UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

JUN 20 2012

The Honorable Daniel K. Inouye
Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The enclosed report responds to language in House Report 111-491, page 314, which accompanied H.R. 5136, the National Defense Authorization Act for Fiscal Year 2011, which requests a report evaluating the comparative effectiveness of neuroimaging modalities as imaging biomarkers for the detection of mild, moderate, and severe traumatic brain injury (TBI). This issue falls under my purview as the Acting Under Secretary of Defense for Personnel and Readiness, and I have been asked to respond. A similar letter is being sent to the Chairmen of the congressional defense committees.

This report concludes that there is no single imaging modality in clinical use that can be universally applied to all patients who experience a TBI. As captured in this report, there is a need for more validation or exploration of nearly every technique in the clinical and research disciplines, as well as consideration of the fact that each modality assesses different aspects of anatomy and/or physiology. Future research efforts must concentrate on addressing these limitations to improve care for individuals with TBI. This report will inform the Department's research plans in TBI with regard to forthcoming funding opportunities.

Thank you for your interest in the health and well-being of our Service members, veterans, and their families.

Sincerely,

Jo Ann Rooney
Acting

Enclosure:
As stated

cc:
The Honorable Thad Cochran
Vice Chairman

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

The Honorable Carl Levin
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

20 2012

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cc:
The Honorable John McCain
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

20 2012

The Honorable Howard P. "Buck" McKeon
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

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As stated

cc:
The Honorable Adam Smith
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

20 2012

The Honorable Harold Rogers
Chairman
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

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Sincerely,

Jo Ann Rooney
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Enclosure:
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cc:
The Honorable Norman D. Dicks
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

20 2012

The Honorable Jim Webb
Chairman
Subcommittee on Personnel
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

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Jo Ann Rooney
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cc:
The Honorable Lindsey Graham
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

20 2012

The Honorable Joe Wilson
Chairman
Subcommittee on Military Personnel
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

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Jo Ann Rooney
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As stated

cc:
The Honorable Susan A. Davis
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

20 2012

The Honorable C.W. Bill Young
Chairman
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

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The Honorable Norman D. Dicks
Ranking Member

Report to Congress in Response to House Report 111-491, page 314, which accompanied H.R. 5136, the National Defense Authorization Act for Fiscal Year 2011

Comparative Effectiveness of Neuroimaging Modalities on the Detection of Traumatic Brain Injury

Preparation of this report/study cost the Department of Defense a total of approximately $150,000 for the 2011 Fiscal Year.

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Comparative Effectiveness of Neuroimaging Modalities on the Detection of Traumatic Brain Injury
Report to Congress

TABLE OF CONTENTS

PURPOSE OF REPORT

House Report 111-491, page 314, which accompanied H.R. 5136, the National Defense Authorization Act for Fiscal Year 2011, requested the Secretary of Defense to prepare a report that evaluates the comparative effectiveness of neuroimaging modalities as imaging biomarkers for the detection of mild, moderate, and severe traumatic brain injuries. The neuroimaging modalities to be evaluated should include, but not be limited to, the following:

(1) Transcranial Doppler Ultrasound
(2) Computed Tomography (CT)
(3) Magnetic Resonance Imaging (MRI)
(4) Single Proton Emission Computed Tomography (SPECT)
(5) Positron Emission Tomography (PET)

The committee requested the Secretary of Defense submit the report to the congressional defense committees by March 31, 2012.

OVERVIEW

In order to evaluate the comparative effectiveness of neuroimaging modalities as imaging biomarkers for the detection of mild, moderate, and severe traumatic brain injuries, governmental subject matter experts were identified for each modality. The most current body of scientific literature on these modalities, consisting of research abstracts and review criteria, were provided to the subject matter expert modality teams for their subsequent review and evaluation and provided the basis of this report. The following sections describe the review methods and findings for each modality. Table 1 (page 16) provides the findings for each modality in terms of its usefulness in the clinic and research settings. The U.S. Army Medical Research and Materiel Command and the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) collaboratively led the technical and scientific activities associated with this evaluation and report.

METHODOLOGY

Design:

Relevant teams of subject matter experts (SMEs) were identified. A total of 491 abstracts (excluding review articles) were identified as relevant to this report. Some overlap among modalities was noted in these papers. In these cases, abstracts were sent to all relevant reviewers. Full articles were furnished as requested by the review teams.

Due to the quantity of articles identified during the data pull, review criteria were devised to facilitate a rapid yet careful review of the literature. The criteria were:

- Relevance of the data to the aforementioned congressional language
- Quality of the data (e.g., statistically significant datasets, good quality imaging data, journal impact factor)

Abstracts were numerically scored (1–5 scale, 5 being best). Scores were justified by each reviewer via comments for each scored abstract. All reviewers could request additional literature or full articles as needed to comprehensively scan the available literature for each modality included in this report. Team sizes varied, but were based on the number of abstracts for each modality. Due to the retrospective nature of this evaluation, estimates of comparative effectiveness are qualitative. The estimates are broken down into clinical relevance and research utility in Table 1 on page 16.

Included Literature:

The data were composed of primary reports that included:

- Meta-analyses and reviews
- Clinical Trials and State-of-the-Art Healthcare Practice

Data acquired for this report include clinical TBI datasets from, but not limited to:

- Occupational Injury
- Motor Vehicle Crashes
- Sports Injury
- Acts of Violence
- Military Combat

The following are examples of TBI studies that were NOT included:

- Malignancy
- Stroke
- Infection
- Ischemia
- Intoxication
- Children
- Penetrating Injuries–because imaging would be of limited value for these types of injuries
- Other diseases or disorders of the brain

These criteria are adapted from "Gulf War and Health," Volume 7[1] and were chosen because they have demonstrated an ability to provide a robust focus on military TBI while excluding related but distinct disease processes, such as pediatric TBI or stroke. The data were limited to publications written in English and published in the past 10 years.

DATA ASSESSMENT

Data quality was assessed using the following qualitative criteria:

- High quality – Further research is very unlikely to change our confidence in the estimate of effect
- Moderate quality – Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
- Low quality – Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
- Very low quality – Any estimate of effect is very uncertain

These qualitative scores were based on the:

- Quality of the data
- Assessment of balance between desired and undesired patient outcomes
- Level of uncertainty in statistical data and other quantitative values
- Assessment of whether the intervention represents a wise use of resources

[1] IOM (Institute of Medicine). 2009. *Gulf War and Health, Volume 7. Long-term Consequences of Traumatic Brain Injury.* Washington, DC: The National Academies Press.

REVIEW OF NEUROIMAGING MODALITIES

COMPUTED TOMOGRAPHY

Introduction

Computed Tomography (CT) scanning is used to detect skull fractures, bleeding, and other anatomical features associated with traumatic brain injury (TBI). Since its introduction in the 1970s, it has revolutionized the management of TBI, and has undoubtedly saved many lives. Although a mature technology, recent advances such as multi-detector CT have allowed the use of CT technology for rapid, non-invasive imaging of brain structure. The following assessment is based on a review of 324 primary abstracts as described in the methods section.

Mild TBI

Approximately 20 percent of patients who sustain mild TBI without significant abnormalities identified by CT have significant problems returning to work. This is likely due to the inadequate sensitivity of CT for microscopic white matter (composed of myelin coated nerve cell fibers) damage, termed diffuse axonal injury (DAI).

One of the most important challenges for physicians in the Emergency Department (ED) is deciding whether subsequent neuroimaging is needed in patients presenting with mild TBI. A CT scan without the use of an intravenous contrast agent is usually the test of choice. This test identifies abnormal features in roughly 10 percent of patients identified with mild TBI. Most of these abnormalities are of little neurosurgical consequence, but the CT scan can be lifesaving for those few diagnosed with potentially dangerous intracranial bleeding for which neurosurgical intervention is necessary. CT scanning is not without drawbacks, which include cost, potential risks of transporting patients outside the ED, and exposure to ionizing radiation. The goal is to perform the minimum number of head CTs while ensuring that patients with potentially dangerous intracranial bleeding are identified.

Numerous studies have addressed clinical criteria that physicians can use to determine whether a patient with mild TBI should undergo head CT. The two most commonly used clinical criteria are the New Orleans Criteria and the Canadian CT Head Rule. Follow-up studies have evaluated the effectiveness of these and other criteria in terms of sensitivity and specificity for identifying clinically significant brain injury in adults. Based on the data available from these studies, the American College of Emergency Physicians (ACEP) and the Centers for Disease Control (CDC) issued a clinical policy statement in 2008 regarding indications for obtaining head CT scans in adults with TBI. These criteria generally take into account mental status or obvious signs of skull fracture, and are very sensitive for identifying the small subset of patients with mild TBI who require neurosurgical interventions.

A normal head CT does not mean that patients will not develop functionally limiting post-concussive symptoms. All patients with mild TBI, including those with normal CT scans, should be counseled about risk of these symptoms.

Moderate and Severe TBI

In moderate and severe TBI, CT is useful in identifying anatomical features that may affect clinical diagnosis and treatment, but it is not useful for predicting long-term outcome. The primary role of CT scanning has been for the acute identification of focal injuries, (e.g., intracranial bleeding) which may require neurosurgical interventions, or for the identification of conditions that may require intensive care monitoring. CT is most beneficial in patients with severe TBI as it can readily identify those patients who require life-saving intervention. The "Guidelines for the Management of Acute Traumatic Brain Injury," 2006, evidence-based guidelines formulated by the Brain Trauma Foundation and widely adopted throughout the world, largely base recommendations for surgical interventions based on CT findings. Approximately 20 percent of patients with severe TBI require surgery based on the findings from the initial CT scan. Patients in whom the initial CT scan demonstrates significant bleeding in or around the brain but do not require immediate surgery are admitted to the hospital and re-scanned within 24 hours, as clinically significant expansion of bleeding is common.

Despite its utility for identifying patients requiring surgery, CT is not useful for predicting outcome after severe TBI. Up to 20 percent of patients with severe TBI have a normal or near-normal CT scan on the day of admission, a reflection of the fact that CT is not a sensitive technique for the detection of DAI. Many patients with medium or even large-size evidence of intracranial bleeding on their initial CT scan make excellent functional recovery with adequate neurosurgical and neurological care.

Conclusion

The quality of evidence is moderate in the use of CT scanning in the evaluation of patients presenting to the ED with mild TBI. Due to variable approaches in clinical practice, CT is likely overused in the evaluation of mild TBI, and further research is needed to more precisely identify which patients with mild TBI are likely to benefit from a CT scan.

The quality of evidence is high in the use of CT scanning in the evaluation of patients presenting to the ED with moderate and severe TBI. In these patients, CT is highly sensitive for identifying intracranial bleeding which requires neurosurgical interventions, which can often be lifesaving. The quality of evidence also is high that CT scanning is not useful for the prediction of functional recovery, even in moderate and severe TBI.

MAGNETIC RESONANCE IMAGING

Introduction

Magnetic resonance imaging (MRI) can create two-dimensional (2D) or three-dimensional (3D) models of the brain. MRI scanners produce a homogeneous magnetic field that causes the nuclei of hydrogen atoms (single protons) to line up like a compass needle. Bursts of radio waves are applied and cause the protons to flip back and forth. When returning to their original orientation, the protons emit a radio wave of their own, which can be used to produce "maps" or images of the human anatomy. The technique is successful since the body is mostly water, which contains

hydrogen atoms. Researchers have used these resonances in a variety of different strategies to determine elements of the anatomy, blood flow and the chemistry of the brain. The following assessment is based on a review of 391 primary abstracts as described in the methods section. The following is a brief list of common techniques used in MRI neuroimaging research:

- Perfusion Weighted Imaging (PWI): Measures blood flow through the brain
- Functional MRI (fMRI): Used for monitoring small changes in the brain's blood oxygenation level that occur when performing a task
- MR Spectroscopy (MRS): Produces maps of the chemical composition of the brain
- Diffusion Tensor Imaging (DTI): Shows the integrity and continuity of the white matter tracts of the brain
- Susceptibility Weighted Imaging (SWI): Used for identifying blood vessels, small bleeds, brain iron, and calcification

Mild TBI

MRI is capable of identifying regions of interest indicative of potential injury in mild TBI patients who have already had a normal CT scan. Some of these markers of potential injuries are apparently reversible, and they may resolve over time. However, there is a subset of lesions noted on MRI that represent real pathology that is below the threshold for detection by CT. Correlation between these markers and pathological assessments has not been validated in the literature, although it may exist.

Investigators have used several MRI techniques to continue investigating the link between these MRI-identified injuries and pathological findings. These techniques include, but are not limited to, PWI, DTI and MRS. PWI may demonstrate brain blood flow changes and may show very small (< 1/8th inch) blood clots. DTI appears to show actual areas of broken nerve cells (axons) in the brain white matter. The chemical composition, as measured by MRS, will change.

Overall, MRI is useful in continued investigations of mild TBI. However, the exact nature of these lesions (CT normal and MRI abnormal), their significance to the individual patient, their ability to predict symptoms, signs, and future disability are still under investigation by researchers.

Moderate and Severe TBI

Patients with moderate and severe TBI usually have an abnormal CT scan. However, the added sensitivity of MRI may show more lesions and in more detail; and, this may allow better definition and distinction between different types of abnormalities. MRI offers a "new camera" to photograph brain damage – including changes in blood flow (PWI) and brain chemistry (MRS) that are invisible to CT. In theory, disability should be proportional to damage visible by these novel MRI techniques. MRI techniques that show the brain "wiring" (DTI) have shown mixed results in many TBI patients. Some patients have functional and clinical recovery – while the brain remains abnormal on the MRI.

Conclusion

MRI, in particular SWI, fMRI, and DTI, may provide improved diagnosis and treatment monitoring in a wide spectrum of patients with TBI. However, the appropriate role of MRI in common practice has yet to be determined and additional studies are needed, especially longitudinal monitoring over months and years after TBI. The quality of evidence for the efficacy of MRI across the spectrum of TBI is moderate; more research is needed in order to fully estimate clinical value.

TRANSCRANIAL DOPPLER ULTRASOUND

Introduction

Transcranial Doppler Ultrasonography (TCD) uses the reflection of sound wave energy to detect the velocity of blood flow within the major arteries and veins of the brain. Elevated blood flow velocities typically indicate narrowing of vessels. However, the blood flow velocity also can be elevated in hyperdynamic states, such as anemia or fever. TCD is capable of monitoring several parameters relevant to blood flow in patients with TBI. The following assessment is based on a review of 49 primary abstracts as described in the methods section.

Mild TBI

Disruption of autoregulation of the blood vessels (vasoreactivity, or abnormal blood pressure) is emerging as a fundamental feature following TBI. In mild TBI, evidence is emerging that autoregulation may be compromised for extended periods. This disturbance is thought to represent a vulnerable state of the brain. In addition, similar to its role in moderate to severe TBI, evidence is emerging that vasoreactivity is altered and linked to persistent deficits following mild TBI.

Moderate and Severe TBI

TCD in moderate and severe TBI has two clinical applications. The first, although only in the experimental stage, is as an alternative, non-invasive method to determine elevated intracranial pressure (ICP). The second is a more well-established method not of detecting TBI itself, but one of the possible sequelae, vasospasm. Vasospasm refers to blood vessel spasms, which can lead to brain damage or death.

Elevated pulsatility indices (EPI), which are calculated from TCD measurements, can be used to identify ICP. Care must be taken with EPI measurements for ICP diagnoses since these values are also sensitive to a variety of other conditions. Currently, algorithmic analyses of systemic blood pressures and TCD blood flow velocities are under investigation to increase the sensitivity and specificity in non-invasive ICP assessment. The advantage of TCD for detecting or diagnosing increased ICP is that it is non-invasive and can be readily used in remote environments unlike CT or MRI. Both CT and MRI would require transfer to higher echelons of care; or in the case of intracranial monitors, a catheter is required. As a disadvantage, TCD data is non-continuous, unlike intracranial monitors. In moderate to severe TBI, continuous

monitoring in an intensive care unit setting is required to detect and intervene prior to neurological deterioration.

Delayed vasospasm can develop and is a common cause of neurological deterioration following TBI. TCD detection of vasospasm is routine because it is non-invasive, and although it is usually performed only daily, it provides data trends that might help predict the onset of vasospasm should it occur. TCD is an emerging technology and, as such, is often used in conjunction with other techniques to validate whether aggressive treatment is needed.

Extracranial vessel dissection (or tears within extracranial blood vessels) in the setting of TBI can result in dangerous, decreased blood flow and oxygen to the brain. Large vessel tears can also result in embolic phenomenon (obstruction in a blood vessel due to a blood clot or other foreign matter that gets stuck while traveling through the bloodstream) which can cause strokes. Screening with TCD in the setting of unexplained deterioration and/or evidence of strokes following TBI can rapidly and noninvasively identify the source of the tear. Additionally, TCD can screen for and identify emboli reaching the brain that would prompt the need for more invasive intervention.

Conclusion

The quality of data is moderate regarding the utilization of TCD as a biomarker of vasoreactivity (abnormal blood pressure in the brain) in mild TBI. More studies are needed as this could provide a tool for diagnosing such conditions in patients whom sustain mild injuries. The quality of the evidence is stronger for the use of TCD to assess changes in vasoreactivity for moderate and severe TBI.

The quality of the data is moderate regarding utilization of TCD parameters in the multimodal assessment of ICP in severe TBI. Further studies are warranted to explore the usefulness of parameters such as pulsatility indices in TCD for more accurate diagnoses of ICP.

Quality of evidence is high regarding the usefulness of monitoring the development of vasospasm in patients with severe TBI. TCD offers the benefit of guiding the timing of interventional studies, and can monitor effectiveness of treatment in response to vasospasm.

Evidence is moderate regarding use of TCD to identify cerebral emboli (blockages in blood flow) and evidence of post-injury sequential neurological events in patients with TBI. Further studies would be needed to determine prevalence of embolic phenomenon following mild to severe TBI.

Quality of data is moderate regarding the assessment of large vessels for tears following TBI. Further studies are needed to determine the optimal use of multiple potential modalities (e.g., TCD, CT angiogram, MR angiogram and conventional angiogram) in this patient setting.

POSITRON EMISSION TOMOGRAPHY

Introduction

Positron emission tomography (PET) is a nuclear medicine imaging technique that provides physiological and biochemical information about tissues in the body. PET images show the distribution in the body of radiopharmaceuticals or "tracers" that are labeled with radioactive, positron-emitting atoms. A wide variety of PET radiopharmaceuticals can be administered to patients for brain studies, to obtain images of brain blood flow; glucose and oxygen metabolism; brain inflammation; and communication between nerve cells. PET research studies are typically combined with anatomic imaging methods, CT and/or MRI. The following assessment is based on a review of 79 primary abstracts as described in the methods section.

Mild TBI

Guidelines issued by the American College of Radiology (ACR) in 1996 (revised 2008) indicate that this technique is of limited use in the clinic for the assessment of mild TBI. The ACR report also notes that the radiation level relative to other comparable techniques (e.g., CT or MRI) is high. Studies using fluorodeoxyglucose (FDG; an analog of glucose for metabolic studies of the brain) in the chronic phase of mTBI have shown decreased metabolism in brain areas involved in decision making and memory function. Correlations have been observed between decreased metabolism in certain brain regions and the degree of cognitive and behavioral abnormalities.

Moderate and Severe TBI

Studies using FDG for acute, severe TBI have reported decreased glucose metabolism in and around contusions (bruises), as well as in distant brain regions. Within a contusion, glucose metabolism is greatly decreased, and there is usually decreased glucose use near the contusion. There also is widespread decreased glucose metabolism in gray matter (composed of nerve cells and blood vessels) involving distant brain areas that appear normal on CT or MRI. This global disruption in metabolism seen in the grey matter may indicate a more generalized alteration in brain function from the injury. During the months after brain injury, glucose use increases throughout the brain, although not necessarily to normal levels.

Other methods that use radioisotopes of oxygen can provide assessments of brain blood flow and oxygen use. These are useful in research for acute, severe TBI as they can be used to estimate whether or not oxygen is accessible to all regions of the brain. Similar to the results with FDG, decreased blood flow is seen in and around injured regions in patients with acute, severe TBI. Ischemia (blood flow insufficient to meet the tissue's need for oxygen) is not a prominent finding in acute TBI and, when present, involves a relatively small volume of brain.

PET scans of blood flow obtained while subjects are performing psychological tasks can used to map what parts of the brain are involved in these tasks, because changes in local blood flow parallel the activity of nerve cells. A few studies have been reported in chronic TBI, mainly while patients perform memory tasks. In general, the pattern of activation was similar to that of subjects without TBI, but the degree of activation was abnormal. Brain mapping with PET has

been supplanted by blood-oxygen level dependence (BOLD) fMRI. BOLD fMRI is the MRI contrast of blood deoxyhemoglobin. BOLD fMRI has greater resolution and is of value in Service members with retained shrapnel who cannot undergo MRI.

Conclusion

PET has been used for three decades to study brain abnormalities in neuropsychiatric diseases and although PET is widely used in the care of patients with cancer, there are few uses for clinical studies of the brain. PET studies of chronic TBI often are compared to the neuropsychological evaluation of patients. However, the clinical utility of PET to diagnose or manage individual TBI patients has not yet been demonstrated. The tool has the potential to investigate processes not easily examined via other modalities (e.g., neuro-inflammation). Overall, the level of evidence in the majority of PET research studies in TBI is moderate.

SINGLE PHOTON EMISSION COMPUTER TOMOGRAPHY

Introduction

Single photon emission computed tomography (SPECT) is a clinical modality for imaging numerous neurological disease processes, including TBI. In most brain SPECT applications, a radioactive material is injected intravenously, and localizes to the brain. The SPECT detector captures light emitted as part of the natural radioactive decay process. This signal can be used to construct images of where the radioactive material accumulates within the brain. The following assessment is based on a review of 34 primary abstracts as described in the methods section. Many of these studies compared SPECT to MRI or CT.

SPECT is an imaging modality that may be used with a variety of radionuclides or radiopharmaceuticals; however, when one discusses SPECT imaging for TBI, it usually refers to the two most common and U.S. Food and Drug Administration-approved cerebral perfusion/blood flow imaging radiopharmaceuticals: Tc99-HMPAO and Tc99-ECD. Several additional research SPECT radiopharmaceuticals, which evaluate central nervous system receptors, include I-123 IMZ and I-123 CIT, which image the benzodiazepine and striato-nigral receptors, respectively. Researchers postulate that as a result of TBI, decreased binding occurs at these receptors.

Mild, Moderate, and Severe TBI

Clinically, SPECT can be used to assess for perfusion deficits when no lesion can be identified using other imaging techniques. Research has shown that SPECT can be used to assess sub-acute and chronic injuries. The technique often is used in concert with other modalities, such as MRI or CT. This is especially true for cases in which the anatomically identified lesion (via CT, as an example) does not explain clinical deficits. One of the greatest benefits to SPECT is its high negative predictive value (NPV): a negative examination usually portents a good prognosis for a TBI patient (e.g., recovery from post-concussive symptoms).

Conclusion

The overall quality of the SPECT published research is moderate. More research is needed to accurately estimate the ability of SPECT to detect mild, moderate and severe TBI when subjects present a neurological deficit. Of particular utility is SPECT perfusion in the evaluation of TBI in the sub-acute and chronic setting. It can reveal abnormalities that may be not be identified by other imaging methods.

CLINICAL ELECTROPHYSIOLOGY

Introduction

Clinical electrophysiology refers to a group of technologies that assess the electrical and magnetic activity of the brain. Electrical activity is measured by placing recording electrodes on the scalp. The most commonly used electrophysiological assessments are conventional electroencephalography (EEG) and evoked and event-related potentials (EPs and ERPs, respectively). Digitally recorded signals can be quantitatively analyzed using advanced software packages; this approach is referred to as quantitative EEG (qEEG). The electrical activity of the brain also generates magnetic fields, which can be recorded by placing around the head a device containing specially designed metal coils cooled to superconducting temperatures. This technology, magnetoencephalography (MEG), produces data about brain activity that are complementary to EEG, qEEG, EPs, and ERPs.

All of these clinical electrophysiologic recording techniques are of particular interest to the study and clinical assessment of persons with TBI because they measure brain activity at the millisecond level – a time resolution far superior to that of fMRI, PET, and SPECT. Recordings made with high-density electrode and/or magnetic sensory arrays also provide information about brain activity with a spatial resolution that is similar to fMRI, PET, and SPECT. The following assessment is based on a review of 17 primary abstracts as described in the methods section.

Mild, Moderate, and Severe TBI

The abnormalities detected by EEG, qEEG, EPs, ERPs, and MEG include local and/or global reductions of brain activity, local and/or global slowing of brain activity, abnormalities of the types and speed of information transfer between brain areas, and abnormal electrical activity (e.g., seizures or seizure-like brain rhythms). When such abnormalities are identified, they serve very effectively as biomarkers of brain dysfunction. However, the types of abnormalities to which clinical electrophysiology is sensitive are not specific to any single brain disorder, including TBI. The EEG, qEEG, EP, ERP, and MEG abnormalities observed among persons with TBI are similar, and in some instances identical, to those observed among persons with post-traumatic stress disorder (PTSD), depression, anxiety disorders, substance use disorders (SUD), and sleep deprivation or sleep disorders. Some of the "abnormal" rhythms observed in these disorders also are observed among healthy individuals.

Conclusion

The quality of the evidence pertaining to clinical electrophysiologic biomarkers of mild, moderate, and/or severe TBI is low. Further research is very likely to have an important impact on our confidence in the estimate of the usefulness of one or more clinical electrophysiologic methods to yield valid, reliable, sensitive, and specific biomarkers of TBI.

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY

Introduction

Functional near-infrared spectroscopy (fNIRs) is an emerging neuroimaging technology to monitor local hemodynamic response of the brain during activation of brain regions in response to stimuli, or in response to an abnormal medical condition (such as TBI). This method uses a series of near infrared (NIR) light sources and detector elements that are in contact with the tissue. NIR light can penetrate deep into the skull to permit noninvasive studies of blood within the human brain. fNIRS can be used to assess blood volume within a specific region of the brain, blood flow, and rate of oxygen consumption. The following assessment is based on a review of six primary abstracts as described in the methods section.

Mild, Moderate, and Severe TBI

While this technique is well established for assessments of brain tissue oxygenation, more data are needed regarding the use of this technique in TBI. Although the pathophysiology of TBI is still not well understood, it is postulated that understanding tissue oxygenation as opposed to tissue deoxygenation may be key in understanding TBI. There are several manufacturers developing devices for these purposes. Assessments can be done within several minutes, and can be used to reveal hematomas (a localized collection of blood outside the blood vessels) associated with changes in oxygen content within specifically studied regions of the brain. One study included 35 TBI patients aged 17–76 admitted to the neurosurgical intensive care unit in a Level I trauma center. The results suggested that the commercial device was reasonably sensitive and specific for detecting abnormalities such as hematomas in this patient cohort. These results could be used as part of the clinical decision making process (e.g., additional imaging, other tests, or surgical intervention). Larger studies are needed in order to validate commercial devices such as the device on which these results were gathered. fNIRs for the assessment of TBI most importantly demonstrates a strong potential to enhance early clinical assessment in the field as it is extremely portable as compared to other modalities, such as CT or MRI.

Conclusion

fNIRs can provide information regarding oxygenation of brain tissue. However, in patients with TBI, it is not clear what is the diagnostic potential and clinical usefulness of measuring the oxygenation. Many groups are currently exploring non-invasive optical brain imaging using fNIRs. Such measurements are typically performed using prototype devices that are interfaced with a personal computer while the time for data analysis is typically on the order of several to

tens of minutes. Other advantages could include cost and portability. Overall, the quality of the data is low. Further research is very likely to have an important impact on determining the potential use of this technique for TBI.

CONCLUSION

A total of 491 articles (excluding review articles) were identified as relevant to this evaluation and report. Data quality (e.g., statistical significance of the studies, quality of the research methods) was assessed for each article to estimate the completeness of our knowledge for each technique with respect to mild, moderate or severe TBI. Data of "high quality" would not necessarily indicate that the technique was applicable to TBI; instead it would indicate that more data were not needed to assess its value in detecting/diagnosing TBI. For the vast majority of the techniques studied in this report, data quality was moderate, indicating data quality was good enough to make an assessment of clinical applicability for TBI, but further research was still needed. For example, CT and PET both had high quality data available, but only CT had high clinical applicability for moderate and severe TBI.

Once data quality was estimated, authors assessed clinical applicability/use and research utility for each imaging modality (page 16, Table 1). An important distinction was made between clinical use and research utility. An indication of "high clinical use" indicates that the technique has high clinical applicability for a given severity of TBI. At this time, only CT and TCD have high clinical applicability for moderate and severe TBI. Research utility also was assessed for each imaging modality. An indication of "high research utility" indicates that the technique could emerge as part of clinic care in the future, and is a target of continued investigation with respect to TBI. All techniques have research utility based on the data in this report.

A "gold-standard test" with which to compare imaging modalities does not exist, and no definitive biomarker has been identified. The limits of this evaluation and report include (but are not limited to) multiple definitions of TBI used in the literature, clinical research protocols that varied from institution to institution, and methods that are, or were, previously non-standardized. In order to perform a truly quantitative analysis, these limitations would need to be addressed. Efforts to mitigate these concerns are underway in the research and clinical communities.

This report concludes that there is no single imaging modality in clinical use that can be universally applied to all patients sustaining a traumatic brain injury. This is a function of the limits described above, the need for more validation or exploration of nearly every technique in the clinical and research disciplines, and the fact that each modality assesses different aspects of anatomy and/or physiology as captured in this report. Future research efforts must concentrate on addressing these limitations to improve care for individuals who sustain TBI. This report will inform the Department's research plans in TBI with regard to forthcoming funding opportunities.

Table 1: Overview of Imaging Modalities with Respect to TBI use in Research and the Clinical Settings

	CT*	MRI	TCD	PET	SPECT	Clinical Electro-physiology (MEG/EEG)	fNIRS
Mild TBI	Moderate Clinical Use Moderate Research Utility	Moderate Clinical Use High Research Utility	Moderate Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility
Moderate TBI	High Clinical Use Moderate Research Utility	Moderate Clinical Use High Research Utility	High Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility
Severe TBI	High Clinical Use Moderate Research Utility	Moderate Clinical Use High Research Utility	High Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility	Limited Clinical Use High Research Utility

*CT - computed tomography; MRI – magnetic resonance imaging; TCD – transcranial doppler, PET - positron emission tomography; SPECT - single photon emission computer tomography; MEG/EEG - magnetoencephalography/electroencephalography; fNIRS - functional near-infrared spectroscopy; TBI – traumatic brain injury