DEFENSE CENTERS OF EXCELLENCE
For Psychological Health & Traumatic Brain Injury

Portable, Field-Based Devices for the Early Diagnosis of Mild Traumatic Brain Injury

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ABSTRACT

Recognizing the need to improve diagnosis of mild traumatic brain injury (mTBI) in the field, the Defense Centers of Excellence (DCoE) for Psychological Health (PH) and Traumatic Brain Injury (TBI) conducted a review of recent literature to identify field-deployable devices that may be able to detect mTBI early after injury. The review included searches for devices that can objectively detect, quantify, and record exposures that may cause mTBI as well as devices capable of measuring changes in brain activity, physiology, or function that may be associated with mTBI. To determine which devices are appropriate for use in theater (the combat zone), device size and ease of use were considered. Findings from this review revealed a wide variety of devices proposed for diagnosing mTBI. Few of them, however, have been appropriately validated, particularly for blast-related mTBI. Furthermore, the results of the review revealed that empirical data characterizing mTBI in humans early after injury are lacking, making it difficult to critically evaluate and compare different devices and the measures they provide. Taken together, these findings indicate that there is a critical need for research to (a) determine the sensitivity and specificity of proposed diagnostic devices in detecting mTBI, (b) compare devices with regard to their ability to discriminate mTBI, and (c) provide a better understanding of the early pathophysiologic changes occurring in mTBI to inform future research and development efforts.

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ABBREVIATIONS

ANAM	Automated Neuropsychological Assessment Metric
AMRMC	Army Medical Research and Materiel Command
AUC	area under the receiver operating characteristic curve
BAM	Brain Acoustic Monitor
BCT	Brigade Combat Team
BESS	Balance Error Scoring System
CBF	cerebral blood flow
CDC	Centers for Disease Control and Injury Prevention
CDMRP	Congressionally Directed Medical Research Program
CPP	cerebral perfusion pressure
CO_2	carbon dioxide
CT	computed tomography
CSI	Concussion Symptom Inventory
DCoE	Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury
DARPA	Defense Advanced Research Project Agency
DoD	Department of Defense
DVBIC	Defense and Veterans Brain Injury Center
EEG	electroencephalography
EHS	Environmental Helmet System
eICP	elevated intracranial pressure
EP	evoked potential
ERP	event-related potential
FDA	Food and Drug Administration
GCS	Glasgow Coma Scale
GFP	glial fibrillary acidic protein
GOS	Glasgow Outcome Scale
Hb	hemoglobin
HbO_2	oxyhemoglobin
HEADS	Headborne Energy Analysis and Diagnostic System
HITS	Head Impact Telemetry System
ICP	intracranial pressure
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
kHz	kilohertz
LOC	loss of consciousness
MACE	Military Acute Concussion Evaluation
MAP	mean arterial pressure
MCA	middle cerebral artery
MCAv	middle cerebral artery blood flow velocity
MB	megabytes
MFEIT	multifrequency electrical impedance tomography
MHz	megahertz
mmHg	millimeters of mercury
MRI	magnetic resonance image

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mTBI	mild traumatic brain injury
NIH	National Institutes of Health
NIR	near infrared
NIRS	near-infrared spectroscopy
NRL	Naval Research Laboratory
NSE	neuron-specific enolase
O_2	oxygen
OIF	Operation Iraqi Freedom
OEF	Operation Enduring Freedom
ONSD	optic nerve sheath diameter
PARC	Palo Alto Research Center
PDA	personal digital assistant
PH	psychological health
PI	pulsatility index
PTA	post-traumatic amnesia
qEEG	quantitative electroencephalography
REG	rheoencephalography
RF	radio frequency
rSO2	regional cerebral oxygenation saturation
SAC	Standardized Assessment of Concussion
SBIR	Small Business Innovation Research
SD	standard deviation
SME	subject matter expert
SPEM	smooth pursuit eye movements
SpO_2	saturation of peripheral oxygen (pulse oximeter saturation)
STTR	Small Business Technology Transfer
TBI	traumatic brain injury
TCD	transcranial Doppler ultrasound
$TipO_2$	brain tissue oxygen pressure
TMD	tympanic membrane displacement
TOI	tissue oxygen index
UCH-L1	ubiquitin C-terminal hydrolase L1
USB	Universal Serial Bus
WHO	World Health Organization
Xe	xenon
Xe-SPECT	xenon-1 33 single photon emission computed tomography

Portable, Field-Based Devices for the Early Diagnosis of Mild Traumatic Brain Injury

Executive Summary

The Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) was founded in November 2007 with the mission to assess, validate, oversee, and facilitate prevention, resilience, identification, treatment, outreach, rehabilitation and reintegration programs for psychological health (PH) and traumatic brain injury (TBI) to ensure that the Department of Defense (DoD) meets the needs of the nation's military communities, warriors and families. Critical to this mission is the ability to diagnose TBI early after exposure, but objective and sensitive field-deployable devices for TBI diagnosis — particularly mTBI — are currently lacking. To help fulfill its mission, DCoE conducted a search of current literature to identify portable or potentially portable devices for diagnosing mTBI within minutes to an hour after injury. This review is also intended to help guide future research and development efforts by providing an overview of devices that may be useful for diagnosing mTBI based on their ability to measure other types of acute neurologic injury.

Methodology

The scope and methodology for this literature review were developed in collaboration with the DCoE Research, Quality Assurance, Program Evaluation, and Surveillance Directorate. The review sought to address three research questions related to identifying portable and potentially portable devices that can be used in theater to diagnose mTBI within minutes to an hour following exposure to injury.

1. What existing devices, techniques, or tests can be used effectively in the field for early diagnosis and detection of mTBI?
2. Which of the diagnostic devices currently in use in the clinical/hospital setting are amenable for use in field-based situations? What would be required to outfit such tests for portability?
3. Is there a combination of subjective and objective methods that will provide a comprehensive picture for diagnosis of mTBI?

A search strategy was designed to identify and review devices currently being used to assess mTBI in research and clinical settings as well as devices that may be useful based on their ability to detect moderate to severe TBI or other types of acute neurologic injury (e.g., stroke or ischemia). In addition, a strategy was developed to identify relevant emerging technologies for device development and provide an overview of devices that may be able to diagnosis mTBI in the future.

Results of the Review

Findings revealed that there are few relevant human studies examining early brain changes following mTBI using diagnostic devices and even fewer studies examining blast-related mTBI. Researchers have proposed many devices for diagnosing mTBI. Some involve measures of brain activity (e.g., electroencephalography [EEG]) or function (e.g., visual tracking goggles and computerized tests of

cognition and executive function), while others attempt to non-invasively assess different aspects of brain hemodynamics (e.g., near-infrared spectroscopy [NIRS] and transcranial Doppler ultrasound [TCD]). Other efforts have focused on devices that attempt to measure intracranial pathology, such as intracranial hypertension, via observation of extracranial phenomena (e.g., optic nerve sheath diameter [ONSD] or otoacoustic emissions).

Some potentially useful diagnostic devices have been evaluated in populations of mTBI sufferers, but others have been used only in studies of moderate to severe TBI patients or of patients suffering from other types of intracranial pathology. As a result, additional research is needed to determine whether these devices are valid for diagnosing mTBI.

Conclusions and Future Directions

Many devices have the potential to benefit mTBI diagnosis in the field, but several knowledge gaps must first be overcome to support their widespread use. There is a need for controlled, clinically relevant research to determine whether any of these devices are effective for identifying mTBI , including combat-related mTBI. Comparison studies are needed to determine which devices are most appropriate for field use and for use in the immediate aftermath of injury. Finally, additional human research to characterize early (in the immediate aftermath of injury) pathologic changes that occur as the result of mTBI is needed; an improved understanding of these changes is necessary for identifying markers that may be detectable in the field.

Introduction

Recent military operations in Afghanistan (Operation Enduring Freedom [OEF]) and Iraq (Operation Iraqi Freedom [OIF]) have taken a significant toll on members of the U.S. military, many of whom have sustained TBIs (Hoge et al., 2004). TBI has become a "signature injury" of contemporary warfare (Defense and Veterans Brain Injury Center (DVBIC), 2010a), and there is growing concern that the effects of TBI on health and well-being may linger well beyond the healing of other, more visible wounds. In particular, mTBI is difficult to detect and diagnose because of its often subtle presentation and a lack of objective, biologically or physiologically based diagnostic tools. Failure to diagnose mTBI threatens servicemembers' health on many fronts. First, undiagnosed servicemembers may not receive follow-up observation to look for signs of deterioration. Second, affected individuals may be returned to duty while they are still vulnerable to a variety of damaging secondary effects that can follow TBI. Finally, in the absence of a correct original diagnosis, persistent or delayed symptoms may not be correctly attributed to mTBI.

The goal of this review is to examine advances in neurodiagnostic technology and identify one or more devices that may allow mTBI to be detected and diagnosed early after sustaining an injury. Early diagnosis promotes early intervention and may improve outcomes. It also provides line leaders the opportunity to make better-informed decisions about which servicemembers should return to duty, receive follow-up, or be triaged for further evaluation and care. Until it is possible to clearly diagnose and document mTBI in the immediate aftermath of trauma, it is impossible to develop a complete understanding of its epidemiology, cumulative effects and long-term sequelae.

DEFINING MTBI

TBI can be caused by a jolt or blow to the head or a penetrating injury, and TBI cases range in severity from mild to severe. The terms *concussion* and *mTBI* are often used interchangeably (DVBIC, 2010b), although the relationship between the two depends on the classification scale used for concussion diagnosis (American Academy of Neurology, 1997; American Psychiatric Association, 2000).

Early after mTBI, an individual may experience loss of consciousness (LOC) or altered mental status, along with a variety of other physical, cognitive, behavioral or emotional symptoms: See Table 1 for examples (Campbell, Greenberg, & Weil, 2010). Notably, not all individuals experience the same clinical symptoms.

Table 1: Examples of mTBI Symptoms (Campbell et al., 2010)

Symptoms
✓ No LOC* to LOC <30 minutes
✓ Post traumatic amnesia (PTA)
✓ Headache/lightheadedness
✓ Confusion
✓ Dizziness
✓ Blurred vision or tired eyes
✓ Ringing in the ears
✓ Bad taste in the mouth
✓ Fatigue or lethargy
✓ Change in sleep patterns
✓ Behavioral or mood changes

MTBI DEMOGRAPHICS

TBI in the General Public

TBI accounts for one-third of all injury-related deaths in the United States (Centers for Disease Control and Injury Prevention (CDC), 2010). Each year, 1.7 million Americans sustain a TBI. Of these, more than 1.3 million are treated and

released from a health care facility, 275,000 are hospitalized, and 52,000 die (CDC, 2010). Approximately 5.8 million people, or 3 percent of the population, experience chronic disability associated with TBI (Kim et al., 2007).

Approximately 75–90 percent of recorded TBI cases (or 100–300 out of every 100,000) are classified as mTBI (Cassidy et al., 2004; Thornhill et al., 2000). The actual number of people who sustain an mTBI, however, is likely much higher than these estimates; individuals having less visible symptoms may not seek medical attention for their injuries or be diagnosed with mTBI at the hospital.

TBI in the Military

Compared to their civilian peers, service members have an increased risk for sustaining head injury, even during times of peace. Servicemembers are generally young and predominantly male, both of which are risk factors for incurring head injury (DVBIC, 2010a). Furthermore, the environmental demands of training and service impart additional risk of injury.

Not surprisingly, the risk of sustaining mTBI increases during times of war. A fairly large study of servicemembers returning from OEF/OIF (*n* = 2525) found that 378 servicemembers (15% of the sample) reported experiencing events associated with mTBI, including LOC; being dazed, confused, or "seeing stars;" or not remembering the injury (Hoge et al., 2008). Others have estimated that up to 28 percent of servicemembers deployed to Iraq or Afghanistan have sustained at least one mTBI (Okie, 2005; Warden, 2006).

In addition to other combat-related risks, servicemembers in Iraq and Afghanistan have been exposed to blast-induced injuries, including injuries sustained following the detonation of improvised explosive devices (IEDs). The prevalence of IEDs has brought about a precipitous change in the nature of the battlefield and combat-related injuries, including an increased threat of blast-related injuries (Table 2). A recent study reported that 88 percent of injuries seen at an echelon II facility were caused by explosions (Murray et al., 2005). Thus, when discussing military mTBI, it is important to consider how exposure to an explosive blast may affect the sensitivity, specificity, and/or feasibility of diagnosis and diagnostic devices.

Table 2: Sources of Injury in Military Personnel during World War II (WWII), Vietnam, and OEF/OIF (Rounded to the Nearest Percentage)

	Thoracic (%)	Head or Neck (%)	Gunshot Wounds (%)	Explosion-Related (%)
WWII	6	21	27	73
Vietnam	13	16	35	65
OEF/OIF	14	31	19	81

Although current statistics provide an informative picture of mTBI sustained in the military setting, they likely fail to capture all mTBI cases. First, servicemembers may not report that they have experienced a TBI because they do not want to be pulled out of combat and away from their comrades. Even when an attempt is made to report exposure, the impact of stress, psychological trauma or mTBI itself may impair accurate reporting of an injury event and subsequent symptoms. Furthermore — and perhaps most relevant to blast-exposed veterans — individuals may simply not recognize that they have been exposed to injury, either because they did not sustain a direct head impact or because they do not

recognize that their exposure to blast could lead to mTBI. Second, because mTBI often occurs without overt signs of injury, it may be missed by clinicians, particularly if the servicemember has more obvious injuries requiring immediate attention. Military operations that result in multiple casualties also tax medical personnel; in these situations, combat medics, corpsmen or echelon medical providers may fail to ask about or identify mTBI (Campbell et al., 2010). Furthermore, mTBI diagnosis may be confounded by symptomatic overlap between mTBI and other potentially co-occurring or co-morbid conditions, such as mood and anxiety disorders, sleep disturbances, pain disorders, and substance use and abuse.

DIAGNOSING MTBI

Diagnostic Criteria

Over the years, different organizations have proposed a variety of diagnostic criteria for mTBI, including the American Congress of Rehabilitation Medicine (Kay et al., 1993), the CDC (CDC, 2003), and the World Health Organization (WHO) Task Force on Mild Traumatic Brain Injury (Holm, Cassidy, Carroll, & Borg, 2005). Currently, military medical providers use criteria for mild, moderate and severe TBI that include Glasgow Coma Scale (GCS)[1] scores and the durations of LOC, altered consciousness, and PTA (The Management of Concussion/mTBI Working Group, 2009; Table 3).

Table 3: mTBI Diagnostic Criteria

TBI Severity	GCS	Alteration in Consciousness	LOC	PTA
Mild	13 to 15	≤24 h	0–30 min	≤24 h
Moderate	9 to 12	>24 h	>30 min to <24 h	>24 h to 7 d
Severe	3 to 8	>24 h	≥24 h	≥7 d

mTBI Assessment in Theater

In the aftermath of a blast or injury to the head, servicemembers are assessed using the Military Acute Concussion Evaluation (MACE), which is a pencil-and-paper assessment of concussion developed by DVBIC (DVBIC, 2009). The MACE contains three sections and can be administered in five minutes by a trained individual. The first section contains indentifying information, and section two contains event and symptom history. Section three is the examination portion. The examination consists of an orientation section, an immediate memory word list section, a brief neurologic assessment, a digits-backward and months-in-reverse-order concentration section, and a delayed recall section. The delayed recall section asks the individual to recall the word list administered earlier in the examination. The MACE options include no concussion, concussion with no LOC, concussion with LOC, and other assessment outcomes. Ultimately, a clinician determines whether an individual has sustained a mTBI based on screening assessment outcomes and clinical observations. At present, no objective, biologically or physiologically based diagnostic measures of mTBI exist.

[1] The GCS is a 15-point scale (3–15-point outcome range) that measures eye opening, verbal, and motor responses (CDC, 2006).

CONSIDERATIONS FOR DEVELOPING AND VALIDATING DEVICES FOR DIAGNOSING MTBI

mTBI Pathophysiology

To identify devices for diagnosing mTBI early after injury, it is necessary first to consider various biologic and neurologic changes evoked by TBI more generally and the ways to potentially measure them. Brain injury is not a discrete entity — it is a continuum of cascading, often interrelated events. Waves of these events occurring over time are represented as "stages" of injury. Primary injury includes contusions, lacerations, hemorrhage, and diffuse axonal injury. This is followed by secondary injuries comprising a wide range of cellular and physiologic changes that lead to additional injury and can exacerbate primary injury. A brief and simplified summary of injury events that may occur following TBI is provided in Table 4. Other authors have provided more comprehensive and detailed analyses (Arciniegas, Anderson, Topkoff, & McAllister, 2005; Czosnyka, Smielewski, Lavinio, Czosnyka, & Pickard, 2007; Golding, Robertson, & Bryan, 1999; Hicks, Fertig, Desrocher, Koroshetz, & Pancrazio, 2010; Morganti-Kossmann, Rancan, Stahel, & Kossmann, 2002; White & Venkatesh, 2008).

Table 4: Examples of Primary and Secondary Events Associated with TBI

Injury Associated with TBI
Primary Injury
✓ Contusion
✓ Laceration
✓ Hemorrhage
✓ Diffuse axonal injury
Secondary Injury
✓ Ischemia
✓ Oxidative stress
✓ Glutamate excitotoxicity
✓ Metabolic dysfunction
✓ Edema
✓ Neurochemical alterations
✓ Inflammation

Ultimately, these changes can alter the functional integrity of brain cells. Cerebral blood flow (CBF) may become impaired (e.g., through decreased cerebral perfusion pressure [CPP][2]) and deleterious sequelae, such as ischemia, may occur. In addition, homeostatic mechanisms designed to maintain cerebral integrity, such as cerebral autoregulation, may become compromised. These events may leave the brain unable to maintain adequate cerebral perfusion in the face of systemic blood pressure changes, and, in turn, vulnerable to insults caused by peripheral hypoxia and hypotension. Another pressing consequence of these injury cascades is edema and subsequent intracranial hypertension (elevated intracranial pressure [eICP]). Edema can result from multiple events, such as metabolic dysfunction and breakdown of the blood-brain barrier. As fluid in the cranium increases, ICP increases, and compensatory mechanisms for maintaining perfusion become exhausted. As a result, CBF is hindered, causing further injury.

The events described above represent a variety of injury-related events that may occur following all severities of TBI—particularly following severe TBI cases. Few mTBI sufferers, if any, will experience the full spectrum of injuries. For mTBI, the precise incidence and timing of injury-related events are not completely clear, which makes it particularly difficult to diagnose. Few studies have evaluated mTBI patients within the first minutes to an hour after injury, and clinically validated devices for assessing intracranial pathology in mTBI patients are not yet available. Thus, it may be useful to consider diagnostic devices that can measure injury-related events such as disturbed CBF, eICP, and ischemia.

[2] CPP is the difference between the pressure in the arteries (mean arterial pressure) and the pressure inside the skull (ICP). A significant drop in CPP can decrease blood flow (cerebral perfusion) throughout the brain, potentially resulting in ischemia.

Additional research and clinical studies will be necessary, to determine their ability to diagnose mTBI in the immediate aftermath of trauma.

Comparing Non-Military and Military Settings

Much of the current knowledge about mTBI has been derived from sports injury literature or studies of civilian emergency room patients. Differences may exist between mTBI sustained in these settings versus military settings, including the context surrounding the injury, source of injury, and extent of polytrauma. Such differences must be carefully considered when evaluating the scientific literature to identify devices for use in the field context of military operations. Contextual differences may also be relevant to the determination of normal versus abnormal clinical values, cut-off thresholds, and classification methods. Methods and measures obtained from civilian or pre-deployment baseline data may or may not be appropriate to the military field setting.

Impact of Context Surrounding the Injury

In combat, human lives are at risk. This is generally not the case in sports settings or in civilian settings not characterized by combat or conflict. Over time, chronic psychological stress caused by a perceived threat of death or other combat-related stressors may induce physiologic changes (e.g., stress hormone secretion) that in turn can influence the brain's vulnerability to injury. Furthermore, military personnel may be more vulnerable to injury because of sleep deprivation, chronic psychological and physical stress, and altered physiologic states associated with extreme environmental demands (e.g., extreme fluctuations in temperature, humidity, and altitude).

Impact of Injury Source

Explosive blast is responsible for many military injuries in combat. Whether or not blast-related TBI differs pathologically from other types of TBI has been the focus of recent debate (French, Mouratidis, Dicianno, & Impink, 2009). Blast can result in exposure to events not necessarily associated with non–blast-related TBI, such as the inherent properties of blast forces (e.g., blast over and under pressure), shrapnel penetrating the head, and toxic gas exposure (for a recent review, see Hicks et al., 2010). Thus, pathologic features that are specific to blast-related-TBI may exist, but it remains to be determined whether or how these features might relate to patient care and management.

Impact of Polytrauma

Polytrauma can occur in any setting, but it is particularly common in the military context. Blast forces can damage the entire body, particularly areas not shielded by protective gear, such as the eyes and ears. One recent study found that 66 percent of OEF/OIF veterans who screened positive for TBI also had combat ocular trauma (Weichel, Colyer, Bautista, Bower, & French, 2009). Organ and tissue injury can result in hypoxia and hypotension, both of which may exacerbate TBI.

Polytrauma can also confound diagnostic measures for mTBI. For example, polytrauma may preclude the use of diagnostic measures that rely on end-organ integrity, such as ocular, audiologic, or balance assessments. Pathologic measures that are not specific to brain injury, for example, indicators of inflammation, physiologic dysfunction, and cellular injury, may not be appropriate for assessing patients with multiple injuries.

Impact of the Field Environment on Device Feasibility

When determining the feasibility of a diagnostic device in the field, environmental demands are a critical consideration. First, device size and weight must be considered. In the combat zone, equipment is generally limited to what can be carried in military backpacks or on convoy transportation vehicles. Second, it is important to consider the expertise that is necessary to operate the device and interpret its results. Immediately following injury, medical assistance is generally provided by fellow servicemembers or combat medics who may not have the specialized expertise required for operating the device or interpreting its results. Although training can be provided prior to deployment, the amount of time allotted for training is limited and must cover many types of medical procedures, assessments and techniques. Finally, the field's physical environment must be considered when developing device features and methods. Terrain and environment are potentially formidable forces. Temperatures may vary from hot to cold. Military personnel may have to operate at high altitude. Weather variables might include dust and sand storms, among other things. All of these factors can interfere with instrumentation and increase the rate of mechanical wear and tear. In the context of combat, devices that are minimally instrumented and ruggedized are likely to fare better than those that are not.

Regulatory Considerations for Device Development

Regulatory requirements are an issue of considerable importance to developing devices for mTBI diagnosis. All medical devices, including those intended for diagnostic purposes, are regulated by the U.S. Food and Drug Administration (FDA). For this reason, well-designed validation studies must be conducted for device approval.

According to the FDA website (FDA, 2010):

> "If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act it will be regulated by the Food and Drug Administration (FDA) as a medical device and is subject to premarketing and postmarketing regulatory controls. A device is:
>
> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
>
> - recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
> - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
> - intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Most Class I devices are exempt from premarket notification 510(k) whereas most Class II devices require premarket notification 510(k) and most Class III devices require premarket approval. For example, most biomarker submissions have been classified as Class III devices and, thus, require premarket approval (Oli, Hayes, Robinson, & Wang, 2009).

Methodology

The scope and methodology for this review were designed in collaboration with the DCoE Research, Quality Assurance, Program Evaluation, and Surveillance Directorate. The overarching goal of this review was to identify diagnostic devices that can be used to detect mTBI in theater immediately (within minutes to an hour) after impact. This review is also intended to help guide future research and development efforts by providing an overview of devices that can potentially diagnosis mTBI based on their ability to detect other types of acute neurologic injury. A list of search terms was developed based on the research questions and areas of interest.

The literature review sought to answer the following questions:

1. What existing devices, techniques, or tests can be effectively used in the field for early diagnosis and detection of mTBI?
2. Which of the diagnostic devices currently in use in the clinical/hospital setting are amenable for use in field-based situations? What would be required to outfit such tests for portability?
3. Is there a combination of subjective and objective methods that will provide a comprehensive picture for diagnosis of mTBI?

In addition, a strategy was developed to identify relevant emerging technologies for device development and provide an overview of devices that may be able to diagnosis mTBI in the future.

Search Strategy

Search terms included broad terms for identifying articles related to mTBI and brain injury diagnosis. Additional terms were used to specifically identify studies conducted early after injury and studies that included military or blast-exposed populations. More than 150 initial searches were conducted, with additional searches for refining results or providing more detailed information about devices identified in the initial searches. Searches were conducted in PubMed, Google Scholar, and Ovid using select search term combinations and limited to English-language articles published between 2000 and 2010. Selected studies were also limited to adult human studies. Subject matter experts (SMEs) provided additional input to help guide efforts and to identify emerging technologies.

Examples of government-funded research efforts relevant to mTBI diagnosis were identified using combinations of search strategy terms. When available, results were presented in table form. Because a full search of awards databases was beyond the scope of this review, three funding sources were chosen for these searches: National Institutes of Health (NIH), DoD Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR), and U.S. Army Medical Research and Materiel Command (USAMRMC). Relevant awards were not successfully identified for all device areas. Supplemental information about commercial efforts identified by initial search was obtained through company websites and press releases, which are not peer-reviewed sources.

The search strategy uncovered a broad spectrum of potential mTBI diagnostic devices and/or technologies. To focus the review and best address the research questions, a *portable, field-based*

diagnostic device was defined as a device that is appropriately sized and powered for use in the combat zone or in evacuation transportation.

ASSUMPTIONS

This review is intended for the research community and is written using a format similar to that used for peer-reviewed scientific literature. Where possible, technical terms are defined in lay language, but some basic scientific terms and principals (e.g., the relationship between wavelength and light) are not defined in depth. To serve a broader audience, device specifications and characteristics that would be of interest only to technical experts or engineers are located in the appendices.

Results of the Literature Review

SENSOR SYSTEMS FOR DETECTING EXPOSURE TO INJURIOUS EVENTS

One of the earliest steps in diagnosing mTBI is identifying and quantifying exposure to injurious events. Currently, this process is subserved by gathering qualitative self-reports and observations of witnesses. These data can be limited by subjectivity as well as by an individual's ability or willingness to report accurately.

One approach for objectively detecting threats to brain health is the development of sensor systems that can detect, record and quantify head impact, acceleration and blast forces. Several such helmet-based sensor systems have been or are in the process of being developed, including two systems that were fielded in Iraq and Afghanistan.

Current Helmet-Based Sensor Systems

Head Impact Telemetry System

In 2007, the Army awarded Simbex, LLC, a $932,000 contract to adapt the Simbex Head Impact Telemetry System (HITS; Simbex, LLC, 2009) for use in the Army's Advanced Combat Helmet. The Simbex HITS system originally gained recognition for its use by the National Football League in Riddell sports helmets. The Army version of HITS comprised eight accelerometers (to measure acceleration forces caused by movement or vibration) built into the helmet's liner. Developed by Endevco, the accelerometers measure linear and rotational acceleration, having high bandwidth to measure both high-magnitude and high-frequency impact. To help better assess blast exposure, Simbex engineers added a pressure transducer for measuring pressure changes caused by shock waves and transducers that turn on the helmet's data acquisition system when triggered by blast forces.

Environmental Helmet Sensor

The Naval Research Laboratory (NRL) developed an Environmental Helmet Sensor (EHS) with features for distinguishing between blast- and non-blast forces (Simmonds et al., 2009). The first prototype comprised a three-axis accelerometer, a triggering circuit, and control algorithms and was designed to be mounted on the back of a helmet. NRL teamed with Allen-Vanguard Corporation to transform the prototype into a more rugged, battlefield-appropriate system with an added pressure sensor and software for downloading 500 events (Simmonds et al., 2009). The EHS can measure acceleration up to 4000 times the force of gravity (G) in three directions, ambient temperature, and peak pressure up to 17 atmospheres, and it is equipped with enough battery power for 7 months of continuous operation. Exposure information is stored on the system until needed, at which point it can be downloaded using a universal serial bus (USB) device. Allen-Vanguard extensively blast-tested the system.

Headborne Energy Analysis and Diagnostic System

The Headborne Energy Analysis and Diagnostic System (HEADS) was introduced by BAE Systems in 2008 (BAE Systems, 2009a). This system is similar to the EHS but has a few key differences. Compared to the EHS, HEADS is more lightweight, can record more events, and sits inside of a helmet instead of being externally mounted. According to company specifications, HEADS has three-axis accelerometers with

5000 G range and 5 kilohertz (kHz) frequency response as well as an embedded pressure sensor with a ≥100 pounds-force per square inch absolute (psia) range and 100-µsec response. This allows the system to record sudden acceleration data in the X, Y, and Z axes as well as overpressure data. Although the number of events the system can capture is not limited, overall data acquisition is limited to 512 megabytes (MB) of memory.

Military Fielding of Generation I and II Sensors

Generation I Sensors

The Program Executive Office Soldier chose two sensor systems for fielding: one from BAE Systems and the other from Allen-Vanguard (Dawson, 2009). The internal sensor system was deployed to Iraq with soldiers of the 1st Brigade Combat Team (BCT), 4th Infantry Division, whereas the external system was fielded in Afghanistan with soldiers of the 4th BCT, 101st Airborne Division (Lamothe, 2008). Data from these generation I sensor systems were collected from March 2008 to March 2009 but have not yet been published in peer-reviewed literature.

Generation II Sensors

The U.S. Army has already begun the process of acquiring and fielding generation II helmet sensors. On June 30, 2010, Allen-Vanguard and BAE Systems were each awarded a $16,999,760 firm-fixed-price contract to develop the generation II helmet sensors. In general, planned enhancements include improved data collection, storage, and power management. In addition, the generation II sensors will measure both linear and angular acceleration as well as the exact times of single or multiple blast events.

BAE Systems unveiled its new HEADS II system at the Farnborough International Air Show in July 2010. Upgrades are reported to include an increased acceleration range from 5000 G to 6000 G and wireless data summary download with a handheld range of ≥3 inches and a fixed range ≥30 feet (BAE Systems, 2009b). The HEADS II system will collect six channels of angular and linear acceleration. The system also has a new battery — a rechargeable lithium-polymer battery with motion sensor and sleep/wake up mode. Company officials claim that the HEADS II system will have a flashing LED light that blinks when blast forces exceed a predetermined threshold and will use radio-frequency (RF) technology so that data the sensors collect can be read by an antenna or hand-held device (BAE Systems, 2010).

Allen-Vanguard's new system, called the *Sensor, Helmet, and Kinematic Recorder* (SHAKR), is expected to include similar upgrades, including wireless data transmission and upgraded electronics (Allen-Vanguard Corporation, 2010).

Future Directions

Although advances have been made in developing sensor systems for detecting and recording forces that may threaten brain health, currently available sensor systems have limitations. Most pressure sensors are direction dependent, such that their output depends on sensor orientation. Furthermore, sensor systems are relatively cost-prohibitive for extensive fielding, maintenance, and replacement. Systems that require less instrumentation may be less expensive, less bulky, and suffer from fewer technical failures. In addition, technologies and methods for linking data obtained from helmet sensor systems to medical data are critical for determining how effective sensor system data are in predicting

whether a servicemember has sustained mTBI. Several research and development efforts are now underway to address the limitations of current sensor systems.

Organic and Printed Electronics for Sensor Development

Low-cost sensor systems may be developed using organic and printed electronics (flexible electronics). These technologies take advantage of recent advances in nanotechnology and print methods, such as microcontact, inkjet, screen, thermal-line patterning and offset printing.

Currently, at least one company, the Palo Alto Research Center (PARC; a Xerox company), is using organic and printed electronics to develop improved sensor systems. In June 2008, the U.S. Defense Advanced Research Project Agency (DARPA) gave PARC a $2 million, 18-month award to develop a flexible, printed blast dosimeter that can be attached to a helmet or other relevant surface. PARC designed a piece of disposable "tape" for recording pressure waves, acceleration, acoustic levels, temperature, and light intensities (Ng et al., 2009, 2010; PARC, 2008; PARC, n.d.; see Appendix A for details).

PARC's blast dosimeter 'tape' is small and lightweight — no larger than a 4 × 4-inch medical pad, with a minimum 1-inch bend radius. The tape uses a thin-film, non-volatile battery with a low device count analog memory. The system is mechanically flexible and relatively robust to stress or deformation, making it suitable for mounting to curved objects such as helmets. Multiple pieces of the tape can be placed in different locations on the helmet, presumably minimizing the influence of direction on data output. Data collected and stored by the tape can be extracted and used to calculate cumulative blast exposure.

PARC states that its blast dosimeter yields results comparable with more expensive, commercially-available technologies and can be fabricated for less than $1 (PARC, 2008).

Early-Stage Research and Development Efforts

Other devices currently under development include sensor systems that are omni-directional and able to measure time of arrival of blast forces. In addition, devices using novel approaches for sensor development include sensors that have optical properties that change when exposed to blast pressure or acceleration forces (Appendix B).

Conclusions

Sensor systems for detecting exposure to blast and acceleration forces have been developed, two of which have been fielded in combat settings. To date, data collected by these systems have not been published in peer-reviewed literature. Generation II sensor systems are being developed with added capabilities, such as wireless data transfer. Many of these systems, however, are currently limited by their cost and the influence of blast force direction on data quality. Research and development efforts are focused on addressing these limitations.

Because data from testing and fielding current sensor systems are not yet available in the peer-reviewed literature, critically evaluating their capabilities, field feasibility, and clinical value is not possible. Notably, a critical need exists for technologies and methods that can be used to link data obtained from the sensor systems to clinical data. In addition, for the data from these systems to be clinically useful, research is needed to determine the thresholds at which acceleration and blast forces cause mTBI and

the factors that influence individual vulnerability to mTBI (e.g., prior brain injury history, genetics, psychological stress). In line with this, sensor systems that can both monitor cumulative exposures to injurious events and link the data to human safety thresholds, which are currently unknown, need to be developed.

POINT-OF-CARE DETECTION DEVICES FOR ASSESSING BIOMARKERS

A chemical biomarker for mTBI could provide an objective, early, and quantitative index of brain injury, even when overt signs of injury are absent. Recent efforts to identify chemical biomarkers for mTBI underscore the need for portable point-of-care devices to analyze samples in the field. An optimal device would be able to prepare and purify samples (e.g., blood samples); analyze biomarker concentrations; and provide real-time, automated results to indicate the presence or absence of mTBI.

Current State of Biomarkers for mTBI Diagnosis

Biomarkers for mTBI Diagnosis

To date, a wide variety of biomarker candidates have been examined for their ability to diagnose mTBI, with some — such as S100B, glial fibrillary acidic protein (GFAP), and neuron-specific enolase (NSE) — receiving considerable attention. (A non-exhaustive biomarker candidate list and related reading can be found in Appendix C). Recent reviews of the literature, however, consistently conclude that none of the proposed candidates appear to have the sensitivity and specificity[3] needed to serve as a stand-alone diagnostic indicator for mTBI (Begaz, Kyriacou, Segal, & Bazarian, 2006; Hergenroeder, Redell, Moore, & Dash, 2008; Kövesdi et al., 2010). Research is needed to address the sensitivity and specificity of newer candidates, such as ubiquitin C-terminal hydrolase L1 (UCH-L1; Kobeissy et al., 2006; Liu et al., 2010; Papa et al., 2010), neurofilament phosphoforms (Säljö, Bao, Haglid, & Hansson, 2000; Siman et al., 2009), 14-3-3 proteins (Berg, Holzmann, & Riess, 2003; Kobeissy et al., 2006; Siman et al., 2009) and others.

Given the complex and heterogeneous nature of TBI, a single biomarker for mTBI diagnosis may not exist. It may, however, be possible to use screening panels that incorporate multiple complementary biomarkers. Such panels have shown promise for detecting and discriminating other forms of brain pathology, such as stroke, within hours of symptom onset (Laskowitz, Blessing, Floyd, White, & Lynch, 2005; Laskowitz et al., 2009; Lynch et al., 2004).

Banyan Biomarkers, Inc. (formerly known as Daimonion Diagnostics, LLC) is undertaking a major initiative that may advance development of biomarker panels for mTBI diagnosis. In 2009, the company began investigating proprietary biomarkers in several hundred TBI patients shortly after injury (Banyan Biomarkers, Inc., 2009). Now, with an expected DoD award of $17 million, Banyan Biomarkers plans to conduct a large scale, 18-month study that will include more than 1000 patients at 20 hospitals (Burton, 2010). Although the exact biomarker panel planned for use in this study could not be identified by a search of the scientific literature, the company has expressed interest in multiple biomarker candidates.

[3] Sensitivity and specifity refer to the ability of a diagnostic device to accurately identify individuals who have or who don't have a condition or disease. Sensitivity refers to the percentage of individuals who have a condition and who are accurately identified as having the condition by the diagnostic device. Specificity is the percentage of individuals who do not have a condition and who are accurately identified as not having the condition by the device.

Banyan Biomarkers holds several patents involving TBI biomarkers, including breakdown products of microtubule-associated proteins (U.S. Patent No. 7,456,027, November 25, 2008), spectrin and spectrin proteolytic cleavage products (U.S. Patent No. 7,291,710, November 6, 2007), and unspecified neural proteins (U.S. Patent No. 7,396,654, July 8, 2008). Scientists at Banyan Biomarkers have also investigated changes in UCH-L1 following brain injury and stroke in animal models (Liu et al., 2010) as well as in patients with severe TBI (Papa et al., 2010).

mTBI Biomarkers in Military Populations

For a biomarker to be useful in the military operational environment, it is important to avoid the need for invasive or potentially dangerous medical procedures. Ideally, the biomarker should be present in blood, saliva, or urine. Because samples from blood and other peripheral sources carry information about the entire body, brain-specific markers are more optimal than general indicators of inflammation, injury, or cell death. This is particularly true in cases of polytrauma. Brain-specific biomarkers, however, are not easily accessed. Unless the biomarker can leave the brain and enter peripheral circulation by crossing the blood-brain barrier (most cannot), it is trapped in the brain. For the biomarker to leave the brain, the integrity of the blood-brain barrier must be disrupted. The incidence and timing of blood–brain barrier breakdown following both blast- and non–blast-related mTBI are unclear.

Research will also be needed to determine whether biomarkers of use in civilian settings are clinically valid in combat settings. For example, some biomarkers may be affected by chronic or acute stress or other factors that are common in military settings. This could be problematic when comparing a Service member's biomarker levels to normal values determined in civilian studies. Finally, it is not yet clear whether blast-specific biomarkers exist (Blennow et al., 2010; Svetlov et al., 2009).

Point-of-Care Biomarker Analysis Devices

As previously mentioned, real-time, point-of-care devices will be needed to analyze samples in the field. Devices of this type should be self-contained and able to perform all steps required for analysis. Traditional laboratory biomarker analysis devices carry out several steps, and multiple devices are often needed to perform analysis from sample collection to result. First, a sample containing the biomarker needs to be separated from the blood or other body fluid and purified. The resulting sample is then run through a system containing factors (e.g., antibodies) that recognize and capture the biomarker, forming capture factor–biomarker complexes. Detection factors are added to the system; these recognize the formed complexes and bind (connect) to them. Detection factors have attached "labels" that can emit a measurable signal. This signal can be fluorescence, radioactivity, or a substance that changes its color or optical properties. The signal is emitted when the detection factor binds to the biomarker complex, and the amount of emitted signal is used to calculate the biomarker concentration. Each step of this process requires materials that may be light or temperature sensitive as well as equipment that can be bulky, expensive, and subject to technical failures, particularly in harsh environments.

Currently, there is no clinically validated, FDA-approved biomarker device for mTBI. Some portable, point-of-care devices are being used in hospitals for other clinical applications. These include devices to assess cardiac biomarkers (the Roche CARDIAC proBNP test and its successor, the cobas h 232 system; Alehagen & Janzon, 2008; Bertsch et al., 2010) and stroke biomarkers (e.g., the triage stroke panel used with the triage meters [Biosite Inc., San Diego, CA, USA]; Laskowitz et al., 2009). Although portable, these devices are still limited by some of the factors mentioned above. New or adapted technologies are needed to develop a system more suitable for use in the military setting.

Future Directions

In addition to portability and clinical validity, there are several characteristics that a point-of-care biomarker analysis device would require for use in the military setting (Table 5).

Table 5: Ideal Characteristic of a Point-of-Care Device Intended for Field Use

Characteristics
✓ Low-cost
✓ Small and lightweight
✓ Disposable or multiuse capability
✓ Reagentless
✓ Able to stabilize samples until data analysis is finished
✓ Able to separate and purify the sample as well as perform the analysis
✓ Rugged
✓ User friendly, requiring little expertise
✓ Real-time output of results
✓ Minimal instrumentation

One effort to develop a hand-held device for TBI diagnosis that may be close to achieving FDA approval is that of SFC Fluidics LLC. The company recently announced that it has received a contract for approximately $4,938,090 from the Congressionally Directed Medical Research Program (Award: DR081211; SFC Fluidics, LLC, 2009) to develop a portable, hand-held device for rapid TBI diagnosis using a pinprick of blood. The device is expected to be low cost and able to provide a read out of TBI severity (i.e., none, mild, moderate, or severe). SFC Fluidics LLC hopes to begin clinical trials for FDA approval in 2013.

Given the lack of point-of-care devices for biomarker analysis, stimulation of additional research and development is needed in this area. Several technologies may provide the platform needed for developing an optimal field-based biomarker analysis device. These include microelectrical sensors, electrochemical immunosensors, microfluidic "chips," photolithography and chromatography (Arruda et al., 2009; Sorger, 2008; Weigl, Domingo, LaBarre, & Gerlach, 2008). Although an exhaustive review of these technologies is beyond the scope of this paper, several are highlighted as examples below (and Appendices D and E) to provide an overview of research and development possibilities.

Immunochromatographic Strips

A biomarker analysis device for mTBI could be as simple as immunochromatographic or lateral flow strips. Immunochromatographic strips are generally stable for many months at ambient temperatures, relatively inexpensive and usually require little, if any, sample preparation. Furthermore, most can be read with the naked eye or commercially available hand-held devices (Weigl et al., 2008). Traditional immunochromatographic strips, however, may not have the sensitivity and specificity needed to detect low-abundance biomarkers. Sensitivity limitations may be overcome by advances in paper- or membrane-based colorimetric technologies (technologies based on measurable color properties). Ornatska and colleagues have suggested using paper-based devices based on changes in the physical–chemical properties of metal oxide nanoparticles, which are used as chromogenic (color producing) indicators (Ornatska, Sharpe, D. Andreescu, & S. Andreescu, 2010). The proposed device would eliminate the need for reagents and electronics, making it more suitable for field use. Similarly, gold-nanoparticle–based immunochromatographic devices for clinical applications are under development (Takahashi et al., 2009).

Microfluidic Technologies

In addition to lateral flow technologies, experts have shown interest in microfluidic technologies for point-of-care biomarker devices. Recently developed integrated microfluidic systems, such as the integrated blood barcode chip and its variants (Fan et al., 2008; Goluch et al., 2009; Qin, Vermesh, Shi, &

Heath, 2009; Sorger, 2008) can rapidly separate plasma from whole blood using microchannels and, in some cases, conduct the biomarker assay in those same channels. This eliminates the need to prepare samples prior to using the analysis device and may advance the development of self-contained, "lab-on-a-chip" designs.

Label-Free Detection Systems

Label-free detection allows biomarkers (proteins and other macromolecules) to be detected without needing to attach fluorescent, radioactive, or other labels (Ray, Mehta, & Srivastava, 2010). This allows analysis to be conducted with minimal reagents and potentially without needing expensive optical imaging systems. For example, capture antibodies may be attached on top of and in between gold electrodes. The sample containing the biomarker is then applied to the electrodes, and the biomarker binds to the capture antibodies. This binding changes the electrodes' electrical properties. Voltage can be applied across the electrodes, and the resulting current can be measured. The measured current reflects the biomarker concentration in the sample (Arruda et al., 2009).

Several technologies may be used to create a label-free system, including electrochemical immunosensors and microelectrical sensors (Arruda et al., 2009; Dungchai, Chailapakul, & Henry, 2009; Maraldo, Garcia, & Mutharasan, 2007; Stoeva, Lee, Smith, Rosen, & Mirkin, 2006; Tang, Yuan, & Chai, 2008; Wilson & Nie, 2006; Appendix D). Electrochemical immunosensors can be economically mass-produced and some are able to detect low-abundance biomarkers in small sample sizes (Wilson & Nie, 2006). Although microelectrical sensors provide technological benefits similar to those provided by electrochemical immunosensors, microelectrical sensors have been limited by cost and issues with fabrication and sensitivity. These technologies have also been limited by biofouling, non-specific binding, degradation of the active surface areas and in some cases, the need for precisely controlled buffers (Arruda et al., 2009; Stern et al., 2010). Using a microfluidic purification chip to first purify the sample may mitigate some of these problems (Stern et al., 2010).

Conclusions

To date, no biomarker candidate has demonstrated the sensitivity and specificity needed to serve as a stand-alone mTBI biomarker. As a result, research is needed both to identify a new biomarker or biomarker panel for mTBI diagnosis and to validate the proposed biomarkers in the military setting.

A need exists for a field-appropriate, point-of-care device that can be used to analyze biomarkers in blood, urine, or other body fluid samples. Efforts should target technologies that are relatively low cost, minimally instrumented, and sensitive to low-abundance mTBI biomarkers. Advanced technologies, such as microfluidics, microelectrical sensors and electrochemical immunosensors, may prove useful in developing field-based point-of-care devices for mTBI diagnosis.

Electrophysiologic Methods and Devices

Many methods and corresponding devices measure brain electrophysiology (electrical brain activity). Of these, several have been used to examine brain activity following mTBI, including EEG, evoked potentials (EPs) and event-related potentials (ERPs).

Electroencephalography

EEG is particularly attractive for field use because it is portable, relatively inexpensive and requires relatively short recording durations (Airoldi, Beghi, Bogliun, Crespi, & Frattola, 1999). Although *routine* EEG lacks sufficient sensitivity and specificity for diagnosing mTBI (Gaetz & Bernstein, 2001; Nuwer, 1997; Nuwer, Hovda, Schrader, & Vespa, 2005; Voller et al., 1999), quantitative EEG (qEEG), together with advanced analyses methods, shows promise for clinical applications.

QEEG has consistently yielded interesting research results in studies of concussed athletes and mTBI patients. For example, multiple qEEG parameters appear to change following mTBI (Geets & Louette, 1985; Nuwer et al., 2005; Thatcher et al., 1999, 2001; Thatcher, Walker, Gerson, & Geisler, 1989; Thatcher, 2010; Watson et al., 1995). QEEG abnormalities can appear early after injury, and, in a subgroup of individuals, can persist over time (for recent reviews, see Nuwer et al., 2005; Thatcher, 2010). Furthermore, qEEG parameters can reflect the effects of multiple mTBI exposures (Slobounov, Cao, & Sebastianelli, 2009), symptom persistence (Chen, Tao, & Chen, 2006; Duff, 2004; Thompson, Sebastianelli, & Slobounov, 2005; Thornton, 1999) and recovery of function (Watson et al., 1995). This suggests that qEEG measures can detect brain changes both early after sustaining mTBI and over a period of time post-injury.

Despite the relationship between mTBI and qEEG abnormalities, there is controversy about the extent to which qEEG can be used for diagnostic purposes (Gaetz & Bernstein, 2001; Nuwer, 1997; Nuwer et al., 2005; Thatcher et al., 1999; Thatcher, 2010). A recent review by Thatcher (2010) arrived at a favorable conclusion about using qEEG to diagnose mTBI, finding that qEEG's clinical validity and reliability is greater than 0.95. One of the largest studies included in the review comprised four cross-validation studies and used a discriminant function analysis[4] to evaluate a sample of 608 mTBI patients (Thatcher, Walker, Gerson, & Geisler, 1989). This approach successfully distinguished mTBI patients from age-matched normal control participants with a classification accuracy of 96.2 percent. All four cross-validations conducted in the study produced similar accuracies, with an overall sensitivity and specificity of 96.6 and 89.2 percent, respectively, and average positive and negative predictive values of 93.6 and 97.4 percent, respectively. Using a similar approach, a subsequent study found that discriminant analysis could predict Glasgow Outcome Scale (GOS) scores with a correlation of 0.85 (Thatcher et al., 2001). Many other studies have used qEEG to assess mTBI patients or concussed athletes and reported similar sensitivities and specificities (Duff, 2004; Leon-Carrion, Martin-Rodriguez, Damas-Lopez, Barroso y Martin, & Dominguez-Morales, 2008; Leon-Carrion, Martin-Rodriguez, & Dominguez-Morales, 2008; Thornton, 2003, 1999).

QEEG can be limited by the lack of standardized protocols and the need for expertise to analyze data. Reports that qEEG abnormalities are more common than clinical symptoms in the initial months following injury have also raised concern (Nuwer et al., 2005). Although it is possible that early qEEG abnormalities reflect exquisite sensitivity to injury-related changes in brain activity, a high rate of false positives may discourage its use in clinical settings.

[4] A *discrimant function analysis* is a statistical method used to predict group membership (e.g., is an individual healthy or injured). *Discriminant functions* are mathematical equations created using values (e.g., different EEG paramaters) that were obtained from individuals whose group was already known.

EEG and Military Populations

Most qEEG studies have evaluated individuals from civilian settings and individuals who have not been exposed to blast forces. Only two peer-reviewed studies have examined EEG-recorded brain activity following blast-related injury, and neither of these investigated brain activity in the early post-injury phase (Cernak, Savic, Ignjatovic, & Jevtic, 1999; Trudeau et al., 1998). Study details can be found in Table 6. Both studies found EEG abnormalities in individuals who were exposed to blast. These data, however, are not sufficient to support the widespread clinical use of qEEG to diagnose blast-related mTBI.

Table 6: EEG Following Blast Exposure

Population	Defining Injury	Key Methods	Main EEG Findings
Trudeau et al. (1998)			
Outpatient combat veterans: • With blast history (*n* = 27) • Without blast history (*n* = 16) *Demographics:* • Age: mean: 52 yr; range: 26–72 yr Male: 100% *Inclusion criteria:* • Post-combat post-traumatic stress disorder (PTSD) *Exclusion criteria:* • Active psychoactive substance abuse disorder • Seizure disorders • Neuroleptic drugs	*Self-Report Questionnaire:* • Present at ordnance detonation • LOC < 20 min or dazed > 1 h without LOC • Did not require medical attention for concussion	*Patient Assessed:* • Years after injury *EEG:* • 19 channel • 30 sec of artifact-free data • Obtained discriminant score (Thatcher et al., 1989) and applied discrimination cutoff score of -1.201	• EEG correctly identified 88% of blast-history-positive group and 75% of the blast-history-negative group. • A history of blast injury in combat veterans with PTSD is associated with EEG findings of mTBI. • Psychoactive substance abuse disorder, prior TBI, or adult residual attention deficit hyperactivity disorder (ADHD) did not influence results.
Cernak et al. (1999)			
War casualties admitted to Belgrade Military Medical Academy: • With blast injury (*n* = 665) • Without blast injury (*n* = 658) *Demographics:* • Age: mean: 27 yr; range 17–50 yr • Male: 94% *Inclusion criteria:* • Explosive wounding of lower extremities without other penetrating injuries • Admitted within 18 h of injury • <50 yr of age *Exclusion criteria:* • Intracranial bleeding • Spinal cord injury • Infection	*Positive indicators on:* • History and questionnaire on subjective symptoms (e.g. vertigo, tinnitus, retrograde amnesia) • Physical examination (e.g., blood excretion in external ear/nose, eardrum rupture) • Clinical examination (i.e., radiography, CT, ultrasound of lung/abdomen)	*Patient assessed:* • within 3 d after injury in patients with neurologic complaints, including headache, insomnia, psychomotor agitation, vertigo and consciousness disturbance	• Acute EEG abnormalities in 36% (241/665) of participants with blast injury and 12% (79/658) of participants without blast injury. • The most common observation was hypersynchronous, discontinuous or irregular brain activity with increased theta activity. • At 1-yr follow-up: persistent alterations in 200 (30%) of participants with blast injury and 26 (4%) of participants without blast injury.

Evoked Potentials and Event-Related Potentials

Like EEG, EPs and ERPs provide indices of brain activity, and all three can use similar recording equipment. Because of these similarities with EEG, EPs and ERPs will be covered here instead of in later sections covering sensory and neuropsychologic assessment devices.

Whereas EEG provides a continuous measure of spontaneous brain activity over time, EPs and ERPs are recorded over brief periods of time that coincide with the presentation of a particular event or stimulus (e.g., sound, flashing light). Multiple time-locked recordings are then averaged to reveal consistent brain response to the stimulus of interest. Although EP and ERP recordings are brief, multiple recordings are necessary to produce a reliable average. Thus, recording sessions for EPs and ERPs tend to be longer in duration than EEG recording sessions, in some cases ranging from 20 minutes to several hours.

For simplicity, EPs can be viewed as measures of primary sensory systems (e.g., visual, auditory, and olfactory response), whereas ERPs represent information processing among distributed brain networks that are responsible for higher-level functions, such as attention and memory (Gaetz & Bernstein, 2001).

EPs

Many types of EPs exist, including brainstem auditory EPs and visual EPs (Appendix F). Although studies have found EP abnormalities both early and late following mTBI, overall, findings have been inconsistent (for a review, please see Gaetz & Bernstein, 2001). In addition, the incidence of EP abnormalities in mTBI patients is relatively low for diagnostic purposes. For example, in a recent study that included non-sports-related mTBI patients (n = 150), abnormal brainstem auditory EPs and middle latency EPs were observed in just 9–18 percent and 5.5 percent of participants, respectively (Munjal, Panda, & Pathak, 2010). Similarly, other studies have found atypical olfactory EPs in 12.8 percent of mTBI patients (n = 16; Haxel, Grant, & Mackay-Sim, 2008) and abnormal visual EPs in only 1 of 9 mTBI patients (Gupta, Verma, Guidice, & Kooi, 1986). Individuals were generally evaluated 6–25 months after injury in these studies; thus, additional studies are needed to determine the incidence of EP abnormalities in mTBI sufferers immediately after injury.

ERPs

Most ERP studies have focused on changes in the N2/P3 (N200 and P300) response parameters of the ERP (Gaetz & Bernstein, 2001). These parameters can be evoked by a wide range of stimuli (e.g., novel sounds or noises) and cognitive tasks, such as detecting mismatches or errors and inhibiting responding to target images or sounds. Contingent negative variation (CNV), which is a brain response that occurs in anticipation of an expected event, has also been examined following mTBI. Most studies have used auditory or visual stimuli in their procedures, although other types of stimuli could be used.

Historically, auditory ERP studies following mTBI have yielded inconsistent results (Gaetz & Bernstein, 2001). More recent findings appear to support the notion that abnormal auditory ERPs may indicate brain injury in concussed athletes (Thériault, De Beaumont, Gosselin, Filipinni, & Lassonde, 2009) and patients with mild head injury (Solbakk, Reinvang, Nielsen, & Sundet, 1999). These abnormalities, however, may reflect the effects of contusion as opposed to concussion, per se (Gosselin, Thériault, Leclerc, Montplaisir, & Lassonde, 2006; Rousseff, Tzvetanov, Atanassova, Volkov, & Hristova, 2006).

Data from visual ERP studies have been slightly more consistent than those from auditory studies (Gaetz & Bernstein, 2001). For example, Sangal & Sangal (1996) found visual but not auditory ERP

abnormalities in individuals with mild closed head injury (six of eight patients). Differences in visual ERPs following mTBI correlate well with postconcussive symptoms (Dupuis, Johnston, Lavoie, Lepore, & Lassonde, 2000; Lavoie, Dupuis, Johnston, Leclerc, & Lassonde, 2004) and can be sensitive to the cumulative effects of concussion (De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007). More research is needed, however, to determine whether ERPs of any type can be used to diagnose mTBI.

EPs, ERPs, and ICP

In addition to providing measures of brain activity following mTBI, electrophysiologic measures may be able to detect ICP changes in head-injured patients. For example, multiple studies have found that flash visual EPs correlate with ICP (Gumerlock, York, & Durkis, 1994; York, Legan, Benner, & Watts, 1984; York, Pulliam, Rosenfeld, & Watts, 1981). Because of this suspected relationship, electrophysiologic devices, such as the Noninvasive ICP Monitoring System (NIP-200/210), have been developed to provide non-invasive ICP measures (Zhao, Zhou, & Zhu, 2005). Zhao et al. (2005) found that NIP-200/210 data correlated with invasive ICP measures (correlation index: 0.651–0.97; standard error: 8–15%). The relationship between electrophysiologic measures and ICP may be imperfect; ICP can change significantly without corresponding electrophysiologic changes (Davenport & Bramley, 1993). Thus, despite a possible association between electrophysiologic measures and ICP, the data do not support using electrophysiologic measures as surrogate ICP measures. Also, the relationship between ICP and mTBI in the immediate aftermath of trauma is unclear, but it is unlikely that they are strongly correlated.

Future Directions

BrainScope Company, Inc. developed an advanced eight-channel, portable, hand-held EEG device intended for deployment in military settings. Their ZOOM-100DC device was cleared for marketing by the FDA under section 510(k) of the FD&C Act in 2009 (BrainScope Company, Inc., 2009b). According to the company, the ZOOM-100DC is designed to be used at the initial point of care. Functional features of the device can be found in Appendix G.

The BrainScope device was recently used to investigate EEG changes following concussion in high school and collegiate football players (BrainScope Company, Inc., 2010; McCrea, Prichep, Powell, Chabot, & Barr, 2010). The study recruited 396 participants; of these, 28 (7%) sustained a concussion. Concussion was defined as an injury resulting from a blow to the head causing an alteration in mental status and accompanied by at least one of the following symptoms: headache; nausea; vomiting; dizziness or balance problems; fatigue; trouble sleeping; drowsiness; sensitivity to light or noise; blurred vision; difficulty remembering or difficulty concentrating. Individuals identified as having sustained a concussion were tested with the Concussion Symptom Inventory (CSI) and the Standardized Assessment of Concussion (SAC) on the sideline immediately after the injury. Of the 28 concussed athletes, 7.1 percent experienced a LOC (mean duration of less than 1 minute), 17.9 percent had PTA (median duration 10 minutes), and 28.6 percent had retrograde amnesia (median duration 60 minutes). At the time of injury, the mean CSI and SAC scores (± standard deviation [SD]) for concussed athletes were 18.82 ± 15.4 and 25.5 ± 3.32, respectively.

Participants with and without concussion were compared using seven EEG features (data for each time point was available for only 18 of the concussed individuals). In concussed athletes, EEG recordings taken on the day of injury were significantly different than baseline EEG recordings (F-value = 2.5; p = 0.039). EEG recordings from injured athletes also differed significantly from those from non-injured controls on the day of injury (F-value = 4.4, p = 0.002). These data suggest that the device may be able

to detect sports-related concussion — and possibly mTBI — early after injury. More evidence, however, is needed to fully support this conclusion.

According to company reports, the BrainScope device is undergoing additional clinical studies in individuals with concussion or general altered mental status across hospitals nationwide, including the Brooke Army Medical Center in Fort Sam Houston, Texas; Washington University in St. Louis, Missouri (Barnes Jewish Hospital); William Beaumont Hospitals in Royal Oak and Troy, Michigan; Wayne State University (Detroit Receiving Hospital and Sinai Grace Hospital) in Detroit, Michigan; University of Virginia Medical Center in Charlottesville, Virginia; University of Maryland (R Adams Cowley Shock Trauma Center) in Baltimore, Maryland and Waukesha Memorial Hospital in Waukesha, Wisconsin (BrainScope Company, Inc., 2009a).

Several other portable electrophysiology systems are also under development (ElMindA, 2008; Engin, Dalbasti, Güldüren, Davasli, & Engin, 2007; Martins, Selberherr, & Vaz, 1998; Appendix H), including devices capable of wireless local area network (WLAN) transmission (Chen, Ye, & Lee, 2007) and those targeted at measuring evoked- or event-related potentials (Gnecchi, Ramirez, & Gordillo, 2009). Helmet-based EEG systems have also been described. These may be able to (or adapted to) take baseline EEG measures each time the helmet is placed on the head or when triggered (Kim et al., 2009; Litscher, 1998), potentially providing a more appropriate 'control' value for comparisons after injury.

Conclusions

Electrophysiologic methods have positive characteristics that make them suitable for use in theater, including portability and automated analyses. Electrophysiologic equipment is also relatively affordable compared to other brain monitoring technologies. Although EPs and ERPs alone may not be optimal for mTBI diagnosis because of their ability to diagnose only a subset of individuals with mTBI, a multimodal device that integrates some combination of EEG, EPs and/or ERPs may provide a more comprehensive picture of injury and, if so, could offer better potential for mTBI diagnosis.

Several issues need to be addressed before widespread clinical use of electrophysiologic devices for mTBI diagnosis. First, it is necessary to develop systems that can provide user-friendly output and automated classification to reduce or eliminate the need for specialized clinical expertise. Discriminant function analysis or other classification algorithms may be useful in this regard (Cao, Tutwiler, & Slobounov, 2008).

Second, additional studies are needed to determine what constitutes an abnormal signal, particularly in individuals who are injured in military settings and those who suffer blast-related mTBI. Normative values taken from civilian settings or from pre-deployment baseline measures may not be appropriate for mTBI sustained in the combat zone. The field can be a harsh environment, affecting sleep, use of pharmaceuticals, and stress. Given that such factors can themselves influence brain activity, more appropriate normative databases, mathematical classification functions, and baseline measures may be needed to assess mTBI in the field. Research is also needed to determine whether additional or different EEG parameters should be assessed for blast-exposed Service members.

Third, many protocols, including those used in the BrainScope study, involve placing EEG electrodes on frontal and/or temporal regions of the head, because data from civilian trauma and sports-related

concussion indicate that these regions are quite vulnerable to mTBI. Ideal placement of electrodes for those exposed to blast forces has yet to be empirically determined.

Considerations more specific to EPs and ERPs also exist. Diagnostic validity can be impeded by end-organ dysfunction (e.g., eye or ear damage) that is not directly related to brain injury, per se. Furthermore, measuring sensory systems in the field environment may prove difficult given the levels of noise, olfactants from munitions, and visual distractions. Finally, it may be necessary to design short-duration ERP recording protocols that have sufficient power for detecting mTBI.

Electrical Impedance Methods and Devices

Electrical impedance methods have been used to study the dynamics of blood circulation in humans for more than 75 years. *Electrical impedance* is defined as the opposition to the flow of an alternating current through a conductor and, as such, will change as a function of the conductor's electrical properties (e.g., volume, resistance). Blood is a relatively good conductor, especially compared to "dry tissues," such as brain tissue. As a result, changes in blood volume or flow can drive changes in the entire region's electrical resistance and be measured using electrical impedance methods.

Although best known for their use in monitoring cardiac output (thoracic electrical bioimpedance or impedance cardiography), electrical impedance methods have been used to investigate cerebral circulation since the 1950s (Polzer & Schufried, 1950). Through the years, clinicians and researchers have used several electrical impedance methods to assess cerebral hemodynamics, but most attention has focused on an adaptation of Polzer's original technique, termed rheoencephalography (REG).

REG

REG is based on monitoring pulse-synchronous variations in electrical impedance over time (Bodo et al., 2003). As blood flows into the cranial cavity, electrical conductance increases, while resistance decreases. This change is represented on the rheoencephalograph as an increase in the REG pulse amplitude. Venous return related to respiration causes another but slower impedance fluctuation.

Early REG studies found a relationship between the REG pulse amplitude and a variety of conditions that affect cerebral hemodynamics and health, including subdural hematoma, eICP, arteriosclerosis, and compression of the ipsilateral carotid artery in healthy participants (Geddes, Hoff, Hall, & Millar, 1964; Hadjiev, 1968; Jacquy et al., 1974; Jacquy, Piraux, Noel, & Henriet, 1973). There was considerable disagreement, however, about REG's true clinical usefulness. Some claimed that REG was unreliable and potentially misleading (Perez-Borja & Meyer, 1964; Waltz & Ray, 1965, 1967). Others supported using REG for clinical applications (Bostem, Thibaut, & Hanton, 1982; Gougerot, Soulairac, & Marstal, 1969; Namon et al., 1967; Seipel, 1967). Fueling the debate was the difficulty in determining the physiologic phenomenon underlying REG and disagreement about the actual intracranial contribution to REG findings. Issues surrounding REG's limitations and clinical value, along with the development of new technologies such as TCD, likely contributed to the decline in REG research.

Recently, interest in using REG to evaluate brain pathology has grown. This renewed interest is likely because REG technologies have improved (e.g., better equipment, automated and computerized methods, new analytical methods; Bodo et al., 2005; Perez, Guijarro, Sancho, & Navarre, 2006). Furthermore, REG may be able to meet the growing and currently unmet need for low-cost, portable

devices that can continuously and noninvasively monitor intracranial hemodynamics and integrity following brain injury. In addition — and of particular relevance to complex pathologies such as mTBI — it may be possible to incorporate REG into a multimodality brain assessment device that includes simultaneous electrophysiologic recordings, such as EEG (Montgomery & Gleason, 1992).

Despite this renewed interest, no recent clinical studies have used REG to evaluate patients who have sustained a TBI. REG's potential for diagnosing mTBI can only be inferred from studies evaluating REG's ability to measure aspects of cerebral dynamics that may be associated with mTBI, such as changes in cerebral autoregulation and ICP. For example, studies show that REG is altered following carbon dioxide (CO_2) inhalation and aortic compression and can measure ICP changes in humans and animals (Bodo, 2010; Brady et al., 2010; McHenry, 1965).

REG and Stroke

REG also appears to be sensitive to other sources of neural injury, such as stroke (Bodo, 2010; Bodo et al., 2005, 2008). REG revealed signs of arteriosclerosis in 54.26 percent of the cases, whereas TCD only detected changes in 30.43 percent. The authors interpreted these findings as a sign that REG is more sensitive to the upstream events that occur before cerebral changes that can be detected using TCD. However, although conditions such as TBI stroke, and ischemia share some similar pathological pathways (e.g., oxidative stress, cellular injury, mitochondrial dysfunction), they are different in many ways. Whether REG can detect early changes in TBI, particularly mTBI, remains to be seen.

REG Devices

REG devices used in human and animal studies have been reviewed elsewhere (Bodo, 2010; Appendix I). At the time of this review, there were no FDA-registered REG devices, but a recent DoD solicitation OSD09-H06 (SBIR) was aimed at developing a TBI diagnostic systems based on REG.

Future Directions

In addition to REG devices, researchers have developed other devices for assessing intracranial pathology based on electrical impedance. Liu et al. (2005) developed a non-invasive electrical impedance brain monitor (Born Science & Technology Corporation, China), comprising three electrodes and measuring electrical impedance from both hemispheres to determine a "perturbative index." They compared their electrical impedance measure to MRI or CT findings in 52 patients with intracranial hemorrhage, 33 patients with ischemic stroke, and 100 healthy volunteers. In the intracranial hemorrhage group, the perturbative index of the hematoma side was lower than that of the other side. Furthermore, the perturbative index and infarction volume correlated significantly ($r = 0.8496$; $p < 0.01$). The authors concluded that their device was useful for monitoring edema and hematoma in stroke. The study did not report statistics for differences among participant groups, nor did it give the number of false positives apart from stating that there were "several false positives." No peer-reviewed studies exist that use the device to evaluate mTBI patients.

Recently, the research and clinical community has shown interest in electrical impedance tomography (Holder, 2005), particularly multifrequency electrical impedance tomography (MFEIT) or electrical impedance spectroscopy (Romsauerova et al., 2006; Yerworth et al., 2003). Several systems have already been developed for MFEIT, with likely many other research labs having their own system (Appendix J). Few clinical studies, however, have used MFEIT, and no published studies on the use of MFEIT in TBI patients exist. In one study, MFEIT failed to differentiate among groups of individuals with

different intracranial pathologies (Romsauerova et al., 2006), suggesting that more research is needed to improve the technique.

Conclusions

Electrical impedance methods, such as REG, can be used to better understand cerebral hemodynamics and pathology. REG is a relatively inexpensive and potentially portable device that may be useful in detecting and diagnosing mTBI by providing measures of hemodynamics, ICP and cerebral autoregulation. No published studies, however, have used REG to diagnose TBI of any severity. Thus, research is needed to evaluate REG's ability to diagnose mTBI.

Acoustical Imaging Methods and Devices

Several methods use principles of acoustics to investigate brain pathology (Appendix K; also Popovic, Khoo, & S. Lee, 2009). Most are based on the assumption that changes in ICP will cause small, measurable changes in skull expansion or tissue rigidity. These changes can be measured by sending a signal to the tissue (e.g., ultrasonic wave) and measuring the resulting acoustic response. Although some of these methods may lead to the development of a portable brain assessment device for mTBI, few have been validated in clinical studies of TBI patients; thus, their ability to diagnose mTBI is unknown.

Passive Acoustical Monitors

A type of passive acoustic monitoring has been used to evaluate patients with mild, moderate and severe TBI. The method is based on a fairly simple principle: measuring the acoustic response to an internal force as opposed to an externally applied force. When the heart's ventricles contract (during cardiac systole) a pulse wave is generated and propogates along the arterial system, causing predictable skull deformation when it enters the head. Passive acoustic monitoring measures the acoustic response to this internal force or arterial excitation signal. The assumption is that the acoustic response changes following brain injury, and this change should be detectable using a passive acoustic monitoring device. Active Signal Technologies, Inc. has developed a device, called the *Brain Acoustic Monitor* (BAM), to measure these internally driven acoustic responses in normal and pathologic conditions (Active Signal Technologies, Inc., 2010). The BAM has been employed in the R. Adams Cowley Shock Trauma Center since 1998, and according to the company, the BAM has been used to detect mTBI at the Air Force Academy in parallel with neuropsychological evaluation (Active Signal Technologies, Inc., 2010; Roudebush, 2008a, 2008b) and is also under evaluation by DoD in the San Antonio Military Medical Center for returning wounded warriors with head injuries.

The early BAM used a circular sensor coupled to the skin of the forehead with an elastic band. The sensor was connected to a signal-processing box, which in turn was connected to a computer. Data from the system was displayed as a continuous wave of amplitude over time, typically 8 seconds per record. The BAM is currently available in a smaller and more rugged form and can be used with a personal digital assistant (PDA). The device performs more sophisticated analyses and uses two sensors — one placed at the surface of the forehead and one placed at a reference point (e.g., radial artery) — for comparison measures. The system has a red/green display indicating the results.

To date, two studies using the BAM in TBI patients have been published in peer-reviewed literature (Dutton, Sewell, Aarabi, & Scalea, 2002; Dutton, Van Der Heijden, Aarabi, Sewell, & Scalea, 2005; see Table 7 for summaries and Appendix L for specifications for a "normal" BAM signal). Findings from these studies suggest that the BAM signal is a more sensitive indicator of TBI than CT findings, invasive ICP and CPP measures and outcome measures (GOS). Notably, in the Dutton et al. (2005) study, most participants were mTBI patients. As a result, study results were likely driven by BAM measures following mTBI.

Future Directions

Advances in acoustical methods may provide more sensitive or comprehensive measures of mTBI, although the feasibility of using these sophisticated and comparatively more complicated technologies is unknown.

Conclusions

Many methods may be able to measure intracranial changes based on the acoustical response to an internal or externally applied force or energy. Few have been evaluated for their ability to diagnose mTBI, and given their complexity and instrumentation, it is possible that not all of these technologies will prove appropriate for field use. Passive acoustical monitoring can be performed using a device called BAM, developed by Active Signal Technologies. The BAM is particularly attractive for field use, because it is reportedly easy to use, rugged, low cost, and has been miniaturized for use with a PDA. Two studies have examined the relationship between the BAM signal and TBI, with one study including a large number of mTBI patients. Findings from these studies suggest that the BAM may prove useful for mTBI screening. Because the BAM appears to register a high number of false positives when evaluating mTBI patients, more research is needed to evaluate the device's diagnostic accuracy and/or improve its data analyses methods.

Table 7: BAM Studies in TBI Patients

Study Population	Comparison Measures	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	Positive Predictive Value % (95% confidence interval)	Negative Predictive Value % (95% confidence interval)	Results
Dutton et al. (2002)						
Patients with severe TBI: *n* = 30 (28 successfully monitored)	CPP	–	–	–	–	Initial BAM recording predicted clinical status at discharge in 25/28 cases ($p < 0.01$). The BAM signal and outcome correlated ($r = 0.81$). Normal signals did not occur at any time point in patients who went on to a poor outcome. The BAM signal correlated with outcome in 63 of 71 sessions ($p < 0.0001$). The BAM signal correlated weakly with average ICP ($r = -0.20$) or CPP ($r = 0.24$).
	ICP	–	–	–	–	
	GOS at discharge	100 (75–100)	77 (46–94)	83	100	
Dutton et al. (2005)						
Patients with TBI (blunt trauma) *n* = 206: • Mild: GCS: 13–15 *n* = 154 (104 with GCS of 15) • Moderate: GCS: 9–12 *n* = 22 • Severe: GCS: ≤8 *n* = 29	CT	93 (86–96)	14 (7–24)	64 (57–71)	55 (32–76)	The BAM was sensitive to GOS and the presence of CT findings but yielded many false positives.
	GOS = severe impairment	100 (90–100)	13 (7–22)	36 (28–45)	100 (71–100)	
	GOS = any impairment	93 (86–97)	13 (7–22)	54 (47–62)	65 (40–83)	

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Optical Imaging Methods and Devices

Transillumination of the head for clinical observation was first described by Richard Bright in 1831 (Bright, 1831). In a case study of a child suffering from hydrocephalus, Bright noted that, "if a candle was held behind his head, or the sun happened to be behind it, the cranium appeared semi-transparent and this was more or less evident till he attained his fourteenth year." Using visible light to provide a window into the cranium proved useful in assessing several types of neonatal intracranial pathologies (Alexander, Davis, & Kitahata, 1956; Barozzino & Sgro, 2002; Cope & Delpy, 1988; Donn et al., 1979; Johns, 1979; Vyhmeister, Schneider, & Cha, 1977), but it was not ideal for penetrating the thick skull and tissues of the adult head.

In 1977, Jobsis proposed using light in the near-infrared (NIR) spectrum (700–1000 nm) for optical imaging of the head (Jobsis, 1977). Light in the NIR spectrum is able to penetrate biologic tissue and bone because neither absorbs significant energy in the NIR range. Over the past several decades, a variety of NIR-based brain monitoring methods have been developed, with some providing basic cerebral hemodynamic measures, such as blood oxygen saturation, while others attempt to measure more complex aspects of brain function. In terms of TBI, most of the relevant research has employed NIR Spectroscopy (NIRS; sometimes termed *cerebral* or *transcranial oximetry*) to assess hemoglobin (Hb) and deoxyhemoglobin (HbO_2). No clinically relevant data are currently available for more complex optical methods, such as optical tomography or functional NIRS; thus, these methods will not be examined in this review.

Near-Infrared Spectroscopy

In NIRS, devices that send and receive light, called *optodes*, are attached to the scalp. These optodes transmit light in the NIR spectrum to the underlying tissue. Portions of the light are absorbed, diffusively scattered, or reflected back based on the composition and respective absorption characteristics of the underlying tissue and on the wavelengths of the transmitted light. NIRS protocols generally transmit wavelengths of light that target the characteristic absorption spectra of the chromophores, HbO_2, Hb, and, in some cases, cytochrome c oxidase. Because of the low absorption of bone and tissue, changes in intracranial chromophore concentration cause measurable changes in the amount of transmitted light that is absorbed and scattered back. By transmitting multiple NIR wavelengths, some of which are better absorbed by HbO_2 and others that are better absorbed by Hb, blood flow and tissue oxygenation can be estimated. It is important to recognize that the NIRS signal represents a *local* oxygenation index from arterial, venous, and capillary compartments; thus, comparisons with methods that measure *global* or *small-volume* oxygenation should be made with caution.

NIRS has been used for neonatal clinical applications (Brazy, D. Lewis, Mitnick, & vander Vliet, 1985) but has been less successful for adult evaluation. Because older children and adults have relatively large heads, transillumination is not feasible. Reflectance-mode NIRS was developed to overcome this issue (Young, Germon, Barnett, Manara, & Nelson, 2000). In reflectance-mode NIRS, NIR light is transmitted through the head in a localized area, and the light that is reflected back is measured at the scalp. Original reflectance-mode NIRS, however, was plagued by the probable extracranial contamination of the NIRS signal (Al-Rawi, 2005). To mitigate the contribution of extracranial blood, spatially and time-

resolved spectroscopy methods were developed (Al-Rawi, 2005; Calderon-Arnulphi, Alaraj, & Slavin, 2009) and have since been implemented in commercially available NIRS devices.

NIRS Methods

NIRS methods come in several types, including continuous wave, frequency domain, and time domain (Appendix M). Because the majority of studies relevant to TBI have employed continuous-wave NIRS and most commercially available NIRS devices are based on spatially resolved continuous-wave methods, this review will not discuss other NIRS methods.

Differences Among NIRS Devices and Methods

Before discussing the relevant literature, it is important to note that spatially resolved, continuous-wave NIRS methods vary among devices and, in turn, studies. Key differences include specific modifications to the Beer-Lambert Law[5], the number and spacing of the light-emitting and receiving optodes, and the algorithms used to produce an output value. For example, in one method, light detectors are positioned at two different distances from the light-emitting optode. The detector close to the emitting optode is assumed to measure light reflected by the superficial tissue layers and extracranial blood, whereas the far detector presumably measures more of the cerebral light reflectance. An algorithm is then used to subtract the "extracranial signal.' This method can be compared to one that uses three emitting and detecting diodes separated by different distances. HbO_2 and Hb are calculated from the regression line between the three values from the three detectors. This method does not directly subtract extracranial contamination but instead attempts to mitigate it through the use of algebraic calculations (Al-Rawi, 2005; Al-Rawi, Smielewski, & Kirkpatrick, 2001). Currently, most protocols are consistent with the general positioning of optodes, which are usually attached to the forehead and presumably provide a local measure of frontal lobe cerebral oxygenation.

The impact of methodological differences on study results is illustrated by a comparison of two relatively common NIRS devices: the NIRO 300 (Hamamatsu Photonics, Hamamatsu City, Japan) and the INVOS 5100 (Somanetics, Troy, Michigan, USA). The two devices differ significantly in several aspects, including their output. The NIRO 300 measures a "tissue oxygen index" (TOI), whereas the INVOS 5100 measures "regional cerebral oxygenation saturation" (rSO2). The reliability, ease of use, and output values of these two devices were examined and compared during hyperoxia and hyperventilation in 10 healthy volunteers (Thavasothy, Broadhead, Elwell, Peters, & Smith, 2002; Appendix N). The study found that rSO2 values were 2.1 percent lower than TOI values (SD of the difference between them = 7.5%; ± 1.96 SD limit of agreement = 14.7%), with results from the NIRO 300 having less variability. This is consistent with questions raised by others over the reliability of the INVOS 3100 (Colier, Haaren, & Oeseburg, 1995; Grubhofer et al., 1999; McKeating, Monjardino, Signorini, Souter, & Andrews, 1997). Furthermore, there were large inter- and intra-individual differences between the outputs of the two monitors. The authors concluded that the overall bias of −2.1 percent and wide limits of agreement make interpretation of the absolute values of rSO2 and TOI difficult. Despite the apparent imprecision of the rSO2 and TOI values, both recorded an increase in cerebral cerebral oxygen (O_2) following hyperoxia and a significant reduction during hypocapnia. Other studies comparing different NIRS devices have also found variability in and among devices. For example, a study comparing INVOS 4100 and NIRO 300 during a CO_2 challenge test in anaesthetized patients found differences between the

[5] The Beer-Lambert Law represents the mathematical relationship between the absorbance and the concentration of the material that is absorbing light.

devices similar to those reported in the Thavasothy et al. (2002) study (bias of −0.5%; ±1.96 SD limit of agreement of 15.6%).

The factors underlying variation in NIRS device measures are not fully understood, but they likely stem from multiple sources. For example, evidence suggests that the type of light emitter (McKeating et al., 1997) and interoptode distance may influence output. Furthermore, even when using the same NIRS data, different published analysis methods produce different results (Matcher, Elwell, Cooper, Cope, & Delpy, 1995). Thus, the sensitivity and specificity of NIRS measures for mTBI diagnosis may be device dependent.

NIRS and Ischemia

Overall, NIRS has good sensitivity and specificity for detecting ischemia. For example, in a large study that included 167 patients undergoing carotid endarterectomy, TOI changes (%DeltaTOI) occurring during internal carotid artery clamping were compared with intracranial blood flow (TCD; middle cerebral artery [MCA] flow velocity) and cerebral function monitoring to identify and quantify periods of cerebral ischemia. MCA flow velocity and TOI changes were significantly correlated on clamping (r = 0.74, p = 0.0001). Of the patients having a %DeltaTOI above −13, none showed evidence of ischemia on clamping. This threshold provided to have a sensitivity and specificity of 100 percent and 93.2 percent, respectively, for patients satisfying the preset criteria for cerebral ischemia (Al-Rawi & Kirkpatrick, 2006).

NIRS and Hematoma

Relatively few clinical studies have examined the relationship between NIRS measures and TBI of any severity. Of those that have included TBI patients, most have focused on the ability of NIRS to detect subdural and epidural hematomas or predict delayed intracranial hematoma in head-injured patients (Table 8). For example, NIR light at 760 nm was able to detect hematomas in head-injured patients (Gopinath, Robertson, Grossman, & Chance, 1993) and, in a subsequent study, was shown to predict hematomas before ICP increases, changes in neurologic exam, or CT clinical findings (Gopinath et al., 1995). In a more recent study, results comparing NIRS to CT findings suggest that NIRS may be useful in screening TBI patients because it has good sensitivity, though the authors also noted that NIRS produced false positives (Ghalenoui et al., 2008).

Table 8: NIRS Detection of Hematoma in Patients with Head Injury

Population	Methods	Results
Gopinath et al. (1993)		
Patients with head injury: *n* = 46	CT Difference in absorption of light (760 nm) between side with and without hematoma	Absorption was greater on side of hematoma in all cases. Mean optical density difference between hematoma and non-hematoma sides: 0.99 +/- 0.30 for epidural hematomas; *n* = 10 0.87 +/- 0.31 for subdural hematomas; *n* = 22 0.41 +/- 0.11 for intracerebral hematomas; *n* = 8 6 patients with diffuse injury had minor differences between sides, similar to non head-injured participants
Gopinath et al. (1995)		
Patients with head injury: *n* = 167	CT Difference in absorption of light (760 nm) between side with and without hematoma	Patients developed late hematoma (*n* = 27; 16%), appearing between 2 and 72 h after injury In 24 of 27 patients, NIRS findings preceded increased ICP and findings on neurological examination or CT scan
Ghalenoui et al. (2008)		
Patients with head injury: *n* = 148	CT NIRS detection of potential hematoma	CT findings: intracranial hematoma in 54 (36.5%) patients NIRS: indentified potential hematoma in 69 (46.6%) patients Sensitivity: 88.9% Specificity: 77.7% Positive Predictive Value: 69.6% Negative Predictive Value: 92.4% GCS did not predict hematoma

NIRS and ICP/CPP

Several studies have found a correlation between NIRS measures and ICP or CPP in severe TBI patients (Dunham, Ransom, Flowers, Siegal, & Kohli, 2004; Dunham et al., 2006; Dunham, Sosnowski, Porter, Siegal, & Kohli, 2002). Most of these studies, however, have had relatively small sample sizes (*n* = 4–18 patients).

NIRS was also used to assess eight head-injured patients with high (>25 mmHg) or low (<25 mmHg) ICP (*n* = 4 for each group; Kampfl, Pfausler, Denchev, Jaring, & Schmutzhard, 1997). NIRS values in the high ICP group were significantly lower than in the low ICP group (<25 mmHg). Following artificial hyperoxygenation (50% O_2) for a period of 3 minutes, rSO2 values in high ICP patients were significantly lower than in the low ICP group. Also, there was a significant increase in rSO2 values at the end of the hyperoxygenation period in the low but not high ICP group. The authors concluded that NIRS may be an additional diagnostic tool in the noninvasive evaluation of impaired cerebral microcirculation in patients with increased ICP.

NIRS and Cerebral Autoregulation

NIRS may be able to detect impaired cerebral autoregulation (Brady et al., 2007; Steiner et al., 2009). For example, NIRS measures appear to reflect CBF and possibly autoregulation in TBI patients. Kim et al. (2010) found that NIRS distinguished the effects of xenon gas inhalation on CBF (xenon CT) in critically brain-injured adults (*n* = 7). Furthermore, other studies have suggested that NIRS can be used to continuously assess cerebral autoregulation, though the evidence supporting this conclusion was drawn from a study of patients with subarachnoid hemorrhage using correlations between TCD and NIRS measures (Zweifel et al., 2010). Research is needed to evaluate the relationship between NIRS measures and cerebral autoregulation following mTBI.

NIRS Versus Other Oxygenation Measures

The ability of NIRS to assess TBI patients has been questioned because NIRS measures sometimes correlate poorly with other oxygenation measures — particularly jugular bulb oximetry measures of cerebral venous oxygen saturation (SjO_2) (Kirkpatrick, Smielewski, Czosnyka, Menon, & Pickard, 1995; Lewis, Myburgh, Thornton, & Reilly, 1996). Using a multimodality recording system that included jugular bulb oximetry (SjO_2), TCD, and laser Doppler flowmetry, Kirkpatrick et al. (1995) monitored 14 ventilated patients with closed head injury. In nine patients, 38 events were recorded that demonstrated CPP changes that were accompanied by hemodynamic changes (TCD measures) and cortical perfusion (measured by laser Doppler flowmetry). Changes in NIRS measures correlated with 37 of these events (97%), whereas jugular venous saturation monitoring registered only 20 (53%). In another multimodality study of 18 patients admitted with coma-producing closed-head injury, 58 cerebral events were recorded in 16 patients, 94 percent of which were associated with NIRS changes 50 percent percent with SjO_2 (Kirkpatrick, 1997). Thus, in patients with head injuries, NIRS appears to detect more cerebral events than jugular bulb oximetry. The clinical significance of this is not quite clear (c.f. Haitsma & Maas, 2007), but the lack of correlation between NIRS measures and SjO_2 is not surprising in a complicated pathology like TBI, where global versus local measures are likely to disagree (McLeod, Igielman, Elwell, Cope, & Smith, 2003).

A comparison of invasively measured cerebral oxygenation (local O_2 pressure; TipO2) and NIRS (rSO2) in severe TBI patients (*n* = 9) and patients with subarachnoid hemorrhage (*n* = 3) found that the two measures contain similar data, although it was noted that their relationship needs further clarification (Brawanski, Faltermeier, Rothoerl, & Woertgen, 2002). Other studies have found generally poor correlation between the two measures (Büchner, Meixensberger, Dings, & Roosen, 2000).

Future Directions

Several avenues are open for exploration in making NIRS a viable option for mTBI diagnosis, although not all may be feasible for use in theater. NIRS may be able to measure cerebral perfusion when NIR absorbents are used as tracers (e.g., indocyanine green, an FDA-approved NIR dye). This method has been used to evaluate perfusion in patients following stroke (Terborg, Bramer, Harscher, Simon, & Witte, 2004; Terborg et al., 2009). More research is likely needed to perfect the technique, though, given data showing that NIRS and indocyanine green measures do not correlate with the standard measure for CBF, (133)Xe-SPECT (Schytz et al., 2009).

NIRS may also be able to monitor early signs of injury apart from cerebral hemodynamics, such as disrupted mitochondrial respiration. As mentioned earlier, cytochrome c oxidase is a chromophore with

characteristic absorption in the NIR range. To date, no studies have evaluated the use of NIRS-measured cytochrome c oxidase to predict mTBI.

Conclusions

NIRS is portable, easy to use and available commercially. It can also be effectively used in helicopter medical transport without causing signal interference (Pointinger et al., 2002), which may make it particularly suited for use in theater. There are, however, technical limitations inherent to NIRS, including the time-consuming process for optimally shielding optodes from ambient light and ensuring appropriate optode spacing. In addition, NIRS can penetrate only the outer few centimeters of the brain cortex, precluding examination of cerebral oxygenation in deeper brain regions. Furthermore, some but not all researchers have experienced technical difficulties with NIRS devices (Büchner et al., 2000). NIRS is also confounded by the fact that devices vary in their methodologic approaches and instrumentation. Research has shown that these differences result in different values of cerebral oxygenation.

NIRS can provide measures of cerebral oxygenation, hematoma, and potentially cerebral autoregulation, but clinical studies are needed to determine whether NIRS has sufficient specificity and sensitivity for mTBI diagnosis. Furthermore, several recent reviews of NIRS have all concluded that improved algorithms, optimized equipment and a better understanding of the extracranial contamination of the NIRS signal are needed prior to widespread clinical use of NIRS (Al-Rawi, 2005; Davis, Iverson, Guskiewicz, Ptito, & Johnston, 2009; Gratton, Toronov, Wolf, Wolf, & Webb, 2005).

Transcranial Ultrasound Methods and Devices

Transcranial Doppler Ultrasound

TCD is the most frequently employed transcranial ultrasound technique in TBI research. It provides a non-invasive measure of CBF velocity. CBF velocity is proportional to CBF as long as the artery diameter remains constant. TCD can thus provide useful information about cerebral circulatory dynamics, which has led to its widespread use for research and clinical applications (Aaslid, Markwalder, & Nornes, 1982; Markus, 2000; Moppett, 2007; Panerai, 2009). Relatively recently, technological advances enabled the development of more portable TCD systems that are capable of monitoring an individual for up to eight hours (Mackinnon, Aaslid, & Markus, 2004, 2005).

TCD generates ultrasonic beams using a piezoelectric transducer — a device that converts energy from one form to another, such as electrical energy to sound waves. These ultrasonic beams are directed through the skull and to large cerebral arteries, where red blood cells reflect the ultrasonic waves. The waves are reflected with a measurable frequency shift that is directly proportional to the blood's velocity (reviewed by Panerai, 2009).

Because the skull absorbs and reflects ultrasonic waves, penetrating the skull using ultrasound proves difficult. TCD methods attempt to maximize transmission by using a low-frequency transducer, typically around 2 megahertz (MHz) for adults (Markus, 2000), and targeting *acoustic windows* — regions of the skull where the ultrasonic beam has better penetration. The transtemporal window is typically used for brain injury assessment, allowing insonation of the MCA. Multiple TCD measures are generally recorded, including systolic flow velocity, diastolic flow velocity, time-averaged mean flow velocity, and ratios of these measures, such as the pulsatility index (PI).

TCD and TBI Severity and Outcomes

In a study of mild, moderate, and severe TBI patients, TCD measures of MCA blood flow velocity (MCAv) correlated with admission GCS scores in the first 24 hours following injury (rank correlation $r = 0.46$; $p < 0.01$; Chan, Miller, & Dearden, 1992). Studies also show that TCD measures taken in the first 24 hours after sustaining TBI can predict outcome measures (Martin et al., 1997; Moreno et al., 2000; van Santbrink, Schouten, Steyerberg, Avezaat, & Maas, 2002; Splavski et al., 2006; Tan, Feng, Gao, Huang, & Liao, 2001; Visocchi, Chiaretti, Cabezas, & Meglio, 2002). Other studies, however, have failed to find an association between TCD and outcome. For example, TCD measures did not correlate with the 1-month GOS scores of mTBI patients (Jünger et al., 1997) or 6-month GOS scores after injury in severe TBI patients (Chan et al., 1992). In the latter study, however, 80 percent of early deaths could be predicted by an admission MCA flow velocity <28 cm/s.

TCD and ICP/CPP

TCD may be able to indirectly measure ICP and CPP (Hassler & Chioffi, 1989; Hassler, Steinmetz, & Gawlowski, 1988; Klingelhöfer, Conrad, Benecke, Sander, & Markakis, 1988) and indicate diffuse cerebral swelling (Shigemori et al., 1990). Bellner et al. (2004) investigated patients with a variety of brain pathologies, including a subset with severe TBI, and concluded that there is a strong correlation between PI and ICP. In severe TBI, cerebral hypoperfusion results in low diastolic velocity and increased PI, both measured by TCD (Shigemori et al., 1989). In head-injured patients with CT findings ($n = 10$), there was a positive exponential correlation between PI and ICP, with increases in PI corresponding to increases in ICP ($r = 0.82$; $p < 0.001$; Homburg, Jakobsen, & Enevoldsen, 1993). Another study found that PI correlated with both ICP and CPP ($p < 0.01$) in severe TBI patients ($n = 96$) when measures were taken within 24 hours of admission (Tan et al., 2001). Moreno et al. (2000) also found significant correlations between PI and ICP/CPP in severe TBI patients within 24 hours of their admission ($n = 125$; GCS < 9; $r^2 = 0.6$; $p < 0.0001$).

In a more recent study, researchers suggested that TCD could be used in situations where neurosurgical expertise is not available for invasive ICP (Splavski et al., 2006). This study looked at 24 consecutive patients admitted to the hospital for severe, non-penetrating traumatic head injury (GCS ≤ 8). ICP was recorded continuously using external ventriculostomy, and initial TCD measurements were taken as early as possible (within 24 hours of admission; authors did not specify the precise time between injury and assessments). In one-third of brain-injured patients, TCD measures were abnormal and overall, TCD parameters were significantly correlated with the daily duration of eICP (Table 9).

Table 9: Correlation Between TCD Measures and ICP/CPP (Splavski et al., 2006)

Patient Subgroup	Relationship	Correlation Coefficient (*r*)	*p*-value	Linear Regression Equation
Patients with normal blood velocities: *n* = 17	MCAv and duration of eICP (>25 mmHg)/day)	−0.498	0.042	ICP = 11.477−0.153 MCAv
Patients with pathologic PI: *n* = 11	PI and duration of eICP	0.753	0.007	ICP = -13.097+10.834 PI
All Patients: *n* = 24	MCAv and duration of decreased CPP (<70 mmHg)/day	−0.619	0.001	CPP = 14.576−0.215MCAv

In addition to standard TCD measures, TCD analyses methods intended to more accurately reflect CPP have been proposed. The proposed calculations were shown to correlate with invasive CPP measures ($r = 0.73$; $p < 10^{-6}$) in head-injured patients (n = 96; GCS < 13; Czosnyka, Matta, Smielewski, Kirkpatrick, & Pickard, 1998).

TCD and Cerebral Autoregulation

TCD may be able to assess cerebral autoregulation early after an injury. Continuous monitoring of blood flow velocities using TCD allows estimates of autoregulation from the relationship between blood pressure and MCAv signals (Asil, Utku, Balci, & Uzunca, 2007; Novak, Novak, Spies, & Low, 1998; Panerai, White, Markus, & Evans, 1998; Panerai, 2009; Tiecks, Douville, Byrd, Lam, & Newell, 1996). In an mTBI case study, TCD detected disrupted cerebral autoregulation 6 days after injury (Strebel, Lam, Matta, & Newell, 1997). Larger studies have confirmed that TCD appears to detect impaired autoregulation in TBI during the acute injury stage (Jünger et al., 1997; Steiner et al., 2003). One study compared TCD measures with a gold-standard CBF measurement, stable xenon-enhanced CBF (XeCBF), following a CO_2 challenge to assess cerebral vasoreactivity in patients with moderate to severe head injury ($n = 14$; GCS < 13; median: 6.5; Ng, Poon, Chan, Lam, & Lam, 2002). Investigators found that TCD measures correlated with XeCBF ($r = 0.34$; $p = 0.006$). In addition, the pressure autoregulatory response ratios determined by TCD and XeCBF correlated well ($r = 0.73$; $p < 0.0005$). The authors concluded that overall, TCD had a sensitivity and specificity of 70.5 percent and 50 percent, respectively, in detecting preserved and impaired cerebral vasoreactivity, and 76.2 percent and 59.1 percent for detecting intact and lost-pressure autoregulatory response.

TCD Early After TBI

In most studies, TCD measures are taken within the first 24–48 hours following an injury, although the precise time between injury and initial TCD measurement is rarely recorded. TCD measures have been recorded following severe head injuries in the emergency department (Burger & Hassler, 1993; Muttaqin et al., 1993; Saunders & Cledgett, 1988), so the assumption is that these were done within hours of injury, but the exact time interval was only recorded in four participants. The authors reported results for three of these patients, finding increases in PI and decreases in average flow velocity in patients with hematomas and brain swelling.

McQuire, Sutcliffe, & Coats (1998) examined 22 severely brain-injured patients (GCS ≤ 8 or Abbreviated Injury Scale ≥ 3) less than three hours after injury (median time: 83.5 minutes; range: 53–187) and found significant changes in PI and MCAv. Of the 22 patients, 86 percent had TCD-recorded abnormalities on either the left or right MCA. Of the 15 patients having CT data along with bilateral NIRS measures, six (40%) had abnormal TCD findings on the side of the head that corresponded with the side of CT-detected injury. Thus, the side of abnormal signal measured by TCD did not appear to be an accurate predictor of the side of injury as seen on initial CT.

In a prospective study that included 57 patients with severe, non-penetrating brain injury (GCS ≤ 8), the lowest blood flow velocities were recorded within the first 8 hours after trauma (between 0 and 8 hours after injury; van Santbrink et al., 2002). Furthermore, TCD measures taken within the first 6 hours after sustaining severe TBI ($n = 32$) predicted oligemia, vasospasm and poor outcome (Ojha, Jha, Kale, & Mehta, 2005).

TCD and mTBI

Several studies included a subgroup of patients with mild brain injury (Table 10). These found a variety of TCD-recorded abnormalities in mTBI in what the authors defined as the 'acute' stages after injury (within 48 hours of injury). For example, TCD identified impaired cerebral autoregulation in 28 percent of patients with GCS scores of 13 to 15 (Jünger et al., 1997). In addition, Chan et al. (1992) found low blood flow velocities in mTBI patients (n = 55) within 24 hours of injury. TCD was also used to detect secondary neurologic deterioration in the first few hours after injury in mild to moderate TBI patients (Jaffres et al., 2005).

Table 10: TCD Studies in mTBI

Population	Methods	Results
Chan et al. (1992)		
Patients with TBI • Mild n = 55 GCS: 13–15 • Moderate n = 16 GCS: 9–12 • Severe n=50 GCS: ≤8	Assessed within 24 h of admission, and then daily measurements	Rank correlation r = 0.46; p < 0.01 between mean MCA velocity and admission GCS. All groups, including the mild TBI group, had lower velocity upon admission than that of the control group.
Junger et al. (1997)		
Patients with mTBI: n = 29 GCS: 13–15	Assessed within 48 h of injury Autoregulation procedure: blood pressure changes induced by removing blood pressure cuff placed on thighs and inflated to 20–40 mmHg above systolic blood pressure for 3 min	28% of patients and 0% of controls had impaired or absent cerebral autoregulation (p = 0.008). Individuals with impaired cerebral autoregulation may be vulnerable to ischemic brain damage and neurologic deterioration if there are reductions in CPP or fluctuations in blood pressure after injury.
Jaffres et al. (2005)		
Patients with TBI: • Mild: n = 42 GCS: 14–15* • Moderate: n = 36 GCS: 9–13	Assessed at admission (see below for time between injury and TCD); CT scan done close in time to TCD Mild: No secondary deterioration 240 min (range: 25–700) Secondary deterioration 210 min (range: 60–690) Moderate: No secondary deterioration 180 min (range: 30–720) Secondary deterioration 203 min (range: 90–600)	Patients with secondary neurologic deterioration: 17% of mild 28% of moderate Patients with secondary deterioration had higher PI than those without secondary deterioration (p < 0.05 for mild and moderate). TCD may help identify those patients who are at risk for neurologic deterioration following mild or moderate TBI.

* Plus the presence of one concomitant clinical finding, including vomiting, post-traumatic seizure, PTA, LOC, focal neurodeficit, skull fracture, multiple trauma, drug or alcohol intoxication, serious facial injury

Future Directions

Although commercial TCD devices are available, design advances may lead to smaller devices that are capable of wireless data transmission and less susceptible to operator dependence. For example, a pocket-sized transcranial ultrasound device has been developed (NeuroDop, MedaSonics, Inc., Mountain View, CA, USA; Kidwell, Martin, & Saver, 2000).

Transcranial color-coded duplex sonography may help eliminate some of the operator dependency found with TCD because of problems finding the artery and determining the angle of insonation. A study using this method that included 12 severe and 12 moderate TBI patients revealed a drop in CBF soon after injury (Kochanowicz et al., 2006). As mentioned earlier, a variety of other methods may prove useful to mTBI diagnosis, but these are currently limited to research applications (Popovic et al., 2009).

Several relatively novel ultrasound-based devices are being developed to assess intracranial pathology, but few have been clinically validated. Such devices include shear mode ultrasound, time-of-flight ultrasound and its variants (e.g., Vittamed; Petkus, Ragauskas, & Jurkonis, 2002; U.S. Patent No. 5,388,583, February 14, 1995; U.S. Patent No. 5,951,477, September 14, 1999) and dispersive ultrasound methods (U.S. Patent Application No. 2005/0033171, February 10, 2005; Stergiopoulos, Toronto, Freibert, Zhang, & Hatzinakos, 2008).

Conclusions

Compared to other devices, TCD has received considerable attention and clinical use in TBI of all severities. TCD can be portable, and TCD measures have been shown to significantly correlate with several measures of cerebral hemodynamics that could be relevant to mTBI, with admission GCS and outcome measures.

Notably, TCD has several limitations that need to be addressed. For example, it is impossible to insonate the cerebral vessels in approximately 5–10 percent of individuals because of the lack of an acoustic window (Markus, 2000). Furthermore, the technique can be operator dependent, especially in finding the angle of insonation and MCA requires training and expertise.

Ocular Imaging Methods and Devices

Methods that examine the eye can provide information about ICP, pupil size and reactivity, and papilledema secondary to eICP. Several portable or potentially portable devices for examining the eye are available (Table 11). Of these, ocular sonography appears currently to have the greatest potential for field-based diagnostics.

Table 11: Ocular Imaging and Assessment Devices

Device	Measures	Limits
Ophthalmoscope and laser scanning ophthalmoscope	Papilledema	• Qualitative • Requires pupil dilation • Requires expertise
Tonometer	Intraocular pressure	• Requires pupil dilation • Requires expertise • External pressure may trigger oculo-cardiac reflex, causing hypotension • Intraocular pressure does not correlate well with ICP (Czarnik et al., 2009, 2007)
Optical coherence tomography of the retina and Doppler optical coherence tomography	Provides information on retinal layers, optic nerve head topography, peripapillary retinal nerve fiber layer thickness, and macular volume; can measure papilledema	• Still early in development • Requires expertise • No studies showing relationship with ICP, CPP, etc.
NIR automated pupillometer (Neuroptics, 2010)	Pupil size and reactivity with little expertise*	• Measures may reflect changes associated with more severe injury or later events after injury
Optic nerve sheath ocular sonography	Optic nerve sheath diameter (ONSD) and potentially ICP	• Feasibility for use by non-experts unclear • Correlation coefficients and ONSD cut-offs for ICP have varied across studies
Retinal Laser Doppler sonography	Ocular blood flow	• No evidence for use in mTBI • No clear relationship to ICP

* The American Association of Neurological Surgeons and the Brain Trauma Foundation Guidelines recommend that papillary light response should be evaluated and used as a prognostic parameter and that pupil dynamics and asymmetry should be documented in the clinical record.

Ocular Sonography

Ocular sonography has been used to determine ONSD for more than a decade. Unlike other methods, it is not limited to measures of papilledema. Papilledema is a surrogate and delayed indicator of eICP (Czarnik et al., 2009, 2007; Hayreh, 1968) and relatively uncommon following mTBI. Furthermore, ocular sonography does not require pupil dilation. Pupil dilation can hinder detection of signs of deterioration and may be particularly problematic for servicemembers in the field, because it can transiently inhibit visual acuity.

On average, ONSD sonography requires less training than that required for other ocular assessment devices; however, ONSD measures can be operator dependent and require some expertise in sonography. ONSD measures appear to be reproducible with good inter- and intra-observer variation in head injury. Karakitsos et al. (2006) reported median intra- and inter-observer variations to be 0.2 mm and 0.3 mm, respectively. Geeraerts et al. (2007) reported a 0.27-mm mean SD for ONSD (two raters, three repeated measurements taken in 1 hour; n = 12 TBI patients). Similar reproducibility has been found when using ONSD to examine patients with intracranial hemorrhage (median inter-observer difference of 0.25 mm; interquartile range: 0.1-0.4 mm; Moretti, Pizzi, Cassini, & Vivaldi, 2009).

Although measuring ONSD requires training, the learning curve for experienced sonologists may include as few as 10 subjects, three with abnormal scan results. Novice sonologists may need to perform closer

to 25 scans (Tayal et al., 2007). Researchers have suggested that the technique could be made more reliable and less operator dependent by using different instrumentation and slightly different scans (Shah, Kimberly, Marill, & Noble, 2009).

ONSD and ICP/CPP

The ocular nerve is surrounded by cerebrospinal fluid and covered in dura mater, which makes up what is known as the *optic nerve sheath* (Figure 1). The optic nerve sheath is responsive to cerebrospinal fluid pressure variations (Hansen & Helmke, 1996, 1997; Hayreh, 1968; Liu & Kahn, 1993) and has been found to be widened in patients with intracranial hypertension (Gangemi, Cennamo, Maiuri, & d'Andrea, 1987). For this reason researchers have suggested that the ONSD may be able to serve as a noninvasive indicator of ICP (Geeraerts & Dubost, 2009).

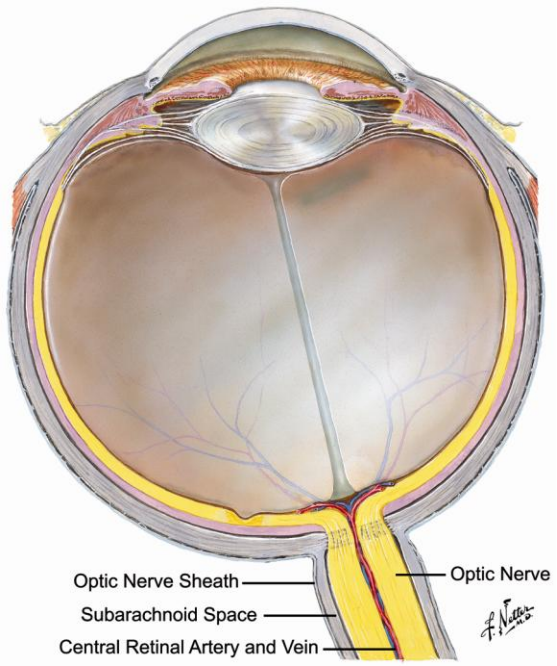

Figure 1: Anatomy of the Eye

ONSD sonography is performed using a relatively standardized protocol (Blaivas, Theodoro, & Sierzenski, 2002; Blaivas, Theodoro, & Sierzenski, 2003; Hansen & Helmke, 1996, 1997; Newman, Hollman, Dutton, & Carachi, 2002). Research has found that ONSD correlates with ICP in neurosurgical patients (Cennamo, Gangemi, & Stella, 1987; Gangemi et al., 1987) and patients with suspected ICP elevation (Major, Girling, & Boyle, 2010). Reports indicate that similar correlations occur following spontaneous intracranial hemorrhage (Moretti & Pizzi, 2009; Moretti et al., 2009). A direct relationship between ONSD and ICP was also found following liquid infusion and removal during lumbar puncture (Hansen & Helmke, 1997).

ONSD and TBI

Several studies have investigated ONSD following TBI, two of which included mTBI patients (see Table 12 for summaries). The precise time of measurement was not recorded in these studies, although for most, initial ONSD measures appear to have been taken within 24 hours of hospital admission. These studies show that ONSD is significantly correlated with invasive ICP measurements after severe TBI (Geeraerts, Duranteau, & Benhamou, 2008; Geeraerts et al., 2007; Kimberly, Shah, Marill, & Noble, 2008; Soldatos, Chatzimichail, Papathanasiou, & Gouliamos, 2009; Soldatos et al., 2008) and with signs of eICP on CT in mild to moderate head injury (GCS > 8; n = 18; Blaivas et al., 2003; Tayal et al., 2007).

ONSD and Military or Blast TBI

To date, no studies of ocular sonography in military populations or following blast exposure have been published.

Future Directions

One of the greatest limitations to ONSD is the need for training to obtain reproducible and reliable measures. Development of more automated systems may mitigate this limitation. Furthermore, because ONSD appears to serve as a surrogate measure of ICP, which may or may not be elevated early after mTBI, incorporating ONSD into a multimodality system that measures other aspects of brain health may prove beneficial.

Conclusions

Of the devices available for ocular assessment, sonographic measures of ONSD appear to be the most feasible for field use and are likely better for assessing early injury than methods limited to detecting papilledema. ONSD appears to provide sensitive measures of ICP in TBI patients, although differences have been reported for cut-off thresholds discriminating normal from eICP. Good correlations have also been found between ONSD and CT findings. A potential limitation in using ONSD for mTBI diagnosis is that the technique cannot be used in cases of ocular trauma, which can occur following blast-related TBI.

Table 12: ONSD in TBI Patients

Study Population	Comparison Method	ONSD Cut-off (mm)	Area Under the Curve (AUC; 95% Confidence Interval)	Sensitivity % (95% Confidence Interval)	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Results
Blaivas et al. (2003)								
Patients with ICH (blunt head trauma induced or spontaneous) : *n* = 35	CT findings *n* = 14 patients with CT signs of eICP	>5	-	100	95	93	100	ONSD signs different among patients with and without CT signs of eICP ($p = 0.001$).
Karaksitos et al. (2006)								
Patients with severe TBI: *n* = 54 GCS: ≤8	CT findings prognosis (brain death)	>5.9	0.805 (0.768–0.911) for predicting brain death	74	65	65	74	ONSD signs different between severe TBI patients and controls ($p < 0.001$). CT and ONSD signs correlated ($p < 0.001$).
Geeraerts et al. (2007)								
Patients with severe TBI: *n* = 31 GCS: <8	CT, TCD, intraparenchymal catheter	>5.9	0.96 (0.83–0.99)	87	94	93	88	ONSD greater in high ICP than in control and normal ICP patients ($p < 0.0001$). Largest ONSD value at admission and baseline ICP correlated ($r = 0.68$; $p < 0.0001$; $n = 31$). Largest ONSD predicted eICP more efficiently than TCD PI.
		>5.7	–	100	–	100	–	
Tayal et al. (2007)								
Patients with suspected head injury: *n* = 56 GCS median of 15 GCS interquartile range 6 -15	CT	≥5.0 CT eICP	–	100 (68–100)	63 (50–76)	30 (12–47)	100 (91–100)	An ONSD < 5 mm excluded eICP, as determined by CT. Eight patients with ONSD ≥5 mm had CT findings consistent with eICP. Two out of eight patients with increased ONSD and eICP had GCS 14 (CT shift) and 15 (CT edema).
		≥5.0 any CT	-	84 (60-97)	73 (59-86)	-	-	

Study Population	Comparison Method	ONSD Cut-off (mm)	Area Under the Curve (AUC; 95% Confidence Interval)	Sensitivity % (95% Confidence Interval)	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Results
Kimberly et al. (2008)								
Patients with traumatic injuries: *n* = 4 Patients with spontaneous intracerebral hemorrhages: *n* = 11	Extraventricular drain ICP	>5.0	0.93 (0.84–0.99)	88 (47–99)	93 (78–99)	–	–	ONSD-ICP Spearman rank correlation coefficient: 0.59 ($p < 0.0005$).
Soldatos et al. (2008)								
Patients with brain injury: *n* = 50 Controls: *n* = 26 GCS: 14 Normal CT Moderate: *n* = 18 GCS: >8 CT Marshall I Severe: *n* = 32 GCS: ≤8 CT Marshal II to VI	Intraparenchymal catheter for severe, CT, TCD	>5.7	0.93 (0.79–0.99) for predicting eICP	74	100	–	–	ONSD measurements correlate well with noninvasive and invasive ICP measures as well as with head CT scan findings in brain-injured adults. ONDS and TCD values did not differ between controls and moderate TBI patients. In severe TBI, ONSD correlated with eICP ($r = 0.8$; 95% CI, 0.62–0.90; $p < 0.0001$). In severe TBI, ONSD correlated with ICP ($r = 0.68$; 95% CI, 0.43–0.83; $p = 0.002$) and CT ($r = 0.82$; 95% CI, 0.66–0.91; $p < 0.0001$).

Study Population	Comparison Method	ONSD Cut-off (mm)	Area Under the Curve (AUC; 95% Confidence Interval)	Sensitivity % (95% Confidence Interval)	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Results
Goel et al. (2008)								
Patients with head injury: *n* = 100 Mild: *n* = 40 GCS: 13–15 Moderate: *n* = 35 GCS: 9–12 Severe: *n* = 25 GCS: ≤8	CT	>5.0	–	99	93	96	97	ONSD correlated with signs of eICP on CT compared to mean ONSD in patients without CT findings. TCD has the potential to serve as an indicator of eICP and intracranial hematoma needing surgical intervention.
Geerarets et al. (2008)								
Patients with severe TBI: *n* = 22 Patients with subarachnoid hemorrhage: *n* = 6 Patients with intracranial hematoma: *n* = 8 Patients with stroke: *n* = 1	Intraparenchymal catheter	5.86	0.91 (0.82–0.96)	95	79	–	100	Mean ONSD correlated with ICP (r = 0.71; $p < 0.0001$; 78 simultaneous measures). ONSD changes were related to ICP variations (r = 0.73; $p < 0.0001$, 39 simultaneous paired measures.

SENSORY ASSESSMENT METHODS AND DEVICES

Individuals who have sustained an mTBI frequently complain about problems with smell and hearing. Thus, interest exists in using devices that can assess smell and hearing systems (olfactory and auditory systems, respectively) to detect mTBI. For reasons mentioned earlier, however, sensory system function cannot serve as a stand-alone indicator of mTBI in all patients and can be confounded by polytrauma and the field environment. Because measures of sensory system function may provide supplemental information in multimodal diagnostic approaches, however, devices that can assess olfaction and hearing are briefly described below.

Olfactory System

Olfactory Dysfunction and mTBI

The olfactory nerve (cranial nerve I) is the most frequently damaged cranial nerve following mTBI (Coello, Canals, Gonzalez, & Martín, 2010); thus, it is not surprising to find olfactory deficits following head injury. In fact, a reported 0–16 percent of individuals with mTBI suffer from olfactory dysfunction (Costanzo, DiNardo, & Reiter, 2003), although studies using newer quantitative testing methods have reported higher numbers. For example, in a cohort of mTBI patients, the incidence of hyposmia and anosmia were 22 percent and 4 percent, respectively (de Kruijk et al., 2003). Notably, it appears that many mTBI sufferers are unaware that they have an olfactory deficit (Callahan & Hinkebein, 1999; Callahan & Hinkebein, 2002). Thus, self-report information about olfactory problems are likely inaccurate.

Research investigating the association between olfactory dysfunction and brain injury severity have yielded mixed results, with some reporting an association (Doty et al., 1997; Green, Rohling, Iverson, & Gervais, 2003; Ogawa & Rutka, 1999) while others report no correlation with GCS (Haxel et al., 2008). Thus, the ability of olfactory tests to accurately diagnose mTBI is unclear.

Olfaction Assessment Devices

Several objective and portable devices for determining olfactory function are available, including the Pocket Smell Test and “Sniffin’ Sticks”(In addition to the tests mentioned in the table, other olfaction tests appear to have good validity and reliability and could potentially be redesigned into portable and affordable devices, including the Connecticut Chemosensory Clinical Research Center Test, a combined odor identification and odor threshold test, and the Alberta Smell Test.
Table 13.) Both of these devices require less expertise and instrumentation than electrophysiologic methods, making them more attractive for field use. Comparatively, both the Pocket Smell Test and Sniffin’ Sticks can reliably assess olfaction, but Sniffin’ Sticks may be more amenable to widespread use in the field, because the system is compact, can be used multiple times, and has a 6- to 12-month shelf life.

In addition to the tests mentioned in the table, other olfaction tests appear to have good validity and reliability and could potentially be redesigned into portable and affordable devices, including the Connecticut Chemosensory Clinical Research Center Test, a combined odor identification and odor threshold test, and the Alberta Smell Test.

Table 13: Portable Devices for Assessing Olfaction

Device	Usage	Description
Pocket Smell Test	Each test can be used one time.	Derived from the clinically validated University of Pennsylvania Smell Identification Test and comprises a three-item microencapsulated "scratch and sniff" measure. Each odor is released by scratching the encapsulating material with a pencil. The patient smells the odor and chooses one of the four response choices (forced choice design).
Sniffin' Sticks	Each test can be used multiple times.	This 12-item test uses pen-like odor-dispensing devices and includes tests for odor identification, discrimination and detection thresholds.

Notably, research findings suggest that tests of effort should be included with measures of olfactory function, given that some individuals may exaggerate their dysfunction or "game" the assessment (Green & Iverson, 2001). How tests of effort would be incorporated into a device intended for diagnosing mTBI in the field is unclear.

Auditory System

Auditory Dysfunction and mTBI

Peripheral and central auditory structure damage occurs following head injury, with peripheral damage perhaps being most prominent in those having skull trauma (Abd Al-Hady, Shehata, El-Mously, & Sallam, 2007; Barber, 1969; Bergemalm & Borg, 2001; Bergemalm, 2003; Nölle, Todt, Seidl, & Ernst, 2004). Auditory problems may be more prominent in military settings where exposure to munitions of all kinds is common. Blast forces may be particularly damaging; both sound and atmospheric pressure changes caused by blast can damage the tympanic membrane, middle ear and outer ear (Figure 2).

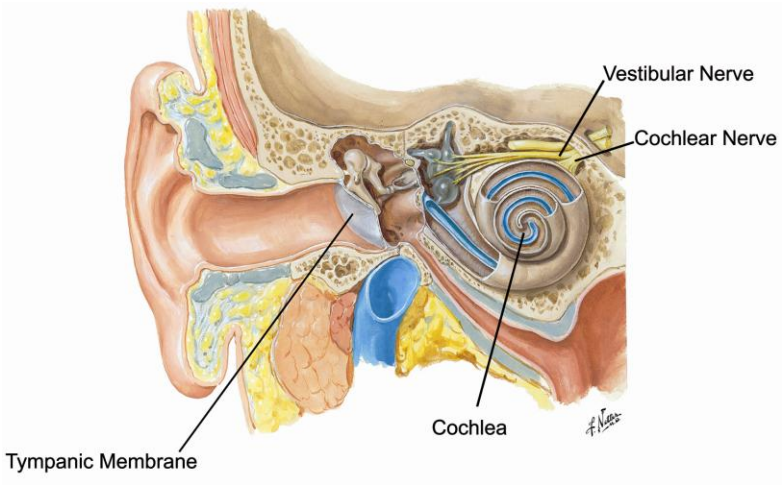

Figure 2: Anatomy of the Ear

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Hearing loss and tinnitus are highly prevalent in soldiers returning from OEF/OIF (Lew, Poole, Alvarez, & Moore, 2005), with a recent study finding that 35.2 percent of blast-exposed veterans had tympanic membrane perforation (Xydakis et al., 2007). It should be noted, however, that damage to auditory structures, such as tympanic membrane perforation, is not an indicator of TBI, per se. Other reports found hearing impairments (either alone or in combination with visual impairment) in 51 percent of patients with blast-related TBI (Lew et al., 2009). Furthermore, hearing loss and tinnitus were more common in OIF veterans who had sustained blast-related TBI compared to individuals who had sustained TBI from other sources (p = 0.04 and 0.007, respectively).

Audiologic Assessment Devices

Standard audiologic examinations are not feasible in the field, requiring lengthy sessions, a low-noise environment and expertise. Several devices capable of assessing the integrity of the auditory system, however, may prove feasible in the field. These include tympanometry, otoacoustic emission measures and electrocochleography for measuring microphonic potentials.

Tympanometry

Tympanometry, also known as *impedance audiometry*, is used to assess the integrity of the middle ear and tympanic membrane through measuring the acoustic reflex. The acoustic reflex is a non-voluntary reflex (muscle contraction) occurring in response to high-intensity sounds. Newer tympanometry devices are available commercially, and several are portable, easy to use and fully automated (Popovic et al., 2009). In mTBI, an examination of both ears revealed that >30 percent of patients had abnormal tympanograms (Munjal et al., 2010). Findings from this study are difficult to interpret, however, because the data did not reveal a significant difference between mTBI and control participants.

Tympanometry and ICP. Tympanometers may also be able to evaluate ICP using tympanic membrane displacement (TMD) procedures (Marchbanks, 1984). Several studies have used TMD to examine ICP, either after postural changes (Phillips & Marchbanks, 1989) or during invasive ICP monitoring (Shimbles, Dodd, Banister, Mendelow, & Chambers, 2005). When compared directly to invasive ICP in pediatric patients, TMD predicted invasive ICP measures with excellent sensitivity (93%) and specificity (100%). Nonetheless, the study authors concluded that TMD was a poor clinical indicator of ICP because of high intersubject variability and low predictive value (Shimbles et al., 2005).

TMD is not suitable for individuals who have middle ear or brainstem dysfunction (Reid et al., 1989). Appropriate clinical studies in mTBI sufferers have not been conducted, but TMD would plausibly not be appropriate for ICP given that mTBI — particularly blast-induced mTBI — is associated with ear dysfunction.

Otoacoustic Emissions

Otoacoustic emissions measure the integrity of the inner ear and cochlea as well as the nerves supporting cochlear function, such as the olivocochlear efferent system. There are several types of otoacoustic emissions. *Transient evoked otoacoustic emissions* result from delivery of a wide band audio burst. *Distortion product otoacoustic emissions* are evoked by a pair of primary tones. The elicited response occurs at frequencies mathematically related to the delivered primary tones. It is important to note that otoacoustic emissions disappear with hearing loss, and measuring otoacoustic emissions generally requires a silent recording environment. Both of these factors potentially limit the

ability to effectively monitor otoacoustic emissions following mTBI in the field or in individuals with prior hearing loss.

Otoacoustic Emissions and ICP. Otoacoustic emissions may be able to detect changes in ICP. Changes in otoacoustic emissions have been reported following changes in posture (Büki et al., 1996; Büki, Giraudet, & Avan, 2009; Büki, de Kleine, Wit, & Avan, 2002; Frank et al., 2000; de Kleine, Wit, Avan, & van Dijk, 2001; Kleine, Wit, van Dijk, & Avan, 2000; Mom, Gilain, & Avan, 2009; Traboulsi & Avan, 2007; Voss et al., 2010; Voss, Horton, Tabucchi, Folowosele, & Shera, 2006), altitude (Olzowy, von Gleichenstein, Canis, & Mees, 2008) and in neurosurgical patients (Büki et al., 1996).

Cochlear Microphonic Potentials

Cochlear microphonic potentials are generated by cochlear hair cells and, like otoacoustic emissions, represent cochlear integrity. They can be measured by transtympanic electrocochleography, the gold-standard method, or by extratympanic electrocochleography (Anastasio, Alvarenga, & Filho, 2008; Büki et al., 2009; Takeda & Kakigi, 2010). Recently, newer methods, such as wet electrocochleography, have also been proposed (Carpi & Migliorini, 2009).

Transtympanic procedures yield better, more reliable data than extratympanic measures (Bonucci & Hyppolito, 2009; Santarelli, Scimemi, Monte, & Arslan, 2006). Transtympanic electrocochleography, however, is not field-appropriate; it is a somewhat invasive procedure that requires sedation. Thus, extratympanic procedures would likely need to be used in the field, and as such, methods for mitigating issues with signal-to-noise ratio and data quality may need to be addressed.

Microphonic potentials may convey some advantage over using otoacoustic emissions for assessing mTBI in theater. Microphonic potentials presumably persist as long as there are sensory cells in the cochlea, and, thus, are more robust in the face of hearing loss. Furthermore, microphonic potential assessment may be more immune to environmental noise (Büki et al., 2009).

Cochlear Microphonic Potentials and ICP. Microphonic potentials have been reported to change in response to posture changes (Büki et al., 2009), suggesting that they may be sensitive to ICP.

Future Directions

Active Signal Technologies, Inc. received DoD funds to integrate cochlear microphonics into their BAM systems (Active Signal Technologies, Inc., 2010; refer to page 25). Other brain monitoring and evaluation systems will also likely attempt to integrate devices for assessing auditory function in order to provide a more complete picture of the central nervous system following mTBI.

Conclusions

Olfactory and auditory deficits can occur in a subset of mTBI sufferers. Portable or potentially portable devices for assessing these two sensory systems exist. Because only a subset of individuals experience olfactory or auditory deficits following mTBI, these devices would not be useful for widespread mTBI screening in the field. Furthermore, as previously mentioned, devices that rely on end-organ function may not be suitable for field-based diagnostics.

Although olfactory and auditory assessment devices may not be appropriate stand-alone indicators of mTBI, they may be able to provide a more complete picture of brain injury when integrated with other brain assessment devices. The feasibility of this integration is not known, but companies such as Active Signal Technologies have already begun to investigate this possibility.

Balance Assessment Methods and Devices

The vestibular system supports balance, sense of orientation in space and gait. It provides information about gravity, rotation, and acceleration and resides in the inner ear. The vestibular system comprises a series of semicircular canals for detecting rotational movement and the otolith organs, which register linear acceleration (e.g., speed). The vestibular system communicates with the visual system to help the eyes remain stable during head movement and with the systems that allow muscles to maintain posture and balance. TBI likely affects the vestibular system because individuals who have experienced a TBI commonly complain of balance problems (Basford et al., 2003).

A number of balance tests that are relatively rapid to administer exist (see Table 14 for examples). Most require baseline scores or a normative value derived from "healthy" populations for comparison. Some — particularly those that require force platforms — can be quite expensive, which has spurred interest in off-the-shelf systems such as the Nintendo Wii Balance Board.

Table 14: Balance Assessment Devices

Test/Device	Necessary Equipment
Balance Error Scoring System (BESS)	Stopwatch and foam surface
Sensory Organization Test (SOT)	Force platform
NeuroCom SMART Balance Master	SMART EquiTest system — force platform
Wii Balance Board	Wii game system
Rhomberg	No equipment required
Fukuda Stepping Test	No equipment required

A number of recent studies have examined the relationship between TBI and balance in concussed athletes. Davis et al. (2009) reviewed balance testing as a marker of status post TBI in concussed athletes, employing four balance measures. BESS scores in concussed athletes were notably different than their non-concussed cohort.

A study by Guskiewicz, Ross, & Marshall (2001) collected two measures of postural stability in concussed athletes. The study employed the SOT and Neurocom Smart Balance System. Postural stability impairment was noted in individuals on post-injury days one, three and five. In a review of postural balance and gait in the aftermath of TBI, dizziness scores were found to be consistent with complaints reported by subjects (Basford et al., 2003). Vestibular and gait impairment were noted in subjects after TBI. Furthermore, these impairments were found to correlate with pervasive physical, emotional and functional impairments in subjects enrolled in the study (Basford et al., 2003). The SOT was also able to detect differences in balance between TBI patients and non–head-injured controls, with the authors concluding that objective, computerized assessment of balance should be used to investigate complaints of balance in TBI patients (Kaufman et al., 2006).

It should be noted that others have found a less consistent relationship between balance measures and TBI. A fairly comprehensive study looked at predictors of outcomes in TBI patients (Dischinger, 2007), and found that balance was not correlated with symptoms, well-being, or the ability to return to work.

Balance testing can be problematic in the field. A wide variety of injury precludes successful balance testing, including injuries to upper or lower extremities, chest injuries, spine injures and others. In addition, like other sensory systems, the vestibular system may be disrupted by end-organ damage that may or may not reflect mTBI. Furthermore, many of the devices for measuring balance are quite large, such as the Neurocom International, Inc. Smart Balance Master®.

Future Directions

Interest is increasing in off-the-shelf systems that are easy to use, portable and relatively inexpensive. Notably, the WII Balance Board may be useful in assessing balance in TBI sufferers (Clark et al., 2010). The WII Balance Board showed requisite test–retest reliability in TBI patients. Moreover, this test demonstrated comparable validity when compared to laboratory-grade force platforms, noted as the gold standard in balance testing.

Conclusions

Balance assessments may provide a better understanding the effects of mTBI on the vestibular system and may be able to be incorporated into a multimodal mTBI assessment procedure. A review of the literature on balance problems in military servicemembers who had experienced a TBI indicates that balance problems are prevalent as a feature of TBI (Hoge et al., 2004). Using balance testing in the field has several limitations. Notably, balance may be affected by injury to body regions needed for balance testing, such as the upper and lower extremities. Fatigue, dehydration and nutrition may also affect balance. Moreover, prior baseline balance of servicemembers may not be known. A lack of a baseline comparison likely reduces the accuracy of data collected in theater.

Neurocognitive/Psychological Testing Methods and Devices

Neuropsychological testing can measure many functions and behaviors that are potentially impaired in the aftermath of a head injury, such as reaction time, memory and attention (Bleiberg, Kane, Reeves, Garmoe, & Halpern, 2000; Iverson, Langlois, McCrea, & Kelly, 2009; Peterson, Stull, Collins, & Wang, 2009). Several studies indicate that mTBI sufferers may have neuropsychological impairments within 24 hours of sustaining the injury. For example, in a sample of emergency department mTBI patients, cognitive deficits were noted in the areas of concentration, memory, and performance on simple mathematical tasks (Peterson et al., 2009). Echemendia et al. (2001) found that neuropsychological performance was worse in concussed athletes as compared to non-injured control participants both 2 and 48 hours after injury. Data from military populations in the immediate aftermath of injury are lacking, as are studies investigating differences between blast- and non-blast mTBI. Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler (2009) did not find differences between blast- and non–blast-related TBI, but more research is needed in this area.

Rigorous debate over the neuropsychological impact of mTBI exists. Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg (2005) conducted a meta-analysis to investigate the relationship between mTBI and neuropsychological function. The analysis included 39 studies involving 1463 mTBI patients

and 1191 control individuals. The overall effect of mTBI on neuropsychological measures was moderate (*d* = 0.54), with larger effect sizes noted for delayed memory and fluency when tested within 3 months of injury (*d* = 1.03 and 0.89, respectively). In a different meta-analysis that examined the impact of sports-related concussion on neuropsychological function, the effect size was moderate (*d* = 0.49) but was much greater when analyzing studies that conducted testing within 24 hours of injury (*d* = 1.0 to 1.42; Belanger, Spiegel, & Vanderploeg, 2010). Frencham, Fox, & Mayberry (2005) also found that time after injury moderated meta-analysis effect size, which moved towards zero as the time between assessment and injury increased (Frencham et al., 2005). Notably, meta-analyses of studies involving mTBI and neuropsychological testing may be confounded by differences among studies included in the types of analyses, sampling methods, time between injury and assessment and patient populations (Pertab, James, & Bigler, 2009).

Standard neuropsychological assessment for a single TBI patient can require up to 12 hours of testing by a highly trained neuropsychologist. Thus, to use neuropsychological measures for mTBI diagnosis in the field, automated testing and data interpretation devices are needed. Automated designs are available, but are still being investigated. For example, Broglio, Macciocchi, & Ferrara (2007) concluded that automated neuropsychological testing platforms show promise, but formal testing batteries are needed to assess mTBI until automated platforms are more consistent and reliable.

Current Automated Testing Platforms for Consideration in Military Service Members

At present, five automated neuropsychological testing platforms are being reviewed by DVBIC to identify which system best meets the needs of military medicine.

ANAM

The Automated Neuropsychological Assessment Metrics (ANAM) system is a battery of computerized neuropsychological and human factors tests that takes about 20 minutes to complete. This model was originally created within DoD as a research tool. The ANAM is a computerized battery designed to detect speed and accuracy across a number of domains associated with neuropsychological functioning. The Assistant Secretary of Defense for Health Affairs released a memorandum dictating that all servicemembers being deployed to combat zones in Iraq or Afghanistan receive a pre-deployment ANAM screening to establish a baseline functioning ("Automated Neuropsychological Assessment Metrics," 2010). This testing would allow for comparison of post-injury function to the servicemember's pre-injury function.

Braincheckers

The Braincheckers system is comparable to earlier versions of the ANAM system. The key difference in this platform is that through Navy Medicine, it has been loaded onto a portable PDA platform. In addition to assessment of neuropsychological constructs, such as simple reaction time, go-no-go reaction time as a time sensitive decision-making measure, and matching to sample, the Braincheckers system includes a sleep scale and a mood scale. Braincheckers shows promise as an affordable and portable system for the measurement of potential cognitive constructs potentially affected by neurologic insult (Reeves et al, 2007).

CNS Vital Signs

CNS Vital Signs is a computerized neurocognitive assessment developed as a screening instrument. This measure contains seven tests measuring key neuropsychological constructs: verbal and visual memory, finger tapping, digit symbol coding, Stroop, shifting attention and continuous performance. Traditionally, this measure was employed in pharmaceutical testing to measure cognitive change after the introduction of a pharmaceutical compound. This measure contains two significant benefits; it has been tested on a global population and has been translated into numerous languages (Gualtieri & Johnson, 2006, 2008).

ImPACT

The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) is a potentially portable system developed in the 1990s as a solution to the need to assess athletes after head injury (ImPACT Applications, Inc., 2010). The system has been widely used in high school, college and professional athletic organizations. It takes approximately 20 minutes to complete and is comprised of the following tests: attention span, working memory, sustained and selective attention time, response variability, non-verbal problem solving and reaction time. ImPACT has been translated into 13 languages and is widely used in athletic communities.

HeadMinder

HeadMinder is a computerized testing system that offers a disease-specific diagnostic indicator (HeadMinder, Inc., 2001). The system is reported to have acceptable sensitivity and specificity as well as statistically viable validity and reliability. HeadMinder is reported to contain a reliable change index, employing high-order statistics, and is simple to administer.

Future Directions

Virtual Reality and Gamer-Based Designs

Virtual reality and gamer-based designs may prove useful in creating a neuropsychological testing device for field-based mTBI diagnostics. Experts have shown interest in gamer technologies for assessment (Davies et al., 1999), and they are already being employed in TBI rehabilitation (Doherty, Bloor, & Cockton, 1999).

Smooth Eye Pursuit and Saccades

Another promising area in measuring cognitive and executive function after mTBI is the evaluation of visual tracking performance (e.g., smooth pursuit eye movements [SPEM]). Unlike other neuropsychological measures of attention, visual tracking can be used to detect momentary lapses in attention, which may be present in mTBI sufferers. Visual tracking involves following slowly moving objects in the visual field with the eyes. The slowly moving object is often a dot traveling in a circular motion on a screen. The eye tracking can be accurately and easily measured using video-oculography, enabling automated assessment with the development of appropriate computerized systems and algorithms.

The neural circuitry mediating SPEM comprises a widely distributed network that is known to be involved in attention and executive functions (e.g., parietal cortex, prefrontal cortex, etc.) as well as motor function (e.g., cerebellum). Because visual tracking requires distributed neural networks, diffuse axonal injury, which is not sufficiently measured using CT or standard MRI imaging, may be able to be

assessed with visual tracking measures (Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010). Indeed, variability in SPEM is associated with cognitive performance (Suh et al., 2006; Suh, Kolster, Sarkar, McCandliss, & Ghajar, 2006) and can predict white matter shear injury detected using diffusion tensor imaging (Maruta et al., 2010).

Suh et al. (2006) found that patients with mTBI (GCS: 13 –15) are impaired on SPEM measures relative to non–brain-injured volunteers. Heitger et al. (2004) did not find similar results, but they averaged performance measures across many trials. Healthy volunteer performance may decrease over trials; thus, it may be more appropriate to use control measures taken in the first few trials. Notably, in another study that found an association between SPEM deficits and mTBI, it was concluded that more studies were needed to develop a standard for normal performance given variability in "normal" performance scores (Contreras et al., 2008).

Testing visual tracking in the field could prove difficult, given the need for stimulus display, shielding of other visual distracters, and recording equipment. There are novel devices for measuring visual tracking though, including a set of 'goggles' developed by Jamshid Ghajar, M.D., Ph.D., of the Brain Trauma Foundation, Inc., with DoD (Congressionally Directed Medical Research Program [CDMRP]) funding ("CDMRP and TATRC Vision Research Portfolio," 2009). The goggles are strapped around the head and project a moving ball, gauging the eye movements of the person watching it.

Conclusions

At present, neuropsychological testing in theater is predominantly achieved via pencil-and-paper formats (MACE). Formal neuropsychological testing in the field is not feasible because of time, cost, and the need for expertise to administer and interpret the assessment. Automated platforms are needed for neuropsychological testing to be a viable option for mTBI diagnosis. DVBIC is currently assessing several such systems, but it should be noted that to date, automated neuropsychological testing has yielded inconsistent findings, and is limited by the lack of appropriate baseline measures for comparison. Newer devices for measuring brain function, such as visual tracking measures, may prove useful in diagnosing mTBI early after injury, but this remains to be seen. One of the greatest stumbling blocks to neuropsychological testing in general is the need for appropriate comparison values. Even when pre-deployment measures are available, these may not be valid as a baseline in the combat environment.

Conclusions

Although there are subjective signs and symptoms (i.e., self-report information) that a health care provider can look for in a servicemember to help diagnose mTBI, there are no objective biologically or physiologically based diagnostic measures of mTBI. The increased incidence of mTBI and the increased understanding of the downstream effects on both the physical and mental health of servicemembers who sustain mTBI highlights the need for objective diagnostic and assessment tools that are sensitive and specific when used within hours of impact.

A wide variety of devices proposed to have value in detecting and/or diagnosing mTBI exist. To determine their clinical value and feasibility for diagnosing mTBI in the field, it is necessary to examine several questions. First, what events occur early in mTBI and in how many individuals do they occur? To have potential for diagnosing mTBI in the field, the device should be able to measure changes that occur in the immediate aftermath of mTBI and should preferably be able to measure changes that occur in the majority of mTBI sufferers. Second, of the devices that can measure events occurring in the acute stages of mTBI, which are most suited for the field? For example, is the device lightweight and portable? Is it operational in harsh environmental conditions with limited supplies and resources, including power? Can the device be easily operated, and does it display real-time results that can be interpreted by field medics? Third, can the device be used to evaluate individuals with polytrauma? Does it rely on end-organ integrity, such as eye or ear function? Are the output measures of the device influenced by stress, medications, sleep deprivation, or other conditions that may be affecting the wounded servicemember at the time of injury? Finally, how is the device used to make a diagnosis: Are output values compared to a baseline or "normal" value and, if so, are the comparison values appropriate for field-incurred injuries?

Without a complete understanding of the events leading to mTBI, it is difficult to assess the validity of devices intended for mTBI diagnosis. As a result, inferences regarding a given device's diagnostic potential must be drawn from its ability to detect neurologic injury and intracranial pathology more broadly. Future research is needed to determine if the reviewed devices are indeed valid for early mTBI diagnosis, both in civilian hospital and military field settings. Furthermore, because so few studies investigated military or blast-related mTBI and no studies were performed in the field, it remains to be seen whether devices used in the field will yield results comparable to those obtained in the civilian setting.

Issues of polytrauma and environmental considerations can possibly preclude the use of devices proven to be clinically valid in non-military settings. It is thus highly likely that a single device may not be able to serve as the stand-alone tool for early mTBI diagnosis. Advances are needed in incorporating several measures into a comprehensive assessment system that still meets the requirements for appropriate field use. The devices uncovered in this review could be categorized into several domain-based categories, such as markers of cellular injury (e.g., biomarkers), electrical brain activity (e.g., EEG, ERPs), hemodynamic s (e.g., REG, BAM), tissue oxygenation and ischemia (e.g., NIRS), intracranial and extracranial indicators of ICP (e.g., ONSD, otoacoustic emissions), and brain function (e.g., visual eye tracking goggles). The optimal multimodal system should likely draw from several of these domains in order to provide a comprehensive picture of injury and maximize that ability to use the system in a majority of individuals.

The focus of this review was portable devices for field-based mTBI diagnosis early after injury. Improved transportation, particularly air transportation, makes it possible for wounded servicemembers to reach higher-echelon care quickly. Devices that are portable but not feasible for use in the early stages of care, such as portable CT for perfusion studies (Rumboldt, Huda, & All, 2009) and micro-Tesla MRI (Matlachov, Volegov, Espy, George, & Kraus, 2004; Zotev, Matlashov, et al., 2008; Zotev, Volegov, et al., 2008), may enable mTBI diagnosis early. Such devices could be used for follow-up assessment in individuals who have screened positive using a sensitive, but perhaps not specific technology (e.g., EEG, BAM).

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Appendix A: Palo Alto Research Center (PARC) Dosimeter 'Tape' Sensor Specifications

Pressure	Acoustic	Acceleration	Optical
5–100 psi pressure pulse range	100–175 dB acoustic range (measured up to ≈500 Hz)	5–1000 G range	Linear response from 100–400 klux
Reduced thermal cross-sensitivity	Reduced thermal cross-sensitivity	High-resonance frequency design	Maximum sensitivity between 300 and 500 nm

Appendix B: Awards Related to Head Impact, Acceleration, and Blast-Exposure Sensor Devices

Principal Investigator	Title	Award or U.S. Patent Application Number	Abstract Summary	Dates
U.S. Patents				
Shu Yang, Douglas H. Smith, and D. Kacy Cullen	Blast Injury Dosimeter	20100073678	The blast sensor will be made of a material with a specific optical property, such as a contained solution, a membrane-bound solution, or a photonic crystal material. The material's optical property will change when exposed to a pressure wave. This change will correspond to the blast level.	Filed March 27, 2009; published March 25, 2010
William C. Moss and Michael J. King	Helmet Blastometer	20100005571	A helmet blast sensor system that uses external sensors placed in multiple locations on the helmet is being developed. The sensors will characterize the speed, magnitude, and duration of a blast event. External sensors will have one or more time-of-arrival gages that produce a time-of-arrival signal in response to blast-induced positive and negative pressure changes above or below a predetermined pressure threshold. The system includes a data processor and warning indicator comprising a visual or RF signal.	Filed July 8, 2009; published January 14, 2010
Federal Government Awards				
Patrick Kalgren, PI and Impact Technologies, LLC	Electronic Blast Level Alert Sensing Technique W81XWH-10-C-0012	W81XWH-10-C-0012	A small, disposable sensing system for dynamic pressure wave exposure is being developed in collaboration with Allen-Vanguard Corporation. The system comprises a piezoelectric-based omni-directional sensor to remove the impact of sensor direction on measuring blast exposure level. The system will also provide adjustable thresholds that can be reconfigured as additional blast research is conducted.	2009
Jeffrey Chu, PI and Simbex, LLC	Personnel Borne Blast Dosimeter	W81XWH-10-C-0018	A low-cost, retrofittable, unobstrusive, and fieldable Head Injury Dosimeter (HID) will be developed. The HID will be able to provide continuous monitoring and of potentially injurious threats to the head from blasts or direct impacts and will provide real-time alerts following exposure.	2009
John A. Judge and Scott A. Mathews	Fabrication and Testing of a Blast Concussion Burst Sensor	W81XWH-08-1-0186	A wearable burst membrane sensor will be designed. High pressure from an incident explosive shock wave will rupture the membrane, releasing a material with optical properties. The optical properties of the material can be measured and used to calculate blast parameters.	2008

Appendix C: Further Reading on Biomarker Candidates for mTBI

Relevant Reviews

- Agoston, D. V., Gyorgy, A., Eidelman, O., & Pollard, H. B. (2009). Proteomic biomarkers for blast neurotrauma: Targeting cerebral edema, inflammation, and neuronal death cascades. *Journal of Neurotrauma, 26*(6), 901-911.
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S100B

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Neuron-Specific Enolase

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Glial Fibrillary Acid Protein

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Cleaved Tau

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Appendix D: Examples of Electrochemical and Microelectrical Sensor Technologies

Electrochemical Immunosensors	Microelectrical Sensors
• Amperometric devices • Sandwich electrochemical immunosensor devices • Macrocantilever devices	• Nanowires • Impedimetric sensors • Surface acoustic wave sensors • Magnetic nanoparticles • Microatennae

Appendix E: Awards Related to Technologies for Developing Point-of-Care Biomarker Analysis Devices

Principal Investigator	Title	Award Number	Abstract Summary	Award Year
NIH				
Tarek Fahmy	Semiconductor Nanosensors for Label-Free Detection of Antigens and Cellular Immunity	5R01EB008260	The ability of nanoscale complementary metal-oxide semiconductor wires to serve as rapid, quantitative diagnostic devices of soluble antigens will be tested.	2010
John McDevitt	Development of a Lab-on-a-Chip System for Saliva-Based Diagnostics	5U01DE017793	This is the renewal of program for developing portable devices that can be used to complete salivary diagnostic tests (integrated biochips and analyzers) that are highly functional and portable systems.	2010
Pavel Anzenbacher	Self-Luminant Micro-Arrays and Reader for Rapid Diagnostics	1R15EB008874	A fluorescence-based microarray diagnostic platform and rugged device capable of reading DNA and/or protein microarrays will be developed. The system will comprise a disposable self-illuminating array slides with integrated back lighting and a flexible, rugged and portable microarray reader.	2009
DoD SBIR/STTR				
Frank Wang, PI and BioMedomics, Inc.	Highly Sensitive Hand-Held Device for Quantitative Multiplex Protein Analysis Using Time-Resolved Assay	W81XWH-09-C-0037	A compact system for multiplex lateral flow immunoassays is being developed by using proprietary technologies in lateral flow immunoassay, novel nanoparticales and time-resolved luminescent detection.	2009
Gregory Zeltzer, PI and Physical Optics Corporation	Multiplex Biomarker Detection Device	W81XWH-09-C-0059	A device that integrates a microfluidic chip, miniature pump, and electro-optical readout subsystem will be developed. The readout system will have a light delivery unit, miniature spectrometer, microprocessor and liquid crystal display.	2009

Appendix F: Types of Evoked Potentials (EPs)

Evoked Potential	Elicited By
Brainstem Auditory EP	Clicks delivered through headphones or earpieces
Middle Latency EP	Auditory stimulation but thought to be of thalamocortical origin
Pattern Visual EP	Visual stimulation, often flashing light or checkerboard patterns displayed on a video screen that may or may not flicker with invert contrast (black on white to white on black)
Olfactory EP	An odorant delivered to the nose
Somatosensory EP	Mechanical “touch” of finger, wrist, or other body part or by air puff
Motor EP	Peripheral, direct, or transcranial motor cortex electrical stimulation or transcranial magnetic stimulation

Appendix G: Functional Features of the ZOOM-100DC EEG Device

- Portable
- Battery operated
- Eight single-ended channels (five differential channels viewable concurrently)
- Automated artifact detection system ensures that EEG measures are derived from "clean" EEG signals
- Spectral averaging and display of power spectra
- Conventional EEG measures displayed in tables
- Pre-test electrode impedance check
- Ergonomic touch screen user interface with easy-to-read displays
- Raw EEG waveforms displayed in real time and playback mode
- Compact flash storage of digitized raw waveforms and processed results
- Disposable compact frontal electrode headset for data collection
- Miniaturized hardware
- Advanced non-linear computer algorithms that perform quantitative analysis of brain electrical activity and calculate the probability that a particular diagnostic profile exists

Appendix H: Awards Related to Electrophysiologic Devices

Principal Investigator	Title	Award No.	Abstract Summary	Award Year
NIH				
Mo Modarres, PI and Neurowave Systems, Inc.	Field Deployable, Automatic, EEG Seizure Detector and Brain Dysfunction Monitor	5U44NS057969	A portable, low-cost, field-deployable, eight-channel automatic EEG-based seizure detector and brain dysfunction monitor is being developed. It will include novel artifact identification and removal algorithms currently supported by National Institute of Neurological Disorders and Stroke (NINDS). The device will initially be attached to a laptop but will eventually be made smaller and will include onboard data processing capabilities and an attached screen for real-time data display. The device will also have the ability to store data and transmit information wirelessly. It will be tested in the emergency departments of two major health facilities, The Cleveland Clinic and University Hospitals of Cleveland, with a combined 255 patients who have been admitted to the departments and who are in need of an emergency EEG examination.	2008
DoD SBIR/STTR				
Don Tucker, PI and Electrical Geodesics, Inc.	Simultaneous EEG Acquisition and Portable Near Infrared Spectroscopy for Recognition of Traumatic Brain Injury Severity and Outcome Assessments in Far [truncated]	W81XWH-05-C-0068	Through laboratory validation and extensive field testing in military and civilian medical settings, an advanced brain monitoring system will be developed. The system will include a dense array EEG system integrated with a NIRS brain imaging system.	2006

Appendix I: Rheoencephalography (REG) Devices

Device	Parameters	Source
Galileo: KR –Ea Rheo Preamp	45 kHz, 3 s	OTE Galileo, Italy
Medicor: ReoRon 61	160 kHz	Medicor, Hungary
Cerberus	125 kHz, 0.3 s	Quintlab, Hungary
UFI: Model 2991 and 2994*	50 kHz	UFI, Inc., Morro Bay, CA
Minnesota Impedance Cardiograph: Model 304B*	100 kHz, 60 Hz (DC)	Surcom, Inc., Minneapolis, MN

*Animal studies only

Appendix J: Multifrequency Electrical Impedance Tomography (MFEIT) Devices

Device	References
UCLH Mk 2 MFEIT system	Romsauerova et al., 2006; Yerworth, Bayford, Cusick, Conway, & Holder, 2002
Sheffield Mk 3.5 MFEIT system	Wilson, Milnes, Waterworth, Smallwood, & Brown, 2001
Dartmouth System	Halter, Hartov, & Paulsen, 2004
Khu Mark 1	Oh et al., 2008

Appendix K: Acoustical Imaging Methods

Technique	Signal Sent to Tissue	Signal Received from Tissue	References
Photoacoustic or Thermoacoustic Tomography	non-ionizing waves (short pulse lasers or RF pulses)	photoacoustic waves detected by ultrasonic transducers	Anastasio, 2010; Tang, Elson, Li, Dunsby, & Eckersley, 2010; Wang, 2008; Wang et al., 2003; Xu & Wang, 2006
Magnetic Resonance Elastography	actuator-induced vibrations	strain waves measured by phase sensitive MRI	Muthupillai et al., 1995, 1996
Shear Wave Elasticity Imaging	radiation force of a focused ultrasonic beam	shear acoustic waves measured by ultrasonic transducers	U.S. Patent No. 5,524,636, June 11, 1996; Sarvazyan, Rudenko, Swanson, Fowlkes, & Emelianov, 1998
Elastography or Ultrasound Speckle Tracking	static force to compress tissue	acoustical signal measured with ultrasonic transducers	O'Donnell, Skovoroda, Shapo, & Emelianov, 1994; Ophir, Céspedes, Ponnekanti, Yazdi, & Li, 1991
Sonoelasticity Imaging	mechanical vibrators to vibrate tissue	displacement detected using Doppler ultrasound	Muthupillai et al., 1995, 1996
Ultrasound Stimulated Vibroacoustic Spectroscopy	localized dynamic radiation force of the ultrasound field	acoustic response	Fatemi, Alizad, & Greenleaf, 2005; Fatemi & Greenleaf, 1998
Passive Acoustic Monitoring	internal force	acoustic response	Dutton et al., 2002; Dutton et al., 2005

Appendix L: Normal Brain Acoutic Monitor (BAM) Measures

Study	Populations Used to Determine Criteria	Data Output	Amplitude Positive Deflection	Positive-to-Negative Deflection Ratio	Other
Dutton et al., 2002	20 severe TBI patients 20 non–brain-injured controls	Time domain	≥0.3 V	2.5:1	A return to baseline following head-down tilt (in healthy volunteers) or suctioning of an intubated patient
Dutton et al., 2005	380 severe TBI patients 50 non–brain-injured controls	Time domain and frequency domain	≥0.8 V	2.5:1	Normal frequency domain signal (the fundamental must be ≥−40 dB, and the difference between the fundamental and the 8th harmonic had to be a minimum of 20 dB)

Appendix M: Types of Near-Infrared Spectroscopy (NIRS) Methods

Continuous wave	Constant illumination of the head, with measurement of the attenuated light
Frequency domain	Head is illuminated with intensity-modulated light; both attenuation and phase shift of the emerging light is measured
Time domain	Based on short pulses of light and the time-resolved detection of the shape of the pulse after propagation through the head

Appendix N: Near-Infrared Spectroscopy (NIRS) Device Comparison

	NIRO 300	INVOS 5100
Light Emitter	Laser diodes: narrow emission bandwidth corresponding with Hb and HbO_2 absorption spectra	Light diodes: broader emission bandwidth (30–40 nm)
Oxygen Index Calculation Algorithms	Modified Beer-Lambert Law and a more rigorous application of spatially resolved spectroscopy Three emitting and detecting diodes separated by different distances; Hb and HbO_2 calculated from the regression line between the values from the three detectors	Modified Beer-Lambert Law, with compensation (subtraction) for extracranial blood Two different emitter–detector separations: 3-cm separation assumed to be mainly extracerebral and 4-cm separation assumed to be cortical and intracerebral
Value Output	TOI THI	rSO2
System Set-up	Optode initialization required; place in rubber holder and attach to the head with a band Light shielding had to be optimized Comparatively slow	No optode initialization; attach adhesive optode patch to head Additional light shielding not needed Comparatively fast but optode failure 2/10 times