



**Department of
Veterans Affairs**
VHA Office of Patient Care Services
Technology Assessment Program

**VISUAL PROBLEMS IN TRAUMATIC BRAIN INJURY:
A SYSTEMATIC REVIEW OF SEQUELAE AND INTERVENTIONS
FOR THE VETERAN POPULATION**

Briefing to the Consensus Validation Panel

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A SUMMARY FOR HTA REPORTS
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Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?	√		
4. Statement on whether report externally reviewed?	√		
5. Short summary in non-technical language?	√		
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of the assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?		√	
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

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ACRONYMS USED IN THE REPORT

AAN, American Academy of Neurology	OT-APST, Occupational Therapy Adult Perceptual Screening Test
AC, altered consciousness	PCM, post concussive migraine
ACRM, American Congress of Rehabilitation Medicine	PCS, post concussion syndrome
AIS, Abbreviated Injury Scale	PCSC, Post Concussion Syndrome Checklist
AMS, altered mental state	PPVT-III, Peabody Picture Vocabulary Test-III
AS, antisaccade task	PSAT, Paced Serial Addition Test
AUDIT, Alcohol Use Disorders Identification Test	PTA, post-traumatic amnesia
BRISC, Barry Rehabilitation Inpatient Screening of Cognition	PTSD, post traumatic stress disorder
CM, consistent mapping	RAVLT, Rey Auditory Verbal Learning Test
COWA, Controlled Oral Word Association test	RBMT, Rivermead Behavioural Memory Test
CT, computerized tomography	RFFT, Ruff Figural Fluency Test
DAI, diffuse axonal imaging	RLA, Ranchos Los Amigos
EMT, electronic maze test	ROC, receiver operating characteristic
EMV, eyes, motor and verbal	RT, reaction time
ERP, event-related potentials	SAT, speed-accuracy trade off method
ETOH, ethyl alcohol	SD, standard deviation
FAM, Functional Assessment Measure	SEM, standard error of the mean
FIM, Functional Independence Measure	SMAST, Short Michigan Alcoholism Screening Test
GCS, Glasgow Coma Scale	SNST, Stroop Neuropsychological Screening Test
GOAT, Galveston Orientation and Amnesia Test	SR, systematic review
HTA, health technology assessment	STM, short term memory
ISS, Injury Severity Score	SVLT, Shum Visual Learning Test
LOC, loss of consciousness	SX, symptoms
LOS, length of stay	TBI, traumatic brain injury
MA, meta-analysis	TEA, Test of Everyday Attention
MCA, motor cycle accident	TMT, Trail Making Test
MHI, mild head injury	USPSTF, US Preventive Services Task Force
MMSE, Mini-Mental State Examination	VEP, visual evoked potential
MRI, magnetic resonance imaging	VGS, visually guided saccade task
MSe, mean squared error	VM, varied mapping
MSIP, modified sickness impact profile	VOSP, Visual Object and Space Perception Battery
MVA, motor vehicle accident	WAIS-III, Matrix Reasoning subtest from the Wechsler Adult Intelligence Scale-3 rd ed
MWM, Morris water maze	WCST, Wisconsin Card Sorting Test
NART, National Adult Reading Test	WRAT-R, Wide Range Achievement Test-Reading subtest
NCT, Number Comparison Test	WTAR, Wechsler Test of Adult Reading
NR, not reported	
OEF/OIF, Operation Enduring Freedom/Operation Iraqi Freedom	

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VISION PROBLEMS ASSOCIATED WITH TRAUMATIC BRAIN INJURY:

A SYSTEMATIC REVIEW OF SEQUELAE AND INTERVENTIONS FOR THE VETERAN POPULATION

“...we take it for granted that we know what we are looking at, that we can find our way around and that our internal percept of the visual world around us provides an accurate three-dimensional map to visually guide all our movements, but when these systems become dysfunctional, profound problems arise...”¹

PURPOSE

A Consensus Validation Panel was assembled in November 2007 to bring together expertise in VA to address vision issues related to rehabilitation of traumatic brain injury (TBI) and polytrauma confronting Veterans of the Afghanistan (Operation Enduring Freedom (OEF)) and Iraq (Operation Iraqi Freedom (OIF)) wars. The consensus validation process is a multidisciplinary process that attempts to close the gap between research and practice by clarifying the state of the art/science and best practices in particular areas of rehabilitation. The consensus validation process consists of three phases:

Phase 1: develop key issue questions to consider that relate to vision problems resulting from TBI in the Veteran population.

Phase 2: assign questions to smaller teams of subject matter experts to summarize the available literature.

Phase 3: convene the final Consensus Validation Conference to evaluate and synthesize available scientific evidence into Consensus Statements and to optimize the dissemination of these findings. Each Consensus Statement is an independent report of that team; it does not represent official policy or practice unless officially accepted by an organization.

This report was produced as a supplement to the Consensus Validation Panel. It is a qualitative systematic review of the best available evidence from the peer reviewed literature addressing:

1. The frequency of visual problems associated with mechanisms of TBI that are most commonly found in the new OEF/OIF Veteran population, and;
2. The effectiveness of rehabilitation interventions for vision problems in patients with these mechanisms of TBI.

¹ Dutton GN. Cognitive vision, its disorders and differential diagnosis in adults and children: knowing where and what things are. *Eye*. 2003;17:289-304.

BACKGROUND

The Centers for Disease Control and Prevention define TBI *“as a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain”*.² TBI is a leading cause of death and life-long disability in the United States. Groups at high risk for TBI are younger (15-24 years) and older (age > 64 years) males. Leading causes of TBI among younger and older males are motor vehicle accidents and falls, respectively, and about half of TBI cases are alcohol-related. In civilian populations, an estimated 1.1% or 3.17 million people (95% CI: 3.02-3.32 million) were living with long-term disability from TBI at the beginning of 2005.³

When combat exposure is added to these demographic data, active duty personnel and Veterans represent groups at high risk for sustaining a TBI. During the Vietnam War, 12-14% of surviving soldiers treated in hospitals had TBI, compared to estimates of at least 22% of surviving OEF/OIF combatants today.⁴ Therefore, TBI appears to account for a larger proportion of morbidity among United States OEF/OIF armed forces than those in previous wars. Reasons for these trends include increased exposure to blast attacks and improvements in acute trauma medicine and in body armor, including helmets, which have reduced the frequency of penetrating injuries and improved overall survival rates. In short, more soldiers today are surviving wartime explosions but often with significant injuries and functional disabilities that require complex rehabilitative support.

Blast injuries from explosive munitions such as rocket-propelled grenades, improvised explosive devices, and land mines are the leading cause of casualties among OEF/OIF service men and women. Injuries from a blast may result from:⁵

- Pressurization waves caused by the rapid and extreme changes in atmospheric pressure (primary);
- Flying debris and collapse of structures onto an individual (secondary);
- The individual being physically thrown by the blast wind (tertiary);
- Burns and/or inhalation of gases and vapors (quaternary).

Classifying TBI

TBI may be classified along a continuum of severity, which is an important determinant of outcome. A TBI can result in short or long-term impairment with independent function. Several schemes exist to classify severity, but few have been compared and validated. In VA, severity is graded as mild, moderate and severe based on one of three indices (Table 1).⁶

² <http://www.cdc.gov/ncipc/tbi/TBI.htm>.

³ Zaloshnja, E. et al. Prevalence of Long-Term Disability From Traumatic Brain Injury in the Civilian Population of the United States, 2005. *J Head Trauma Rehabil* 2008;23(6): 394-400.

⁴ Okie, S. (2005). "Traumatic brain injury in the war zone." *New England journal of medicine* 352(20): 2043-7.

⁵ Scott, S. G., R. D. Vanderploeg, et al. (2005). "Blast injuries: evaluating and treating the postacute sequelae." *Federal practitioner* 22(1): 67-75.

⁶ Veterans Health Initiative: Traumatic Brain Injury. Independent Study Course Released: January 2004. Employee Education System. Department of Veterans Affairs.

Table 1. Severity Grades of TBI

Scale	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3&4)
LOC	Altered or < 30 min with normal CT &/or MRI	< 6 hours with abnormal CT &/or MRI	> 6 hours with abnormal CT &/or MRI
GCS	13-15	9-12	< 9
PTA	< 24 hours	< 7 days	> 7 days

See abbreviations list Page iv

Severity of TBI depends on many factors including the pre-injury condition of the brain, primary versus secondary pathophysiology of TBI, mechanisms of TBI and focal versus diffuse damage after TBI.⁷ Primary pathophysiology is induced by mechanical forces at the moment of injury, while secondary pathophysiology injury results from the cascade of cellular, neurochemical and metabolic processes set in motion following the initial injury.

Contact mechanisms of TBI result either from an object striking the head or from contact between brain and skull, while acceleration/deceleration mechanisms of TBI result from unrestricted head movement that leads to shear, tensile and compressive strains resulting in widespread damage to axons and blood vessels. Research is underway to study the biological effects of primary blast exposure on brain cells, one theory being that certain genes trigger a cascade of negative events when exposed to overpressure from a blast.⁸

Classification of damage after TBI can be described as focal, diffuse, or mixed. Primary focal injury is usually the result of direct impact of the brain against the cranium resulting in contusions on the surface of the brain and subdural hemorrhage. It may occur in any head trauma case but occurs primarily in moderate to severe TBI and can be observed on standard neuroimaging studies such as CT or MRI. Typical areas of focal injury are the frontal, orbital frontal, anterior temporal and lateral temporal areas.

Primary diffuse injury is an ongoing process consisting of hypoxic brain damage, brain swelling, vascular injury, and axonal injury.⁹ The most common form of primary diffuse injury, diffuse axonal injury (DAI), is defined as widespread disruption of neuronal circuitry resulting from rotational shearing and stretching from acceleration-deceleration forces that pull on axons and small vessels. Normal findings or presence of small white matter changes on standard neuroimaging in the presence of neurological symptoms may infer DAI. The most common locations for DAI are the corticomedullary (grey matter-white matter) junction (particularly in the frontal and temporal areas), internal capsule, deep gray matter, upper brainstem, and corpus callosum. MRI is reportedly more sensitive than CT in detecting DAI.

In the combat environment, the brain is vulnerable to both secondary and tertiary blast injury. A limited number of animal and human studies and increasing cumulative experience with OEF/OIF service personnel and Veterans suggest that the primary blast wave may also cause diffuse closed head injuries, particularly among those with repeat blast exposure.

Identifying TBI

While open head injuries are easier to detect, they are less common than closed head injuries. The Defense and Veterans Brain Injury Center (DVBIC) reports that more than 90% of combat-

⁷ Gennarelli TA and Graham DI. (2005). Neuropathology In JM Silver, TW McAllister, and SC Yudofsky Textbook of Traumatic Brain Injury (pp. 27-50) Washington DC: American Psychiatric Publishing, Inc.

⁸ http://www.research.va.gov/resources/pubs/docs/va_research_currents_apr-may_08.pdf accessed August 26, 2008.

⁹ Taber, K. H., D. L. Warden, et al. (2006). "Blast-related traumatic brain injury: what is known?" *The Journal of neuropsychiatry and clinical neurosciences* 18(2): 141-5.

related TBI are closed head injuries often with no external sign of injury.¹⁰ Despite no universally agreed-upon definition of mild TBI, the majority of all brain injuries are reportedly classified as mild; however, precise estimates are difficult to determine because mild TBI cases can be overlooked or misdiagnosed.

Most persons who suffer mild TBI experience few post-injury problems and recover completely within three to six months. A minority of mild TBI cases suffer from postconcussion syndrome, which is defined as persistent physical, emotional and cognitive symptoms lasting longer than three months; symptoms may include poor concentration, memory difficulty, intellectual impairment, irritability, fatigue, headache, depression, anxiety, dizziness, blurry or double vision, light sensitivity and sound sensitivity.

Military personnel with TBI may present with symptoms and findings that affect multiple areas of brain function resulting in impairments in cognitive, behavioral and sensory functions. Other bodily injuries and overlapping symptoms associated with post traumatic stress disorder (PTSD) and persistent post concussion symptoms may further complicate recovery.^{11,12}

“Although symptoms of PTSD and post concussion syndrome do overlap (eg, attentional problems, depression), some symptoms are characteristic only of PTSD (eg, flashbacks and other re-experiencing phenomena); other symptoms are characteristic of post concussion syndrome, but not PTSD (eg, headache, nausea/vomiting, dizziness). Clinicians will need to consider each diagnosis and the possible co-occurrence of the two diagnoses in war veterans presenting with co-occurring symptoms, for example, anxiety, depression, difficulty concentrating, or attentional problems.”¹³

Improving identification of primary blast-related brain injury has stimulated efforts in the military and in VA to increase awareness of TBI among active military personnel and Veterans, especially mild cases. VA created a task force comprising a range of clinical experts to develop a screening tool to assist in identifying OEF/OIF Veterans who may be suffering from TBI and to develop a protocol for further evaluation and treatment of those who test positive on screening. From these efforts, VA established a policy that *“all OEF and OIF veterans receiving medical care, within VA, must be screened for possible TBI; those who, on the basis of the screen, might have TBI must be offered further evaluation and treatment by clinicians with expertise in the area of TBI.”¹⁴*

Interest in finding the optimal screening tool prompted a request to the VATAP for a systematic review of functional neuroimaging for screening TBI.¹⁵ It found that the research evidence had focused largely on the use of CT, and research into the clinical utility of alternate functional imaging was preliminary or absent. Therefore there was insufficient information to guide the design of TBI screening programs using functional imaging in soldiers’ pre- and post-deployment. *“Precision of diagnosis and prediction in the majority of mildly injured patients*

¹⁰ www.dvbic.org, accessed January 31, 2009.

¹¹ Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *The New England journal of medicine* 2008;358(5):453-63.

¹² Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *American journal of epidemiology* 2008;167(12):1446-52.

¹³ Warden, D. (2006). "Military TBI during the Iraq and Afghanistan wars." *J Head Trauma Rehabil* 21(5): 398-402.

¹⁴ VHA Directive 2007-013. Screening and Evaluation of Possible Traumatic Brain Injury in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) Veterans. Veterans Health Administration. Department of Veterans Affairs. April 13, 2007.

¹⁵ Patrick K. Brief Services, Veterans Health Administration, September 2007. *injury*. VA Technology Assessment Program, Office of

clearly needs improvement and remains an area of active research... Clearly, this level of research is inadequate to the potential use in screening of expensive tests involving injected contrast agents and whose diagnostic performance and clinical impact remain undefined.”

Visual sequelae of brain injury¹⁶

“The extent and impact of a TBI on overall sensory function can be quite profound but due to the true nature and primary influence of visual processing, no interference can be as significant as that of the visual system following a TBI.”

The visual system plays a vital role in influencing overall sensory-motor function. The retina transmits information to visual and nonvisual centers in the brain and integrates information with other sensory systems. Seventy percent of all sensory processing in the entire body is directly affected by information captured through the retina, most of which is directed to the occipital cortex to receive and process visual detail. This enables the person to attend to a task or concentrate. The remaining is directed to the midbrain responsible for controlling eye movement and relaying signals for auditory and visual reflexes and is integrated with other sensory signals that coordinate balance, movement and orientation in space.

TBI can result in impairment at the unconscious, subconscious and conscious levels of visual processing with deficits ranging from mild to severe, depending on the location and severity of the injury. For example, damage to the occipital cortex can result in visual deficits ranging from visual field defects to the inability to recognize known objects to blindness. Injury to the right temporal lobe can result in difficulty storing new visual memories while preserving old visual memories. Damage to the right parietal lobe, which is associated with processing visual-spatial information, can result in disorientation in familiar and unfamiliar surroundings. Cranial nerves involved in vision are the Optic (II), Oculo-motor (III), Trochlear (IV), Abducens (VI) and Trigeminal (V) (for corneal sensation). The same mechanisms that cause cortical injury may also injure the cranial nerves resulting in impaired sensation (smell, sight, hearing and taste) and motor function involved in facial expression, chewing, swallowing and speech.

TBI-associated vision problems can be confused with psychological, motor or developmental symptoms which can complicate accurate diagnosis and treatment. Common complaints are traumatic visual acuity loss, binocular dysfunction (presented as convergence insufficiency or strabismus leading to diplopia), headaches, blurred vision, visual field defects (compression of peripheral fields and homonymous hemianopia), and exotropia caused by oculo-motor nerve palsy and optic nerve abnormalities. Other problems may include visual perceptual and cognitive deficits. Persons with visual perceptual disorders may have: *“...difficulties moving accurately through visual space, difficulties handling complex visual scenes, problems recognising certain aspects of the world around them, or they may be troubled by seeing visual phenomena that they know not to be present.”¹⁷*

Evidence of DAI has been found in persons who have sustained a brain injury. DAI typically results in a generalized slowing of information processing tasks, including slowed thinking and difficulty accomplishing tasks, thus limiting the number of cognitive operations that the brain can engage in at any given time. Military personnel who have sustained primary blast-related brain injuries are susceptible to diffuse damage that may interfere with visual processing.

¹⁶ Padula, WV et al. (2007) Evaluating and Treating Visual Dysfunction In ND Zasler, DI Katz, and RD Zafonte Brain Injury Medicine (pp.511-528) New York: Demos Medical Publishing, LLC.

¹⁷ Dutton (2003).

Rehabilitating TBI-related visual system dysfunction

“... adequate vision is a requisite for evaluation and treatment performed during most types of rehabilitation, such as optometric, ophthalmological, neuropsychological, physical, vestibular, occupational, and speech and language therapies.”¹⁸

In VA, the goal of rehabilitation is:

“...to facilitate the veteran's ability to remain in the most independent and least restrictive living environment via therapeutic interventions. Rehabilitative services in the VA are provided in a variety of settings such as on acute medical, surgical, and psychiatric units, in nursing homes, in substance abuse programs, in programs for the chronic mentally ill, in outpatient clinics, and in the home.”¹⁹

The knowledge gained through neuroscience research and clinical experience is helping to advance the understanding of both the extent of visual system disturbances in persons with TBI and the plasticity (i.e. adaptive capacity) of the adult brain.²⁰ Most visual-related symptoms are not visible on imaging or detected on standard eye examinations and therefore, may go undiagnosed. However, an individual with unmanaged sensory input to an injured visual system may experience physical, cognitive or behavioral symptoms that can interfere with their quality of life and adversely affect the quality and effectiveness of their rehabilitation.

Prior beliefs held that the adult brain was unable to develop new neural circuitry and that once injured, its function could not be restored. Newer research now favors thinking of the functional brain as a dynamic organ, capable of adapting new and constant sensory input to new neural roadmaps to restore or modify function. As a consequence, this knowledge is changing the way persons with TBI are rehabilitated. Increasingly, rehabilitation is incorporating multidisciplinary care management and exploiting brain plasticity as a means of improving brain reorganization and functional outcome.

The VA Physical Medicine and Rehabilitation Service uses a multidisciplinary rehabilitation model across health care settings to achieve successful rehabilitation. One of their specialty programs is TBI/Polytrauma. VA's TBI/Polytrauma System of Care model was implemented to provide injured Veterans and active duty service members with a spectrum of medical and rehabilitation care for TBI and its co-morbidities, including visual problems.²¹ At the forefront are new subspecialties devoted to clinical assessment and rehabilitation of visual binocular and processing disorders associated with TBI.

¹⁸ Kapoor, N. and Ciuffreda, KJ (2005). Chapter 23 Vision Problems. In JM Silver, TW McAllister, and SC Yudofsky. Textbook of Traumatic Brain Injury. 1st ed. Arlington, VA: American Psychiatric Publishing, Inc.

¹⁹Physical Medicine and Rehabilitation Home Page, Office of Patient Care Services, Veterans Health Administration, Department of Veterans Affairs. <http://vaww1.va.gov/rehab4veterans/>. Accessed April 16, 2009.

²⁰Zelinsky D. Neuro-optometric diagnosis, treatment and rehabilitation following traumatic brain injuries: a brief overview. Physical medicine and rehabilitation clinics of North America 2007;18(1):87-107, vi-vii.

²¹Lew H, Cifu D, Sigford B, Scott S, Sayer N, Jaffe M. Team approach to diagnosis and management of traumatic brain injury and its comorbidities. Journal of Rehabilitation Research and Development 2007;44(7):vii.

SCOPE OF THE REPORT

The focus of this report is on visual sequelae related to TBI that are experienced by OEF/OIF troops and Veterans. For this report visual sequelae will be defined as oculo-motor disorders and visual processing, or perceptual, disorders that hinder the ability of the brain to make sense of information taken in through the eyes.

Scott and colleagues describe a rationale for focusing on mechanisms of injury as a preferred model for improving detection and management of traumatic brain injuries in post deployment service members and Veterans.²² While blast injuries are not new to the Veteran population, the diffuse injury experienced in closed head injuries as a result of detonation exposure is regarded as a “signature injury” among new Veterans and post-deployed troops. Therefore, this report will include clinical research of TBI caused by detonation or other mechanisms of diffuse closed head injury such as diffuse axonal injury from motor vehicle accidents, falls and sport/recreational activities that are likely to resemble the types of exposure experienced by our newest Veteran population; it will exclude causes of focal brain injury such as stroke, infection, and tumors.

ORGANIZATION OF THE REPORT

The findings of the report will be divided into two sections, as indicated below. Some methods are used in both sections of this report. These methods are included in the General Methods section below.

Part 1. Frequency of TBI-related visual sequelae (Page 9)

Part 2. Rehabilitation of TBI-related visual dysfunction (Page 26)

GENERAL METHODS

For this report VATAP generated a qualitative systematic review, which approaches the process of literature review as a scientific endeavor. A systematic review applies explicit, reproducible methods that emphasize study quality and minimize potential biases in addressing a focused question usually about a health care intervention.²³ In contrast, a traditional narrative review frequently addresses a broad topic, fails to report objectives of the review, identification of articles, or methods for critical appraisal, and may be susceptible to bias in the selection, analysis, and synthesis of studies.

VATAP conducted extensive searches of the published clinical research literature, applied inclusion criteria as a filter for selecting the best evidence from published research for addressing the questions in this review, and critically appraised the included studies by applying scientific rules of evidence to help interpret the persuasiveness of the evidence for linking cause to effect based primarily on the type and quality of the research design. Ultimately, the conclusions do not overstate the evidence appraised in the review, and the recommendations for policy are linked to the strength (or quality) of the evidence.

²²Scott et al. (2005).

²³Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med* 1997;126(5):376-80.

Critical appraisal framework

Critical appraisal of epidemiological studies of disease frequency and association as well as treatment effects requires consideration both of the study question and of the strengths and limitations of each study type. For this review VATAP applied widely accepted principles of epidemiology to its critical appraisal of included studies.²⁴

Many frameworks exist to express the range of epidemiologic studies; common to all is placing studies along a continuum of the weakest method to the strongest method for linking cause and effect. For example:

Table 2. A continuum of study designs and their causal implications²⁵

Study designation		Hypothesis generating	Hypothesis testing	Inference
I.	Anecdotes	X		Speculative
	Clinical hunches	X		
	Case history	X		
II.	Time series	X		Suggestive
	Ecologic correlations	X		
	Cross-sectional	X		
III.	Case-control	X	X	Moderately suggestive
IV.	Before-after with controls		X	Highly suggestive
	Historical cohort		X	
V.	Prospective cohort		X	Moderately firm
VI.	Clinical randomized trials		X	Firm
	Community randomized trials		X	

In some evidence frameworks, systematic reviews and meta-analyses of primary studies may be considered firm evidence of an association provided that the systematic review process is comprehensive, rigorous and transparent and the included studies are of high quality and absent of heterogeneity to permit confidence in the analyses.²⁶

²⁴(1987). Chapters 2-7 In C.H. Hennekens and J.E. Buring. *Epidemiology in Medicine*. (pp. 16-177) Boston: Little, Brown and Company.

²⁵Adapted from Ibrahim, MA. (1985). *Rules of Evidence in M.A.* Ibrahim. *Epidemiology and Health Policy* (pp. 39-49). Rockville, MD: Aspen Systems.

²⁶Jovell AJ and Navarro-Rubio MD. Evaluación de la evidencia científica (Evaluation of the scientific evidence). *Medicine Clínica (Bar)* 1995;105:740-3.

PART 1. FREQUENCY OF TBI-RELATED VISUAL SEQUELAE

METHODS

Critical appraisal framework

Measuring disease frequency such as visual sequelae in a population with TBI can be achieved in several ways: 1) by a simple count of affected individuals; or 2) by understanding the pattern and determinants of disease occurrence in a given population. The latter has greater utility in epidemiology as it requires knowledge of the size of the source population and the time period during which the data were collected using either descriptive or analytical design strategies.

Descriptive epidemiological studies address patterns of disease occurrence and allow the generation of etiologic hypotheses. Types of descriptive studies are case reports/series, correlation studies, and case-control studies. They provide valuable information about populations, place and time to health care providers and administrators for effective planning and resource allocation decisions. However, they provide data on populations rather than individuals, lack a comparison group and cannot discern a temporal relationship between the exposure and disease.

Analytical epidemiological studies are designed explicitly to determine whether or not the risk of disease (i.e. visual sequelae) is different for individuals exposed or not exposed to a factor of interest, in this case TBI, by use of a control group. Analytical studies include case-control studies, cohort studies, and experimental studies (clinical trials).

The most common categories of disease frequency used in epidemiological studies are prevalence and incidence. Prevalence provides information, or a “snapshot”, of the state of disease occurrence at a point in time, whereas incidence quantifies the number of new cases of disease that develop in a population at risk during a specified time interval.

Two frequencies being compared between groups can be combined into a single summary measure to estimate the strength of an association between exposure and disease occurrence. The most common measures of association used in epidemiology are relative risk (a.k.a. risk ratio or odds ratio in case-control studies) and attributable risk (or risk difference or rate difference). Of the two, relative risk is used most commonly by epidemiologists, because it can be estimated from a wider range of study designs, including case-control studies. Relative risk measures the likelihood the exposed group will develop a disease relative to the unexposed group. It provides information about whether a valid observed association is likely to be causal.

However, once causality is assumed, the difference in the disease rate between an exposed population and an unexposed population become more important to public health decisions. Attributable risk quantifies the disease rate in exposed individuals that can be attributed to the exposure, or the reduction in incidence of disease that would be observed if the population was entirely unexposed, compared with its current exposure pattern. When comparing the potential impact of public health strategies, risk attributable to a population can be used to associate causality and public health action.

As with any study design type, the validity of the results, and hence, the degree of certainty derived from them, will depend on the extent to which bias and confounders are minimized in

the conduct of the study. For the literature on the frequency of visual sequelae of TBI, the following is of particular importance:

- Selection of study subjects: detailed information about the exposed population of interest and the comparison population including recruitment of the study populations, adequate power calculations, criteria used to define injury severity and time since injury;
- Exposure: defining visual sequelae, mechanism of TBI;
- Confounding factors: age, gender, prior injury, concurrent mental illness, substance abuse or physical injury that may affect the ability to assess oculo-motor or perceptual function;
- Outcome measures used.

Search strategy-identifying visual sequelae

VATAP conducted multiple comprehensive literature searches from July 2007 to January 2009 on The Cochrane Library[®], MEDLINE[®], EMBASE[®], and Current Contents[®] electronic databases, via the Dialog OneSearch[®] feature, for systematic reviews, meta-analyses and primary studies published in English from 1990 to January 2009. VATAP also conducted complementary searches on PubMed[®] to retrieve additional citations plus related references from specific key on-point articles. Searches were conducted repeatedly using differing strategies to exhaustively address the multidisciplinary nature of TBI and its sequelae: neuropsychological, visual, auditory, attentional, behavioral and perceptual. Incidence and prevalence of mild and severe TBI with the specific attendant sequelae were also thoroughly addressed.

The search terms fell into three broad concepts: **brain injury** (brain injuries, blast, head, explosion, concussion, trauma, closed-head, diffuse axonal injury, etc); **study types** (controlled studies, randomized trials, meta-analyses, guidelines, consensus development, recommendations, systematic reviews, evidence reports, etc); and **sequelae** (neuro-ophthalmology, neuro-optometry, neuro-psychology, auditory, multi-sensory, spatial integration, oculo-motor, ocular motility, visual, visual inattention, etc). All terms were searched as descriptors (exploded when appropriate) from all the databases' thesauri. Free text terms as well as title words (from on point articles) were used to further enhance retrieval.

Other data sources

Following the initial VATAP searches, in November 2007 the VA Journal of Rehabilitation Research and Development²⁷ published a special, single-topic issue on TBI and polytrauma. This issue examined the clinical characteristics of military personnel returning from combat and described several healthcare models providing diagnosis and treatment of TBI. VATAP hand searched the articles and their end references for studies meeting inclusion criteria.

Inclusion criteria

Studies were included that met the following criteria:

- Adult subjects only;
- Case series \geq 10 subjects who were Veterans seen in VA;
- Controlled studies \geq 10 subjects with the condition of interest;
- Health technology assessments, systematic reviews or meta-analyses on the topic (studies analyzed in systematic reviews or meta-analyses that met criteria for inclusion were excluded from further analysis in this review);
- Largest or most comprehensive study from the same study group on the same objective to avoid redundancy;

²⁷ http://www.research.va.gov/news/features/JRRD_TBI.cfm

- Closed head injury caused by blast or acceleration/deceleration type mechanisms of injury (stroke was excluded as a mechanism of injury, as were studies which lacked a clear description of mechanism of injury);
- Clear description of the severity of TBI in the study population (studies which lacked a clear description were excluded);
- Visual sequelae included either oculo-motor or visual perceptual problems.

RESULTS

While the goal of the searches was to retrieve from the years 1990 to 2009, the numerous electronic searches and hand searching of retrieved articles identified 5,118 citations ranging from 1964 to the present. Based on appraisal of title and abstract information in the searches, VATAP retrieved 302 articles that appeared relevant to the review, of which 24 met inclusion criteria for studies of frequency (see End References). A detailed data abstraction of included studies is presented in Tables A and B in Appendix 1. A breakdown of these studies by injury severity and study type is presented in the following table:

Table 3. Overview of included studies of frequency

TBI severity	Primary Study Type (number of studies)				Systematic Reviews / Meta-analyses
	Case series (Level 1)	Case-control (Level III)	Before-after with controls (Level IV)	Prospective Cohort (Level V)	
Mild severity	1	8*	--	2	2
Moderate-severe injury	1	9	--	--	1

*includes one before-after study with cases used as own internal controls

For determining an association between visual problems and mild TBI, case series provide speculative evidence, case-control studies provide moderately suggestive evidence, prospective cohort studies provide moderately firm evidence and rigorous meta-analyses provide firm evidence.

Mild TBI

A summary of the evidence of visual dysfunction in individuals with mild TBI is presented in Table 4. Five primary studies met inclusion criteria for evaluation of oculo-motor dysfunction; six studies and two meta-analyses met inclusion criteria for evaluation of visual perceptual disorders.

Included studies of oculo-motor dysfunction in individuals with mild TBI were one Level 1 case series (Lew 2007), two Level III case-control studies (Kraus 2007; Bohnen 1992) and two Level V prospective cohort studies (Heitger 2006; Kraus 2005). Evidence of visual perceptual dysfunction was found in two meta-analyses of the neuropsychological dysfunction following mild TBI that included visual domains (Frenchem 2005; Belanger 2005, which was funded by VA) and six additional Level III case-control studies.

The majority of study subjects were males in their late teens to mid thirties. Causes of injury were either combat-related in the Veteran population (Lew 2007) or motor vehicle accidents, sports, falls and assault in the civilian study populations.

Oculo-motor dysfunction

While the case series by Lew (2007) is categorized lower than the other study types, it was the only one to include a Veteran population, in this case those seen at the VA Palo Alto Polytrauma Network Site outpatient clinic. Thus, it can provide useful information for generating hypotheses about new or unusual health problems observed in Veterans, particularly in the newest OEF/OIF Veteran population seeking medical care.

Included case-control studies comprised cases who were defined by a history of suspected or confirmed head trauma from ambulance or hospital records or by self-reported symptoms and who were seen in emergency room or trauma centers at tertiary care facilities. Persons with visible head injuries, a history of substance abuse, psychiatric disorders or TBI, or other causes of TBI were usually excluded. Kraus (2007) explicitly excluded subjects with mild TBI who were in litigation, although Heitger (2006) reported that none of their subjects was in litigation.

These studies employed concurrent controls who were healthy volunteers (Bohnen 1992; Heitger 2006), from the general community (Kraus 2007) or hospitalized patients admitted through the emergency or trauma departments with complaints other than head injuries (Kraus 2005). Controls were matched for age and gender and occasionally educational level or premorbid IQ. Only Bohnen (1992) reported on the consecutive enrollment of study subjects, while none of the other studies reported on the systematic nature of the selection process. Only Kraus (2005) presented power calculations that guided the sample size needed to obtain a desired power of at least 90% with an alpha of 10% to detect a 15% difference in outcomes between comparison groups.

Injury severity criteria varied across all studies with altered mental status or loss of consciousness ranging from a few seconds to several minutes and a history of head trauma confirmed or inferred along with other variables. Nonetheless, cases in all studies represented the wider mild TBI population. Similarly, time since injury varied; most studies addressed the acute phase within a few hours to weeks of injury, while Heitger (2006) followed the study cohort up to one year post-injury, Kraus (2007) studied the chronic stage of injury, and Lew (2007) did not report on the variable.

Visual-related outcome measures were subjective complaints (Lew 2007; Kraus 2005) or objective testing for versional oculo-motor deficits (Kraus 2007; Heitger 2006) and photosensitivity (Bohnen 1992). All studies provided estimates of prevalence. Kraus (2007) conducted receiver operating characteristic analysis to graphically compare true- and false-positive rates between testing options through a series of cutoff points for each test; such a comparison will help indicate where one test has an advantage over the other.

Perceptual dysfunction

Evidence from two meta-analyses of neuropsychological studies that included visual domains is presented in this section. Frencham (2005) updated an earlier meta-analysis²⁸ which was not included in this review because of insufficient detail regarding visual domains. Belanger (2005) and Frencham (2005) quantitatively synthesized evidence from controlled studies of adult

²⁸Binder LM, Rohling ML, LarrabeeGJ. A Review of Mild Head Trauma. Part I: Meta-analytic Review of Neuropsychological Studies. J Clin and Experimental Neuropsychol. 1997; 19(3): 421-31.

subjects at any time post injury from which the effect of mild TBI on neuropsychological impairment could be measured.

While there was some variability in inclusion criteria for primary studies, both meta-analyses examined a range of neuropsychological domains, some of which have a visual component. Both analyses incorporated weighted effect sizes in calculations to control for the confounding effects of sample size. Frencham (2005) also examined the potentially confounding effects of time since injury across specific neuropsychological domains, and Belanger (2005) considered the effect of time since injury as well as the context of study participants (i.e. litigation vs. clinic-based vs. unselected samples).

Evidence from case-control studies comprised hospital cases of emergency room or trauma clinic admissions with physician diagnosed mild TBI (Mathias 2004; Malojcic 2008) or cases of university students with self reported head injury with loss of consciousness or altered consciousness in the previous six years (Chua 2004), at risk of head injury (Sosnoff 2007), or with physician-diagnosed mild TBI (Drew 2007; Halterman 2006). Persons with more severe head injury, physical or language limitations that would impede certain tasks, or a history of substance abuse, psychiatric disorders, learning disabilities or TBI were excluded.

Concurrent controls were from the general community (Mathias 2004), healthy volunteers (Malojcic 2008), and healthy students (Sosnoff 2007; Drew 2007; Halterman 2006; Chua 2004). Only Chua (2004) reported on the systematic nature of the selection process for study participants: both cases and controls were selected randomly from the same recruitment source and were blinded to the study objective. Controls were matched for age and gender and occasionally educational level, premorbid IQ, activity level and alcohol use. None used power calculations to guide optimal study size.

As with studies of oculo-motor dysfunction, the injury severity criteria varied across studies in degree of stringency and completeness of reporting, but case samples are believed to represent the wider mild TBI population.

The chronicity of injury varied among studies with the majority addressing the acute stage of injury (Malojcic 2008; Drew 2007; Halterman 2006, Mathias 2004) and the remaining addressing chronic stage (Sosnoff 2007; Chua 2004).

Outcomes in primary studies and in both systematic reviews included prevalence data from a number of objective cognitive tasks. Evidence of the visual-related cognitive tasks included aspects of attention, speed of processing and working memory.

Table 4. Summary of results of frequency of visual dysfunction in mild TBI

Note: See Page iv for list of abbreviations

Study	Study Type	Size (N) Mild TBI/Controls	Time since injury (mean)	Injury severity criteria	Outcome Measures	Findings
Oculo-motor dysfunction						
Lew 2007	I	62/0 Veterans	NR	Not specified, some AC	Self reported symptoms	Despite normal or near normal corrected visual acuity and visual fields, mild TBI vets displayed: <ul style="list-style-type: none"> • Photosensitivity (59%) • Convergence dysfunction (46%) • Pursuit or saccadic dysfunction (25%) • Accommodation dysfunction (21%) • Strabismus (11%) • Fixation dysfunction or nystagmus (5%) • Reading difficulties after TBI (70%)
Kraus 2007	III	20/19	65.2 months	ACRM Mild TBI: any period of LOC, acute PTA, any AC during accident, or focal neurologic deficit that may be transient or not.	Visually guided saccades, antisaccades (AS)	<ul style="list-style-type: none"> • AS task: mild TBI had more prosaccade errors than controls [gap: $F(1,38)=4.84, P=0.034$; overlap $F(1,38)=5.15, P=0.029$] • AS latencies: mild TBI had increased prosaccade response latencies than controls [$F(1,38)=6.95, P=0.012$] • ROC analysis=prosaccade error rates performed better than executive domain score for differentiating mild TBI from controls, whereas the opposite was true for differentiating mild TBI from mod-severe TBI cases.
Heitger 2006	V	37/37	1 week 3 months 6 months 12 months	GCS=13-15	<ul style="list-style-type: none"> • Saccadic reaction times, velocity, motor accuracy, directional errors, and timing and rhythm of memory-guided sequences using computerized testing • RPSQ 	<ul style="list-style-type: none"> • Unsuspected persistent deficits noted in oculo- and arm- motor function up to one year post injury ($p \leq 0.05$). • Persistent post-concussional symptoms at one year post injury ($p < 0.05$); only 38.7% entirely free of post-concussional symptoms after one year post injury
Kraus 2005	V	235/235	< 72 hours	GCS=13-15 Any AC or LOC < 30 min or PTA < 24 hrs Evidence of blow/impact to head or accel/decel exposure	Self reported symptoms	<ul style="list-style-type: none"> • Blurred vision (23%) Adjusted RR=1.50 (90% CI 1.07-2.11) • Double vision (9.8%) Adjusted RR=1.81 (90% CI 1.02-3.21)
Bohnen 1992	III	43/43	10 days & 5 weeks	LOC=sec-15 min PTA < 60 min EMV score on admission=15	Light stimuli Sound stimuli Behavior rating scales	<ul style="list-style-type: none"> • Light sensitivity (42%) at 10 days ($p < 0.01$), 23% persisted at 5 weeks ($p < 0.05$) • Light sensitivity correlated with post-concussive cognitive complaints ($R_s=0.36, p < 0.05$)

Study	Study Type	Size (N) Mild TBI/Controls	Time since injury (mean)	Injury severity criteria	Outcome Measures	Findings
Perceptual dysfunction						
Malojic 2008	III	37/53	45 days (median reported)	ACRM (1993) LOC < 30 min, PTA < 24 hrs, any AC during accident, focal neurologic deficit that may be transient or not GCS falling < 13 after 30 min. .	Sustained visual attention RT and accuracy on Sternberg Memory Scanning Paradigm Decision RT=Choice RT-Simple RT	Deficits in: <ul style="list-style-type: none"> • Sustained visual attention $F(1,68) = 4.2, p=0.045$ • Short term memory scanning $F(1,86) = 10.8, p=0.001$ • Trend toward slowing at making simple perceptual decisions but NS
Sosnoff 2007	III	22/22	173.1 days (median reported)	Physician diagnosed, not specified	Baseline Headminder Concussion Resolution Index consisting of 6 subtests: simple RT, cued RT, 2 visual recognition tasks, animal decoding, symbol scanning	<ul style="list-style-type: none"> • Slowed response (increased mean RT) across all cognitive tasks ($p<.05$) • Lower accuracy in cued RT ($p<.05$) <p>Increases in mean RT after injury suggests transient alterations in the attentional network.</p>
Drew 2007	III	20/20	37 hrs	AAN, AMS>15 min.	Attentional disengagement in orienting visuospatial attention using saccadic reaction time (RT) and gap duration using the gap saccade task	Longer saccadic RT at shorter gap durations (0-100 ms) at 2 days post injury ($F[6,228] = 2.824, p=0.32$) which resolved within 1 week.
Halterman 2006	III	20/20	37 hrs	AAN	Orienting, alerting and executive components of attention using Attentional Network Test (ANT) as measured by median reaction times (RTs) and response accuracy	<ul style="list-style-type: none"> • Deficits in orienting ($p < 0.01$) and executive ($p<0.001$) components of visuospatial attention • Degree and rates of recovery vary across brain regions; orienting deficit resolved within 1 mo of injury but executive deficit did not.
Mathias 2004	III	40/40	26.3 days	GCS=13-15 LOC \leq 20 min.	<ul style="list-style-type: none"> • Attention • Memory • Visual and tactile RT • Fluency • Premorbid IQ • Injury-related Stress 	Deficits in: <ul style="list-style-type: none"> • Selective attention (speed and accuracy) ($p<0.05$), • Non-verbal fluency ($p<0.01$) • Verbal memory ($p<0.01$) • Slower processing speed on visual ($p<0.05$) and tactile ($p<0.01$ and $p<0.05$) tasks • Visual tasks requiring inter-hemispheric transfer of information and task difficulty were affected more.
Chuah 2004	III	16/16	2.64 yrs	LOC < 30 min or disorientation	Memory span tasks (visual, spatial and visual-spatial)	Deficit in: <ul style="list-style-type: none"> • Spatial memory ($p=.01$), but not on visual or visuospatial memory suggesting that subtle long-term cognitive changes may be present after a mild TBI

Study	Study Type	Size (N) Mild TBI/Controls	Time since injury (mean)	Injury severity criteria	Outcome Measures	Findings
Belanger 2005 *funded by VA	SR	39 studies: 1463 cases 1191 controls Mean age NR Gender NR	No limits	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> • Controlled studies published from 1970-March 2004 in English • Defined by severity level • Sought medical attention at a medical facility (not sporting event) • Clinically validated or experimental tests used for cognitive measurement • Reported time since injury 	<ul style="list-style-type: none"> • Global cognitive ability • Attention • Executive functioning • Fluency • Memory acquisition • Delayed memory • Language • Visuospatial ability • Motor abilities 	<ul style="list-style-type: none"> • Overall effect size was moderate: $d=0.54$ ($p < .05$); All domains except motor functions showed significant effect sizes • Controlling for time since injury, sample selection context, visuospatial skill was the only domain with an increasing effect size across time (< 90 days, $d=.48$; ≥ 90 days, $d=.73$ $p < .05$); studies conducted at ≥ 90 days time since injury involved participants in litigation, while those studies conducted at < 90 days were unselected samples. • <i>"In unselected or prospective samples, the overall analysis revealed no residual neuropsychological impairment by 3 months postinjury ($d = .04$). In contrast, clinic-based samples and samples including participants in litigation were associated with greater cognitive sequelae of mild TBI ($d = .74$ and $.78$, respectively at ≥ 3 mo)."</i> • Litigation was associated with stable or worsening of cognitive functioning over time.
Frencham 2005 (updated Binder 1997)	SR	<ul style="list-style-type: none"> • 17 studies: • 634 cases • 485 controls • Mean age=28.46 • 71% male • Educ level=12.3 • Mean time since injury=1.13 yrs (SD=2.44) 	No limits	<ul style="list-style-type: none"> • Inclusion criteria: Controlled studies published during or since 1995 in English • mild TBI not based on sx • GCS ≥ 13 • Attrition rates $< 50\%$ • No whiplash or non-impact head injuries 	<ul style="list-style-type: none"> • Working memory and attention • Perceptual organization • Verbal organization • Motor skills • Memory • Executive functioning • Processing speed 	<ul style="list-style-type: none"> • Overall effect size: $g = 0.32$, $p < .001$. • Weighted effect sizes were significant for working memory/attention ($g = 0.32$, $p < .005$), perceptual organization ($g = -0.25$, $p < .36$), memory ($g = 0.30$, $p < .05$), executive functioning ($g = 0.30$, $p < .05$), and processing speed ($g = 0.47$, $p < .0005$). • The merging of post-acute effect sizes with those reported in Binder 1997 yielded a nonsignificant result, $g = 0.11$. • <i>"Time since injury was found to be a significant moderator variable, with effect sizes tending to zero with increasing time post injury."</i>

Moderate-severe TBI

A summary of the evidence of the frequency of visual dysfunction in individuals with moderate-severe TBI is presented in Table 5. Two primary studies met inclusion criteria for evaluation of oculo-motor dysfunction; eight studies and one meta-analysis met inclusion criteria for evaluation of visual perceptual disorders.

Included studies of oculo-motor dysfunction in individuals with moderate-severe TBI comprised one Level 1 case series (Goodrich 2007) and one Level III case-control study (Kraus 2007). Evidence of visual perceptual dysfunction was found in one meta-analysis examining attention following severe TBI (Mathias 2007), seven additional Level III case-control studies (Battistone 2008; Summers 2006; Skelton 2006; Du 2005; Mathias 2004; Lew 2004; Shum 2000), and one Level V historical cohort study (McKenna 2006).

The majority of study subjects were males with mean ages in their twenties and thirties but included a range of subjects in their fifties and sixties who were older than those in the studies of mild TBI. Causes of injury were largely combat-related in the Veteran population (Lew 2007) or motor vehicle accidents, motorcycle accidents, sports, falls and assault in the civilian study populations.

Oculo-motor dysfunction

Using both self-reported symptomatology and diagnosis, the retrospective case series by Goodrich (2007) provides important information for generating hypotheses about visual problems observed in an inpatient setting of Veterans at a VA Optometry Polytrauma Inpatient Clinic with moderate-severe TBI, particularly in the newest OEF/OIF Veteran population seeking medical care. Accommodation, convergence and spatial deficits occurred in at least 20% of all subjects, and reading impairment occurred in at least 60%, regardless of mechanism of injury and despite having normal or near normal visual acuity and visual fields.

The case-control study by Kraus (2007) comprised cases with chronic moderate-severe TBI defined by a history of closed head trauma with at least six months post injury. Cases were referred from an inpatient setting at a tertiary care facility. Subjects with a history of psychiatric problems or substance abuse, litigation pending, and on current treatment for cognitive problems were excluded. Mean time since injury was approximately 9 years. Cases had an average loss of consciousness post injury of 549 hours (range 4 to 2880 hours). Controls were recruited from the general community with no history of psychiatric illness, TBI, substance abuse or dependency or significant medical or neurologic illness associated with significant changes in brain function. Controls were matched for age, but had higher premorbid IQ and educational level than cases. No power calculations were conducted.

Visual-related outcomes measured oculo-motor function using visually guided saccade and antisaccade tasks, as well as neuropsychological testing. In addition, Kraus (2007) conducted receiver operating characteristic analysis to graphically compare true- and false- positive rates between testing options through a series of cutoff points for each test; such a comparison will help indicate where one test has an advantage over the other.

Perceptual dysfunction

Evidence from one meta-analysis of studies of deficits in attention following severe TBI was included in this section (Mathias 2007). The meta-analysis comprised 41 controlled studies with 1,651 participants published from 1980 to November 2005 in English. The studies used a total of 48 different tests, subtests and scoring procedures, some of which were investigational, to

measure aspects of attention. The results were categorized into one of seven aspects of attention: information processing speed; orienting of attention; attention span; focused/selective attention; divided attention; sustained attention/vigilance; and supervisory control.

Ninety-three percent of the studies did not report recruiting a selected sample of TBI patients (eg. patients complaining of attentional problems). Control groups were generally well-matched on age, educational level and premorbid IQ estimates, suggesting that group differences in these variables were not contributing to the results. However, fewer than half of the studies reported estimates of premorbid IQ for the study groups or injury severity data, and none reported depression scores, which may contribute to some of the deficits in attention. The mean time since injury was 1,178 days, but this variable was not reported in 22% of the studies.

Mathias (2007) incorporated weighted effect sizes to control for the confounding effects of sample size. The investigators calculated a fail safe statistic for each effect size to estimate the number of unpublished studies with nonsignificant findings that would be needed to call into question the current findings. This would assist the reader in estimating the impact of publication bias in the evidence base, and therefore, the degree of confidence in the findings.

For primary studies included in this review, case-control studies of cases with moderate-severe TBI represented residents from community facilities (Summers 2006), residential facilities (Skelton 2006) and a trauma unit (Mathias 2004), while the remaining studies represented populations of inpatients or referrals from rehabilitation units at tertiary care facilities. Cases with a history of diagnosed TBI with or without vision symptoms were generally included. Persons with obvious visual or motor deficits that would affect test performance were excluded.

Injury severity criteria varied across studies but generally considered subjects with a PTA > 1 day or GCS between 9 and 12 for moderate TBI or < 9 for severe cases with or without loss of consciousness. Two studies did not report criteria (Skelton 2006; Du 2005). Mean time since injury was reported in all but one (Battistone 2008) and ranged from approximately 3 months to several years. Shum (2000) was the only study to report separate outcomes of cases early in their recovery (< 1 year) from those in late recovery. Therefore, the study base for this review represents individuals with moderate-severe TBI in the chronic stages of recovery.

Controls were recruited generally from the community or university settings. Lew (2004) did not report the referral source. Controls were matched for age and educational level, but, where reported, gender composition and premorbid IQ often was not matched to cases.

Outcomes measured aspects of information processing speed, visual perceptual impairment, attention, spatial navigation, dark adaptation, and visual memory using a variety of neurocognitive and visual perceptual tests. In addition, three studies evaluated diagnostic test performance in detecting brain injury using new tests (Skelton 2006; Du 2005) or less frequently used tests (Lew 2004).

Table 5. Summary of results of visual dysfunction in moderate-severe TBI

Note: See Page iv for list of abbreviations

Study	Study Type	Size (N) mod-severe TBI/Controls	Time since injury (mean)	Injury severity criteria	Outcome Measures	Findings
Oculo-motor dysfunction						
Goodrich 2007	I	50/0	NR	NR	Comprehensive exam	<ul style="list-style-type: none"> • 74% had vision complaints, but only 24% had abnormal visual fields. • Accommodation, convergence and spatial deficits occurred in 20% or more of all subjects regardless of mechanism of injury • % visual impairment in blast v. nonblast TBI = 52% v. 20% • Reading deficits occurred in ~60% regardless of mechanism of injury • Modest correlation between visual acuity and reading deficits ($r = 0.419$, $p < 0.001$), but accounted for < 18% of the variance • Persons with blast injury-related visual impairment were more likely to have damage to the eye, orbit and/or cranial nerves (p not reported). • Similar rates of binocular or perceptual dysfunction between blast-related and non-blast related injuries. • Non-blast-related injuries were associated with higher rates of convergence (23.8% v. 36%), pursuit/ saccades dysfunction (4.8% v. 32%), fixation/ nystagmus (0% v. 4%), and diplopia (0% v. 12%)
Kraus 2007	III	17/19	107.12 mo (SEM 22.04)	ACRM: <ul style="list-style-type: none"> • GCS < 13 +/-0 • LOC > 30 min 	<ul style="list-style-type: none"> • Visually guided saccade task (VGS) latency, velocity, and gain • Antisaccade task (AS) prosaccade error rate, latency • Neuropsychological testing battery 	<p>The mod-severe TBI group showed significant persistent impairment of attentional and sensorimotor function:</p> <ul style="list-style-type: none"> • Greater latencies on the VGS task overlap condition [$F(1,35)=5.79$, $P=0.022$] which accounted for their increased gap effects, suggesting that TBI group had greater difficulty disengaging attention from the fixation point in the overlap condition. • More prosaccade errors [$F(1,35)=8.97$, $P=0.005$] on the AS task overlap condition • AS latencies and prosaccade error rate scores correlated with executive, attention and memory domain scores. • ROC analysis: executive domain score was more sensitive and specific than prosaccade error rates for differentiating mod-severe TBI from either mild TBI or controls.
Perceptual dysfunction						
Battistone 2008	III	17/17	NR	<ul style="list-style-type: none"> • PTA 1-28 days • Any LOC • ≥ 1 year post injury 	<ul style="list-style-type: none"> • Speed-accuracy trade-off methodology (SAT) • Peabody Picture Vocabulary Test-III (PPVT_III) • Number Comparison Test (NCT) • Matrix Reasoning subtest from the Wechsler Adult Intelligence Scale-3rd ed. (WAIS-III) 	<p>TBI group demonstrated impairment in:</p> <ul style="list-style-type: none"> • Resource capacity resulting in slowing of cognitive tasks across all measures • Self-regulation resulting in a more cautious approach despite no improvement in accuracy.

Study	Study Type	Size (N) mod-severe TBI/Controls	Time since injury (mean)	Injury severity criteria	Outcome Measures	Findings
McKenna 2006	III	31/195 *Statistically significant differences between groups for: age, education level, employment type	106.8 days (range 21-440, SD 96.5)	Length of PTA: • Mean PTA=61 days (range 11-204 days, SD 45.9)	Cases: • OT-APST • FIM • BRISC • RBMT Normative sample: Above plus MMSE	Among TBI cases: • Most common impairments on the OT-APST were unilateral neglect (45.2%), body scheme (25.8%) and constructional skills (25.8%). • 64.5% had one or more impairments across the OT-APST subscales v. 11.8% of the normative sample. • Higher frequency of agnosia, apraxia, unilateral neglect, and impairments in body scheme and constructional skills. • No significant relationship between the presence of visual perceptual impairment and level of cognitive and functional impairment after TBI. • "Routine use of a screening tool such as the OT-APST may help identify visual perceptual impairments in these patients and the need for more detailed assessment."
Summers 2006	III	10/10	52.90 mo (range 24-112; SD 29.05)	• Severe= 1-7 days • Very severe= 1-4 wks duration • Extremely severe= > 4 wks	• Stroop test • TMT Parts A and B, TMT Ratio score (B-A)/A • VOSP Incomplete Letters subtest and Object Decision subtest • Luminance and basketball tasks	TBI group was: • Comparable on visual perception using the either VOSP subtests • Slower on the Stroop test and TMT and had higher Stroop interference and TMT ratio scores. • Less able to identify a distracting stimulus on luminance and basketball tasks of inattention blindness. • Conclusion: Severe TBI is associated with deficits to focused and divided attention and with a potentially more debilitating consequence of reduced distractibility. Current models of attention may need to be reconceptualized to incorporate the notion of functionally adaptive distraction.
Skelton 2006	III	14/12	15.9 yrs, (range 0.5-48; SD 0.9)	NR	• Arena Maze task= • Probe trials to test knowledge of platform location • Everyday Spatial Questionnaire	TBI group showed: • Severe impairment in spatial navigation on Arena maze task and Everyday Spatial Questionnaire. • No significant differences between the groups and no correlations found between any Arena Maze variables and age, gender, time-since-injury or computer experience. Other findings: • Spatial score was the best measure of performance in Arena maze. • Path efficacy was a better measure of discriminating TBI from non-injury than distance or latency. • Results support the need for further study of the frequency and impact of spatial navigational impairment in a TBI population to determine its significance and the need for testing.
Du 2005	III	17/21	≥ 6 months	Not reported, but authors stated many cases had co-existing mobility and balance problems from their injury	Scotopic thresholds (dB) in undilated conditions	• TBI group had higher mean scotopic thresholds and greater variability than controls [TBI mean=9.4 dB (range 0-20; SD 5.0; SEM 1.2) vs. Control mean=4.1 dB (range 0-9; SD 2.4; SEM 0.5) (t=4.255, p=0.0004 for mean thresholds)] • Using a cutoff threshold of 9 dB, 9/17 (53%) TBI subjects had elevated dark adaptation thresholds • Among TBI cases who reported elevated photosensitivity, final dark adaptation threshold values were frequently elevated when compared with controls, but the degree of elevation did not correlate with the self-reported degree of photosensitivity. • The lack of abnormal dark adaptation thresholds in 47% of TBI subjects who complained of photosensitivity may be due to difference in site and pervasiveness of the injury. • Further study is needed to better understand the neurological mechanism and neural sites underlying photosensitivity.

Study	Study Type	Size (N) mod-severe TBI/Controls	Time since injury (mean)	Injury severity criteria	Outcome Measures	Findings
Mathias 2004	III	25/25	212.9 days, SD=86.6	<ul style="list-style-type: none"> Moderate TBI: GCS 9-12 and LOC between 20-60 min. Severe TBI= GCS \leq 8 and LOC > 1 hr 	<ul style="list-style-type: none"> Self reported symptoms and history Visual Elevator, Telephone Search, Telephone Search While Counting, TEA COWA RFFT WCST RAVLT Interhemispheric processing tasks Rivermead Head Injury Follow-up Questionnaire Rivermead Post Concussional Symptoms Questionnaire (PCS) 	<p>TBI group showed:</p> <ul style="list-style-type: none"> Poorer performance on measures of visual and verbal fluency (COWA and RFFT) and verbal memory (RAVLT total Trials 1 through 5 and 20-min delayed recall), but showed minimal problems with attention or set shifting. Slower response to the visual RT tasks [$F(1,48)=8.61, p < .01$], Affected by more stimulus-response choices [$F(1,48)=9.82, p < .01$], Slower on measures using incompatible response [$F(1,48)=4.36, p < .05$] Slower on tasks designed to require the inter-hemispheric transfer of information. <p>Other findings:</p> <ul style="list-style-type: none"> Correlation between COWA and six-choice incompatible tactile RT task ($r = -.61, n=20, p < .01$). Correlations between outcome on Rivermead indices and tactile six-choice compatible RT task ($r = .56, n=20, p < .01$) and between PCS and tactile six-choice compatible RT task ($r = .65, n=20, p < .01$), i.e. poor outcome was associated with slower information processing speed. Effect size was largest for the interhemispheric process task i.e. six-choice, two sequence incompatible tactile RT task (Cohen's $d = 1.15$).
Lew 2004	III	11/11	9.3 mo	GCS \leq 8	<ul style="list-style-type: none"> ERP amplitude and latency Behavioral data = reaction time and response accuracy 	<p>TBI patients had:</p> <ul style="list-style-type: none"> Lower P300 amplitude in both auditory (11.2 vs. 22.7 $\mu V, P < 0.01$) and visual (11.6 vs. 20.9 $\mu V, P < 0.01$) domains Longer P300 latency in both auditory (355 vs. 294 msec, $P < 0.0001$) and visual (376 vs. 341 msec, $P < 0.01$) modalities Comparable response accuracy. Longer mean reaction time for both auditory and visual tasks (auditory, 404 vs. 277 msec, $P < 0.05$; visual, 397 vs. 346 msec, $P < 0.05$).
Shum 2000	III	<ul style="list-style-type: none"> Early recovery group (ERG) with TBI < 1 yr=14 Late recovery group (LRG) with TBI > 1 yr=14 Controls=18 	<ul style="list-style-type: none"> ERG Median=4 mo 1.5 wks, (range = 2 mo - 9 mo 1 wk) LRG Median=2 yrs 1 wk, (range=1 yr 2 wks - 6 yrs 3 mo) 	<ul style="list-style-type: none"> GCS \leq 8 or PTA > 7 days 	<ul style="list-style-type: none"> SVLT RAVLT Electronic maze test (EMT) Perceptual discrimination task with Chinese characters to screen out visual perceptual problems 	<p>TBI individuals had:</p> <ul style="list-style-type: none"> Impairment on verbal and visual memory, but the patterns of impairment were not identical. A similar rate of learning on verbal memory test (RAVLT) but a slower rate of learning on the visual memory test (SVLT) Comparable performance on EMT for spatial memory Conclusion: Using unfamiliar stimuli such as Chinese characters in the SVLT rather than familiar verbal stimuli used in RAVLT may uncover impairment that is masked by a retroactive interference effect from using familiar stimuli in testing. More research is needed to determine if severe TBI has a differential effect on visual and verbal memory processes.

Study	Study Type	Size (N) mod-severe TBI/Controls	Time since injury (mean)	Injury severity criteria	Outcome Measures	Findings
Mathias 2007	MA	41 studies: <ul style="list-style-type: none"> • 823 cases • 828 controls • Mean age, educ level and premorbid IQ matched where reported 	Mean=1,178 days (SD 1151.7; range 59.9-4015 days)	<ul style="list-style-type: none"> • GCS range 4.7-6.6 • Mean PTA=30.2 (6.0-125) • Mean LOC=863.3 (8.25-4,937.5) <p>Where reported</p>	<p>Various tests for:</p> <ul style="list-style-type: none"> • Information processing speed • Attention span • Focused/selective attention • Divided attention • Sustained attention/vigilance • Supervisory attentional control 	<p>Only effect sizes for tests used by two or more studies (N=37 studies) reported:</p> <ul style="list-style-type: none"> • Speed of information processing was significantly impaired following severe TBI using simple and choice RT tasks (N=21) • Specific measures of attention span (eg. reading span, digit span) were affected more by severe TBI than other tests (eg. alphabet span, digits forward and backward) (N=13) • Focused/selective attention was the most commonly studied. Large and significant effect sizes noted using Stroop, Symbol Digit, Digit Symbol, Trails Inhibition Task, and TMT A,B and A:B tests (N=11) • On divided attention, RT under dual tasks conditions and PSAT suggested modest deficits and smaller than those found on measures of info-processing speed (N=8) • On sustained attention/vigilance, visual search and cancellation tasks showed deficits when based on a combination of speed and accuracy or speed alone. (N=8) • Supervisory attention control-card sorting tests and the Tower of London tests showed only small to moderate effect sizes.

CONCLUSIONS

Mild TBI

Overall, the findings from this qualitative systematic review provide moderately suggestive evidence for a range of vision sequelae primarily in the acute stages of mild TBI in younger clinically-based adult populations. The evidence is limited by small sample size and heterogeneity in the selection of cases and controls, injury severity criteria and outcome measures.

In the acute stages following mild TBI, photosensitivity is a common complaint particularly in the Veteran population. The evidence suggests that while nearly half of the cases tend to experience photosensitivity in the acute phase following injury; this problem can persist for several weeks especially in the presence of post-concussive cognitive complaints. Moderately firm evidence exists for the presence of self-reported vision disorders (blurred vision and double vision) and saccadic deficits in the acute and chronic stages post injury. These common symptoms are not representative of the range of possible symptoms and impairments found in individuals with mild TBI, nor are they necessarily specific to an underlying mechanism of TBI.

Findings from both meta-analyses and primary studies of neurocognitive dysfunction following mild TBI suggest resolution of these effects generally within 3 months, but data from longer time since injury are lacking. Preliminary evidence suggests that some domains of neurocognitive testing with respect to visual processing speed, visuospatial attention, and spatial memory may be sensitive to detecting persistent mild TBI.

Moderate-severe TBI

These findings provide preliminary speculative evidence from one case series of Veteran patients and moderately-suggestive evidence from case-control studies of diffuse deficits to oculo-motor function and visual perception in clinically- and community-based populations with chronic moderate-severe TBI. Results suggest deficits often persist many years after injury. As with studies of mild TBI, the evidence base is limited by conduct and reporting of key study elements, specifically, small sample sizes, selection process of cases and controls, injury severity criteria and testing measures.

Among Veterans with moderate-severe TBI, binocular dysfunction, pursuit and/or saccade deficits and visual spatial deficits were common. The rate of visual impairment with either overt blast injury or blast exposure was more than twice that of other mechanisms of injury, suggesting a need to conduct more comprehensive eye examination beyond refractive correction to uncover more pervasive visual deficits in this population, particularly those who complain of reading difficulty or photosensitivity.

The preponderance of evidence from multiple studies suggests that moderate-severe TBI is associated with widespread deficits in attention, in particular in information processing speed and executive control of task switching in focused/selective and divided attention. Possible reasons underlying these impairments are a reduced resource capacity and impairment in self-regulation (Battistone 2008). Mathias (2007) stressed the need to account for the effect of the impairment in information processing speed when measuring other aspects of attention. Summers (2006) highlighted the role of inattentive blindness, i.e. the failure to identify significant but unexpected events that occur within a person's visual field, and its implications on function and in design of rehabilitative models of care.

Results from single case-control studies found higher frequencies of agnosia, apraxia and unilateral neglect, dark adaptation dysfunction and visual memory as well as impairment in body scheme and constructional skills in moderate-severe TBI subjects than in noninjured subjects.

RECOMMENDATIONS FOR FUTURE RESEARCH

To minimize the effect of bias (and consequently maximize the internal validity and generalizability) in the design of descriptive epidemiological studies, this VATAP systematic review and included meta-analyses stress the importance of clearly reported systematic sample selection (criteria, context, heterogeneity and method) and time since injury in designing prospective research and interpreting data, as well as the sources from which information about exposure and disease are obtained.

Valid estimates of the association between visual disorders and TBI require that the source data and selection process for choosing cases and controls be similar except for the disease of interest. Ideally, exclusion criteria for cases should apply equally to controls. The appropriate source for a control population may be the general community, special groups within the general community or clinically based groups. Included studies of acute mild TBI generally achieved this goal, while studies of individuals with chronic TBI of all severity levels may have overestimated the association between vision disorders and TBI by using cases from a university hospital-based referral source and controls from the general community.

Classification and effects of TBI are often described as “mild” or “subtle”. In fact, effects of TBI may be very debilitating despite inconclusive or negative clinical results. Reasons for this include incomplete or poorly understood information about the exposure (TBI) or the disorder (visual sequelae). Information about the exposure will depend on the mechanism and time of injury and the stringency of injury severity criteria. Information about the disorder (visual sequelae) may be based on symptomatology, which brings inherent recall bias, or on findings from physical examination or an array of objective testing, which may or may not be uniformly available or applied.

Choice of testing and methodological considerations must be taken into account when evaluating epidemiological studies. Certain tests of perceptual impairment may not be sufficiently sensitive to detect the effects of mild TBI. Pooling data from multiple studies may mask more subtle effects of mild TBI in individual studies or more significant effects from a small subset of the study population. Correlation between testing and functional impairment requires further study along the spectrum of TBI, as does understanding the potential confounding effects of depression and premorbid IQ on various aspects of attention as well as the moderating influences of age, education and post-injury interval on specific testing measures.

Limited availability of commercial programs, computerized tools and normative data limit the generalizability of test results from many of the included studies and, therefore, their widespread clinical use. Research is needed to refine existing testing for routine clinical use, validate preliminary findings of novel testing, and understand the underlying mechanisms and neural sites involved in impairments detected by these tests.

VATAP identified several preliminary studies whose secondary objectives were to identify improved methods of detecting TBI using oculo-motor and perceptual testing. This review and a

prior VATAP review of functional neuroimaging used to screen TBI²⁹ found that such tests would need to be studied in larger, prospective samples with sufficient power to reliably determine their operating characteristics. Specifically, positive and negative predictive values are needed to better understand their clinical value in this population. Predictive values must incorporate the clinician's estimate of the probability of disease before testing to determine the likelihood of the disease when the test is positive or negative. Studies that suggest a role for oculo-motor or visual perceptual testing in screening individuals with TBI would need to follow this construct before drawing firm conclusions of a test's clinical utility.

In this review, VATAP attempted to confine the literature to results that would be generalizable to the new, younger Veteran population. The evidence is based on those who sought medical care in a hospital emergency room, trauma clinic or university health clinic setting. It does not reflect the unknown numbers of cases seen outside those settings with undiagnosed, misdiagnosed or untreated TBI or its consequences. Both Goodrich (2007) and Lew (2007) suggest significant visual perceptual problems even among Veterans with known TBI who have normal or near normal corrected visual acuity and visual fields. Confirmation of their results in prospective, controlled studies would improve understanding of the magnitude of the problem among Veterans.

The importance of raising awareness among Veterans about TBI and its consequences, particularly mild TBI, cannot be overstated at a time when Veterans have been placed at high risk for sustaining an injury, and they and their families are at risk of suffering needlessly in the presence of available care. Connecting these Veterans to VA care will assist in conducting the research that is so desperately needed to advance identification and understanding of the mechanisms and range of effects of TBI on the visual system.

²⁹ Flynn (2007).

PART 2. REHABILITATION OF TBI-RELATED VISUAL DYSFUNCTION

METHODS

Critical appraisal framework

As with any study design type, the validity of the results, and hence the degree of certainty derived from them, will depend on the extent to which bias and confounders are minimized in the conduct of the study. For evaluating the validity of treatment studies, the JAMA Users' Guides to Evidence Based Medicine offer a widely accepted evidence-based framework with which to critically appraise the evidence on visual rehabilitation in individuals with TBI.³⁰

Specifically, the following aspects of study validity will be considered:

- Similarity of study arms with respect to baseline characteristics, follow up, application of additional treatments other than the intervention of interest;
 - Randomized assignment to treatment;
 - Aspects of treatment;
- Completeness of follow-up;
- Adherence to principles of intention-to-treat analysis (subjects were analyzed in the groups to which they were randomized);
- Degree of blinding employed (critical if subjective outcome measures were used, less critical if objective outcome measures were used);
- Results: magnitude and precision of the treatment effect;
- Generalizability of findings to clinical practice;
- Consideration of all clinically important outcomes;
- Consideration of all risks and benefits of treatment.

Linking evidence to policy recommendations

In addition to Ibrahim's evidence hierarchy presented earlier (Table 2), individual studies of treatment interventions will be critically appraised by applying the framework developed by the US Preventive Services Task Force.³¹ This framework is designed to ensure that the critical appraisal process and final product are "*methodologically sound, scientifically defensible, reproducible, and well documented.*"³² The framework includes:

- Classifying individual studies according to a revised hierarchy of research design
- Assessing internal validity of individual studies and assigning to one of three categories—"good," "fair," and "poor";
- Assessing external validity and applicability;
- Assessing both the certainty of the evidence about, and the magnitude of, the net benefits of an intervention;
- Assigning a recommendation grade for that intervention.

A detailed description of the USPSTF framework is available at www.ahrq.gov. A modified summary is presented in Appendix 2.

³⁰Users' Guides to Evidence-based Medicine. How to Use an Article About Therapy or Prevention. Reproduced from JAMA (1993;270(21):2598-2601) and (1994;271(1):59-63) <http://www.cche.net/text/usersguides/therapy.asp> accessed April 16, 2009.

³¹U.S. Preventive Services Task Force Procedure Manual. Agency for Healthcare Research and Quality (AHRQ). AHRQ Publication No. 08-05118-EF. July 2008. www.ahrq.gov.

³²Ibid.

Search strategy

VATAP conducted multiple comprehensive literature searches from July 2007 to January 2009 on The Cochrane Library[®], MEDLINE[®], EMBASE[®], and Current Contents[®] electronic databases, via the Dialog OneSearch[®] feature, for systematic reviews, meta-analyses and primary studies published in English from 1990 to 2009, with the treatment searches focusing on the years 2000 to the present. VATAP also conducted complementary searches on PubMed[®] to retrieve additional citations plus related references from specific key on point articles. Searches were conducted repeatedly using differing strategies to exhaustively address the multidisciplinary nature of TBI rehabilitation for visual disorders: neuropsychological, visual, auditory, attentional, behavioral and perceptual.

The search terms addressed four concepts: **brain injury** (brain injuries, blast, head, explosion, concussion, trauma, closed-head, diffuse axonal injury, etc); **visual sequelae** (neuro-ophthalmology, neuro-optometry, neuro-psychology, auditory, multi-sensory, spatial integration, oculo-motor, ocular motility, visual, visual inattention, etc); and **treatment** (treat, therapy, rehabilitation, intervention, manage, counsel, care, nurture, progress, outcome, prognosis, quality of life; also included were terms for rehabilitative or therapeutic devices). Results were limited to **adults** only (adult, middle age, elderly). All terms were searched as descriptors (exploded when appropriate) from all the databases' thesauri. Free text terms as well as title words (from on point articles) were used to further enhance retrieval.

Other data sources

Following initial VATAP searches, in November 2007 the VA Journal of Rehabilitation Research and Development³³ published a special, single-topic issue on TBI and polytrauma. This issue examined the clinical characteristics of military personnel returning from combat and described several healthcare models providing diagnosis and treatment of TBI. VATAP hand searched the articles and their end references for studies meeting inclusion criteria.

Inclusion criteria

For examining effectiveness of treatment for visual problems associated with TBI, studies were included that met the following criteria:

- Adult subjects only;
- Controlled studies with the experimental group size >10;
- Primary clinical studies, health technology assessment or systematic review evaluating interventions used to treat visual problems after TBI;
- Largest or most comprehensive study from the same study group on the same objective to avoid redundancy;
- Closed head injury caused by blast or acceleration/deceleration type mechanisms of injury (stroke was excluded as a mechanism of injury, as were studies which lacked a clear description of mechanism of injury);
- Severity of TBI in the study population was clearly described (studies which lacked a clear description were excluded);
- Visual sequelae included either oculo-motor or visual perceptual problems.

³³ http://www.research.va.gov/news/features/JRRD_TBI.cfm

RESULTS

The searches retrieved more than 700 citations. Based on appraisal of title and abstract information in the searches, VATAP retrieved 92 articles that appeared relevant to the review. Of these, three met inclusion criteria for studies of treatment (see End References). A detailed data abstraction of included studies is presented in Table C in Appendix 1. A breakdown of included articles by injury severity and publication type is presented in the following table:

Table 7. Overview of included studies of treatment effectiveness

TBI Severity	Primary Study Types (number of studies)				Systematic Reviews / Meta-analyses
	Case series (Level 1)	Case-control (Level III)	Before-after with controls (Level IV)	Prospective Cohort (Level V)	
Mild injury	--	--	--	--	--
Moderate-severe injury	--	--	2	1	--

Mild TBI

No studies met the inclusion criteria for evaluating the effectiveness of visual rehabilitation interventions in persons with mild TBI.

Moderate to severe TBI

Using the Ibrahim hierarchy of study designs, two Level IV before-after with controls (Padula 1994; Schmitter-Edgecombe 2001) and one Level V prospective cohort study (Pavawalla 2006) met the inclusion criteria. For determining the strength of the association between a rehabilitation intervention and outcomes in persons with TBI-related visual problems, studies using a before-after with controls design provide highly suggestive evidence and prospective cohort studies provide moderately firm evidence.

The study objectives varied from studying the effects of refraction correction with and without prisms and bi-nasal occluders on ambient vision disturbances using visual evoked potentials (Padula 1994), to evaluating skill acquisition and automatic process training in severe closed head injury using a semantic-category visual search task (Schmitter-Edgecombe 2001), to retention of learned automatic cognitive processes in the same study population 5-months and 10-months post training (Pavawalla 2006). Schmitter-Edgecombe (2001) built on previous work in this area. Therefore only the most recent study was included in this review. Study sizes were small (N < 20 in each arm) and no power calculations were performed.

The majority of study subjects were males in their twenties and thirties. Causes of injury were motor vehicle accidents and falls. Schmitter-Edgecombe (2001) and Pavawalla (2006) recruited both TBI subjects with chronic injury and healthy volunteers from the community and matched controls for gender, age and educational level. Persons were excluded if they had a history of neurological disorders other than TBI, treatment for substance abuse, multiple head injuries, dementia, or if they had either reading impairment or motor impairment to their upper limbs that would affect their ability to perform training. Padula (1994) used hospital records to recruit TBI subjects and recruited healthy volunteers from hospital staff, but there were insufficient details reported to determine chronicity. Persons with measurable strabismus were excluded.

All authors noted that TBI subjects experienced greater visual deficits or cognitive deficits than controls, which may lead to an overestimation of the effect of the intervention on outcomes. Of the three, Schmitter-Edgecombe (2001) and Pavawalla (2006) minimized selection bias in their study design and analyses by analyzing the relative level of comparable skill learning and retention for each group and analyzing the effects of potential confounders.

As these studies were not randomized control trials, no randomization or intention to treat analysis was applied. Before-after designs allowed for the intervention to be applied to all subjects, with each subject serving as its own internal control, and the mean difference in objective outcome measures for each group was then compared. Therefore, blinding treatment allocation is less critical. Follow-up was complete in both Schmitter-Edgecombe (2001) and Padula (1994) studies. Pavawalla (2006) had nearly complete follow-up (94%) of the TBI subjects but only 56% of controls.

VATAP also appraised these studies using the USPSTF framework (Table 8). A summary of study findings is presented in Table 9; full study details are abstracted in Table C in Appendix 1.

Table 8. Appraisal of included studies using the USPSTF framework

Study	Research design	Internal validity	External validity	Level of certainty	Recommendation grade
Padula 1994	II-1	Poor	Poor	Low	I
Schmitter-Edgecombe 2001	II-1	Good	Good	Low	I
Pavawalla 2006	II-2	Fair	Fair	Low	I

Table 9. Summary of studies of rehabilitation interventions for visual perceptual disorders in moderate to severe TBI

Note: See Page iv for list of abbreviations

Study	Study Type Ibrahim/USPSTF	Size (N) Mod-severe TBI/Controls	Time since injury (mean)	Injury severity criteria	Intervention	Outcome Measures	Findings
Perceptual dysfunction							
Padula 1994	IV/II-1	10/10	NR	RLA Disability rating	Refraction correction with & without base in prisms + binasal occluders	<ul style="list-style-type: none"> • Mean amplitude of P1 using binocular VEP • Absolute latency 	The use of base in prisms and binasal occluders with refraction correction are an effective means to treat ambient vision disturbances resulting from post-traumatic vision syndrome caused by TBI
Schmitter-Edgecombe 2001	IV/II-1	18/18	Range 1-27 years; 83% > 2 yrs; 56% > 6 yrs	<ul style="list-style-type: none"> • Duration of coma > 48 hrs, • GCS ≤ 8, or • Subject or significant other reported coma duration > 48 hrs and PTA ≥ 14 days 	CM training VM training	Visual search rate	<ul style="list-style-type: none"> • In both study groups, visual search rate decreased with CM training but not VM training [$F(11,374) = 2.33, MSE = 2561.28, p < 0.009$] • Difference in visual search rate between study arms was greater for VM training (55 ms) than for CM training (31 ms) [$F(1,34) = 2.33, MSE = 29855.35, p < 0.06$]
Pavawalla 2006 (follow up to Schmitter-Edgecombe 2001)	V/III-2	17/10	Range 1-27 years; 83% > 2 yrs; 56% > 6 yrs	<ul style="list-style-type: none"> • Duration of coma > 48 hrs • GCS ≤ 8, or • Subject or significant other reported coma duration > 48 hrs & PTA ≥ 14 days 	CM training	Visual search rate	<ul style="list-style-type: none"> • Individuals with severe TBI were able to retain the learned skills over a long-term retention interval at a level comparable to controls • A statistically significant loss in stimulus-specific skills from 5-months to 10-months ($p < .01$); a trend noted in loss of task-specific skills from 5-months to 10-months ($p > .05$) • Passage of time is likely the most significant contributor

CONCLUSIONS

Findings from this review provide very limited evidence of effectiveness for rehabilitation of TBI-related visual dysfunction; at best the evidence is in its early stages of discovery. No studies met the inclusion criteria using populations with mild TBI. Only three small, preliminary studies of interventions used to treat chronic visual perceptual defects in moderate to severe TBI were included, two of which used the same study population. No studies met the inclusion criteria that evaluated treatment for oculo-motor dysfunction. Overall, studies were hampered by small sample sizes.

Selection bias was most evident in Padula (1994) but was mitigated by design and analysis in the other two studies. Padula (1994) provided the weakest evidence linking the effects of an intervention to outcome because of overall design and of insufficient reporting of critical study details. The investigators used too few subjects for multiple study objectives, namely, determining both the value of visual evoked potentials (VEPs) in identifying ambient visual disturbances and the effects of treatment. Establishing the diagnostic value of VEPs should be conducted using rigorous studies of diagnostic efficacy, and treatment intervention should be studied separately using appropriate experimental and control groups with TBI with randomized treatment allocation.

For the purpose of this review, Schmitter-Edgecombe (2001) and its follow up study (Pavawalla 2006) provided the strongest evidence for linking the effects of a rehabilitation intervention to outcome in persons with visual perceptual disorders related to TBI. The results of their study suggest that persons with severe TBI can acquire and use automatic cognitive processes to develop skill performance using semantic-category visual search tasks, and these skills can be maintained over time with retraining. Pavawalla (2006) noted that these findings, if validated in more rigorous studies, may have implications for the design of rehabilitation programs for TBI-related visual perceptual disorders:

“...breaking down complex cognitive skills and consistently training individuals on smaller components of the task in order to develop automatic cognitive process is a worthwhile strategy since such skills are likely to be retained over a long-term interval, perhaps more so with follow-up “booster” or retraining sessions.”

Given the low level of certainty in the results, there was insufficient evidence (USPSTF Grade I) to assess the net benefits of the interventions in this review, and if offered, patients should understand the uncertainty about the balance of benefits and harms of the interventions.

Of note, no interventions for treating homonymous hemianopia met inclusion criteria in this review. Homonymous hemianopia is a visual field deficit resulting from injury most commonly from stroke, tumors and TBI, and a range of rehabilitative interventions are used to address the significant functional impairment that may result. Results of a recent literature review of optical devices, compensatory training, and visual restoration therapy marketed by NovaVision (Boca Raton, FL) for treatment of homonymous hemianopia confirms the findings of this VATAP report:³⁴

³⁴Pelak VSDMWE. Homonymous hemianopia: A critical analysis of optical devices, compensatory training, and Nova vision. Current Treatment Options in Neurology 2007;9(1):41-7.

“In regard to compensatory training and optical devices, a standardized methodology is lacking, and very few controlled studies exist in regard to efficacy. Outcome data regarding effectiveness of VRT [visual restoration therapy] are conflicting, as are the opinions of investigators who have studied and reviewed VRT. There is some evidence that expansion of visual fields by VRT may be the result of very small eye movements. Functional outcomes for each strategy reveal subjective, but limited evidence or no objective evidence of functional improvement; therefore, it is difficult to recommend a specific treatment based on evidence for most patients. The decision to treat and the type of treatment to pursue for patients with HH [homonymous hemianopia] should be individualized and guided by the type of injury, associated deficits, available resources, and the level of functional impairment manifested by the HH.”

RECOMMENDATIONS FOR FUTURE RESEARCH

The preponderance of general and vision-specific rehabilitation literature in TBI in terms of overall size and research quality represents older adult populations with moderate to severe stroke. Far less rigorous evaluation has emerged in persons with diffuse TBI such as that seen in our newest Veteran population. Existing studies of diffuse TBI have examined moderate to severe injury, as corroborated by the results of this review. Given the escalating prevalence of Veterans with mild, diffuse TBI in VA, the absence of literature in this population must be addressed.

The limitations in the evidence for the effectiveness of TBI-related visual rehabilitation, including visual domains of cognitive rehabilitation, identified in this review are aligned with the limitations identified in the broader evidence base for studying the effectiveness of TBI rehabilitation. In general, all authors agree the limitations below should be addressed in future research.^{35,36,37,38,39}

- Insufficiently powered studies;
- Heterogeneity with respect to study subjects, pathologies, impairments, rehabilitative services and outcome measures;
- Inadequate reporting of information that would allow determination of effect sizes and the clinical significance of the statistical improvements associated with the intervention within a study and across studies;
- The use of the multidisciplinary model of care to optimize function and outcomes in rehabilitation, which makes it challenging to employ RCTs to study its effectiveness.

Other authors point to:

- The need to identify valid relationships between rehabilitative processes and patient outcomes in clinical practice.⁴⁰

³⁵Chua KSG, Ng Y-S, Yap SGM, Bok C-W. A brief review of traumatic brain injury rehabilitation. *Annals of the Academy of Medicine, Singapore* 2007;36(1):31-42.

³⁶Cullen N, Chundamala J, Bayley M, Jutai J. The efficacy of acquired brain injury rehabilitation. *Brain injury - BI* 2007;21(2):113-32.

³⁷Kennedy Mary RT, Coelho C, Turkstra L, et al. Intervention for executive functions after traumatic brain injury: a systematic review, meta-analysis and clinical recommendations. *Neuropsychological rehabilitation* 2008;18(3):257-99.

³⁸Cicerone KD, Dahlberg C, Malec JF, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. *Archives of physical medicine and rehabilitation* 2005;86(8):1681-92.

³⁹Pelak 2007.

⁴⁰Johnston MV, Wood KD, Fiedler R. Characteristics of effective and efficient rehabilitation programs. *Arch Phys Med Rehabil* 2003;84(3):410-8.

- The need to examine outcomes post-discharge from acute rehabilitation, including modifiable factors and treatment barriers that influence outcomes in the VA Polytrauma System of Care, which would align the research with the complex lifelong needs of Veterans with a spectrum of TBI.⁴¹
- The paucity of visual information reported in the cognitive rehabilitation literature for TBI populations.^{42,43}

Consequently, comparative studies are often lacking, and questions of how to achieve optimal cost-effectiveness across the continuum of rehabilitative care remain. For rehabilitation of TBI-related vision disorders, future studies that address these limitations will improve the internal and external validity of the evidence base substantially, as so little quality evidence currently exists.

Finally, there is a need for basic neuroscientific research to advance the understanding of TBI and identify optimal rehabilitation interventions for this population of Veterans. As Kleim eloquently states:⁴⁴

“Neuroscience research has yielded a great deal of information on the nature of experience-dependent brain plasticity, and there is reason for optimism that our understanding of this can be capitalized upon to improve functional outcome after brain damage. This work strongly supports the use of rehabilitative training as a tool to improve brain reorganization and functional outcome. However, many issues that are likely to be critical for optimizing rehabilitation remain poorly understood and require greater attention by neuroscientists. A better understanding is needed of how training experiences interact with neural reactions to brain damage, with self-taught compensatory behavioral changes, and with age, as well as how to combine rehabilitative training with other treatment approaches. Of particular importance is the need to understand time windows in which training can be optimally and safely applied. Translation of these findings to rehabilitative treatment will also normally require intermediate steps, including experimental research using human subjects and computational models. This may be especially true for disorders that are challenging to model in detail in animals, such as some cognitive and motor disorders of speech and language...Hopefully, the translational relevance of future research will be improved by greater interaction between basic and clinical researchers and a better awareness, on the part of the neuroscientists, of the problems faced by those in the clinical who are administering and receiving rehabilitation.”

⁴¹Sayer NA, Chiro CE, Sigford B, et al. Characteristics and Rehabilitation Outcomes Among Patients With Blast and Other Injuries Sustained During the Global War on Terror. *Archives of Physical Medicine and Rehabilitation* 2008;89(1):163-70.

⁴²Cullen 2007.

⁴³Kennedy 2008.

⁴⁴Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res* 2008;51(1):S225-39.

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APPENDIX 1. DATA ABSTRACTION OF INCLUDED STUDIES

Table A. Frequency of visual sequelae associated with diffuse mild TBI

Note: See Page iv for list of abbreviations

Study attributes	Malojic (2008)	Lew (2007)	Sosnoff (2007)	Kraus (2007)	Drew (2007)	Halterman (2006) (same study group as Drew 2007)
Study objective(s)	To study the effect of mild TBI on short-term or working memory, and attention	To report the clinical characteristics of the first 62 patients in the VA Palo Alto Polytrauma Network Site (PNS) outpatient clinic	To evaluate the effect of concussion on intraindividual variability in processing speed	To characterize oculo-motor function in chronic TBI across all severities versus healthy controls Data for mild TBI only Moderate to severe TBI (mod-severe TBI) reported in Table B.	To study the role of attentional disengagement in orienting visuospatial attention within a month following mild TBI	To study the presence of, rate and degree of recovery of visuospatial attention (alerting, orienting, and executive components) within a month following mild TBI
Study size	Cases=37 Controls=53	Cases=62	Cases=22 Controls=22	Cases=20 Controls=19	Cases=20 Controls=20	Cases=20 Controls=20
Perspective	Prospective	Retrospective	Retrospective	Prospective	Prospective	Prospective
Injury severity criteria	ACRM (1993)	Not specified, but determined through history of trauma with alteration of consciousness. Most subjects were regarded as having mild TBI	Physician diagnosed, details not specified	ACRM mild TBI: any period of LOC, acute PTA, any altered mental status during accident, or focal neurologic deficit that may be transient or not.	AAN Grade 2=AC > 15 min	AAN Grade 1=AC < 15 min Grade 2=AC > 15 min Grade 3=any LOC or prior TBI within 6 months
Recruitment source	<ul style="list-style-type: none"> Cases=127 patients and staff at the Zagreb Trauma Clinic Controls=63 volunteers 	Cases referred to Palo Alto PNS outpatient clinic from July 2006 to February 2007	Student athletes at two universities between 2001-2003	<ul style="list-style-type: none"> Cases=Tertiary hospital (Univ Ill Med Center) Controls=community 	University student athletes seen in athletic program or student health center identified by certified athletic trainers or attending MDs	University student athletes seen in athletic program or student health center identified by certified athletic trainers or attending MDs
Inclusion criteria	Diagnosed mild TBI	<ul style="list-style-type: none"> Scheduled and evaluated at the clinic, including screening for TBI or Directly referred from Nat'l Center for PTSD 	<ul style="list-style-type: none"> Cases= high risk for concussion with valid baseline neurocognitive assessment prior to competitive season Controls=123 subjects evaluated twice using CRI in 2005; 	<ul style="list-style-type: none"> Hx of closed head type TBI > 6 mo post injury 	Grade 1 or 2 mild TBI	Grade 1 or 2 mild TBI

Study attributes	Malojic (2008)	Lew (2007)	Sosnoff (2007)	Kraus (2007)	Drew (2007)	Halterman (2006) (same study group as Drew 2007)
Exclusion criteria	<ul style="list-style-type: none"> > 60 years old Self-reported or documented history of ETOH or drug abuse, functional headaches or peripheral nerve injury Diagnosed with DSM-IV (1994) criteria for cognitive, psychotic or mood disorders 	Not reported	Subjects with attention deficit disorder or other learning disabilities	<p>Cases:</p> <ul style="list-style-type: none"> Hx of psychiatric disorder before injury or substance abuse Current pending litigation Any neurologic or medical condition that could result in cognitive changes Current use of psychiatric meds or meds used for cognitive enhancement <p>Controls:</p> <ul style="list-style-type: none"> Hx of psychiatric illness or TBI, substance abuse or dependency, significant medical or neurologic illness associated with significant changes in the brain eg. Diabetes, seizures, stroke 	<ul style="list-style-type: none"> Grade 3 TBI based on a LOC for any period of time Previous mild TBI within the last 12 months 	<ul style="list-style-type: none"> Grade 3 TBI based on a LOC for any period of time Previous mild TBI within the last 6 month
Time since injury	Median= 45 days, range 6-155	Not reported	<ul style="list-style-type: none"> Cases: Median interval between baseline testing and injury=173.1 days (\pm 171.3; range=16-514 days) Controls: Median interval between 1st and 2nd CRI evaluation=44.8 days (\pm 1.8 days) 	<p>At least 6 months</p> <ul style="list-style-type: none"> mild TBI= Mean 65.20 mo (SEM 18.13) 	Mean interval=37 \pm 11.5 hrs, range 12-50 hrs	Mean interval= 37 \pm 11.5 hrs, range 12-50 hrs)
Characteristics of cases/controls	<ul style="list-style-type: none"> Causes of injury: not reported 23 males, 14 females Mean age (\pm1 SD)=31.3 yrs (11.2) Mean education level (\pm1 SD)=13.2 yrs (2.3) Mean MMSE (\pm1 SD)=28.3 (3.1) <p>Controls matched for age, gender, education level and MMSE</p>	<ul style="list-style-type: none"> Causes of injury: blast (79%); MVA (8%); blunt trauma (8%); penetrating head injury (3%); 1 no physical injury 59 males, 3 females 89% OEF/OIF returnees; 5% older vets; 6% no combat-related injuries LOC (50%); altered consciousness (31%) 	<ul style="list-style-type: none"> Causes of injury: not specified, likely sports-related 20 males, 2 females Mean age=19.8 yrs (\pm 2.2 yrs) 13 had 1-3 prior concussions <p>Controls=matched for age and gender</p>	<ul style="list-style-type: none"> Cause of TBI: MVA (57%), fall or blow to head (34%), sports (8%) Mild TBI mean age=33.75 (range 20-47 yrs) Mild TBI mean educ/employment level=16.05 (range 10-21 yrs) Mild TBI mean WTAR premorbid IQ=112.65 <p>Controls=statistically similar re age, No yrs of education and premorbid IQ</p>	<ul style="list-style-type: none"> Causes of injury: Fall (7), knee to head (4), helmet to helmet (4), blunt injury (2), head to head (2), bicycle accident (1) 12 males, 8 females Mean age: 21 \pm 1.74 years, range 18-24 years Education level: 16 \pm 1.65 years <p>Controls=matched for age, gender, activity level, and educational level</p>	<ul style="list-style-type: none"> Causes of injury: Fall (7), knee to head (4), helmet to helmet (4), blunt injury (2), head to head (2), bicycle accident (1) 12 males, 8 females Mean age: 21 \pm 1.74 years, range 18-24 years Education level: 16 \pm 1.65 years <p>Controls=matched for age, gender, activity level, and educational level</p>
Outcome measures	<ul style="list-style-type: none"> Sustained visual attention RT and accuracy on Sternberg Memory Scanning Paradigm (STM) 	Self reported symptoms of post concussion symptoms and pain	Baseline Headminder Concussion Resolution Index (CRI) consisting of 6 subtests: simple response time (SRT), cued RT (CuRT), 2	<ul style="list-style-type: none"> Visually guided saccade (VGS) latency (time taken to initiate a saccade), velocity, and gain Antisaccade (AS) tasks= 	Saccadic reaction time (RT) and gap duration using the gap saccade task	Median reaction times (RTs) and response accuracy using Attentional Network Test (ANT)

Study attributes	Malojcic (2008)	Lew (2007)	Sosnoff (2007)	Kraus (2007)	Drew (2007)	Halterman (2006) (same study group as Drew 2007)
	<ul style="list-style-type: none"> Decision RT= Choice RT- Simple RT 		visual recognition tasks (VR1, VR2), animal decoding, symbol scanning (SS)	prosaccade error rate (# times subject looks at the target instead of opposite direction as instructed), latency <ul style="list-style-type: none"> Neuropsychological testing battery 		
Results (only vision-related reported)	<ul style="list-style-type: none"> Sustained visual attention: mild TBI subjects had longer RT than controls $F(1,68)=4.2$, $p=0.045$ at delay intervals > 60 sec ($p<0.05$). STM scanning: mild TBI individuals had slower search times compared with controls $F(1,86)=10.8$, $p=0.001$. Results suggest that either motor response or central cognitive processes, and not search speed, is responsible for the cognitive deficit observed among mild TBI subjects Decision RT: mild TBI group was on average 26% slower at making simple perceptual decisions than controls $F(1,87)=2.987$, $p=0.087$. (NS but trends toward). 	<ul style="list-style-type: none"> Most prevalent symptom=pain: 71% headache; 32% eye pain Frequency of neuropsychological dx: 71% PTSD; 55% cognitive disorders; 42% both Frequency of visual dysfunction: <ul style="list-style-type: none"> Majority showed normal or near normal corrected visual acuity and visual fields 75% with self-reported vision problems, including photosensitivity (59%) 84% with self-reported reading difficulties, 70% of which began after TBI 70% with oculo-motor problems: 46% convergence dysfunction; 25% pursuit or saccadic dysfunction; 21% accommodation dysfunction; 11% strabismus; 5% fixation dysfunction or nystagmus 	At $p<.05$: <ul style="list-style-type: none"> Concussed individuals had increased RTs across all tasks and were less accurate than controls in the CuRT. RT variability for all tasks was elevated in concussed individuals, but controlling for mean RT at follow-up eliminated group differences. Increases in RT variability in concussed individuals are proportional to processing-time increases. Therefore, RT variability is not a unique identifier of cognitive dysfunction following concussion. Results suggest that transient brain injury and chronic brain injury have significantly different neurobiological consequences. 	<ul style="list-style-type: none"> VGS task: mild TBI showed no significant impairment of attentional or sensorimotor function compared with controls AS task: mild TBI had more prosaccade errors than controls [gap: $F(1,38)=4.84$, $P=0.034$; overlap $F(1,38)=5.15$, $P=0.029$] AS latencies: prosaccade response latencies were increased in mild TBI group compared with controls [$F(1,38)=6.95$, $P=0.012$] On neuropsych testing, mild TBI group showed no significant impairment compared to controls Other findings: <ul style="list-style-type: none"> ROC analysis showed that prosaccade error rates were more sensitive and specific than executive domain score for differentiating mild TBI from controls, whereas the opposite was true for differentiating mild TBI from MOD-SEVERETBI cases. Results suggest that neuropsychological testing has greater clinical utility in detecting and scaling TBI severity and oculo-motor testing has greater clinical utility in characterizing neurobehavioral deficits in mild TBI cases. 	<ul style="list-style-type: none"> Both mild TBI and controls exhibited a gap effect across all testing sessions consistent with previous studies. Mild TBI group had significantly longer saccadic RT than controls at shorter gap durations (0-100 ms) but not at longer durations (> 100 - ≤ 300 ms) ($F[6,228] = 2.824$, $p=0.32$). This difference was present at 2 days post injury and resolved within 1 week. 	<ul style="list-style-type: none"> Overall, mild TBI cases had significantly slower RT than controls (group effect: [$F(1,7) = 12.4$, $P=0.001$]) Mild TBI significantly affected executive component compared with controls (group effect [$F(1,7) = 18.7$, $P=0.001$]; day effect [$F(3,7) = 5.6$, $P=0.001$]) Mild TBI significantly affected the orienting component within the first week post injury but the effect recovered during the month of testing post injury (group effect [$F(1,7) = 6.8$, $P=0.01$]; day effect NS; group and day effect [$F(3,7) = 3.97$, $P=0.009$]. mild TBI did not affect the alerting component of attention The RT cost to generate accurate vs. inaccurate responses was significantly > in mild TBI subjects than in controls (group effect [$F(1,7) = 12.91$, $P=0.0001$], and this difference was maintained throughout the 1 month testing period (group and day effect NS).

Study attributes	Malojcic (2008)	Lew (2007)	Sosnoff (2007)	Kraus (2007)	Drew (2007)	Haltermann (2006) (same study group as Drew 2007)
<p>Author's conclusions</p>	<p>"...our results support several premises. The first is that individuals who have suffered mild TBI may still show symptoms more than a month and a half post-injury. A second conclusion is that complaints of cognitive deficit following mild TBI, while not often supported by standard imaging or neuropsychological exams, represent real cognitive deficits although standardized neuropsychological assessment tools may not be sensitive enough to detect these deficits. Finally, our data suggest that the nature of these deficits lies almost wholly in controlled cognitive processes, which indicates that some central measure of resource or decision making is being disrupted in individuals who experience residual cognitive deficits resulting from mild brain trauma."</p>	<p>"These data indicate a very high prevalence of vision-related problems in this post-combat population. These problems could result from brain concussion and/or peripheral optical injuries, and further research to identify causative factors is warranted."</p>	<p>"The current investigation demonstrated that the transient neurological dysfunction induced by exogenous impacts resulting in concussion is responsible for increases in mean RT but not for elevated intraindividual cognitive variability (i.e. RT SD). This observation supports the proposition that the mean RT and RT variability are independent neurocognitive mechanisms (MacDonald et al., 2006). Although evidence suggests that alterations in the attentional network are contributing to increases in mean RT following injury (Haltermann et al., 2006), further investigations using more sophisticated evaluative measures are needed to identify these networks."</p>	<p>"...The mild TBI group showed impaired performance primarily on the AS task, consistent with prefrontal system dysfunction. Hence, oculo-motor testing is sensitive to the range of neuropathology in chronic TBI, and importantly, may be more sensitive to neuropathology in mild TBI."</p> <p>In summary, this study places chronic mild severity TBI cases in the middle of the functional spectrum between health controls with no history of TBI and subjects with moderate to severe chronic injuries, in terms of certain aspects of oculo-motor function that may be particularly sensitive to the effects of trauma. AS task performance seems to be sensitive to more selective and subtle prefrontal effects of mild TBI in ways that standard neuropsychologic and sensorimotor testing are not. Although the neuropsychologic testing did not clearly identify deficits in the mild TBI group, it was effective at discriminating functional neurobehavioral impairments in the moderate and severe injury group."</p>	<p>"In conclusion, we have demonstrated that individuals with mild TBI present with deficits with the disengagement process of attentional orienting. This implies that the cortical and subcortical locations involved in the disengagement process are vulnerable to mild TBI. This information could be of particular value to researchers investigating the decreased attentional capabilities following this form of brain injury."</p>	<p>"These findings indicate that the regions of the brain associated with the orienting and executive components of visuospatial attention may be most susceptible to neural damage resulting from mild TBI. Moreover, the lack of recovery in the executive component indicates that the degree and time course for recovery may be regionally specific."</p>

Table A (continued). Frequency of visual sequelae associated with diffuse mild TBI

Note: See Page iv for list of abbreviations

Study attributes	Kraus (2005)	Heitger (2006)	Mathias (2004)	Chuah (2004)	Bohnen (1992)
Study objective(s)	To derive and compare frequencies of self reported symptoms, medical service use, and social and employment changes in patients with mild TBI vs. matched controls	<ul style="list-style-type: none"> To study the incidence of eye and visuomotor arm movement one year post mild TBI (Note: only oculo-motor results reported)	To examine cognitive performance following mild TBI, specifically functions mediated by those areas of the brain susceptible to diffuse damage following TBI	To investigate the long-term effects of mild TBI on visual, spatial and visual-spatial short-term memory in well-functioning university students	<ul style="list-style-type: none"> To study the extent to which patients recover from visual and acoustic hyperaesthesia after mild TBI To study whether visual or acoustic hyperaesthesia is related to a particular pattern of post-traumatic behavioral dysfunction
Study size	Case cohort=235 Control cohort=235 Study size based on power calculations	Cases=37 Controls=37	Cases=40 Controls=40	Cases=16 Controls=16	Cases=43 Controls=43
Perspective	Prospective	Likely prospective	Prospective	Retrospective	Prospective
Injury severity criteria for mild TBI	<ul style="list-style-type: none"> Evidence of a blow to or impact on the head, including acceleration/deceleration exposures GCS score 13-15 Confusion or disorientation or observed or reported LOC < 30 min or PTA < 24 hours 	<ul style="list-style-type: none"> GCS 13-15 (main criterion) PTA estimated < 24 hours 	<ul style="list-style-type: none"> GCS 13-15 LOC ≤ 20 min 	LOC < 30 min or disorientation	<ul style="list-style-type: none"> LOC several sec to 15 min PTA < 60 min, and EMV score on admission = 15
Recruitment source	Persons screened at the ER or Level-2 trauma center within 72 hours of admission to an urban area of San Diego County, CA from June 2000-December 2003	Cases=Ambulance records of persons presenting with acute head injury to a tertiary hospital Controls=volunteer database from Dept. of Psychology at tertiary hospital or family or friends of injured	Cases= ER admissions of a major hospital evaluated initially by ambulance paramedics Controls=general community (friends of cases group and members of community groups)Initially attended to by ambulance paramedics	<ul style="list-style-type: none"> 482 university students in a first year psychology class Cases and controls randomly selected, blinded to study objective 	<ul style="list-style-type: none"> Cases=71 patients from a population of consecutively admitted patients with mild TBI to university hospital Controls=healthy volunteers
Inclusion criteria	Cases: <ul style="list-style-type: none"> Age 18-60 Physician-diagnosed mild TBI Understands English or Spanish Controls: <ul style="list-style-type: none"> Physician-diagnosed AIS level 1,2 or 3 non-head injuries 	Cases=diagnosed with mild TBI Controls=no history of any TBI	Cases: <ul style="list-style-type: none"> Age 18-60 Diagnosed with mild TBI from MVA, assault, fall or blow to the head Initially attended by ambulance paramedics Controls= No hx of head injury or LOC	Cases=self-reported head injury involving any LOC or altered consciousness within the preceding 6 years Controls=no self-reported head injury	Cases= mild TBI who were not excluded based on criteria below Controls=healthy volunteers

Study attributes	Kraus (2005)	Heitger (2006)	Mathias (2004)	Chuah (2004)	Bohnen (1992)
Exclusion criteria	<ul style="list-style-type: none"> • AIS score ≥ 4 to any body region • Patients requiring invasive neurosurgical procedures • Patients with hypoxia induced mild TBI • Patients who were under arrest 	<ul style="list-style-type: none"> • History of ETOH, psychoactive drug use, drug abuse, CNS disorders, psychiatric conditions, any brain injury with persisting symptoms or complaints • Structural brain damage or hematoma on CT • Oculo-motor or somatomotor deficits on clinical exam • Presence of strabismus, visual acuity $\leq 6/12$ • Skull fractures 	<ul style="list-style-type: none"> • History of neurological or psychiatric problems • English is second language • Physical problems that would prevent them from completing the RT tasks 	<p>Recreational drug use or medicine, neurological or psychiatric illness that could adversely impact memory functioning</p>	<ul style="list-style-type: none"> • Evidence of focal neurological deficit or skull fracture • ETOH abuse at time of the injury • Concomitant orthopedic injury • Previous head injury • History of emotional, visual or hearing problems • Loss to follow up
Time since injury	< 72 hours p/t admission	<ul style="list-style-type: none"> • Within 1 week of injury, at 3 mo, 6 mo, 12 mo post-injury • Controls measured simultaneously 	4 weeks post injury (Mean=26.3 days, SD=6.1)	<ul style="list-style-type: none"> • ≤ 6 yrs • Mean= 2.64 yrs (SD=1.86 yrs, range = 6 mo-6 yrs) 	10 days and five weeks post injury
Characteristics of cases/controls	<ul style="list-style-type: none"> • Causes of injury: MVA (70%), fall (17%), blunt object (7%), assault (6%) • 150 males, 80 females • Ages 18-25 75/235 (32%) • Ages 26-34 53/235 (23%) • Ages 35-49 80/235 (34%) • Ages 50-60 27/235 (12%) • LOC < 30 min=113/235 (48%) • Hx of concussion (40%) • Hx of neurological problems (11%) • Current sleeping problems (36%) <p>Controls matched for age and gender</p>	<ul style="list-style-type: none"> • Causes of injury not reported • 24 male, 13 female • Mean age=22.2 \pm 7.1 yrs • Mean educ level = 13.6 \pm SD2.56 yrs, range 8=19 yrs • Mean PTA=160 min, range 2 min-22 hours • 32/37 with confirmed LOC mean = 3.96 min, range 0.5-15 min); • All employed or in school, none involved in litigation <p>Controls matched for age, gender and education level; equivalent IQ reported</p>	<ul style="list-style-type: none"> • Causes of injury: MVA, assault, fall or accident involving blow to the head (% not reported) • 32 males, 8 females • Mean age=32.4 yrs, range 18-60, SD 12.7 • Mean education level=12.4 yrs SD 2.3 • Mean GCS=14.7, SD=5.3 • LOC: 5(13%) >5 min but < 20 min, 9(23%) 1-5 min, 18 (44%) < 1 min, 8(20%) no LOC • Premorbid IQ= mean 102.5 (SD 10.5) • 17 (43%) hospitalized • CT=12, MRI=2 negative scans • 11(28%) considering litigation • Impact of Events Scale scores=mean 22.8, SD 16.7 indicating mild levels of injury-induced psychological distress <p>Controls were matched for age, ETOH use, years of education, and estimated premorbid IQ</p>	<ul style="list-style-type: none"> • Causes of injury: sports-related (37%); MVA (25%); unexpected accidents falls or blow to head (25%); fight-related (13%) • 7 males, 9 females • Mean age=19.31 yrs, range 17-26, SD=2.89 • LOC < 30min (68%) • 31% with extended period of disorientation (mean=6.15 hrs) • 18% hospitalized due to injury <p>Controls were similar for age, gender, for premorbid intellect, total score on post concussion syndrome checklist, and ETOH intake</p>	<p>Data available for 46 original subjects, 3 were eventually excluded for failure to follow up:</p> <ul style="list-style-type: none"> • 23 males, 23 females • Mean age 28.3 (\pm 14.9) years <p>Controls matched for age and gender, but gender breakdown not reported</p>
Outcome measures	Self-reported physical complaints and social and employment changes	Reflexive saccades, antisaccades, sequences of memory-guided saccades, self-paced saccades, and smooth pursuit using a computerized IRIS infrared limbus tracker (Skalar Medical, BV, The Netherlands), Rivermead Post-Concussion Symptoms Questionnaire,	<ul style="list-style-type: none"> • Attention (TEA) • Memory (RAVLT) • Visual and tactile RT • Fluency (COWA, RFFT) • Premorbid IQ (NART) • Injury-related Stress (IES) 	Memory span tasks (visual, spatial and visual-spatial)	<ul style="list-style-type: none"> • PCS checklist • Light stimuli (up to 95dB) • Sound stimuli (up to 1500 llux) • Behavioral rating scales for post-concussive, cognitive, emotional and psychovegetative complaints

Study attributes	Kraus (2005)	Heitger (2006)	Mathias (2004)	Chuah (2004)	Bohnen (1992)
		neuropsychological testing			
Results (only vision-related results reported)	<p>Statistically significant common symptoms, reported as frequencies (%) mild TBI vs. Control, adjusted RR* (90% CI):</p> <ul style="list-style-type: none"> • Blurred vision: 54/235 (23%) vs. 33/235 (14%), RR 1.50 (1.07-2.11) • Double vision: 23/235 (9.8%) vs. 12/235 (5.1%), RR 1.81 (1.02-3.21) • More headaches: 85/235 (36%) vs. 64/235 (27%), RR 1.31 (1.04-1.64) • Dizziness: 54/235 (23%) vs. 33/235 (14%), RR 1.50 (1.16-1.94) • Memory problems: 95/235 (40%) vs. 59/235 (25%), RR 1.52 (1.21-1.91) • Learning problems: 40/235 (17%) vs. 26/235 (11%), RR 1.52 (1.03-2.25) <p>*adjusted for history of concussion, neurological problems, ETOH use, and ISS at baseline</p> <p>Additional findings:</p> <ul style="list-style-type: none"> • 82.6% of mild TBI cohort had \geq one symptom during the 6 months after their injuries • no specific or consistent pattern was observed in their occurrence 	<p>At $p < 0.05$</p> <ul style="list-style-type: none"> • the CHI (closed head injury) group reported elevated levels of post-concussive symptoms up to 12 mo post injury • At week one, the CHI group exhibited prolonged saccadic latencies, increased directional errors, decreased saccade accuracy and impaired fast sinusoidal smooth pursuit concomitant with increased arm movement reaction time, decreased arm movement speed and decreased motor accuracy on upper-limb visuomotor tracking tasks, and neuropsychological deficits in verbal learning and speed of processing. • At 3 and 6 months, the CHI continued to show deficits on several oculomotor and upper-limb visuomotor measures in combination with some improvement in verbal learning • At 12 months, the CHI group had no cognitive impairment but residual deficits in eye and arm motor function 	<ul style="list-style-type: none"> • Mild TBI group demonstrated deficits in attention ($p < 0.05$), non-verbal fluency ($p < 0.01$), and verbal memory (immediate and delayed recall) ($p < 0.01$) vs. controls. • Mild TBI group demonstrated slower visual RT ($p < 0.05$) and tactile RT tasks ($p < 0.01$ and $p < 0.05$) vs. controls. • Visual RTs of mild TBI patients were affected more by increased task difficulty and tasks requiring inter-hemispheric transfer of information vs. controls. • Accuracy was not adversely affected in mild TBI group. 	<ul style="list-style-type: none"> • MHI participants were impaired on spatial memory ($p = .01$) vs. controls, but no statistically significant differences between cases and controls were noted on visual span or visual-spatial span suggesting that tasks of spatial STM may be more sensitive, compared to tasks of visual STM, to the subtle long-term cognitive changes that may be present after a MHI. • Subsidiary analyses suggested that performance levels and differences in the ranges of scores were unlikely to explain the lower spatial span scores between groups. 	<ul style="list-style-type: none"> • 17/43 mild TBI patients had reduced tolerance to sound at 10 days and 11/43 at 5 weeks. • 18/43 mild TBI patients had reduced tolerance to light at 10 days and 10/43 at 5 weeks. • At 10 days, mild TBI patients had a significantly lower tolerance for both sound ($p < .01$) and light ($p < .0001$) than controls. • At five weeks, patients with PCS (N=31) had a significantly lower tolerance for both sound ($p < .01$) and light ($p < .05$) than controls. • Reduced tolerance to light was significantly correlated with post-concussive cognitive complaints ($R_s = 0.36$, $p < 0.05$) but not with emotional/ vegetative complaints.

Study attributes	Kraus (2005)	Heitger (2006)	Mathias (2004)	Chuah (2004)	Bohnen (1992)
<p>Author's conclusion</p>	<p>"Although our findings demonstrate that persons experiencing mild TBI and other injuries of comparable severity can have similar symptoms, a greater incidence of certain neurological symptoms exists following mild TBI. These findings suggest the need for diagnostically directed postinjury medical management for this patient population."</p>	<p>"The findings indicate that multiple motor systems are measurably impaired up to 12 months following mild CHI and that instrumented motor assessment may provide sensitive and objective markers of cerebral dysfunction during recovery from mild head trauma independent of neuropsychological assessment and patient self-report."</p> <p>Further research is needed to verify.</p>	<p>"...the present study suggests that in the early stages after a mild TBI, patients experienced problems with selective attention (speed and accuracy), non-verbal fluency, the initial learning and free recall of verbal information, the speed with which they were able to process visual and tactile, information, and with visual tasks requiring the inter-hemispheric transfer of information. These deficits...are consistent with what would be expected to occur as a result of disruptions to integrated white matter pathways. In addition, deficits in the visual RT tasks requiring the inter-hemispheric transfer of information may reflect damage or disruption to callosal pathways."</p>	<p>"...this study demonstrated that spatial STM tasks may be more sensitive, compared to visual STM tasks, to the subtle long-term cognitive deficits related to a MHI. However, the results are preliminary, and replication of the effects with larger samples is necessary before generalizations can be made."</p> <p>"...the neurological mechanisms underlying the relationship between MHI and spatial STM remain unclear and further research investigating possible mechanisms (eg. Dopaminergic imbalance) may be fruitful."</p> <p>Study limitations include: effect of verbal rehearsal strategies, modest sample size, retrospective design which prevents exploring the possible causal role of spatial STM impairment in the head injury</p>	<p>"Assessment of visual and acoustic hyperaesthesia can be used as an objective measure of MHI...Patients who still complained of persisting PCS tolerated the intense light and sound stimuli less well than those patients who had no PCS..."</p> <p>"Analysis of data obtained with two behavioural rating scales (one with post-concussive/cognitive complaints and a second with emotional/vegetative complaints) indicated that visual hyperaesthesia was specifically related to the post-concussive/cognitive complaints scale."</p> <p>Further study is needed to determine if recovery from PCS is best assessed using visual hyperaesthesia or acoustic hyperaesthesia parameters.</p>

Table B. Frequency of visual sequelae associated with moderate to severe TBI

Note: table includes published articles not reviewed in Mathias 2007 meta-analysis

Note: See Page iv for list of abbreviations

Study attributes	Battistone 2008	Goodrich (2007)	Kraus (2007)	McKenna (2006)	Summers 2006
Study objective(s)	To test competing explanations for slowed processing speed due to moderate to severe TBI: 1) fixed limited capacity due to the diffuse nature of the neurologic injury vs. 2) volition changes to executive skills involved in performance monitoring and self-regulation	To assess visual function in VA patients experiencing deployment-related polytrauma	To characterize oculo-motor function in chronic TBI across all severities using visually guided saccade (VGS) and antisaccade (AS) tasks and neuropsychological testing Only moderate/severe TBI (mod-severe TBI) reported Mild TBI (mild TBI) reported in Table A.	<ul style="list-style-type: none"> To compare the frequency of visual perceptual impairment in patients with severe TBI to a normative sample using the OT-APST To evaluate the relationship between cognitive, memory and functional status and length of PTA vs. presence of visual perceptual impairments in patients with severe TBI 	To study the role of selective attention and visual perception in mediating inattentive blindness in individuals with very severe TBI
Study size	N= 20 cases* N= 20 controls* *3 eliminated from analysis due to SAT performance data that could not be accurately modeled	Cases=50	Cases=17 Controls=19	Cases=31 Normative sample=195	Cases=10 Controls=10
Perspective	Prospective	Retrospective	Prospective	Retrospective? Historical cohort	Retrospective
Injury severity criteria	<ul style="list-style-type: none"> PTA from 1-28 days Any LOC At least 1 year post injury 	Not reported	Amer Congress of Rehab Medicine <ul style="list-style-type: none"> mod-severe TBI: GCS < 13 +/-0 LOC > 30 min. 	Based on length of PTA: <ul style="list-style-type: none"> Mean PTA=61 days (range 11-204 days, SD 45.9) 	<ul style="list-style-type: none"> Severe= 1-7 days Very severe= 1-4 wks duration Extremely severe= > 4 wks Verified by ambulance/hospital records
Recruitment source	Cases= not reported Controls=university undergraduates	<ul style="list-style-type: none"> All inpatient admissions to VA Palo Alto Polytrauma Rehab Center (PRC) between December 2004 and November 2006 N=71 	Cases=Tertiary hospital (Univ Ill Med Center) Controls=community	Cases=Convenience sample from the Brain Injury Rehab Unit of a large public hospital in Brisbane Australia between September 2003-March 2004 Normative sample =Normative convenience sample of healthy subjects collected between July 2002-March 2004	Cases=local Head Injury Support groups, referrals from clinicians, clients of the investigator Controls=University of Tasmania and general community
Inclusion criteria	Cases=not reported Controls=approximately matched with respect to verbal and reasoning ability scores	<ul style="list-style-type: none"> Seen by the Optometry Polytrauma Inpatient Clinic (OPTIC) with or without visual complaints Did <u>not</u> include history of TBI Scheduled or completed visual exam Referred during start-up phase of clinic 	<ul style="list-style-type: none"> Hx of closed head type TBI > 6 mo post injury 	Cases: <ul style="list-style-type: none"> Age >15 years Dx with TBI and emerged from PTA Consented Proficient in English to provide informed consent, understand and complete test or have interpreter 	<ul style="list-style-type: none"> Sustained injury as a result of a MVA or MCA PTA ≥ 1 day ≥ 2 years post injury Controls matched for age and educational level

Study attributes	Battistone 2008	Goodrich (2007)	Kraus (2007)	McKenna (2006)	Summers 2006
		<ul style="list-style-type: none"> • Able to respond to exam 		<p>available</p> <ul style="list-style-type: none"> • Be able to hold a pen • Medically stable • Identified by occupational therapist as suitable to take OT-APST • Available on research days. <p>Normative sample:</p> <ul style="list-style-type: none"> • Ages 16-68 • Good health • Able to read and understand English • Able to give informed consent 	
Exclusion criteria	<ul style="list-style-type: none"> • Obvious visual or motor deficits • Seizure disorders • Reported history of learning disabilities or attentional difficulties pre injury 	N/A	<p>Cases:</p> <ul style="list-style-type: none"> • Hx of psychiatric disorder before injury or substance abuse • Current pending litigation • Any neurologic or medical condition that could result in cognitive changes • Current use of psychiatric meds or meds used for cognitive enhancement <p>Controls:</p> <ul style="list-style-type: none"> • Hx of psychiatric illness or TBI, substance abuse or dependency, significant medical or neurologic illness associated with significant changes in the brain eg. Diabetes, seizures, stroke 	<p>Cases:</p> <ul style="list-style-type: none"> • Severely impaired bilateral hand function visual impairment affecting functional reading ability; • Receptive aphasia; • Hx of psychiatric illness, intellectual disability, previous ABI, substance abuse; • Diminished level of alertness or consciousness impeding the assessment process; • Memory or cognitive deficits unrelated to TBI. <p>Normative sample:</p> <ul style="list-style-type: none"> • History of any neurological condition resulting in visual perceptual impairments, a visual impairment interfering with functional reading or an auditory comprehension impairment 	<ul style="list-style-type: none"> • Loss of vision • Hemiparesis • Significant motor control deficit • Significant visual impairment not corrected to normal bilateral vision with corrective lenses • History of any neurological condition including previous head injury (Controls only)
Time since injury	Not reported	Not reported	<ul style="list-style-type: none"> • At least 6 months • Mean= 107.12 mo (SEM 22.04) 	Mean=106.8 days (range 21-440, SD 96.5)	Mean= 52.90 months (range 24-112; SD 29.05)
Characteristics of cases/controls	<p>Cases</p> <ul style="list-style-type: none"> • 14 males, 6 females • Mean age=30.2 yrs (SD=7.75) • Moderate to severe TBI <p>Controls</p> <ul style="list-style-type: none"> • 5 males, 15 females • Mean age=24.2 (SD=7.62) 	<ul style="list-style-type: none"> • Cause of TBI: blast (50%); MVA (26%); assault (8%); falls (8%); gunshot +/- shrapnel (4%); anoxia (4%) • 45/50 (90%) male • Mean age=28.1 yrs (median 26 yrs, range 19-56 yrs) • 100% experienced a TBI • 59% occurred in combat • 44% of penetrating injuries caused by 	<p>Cases</p> <ul style="list-style-type: none"> • Cause of TBI: MVA (57%), fall or blow to head (34%), sports (8%) • Mean age=33.82 (range 22-51 yrs) • Mean educ/employment level=15.12 (range 8-20 yrs) • Mean WTAR premorbid IQ=103.59 (lower than controls ($P<0.01$)) • Ave. LOC=549 hrs (range 4-2880 hrs) 	<p>Cases</p> <ul style="list-style-type: none"> • Cause of TBI=MVA or MCA (48.4%) • 84% Male • Mean age=29.0 yrs (range 18-68 yrs; SD 12.5) • Education level \leq 10 years=35.5% • Employment type: Laborer 39%; tradesperson 19.4% • 98% with CHI • LOS in Rehab=76 days (range 23- 	<p>Cases:</p> <ul style="list-style-type: none"> • Cause of TBI=MVA or MCA (100%) • 70% male • Mean age=38.60 (range=22-58, SD=14.19) years • Mean education=10.50 (range=9-13, SD=1.27) years • Mean duration since accident= 52.90 (range=24-112, SD=20.05) months • Mean GCS on admission= 4.63

Study attributes	Battistone 2008	Goodrich (2007)	Kraus (2007)	McKenna (2006)	Summers 2006
		blast	Controls <ul style="list-style-type: none"> Higher premorbid IQ ($P<0.01$) and no yrs of education ($P<0.05$) than mod-severe TBI group 	225 days, SD 61.2) <ul style="list-style-type: none"> Mean Initial GCS=6.7 (3-14) Normative sample: <ul style="list-style-type: none"> Mean age=49.6 yrs (range 16-68; SD 12.5) 53% Male Education level ≤ 10 years=44.1% Employment type: clerical/sales 34.9%; professional 26.2% MMSE score=28.8 (24-30; SD 1.4) 	(range=3-8 with 2 unknowns, SD=2.26) <ul style="list-style-type: none"> PTA duration= 72.00 (range=14-210, SD=57.52) days 9 right-hand dominant, 1 left hand dominant Controls <ul style="list-style-type: none"> 40% males Matched for age and educational level 7 right-hand dominant, 3 left hand dominant
Outcome measures	<ul style="list-style-type: none"> Speed-accuracy trade-off methodology (SAT) to study the relationship between processing time and response accuracy the Peabody Picture Vocabulary Test-III (PPVT_III) to assess group differences in receptive verbal abilities Number Comparison Test (NCT) to assess simple perceptual speed Matrix Reasoning subtest from the Wechsler Adult Intelligence Scale-3rd ed. (WAIS-III) 	<ul style="list-style-type: none"> Self-report questionnaire re vision status before and after injury Visual acuity, visual fields, plus reading ability, comprehension, accommodation, convergence, fixation/nystagmus, saccades, extraocular muscle range of motion and quality between eyes, visual perception and spatial ability, color vision, cranial nerve status 	<ul style="list-style-type: none"> VGS latency (time taken to initiate a saccade), velocity, and gain AS= prosaccade error rate (# times subject looks at the target instead of opposite direction as instructed), latency Neuropsychological testing battery 	Cases: <ul style="list-style-type: none"> OT-APST FIM BRISC RBMT Normative sample: <ul style="list-style-type: none"> MMSE 	<ul style="list-style-type: none"> Focused attention (Stroop test) Divided attention (Trail Making Test-TMT Parts A and B, TMT Ratio score (B-A)/A) Visual perception (selected subtests of the Visual Object and Space Perception Battery (VOSP)-Incomplete Letters subtest and Object Decision subtest) Two tasks of inattention blindness (luminance and basketball tasks).
Results	Significant results reported <ul style="list-style-type: none"> TBI group was slower on information accrual across NCT, PPVT and Matrix reasoning measures; largest difference on perceptual speed [NCT: TBI (Mean 15.93, SD 4.09) vs. Control (Mean 15.93, SD 4.09)] (supporting a fixed limit explanation) The TBI group showed slower response speeds ($M= .49$ responses/sec, $SD=.19$) vs. controls ($M=.81$ responses/sec, $SD=.13$), $F(1,38)=39.28$, $MSe=.026$, $\eta^2 = .51$) Differences in cognitive ability across groups could not account for performance differences in SAT tasks, but when early responding was allowed both groups chose to hold off responding despite being no more 	<ul style="list-style-type: none"> 74% had vision complaints, with one or more of: blurred distance vision, light sensitivity, missing part of their vision, bumping into objects, blurred near-reading vision, inability to comfortably read continuous text. 64% had a refractive error that required correction (probably unrelated to injury) Majority had normal or near normal visual fields; ~24% with visual field deficits 38% sustained vision loss ranging from moderate to total blindness from visual acuity, visual field loss, and/or bilateral enucleation Patients whose injury resulted in a visual impairment were more likely to have damage to the eye, orbit and/or 	<ul style="list-style-type: none"> VGS task: In the gap condition saccade gain was greater in mod-severe TBI group v. controls [$F(1,35)=5.79$, $P=0.022$] (Saccade gain indicates the extent to which the eye movement either overshot or undershot the target). AS task: in the overlap condition, controls committed fewer prosaccade errors than mod-severe TBI group [$F(1,35)=8.97$, $P=0.005$] mod-severe TBI was significantly impaired compared to controls and mild TBI on a 3 neuropsychological domain scores mod-severe TBI showed significant impairment of attentional and sensorimotor function, specifically having greater difficulty disengaging 	Statistically significant differences between cases and normals for: <ul style="list-style-type: none"> Age ($t(224)=7.7$, $p<0.001$) Education level ($\chi^2=9.0$, $p=0.011$) Employment type ($\chi^2=80.8$, $p<0.001$) Only statistically significant results reported as TBI mean (SD, range) vs. Normative sample mean (SD, range): <ul style="list-style-type: none"> Agnosia: 25.7 (0.8,23-26) vs. 25.9 (0.3, 24-26) ; $\chi^2=7.2$, $p=0.007$ Unilateral neglect: 12.4 (0.8,10-13) vs. 13.0 (0.2, 12-13) ; $\chi^2=48.1$, $p=0.001$ Body scheme: 21.6 (0.8,20-22) vs. 22.0 (0.3, 20-22) ; $\chi^2=26.7$, $p=0.001$ Constructional skills: 51.7 (2.3, 41-53) vs. 52.7 (0.6, 49-53) ; $\chi^2=21.3$, $p=0.001$ 	<ul style="list-style-type: none"> No statistically significant difference between study groups on either the VOSP object decision or incomplete letters subtests On inattention blindness tasks, fewer TBI individuals identified a distracting stimulus than the controls: luminance task=40% of controls saw the stimulus vs. 10% of TBI group (Fisher's Exact $p=0.303$); basketball task=50% of controls saw the stimulus vs. 0% of TBI group (Fisher's Exact $p=0.033$). TBI group performed significantly slower on both trails of the TMT: <ul style="list-style-type: none"> TMT A: $M=53.60$ ($SD=29.91$) sec vs. Controls $M=28.40$ ($SD=8.17$) sec, $t=2.570$, $p=0.027$; TMT B: $M=170.40$ ($SD=92.02$) sec

Study attributes	Battistone 2008	Goodrich (2007)	Kraus (2007)	McKenna (2006)	Summers 2006
	<p>accurate in their responses with the additional time (a finding supporting a volitional explanation).</p> <ul style="list-style-type: none"> When controlling for differences in rate of information accrual, TBI individuals took longer than controls to initiate the accrual of information [F(1,38)=10.77, MSe=.06, $\eta^2 = .22$]. Neither group traded off any degree of accuracy for speed when given the opportunity to respond early [F(1,38) <1] (a finding that contradicts a volitional explanation for the control group). TBI individuals took longer to respond than controls [F(1,38) = 31.31, MSe=3.19, $\eta^2 = .45$], and the differences grew larger at longer exposures F(1,48)=16.35, MSe=1.33, $\eta^2 = .30$). 	<p>cranial nerves</p> <ul style="list-style-type: none"> % visual impairment in blast v. nonblast TBI = 52% v. 20% Blasts associated with higher rates of damage to the eye, orbit, and/or cranial nerves % visual dysfunction blast v. nonblast: <ul style="list-style-type: none"> - Accommodation= 23.8% v. 20% - Convergence=23.8% v. 36% - Pursuit/saccade=4.8% v. 32% - Fixation/nystagmus=0% v. 4% - Diplopia=0% v. 12% - Suppression= 14.3% v. 10% - Neglect 9.5% v. 8.0% - Visual spatial=28.6% v. 32% - Reading 61.9% v. 60% 	<p>attention from the fixation point during the overlap condition</p> <ul style="list-style-type: none"> "Across all TBI subjects, there were significant correlations between AS measures and executive, attention and memory neuropsych domain scores, indication that the oculomotor deficits may reflect a common underlying neuropathology." <p>ROC analysis showed that:</p> <ul style="list-style-type: none"> Executive domain score was more sensitive and specific than prosaccade error rates for differentiating mod-severe TBI from either mild TBI or controls. 	<ul style="list-style-type: none"> Apraxia: 9.8 (0.5,8-10) vs. 10.0 (0.1, 9-10) ; $\chi^2=12.9, p=0.001$ 64.5% of TBI cases had one or more impairments across the OT-APST subscales compared to 11.8% of the normative sample "The severity of cognitive or functional impairment following TBI was not significantly related to the incidence of visual perceptual impairment on the OT-APST in this study." Persons with unilateral neglect had lower FIM scores 	<ul style="list-style-type: none"> vs. Controls M=62.40 (SD=18.06) sec; t=3.642, p=0.005, TBI group displayed a greater impairment on the ratio score [TMT B-A/A: M=2.35 (SD=1.23) sec vs. Controls M=1.24 (SD=0.44) sec, t=2.669, p=0.021] TBI group was significantly slower on SNST color-word score [TBI M=70.00 (SD=17.09) vs. Controls M=101.90 (SD=14.55), t=4.396, p=0.001] and made more errors [TBI M=5.44 (SD=3.61) vs. Controls M=2.10 (SD=2.60, t=2.336, p=0.032] TBI group displayed a significantly elevated interference effect on the SNST [TBI M=0.33 (SD=0.18) vs. Controls M=0.09 (SD=0.13), t=3.355, p=0.004]
<p>Author's conclusions</p>	<ul style="list-style-type: none"> The findings support roles for both the fixed-limited capacity and volition in processing speed deficits in individuals with moderate to severe TBI. "Although the current study was not intended to evaluate treatment for cognitive problems, the results do suggest that multifaceted, cross-paradigm approaches may be essential for dealing with the processing speed deficits found among individuals who sustain brain injuries." 	<ul style="list-style-type: none"> Accommodation, convergence and spatial deficits occurred in 20% or more of all subjects regardless of mechanism of injury Reading deficits occurred in ~60% regardless of mechanism of injury Binocular, perceptual and reading difficulties were common in subjects regardless of the mechanism of injury Blast-related and non blast-related TBI were associated with similar rates of binocular or perceptual dysfunction Non-blast related TBI was associated with somewhat higher rates of convergence and pursuit and/or saccade dysfunction, fixation and/or nystagmus, and diplopia than blast-related TBI "This finding suggests that comprehensive eye examinations should be routinely administered, particularly when the mechanism of injury involves a blast." "Such studies should not be limited to patients with overt blast-related 	<p>Results suggest that neuropsychological testing has greater clinical utility in detecting and scaling TBI severity and oculomotor testing has greater clinical utility in characterizing neurobehavioral deficits in mild TBI cases.</p> <p>"The mod-severe TBI group was impaired on both oculomotor tasks and neuropsychologic testing, consistent with more global neuropathology. The mild TBI group showed impaired performance primarily on the AS task, consistent with prefrontal system dysfunction. Hence, oculomotor testing is sensitive to the range of neuropathology in chronic TBI, and importantly, may be more sensitive to neuropathology in mild TBI."</p>	<ul style="list-style-type: none"> "...in the TBI sample, the most commonly impaired sub-scales on the OT-APST were unilateral neglect (45.2%), body scheme (25.8%) and constructional skills (25.8%)." Regardless of cause, persons with TBI may have a discrete number of visual perceptual impairments which are unrelated to cognitive impairment or severity of injury "Routine use of a screening tool such as the OT-APST may help identify visual perceptual impairments in these patients and the need for more detailed assessment." 	<ul style="list-style-type: none"> "The results of the present study contradict those of previous studies [internal ref 47] in that it identified a pervasive deficit to speed of information processing superimposed on a deficit to selective attention evident on both tasks of focused (Stroop) and divided (TMT) attention. The results of the present study are in keeping with Posner's model of attention [refs17-20], indicating that severe TBI results in widespread deficits to the anterior attentional system." "This suggests that following severe TBI the capacity to inhibit irrelevant distractors remains intact, but that the ability to enable distraction by a central salient stimulus is profoundly impaired. It is imperative to recognize that current models of attention view distraction as a failure in attentional control. The present study illustrates the potential negative functional consequences of reduced

Study attributes	Battistone 2008	Goodrich (2007)	Kraus (2007)	McKenna (2006)	Summers 2006
		<i>injuries...Such study would be particularly relevant for those troops exposed to a blast who report any level of visual difficulty, such as decreased reading ability, reduced reading duration, inability to track printed materials, or photo-sensitivity..."</i>			<i>distractibility and indicates that current models of attention may need to be reconceptualized to incorporate the notion of functionally adaptive distraction."</i>

Table B (continued). Frequency of visual sequelae associated with moderate to severe TBI

Note: table includes published articles not reviewed in Mathias 2007 meta-analysis

Study attributes	Skelton (2006)	Du (2005)	Mathias (2004)	Lew (2004)	Shum (2000)
Study objective(s)	<ul style="list-style-type: none"> To examine spatial navigation deficits in individuals with moderate to severe TBI To examine which measures of Arena Maze performance were best able to detect brain injury vs. no brain injury 	To study the extent of dark adaptation in moderate to severe TBI subjects using a new dark adaptometer that employs a nearly full retinal field stimulus	<p>To compare in persons with moderate to severe TBI with diffuse damage to matched controls:</p> <ul style="list-style-type: none"> the frequency of impairment of attention, fluency, set shifting and memory the frequency of impairment on visual and tactile RT tasks that required the intra- or inter-hemispheric information processing <p>To correlate quantitative MRI measures with information processing speed and other neuropsychological testing [data excluded]</p>	<ul style="list-style-type: none"> To study the efficacy of event-related potentials (ERP) in detecting residual cognitive impairments in patients with severe TBI at VA Palo Alto 	<ul style="list-style-type: none"> To study the effects of severe TBI on visual memory
Study size	Cases=14 Controls=12	Cases=17 Controls=21	Cases=25 Controls=25	Cases=11 Controls=11	<ul style="list-style-type: none"> Early recovery group with TBI < 1 yr=14 Late recovery group with TBI > 1 yr=14 Controls=18
Perspective	Prospective?	Prospective?	Prospective	Prospective?	Prospective
Injury severity criteria	Not reported	Not reported, but authors stated many cases had co-existing mobility and balance problems from their injury	<ul style="list-style-type: none"> Moderate TBI:GCS 9-12 and LOC between 20-60 min. Severe TBI= GCS ≤ 8 and LOC > 1 hr 	GCS ≤ 8	GCS ≤ 8 or PTA > 7 days

Study attributes	Skelton (2006)	Du (2005)	Mathias (2004)	Lew (2004)	Shum (2000)
Recruitment source	Cases=17 from residential facility and community Controls=16 from community?	Cases=University-based rehabilitation center Controls=University students and faculty	Cases= hospital accident and ER records at Royal Adelaide Hospital Controls= general community	Cases=discharged from inpatient rehab program Controls=not reported	ERG=clinical referrals, Head Injury Unit of the Princess Alexandra Hospital LRG=mail and telephone survey of names from Head Injury Unit of the Princess Alexandra Hospital Controls=advertisements, friends from general community
Inclusion criteria	Cases: • Adults • Hx of TBI Controls: • Not hospitalized for LOC • Age 18 or older	Cases: • Hx of TBI ≥ 6 months prior to study • Self-reported photosensitivity Controls: • Self-reported normal binocular vision • Able to identify the dim luminous test stimulus during pre-testing period with out refractive correction	Cases: • Ages 18-58 • With moderate or severe TBI Controls: • No history of head injury or LOC	Cases: • Discharged with favorable outcome GCS=5 • Hx of severe TBI within last 3 yrs Controls: • Similar age and educational background as controls	Cases: • Hx of severe TBI Controls: • No hx of TBI or other neurological problems
Exclusion criteria	Cases (N): • Inability to find invisible platform within 3 trials (1) • Unclear dx of brain injury (2) Controls: • Ongoing psychological disorders (2) • Intentional failure to follow instructions (1) • Dizziness during testing (1)	Cases: • No hx of media, retinal or optic nerve abnormalities Controls: • No hx of elevated light sensitivity, acquired brain injury, or retinal/neurological disease	• Prior history of neurological or psychiatric problems • English was second language • Physical problems that would interfere with their performance on RT tasks (eg. Visual field loss, visual neglect, hemiparesis, paralysis)	• Hx of hearing loss or color blindness • Consumption of sedatives, anticholinergics, dopamine agonists or antagonists within 72 hrs of testing • Possessed rare talent of absolute pitch	• No prior exposure to Asian languages
Time since injury	Ave =15.9 yrs, (0.5-48; SD 0.9)	≥ 6 months	Mean = 212.9 days, SD=86.6	Mean = 9.3 mo	• ERG Median=4 mo 1.5 wks, (range = 2 mo - 9 mo 1 wk) • LRG Median=2 yrs 1 wk, (range=1 yr 2 wks – 6 yrs 3 mo)
Characteristics of cases/controls	Cases: • Cause of injury (N)= MVA (9), sports injury(3), assault (2) • 79% male • Mean age=39.3 yrs (23-67; SD 0.9) • Mean educ level=12.9 yrs (8-16; SD 0.2)	Cases: • Cause of injury (N)= MVA (7), fall (5), assault (2), accident (1), encephalopathy (1) • Gender=NR • Mean age=45.9 yrs (24-78; SD 16.4) • Mean educ level=NR	Cases (range, SD): • Cause of TBI=MVA (60%); Assaults (20%); falls (12%); sporting injuries (4%); hit by car (4%) • 84% Male • Mean age=28.0 yrs (18-58 yrs; SD 10.2) • Educ level =12 yrs (SD=2.4)	Cases: • Cause of TBI=not reported • % male not reported • Mean age=33.4 ± 12.9 yrs Controls: • % male not reported* • Mean age=36.0 ± 2.8 yrs*	ERG cases: • Cause of TBI=MVA (64%); fall (14%); MBA(14%); sports (7%) • 71% male • Mean age=28.214 yrs (SD=10.635) • Educ level=10.714 yrs (SD=1.541) LRG cases:

Study attributes	Skelton (2006)	Du (2005)	Mathias (2004)	Lew (2004)	Shum (2000)
	<p>Controls:</p> <ul style="list-style-type: none"> • 58% male • Mean age=36.2 yrs (19-52; SD 0.9) • Mean educ level=13.8 yrs (7-17; SD 0.2) <p>No statistically significant difference between group re age or educ level</p>	<ul style="list-style-type: none"> • Self-reported photosensitivity (N) =mild (8); moderate (5); marked (4) <p>Controls (random, unmatched):</p> <ul style="list-style-type: none"> • Mean age=39 yrs (22-72; SD 15) • Gender=NR • Educ=NR 	<ul style="list-style-type: none"> • Mean NART estimated premorbid IQ score=107.1 (SD=5.2) • PTA=61 days (11-204) • Mean GCS=8.8 (SD=3.6); • Moderate TBI (n=15); Severe (n=10) • Mean LOS=23.7 days (SD=35.8) <p>Controls=matched for age $t(1,48)=0.55, p > 0.05$; education $t(1,48)=0.062, p > 0.05$; ETOH consumption $t(1,48)=0.55, p > 0.05$; gender (no data reported), with differences on premorbid IQ $t(1,48)=3.09, p > .01$. (TBI group had a lower mean IQ but may be a consequence of the injury).</p>	<p>*authors reported no significant difference between group re age or sex</p>	<ul style="list-style-type: none"> • Cause of TBI=MVA (43%); MBA (21%); hit by train/car (21%); assault (14%) • 79% male • Mean age=24.071 yrs (SD=7.364) • Educ level=11.286 yrs (SD=1.326) <p>Controls:</p> <ul style="list-style-type: none"> • 67% male • Mean age=24.667 yrs (SD=9.127) • Educ level=10.944 yrs (SD=1.589) <p>No significant difference between 3 groups in age or educ level</p>
Outcome measures	<ul style="list-style-type: none"> • Arena Maze task= Virtual MWM for testing spatial learning and memory <ul style="list-style-type: none"> • Probe trials to test knowledge of platform location • Everyday Spatial Questionnaire to assess wayfinding and object location 	<p>Scotopic thresholds (dB) in undilated conditions</p>	<ul style="list-style-type: none"> • Self reported symptoms and history • Attention=Visual Elevator, Telephone Search, Telephone Search While Counting, TEA • Verbal fluency=COWA • Nonverbal fluency=RFFT • Set shifting=WCST • Verbal memory=RAVLT • Interhemispheric processing=Visual and tactile RT tasks • Outcome=Rivermead Head Injury Follow-up Questionnaire • Outcome=Rivermead Post Concussional Symptoms Questionnaire (PCS) 	<ul style="list-style-type: none"> • ERP amplitude and latency • Behavioral data = reaction time and response accuracy 	<ul style="list-style-type: none"> • SVLT for visual memory • RAVLT for verbal memory • Electronic maze test for spatial memory • Perceptual discrimination task with Chinese characters to screen out visual perceptual problems
Results	<p>(Selected outcomes reported)</p> <p>Arena Maze performance:</p> <ul style="list-style-type: none"> • There was a significant effect of TBI on both distance [$F=9.625$; df 1,24; $p<0.005$] and latency [$F=13.1$; df 1,24; $p<0.001$]. • There was a significant learning effect over trials among non-injured [$F=4.95$; df 2.2, 23.9; $p<0.014$] but not among TBI [$F=1.43$; df 3.8, 48.8; $p<0.240$]. • Probe trials: TBI group searched the correct location less than the 	<ul style="list-style-type: none"> • Mean scotopic threshold was significantly higher in the TBI group and showed greater variability than in the controls [TBI mean=9.4 dB (range 0-20; SD 5.0; SEM 1.2) vs. Control mean=4.1 dB (range 0-9; SD 2.4; SEM 0.5) ($t=4.255, p=0.0004$ for mean thresholds)] • Using a cutoff threshold of 9 dB, 9/17 (53%) TBI subjects had elevated dark adaptation thresholds <p>Self-reported degree of photo-</p>	<ul style="list-style-type: none"> • After controlling for the effects of IQ, TBI group performed significantly poorer on measures of visual and verbal fluency (COWA and RFFT) and verbal memory (RAVLT total Trials 1 through 5 and 20-min delayed recall), but showed minimal problems with attention or set shifting. • RT tasks of TBI group vs. controls: <ul style="list-style-type: none"> • Slower to respond to the visual RT tasks $F(1,48)=8.61, p< .01$. 	<p>(TBI patients vs. controls)</p> <ul style="list-style-type: none"> • TBI patients had significantly lower P300 amplitude in both auditory (11.2 vs. 22.7 $\mu V, P<0.01$) and visual (11.6 vs. 20.9 $\mu V, P<0.01$) domains • TBI patients had significantly longer P300 latency in both auditory (355 vs. 294 msec, $P<0.0001$) and visual (376 vs. 341 msec, $P<0.01$) modalities • There was no significant difference in response accuracy (97.7% vs. 	<p>SVLT:</p> <ul style="list-style-type: none"> • ERG and LRG groups performed significantly more poorly than the controls (t-test, $p<.001$) • Both ERG and LRG were learning the target stimuli at a significantly slower rate across the five trials than the controls and the learning rates of each TBI group were similar. • Controls obtained significantly higher scores on overall learning ($p<.001$) and learning indices

Study attributes	Skelton (2006)	Du (2005)	Mathias (2004)	Lew (2004)	Shum (2000)
	<p>non-injured group [$t(24)=5.48$, $p<0.00001$] suggesting that the brain injured either didn't know where it was or had little confidence in their knowledge.</p> <p>Comparison of dependent variables</p> <ul style="list-style-type: none"> Spatial score was best measure of performance in Arena maze: $d=2.25$, $t(24)=5.74$, $P<0.0001$; $Se=93\%$, $Sp=92\%$, $PPV=93\%$, $NPV=92\%$, $Pos LR=11.14$, $NegLR=0.08$ Path efficacy was a better measure of discriminating TBI from non-injury than distance or latency Everyday Spatial Questionnaire: Overall those with TBI reported more frequent spatial problems than those with no injury ($t(24) = -2.96$, $p<0.01$, Cohen's $d=1.16$) No significant differences between the groups and no correlations with any Arena Maze variables in age, gender, time-since-injury or computer experience 	<p>sensitivity (mean threshold):</p> <ul style="list-style-type: none"> Mild = 8.63dB vs. moderate = 11.2dB vs. marked =8.75dB There were statistically significant differences in final thresholds for mild ($p=0.008$), moderate ($p=0.001$) and marked ($p=0.034$) compared with controls. 	<ul style="list-style-type: none"> Affected by more stimulus-response choices $F(1,48)=9.82$ $p<.01$ Slower when making an incompatible response $F(1,48)=4.36$, $p<.05$ Slowed to a greater extent by tasks designed to require the inter-hemispheric transfer of information Effect size was largest for the interhemispheric process task i.e. six-choice, two sequence incompatible tactile RT task (Cohen's $d=1.15$) Correlation between RT tasks and neuropsychological tests found that for TBI group, there was a single significant correlation between COWA and six-choice incompatible tactile RT task ($r=-.61$, $n=20$, $p<.01$) <p>Significant correlation between testing measures and outcome was found between:</p> <ul style="list-style-type: none"> outcome and tactile six-choice compatible RT task ($r=.56$, $n=20$, $p<.01$) PCS and tactile six-choice compatible RT task ($r=.65$, $n=20$, $p<.01$), i.e. poor outcome was associated with slower information processing speed 	<p>100%),</p> <ul style="list-style-type: none"> Mean reaction time for both auditory and visual tasks were significantly longer in TBI patients (auditory, 404 vs. 277 msec, $P<0.05$; visual, 397 vs. 346 msec, $P<0.05$). 	<p>($p<.05$) and mean false-positive errors ($p<.001$) than the LRG or ERG.</p> <ul style="list-style-type: none"> SVLT scores between both ERG and LRG were not significantly different. Electronic Maze Test: <ul style="list-style-type: none"> No significant differences between groups RAVLT <ul style="list-style-type: none"> Controls recalled significantly more words than LRG ($p<.01$) and ERG ($p<.001$) The number of words recalled by the two TBI groups was not sig different. On the overall learning index controls recalled more words over the five trials than the LRG ($p<.01$) and ERG ($p<.001$), the number of words recalled for the two TBI groups were not significantly different. On the retention after interference index, ERG scored significantly lower on this ratio score than controls ($p<.05$), but no difference found between LRG and either ERG or controls.
<p>Author's conclusions</p>	<ul style="list-style-type: none"> TBI survivors showed severe impairment in spatial navigation using a virtual version of MWM Results confirm the feasibility of testing with virtual procedures in a community-based or institution-alized severe TBI population, however further research is needed to refine and shorten the procedure. Results support the need for further study of the frequency and impact of spatial navigational impairment in 	<ul style="list-style-type: none"> In subjects with TBI who report elevated photosensitivity, final dark adaptation threshold values were frequently elevated when compared with controls, but the degree of elevation did not correlate with the degree of photosensitivity The lack of abnormal dark adaptation thresholds in 47% of TBI subjects who complained of photosensitivity may be due to difference in site and pervasiveness 	<ul style="list-style-type: none"> "...there was evidence of a general slowing in the processing of visual and tactile information following TBI. Moreover, the TBI participants were disproportionately slower on the more difficult visual and tactile RT tasks, suggesting that they were more affected by increased information processing demands." Lack of effect of attention in TBI group may have been influenced by premorbid IQ rather than injury 	<ul style="list-style-type: none"> "Although TBI patients with good recovery showed similar response accuracy when compared with control subjects, they demonstrated significantly poorer performance in both electrophysiologic and behavioral responses. Diminished amplitudes and prolonged latencies in P300 responses indicate impaired organization and categorization of incoming sensory information; prolonged behavioral 	<ul style="list-style-type: none"> Results suggest that individuals with severe TBI were impaired on verbal and visual memory, but the patterns of impairment were not identical. Compared to controls, those with severe TBI showed a similar rate of learning on verbal memory test but a slower rate of learning on the visual memory test. Using unfamiliar stimuli such as Chinese characters in the SVLT

Study attributes	Skelton (2006)	Du (2005)	Mathias (2004)	Lew (2004)	Shum (2000)
	<p>a TBI population to determine its significance and the need for testing.</p>	<p>of the injury.</p> <ul style="list-style-type: none"> • Further study is needed to better understand the neurological mechanism and neural sites underlying photosensitivity. 	<p>status, but requires further study</p> <ul style="list-style-type: none"> • Further study is needed to better control for premorbid IQ across samples and to determine the accuracy of the NART in moderate to severe TBI, particularly in the first year post injury • Improvements in visual and tactile task methodology is needed with larger groups of TBI and controls who have undergone MRI at the time of their cognitive assessments 	<p><i>reaction times suggest slowing in the response execution process."</i></p> <ul style="list-style-type: none"> • Future research should include prospective study of ERP with neuropsychological testing on the same day, refining ERP paradigms to incorporate more ecologically valid stimuli (eg. Semantic categorization and facial expressions) without compromising operating characteristics, and combining ERP with (functional) neuroimaging to delineate both eletrophysiologic, anatomic and biochemical basis of recovery in TBI. 	<p>rather than familiar verbal stimuli used in RAVLT may uncover impairment that is masked by a retroactive interference effect from using familiar stimuli in testing.</p> <ul style="list-style-type: none"> • More research is needed to determine if severe TBI has a differential effect on visual and verbal memory processes.

Table C. Studies of rehabilitation interventions for TBI-related vision disorders in moderate to severe TBI

Note: See Page iv for list of abbreviations

Study Attributes	Pavawalla 2006 (follow up to Schmitter-Edgecombe 2001)	Schmitter-Edgecombe 2001	Padula 1994
Study objective	To study the long-term retention of a learned automatic cognitive process	To study skill acquisition and automatic process development in severe closed head injury using a semantic-category visual search task	To study the effect of prisms and bi-nasal occluders on ambient vision disturbances using visual evoked potentials (VEP)
Study size	Experimental subjects=17 Controls=10	Experimental subjects=18 Controls=18	Experimental subjects=10 Controls=10
Perspective	Prospective		Prospective
Injury severity criteria	Severe: <ul style="list-style-type: none"> • Duration of coma > 48 hrs, or • GCS \leq 8, or • Subject and significant other reported coma duration > 48 hrs and PTA \geq 14 days 		Disability rating: Mean Ranchos Los Amigos=VI, range V-VII
Recruitment source	Cases= Former clients of TBI brain injury rehab program, local chapter of national head injury foundation, or support groups Controls = community through advertisement		Hospital subjects = TBI confirmed by medical records chosen at random, randomization process not described Controls = hospital staff who denied having TBI
Inclusion criteria	Severe TBI <ul style="list-style-type: none"> • > 1 year post injury • \geq 15 years of age at the time of injury • < 55 years of age at testing Controls-not reported		Cases = TBI Controls = no history of TBI
Exclusion criteria	<ul style="list-style-type: none"> • Hx of neurologic disorder other than TBI, treatment for substance abuse, multiple head injuries, or dementia (DRS < 122) • Vision problems (Snellen ratio < 0.50 at a distance of 45 cm or visual field deficit that would impair viewing a computer screen) • Reading impairment, inability to understand simple words • Motor impairment to upper limbs 		<ul style="list-style-type: none"> • Subjects with measurable strabismus
Time since injury	<ul style="list-style-type: none"> • At least one year (range 1-27 years); 83% > 2 yrs; 56% > 6 yrs 		<ul style="list-style-type: none"> • Not reported

Study Attributes	Pavawalla 2006 (follow up to Schmitter-Edgecombe 2001)	Schmitter-Edgecombe 2001	Padula 1994
Characteristics of study subjects	<ul style="list-style-type: none"> • Cause of injury (N)= MVA (16), fall (2) • 83% male • Mean age=34.12 (SD 9.41) • Mean educ level=13.82 yrs (SD 1.91) • 50% receiving Social Security Disability; 33% supported by parent or spouse; 17% actively employed and self-supporting • Cases had residual cognitive difficulties in verbal learning, verbal and visual memory, category fluency and processing speed <p>Controls matched for sex, age, educational level and occupational status of mothers or fathers</p> <ul style="list-style-type: none"> • No difference between study arms in occupational status of mothers or fathers, premorbid intelligence, current intellectual abilities, or on cognitive tests for short-term memory span or working memory span 	<ul style="list-style-type: none"> • Cause of injury (N)= MVA (16), fall (2) • 83% male • Mean age=32.53 (SD 10.03) • Mean educ level=13.61 yrs (SD 1.79) • 50% receiving SSD; 33% supported by parent or spouse; 17% actively employed and self-supporting • Cases had residual cognitive difficulties in verbal learning, verbal and visual memory, category fluency and processing speed <p>Controls matched for sex, age and educational level</p> <ul style="list-style-type: none"> • No difference between study arms in occupational status of mothers or fathers, premorbid intelligence, current intellectual abilities, or on cognitive tests for short-term memory span or working memory span 	<ul style="list-style-type: none"> • Cause of injury (N) = MVA (8), fall (1), MVA/PED (1) • 70% male • Mean age=24 yrs, range 22-46 yrs • Authors reported a common symptom among cases was perceived movement and shift of chart <p>Controls:</p> <ul style="list-style-type: none"> • 10% male • Mean age=27 yrs, range 23-46 yrs <ul style="list-style-type: none"> • Relative to controls, subjects with TBI experienced reduced monocular and binocular visual acuity and higher frequencies of tracking and convergence difficulty, exophoria, myopia, and lack of accommodative ability.
Random assignment	No		No
Intention-to-treat analysis	N/A		N/A
Follow up	<ul style="list-style-type: none"> • TBI=missed appt (1) • Controls= could not be located (2), did not respond (4) or failed to attend (2) 	<ul style="list-style-type: none"> • Complete • 10 training sessions 	<ul style="list-style-type: none"> • Complete • Evaluated in one day
Outcome measures	<ul style="list-style-type: none"> • Slope estimates = Visual search rate, i.e. the time needed to search an item in the visual display 		<ul style="list-style-type: none"> • Mean amplitude of P1 using binocular VEP • Absolute latency
Intervention (s)	<ul style="list-style-type: none"> • Consistent mapping (CM) training used in both arms 	<ul style="list-style-type: none"> • Consistent mapping (CM) training • Varied mapping (VM) training <p>Both training methods used in case and control arms, with individual subjects used as own internal controls</p>	<ul style="list-style-type: none"> • Refraction correction vs. refraction correction with bi-nasal occluders and base in prisms • A before-after design was used with both experimental and control groups, with individual subjects used as own internal controls
Results	<ul style="list-style-type: none"> • Returning TBI and control groups demonstrated comparable levels of stimulus-specific and task-specific skill learning at the beginning of the study ($p < .01$). • No significant group differences were found in the level of retention for either skill type, indicating that individuals with severe TBI were able to retain the learned skills over a long-term retention interval at a level comparable to controls • TBI subjects who returned at the 5-month retention interval showed nearly complete skill retention, and greater skill retention, than TBI subjects who returned at the 10-month interval. [A statistically significant loss in stimulus-specific skills from 5-months to 10-months ($p < .01$); a trend noted in loss of task-specific skills from 5-months to 10-months ($p > .05$)] • No statistically significant difference in demographic, 	<p>(Only results using training method as an independent variable were reported)</p> <p>CM vs. VM training:</p> <ul style="list-style-type: none"> • Visual search rate decreased with practice in the CM condition but not the VM condition [$F(11,374) = 2.33$, $MSE = 2561.28$, $p < 0.009$] • Difference in visual search rate between study arms was greater for VM training (55 ms) than for CM training (31 ms) [$F(1,34) = 2.33$, $MSE = 29855.35$, $p < 0.06$] 	<ul style="list-style-type: none"> • "The results indicated that the use of base-in prisms and bi-nasal occluders produced a large increase in the experimental group, and that the difference was statistically significant ($p < 0.01$)." • Mean=relative change in amplitude before and after intervention • Cases (mean = 1.375) vs. controls (mean = -0.405); Difference=1.780, t-value=3.76, d.f. 18, $p < 0.01$] • Caution: Questionable baseline comparability of study groups and small sample size limits interpretation of t-test results.

Study Attributes	Pavawalla 2006 (follow up to Schmitter-Edgecombe 2001)	Schmitter-Edgecombe 2001	Padula 1994
	<p>injury-related, or neuro-psychological variables between the 5-month and 10 month returning groups, indicating the passage of time is likely the most significant contributor to this pattern of data.</p>		
<p>Authors' conclusions</p>	<ul style="list-style-type: none"> • Together with the earlier study, the results suggest that: • "...breaking down complex cognitive skills and consistently training individuals on smaller components of the task in order to develop automatic cognitive process is a worthwhile strategy since such skills are likely to be retained over a long-term interval, perhaps more so with follow-up "booster" or retraining sessions." • Future research with larger sample sizes is needed to explore optimal time for booster sessions and other training related variables, participant and injury-related factors that might influence skill acquisition rate and retention capacity to clarify the parameters necessary to develop and sustain an automatic cognitive skill. 	<ul style="list-style-type: none"> • "CM training resulted in a significant decrease in visual search rate across practice, whereas search rates did not change following extended VM practice." • "In both CM memory and visual search situations, we have shown that CHI participants can acquire and use automatic processes in the development of skilled performance. In contrast, for VM task situations, where controlled processing dominates performance, CHI participants continue to perform poorly than controls even after extended practice. These findings suggest that remediation programs should try to capitalize on processes that can be made automatic through practice..." • "...In the CHI literature, retention of newly acquired skills has not been systematically evaluated..." 	<ul style="list-style-type: none"> • "... the study indicates that the symptoms presented may be due to a disturbance of the ambient visual process, which in turn interferes with binocularity. • The ambient visual process is a spatial orienting process that is part of the sensory-motor feedback loop. When used properly it supports the focal process by orienting this system spatially. In order for the focal process to function effectively the ambient process must initially organize and stabilize the field. • This study further indicates that the ocular conditions diagnosed after a TBI may be due to a dysfunction of the ambient visual process in its inability to organize spatial information with other sensory-motor systems. This in turn causes a compromise of the focal process. • The increase in amplitude of the binocular VEP for the experimental group when using base-in prisms and bi-nasal occluders suggests that by affecting the ambient visual process through structure from the bi-nasal occluders and field expansion from the base-in prisms, the binocular cortical cells increase in effectiveness of function." • Authors recommend confirming results in larger studies and studying the effectiveness of bi-nasal occluders and base-in prisms separately. • Analyst notes: baseline comparability of study groups is also needed.

APPENDIX 2. SUMMARY OF US PREVENTIVE SERVICES TASK FORCE PROCEDURE MANUAL: MODIFIED FOR THIS SYSTEMATIC REVIEW

1. Classify individual studies according to a hierarchy of research design.

I:	Properly powered and conducted RCT; well-conducted systematic review or meta-analysis of homogeneous RCTs
II-1:	Well-designed controlled trial without randomization
II-2:	Well-designed cohort or case-control analytic study
II-3:	Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III:	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

2. Assess internal validity of individual studies and assigning to one of three categories—“good,” “fair,” and “poor”

Good	Meets all internal validity criteria: comparable groups are assembled initially and maintained throughout the study (follow up at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. For RCTs, intention to treat analysis is used.
Fair	If any or all of the following problems occur, without fatal flaws noted in the “poor” category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.
Poor	If any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or not attention. For RCTs, intention to treat analysis is lacking.

3. Global rating of external validity

Good	The study differs minimally from the Veteran population, and only in ways that are unlikely to affect the outcome; it is highly probable (>90%) that the clinical experience with the intervention observed in the study will be attained in the Veteran setting.
Fair	The study differs from the Veteran population in a few ways that have the potential to affect the outcome in a clinically important way; it is only moderately probably (50%-89%) that the clinical experience with the intervention in the study will be attained in the Veteran setting.
Poor	The study differs from the Veteran population in many ways that have a high likelihood of affecting the clinical outcomes; the probability is low (<50%) that the clinical experience with the intervention observed in the study will be attained in the Veteran setting.

4. Levels of certainty regarding net benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative Veteran populations. These studies assess the effects of the intervention on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the intervention on health outcomes, but confidence in the estimate is constrained by factors such as: <ul style="list-style-type: none"> ○ the number, size, or quality of individual studies ○ inconsistency of findings across individual studies ○ limited generalizability of findings to the Veteran population, or ○ lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of; <ul style="list-style-type: none"> ○ the limited number or size of studies ○ important flaws in study design or methods ○ inconsistency of findings across individual studies ○ gaps in the chain of evidence ○ findings not generalizable to routine VA care, or ○ a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

5. Putting it all together: Assigning a recommendation grade for that intervention

Certainty of Net Benefit	Magnitude of Net Benefit			
	Substantial	Moderate	Small	Zero/Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	Insufficient (I)			

6. Defining USPSTF grades and suggestions for practice

Grade	Grade definitions The VA consensus validation panel...	Suggestions for Practice
A	...recommends the intervention. There is high certainty that the net benefit is substantial.	Offer/provide this intervention.
B	...recommends the intervention. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial	Offer/provide this intervention.
C	...recommends against routinely providing the intervention. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.	Offer/provide this intervention only if there are other considerations in support of offering/providing the intervention in an individual patient.
D	...recommends against the intervention. There is moderate or high certainty that the intervention has no net benefit or that the harms outweigh the benefits.	Discourage the use of this intervention.
I statement	...concludes that the current evidence is insufficient to assess the net benefit of the intervention. Evidence is lacking, of poor quality or conflicting, and the balance of benefits and harms cannot be determined.	If offered, patients should understand the uncertainty about the balance of benefits and harms.

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