



Reference List - Expert Opinion Report

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Post-concussion syndrome

Overview

Post-concussion syndrome is a complex disorder in which various symptoms — such as headaches and dizziness — last for weeks and sometimes months after the injury that caused the concussion.

Concussion is a mild traumatic brain injury that usually happens after a blow to the head. It can also occur with violent shaking and movement of the head or body. You don't have to lose consciousness to get a concussion or post-concussion syndrome. In fact, the risk of post-concussion syndrome doesn't appear to be associated with the severity of the initial injury.

In most people, symptoms occur within the first seven to 10 days and go away within three months. Sometimes, they can persist for a year or more.

The goal of treatment after concussion is to effectively manage your symptoms.

Symptoms

Post-concussion symptoms include:

- Headaches
- Dizziness
- Fatigue
- Irritability
- Anxiety
- Insomnia
- Loss of concentration and memory
- Ringing in the ears
- Blurry vision
- Noise and light sensitivity
- Rarely, decreases in taste and smell

Post-concussion headaches can vary and may feel like tension-type headaches or migraines. Most often, they are tension-type headaches. These may be associated with a neck injury that happened at the same time as the head injury.

When to see a doctor

See a doctor if you experience a head injury severe enough to cause confusion or amnesia — even if you never lost consciousness.

If a concussion occurs while you're playing a sport, don't go back in the game. Seek medical attention so that you don't risk worsening your injury.

Causes

Some experts believe post-concussion symptoms are caused by structural damage to the brain or disruption of the messaging system within the nerves, caused by the impact that caused the concussion.

Others believe post-concussion symptoms are related to psychological factors, especially since the most common symptoms — headache, dizziness and sleep problems — are similar to those often experienced by people diagnosed with depression, anxiety or post-traumatic stress disorder.

In many cases, both physiological effects of brain trauma and emotional reactions to these effects play a role in the development of symptoms.

Researchers haven't determined why some people who've had concussions develop persistent post-concussion symptoms while others do not. There's no proven connection between the severity of the injury and the likelihood of developing persistent post-concussion symptoms.

However, some research shows that certain factors are more common in people who develop post-concussion syndrome compared with those who don't develop the syndrome. These factors include a history of depression, anxiety, post-traumatic stress disorder, significant life stressors, a poor social support system and lack of coping skills.

More research is still needed to better understand how and why post-concussion syndrome happens after some injuries and not others.

Risk factors

Risk factors for developing post-concussion syndrome include:

- **Age.** Studies have found increasing age to be a risk factor for post-concussion syndrome.
- **Sex.** Women are more likely to be diagnosed with post-concussion syndrome, but this may be because women are generally more likely to seek medical care.

Prevention

The only known way to prevent post-concussion syndrome is to avoid the head injury in the first place.

Avoiding head injuries

Although you can't prepare for every potential situation, here are some tips for avoiding common causes of head injuries:

- **Fasten your seat belt** whenever you're traveling in a car, and be sure children are in age-appropriate safety seats. Children under 13 are safest riding in the back seat, especially if

your car has air bags.

- **Use helmets** whenever you or your children are bicycling, roller-skating, in-line skating, ice-skating, skiing, snowboarding, playing football, batting or running the bases in softball or baseball, skateboarding, or horseback riding. Wear a helmet when riding a motorcycle.
- **Take action at home to prevent falls**, such as removing small area rugs, improving lighting and installing handrails.

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ORIGINAL ARTICLE

Vision Therapy for Post-Concussion Vision Disorders

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ABSTRACT

Purpose. To determine the frequency and types of vision disorders associated with concussion, and to determine the success rate of vision therapy for these conditions in two private practice settings.

Methods. All records over an 18-month period of patients referred for post-concussion vision problems were reviewed from two private practices. Diagnoses of vergence, accommodative, or eye movement disorders were based on pre-established, clinical criteria. Vision therapy was recommended based on clinical findings and symptoms.

Results. Two hundred eighteen patient records were found with a diagnosis of concussion. Fifty-six percent of the concussions were related to sports, 20% to automobile accidents, and 24% to school, work, or home-related incidents. The mean age was 20.5 years and 58% were female. Eighty-two percent of the patients had a diagnosis of an oculomotor problem [binocular problems (62%), accommodative problems (54%), eye movement problems (21%)]. The most prevalent diagnoses were convergence insufficiency (CI, 47%) and accommodative insufficiency (AI, 42%). Vision therapy was recommended for 80% of the patients. Forty-six per cent (80/175) either did not pursue treatment or did not complete treatment. Of the 54% (95/175) who completed therapy, 85% of patients with CI were successful and 15% were improved, and with AI, 33% were successful and 67% improved. Clinically and statistically significant changes were measured in symptoms, near point of convergence, positive fusional vergence, and accommodative amplitude.

Conclusions. In this case series, post-concussion vision problems were prevalent and CI and AI were the most common diagnoses. Vision therapy had a successful or improved outcome in the vast majority of cases that completed treatment. Evaluation of patients with a history of concussion should include testing of vergence, accommodative, and eye movement function. Prospective clinical trials are necessary to assess the natural history of concussion-related vision disorders and treatment effectiveness.

(Optom Vis Sci 2017;94:68–73)

Key Words: vision therapy, vision rehabilitation, concussion, convergence insufficiency, accommodative insufficiency, near point of convergence

Up to 3.6 million concussions are reported annually from causes such as motor vehicle accidents, sports, and household injuries.^{1,2} Traumatic brain injury (TBI) from blast injuries was the signature injury of the Iraq and Afghanistan wars. Studies with both military^{3–8} and civilian^{9–11} populations have found that oculomotor deficits such as convergence insufficiency (CI), accommodative insufficiency (AI), and saccadic dysfunction (SD) occur 30 to 42% of the time after concussion, which is much higher than the 5 to 15% estimated in the general population.^{12,13} A recent hospital-based study by Master

et al. found very similar prevalence rates in adolescents after concussion, with CI and AI reported in approximately 50% of the sample.¹⁴

Treatment of concussion-related vision disorders often involves the use of vision therapy/rehabilitation to remediate vergence, accommodation, and versional eye movements. In a retrospective study in a university optometric clinic, Ciuffreda et al. reported that 90% of patients ($n = 33$) with TBI-related oculomotor abnormalities experienced improvement in signs and symptoms after vision therapy.¹⁵ In a recent placebo-controlled randomized clinical trial, the authors found clinically and statistically significant improvements in vergence, accommodative, and versional findings and visual attention.^{16–18}

As awareness of concussion-related vision disorders has grown over the past 5 to 10 years, more optometrists are diagnosing and treating these disorders. Although there is strong evidence for the

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effectiveness of vision therapy for CI and accommodative dysfunction in non-concussed patients,^{19–22} there are limited published data on the treatment of concussion-related vision disorders. The purpose of the current study was to assess the frequency and types of concussion-related vision disorders and the effectiveness of treatment for these conditions in a private practice setting.

METHODS

Institutional Review Board approval was obtained to perform this retrospective chart review. A record search (18-month period from January 2012 to July 2013) was completed in two private practice settings that specialize in vision therapy/neuro-optometric rehabilitation. Eligibility criteria included all patients who were referred for visual evaluation after a medical diagnosis of concussion. Referral sources included sports medicine physicians, physiatrists, neurologists, pediatricians, athletic trainers, and physical therapists.

The diagnosis of concussion included a history of a direct or indirect force transmitted to the head causing signs or symptoms of headache, dizziness, nausea, balance problems, fatigue, light and noise sensitivity, sleep problems, cognitive deficits (memory, attention, executive functioning, reaction time), and emotional issues (irritability, sadness, nervousness, anxiety and depression).^{23,24} Patients were generally referred to the authors' offices due to visual symptoms such as blur, diplopia, eye fatigue, headaches, and loss of place with reading and close work.

Vision testing included well-established clinical measures of accommodation, vergence, and ocular motility.²⁵ Ocular alignment/phoria was measured with the cover test at distance and near with prism bar neutralization. Near point of convergence (NPC) break and recovery were measured with a 20/30 accommodative target and an accommodative convergence rule from the patient's mid-brow. Step vergences to assess positive and negative fusional vergence blur, break, and recovery at 40 cm were performed with a prism bar. Vergence facility was assessed at 40 cm with a 12BO/3BI prism. Accommodative amplitude was measured with a push-up technique and 20/30 target to first sustained blur. Accommodative facility was assessed monocularly and binocularly with +2.00/–2.00 lens flipper. Saccadic speed and accuracy was measured with the Developmental Eye Movement Test (DEM), a timed visual-verbal test. In addition, the Convergence Insufficiency Symptoms Survey (CISS)^{26,27} was administered to monitor changes in symptoms with patients who were subsequently treated with vision therapy.

Diagnosis of vision disorders was based on the criteria listed in Table 1. Some patients had more than one diagnosis. Patients with convergence excess or accommodative insufficiency without CI were offered a reading prescription in addition to vision therapy.

Vision therapy consisted of once or twice weekly, 45-minute in-office sessions with approximately 15 min/day and 3 to 5 days per week of home activities. Therapy procedures were similar to those used in the Convergence Insufficiency Treatment Trials (CITT)^{19,21,22,28} with the addition of saccadic and pursuit activities such as Hart Chart, thumb rotations, rotating pegboard, and the Sanet Vision Integrator (SVI).²⁵ Balance and head movements were added as needed for vestibular and vestibulo-ocular reflex stimulation. Criteria for success or improvement in signs and symptoms are listed in Table 2.

Statistical analyses were completed using SAS version 9.3 and SPSS version 21. One-sample *t*-tests were used to compare

treatment improvements to zero. The area under the receiver-operator characteristic (ROC) curve is used as an indicator of the accuracy of the given patient characteristic to identify a patient with any vision disorder. It is constructed by plotting the value of sensitivity versus specificity for all possible cut-points for a given

TABLE 1.

Diagnostic criteria for binocular vision, accommodative, and eye movement disorders

Convergence insufficiency
(A) 3-Sign CI
Requires: 1, 2 plus at least 1 finding from 3–4
1. Near point of convergence of ≥ 6 cm break
2. Exophoria at near at least 4 pd greater than at distance
3. Reduced positive fusional vergence at near (<20 pd or fails Sheard's criterion)
4. Vergence facility (D or N) ≤ 9 cpm with difficulty with base-out
(B) 2-Sign CI
Requires: 1, plus at least 1 finding from 2–4
1. Near point of convergence of ≥ 6 cm break
2. Exophoria at near at least 4 pd greater than at distance
3. Reduced positive fusional vergence at near (<20 pd or fails Sheard's criterion)
4. Vergence facility (D or N) ≤ 9 cpm with difficulty with base-out
Convergence excess
Requires: 1 plus at least 1 finding from 2–3
1. ≥ 3 pd esophoria at near
2. Reduced negative fusional vergence at near (<8 pd or fails Sheard's criterion)
3. Vergence facility (D or N) ≤ 9 cpm with difficulty with base-in
Fusional vergence dysfunction
Requires: 1 and 2, or 3
1. Reduced negative fusional vergence at near (<8 pd or fails Sheard's criterion)
2. Reduced positive fusional vergence at near (<20 pd or fails Sheard's criterion)
3. Vergence facility (D or N) ≤ 9 cpm with difficulty with both base-in and base-out
Accommodative insufficiency
Requires: 1 or 2
1. Amplitude of accommodation ≥ 2 D below mean for age (15–1/4 age)
2. Monocular accommodative facility ≤ 6 cpm (difficulty with minus lenses)
Accommodative excess
Requires: 1
1. Monocular accommodative facility ≤ 6 cpm (difficulty with plus lenses)
Accommodative infacility
Requires: 1
1. Monocular accommodative facility ≤ 6 cpm (difficulty with plus AND minus lenses)
Saccadic dysfunction
Requires: 1 or 2
1. Ratio score: 1 SD or more below the mean on DEM
2. Error score: 1 SD or more below the mean on DEM

CI, convergence insufficiency; DEM, Developmental Eye Movement Test.

TABLE 2.

Criteria for success with vision therapy

Convergence insufficiency
Success: (all 3) NPC <6 cm, BO >20 or pass Sheard's criteria, and CISS <16
Improved: improved CISS by 10 or more, and either improved NPC >4 cm or normal or improved BO >10
Accommodative insufficiency
Success: (all 3) Normal accommodative amplitude (15–1/4 age), MAF/BAF >6, CISS <16 or improved by >10
Improved: (1 or 2) Normal accommodative amplitude (15–1/4 age), or MAF/BAF >6
Saccadic dysfunction
Success: Both ratio and error scores \geq 50th percentile
Improved: Either ratio or error scores \geq 50th percentile

BO, base-out; CISS, Convergence Insufficiency Symptom Survey; NPC, near point of convergence.

characteristic. An area of 1.0 represents a perfect test whereas an area of 0.50 represents a test no better than flipping a fair coin. Commonly used classification schemes characterize values over 0.90 as excellent, 0.80 to 0.90 as good, 0.70 to 0.80 as fair, 0.60 to 0.70 as poor, and values less than 0.60 as failure to discriminate.²⁹ The ability of combinations of patient characteristics to discriminate was completed by first using a logistic regression to calculate the probability of vision disorder. These probabilities were then used to construct the ROC curve.

RESULTS

Two hundred eighteen records were found for patients who were referred after a concussion during the 18-month period. The mean age was 20.5 years and 58% were female. Sixty-seven percent of the patients were between the ages of 12 and 19. The causes of concussion were 56% sports-related accidents, 20% motor vehicle accident, 17% home accident, and 7% school or workplace accident. This was the first documented concussion in 70% of the patients. A summary of descriptive statistics for the sample is listed in Table 3.

Eighty-two percent of patients had at least one diagnosis. Sixty-two percent (135/218) of the sample had a binocular vision disorder, 54% (118/218) had an accommodative disorder, and 21.6% (47/218) had saccadic dysfunction. Table 4 lists the specific diagnoses.

TABLE 3.

Descriptive statistics (n = 218)

Mean age	20.5 yrs
Range	6–72 yrs
	67% ages 12–19
Females	58%
Mean no. of concussions	1.5
1 concussion/2>2	70%/17%/13%
Time since concussion (mean no. of weeks)	31 wks
Range	1 wk to 5 yrs
	83% >4 wks
History of vestibular therapy	78%
Previous vision therapy pre-concussion	5% (11/218)

TABLE 4.

Frequency of specific vision diagnoses

Binocular vision diagnoses	Frequency
Convergence insufficiency	47.5%
Convergence excess	7.8%
Vertical deviations	3.7%
Other	3.3%
Total	62.3%

Accommodative diagnoses	Frequency
Accommodative insufficiency	41.9%
Accommodative infacility	11%
Accommodative excess	1.3%
Total	54.2%

Saccadic dysfunction	Frequency
	21.6%

Vision therapy was recommended for 175 of the 218 patients (80%). Of these, 80 (45.7%) either chose not to begin therapy (52) or did not complete therapy (28) (discussed below). Of the 95 patients who completed treatment, the most common diagnoses were CI, AI, and SD. For patients treated for CI, 85% (35/41) had a successful outcome and 15% (6/41) were improved. Among the patients with AI, 33% (13/39) were successful and 67% (26/39) were improved, and for patients treated for SD, 83% (15/18) were successful and 5% (1/16) were improved. The mean number (\pm SD) of VT sessions for patients who completed treatment was 14.6 (\pm 5). The variability in the number of sessions reflects the variable time course of post-concussion treatment, which is less predictable than with non-concussion accommodative and vergence disorders.

Clinically and statistically significant changes were seen in NPC, positive fusional vergence (base out break and recovery) and CISS for patients with CI, and in accommodative amplitude and CISS in patients with AI (Table 5). Improved speed was seen on the DEM in patients with SD. Data on accommodative facility and vergence facility are not reported because these test results were often recorded as pass/fail and not quantified.

The ability of any one patient characteristic to discriminate those with and without a concussion-related vision disorder varied (Table 6). NPC break and recovery along with accommodative amplitude and DEM ratio percentile have fair accuracy (ROC area between 0.70 and 0.80). For example, the probability of a more receded NPC break observed in a patient with any vision disorder (relative to a patient with normal vision) is 0.79. The accuracy of DEM vertical time percentile and DEM errors is poor (values between 0.60 and 0.70). A combination of NPC break, accommodative amplitude, and DEM ratio percentile offers the greatest ability to discriminate between those with and without a vision disorder with an area under the ROC curve of 0.89 (95% CI 0.84–0.95).

DISCUSSION

The results of this retrospective study provide additional evidence about the prevalence of concussion-related vision disorders in patients referred to optometrists after concussion. The data also indicate an excellent success rate for patients electing to be treated with vision therapy. A recent review article³⁰ confirmed that

TABLE 5.

Changes in clinical measures after VT for subjects who completed VT

Diagnosis	Test	Mean pre-VT	Mean post-VT(±SD)	Mean change	p-value
CI (n = 43)					
	CISS	31.1	11.0	-21.1 (±8.8)	<0.0001
	NPC break (cm)	13.0	3.3	-9.7 (±10.1)	<0.0001
	NPC recovery (cm)	17.7	5.6	-12.0 (±8.5)	<0.0001
	BO break (pd)	18.1	38.9	20.8 (±8.6)	<0.0001
	BO recovery (pd)	11.2	32.1	20.9 (±7.0)	<0.0001
AI (n = 39)					
	CISS	28.6	8.6	-20.0 (±9.8)	<0.0001
	Accommodative amplitude (cm)	14.1	9.5	-4.6 (±3.6)	<0.0001
SD (n = 23)					
	DEM horizontal speed (sec)	49.9	33.8	-16.1 (±14.3)	<0.0001
	DEM errors	1.82	0.59	-1.24 (3.6)	0.45

AI, accommodative insufficiency; BO, base-out; CI, convergence insufficiency; CISS, Convergence Insufficiency Symptom Survey; DEM, Developmental Eye Movement Test; NPC, near point of convergence; SD, saccadic dysfunction; VT, vision therapy.

oculomotor abnormalities are much more common after concussion than the prevalence rates in the general population. This may be due to the widespread neural architecture of the visual system, which includes frontal and posterior cortical regions, cerebellum, cranial nerves, and interconnections between these areas. The neurometabolic and structural impacts of concussion in the form of diffuse axonal injury render the visual brain especially vulnerable.³¹ As a result, vision therapy is emerging as a treatment modality in concussion treatment, although more data are needed to assess effectiveness.³²

The most common types of concussion-related vision disorders in this sample were CI, AI, and SD. This finding is consistent with previous literature in military subjects,^{3–8} the adult civilian population,^{9,33} and children.¹⁴ Other conditions such as convergence excess, comitant vertical deviations, and accommodative infacility were diagnosed less frequently. It is possible that some of these problems were premorbid, and that concussion may have exacerbated symptoms or increased the level of oculomotor dysfunction. It is interesting that there were no cranial nerve palsies in this sample, underscoring the notion that cranial nerve palsies are much more likely to occur from more focal damage seen in moderate or severe TBI.³⁴

Seventy-eight percent of the patients reported having previous or concurrent vestibular therapy, reflecting the high prevalence of vestibular disorders after concussion.^{23,24} It may also reflect practice patterns in the authors' practice area, where vestibular therapy administered by physical therapists sometimes includes convergence and ocular motor activities. Pre-existing vestibular dysfunction may also have contributed to this high prevalence.

Nearly 46% of patients for whom vision therapy was recommended either did not finish treatment or did not elect treatment in the authors' practices. Some patients may have sought treatment elsewhere (including with physical therapists) or waited to see if resolution or improvement of their problems occurred through natural healing. Some were also prescribed reading glasses that may have lessened symptoms and reduced the motivation for therapy, whereas others may not have been able to afford the cost of vision therapy.

The ROC curve analysis suggests that a combination of NPC break, accommodative amplitude, and DEM ratio score has very good ability to predict the presence of a vision disorder. This

information may be helpful for screening purposes for physicians and primary care optometrists.

In our sample, the success rates for vision therapy suggest that cortical neuroplasticity is still present and that treatment can be effective in this population. Strengths of this study were that all patients with concussion-related vision disorders over an 18-month period were included. In addition, the two investigators used similar assessment and treatment methods. Limitations of this study were its retrospective design, the use of unmasked examiners, the high percentage of patients who did not start or complete vision therapy, and a lack of a control group. It is possible that factors such as a placebo effect, regression to the mean, and continued natural healing accounted for some of the treatment effect. Despite these limitations, these data provide insight into the prevalence of vision problems of patients referred to optometrists post-concussion and about the effectiveness of vision therapy for concussion-related vision disorders. Currently, there is only one randomized clinical trial comparing treatments for concussion-related oculomotor problems. In this study by Ciuffreda and colleagues,^{16–18} all of the subjects (n = 12) were at least 1 year removed from their brain injury, and they still demonstrated significant ocular motor plasticity as the result of vision therapy. The evidence from the Ciuffreda study, plus the data from this large retrospective study, suggests that vision therapy is a valuable treatment for concussion-related vision disorders and argue for a large, multicenter randomized clinical trial that would be able to minimize factors that introduce bias in study results.

TABLE 6.

Predicting any vision disorder

Characteristic	Area under ROC	95% CI
NPC break	0.79	0.72, 0.86
NPC recovery	0.74	0.67, 0.82
Accommodative amplitude	0.76	0.69, 0.84
DEM vertical time (percentile)	0.61	0.51, 0.72
DEM ratio (percentile)	0.71	0.63, 0.80
DEM errors	0.63	0.53, 0.73

DEM, Developmental Eye Movement Test; NPC, near point of convergence.

In summary, the high prevalence of concussion-related vision disorders supports the need for appropriate clinical testing of vergence, accommodation, and eye movements. Our data suggest vision therapy can be an effective intervention, but a large-scale randomized clinical trial is warranted to rigorously determine the effectiveness of vision therapy for concussion-related vision disorders and to better understand the time course of natural healing.

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REVIEW

Visual impairments in the first year after traumatic brain injury

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Abstract

Background: This article reviews literature regarding individuals with traumatic brain injury who have vision related impairments up to one year, post-injury. Such impairments may impact rehabilitation of activities of daily living and mobility since vision is integral in much of what one does on a daily basis.

Methods: Search of Medline, Ovid, and PubMed was performed using terms including: traumatic brain injury, visual deficits after brain injury, vision and traumatic brain injury, and ADLs after brain injury.

Results: Eighteen studies were analyzed and reviewed. A range of visual and visual-motor impairments are seen across the severity of traumatic brain injury. Visual impairment negatively impacts independence in mobility and activities of daily living. Common sensorimotor visual symptoms reported by those with traumatic brain injury include blurred vision, reading problems, double vision or eyestrain, dizziness or disequilibrium in visually-crowded environments, visual field defects, light sensitivity, and color blindness.

Conclusions: This review should alert the reader to common visual complaints and defects seen after traumatic brain injury. It is important to screen persons who have suffered traumatic brain injury for sensorimotor vision deficits early on in recovery so that these issues may be addressed and recovery of function and independence in the community are not delayed.

Keywords: Traumatic brain injury, visual deficits, visual field deficit, oculomotor dysfunction, photosensitivity, blurred vision, light sensitivity, accommodative dysfunction

Introduction

Traumatic brain injury (TBI) may impair an individual's cognition, affect, behaviour and sensorimotor function, including vision [1–13]. Dysfunction of the visual system is a serious problem that has adverse effects on rehabilitation, as well as the recovery of mobility and activities of daily living (ADL) for those with TBI. Blurred vision, reading problems such as slower reading speed and loss of place when reading, diplopia or eyestrain, vestibular symptoms in visually-crowded environments, peripheral vision restrictions, increased sensitivity to light and colour vision deficits are common symptoms following TBI [3, 6, 8, 10, 11, 14–19].

Such symptoms may be associated with anomalies of accommodation, versional ocular motility, vergence ocular motility, visual–vestibular interactions, visual field integrity, light and dark adaptation and optic nerve function, respectively [3, 6, 8, 10, 11, 14–19]. These vision anomalies may occur due to traumatic lesions to the primary and secondary visual pathways, as well as possibly the primary and associated visual cortices.

Sensorimotor vision deficits may affect rehabilitation in a number of ways because of vision's prominent role in balance, gait, attention and other functions related to ADLs. Vision is integral to many basic ADLs including reading, writing, driving, mobility, dressing, grooming and eating, to name a

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few. Therefore, sensorimotor visual impairment may have an adverse global impact on physical and cognitive function. Failure to recognize and treat a sensorimotor visual dysfunction early in rehabilitation may delay functional recovery.

Despite how common vision impairments are in the first year following TBI, there is a dearth of literature on the topic. The first year after TBI is an important time period for natural recovery, during which the most rapid improvements in function occur [20]. Although the patient continues to make progress beyond this first year, improvements made after this time are more gradual. Therefore, a comprehensive search of Medline, Ovid and PubMed was performed using terms including: traumatic brain injury, visual deficits after brain injury, vision and traumatic brain injury and ADLs after brain injury. Using this search, this paper reviews the current literature regarding visual impairments in the first year after traumatic brain injury.

Normal physiology of visual pathways

The Retina-Geniculate-Striate Pathway is an important pathway in visual perception, which is responsible primarily for object recognition and localization, as well as perceiving form, colour, depth and motion (Figure 1).

Visual perception begins with light being refracted through the cornea, passing through the pupil and then being refracted by the lens and vitreous to focus light on the retina. The lens can accommodate (i.e. alter focus) in order to allow for near or distant vision through contraction of ciliary muscles innervated by the oculomotor nerve. Once the light reaches the retina, it passes through the nerve fibre layer to the retinal photoreceptor layer, within which it is converted to a neural signal to be transmitted to the retinal ganglion cells [7].

The retinal ganglion cells form the optic nerve, which carries the initial information for the visual image via the Retina-Geniculate-Striate pathway [7]. Retinal ganglion cell axons of the optic nerve from the nasal portion of the retina decussate via the optic chiasm, while axons from the temporal portion of the retina remain on the ipsilateral side. After crossing over, the axons are referred to as optic tracts, which provide input to the lateral geniculate nucleus (LGN) cells. From the LGN, 90% of the fibres continue on the primary visual cortex, while the remainder travel to the superior colliculus in the midbrain [7].

The primary visual cortex consists of the Striate Visual Cortex (V1 and Brodmann's Area 17) and the Extrastriate Visual Cortex (V2, V3, V4, V5,

Brodmann's area 18 and 19). The primary visual cortex is divided into six layers, with the LGN providing almost all of the input to layer 4 of the primary visual cortex. It is located in the calcarine fissure of the occipital lobe and each hemisphere receives input from the ipsilateral LGN. The visual cortex of the right hemisphere receives information from the left visual field of each retina and vice versa. The upper bank of the calcarine sulcus receives information from the lower visual field of both retinas while the lower bank receives upper visual field information. It is organized retinotopically, with more cortex devoted to central vision (fovea) [7, 21].

V1 transmits information primarily through two pathways, which interact with each other, as well as other areas of the cortex: ventral and dorsal streams [22–24]. The ventral stream starts with the LGN, then V1, progresses to V2, then V4 and the inferior temporal cortex. This ventral (or predominantly parvocellular) pathway is associated with object identification, object representations and storage of long-term and visual memory. The dorsal stream begins at the LGN, on to V1 then projects to V2 and the dorsomedial area, ventral tegmental and posterior parietal cortex. More recently, evidence of an extended dorsal visual stream has become evident, including parieto-prefrontal, parieto-premotor and parieto-medial-temporal pathways responsible for enhanced visual-motor processing in terms of location of objects relative to self, ability to co-ordinate movement to reach the object accurately and ability to maintain balance and navigate while moving through one's environment [23]. The primary dorsal (or predominantly magnocellular) and extended dorsal streams are associated with motion perception, object location, visual motor responses and visual information used to guide saccades and reaching for objects [22–24].

Common sensorimotor visual problems associated with TBI

Within the first year after TBI, patients may present with symptoms attributable to the visual system (Table 1). Some of the most common symptoms include blur, reading difficulties, diplopia or eye-strain, dizziness or disequilibrium exacerbated in visually-stimulating environments, visual field loss or restriction, light sensitivity and colour-blindness. These symptoms correspond to damage of the refractive ocular structures, primary and secondary visual pathways, cranial nerve pathways and nuclei, brainstem, superior colliculus, cerebellum, mid-brain, occipital and parietal lobes and frontal eye fields, to name a few [3, 6, 8, 10, 11, 14–19].

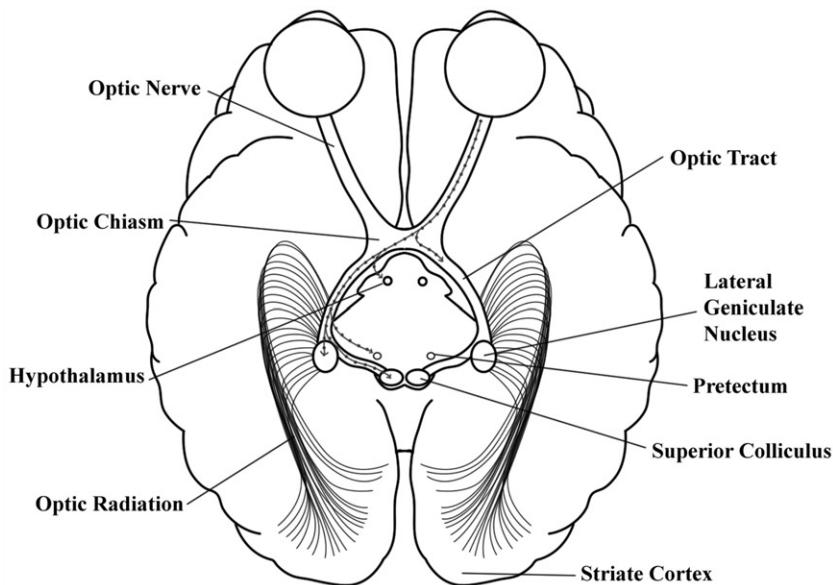


Figure 1. Neuroanatomy of vision.

Blurred vision

Blurred vision in those with TBI may be due to changes in refractive error or structural components of the eye, cortical changes along the primary visual pathway or anomalies along the oculomotor pathway [3, 6, 8, 16, 25].

Refractive error changes evident following a TBI may result in blurred vision and require an updated correction to minimize or reduce the blur. Structural ocular damage may be evident following TBI and may include altered integrity of the tear film, cornea, crystalline lens, vitreous and retina [6, 8, 25]. Changes in tear film integrity may result in intermittent distorted clarity of vision with or without a gritty sensation. Corneal damage may result in a keratitis or corneal scar with reports of central, paracentral or peripheral areas of blur, depending upon the location of the damage on the cornea. Crystalline lens anomalies may present as a traumatic cataract or dislocation of the lens, either of which may be associated with blurring or distortion of the visual image. Vitreo-retinal changes including vitreal haemorrhages, vitreal floaters, vitreal detachments, retinal haemorrhages, retinal detachments, macular changes and retinopathies may impair or distort clarity of vision.

Damage along the primary visual pathway in the cortex may occur following TBI, resulting in loss of vision or reduced clarity of vision, which may or may not be amenable to changes in refractive correction [3, 6, 8, 16]. Anomalies along oculomotor nerve-mediated accommodative pathway may occur following TBI, resulting in constant or intermittent blur, difficulty reading due to impaired ability to

maintain clear vision of near objects for sustained time periods without fatigue, headache, eyestrain, decrease visual efficiency and difficulty looking from far to near and far again [3, 6, 8, 16]. Accommodation refers to the crystalline lens-based mechanism of the eye to change focus in terms of clarity of vision. The optical power of the crystalline lens is altered by the expansion or contraction of the lens to focus an image on the retina. The ciliary muscles of the eye are responsible for this function and are innervated by the oculomotor nerve (i.e. cranial nerve III) and autonomic nervous system. Therefore, damage between the Edinger Westphal nucleus in the pretectum, where the autonomic fibres join the oculomotor fibres along the path of cranial nerve III and the ciliary muscle, may impair accommodation [3, 6, 8, 16]. The most common accommodative dysfunction in those with mild TBI and moderate TBI is accommodative insufficiency, which is diagnosed by the examination finding of reduced accommodation amplitude [3].

Versional oculomotor deficits

Versional ocular motility refers to conjugate eye movements with regard to objects in the field of view [1, 3, 6, 8, 16, 26, 27]. This includes oculomotor functions such as smooth pursuit, saccades and fixation [1, 3, 6, 8, 16, 26, 27], all of which may be evaluated during the extra-ocular motility assessment.

Smooth pursuit refers to the ability to track objects smoothly or to move one's eyes smoothly [3, 26]. Conversely, saccades refer to one's ability to track objects visually as they move rapidly from one

position to another or to move one's eyes rapidly from one target to another, as with reading-related eye movements [3, 26]. Fixation refers to the ability to maintain one's eyes on a target [3, 26]. Deficits of pursuit and deficits of saccades may be due to lesions in the frontal eye fields, paramedian pontine reticular formation, rostral mesencephalon, parietal cortex, basal ganglia, superior colliculus or cerebellum. Changes in neurological functioning in the frontal eye fields, supplemental eye fields, parietal eye fields, right pre-frontal cortex, right posterior parietal cortex or cerebellum may impair fixation, resulting in unsteady fixation, drift, saccadic intrusions or even nystagmus [3, 26]. Individuals with any of the above versional ocular motor deficits may report difficulty reading due to slow reading speed, loss of place when reading, misreading/re-reading words or paragraphs, text appearing to float or shimmer and dizziness or visual motion sensitivity [3, 6, 8, 16].

Vergence ocular motility deficits

Vergence ocular motility refers to disjunctive changes in eye position as one regards objects at varying distances in the visual field, in contrast to versional ocular motility where the eyes move conjugately (i.e. change position together as a unit) [1, 6, 8, 16, 26]. Vergence deficits may be non-strabismic or strabismic (such as due to damage to cranial nerves III, IV or VI) in nature. Symptoms related to vergence deficits occur under binocular viewing conditions and may include diplopia, eyestrain, vision-related headaches, dizziness, exophoria (outward deviation of the eyes), intermittent exotropia (strabismus) during near vision and fatigue [3, 6, 8, 16]. Diplopia and eyestrain evident under binocular viewing conditions are common in those with TBI, which may affect rehabilitation of ADLs and mobility adversely. Diplopia and eyestrain under binocular viewing conditions may occur when both eyes are verged incorrectly (i.e. unable to align correctly) towards the object of regard. The most common type of vergence dysfunction among those with TBI is convergence insufficiency (CI) [3, 4], which may result from trauma along the oculomotor nerve and/or to the medial recti muscles, thereby impairing convergence [3, 4, 6]. CI is characterized by exophoria at near distances more so than far, a reduced near point of convergence (i.e. an inability to maintain adequate vergence as an object approaches from a farther to closer viewing distance) and insufficient positive fusional vergence ranges [3, 4, 6].

Visual vestibular disturbances

Gaze stabilization refers to the control of the vestibular-ocular-reflex (VOR). The VOR's primary

responsibility is to stabilize images on the retina while the head is in motion by producing eye movements in the opposite direction of head movements [8, 18, 26, 28–31]. VOR depends indirectly on visual input, but it is directed by signals from the vestibular apparatus of the inner ear [26, 28, 29, 32, 33]. Head rotation is detected by the semicircular canals and translation is detected by the otoliths [26, 28, 29, 32, 33].

The pathway for horizontal VOR commences with the semicircular canals being stimulated by head rotation. This initial stimulation is followed by a consequent interaction among the oculomotor (CN III), abducens (CN VI) and acoustic nerve (CN VIII) via the medial longitudinal fasciculus to move the eyes in a direction opposite to the head movement to stabilize gaze [3, 8, 26, 29–31].

Those with TBI may have visual-vestibular disturbances, which are often abnormalities of the VOR system, resulting in symptoms of dizziness, disequilibrium, vertigo, nausea, oscillopsia, photosensitivity to fluorescent lighting and increased sensitivity to visual motion in visually stimulating environments (i.e. malls, supermarkets, crowds) [3, 8, 30]. Reading may be difficult because words may seem to float or shimmer and computer tasks may be troublesome because of difficulty with scrolling or flickering of the screen [3, 8, 30].

Visual field defects

Visual field defects (VFDs) in those with TBI may be restricted overall, present with scattered defects throughout the visual field or manifest as a lateralized visual defect evident with or without visual inattention. VFDs may be due to trauma along the visual pathway anywhere from the optic chiasm through the optic radiations of the visual cortex. Those with lateralized VFDs, such as homonymous hemianopias, may cause a patient to ignore one half of the objects in space because they are located on his affected side. Associated symptoms with lateralized VFDs include difficulty reading with a slower speed of reading, bumping into objects on one side, forgetting food on one side of their plate, difficulty dressing one side of their body or difficulty navigating streets. Homonymous hemianopsia may pose a safety hazard because affected patients are not always aware of their visual field defect, which is referred to as visual inattention or, in more severe cases, visual anosognosia [8, 12, 16].

Light sensitivity

Photosensitivity (i.e. increased sensitivity to light) is ocular discomfort in the presence of light without ocular inflammation or pain [8, 14–16, 19]. Photosensitivity may be evident with all lighting or

selectively fluorescent lighting. While the exact underlying neurology for photosensitivity remains unclear, some hypothesize that it may be related to anomalous light and dark adaptation regarding general photosensitivity [8, 15]. Regarding selective light sensitivity to fluorescent lighting, anomalous critical flicker fusion frequency threshold may be contribution components [8, 14, 16, 19].

Light adaptation involves cones predominantly and occurs very quickly in a normal individual permitting the eyes to adjust progressively to increased magnitudes of light [15]. It is often determined by recording the stimulus contrast level perceived by the individual [15]. Conversely, dark adaptation, which involves rods predominantly, occurs more slowly than light adaptation and it refers to the recovery of contrast sensitivity in the dark following stimulation by bright light [15]. *Critical flicker frequency threshold* refers to the minimal (or extent of) magnitude of flicker frequency for which the individual reports perceiving a steady-state (rather than flickering) presentation of light [14, 19].

Colour blindness

Colour blindness refers to the inability to perceive colours as they are. Although this is most often due to a congenital genetic defect, TBI can result in this visual dysfunction. Damage as a result of trauma to areas such as the retina, optic nerve, parvocellular pathway of LGN or visual area V4 can result in defective colour perception [17].

Evaluation tools

Vision defects affect rehabilitation of ADLs and mobility and recovery of function in TBI patients. Outcomes of these patients post-injury may also be affected by their vision status. Some useful ways to measure the effect of vision deficit on the outcome of patients are Useful Field of Vision Test (UFOV) and Vestibulo-Ocular Monitoring (VOM).

Useful field of vision

The Useful Field of Vision (UFOV) test is a computer-operated measure of focused and divided visual attention [34]. It requires the participant to complete a task prompted by the computer. UFOV consists of three sub-tests: UF1, UF2 and UF3. UF1 measures focused visual attention on a single target with varied target durations. UF2 measures the ability to divide one's visual attention and identify a central target in addition to a peripheral target simultaneously. UF3 measures visual attention divided by background 'visual noise' [34]. This is used to assess one's ability to respond although there are many visual distractions.

There are many other uses for the UFOV test. It can be used to measure aspects of cognition in TBI patients or for ongoing evaluations to track patient progress and effectiveness of medications and interventions. Patient progression over treatment and expected time of hospital stay can be estimated [34]. In Calviano et al. [35] study, the UF2 test was highly correlated with other traditional tests of visual attention. In addition, functional independence measure (FIM) scores on admission and UF2 correlate with traditional outcome measures (FIM change and length of stay-LOS) as well.

Vestibulo-ocular monitoring

Vestibulo Ocular Monitoring (VOM) is based on video-oculographic recording of eye movements during galvanic labyrinth polarization (GaLa). The VOR is assessed from the eye movement response. VOM with GaLa performed during the first few days after TBI can predict favourable vs unfavourable outcomes [23]. It indicates function of the brainstem and can be a useful test in addition to standard imaging techniques (MRI, CT, etc.).

The VOM technique is performed by video-oculographic recordings of oculomotor responses (by VOR) during GaLa polarization of both labyrinths. Each exam consists of 1 minute of spontaneous eye movements elicited without stimulation followed by 1 minute of eye movements elicited by stimulation. It is used to examine comatose and neurologic intensive care patients with severe TBI.

Prediction of outcome is based on the production of eye movements by stimulation. Although sedative therapy does not affect this test, muscle relaxants paralyze extra-ocular muscles and mask VOM effects.

Treatment options

A compensatory treatment for accommodative disorders involves prescribing lenses for prolonged near vision tasks in lieu of, in conjunction with or following restorative accommodative treatment. Restorative treatment for accommodative disorders involves equalizing the accommodative amplitudes, improving the facility (i.e. the ability to *change* focus from far to near to far, on command repeatedly) of accommodation and the sustainability of accommodation. Restorative training techniques may involve using lenses to alter the virtual image of targets or viewing targets at various different viewing distances in free space [8, 16].

Compensatory treatment approaches for versional ocular motor deficits includes providing patients with large-print text if their visual acuity is reduced. Many of those with mild-to-moderate TBI who

Table I. Studies addressing vision impairment after traumatic brain injury.

Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
Astereopsis caused by TBI [37]	<ul style="list-style-type: none"> • 93 admissions from Emergency Department due to motor vehicle accidents (MVA). • Mean age 33.05. • Control: 30 admissions who presented for treatment of orthopaedic injuries w/o head trauma/neurologic deficit. <p>On admission to ED 79% of patients had a GCS of 13–15, 13% had a GCS of 9–12 and 8% had a GCS of 8 or less.</p> <p>Intracranial abnormalities were found in 44 patients, and skull fractures in 25.</p>	Unknown.	<p>Posterior parietal lobe injuries are observed to cause impairment in depth perception.</p> <p>Stereoaclity was assessed using Stereo Optical Company Test 004 after resolution of post-traumatic amnesia (PTA).</p> <p>The test consists of six items of graded difficulty that measures sensitivity to binocular disparities of 591–32 seconds of arc. Each item consists of a row of circles, one of which appears raised from the background when viewed through polarized glasses if stereopsis is adequate.</p>	<ul style="list-style-type: none"> • Stereopsis was significantly impaired by TBI when compared to orthopaedic injured controls. • Clinically significant impairment of stereoaclity was found in 41% of the head trauma group (performance was >2 SD below the orthopaedic control group mean). • Patients admitted with skull fractures had significantly lower stereopsis scores than those without, no difference was found in those with unilateral vs bilateral fractures. • Intracranial pathology was significantly associated with reduced stereopsis. Localization of lesions were examined, statistically significant reductions in stereoaclity were noted in trauma involving the parietal lobe. Damage to other cortical regions was not associated with significant reduction in stereopsis beyond diffuse injury from TBI. <p>The relationship between stereoaclity and cognitive test performance in the head trauma group demonstrated reduced stereoaclity associated with decreased visuospatial abilities and reduced visual/verbal memory efficiency.</p>
Antisaccades (AS) and remembered saccades (RS) in mild traumatic brain injury [38].	<ul style="list-style-type: none"> • 31 TBI patients. • 6 injury after alcohol intoxication (BAC 1.89–3.84). • 25 non-intoxicated (mean age 27.6). <p>Loss of consciousness (LOC) occurred in 15 patients, PTA was less than 1 hour and 7 patients had no amnesia.</p> <p>All patients scored 15/15 on the GCS and had normal clinical</p>	Eye movements studied 24 hours after trauma.	<ul style="list-style-type: none"> • Prospective study which defined mild TBI (mTBI) as traumatically induced brain dysfunction including LOC, loss of memory immediately before or after accident, focal neurologic deficit if LOC is <30 minutes with a 30 minute GCS of 13–15 and PTA less than 24 h • Eye movements were recorded 24 hours after trauma using infrared 	<ul style="list-style-type: none"> • The median latency time and percentage error for RS test were comparable between mTBI patients and control subjects, showing no significant difference between the two. The median percentage of errors on AS test was similar in control and non-intoxicated groups, demonstrating no significant difference between the two. • Weakly significant differences were found between the overall comparison

(continued)

Table I. Continued.

Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
	neurological exam at the time of antisaccades (AS) and remembered saccades (RS) testing.		<ul style="list-style-type: none"> • oculography (OBER-2 system) and analysed off-line. • Spontaneous saccadic intrusions were rejected (square wave jerks). • Both AS and RS tests consisted of 15 stimuli to the left and right in randomized order. The subjects were allowed to practice until the task was understood. 	<p>of the three groups among latency times for RS tests and error percentages in AS tests.</p> <p><i>Conclusions:</i></p> <p>Frontal lobe injuries are likely to occur in mTBI, however no significant difference in AS or RS was found between mTBI patients without intoxication and control groups. This may be because brain injury sustained by subjects was too mild to incur enough damage to the frontal lobe, AS and RS are not sensitive enough tests to evaluate mTBI and there may also be a negative effect from alcohol on the AS and RS results.</p>
	Assessment of vision and visual attention in minimally responsive brain injured patients [39].	3–16 weeks.	<ul style="list-style-type: none"> • 2F, 4M with severe brain injury. • Admission disability rating score 21–23. 	<p>Visual perception and attention are difficult to assess in minimally responsive brain injured patients. This article has examined each of six subjects with presentation of six combinations of a photograph and blank white card for six trials. This method has diagnosed hemi-field defects in three patients studied, hemispatial extinction in two patients and monocular pathology in two patients, one patient was found to have normal visual fields and perception, although he had monocular pathology. However, the sample in this study is too small for the results to be clinically and statistically significant. The overall conclusion of this paper states that the observation of a few responses is not sufficient to draw any firm conclusions.</p> <p>Visual assessment was performed with a set of 6–10 brightly coloured photographs obtained from each patient's family and a plain white card. A response was recorded as the first lateral eye movement made after presentation of the stimuli. Six trials of stimuli were presented with the order of presentation changing each time.</p> <p>Unilateral photo condition was thought to be the best test of vision in each field, triggering a large number of eye movements to the side of the stimulus in a patient with normal vision. The unilateral card should produce a similar pattern of results with fewer movements and responses because it is less visually stimulating. Then, by comparing the number of left eye movements to a left photo with a right card a measure of left-sided extinction can be developed.</p>

- 20 mTBI patients.
 - Undergraduates who were injured in sports, physical activities and falls.
 - All had grade 2 concussions according to the American Academy of Neurology: disorientation to time and place lasting greater than 15 minutes.
 - Controls were from the same undergraduate population and were matched for age (mean 21), gender (12 M, 8F), activity and education level to individual mTBI patients.

Attentional Disengagement Dysfunction after mild TBI assessed with gap saccade [40].

2 days after injury patients received initial exam. Re-evaluations performed at 1 week, 2 weeks, 1 month.

Participants with mTBI and controls exhibited a gap effect across all test sessions. However, during the first session the mTBI group demonstrated a significantly longer saccade latency at the 0, 50 and 100 ms gap durations, but not at the longer gap durations. This implies that the saccadic reaction times of participants with mTBI normalized as the contribution of disengagement process was decreased with increasing gap durations. The authors conclude that deficits in orientation of visuospatial attention in mTBI patients is due to difficulty disengaging attention and not problems with orientation and reengaging attention. Alteration in the gap effect also may signify that mTBI patients are unable to perceive the alerting cue that occurs when the fixation target disappears.

The authors hypothesized that alterations in gap effect compared to control subjects would signify that the difficulty mTBI patients have in directing their attention to space is related to a dysfunction in disengaging attention from the current fixation point. Subjects were asked to fixate on a target presented to them on a screen which disappeared after a variable delay and made them saccade to fixate on a new target. On gap trials a temporal interval of 50, 100, 150, 200, 250, and 300 ms was inserted between the disappearance of one target and appearance of new fixation point. 'No gap' trials the temporal interval was zero.

The horizontal movement of the subjects eyes was monitored at 200 Hz using an infrared corneal reflection device, which relayed information about the position of the eye with respect to the head. Participants were allowed 10 practice trials and subjects performed 8 blocks of 20 trials: 5 were no gap trials and 12 were trials where the saccade target was right of the fixation point and 12 to the left of the fixation point.

- Control group: 25 healthy students and collaborators (mean age 34) without history of soft tissue neck injury or head injury.
- 27 patients in MVA (14M, 13F).

Patients included in the study sustained whiplash injury grades II and III according to the Quebec Task Force Classification on whiplash-

1–2 years after whiplash.

The authors hypothesized that alterations in gap effect compared to control subjects would signify that the difficulty mTBI patients have in directing their attention to space is related to a dysfunction in disengaging attention from the current fixation point.

Subjects were asked to fixate on a target presented to them on a screen which disappeared after a variable delay and made them saccade to fixate on a new target. On gap trials a temporal interval of 50, 100, 150, 200, 250, and 300 ms was inserted between the disappearance of one target and appearance of new fixation point. 'No gap' trials the temporal interval was zero.

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Subjects underwent a kinesthetic sensibility test in which they were asked to fixate on a target, move their head to various positions and then relocate to the initial reference position. Oculomotor tests were performed 2 years post-injury:

- horizontal eye movements were recorded with electrodes placed bitemporally, smooth pursuit tests consisting of tracking a pendular light to the right and left were

Kinesthetic Sensibility Test:

- Whiplash patients showed higher errors in repositioning than in control subjects. Significant differences in repositioning were found between whiplash patients and the control group for all four directions (left, right, extension and flexion).
- Whiplash patients who were free of symptoms after injury had fewer repositioning errors after neck rotation to the left compared with those who

(continued)

Table I. Continued.

Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
Critical Flicker Frequency and Related Symptoms in mild TBI [14].	<ul style="list-style-type: none"> associated disorders. (Grade II includes neck complaints and skeletal signs; Grade III includes additional signs such as decreased or absent deep tendon reflexes, weakness and sensory deficits.) 	<ul style="list-style-type: none"> performed. Velocity of pursuit and number of superimposed saccades were recorded. Voluntary saccade test was performed by fixation on a light on a screen at angles of 30, 40 and 50 on either side of midline. Active cervical range of motion was recorded. 	<ul style="list-style-type: none"> had symptoms after injury. <i>Oculomotor Testing:</i> <ul style="list-style-type: none"> 62% of whiplash patients showed pathologic results in one of the smooth pursuit scales and at least one of the saccadic scales for two directions at the 2-year follow-up exam. Significant association was found between oculomotor dysfunction and repositioning dysfunction. Significant associations found between smooth pursuit scales and active range of motion Patients found to have oculomotor dysfunction were less likely to be accurate with head repositioning than those with normal oculomotor function. 	<ul style="list-style-type: none"> CFF was examined as a function of age in the control and mild TBI (mTBI) group. In the control group, no significant changes with age were noted; similar findings were seen in the mTBI group. CFF was found to be related to degree of light sensitivity, mTBI patients who were 'light sensitive' had a significantly higher CFF threshold value than those 'not light sensitive'. CFF is also related to degree of motion sensitivity. Mild TBI patients who were 'motion-sensitive' had significantly higher CFF threshold values than those 'not motion sensitive'. CFF was also found to be higher in groups who rated light sensitivity as 'very bothersome' compared to those with 'no symptoms'. <p><i>Conclusion:</i></p> <ul style="list-style-type: none"> Foveal CFF is not significantly different between mTBI patients and visually normal groups. However, individuals

Critical Flicker Frequency and Related Symptoms in mild TBI [14].

- 56 faculty and students of SUNY State College of Optometry as control subjects (ages 22–83, 25 M, 31F).
- TBI group = 18 patients from Raymond J. Greenwald Rehabilitation Center at SUNY State College of Optometry (ages 19–72, 6M 12F).

All patients were tested at least 3 months post-injury, with a range of 3 months to 15 years and a mean of 5.2 years.

- Subjects placed their chins into the CFF device and fixated on the centre of the test field. Subjects depressed a handheld clicker when they initially saw the flickering light appear to stop flickering and again when flickering resumed.
- Subjects were also asked to complete a questionnaire in which they were asked to rate the degree of light sensitivity and visual motion sensitivity on a scale of 1–4 (1 = never, 2 = mild, 3 = moderate, 4 = marked). They rated their discomfort associated with light sensitivity on a scale of 1–5 (1 = none, 2 = somewhat bothersome, 3 = bothersome without pain, 4 = bothersome with some pain associated and 5 = very bothersome and very painful).
- Additional questions were asked about types of illumination that were most troubling for patients

- and onset of light sensitivity.
- Subjects were also asked to identify exacerbating or alleviating factors for their light sensitivity.

who sustained mTBI's that exhibited photosensitivity had a higher CFF than those without photosensitivity. This is due to relative hypersensitivity to normal light conditions. TBI patients may develop a neurological disinhibition through injury which results in hypersensitivity to normal visual stimuli.

- 26 control (ages 15–60)
- 21 mild TBI (mTBI) patients with GCS score of 13–15 at time of injury.
- Patients had significant symptoms of TBI scoring >2 on the Head Injury Symptom Checklist.
- Conditions for study inclusion:

 - blunt, isolated TBI, PTA and non-intoxication at the time of testing. Patients were excluded if there was prior incidence of TBI, LOC, pregnancy, substance abuse, neurological or psychological diagnosis, seizure or general anaesthesia within 2 weeks of testing.

Deficits in predictive smooth pursuit after mild TBI [13].

- 6 patients examined 10 days after TBI (acute group).
- 15 patients evaluated 5 years after TBI (chronic group).

- Investigation of SPEM in mTBI patients was performed using a predictable sinusoidal stimulus, circular target tracking and patients were monitored over 50 second periods with 12.5 second sub-divisions.
- Eye movements were recorded by a human infrared video-based eye tracking system (Eyelink II).

The authors hypothesized that predictive smooth pursuit eye movements (SPEM) would be impaired in patients with TBI and this would be associated with deficits in attention, anticipation and executive function.

Conditions for study inclusion:

- blunt, isolated TBI, PTA and non-intoxication at the time of testing. Patients were excluded if there was prior incidence of TBI, LOC, pregnancy, substance abuse, neurological or psychological diagnosis, seizure or general anaesthesia within 2 weeks of testing.

The lack of difference in the TBI group vs control group after the first five cycles suggests that the control subjects were unable to maintain the generation of predictive SPEM, which resulted in the decline of their performance to the level of TBI subjects. TBI patients showed no changes in performance with each block.

- Greater eye position error was found in the TBI group compared to control subjects, correlations were found between eye position error and decreased target prediction.
- Increased intra-individual and inter-individual SPEM variability seen in TBI patients compared to controls.

- 17 TBI patients.
- 24–78y/o (mean age 45.9).
- 21 control subjects: students and faculty of SUNY College of Optometry (age 22–72, mean 39).

TBI at least 6 months prior to study.

- Subjects reported light sensitivity of mild, moderate and marked intensity.
- Instrument used was a LKC Technologies SST-1 Dark Adaptorometer. This desensitizes
- Individuals with TBI were found to have higher average threshold primarily on the rod portion of the dark adaptation curve.
- The final thresholds were considered elevated in TBI patients when

(continued)

Table I. Continued.

Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
Impaired eye movement in post-concussion syndrome [42].	• 36 Post-concussion syndrome (PCS) participants were compared with 36 individually matched controls (patients who sustained mild closed head injury but recovered well). • Injuries were sustained in MVA, falls.	3–6 months after mild closed head injury.	retinal photopigments to a zero baseline and measures sensitivity to light. • Testing was performed with the hand-held stimulator placed at the orbital rim of each subject presenting the pre-adapting field for 60 seconds. After being extinguished, measurements begin immediately. This is continued until the subject reports that the stimulus cannot be detected, threshold level and time to reach final threshold were recorded. Thresholds were determined at 30 second intervals over 12 minute test periods for each eye.	compared to the visually normal. Statistically significant differences were found in final thresholds of the TBI subjects who reported mild, moderate and marked photosensitivity when compared to the visually normal. However, the degree of threshold elevation did not correlate with degree of photosensitivity.
			Oculomotor testing: Measurements were recorded of reflexive saccades, anti-saccades, memory-guided sequences of saccades, self-paced saccades, sine and random oculomotor smooth pursuit. Eye movements were tracked using an IRIS infrared limbus tracker. Eye movements were achieved by instructing the subject to follow computer-generated stimuli on a computer monitor 45 cm in front of the subject. Neuropsychological tests and health status questionnaires were also performed.	Oculomotor tests: • PCS group had greater directional errors on anti-saccades and memory-guided saccades. The final eye position on anti-saccades was found to be hypermetric when compared with controls. • PCS group also had a larger number of positional errors of final eye position in anti-saccades and memory-guided sequences and a larger final amplitude error in memory guided sequences. • In memory guided sequences the PCS group showed poor timing and rhythm keeping, they also executed less self-paced saccades which had longer inter-saccadic intervals. • Slower peak velocity of self-paced saccades and longer saccade durations were also seen in the PCS group. • Tracking velocity was slower in the PCS group, there were a greater number of absolute errors and a larger number of 'catch-up' saccades.

- The incidence of visual perceptual impairment in severe TBI [43].
- TBI sample: 31 patients aged 15–30.
 - Mostly males who were labourers or trade workers.
 - To be included in the study patients had to have been diagnosed with a TBI and emerged from PTA, be able to speak, read and understand English, be able to hold a pen and be in stable medical condition.
 - Severe TBI patients.
 - Control group: 195 healthy males and females aged 16–68. Inclusion criteria: >15 years old, good health, able to read and understand English, ability to give informed consent.

3–13 months.

Measures of cognitive and functional impairment used with the TBI sample:

- The Functional Independence Measure (FIM).
- The Barry Rehabilitation Inpatient Screening of Cognition.
- The Rivermead Behavioural Memory Test.
- Cognitive screening measures used in control sample:
 - Mini-Mental Status Exam (MMSE).

- There are significant differences between the groups for incidence of agnosia, unilateral neglect, body scheme, constructional skills and apraxia. Impairment was higher in the TBI sample in all cases.
- No significant differences between the two groups were noted for impairment of acalculia or performance on the functional skills sub-scale.
- A small proportion of patients with TBI showed visual perceptual impairment on four of the seven OT-APST sub-scales, unilateral neglect was found as the most common impairment. More TBI participants were found to have a number of impairments on this test than the normal sample.
- 25% of TBI patients were found to have body scheme impairment, experiencing more difficulty with left/right discrimination and directionality than naming parts of the body.
- 25% of TBI sample demonstrated impairment in constructional skills.
- One third of the TBI sample had no impairment in visual perception or praxis skills according to the OT-APST.
- There was a higher incidence and frequency of perceptual impairment in the TBI group than the normal group, however there was no significant difference between samples for test duration. This may seem to be a strange finding since TBI patients typically have a slower processing speed on most tasks compared to healthy individuals, however the simple instructions of OT-APST may facilitate participants understanding and minimize the influence of their cognitive impairments.

(continued)

Table I. Continued.

Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
Occurrence of ocular disease in TBI [25].	<ul style="list-style-type: none"> 141 TBI subjects. 50 CVA subjects. ages 8–91. 	1 month–42 years. Mean 4.5 years.	The main categories of ocular disease examined include: anterior segment, pupil, crystalline lens and posterior segment the posterior segment. Frequency of occurrence of each targeted condition was recorded and tabulated. Determination of relative risk (RR) of each ocular disease was performed.	<ul style="list-style-type: none"> Ocular disease of the anterior segment, crystalline lens and posterior segment with a RR > 1 in TBI patients include: corneal abrasion, superficial epithelial keratitis, lagophthalmos, blepharitis, lid lesion, chalazion/hordoleum, dry eye, traumatic cataract of the lens. Disease of the posterior segment with a RR > 1 include vitreal prolapse, vitreous degeneration, optic atrophy, traumatic optic atrophy, peripheral retinal degeneration.
Occurrence of oculomotor dysfunction in acquired brain injury [3].	<ul style="list-style-type: none"> Ambulatory outpatients with vision symptoms. Majority of patients were referred from various rehabilitation institutions in New York City. 160 subjects with TBI. 	Mean of 4.5 years post-injury.	<ul style="list-style-type: none"> Five major categories of oculomotor dysfunction were examined: accommodation, version, vergence, strabismus and cranial nerve (CN) palsy. Frequency of occurrence of each targeted condition was recorded and tabulated. 	<ul style="list-style-type: none"> Accommodative dysfunction in the TBI group was seen in 41% of patients and the most common anomaly was accommodative insufficiency. The second most prominent oculomotor dysfunction was in vergence (seen in 56.3% of TBI patients). The most common anomaly of vergence was convergence insufficiency. Versional dysfunction was seen in 51.3% of TBI patients with the most common problem being deficits of saccades. Strabismus at near was seen in 25.6% of patients with TBI. Cranial nerve III and IV palsies were the most common CN dysfunctions in TBI patients.
Pilot study on ADL limitations in adults with homonymous hemianopsia [44].		2–300 weeks. Median time post-injury: 13 weeks.	Assessments include: distance visual acuity test, automated perimetry visual field test, hemi-inattention screening, reading performance test, ADL interview. Each evaluation was followed by an occupational therapy assessment: hemi-inattention screening, reading performance assessment, ADL interview.	<p>ADL's identified by participants as being difficult to complete because of their visual field defects (VFD) include personal hygiene and grooming (41% patients) and feeding (13% of patients). Instrumental ADLs that participants found difficult include: driving (98%), Shopping (94%), Meal preparation (50%), Financial Management (89%), Telephone use (15%).</p> <p><i>Instruments:</i></p>

- no physical impairment that affects ADLs.
- Most patients had complete homonymous hemianopia: central, foveal and peripheral field involvement in both eyes.
 - All other patients had homonymous quadrantanopsia.
 - More patients with left than right sided VFD.
 - Only 1 TBI patient, all others have VFD due to stroke.

Early Treatment Diabetic Retinopathy Study charts were used to measure distance acuity; Four tests from the Behavioural Inattention Test used for hemi-inattention (line crossing, letter cancellation, star cancellation and line bisection.) Reading performance was measured using Visual Skills for Reading Test (VSRT). A semi-structured interview was used to gather information about ADLs.

- Limitations of ADLs:*
- Challenges participants faced with grooming included applying make-up, shaving, cutting nails.
 - Difficulties encountered with feeding include not being aware of food on one side of the hemianopsia, knocking over unseen items.

Limitations in IADLs:

- Difficulties shopping are associated with mobility challenges (getting to the store), orientation while in the store, prevention of collisions with people, displays and objects, difficulty reading labels, identifying food items, paying for items with check or credit card, credit card readers.
- Financial management challenges include difficulty reading numbers on bills, staying on line and accurately positioning handwriting on bills and checks resulting in reduced legibility.
- Meal preparation is difficult for patients with VFDs due to problems reading recipes, measuring food, locating items on shelves and in the refrigerator, safely cutting/chopping items.
- Communication is difficult due to problems dialling telephone numbers.

More than 50% of cases had multiple cerebral lesions, 79.8% had additional neurological deficits.
HH results in difficulties with ADLs. May be caused by multiple lesions/diffuse injuries to brain.

- HH have a major legal and financial impact on patients due to effects on their driving and rehabilitation. Other activities such as reading and activities of daily living are also affected.
- In this study traumatic HH were found to occur more in men than women, African Americans than the general population and with a higher

(continued)

Median time from injury to initial VF test was 5 months (range 0.5–360 months).

Patients with history of TBI (103) and homonymous hemianopias (HH) (74F, 29M).

Traumatic homonymous hemianopia [45].

Retrospective review of medical records of patients with homonymous hemianopsia in the Neuro-Ophthalmology Unit at Emory University of Atlanta, GA.

Table I. Continued.

Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
Useful field of view (UFOV) after traumatic brain injury [34].	<ul style="list-style-type: none"> 23 TBI subjects who sustained closed head injuries from MVAs, GSW, falls, assault. Median PTA was 1–7 days. Control group: 18 subjects without neurological complaints. 	3–13 months.	<ul style="list-style-type: none"> Visual Acuity was tested with a Snellen chart at 20 feet. UFOV was measured with the Visual Attention Analyzer Model 2000. UFOV is a composite of three measures of visual processing: processing speed threshold for central vision, divided attention sub-test, selective attention sub-test. All sub-tests began with long stimulus durations that were gradually reduced to increase the difficulty. The scores from each sub-test were summed and higher UFOV scores indicate greater impairment, scores >40 indicate significant functional deficit. Each subject also participated in a neuropsychological evaluation. 	<p>frequency of multiple brain lesions accounting for VFDs and are associated with other neurologic deficits.</p> <ul style="list-style-type: none"> The TBI group had higher overall UFOV scores than the control group, which implies greater UFOV impairment. Significantly higher scores in the TBI group were seen in the divided attention and selective attention sub-tests than the control group. There was no difference seen between groups on the processing speed sub-test. Correlations between the UFOV and the Trail Making Test B were found to be statistically significant, other neuropsychological tests were not found to be correlated with statistical significance. Trail Making Test B is a measure of visuomotor tracking skills, its relationship with UFOV is correlated with driving evaluation outcomes. UFOV is not related to other psychological tests because it is not a measure of intelligence or cognitive function but more so a specific measure of attention and visual processing. <p><i>Conclusions:</i></p> <ul style="list-style-type: none"> TBI patients were found to have slower processing speeds and reach threshold performance at longer stimulus durations. There is a greater VF impairment in TBI patients than in visually normal participants; this suggests that TBI patients have more visual processing deficits as well. These include: slower information processing, mild impairment at eccentricities and greatest impairment on selective attention sub-test of UFOV. TBI patients may need more time to locate stimuli in cluttered

backgrounds and may be less accurate than visually normal people.

- Visual Field Defects in relation to head injury severity [46].
159 patients, who had CT scan within 96 hours of head injury and neuropsychologic exam within 10–19 months after injury were included. All patients had CT 96 hours post-injury, neuro-psychologic follow up 10–19 months later.
- At the time of injury 139 patients were under the care of neurosurgical ICU, the remaining 20 received medical care in the emergency department. CTs were obtained and intracranial pressure was managed. During the first 20 months follow-up was maintained.
- Neuropsychological tests were administered when patients were oriented to person, place and time.
- VF tests and visual acuity were measured.

- A statistically significant difference was found between the no VFD group and the VFD group with severe head injury; for learning, short-term recall and visuomotor speed. This difference did not exist for intelligence, acquired verbal skills and visuospatial skills.
- groups, average scores of the VFD groups were lower than the no VFD groups within each injury severity classification. This suggests greater dysfunction in the groups with VFD.
- Lower neuropsychological scores also suggest greater impairment of both severe head injury groups (VFD and no VFD) than both minor-moderate head injury groups.

- Average short-term memory measures, including immediate recall and savings of verbal and figural materials, were lower in VFD groups than for no VFD groups after both minor-moderate and severe injury.

Evaluation tools

Acquired brain injury, visual attention and Useful field of view test [35].

30–90 days.

15 patients with severe brain injury.

Three sub-tests administered by Visual Attention Analyzer.
• Primary factors affecting the size of the UFOV include: length of time the stimulus is visible, difficulty of the central vision task, eccentricity of the peripheral target, presence or absence of clutter in the field.

- Variables investigated across three tasks: UF1, UF2, UF3.
- UF1: Measures focused visual attention with single visual target identification in conditions of variable target duration.
- UF2: Measures divided visual attention.
- UF3: Measures divided visual attention with background visual noise conditions.

UFOV and Rehabilitation outcomes:

- Adminstration functional independence measure (FIM) and UF2 score are correlated with significance to FIM change and length of stay (LOS). UF2 is a major contributing factor of the outcome variance, this implies that rehabilitation progress in brain injured patients depends on visual attention and the ability to divide it.

UFOV Test as a Measurement of Impairment:

- UFOV test measured cognitive impairments in brain injured patients. The UF2 test correlates significantly with UF1 and with UF3 (which are at the upper and lower end of processing demand, respectively).
- Patients at the upper end of

(continued)

Table I. Continued.

Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
			<p>performance are discriminated by the UF1 test and at the lower end by the UF3 test. Patients whose total score (sum of UF1, UF2, UF3) range from very high to low are distinguished from one another by the UF2 score.</p> <p><i>UFOV Correlations with control measures:</i></p> <ul style="list-style-type: none"> • UFOV does not measure dementia, general properties of attention (that are non-visual) • UFOV measures visual attention ability <p><i>UF2 Correlations with selected visual attention tests:</i></p> <p>Correlations between UF2 and six measures of visual attention (visual span, forward and backward raw scores, TMT-A time, TMT-B time and number correct, digit symbol number correct).</p> <p><i>Clinical Implications:</i></p> <ul style="list-style-type: none"> • UFOV can be used to measure the effect of medications used to improve the patients' attention. • Assessment of attention over the course of recovery can be performed with the use of UFOV. • Provides three component measures of visual attention that can be used to characterize the patient's current visual attention and tasks that can be recommended to improve attention. <p><i>Main conclusion:</i> UFOV determines the degree to which patients with brain injury can divide their visual attention.</p> <ul style="list-style-type: none"> • Monocular and binocular visual acuity (VA) were reduced in TBI patients compared to controls. TBI patients complained that the stationary vision charts appeared to move or shift, which was not reported in the control group. 	
			<p>Visual evoked potentials evaluating treatment for post-trauma vision syndrome (PTVS) in patients with TBI [11].</p> <ul style="list-style-type: none"> • Experimental group: Mean age 24y/o, 3F, 7M. • Control group: 10 subjects chosen at random among hospital staff without TBI, 9F, 1M. 	<p>Unknown.</p> <ul style="list-style-type: none"> • History and review of medical records was performed for all participants. Each subject was given a visual acuity test at distance and near using Feltlloon Acuity and Lighthouse Near Acuity Charts, respectively.

- Visual skills testing included tracking and convergence. Tracking was recorded as smooth, jerky or fixation loss according to subjects' ability to follow movement of a ball. Convergence ability was recorded when diplopia was reported as the ball moved towards the subject.
- Cover test at distance and near was used to discover phorias and prisms were used to neutralize deviations.
- Refraction was determined on each subject.
- Accommodative tests included Bell and Book retinoscopy. Bell retinoscopy was performed by suspending the ball 40 cm in front of the subject while the retinoscopic reflex was examined for accommodative response, duration and loss of response. Book retinoscopy was performed by having the subject read 20/40 sized font at 40 cm, while the retinoscopic reflex analysed for focusing at the plane of fixation, focusing behind plane of fixation or focusing inside plane of fixation.
- After visual examination with direct and indirect ophthalmoscope, VEPs were performed using a Nicolet Compact Four Electrodagnostic System and a NIC 1015 Visual Stimulator. Full field binocular stimulation was performed, using chessboard-pattern reversal stimulation.
- During control conditions subjects were tested without bi-nasal occluders and base prisms. In experimental conditions subjects were tested with bi-nasal occluders and two diopters of base prism. In the final measurement the occluders and base prisms were removed and the participant was re-evaluated. Measurements included
 - Tracking and convergence difficulties were found in the experimental group with greater frequency than in the control group.
 - TBI patients were found to have a large amount of exophoria, causing the spatial perception of objects to appear far away.
 - Higher incidence of myopia was noted on refraction in the group of TBI patients, along with a lack of accommodative ability according to Bell and Book retinoscopy.
 - Other visual anomalies found in the TBI group include convergence insufficiency and third nerve palsy.
- The VEP of the TBI group shows a statistically significant increase in the amplitude when base-in prisms and bi-nasal occluders were introduced. This implies that there is some damage to the binocular cortical cells which function as part of the focal process. After TBI there is interference in organization of the VF which affects focalization, this causes the amplitude to be reduced on binocular VEP testing due to the compromised focal process. This process is related to attention, concentration and cognitive functions. Disturbances in this process affects binocularity, accommodation, convergence and oculomotor dysfunction.
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(continued)

Table I. Continued.

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Study	Subjects	Time post-injury	Methods/pertinent study information	Results/conclusions
Vestibulo-ocular monitoring (VOM) as a predictor of outcome after severe traumatic brain injury [18].	<ul style="list-style-type: none"> 26 patients with severe TBI (21M, 5F). Mean age of participants was 44.6. GCS <9. Patients admitted to the NICU for therapy of severe TBI. Participants are intubated and ventilated during tests. All patients had structural lesions on CT scan due to trauma. Patients with orbital and ocular lesions were excluded from the study. <p>The mean APACHE II score was 20.9 and mean SAPS was 45.3.</p>	VOM was performed 3 days after TBI.	<p>VOM technique is based on video-oculographic (VOG) recording of eye movements during galvanic labyrinth polarization (GaLa) stimulation of both labyrinths. Eye movement response is due to afferents of the peripheral neurons to the vestibular nuclei and to the oculomotor neurons (vestibulo-ocular reflex- VOR).</p> <ul style="list-style-type: none"> Each examination consisted of 1 minute of spontaneous eye movement recording, followed by 1 minute recording of GaLa stimulation. Eye movements were recorded by VOG and spontaneous eye movements were compared with GaLa elicited movements. If the oculomotor response power spectrum showed a clear peak at the frequency of the stimulus, the patient was determined to be a responder. Patients and caretakers were seen for follow-up in outpatient clinic or telephone interview 6 months after the trauma as well. 	<ul style="list-style-type: none"> GaLa induced eye movements were recorded in 15 patients, no oculomotor response (OMR) was elicited in the remaining 11. Those without OMR had an unfavourable outcome with a Glasgow outcome score <3 (GOS). Ten of the 11 patients without an OMR response expired. All of the non-OMR patients died within 15 days post-trauma, six were operated on to reduce intracranial pressure. From the group with positive OMRs, 13 patients had an outcome of GOS ≥3. The other two patients had unfavourable outcomes. Pupillary dilation was also found to be a prognostic indicator: dilated pupil was found in three patients with unfavourable outcomes, while normal pupillary diameter was noted in the remaining 23. This parameter is associated with a low sensitivity when compared to VOM. Use of VOM as an indicator of outcome prognosis in severe TBI based on GaLa induced OMR is possible. The use of VOM avoids limitations of other tests such as caloric and oculcephalic testing, no physical manipulation of the patient is required. Time required for testing is short (minutes) and stimulus parameters are defined and GaLa stimulation can be repeated as necessary. VOM represents a solution to technical restrictions, positioning tolerance and complexity of patient transportation/transfer involved in imaging studies such as MRI/CT used to monitor or measure outcomes. VOM is a useful alternative and complementary approach to identification of brainstem lesions by imaging.

present with versional ocular motor defects do not manifest reduced best-corrected clarity of vision and, for these individuals, the space between the lines and words is a greater issue. Therefore, for all presenting with impaired versional oculomotility, a typoscopic approach, in which an aperture/window is created to highlight the text of regard while obscuring non-pertinent text, is beneficial. Restorative treatment for versional ocular motor deficits includes basic visual scanning and searching techniques, during which the patient is encouraged to slow down and concentrate on accuracy first. Once accuracy has been achieved, then speed of visual processing may be addressed [8, 16].

Regarding vergence dysfunctions, the initial component of treatment is to aid the person in seeing singly with both eyes open simultaneously. For strabismic vergence dysfunction or non-strabismic, large magnitude vergence dysfunction, the first step in compensatory treatment is to apply fusional prism, if possible, to result in single binocular vision. If fusion cannot be obtained, then occlusion is to be incorporated in varying degrees (partial, graded or complete). In terms of restorative treatment for vergence, once fusion is achieved, vergence is stabilized in primary gaze (ramp and step) at far and near viewing distances. Then, the facility and sustainability of fusional vergence is addressed, while integrating vision with motor and/or audition [8, 16].

Optometric treatment options for visual–vestibular dysfunction are a combination of restorative, adaptive and compensatory [8, 16, 30].

For versional ocular motor and vestibular aspects, basic visual searching and visual scanning techniques are employed while encouraging accuracy initially and then concentrating on visual speed of processing. The difference is that the speed of the saccades and pursuit begin at a slower velocity, while the patient is seated and with minimal background distractors. Systematically, the velocity of the ocular motility and background distractors are increased, followed by the patient moving from being seated to standing to moving in place [8, 16, 30].

For vergence ocular motor and vestibular aspects, vergence (ramp and step) is stabilized at various viewing distances in primary gaze. It is then stabilized at various viewing distances at 30° right gaze and 30° left gaze to prepare for insuring accurate dynamic vergence while a patient performs a slow horizontal VOR. Once horizontal VOR and associated vergence has been trained and is accurate, then vergence (ramp and step) is stabilized at 25° upgaze and 25° downgaze. This prepares the patient to then train and insures accurate dynamic vergence while a patient performs a slow vertical VOR [8, 16, 30].

To improve function for basic ADLs in those with lateralized visual field defects, the treatment options

are compensatory. For all post-chiasmal lateralized visual field defects, spotting prisms, visual scanning strategies and compensatory/adaptation approaches may benefit the patient. In addition, for post-chiasmal lateralized visual field defects with inattention, the application of yoked prisms, mirrors and field expanding lenses may also benefit the patient [8, 16].

Treatment options for photosensitivity are compensatory, including the incorporation of tints with spectacle correction (30–40% tint for indoors, 80–85% tint for outdoors) for photosensitivity that is general to all types of lighting (using either brown or grey tints) or selective to fluorescent lighting (using either blue or grey tints). In addition, patients are often advised to wear brimmed hats to reduce the amount of illumination from above [8, 16].

Discussion

Traumatic brain injury is a common cause for visual dysfunction simply because of the proportion of the nervous system devoted to vision. Vision is a primary sensory input for most aspects of TBI rehabilitation. Despite increasing knowledge of the frequency, evaluation and management of visual impairment after TBI it is frequently overlooked [36].

Gait disturbance may be caused by several types of vision anomalies, including anomalies of visual field integrity, visual–vestibular function, vergence, accommodation and/or refractive status. VFDs may result in gait disturbance and these patients are often unaware of their VFD due to visual neglect or, in severe cases, visual anosognosia. Visual–vestibular defects may cause dizziness and loss of balance, which may impair gait training and also increase the patient's risk for falls. Diplopia due to vergence deficits and blurred vision due to anomalies of accommodation and/or refractive status may also impair ambulation.

Although sensorimotor vision defects are quite different from cognitive defects, they may exacerbate cognitive dysfunctions such as memory, attention, concentration and perception. Memory impairments such as amnesia and dementia may be exacerbated by lack of an adequate visual memory due to vision problems. Inaccurate smooth pursuit, tracking and fixation may also impair memory and attention.

Many vision problems discussed in this paper result in difficulty reading, which may present as slower reading pace, loss of place while reading, misreading/rereading text, dizziness and headache while reading. These may be mistaken for learning disabilities when, in fact, they are simply due to sensorimotor vision deficits following TBI. Attention and concentration are affected by ocular motility

problems such as versional and vergence ocular motor dysfunctions which make concentration increasingly difficult. Perception is adversely affected by VFD, colour blindness and inadequate depth perception as described earlier.

Conclusion

Common vision problems associated with TBI within the first year of injury include diplopia, VFD, blurred vision, photosensitivity, dizziness, vestibular-ocular dysfunction and versional ocular motor anomalies. It is important to screen TBI patients for sensorimotor vision deficits early on in recovery so that these issues may be addressed and recovery of function and independence in the community are not delayed.

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Optometric vision therapy in rehabilitation of cognitive dysfunctions caused by traumatic brain injury

Evidence-based review

Business Group	Clinical Services Directorate
Date requested	1 March 2015
Date completed	2 November 2015
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Important note

- The main purpose of this report is to review research evidence on the effectiveness of optometric vision therapy in rehabilitation of cognitive dysfunctions following traumatic brain injury.
- The systematic literature search for primary studies was undertaken for the period from January 2007 to May 2015.
- A reasonable attempt has been made to find and review all papers relevant to this topic; however, the search does not claim to be exhaustive.
- The report has been prepared by the Knowledge Management Team, Clinical Services Directorate.

Abbreviations used in this report

ADL – activities of daily living
CI – convergence insufficiency
mTBI – mild traumatic brain injury
OMT – oculomotor therapy
OVT – optometric vision therapy
RCT – randomised controlled trial
SIGN – Scottish Intercollegiate Guidelines Network
TBI – traumatic brain injury

Glossary of terminology (adapted from (Suter & Harvey, 2011))

Accommodation	The act of focusing the eyes to provide a clear image.
Active Optometric Vision Therapy	Treatment of visual problems with a range of equipment and techniques, such as penlights and mirrors and electronic optical instruments etc. Involves eye movement tasks designed to improve visual dysfunctions.
Attention	The cognitive process of allocation of processing resources, or selectively concentrating on one aspect of the environment.
Binocular	The organised simultaneous perception of information from the right eye and the left eye.
Convergence	See Vergence.
Oculomotor	Pertaining to eye movements, such as pursuits or saccades, or the muscle system controlling the eyes.
Optometric Vision Therapy	An umbrella term used to refer to a broad range of non-surgical treatments of a range of vision dysfunctions.
Passive Optometric Vision Therapy	Treatment of visual problems with eye patches, miotics, prisms, lenses etc
Pursuit	Ocular movement that holds the image of a target on the fovea, when either self, the target, or both are moving, to keep the dynamic image from blurring.
Saccade	A relatively rapid jump movement of the eyes from one place in space to another to bring images of objects of interest onto the fovea.
Vergence	Eye movements involving both eyes in which each eye moves in opposite directions. Vergence movements help to attain and

	maintain fusion at various distances. Convergence is the turning inward of the lines of sight to attain or maintain single vision while viewing objects or print at nearpoint.
Version	The movement of both eyes in a coordinated and conjunctive manner.
Saccadic latency	Time from stimulus change to saccadic onset.

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1 EXECUTIVE SUMMARY

Background

ACC receives requests to fund optometric vision therapy for clients with cognitive and visual dysfunctions following traumatic brain injury (TBI).

The purpose of this report is to review research evidence on the effectiveness of optometric vision therapy (OVT) in rehabilitation of cognitive dysfunctions secondary to TBI. The report attempts to answer two research questions:

1. Is OVT effective in cognitive rehabilitation of clients with TBI?
2. Is OVT better than no treatment in cognitive rehabilitation of clients with TBI?

Methodology

This report is based on a systematic review of relevant research published from January 2007 to May 2015. A detailed search strategy is provided in Appendix A.

The research on the effectiveness of OVT is critically appraised. The two authors of this report independently applied SIGN (Scottish Intercollegiate Guidelines Network, 2014) criteria to assess the quality of the primary studies identified through the literature search.

Results

The systematic search found five published papers relevant to the research questions. Overall these studies provide some evidence that OVT results in improvements in essential oculomotor functions such as vergence, version and accommodation. However, only one paper reports on a functional rehabilitation outcome, such as reading, from this type of therapy.

Furthermore, the following research limitations have to be noted:

- Four out of the five papers are based on one PhD research project with a sample size of 12 participants.

- The total length of treatment varies considerably, from 6 to 26 weeks, and the results suggest that in many cases this duration wasn't sufficient to bring about positive changes.
- The different treatment durations don't specify a treatment effect that could be achieved. Hence it is unclear what length of treatment is needed to achieve successful outcome(s).
- No follow-up beyond 3 months was reported; therefore it is not known whether the improvements in oculomotor function(s) are sustainable over a longer duration of time.
- Only one paper reported on cognitive functional outcomes (ie reading and attention).
- None of the studies measured how improvements in the oculomotor functions led to improved rehabilitation outcomes, such as return to work and activities of daily living.
- Placebo effect cannot be discounted. It has been highlighted that, while eye exercises appear to be effective in improving oculomotor functions, the motivation and encouragement effects of this therapy cannot be dismissed (Horwood, Toor, & Riddell, 2014).
- Individuals over 40 years of age were excluded from the trial, so it is unclear whether the findings of the studies can be generalised to older populations.
- Studies are done mostly on patients with mTBI and it has not been determined whether the results are applicable to individuals with the sequelae of moderate to severe TBI.

Conclusion

While some quality research has been done over the last decade, there is insufficient evidence that OVT has significant positive effects on the rehabilitation of patients with TBI.

Recommendation

The current available evidence is insufficient to support the use of OVT in post-TBI cognitive rehabilitation.

Based on this evidence the recommendation for OVT is: Do not purchase.

2 BACKGROUND

Visual pathways are vulnerable to insult in brain injuries, and traumatic brain injury (TBI) often results in compromising the integrity of the visual system. Hence visual complaints and problems are routinely observed following TBI, and the adverse effects of TBI on vision have been well described (Barnett & Singman, 2015; Greenwald, Kapoor, & Singh, 2012; Ventura, Balcer, & Galetta, 2014).

A review of 18 studies from the late 1990s to 2009 identifies common visual complaints and deficits in the first year after TBI. Common self-reported vision-related symptoms included blurred vision, reading difficulties, diplopia, eye strain, dizziness, visual field defects, colour blindness and light sensitivity. These symptoms were linked to damage of the visual and brain pathways and structures (Greenwald et al., 2012).

The common post-TBI clinical presentations include oculomotor dysfunctions, binocular dysfunctions, visual field deficits and/or reduced visual acuity (Alvarez et al., 2012; Ciuffreda et al., 2007). The common oculomotor dysfunctions are problems with vergence, version and accommodation (Ciuffreda et al., 2007; Ciuffreda & Ludlam, 2011; Suter & Harvey, 2011).

Cognitive dysfunctions are a common consequence of TBI. The cognitive sequelae include poor concentration and problems with cognitive processing speed, memory and executive function (Ubukata et al., 2014). The most common neurocognitive effects of TBI relevant in the context of OVT are problems with attention, memory, reading and the ability to concentrate.

OVT is an umbrella term used to refer to a broad range of non-surgical treatments of a range of vision dysfunctions. OVT is also referred to as oculomotor training, behavioural vision therapy, vision or visual training, and orthoptics. Another commonly used term is behavioural optometry, but there does not appear to be an agreed definition of behavioural optometry. This concept may reflect the extension of an optometrist's role beyond the traditional optometry model and include an optometrist's holistic approach to treatment of visual disorders (Barrett, 2009).

The range of vision therapy techniques is diverse. These techniques are categorised into passive and active. Passive methods include treatment of visual problems with eye patches, miotics, prisms, lenses etc. Active vision therapy is therapy that uses a range of equipment and techniques, such as penlights and mirrors, video games, biofeedback,

electronic optical instruments etc. The active approach involves eye movement and eye focusing exercises that are designed to remediate a person's vision dysfunctions and improve their overall visual function and performance.

While there is a range of active OVT equipment and techniques (and our review did not exclude any particular one), the studies that met the inclusion criteria all used a particular form of OVT - oculomotor training (OMT) via electronic computerised optical instruments. This OVT technique involves a person performing eye movement activities in response to visual stimuli presented to them via electronic or computerised optical instruments. For instance, a person is asked to track a light across a screen, or look to where a light flashed on the screen, and their saccadic or pursuit eye movements are recorded. A base-line recording is then compared to a normal range of eye movement responses for these tasks, and it is used to assess any improvement gained from trials of these eye tasks over a number of sessions. Measures for cognitive tasks such as reading are also pre and post assessed alongside the therapy sessions. This form of OVT uses OMT combined with attention training aimed at helping patients with mTBI to improve the function of their visual system and correct visual deficits (Barnett & Singman, 2015).

The business need

ACC receives requests to approve funding for ACC clients for treatment of visual dysfunctions secondary to TBI. Such requests are based on the premise that improvements in visual function support clients' cognitive rehabilitation following TBI and expedite return to work and activities of daily living (ADL).

ACC's current position on optometric vision therapy

ACC has not made formal purchasing recommendations in the past. ACC's current position is based on the brief report published in 2007 (Accident Compensation Corporation, 2007). The report concluded that at that time no studies had been published to assess the effectiveness of OVT in rehabilitation of cognitive dysfunctions secondary to TBI.

The purpose of this report

The main purpose of this report is to review clinical research on the effectiveness of vision therapy in rehabilitation of cognitive dysfunctions caused by TBI.

This paper focuses on the research questions:

1. Is OVT effective in cognitive rehabilitation of clients with TBI?
2. Is OVT better than no treatment in cognitive rehabilitation of clients with TBI?

This evidence review will inform ACC purchasing recommendations.

Structure of the report

This report covers a critical appraisal of primary research on OVT. It includes a brief background, describes the methodology of this review, summarises the key research papers and presents a critical appraisal of primary studies on OVT in rehabilitation of cognitive dysfunctions. The quality of these studies has been graded by the two authors of this report according to SIGN (Scottish Intercollegiate Guidelines Network, 2014) quality criteria. Detailed evidence tables are presented in Appendix A.

3 REVIEW OF PRIMARY STUDIES 2007-15

This section outlines the methodology of this review, presents its key findings and provides a summary of the five research papers selected through the systematic search.

Methodology

Two researchers systematically searched the key medical and psychology databases. The search strategy is explained in detail in Appendix B.

The search identified 12 primary OVT research papers related to TBI-induced cognitive dysfunctions. Out of these publications five papers were selected using the inclusion and exclusion criteria outlined below. The seven excluded studies were related either to establishing vision therapy measurements only or to non-TBI conditions (ie stroke, convergence insufficiency in children).

Despite further research carried out since 2007, only one study was found that directly answers the main research question: whether vision therapy may improve rehabilitation outcomes for patients with TBI.

Study inclusion criteria

- study design level 2 and above (cohort studies, interventional design, randomised controlled trials (RCTs))
- studies that included patients with visual sequelae of TBI

- all degrees of TBI severity were included (mild, moderate and severe)
- studies on 'active' vision therapy, eg eye exercises carried out under the direction of a trained optometrist
- publications in English language
- studies published since January 2007.

Study exclusion criteria

- non-analytical studies (eg case control studies, case series, case studies)
- publications in languages other than English
- studies that included patients with acquired brain injuries (eg stroke) and children with vision dysfunctions unrelated to TBI
- studies on 'passive' vision therapy, eg lenses, prescription glasses
- studies published before January 2007.

Main findings

This appraisal includes five papers: one report on a retrospective study and one cross-over interventional trial. Studies were critically appraised using the SIGN criteria and detailed evidence is presented in Table 2 in Appendix A.

Primary studies

RETROSPECTIVE COHORT STUDY

In a retrospective study, Ciuffreda et al. (2008) analysed the records of 33 patients with TBI. All patients were referred to and completed a full course of an OMT programme. The patients' oculomotor symptoms and signs were measured at the start and after the completion of the programme. An improvement in at least one of the signs and symptoms on the completion of the programme was deemed a success. Ninety percent of patients had either complete, or significant, reduction in their oculomotor-based symptoms and clinical signs, and these improvements remained when measured at 2 to 3 months after the therapy. The authors concluded that the findings demonstrate the effectiveness of OMT in rehabilitation of oculomotor abnormalities associated with TBI (Ciuffreda et al., 2008).

STUDIES USING SAME COHORT OF PARTICIPANTS

The four studies described below are based on one PhD research project (Thiagarajan, 2012). This research used the same sample of 12 patients, but the papers report on the effects of OMT on three different oculomotor dysfunctions and one functional outcome (ie reading). The first paper reports on the effects of OMT on version (Thiagarajan & Ciuffreda, 2014a), the second paper analyses the effects of OMT on vergence (Thiagarajan & Ciuffreda, 2013), the third study measures the OMT effects on accommodation (Thiagarajan & Ciuffreda, 2014b), and the fourth article presents the reading-related measures (Thiagarajan, Ciuffreda, Capo-Aponte, Ludlam, & Kapoor, 2014).

The study was designed as a cross-over interventional experimental trial where subjects were blinded to the nature of the intervention. During phase 1, odd-numbered participants received OMT and every even-numbered subject received placebo treatment. During phase 2, the groups swapped interventions. Each phase lasted for 6 weeks, with a 1-week interval between the phases. The total duration of the study was 15 weeks, and it included taking baseline measurements 1 week before the start of the programme and the repeat baseline measurements 1 week following phase 2. Each subject received two 60-minute training sessions per week, with total training time of 9 hours.

CHARACTERISTICS OF THE PARTICIPANTS INCLUDED IN THESE STUDIES

The characteristics of the participants included in these studies are shown in Table 1 below. All patients were classed has having mTBI and the table below shows that the aetiology of their TBI was mainly from motor vehicle accidents (MVAs), followed by falls, assaults and hitting head against a metal rod-shaped device. The patients were young, aged between 24 and 33 years, and had variable visual symptoms, although the majority reported they had 'eye strain'. Time lapse after initial TBI was variable.

Also of note, there is nothing about imaging in these patients so their inclusion is done from the aetiological effects of their TBI rather than what is known about their structural damage, so it is not identified what parts of their brain were affected.

To be included in these studies the participants had to have at least one clinical sign reflecting accommodative dysfunction, stable health and no significant cognitive dysfunction.

Table 1: Demographics of study participants - Thiagarajan & Ciuffreda (2014b)

Age (yrs)	Age at mTBI (yrs)	Mechanism of mTBI	Visual symptoms/complaints
25	23	Head hit against metal rod	Slow reading, skipping lines
27	22	Head hit with baseball bat	Intermittent diplopia, poor concentration, intermittent blur at near
30	27	Assault	Eye strain, difficulty reading, poor focusing ability
31	25	MVA	Eye strain, headache
25	22	MVA	Difficulty performing computer work, eye strain
24	22	Fall	Difficulty performing ophthalmoscopy, eye strain
29	27	MVA	Intermittent blur, intermittent diplopia, difficulty reading, skipping lines, visual motion sensitivity
28	27	Fall	Headache, near vision blur, intermittent diplopia
33	31	MVA	Blurry vision, intermittent diplopia, difficulty reading, peripheral visual motion sensitivity
29	25	MVA	Headache, intermittent diplopia at near, trouble focusing at near, dry eye, hyperacusis, photosensitivity, eye strain
33	31	Assault	Difficulty shifting focus, blur at near, loss of place while reading, visual fatigue, headache, nausea, loss of balance
31	25	Fall	Intermittent diplopia, imbalance, difficulty reading

Study 1: Thiagarajan & Ciuffreda (2013)

A single-blinded cross-over interventional study compares the results of OMT to placebo training in a group of 12 patients with mTBI. Each patient received vision training (Treatment A) as well as placebo training (Treatment B). The training was delivered by an optometrist in a college-based laboratory. The study lasted for 15 weeks. During the first phase (first 6 weeks) half of the group received Treatment A, while the other half received Treatment B, both for 9 hours a week. In the second phase, after 6 weeks of training and a 1-week break the groups swapped the interventions. Objective laboratory and subjective clinical measures of vergence were measured before and after vergence-based OMT. The authors reported subjective and objective improvements in nearly all of the measures of vergence, and increased visual attention concurrent with OMT (Thiagarajan & Ciuffreda, 2013).

Study 2: Thiagarajan & Ciuffreda (2014a)

The second paper in the series describes the effects of the OMT on version. The vision parameters were assessed before the start of the interventions, and 1 week after each phase. The study measured versional eye movements: binocular central fixation, saccadic gain, saccadic latency and saccade ratio.

The results indicated significant and statistically significant improvement in overall oculomotor function following the OMT. The authors suggested that OMT had a positive impact on version; however, the duration of treatment was not long enough to normalise oculomotor control, and treatment protocols needed to be further refined (Thiagarajan & Ciuffreda, 2014a).

Study 3: Thiagarajan & Ciuffreda (2014b)

The third paper in the series reports on the effects of OMT on accommodative dysfunction. The participants' common symptoms and complaints were difficulties with reading, eye strain, headaches, intermittent diplopia, blurry vision, poor focusing and concentration, and visual fatigue. The study assessed the following parameters: clinical measures using vision-related tests, laboratory measures of accommodative dynamics, subjective visual attention using a validated tool, and a near vision symptom-related scale. The authors concluded that subjectively and objectively nearly all abnormal parameters of accommodation were improved as a result of OMT (Thiagarajan & Ciuffreda, 2014b).

Study 4: Thiagarajan et al. (2014)

The fourth paper presented the effects of OMT on reading and attention. The authors made references to the effects of TBI on reading through disruptions in coordination in the oculomotor (vergence, version and accommodation) and non-oculomotor (eg attention, speech, memory) processes. The paper analysed the results of the study in relation to reading. The study used the same pool of 12 participants to record reading eye movements, and to compare a range of reading-related measures, such as reading rate in words per minute, number of progressive and regressive saccades, and comprehension. The study also tested visual attention and self-reported symptoms. The results demonstrated improvements in the vast majority of measured oculomotor parameters. Sham treatment had no significant effect on any of the measured parameters.

However, many of the measures didn't normalise, and the authors hypothesised that increasing the time for oculomotor rehabilitation could lead to more positive results (Thiagarajan et al., 2014).

Limitations of these studies

The authors listed the following limitations of this research:

- Only patients with mTBI were included; hence any positive or negative effects found with OMT for less or more severe TBI are limited.
- The duration of training was limited to 9 hours. Future studies need to determine whether longer durations may be more effective.
- A longer-term follow-up is required at regular intervals up to 4 years after the initial treatment (Thiagarajan et al., 2014).

In addition, the cross-over intervention's experimental design is a limitation as it doesn't allow control for carry-over effect. Furthermore, the fact that the studies come from the same group of researchers introduces a risk of researcher bias, as these results have not been replicated yet by any other research groups.

The SIGN ratings given to these studies by the two authors of this report (see Table 1 in Appendix A) suggest that research in this area is of an acceptable quality.

HORIZON SCANNING

This appears to be an emerging area of research. The authors of these papers indicated that further follow-up will be carried out on the participants three and six months after the

intervention. It may be warranted to revise this review in the future when new research relevant to the research questions is published.

4 DISCUSSION

The key research question this report attempted to answer was whether OVT is an effective treatment modality and provides tangible and sufficient benefits to people recovering from TBI.

The systematic search found five papers directly relevant to the research questions, and these studies were critically appraised using the SIGN criteria.

Overall, the studies provide some evidence that OVT results in improvements in some specific oculomotor functions (such as vergence, version and accommodation). One of these studies reports how the improvements in oculomotor function translate into improved cognitive outcomes (ie improvement in reading).

However, the following research limitations have to be noted:

- four out of the five papers are based on one PhD research project, with a sample size of 12 participants
- the total length of treatment varies considerably, from 6 to 26 weeks, and the results suggest that in many cases this duration wasn't sufficient to bring about positive changes
- the different treatment durations do not specify a treatment effect that could be achieved. Hence it is unclear what length of treatment is needed to achieve successful outcome(s)
- no follow-up beyond 3 months was reported; therefore it is not known whether the improvements in oculomotor function(s) are sustainable over a longer duration of time
- only one paper reported on cognitive functional outcomes (ie reading and attention)
- none of the studies measured how improvements in oculomotor functions led to improved rehabilitation outcomes, such as return to work and activities of daily living
- placebo effect cannot be discounted. Horwood et al. (2014) highlighted that, while eye exercises appear to be effective in improving oculomotor functions, the

motivation and encouragement effects of this therapy cannot be dismissed (Horwood et al., 2014)

- individuals over 40 years of age were excluded from the trial, so it is unclear whether the findings of the studies can be generalised to older populations
- studies are done mostly on patients with mTBI and it has not been determined whether the results are applicable to individuals with the sequelae of moderate to severe TBI.

5 CONCLUSIONS AND RECOMMENDATION

While some research has been done over the last decade, no studies have been found to demonstrate that OVT has a significant positive effect on cognitive rehabilitation following TBI. It should be noted, however, that this is an emerging area of research.

There is evidence of some benefits in using this treatment modality for improving oculomotor functions, such as vergence, version and accommodation. However, this research does not translate the positive effects into functional gains, and it does not answer the key research question of whether OVT expedites or enhances post-TBI recovery of cognitive function.

Overall, the current published evidence is insufficient to determine that OVT is more effective than no treatment in rehabilitation of clients with TBI-related cognitive dysfunction.

Based on this evidence, the recommendation for optometric vision therapy is: Do not purchase.

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APPENDIX A – CRITICAL APPRAISAL

Table 2: Critical appraisal of primary studies on effectiveness of optometric vision therapy in rehabilitation of TBI patients.

Reference Study design SIGN grade	Participants	Intervention	Outcome measure(s)	Limitations	Results and conclusions
Ciuffreda, Rutner, Kapoor, Suchoff, Craig, & Han (2008) Retrospective Single Cohort Study Level = 2+	33 TBI patients who were prescribed and completed an optometric vision therapy programme in one optometry clinic. All patients had accommodative, versional and/or vergence oculomotor dysfunctions following TBI. Age range 11-66 years. Range of years post-injury 0.25-20.17 years.	Conventional vision therapy: vergence, version, and accommodative therapies. The number of sessions per participant: from 10-14 to 26-30. The sessions were conducted over 2-8 month period.	Measured symptoms and signs before and after the intervention. Most common self-reported symptoms: ocular motility when reading, eyestrain, diplopia, headaches and visual fatigue. The most common signs detected by optometrists: Preceded nearpoint convergence; abnormal developmental eye movement (DEM); reduced near convergence range. Success defined as improvement in at least one primary symptom and sign.	<ul style="list-style-type: none"> no control group no information on the severity of TBI no follow-up beyond 3 months no measurements of the impact of the improvements in signs and symptoms on quality of life or functional outcomes no method for excluding those who had had visual difficulties before their mTBI the selection of cases and assessment of success was not blinded but done by a single therapist; hence researcher's bias can't be discounted. 	<p>Improvements or normalisation of symptoms and signs were recorded in 90% of sample.</p> <p>Improvements remained stable at retesting 2-3 months later.</p> <p>Authors' conclusions: Optometric vision therapy can be an important modality in the vision rehabilitation for oculomotor dysfunctions subsequent to TBI.</p> <p>Reviewers' comments: This study shows that nearly all participants had an improvement in at least one clinical sign and/or symptom after several weeks of conventional vision therapy. It doesn't measure the impact of this intervention on quality of life or effects on activities of daily living or vocational rehabilitation.</p>

Reference Study design SIGN grade	Participants	Intervention	Outcome measure(s)	Limitations	Results and conclusions
Thiagarajan & Ciuffreda (2014a) PhD research Single-blinded individual cross-over interventional experimental design Level = 1-	12 participants (8 females; 23-33 years old), diagnosed with mTBI, 1-10 years post-injury. Inclusion criteria: TBI at least 1 year post-insult to control for natural 6-9 months neurological recovery. At least one symptom (eg diplopia) and 1 clinical sign (eg receded nearpoint of convergence). Intact cognition and no other significant comorbidities. Exclusion criteria: Age over 40 as in older age accommodation can't be measured reliably. Vision acuity is poorer than 20/30 in either eye. Strabismus, amblyopia or ocular disease. Medications affecting oculomotor function and/or attention.	Each subject received oculomotor training (OMT) (Treatment A), as well as placebo training (P) (Treatment B) in two separate phases – 6 weeks each, 2x45 min sessions a week. 15 min was allocated to training three oculomotor functions: version, vergence and accommodation. Version (fixation, predictable saccades and simulated reading) was trained via the computerised oculomotor rehabilitation (COR) software.	Measured version: Binocular central fixation Saccadic gain Saccadic latency Saccade ratio.	<ul style="list-style-type: none"> • small sample size • no data on whether the subjects had vergence problems before the mTBI • no follow-up beyond 1 week after treatment (authors indicated that a follow-up at the 3rd and 6th months was on-going) • the problem with using patients as their own control in this cross-over pattern is that it assumes that those who have the active treatment in the first 6 weeks don't carry over any change (better or worse) into their 2nd control period • Symptoms may have been erroneously attributed to mTBI, and patients not screened for other diagnoses, such as orbital fractures or depression. 	Significant reduction in horizontal fixational error. Saccadic gain increased horizontally and vertically. Saccade ratio for the simulated reading, multiple-line paradigm reduced significantly. No measures changed significantly following the P training. Authors' conclusion: Versional tracking significantly improved with the oculomotor training. Reviewers' comments: Authors commented that the 6-week course of OMT was not sufficient to normalise oculomotor control in many cases. They suggest the need for further research to determine the optimal duration of training.

Reference Study design SIGN grade	Participants	Intervention	Outcome measure(s)	Limitations	Results and conclusions
Thiagarajan & Ciuffreda (2013) PhD research Single-blinded individual cross-over interventional experimental design Level = 1-	12 participants (8 females; 23-33 years old), diagnosed with mTBI, 1-10 years post-injury. Inclusion criteria: TBI at least 1 year post-insult to control for natural 6-9 months neurological recovery. At least one symptom (eg diplopia) and one clinical sign (eg receded nearpoint of convergence). Intact cognition and no other significant co-morbidities. Exclusion criteria: Age over 40 as in older age accommodation can't be measured reliably. Vision acuity is poorer than 20/30 in either eye. Strabismus, amblyopia or ocular disease. Medications affecting oculomotor function and/or attention.	Each subject received oculomotor training (OMT) (Treatment A) as well as placebo training (P) (Treatment B) in two separate phases – 6 weeks each, 2x45 min sessions a week. The placebo treatment was rapidly changing the lenses in the test without changing the refractive power of the lens.	Measured vergence: a range of static and dynamic vergence responses. A single outcome only was tested for: whether the subjects improved. Worsening wasn't tested for, but this makes a difference to the statistical tests applied.	<ul style="list-style-type: none"> • small sample size • no information on whether the subjects had vergence problems before the mTBI • no follow-up beyond 1 week after treatment (authors indicated that a follow-up at the 3rd and 6th months was ongoing) • using patients as their own control in this cross-over pattern assumes that those who have the active treatment in the first 6 weeks don't carry over any change (better or worse) into their 2nd control period • symptoms may have been erroneously attributed to mTBI, and patients not screened for other diagnoses, such as orbital fractures or depression. 	<p>Significant improvement in most aspects of vergence eye movements affecting positively on nearwork-related symptoms and visual attention.</p> <p>None of the measures changed significantly following the P training.</p> <p>Authors' conclusions: Vergence-based OMT is effective in improving abnormal measures of vergence. Reduction in symptoms and improvement in visual attention were attributed to the plasticity of neural visual system and oculomotor learning effects.</p> <p>Reviewers' comments: The authors report that while most of the vergence parameters improved with OMT, many did not normalise. They suggest OMT needs to be increased two-fold or more to obtain a more robust result.</p> <p>This trial proves that training improves performance of tests, and any interest shown in a patient may improve their subjective feelings.</p>

Reference Study design SIGN grade	Participants	Intervention	Outcome measure(s)	Limitations	Results and conclusions
Thiagarajan & Ciuffreda (2014b) PhD research Single-blinded individual cross-over interventional experimental design Level = 1-	12 participants (8 females; 23-33 years old), diagnosed with mTBI, 1-10 years post-injury. Inclusion criteria: TBI at least 1 year post-insult to control for natural 6-9 months neurological recovery. At least one symptom (eg diplopia) and one clinical sign (eg receded nearpoint of convergence). Intact cognition and no other significant co-morbidities. Exclusion criteria: Age over 40 as in older age accommodation can't be measured reliably. Vision acuity is poorer than 20/30 in either eye. Strabismus, amblyopia or ocular disease. Medications affecting oculomotor function and/or attention.	Each subject received oculomotor training (OMT) (Treatment A) as well as placebo training (P) (Treatment B) in two separate phases – 6 weeks each, 2x45 min sessions a week. The placebo treatment was rapidly changing the lenses in the test without changing the refractive power of the lens.	<ul style="list-style-type: none"> • accommodation: • clinical measures using vision-related tests • laboratory measures of accommodative dynamics • subjective visual attention using a validated tool • near vision symptom-related scale (CISS). 	<ul style="list-style-type: none"> • small sample size • no information if subjects had vergence problems before mTBI • no follow-up beyond 1 week post treatment (authors report ongoing 3 and 6 mth follow up) • using subjects as their own control in cross-over pattern assumes those doing active treatment first don't carry over any change (better or worse) into their 2nd control period • symptoms may have been erroneously attributed to mTBI, and subjects not screened for other diagnoses, such as orbital fractures. • authors report accommodation velocity and latency not tested for sensory processing. 	<p>Significant increase in the maximum accommodative amplitude both monocularly and binocularly.</p> <p>Near vision symptoms reduced along with improved visual attention. No measures changed significantly following P training.</p> <p>Authors' conclusion: OMT was effective in improving nearly all of the abnormal parameters of accommodation.</p> <p>Reviewers' comments: The authors report that this is the first objectively based study demonstrating positive effects of OMT on accommodative responsivity for mTBI people. This study provides a very good starting point for future research. It highlights relevant factors in vision therapy such as task repetition, increasing complexity, participants' active participation, and motivation. It also sets out specific accommodation measures that may be used in future research.</p>

Reference Study design SIGN grade	Participants	Intervention	Outcome measure(s)	Limitations	Results and conclusions
Thiagarajan , Ciuffreda, Capo-Aponte, Ludlam, & Kapoor (2014) PhD research Single-blinded individual cross-over interventional experimental design Level = 1-	12 participants (8 females; 23-33 years) with diagnosed mTBI 1-10 years post-injury. Inclusion criteria: TBI at least 1 year post-insult to control for 6-9 months natural neurological recovery. At least one symptom (eg diplopia) and one clinical sign (eg receded nearpoint of convergence). Intact cognition and no other significant co-morbidities. Exclusion criteria: Age over 40 as in older age accommodation can't be measured reliably. Vision acuity is poorer than 20/30 in either eye. Strabismus, amblyopia or ocular disease. Medications that affect oculomotor function and/or attention.	Each participant received oculomotor training (OMT) (Treatment A), as well as placebo training (P) (Treatment B) in two separate phases – 6 weeks each, 2x45 min sessions a week. 15 min was allocated to training three oculomotor functions: version, vergence and accommodation.	<i>Clinical parameters:</i> Nearpoint of convergence (NPC) Nearpoint of accommodation (NPA) Reading eye movements <i>Laboratory parameters:</i> Binocular horizontal versional eye movements Saccade ratio <i>Subjective visual attention test</i> <i>Symptom scale (CISS).</i>	<ul style="list-style-type: none"> performed 9 hours training and suggested more training sessions are needed but unclear how many. small sample size. no information on whether subjects had vergence problems pre-mTBI no follow-up past 1 week post treatment (authors indicated 3 and 6 mth follow-up ongoing) using subjects as their own control in this cross-over pattern assumes those who do active treatment in the first don't carry over any change (better or worse) into their 2nd control period symptoms may be erroneously attributed to mTBI, and subjects not screened for other diagnoses such as orbital fractures. 	<p>Over 80% of abnormal parameters significantly improved. Reading rate, vergence amplitudes and accommodation improved markedly. Saccadic eye movements showed rhythmicity and accuracy. Improved reading-related oculomotor behaviour shown in reduced symptoms and increased visual attention. No parameters changed with placebo therapy.</p> <p>Authors' conclusion: OMT resulted in significant improvement in oculomotor control, reading rate and overall reading ability.</p> <p>Reviewers' comments: This is the only paper that reports improvement in a specific cognitive function (reading). The authors note that except for accommodative facility rate, the oculomotor significant parameters did not normalise; thus future research is needed to test therapeutic protocols. Only 7 out of 12 subjects complained of reading difficulty; however, all 12 were assumed to have reading difficulty, and same statistical methods were used.</p>

APPENDIX B – METHODOLOGY

Literature search strategy

SCOPE

The objective of the search strategy was to conduct a systematic search looking for primary studies that would answer the research questions:

1. Is vision therapy effective in rehabilitation of clients with TBI?
2. Is vision therapy better than no treatment in rehabilitation of clients with TBI?

The systematic literature search time period was January 2007 to May 2015. This search interval extends an ACC literature review on this topic completed in 2007. This literature search was open to all degrees of TBI severity.

A SIGN (2014) critical appraisal checklist was completed for each primary study identified and rated according to SIGN criteria.

SEARCH CRITERIA

This literature review is based on the following PICO (population, intervention, controls and outcomes) framework (Richardson, Wilson, Nishikawa, & Hayward, 1995) principles for formulating search criteria:

- Population of interest is open to gender, age range, ethnicity, socio-economic status, education, occupation, culture, and residential location.
- Intervention is vision therapy for cognitive dysfunction (eg reading, memory, attention) in relation to ocular dysfunctions (eg convergence insufficiency) related to mTBI.
- Where control/comparison groups are utilised in the research they will typically be a ‘no vision therapy’ control group or ‘normal vision’ comparison groups. Other control/comparison groups will be taken into account if they meet SIGN (2014) standards.
- Outcomes relate to improving ocular defects, which in turn improve cognitive functions such as reading, memory and attention tasks. Measures of these outcomes will be reliable and valid optical medicine tests.
- The time period is from January 2007 to 31 May 2015.
- The SIGN (2014) guidelines for quality of evidence-based medicine (EBM) research are to be adhered to.

DATABASES SEARCHED

1. Cochrane Library
2. OvidSP 1956 to current (bibliographic databases, academic journals, and other products, chiefly in the area of health sciences – MeSH terms). Includes MEDLINE(R) without Revisions 1996 to May Week 4 2015
3. PsycINFO (abstracts of literature in the field of psychology)
4. Scopus (scientific, technical, medical, and social sciences – including arts and humanities)
5. Web of Science (scientific and academic cross-disciplinary research citation indexing; highly cited articles and most recent publications)
6. EBSCO: MEDLINE, CINAHL Plus with full text, Biomedical Reference Collection: Comprehensive, Psychology & Behavioral Sciences Collection, PsycARTICLES, CINAHL Select
7. EBM Reviews – Cochrane Central Register of Controlled Trials
8. EBM Reviews – Database of Abstracts of Reviews of Effects
9. EBM Reviews Full Text – Cochrane DSR, ACP Journal Club, and DARE
10. All EBM reviews – Cochrane DSR, ACP Journal Club, DARE, and CCTR
11. ProQuest
12. References to relevant research listed in the referenced articles
13. References on the NORA website by the Australasian College of Behavioural Optometrists.

SEARCH KEYWORDS

traumatic brain injury (TBI), acquired brain injury (ABI), behavioural optometry, optometry, optometric vision therapy, optometric therapy, vision therapy, vision training, orthoptics, eye training, eye exercise, oculomotor rehabilitation, vision rehabilitation, oculomotor vision rehabilitation.

SEARCH TIME-FRAME

January 2007 to Week 4 May 2015

EVIDENCE GRADING SYSTEM

Scottish Intercollegiate Guidelines Network (SIGN) Retrieved from
<http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html>

- 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- 2++ High-quality systematic reviews of case control or cohort studies
 - High-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

Current and Emerging Rehabilitation for Concussion: A Review of the Evidence

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KEYWORDS

- Concussion • Physical rest • Cognitive rest • Vestibular rehabilitation
- Pharmacologic interventions

KEY POINTS

- Concussion rehabilitation policies are largely consensus based.
- Emerging evidence is suggesting that exercise and cognitive activity in a controlled and prescriptive manner may benefit recovery.
- Additional rehabilitation strategies (eg, vestibular, oculomotor, and pharmacologic) also have mounting evidence and should be incorporated by an appropriately trained professional when appropriate.

INTRODUCTION

The clinical signs and symptoms of sport concussion have long been recognized as^{1,2} brought about by an extrinsic force applied directly or indirectly to the head or body.³ Much of the scientific literature surrounding this injury has focused on injury incidence,⁴ assessment tools,^{5,6} and recovery patterns among athletes.⁷ Absent from the literature are reviews of empirical studies assessing the effectiveness of different rehabilitation approaches for concussed patients. Therefore, this article reviews and evaluates the evidence supporting consensus-based standard of care (eg, physical and cognitive rest) and emerging, targeted (eg, vestibular, oculomotor, exertional, pharmacologic) rehabilitation approaches for concussion based on an evolving model of clinical concussion care.⁸

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The concept of physical and cognitive rest as the cornerstone of concussion management was developed by the International Concussion in Sport Group and currently states, “The cornerstone of concussion management is physical and cognitive rest until the acute symptoms resolve and then a graded program of exertion prior to medical clearance and return to play.”³ The rationale for rest asserts that during the acute (1–7 days, possibly longer in youth) postinjury period of increased metabolic demand and limited adenosine triphosphate reserves, nonessential activity draws oxygen and glycogen away from injured neurons. The Concussion in Sport Group recommendation has been interpreted by many clinicians to mean that all concussed athletes should be restricted from all physical and cognitive activity until symptoms resolve, at which point, the athlete could be cleared to begin a return to play progression. This “shut-down” or “dark-closet” approach following concussion is wrought with potential pitfalls for patients, including hyperawareness of symptoms, somatization, social isolation, and other potential comorbid concerns. Citing the risk for prolonged and exacerbated symptoms that may not be directly related to the concussive injury, other medical organizations have recommended that athletes be permitted to engage in limited physical and cognitive activity so long as it does not worsen symptoms.⁹

These 2 perspectives regarding strict rest versus physical and cognitive activity as tolerated are seemingly at odds with each other, in part because there is no agreed on definition of what constitutes rest following a concussion in the literature. Such recommendations are also limited because they do not take into account the individualized nature of the injury, potential risk factors that may influence outcomes, and differential responses to recovery. Moreover, and most importantly, there are no known prospective randomized control trials (RCTs) evaluating rest in concussed athletes immediately following a concussion.¹⁰ In fact, the evidence for physical and cognitive rest is limited, relying on observational studies and studies of patients from sports medicine clinics during the subacute stage.^{11,12} With a dearth of literature to support clinical guidelines, expert consensus has been used in its place.

The premise that rest is the most effective management strategy for all concussed patients assumes that all concussions are alike, yet concussion recovery is known to be influenced by several modifying factors including sex,¹³ concussion history,¹⁴ and age.¹⁵ Even for injuries occurring within these populations, concussions manifest in varied symptoms (eg, headache, dizziness, fogginess), cognitive (eg, memory, reaction time, processing speed),¹⁶ psychological (eg, depression, anxiety),¹⁶ and vestibular (eg, dizziness, imbalance, gait, vestibulo-ocular)¹⁷ impairments. As such, this highly individualized injury results in a varied injury presentation, indicating no single rehabilitation strategy will be effective for all patients following concussion necessitating distinct treatment.⁸

PHYSICAL REST

Declines in neurocognitive function and motor control and increases in self-report symptoms following concussion are well documented.^{5,18} Among the most commonly reported symptoms are headache, dizziness, and confusion immediately following a concussion.^{19–25} Other research has reported increased rates of depression and fatigue among the same cohort.²⁶ Between 80% and 90% of concussed individuals will return to preinjury levels of functioning within 2 weeks without intervention, but a small percentage (2.5%) will remain symptomatic 45 days after injury, despite resolution of other objective measures (eg, neurocognitive and balance assessments).²⁷ Therefore, management of athletes falling within and outside the range of normal recovery may require different approaches.

Evidence for Physical Rest

Consensus supporting physical rest recommendations is partly predicated on risk management and animal studies demonstrating impaired recovery with the early onset of physical activity. Although secondary to restricting activity to facilitate recovery, restricting physical activity to reduce risk for a second injury has broad support as the sole means to eliminate Second Impact Syndrome.²⁸ Even in the absence of a catastrophic outcome, animal models show metabolic dysfunction in the days immediately following injury^{1,29} with an increased energy demand within the cerebral tissue as ion imbalances are returned to preinjury levels. During this time, the risk for second injury seems to be highest²³ and an additional injury sustained shortly after the first increases recovery time and impairs the ability to learn among rodents.³⁰ Similar metabolic dysfunction findings among concussed athletes were reported by Vagnozzi and colleagues.³¹ That is, altered cerebral metabolism lasting up to 30 days was documented using magnetic resonance spectroscopy imaging in concussed athletes and up to 45 days in those sustaining a second injury before resolution of the first.³²

In addition, subsequent injury risk and prolonged recovery brought about by sport participation, unrestricted physical activity in a controlled and safe environment during the acute recovery stage, may be detrimental. For example, rats exposed to a fluid percussion injury and provided unrestricted running wheel access within the first 6 days of injury showed poorer performance on a cognitive task (ie, Morris water maze) compared with similarly injured rats that were restricted from activity until day 14 after injury.³³ In addition, a review of medical records from 159 concussed patients found that those returning to play before concussion symptom resolution reported worsening concussion-related symptoms.³⁴ The mechanistic underpinnings explaining these findings are not entirely clear, but it is possible that early exercise may draw energy (ie, glycogen) away from the brain and inhibit the recovery process.

Evidence for Physical Activity

The evidence supporting physical activity following concussion is sparse, but other medical literature suggests that withholding injured, but nonconcussed athletes from exercise increases reports of depression, anxiety, and lower self-esteem when evaluated both at the time of injury and 8 weeks later.³⁵ Injured (nonconcussed) high school athletes missing a minimum of 3 weeks of athletic participation also showed higher rates of depression than noninjured athletes. The authors indicated that high levels of athletic identity partly explained the finding.³⁶ Moreover, onset of migraine has been shown to occur in patients with limited or minimal physical activity.³⁷ Ultimately, removing an athlete from sport may increase the risk for depression and other concussionlike symptoms to develop, yet the point at which an athlete can begin physical activity following concussion is unclear.

In the single human study evaluating exercise shortly after concussion, 95 concussed student-athletes retrospectively self-reported physical and cognitive activity in the 30 days following injury and compared the findings to a neurocognitive assessment. Each athlete was categorized into 1 of 5 groups ranging from “no school or exercise activity” to “school activity and participation in sports games” and completed a computerized neurocognitive assessment for both cognitive functioning and self-report symptoms. The results indicated that athletes engaging in a medium level of physical and cognitive activity (ie, school activity and light activity at home, such as slow jogging or mowing the lawn) performed better on the neurocognitive test than those with no physical and cognitive activity and those reporting the highest levels of physical and cognitive activity.³⁸ These findings should be cautiously interpreted

however, because the physical and cognitive activity was self-report recall by the injured athlete. In addition, it is not known at what point after the injury the athletes elected to begin physical activity. Coupled with the previously discussed animal work, this investigation set the groundwork to suggest that unrestricted exercise in the immediate acute phase of concussion recovery may increase the risk of subsequent injury and/or delay recovery, yet some level of exercise may be beneficial to the recovery process once the athlete has moved beyond the acute injury stage.

When dealing with athletes continuing to experience concussion-like symptoms beyond the acute injury stage, stronger literature is available showing the benefit of physical activity as a means to mitigate symptom reports. Leddy and colleagues³⁹ implemented a graded return to activity protocol on 6 concussed athletes that had been symptomatic for a minimum of 6 weeks (mean 19 weeks) following a concussive event. Once enrolled, the athletes were monitored for an additional 2 weeks, wherein there was no change in their symptom reports. They then began an exercise protocol 5 to 6 days a week with intensity monitored by heart rate. After 6 weeks of the intervention, the athletes had a significant decrease in their symptom reports and were able to return to sport. Interestingly, a concussed nonathlete group completed an identical protocol, but did not show the same decline in symptom reports as the athlete cohort. A follow-up investigation enrolled 91 participants that had been experiencing symptoms following a concussion for a minimum of 3 weeks. Each participant completed a baseline graded exercise test, whereby 26 were able to reach maximum exertion. These individuals were determined to be experiencing symptoms related to something other than concussion, whereas 35 of the remaining 65 continued with the same heart rate-based exercise protocol described above. A return to full functioning by means of the exercise protocol was achieved in 77% of the subset ($n = 27$).⁴⁰

Exercise has been proven to be a powerful modality for cognitive health,⁴¹ but the implementation of postconcussion exercise should be carefully considered relative to the time from injury. The limited literature available to date suggests that athletes experiencing symptoms in the acute stage of injury should avoid full sport participation to avoid secondary injury as well as exercise in a controlled environment because it may increase recovery time. Animal and retrospective human studies, however, suggest that athletes continuing to report symptoms beyond the acute stage of injury may benefit from moderate levels of exercise. Last, those athletes that continue to report concussion-related symptoms well beyond the acute stage of injury may benefit from a progressively intensive exercise protocol to return them to their sport.

COGNITIVE REST AND ACADEMIC ACCOMMODATIONS

Cognitive impairment following concussion is common among student-athletes and cognitive rest has been suggested to enhance recovery. The cognitive rest theory is based on the premise that increasing cognitive activities following concussion will increase symptom recovery time and prolong recovery. Cognitive rest includes the reduction of brain stimulating activities (eg, television, video games, school work, reading, and writing) and, despite the limited data to support the use of cognitive rest, it is widely recommended in consensus statements and concussion guidelines.^{3,9,42–45}

To date, few studies have evaluated cognitive rest; however, these studies have found that increased cognitive activity does delay symptom recovery. Moser and colleagues¹¹ studied 49 high school and collegiate athletes prescribed a minimum of a week of cognitive and physical rest. Both before and after rest periods, individuals performed the ImPACT and cognitive testing measures. The study concluded with a

period of cognitive and physical rest with individuals showing increased performance on the ImPACT and cognitive testing as well as decreased symptom reporting. Similarly, Brown and colleagues¹² studied 335 patients (mean age, 15 years) on level of cognitive activities between clinical visits, finding that longer concussion recovery time was related to higher cognitive activity levels. Indeed, those participating in the lowest 50% of cognitive activity were completely asymptomatic within 100 to 150 days of injury, whereas those engaging in the third and fourth quartiles of cognitive active took up to 300 and 500 days to recover, respectively.

School is a major component of a student's life, requiring the attainment of new knowledge, development of academic skills, and diligent work to complete assignments and prepare for examinations. To be successful in academic endeavors, students must engage in classroom learning requiring attention, material memory recall, critical thinking, and problem-solving. Students who sustain a sports-related concussion (SRC) may also experience physical, mental, behavioral, and social changes that impact their daily life and threaten their ability to learn and succeed academically.⁴⁶ Limiting school activity is one mechanism that affords the injured athlete time to mitigate concussion-related symptoms.

Despite limited research on cognitive load following concussion, it has been suggested that some concussed students may benefit from excused or reduced academics (eg, classroom attendance, homework, examinations) immediately following injury.^{47–49} Returning to academic work while symptomatic may cause symptoms to worsen, resulting in a decline in academic performance.^{48,50} Although there are more formal accommodations available for long-term or prolonged cases, temporary and targeted accommodations during the acute recovery time is an easy tool to assist a student's return to the classroom.⁴⁷ Temporary accommodations may include, but are not limited to, excused absences, lighter homework, breaks during the day, starting later or ending the school day earlier, and extended examination or homework dates.⁴⁹ Once the athlete no longer reports concussion-related symptoms, a transition period to partial and then full days is recommended.⁵¹

Requiring a student-athlete to attend school immediately following a concussion may place him or her in a compromised academic position. Concussed student-athletes engaging in moderate to intense cognitive activity may exacerbate symptoms,¹² resulting in incomplete school work, making excused absences important to the recovery process. During this period, a time extension to complete academic assignments including homework and examinations allows the student-athlete to make up missed schoolwork and take their time with completion of assignments. Implementing delayed testing or project due dates can help the student maintain good academic standing without the penalty of decreased scores. Temporary accommodations such as these are commonly implemented quickly and without burdensome paperwork. To ensure these tools are available, the concussion management team should prearrange their use with school personnel as part of the concussion management plan before the athletic season.

Those individuals experiencing a prolonged concussion recovery or those with recurrent injuries may need additional testing to better accommodate or intervene with school as needed.⁵¹ In some cases, implementing an individualized academic plan can help with the management of accommodations. If a student-athlete is having symptoms or displays challenges greater than 3 weeks, a 504 Plan may be implemented.⁴⁷ A 504 Plan refers to the proper section of the Rehabilitation Act that provides medical need accommodations. In order for formal accommodations to be implemented, the student would have to display mental impairments that limit greater than one major life activity.⁵² Clinicians may also consider an Individualized Education

Plan (IEP) for those with prolonged concussion recovery. An IEP allows for the school personnel to collaborate with the physician, student-athlete, and parents to create a plan that will best help that student receive special education.⁵³ Both IEPs and 504 Plans require extensive medical documentation and are a more permanent measure that are embedded into the school system documents, but allow for changes to the student-athlete's academic plan for classroom success.

Despite consensus for cognitive rest, it is important to note that prolonged cognitive rest and reduction of school events have the potential to exacerbate symptoms or cause negative mental health issues. Depression, behavioral issues, and social issues have been shown to increase following a concussion as well as many other injuries when the student-athlete is eliminated from team activities, school events, and social outings.⁵⁴ Decreasing school attendance and other social activities can negatively impact some student-athletes and prevent them from going through proper injury-coping mechanisms. Decreased school attendance can also add an increased burden and sense of anxiety to the student-athlete because they are not attending school nor completing school assignments. The mental image of being behind in academics can create a highly anxious environment for student-athletes, especially those who already place high priority on increased academic achievement. Ultimately, the medical team, in conjunction with a trained professional, should balance the neurocognitive and behavioral accommodations of the concussed student-athlete in a way that restricts cognitive activities that trigger or introduce symptom exacerbation, but allow for him or her to become involved in school activities again.

VESTIBULAR AND OCULOMOTOR REHABILITATION

In a new clinical model of SRC care, researchers have suggested that oculomotor and vestibular symptoms and impairment may constitute unique clinical subtypes of SRC—along with cognitive fatigue, anxiety-mood, cervical, and posttraumatic migraine (PTM).⁸ These clinical subtypes of concussion, which can occur concurrently or independently, require targeted therapies and treatments to be managed most effectively.⁸ For example, an athlete with an oculomotor concussion subtype will benefit most from vision and oculomotor-specific therapies. Without such targeted intervention strategies, an athlete may experience an unnecessarily prolonged recovery from SRC. In a prospective study of recovery times following SRC, researchers reported that 17% of athletes experience prolonged recovery lasting greater than 3 weeks.⁵⁵ The identification of specific clinical subtypes of concussion together with the application of targeted treatments and rehabilitation strategies will yield the best clinical outcomes for athletes with SRC. Two clinical subtypes that have been associated with poor clinical outcomes, but that may be amenable to rehabilitation and treatment interventions, are vestibular and oculomotor.

Vestibular and Oculomotor Impairment and Symptoms

Vestibular and oculomotor impairment and symptoms occur in approximately 60% of athletes following SRC.¹⁷ The vestibular system plays an integral role in balance function and in maintaining visual and spatial orientation. Sensory information from each inner ear is used to inform the adjustment of eye movements for clear, stable vision and to adjust muscle reactions of the head and body for balance and gait. Vestibular impairment and dysfunction may involve either the peripheral or the central structures of the vestibulospinal system and may result in disequilibrium and impaired balance.⁵⁶ In contrast, dizziness, vertigo, blurred/unstable vision, discomfort in busy environments, and nausea often occur with disruption to the vestibulo-ocular system.⁵⁶

Vestibular symptoms at the time of injury may predict prolonged recovery following SRC. In fact, Lau and colleagues²⁵ reported that on-field dizziness was the only significant predictor of a prolonged recovery (>21 days) following SRC. This expression of post-SRC dizziness acutely may be the result of disruption to the vestibulo-ocular and gaze stability systems at the time of the injury.

Similar to vestibular dysfunction, impairment in oculomotor control and visual dysfunction are observed frequently following SRC.^{57–61} Ciuffreda and colleagues⁶² indicated that visual dysfunction involving accommodation, version and vergence, strabismus, and cranial nerve palsy occurred following mild traumatic brain injury (mTBI). Symptoms attributed to poor oculomotor function may include blurred vision, diplopia, difficulty reading, eyestrain, headache, reading difficulties, and problems with visual scanning. Vestibular and oculomotor impairment and symptoms are prevalent following SRC and may play a role in prolonged recovery and related clinical outcomes. Therefore, vestibular rehabilitation and vision therapy interventions are presented and discussed that can be used with athletes experiencing vestibular and oculomotor impairment and symptoms following SRC.

Vestibular Rehabilitation Interventions

There are many different types of vestibular rehabilitation interventions that may be implemented to mitigate vestibular symptoms and dysfunction following SRC. Among the most common vestibular issues following SRC are benign paroxysmal positional vertigo (BPPV), vestibulo-ocular reflex (VOR) impairment, visual motion sensitivity, balance dysfunction, cervicogenic dizziness, and exercise-induced dizziness. **Table 1** summarizes these and other vestibular problems along with targeted therapeutic interventions. It is important to note that these interventions should be performed by licensed physical therapists specializing in vestibular rehabilitation.

Benign paroxysmal positional vertigo is the most common disorder of the vestibular system and can occur posttraumatically after SRC. In BPPV, small calcium carbonate crystals (otoconia), which are normally housed in the otolith organs of the inner ear, become dislodged and relocate to one or more of the adjacent semicircular canals. With head movement in the plane of the affected semicircular canal, the otoconia shift position and create a false excitatory stimulus and resultant vertigo. Reproduction of vertigo and a characteristic nystagmus pattern during positional testing (Dix-Hallpike and Roll Test) are necessary to diagnose BPPV. Canalith repositioning maneuvers, designed to shift the displaced otoconia out of the affected semicircular canal, is the treatment of choice for BPPV.⁶³

Gaze stability refers to the ability to maintain visual focus while the head is moving. Although gaze stability is mediated by different vestibular and ocular motor systems depending on the velocity and context of the task, the VOR is the primary mechanism for maintaining eye position during head movement. The VOR is a fast-acting reflex that keeps the eyes stable by generating ocular movements precisely in proportion, but opposite in direction, from the head motion. In sport, where rapid acceleration and high-velocity movement necessitate quick visual responses, intact VOR functioning is particularly important. When the VOR is impaired, visual blurring, dizziness, poor visual focus, and oscillopsia may occur with head motion. The responses of the VOR can be adapted through exercise designed to induce movement of a visual image on the retina. This motion, inducing retinal slip, is the primary error signal that drives adaptation of the VOR. Thus, vestibular physical therapy exercises for VOR adaptation require patients to maintain visual focus on a target while moving their head. VOR adaptation exercises are manipulated in multiple ways to gain maximal benefit,

Table 1
Common interventions for vestibular impairment following sport-related concussion

Impairment	Cause	Symptoms	Associated Problems/Risk Factors	Physical Therapy Treatment
Benign paroxysmal positional vertigo ⁶³	Mechanical disruption in the vestibular labyrinth (end organ). Otoconia from otoliths become dislodged and displace in semicircular canal	Vertigo with changes in head position	Older age High impact forces	Canalith repositioning maneuvers
VOR impairment ⁸⁰	Disrupted function in the VOR pathways, peripherally or centrally	Dizziness	Labyrinthine concussion	Gaze stability training
Visual motion sensitivity ⁹⁰	Impaired central processing/integration of vestibular information with visual and other sensory information	Dizziness	Posttraumatic migraine Anxiety	Graded exposure to visually stimulating environments Virtual reality Optokinetic stimulation
Impaired postural control ⁹¹	Disruption/damage to vestibular-spinal reflex pathways, peripherally or centrally	Impaired balance, particularly with: <ul style="list-style-type: none"> • Vision and/or somatosensation reduced • Cognitive dual/task demand 	Common early finding after concussion; typically resolves before other vestibular deficits	Balance rehabilitation strategies Sensory organization training Divided attention training Dynamic balance training
Cervicogenic dizziness ^{92,93}	Cervical injury results in abnormal afferent input to CNS; mismatch with other sensory information	Dizziness, related to cervical movement/posture Imbalance Impaired oculomotor control	Cervical pathologic abnormality Cervicogenic headaches	Manual therapy for cervical spine Balance training Oculomotor training
Exercise-induced dizziness ⁹⁴	Inadequate central response to cardiovascular and vestibular/ocular demands of exercise	Dizziness with movement-related cardiovascular exercise	<ul style="list-style-type: none"> • VOR/gaze stability impairment • Visual motion sensitivity • Autonomic dysregulation 	Progressive dynamic exertion exercise program

including varying target size and complexity, postures, duration, direction, amplitude, and velocity.

Visual motion sensitivity refers to an increased sense of disorientation, dizziness, or postural instability in situations with visual and vestibular conflict. It is thought to arise from inability of the central nervous system (CNS) to effectively integrate sensory information, particularly vestibular information, creating overreliance on vision. Patients with visual motion sensitivity become particularly symptomatic when exposed to visually disorienting stimuli or environments, such as malls, grocery stores, or even busy patterns. Visual motion sensitivity has also been described as “visual vertigo,” “space and motion discomfort,” and “visual vestibular mismatch” in the literature. Visual motion sensitivity has been reported in patients following peripheral vestibular disorders⁶⁴ and in those with migraine⁶⁵ and anxiety.⁶⁶ It has also recently been recognized in patients following SRC.¹⁷ Treatment of visual motion sensitivity involves gradual and systematic exposure to provocative stimuli to habituate the abnormal responses. Because treatment of visual motion sensitivity has the potential to exacerbate symptoms from concussion, intervention should be introduced in a step-by-step progression that is carefully monitored by a trained vestibular therapist.

Restoring postural control, or balance, is an area of focus for vestibular rehabilitation following SRC.^{67–69} Because sensory organization is often impaired^{70,71} early after concussion, training the ability to effectively alternate between using visual, somatosensory, and vestibular information for postural control is a key component of balance retraining. Graded exercises for sensory organization deficits involve manipulation of these 3 sensory systems. Examples of sensory organization training activities include performing tasks with eyes closed, while turning the head, with narrowed base of support, on an uneven or soft surface. In addition to sensory organization issues, several studies have shown patients following mTBI have greater difficulty maintaining balance under conditions of divided attention.^{72–74} Therefore, dual task condition practice and dynamic balance activities may also be incorporated into vestibular rehabilitation.

Although dizziness is most often attributed to vestibular system dysfunction, it may also arise from other impairment following SRC, which may be responsive to intervention. In cervicogenic dizziness, pathologic abnormality in the cervical spine creates abnormal muscle activity in the deep layers of the upper cervical spine responsible for providing proprioceptive input to the CNS. Dizziness is thought to occur because of the mismatch between aberrant cervical proprioceptive information in relation to vestibular and visual inputs. Because this cervical afferent information also participates in reflex activity for postural control and eye movements, imbalance and impaired eye movements may occur in addition to dizziness. Management of cervicogenic dizziness is directed toward therapies that treat the underlying cervical spine injury to normalize proprioceptive input with visual and vestibular information, along with treatment of any additional balance or oculomotor impairment through targeted exercises (Treleaven 2011).

Last, following concussion, dizziness may arise with exertional activity.⁷⁵ In a study of soldiers following blast-related concussion, exercise-induced dizziness was categorized as one type of dizziness typically seen by physical therapists in vestibular rehabilitation. Although there are no studies that confirm the cause of exercise-induced dizziness, the authors postulate that inadequate response of the CNS to combined cardiovascular and vestibular/visual demand may be responsible. Anecdotally, it was found in the authors' clinic that stationary cardiovascular activities at high levels of exertion (eg, stationary cycling) rarely cause dizziness, whereas cardiovascular

activity maintaining similar levels of exertion, when combined with motion (eg, forward/backward line drills), often produces significant levels of dizziness. Clearly, more research is needed to validate this hypothesis. Treatment of individuals with exercise-induced symptoms is controversial; however, preliminary evidence suggests that graded exercise may be useful in modifying these postconcussive symptoms when chronic.^{39,76}

The value of vestibular rehabilitation in managing individual vestibular conditions is well documented. A *Cochrane Review*⁷⁷ concluded that there is moderate to strong evidence for efficacy of vestibular rehabilitation in improving VOR impairment and balance deficits due to peripheral vestibular dysfunction, and for the use of canalith repositioning maneuvers performed by vestibular therapists in the management of BPPV. Dizziness due to migraine as well as patients with central vestibular dysfunction has been shown in studies to improve with vestibular physical therapy intervention (Whitney and colleagues, 2000; Brown and colleagues, 2006). Therapies for visual motion sensitivity, such as optokinetic stimulus exposure, have been shown to be effective with peripheral vestibular disorders (Pavlou 2013). Several studies have investigated the efficacy of physical therapy treatment of the cervical spine for cervicogenic dizziness (Malmstrom 2007, Heidenreich 2008, Reid 2008), including a recent RCT (Reid 2014) demonstrating significant reduction in intensity and frequency of cervicogenic dizziness with 2 different manual therapy techniques over placebo. Although vestibular therapies have been shown to be beneficial in the treatment of various vestibular-related impairments, the evidence for using vestibular physical therapy for impairment attributed to SRC is limited and consists primarily of retrospective, cross-sectional, and small cohort studies.

A recent study by Schneider and colleagues⁷⁸ conducted an RCT with a sample of 12- to 30-year-olds with dizziness, neck pain, and/or headache following SRC. After 8 weekly physical therapy sessions consisting of vestibular and cervical spine rehabilitation, subjects in the treatment group were nearly 4 times more likely to be medically cleared when compared with a control group. In a retrospective chart review, Alsalaheen and colleagues⁷⁹ examined the response of a population of concussed patients to vestibular physical therapy. Data from 114 patients referred for vestibular rehabilitation following concussion demonstrated a significant treatment effect for 15 different measures of dizziness severity, balance confidence, gait, and static/dynamic balance. Gottshall and Hoffer⁷⁵ assessed computerized VOR and gaze stability measures in 82 military individuals who experienced blast-related mTBI. Impairment was significant at the time of initial evaluation, but returned to normative levels after 4 to 12 weeks of vestibular physical therapy. Hoffer and colleagues⁸⁰ examined the effect of vestibular rehabilitation in a population of 58 active duty military individuals with postconcussive dizziness. They found that after a 6- to 8-week vestibular rehabilitation program, patients had improved with respect to symptoms of dizziness, perception of balance function, and measures of VOR function. However, the effectiveness of vestibular rehabilitation differed based on type of posttraumatic dizziness. Specifically, patients with PTM-associated dizziness were most responsive to treatment (84%) in contrast with the spatial disorientation group (27%).

Vision Therapy

Most oculomotor problems following SRC, such as convergence insufficiency, accommodative insufficiency, impaired version movements, and minor ocular misalignments, may be managed conservatively with vision therapy.⁵⁷ However, in rare instances, surgical/medical intervention by an ophthalmologist or neuro-ophthalmologist may be warranted for complex diplopia, strabismus that is due to

muscle paralysis or nerve palsy, or other concurrent ocular-health issues. Typically, vision therapy involves vision exercises using eye patches, penlights, mirrors, lenses, prisms, and other nonsurgical interventions to improve the function of the ocular muscles.

Despite anecdotal evidence for the effectiveness of vision therapy following SRC, there is limited empirical support for vision therapy in the literature. However, a 2011 *Cochrane Review* of RCTs for nonsurgical intervention for convergence insufficiency, and another RCT by Scheiman and colleagues for treatment of accommodative insufficiency, pointed to the effectiveness of vision therapy in children in managing these 2 conditions.^{81,82} Although empirical support for oculomotor and vision-related therapies following SRC is limited and does not include any RCTs, emerging evidence supports the effectiveness of visual exercises for specific oculomotor problems. A retrospective study by Ciuffreda and colleagues⁶² examined patients with mTBI who were enrolled in a vision therapy program consisting of combined vergence, version, and accommodative exercises. They reported that 90% of patients improved markedly or completely in symptoms and subjective reports of enhanced reading at a 2 – to –3-month follow-up. In a recent study involving 12 subjects following mTBI, Thiagarajan and Ciuffreda⁸³ demonstrated that an oculomotor training program targeting the version, vergence, and accommodation components of the ocular motor system significantly improved the amplitudes of vergence and accommodation, accuracy of saccadic eye movements, and overall reading.

PHARMACOLOGIC INTERVENTIONS

It has been reported that as much as 89% of clinicians manage symptoms of athletes with SRC using over-the-counter (OTC) or prescription medications.⁸⁴ The most common interventions involve OTC medications such as nonsteroidal anti-inflammatory drugs and acetaminophen. However, many other prescription pharmacologic interventions are used with athletes who are not following a normal recovery trajectory (ie, recovered within 10–14 days) following SRC. Research indicates that pharmacologic treatments usually begin at approximately 10 days after injury.⁴² As with vestibular and oculomotor therapies, pharmacologic interventions are most effective when they target specific clinical subtypes of SRC. For example, an athlete with a primary cognitive-fatigue subtype following SRC may be prescribed a neurostimulant such as amantadine. In addition to cognitive fatigue, other clinical subtypes that are amenable to pharmacologic treatment include PTM and anxiety/mood.^{3,8} In addition, sleep-related issues are often treated using pharmacologic interventions. It is important to acknowledge that there is still no US Food and Drug Administration-approved pharmacologic treatment for SRC. As such, all pharmacologic interventions discussed later involve off-label use of medications that were approved for other primary purposes. Moreover, each medication discussed may involve side effects that warrant close monitoring from prescribing clinicians. In addition, the use of certain medications, such as neurostimulants, may be in violation of the medication and performance enhancement policies of specific sport governing bodies; thus, proper documentation is very important.

Targeted Pharmacologic Interventions: Matching Treatments to Clinical Subtypes

Cognitive fatigue is a commonly targeted clinical subtype for pharmacologic intervention. Athletes with this subtype experience difficulty concentrating, memory problems, attentional issues, decreased vigor, and headaches that worsen throughout

the day. These symptoms are often treated effectively with the use of a neurostimulant. The most commonly used neurostimulant is amantadine, with 10% of clinicians reporting that they prescribe amantadine to athletes following SRC.⁸⁴ There is some empirical evidence that amantadine, a dopaminergic neurostimulant primarily purposed as an antiviral medication, can improve cognitive-fatigue symptoms and memory in athletes experiencing prolonged recovery following SRC.⁸⁵ Other neurostimulants that can be used to treat athletes with cognitive fatigue include methylphenidate, Adderall, and atomoxetine. There is some evidence of the effectiveness of methylphenidate on improving processing speed in moderate TBI (eg,⁸⁶), but not in athletes with SRC. Of note, some athletes may already be taking these medications for attention deficit hyperactivity disorder and related conditions, thereby necessitating close monitoring from clinicians; medications may need to be adjusted during their recovery period.

Some athletes may develop anxiety or mood issues as a direct result of an SRC or secondary to the injury recovery process with its concomitant frustrations and feelings of isolation and loss of control.¹⁶ Other athletes may have pre-existing anxiety/mood issues before injury that may be exacerbated following an SRC. Regardless of its underlying cause, anxiety and mood issues following SRC can be treated with tricyclic antidepressants (eg, amitriptyline). In fact, tricyclic antidepressants are used by up to 23% of clinicians in treating young athletes with SRC.⁸⁴ It is likely that this relatively high percentage of clinicians prescribing tricyclic antidepressants is due in part to its use across multiple clinical subtypes, including anxiety and mood, sleep, and PTM. Other common medications used for athletes in the anxiety and mood clinical subtype include selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors. There is some anecdotal evidence that short-term, low-dosage use of certain benzodiazepines such as Klonopin may be effective in athletes with vestibular-related anxiety. Klonopin and other benzodiazepines are also thought to act on neurons in the vestibular nuclei of the brain to decrease vestibular-related symptoms and in turn decrease anxiety. Klonopin can be effective for vestibular-related migraines. However, Klonopin can result in elevated anxiety and sleep disruption in some athletes and its use should be monitored closely.

The symptoms of PTM include headache, nausea, photo-sensitivity or phonosensitivity, and dizziness. These symptoms have been associated with prolonged recovery and impairment following SRC.⁸⁷ Clinicians may use a variety of pharmacologic interventions to treat the symptoms of PTM, including tricyclic and SSRI antidepressants, anticonvulsants (eg, topiramate, gabapentin, valproic acid), or β-blockers. In addition, triptans (eg, Imitrex, Maxalt) are often prescribed as abortive medications for PTM. Despite anecdotal evidence regarding the effectiveness of these treatments, there are no empirical studies of the effectiveness of these medications in athletes with SRC.

There is often a sleep overlay that permeates across each clinical subtype of SRC. Consequently, clinicians often prescribe OTC and prescription sleep medications for athletes with persistent sleep disruptions following SRC. After all, if an athlete is not sleeping well following an SRC, it will be difficult for that athlete to recover. The most commonly used sleep medication is melatonin with one-fifth of clinicians reporting that they prescribe melatonin to athletes with sleep disruptions following SRC.⁸⁴ Melatonin together with basic sleep hygiene can help regulate circadian rhythms and promote better sleep-wake cycling.^{88,89} Other medications used to improve sleep disruption in athletes following SRC include antidepressants (eg, amitriptyline, trazodone) and nonbenzodiazepine hypnotics (eg, Ambien, Lunesta).⁸⁹

SUMMARY AND RECOMMENDATIONS

Despite limited empirical support, physical and cognitive rest have been deemed essential components of initial concussion management and treatment. Such recommendations have been developed by consensus and introduced by the International Concussion in Sport Group in 2008. Since that time, there has been limited empirical work evaluating the efficacy of physical and cognitive rest protocols. Some research suggests that prescribed physical and cognitive rest in the acute stage of concussion may be of benefit to some athletes. However, other studies have indicated that an early return to light to moderate physical activity may be effective for other athletes following concussion. The heterogeneous nature of concussion renders a universal prescription of strict rest for all concussed athletes an ineffective strategy. As such, strict rest extending beyond the acute injury stage may result in the athlete developing concussionlike symptoms that are unrelated to the injury (eg, anxiety, migraine, sleep disorders) and may complicate injury management, which may in turn lead to psychological and other concurrent problems. Student-athletes who are unable to attend or participate in academics to the fullest may benefit from a reduced cognitive load following injury, with a graduated return to academics that does not exacerbate symptoms. Reduction of cognitive load requires a coordinated effort between the medical and school academic support staff with short-term or long-term academic accommodations. Any accommodations may be lifted once a complete academic schedule can be completed without symptom exacerbation, at which time a return to play protocol be undertaken.

Sport-related concussions can involve several different clinical subtypes that warrant a comprehensive clinical assessment and subsequent targeted treatment and rehabilitation strategies. Recent advances in screening for vestibular and oculomotor impairment and symptoms (eg, Mucha and colleagues¹⁷) have revealed that many athletes experience these issues following SRC. Research also suggests that athletes with these issues often have longer recovery times and more pronounced impairment and symptoms following SRC.²⁵ In response to these findings, vestibular and vision therapists have begun to apply specific rehabilitation interventions to enhance the recovery process for those athletes with vestibular or oculomotor impairment and symptoms following SRC. Initial empirical evidence indicates that these vestibular and oculomotor interventions may be useful in mitigating these issues and enhancing the recovery of athletes with SRC. However, additional research regarding which interventions are most effective for each type of impairment and symptoms as well as the optimal number and length of therapeutic sessions needed to obtain the desired effect is warranted.

Most clinicians use some sort of OTC or prescription pharmacologic intervention to help manage lingering symptoms and impairment following SRC.⁸⁴ It is clear from clinical experience that when pharmacologic treatments are matched appropriately with patients' clinical subtypes and symptoms, they can be an effective intervention. However, there is some overlap for the effectiveness of certain pharmacologic interventions across more than one clinical subtype. Most pharmacologic treatments are implemented in patients with lingering (10–14 + days) or chronic (3 + months) symptoms and impairments. It is atypical for a patient to be prescribed a medication in the acute and subacute phases following a concussion. This "wait-and-see" approach may result in missed opportunities for effective early pharmacologic intervention following SRC. However, researchers have yet to determine how soon after injury the preceding pharmacologic treatments should be implemented to have the greatest therapeutic effect. In fact, it has been suggested that clinicians could accelerate recovery for some patients if pharmacologic treatments were implemented earlier in

the injury process. In addition, researchers need to explore the effectiveness of various dosage levels, treatment regimens, and administration methods in patients following concussion.

This review was conceived to evaluate the evidence supporting current and emerging rehabilitation approaches for sport concussion. Consensus opinion for prescribed physical and cognitive rest is the most common rehabilitation approach for patients with concussion. However, more active and targeted rehabilitation strategies including vestibular and oculomotor rehabilitation and pharmacologic interventions have emerging evidence supporting their use. Ultimately, there is limited empirical support for the rehabilitation strategies discussed in this article, necessitating additional research on their effectiveness following concussion. This research should use multisite, RCT research designs to better elucidate the specific effects of individual interventions. In addition, future research should use comprehensive outcome assessments and targeted rehabilitation strategies that account for the heterogeneous nature of this injury.

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Prevalence of Dual Sensory Impairment and Its Association With Traumatic Brain Injury and Blast Exposure in OEF/OIF Veterans

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Objective: To describe the prevalence of self-reported rates of auditory, visual, and dual sensory impairment (DSI) in Afghanistan and Iraq war Veterans receiving traumatic brain injury (TBI) evaluations. **Design:** Retrospective medical chart review. **Participants:** Thirty-six thousand nine hundred nineteen Veterans who received a TBI evaluation between October 2007 and June 2009. Final sample included 12,521 subjects judged to have deployment-related TBI and a comparison group of 9106 participants with no evidence of TBI. **Main Outcome Measure:** Self-reported auditory and visual impairment. **Results:** Self-reported sensory impairment rates were: 34.6% for DSI, 31.3% for auditory impairment only, 9.9% for visual impairment only, and 24.2% for none/mild sensory impairment. Those with TBI and blast exposure had highest rate of DSI. Regression analyses showed that auditory impairment was the strongest predictor of visual impairment, and vice versa, suggesting these impairments may derive from a common source. **Conclusions:** Veterans who self-report clinically significant hearing or vision difficulty during routine TBI evaluation should be evaluated systematically and comprehensively to determine the extent of sensory impairment. Identifying DSI could allow clinicians to collaborate and maximize rehabilitation. **Keywords:** *blast injuries, hearing impairment, traumatic brain injury, vision impairment*

SINCE 2001, more than 1.7 million troops have been deployed to Afghanistan or Iraq for Opera-

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tion Enduring Freedom and Operation Iraqi Freedom (OEF/OIF).¹ Although most troops are returning from war with no physical injury, approximately 15% to 19% of returnees have been judged to have experienced a traumatic brain injury (TBI), termed a "signature injury" of these military operations.²⁻⁴ The majority of TBIs are mild and symptoms usually resolve within hours or days, but for some they can persist for months or years after a traumatic event.⁵

Due to enhancements in protective gear and better medical knowledge of closed head injury, soldiers are surviving injuries, such as those caused by blast, which would have been fatal in previous wars.^{6,7} Primary blast waves, which cause a sudden change in atmospheric

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pressure that impacts the body's surface and internal structures, have been a leading cause of closed head TBI.^{6–8} Among 125 patient-events reported in OIF marines, 97% of the patients were injured due to improvised explosive devices (IEDs) or mines,⁹ and in another study nearly 60% of blast-exposed OEF/OIF troops admitted to an army hospital were judged to have a TBI.⁶

Numerous injuries can result from blast or non-blast events (eg, gunshot wounds, motor vehicle accidents, falls), but hearing and vision deficits may not be obvious in patients with TBI due to the lack of visible symptoms.^{10,11} However, sensory impairment is likely to impact patients' functional improvement⁴ and activities of daily living by diminishing their ability to interact with their immediate environment and with others. The ears are air-filled organs that are likely to sustain primary blast wave injury. Blast waves can overpressurize the auditory pathway, resulting in damage to the tympanic membrane, middle ear, inner ear, or auditory cortex.^{10,12–15} Signs of auditory injury include hearing loss, tinnitus (any type of sound such as ringing, humming, or buzzing that is heard without an identifiable outside source), and otalgia (ear pain). Many studies have reported auditory disturbance in OEF/OIF troops,^{2,4,11,15–17} and in one 6-month study of OIF marines, auditory injury was the most frequently reported single injury type (23%).⁹ Sixty-two percent of blast-exposed Veterans with TBI reported hearing loss (compared to 44% of patients with nonblast related TBI), with 58% diagnosed with pure sensorineural loss after undergoing audiometric evaluation.¹⁵ Another blast-exposed Veteran patient group with sensorineural hearing loss¹⁸ reported hearing and communication impairment, despite audiometric results appearing in the normal range, suggesting potential central auditory processing deficits.^{16,19}

The eyes are also vulnerable to the primary and other effects of blast, especially when unprotected.²⁰ Trauma to the visual system can create a variety of symptoms stemming from damage that ranges from injuries of the eye globe to the visual cortex.^{19,21} Eye trauma in OEF/OIF is more frequent than in prior conflicts.²² In one 8-month study of OIF troops who were deployed during an Iraqi insurgency, blast fragmentation was responsible for 82% of all ocular injuries, with IEDs accounting for the majority of these injuries.²³ A recent study documented vision impairments in 38% of OEF/OIF Veterans receiving inpatient care.²⁴ Vision loss was confirmed at a rate approximately 2.5 times higher in individuals exposed to blast versus not exposed to blast, and damage to the eye or orbit was highly associated with blast injury.²⁴ In another Veteran sample, self-reported visual impairment was 1 of 4 major symptoms that differentiated patients who sustained TBI in combat versus noncombat.²⁵

Given the prevalence of auditory and visual impairment in OEF/OIF Veterans, it is likely that a portion of this population experiences impairment in both sensory modalities, a condition termed dual sensory impairment (DSI).⁴ In a study of 62 OEF/OIF returnees (mean age of 27 years) who had incurred blast-related TBI, professional evaluations determined that hearing impairment only, vision impairment only, and dual sensory impairment were present in 19%, 34%, and 32% of these patients, respectively.⁴ After controlling for TBI severity, DSI was predictive of poorer functional improvement, signifying the importance of hearing and vision for rehabilitation outcomes. In an older non-TBI outpatient Veteran population, DSI was documented in 0% younger than the age of 65 years and in 20% older than the age of 85 years.²⁶ Together, these results suggested that DSI appearing in the current and younger Veteran cohort may indicate a premature deterioration in hearing and vision that may potentially have long-lasting effects.^{4,26}

DSI among patients with TBI is a challenge for clinicians providing rehabilitative care,¹⁹ but its prevalence in OEF/OIF returnees beyond studies with modest sample sizes is currently unknown. Using large national Veterans Health Administration (VHA) and Department of Defense (DoD) databases, the goals of the present study were to determine the prevalence rates of self-reported auditory, visual, and dual sensory impairment, and to identify demographic and deployment-related factors associated with sensory impairment. To date, this is the largest study that we are aware of on self-reported auditory and visual impairment in OEF/OIF Veterans who completed a TBI evaluation.

METHODS

Design

We performed a retrospective database review of 36,919 medical records that included information on demographics and results of comprehensive TBI evaluations performed in VHA between October 2007 and June 2009. Military service information was gathered from the DoD's Defense Management Data Center.

Instruments

Comprehensive TBI evaluation

Approximately, 20% of OEF/OIF Veterans seeking VHA healthcare services screen positive for TBI and are then referred for a comprehensive second-level TBI examination.²⁷ During this comprehensive TBI evaluation, patients undergo a physical examination by a specialist and are asked a series of standardized questions about their deployment-related experiences regarding blast exposure and nonblast related injuries and

pre- and postdeployment related trauma history. The protocol also includes the 22-item Neurobehavioral Symptom Inventory (NSI-22), which asks patients to self-report the extent to which any cognitive, affective, somatic, or sensory symptoms²⁸ have impacted them within the past 30 days. The evaluator then determines whether the patient history and clinical course is consistent with TBI or other physical or behavioral conditions, and develops a treatment plan.

The presence or absence of self-reported blast exposure and the clinical judgment of TBI (yes, no) were the stratifying variables, and demographic characteristics (age, sex) served as control variables.

Main measures

Auditory and visual variables were based on patients' self-reports of the extent to which "vision problems, blurring, trouble seeing" and "hearing difficulty" had affected them over the past 30 days on a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe). These data were treated in 2 ways, as a: (a) quantitative scale or (b) dichotomous categorical variable with "none" and "mild" difficulty combined.

Participants

Of the 36,919 comprehensive TBI evaluations performed for 36,426 unique patients included in the original dataset, test cases, and duplicate TBI evaluations ($n = 518$), as well as cases involving inconsistent responses regarding blast exposure ($n = 187$) were eliminated to yield 36,214 cases from which to sample (Figure 1).

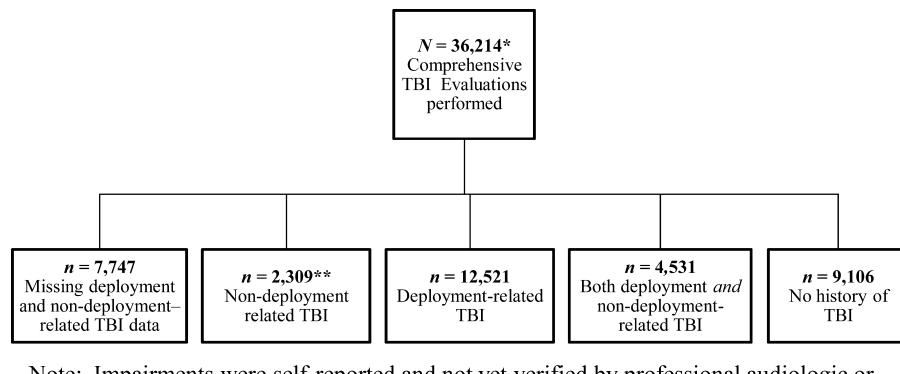
Of these, we focused on 2 groups, those who were judged to have deployment-related TBI ($n = 12,521$), and those who were not judged to have TBI ($n = 9,106$),

for a study sample size of 21,627. We excluded patients who had reported sustaining a TBI at a time other than deployment to control for conditions under which a TBI may have been experienced ($n = 6,840$), and those who did not have complete data ($n = 7,747$). We included non-TBI patients as a comparison group that was likely exposed to similar conditions ($n = 9,106$). Table 1 summarizes the sample characteristics. The majority of TBIs identified through this VHA evaluation process were mild (85.4%), thus reported results do not distinguish among levels of TBI severity.

DATA ANALYSIS STRATEGY

Frequencies for categorical variables and means and standard deviations for quantitative variables were calculated. Chi-square tests were used to examine the association of levels of sensory impairment severity (categorical) with blast exposure and TBI, and Pearson product moment correlations were used to examine associations between auditory and visual impairment.

Separate multiple linear regression analyses were conducted to predict severity of self-reported auditory or visual disturbance using simultaneous solutions in a hierarchical manner. Predictor variables included demographic factors (age, sex), impairment of the other sensory modality, blast exposure, TBI, and the 2- and 3-way interactions among TBI status, blast exposure, and sex. Variables were entered in blocks, with the main effects entered first followed by the set of 2-way interactions and then the 3-way interaction. To determine the unique contribution of each set of predictor variables, each block was entered last relative to all other blocks of predictors. The change in variance associated



Note: Impairments were self-reported and not yet verified by professional audiologic or visual testing.

*Excludes 518 test cases or repeat TBI evaluations and 187 cases with inconsistent blast responses (85 from Deployment-related TBI only, and 102 from No history of TBI groups)

**Non-deployment related TBI documented in notes, but no overall history of TBI indicated.

Figure 1. Prevalence of self-reported sensory impairment in OEF/OIF returnees who completed a comprehensive TBI Evaluation.

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TABLE 1 Demographic and event-related factors ($N = 21,627$)

Factors	n (%)
Sex	
Female	1,319 (6.1)
Male	20,306 (93.9)
Age	$M = 31.3$, SD = 8.6 Range: 18–65 years
Married/partnered	10,852 (50.3)
Pre-military education	
High school or less	12,032 (56.0)
Some college	7,909 (36.8)
College degree or postbaccalaureate	1,541 (7.1)
Current employment	
Working part-time/full-time	11,423 (55.0)
Student	2,233 (10.8)
Volunteer	49 (0.2)
Homemaker	126 (0.6)
Unemployed	6,930 (33.4)
Branch of service	
Army	15,856 (73.3)
Marines	3,763 (17.4)
Air Force, Navy, Other	1,766 (8.1)
Years of service	Median = 4.0 Range: 0–36 years
Number of deployments	Median = 1.0 Range: 1–19 ^a
Deployment-related TBI (Yes)	12,521 (57.9)
Blast exposure (Yes)	16,909 (78.2) $M = 3.0$, SD = 1.7

^aThe number of deployments can be high due to the methodology used to count the deployments. For example, each flight mission undertaken can be considered as a deployment resulting in a high number of deployments for Air Force personnel.

with the last step represents the unique contribution of that set of predictors. This procedure was used to evaluate the unique contribution of the main effects prior to any interaction effects, the unique contribution of the 2-way interactions over and above the main effects but prior to the 3-way interaction, and the unique contribution of the 3-way interaction over and above all other predictors.

RESULTS

Rates of Auditory, Visual, and Dual Sensory Impairment

Statistical analyses were performed with the use of SPSS software, version 18.0. The average patient was a 31.3-year-old man with 4.5 years of military service and 1.4 deployments. Among those who were judged to have deployment-related TBI (both blast exposed and nonblast exposed), self-reported sensory impairment rates

were: 24.2% for none to mild sensory impairment, 9.9% for visual impairment only, 31.3% for auditory impairment only, and 34.6% for DSI.

The distributions of sensory impairment as a function of blast exposure and TBI are presented in Figure 2.

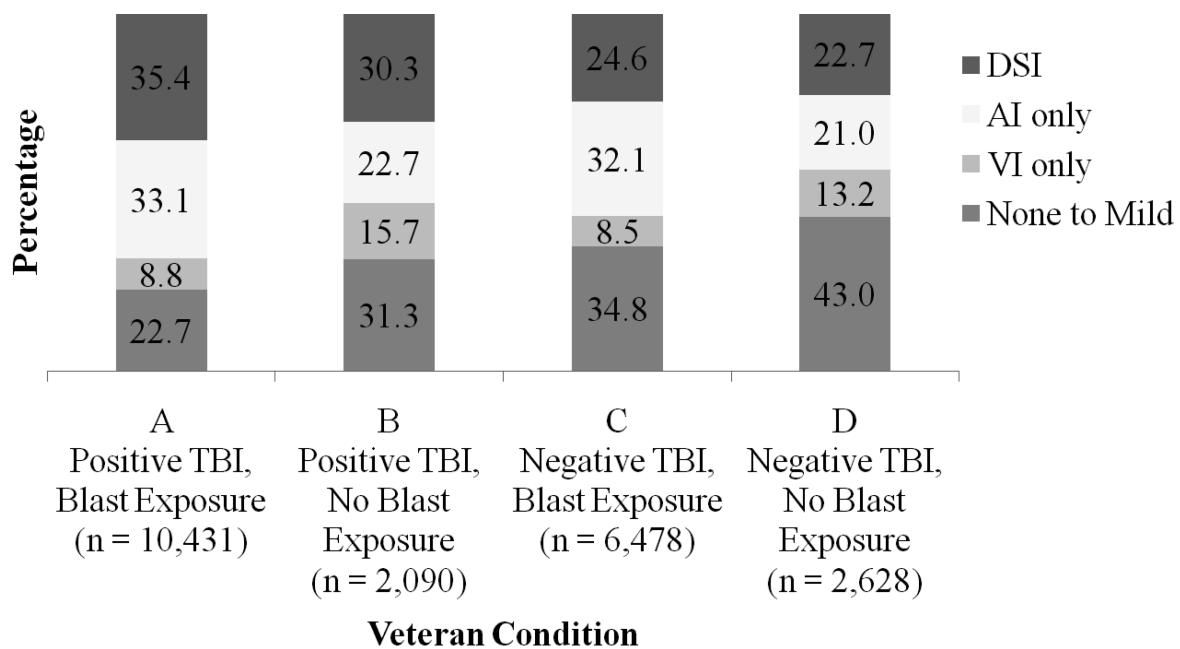
Across all 4 groups, approximately 78% were exposed to blast, and 58% were evaluated as having TBI. The 2 groups with the most pronounced differences in distributions of sensory impairment were the “Positive TBI, blast exposure” group (Graph A) and the “Negative TBI, no blast exposure” group (Graph D). Visual comparisons of these panels show that nearly twice the proportion of patients in Graph D reported minor rates of sensory impairment and also higher rates of visual impairment, whereas auditory and dual sensory impairment were markedly higher among those in Graph A. Patients in the “Negative TBI, blast exposure” group (Graph C) reported higher rates of auditory impairment and lower rates of visual impairment compared to the “Positive TBI, no blast exposure” group (Graph B). Among all 4 conditions, rates of DSI ranged from approximately 1 in 3 (Graph A) to approximately 1 in 5 (Graph D). For auditory impairment, there was a significant association between history of blast exposure and severity of sensory complaint, $\chi^2(3) = 198.20$, $P < .0001$; Cramer’s $V = .13$. Specifically, a higher percentage of positive TBI, blast-exposed patients reported moderate to very severe levels of impairment as compared to positive TBI, nonblast exposed patients. An association with blast exposure was also observed regarding visual impairment, $\chi^2(3) = 16.96$, $P = .001$, but the effect was weaker (Cramer’s $V = .04$) and in the opposite direction, with more patients in the positive TBI, nonblast group reporting very severe visual impairment.

Those who were exposed to blast reported higher rates of moderate to very severe auditory impairment compared to visual impairment. In the nonblast conditions, a similar trend is observed, although the rates of auditory and visual impairment were more comparable to one another.

Contributors to Sensory Impairment

Auditory and visual impairment were significantly correlated, $r(21625) = .33$, $P < .0001$, and therefore auditory impairment was included as a control variable in the regression model predicting visual impairment, and vice versa. The linear multiple regression model predicting auditory impairment was significant, $F(9, 21603) = 370.05$, $P < .0001$, accounting for 13.3% of the variance in impairment (Table 2).

The block of demographic and sensory impairment predictors accounted for the most variance (10.8%). Visual impairment was the largest predictor of auditory impairment, accounting for 9.2% of the variance,



VI = Visual Impairment; AI = Auditory Impairment; DSI = Dual Sensory Impairment

Figure 2. Association of sensory impairment with TBI and blast exposure in OEF/OIF Veterans who completed a comprehensive TBI evaluation (N = 21,627).

TABLE 2 Multiple linear regression results predicting auditory and visual impairment^a

	Auditory Impairment		Visual Impairment	
	Domain Unique Variance	Variable Unique Variance	Domain Unique Variance	Variable Unique Variance
Demographic and sensory impairment characteristics	10.8%		11.7%	
Age		0.1% ^c		1.1% ^c
Sex		0.5% ^c		0.5% ^c
Auditory impairment		—		9.3% ^c
Visual impairment		9.2% ^c		—
Deployment-related event	2.5%		0.008%	
TBI		0.8% ^c		0.7% ^c
Blast		1.3% ^c		0.1% ^c
Two-way interactions	<0.001%		<0.001%	
TBI × blast		0.02% ^b		<0.001%
TBI × sex		0.02% ^b		<0.001%
Blast × sex		<0.001%		<0.001%
Three-way interaction	<0.001%		<0.001%	
TBI × blast × sex		<0.001%		0.02%
Total domain variance before 2-way interactions	13.3%		12.4%	
Total domain variance before 3-way interaction	13.3%		12.4%	
Total domain variance including all interactions	13.3%		12.4%	

^aUnique variance of each demographic, deployment-related event, and interaction entered into the models is presented. Variables with b or c indicate statistically significant predictors of sensory impairment.

^bP ≤ .05, ^cP ≤ .001.

followed by sex (0.5%) and age (0.1%). Deployment-related events were the second strongest block of predictors (2.5%), with both blast exposure (1.3%) and TBI (0.8%) contributing significantly. The block of 2-way interactions was not significant overall (accounting for <0.001% of the variance), although the TBI \times blast interaction accounted for a very small (0.02%) but significant amount of variance in auditory impairment. We further explored the means of the TBI \times blast interaction and found that patients who were exposed to blast and were judged to have had a TBI reported the highest levels of auditory impairment ($M = 2.0$, SD = 1.2), whereas those with no blast exposure or TBI had the lowest levels of auditory impairment ($M = 1.3$, SD = 1.2). The 3-way TBI \times Blast \times sex interaction did not contribute any significant variance (<0.001%).

The linear multiple regression model for visual impairment was also significant, $F(9, 21603) = 342.40$, $P < .0001$. The block of demographic and sensory impairment variables accounted for the largest percent of variance in visual impairment (11.7%), with auditory impairment accounting for the most within this block (9.3%), followed by age (1.1%) and sex (0.5%). The deployment-related events block accounted for 0.008% of the total variance, with TBI significantly contributing the most variance (0.69%), followed by blast exposure (0.14%). The 2-way and 3-way interactions were not significant predictors of visual impairment.

DISCUSSION

The goals of this study were to document the prevalence of self-reported DSI and to identify contributing factors related to self-reported auditory and visual impairment in OEF/OIF service members who completed a VA comprehensive TBI evaluation. A main finding was that the coexistence of sensory impairment was common. Depending on exposure to blast and TBI status, rates of visual impairment ranged from 8.5% to 15.7%; auditory impairment from 21.0% to 33.0%; and DSI from 22.7% to 35.4%.

The regression models showed that sensory impairment in one modality (ie, auditory or visual) was the largest predictor for sensory impairment in the other modality. This finding suggests that either these impairments have a single source (eg, brain trauma with associated dysfunction) or that damage to the 2 systems stems from a common source (eg, blast wave, shrapnel). There is no evidence to suggest that impairment to one system leads to impairment in the other.

Independently, blast exposure and TBI were significant but small contributors to sensory impairment, with blast exposure accounting for more variance in auditory impairment than visual impairment. The interaction of TBI and blast showed that those who experienced blast

exposure and were evaluated as having TBI reported higher rates of auditory impairment than any other condition; this result was consistent with other studies reporting the deleterious effects of blast-related TBI on hearing.^{4,15,16,19}

A striking finding was that 1 in 5 patients who reported no exposure to blast and were not judged to have a TBI still self-reported moderate to very severe DSI. Although it is impossible to know about all premilitary, general military, and battlefield conditions, several situations may help explain these findings. We note that auditory impairment was more prevalent than visual impairment regardless of blast exposure or TBI. Some service members have complained that wearing earplugs prevents them from being keenly attuned to their environment.²⁹ Exposure to noise from the general military environment and weaponry,^{15,19} coupled with the tendency of some service members to forgo ear protection,⁹ may create an extra vulnerability to auditory system damage. Regarding vision, one study⁹ reported eye problems occurring in only 0.5% of troops, citing ballistic eye gear as a likely protectant. Nearly 100% of these marines wore ballistic eye protection, which typically sustained shrapnel and debris damage.⁹ However, polycarbonate ballistic eyewear cannot protect against all ocular trauma, such as targeted hits from bullets or projectiles that impact the eye via other parts of the face.²³ As was the case with earplugs, some combat troops have viewed protective eye armor as intrusive,²¹ which could decrease its rate of utilization.

LIMITATIONS

We note several limitations of this study. First, degree of sensory impairment was based on patient self-report, which is subjective and potentially inaccurate. We also do not know whether any of the self-report data were attributable to preexisting or nondeployment related sensory conditions. Relatedly, because the types of hearing and vision problems experienced by the patients were not specified in the databases, the nature of self-reported sensory impairment was not clear. However, we note that the TBI evaluation process is meant to evaluate whether the patient experienced a TBI or is experiencing other conditions that may require further assessment. Information obtained during the TBI evaluation provides a good gateway for additional discussion about patient complaints and an opportunity to refer for specialty care. Finally, we caution that this sample may not be characteristic of OEF/OIF returnees as a whole, but rather may only be representative of OEF/OIF returnees who (a) used VA healthcare services, (b) were referred for additional TBI evaluation after a positive preliminary TBI screen, and (c) came to the clinic and completed the comprehensive evaluation. Therefore, compared to the

general OEF/OIF Veteran population, the rates of visual and auditory impairment reported here may be slightly inflated by the fact that these patients referred for a TBI evaluation had an increased likelihood of having experienced a TBI.

IMPLICATIONS

Vision and hearing are 2 key modalities through which people interact with and make sense of their environment. Patients with impairment in one sensory modality may be able to compensate by relying on a different sensory modality.^{30,31} Without vision³² or hearing therapies,^{16,19} untreated impairment can challenge patients' abilities to read, drive, communicate, interact, and participate in some work environments. Rehabilitation efforts can be compromised further if the patient has TBI.³³

The prevalence of single and dual sensory impairment in our sample suggests that patients undergoing a comprehensive TBI evaluation who report at least moderate hearing or visual difficulty on the NSI-22 should be referred on for further evaluation. Hearing and vision ex-

aminations could identify existing sensory deficits and may also lead to collaborative efforts among clinicians to diagnose, or rule out, any other conditions, such as neuropsychological dysfunction.¹⁹ In this relatively young cohort of Veterans that could require decades of care, a comprehensive, multidisciplinary evaluation may provide early detection of impairment that sets the patient on the appropriate rehabilitation course.

CONCLUSIONS

In the largest study of its kind to date, we found that self-reported auditory and visual impairment were prevalent among OEF/OIF Veterans receiving a VA comprehensive TBI evaluation, and that DSI ranged from 1 in 3 (positive TBI, blast exposed) to 1 in 5 (negative TBI, non-blast exposed). These results highlight the importance of a comprehensive, interdisciplinary team approach during the evaluation and rehabilitation process of Veterans returning from OEF/OIF. Patients who report clinically significant hearing or vision difficulty during the routine TBI evaluation should be offered referrals for complete audiology and visual examinations.

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ORIGINAL ARTICLE

Mild Traumatic Brain Injury After Motor Vehicle Collisions: What Are the Symptoms and Who Treats Them? A Population-Based 1-Year Inception Cohort Study

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Abstract

Objective: To describe the 1-year course of symptoms following mild traumatic brain injury (MTBI) sustained in a motor vehicle collision as well as patterns of care-seeking.

Design: One-year follow-up of a population-based inception cohort.

Setting: The province of Saskatchewan, Canada, with a population of about 1,000,000 inhabitants.

Participants: Persons (N=1716) sustaining an MTBI during a car collision between November 1997 and December 1999.

Interventions: Not applicable.

Main Outcome Measures: We report the prevalence of sleep disturbances, tiredness, dizziness, forgetfulness, vision problems, hearing problems, headache, neck pain, mid back pain, and low back pain at 6 weeks and 3, 6, 9, and 12 months postcollision. At the same time points, we report self-reported care-seeking from registered health care professionals.

Results: A total of 1716 adults suffered MTBI after a motor vehicle collision over the 2-year inception period. Six weeks after the collision, 75% reported having more than 3 symptoms and 30% had clinically significant pain in more than 3 body sites. Over time, the prevalence of symptoms and pain decreased but they were still common after 1 year. Almost all participants sought care for their symptoms at all time points, most commonly from a physician. Care-seeking from physiotherapists, chiropractors, and massage therapists was also very common, and most participants sought care from 2 or 3 providers at all follow-up points.

Conclusions: Up to 1 year after sustaining an MTBI during a motor vehicle collision, multiple symptoms and pain in several anatomical sites are common. Care-seeking from multiple providers continues throughout the first year postinjury.

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While the true incidence of traumatic brain injury (TBI) and concussion is not known, it is estimated that as many as 600 of

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every 100,000 Americans are affected every year,¹ resulting in approximately 1.4 million visits to emergency departments yearly.² There is evidence that the incidence of TBI is increasing, especially during sports activities, possibly reflecting both true increase and increased reporting.^{3,4}

TBI severity is usually categorized into mild, moderate, or severe, most often on the basis of the Glasgow Coma Scale

score,⁵ with the most common being mild traumatic brain injury (MTBI), also commonly known as concussion.² Symptoms after MTBI vary but may include headache, blurred vision, confusion, dizziness, memory problems, fatigue, and sleep difficulties to varying degrees.⁶ Imaging of the brain in persons having suffered an MTBI is usually normal.⁷ Most patients with MTBI recover within the first year even though a significant minority continues to report symptoms.⁸ The International Collaboration on MTBI Prognosis reviewed and critically appraised the literature relating to subjective symptoms after adult MTBI and found that although self-reported symptoms such as headache and fatigue are common even after 1 year, they are not specific to MTBI but are equally present in those with other nonhead injuries.⁹ For instance, Lannsjo et al¹⁰ reported that 44% of the persons presenting to an emergency department after MTBI still had 1 or more symptoms after 3 months, most commonly fatigue, headache, and dizziness. However, it is unclear what the source population was in this and other studies, and they did not collect data on a range of symptoms such as neck and back pain.¹⁰ This is important because many cases of MTBI are not treated at hospitals and are therefore mostly not registered in health databases.¹¹ Of those who do not present to hospital emergency departments, some do not seek any care¹² while others seek care for symptoms in the primary health care sector through family physicians, physiotherapists, chiropractors, massage therapists, or others for symptoms relating to MTBI.² Evidence suggests that persons not experiencing persistent symptoms after the injury are less likely to seek care,¹³ and indeed individuals who experience a more severe TBI access health care at a much higher rate than do persons having suffered mild or moderate TBI.¹⁴

Allied health professions, predominantly physiotherapists, are involved in care for individuals with MTBI.¹⁴ This may reflect guideline recommendations for the management of MTBI, which include information about the injury, how to handle common complaints, and how to cope with them, including reassurance about the good prognosis and gradual reintegration of normal activities.^{15,16} Little is known, however, about the course of common symptoms during the first year after sustaining an MTBI and how these symptoms are associated with health care-seeking from both physicians and other care providers. Such information is important and a prerequisite for subsequent analytic studies examining associations between symptoms, care-seeking, and recovery and could help formulate future intervention studies.

In this article, we describe the 1-year course of symptoms following MTBI sustained in a motor vehicle collision and the primary sector care-seeking patterns for individuals who experienced MTBI. Specifically, we sought to answer the following research questions: (1) What are the symptoms after MTBI sustained in a motor vehicle collision at 6 weeks and 3, 6, 9, and 12 months after the injury? and (2) What types of care and combinations of care do persons who have sustained an MTBI in a motor vehicle collision seek at these follow-up points?

List of abbreviations:

- MTBI mild traumatic brain injury
- NRS numeric rating scale
- TBI traumatic brain injury

Methods

Participants and setting

Between December 1, 1997, and November 30, 1999, a population-based inception cohort of all traffic injuries in persons 18 years and older was formed in the province of Saskatchewan, Canada. The cohort included all injured individuals who were treated by registered health professionals, who were obliged to make a claim to receive reimbursement for treatment, or individuals who made an insurance claim independent of the health care provider. We excluded individuals who made such a claim more than 42 days after their injury. We also excluded individuals who had died as a result of the collision, could not answer the baseline questionnaire because of language or serious disease or injury, and Workers' Compensation claims, which are covered by a different public insurance scheme. Baseline information was collected on insurance claim forms on all subjects. This included sociodemographic characteristics, collision-related factors, injury-related symptoms, body areas with pain and intensity of the pain, depressive symptoms, health care provision, comorbid health conditions, general health, previous injury, and work status. MTBI cases were identified using a 3-step process: first the person had to answer "yes" to the question "Did you hit your head in the collision?" Then, the person had to answer either "yes" or "don't know" to one of the following questions: "Did you lose consciousness immediately after the accident?" "Immediately after the accident, did you experience amnesia or loss of memory?" "Immediately after the accident, did you experience disorientation or confusion?" In addition, the study participant had to have answered "yes" to at least one of the following questions for cohort inclusion: "Did the accident cause dizziness or unsteadiness?" "Did the accident cause memory problems or forgetfulness?" "Did the accident cause concentration of attention problems?" We excluded study participants who reported that they lost consciousness for more than 30 minutes after the collision.

Subjects were followed by computer-aided telephone interviews at 6 weeks and 3, 6, 9, and 12 months. For this study, we examined the health care utilization patterns and symptoms starting at the 6-week follow-up because the baseline questionnaire was answered any time from the day of collision to 42 days after the collision. Study participants who completed the baseline questionnaire later would have had more opportunity to visit different types of health care providers than study participants who completed the questionnaire within a couple of days of the collision. The Research Ethics Board of the University of Saskatchewan and the University of Alberta approved the original study. The University Health Network at the University of Toronto approved our current analysis.

Variables

Symptom variables at baseline included answers to the following question: "Did the accident cause any of the following symptoms?" Checklist response options included the following: sleep problems, concentration and attention problems, dizziness or unsteadiness, memory problems or forgetfulness, sleep problems, hearing problems, or vision problems. Depression was assessed at baseline using the Centre for Epidemiological Studies—Depression Scale. The Centre for Epidemiological Studies—Depression Scale, which has been shown to have good test-retest reliability and validity, was

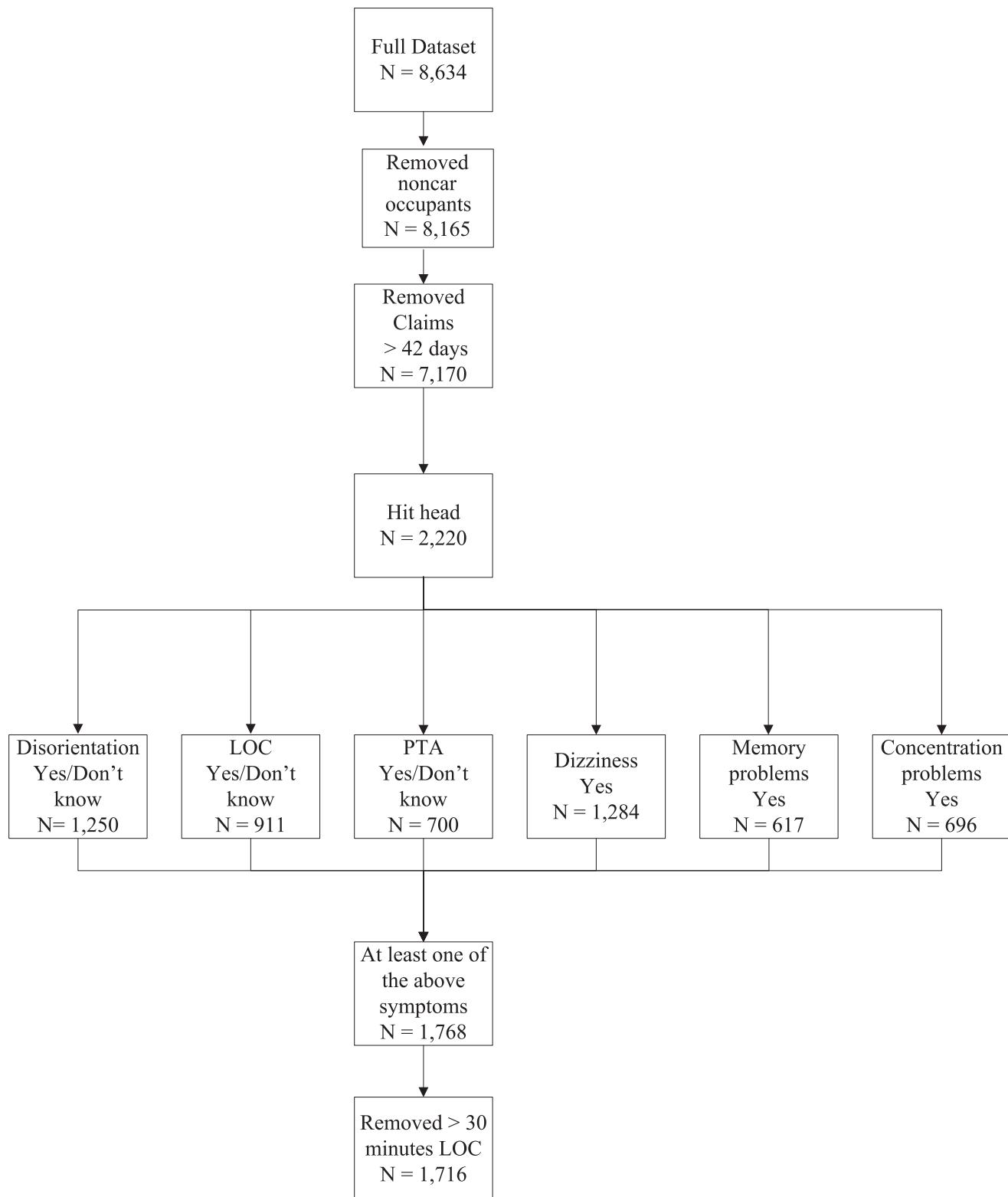


Fig 1 Flow diagram of cohort assembly.

designed to measure the current level of depressive symptoms in the general population with a score range of 0 to 60, where a higher score indicates greater depressive symptoms. The Centre for Epidemiological Studies—Depression Scale asks questions with

reference to the past week, and we used a cutoff of 16 points to define depression.^{17,18} This cutoff point has been used previously in population-based studies of patients with whiplash injury.¹⁹ Self-rated health was assessed at baseline and follow-up by asking the

Table 1 Descriptive characteristics for an inception cohort of 1716 persons who sustained MTBI during a car collision

Characteristic	n (%)
Sex: female	904 (52.7)
Age (y), mean \pm SD	37.7 \pm 16.1
18–23	435 (25.4)
24–29	258 (16.0)
30–39	359 (20.9)
40–49	304 (17.7)
\geq 50	360 (21.0)
Education	
Less than high school	520 (30.3)
High school graduate	434 (25.3)
More than high school	761 (44.4)
Missing	1 (0.0)
Income (\$)	
0–20,000	625 (37.2)
20,001–\$40,000	513 (30.6)
40,001–\$60,000	298 (17.8)
\geq 60,000	242 (14.4)
Missing	38 (2.2)
Driver of the car	
Days in hospital (d), mean \pm SD	1.6 \pm 4.1
0	1249 (73.0)
1–2	175 (10.2)
3–7	175 (10.2)
$>$ 7	113 (6.6)
Missing	4 (0.0)
Accident caused	
Fracture any bones	
No	1263 (73.6)
Yes	362 (21.1)
Uncertain	90 (5.3)
Missing	1 (0.0)
Loss of consciousness	
No	855 (50.0)
Yes	473 (27.6)
Do not know	386 (22.5)
Missing	2 (0.0)
Amnesia	
No	1059 (61.7)
Yes	393 (22.9)
Do not know	264 (15.4)
Confusion	
No	505 (29.5)
Yes	1019 (59.5)
Do not know	190 (11.1)
Missing	2 (0.0)
Pain intensity baseline, mean \pm SD*	
Neck	6.1 \pm 2.9
Headache	5.7 \pm 3.4
Back	4.1 \pm 3.6
Mid back	3.8 \pm 3.6
Arm	3.1 \pm 3.5
Hand	1.7 \pm 2.9
Abdomen, chest, groin	3.2 \pm 3.7
Face	2.4 \pm 3.4
Leg	3.2 \pm 3.6
Foot	1.1 \pm 2.6

Table 1 (continued)

Characteristic	n (%)
Prior health	
Excellent	738 (43.0)
Very good	567 (33.0)
Good	332 (19.3)
Fair/poor	79 (4.6)
Health now	
Excellent/very good	154 (9.0)
Good	385 (22.4)
Fair	682 (39.8)
Poor	494 (28.8)

* Item missing for pain questions up to 25 (1.5%).

following question: “In general would you say your health is: excellent; very good; good; fair; poor?” Headache and spine pain were assessed by asking the following question: “Did the accident cause headache, neck pain, shoulder pain, mid back pain, or low back pain?” If the answer was yes to any one of the separate questions, participants were asked to rate their pain on an 11-point numeric rating scale (NRS), where 0 was labeled as “no pain” and 10 was labeled as “pain as bad as could be.”

At 3, 6, 9, and 12 months, the same questions regarding depression, symptoms, headache, neck/shoulder, mid back, and low back pain were asked in relation to the past week.

Care-seeking at the first follow-up interview at 6 weeks was assessed by asking the following question: “Since the accident, have you seen health care practitioners?” Response options were as follows: No, yes physician, yes physiotherapist, yes chiropractor, yes massage therapist, or yes other. At the 3-, 6-, 9-, and 12-month follow-up, care-seeking was assessed by asking about provider type: “Have you seen a physician or chiropractor or physiotherapist or massage therapist or any other health care provider as a result of the accident since the last follow-up?” Response options for each provider type were “yes” and “no.”

Analysis

Proportions of participants with symptoms were tabulated for each follow-up time point. Pain measured from the NRS is reported as means and SDs. To distinguish trivial from nontrivial pain, we arbitrarily dichotomized answers into intensity of pain less than 5 and intensity of pain 5 or more on the NRS. We then reported proportions of participants in each category and proportion of participants with pain intensity of 5 or more at more than 3 body sites. Care-seeking from physicians, physiotherapists, chiropractors, massage therapists, and others was calculated at each follow-up point as well as the number of providers and the most common combinations of providers if more than 1 provider had been seen. Finally, symptom profiles for participants seeking care from the different providers were tabulated. The analysis was purely descriptive, and no statistical comparisons were performed.

Results

In total, 8634 persons were involved in a motor vehicle collision during the study period. We excluded 469 persons because they were not occupants of a motor vehicle (eg, pedestrians or bikers),

Table 2 Symptoms up to 1y for 1716 persons who had suffered an MTBI during a car collision

Symptoms	6wk (n=1442)	3mo (n=1415)	6mo (n=1321)	9mo (n=1193)	12mo (n=1158)
Sleep disturbances	921 (64.5)	729 (53.2)	613 (48.0)	498 (44.3)	480 (44.4)
Tiredness	845 (59.2)	721 (52.7)	573 (45.1)	457 (40.7)	426 (39.4)
Dizziness	554 (38.9)	441 (32.2)	358 (28.2)	290 (25.8)	275 (25.4)
Forgetfulness	468 (32.8)	443 (32.2)	378 (29.8)	310 (27.6)	288 (26.6)
Depression	463 (27.0)	371 (21.6)	280 (16.3)	224 (13.1)	209 (12.2)
Vision problems	276 (19.3)	232 (16.9)	208 (16.4)	178 (15.9)	156 (14.4)
Hearing problems	167 (11.7)	165 (12.1)	150 (11.8)	126 (11.2)	111 (10.3)
Headache*	540 (38.8)	373 (27.4)	305 (23.9)	234 (20.7)	207 (18.6)
Neck pain*	706 (50.0)	508 (36.9)	394 (30.7)	327 (28.5)	283 (25.4)
Mid back pain*	265 (18.6)	175 (12.7)	129 (10.0)	97 (8.4)	87 (7.8)
Low back pain*	487 (34.7)	376 (27.4)	273 (21.4)	248 (21.7)	209 (18.8)

NOTE. Values are presented as n (%).

* ≥5 on the NRS.

and a further 995 were excluded because they claimed an injury more than 42 days after the collision. To form our cohort, we identified 1768 subjects who answered “yes” to having hit their head in the collision and reported having at least 1 of the following symptoms as the result of the collision: confused, passed out, amnesia, dizziness, forgetfulness, or concentration problems. We then excluded 52 study participants who stated that they lost consciousness for more than 30 minutes. The final MTBI cohort had a sample size of 1716 (fig 1). The total follow-up rate over the duration of the study was 84%.

The mean age of the cohort was 37.7 years, and 53% were women (table 1). Slightly under a third reported that they had not

completed high school, and 68% reported their income to be less than or equal to \$40,000 per year. A majority of the cohort members were the driver of the car, and 27% had spent at least 1 day in hospital postcollision. Most reported that their current health status was fair to poor after the collision, which contrasted remarkably with their self-reported health status 1 year earlier, which they classified as either excellent to very good.

Six weeks after the collision, the most common symptoms were sleep disturbances (65%), tiredness (59%), neck pain (50%), headache (39%), dizziness (39%), and low back pain (35%), whereas the other symptoms were somewhat less common (table 2). Three-fourths reported more than 3 symptoms, and 26% reported

Table 3 Care-seeking over the first year for 1716 persons who had suffered an MTBI during a car collision

	6wk (n=1420)	3mo (n=1367)	6mo (n=1134)	9mo (n=1116)	12mo (n=1078)
No care	22 (1.5)	23 (1.7)	37 (3.3)	50 (4.5)	59 (5.5)
All contacts*					
MD	1364 (95.9)	1312 (95.7)	1188 (93.8)	1042 (93.0)	988 (91.4)
PT	592 (41.7)	641 (46.8)	679 (53.8)	618 (55.4)	606 (56.2)
DC	282 (19.9)	356 (26.2)	390 (30.9)	373 (33.4)	375 (34.7)
MT	346 (24.4)	393 (28.7)	385 (30.5)	382 (34.2)	370 (34.4)
Other	143 (10.1)	162 (11.8)	174 (13.8)	149 (13.3)	133 (12.3)
Care only from					
MD	425 (29.9)	341 (24.9)	275 (24.3)	209 (18.7)	194 (17.9)
PT	4 (0.2)	6 (0.4)	3 (0.3)	6 (0.5)	10 (0.9)
DC	16 (1.1)	16 (1.2)	8 (0.7)	8 (0.7)	12 (1.1)
MT	1 (0.1)	1 (0.1)	5 (0.4)	1 (0.1)	2 (0.2)
Other	0	4 (0.3)	2 (0.2)	1 (0.1)	0
Combinations of care					
MD + PT	310 (21.8)	326 (23.8)	256 (22.6)	238 (21.3)	201 (18.6)
MD + DC	85 (5.9)	85 (6.2)	68 (5.9)	59 (5.3)	61 (5.7)
MD + MT	111 (7.8)	94 (6.9)	52 (4.6)	64 (5.7)	51 (4.7)
PT + DC	1 (0.1)	0	4 (0.4)	1 (0.1)	2 (0.2)
PT + MT	0	0	3 (0.3)	0	1 (0.1)
DC + MT	10 (0.7)	6 (0.4)	5 (0.4)	7 (0.6)	7 (0.6)
MD + PT + DC	176 (12.4)	58 (4.2)	77 (6.8)	75 (6.7)	78 (7.2)
PT + DC + MT	2 (0.1)	1 (0.1)	1 (0.1)	2 (0.1)	0
Missing	22 (1.5)	48 (3.5)	187 (16.4)	77 (6.9)	80 (7.4)

NOTE. Values are presented as n (%).

Abbreviations: DC, chiropractor; MD, physician; MT, massage therapist; PT, physiotherapist.

* Denominator = everyone who completed at least 1 question at a follow-up.

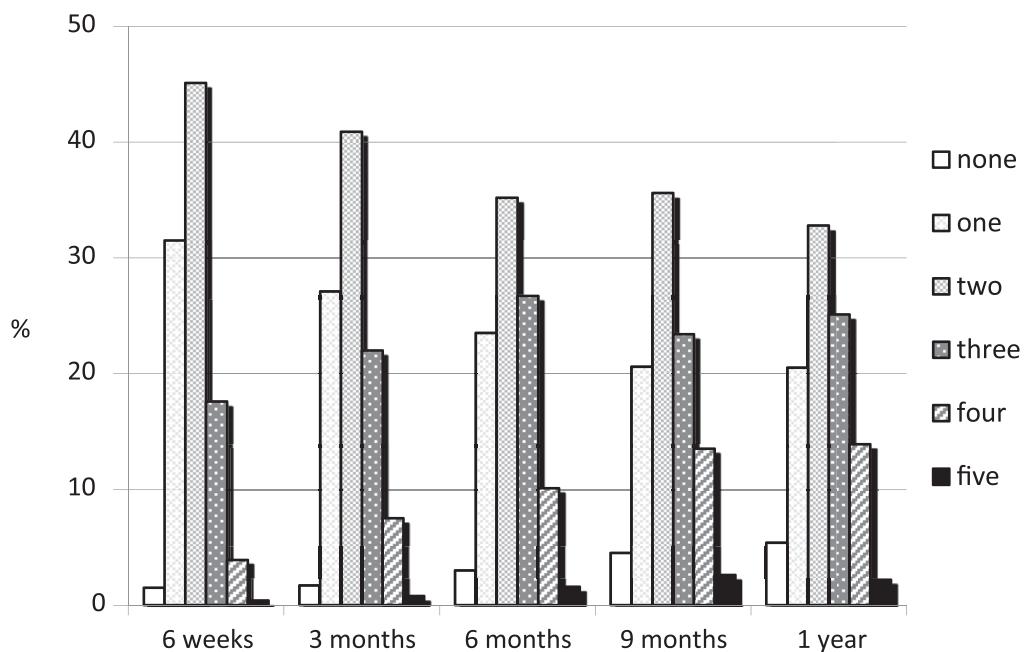


Fig 2 Number of health care providers over 1 year for 1716 individuals who had experienced MTBI after a motor vehicle collision.

more than 8 symptoms. Thirty percent had a pain score of 5 or more on the NRS at more than 3 body sites. Over time, the prevalence of all symptoms decreased. However, after 1 year, sleep disturbances (44%), tiredness (39%), forgetfulness (27%), dizziness (25%), neck pain (25%), and low back pain (19%) were still common symptoms that participants related to the collision. More than half still reported more than 3 symptoms, and 17% reported more than 8 symptoms. The number of pain sites decreased considerably over time, and only 10.5% reported a pain score of 5 or more on the NRS at more than 3 body sites at the 1-year follow-up.

Almost all participants had sought care for symptoms related to the collision within the first 6 weeks: 95.9% had seen a physician, 41.7% a physiotherapist, 19.9% a chiropractor, 24.4% a massage therapist, and 10.1% had seen another type of provider (table 3). Over the 1 year, care-seeking from physicians remained constant and high (>90%) and care-seeking from physiotherapists, chiropractors, massage therapists, and others increased. After 1 year, 74% of the participants had sought care from more than 1 provider. If participants had only 1 care provider, this was by far most commonly a physician. The majority of the participants received care from more than 1 provider at all time points, with most still seeing 2 or 3 providers after 1 year (fig 2). The most common combination of caregivers was a physician and a physiotherapist at all time points. Combinations not involving physicians were rare (see table 3), and less than 1% reported not having seen a physician at any follow-up point. Generally, a greater proportion of persons seeking care from nonphysicians reported symptoms at all time points, and this was particularly pronounced for neck pain but was true for practically all symptoms at all follow-up time points (table 4).

Discussion

To our knowledge, this is the first population-based study describing the prevalence and development of self-reported

symptoms and care-seeking in individuals who have experienced a traffic-related MTBI. Being involved in a motor vehicle collision and sustaining an MTBI has a significant negative effect on a person's health status. One year later, multiple symptoms are very common and the majority (74%) continues to seek care from multiple providers. Physicians provide most of the care, but patients may also seek care from allied health professionals such as physiotherapists, chiropractors, and massage therapists. Individuals seeking care from allied health professionals have in general more symptoms than do persons seeking care from physicians. The symptom profile of this cohort is comparable to known symptom profiles from other studies of MTBI after traffic collisions²⁰; however, the course and persistence of symptoms during the first year has not been mapped in detail before.

Motor vehicle collisions can result in multiple injuries and various symptoms that are similar to MTBI. For example, mechanical injury and stress to the neck and spine can also cause headache, fatigue, concentration problems, and other symptoms similar to MTBI.²¹ Certainly, there can be overlap and whiplash injuries have a substantial effect on future health in terms of persistent headache, spine pain, fatigue, and sleep disturbances²² and other pain complaints.²³ It is possible that MTBI could be caused by sudden acceleration-deceleration of the head during motions similar to whiplash injury. However, the extent of MTBI caused by indirect injury is not known in our study or in general. Differentiating symptoms of MTBI from whiplash injury is a major challenge because they probably co-occur in many cases. Also, depression is common after whiplash injury,²⁴ and the prevalence of both depression and spine pain decreased in our cohort over the first year after sustaining an MTBI (see table 2). Finally, in another publication based on this cohort, ratings of self-rated health were found to decrease dramatically after sustaining an MTBI in a traffic collision.²⁵

We found that almost all participants received continuous care over the first year from primarily a physician, but a large proportion also consulted allied health professionals such as physiotherapists, chiropractors, and massage therapists. These providers

Table 4 Symptoms per provider up to a year for 1716 persons who had suffered an MTBI during a car collision*

Symptoms	6wk				
	Physician (n=1364)	Physiotherapist (n=592)	Chiropractor (n=282)	Massage therapist (n=346)	Other (n=143)
Sleep disturbances	891 (65.2)	431 (72.8)	202 (71.6)	233 (67.3)	107 (74.8)
Tiredness	814 (59.7)	395 (66.7)	190 (67.4)	223 (64.4)	94 (65.7)
Dizziness	529 (38.9)	269 (45.5)	120 (42.6)	134 (38.7)	75 (52.4)
Forgetfulness	447 (32.8)	220 (37.2)	114 (40.4)	133 (38.4)	60 (41.9)
Depression	445 (32.6)	223 (37.7)	99 (35.1)	121 (35.0)	65 (45.5)
Vision problems	266 (19.5)	126 (21.3)	58 (20.6)	74 (21.4)	44 (30.8)
Hearing problems	160 (11.7)	76 (12.8)	42 (14.9)	44 (12.7)	20 (13.9)
Headache*	521 (39.4)	272 (47.4)	127 (47.0)	160 (47.2)	67 (48.2)
Neck pain*	674 (50.1)	343 (58.7)	183 (65.8)	223 (65.0)	79 (55.3)
Mid back pain*	259 (19.1)	130 (22.1)	66 (23.5)	77 (22.3)	31 (21.7)
Low back pain*	471 (35.2)	234 (40.1)	124 (45.3)	143 (41.8)	57 (39.9)
6mo					
	Physician (n=1188)	Physiotherapist (n=679)	Chiropractor (n=385)	Massage therapist (n=390)	Other (n=174)
Sleep disturbances	583 (49.1)	401 (59.1)	227 (58.9)	221 (56.7)	108 (62.1)
Tiredness	550 (46.3)	364 (53.6)	198 (51.4)	194 (49.7)	104 (59.8)
Dizziness	342 (28.8)	222 (32.7)	133 (34.5)	127 (32.6)	75 (43.1)
Forgetfulness	364 (30.7)	231 (34.0)	137 (35.6)	134 (34.4)	79 (45.4)
Depression	270 (22.7)	171 (25.2)	102 (26.5)	95 (24.4)	65 (37.4)
Vision problems	198 (16.7)	129 (18.9)	69 (17.9)	60 (15.4)	47 (27.0)
Hearing problems	141 (11.9)	84 (12.4)	56 (14.5)	38 (9.7)	25 (14.4)
Headache*	291 (24.9)	201 (29.9)	112 (29.6)	118 (30.9)	69 (40.4)
Neck pain*	370 (31.4)	271 (40.2)	164 (42.3)	159 (41.2)	74 (42.8)
Mid back pain*	124 (10.5)	95 (14.1)	58 (15.1)	41 (10.5)	32 (18.5)
Low back pain*	257 (21.9)	183 (27.3)	112 (29.5)	93 (24.3)	52 (29.9)
12mo					
	Physician (n=988)	Physiotherapist (n=606)	Chiropractor (n=375)	Massage therapist (n=370)	Other (n=133)
Sleep disturbances	453 (45.9)	316 (52.1)	186 (49.6)	194 (52.6)	80 (60.2)
Tiredness	401 (40.6)	278 (45.9)	166 (44.2)	170 (46.1)	68 (51.1)
Dizziness	255 (25.8)	171 (28.2)	101 (26.9)	105 (28.5)	50 (37.6)
Forgetfulness	273 (27.7)	179 (29.5)	115 (30.7)	109 (29.5)	55 (41.4)
Depression	194 (19.6)	132 (21.8)	69 (18.4)	70 (18.9)	35 (26.3)
Vision problems	153 (15.5)	99 (16.3)	56 (14.9)	64 (17.3)	27 (20.3)
Hearing problems	99 (10.0)	67 (11.1)	44 (11.7)	46 (12.5)	15 (11.3)
Headache*	196 (20.2)	137 (23.1)	82 (22.3)	97 (26.5)	43 (33.6)
Neck pain*	268 (27.4)	192 (32.2)	133 (36.0)	141 (38.6)	54 (40.1)
Mid back pain*	85 (8.7)	64 (10.7)	45 (12.1)	43 (11.7)	21 (15.8)
Low back pain*	201 (20.7)	144 (24.2)	99 (26.8)	94 (25.7)	40 (30.1)

NOTE. Some patients use more than 1 provider. Values are presented as n (%).

* ≥ 5 on the NRS.

likely provide symptomatic treatments for back pain, neck pain, and headaches (see table 4). Consulting health care providers is dependent on many factors including habits, preferences, access, financial ability/insurance systems, and of course type and severity of injuries and symptoms. Notably, frequent attendance in family practice has been associated with psychological distress in patients,²⁶ and indeed emotional distress and personality changes have been found in persons who sustained a head injury in a car collision.²⁷ Using our same Saskatchewan data, Carroll et al²⁴ found that almost half of the individuals in a cohort who had experienced whiplash injury could be classified as depressed shortly after the accident and that approximately 20% had recurrent or persistent depressive symptoms.¹⁹ In addition, the personal perception of one's injury and its potential negative consequences

have been shown to significantly affect the persistence of symptoms.²⁸ In fact, persons who expect to get better after the collision recover more than 3 times faster than do persons who never expected to get better after a whiplash injury.²⁹ At the same time, evidence suggests that general practitioners underestimate the degree of patient distress in the postinjury period.³⁰ Thus, a greater focus on depression, emotional distress, and patient expectations instead of on bodily symptoms may result in less seeking of care and faster recovery.

There is an urgent need for clinical trials that evaluate the effectiveness of interventions that are provided to patients with MTBI by both medical and allied health professionals. Clearly, these interventions need to target a broad range of symptoms that are not unique to MTBI. Furthermore, it could be helpful

to coordinate care among various health professionals who target these conditions.

Study limitations

Our findings must be interpreted in light of several potential limitations. We formed our cohort of patients with MTBI without using the Glasgow Coma Scale. We did include subjects who had “hit their head” during the traffic collision and experienced at least 1 common MTBI symptom. However, these symptoms are not specific to MTBI and our cohort likely included some patients with whiplash injury to the neck. However, as previously discussed, distinguishing MTBI from whiplash injury is problematic because they can share the same mechanism of injury and the same symptoms. In addition, symptoms may vary across time points and patients. Furthermore, symptom reporting and care-seeking behaviors are highly affected by cultural and societal factors and our findings may not be generalizable to other settings. Because both symptoms and health care use were so frequent, we did not perform further analyses of symptom and care-seeking patterns for subgroups of participants based on personal or injury characteristics. Such analyses would require further stratification and multivariate analysis. Our data are 15 years old, and although we are not aware of any secular trends in the treatment and prognosis of MTBI, this is a potential limitation. Finally, definitions of MTBI are known to vary across studies and our findings may not be comparable to other studies that use clinician-defined MTBI. However, there is great variation in definitions of MTBI and we have addressed this issue in a companion article in this issue of the journal.³¹

An important strength of our study is that it is population based and includes all treated MTBIs after traffic collisions. Although we had no data from clinical examinations, we did have an impressive spectrum of self-reported outcomes on a large number of patients followed frequently over 1 year. Our questions came from valid measures of symptoms, which limit information bias. Our follow-up rate of 84% limits the potential for selection bias.

Conclusions

In this first population-based inception cohort study of individuals who have experienced an MTBI during a car collision, we found a high prevalence of multiple symptoms and pain at several body sites. In addition, care-seeking from multiple providers continued throughout the first year postinjury. Studies investigating how clusters of symptoms interact and affect prognosis are needed. Most urgently however, high-quality clinical trials investigating the effectiveness and cost-effectiveness of the many kinds of treatments given to these patients are needed.

Keywords

Brain concussion; Cohort studies; Health care seeking behaviour; Rehabilitation

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ORIGINAL ARTICLE

Visual dysfunction following blast-related traumatic brain injury from the battlefield

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Abstract

Primary objective: To assess the occurrence of ocular and visual disorders following blast-related traumatic brain injury (TBI) in Operation Iraqi Freedom.

Research design: Retrospective cohort study.

Methods and procedures: A total of 2254 US service members with blast-related combat injuries were identified for analysis from the Expeditionary Medical Encounter Database. Medical record information near the point of injury was used to assess factors associated with the diagnosis of ocular/visual disorder within 12 months after injury, including severity of TBI.

Main outcomes and results: Of 2254 service members, 837 (37.1%) suffered a blast-related TBI and 1417 (62.9%) had other blast-related injuries. Two-hundred and one (8.9%) were diagnosed with an ocular or visual disorder within 12 months after blast injury. Compared with service members with other injuries, odds of ocular/visual disorder were significantly higher for service members with moderate TBI (odds ratio (OR) = 1.58, 95% confidence interval (CI) = 1.02–2.45) and serious to critical TBI (OR = 14.26, 95% CI = 7.00–29.07).

Conclusions: Blast-related TBI is strongly associated with visual dysfunction within 1 year after injury and the odds of disorder appears to increase with severity of brain injury. Comprehensive vision examinations following TBI in theatre may be necessary.

Keywords: *TBI, ocular and visual disorder, combat injury, military*

Introduction

Changes in the nature of warfare during the current military conflicts in Iraq and Afghanistan have led to an increase in traumatic brain injuries (TBIs) not experienced in previous wars [1–3]. These injuries are often associated with explosive weaponry, such as improvised explosive devices, that can cause a wide range of penetrating and non-penetrating injuries [4, 5]. Blasts have been responsible for ~75% of all combat casualties in Iraq and Afghanistan [6] and for more than 85% of all head, face and neck injuries [5]. Improvements in protective equipment have reduced the frequency

and severity of penetrating injuries, but they provide limited protection for non-penetrating injuries, such as concussion resulting from the blast wave of a high-energy explosion [7]. In addition, advances in battlefield medicine and medical response times have improved the survivability of wounds that were fatal in previous wars [8]. Together, these changes have resulted in a new pattern of injuries among survivors. TBI has emerged as a preponderant injury of Operations Enduring Freedom and Iraqi Freedom [9].

Survivors of TBI experience a wide range of physical, cognitive and emotional symptoms and

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often require a complex and integrative approach to rehabilitative care [10, 11]. Visual problems are among the most common physical sequelae following a TBI [12, 13]. The occurrence of TBI-related ocular and visual disorders is varied, depending on the diagnostic criteria, condition and patient population, but has primarily been studied in civilian settings where blunt force trauma is often cited as the cause of injury [12, 14–16]. Visual dysfunction following TBI in a combat setting has not been widely examined, nor have the effects of blast-related TBI on vision. The aim of the present study was to assess the occurrence of visual dysfunction following blast-related TBI among US service members injured during combat deployment in Operation Iraqi Freedom.

Methods

Study sample

The study sample was identified from the Expeditionary Medical Encounter Database (EMED), formerly the Navy-Marine Corps Combat Trauma Registry, which is maintained by the Naval Health Research Center in San Diego, CA. The EMED contains information abstracted from US service members' medical records completed by military providers at forward-deployed treatment facilities in the combat zone, nearest to the point of injury, and is merged with inpatient and outpatient medical record information obtained from other US Department of Defense databases [17].

From the EMED, US service members who met the following criteria were included in this study: (a) having survived injury due to an explosion (or blast) in Operation Iraqi Freedom between 1 March 2004 and 28 February 2007, (b) having only one recorded injury event and (c) having not received a diagnosis of ocular or visual disorder prior to the injury event. Those who sustained eye injury were excluded from analysis in order to minimize confounding. This research was conducted in compliance with all applicable US federal regulations governing the protection of human subjects.

Measures

Demographic information included age and military rank (enlisted or officer) at the time of injury and gender. The cause of injury was indicated on service members' clinical records from theatre and was categorized as improvised explosive device, landmine, mortar, rocket-propelled grenade and blast, other/unspecified. Traumatic brain injury, the exposure of interest, was defined according to criteria established by the Centers for Disease Control and

Prevention as indicated by any one of the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes: 800.0–801.9, 803.0–804.9 or 850.0–854.1 [18]. The Abbreviated Injury Scale (AIS) 2005 was used to describe severity of brain injury [19]. The AIS details the severity of each injury in nine body regions and ranges from 0 (no injury) to 6 (unsurvivable injury). Due to a small number of TBI observations with scores of 4 (severe injury) and 5 (critical injury) in the present study, TBI severity was categorized as follows: 0 = no TBI, 1 = minor, 2 = moderate and 3–5 = serious to critical. Service members with AIS scores of 6 were not eligible for inclusion in this study.

The main outcome measure, ocular/visual disorder, was indicated by the ICD-9-CM diagnostic codes for 'disorders of the eye and adnexa' (360.0–379.9) obtained from electronic outpatient medical records (Standard Ambulatory Data Record) and diagnosed within 12 months after blast-related combat injury.

Statistical analysis

Descriptive and univariate analyses were performed using SPSS software, v. 17.0 (SPSS Inc., Chicago, IL). The prevalence of ocular/visual disorder was calculated for the sample. Differences in demographic and injury characteristics between groups with and without TBI were assessed with the Mann-Whitney U-test for non-normally distributed, continuous data (i.e. age) and with chi-square (χ^2) tests for categorical data. Simple logistic regression was performed to ascertain odds ratios and 95% confidence intervals for characteristics associated with diagnosis of ocular/visual disorder. The StatCalc program in Epi Info software version 6 was used to perform the Mantel extension of chi-square test for trend (χ_{trend}) to assess a dose-dependent relationship between severity of TBI and diagnosis of ocular/visual disorder. An alpha level of 0.05 was used to determine statistical significance for all tests.

Results

The study sample consisted of 2254 US service members injured by an explosive weapon during a 3-year period of Operation Iraqi Freedom. Median age at the time of injury was 23 years and ranged from 18–59 years. The majority of service members were male (99.0%) and were enlisted (95.9%). Approximately 8.9% (201 of 2254) were diagnosed with ocular/visual disorder within 12 months after injury in a blast event.

Thirty-seven per cent of the sample ($n=837$) were diagnosed with a blast-related TBI during

Table I. Demographic and injury characteristics of blast-injured US service members from Operation Iraqi Freedom by TBI status.

Characteristic	Total (n=2254)	TBI (n=837)	Other injury (n=1417)	p
Ocular/visual disorder, no. (%)				0.01
Yes	201 (8.9)	91 (10.9)	110 (7.8)	
No	2053 (91.1)	746 (89.1)	1307 (92.2)	
Median age (range), years	23 (18–59)	22 (19–53)	23 (18–59)	0.19
Gender, no. (%)				0.13
Male	2231 (99.0)	832 (99.4)	1399 (98.7)	
Female	23 (1.0)	5 (0.6)	18 (1.3)	
Military rank, no. (%)				0.04
Enlisted	2162 (95.9)	812 (97.0)	1350 (95.3)	
Officer	92 (4.1)	25 (3.0)	67 (4.7)	
Blast mechanism, no. (%)				<0.001
Improvised explosive device	1563 (69.3)	703 (84.0)	860 (60.7)	
Mortar	188 (8.3)	19 (2.3)	169 (11.9)	
Rocket-propelled grenade	113 (5.0)	26 (3.1)	87 (6.1)	
Landmine	111 (4.9)	47 (5.6)	64 (4.5)	
Other/unspecified	279 (12.4)	42 (5.0)	237 (16.7)	

the study period. The characteristics of service members with TBI and with other injury are compared in Table I. Median age and gender did not statistically differ by TBI status. Traumatic brain injury status differed, however, by military rank, injury mechanism and ocular/visual disorder outcome. Compared with service members without TBI, higher proportions of those with TBI were enlisted (97.0% vs 95.3%, $p=0.04$) and were injured by an improvised explosive device (84.0% vs 60.7%, $p<0.001$). Ocular/visual disorder diagnosis was more common among those with TBI than service members with other injuries (10.9% vs 7.8%, $p=0.01$).

Ocular/visual disorder diagnoses by TBI status, based on the ICD-9-CM category descriptions, are shown in Table II. Overall, the most common disorders were ‘disorders of refraction and accommodation’ and ‘visual disturbances’ (see Appendix for a detailed list of diagnoses within these categories). Although ‘disorders of refraction and accommodation’ were proportionally higher among service members with TBI than those without (7.3% vs 5.8%), the difference was not statistically significant. ‘Visual disturbance’ disorders and ‘disorders of conjunctiva’, however, were statistically more common in the TBI than the other injury group (1.9% vs 0.6%, $p=0.003$, and 1.6% vs 0.6%, $p=0.03$, respectively).

In Table III, simple logistic regression (univariate) analyses show the odds of new-onset ocular/visual disorder following blast-related injury by sample characteristics. Age, gender, military rank and blast mechanism were not associated with diagnosis of ocular/visual disorder. In order to assess for difference in odds by severity of brain injury, service

members were categorized as no TBI, minor, moderate and serious-to-critical. Compared with service members without TBI, those with minor TBI did not have statistically different odds of new-onset ocular/visual disorder ($p=0.88$). The odds of new-onset ocular/visual disorder were statistically higher, however, among service members with moderate TBI (odds ratio (OR)=1.58, 95% confidence interval (CI)=1.02–2.45) and serious-to-critical TBI (OR=14.26, 95% CI=7.00–29.07). Figure 1 demonstrates the upward trend in odds of ocular/visual disorder by increasing brain injury severity (Mantel $\chi_{\text{trend}}^2=28.063$, $p<0.001$).

Discussion

In the present study, 37% of service members sustained a blast-related TBI during combat deployment. These personnel were significantly more likely to be diagnosed with an ocular or visual disorder than service members with other blast-related injuries. Furthermore, the findings demonstrate a dose-dependent effect of brain injury severity on visual dysfunction, in that the odds of ocular or visual disorder diagnosis increases with brain injury severity. This finding is not altogether surprising as injury severity is known to be linearly associated with morbidity, mortality, hospitalization and other measures of severity [19–21].

Previous literature has demonstrated an occurrence of visual dysfunction in 30–85% of civilian and military samples with occult TBI [7, 12, 22]. In the present study, only 11% of those with TBI, overall, were diagnosed with visual dysfunction within 1 year of blast-related combat injury. This discrepancy in the occurrence of visual dysfunction following TBI

Table II. Number and percentage of US service members in each ocular/visual disorder diagnostic category by TBI status.

ICD-9-CM code and category ^a		TBI (n=837)	Other injury (n=1417)
360 Disorders of the globe	0	1	<0.1%
361 Retinal detachments and defects	0	1	<0.1%
362 Other retinal disorders	2	0.2%	4
363 Chorioretinal inflammations, scars and other disorders of choroid	1	0.1%	0
364 Disorders of iris and ciliary body	1	0.1%	3
365 Glaucoma	3	0.4%	2
366 Cataract	1	0.1%	1
367 Disorders of refraction and accommodation	61	7.3%	82
368 Visual disturbances*	16	1.9%	8
369 Blindness and low vision	3	0.4%	2
370 Keratitis	3	0.4%	3
371 Corneal opacity and other disorders of cornea	2	0.2%	5
372 Disorders of conjunctiva**	13	1.6%	9
373 Inflammation of eyelids	1	0.1%	1
374 Other disorders of eyelids	3	0.4%	5
375 Disorders of lacrimal system	1	0.1%	4
376 Disorders of orbit	1	0.1%	0
377 Disorders of optic nerve and visual pathways	1	0.1%	4
378 Strabismus and other disorders of binocular eye movements	5	0.6%	5
379 Other disorders of eye	5	0.6%	5

Individuals may be represented in multiple diagnostic categories.

^aEach category is calculated as a separate variable.

* $\chi^2 = 9.063$, $p = 0.003$. ** $\chi^2 = 4.585$, $p = 0.03$.

Table III. Descriptive and univariate analyses of ocular/visual disorder outcome among blast-injured US service members from Operation Iraqi Freedom (n=2254).

Variable	Ocular/visual disorder (n=201)	No disorder (n=2053)	Odds ratio	95% CI	p
Traumatic brain injury, no. (%)					<0.001
No	110 (54.7)	1307 (63.7)	Ref		
Minor	45 (22.4)	520 (25.3)	1.03	0.72–1.48	0.88
Moderate	28 (13.9)	211 (10.3)	1.58	1.02–2.45	0.04
Serious-to-critical	18 (9.0)	15 (0.7)	14.26	7.00–29.07	<0.001
Median age ^a (range), years	22 (19–53)	23 (18–59)	1.38	0.66–2.87	0.39
Gender, no. (%)					0.49
Male	193 (98.5)	2033 (99.0)	Ref		
Female	3 (1.5)	20 (1.0)	1.54	0.45–5.23	
Military rank, no. (%)					0.30
Enlisted	190 (94.5)	1972 (96.1)	Ref		
Officer	11 (5.5)	81 (3.9)	1.41	0.74–2.69	
Blast mechanism, no. (%)					0.47
Improvised explosive device	140 (69.7)	1423 (69.3)	Ref		
Mortar	15 (7.5)	173 (8.4)	0.88	0.51–1.54	0.66
Rocket-propelled grenade	9 (4.5)	104 (5.1)	0.88	0.44–1.78	0.72
Landmine	15 (7.5)	96 (4.7)	1.59	0.90–2.81	0.11
Other/unspecified	22 (10.9)	257 (12.5)	0.87	0.55–1.39	0.56

CI, confidence interval; Ref, reference group.

^aAge was log transformed for univariate analysis due to non-normal distribution.

may be explained by the difference in assessment of outcome. Generally, previous studies used prospective visual screening, clinical evaluation measures or self-report data to identify visual problems, whereas, in the present study, the occurrence of dysfunction was retrospectively assessed by the presence of an

ocular or visual disorder diagnosis in the service members' existing medical record. Without thoroughly evaluating all patients, one is likely underestimating the occurrence of ocular and visual problems among service members with blast-related combat injury.

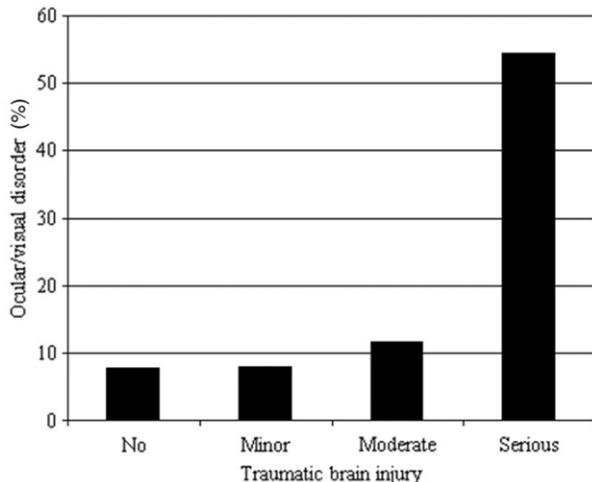


Figure 1. Percentage of US service members with ocular/visual disorder by traumatic brain injury status.

Note: Mantel χ^2 trend = 28.063, $p < 0.001$.

The primary finding of the present study was the strong dose-dependent relationship between severity of TBI and the occurrence of visual dysfunction. These disorders should be considered common sequelae of moderate and serious-to-critical TBI among blast-injured combat veterans and clinical interventions should be applied appropriately. Although the association between minor TBI and ocular/visual disorder did not achieve statistical significance, those with minor blast-related TBI (or concussions) may still be at risk for developing vision problems. In a recent study of combat-injured service members with self-reported mild TBI, the majority reported visual complaints and presented with visual dysfunctions, such as accommodative insufficiency [22]. Many patients with minor injuries, including mild TBI, are immediately returned to duty following treatment in theatre [5, 23]. Because visual problems reduce the ability to perform daily activities (e.g. reading) [12] and might further affect one's abilities to perform duties required during combat deployment, administration of comprehensive visual examinations in theatre following any severity of TBI and especially blast-induced injury should be considered.

The primary limitation of this study was the retrospective nature of the analysis; data were not collected for the purpose of this study. Further, in order to minimize confounding, the analysis included only those without eye injury. Future research should assess the potential cumulative effects blast-related eye injury and TBI may have on the short- and long-term visual outcomes among combat veterans. As mentioned previously, because the outcome data were diagnoses of patients who

presented for care rather than a vision assessment of all patients in the sample, this analysis may underestimate the true prevalence of impairment.

Despite these limitations, this study is unique because it examined new-onset visual dysfunction in a large cohort of blast-injured veterans and assessed the outcome in US service members with all types of injuries, ranging from minor to severe. Furthermore, it is the first to identify a statistical relationship between severity of TBI and subsequent diagnosis of ocular/visual disorder in a blast-injured population. As blast mechanisms, such as improvised explosive devices, continue to cause the majority of injuries among military personnel serving in Operations Enduring Freedom and Iraqi Freedom, further research of the effects of blast-related brain injury will be needed.

Conclusion

Given the occurrence of vision problems in the growing population of service members with blast-related TBI, strategies for diagnosis and management of these conditions are needed and should be included in TBI treatment protocols. Comprehensive vision examinations after TBI in theatre may be necessary in order to identify undiagnosed cases of ocular/visual disorder. For veterans with undiagnosed TBI, Post-Deployment Health Assessments, which contain questions about exposure to blasts and brain injury experience (e.g. losing consciousness), may be used to identify service members who may require vision assessments and/or rehabilitation. Future research should include population-based studies and screening among returning service members to elucidate specific ocular and visual conditions associated with blast-related TBI, in order to develop appropriate rehabilitation guidelines.

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Appendix: ICD-9-CM codes and diagnoses for ‘disorders of refraction and accommodation’ and ‘visual disturbances’

Disorders of refraction and accommodation

- 367.0 Hypermetropia (farsightedness, hyperopia)
- 367.1 Myopia (nearsightedness)
- 367.2 Astigmatism
- 367.3 Anisometropia and aniseikonia
- 367.4 Presbyopia
- 367.5 Disorders of accommodation
- 367.8 Other disorders of refraction and accommodation
- 367.9 Unspecified disorder of refraction and accommodation

Visual disturbances

- 368.0 Amblyopia ex anopsia
- 368.1 Subjective visual disturbances
- 368.2 Diplopia (double vision)
- 368.3 Other disorder of binocular vision
- 368.4 Visual field deficits
- 368.5 Colour vision deficiencies (colour blindness)
- 368.6 Night blindness (nyctalopia)
- 368.8 Other specified visual disturbance
- 368.9 Unspecified visual disturbance

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Visual symptomatology and referral patterns for Operation Iraqi Freedom and Operation Enduring Freedom veterans with traumatic brain injury

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Abstract—Advances in protective armor technology and changes in the “patterns of war” have created a population of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans with traumatic brain injury (TBI) that provide a unique challenge to Department of Veterans Affairs (VA) healthcare practitioners. The purpose of the study was to determine the frequency of symptomatic ocular and visual sequelae of TBI in OIF/OEF veterans at the Portland VA Medical Center, a Polytrauma Support Clinic Team site. A retrospective analysis of 100 OIF/OEF veterans with TBI was conducted to determine the prevalence of ocular and visual complaints. Referral patterns were also investigated. Visual symptoms were reported in approximately 50% of veterans with TBI. Loss of consciousness, but not number of deployments or number of blast exposures, was found to have a statistically significant association with severity of reported visual symptoms. The most commonly reported symptoms included blurred vision (67%), photosensitivity (50%), and accommodative problems (40%). Visual symptoms of OIF/OEF veterans at the Portland VA Medical Center are reported at slightly lower rates than similar studies conducted at the Palo Alto and Edward Hines Jr VA facilities.

INTRODUCTION

The high incidence of nonpenetrating injuries from explosive blasts has made mild traumatic brain injury (TBI) the “signature wound” of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) [1]. Estimates state that 10 to 20 percent of OIF/OEF veterans return from the theater of operations having sustained a TBI [2]. Improvised explosive devices (IEDs) have been estimated to be responsible for approximately 60 percent of these TBIs, as well as 40 percent of Coalition casualties [3–4]. TBIs from IEDs can occur through several mechanisms. Primary blast injuries include those sustained from the initial blast wave itself. The extreme pressure changes associated with the blast wave tend to preferentially damage organs with air-fluid interfaces,

Abbreviations: IED = improvised explosive device, NSI = Neurobehavioral Symptom Inventory, OEF = Operation Enduring Freedom, OIF = Operation Iraqi Freedom, PNS = Polytrauma Network Site, PRC = Polytrauma Rehabilitation Center, PSCT = Polytrauma Support Clinic Team, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury, VA = Department of Veterans Affairs, VHA = Veterans Health Administration.

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Key words: Neurobehavioral Symptom Inventory, Operation Enduring Freedom, Operation Iraqi Freedom, postconcussive syndrome, postdeployment, posttraumatic stress disorder, symptom, traumatic brain injury, veteran, vision.

such as rupturing of the tympanic membranes. A secondary injury occurs as a result of propulsion of shrapnel within the radius of the blast exposure. A tertiary injury occurs when an individual is physically displaced from his or her position either to the ground or into a stationary object. Finally, the heat wave generated by the blast may result in burns or exposure to noxious chemicals: a quaternary injury [4].

In April 2007, the Department of Veterans Affairs (VA) issued a directive requiring all OIF/OEF veterans to be screened for TBI. This screening includes a military history questionnaire and the Neurobehavioral Symptom Inventory (NSI). The goal of these surveys is to ascertain a history of potentially traumatic events sustained in the combat zone, including exposure to blasts, explosions, and artillery, as well as symptoms immediately after such traumatic events and persistence of these symptoms into the present. A positive screening results in a referral to the appropriate provider for additional clinical evaluation [1,5].

The Polytrauma System of Care was designed to manage veterans diagnosed with TBI [6]. A summary of the Polytrauma System of Care is available from <http://www.polytrauma.va.gov/system-of-care/care-facilities/>. Polytrauma Rehabilitation Centers (PRCs) are inpatient facilities for the most severe injuries and are located in Minneapolis, Minnesota; Palo Alto, California; Richmond, Virginia; and Tampa, Florida. Regional Polytrauma Network Sites (PNSs) provide the second tier of care by managing postacute injuries; there are 21 such sites across the country. Finally, 130 Polytrauma Support Clinic Teams (PSCTs) consist of interdisciplinary teams that manage postacute sequelae in an outpatient setting and make referrals to the PRCs and PNSs as appropriate. The Portland VA Medical Center serves as one of these PSCTs.

In addition to these general screenings, Veterans Health Administration (VHA) Directive 065, issued October 2008, states “every prior (since February 2005), current, and future patient with a diagnosis of TBI admitted to a VA PRC must have a TBI specific ocular health and visual functioning eye examination performed by an optometrist or ophthalmologist” [7] (available online from http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=1783).

The tests required under this directive are extensive and apply specifically to PRCs. This directive has been successful in evaluating and managing veterans with the most

severe TBIs, as well as spreading public awareness about the ocular and visual consequences of TBI.

The ocular and visual sequelae of TBI in the general population have been well documented. Anomalies of the accommodative, binocular, and oculomotor systems, as well as vestibular dysfunction and perceptual and cognitive delays, are often reported following TBI [8]. Visual field defects, photosensitivity, and ocular surface disease are also common ocular health sequelae of mild TBI [9]. In populations recovering from TBI, the prevalence of these visual disturbances has been reported as ranging from 30 to 85 percent [10]. Recent studies have described the occurrence of visual and vestibular symptoms in OIF/OEF veterans with TBI. Stelmack et al. reported that visual symptoms were self-reported in 75 percent of OIF/OEF veterans with TBI at the Edward Hines Jr VA Hospital (PNS) [11]. In a retrospective study of the Palo Alto VA (PRC) healthcare system, Brahm et al. found that 75.4 percent of OIF/OEF veterans at PRCs reported subjective visual complaints [12]. For OIF/OEF veterans with presumed TBI being seen at the center’s outpatient PNS, 75.8 percent of patients reported a subjective visual complaint. An earlier study of polytrauma patients at the Palo Alto VA (PRC) revealed self-reported visual symptoms in 74 percent of the population [13]. Similarly, Lew et al. observed that 75 percent of veterans with TBI reported visual symptoms at the Palo Alto VA (PNS) [5]. Thus, it is clear that OIF/OEF veterans with TBI are very likely to complain of visual symptoms during screenings.

The goal of the present study is to determine the frequency of self-reported ocular and visual symptoms in OIF/OEF veterans with TBI at the Portland VA Medical Center, a PSCT. Further, this study will examine the referral patterns to the eye care team to determine whether visual symptoms are being adequately addressed in this population.

METHODS

We reviewed 185 records from OIF/OEF veterans examined in the postdeployment clinic from January 2009 to the present. Patient records were included in the present study if a diagnosis of TBI was given at the initial postdeployment evaluation with the medical doctor. The records of those OIF/OEF veterans who were evaluated in the postdeployment clinic by a medical doctor but not given a diagnosis of TBI were excluded. The present

study examines 100 OIF/OEF veteran records with a diagnosis of TBI based on the postdeployment evaluation. The information from each electronic medical record was extracted, de-identified, and entered into a secure database. Specific information from each veteran's initial evaluation by a medical doctor in the post-deployment clinic was reviewed. These records included a military history questionnaire eliciting specific information about blast exposures capable of inducing a TBI during deployment, as well as the NSI to determine the severity of neurological and psychological symptoms that have caused disturbance since deployment. For the purposes of this study, a score of 2 or greater out of 4 on the NSI was considered to be significant. This level corresponded to symptoms of moderate or greater intensity and was determined by Stelmack et al. to have an adverse effect on daily activities [11]. Statistical analysis was performed using SPSS for descriptive statistics, correlations, and *t*-tests (PASW v18, IBM; Armonk, New York) and Linacre (v3.66, Winsteps; Berkeley, California) for Rasch analysis.

RESULTS

The mean age of veterans in this study was 29.9 yr (range: 21–55 yr), and 99 percent of veterans were male. Of the records studied, 59 percent of these veterans reported a single deployment, while two, three, and four or greater deployments were reported by 28 percent, 10 percent, and 3 percent of subjects, respectively. Multiple blast injuries accounted for the majority (69%) of TBIs, with the other causes being blasts associated with motor vehicle accidents (13%), single blasts (10%), falls (7%), and isolated motor vehicle accidents (1%). Loss of consciousness was reported by 27 percent of subjects.

The frequencies of reported symptoms on the NSI in the present study are compared with those of Stelmack et al. in **Figure 1** [11]. A score of 2 or greater was reported by 47 percent of veterans for "Blur/Trouble Seeing" compared with 63 percent in the Stelmack et al. study, while 54 percent responded with a score of 2 or greater for "Light Sensitivity" compared with 59 percent per Stelmack et al. **Figure 1** also compares the frequencies compiled in the

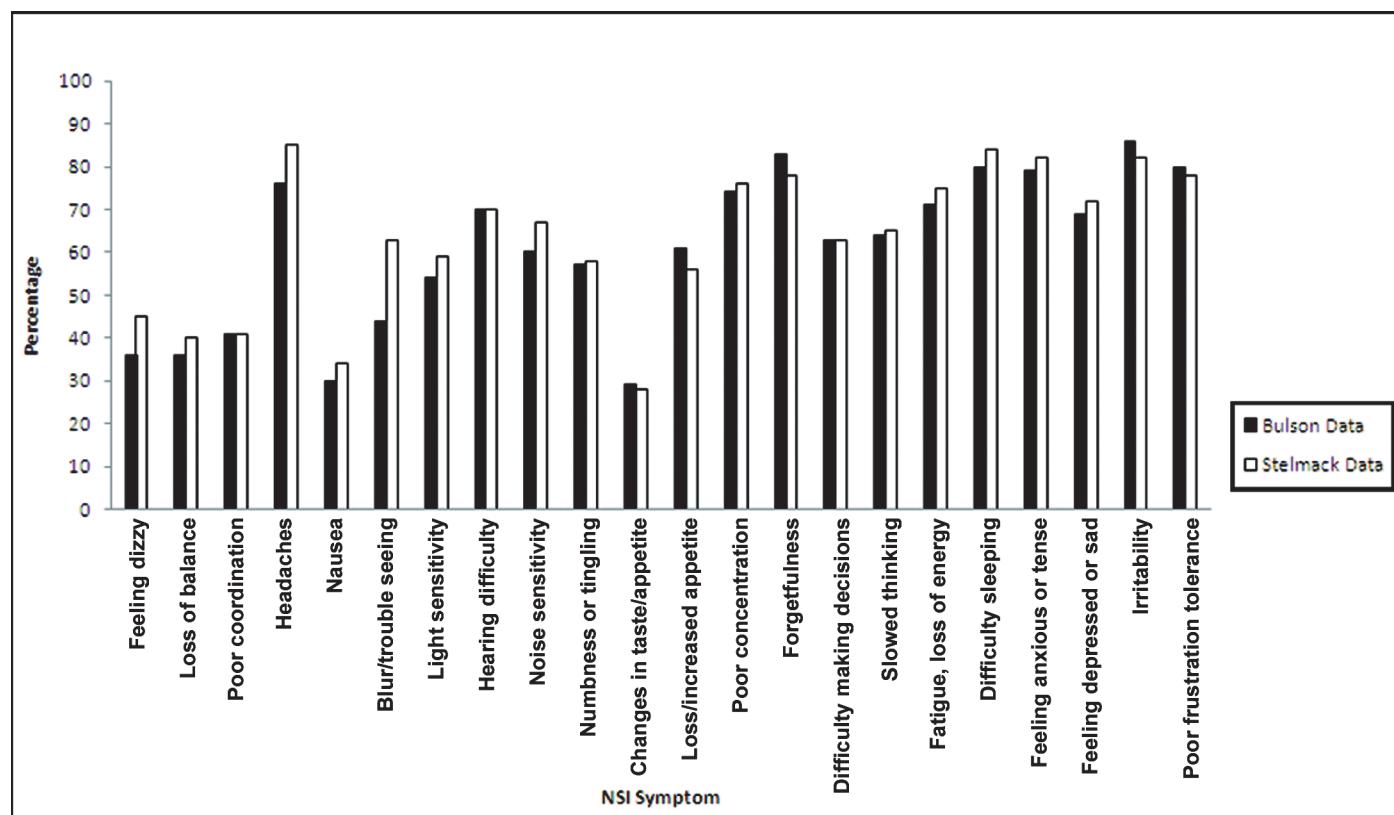


Figure 1.

Percentage reporting Neurobehavioral Symptom Inventory (NSI) score of ≥ 2 : comparison of present study versus Stelmack et al. [11].

present study with those reported by Stelmack et al. [11]. Only the frequency of reported problems with “Blur/Trouble Seeing” were statistically different from the findings of Stelmack et al. via Chi square analysis ($\chi^2 = 5.71$, $p = 0.02$).

Rasch analysis was used to provide composite scores for the NSI. The overall single factor scale had Item separation = 3.5 and Person separation = 5.94, with reliabilities equal to 0.92 and 0.97, respectively. Four items—difficulty sleeping, numbness or tingling, feeling anxious or tense, and poor coordination—had infit scores > 2 . The outlier questions were not deleted from the scale since a subscale created with them correlated ($r = 0.75$) with the reduced total scale score. The composite Rasch measure was used to test the associations with other variables.

There were no significant correlations between severity of symptoms reported on the NSI and number of blasts ($t = 1.56$, $p = 0.12$) or number of deployments ($r = -0.04$, $p = 0.67$). Loss of consciousness was determined to be statistically correlated with more severe symptoms on the NSI ($t = 3.92$, $p < 0.001$). A comparison of NSI symptom scores between veterans reporting loss of con-

sciousness and those reporting no loss of consciousness is shown in **Figure 2**.

During the postdeployment evaluation with the primary care physician, 33 percent of veterans self-reported a visual problem. The most commonly self-reported visual symptoms during the initial postdeployment evaluation were blurred vision (67%), photosensitivity (50%), focusing problems (40%), peripheral vision defects (17%), tracking problems (10%), and double vision (7%). Of those veterans reporting visual symptoms on either the NSI or during the postdeployment evaluation, 91 percent were referred to the eye clinic; however, 23 percent of these veterans “no-showed” for their evaluation in the eye clinic.

Of the visually symptomatic veterans examined in the eye clinic, 96 percent had best corrected visual acuities of 20/20 or better. The most common diagnoses of those veterans evaluated in the eye clinic were uncorrected refractive error (96%), photosensitivity (22%), accommodative dysfunction (13%), dry eye syndrome (9%), and visual field defect (9%).

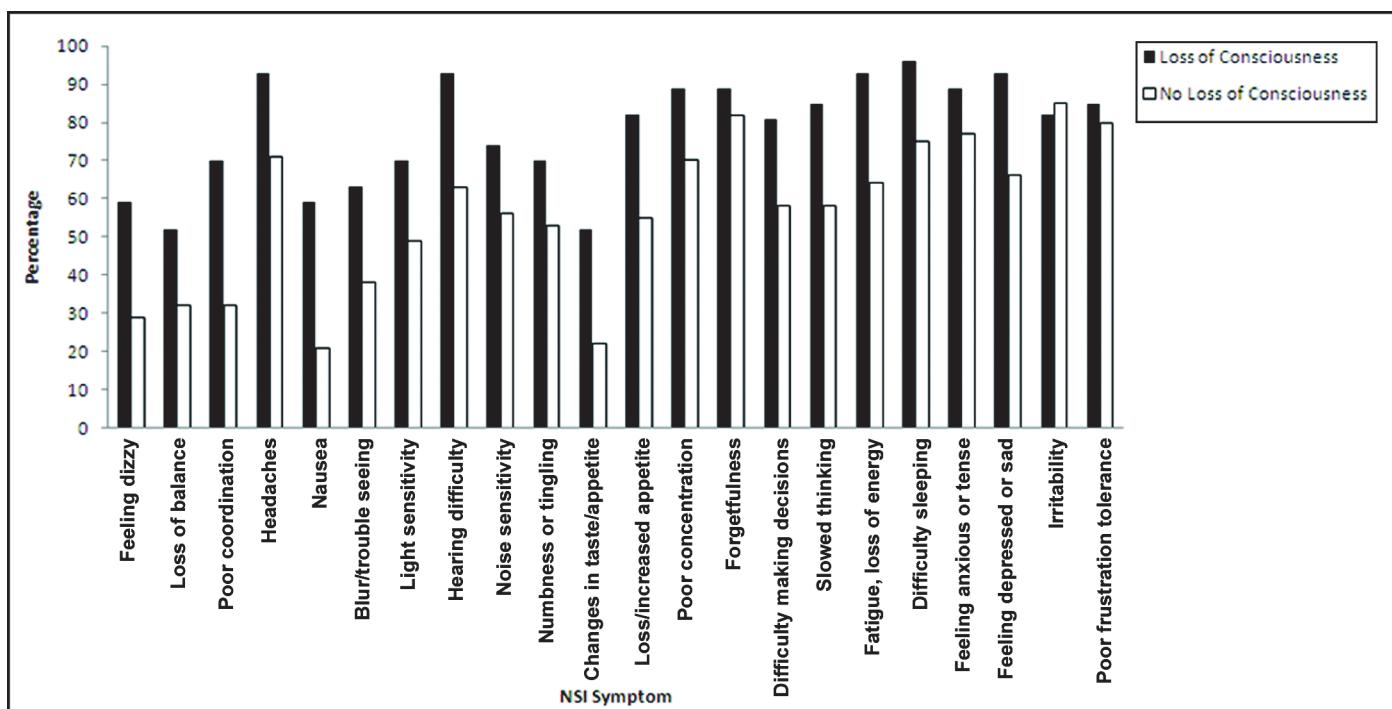


Figure 2.

Percentage reporting Neurobehavioral Symptom Inventory (NSI) score of ≥ 2 : comparison of reported loss of consciousness.

DISCUSSION

Self-reported visual symptoms in OIF/OEF veterans with TBI at the Portland VA Medical Center (PSCT) occurred with a frequency of 44 to 54 percent via the NSI and 33 percent during the initial postdeployment evaluation. Previous studies at the Palo Alto VA Health Care System (PRC) and Edward Hines Jr VA Hospital (PNS) have consistently reported visual symptoms with a frequency of approximately 75 percent [5,11–13]. The discrepancy observed in the current study is likely related to the VA polytrauma rehabilitation hierarchy discussed in the “Introduction” section. The Palo Alto VA Health Care System includes both a PRC and PNS, while the Edward Hines Jr VA Hospital features a PNS. The Portland VA Health Care System serves as a PSCT managing the least severe TBI patients in an outpatient setting, which is one explanation for the lower incidence of self-reported symptoms in the Portland VA population. Interestingly, in comparing the NSI symptom frequencies with those reported by Stelmack et al. [11], the only significant difference observed was a higher frequency of “Blur/Trouble Seeing” at the Edward Hines Jr VA PNS. It is not entirely clear why veterans at a PNS, a higher tier on the Polytrauma System of Care than the Portland VA Medical Center, would report a higher frequency of this visual symptom but no other symptoms on the NSI. Based on the Polytrauma System of Care, veterans at a PNS are generally recovering from more severe injuries than those at a PSCT, so it is possible that the ocular and visual sequelae in this population are having a greater effect on quality of life than other symptoms and are therefore reported at higher rates on the NSI.

Among the most frequently reported visual symptoms at the Portland VA Medical Center were blurred vision and focusing problems. The most common etiologies for these visual complaints were uncorrected refractive error and accommodative dysfunction. Of those veterans that were referred to the eye care team, 96 percent were found to have some type of uncorrected refractive error. Given the young demographic of OIF/OEF veterans in this study (mean age 29.9 yr), accommodative dysfunction likely contributed to symptoms of blurred vision and problems focusing. Accommodation refers to the ability of the eye to form and maintain a focused retinal image on an object of interest. The frequency of occurrence of accommodative dysfunction in presbyopic patients with TBI ranges from approximately 10 to 40 percent [8]. The most common dysfunctions of accommodation include accommodative insuf-

ficiency (underaccommodation), accommodative excess/spasm (overaccommodation), and accommodative infacility (inflexibility of accommodation) [10]. Green et al. recently investigated both the static and dynamic accommodation levels in a population of patients with mild TBI [14]. Accommodative responses, including both monocular and binocular accommodative amplitude, accommodative convergence to accommodation ratio, and negative and positive relative accommodation, were reduced in the TBI population compared with normative values. In addition, the TBI cohort also exhibited a significant fatigue effect during accommodative facility testing, which is atypical in the non-TBI population. Thus, reported problems with blurred vision and focusing problems may have been related to both uncorrected refractive error and accommodative dysfunction.

A statistically significant association was observed between severity of symptoms on the NSI and reported loss of consciousness. These findings are not surprising given that loss of consciousness is often used to classify the severity of a TBI [3,15]. Hoge et al. observed that veterans with TBI reporting loss of consciousness were at a significantly higher risk for developing physical and mental health problems than those who did not lose consciousness [2]. Furthermore, 40 percent of these veterans met the criteria for posttraumatic stress disorder (PTSD). Thus, it is clear that veterans with TBI associated with loss of consciousness are likely to develop more severe posttraumatic symptoms. Note, however, that symptoms were also reported at relatively high rates even in those veterans not reporting loss of consciousness.

The findings of the present study indicate that no significant correlation exists between severity of symptoms on the NSI and number of deployments. Previous studies have demonstrated a statistically significant correlation between prevalence of PTSD and both duration and number of deployments [16–17]. In contrast, a more recent study by Fear et al. revealed no association between number of deployments and PTSD, mental health disorders, or alcohol misuse [18]. In agreement with the latter study, one may expect to find a lack of association between severity of symptoms and number of deployments given that the NSI questionnaire used in the present study includes many symptoms of PTSD. Indeed, recent reports have acknowledged that the overlap of symptoms between PTSD and TBI, as well as the commonality of their comorbidity, can make differentiating the two conditions clinically challenging [4,15].

No significant association was observed between severity of symptoms on the NSI and number of blasts. One possible explanation for this finding is that veterans may be overestimating the number of blasts to which they have been exposed. A similar possibility is that veterans reporting exposure to multiple blasts were within sight or sound of multiple blasts but outside the radius capable of inducing a TBI. It is not clear whether exposure to several of these less forceful, nontraumatic blasts is capable of producing significant long-term injury [4]. If the veterans were indeed exposed to multiple traumatic blasts, the resulting injuries may have caused a disconnect from true symptoms, thereby masking the severity of NSI symptoms. A recent report demonstrated that specific regions of the brain may be more susceptible to blast injuries, specifically areas of the prefrontal cortex near the orbital sockets and nasal sinuses responsible for integration of information from subcortical structures, as well as disinhibition of responses to emotions such as fear and anxiety [19]. Damage to these regions may cause inappropriate activation of normal physiological systems, resulting in cognitive misperception of a person's environment and their symptoms in day to day life.

Nearly 10 percent of visually symptomatic veterans were not referred to the eye clinic for further evaluation. Perhaps more concerning is that 23 percent of visually symptomatic veterans no-showed for their consultations with the eye clinic. The average no-show rate for the Portland VA eye clinic is below 10 percent. A number of causes are likely to blame for a higher no-show rate. First, OIF/OEF veterans are generally a younger demographic than the typical VA population. As a result, these veterans likely have more time demands, including work and family obligations, that make scheduling difficult. Indeed, previous surveys in this population have shown lack of availability because of work schedules [2]. Second, in the present study 83 percent of veterans reported a score of 2 or greater on the NSI category for "forgetfulness." Cognitive deficits and memory problems are well-documented long-term sequelae of TBI [15]. Konrad et al. recently investigated a comprehensive battery of neuropsychological testing in subjects with TBI [20]. Compared with controls, the TBI group performed statistically worse in assessments of learning, recall, working memory, attention, and executive function. Another recent study demonstrated a significant inverse relationship between severity of TBI and declarative memory performance [21]. The authors used functional magnetic reso-

nance imaging studies to determine that reduced medial temporal lobe functionality may be contributing to the memory deficits. Given these findings, it is reasonable to posit that traditional recall systems may not be adequate for this population because of the high frequency of cognitive deficits and memory problems. A final explanation for the high no-show rate of veterans with TBI is the necessity of multiple specialty providers to manage the complex nature of their injuries. These veterans may require multiple appointments each week, potentially resulting in considerable time and financial expense as they are simultaneously working to assimilate back into civilian culture. This is likely to be more problematic for this younger demographic for the reasons previously stated.

The most commonly reported ocular and visual conditions in the current study were uncorrected refractive error (96%), photosensitivity (22%), and accommodative dysfunction (13%). While these conditions were reported at relatively high rates, ocular and visual conditions in this population may have been underrepresented because of the lack of a standardized protocol for evaluating patients with TBI by the eye care team at the Portland VA Medical Center. The Portland VA eye care team TBI template was modeled from VHA Directive 2008–065, which outlines a standardized protocol for evaluating patients with TBI at PRCs; however, this template was not universally accepted and implemented by the eye care team at the time of the study [7]. Optometric evaluations at the Portland VA Medical Center were problem-oriented such that they addressed the patient's primary complaint. The baseline optometric examination included corrected distance visual acuity, corrected near visual acuity, distance and near cover test, extraocular motilities, pupil testing, confrontation visual fields, distance refraction, anterior segment evaluation, intraocular pressure measurement, and dilated fundus examination. Patients presenting to the eye clinic after referral from the postdeployment clinic with a binocular vision-related complaint, for example intermittent blurred vision, blurred vision at near, diplopia, and/or slow focusing, had additional binocular vision testing performed. This testing was conducted at the discretion of the attending optometrist and may have included additional accommodative testing (positive/negative relative accommodation, fused cross cylinder, accommodative amplitudes, accommodative facility) and vergence testing (distance and near lateral and vertical phorias, distance and near convergence and divergence ranges, vertical vergence ranges).

Because the individual binocular testing varied from provider to provider, it is difficult to determine whether the evaluations reviewed in the present study were adequately identifying binocular vision issues. Thus, a future goal at the Portland VA Medical Center is for all OIF/OEF veterans with confirmed TBI to be evaluated per the testing recommended by VHA Directive 2008–065. In addition, the present study demonstrates a need for standardized testing batteries such as that described by VHA Directive 2008–065 for this population at all PNS and PSCT sites.

CONCLUSIONS

OIF/OEF veterans at the Portland VA Medical Center, a PSCT site, generally reported visual symptoms at lower rates than those veterans at PRCs and PNSs in Palo Alto and Edward Hines Jr VA medical centers. Loss of consciousness was found to be the best predictor for severity of symptoms reported on the NSI, while number of deployments and number of blast exposures were not correlated with severity of symptoms. Most veterans reporting visual symptoms on either the NSI or during their initial postdeployment evaluation were appropriately referred to the eye clinic and, of those who presented to the eye clinic, the vast majority were deemed to have had their visual concerns addressed by the eye care team. However, OIF/OEF veterans with TBI no-showed at double the rate of the normal VA eye clinic population, indicating that traditional VA protocols, including screening batteries, locations, hours, and recall methods, may not adequately address the needs of this population.

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Author Contributions:

Study concept and design: R. Bulson, W. Jun.

Acquisition of data: R. Bulson, W. Jun.

Analysis and interpretation of data: R. Bulson, W. Jun, J. Hayes.

Drafting of manuscript: R. Bulson, W. Jun.

Critical revision of manuscript for important intellectual content: R. Bulson, W. Jun.

Statistical analysis: J. Hayes.

Administrative, technical, or material support: R. Bulson, W. Jun.

Study supervision: R. Bulson, W. Jun.

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Occurrence of oculomotor dysfunctions in acquired brain injury: A retrospective analysis

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KEYWORDS

Acquired brain injury;
Traumatic brain
injury;
Cerebrovascular
accident;
Stroke;
Oculomotor
dysfunction;
Strabismus;
Accommodation;
Eye movements;
Cranial nerve palsy

Abstract

BACKGROUND: The purpose of this retrospective study was to determine the frequency of occurrence of oculomotor dysfunctions in a sample of ambulatory outpatients who have acquired brain injury (ABI), either traumatic brain injury (TBI) or cerebrovascular accident (CVA), with associated vision symptoms.

METHODS: Medical records of 220 individuals with either TBI ($n = 160$) or CVA ($n = 60$) were reviewed retrospectively. This was determined by a computer-based query spanning the years 2000 through 2003, for the frequency of occurrence of oculomotor dysfunctions including accommodation, version, vergence, strabismus, and cranial nerve (CN) palsy.

RESULTS: The majority of individuals with either TBI (90%) or CVA (86.7%) manifested an oculomotor dysfunction. Accommodative and vergence deficits were most common in the TBI subgroup, whereas strabismus and CN palsy were most common in the CVA subgroup. The frequency of occurrence of versional deficits was similar in each diagnostic subgroup.

CONCLUSION: These new findings should alert the clinician to the higher frequency of occurrence of oculomotor dysfunctions in these populations and the associated therapeutic, rehabilitative, and quality-of-life implications.

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Acquired brain injury (ABI) typically includes both traumatic brain injury (TBI) and cerebrovascular accident (CVA), more commonly referred to as stroke.¹ Statistics regarding the frequency of occurrence and impact in the United States are striking. Approximately 8 million people per year suffer a TBI, with 1.5 million of those injuries categorized as "major."² About 60% of those affected do not return to the workforce, with an estimated national economic loss of \$4 billion.³ The

findings are similar for CVA. Stroke is the leading cause of chronic disability,⁴ affecting 500,000 individuals per year.⁵ Only 50% of those affected return to the workforce with little, if any, residual disability.⁶ Hence, both TBI and CVA, and, more broadly, ABI in general, are major economic, social, medical, and public health concerns.⁷

Because of the global nature of a brain injury, many brain areas and their associated functions are adversely affected.³ One such area is vision, a primary sensory modality; half of the cranial nerves relate to vision. Injury to vision-related areas of the brain can result in a range of dysfunctions, including the oculomotor, color vision, and visual field systems.⁸⁻¹⁰ An important area of vision-based concern is the oculomotor system, which broadly includes

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Table 1 Age range, mean, and standard deviation of the subgroups

Subgroup	Age range (yr)	Mean (yr)	Standard deviation (yr)
TBI (n = 160)	8 to 91	44.9	15.8
CVA (n = 60)	24 to 90	61.2	14.7
ABI (n = 220)	8 to 91	49.3	17.1

the versional, vergence, and accommodative systems.¹¹ Resultant symptoms are diverse and may include diplopia, blur, difficulty following targets, oculomotor-based reading problems, and asthenopia.¹² While producing vision discomfort and possible loss of visual efficiency (e.g., reading speed and reading duration),^{13,14} oculomotor problems may negatively affect the overall rehabilitative process (e.g., cognitive therapy)^{15,16} thus impacting adversely on an individual's quality of life.

The frequency of occurrence of oculomotor dysfunction in these studies is dependent on the tests used, the method of categorizing the deficits, and the subgroupings used. Despite methodologic differences, the frequency of occurrence of oculomotor dysfunctions in these populations has been found to be universally high in earlier studies. In the TBI population, convergence insufficiency was found to be about 40%^{9,17}; some type of oculomotor dysfunction was 60% to 85%^{18,19}; cranial nerve (CN) palsy was 33%,²⁰ and accommodative dysfunction was about 20%.²¹ In the ABI population, accommodative dysfunction ranged from 10% to 70%.^{9,22} For example, a recent study in this area was conducted by Suchoff et al.⁹ Their adult (ages 19 to 70 years) ABI population (n = 62) was derived from 2 extended-care facilities, and subjects were unselected with respect to suspected vision problems and related symptoms. All vision examinations were part of their routine annual physical examinations and were performed at least 6 months after injury. They found considerably increased frequency of occurrence of dysfunctions in all oculomotor areas tested compared with a non-ABI cohort: strabismus and convergence insufficiency (approximately 45%), abnormal oculomotor tracking (approximately 40%), and impaired accommodation (approximately 10%).

Although these studies provided valuable information, most of them had several limitations: (1) some had small sample sizes, (2) some lacked diagnostic subgroupings, (3) not all patients tested had vision-based symptoms, (4) there was broad categorization of the oculomotor dysfunctions, and (5) CVA was not assessed separately as a subgroup. In the current retrospective study, all of these limitations were addressed.

Methods

A computer-based query was obtained for ABI patients examined between October 1, 2000, and October 7, 2003,

using either the 99203 (new patient evaluation) or 99213 (established patient evaluation) procedure codes. All patients were ambulatory outpatients with vision-based symptoms. Optometrists from the Raymond J. Greenwald Rehabilitation Center (RJGRC) at the State University of New York (SUNY) State College of Optometry performed the vision examinations. The majority of patients were referred from rehabilitation professionals at the following institutions: Rusk Institute of Rehabilitative Medicine at NYU Medical Center, Bellevue Hospital at NYU Medical Center, Department of Rehabilitative Medicine at Mount Sinai Medical Center, Lenox Hill Hospital, New York Hospital, and the International Center for the Disabled. Other referrals were made by rehabilitation professionals in private practice in the greater New York City area. Referrals were also received from other services within the SUNY College of Optometry's University Optometric Center including primary care, low vision, contact lenses, and ocular disease and special testing. Referred patients were not limited to those with either TBI or CVA; individuals with other neurologic conditions that affect the visual system, such as vestibular dysfunctions, cranial postsurgical complications, and brain tumors, comprised a sizeable patient base. **Table 1** lists the age characteristics of the patients in each group at the initial evaluation at the RJGRC. **Table 2** describes the range of years after injury and the mean for each category at initial presentation at the RJGRC.

The computer query yielded 486 records, of which 300 were selected randomly. Each of 3 members of the RJGRC's clinical staff then randomly chose 100 of the records. Of these, only those patients with either TBI (n = 160) or CVA (n = 60) were reviewed. Several patients whose records were selected for the retrospective review and analysis had received dilated fundus examinations 4 months or less before their evaluations at RJGRC, and, as such, a dilated fundus examination was not repeated.

The RJGRC's diagnostic evaluation included assessment of the following areas: distance and near visual acuity, distance and near refraction, distance and near binocular and oculomotor status, color vision, visual fields, and ocular health. In some instances, not all areas could be evaluated because of limitations in the patient's cognitive status, language ability, or physical state.

The 5 major categories of oculomotor dysfunction investigated were accommodation, version, vergence, strabismus, and CN palsy. Conditions included under each category were determined by consensus. Criteria for inclusion into 1

Table 2 Range and mean of the number of years (postinjury) upon initial presentation for the subgroups

Subgroup	Range (yr)	Mean (yr)
TBI (n = 160)	0.1 to 42.0	4.5
CVA (n = 60)	0.1 to 18.0	2.7
ABI (n = 220)	0.1 to 42.0	4.0

Table 3 Summary of the percentage of individuals in each subgroup (where for TBI n = 160 and for CVA n = 60) within a given category of ocular motor dysfunction and the most common anomaly present

Ocular motor dysfunction	TBI (%)	Most common anomaly (TBI)	CVA (%)	Most common anomaly (CVA)
Accommodation	41.1	Accommodative insufficiency	12.5	Accommodative infacility
Versional	51.3	Deficits of saccades	56.7	Deficits of saccades
Vergence	56.3	Convergence insufficiency	36.7	Convergence insufficiency
Strabismus	25.6	Strabismus at near	36.7	Strabismus at far
CN palsy	6.9	CN III	10	CN III

Note: The "n" represents the number of persons tested for accommodation, which only included those under the age of 40 years (i.e., presbyopic). TBI = 51 and CVA = 8.

or more of the oculomotor dysfunction categories were per conventional clinical standards.²³⁻²⁵

The reviewers then recorded the frequency of occurrence (percentage) of the targeted conditions that were diagnosed at the patient's initial evaluation. These conditions were tabulated separately for the TBI and CVA subgroups.

Results

The percentage of individuals in the 2 subgroups manifesting the 5 basic categories of oculomotor dysfunctions are presented in **Table 3**. The majority of individuals with either TBI or CVA exhibited some type of oculomotor dysfunction. This ranged from 6.9% to 56.3% in the TBI subgroup and from 10.0 to 56.7% in the CVA subgroup. Deficits in accommodation (41.1%) and vergence (56.3%) were more prominent in the TBI subgroup, whereas those of strabismus (36.7%) and CN palsy (10%) were more prominent in the CVA subgroup. The frequency of versional deficits was similar in each subgroup (approximately 55%). When assessed across the 5 categories, 90% of the TBI subgroup manifested some type of oculomotor dysfunction, whereas 86.7% of the CVA subgroup manifested the same.

The number of individuals under the age of 40 years with 1 or more types of accommodative dysfunctions is presented in **Table 4**. More than 40% of those with TBI exhibited an accommodative dysfunction, with nearly all showing accommodative insufficiency (AI). In contrast, only 1 in 8 (12.5%)

patients with CVA exhibited an accommodative deficit, specifically a slowed dynamic facility.

The number of individuals with 1 or more vergence dysfunctions is presented in **Table 5**. Convergence insufficiency (CI) was the main dysfunction found in both subgroups, occurring in 42.5% and 35% of the TBI and CVA patients, respectively. Other diagnostic categories with high frequency of occurrence were binocular instability (BI; i.e., restricted vergence ranges) in TBI (10%) and basic esophoria in CVA (18.3%). Furthermore, the presence of each abnormal vergence type was reasonably well segregated by diagnostic subgroup.

The number of individuals manifesting 1 or more versional oculomotor dysfunctions in each subgroup is presented in **Table 6**. The overall percentage within each subgroup was similar (approximately 55%), except for nystagmus, which was nearly 30 times more frequent in CVA than in TBI.

The number of individuals with strabismus in each subgroup is presented in **Table 7**. Strabismus was found in 25.6% of the patients with TBI and in 36.7% of the patients with CVA. Two of the strabismic categories did not reflect the predicted ratio of the dysfunction based purely on subgroup sample size (i.e., 160TBI:60CV = 2.66). There was a higher relative frequency of a hyper component (ratio = 4.75) and a nearly equal relative frequency of an esophoria component (ratio = 0.83).

The number of individuals manifesting CN palsy in each subgroup is presented in **Table 8**. The most common deficits were CN III and IV for TBI and CN III for CVA. The

Table 4 Individuals in each subgroup with accommodative dysfunction

Subgroup	No. with accommodative insufficiency	No. with accommodative infacility	No. with accommodative excess	No. with ill-sustained accommodation	Total no. with accommodative dysfunction
TBI (n = 51)	19	2	2	0	21
CVA (n = 8)	0	1	0	0	1

Note: Some persons presented with more than 1 accommodative dysfunction. The "n" represents the number of persons tested for accommodation, which only included those under the age of 40 years (i.e., presbyopic).

≥21/51 = 41.1% of persons with TBI presenting with accommodative dysfunction.

≥1/8 = 12.5% of persons with CVA presenting with accommodative dysfunction.

Table 5 Individuals in each subgroup with vergence oculomotor dysfunction

Subgroup	No. with CI	No. with CE	No. with DE	No. with DI	No. with BI	No. with basic exo	No. with basic eso	Total no. with vergence dysfunction
TBI (n = 160)	68	4	0	2	16	2	3	90
CVA (n = 60)	21	0	0	0	1	0	11	22

CI = convergence insufficiency; CE = convergence excess; DE = divergence excess; DI = divergence insufficiency; BI = binocular instability; basic exo = basic exophoria; basic eso = basic esophoria.

Note: Some persons presented with more than 1 vergence oculomotor dysfunction. The "n" represents the number of persons tested for vergence oculomotor dysfunctions, which includes the entire sample for each subgroup.

≥82/160 = 51.3% of persons with TBI presenting with vergence oculomotor dysfunction.

≥34/60 = 56.7% of persons with CVA presenting with vergence oculomotor dysfunction.

frequency of occurrence of CN palsy was 6.9% in TBI and 10.0% in CVA.

Discussion

The current retrospective analysis conducted in a large sample of ambulatory outpatients with either TBI or CVA and related vision symptoms supports previous reports of the markedly increased frequency of occurrence of oculomotor dysfunctions in these populations versus the non-ABI population.^{7,9,28} Furthermore, it extends these studies to include CVA, because CVA had not been investigated previously as its own subgroup.

The frequency of occurrence of oculomotor dysfunctions in the TBI and CVA populations is much larger than that found in their non-ABI cohort.²⁶⁻²⁸ For example, in a nonpresbyopic clinic population with near work symptoms,²⁶ convergence insufficiency was found in about 4% of the cases, whereas in the current study, it was found in 43% of the TBI subgroup and in 35% of the CVA subgroup, with similarly symptomatic individuals. The same was true for accommodative insufficiency, which was found in 9% in the non-ABI population²⁶ and in 40% of the current TBI population. Lastly, the overall frequency of occurrence of oculomotor dysfunctions in the non-ABI symptomatic sample was 20%²⁶ versus 90% in the current study, representing a 4.5-fold increase in frequency in the brain-injured sample. Thus, in the TBI and CVA popula-

tions, if some type of an oculomotor dysfunction is not found after careful and comprehensive testing, it is unexpected and represents an exception to the rule.

Underlying neurophysiology of the oculomotor system and its dysfunctions resulting in diffuse versus local brain insult

Within the TBI and CVA populations, the frequency of occurrence of specific oculomotor conditions appeared to be dependent on the nature of the neurologic insult: diffuse versus localized. Because of the global coup-contrecoup nature of the injury in TBI, brain consequences tend to be diffuse. In contrast, because of the more regional vascular nature of the injury in CVA, brain consequences tend to be more localized.

Accommodation. The innervation for accommodation is comprised of premotor and cortical neural components.² The premotor neural component for accommodation is the autonomic nervous system, with the parasympathetic system initiating the accommodative response and the sympathetic system assisting in maintaining the response. The cortical innervation for accommodation begins with fibers from the primary visual cortex (V1) going to the parieto-temporal area and the cerebellum. The fibers continue on to the Edinger-Westphal nucleus in the pretectum, where input

Table 6 Individuals in each subgroup with versional oculomotor dysfunction

Subgroup	No. with deficits of saccades	No. with deficits of pursuit	No. with saccadic intrusions	No. with nystagmus	Total no. with versional dysfunction
TBI (n = 160)	62	52	19	1	82
CVA (n = 60)	23	13	6	10	34

Note: Some persons presented with more than 1 versional oculomotor dysfunction. The "n" represents the number of persons tested for versional oculomotor dysfunctions, which includes the entire sample for each subgroup.

≥82/160 = 51.3% of persons with TBI presenting with versional oculomotor dysfunction.

≥34/60 = 56.7% of persons with CVA presenting with versional oculomotor dysfunction.

Table 7 Individuals in each subgroup with strabismus

Subgroup	No. with an intermittent strabismus	No. with a constant strabismus	No. with a unilateral strabismus	No. with an alternating strabismus	No. with a distance strabismus	No. with a near strabismus	No. with an exophoria component	No. with an esophoria component	No. with an hyperopia component	No. with a hypo component	No. with a strabismus component	Total no. with a strabismus
TBI (n = 160)	20	20	20	20	23	31	25	5	19	6	4	41
CVA (n = 60)	10	10	10	11	14	11	13	6	4	2	22	

Note: Some persons presented with more than 1 type of strabismus. The "n" represents the number of persons tested for strabismus, which includes the entire sample for each subgroup.
 $\geq 41/160 = 25.6\%$ of persons with TBI presenting with strabismus.
 $\geq 22/60 = 36.7\%$ of persons with CVA presenting with strabismus.

is received and processed from the autonomic nervous system to form the motor command.

From the pretectum, the motor fibers innervating accommodation travel with the oculomotor nerve (i.e., CN III) on to the ciliary ganglion. Finally, these motor fibers continue to travel with the short ciliary nerve to the ciliary muscle to produce a change in accommodation.

Thus, the accommodative pathway is susceptible to diffuse axonal injury, with its numerous stages of neural motor innervation being prone to impact on neurologic insult. However, it is also possible to have a localized lesion (for example in the pretectum), which would paralyze accommodation.²⁹ Finally, there is normal physiologic reduction of accommodative amplitude and dynamic accommodative facility as one ages, which may confound the contribution of the neurologic injury on accommodation, especially for persons between 35 and 45 years of age (i.e., incipient presbyopia).²⁹ Moreover, this process may be exacerbated in TBI patients, especially those with hyperopia.^{10,30}

Vergence oculomotility. The neuromotor control for vergence oculomotility is less clearly elucidated.^{11,31} The premotor neural components in the brainstem are located in the mesencephalic reticular formation 1 to 2 mm dorsal and dorsolateral to the nucleus of the oculomotor nerve. Three types of vergence cells have been isolated: tonic, burst, and burst-tonic. Tonic cells are correlated with changes in vergence angle, whereas burst cells are correlated with changes in vergence velocity. The burst-tonic cells respond to combined vergence angle and vergence velocity. The additional premotor neural components include the medial longitudinal fasciculus, cerebellum, and frontal eye fields. Finally, to elicit convergence at the peripheral level, decreased stimulation to the bilateral abducens nerves and increased stimulation to the inferior division of bilateral oculomotor nerves are evident, with the converse being necessary to elicit divergence.

Thus, with its numerous premotor and motor contributions for vergence, there are multiple axonal pathways susceptible to the diffuse axonal injury pathophysiology of traumatic brain injury. However, localized brainstem lesions to cranial nerves III, IV, or VI, as well as either localized lesions or diffuse axonal shearing along the motor pathways of cranial nerves III, IV, and VI in the cavernous sinus, will result in a restriction of ocular motility to one or both eyes, thus producing a CN palsy/paresis and strabismus.

Versional oculomotility. Versional oculomotility includes components such as fixations, saccades, and pursuit, among others.^{11,31} With respect to fixation, it is the most poorly understood of the versional oculomotor pathways. The premotor neural components have been specified as being the frontal eye fields, supplemental eye fields, parietal area, right prefrontal cortex for attentional aspects, and right posterior parietal cortex for attentional aspects.³² With re-

Table 8 Individuals in each subgroup with CN palsy

Subgroup	CN III	CN IV	CN VI	INO	WEBINO	Total no. with CN palsy
TBI (n = 160)	6	5	2	0	0	11
CVA (n = 60)	6	1	0	1	0	6

Note: Some persons presented with more than 1 CN palsy. The "n" represents the number of persons tested for CN palsy, which includes the entire sample for each subgroup.

≥11/160 = 6.9% of persons with TBI presenting with CN palsy.

≥6/60 = 10.0% of persons with CVA presenting with CN palsy.

spect to saccades, the premotor neural area differs for vertical versus horizontal saccades; for vertical saccades, it is the rostral mesencephalon (RM), whereas for horizontal saccades, it is the paramedian pontine reticular formation (PPRF). And, with respect to horizontal pursuit, the premotor neural components include pursuit neurons in V1, the medial vestibular nuclei (MVN), and the prepositus hypoglossi. The associated integrated premotor neural areas for vertical saccades, horizontal saccades, and horizontal pursuit are similar and include the frontal eye fields, parietal area, basal ganglia, superior colliculus, and cerebellum.

For horizontal saccades and horizontal pursuit, there is a common motor neural pathway for the motor fibers traveling with the inferior division of the oculomotor nerve. In addition, recent evidence suggests a shared saccade/pursuit premotor neural pathway.³³ The joint premotor pathway includes common inhibitory omnipause neurons and common saccade/pursuit neurons in the PPRF responsible for modulating velocity of the motor response.^{11,33} Thus, with its multiple localized premotor neurologic substrates, as well as multiple neural motor cortical axonal pathways for these 3 components of versional oculomotor control, of versions appears to be prone to both localized and diffuse axonal injury.

Comparison of oculomotor dysfunctions for the 2 subgroups of ABI. Individuals with TBI presented with an increased frequency of accommodative and vergence deficits relative to that found in individuals with CVA. This may be because of the involvement of multiple premotor and motor neurologic sites for both accommodation and vergence, which makes sensorimotor vision aspects particularly susceptible to diffuse axonal injury. However, local lesions are possible, with their more discrete and restricted motor involvement.

Individuals with CVA presented with an increased frequency of strabismus and CN palsies. The 3 cranial nerves responsible for innervating the extraocular muscles are particularly vulnerable to localized lesions and disturbances at the level of the brainstem cranial nerve nuclei as well as in the cavernous sinus just before innervating the extraocular muscles. This may account for the increased frequency of occurrence of strabismus and CN palsies in those with CVA versus TBI.

Deficits of versional oculomotor were present with similar frequencies in TBI and CVA. The similarity may be

attributed to the fact that versional oculomotor can be impaired by either localized lesions or diffuse axonal injury. Localized infarcts to any of the premotor neurologic substrates, such as the frontal eye fields, the parietal lobe, and the cerebellum, may be evident in those with CVA. However, diffuse axonal injury could occur in those with TBI just as frequently, thus resulting in shearing of the axons for cranial nerves III, IV, and VI caused by a coup-contrecoup injury,³ with consequent less accurate and poorly sustained versional oculomotor responses.

Knowledge of expected oculomotor sequelae. Optimal management of individuals with either TBI or CVA requires that the clinician be aware of the expected oculomotor dysfunctions found in these patients as well as the potential adverse effects on basic eye tracking, reading, visual scanning, and higher-order visual information processing (e.g., perceptual interpretation). Thus, the case history and diagnostic evaluation should be tailored with this notion in mind. For example, the expected occurrence of nystagmus in the CVA population is 17% based on the current study. This is nearly 30 times greater than expected in a matched TBI cohort (0.625%). Hence, when examining a CVA patient, if nystagmus is not obvious by gross visual observation, then more sensitive techniques should be used, such as high magnification biomicroscopy and careful visuoscopy. Then, if found, the negative impact of acquired nystagmus on reading ability^{34,35} and other visual tasks must be addressed with respect to vocational, avocational, and rehabilitative aspects.

Impact on global rehabilitation. Most types of brain injury rehabilitation involve the visual system, as it is a primary sensory modality. For example, cognitive rehabilitation and speech/language rehabilitation involve saccadic visual search and visual scanning activities in conjunction with intervening periods of accurate fixation. Vestibular rehabilitation also involves dynamic interaction with the vergence and accommodative systems as targets are displaced in depth.¹¹ The notion that the presence of an oculomotor dysfunction may adversely affect the progress of brain injury rehabilitation is well accepted.^{15,16} This is important because approximately 90% of individuals in each of the TBI and CVA subgroups in the current study had at least 1 type of oculomotor dysfunction. Thus, nearly

all patients in each subgroup presented with some type of oculomotor dysfunction. For example, convergence insufficiency, evident in the majority of those with TBI, may produce intermittent diplopia during near work. Saccadic deficits, found in the majority of those with CVA, may result in inefficient and error-prone saccadic tracking.

Impact on quality of life. The first step in patient management for any vision dysfunction is to identify and understand the basic abnormal vision condition along with its associated symptoms. Only then can appropriate therapy be implemented for its remediation (e.g., vision therapy) or a proper referral made for additional guidance and assistance (e.g., neuropsychological evaluation). With success in this management phase, an increased quality of life can result.

If an appropriate vision diagnosis is not made, the patient's visually based symptoms will persist and perhaps even become exacerbated. Thus, the patient will likely continue to have difficulty reading, writing, scrutinizing written instructions, and ambulating through complex environments.^{7,10}

Future directions. The frequency of occurrence for the various categories and types of oculomotor dysfunctions in the TBI and CVA subgroups has been determined. The next logical step is to investigate therapeutic efficacy using a large sample size, with emphasis on both clinical and laboratory-based neurophysiologic aspects (e.g., functional magnetic resonance imaging), as well as a study of the impact on vocational, avocational, and other aspects of overall quality of life. Correlation of damaged structure and related degree of dysfunction, using neuroimaging techniques, would be informative in terms of predicted adverse effects and subsequent treatment outcomes.

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Vision Diagnoses Are Common After Concussion in Adolescents

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Abstract

Objective. To determine the prevalence of vision diagnoses after concussion in adolescents. **Methods.** Cross-sectional study from July 1, 2013 to February 28, 2014, of patients aged 11 to 17 years with concussion evaluated in a comprehensive concussion program. **Results.** A total of 100 adolescents were examined, with a mean age of 14.5 years. Overall, 69% had one or more of the following vision diagnoses: accommodative disorders (51%), convergence insufficiency (49%), and saccadic dysfunction (29%). In all, 46% of patients had more than one vision diagnosis. **Conclusions.** A high prevalence of vision diagnoses (accommodative, binocular convergence, and saccadic eye movement disorders) was found in this sample of adolescents with concussion, with some manifesting more than one vision diagnosis. These data indicate that a comprehensive visual examination may be helpful in the evaluation of a subset of adolescents with concussion. Academic accommodations for students with concussion returning to the classroom setting should account for these vision diagnoses.

Keywords

concussion, mild traumatic brain injury, convergence insufficiency

Background

Up to 3.6 million concussions occur annually, as estimated by the Centers for Disease Control and Prevention, and this likely represents an underestimate of the clinical problem.^{1,2} Approximately 65% of these injuries occur in the pediatric and adolescent population, 5 to 18 years of age, with the 11- to 14- and 15- to 18-year-old age groups representing the largest proportion of those injured.^{3,4} There are increasing concerns that children may be particularly vulnerable to the consequences of concussion and may have more prolonged and complicated outcomes from a cognitive and developmental perspective.⁵⁻⁹

Common problems in concussion that are observed in both the adult and pediatric populations include physical signs and symptoms (headache, dizziness, nausea, balance problems, fatigue, light and noise sensitivity, sleep problems), cognitive deficits (memory, attention, executive functioning, reaction time), and emotional issues (irritability, sadness, nervousness, anxiety and depression).^{10,11} In particular, concussion-related visual complaints, including blurred or double vision, eye fatigue, the appearance of words moving on the page,

loss of place when reading, and difficulty sustaining attention on a visual task have been reported in the adult population.¹²⁻¹⁴ While significant deficits in binocular vision (convergence), accommodative (focusing) and saccadic (eye movement) disorders have been reported in adults with concussion in both the civilian and military populations with a prevalence of up to 30% to 42%,¹⁵⁻²¹ the prevalence of visual diagnoses in adolescents with concussion is unknown. The adolescent population may be at significant risk for morbidity due to such concussion-related vision disorders because of the amount of reading and visual work involved with

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full-time schoolwork.²²⁻²⁴ A recent study using a brief Vestibular/Ocular Motor Screening Assessment (VOMS) tool that clinically assesses saccades, smooth pursuits and convergence, showed that VOMS accurately distinguished concussed patients who had symptoms of oculomotor impairment from uninjured controls, aged 9 to 18 years.²⁵ This study indicates that further investigation into the prevalence of vision diagnoses following concussion is warranted.

Reading is a complex higher order integrative function, which requires adequate accommodative, vergence, and saccadic response at the initial stage of gathering visual information. These processes are necessary to initiate and sustain visual function during reading.²⁴ Areas of the brain involved in these complex tasks include the dorsolateral prefrontal cortex (DLPC), the posterior parietal cortex, and frontal and supplemental eye fields, as well as the brainstem and cerebellum. Each of these regions can be affected by concussion injury.^{14,26} The DLPC plays a significant role in attention and working memory while also interacting with multiple other regions of the brain in carrying out tasks of executive function. In addition, from an oculomotor perspective, saccadic function and vergence are also among the many tasks influenced by the DLPC. Injury to this area may result in oculomotor deficits after concussion, which may negatively affect the task of reading, and thereby, learning in adolescents. Such deficits affecting reading have been reported in adults following concussion.¹²⁻²¹ Due to the high visual work load of adolescents in school, identifying such deficits after concussion is imperative in order to properly direct their postinjury management in school, which is their occupational setting.

The objective of this study was to use comprehensive vision testing to determine the prevalence of vision diagnoses in adolescents aged 11 to 17 years presenting to an outpatient specialty concussion program for evaluation and treatment of concussion. Secondary objectives were to determine if a symptom questionnaire, the Convergence Insufficiency Symptom Survey (CISS),^{27,28} is useful in identifying adolescent patients with vision diagnoses after concussion. The CISS was not originally designed as a screening tool for convergence insufficiency; rather, it was intended for use in clinical trials to assess change in symptoms as an outcome after treatment for convergence insufficiency. We sought to evaluate the utility of the CISS as a screening tool for visual complaints in the setting of concussion as compared with the Post Concussion Symptom Scale (PCSS), which is a validated 22-point symptom questionnaire administered independently or as part of computerized neurocognitive testing.¹¹ An additional secondary

objective was to identify any associations between visual diagnoses and changes in computerized neurocognitive testing scores after injury.

Methods

We conducted a single-center, cross-sectional study of patients who presented to the Minds Matter Concussion Program at The Children's Hospital of Philadelphia. All patients who presented for clinical care between July 1, 2013 and February 28, 2014 were eligible for the study. Our institutional review board approved this study prior to the commencement of subject enrollment and data collection. Study participants were enrolled by trained research assistants during their office visit after parental informed consent and child assent was obtained. We included patients with the medical diagnosis of concussion who were 11 to 17 years old at the time of enrollment. We excluded those who were unable to participate in vision testing for any reason, did not have corrected 20/30 visual acuity, or had a preexisting history of strabismus, amblyopia, surgery, patching, or vision therapy.

A diagnosis of concussion was based on the history of any direct or indirect force transmitted to the head resulting in the temporally-associated onset of signs or symptoms of concussion as defined by the Consensus Statement on Concussion in Sport.¹¹ Vision diagnoses were made based on objective criteria obtained in vision testing as described in Table 1.²⁹ Computerized neurocognitive testing using Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), which includes the PCSS questionnaire, was performed as part of the routine clinical evaluation of the patient for concussion.^{30,31}

Standardized historical and physical examination data,³² as well as computerized neurocognitive testing results with ImPACT, were abstracted from the electronic medical record into Research Electronic Data Capture (REDCap) for analysis. As part of the study, the Convergence Insufficiency Symptom Survey (CISS), a validated questionnaire for the assessment of change in visual symptoms after treatment for convergence insufficiency, was administered to all participants. This tool has been used as an outcome measure in several randomized clinical trials studying the treatment of convergence insufficiency. It is a 15-question instrument with Likert-type scale responses and the expected score for a normal child aged 11 to 17 years is <16.^{27,28} A standardized, comprehensive vision examination, including administration of the CISS, separate from the routine clinical assessment for concussion, was performed by either a developmental optometrist or trained research

Table 1. Diagnostic Criteria for Binocular Vision, Accommodative, and Eye Movement Diagnoses.

<i>Convergence insufficiency</i>
Requires: 1
Plus at least 1 finding from 2-4
Near point of convergence of ≥ 6 cm break
Exophoria at near at least 4 pd greater than at distance
Reduced positive fusional convergence at near (< 20 pd or fails Sheard's criterion ^a)
Vergence facility (distance or near) ≤ 9 cpm with difficulty with base-out
<i>Convergence excess</i>
Requires: 1
Plus at least 1 finding from 2-3
≥ 3 pd esophoria at near
Reduced negative fusional convergence at near (< 8 pd or fails Sheard's criterion ^a)
Vergence facility (distance or near) ≤ 9 cpm with difficulty with base-in
<i>Accommodative insufficiency</i>
Requires: 1 or 2
Amplitude of accommodation ≥ 2 diopters below mean for age (15-1/4 age)
Monocular accommodative facility ≤ 6 cpm (difficulty with minus lenses)
<i>Saccadic dysfunction</i>
Requires: 1 or 2
Developmental Eye Movement Test ratio score: 1 SD or more below the mean
Developmental Eye Movement Test error score: 1 SD or more below the mean

Abbreviations: pd, prism diopters; cpm, cycles per minute; SD, standard deviation.

^aFailing Sheard's criterion = positive fusional vergence is less than twice the near phoria.

assistants. This evaluation included an assessment of visual acuity, eye alignment (Modified Thorington Test), fusional vergence (Step Vergence Test and Vergence Facility Test), convergence (Near Point of Convergence Test), accommodative amplitude and accommodative facility (Push-up Test and +2/-2 test) and eye movements (Developmental Eye Movement Test)²⁹ (Table 1).

Descriptive statistics were calculated for the outcome measures. Fisher's exact test was used for 2-way categorical comparisons of count data. Mann-Whitney analysis for nonparametric data was performed to determine the relationship between neurocognitive test scores and vision diagnoses. All significance levels were set at $P < .05$. Statistical analysis was performed using R version 3.0.3.³² Bootstrap 95% confidence intervals (CIs) were estimated using the boot package.^{34,35} Prevalence ratios (PRs) and 95% CIs were calculated using the epiR package.³⁶

Results

One hundred participants were enrolled during the study period. The mean age was 14.5 years (age range 13.5-14.8 years). Of the study subjects, 42% were male and 65% sustained their concussion as the result of sports participation, while the remainder sustained their concussions in nonsports activities such as falls. Among the

enrolled subjects, 29% were seen within 1 month of their injury, 26% were evaluated between 1 and 3 months after their injury, and 45% were seen > 3 months after their injury. Patients seen within 1 month of injury were more likely to have a vision diagnosis than those evaluated greater than 3 months after injury. Patients who were evaluated early after injury (within 30 days) were more likely to have a vision diagnosis than those evaluated later after injury (> 90 days) ($P = .03$, PR = 1.41; 95% CI = 1.04-1.92). A total of 32% of subjects had a history of prior concussion, which was not associated with an increased risk of vision problems after concussion ($P = .36$).

The primary objective of this study was to determine the prevalence of vision diagnoses after concussion in an adolescent population age 11 to 17 years. Overall, 69% of enrolled subjects had at least one vision diagnosis after concussion, with 51% presenting with accommodative insufficiency or infacility, 49% with convergence insufficiency, and 29% with saccadic dysfunction. Of note, a substantial number of subjects had more than one vision diagnosis following concussion: 22% of patients with convergence insufficiency also had accommodation deficits, while 14% of those with both convergence insufficiency and accommodation deficits also had saccadic dysfunction on exam simultaneously (Figure 1).

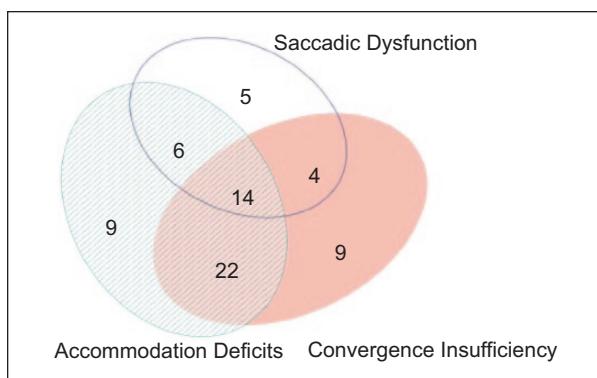


Figure 1. Vision diagnoses after concussion.

Table 2. Association of Convergence Insufficiency Symptom Score (CISS) With Vision Diagnosis.

Vision Diagnosis	CISS <16	CISS ≥16	
(-) Any vision diagnosis	19	12	
(+) Any vision diagnosis	15	54	<i>P</i> = .0002
(-) Convergence insufficiency	24	27	
(+) Convergence insufficiency	10	39	<i>P</i> = .006
(-) Accommodative dysfunction	23	27	
(+) Accommodative dysfunction	11	39	<i>P</i> = .02

A score of ≥ 16 on the CISS indicates that the patient may be symptomatic from convergence insufficiency. A secondary objective of this study was to determine if the CISS could be useful as a screening tool for identifying vision diagnoses in concussion as compared with the widely used PCSS. Among our study subjects, only 29% of patients specifically reported vision problems on the PCSS. In our study, the mean CISS score was 19.8 for all study participants. Overall, the mean CISS score was 22.9 for those with a vision diagnosis, as compared to a score of 13.0 in those without any vision diagnoses (Mann-Whitney $P < .001$), and a high CISS score of ≥ 16 was strongly associated with a vision diagnosis ($P < .001$, PR = 1.85; 95% CI = 1.25-2.75). (Table 2.) More specifically, a CISS score of ≥ 16 was highly correlated with the diagnosis of convergence insufficiency ($P = .006$, PR = 2.01; 95% CI = 1.15-3.51) and accommodative dysfunction ($P = .02$, PR = 1.83; 95% CI = 1.08-3.09). In contrast, a high CISS score of ≥ 16 was not associated with the presence of saccadic dysfunction ($P = .25$) (Table 2).

Another secondary objective of this study was to determine if there was any relationship between vision diagnoses after concussion and scores on computerized neurocognitive testing. Specifically, we examined the relationship between the presence of a visual diagnosis and test-derived verbal memory composite score, visual memory composite score, visual motor speed composite score, reaction time, and impulse control (Table 3). Poor verbal memory composite scores ($P = .002$) and visual motor speed scores ($P = .005$) were significantly correlated with the presence of a vision diagnosis.

Discussion

Vision problems are very common in adults following concussion,¹²⁻²¹ and vision complaints have been described in the adolescent population with concussion.²⁵ We found that a substantial proportion of adolescents in our clinical population with concussion have visual diagnoses identifiable with a comprehensive vision assessment beyond visual acuity.²⁹ Our findings indicate a much higher prevalence of vision diagnoses in adolescents with concussion, as compared with reported prevalence rates in the general pediatric population without concussion. The prevalence of convergence insufficiency in children has been reported between 2% and 8% and the prevalence of accommodative dysfunction has been reported as 5% in the general population, as compared with 49% and 50%, respectively,³⁷⁻³⁹ in our study of adolescents with concussion. While our study excluded patients with binocular vision disorders, it is possible that undiagnosed binocular vision problems comprise a portion of our patients with binocular vision problems following concussion. Despite this limitation, it is unlikely that undiagnosed preexisting binocular issues account for the notable difference observed between the prevalence of convergence insufficiency in our cohort with concussion as compared with the reported prevalence in the general population.

Oculomotor functioning is supported by the occipital lobe, brainstem, frontal lobe, parietal lobe, and cerebellum, with significant integration between these areas and the language areas of the brain to support reading.^{14,26} Because of the diffuse nature of concussion injury, both specific areas of the brain, as well as the integrative pathways needed for accurate and automatic oculomotor functioning, may be affected. The high prevalence of vision diagnoses after concussion reflects the widespread neural architecture involved in visual processing, which may make the visual oculomotor system particularly susceptible to the diffuse stretch injury seen in concussion.

Table 3. Relationship Between Neurocognitive Test Scores and Vision Diagnoses.

	(-)Vision Diagnosis	(+)Vision Diagnosis	P
Verbal memory composite score	88.4	76.9	.002
Visual memory composite score	75.8	68.0	.66
Visual motor speed composite score	37.6	32.0	.005
Reaction time	0.58	0.66	1
Impulse control	6.8	7.8	.88

Identification of concussion-related vision diagnoses is important because of the extensive visual demands of adolescents engaged in full-time school. In today's modern classroom, the use of technology is widespread and these electronic interfaces may add an additional level of visual demand when recovering from a concussion. The high prevalence of vision diagnoses following concussion in this study highlights the importance of implementing appropriate academic accommodations for students returning to the classroom.^{22,23} Since accommodative, binocular vision, and eye movement problems can cause significant symptoms related to visual activities,²⁷ it is important for physicians to suggest specific school-based accommodations to optimally manage these vision-related symptoms. Strategies that include frequent visual breaks, oral teaching, audio-books, large-font printed material (vs. small font electronically displayed material), or preprinted notes may be extremely helpful to a student returning to learn after a concussion.^{22,23}

The PCSS is a widely used tool for diagnosis of concussion and for monitoring recovery over time.³¹ In our study population, fewer than one-third of the study subjects reported visual symptoms using this scale. In comparison, the CISS is a validated 15-point questionnaire developed as a tool to monitor changes in symptoms after treatment for convergence insufficiency.^{27,28,39} In our study, the CISS identified patients with vision diagnoses following concussion, and shows promise as a potential screening tool for vision diagnoses following concussion.

For the general pediatrician, the CISS may prove to be a highly cost-effective means of identifying patients with concussion-related vision deficits who might benefit from referral to a concussion specialist or an eye care professional for a comprehensive visual and oculomotor evaluation beyond visual acuity testing and for possible treatment of accommodation, binocular vision, and eye movements. Future studies to determine potential cutoff scores for the CISS in identifying vision diagnoses after concussion would be helpful.

Computerized neurocognitive testing with tools such as ImPACT are commonly used to aid in the diagnosis and management of acute concussions. In our study,

vision disturbances were correlated with poorer composite scores on visual motor speed, which might be expected in disorders of vision. In addition, vision diagnoses were also associated with poorer verbal memory composite scores, which may reflect the role of the DLPC in both working memory and oculomotor function. This correlation may be due to multiple factors, including the visual nature of the computerized neurocognitive test, as well as the overlapping function of the DLPC in executive function, memory, and oculomotor visual function. The fact that computerized neurocognitive testing, in general, requires sustained visual attention on a computer screen and, therefore presents a high visual demand, may prove problematic for patients with vision diagnoses following concussion. The possibility of concussion-related vision diagnoses may need to be accounted for when interpreting the ImPACT test results much in the same way that adolescents with attention or other learning disorders may have global difficulty with neurocognitive testing.⁴⁰

In the general population without concussion, there have been randomized clinical trials demonstrating the effectiveness of vergence/accommodative therapy for the treatment of convergence insufficiency and accommodative insufficiency.⁴¹⁻⁴⁴ In addition, preliminary studies have shown promise for this type of therapy for the vision deficits following concussion in adults.⁴⁵ Our results suggest that office-based vergence/accommodative therapy for vision disorders following concussion in adolescents warrants further study.

Limitations of our study include a potentially more clinically complicated sample than is seen in the general population with concussion. The Minds Matter Concussion Program at The Children's Hospital of Philadelphia is a subspecialty referral program, and as such, our cohort may represent a concussion population with a greater likelihood of prolonged/complicated recovery or vision diagnoses than is seen in the general pediatric concussion population. Although we did not have a control group, published prevalence rates of these vision diagnoses in the general pediatric population are much lower than the high prevalence of vision diagnoses following concussion in our cohort.

In our study, the 29% of patients less than 1 month postinjury were more likely to have vision deficits than the 22% of patients greater than 3 months postinjury, which was statistically significant. This may indicate that vision diagnoses are a significant component of immediate postconcussion symptomatology, and, in some cases, may recover spontaneously on their own. It is possible that vision diagnoses are present in the estimated 80% to 90% of concussion patients who recover spontaneously over the course of a few weeks,⁴⁶ and therefore, presumably, their vision problems have also spontaneously recovered. While vision diagnoses are also seen in those with prolonged recoveries in our study, further study is needed to determine if they represent a negative prognostic predictor for complicated concussion recovery. Future study is also needed to determine which symptoms are an accurate predictor of the presence of these vision diagnoses, as the PCSS does not appear to identify a majority of patients with vision diagnoses while the CISS appeared to do better. A prospective longitudinal study will be required to answer these important questions.

Given the high prevalence of vision diagnoses after concussion in the adolescent population, future studies should try to establish efficient clinical screening tools, such as the VOMS or CISS, that could be used by a pediatrician to identify the subset of patients who require further concussion care and comprehensive vision evaluation. In addition, a randomized controlled clinical trial is necessary in order to evaluate the potential benefits of possible interventions, such as vergence/accommodative therapy, for patients with vision diagnoses after concussion.

Conclusion

Vision diagnoses are prevalent in adolescents with concussion and include convergence insufficiency, accommodative disorders and saccadic dysfunction. Symptoms of these problems may include double vision, blurry vision, headache, difficulty with reading or other visual work, such as the use of a tablet, smartphone, or computer monitor in the school setting. This likely represents a significant morbidity for adolescents whose primary work is school, which is heavily visually oriented. Recognition of these deficits is essential for clinicians who care for patients with concussion and the CISS may prove to be a useful screening tool for use in the future. Identification of these vision diagnoses will help physicians design necessary academic accommodations for patients who have visual deficits and are attempting to reintegrate into school and learning while recovering from concussion.

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Author Contributions

CLM made a substantial contribution to the concept and design, acquisition of data and analysis and interpretation of data, drafted the article and revised it critically for important intellectual content and approved the version to be published.

MS, MG, AG, RLR and MFG made a substantial contribution to the concept and design, acquisition of data and analysis and interpretation of data, revised the article critically for important intellectual content and approved the version to be published.

SRM made a substantial contribution to the analysis and interpretation of data, revised the article critically for important intellectual content and approved the version to be published.

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ORIGINAL ARTICLE

Prevalence of General Binocular Dysfunctions in a Population of University Students

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ABSTRACT: Purpose. Although some authors report that the prevalence of general binocular dysfunctions (nonstrabismic) for nonpresbyopes in the clinical population is greater than any condition except refractive error, limited research is available to support this statement. This clinical study determined the presence and clinical implications of these conditions in a population of university students with heavy near visual demands. Methods. From a group of second year students who were given a thorough eye examination, 65 students were selected. The criteria for selection were the absence of significant uncorrected refractive error, healthy eyes, and no strabismus or amblyopia. Results. 32.3% of the subjects showed general binocular dysfunctions. In 10.8% of the cases, accommodative excess was present. 7.7% had convergence insufficiency with accommodative excess. 6.2% showed accommodative insufficiency. 3.1% had basic exophoria. Convergence excess with accommodative insufficiency, basic esophoria, and fusional vergence dysfunction all showed the same prevalence of 1.5%. Conclusions. Accommodative and nonstrabismic binocular vision problems are prevalent in this population. Accommodative excess is the most common condition. Because these dysfunctions may have a negative effect on performance, appropriate vision evaluation for this population is important. (Optom Vis Sci 1997;74:111-113)

Key Words: general binocular dysfunctions, accommodative insufficiency, accommodative excess, basic exophoria, basic esophoria, fusional vergence dysfunction, convergence excess, convergence insufficiency

The presence of general binocular dysfunctions (nonstrabismic) in nonpresbyopes is commonly reported, but there are few studies on their prevalence.¹⁻³ Purcell et al.² provided an indirect comparison figure for symptomatic binocular dysfunctions. They reviewed the records of 120 patients at an optometry college clinic. The patients were between 25 and 35 years of age without strabismus, amblyopia, eye pathology, or current contact lens wear. They found that in addition to refraction, 30.8% of patients needed treatment, e.g., vision training, prism, bifocals, or nearpoint lenses, for symptoms associated with their vision, namely headache, eye strain or "pulling," watering, tearing, redness, photophobia, and double vision.

In a sample of 119 patients (39.5% were students), Hokoda³ found that 21% (25 patients) had general binocular dysfunctions with asthenopia. The most commonly encountered conditions were accommodative dysfunctions, which was seen in 16.8% of all patients, 80% of those with dysfunctions. In a study by Hoffman et al.⁴ of 129 individuals diagnosed with binocular vision disorders,

62% had accommodative dysfunctions. In Hokoda's study³ the prevalence of the different types of accommodative dysfunctions was 55% (11 patients) with accommodative insufficiency, 30% (6 patients) with accommodative infacility, and 15% with accommodative spasm (3 patients). Other studies also report that the most common accommodative dysfunction is insufficiency. Daum,⁵ for example, reported 84% with accommodative insufficiency and 2.6% with accommodative excess of 114 patients with accommodative dysfunctions.

Nonstrabismic binocular vision problems have also been found to be prevalent. Morgan's normative data⁶ predict that approximately 12% of nonpresbyopes will have significant near esophoria (greater than 2 Δ), but the prevalence of symptomatic near esophoria was not reported. In his study, Hokoda³ found 5.9% (7 patients) with near esophoria greater than 2 Δ, and 5 of these patients showed an accommodative dysfunction. In the same study, convergence insufficiency occurred in 4.2% (5 patients) and 2 of these patients had associated accommodative dysfunctions.

Other authors^{7–9} report an incidence of convergence insufficiency in 3 to 5% of the population. Daum¹⁰ found that of 177 patients with exo deviation 62.1% had convergence insufficiency and 27.6% showed basic exophoria.

This study was designed to fill a void in the literature by investigating prevalence of nonstrabismic general binocular dysfunctions among university students.

METHODS

A group of 2nd year university students aged 22 years (± 3 years) were given a thorough eye examination over a period of 3 months. From these, 65 students were selected. The criteria for selection were the absence of significant uncorrected refractive error, healthy eyes, and no strabismus or amblyopia.

The examination consisted of the following:

1. History: a questionnaire about symptoms while studying, e.g., appearance, severity, and duration.
2. Preliminary tests: distance and near visual acuity, distance and near cover test in the nine positions of gaze, nearpoint of convergence, ocular motility, pupils, fusion (Worth Four-Dot Test) and stereopsis (Randot Stereotest).
3. Distance refraction: retinoscopy and distance subjective.
4. Binocularity and accommodation tests: distance and near lateral and vertical phorias (von Graef's technique), distance and near lateral and vertical fusional vergence (smooth and step vergence testing), AC/A measured by the gradient method, jump vergence testing (8 Δ base-out and 8 Δ base-in), fixation disparity (with the Mallet unit), monocular estimation method (MEM) retinoscopy, fused cross-cylinder, NRA and PRA (negative and positive relative accommodations), monocular and binocular accommodative facility with ± 2.00 D flipper lenses (the target for binocular testing is the Bernell no. 9 Vectogram), and accommodative amplitude using both the push-up method and the minus lens procedure.
5. Evaluation of ocular health: direct ophthalmoscopy, biomicroscopy, visual fields, and color vision test.

The results of each of the tests were compared first with the population norms,¹¹ derived from Morgan's data⁶ and new data from other tests such as accommodative facility, fusional facility, step vergence, ocular motor test, MEM retinoscopy, and fixation disparity. The results were then grouped according to their deviation from the normal values. The syndrome or anomaly was then identified. Table 1 lists the classification criteria for general binocular dysfunctions used in this study.

RESULTS

Subjects with both abnormal signs and symptoms were considered to have general binocular dysfunctions. Asymptomatic subjects with abnormal clinical findings were excluded and counted as normals, as were those subjects with symptoms but whose accommodative-convergence findings were normal.

The most prevalent symptoms among the students (see Table 2) were 21.5% with asthenopia or eyestrain, followed by 18.5% with headaches, 12.3% had intermittent blurred vision at distance and difficulty in focusing when looking from near to far, 9.2% showed sensitivity to light, 4.6% had intermittent blurred near vision or

TABLE 1.

Classification criteria for general binocular dysfunctions.

Binocular Vision Disorders

Convergence Insufficiency

1. Symptoms associated with reading
2. Signs:
Moderate to high exophoria at near $>6 \Delta$
Low AC/A ratio (less than 3/1)
Reduced positive fusional vergence at near
Receded nearpoint of convergence

Basic Exophoria

1. Symptoms associated with distance and near tasks
2. Signs:
Exophoria of approximately equal magnitude at near and at distance
Normal AC/A ratio (4/1 with a SD of ± 2)
Reduced positive fusional vergence at distance and near

Basic Esophoria

1. Symptoms associated with distance and near tasks
2. Signs:
Esophoria of approximately equal magnitude at near and at distance
Normal AC/A ratio (4/1 with a SD of ± 2)
Reduced negative fusional vergence at distance and near

Fusional Vergence Dysfunction

1. Symptoms associated with reading
2. Signs:
Orthophoria at distance and near, or a low degree of exophoria or esophoria at distance and near
Normal AC/A ratio (4/1 with a SD of ± 2)
Reduced negative and positive fusional vergence at distance and near

Convergence Excess

1. Symptoms associated with reading
2. Signs:
Significant esophoria at near $>2 \Delta$
High AC/A ratio (greater than 7/1)
Reduced negative fusional vergence at near

Accommodative Anomalies

Accommodative Insufficiency

1. Symptoms associated with reading
2. Signs:
Push-up accommodative amplitude at least 2 D below Hofstetter's calculation for minimum age-appropriate amplitude: $15 - 0.25 \times \text{age in years}^{12}$
Decreased positive relative accommodation, ≤ 1.25 D
Difficulty clearing -2.00 D with monocular and binocular accommodative facility (monocular ≤ 6 cpm, binocular ≤ 3 cpm)
High MEM, ≥ 0.75 D
High fused cross-cylinder, ≥ 1.00 D

Accommodative Infacility

1. Symptoms associated with reading
2. Signs:
Difficulty clearing -2.00 D and $+2.00$ D with monocular and binocular accommodative facility (monocular ≤ 6 cpm, binocular ≤ 3 cpm)
Low positive and negative relative accommodation. PRA ≤ 1.25 D and NRA ≤ 1.50 D

Accommodative Excess

1. Symptoms associated with reading
2. Signs:
Variable static and subjective
Possibly low degree of against-the-rule cylinder
Variable visual acuity findings
Difficulty clearing $+2.00$ D with monocular and binocular accommodative facility (monocular ≤ 6 cpm, binocular ≤ 3 cpm)
Low MEM, ≤ 0.25 D
Low fused cross-cylinder, ≤ 0.00 D

TABLE 2.
Prevalence of students' symptoms.

Symptom	Frequency of Occurrence (%)	No. Subjects
Asthenopia after 1 or 2 h	7.7	5
Asthenopia toward the end of the day	13.8	9
Headaches after 1 or 2 h	10.8	7
Headaches toward the end of the day	7.7	5
Intermittent blurred vision at distance and difficulty in focusing when looking from near to far	12.3	8
Sensitivity to light	9.2	6
Intermittent blurred near vision or words appearing to move	4.6	3
Intermittent diplopia	3.1	2
Poor concentration	3.1	2

words appearing to move, and 3.1% presented intermittent diplopia, with a similar percentage reporting loss of concentration.

The prevalence of general binocular dysfunctions detected in the students (see Table 3) was 32.3% (21 subjects); 10.8% had accommodative excess; 7.7% convergence insufficiency with accommodative excess; 6.2% accommodative insufficiency; and 3.1% basic exophoria. Convergence excess with accommodative insufficiency, basic esophoria, and fusional vergence dysfunction all showed the same prevalence of 1.5%.

DISCUSSION

Accommodative and nonstrabismic binocular vision problems were prevalent (32.3%) in a population of university students. Accommodative excess was the most common dysfunction detected.

The term accommodative excess is used in the literature to refer to several conditions such as accommodative spasm, spasm of the near reflex, ciliary spasm, and pseudomyopia. Scheiman and Wick,¹³ suggested a definition of accommodative spasm, spasm of the near reflex, and ciliary spasm. These conditions are a very severe form of the more mild condition they described as accommodative excess. With accommodative excess there is no dramatic overaccommodation, miosis, or limitation of abduction. It should be noted that, as Scheiman and Wick¹² suggested, accommodative

TABLE 3.
Prevalence of general binocular dysfunctions.

Classification	Prevalence (%)	No. Subjects
Accommodative excess	10.8	7
Convergence insufficiency with accommodative excess	7.7	5
Accommodative insufficiency	6.2	4
Basic exophoria	3.1	2
Convergence excess with accommodative insufficiency	1.5	1
Basic esophoria	1.5	1
Fusional vergence dysfunction	1.5	1

excess is not as rare as accommodative spasm. It is in fact very common among university students as is the case in this study. The impact of near visual demands may be responsible for this type of primary accommodative disorder, which was found in 10.8% of the subjects and as a secondary problem in 7.7% of the subjects with convergence insufficiency.

These findings suggest that in university students it is important to give a thorough eye examination to detect these general binocular dysfunctions (particularly accommodative excess) and to consider applying the appropriate treatment in the form of lenses, prisms, and/or visual therapy to help improve performance and visual efficiency.

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Non-surgical interventions for convergence insufficiency (Review)

Scheiman M, Gwiazda J, Li T

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[Intervention Review]

Non-surgical interventions for convergence insufficiency

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ABSTRACT

Background

Convergence insufficiency is a common eye muscle co-ordination problem in which the eyes have a strong tendency to drift outward (exophoria) when reading or doing close work. Symptoms may include eye strain, headaches, double vision, print moving on the page, frequent loss of place when reading, inability to concentrate, and short attention span.

Objectives

To systematically assess and synthesize evidence from randomized controlled trials (RCTs) on the effectiveness of non-surgical interventions for convergence insufficiency.

Search methods

We searched *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index, the *metaRegister of Controlled Trials (mRCT)* (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov) on 7 October 2010. We manually searched reference lists and optometric journals.

Selection criteria

We included RCTs examining any form of non-surgical intervention against placebo, no treatment, sham treatment, or each other.

Data collection and analysis

Two authors independently assessed eligibility, risk of bias, and extracted data. We performed meta-analyses when appropriate.

Main results

We included six trials (three in children, three in adults) with a total of 475 participants. We graded four trials at low risk of bias.

Evidence from one trial (graded at low risk of bias) suggests that base-in prism reading glasses was no more effective than placebo reading glasses in improving clinical signs or symptoms in children.

Evidence from one trial (graded at high risk of bias) suggests that base-in prism glasses using a progressive addition lens design was more effective than progressive addition lens alone in decreasing symptoms in adults. At three weeks of therapy, the mean difference in Convergence Insufficiency Symptoms Survey (CISS) score was -10.24 points (95% confidence interval (CI) -15.45 to -5.03).

Evidence from two trials (graded at low risk of bias) suggests that outpatient (or office-based as used in the US) vision therapy/orthoptics was more effective than home-based convergence exercises (or pencil push-ups as used in the US) in children. At 12 weeks of therapy, the mean difference in change in near point of convergence, positive fusional vergence, and CISS score from baseline was 3.99 cm (95% CI 2.11 to 5.86), 13.13 diopters (95% CI 9.91 to 16.35), and 9.86 points (95% CI 6.70 to 13.02), respectively.

In a young adult population, evidence from one trial (graded at low risk of bias) suggests outpatient vision therapy/orthoptics was more effective than home-based convergence exercises in improving positive fusional vergence at near (7.7 diopters, 95% CI 0.82 to 14.58), but not the other outcomes.

Evidence from one trial (graded at low risk of bias) comparing four interventions, also suggests that outpatient vision therapy/orthoptics was more effective than home-based computer vision therapy/orthoptics in children. At 12 weeks, the mean difference in change in near point of convergence, positive fusional vergence, and CISS score from baseline was 2.90 cm (95% CI 0.96 to 4.84), 7.70 diopters (95% CI 3.94 to 11.46), and 8.80 points (95% CI 5.26 to 12.34), respectively. Evidence was less consistent for other pair-wise comparisons.

Authors' conclusions

Current research suggests that outpatient vision therapy/orthoptics is more effective than home-based convergence exercises or home-based computer vision therapy/orthoptics for children. In adult population, evidence of the effectiveness of various non-surgical interventions is less consistent.

PLAIN LANGUAGE SUMMARY

Non-surgical treatments for eyes with convergence insufficiency

Convergence insufficiency is a common eye muscle co-ordination problem in which the eyes have a strong tendency to drift outward (exophoria) when reading or doing close work. This systematic review aimed to search for, assess, and synthesize evidence from randomized controlled trials (RCTs) on the effectiveness of non-surgical interventions for convergence insufficiency.

We included six RCTs conducted in the United States with a total of 475 participants. We assessed four trials at low risk of bias. Evidence suggests that:

1. Base-in prism reading glasses was no more effective than placebo reading glasses in improving clinical signs or symptoms in children;
2. Outpatient vision therapy/orthoptics is more effective than home-based convergence exercises or home-based computer vision therapy/orthoptics in improving clinical signs and symptoms in children; and
3. The effectiveness of various non-surgical interventions in adult population is less consistent.

BACKGROUND

Description of the condition

Convergence insufficiency is a common binocular vision disorder (eye muscle co-ordination problem) in which the eyes have a strong tendency to drift outward (exophoria) when reading or doing close work. As a result the eyes do not converge adequately and this condition may lead to symptoms including eye strain, headaches, double vision, print moving on the page, frequent loss of place when reading, inability to concentrate, and short attention span.

Convergence insufficiency is diagnosed when exophoria is greater at near than at distance and the patient has one or both of the following: a remote near point of convergence or decreased positive fusional vergence.

There is considerable variability in the reported prevalence of convergence insufficiency. The estimates of prevalence based on population studies range from 2.25% to 8.3% ([Letourneau 1979](#); [Letourneau 1988](#); [Porcar 1997](#); [Rouse 1999](#)). There is a paucity of data regarding whether the prevalence of convergence insufficiency varies by ethnicity, race, age, sex, geographic location, or socioeconomic status.

Description of the intervention

Various non-surgical treatments are prescribed for treating convergence insufficiency including base-in prism reading glasses, home-based convergence exercises (or pencil push-ups as used in the US), home-based vision therapy/orthoptics, and outpatient (or office-based as used in the US) vision therapy/orthoptics (Chin 1995; Gallaway 2002; Griffin 2002; Grisham 1998; Hugonnier 1969; Pratt-Johnson 2001; Press 1997; Scheiman 2002a; Scheiman 2002b; von Noorden 1994; von Noorden 1996). Although surgery is a potential treatment option for convergence insufficiency, it is rarely used because of the comparative invasive nature of surgery with its potential complications.

Base-in prism reading glasses

There are various methods for determining the amount of prism to prescribe (Scheiman 2008). In a Convergence Insufficiency Treatment Trial (CITT) trial of children nine to 17 years of age (CITT 2005a), the investigators prescribed prism based on Sheard's Criterion (Sheard 1930). This criterion states that the magnitude of the prism should be sufficient to insure that the compensatory fusional vergence is equal to twice the magnitude of the phoria. The adult base-in prism study (Teitelbaum 2009) based the prescription of prism on the associated phoria measurement.

Home-based convergence exercises

The home-based convergence exercises are described by Duke-Elder (Duke-Elder 1973). "Exercises to improve the near point of convergence are carried out simply by the subject holding a target at arm's length and then gradually bringing it towards the eye, all the time maintaining binocular fixation. These exercises should be carried out several times each day for a few minutes." Use of a target providing physiological diplopia is often recommended (Hugonnier 1969; Press 1997; Scheiman 2002a; Scheiman 2002b; von Noorden 2001). Recent studies surveying the ophthalmic community suggest that home-based convergence exercises is the most commonly prescribed treatment by both ophthalmologists and optometrists (Chin 1995; Scheiman 2002a; Scheiman 2005). In two CITT trials (CITT 2005c; CITT 2008), the home-based convergence exercises procedures (referred to as pencil push-ups in the trials) used a pencil with 20/60 size letters and a white index card placed in the background to provide a suppression check by using physiological diplopia awareness. The goal of the procedure was to move the pencil to within 2 cm to 3 cm of the brow, just above the nose on each push up while trying to keep the target single and clear. Patients were instructed to perform the pencil push-ups procedure 15 minutes per day, five days per week.

Home-based computer vergence/accommodative therapy

Some clinicians recommend home-based therapy that is more intensive than pencil push-ups (Scheiman 2002a; Scheiman 2002b). Additional home-based techniques include the use of prism, stereoscopes, and computer software programs designed for vision therapy/orthoptics (Scheiman 2002a; Scheiman 2005). In the large-scale CITT trial (CITT 2008) patients in this group were taught to perform the aforementioned pencil push-up procedure as well as procedures on the Home Therapy System (HTS/ CVS; www.visiontherapysolutions.com) computer software. Using this program, the patients performed fusional vergence and accommodative therapy procedures. These procedures were designed to improve convergence and divergence amplitudes and accommodative ability. Patients were instructed to do pencil push-ups five minutes per day and the HTS software program for 15 minutes per day.

Outpatient vision therapy/orthoptics

Outpatient vision therapy/orthoptics involves a sequence of activities prescribed and monitored by an eye care professional to develop efficient visual skills. It incorporates purposeful, controlled manipulation of target blur, disparity, and proximity, with the aim of normalizing the accommodative and vergence systems and their mutual interactions (Ciuffreda 2002).

In two CITT trials (CITT 2005b; CITT 2008), patients in the outpatient (referred to as office-based in the trials) vergence/accommodative therapy group received weekly 60-minute in-office therapy with additional prescribed procedures to be performed at home for 15 minutes a day, five days per week. At each office-based therapy session, the patient performed four to five procedures with constant supervision and guidance from the therapist. The therapist followed a detailed and specific protocol from the CITT Manual of Procedures (accessed at www.optometry.osu.edu/research/CITT/4363.cfm); this document describes each procedure, amount of time used, expected performance, and criteria for ending the procedure and advancing to a more difficult level.

Outpatient placebo therapy

In two CITT trials (CITT 2005b; CITT 2008) patients in the outpatient (referred to as office-based in the trials) placebo therapy group received placebo therapy during a weekly 60-minute office visit and were prescribed procedures to be performed at home for 15 minutes per day, five days per week. The placebo therapy program consisted of 16 in-office therapy procedures and four home therapy procedures, which were designed to look like real vergence/accommodative therapy procedures yet not stimulate vergence, accommodation or fine saccadic eye movement skills beyond normal daily visual activities. The therapist followed a detailed protocol from the CITT Manual of Procedures (accessed at www.optometry.osu.edu/research/CITT/4363.cfm).

How the intervention might work

The two main categories of intervention for convergence insufficiency are base-in reading glasses and vision therapy/orthoptics. Vision therapy/orthoptics can be subdivided into convergence exercises (i.e., pencil push-ups), more intensive home-base vision therapy/orthoptics, and outpatient vision therapy/orthoptics, as described above.

Patients with convergence insufficiency are often symptomatic because they need to use excessive convergence to compensate for high exophoria at near. Base-in prism reading glasses are believed to work by relieving the need to use this excessive convergence, thereby relieving discomfort. While the exact mechanism is not known for how vision therapy works, the hypothesis is that vision therapy increases positive fusional vergence and convergence ability, thereby relieving the symptoms associated with convergence insufficiency.

The three vision therapy/orthoptics treatment approaches (home-based convergence exercises, home-based computer vergence/ accommodative therapy, and outpatient vision therapy/orthoptics) differ in: 1) ability to control/manipulate stimulus parameters; 2) dosage; 3) mode of administration; 4) use of motor learning theory and patient feedback; and 5) cost.

Controlling/manipulating stimulus parameters

To increase fusional vergence amplitudes a therapy procedure must either maintain accommodation at the plane of regard and change the vergence stimulus, or maintain vergence at the plane of regard and change the stimulus to accommodation (Scheiman 2002b). Instrumentations using a variety of stimuli are available that allow manipulation of these variables to create a vergence demand that is appropriate for an individual patient.

The three vision therapy/orthoptics treatment approaches described above vary significantly in their ability to allow the manipulation of stimulus parameters. With home-based convergence exercises, the stimulus is a small letter on a pencil that is moved closer to the patient. To maintain single vision, a combination of proximal, accommodative, and fusional vergence is used with accommodation and convergence synchronized. In contrast, outpatient vision therapy/orthoptics uses a wide variety of instrumentation that is designed to improve the dynamics of the fusional vergence and accommodative systems, typically using stimuli that require an accommodative demand different from the vergence demand. Hence, fusional vergence must be used while proximal and accommodative vergence is minimized. Home-based convergence exercises plus computer-based vergence/ accommodative therapy provides an intermediate level of manipulation of the vergence/ accommodative relationship, but lacks the variety of stimuli available with outpatient vergence/ accommodative therapy.

Dosage

More time is generally spent in outpatient vision therapy/orthoptics than either home-based option. In all three therapy approaches the patient must practice procedures at home. In the outpatient treatment there is an additional 60 minutes per week of therapy in the doctor's office. Total therapy time prescribed tends to be least with home-based convergence exercises and most with outpatient vision therapy/orthoptics.

Mode of administration

In outpatient vision therapy/orthoptics a trained therapist administers the treatment, providing the patient with motivation and feedback regarding performance and varying procedures based on the patient's progress. In the two home-based vision therapy/orthoptics approaches, close supervision from a trained therapist is not available, although parents are expected to supervise children prescribed this therapy.

Motor learning principles and patient feedback

Learning is a set of internal processes associated with practice or experience that results in a relatively permanent change in responding (Schmidt 1988). These processes are believed to be central nervous system phenomena in which sensory and motor information is organized and integrated (Aikon 1988; Arbib 1981; Lisberger 1988) with an ultimate goal of transferring the motor learning outside of the therapy setting.

For motor learning, numerous variables are considered important determinants. These include use of feedback, modeling and demonstration, transfer of training, part to whole task practice, variability in practice, and positive reinforcement. Of the three therapy approaches, outpatient vision therapy/orthoptics uses these principles of motor learning and patient feedback most frequently and consistently (Birnbaum 1977; Scheiman 2002b).

Why it is important to do this review

Although various treatments are prescribed for patients with convergence insufficiency there is a lack of consensus regarding the most effective treatment. Significant differences exist in the time commitment for the patient, number of office visits, cost, and complexity of the treatment. A systematic review of clinical trials will help summarize the available evidence on the effectiveness of interventions for patients with convergence insufficiency and will help clinicians select the most appropriate treatments for patients with this condition.

OBJECTIVES

The objective of this review was to systematically assess and synthesize evidence from randomized controlled trials (RCTs) on the effectiveness of non-surgical treatment options for convergence insufficiency.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and quasi-randomized clinical trials in this review.

Types of participants

We included trials in which participants had been treated for convergence insufficiency using non-surgical treatment. The definition of convergence insufficiency varies considerably from study to study. For this review convergence insufficiency is defined as a condition characterized by higher exophoria at near than at far distance, and one or both of the following objective clinical signs:

1. A receded near-point of convergence (6 cm or greater) ([Hayes 1998](#); [Scheiman 2003](#));
2. Insufficient positive fusional vergence at near (i.e., less than twice the near phoria (Sheard's criterion) or positive fusional vergence less than 15 prism diopters) which is one standard deviation below the mean ([Sheard 1930](#); [Scheiman 2002b](#)).

Types of interventions

We included RCTs examining any form of non-surgical intervention against placebo, no treatment, sham treatment, or each other for patients with convergence insufficiency.

Types of outcome measures

Primary outcomes

The primary outcomes for this review were near point of convergence and positive fusional vergence at near at 12 weeks of intervention. We analyzed the primary outcomes as continuous variables whenever data were available. We planned to analyze the primary outcomes as dichotomous variables if continuous data were not reported in the included trials.

We used currently accepted normative data to determine whether patients had achieved normal levels for these clinical findings. A near point of convergence that was < 6 cm after completion of

treatment was considered a normal finding (Yes/No); positive fusional vergence at near that was either twice the magnitude of the exophoria at near or > 15 prism diopters after completion of treatment was considered normal (Yes/No).

We analyzed primary outcomes at other follow-up times when long-term follow-up data were available.

Secondary outcomes

The secondary outcome for this review was patient symptoms at different follow-up times as reported in the included studies. We assessed patient symptoms whenever trials had used some formal instrument for examining symptoms ([Borsting 2003](#); [Maples 2002](#); [Rouse 2004](#)). One instrument that has been developed and validated for assessing convergence insufficiency symptoms before and after treatment is the Convergence Insufficiency Symptom Survey (CISS) Version -15, a 15-item questionnaire that measures symptoms experienced when reading or doing other close work ([Borsting 2003](#)). The higher the CISS score, the more symptoms. CISS has demonstrated a sensitivity of 96% and a specificity of 88%, when using a score of ≥ 16 for children and ≥ 21 for adults differentiating individuals with symptomatic convergence insufficiency from those with normal binocular vision ([Borsting 2003](#)). We reported compliance to treatment as an *ad hoc* secondary outcome because the success of treatment depends on compliance. Three trials included in our review reported compliance data.

Adverse outcomes

Adverse effects of interest included:

1. Worsening of diplopia (double vision);
2. Worsening of headaches;
3. Convergence spasm.

We summarized the reported adverse effects related to each intervention.

Quality of life data

We planned to describe data on quality of life when available from included trials.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2010, Issue 10, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 7 October 2010), MEDLINE (January 1950 to October 2010), EMBASE (January 1980 to October 2010), the *metaRegister of Controlled Trials*

(mRCT) (www.controlled-trials.com) (October 2010) and ClinicalTrials.gov (www.clinicaltrials.gov) (October 2010). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 7 October 2010. See: Appendices for details of search strategies for CENTRAL ([Appendix 1](#)), MEDLINE ([Appendix 2](#)), EMBASE ([Appendix 3](#)), mRCT ([Appendix 4](#)) and ClinicalTrials.gov ([Appendix 5](#)).

Searching other resources

We searched the reference lists of identified trial reports to find additional trials. We used the Science Citation Index (SCI) to find studies that had cited the reports of included trials. We contacted the primary investigators of identified trials for details of additional trials.

We also conducted manual searches of the following optometric journals:

Optometry, Journal of Behavioral Optometry (1990 to 2009);
Optometry Vision Development (1969 to 2009);
American Orthoptic Journal (1951 to 2009);
Australian Orthoptic Journal (1973 to 2009); and
British and Irish Orthoptic Journal (formerly the *British Orthoptic Journal*) (1954 to 2009).

Data collection and analysis

Selection of studies

At least two authors independently reviewed the titles and abstracts resulting from the electronic and manual searches according to the inclusion criteria stated above. We classified abstracts as 'definitely exclude', 'unsure' or 'definitely include'. We obtained the full text for articles in the 'unsure' and 'definitely include' categories and re-assessed them for final eligibility. After examining the full text, studies labeled as 'excluded' by both authors were excluded from the review and the reasons for exclusion documented. Included studies were further assessed for their methodological quality. We resolved discrepancies through discussion and consensus.

Data extraction and management

At least two review authors independently extracted the data onto paper data collection forms. We resolved discrepancies through discussion. One review author (TL) entered all data into Review Manager ([RevMan 2008](#)). Data entered were verified by a second author (MS). We extracted the following details from the studies: methods, participants, interventions, outcomes, adverse events, quality of life issues, economic data and important information on captured otherwise.

Assessment of risk of bias in included studies

At least two review authors assessed the sources of potential systematic bias in trials according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)). The following parameters were considered: a) randomization sequence generation; b) allocation concealment; c) masking (blinding) of the primary and secondary outcome assessors; d) completeness of outcome data for the primary and secondary outcomes; e) selective outcome reporting; and f) intention-to-treat analysis. Each of the parameters was graded as: 'Yes', at low risk of bias, 'No', at high risk of bias, and 'Unclear', at unclear risk of bias. Because of the nature of the intervention, masking of participants and care providers was not possible in all trials, and consequently was not used as a quality parameter in this review.

Measures of treatment effect

We followed the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2008](#)) for data analyses. We calculated a summary risk ratio for dichotomous outcomes and mean difference between intervention arms for continuous outcomes. We reported estimate of effect and associated confidence intervals (CI).

Unit of analysis issues

We conducted a person-based analysis because convergence insufficiency is a binocular vision disorder. None of the trials included in this review used cluster or cross-over design. If cluster-randomized trials and cross-over trials are to be included in future updates of this review, we will extract data from an analysis that properly accounts for the non-independence of the cluster and cross-over design. If the primary studies fail to report appropriate analyses, we will perform the analyses following section 9.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2008](#)).

Dealing with missing data

We contacted the lead investigator of the trial in an attempt to obtain additional information. We pre-specified that whenever the authors did not respond within four weeks, we would continue the review based on the available information.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity qualitatively by examining the characteristics of each included trial. We assessed statistical heterogeneity quantitatively using the Chi² test and the I² values. We pre-specified that a P-value of less than 0.1 from the Chi² test and I² statistic of greater than 50% indicated substantial statistical heterogeneity.

Assessment of reporting biases

We planned to use a funnel plot to assess publication bias when a sufficient number of trials were identified.

Data synthesis

We pre-specified that we would combine the results in a meta-analysis using both the fixed-effect and random-effects models if little clinical, methodological, and statistical heterogeneity were present. Whenever substantial variation were detected between trials, we would not combine study results but would present them with estimates of effect and associated confidence intervals.

Subgroup analysis and investigation of heterogeneity

We examined potential sources of heterogeneity qualitatively. Variables that could be related to heterogeneity and were candidates for stratified analysis included patient age, types of test and comparison intervention, and study design parameters.

Sensitivity analysis

We pre-specified that we would conduct sensitivity analyses to determine the impact of exclusion of studies at higher risk of bias, unpublished studies, and industry-funded studies.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The electronic searches identified 529 titles and abstracts of which 27 appeared to be relevant on initial review. After reading the full text reports of these 27 titles and abstracts, 18 were excluded; 13 were not RCTs, and the other five studies were not conducted in the study population of interest.

The remaining nine articles reporting six trials were relevant to this systematic review ([Birnbaum 1999](#); [CITT 2005a](#); [CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#), [Teitelbaum 2009](#)).

We did not find any additional trials by searching the reference lists of the included studies, the WHO ICTRP, the SCI website, or by manually searching the above mentioned optometry journals.

Included studies

We have presented the clinical characteristics for each included study in the '[Characteristics of included studies](#)' table.

Types of participants

We included six trials with a total of 475 participants with convergence insufficiency. All six trials were conducted in the United States. The trials varied in size with the smallest enrolling 29 participants ([Teitelbaum 2009](#)) and the largest enrolling 221 participants ([CITT 2008](#)). Four of the six trials were conducted by the Convergence Insufficiency Treatment Trial (CITT) Study Group ([CITT 2005a](#); [CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#)). These four CITT trials randomized 81.3% (386/475) of all participants included in this systematic review. Symptomatic convergence insufficiency was defined consistently across the four CITT trials and the eligibility criteria were comparable. Of the remaining trials, [Birnbaum 1999](#) enrolled 60 adult male participants from a Veterans Medical Center, and [Teitelbaum 2009](#) enrolled 29 patients affected by presbyopia (a condition in which the lens of the eye loses its ability to focus, making it difficult to see objects up close) from a private practice.

We found clinical heterogeneity in several aspects, mainly in the age distribution of trial participants. Three trials were conducted in children nine to 17 or 18 years old ([CITT 2005a](#); [CITT 2005b](#); [CITT 2008](#)); one trial was conducted in adults 19 to 30 years old ([CITT 2005c](#)); the remaining two trials were conducted in adults aged 40 years or older ([Birnbaum 1999](#), [Teitelbaum 2009](#)). [Birnbaum 1999](#) did not report explicitly the baseline characteristics of included participants.

[CITT 2005b](#) included participants with higher accommodative amplitude (a measurement of the eye's ability to focus clearly on objects at near distances) and less exophoria at distance than the other three trials. The lower accommodation is due to the age difference since accommodation is indirectly related to age. The baseline refractive error also varied across trials.

Because of potential differences in accommodation and accommodative vergence with aging, it is important to analyze findings for children separately from young adults and presbyopes.

Types of test interventions and comparison interventions

The included trials evaluated a variety of interventions, including passive treatment with base-in prism reading glasses, and active treatments such as a specific outpatient vision therapy/orthoptics called office-based vergence/ accommodative therapy, home-based convergence exercises, home-based computer vergence/ accommodative therapy plus convergence exercises, and placebo or sham procedures. The interventions and comparison interventions are described in detail in the '[Characteristics of included studies](#)' table and [Table 1](#). We kept the same terms that were used in the trials to refer to each intervention (e.g., instead of convergence ex-

ercises, we used pencil push-ups to describe the intervention tested in the CITT trials).

[CITT 2005a](#) randomly assigned 72 children nine to 18 years of age with symptomatic convergence insufficiency to wear either base-in prism reading glasses or placebo reading glasses. Patients assigned to base-in prism reading glasses received glasses that corrected for the patient's refractive error, when necessary, and base-in prism. Patients in the placebo reading glasses group received glasses that corrected their refractive error, or plano lenses for those who did not require refractive correction. Patients were asked to wear these glasses for all reading and near tasks requiring more than five minutes for six weeks.

[Teitelbaum 2009](#) randomly assigned 29 presbyopic patients aged 45 to 68 years with symptomatic convergence insufficiency to either base-prism in a progressive addition lens or progressive addition lenses with no prism. Participants wore each pair of glasses for three weeks and completed the CISS at the end of three weeks.

[CITT 2005b](#) was considered as a pilot study by the CITT Study Group. In this study, 47 children were randomly assigned to receive a 12-week program of home-based pencil push-ups, office-based vision therapy/orthoptics, or office-based placebo therapy. The same treatment modalities were further tested in 46 adults in [CITT 2005c](#).

[CITT 2008](#) randomly assigned 221 children to receive a 12-week program of home-based pencil push-ups, home-based computer vergence/accommodative therapy plus pencil push-ups, office-based vergence/accommodative therapy with home reinforcement, or office-based placebo therapy. The home-based computer vergence/accommodative therapy plus pencil push-ups group was considered a more intensive regimen than pencil push-ups alone, sometimes used by both ophthalmologists and optometrists. The other three treatment modalities were essentially the same as those in the aforementioned CITT trials.

[Birnbaum 1999](#) randomly assigned 60 male adult patients to receive office-based vision therapy/orthoptics with supplemental home therapy, home vision therapy, or no treatment. The exact

treatment modalities differed from those used in the CITT trials.

Types of outcomes

The four CITT Study Group trials and [Teitelbaum 2009](#) used a consistent method to measure outcomes.

The primary outcome measure for four CITT trials was the Convergence Insufficiency Symptom Survey (CISS) V-15 ([Borsting 2003](#)). [CITT 2005a](#) measured the primary outcome after six weeks of therapy, and the other three CITT trials ([CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#)) measured the primary outcome after 12 weeks of therapy. Secondary outcome measures in these four trials were near point of convergence and positive fusional vergence at near. [Teitelbaum 2009](#) measured symptoms with CISS V-15 after three weeks of therapy.

[Birnbaum 1999](#) did not specify the primary or secondary outcome, although the author reported "success" and "failure" for each individual participant on the basis of improvement shown with respect to the asthenopia (eye strain) and functional criteria. No harms were reported from any of the six trials.

Excluded studies

We excluded 18 studies that initially appeared to be relevant; 13 were not RCTs or CCTs, and the other five did not address the study population of interest. We have listed reasons for excluding each study in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

We evaluated the risk of bias in each of the six included trials using eight pre-specified criteria. Two trials ([Birnbaum 1999](#); [Teitelbaum 2009](#)) were judged to have high potential for bias, and the other four trials ([CITT 2005a](#); [CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#)) were judged to have low potential for bias (see Figure 1: Methodological quality summary).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding? (Primary outcome)	Blinding? (Secondary outcomes)	Incomplete outcome data addressed? (Primary outcome)	Incomplete outcome data addressed? (Secondary outcomes)	Free of selective reporting?	Intention-to-treat (ITT) analysis?
Birnbaum 1999	?	?	?	?	+	+	?	+
CITT 2005a	+	+	+	+	?	?	+	+
CITT 2005b	+	+	+	+	?	?	+	+
CITT 2005c	+	+	+	+	?	?	+	+
CITT 2008	+	+	+	+	?	?	+	+
Teitelbaum 2009	?	?	+	+	?	?	?	?

Allocation

[Birnbaum 1999](#) and [Teitelbaum 2009](#) did not report the procedure used to generate random sequences and whether the intervention allocation was concealed until assigned. When patient assignment involves a non-random approach, confounding and selection bias may be introduced. The other four RCTs ([CITT 2005a](#); [CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#)), designed and conducted by the CITT Study Group, used a central study website to randomize study participants and the treatment assignment was concealed to researchers enrolling and allocating participants until that time.

Blinding

[Birnbaum 1999](#) did not report whether the primary or the secondary outcomes were measured by masked personnel. Inadequate masking may introduce information bias. The other five trials ([CITT 2005a](#); [CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#); [Teitelbaum 2009](#)) reported that masking was used for measuring the primary and secondary outcomes.

Incomplete outcome data

No participants were lost to follow-up in [Birnbaum 1999](#) or [Teitelbaum 2009](#). The remaining four trials had missing data. Personal contact with the CITT trial statistician revealed that missing data were not imputed in the four CITT trials ([CITT 2005a](#); [CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#)), and therefore, only available outcome data were used in the analyses. One participant in [CITT 2008](#) was excluded from the analysis because of early withdrawal. Three participants from [CITT 2005a](#) and five participants from [CITT 2005b](#) were excluded from analyses because only baseline data were available. [Birnbaum 1999](#), [CITT 2005a](#), [CITT 2005b](#), [CITT 2005c](#) and [CITT 2008](#) reported that participants were analyzed by the treatment group to which they were assigned.

Selective reporting

We had insufficient information to assess the risk of selective reporting bias in [Birnbaum 1999](#) and [Teitelbaum 2009](#). All the outcomes described in the study protocol of the four CITT trials ([CITT 2005a](#); [CITT 2005b](#); [CITT 2005c](#); [CITT 2008](#)) were reported.

Other potential sources of bias

The primary outcome was not defined in [Birnbaum 1999](#). Further, although the authors reported data for each individual participant in this trial, no between treatment group comparison was made in the analyses except one outcome.

Effects of interventions

Two of the six trials included in the review reported data for the comparison between base-in prism reading glasses and other reading glasses; the remaining four trials reported data for the comparisons between various types of vision therapy (office- and home-based vision therapy/orthoptics). We present outcomes by interventions compared in the trials, and report outcomes in children and adult populations separately.

We reported difference in change scores between two arms whenever possible except for Analysis 2, where only follow-up values were available to us. Patients with more severe signs and symptoms would have higher baseline values for the CISS score and near-point of convergence, and a lower value for positive fusional vergence at near. If an intervention is effective, one would expect CISS score and near-point of convergence go from a higher value to a lower value, while positive fusional vergence at near goes from a lower to a higher value. To facilitate interpretation of the treatment effect based on a difference in change scores between two arms, change in near-point of convergence and CISS score was defined as baseline value minus follow-up value, and change in positive fusional vergence at near was defined as follow-up value minus baseline value. Using this definition, if the test intervention is more effective than the comparison intervention, all three estimates would be greater than 0.

• EFFECTIVENESS OF BASE-IN PRISM READING GLASSES

Analysis 1. Base-in prism reading glasses versus placebo reading glasses in children

One trial examined this comparison in 72 children up to age 18 ([CITT 2005a](#)). At six weeks of therapy, there was no statistically significant effect of base-in prism reading glasses compared with placebo reading glasses in children in terms of change in near point of convergence, change in positive fusional vergence, or decrease in convergence insufficiency symptoms measured by CISS. At six weeks of therapy:

- the mean difference in change in near point of convergence between the prism reading glasses and the placebo reading glasses was 2.81 cm (95% CI -1.67 to 7.29) ([Analysis 1.1](#));
- the mean difference in change in positive fusional vergence was -0.69 diopters (95% CI -3.96 to 2.58) ([Analysis 1.2](#));
- the mean difference in decrease in CISS score was -4.26 (95% CI -10.42 to 1.90) ([Analysis 1.3](#)).

Few participants in either group achieved a normal near point of convergence or positive fusional vergence at near.

Analysis 2. Base-in prism reading glasses using a progressive addition lens design versus progressive addition lens alone in adults

One trial examined this comparison ([Teitelbaum 2009](#)) in adults. This trial did not report near point of convergence or positive fusional vergence after the treatment. At three weeks of therapy, base-in prism glasses using a progressive addition lens design was found to be more effective than progressive addition lens alone in decreasing convergence insufficiency symptoms measured by CISS in adults. At three weeks of therapy:

- the difference in CISS score between the base-in prism glasses using a progressive addition lens design and progressive addition lens alone was -10.24 (95% CI -15.45 to -5.03) ([Analysis 2.1](#)). We were not able to calculate a change in CISS score from baseline between the two treatment arms because the standard deviation for the change was not reported.

• EFFECTIVENESS OF VISION THERAPY

Analysis 3. Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults

Two trials examined this comparison in children ([CITT 2005b; CITT 2008](#)). At 12 weeks of therapy, based on a meta-analysis of the two trials ([CITT 2005b; CITT 2008](#)), office-based vision therapy/orthoptics was found to be more effective than home-based pencil push-ups in terms of change in near point of convergence, positive fusional vergence at near, and convergence insufficiency symptoms measured by CISS in children. At 12 weeks of therapy:

- the mean difference in change in near point of convergence between office-based vision therapy/orthoptics and home-based pencil push-ups was 3.99 cm (95% CI 2.11 to 5.86) ([Analysis 3.1](#));
- the mean difference in change in positive fusional vergence at near was 13.13 diopters (95% CI 9.91 to 16.35) ([Analysis 3.2](#));
- the mean difference in change in CISS score was 9.86 (95% CI 6.70 to 13.02) ([Analysis 3.3](#)).

One trial examined this comparison in young adults between 19 to 30 years old ([CITT 2005c](#)). At 12 weeks of therapy, office-based vision therapy/orthoptics was found to be more effective than home-based pencil push-ups in terms of change in positive fusional vergence at near, but not more effective than home-based pencil push-ups in change in near point of convergence or patient symptoms measured by CISS in a young adult population. At 12 weeks of therapy:

- the mean difference in change in near point of convergence between office-based vision therapy/orthoptics and home-based pencil push-ups was 2.8 cm (95% CI -2.41 to 8.01) ([Analysis 3.1](#));
- the mean difference in change in positive fusional vergence at near was 7.7 diopters (95% CI 0.82 to 14.58) ([Analysis 3.2](#));
- the mean difference in change in CISS score between the two arms was 4.7 (95% CI -1.45 to 10.85) ([Analysis 3.3](#)).

Analysis 4. Office-based vision therapy/orthoptics versus home-based computer assisted vision therapy/orthoptics in children

One trial examined this comparison ([CITT 2008](#)) in children. At 12 weeks of therapy, office-based vision therapy/orthoptics was found to be more effective than home-based computer assisted vision therapy/orthoptics in terms of change in near point of convergence, positive fusional vergence, and convergence insufficiency symptoms measured by CISS in children. At 12 weeks:

- the mean difference in change in near point of convergence between office-based vision therapy and home-based vision therapy was 2.90 cm (95% CI 0.96 to 4.84) ([Analysis 4.1](#));
- the mean difference in change in positive fusional vergence at near was 7.70 diopters (95% CI 3.94 to 11.46) ([Analysis 4.2](#));
- the mean difference in change in CISS score was 8.80 (95% 5.26 to 12.34) ([Analysis 4.3](#)).

Analysis 5. Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children

One trial examined this comparison ([CITT 2008](#)) in children. At 12 weeks of therapy, there was no statistically significant effect of home-based pencil push-ups compared with home-based computer assisted vision therapy/orthoptics in terms of change in near point of convergence or patient symptoms in children. At 12 weeks:

- the mean difference in change in near point of convergence between home-based pencil push-ups and home-based vision therapy was -1.10 cm (95% CI -3.07 to 0.87) ([Analysis 5.1](#));
- the mean difference in change in CISS score was 1.10 (95% CI -2.55 to 4.75) ([Analysis 5.3](#)).

Based on the same trial ([CITT 2008](#)), home-based computer vision therapy/orthoptics was found to be more effective than home-based pencil push-ups alone in change in positive fusional vergence. At 12 weeks:

- the mean difference in change in positive fusional vergence between home-based pencil push-ups and home-based computer vision therapy/orthoptics was -4.10 diopters (95% CI -7.93 to -0.27) ([Analysis 5.2](#)) in favor of home-based computer vision therapy/orthoptics plus pencil push-ups.

Analysis 6. Home-based pencil push-ups versus office-based placebo in children

One trial examined this comparison ([CITT 2008](#)) in children. At 12 weeks of therapy, home-based pencil push-ups was found to be more effective than office-based placebo in change in near point of convergence. There was no statistically significant effect of home-based pencil push-ups compared with office-based placebo in terms of change in positive fusional vergence or patient symptoms measured by CISS. At 12 weeks:

- the mean difference in change in near point of convergence between home-based pencil push-ups and office-based placebo was 2.50 cm (95% CI 0.53 to 4.47) ([Analysis 6.1](#));
- the mean difference in change in positive fusional vergence was 1.00 diopters (95% CI -2.77 to 4.77) ([Analysis 6.2](#));
- the mean difference in change in CISS score was -0.70; (95% CI -4.32 to 2.92) ([Analysis 6.3](#)).

Analysis 7. Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children

One trial examined this comparison ([CITT 2008](#)) in children. At 12 weeks of therapy, home-based computer assisted vision therapy/orthoptics was found to be more effective than office-based placebo in change in near point of convergence and positive fusional vergence. There was no statistically significant effect of home-based computer vision therapy/orthoptics compared with office-based placebo in change in patient symptoms measured by CISS. At 12 weeks:

- the mean difference in change in near point of convergence between home-based computer vision therapy/orthoptics and office-based placebo was 3.60 cm (95% CI 1.64 to 5.56) ([Analysis 7.1](#));
- the mean difference in change in positive fusional vergence was 5.10 diopters (95% CI 1.31 to 8.89) ([Analysis 7.2](#));
- the mean difference in change in CISS score was -1.80; (95% CI -5.46 to 1.84) ([Analysis 7.3](#)).

Analysis 8. Office-based vision therapy/orthoptics versus office-based placebo in children

One trial examined this comparison ([CITT 2008](#)) in children. At 12 weeks of therapy, office-based vision therapy/orthoptics was found to be more effective than office-based placebo in change in near point of convergence, positive fusional vergence, and patient symptoms measured by CISS. At 12 weeks:

- the mean difference in change in near point of convergence between home-based computer vision therapy/orthoptics plus pencil push-ups and office-based placebo was 6.50 cm (95% CI 4.56 to 8.44) ([Analysis 8.1](#));
- the mean difference in change in positive fusional vergence was 12.80 diopters (95% CI 9.09 to 16.51) ([Analysis 8.2](#));
- the mean difference in change in CISS score was 7.00; (95% CI 3.49 to 10.51) ([Analysis 8.3](#)).

Compliance with treatment

Compliance to treatment was reported in all four of the CITT trials but in neither of the other two trials. In the base-in prism study ([CITT 2005a](#)) compliance was assessed by asking the patient “What percentage of the time did you wear the glasses we gave you while you were reading or doing near work (0%, 25%, 50%, 75%, or 100%)?” The child was also asked “How sure are you about this answer (very sure, pretty sure, somewhat sure, a little

sure, not sure at all)?” Parents were asked the same questions about their child’s wearing of the reading glasses. In the base-in prism group, 90% of patients reported wearing their glasses at least 75% of the prescribed time and 81% of parents said their child wore his or her glasses at least 75% of the prescribed time. There was agreement between child and parent on percentage of time worn for 55% of the responses. In the placebo group, 79% of patients reported wearing their glasses at least 75% of the prescribed time and 79% of parents said their child wore his or her glasses at least 75% of the prescribed time. Patient and parent agreed on the percentage of time the placebo glasses were worn 42% of the time. Reported wearing time was not statistically different between the two reading glasses groups using the patients’ ($P = 0.18$) or parents’ responses ($P = 0.24$).

In the three studies in which office- and home-based vision therapy/orthoptics were evaluated, the therapist asked the patient questions about the home-based treatment component and then answered the following question on the CITT follow-up form “What percent of the time do you feel the patient adhered to the treatment protocol?” The choices were: 0%, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99% or 100%.

In the CITT pilot study ([CITT 2005b](#)), there were no differences in the therapist’s assessment of patient compliance between the three treatment groups at any visit. After 12 weeks of treatment, the therapists estimated that 73% of patients in the office-based vision therapy/orthoptics group, 92% of patients in the placebo office-based vision therapy/orthoptics group, and 73% of the patients in the pencil push-ups group were performing their home therapy at least 75% of the time (Kruskal-Wallis $P = 0.3454$).

In the larger CITT study ([CITT 2008](#)), at 12 weeks the percentage of CITT patients rated by therapists as compliant with the home therapy protocol at least 75% of the time was 67.3% in the home-based computer therapy group, 84.9% in the pencil push-ups group, 87% in the office-based placebo group, and 91.4% in the office-based vision therapy group. Accounting for the observed differences in estimated adherence did not affect the results of the treatment group comparisons for symptom score, near point of convergence, and positive fusional vergence.

Economic data

The cost of materials and equipment is lowest for home-based pencil push-ups and estimated to be equivalent for base-in prism reading glasses, home-based computer vision therapy/orthoptics, and office-based vision therapy/orthoptics. If office visits are considered, costs are expected to be highest for office-based vision therapy/orthoptics, followed by home-based vision therapy/orthoptics and least expensive for base-in reading glasses. Although cost analysis data were not reported from any of the studies, it is possible to estimate the cost of office-based vision therapy/orthoptics, the most effective treatment option based on findings from this systematic review. The office visit fee varies from \$75 to \$100

per session across regions in the United States. Twelve sessions would, therefore, cost about \$900 to \$1200 per patient. Office-based vision therapy/orthoptics is a covered service by most insurance companies in the United States. The direct patient cost would be reduced significantly depending on insurance coverage.

Harms

No adverse effects related to study treatments were reported for any of the included studies.

DISCUSSION

Summary of main results

This systematic review aimed to identify and synthesize available RCT evidence on the effectiveness of various non-surgical treatments for symptomatic convergence insufficiency in children and adults.

Summary of main results in children

The CITT Study Group, a group of almost 100 investigators (optometrists, pediatric ophthalmologists, and orthoptists), completed four randomized clinical trials (all assessed as having low potential for bias) in recent years investigating the effectiveness of non-surgical treatments for convergence insufficiency in children. Treatments evaluated included both passive therapy (base-in prism reading glasses) and active therapy (office or home-based vision therapy/orthoptics).

In this systematic review, evidence from the CITT clinical trials suggests that office-based vision therapy/orthoptics with home reinforcement is more effective than home-based pencil push-ups and home-based computer vision therapy/orthoptics for improving both the clinical signs and symptoms of children with symptomatic convergence insufficiency. Base-in prism was found to be no more effective than placebo reading glasses for improving either clinical signs or symptoms.

The evidence also shows that home-based computer vision therapy/orthoptics was more effective than home-based pencil push-ups for improving near point of convergence and positive fusional vergence. However, home-based computer vision therapy/orthoptics was no more effective than home-based pencil push-ups for improving symptoms. In fact, neither home-based treatment option was more effective than placebo treatment for improving symptoms.

Summary of main results in adults

Data from three clinical trials were available for the adult population. However, only one of these studies ([CITT 2005c](#)) was graded at low risk of bias. The other two ([Birnbaum 1999](#); [Teitelbaum 2009](#)) were graded at high risk of bias. In [Teitelbaum 2009](#), base-in prism progressive addition lenses were more effective than placebo glasses for improving symptoms in presbyopic adults. Because the authors used a lens design that is not commercially available the ability to generalize their data is limited.

The two clinical trials of adults studied heterogeneous populations. The CITT study of adults ([CITT 2005c](#)) included young adults (19 to 30 years of age, mean age 24.4), while the [Birnbaum 1999](#) included older adults only (40 and older, mean age 63.9 years). Evidence from [CITT 2005c](#) suggests that office-based vision therapy/orthoptics with home reinforcement is more effective than home-based pencil push-ups, and office-based placebo therapy/orthoptics for improving both the clinical signs of young adults with symptomatic convergence insufficiency. There was no difference among treatment groups for reducing symptoms in these patients. The trial investigators speculated ([CITT 2005c](#)) that perhaps young adults in college or in the work force spend more time reading or on computers; and/or experience more non-visually related symptoms that mimic symptoms tested on the CISS. Evidence for this speculation exists in the higher mean scores for patients 19 to 30 years compared to those patients nine to 18 years and in the higher cut-point for an asymptomatic score on the CISS V-15.

Placebo effect

Could the improvement in the office-based vision therapy/orthoptics group be due to patient-provider interaction or the patient's belief in the effectiveness of the treatment in the absence of full masking? The placebo effect is viewed as a change in a patient's condition or symptoms attributable to the symbolic aspect of a treatment and not to any specific pharmacologic or physiologic properties ([Brody 1985](#)). Placebo response rates for a variety of medical conditions have been reported to range from 15% to 58% with an average placebo effectiveness of 35% ([Beecher 1955](#)). While this rate is similar to the effectiveness rates found in the CITT office-based placebo therapy and placebo glasses groups, it is unknown how much of the effect in these groups was from the placebo effect versus regression to the mean and/or natural history of the disease because a no-treatment control group was not included. The effect sizes for all three outcome measures were large between the office-based vision therapy/orthoptics and placebo groups. Therefore, the presence of the office-based placebo group provide strong evidence for a real treatment effect with office-based vision therapy/orthoptics.

Overall completeness and applicability of evidence

The four CITT clinical trials, graded at low risk of bias, used a consistent definition of convergence insufficiency, and consistent outcome measures. The most commonly prescribed clinical treatments were evaluated in these trials leading to high quality evidence that can be applied in clinical practice, particularly for children with symptomatic convergence insufficiency. Only one of the four CITT trials enrolled adult participants. This small trial was limited to participants aged between 19 and 30 years old (CITT 2005c). Thus, the completeness and applicability of the evidence is limited for the adult population. In addition, the length of the treatment was purposely limited to 12 weeks in the four CITT trials because of the ethical and logistical challenges of successfully following a group of symptomatic patients in a placebo group. Thus, findings from these trials do not reveal the maximum treatment effect that could be achieved with the various treatments. Finally, none of the included trials reported changes in reading, attention, quality of life, or the cost utility of the various treatments for convergence insufficiency.

Quality of the evidence

Four trials (CITT 2005a; CITT 2005b; CITT 2005c; CITT 2008), including 81.3% of participants of this review were graded at low risk of bias. Teitelbaum 2009 and Birnbaum 1999 were graded at high risk of bias because of inadequate random sequence generation and inadequate allocation concealment. In addition, Birnbaum 1999 did not define the primary and secondary outcomes.

Clinical heterogeneity was reflected in differences in the age distribution of study participants and variation in treatment methods across trials. Such clinical heterogeneity and methodological limitations made it difficult to pool the effect estimates in a meta-analysis for the adult population.

Potential biases in the review process

We took several measures to prevent potential bias in the systematic review process, including having pre-specified eligibility criteria, performing an extensive literature search, and having two review authors working independently to evaluate eligibility, assess risk of bias, and abstract data. We also contacted trial investigators for additional information.

There is a potential conflict of interest as the lead author of this review (Dr. Mitchell Scheiman) is also the Principal Investigator for the four CITT trials. Another limitation is that compliance to treatment was reported incompletely, as an *ad hoc* secondary outcome, and not assessed by any validated method.

Agreements and disagreements with other studies or reviews

Findings from our systematic review are consistent with findings from recent narrative reviews on the same topic (Cacho 2009; Scheiman 2009). There of the six trials included in our systematic review were also included in a non-Cochrane systematic review addressing a related topic (Lavrich 2010).

A U T H O R S ' C O N C L U S I O N S

Implications for practice

This systematic review provides an up-to-date summary of the best available evidence for doctors, patients, and other decision makers about the effectiveness of various non-surgical interventions for symptomatic convergence insufficiency in children and adults. Current research suggests that office-based vision therapy/orthoptics is more effective than home-based pencil push-ups or home-based computer vision therapy/orthoptics for children. Evidence is less consistent for the adult population.

Evidence from the included trials suggests that:

- Office-based vision therapy/orthoptics is more effective than either home-based pencil push-ups or home-based computer vergence/accommodative therapy in children and young adults.
- Home-based computer vergence/accommodative therapy may provide greater improvement in positive fusional vergence than home-based pencil push-ups.
- Base-in prism reading glasses are no more effective than placebo glasses in children.
- Base-in reading glasses may be an effective treatment for symptomatic convergence insufficiency in presbyopic patients.

Implications for research

This systematic review identified key gaps in research including:

- Would a longer duration of office- and home-based therapies have been effective in a higher percentage of children?
- Are certain office-based vergence/accommodative therapy procedures more effective than others in treating convergence insufficiency? Is there an office-based therapy program that would be equally as effective or perhaps even more effective but could be administered for a shorter duration?
- Would a protocol that more closely monitors and encourages adherence affect the outcome for home-based computer vergence/accommodative therapy groups?

- Are there different home-based therapy combinations (e.g., computer therapy combined with therapy procedures such as loose prism or free-space fusion cards rather than pencil push-ups) and/or a modified computer therapy program that might be more effective than the combined computerized therapy and pencil push-up approach that has been prescribed?
- Is there a better method of prescribing prism, such as based on fixation disparity testing, that might be more effective in reducing symptoms of convergence insufficiency?
- What effect does successful treatment of symptomatic convergence insufficiency have on various aspects of reading performance?
- What effect does the successful treatment of convergence

insufficiency have on behavior rating scales in children with convergence insufficiency and Attention-Deficit Hyperactivity Disorder whose behaviors are still an issue despite medical management for the latter?

- What exactly is the cost utility of each of the various treatments for convergence insufficiency?

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Birnbaum 1999

Methods	<ul style="list-style-type: none">• Study design: RCT• Number randomized: 60 (21 assigned to office-based therapy with supplemental home therapy; 20 assigned to home therapy group; and 19 assigned to control group)<ul style="list-style-type: none">• Unit of randomization: individual participant (convergence insufficiency is a binocular vision disorder)• Number analyzed: 60 (100%)• Number of centers: 1• Date of first enrolment: not reported• Length of follow-up: planned: 26 weeks after initiation of treatment; actual: varied• Sample size estimation: not reported
Participants	<ul style="list-style-type: none">• Country of recruitment: United States• Mean age: 63.9 years in the office-based therapy group, 61.1 in home therapy group, and 62.9 in control group• Sex: 100% male• Key inclusion criteria: male adults aged 40 years with symptomatic convergence insufficiency; demonstrated asthenopic symptoms; and failed at least two of the four criteria for convergence insufficiency.• Key exclusion criteria: patients with systemic neurologic disease; use of psychotropic medications that might influence vergence or accommodation; constant or noncomitant strabismus; visual acuity poorer than 20/40 in either eye, or previous vision therapy.
Interventions	<ul style="list-style-type: none">• Intervention regimen #1: office-based therapy with supplemental home therapy Patients assigned to this group were scheduled for 24 weekly 45 minute office-based therapy sessions (some patients discharged earlier, once their treatment was successfully concluded; some patients required somewhat longer treatment periods). The office therapy procedures typically used include series of eye movement procedures and binocular fusion procedures. Procedures were assigned for practice at home to supplement office therapy• Intervention regimen #2: home therapy group Patients were seen for one office visit for instruction on the home therapy procedures. The home therapy procedures include four-corner oculomotor calisthenic fixations; Brock string; eccentric circles base-in and base-out; red-green lifesaver cards, base-in and base-out; and pointer-straw• Intervention regimen #3: control group Patients were given a handout "Care of Your Eyes" (which was also given to patients in the two treatment groups). This handout provided general information on ocular health, but provided no specific information relative to convergence insufficiency
Outcomes	<ul style="list-style-type: none">• Primary outcome: not explicitly specified, might be "success" and "failure" defined by the investigators on the basis of the improvement shown with respect to the asthenopia and functional criteria• Secondary outcome: unclear

Birnbaum 1999 (Continued)

	<ul style="list-style-type: none">• No harm was reported.
Notes	<ul style="list-style-type: none">• Funding sources: none reported• Subgroup analyses: none reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported.
Allocation concealment?	Unclear	Not reported.
Blinding? Primary outcome	Unclear	Not reported.
Blinding? Secondary outcomes	Unclear	Not reported.
Incomplete outcome data addressed? Primary outcome	Yes	There was no lost to follow-up.
Incomplete outcome data addressed? Secondary outcomes	Yes	There was no lost to follow-up.
Free of selective reporting?	Unclear	No access to the protocol.
Intention-to-treat (ITT) analysis?	Yes	All participants were analyzed in the group they were assigned to

CITT 2005a

Methods	<ul style="list-style-type: none">● Study design: RCT● Number randomized: 72 (36 assigned to base-in prism reading glasses; 36 assigned to placebo reading glasses)● Unit of randomization: individual participant (convergence insufficiency is a binocular vision disorder)● Number analyzed: 65 (90%) (31 of 36 assigned to base-in prism reading glasses; 34 of 36 assigned to placebo reading glasses)● Number of centers: 9● Date of first enrollment: July 21, 2003● Length of follow-up: planned: 6 weeks after initiation of treatment; actual: 6 weeks after initiation of treatment● Sample size estimation: all sample size calculations were performed using PASS 2000 software assuming a two-sided test with $\alpha=0.05$ and $\beta=0.10$ (90% power). Preliminary data from CITT 2005b were used to obtain estimates of variability to be used in the calculations. With 32 patients per group, the study would have 90% power to find differences in the mean near point of convergence as small as 3.7 cm.
Participants	<ul style="list-style-type: none">● Country of recruitment: United States● Mean age: 11.5 ± 2.3 (SD) years in the base-in prism reading glasses group; 11.0 ± 2.0 (SD) years in the placebo reading glasses group● Sex: 63.9% were female in base-in prism reading glasses group; 47.2% were female in placebo reading glasses group● Key inclusion criteria: age 9 to 18 years; best corrected visual acuity of 20/25 or better in both eyes at distance and near; willingness to wear eyeglasses to correct refractive error, if necessary; exophoria at near at least 4 D greater than at far; insufficient positive fusional convergence at near (fails Sheard's criterion); receded near point of convergence of > 6 cm break; appreciation of at least 500 seconds of arc on the forms part of the Randot Stereotest; Convergence Insufficiency Symptom Survey-V15 score > 16; informed consent and willingness to participate in the study and be randomized.● Key exclusion criteria: convergence insufficiency previously treated with prism, pencil push ups, or office based vision therapy/orthoptics (no more than 2 months of treatment within the past year); amblyopia; constant strabismus; history of strabismus surgery; anisometropia > 1.50 D (spherical equivalent) difference between eyes; previous refractive surgery; vertical heterophoria greater than 1 D; systemic diseases known to affect accommodation, vergence, and ocular motility such as multiple sclerosis, Grave's thyroid disease, myasthenia gravis, diabetes, and Parkinsons disease; any ocular or systemic medication known to affect accommodation or vergence; monocular accommodative amplitude less than 4 D in either eye as measured by the push up method; manifest or latent nystagmus; attention deficit hyperactivity disorder or learning disability diagnosis by parental report that, in the investigator's opinion, would interfere with treatment.
Interventions	<ul style="list-style-type: none">● Intervention regimen #1: base-in prism reading glasses <p>Patients in this group received glasses that corrected for the patient's refractive error, if necessary, and base-in prism. The amount of prism was based on the minimum amount necessary to meet Sheard's criterion with no less than 1 D prescribed. To determine the amount of prism necessary to achieve this relationship he proposed the following formula: prism to be prescribed = $2/3$ phoria - $1/3$ compensating fusional vergence. The amount of prism was rounded up to the nearest half prism diopter and split equally</p>

CITT 2005a (Continued)

	<p>between the two eyes if the magnitude exceeded 1 D. The patient was asked to wear these glasses for all reading and near tasks requiring more than 5 minutes</p> <ul style="list-style-type: none"> • Intervention regimen #2: placebo reading glasses <p>Patients in this group received glasses that corrected their refractive error, or plano lenses were prescribed for those who did not require a refractive correction. The patient was asked to wear these glasses for all reading and near tasks requiring more than 5 minutes</p>
Outcomes	<ul style="list-style-type: none"> • Primary outcome: convergence insufficiency symptoms measured using Convergence Insufficiency Symptom Survey V-15 after 6 weeks of therapy. • Key secondary outcomes: near point of convergence, and positive fusional vergence at near at 6 weeks of therapy. • No harm was reported.
Notes	<ul style="list-style-type: none"> • Funding sources: grants from the Pennsylvania and Ohio Lions. • Subgroup analyses: none reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"The data coordinating centre randomly assigned eligible patients with equal probability to either base-in prism reading glasses or placebo reading glasses. Randomization was accomplished with the study's web site using a permuted block design stratified by site."
Allocation concealment?	Yes	"Allocation to treatment group was achieved using a secure web site. Researchers entered eligibility data and were then given the group membership information (personal communication with the lead investigator)"
Blinding? Primary outcome	Yes	"Neither the patient nor the examiner performing testing at the outcome examination was aware of the treatment assignment. To prevent potential examiner unmasking by observation of the glasses, the study coordinator placed Tac 'N Stik reusable adhesive around the edges of the eyeglasses. The edges of the lenses were therefore obscured, making it impossible for the examiner to see the edge thickness of the lenses."
Blinding? Secondary outcomes	Yes	See above.

CITT 2005a (*Continued*)

Incomplete outcome data addressed? Primary outcome	Unclear	<p>“Thirty one of the 36 patients (86%) assigned to receive base-in prism reading glasses and 34 of the 36 (94%) assigned to placebo reading glasses completed their 6 week outcome examination. There was no statistically significant difference in the percentage loss to follow up between the two treatment groups ($p=0.43$).”</p> <p>“Statistical analyses techniques were employed which allowed for incomplete data. No imputation or sensitivity analyses were performed (personal communication with the lead investigator)”</p>
Incomplete outcome data addressed? Secondary outcomes	Unclear	See above.
Free of selective reporting?	Yes	All outcomes listed in the study protocol were reported.
Intention-to-treat (ITT) analysis?	Yes	Not reported in the article. The lead investigator described through personal communication “All subjects were analyzed in the group to which they were randomized. There were no subjects switch groups.”

CITT 2005b

Methods	<ul style="list-style-type: none">● Study design: RCT● Number randomized: 47 (15 assigned to pencil push-ups; 17 assigned to vision therapy/orthoptics; 15 assigned to placebo vision therapy/orthoptics)● Unit of randomization: individual participant (convergence insufficiency is a binocular vision disorder)● Number analyzed: 38 (81%) (11 of 15 assigned to pencil push-ups; 15 of 17 assigned to vision therapy/orthoptics; 12 of 15 assigned to placebo vision therapy/orthoptics)● Number of centers: 6● Date of first enrolment: October 2000● Length of follow-up: planned: 12 weeks after initiation of treatment; actual: 12 weeks after initiation of treatment● Sample size estimation: no formal sample size calculations were performed <i>a priori</i> because one goal of this pilot trial was to estimate the variability of the outcome measure. At the study completion, using the observed variability in the Convergence Insufficiency Symptom Survey, with $\alpha=0.05$, assuming a 2-sided test, and assuming the post treatment mean of the most effective treatment group would approximate the mean among patients with normal binocular vision, the mean for the placebo group would decrease 20% from its baseline value, and the mean for the other treatment group would fall in the middle of these two groups, the sample size of 47 yields a power of 92.8%.
Participants	<ul style="list-style-type: none">● Country of recruitment: United States● Mean age: 11.2 ± 2.2 (SD) years● Sex: 57% were female● Key inclusion criteria: ages 9 to 18 years inclusive; best-corrected visual acuity of 20/25 OU at distance and near; willingness to wear eyeglasses or contact lenses to correct refractive error, if necessary; exophoria at near at least 4Δ greater than at far; insufficient positive fusional convergence (i.e., failing Sheard's criterion or $< 15\Delta$ break on positive fusional vergence testing using a prism bar); receded near point of convergence of greater than or equal to 6 cm break; appreciation of at least 500s of arc on the forms part of the Randot Stereotest; Convergence Insufficiency Symptom Survey-V13 (original 13-item version) score > 9; informed consent and willingness to participate in the study and be randomized.● Key exclusion criteria: convergence insufficiency previously treated with pencil push-ups (no more than 2 mo of treatment within the past year); convergence insufficiency previously treated with office-based vision therapy/orthoptics (no more than 2 mo of treatment within the past year); amblyopia; constant strabismus; history of strabismus surgery; anisometropia $> 1.50\text{-D}$ difference between eyes; prior refractive surgery; vertical heterophoria $> 1\Delta$; systemic diseases known to affect accommodation, vergence, and ocular motility, such as multiple sclerosis, Graves thyroid disease, myasthenia gravis, diabetes, and Parkinson disease; any ocular or systemic medication known to affect accommodation or vergence; monocular accommodative amplitude $< 4\text{ D}$ in either eye as measured by the Donder push-up method; manifest or latent nystagmus; attention-deficit/hyperactivity disorder or learning disability diagnosis by parental report; household member or sibling already enrolled in the CITT; any eye care professional, technician, medical student, or optometry student.

Interventions	<ul style="list-style-type: none">● Intervention regimen #1: pencil push-ups Patients in the pencil push-ups group were taught a pencil push-up procedure that included monitoring for suppression. Patients were instructed to hold a pencil at arm's length directly between their eyes, and an index card, serving as a suppression control, was placed on the wall 6 to 8 feet away. Patients were instructed to look at the very tip of the sharpened pencil and to try and keep the pencil point single while moving it toward their nose. If one of the cards in the background disappeared, patients were instructed to stop moving the pencil and blink their eyes until both cards were present. Patients were told to continue moving the pencil slowly toward their nose until it could no longer be kept single and then to try and get the pencil point back into one. If patients were able to regain single vision, they were asked to continue moving the pencil closer to their nose. If patients could not get the pencil back to one, they were instructed to start the procedure again. Patients were instructed to do three sets of 20 pencil push-ups per day at home, 5 days per week for 12 weeks, and this treatment required an average of 15 minutes per day. Prior to doing the procedure at home, children had to demonstrate their understanding and ability to perform the procedure according to protocol● Intervention regimen #2: office-based vision therapy/orthoptics The vision therapy/orthoptics group received therapy administered by a trained therapist during a weekly, 60-minute office visit, with additional procedures to be performed at home for 15 minutes a day, five times per week for 12 weeks. The items are listed in the article. In addition, treatment procedures were practiced at home. During a typical office-based treatment session, the patient practiced four to five procedures with constant supervision and guidance from the therapist. There were no diagnostic tests performed during these sessions. The therapist followed a very detailed and specific CITT protocol from the manual of procedures, which described the proper treatment technique, amount of time the technique was to be used, expected performance, and criteria for ending the procedure and advancing to a more difficult level● Intervention regimen #3: placebo office-based vision therapy/orthoptics Like the vision therapy/orthoptics group, the placebo vision therapy/orthoptics group received therapy administered by a trained therapist during a 60-minute office visit and was prescribed procedures to be performed at home for 15 minutes, five times per week for 12 weeks. The procedures for placebo vision therapy/orthoptics were designed to simulate real vision therapy/orthoptics procedures without the expectation of affecting vergence, accommodation, or saccadic function
Outcomes	<ul style="list-style-type: none">● Primary outcome: convergence insufficiency symptoms measured using Convergence Insufficiency Symptom Survey V-15 after 12 weeks of therapy. A symptom score of 16 or higher differentiated children with symptomatic convergence insufficiency from those with normal binocular vision (sensitivity = 95.7%; specificity = 85.7%). The primary outcome was also measured at 4 and 8 weeks of therapy.● Key secondary outcomes: near point of convergence measured with the Astron International Accommodative Rule; positive fusional vergence at near measurements: measured with a horizontal prism bar while the patient viewed a 20/30-size column of letters held at 40cm. The secondary outcomes were measured at 4, 8 and 12 weeks of therapy.● No harms were reported.

CITT 2005b (Continued)

Notes	<ul style="list-style-type: none"> • Funding sources: National Eye Institute, National Institutes of Health, Bethesda, MD USA. • Subgroup analyses: none reported 	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"The data-coordinating center for the study, randomly assigned eligible patients with equal probability to either pencil push-ups, vision therapy/orthoptics, or placebo vision therapy/orthoptics. Randomization was accomplished with the study's Web site using blocks of 6 so that the investigator could not predict the sequence of treatment assignments. To ensure approximately equal numbers of patients in each treatment arm, randomization was performed separately for each site."
Allocation concealment?	Yes	See above.
Blinding? Primary outcome	Yes	"At these follow-up visits, an examiner who was masked to the patient's treatment group administered the Convergence Insufficiency Symptom Survey V-15, the cover test, and near point of convergence and positive fusional vergence at near measurements."
Blinding? Secondary outcomes	Yes	See above.
Incomplete outcome data addressed? Primary outcome	Unclear	<p>"The completion rate was not related to treatment assignment ($p = .59$). Of the nine patients not completing the primary outcome examination, four were lost to follow-up, two parents decided after randomization that they preferred to have their children treated outside of the study, and three did not complete the outcome examination within the visit window."</p> <p>"There were no statistically significant or clinically relevant differences in demographic or clinical measures at eligibility found between these patients and those</p>

CITT 2005b (Continued)

		who completed the study within the treatment window.” “Statistical analyses techniques were employed which allowed for incomplete data. No imputation or sensitivity analyses were performed (personal communication with the lead investigator)”
Incomplete outcome data addressed? Secondary outcomes	Unclear	See above.
Free of selective reporting?	Yes	All outcomes listed in the study protocol were reported.
Intention-to-treat (ITT) analysis?	Yes	Not reported in the article. The lead investigator described through personal communication “all participants were analyzed in the group to which they were randomized. No participants switched groups.”

CITT 2005c

Methods	<ul style="list-style-type: none"> ● Study design: RCT ● Number randomized: 46 (17 assigned to pencil push-ups; 15 assigned to vision therapy/orthoptics; 14 assigned to placebo vision therapy/orthoptics) ● Unit of randomization: individual participant (convergence insufficiency is a binocular vision disorder) ● Number analyzed: 40 (87%) (15 of 17 assigned to pencil push-ups; 12 of 15 assigned to vision therapy/orthoptics; 13 of 14 assigned to placebo vision therapy/orthoptics) ● Number of centers: 6 ● Date of first enrolment: November 2000 ● Length of follow-up: planned: 12 weeks after initiation of treatment; actual: 12±2 weeks after initiation of treatment ● Sample size estimation: no formal sample size calculations were performed <i>a priori</i> because one goal of this pilot trial was to estimate the variability of the outcome measure. At the study completion, using the observed variability in the Convergence Insufficiency Symptom Survey, with $\alpha=0.05$, assuming a 2-sided test, and assuming the post treatment mean of the most effective treatment group would approximate the mean among patients with normal binocular vision at 12 weeks, the mean for the placebo group would decrease 20% from its baseline value, and the mean for the other treatment group would fall in the middle of these two groups, the sample size of 46 yields a power of 99.6%.
Participants	<ul style="list-style-type: none"> ● Country of recruitment: United States ● Mean age: 24.4 ± 3.4 (SD) years in the pencil push-ups group; 23.7 ± 3.9 (SD) years in the vision therapy/orthoptics group; 25.1 ± 3.5 (SD) years in the placebo vision therapy/orthoptics group

	<ul style="list-style-type: none">● Sex: 70.6% were female in the pencil push-ups group; 73.3% were female in the vision therapy/orthoptics group; 71.4% were female in the placebo vision therapy/orthoptics group● Key inclusion criteria: age 19 to 30 years; best corrected visual acuity of 20/25 or better in both eyes at distance and near; willingness to wear eyeglasses or contact lenses to correct refractive error, if necessary; exophoria at near at least 4 D greater than at far; insufficient positive fusional convergence at near (i.e., failing Sheard's criterion 21 or less than 15 break); receded near point of convergence of ≥ 6 cm break; appreciation of at least 500 seconds of arc on the forms part of the Randot Stereotest; Convergence Insufficiency Symptom Survey V-13 score > 9; informed consent and willingness to participate in the study and be randomized.● Key exclusion criteria: convergence insufficiency previously treated with pencil push ups, or office-based vision therapy/orthoptics (no more than 2 months of treatment within the past year); amblyopia; constant strabismus; history of strabismus surgery; anisometropia > 1.50 D (spherical equivalent) difference between eyes; prior refractive surgery; vertical heterophoria greater than 1 D; systemic diseases known to affect accommodation, vergence, and ocular motility such as multiple sclerosis, Grave's thyroid disease, myasthenia gravis, diabetes, and Parkinsons disease; any ocular or systemic medication known to affect accommodation or vergence; monocular accommodative amplitude less than 4 D in either eye as measured by the push up method; manifest or latent nystagmus; household member already enrolled in the CITT; any eye care professional, ophthalmic technician, medical student, or optometry student.
Interventions	<ul style="list-style-type: none">● Intervention regimen #1: pencil push-ups <p>Patients in the pencil push-ups group were taught a pencil push-up procedure that included monitoring for suppression. Patients were instructed to hold a pencil at arm's length directly between their eyes, and an index card, serving as a suppression control, was placed on the wall 6 to 8 feet away. Patients were instructed to look at the very tip of the sharpened pencil and to try and keep the pencil point single while moving it toward their nose. If one of the cards in the background disappeared, patients were instructed to stop moving the pencil and blink their eyes until both cards were present. Patients were told to continue moving the pencil slowly toward their nose until it could no longer be kept single and then to try and get the pencil point back into one. If patients were able to regain single vision, they were asked to continue moving the pencil closer to their nose. If patients could not get the pencil back to one, they were instructed to start the procedure again. Patients were instructed to do three sets of 20 pencil push-ups per day at home, 5 days per week for 12 weeks, and this treatment required an average of 15 minutes per day. Prior to doing the procedure at home, the patient had to demonstrate their understanding and ability to perform the procedure according to protocol</p> <ul style="list-style-type: none">● Intervention regimen #2: office-based vision therapy/orthoptics <p>The vision therapy/orthoptics group received therapy administered by a trained therapist during a weekly, 60-minute office visit, with additional procedures to be performed at home for 15 minutes a day, five times per week for 12 weeks. The items are listed elsewhere. In addition, treatment procedures were practiced at home. During a typical office-based treatment session, the patient practiced four to five procedures with constant supervision and guidance from the therapist. There were no diagnostic tests performed during these sessions. The therapist followed a very detailed and specific CITT protocol from the manual of procedures, which described the proper treatment technique, amount</p>

CITT 2005c (Continued)

	<p>of time the technique was to be used, expected performance, and criteria for ending the procedure and advancing to a more difficult level</p> <ul style="list-style-type: none"> • Intervention regimen #3: placebo office-based vision therapy/orthoptics <p>Like the vision therapy/orthoptics group, the placebo vision therapy/orthoptics group received therapy administered by a trained therapist during a 60-minute office visit and was prescribed procedures to be performed at home for 15 minutes, five times per week for 12 weeks. The procedures for placebo vision therapy/orthoptics were designed to simulate real vision therapy/orthoptics procedures without the expectation of affecting vergence, accommodation, or saccadic function</p>	
Outcomes	<ul style="list-style-type: none"> • Primary outcome: convergence insufficiency symptoms measured using Convergence Insufficiency Symptom Survey V-15 after 12 weeks of therapy. The primary outcome was also measured at baseline, 4 and 8 weeks of therapy. • Key secondary outcomes: near point of convergence, and positive fusional vergence at near. The secondary outcomes were measured at baseline, 4, 8 and 12 weeks of therapy. • No harms were reported. 	
Notes	<ul style="list-style-type: none"> • Funding sources: Grant EY13164-01, National Eye Institute, National Institutes of Health, Bethesda, MD USA. • Subgroup analyses: none reported 	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"The data-coordinating center for the study, randomly assigned eligible patients with equal probability to either pencil push-ups, vision therapy/orthoptics, or placebo vision therapy/orthoptics. Randomization was accomplished with the study's Web site using blocks of 6 so that the investigator could not predict the sequence of treatment assignments. To ensure approximately equal numbers of patients in each treatment arm, randomization was performed separately for each site."
Allocation concealment?	Yes	See above.
Blinding? Primary outcome	Yes	"Examiners were masked to the treatment assignment (personal communication with the lead investigator)."
Blinding? Secondary outcomes	Yes	See above.

CITT 2005c (*Continued*)

Incomplete outcome data addressed? Primary outcome	Unclear	"All results are reported for only those patients with data at the 12-week visit. Further analyses were performed after imputing outcome values for those patients lost to follow-up. That is, the value at the last available examination was used for each patient who did not complete the study. For 5/6 patients, the only data available were collected at the eligibility visit. When difference in statistical analyses were found, the results from analyses with imputed data are also reported."
Incomplete outcome data addressed? Secondary outcomes	Unclear	See above.
Free of selective reporting?	Yes	All outcomes listed in the study protocol were reported.
Intention-to-treat (ITT) analysis?	Yes	Not reported in the article. The lead investigator described through personal communication "All participants were analyzed in the group to which they were randomized. No participants switched groups."

Methods	<ul style="list-style-type: none"> • Study design: RCT • Number randomized: 221 (54 assigned to home-based pencil push-ups (HBPP); 53 assigned to home-based computer vergence/accommodative therapy and pencil push-ups (HBCVAT+); 60 assigned to office-based vergence/accommodative therapy with home reinforcement (OBVAT); 54 assigned to office-based placebo therapy with home reinforcement (OBPT)) • Unit of randomization: individual participant (convergence insufficiency is a binocular vision disorder) • Number analyzed: 219 (99%) (53 of 54 assigned to HBPP; 52 of 53 assigned HBCVAT+; 59 of 60 assigned to OBVAT; 54 of 54 assigned to OBPT) • Number of centers: 9 • Date of first enrolment: July 2005 • Length of follow-up: planned: 1 year after initiation of treatment; actual: this article reported outcomes at 12 weeks after initiation of treatment • Sample size estimation: all sample size calculations were performed using PASS 2000 software³⁵ and assuming a 2-sided test with 90% power. For a given outcome measure, the common standard deviation (SD) obtained from the CITT pilot study was used as an estimate of variability. To control for multiple comparisons (4 groups, with 2 compared at a time [6 pair-wise comparisons]), the α level used for determining sample size was set at 0.0083 (0.05/6). The sample size of 52 children per group was based on the required sample size for the 3 outcome variables and adjusted for a 10% loss to follow-up.
Participants	<ul style="list-style-type: none"> • Country of recruitment: United States • Mean age: 11.9 ± 2.2 (SD) years in the HBPP group; 11.6 ± 2.3 (SD) years in the HBCVAT+ group; 12.0 ± 2.6 (SD) years in the OBVAT group; 11.8 ± 2.2 (SD) years in the OBPT group • Sex: 27% were female in the HBPP group; 31% were female in the HBCVAT+ group; 41% were female in the OBVAT group; 32% were female in the OBPT group • Key inclusion criteria: aged 9 to 17 years; exodeviation at near of at least 4 prism diopters greater than at far; receded near point of convergence (NPC) break (≥ 6 cm); insufficient positive fusional vergence at near (PFV) (i.e., failing Sheard's criterion; Convergence Insufficiency Symptom Survey score of 16 or greater; best-corrected visual acuity of 20/25 or better in both eyes at distance and near; willingness to wear eyeglasses or contact lenses to correct refractive error, if necessary; exodeviation at near at least 4Δ greater than at far; insufficient positive fusional convergence; receded near point of convergence of ≥ 6 cm break; appreciation of at least 500 seconds of arc on the forms part of the Randot Stereotest; Convergence Insufficiency Symptom Survey score ≥ 16. • Key exclusion criteria: convergence insufficiency previously treated with pencil push-up therapy (> 2 wks of treatment), home- or office-based vergence/accommodative therapy/orthoptics; amblyopia; constant strabismus; history of strabismus surgery; high refractive error; prior refractive surgery; vertical heterophoria $>1\Delta$; systemic diseases known to affect accommodation, vergence and ocular motility; accommodative amplitude < 5 D in either eye as measured by the Donders' push-up method Manifest or latent nystagmus; developmental disability, mental retardation, attention-deficit/hyperactivity disorder, or a learning disability; family or household member or sibling already enrolled in the CITT; family or household member of an eye care professional, ophthalmic technician, ophthalmology or optometry resident, or optometry student; convergence insufficiency secondary to acquired brain injury or any other neurological disorder.

Interventions	<ul style="list-style-type: none">● Intervention regimen #1: home-based pencil push-ups The pencil push-ups procedure involved using a pencil with 20/60 reduced Snellen letters and a white index card placed in the background to provide a suppression check by using physiological diplopia awareness. The goal of the procedure was to move the pencil to within 2 to 3 cm of the brow, just above the nose on each push-up while trying to keep the target single and clear. Patients were instructed to perform the pencil push-ups procedure 15 minutes per day, 5 days per week. They maintained home therapy logs, recording the closest distance that they could maintain fusion after each 5 minutes of therapy● Intervention regimen #2: home-based computer vergence/accommodative therapy and pencil push-ups Patients in this group were taught to perform the pencil push-up procedure as well as procedures on the Home Therapy System/Computerized Vergence System (HTS/CVS) computer software system (Computer Orthoptics, Gold Canyon, Arizona). Using this program, they performed fusional vergence and accommodative therapy procedures, including vergence base-in, vergence base out, autoslide vergence, and jump ductions vergence programs using random-dot stereopsis targets. The accommodative rock program was used for accommodative therapy. Much like a clinician would do at each follow-up visit, this computer program automatically modified the therapy program after each session based on the patient's performance. Patients were instructed to do pencil push-ups 5 minutes per day, 5 days per week, and the HTS software program for 15 minutes per day, 5 days per week, and to save their data on a disk provided by the study and to bring the disk to each follow-up visit● Intervention regimen #3: office-based vergence/accommodative therapy with home reinforcement The OBVAT group received a weekly 60-minute in-office therapy visit with additional prescribed procedures to be performed at home for 15 minutes a day, 5 days per week. The therapy procedures are described in detail elsewhere (CITT 2008). At each office-based therapy session, the patient performed 4 to 5 procedures with constant supervision and guidance from the therapist. There were no diagnostic tests performed during these sessions. The therapist followed a detailed and specific protocol from the CITT manual of procedures (http://optometry.osu.edu/research/CITT/4363.cfm); this document describes each procedure, amount of time procedure was performed, expected performance, and criteria for ending the procedure and advancing to a more difficult level● Intervention regimen #4: office-based placebo therapy with home reinforcement Patients in the OBPT group received therapy during a weekly 60-minute office visit and were prescribed procedures to be performed at home for 15 minutes per day, 5 days per week. The placebo therapy program consisted of 16 in-office therapy procedures and 4 home therapy procedures, which were designed to look like real vergence/accommodative therapy procedures yet not to stimulate vergence, accommodation, or fine saccadic eye movement skills beyond normal daily visual activities. The therapist followed a detailed protocol from the CITT manual of procedures. Five procedures were performed during each office therapy visit and 2 procedures were assigned for home therapy each week. Objectives and goals were established for each placebo procedure to simulate real therapy. For motivational purposes, the therapist told the patient the objective of each procedure before beginning the technique
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CITT 2008 (Continued)

Outcomes	<ul style="list-style-type: none"> Primary outcome: convergence insufficiency symptoms measured using Convergence Insufficiency Symptom Survey V-15 after 12 weeks of therapy. The CI symptoms was also measured at baseline, 4 and 8 weeks of therapy. Key secondary outcomes: near point of convergence, and positive fusional vergence at near. The secondary outcomes were measured at baseline, 4, 8 and 12 weeks of therapy. Harms were reported.
Notes	<ul style="list-style-type: none"> Funding sources: National Eye Institute, National Institutes of Health, Bethesda, MD USA. Subgroup analyses: none reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was achieved using a secure web site created and managed by the data coordinating center. The web site generated the patient's group assignment and assigned the patient a unique study identification number using a pre-determined list generated by the data coordinating center. The randomization algorithm assigned patients to the four treatment groups with equal probability using a randomized permuted block design so investigators could not predict the sequence of treatment assignments. To ensure approximately equal numbers of patients in each treatment arm, randomization was performed separately for each clinical site
Allocation concealment?	Yes	Access to the list was limited to the programmer and principal investigator of the data coordinating center (personal communication with the lead investigator)
Blinding? Primary outcome	Yes	The examiners responsible for obtaining the outcome measures were masked to patient treatment assignment. None of the examiners felt that they could identify the patients' group assignment at the 4 or 8 week masked examinations, and only one examiner felt that he could identify the group assignment at outcome. One third of the examiners responded that their patient was assigned to the OBVAT group,

CITT 2008 (Continued)

		24% responded that he/she was assigned to HBCVAT+, 21% said their patient was assigned to HBPP, and 21% said their patient was assigned to the OBPT group. Examiners, when asked to guess, were correct in identifying the patient's group assignment only 34% of the time, which is less than is expected by chance. There was low agreement between the actual group assignment and the examiner's guess of assigned treatment group (0.11, 95% confidence interval, 0.04 to 0.20)
Blinding? Secondary outcomes	Yes	See above.
Incomplete outcome data addressed? Primary outcome	Unclear	"Statistical analyses techniques were employed which allowed for incomplete data. No imputation or sensitivity analyses were performed (personal communication with the lead investigator)"
Incomplete outcome data addressed? Secondary outcomes	Unclear	See above.
Free of selective reporting?	Yes	All outcomes listed in the study protocol were reported.
Intention-to-treat (ITT) analysis?	Yes	All participants were analyzed in the group to which they were randomized

Teitelbaum 2009

Methods	<ul style="list-style-type: none"> ● Study design: RCT with cross-over design ● Number randomized: 29 ● Unit of randomization: individual participant (convergence insufficiency is a binocular vision disorder) ● Number analyzed: 29 ● Number of centers: 1 ● Date of first enrolment: not reported ● Length of follow-up: 3 weeks after initiation of each treatment (total study period was 6 weeks) ● Sample size estimation: estimated <i>post hoc</i> using data from the first 18 participants. "A sample size of 21 would be required to give 80% power at the 0.05 level, and 28 subjects are needed to given the 90% power."
Participants	<ul style="list-style-type: none"> ● Country of recruitment: United States ● Mean age: 54.14 ± 2.2 (SD) years

Teitelbaum 2009 (Continued)

	<ul style="list-style-type: none">• Sex: 86% female• Key inclusion criteria: age \geq 45 years; best-corrected visual acuity of 20/25 or better in each eye at distance and near; currently wearing progressive addition lenses; a minimum of 1.50 add in subjects' habitual prescription; a minimum of 2 hours spent on reading or close work on a daily basis; associated phoria at near $\geq 1\Delta$ BI; no associated phoria with the potential BI prism at distance; exophoria at near at least 4Δ greater than at distance; Convergence Insufficiency Symptom Score ≥ 16; willingness to participate in the study and wear two pairs of eyeglasses consecutively.• Key exclusion criteria: constant strabismus at distance or at near; convergence insufficiency previously treated with prism; vertical heterophoria greater than 1Δ.	
Interventions	<ul style="list-style-type: none">• Intervention regimen #1: base-prism, using a novel progressive addition lens design which incorporates base-in prism in the near portion only• Intervention regimen #2: progressive addition lenses	
Outcomes	<ul style="list-style-type: none">• Primary outcome: convergence insufficiency symptoms measured using Convergence Insufficiency Symptom Survey V-15 after 3 weeks of therapy.• Key secondary outcomes: not reported• No harms were reported.	
Notes	<ul style="list-style-type: none">• Funding sources: Signet Armorlite funded the study and provided the spectacle lenses.• Subgroup analyses: none reported	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Patients were assigned two pairs of progressive addition lenses (PAL) fabricated by Signet Armorlite with an updated lens prescription, in a randomized sequence."
Allocation concealment?	Unclear	Not reported.
Blinding? Primary outcome	Yes	"The study had a double-blind design as neither the examiner nor subject was aware of the glasses assignment."
Blinding? Secondary outcomes	Yes	See above.
Incomplete outcome data addressed? Primary outcome	Unclear	Unclear how many participants were analyzed for the primary outcome
Incomplete outcome data addressed? Secondary outcomes	Unclear	Not reported.

Teitelbaum 2009 (*Continued*)

Free of selective reporting?	Unclear	Insufficient information to assess.
Intention-to-treat (ITT) analysis?	Unclear	Insufficient information to assess.

CITT: Convergence Insufficiency Treatment Trial

HBPP: Home-based pencil push-ups

HBCVAT+: Home-based computer vergence/accommodative therapy and pencil push-ups

OBVAT: Office-based vergence/accommodative therapy with home reinforcement

OBPT: Office-based placebo therapy with home reinforcement

RCT: Randomized controlled trial

SD: Standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al-Qurainy 1995	Not in patients with convergence insufficiency
Daum 1986	Not a RCT
Daum 1987	Not in patients with convergence insufficiency
Dragomir 2001	Not a RCT
Frantz 1993	Not a RCT
Gall 1998	Not a RCT
Gallaway 2002	Not a RCT
Granet 2005	Not a RCT
Grisham 1996	Unclear how many patients were affected by convergence insufficiency
Harele 2006	Not a RCT
Kerkhoff 1994	Not a RCT
Kommerell 2002	Not a RCT
Ludlam 1988	Not in patients with convergence insufficiency
O'Leary 2006	Not a RCT

(Continued)

Rawstron 2005	Not a RCT
Rutstein 1988	Not in patients with convergence insufficiency
Stavis 2002	Not a RCT
Worrell 1971	Not a RCT

RCT: Randomized controlled trial

DATA AND ANALYSES

Comparison 1. Base-in prism reading glasses versus placebo reading glasses in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in near point of convergence at 6 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Change in positive fusional vergence at near at 6 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Change in Convergence Insufficiency Symptom Survey (CISS) score at 6 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Base-in prism reading glasses using a progressive addition lens design versus progressive addition lens alone in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Convergence Insufficiency Symptom Survey (CISS) score at 3 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in near point of convergence at 12 weeks of therapy	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Children	2	138	Mean Difference (IV, Fixed, 95% CI)	3.99 [2.11, 5.86]
1.2 Young adults	1	27	Mean Difference (IV, Fixed, 95% CI)	2.8 [-2.41, 8.01]
2 Change in positive fusional vergence at near at 12 weeks of therapy	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Children	2	138	Mean Difference (IV, Fixed, 95% CI)	13.13 [9.91, 16.35]
2.2 Young adults	1	27	Mean Difference (IV, Fixed, 95% CI)	7.70 [0.82, 14.58]

3 Change in Convergence Insufficiency Symptom (CISS) score	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Children	2	138	Mean Difference (IV, Fixed, 95% CI)	9.86 [6.70, 13.02]
3.2 Young adults	1	27	Mean Difference (IV, Fixed, 95% CI)	4.70 [-1.45, 10.85]

Comparison 4. Office-based vision therapy/orthoptics versus home-based computer assisted pencil push-ups in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in near point of convergence at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Change in positive fusional vergence at near at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Change in Convergence Insufficiency Symptom (CISS) score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 5. Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in near point of convergence at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Change in positive fusional vergence at near at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Change in Convergence Insufficiency Symptom (CISS) score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 6. Home-based pencil push-ups versus office-based placebo in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in near point of convergence at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Change in positive fusional vergence at near at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Change in Convergence Insufficiency Symptom (CISS) score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 7. Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in near point of convergence at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Change in positive fusional vergence at near at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Change in Convergence Insufficiency Symptom (CISS) score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 8. Vision therapy/orthoptics versus office-based placebo in children

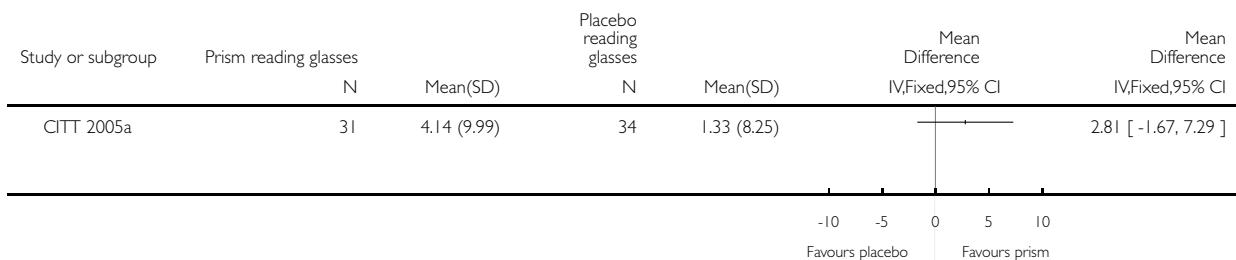
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in near point of convergence at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Change in positive fusional vergence at near at 12 weeks of therapy	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Change in Convergence Insufficiency Symptom (CISS) score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis I.1. Comparison I Base-in prism reading glasses versus placebo reading glasses in children, Outcome I Change in near point of convergence at 6 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: I Base-in prism reading glasses versus placebo reading glasses in children

Outcome: I Change in near point of convergence at 6 weeks of therapy



Analysis I.2. Comparison I Base-in prism reading glasses versus placebo reading glasses in children, Outcome 2 Change in positive fusional vergence at near at 6 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: I Base-in prism reading glasses versus placebo reading glasses in children

Outcome: 2 Change in positive fusional vergence at near at 6 weeks of therapy



Analysis 1.3. Comparison I Base-in prism reading glasses versus placebo reading glasses in children, Outcome 3 Change in Convergence Insufficiency Symptom Survey (CISS) score at 6 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 1 Base-in prism reading glasses versus placebo reading glasses in children

Outcome: 3 Change in Convergence Insufficiency Symptom Survey (CISS) score at 6 weeks of therapy

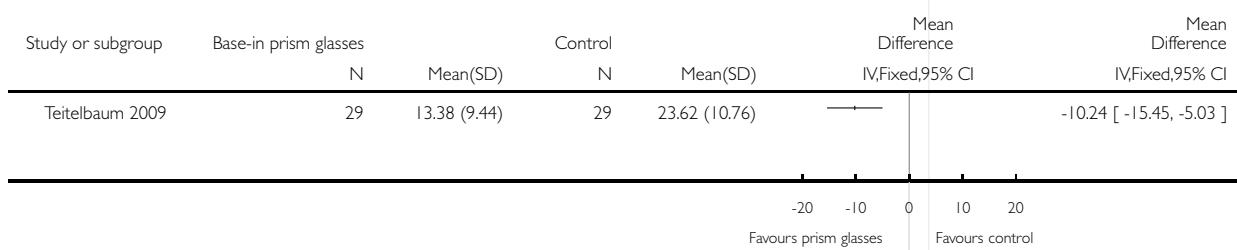


Analysis 2.1. Comparison 2 Base-in prism reading glasses using a progressive addition lens design versus progressive addition lens alone in adults, Outcome 1 Convergence Insufficiency Symptom Survey (CISS) score at 3 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 2 Base-in prism reading glasses using a progressive addition lens design versus progressive addition lens alone in adults

Outcome: 1 Convergence Insufficiency Symptom Survey (CISS) score at 3 weeks of therapy

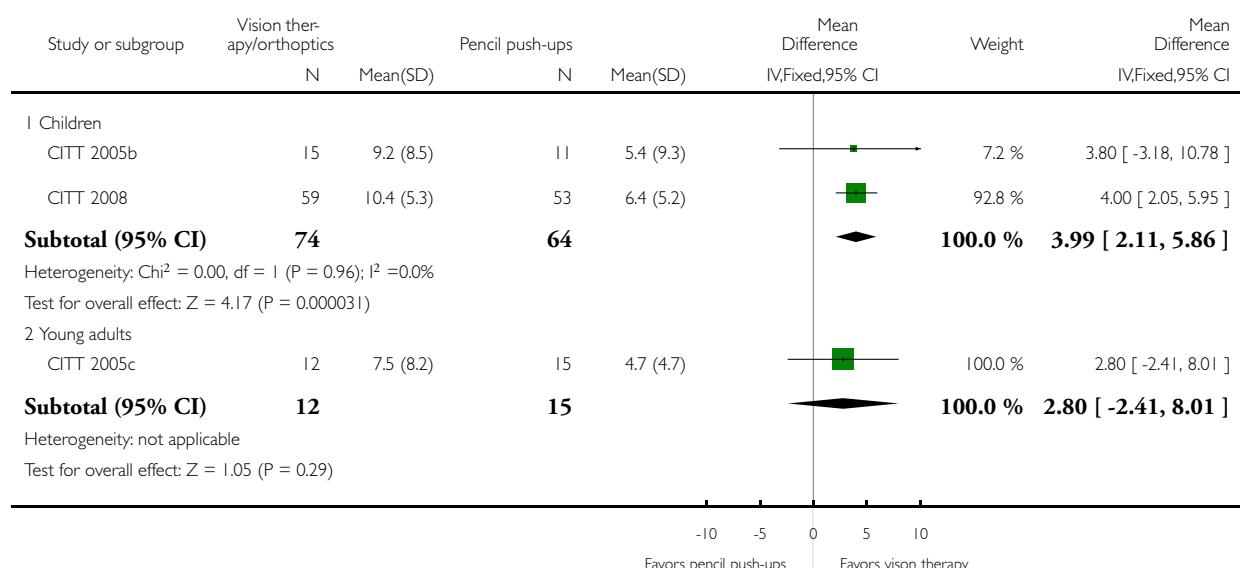


Analysis 3.1. Comparison 3 Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults, Outcome I Change in near point of convergence at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 3 Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults

Outcome: I Change in near point of convergence at 12 weeks of therapy

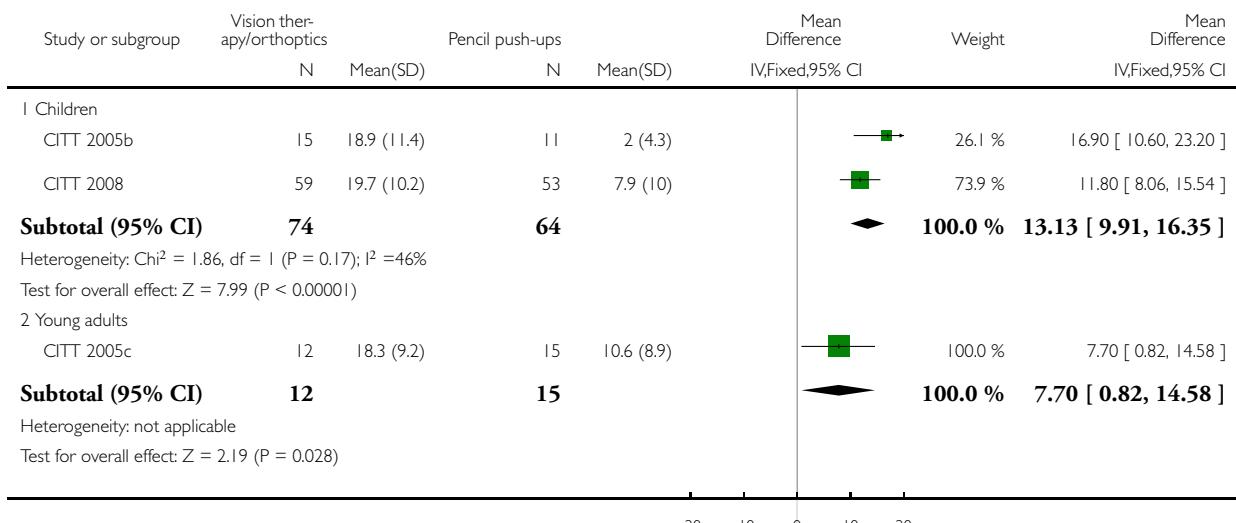


Analysis 3.2. Comparison 3 Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults, Outcome 2 Change in positive fusional vergence at near at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 3 Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults

Outcome: 2 Change in positive fusional vergence at near at 12 weeks of therapy

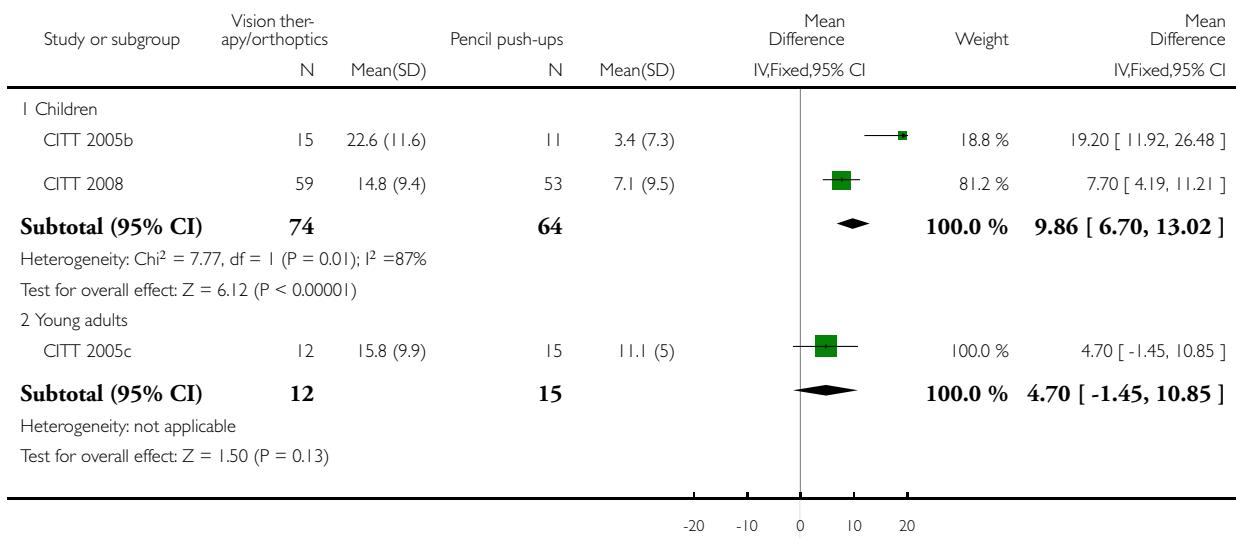


Analysis 3.3. Comparison 3 Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults, Outcome 3 Change in Convergence Insufficiency Symptom (CISS) score.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 3 Office-based vision therapy/orthoptics versus home-based pencil push-ups in children and young adults

Outcome: 3 Change in Convergence Insufficiency Symptom (CISS) score

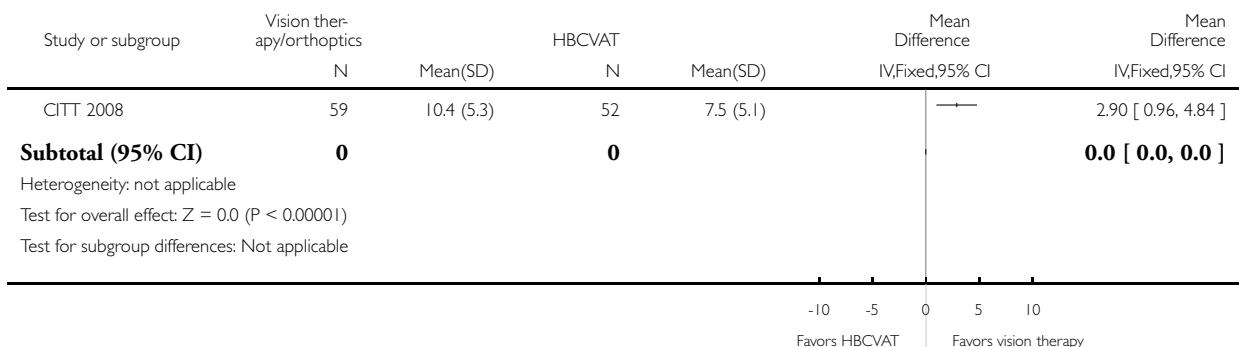


Analysis 4.1. Comparison 4 Office-based vision therapy/orthoptics versus home-based computer assisted pencil push-ups in children, Outcome I Change in near point of convergence at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 4 Office-based vision therapy/orthoptics versus home-based computer assisted pencil push-ups in children

Outcome: 1 Change in near point of convergence at 12 weeks of therapy

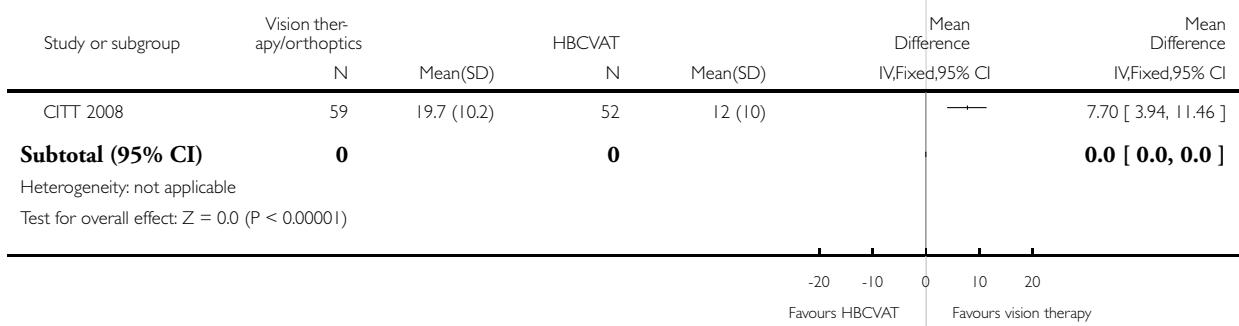


Analysis 4.2. Comparison 4 Office-based vision therapy/orthoptics versus home-based computer assisted pencil push-ups in children, Outcome 2 Change in positive fusional vergence at near at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 4 Office-based vision therapy/orthoptics versus home-based computer assisted pencil push-ups in children

Outcome: 2 Change in positive fusional vergence at near at 12 weeks of therapy

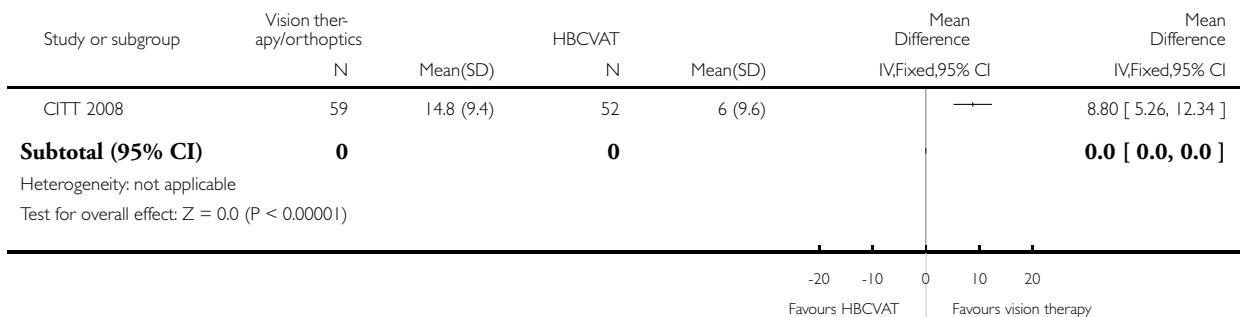


Analysis 4.3. Comparison 4 Office-based vision therapy/orthoptics versus home-based computer assisted pencil push-ups in children, Outcome 3 Change in Convergence Insufficiency Symptom (CISS) score.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 4 Office-based vision therapy/orthoptics versus home-based computer assisted pencil push-ups in children

Outcome: 3 Change in Convergence Insufficiency Symptom (CISS) score

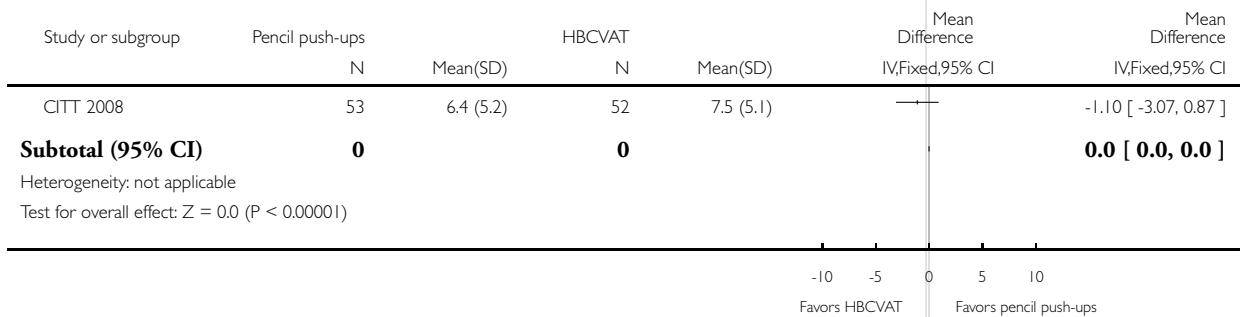


Analysis 5.1. Comparison 5 Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children, Outcome 1 Change in near point of convergence at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 5 Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children

Outcome: 1 Change in near point of convergence at 12 weeks of therapy

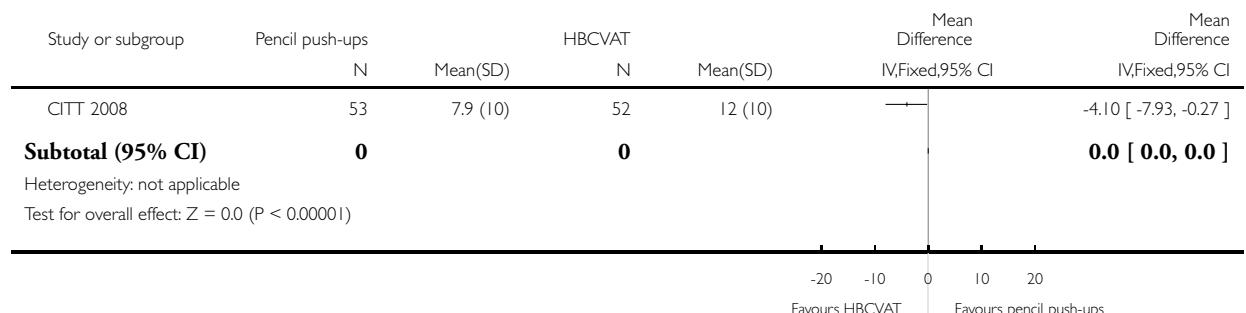


Analysis 5.2. Comparison 5 Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children, Outcome 2 Change in positive fusional vergence at near at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 5 Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children

Outcome: 2 Change in positive fusional vergence at near at 12 weeks of therapy

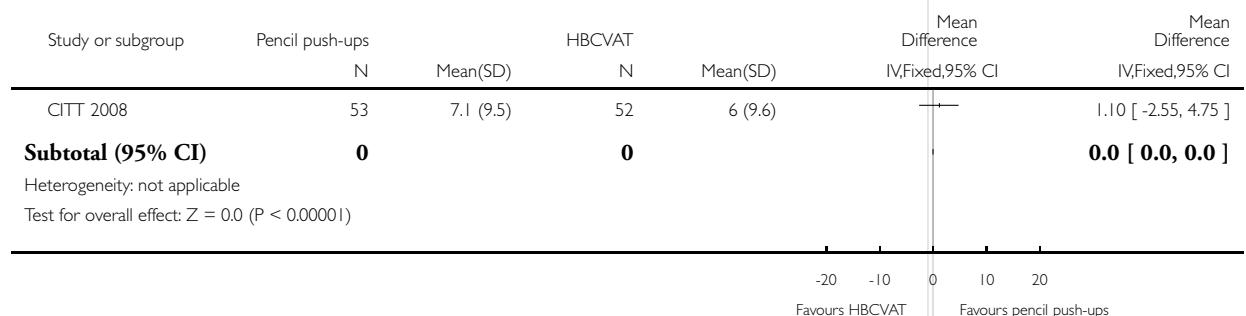


Analysis 5.3. Comparison 5 Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children, Outcome 3 Change in Convergence Insufficiency Symptom (CISS) score.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 5 Home-based pencil push-ups versus home-based computer assisted vision therapy/orthoptics in children

Outcome: 3 Change in Convergence Insufficiency Symptom (CISS) score

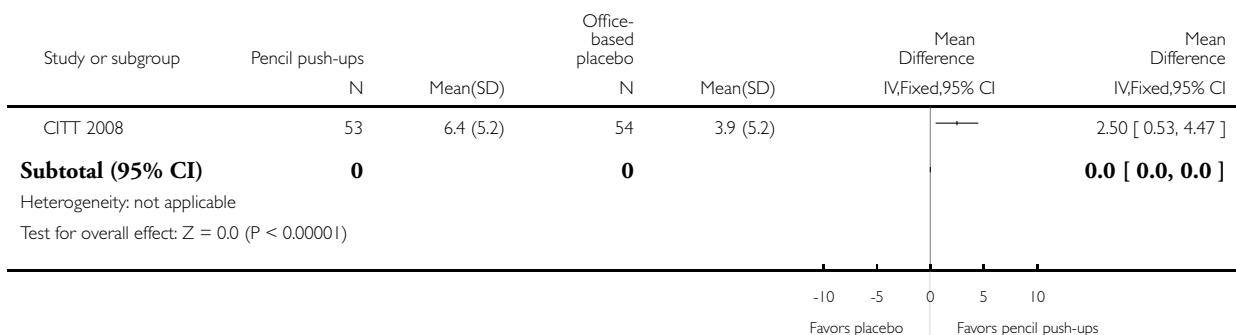


Analysis 6.1. Comparison 6 Home-based pencil push-ups versus office-based placebo in children, Outcome 1 Change in near point of convergence at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 6 Home-based pencil push-ups versus office-based placebo in children

Outcome: 1 Change in near point of convergence at 12 weeks of therapy

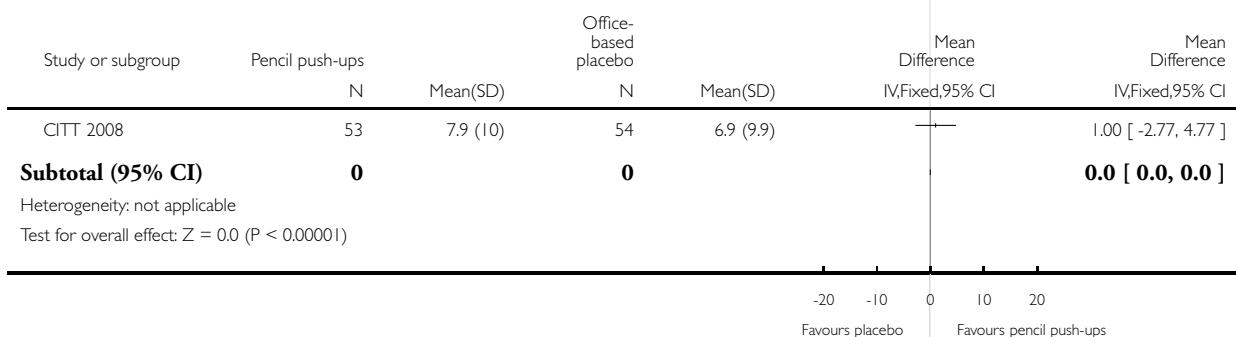


Analysis 6.2. Comparison 6 Home-based pencil push-ups versus office-based placebo in children, Outcome 2 Change in positive fusional vergence at near at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 6 Home-based pencil push-ups versus office-based placebo in children

Outcome: 2 Change in positive fusional vergence at near at 12 weeks of therapy

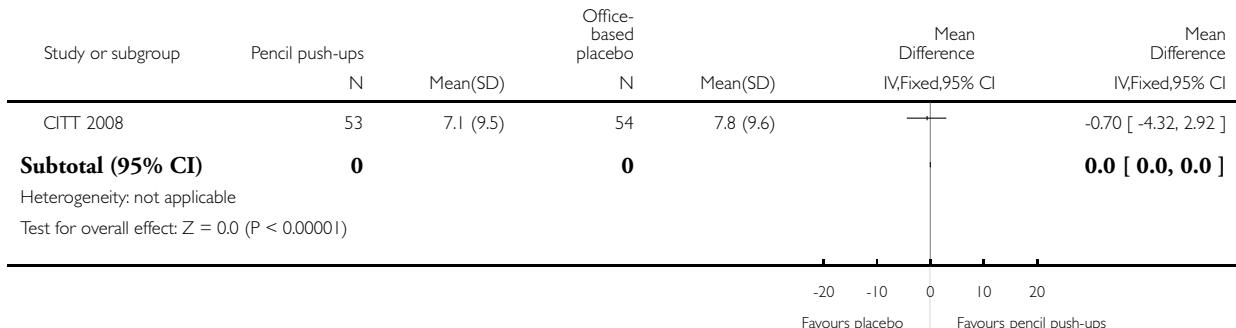


Analysis 6.3. Comparison 6 Home-based pencil push-ups versus office-based placebo in children, Outcome 3 Change in Convergence Insufficiency Symptom (CISS) score.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 6 Home-based pencil push-ups versus office-based placebo in children

Outcome: 3 Change in Convergence Insufficiency Symptom (CISS) score

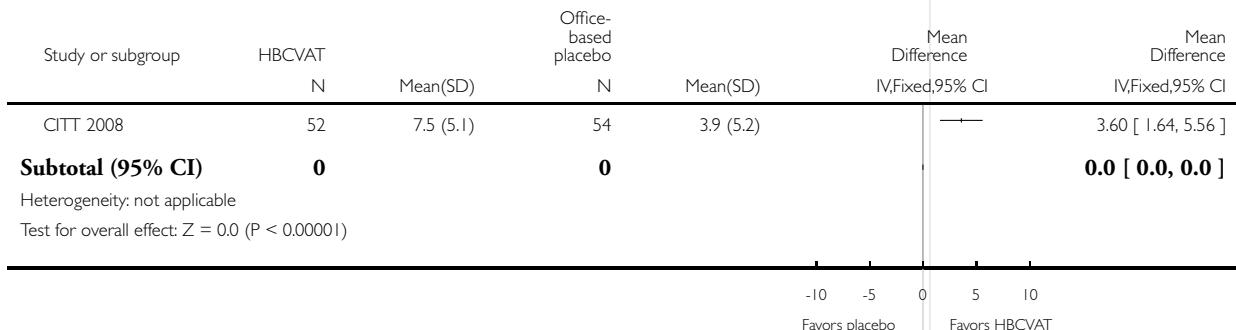


Analysis 7.1. Comparison 7 Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children, Outcome I Change in near point of convergence at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 7 Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children

Outcome: I Change in near point of convergence at 12 weeks of therapy

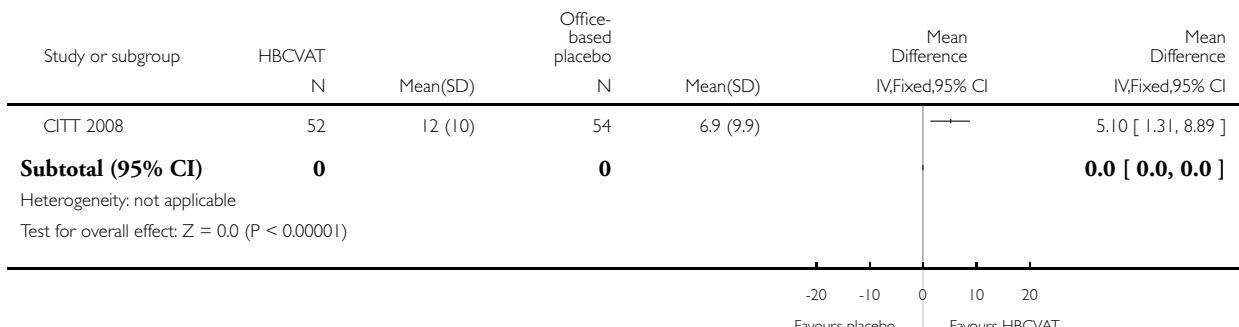


Analysis 7.2. Comparison 7 Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children, Outcome 2 Change in positive fusional vergence at near at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 7 Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children

Outcome: 2 Change in positive fusional vergence at near at 12 weeks of therapy

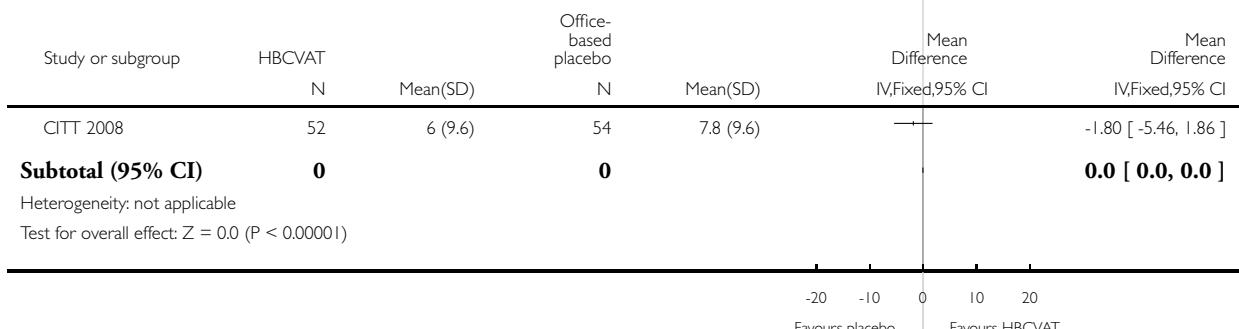


Analysis 7.3. Comparison 7 Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children, Outcome 3 Change in Convergence Insufficiency Symptom (CISS) score.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 7 Home-based computer assisted vision therapy/orthoptics versus office-based placebo in children

Outcome: 3 Change in Convergence Insufficiency Symptom (CISS) score



Analysis 8.1. Comparison 8 Vision therapy/orthoptics versus office-based placebo in children, Outcome I Change in near point of convergence at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 8 Vision therapy/orthoptics versus office-based placebo in children

Outcome: 1 Change in near point of convergence at 12 weeks of therapy

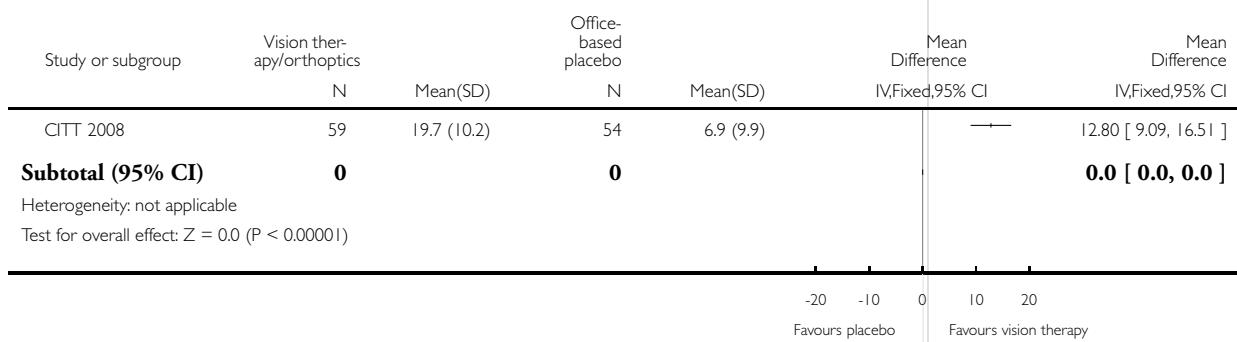


Analysis 8.2. Comparison 8 Vision therapy/orthoptics versus office-based placebo in children, Outcome 2 Change in positive fusional vergence at near at 12 weeks of therapy.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 8 Vision therapy/orthoptics versus office-based placebo in children

Outcome: 2 Change in positive fusional vergence at near at 12 weeks of therapy

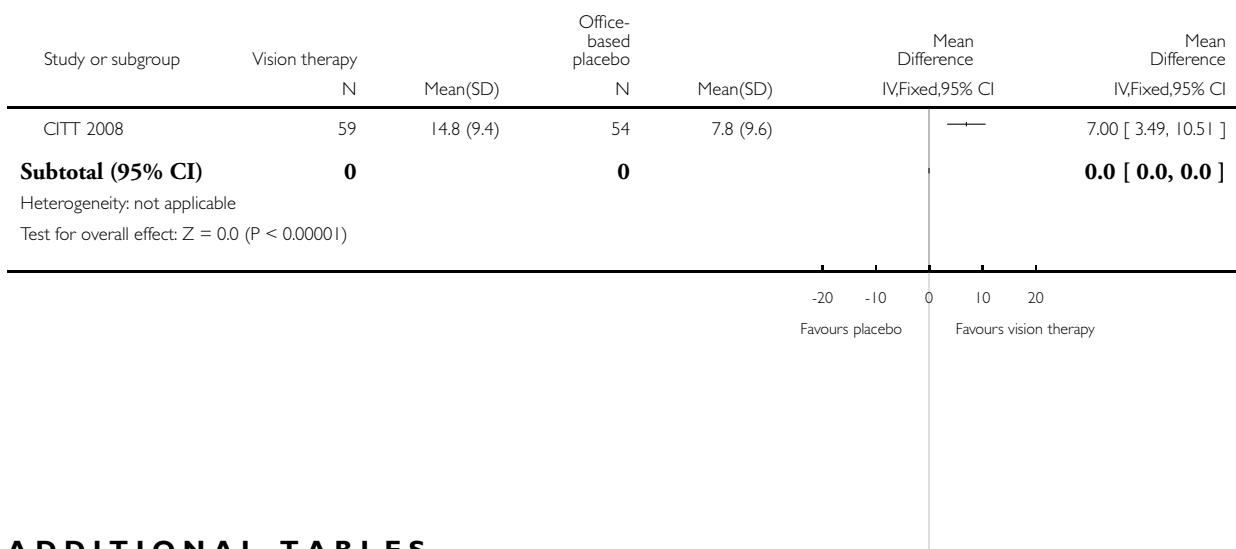


Analysis 8.3. Comparison 8 Vision therapy/orthoptics versus office-based placebo in children, Outcome 3 Change in Convergence Insufficiency Symptom (CISS) score.

Review: Non-surgical interventions for convergence insufficiency

Comparison: 8 Vision therapy/orthoptics versus office-based placebo in children

Outcome: 3 Change in Convergence Insufficiency Symptom (CISS) score



ADDITIONAL TABLES

Table 1. Types of comparisons in the included trials

Study ID	Office-based vision therapy/orthoptics	Home-based pencil push-ups	Placebo vision therapy/orthoptics or other placebo intervention	Home-based computer convergence/accommodative therapy and pencil push-ups	Other therapy	Prism reading glasses	Placebo reading glasses	Progressive addition lens	Population
Birnbaum 1999	✓		✓		✓				Male adult ≥ 40 years old
CITT 2005a						✓	✓		Children aged 9 to 18 years
Teitelbaum 2009						✓		✓	

Table 1. Types of comparisons in the included trials (Continued)

CITT 2005b	✓	✓	✓						Children aged 9 to 18 years
CITT 2005c	✓	✓	✓						Young adults aged 19 to 30 years
CITT 2008	✓	✓	✓	✓					Children aged 9 to 17 years

APPENDICES

Appendix I. CENTRAL search strategy

#1 MeSH descriptor Ocular Motility Disorders
 #2 MeSH descriptor Convergence, Ocular
 #3 MeSH descriptor Accommodation, Ocular
 #4 MeSH descriptor Vision, Binocular
 #5 MeSH descriptor Exotropia
 #6 convergence near insufficiency*
 #7 heterophoria*
 #8 exotropi*
 #9 exophori*
 #10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
 #11 prism*
 #12 pencil near push*
 #13 orthoptic*
 #14 (exercis* or therap* or treat*) near (home*)
 #15 (exercis* or therap* or treat*) near (office*)
 #16 vision therap*
 #17 stereogram*
 #18 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
 #19 (#10 AND #18)

Appendix 2. MEDLINE search strategy

1 randomized controlled trial.pt.
2 (randomized or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/
10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp ocular motility disorders/
14 exp convergence ocular/
15 exp accommodation ocular/
16 exp vision binocular/
17 exp exotropia/
18 (convergence adj3 insufficienc\$).tw.
19 heterophoria.tw.
20 exotropi\$.tw.
21 exophori\$.tw.
22 or/13-21
23 prism\$.tw.
24 (pencil adj2 push\$).tw.
25 orthoptics.tw.
26 ((exercise\$ or therap\$ or treat\$) adj10 home\$).tw.
27 ((exercise\$ ortherap\$ or treat\$) adj10 office\$).tw.
28 vision therapy.tw.
29 stereogram\$.tw.
30 or/23-29
31 22 and 30
32 12 and 31

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al ([Glanville 2006](#)).

Appendix 3. EMBASE search strategy

1 exp randomized controlled trial/
2 exp randomization/
3 exp double blind procedure/
4 exp single blind procedure/
5 random\$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin\$ adj3 trial\$).tw.
14 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15 exp placebo/

16 placebo\$.tw.
17 random\$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control\$ or prospectiv\$ or volunteer\$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp eye movement disorder/
34 exp binocular convergence/
35 exp accommodation/
36 exp binocular vision/
37 exp divergent strabismus/
38 (convergence adj3 insufficienc\$).tw.
39 heterophoria.tw.
40 exotropi\$.tw.
41 exophori\$.tw.
42 or/33-41
43 prism\$.tw.
44 (pencil adj2 push\$).tw.
45 orthoptics.tw.
46 ((exercise\$ or therap\$ or treat\$) adj10 home\$).tw.
47 ((exercise\$ or therap\$ or treat\$) adj10 office\$).tw.
48 vision therapy.tw.
49 stereogram\$.tw.
50 or/43-49
51 42 and 50
52 32 and 51

Appendix 4. metaRegister of Controlled Trials search strategy

convergence insufficiency

Appendix 5. ClinicalTrials.gov search strategy

Convergence Insufficiency

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 3, 2011

Date	Event	Description
19 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: MS, JG, TL

Designing the review: MS, JG, TL

Coordinating the review: TL

Data collection for the review

- Designing search strategies: CEVG Trials Search Co-ordinator, MS, JG

- Undertaking electronic searches: CEVG Trials Search Co-ordinator

- Undertaking manual searches: MS

- Screening search results: TL, MS, JG

- Organizing retrieval of papers: TL

- Screening retrieved papers against inclusion criteria: TL, MS, JG

- Appraising quality of papers: TL, MS, JG

- Extracting data from papers: TL, MS, JG

- Writing to authors of papers for additional information: TL, MS

- Providing additional data about papers: MS

- Obtaining and screening data on unpublished studies: MS, TL

Data management for the review

- Entering data into RevMan: TL, MS

Analysis of data: TL

Interpretation of data

- Providing a methodological perspective: TL

- Providing a clinical perspective: MS, JG

- Providing a policy perspective: MS

- Providing a consumer perspective: MS

Writing the review: MS, TL, JG

Providing general advice on the review: MS, JG, TL

Securing funding for the review: TL

Performing previous work that was the foundation of the current study: MS, TL

DECLARATIONS OF INTEREST

Mitchell Scheiman, OD is the Study Chair of the Convergence Insufficiency Treatment Trial (CITT) Study Group. This group completed three of the clinical trials described in this paper and the group continues to investigate treatment of convergence insufficiency in children and adults.

SOURCES OF SUPPORT

Internal sources

- Johns Hopkins Bloomberg School of Public Health, USA.

External sources

- Contract N-01-EY-2-1003 and Grant 1 U01 EY020522-01, National Eye Institute, National Institutes of Health, USA.
- Grant EY11756, National Eye Institute, National Institutes of Health, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Compliance to treatment is reported as an *ad hoc* secondary outcome because the success of treatment depends on compliance and three trials included in our review reported compliance data
- Cochrane methodology regarding assessments of the risk of bias in included studies have been modified and the review authors updated the 'Assessment of risk of bias in included studies' section of the methods to reflect updated methodological considerations

INDEX TERMS

Medical Subject Headings (MeSH)

*Eyeglasses; Ocular Motility Disorders [*therapy]; Orthoptics [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans

Improvement of Vergence Movements by Vision Therapy Decreases K-ARS Scores of Symptomatic ADHD Children

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Abstract. [Purpose] To determine whether the improvement of vergence movements by vision therapy can decrease the K-ARS scores of symptomatic ADHD children. [Methods] Eighty-one out of 1,123 children surveyed using the K-ARS, a parents'-reported questionnaire, led to 16 of these 81 children being showed scores of ≥ 19 , and measurement of binocular function diagnosed as having convergence insufficiency. The 16 children were divided equally into a control group and a vision therapy group. [Results] After vision therapy for 12 weeks, near point convergence (4.38 ± 0.69 cm) significantly neared compared to the near point convergence before vision therapy (11.50 ± 2.28 cm), and both the break point (32.38 ± 2.53 Δ) and recovery point (19.75 ± 2.11 Δ) of near positive fusional vergence significantly improved compared to their values before vision therapy (15.88 ± 2.64 Δ, 6.38 ± 6.70 Δ, respectively). Near exophoria after vision therapy (7.81 ± 2.00 Δ BI) significantly decreased compared to its value before vision therapy (12.00 ± 1.16 Δ BI). The K-ARS scores referring to symptomatic ADHD significantly decreased after vision therapy (17.13 ± 2.84) compared to before vision therapy (23.25 ± 1.49). [Conclusions] Convergence insufficiency symptoms are closely related to symptoms screened for ADHD, and vision therapy to improve vergence movements is an effective method of decreasing the K-ARS scores.

Key words: Convergence insufficiency, Vision therapy, ADHD

(This article was submitted Jul. 24, 2013, and was accepted Sep. 1, 2013)

INTRODUCTION

Convergence is one of the most important binocular functions of stereopsis and is a common vision disorder characterized by excess and insufficiency. Convergence insufficiency (CI) has great potential to induce exophoria at near^{1, 2)}. The adverse impact of CI, during near viewing, results in typical symptoms including double vision, blurred vision, eye strain, difficulty with concentration, and slow reading^{3, 4)}. These symptoms are closely related to attention deficit hyperactivity disorder (ADHD) and the academic achievement of school children^{5–7)}. Several investigators have concluded that children with ADHD exhibit more visual and quality-of-life symptoms than children without ADHD. Some of the symptoms of ADHD overlap with those of CI. The symptoms frequently reported in CI such as loss of concentration when reading, or reading slowly, are similar to behaviors associated with ADHD (inattentive type), such as failure to complete assignments, and trouble of concentration in class⁸⁾. A diagnosis of ADHD

for a child has an impact not only on the life of the child, but also on the family, the school, and society as a whole⁹⁾. For a complete diagnosis, a medical evaluation should be performed. Furthermore, an evaluation of binocular functions should be made, because some visual problems may be the cause of a child's academic underachievement and/or lack of concentration^{10, 11)}. Recently, the relationship between CI and ADHD has been investigated^{8, 10, 12)}, but the effect on ADHD of convergence improvement has rarely been studied. We are confident that symptomatic ADHD with CI can be significantly relieved by continuous and self-conscious training for vergence improvement, because vergence movements are controlled by voluntary motor innervation.

In this study, we selected children with symptomatic ADHD, as reported by their parents on the Korea-ADHD Rating Scale (K-ARS) questionnaire, and CI evaluated by a binocular function test, and investigated whether vision therapy (VT) for improvement of vergence movement can relieve the symptoms of ADHD evaluated by K-ARS.

SUBJECTS AND METHODS

For the selection of children with symptomatic ADHD, a total of 1,123 parents participated in a questionnaire survey using the K-ARS^{13, 14)}. Their children, ranging from 8–13 years of age, were attending the 1st, 2nd, 3rd, 4th, 5th, and 6th grades of a public primary school in G City, Korea. A

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child is identified with symptomatic ADHD when their score is ≥ 19 on the K-ARS questionnaire¹⁵⁾. The number of subjects reporting K-ARS scores ≥ 19 totaled 81 children. The binocular functions test found that 16 of these 81 exhibited CI without accommodative dysfunctions. These 16 children were divided equally into a control group and a VT group. Each subject and his or her parent provided informed consent to participation in this study after receiving an oral explanation of its method. The study was conducted in adherence to the ethical principles of the Declaration of Helsinki. All subjects were without physical problems, receiving no medical care, taking no medication, and exhibiting no signs of strabismus, or amblyopia.

Measurements of binocular functions are as follows. The examiner corrected refractive errors by subjective refraction with a phoropter (CV-3000, Topcon, Japan) using a decimal visual chart (ACP-7, Topcon, Japan) at 5 m (25–35 lux of interior illuminance and 110–120 lux of chart illuminance). The near point of convergence (NPC) was measured using a fixation stick (Bernell, Indiana, USA) and a ruler. The examiner moved (1–2 cm/sec) the target toward the midpoint of the subject's eyes from 40 cm away. When the subject reported a double target or one eye lost target fixation, the distance measured from the midpoint of eyes to target was recorded as NPC. The fusional vergence facility (FVF) was measured using flipper lenses mounted 3 Δ base in (BI)/12 Δ base out (BO) and Vectogram 9 (Bernell, Indiana, USA) at 40 cm. The examiner placed the 12 Δ BO lenses in front of subject's eyes and as soon as the subject reported that the print became single and clear, flipped the lenses to 3 Δ BI. The number of full cycles that consisted of both the BI and BO lenses in 60 seconds was recorded as FVF. A 6 Δ base up (BU) was placed over the left eye and a 12 Δ BI was placed over the right eye in the subject who was seated behind the phoropter. A vertical arrow target was held at 40 cm from the subject by the examiner. Subjects were instructed to keep the target clear at all times. If subjects didn't see target dissociation vertically, the examiner adjusted the Risley prism over the left eye until dissociation occurred. The examiner then checked the relative direction of the upper target to the lower one, right or left. The horizontal prism over the right eye was slowly moved until the subject said that two targets were aligned vertically. At this point, prism power and base direction were recorded as horizontal phoria. The horizontal vergence at near and at distance was measured using an isolated vertical line of 0.7 letters with subjects seated behind the phoropter. Risley prisms set to zero were placed before both eyes. The examiner instructed the subject to look at the target and try to keep it clear, and introduced the BI prism before both eyes at a speed of approximately 1 prism diopter per second. As prism is added, the total amount of prism before the two eyes was noted when the subject reported the line of letters had broken into two (break point of negative fusional vergence; NFV). After overshooting the break point slightly by adding a little more prism in the same direction, the examiner instructed the subject to acknowledge when the target became single again, and reduced prism until the subject reported the target was single (recovery point). The total

Table 1. The program of vision therapy for children having symptomatic ADHD and convergence insufficiency

Phase 1

Office based

- Block string and Barrel card: convergence and accommodation exercise
- Vectograms and Tranaglyphs: convergence exercise
- Synoptiscope: convergence and divergence exercise

Home based

- Block string and Barrel card: convergence and accommodation exercise
- HTS: convergence and divergence exercise

Phase 2

Office based

- Vectograms, Tranaglyphs, and Aperture rule: convergence exercise
- Synoptiscope and Prism flipper: convergence and divergence exercise

Home based

- HTS and Prism flipper: convergence and divergence exercise

Phase 3

Office based

- Aperture rule, Life saver cards, and Eccentric circles: convergence exercise
- Prism flipper: convergence and divergence exercise

Home based

- Life saver cards and Eccentric circles: convergence exercise
- HTS and Prism flipper: convergence and divergence exercise

HTS, home therapy system

amount of prism before both eyes was noted. The examiner repeated the measurement with the BO prism before both eyes (positive fusional vergence; PFV).

Major eligibility criteria for VT were: high exophoria at near (6 Δ or greater), exophoria at near at least 4 Δ greater than at distance, a receded NPC break (6 cm or greater), or insufficient PFV at near; or failing Sheard's criterion (PFV less than twice the near phoria¹⁶⁾), or minimum PFV $\leq 15 \Delta$ BO blur or break. The program of VT was composed of three phases lasting for 12 weeks, which were divided into home-based VT and office-based VT (Table 1), and three optical practitioners conducted the VT. Each subject in the VT group was instructed how to perform their therapy both at home and with a practitioner every week, and performed 30 minutes of the program, five days a week, at home and at the practitioner's office. To arouse the children's interest in VT, different types of tools were used for the same training. The subjects in the control group continued living their typical day-to-day lives without VT. After VT for 12 weeks, the questionnaire survey using K-ARS was answered again by the children's parents.

Data analysis was performed using SPSS for Windows (SPSS Inc., Chicago, USA). The Mann-Whitney U test was used to compare the mean difference of binocular functions before and after VT, and ANCOVA was used to compare the mean difference of symptomatic ADHD by K-ARS

Table 2. Changes of near point of convergence and fusional vergence facility after vision therapy for children having symptomatic ADHD and CI

Parameters	Control group (8)		VT group (8)	
	Before VT	After VT	Before VT	After VT
NPC (cm)	13.59±2.12	11.20±1.75	11.50±2.28	4.38±0.69*
FVF (cycles/min)	7.38±1.69	8.13±1.77	12.75±1.81	14.75±0.92

Data are expressed as mean±SD.

*p<0.05: significantly different in the same group according to the Mann-Whitney U test

The number of subjects is in parentheses.

VT, vision therapy; NPC, near point of convergence; FVF, fusional vergence facility

Table 3. Changes of binocular vergence and horizontal phoria at near after vision therapy for children having symptomatic ADHD and CI

Parameters	Control group (8)		VT group (8)	
	Before VT	After VT	Before VT	After VT
PFV break point (Δ)	16.13±1.20	15.25±2.00	15.88±2.64	32.38±2.53**
PFV recovery point (Δ)	6.13±2.08	5.75±2.68	6.38±6.70	19.75±2.11**
NFV break point (Δ)	21.88±1.11	20.63±0.75	19.50±1.63	26.25±1.81**
NFV recovery point (Δ)	16.50±1.48	12.88±0.83	15.38±2.11	18.50±2.53
Horizontal phoria (Δ)	-9.19±1.04	-8.81±1.16	-12.00±1.16	-7.81±2.00*

Data are expressed as mean±SD.

*p<0.05, **p<0.01: significantly different in the same group according to the Mann-Whitney U test

The number of subjects is in parentheses.

Minus sign denotes exophoria in phoria measurement.

VT, vision therapy; PFV, positive fusional vergence; NFV, negative fusional vergence

Table 4. Changes of binocular vergence and horizontal phoria at distance after vision therapy for children having symptomatic ADHD and CI

Parameters	Control group (8)		VT group (8)	
	Before VT	After VT	Before VT	After VT
PFV break point (Δ)	11.25±1.06	10.13±1.57	15.50±3.40	27.25±1.94**
PFV recovery point (Δ)	2.38±1.87	2.63±1.66	3.38±0.65	15.00±2.65**
NFV break point (Δ)	7.38±1.07	8.00±0.98	10.88±2.86	12.38±2.54
NFV recovery point (Δ)	3.25±0.37	3.13±0.35	6.25±2.55	7.63±2.34
Horizontal phoria (Δ)	-1.31±0.63	-1.13±0.58	-2.38±0.74	-2.75±0.89

Data are expressed as mean±SD.

**p<0.01: significantly different in the same group according to the Mann-Whitney U test

The number of subjects is in parentheses.

Minus sign denotes exophoria in phoria measurement.

VT, vision therapy; PFV, positive fusional vergence; NFV, negative fusional vergence

scores before and after VT while adjusting for differences at baseline. The two tests were analyzed using a 95% confidence level.

RESULTS

The changes of NPC and FVF after VT over 12 weeks are given in Table 2. NPC of 11.50±2.28 cm before VT significantly neared (p<0.05) to 4.38±0.69 cm after VT. FVF after VT increased by 2 cycles compared to before VT, but the difference was not significant.

The changes of vergence functions at near such as PFV, NFV, and horizontal phoria after VT are given in Table

3. The prism diopters in both the break point and recovery point of PFV after VT significantly increased (p<0.01) compared to before VT. The break point was measured as 32.38±2.53 Δ , an increase of BO 16.5 Δ , and the recovery point was measured as 19.75±2.11 Δ , an increase of BO 13.4 Δ . In NFV, though both the break point and recovery point showed increases of BI prism diopters, only the break point showed a significantly increase (p<0.01) of BI 6.8 Δ . Horizontal phoria, measured as 12.0 Δ of exophoria before VT, significantly decreased (p<0.05) to 7.8 Δ of exophoria after VT.

The changes of vergence functions at distance after VT are given in Table 4. The change pattern of all functions was

similar to that of at near. After VT, the break point of PFV was measured as 27.25 ± 1.94 Δ, a significant increase of BO 11.8 Δ ($p < 0.01$), and the recovery point of PFV was measured as 15.00 ± 2.65 Δ, a significant increase of BO 11.6 Δ ($p < 0.01$). However, horizontal phoria showed no significant difference between before and after VT.

The scores of symptomatic ADHD as assessed by the K-ARS questionnaire are given in Table 5. The score before VT was 23.25 ± 1.49 , and it significantly decreased ($p < 0.05$) to 17.13 ± 2.84 after VT.

DISCUSSION

A specific vision condition is closely related to the diagnosis of symptomatic ADHD in children³⁾. CI causes symptoms of asthenopia, blurred vision, and the sensation that words and letters run away in reading or near work¹⁷⁾. Some patients complain of near diplopia, nausea, or occasional headaches¹⁸⁾. Many cases of CI show poor or delayed reading, or simply lag behind in schoolwork. CI could impede the academic achievements of patients with ADHD. This implies that CI has the possibility of being a comorbid disorder in ADHD patients. Considering that CI is a treatable disorder, management with orthoptic intervention may help patients with ADHD who also suffer from CI¹⁰⁾. However, it is not obvious that the successful treatment of CI improves symptomatic ADHD. In the present study, we found that improvement of convergence functions significantly decreases the K-ARS scores of children with symptomatic ADHD.

The parents' K-ARS questionnaire for symptomatic ADHD is based on the DSM-IV criteria for ADHD, and 5 of the 9 symptoms of inattention could also be applicable for CI¹⁹⁾. Our K-ARS questionnaire survey of 1,123 parents found the percentage of children with reported scores of ≥ 19 , suggestive of ADHD symptoms, was 7.2%. Of these, 19.5% had CI without accommodative dysfunctions.

To achieve optimum improvement of CI, clinical guidelines suggest the length of treatment of office-based therapy should generally be 12–24 weeks²⁰⁾, and the shortest recommended duration is 12 weeks²¹⁾. These suggestions were made for both home-based and office-based treatments, such as computer vergence therapy and pencil push-up, for children with symptomatic CI. In the VT program of this study, the duration of therapy was 12 weeks, and both home-based and office-based therapies were conducted for the subjects. Scheiman et al.²²⁾ found that only office-based vergence/accommodative therapy and home reinforcement resulted in significant improvements in symptoms between visits ($p < 0.001$). The rate of improvement was more rapid for clinical signs (NPC and PFV) than for the symptoms of the children undergoing treatment for CI. NPC and PFV improved to within their normal ranges after 12 weeks of VT. Borsting et al.²³⁾ documented that successful treatment of CI induced a significant decrease in exophoria at near ($p < 0.001$). The important markers of improvement in CI are NPC, PFV, and exophoria at near. In our results, the NPC after VT (4.38 ± 0.69 cm) significantly neared, compared to before VT (11.50 ± 2.28 cm), to within its normal ranges. The

Table 5. Changes of scores reported by parents answering the K-ARS questionnaire after vision therapy for children having symptomatic ADHD and CI

Groups	Scores of symptomatic ADHD by K-ARS	
	Before VT	After VT
Control group (8)	25.88 ± 1.97	23.38 ± 2.23
VT group (8)	23.25 ± 1.49	$17.13 \pm 2.84^*$

Data are expressed as mean \pm SD.

* $p < 0.05$: significantly different in the same group according to ANCOVA

The number of subjects is in parentheses.

VT, vision therapy; ADHD, attention deficit hyperactivity disorder; K-ARS, Korea-ADHD Rating Scale

break point (32.38 ± 2.53 Δ) and recovery point (19.75 ± 2.11 Δ) of PFV at near after VT significantly improved compared to before VT (15.88 ± 2.64 Δ, 6.38 ± 6.70 Δ, respectively). The exophoria at near after VT (7.81 ± 2.00 Δ BI) significantly decreased compared to before VT (12.00 ± 1.16 Δ BI). Although the near exophoria after VT remained outside of its normal range, high exophoria > 6 Δ, the other criteria, such as PFV less than twice the near phoria, or minimum PFV ≤ 15 Δ BO blur or break, had improved to within their normal ranges. In the successful treatment conducted by Borsting et al.²³⁾, even when the near exophoria significantly decreased, the mean of exophoria after 12 weeks of treatment was high (8.90 Δ). Thus, our results indicate that CI is improved by a VT program. With these improvements in CI, the K-ARS score of symptomatic ADHD significantly decreased after VT to 17.13 ± 2.84 , a score below the level, 19, suggestive of ADHD. Moreover, the significant decrease K-ARS score after VT was not dependent on the relief of a specific symptom, but was based on the relief of various symptoms.

Based on our results, binocular dysfunction should always be considered in conjunction with the questionnaire survey for diagnosis of ADHD symptoms, especially, insufficient convergence, because several questions in the survey of ADHD symptoms could also be used in the diagnosis of symptomatic CI. Though a VT program for successful improvement of CI, including both long-term and maintenance therapy is needed²⁴⁾, improvements in NPC, PFV, and horizontal phoria were coincident with improvements in symptomatic ADHD of children. Consequently, the results of this study demonstrate the beneficial impact of treating children with CI on symptomatic ADHD based on parental report.

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Vision therapy for oculomotor dysfunctions in acquired brain injury: A retrospective analysis

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KEYWORDS

Acquired brain injury;
Oculomotor
dysfunction;
Vision therapy;
Eye movements;
Reading;
Quality of life

Abstract

BACKGROUND: Oculomotor dysfunctions are among the most common abnormalities found in the brain-injured population. The purpose of the current study was to determine retrospectively the effectiveness of conventional optometric vision therapy for oculomotor disorders of vergence and version in a sample of ambulatory, visually symptomatic, predominantly adult outpatients who had either mild traumatic brain injury (TBI) or cerebrovascular accident (CVA).

METHODS: A computer-based query for acquired brain injury patients examined between the years of 2000 and 2003 was conducted in our clinic. This yielded 160 individuals with mild TBI and 60 with CVA. Of these patients, only those for whom vision therapy was prescribed and who completed an optometric vision therapy program for remediation of their oculomotor dysfunctions were selected. This included 33 with TBI and 7 with CVA. The criterion for treatment success was denoted by marked/total improvement in at least 1 primary symptom and at least 1 primary sign.

RESULTS: Ninety percent of those with TBI and 100% of those with CVA were deemed to have treatment success. These improvements remained stable at retesting 2 to 3 months later.

CONCLUSION: Nearly all patients in the current clinic sample exhibited either complete or marked reduction in their oculomotor-based symptoms and improvement in related clinical signs, with maintenance of the symptom reduction and sign improvements at the 2- to 3-month follow-up. These findings show the efficacy of optometric vision therapy for a range of oculomotor abnormalities in the primarily adult, mild brain-injured population. Furthermore, it shows considerable residual neural plasticity despite the presence of documented brain injury.

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Oculomotor dysfunctions are among the most common vision problems found in the general population presenting to the optometrist.¹⁻⁴ These include abnormalities of version, vergence, or accommodation. Presence of such problems can produce a variety of visual performance deficits,

such as slowed reading and impaired visual search.⁵ Fortunately, there is evidence showing success with optometric vision therapy in these cases, with both objective and subjective evidentiary documentation,^{2,5} including a recent randomized clinical trial for the condition of convergence insufficiency in adults.⁶

Oculomotor dysfunctions are also among the most common vision problems in individuals with acquired brain injury (ABI).^{2,3} In fact, a recent large-scale retrospective study documented that approximately 90% of individuals

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with either a mild traumatic brain injury (TBI) or a cerebrovascular accident (CVA) manifested some type of oculomotor dysfunction after the acute phase of care.⁷

There is a small but growing body of evidence showing successful treatment of oculomotor deficits in the TBI and CVA populations.^{5,8-10} Although the reported percentages of successful treatment have been high, many were either case reports^{11,12} or case series.^{6,8} However, some small-scale, prospective population studies have been conducted showing objective improvements and high success rates using either electrophysiologic¹³ or eye movement measures.¹⁰ Despite the above studies, large-scale investigations remain warranted.

Thus, the purpose of the current study was to determine retrospectively the effectiveness of conventional optometric vision therapy for oculomotor dysfunctions in a relatively large sample of ambulatory, visually symptomatic, predominantly adult outpatients having either a mild TBI or a CVA.

Methods

A computer-based query was obtained for ABI patients examined between October 1, 2000, and October 7, 2003, using either the 99203 (new patient evaluation) or 99213 (established patient evaluation) procedure codes. All patients were ambulatory, predominantly adult (all but 3 were older than 18 years of age) outpatients with associated vision-based symptoms. Optometrists from the Raymond J. Greenwald Rehabilitation Center (RJGRC) at the State University of New York (SUNY) State College of Optometry performed the vision examinations. The majority of patients were referred by rehabilitation professionals from the following institutions: Rusk Institute of Rehabilitative Medicine at NYU Medical Center, Bellevue Hospital at NYU Medical Center, Department of Rehabilitative Medicine at Mount Sinai Medical Center, Lenox Hill Hospital, New York Hospital, and the International Center for the Disabled. Other referrals were made by rehabilitation professionals in private practice in the greater New York City area. Referrals were also received from other services within the college's University Optometric Center including primary care, low vision, contact lens, and ocular disease and special testing. Referred patients were not limited to those with either a TBI or CVA; individuals with other neurologic conditions that affect the visual system, such as vestibular dysfunctions, cranial postsurgical complications, and brain tumors, comprise a sizeable patient base.

The RJGRC's diagnostic evaluation included assessment of the following areas: visual acuity, distance and near refraction, distance and near binocular and oculomotor status, color vision, visual fields, and ocular health. In some instances, not all of these areas could be evaluated fully because of limitations in the patient's cognitive status, language ability, and/or physical state.

The computer query yielded 486 records of which 300 were selected randomly. Each of 3 members of the

RJGRC's clinical staff (coauthors D.R., S.C., and M.E.H.) then randomly chose 100 of the records. Of these, only those patients with either a mild TBI ($n = 160$) or CVA ($n = 60$) were reviewed. Of the above 220 selected patients (with an age range of 11 to 80 years), only those who had been recommended and completed a full course of optometric vision therapy for accommodative, versional, and/or vergence oculomotor dysfunctions at the time of the computer query were incorporated in the analysis.

Regarding TBI, 144 of 160 presented with oculomotor signs and symptoms. Of those 144, only 87 were recommended for vision therapy, with the remaining 57 persons deemed inappropriate for vision therapy because of excessive fatigue factors, too many other concurrent therapies, unstable systemic/neurologic health, severe cognitive deficits, and/or behavioral issues.

Of the 87 with TBI who were referred for vision therapy, 59 followed the recommendation. Of those 59, only 33 had completed vision therapy at the time the analysis was performed, with 26 still in progress.

Regarding CVA, 52 of 60 presented with ocular motor signs and symptoms. Of those 52, only 23 were recommended for vision therapy, with the remaining 29 persons deemed inappropriate for vision therapy for the reasons stated above for TBI. Of the 23 with CVA referred for vision therapy, 15 followed the recommendation, whereas 8 did not. Of the 15 with CVA who followed through with vision therapy, 7 had completed vision therapy at the time the analysis was performed, with 8 still in progress. Therefore, a total of 40 patients were included in this study: 33 TBI and 7 CVA. This study excluded the results for those patients who were still in training at the time of analysis and classified as being "in progress" at the time.

Table 1 summarizes the age and postinjury years in terms of mean, standard deviation, and range. Note that although the sample population was predominantly adult, 3 11-year-old individuals were also evaluated and treated with

Table 1 Patient demographics and diagnostic breakdown for TBI ($n = 33$) and CVA ($n = 7$)

	TBI	CVA
Parameter		
Mean age (y) at initial visit	42.3	56.6
Standard deviation of age (y) at initial visit	15.2	20.3
Range of age (y) at initial visit	11-66	29-80
Mean years after injury	3.2	1.1
Standard deviation of years after injury	4.1	0.6
Range of years after injury	0.25-20.17	0.6-2.2
Diagnostic category		
Strabismus	3	2
Phoria	29	5
Accommodative deficit	3	1
Oculomotor deficit	31	7
Visual field defect	12	5

Table 2 Categories of oculomotor symptoms and signs

Symptom
Blur
Diplopia
Impaired global sense of depth perception
Increased sensitivity to visual motion (caused by oculomotor-based impairment of dynamic version and/or vergence)
Eye strain
Headache
Avoidance of near vision tasks
Oculomotor-based reading difficulty (e.g., loss of place when reading, skipping lines when reading, and misreading or missing words when reading)
Difficulty with global scanning (e.g., problems navigating in busy streets, stores, malls, etc.)
Sign
Reduced amplitude of accommodation
Increased lag of accommodation
Reduced relative accommodation
Slowed accommodative facility
Uncorrected hyperopia/astigmatism (caused by inability to compensate)
Receded near point of convergence
Restricted relative convergence (BO) at far and near
Restricted overall fusional vergence ranges at far and near
Abnormal Developmental Eye Movement (DEM) test results
Low grade-level equivalent performance on the Visagraph II
Impaired versional ocular motility

vision therapy. **Table 1** also summarizes the number of patients with strabismus, phoria, accommodative deficits, versional oculomotor deficits, and visual field defects.

A summary of the symptom and sign categories is presented in **Table 2**. This included a wide range of areas dealing specifically with the oculomotor subsystems of version, vergence, and accommodation.

Conventional vision therapy paradigms were used.⁴ This included vergence, version, and accommodative therapy (**Table 3**). Accommodative therapy was only incorporated in the treatment plan for the 4 individuals who were younger than 40 years and manifested an accommodative deficit: 3 with TBI (2 11-year-old patients and 1 38-year-old patient) and 1 with a CVA (a 29-year-old patient). Those older than 40 years had either markedly reduced or absent accommodation (i.e., presbyopia), and thus vision therapy was not prescribed for their accommodative deficits. **Table 4** presents tabulated data describing the number of vision therapy sessions conducted over a 2- to 8-month period. The criterion for treatment success was either marked improvement or normalization of at least 1 primary symptom and at least 1 primary sign. The former was based on a 3-category, symptom specification: no improvement, some improvement, and marked/total improvement, as is typically done clinically. The latter was based on the clinical signs moving toward the appropriate compensatory values or, in the absence of a heterophoria, the normative values in the literature.¹⁴⁻¹⁶

Results

Symptoms and signs: Mild traumatic brain injury

Symptoms reported in the mild TBI patients are presented in **Table 5**. The most common symptoms were oculomotor-based reading difficulty, eyestrain, diplopia, and headaches. Signs found in the mild TBI patients are also presented in **Table 5**. The most common signs were receded near point of convergence, abnormal Developmental Eye Movement (DEM) test results, and reduced near convergence range.

Symptoms and signs: Cerebrovascular accident

The only symptom reported in the CVA patients is presented in **Table 6**. This was oculomotor-based reading difficulty, which was found in all of the individuals. Signs

Table 3 Training areas

Vergence oculomotor
Small disparity steps to increase the fusional range
Small disparity ramps to increase the fusional range
Large disparity steps to enhance fusional vergence facility
Large disparity steps with opposing accommodative demands to enhance fusional facility
Sustained vergence at different disparity demands
Versional oculomotor
Stationary target to enhance fixational oculomotor stability
Predictable horizontal, vertical, and oblique steps to enhance saccadic accuracy
Predictable horizontal and vertical ramps to enhance smooth pursuit accuracy
Visual scanning to enhance detection of targets in one's environment
Visual search to enhance detection of targets embedded within a complex array
Accommodative
Monocular stationary target to determine and enhance accommodative stability
Monocular predictable small, moderate, and large dioptric step changes to enhance the accommodative facility, accuracy, and sustainability over time (performed in free space and/or using loose lenses)
Monocular predictable small, moderate, and large dioptric ramp changes in the accommodative stimulus to enhance the accuracy and sustainability of gradual changes in accommodation (performed in free space and/or using loose lenses)
Binocular (with suppression control) predictable small and moderate dioptric step changes to enhance the accommodative facility, accuracy, and sustainability over time (performed in free space and/or using loose lenses)
Binocular (with suppression control) predictable small and moderate dioptric ramp changes in the accommodative stimulus to enhance the accuracy and sustainability of gradual changes in accommodation (performed in free space and/or using loose lenses)

Table 4 Vision therapy patient information

Subgroup	Total completing vision therapy	Total improving after vision therapy	Number of sessions			
			10-14	15-20	21-25	26-30
TBI	33	30	4	9	10	12
CVA	7	7	3	4	0	0

found in the CVA patients are also presented in **Table 6**. These included impaired versional ability and abnormal DEM. Each sign was found in all 7 patients.

Treatment improvement: Mild traumatic brain injury

Thirty of 33 (~90%) showed either complete or marked reduction in 1 or more of their primary symptoms. Twenty-seven of 30 (90%) showed either marked improvement or normalization in 1 or more of their primary clinical signs.

Treatment improvement: Cerebrovascular accident

All 7 (100%) showed either complete or marked reduction of their only primary symptom. All 7 (100%) exhibited either marked improvement or complete normalization of their 2 primary signs.

Table 5 Symptoms/signs initially reported by patients with TBI (n = 33)

	Number of patients reporting the symptom/sign
Symptom	
Ocular motility difficulty when reading	27
Eyestrain	18
Diplopia (at near more so than far viewing distances)	18
Headaches	11
Visual fatigue	5
Near blur	3
Sliding together of text words	1
Increased sensitivity to visual motion	1
Avoidance of near tasks	1
Sign	
Receded near point of convergence	23
Abnormal DEM test	23
Reduced near convergence (BO) range	16
Reduced near vergence ranges	9
Binocular suppression during testing	3
Impaired versional ocular motility	2
Nausea during near testing	1

Note: some patients may have presented with more than 1 symptom/sign.

All patients were reevaluated 2 to 3 months after the termination of vision therapy. Their symptoms and signs remained stable.

Discussion

This has been the first relatively large (n = 40) and comprehensive retrospective analysis of oculomotor dysfunctions in a visually symptomatic, ambulatory, predominantly adult mild ABI sample, which incorporated the 2 primary subgroups of mild TBI and CVA. The current findings showed a wide range of vergence, versional, and accommodative problems that could be remediated successfully, at a level of 90% or better, incorporating conventional optometric vision therapy in the affected oculomotor areas.¹⁴⁻¹⁶ Both symptoms and signs, with most being related to near vision activities, were either markedly reduced or totally eliminated. These findings suggest the presence of considerable visual system plasticity in response to the targeted vision rehabilitation in this brain-injured sample. Thus, despite the presence of brain damage in this predominantly adult population, considerable improvement in oculomotor skills was evident.

The current study is complementary to our earlier retrospective investigation involving the frequency of occurrence of oculomotor problems (~90%) derived from this same initial clinic sample.⁷ This earlier study included a wider age range and sample size (11 to 80 years of age, n = 220), of which these 40 individuals made up a subgroup. In both the present mild TBI and CVA subgroups, vision therapy resulted in symptom and sign reduction as well as

Table 6 Symptoms/signs initially reported by patients with stroke (n = 7)

	Number of patients with the symptom/sign
Symptom	
Ocular motor difficulty when reading	7
Sign*	
Impaired versional ocular motility	7
Abnormal DEM test	7

* Some patients may have presented with more than 1 sign.

related subjectively based reading improvements per the case history.

The current results show that optometric vision therapy can be an important modality in the vision rehabilitation of those with acquired brain injury having oculomotor dysfunctions. Except for those with strabismus, these patients can be regarded simply to be more difficult and challenging “oculomotor skills cases.” Many of the signs and symptoms, as well as the basic therapeutic paradigms, are similar.^{6,17,18} However, progress may be slower and more variable, perhaps attained with a lesser level of final improvement. In addition, the vision therapy may be hindered by memory and cognitive deficits as well as physical health setbacks. Despite these potential obstacles, based on the current findings, a 90% “success” rate is impressive. Although all patients may not normalize, the improvements can be considerable. Thus, given the constellation of both vision-based and non-vision-based residual problems in this population,^{18,19} it is important for the optometrist to attempt a regimen of vision therapy, with likely symptom reduction.

In addition to performing vision therapy in the ABI population to improve their numerous oculomotor deficits and related symptoms,⁵ it can also exert a broader positive influence on the overall quality of life (QOL). Furthermore, the presence of residual vision problems, including oculomotor deficits, will adversely affect other forms of rehabilitation.^{20,21} Thus, such oculomotor deficits would hinder one’s overall rehabilitative progress. For example, presence of accurate and steady fixation as well as efficient saccadic tracking is required in many aspects of cognitive therapy, such as completing a complex visual search matching task.²²

Lastly, there are several areas of future investigation that should be explored in this population. First, a large prospective analysis is warranted. This would allow for better control of the therapeutic components and overall case management, such as specification of precise and consistent times allotted for each category of procedure on all patients. In addition, a control group that did not receive vision therapy would be included. Second, the therapeutic “dose” effect should be studied. That is, what are the minimal amounts and types of vision therapy procedures that yield the best short- and long-term effects with respect to related oculomotor symptoms and signs? And, related to this, does the improvement transfer to other domains, such as general and visual attention? Third, there is the need for long-term follow-up, perhaps up to 1 year or more. And, lastly, the impact of successful vision therapy on one’s QOL should be assessed formally. It is important to determine quantitatively the effect of vision therapy on the patient’s vocational and avocational goals. In this way, both the personal and socioeconomic impact can be ascertained with respect to the individual’s overall satisfaction level.

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Effect of oculomotor rehabilitation on vergence responsivity in mild traumatic brain injury

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Abstract—A range of dynamic and static vergence responses were evaluated in 12 individuals with mild traumatic brain injury (age: 29 \pm 3 yr) having near vision symptoms. All measures were performed in a crossover design before and after oculomotor training (OMT) and placebo (P) training. Following OMT, peak velocity for both convergence and divergence increased significantly. Increased peak velocity was significantly correlated with increased clinically based vergence prism flipper rate. Steady-state response variability for convergence reduced significantly following OMT. The maximum amplitude of convergence, relative fusional amplitudes, and near stereoacuity improved significantly. In addition, symptoms reduced significantly, and visual attention improved markedly. None of the measures were found to change significantly following P training. The significant improvement in most aspects of vergence eye movements following OMT demonstrates considerable residual brain plasticity via oculomotor learning. The improved vergence affected positively on nearwork-related symptoms and visual attention.

Key words: acquired brain injury, mild traumatic brain injury, nearwork symptoms, neuroplasticity, oculomotor dysfunction, oculomotor learning, oculomotor rehabilitation, traumatic brain injury, vergence, vergence dysfunction, visual attention.

INTRODUCTION

Traumatic brain injury (TBI) is defined as any structural damage caused by an external force to the brain and its associated structures (e.g., cranium) resulting in physiological disruption of brain function [1]. The Centers for Disease Control and Prevention estimated that approximately 1.7 million people have experienced a TBI in the

United States, with it being the leading cause of death and disability [2]. TBI is a major medical, optometric, social, economic, and public health issue in the United States [3]. Motor vehicle accidents, falls, assaults, sports-related concussion, gunshot wounds, work-related injuries, etc., are some of the most common causes of TBI [1], with 70 to 80 percent of all TBI being classified as mild TBI (mTBI) [1,4].

Based on the severity and location of the injury, TBI results in a spectrum of dysfunctions involving sensory, motor, perceptual, physical, behavioral, cognitive, linguistic, and emotional aspects [5]. Being a primary modality of sensation, vision and its deficits following TBI will likely have an adverse effect on many activities of daily living (ADLs). Due to the pervasive nature of TBI (e.g.,

Abbreviations: Δ = prism diopter, ADL = activity of daily living, BI = base-in, BO = base-out, CI = convergence insufficiency, CISS = Convergence Insufficiency Symptom Survey, LED = light-emitting diode, mTBI = mild traumatic brain injury, NFV = negative fusional vergence, NPC = near point of convergence, OMT = oculomotor training, OR = oculomotor rehabilitation, P = placebo, PFV = positive fusional vergence, PRII = Power Refractor II, SEM = standard error of mean, SS = steady-state, SUNY = State University of New York, TBI = traumatic brain injury, VSAT = Visual Search and Attention Test.

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coup-contrecoup), numerous vision-related areas can be adversely affected [3,6]. For example, approximately 90 percent of individuals with mTBI having vision-related symptoms examined in an optometric clinic setting were diagnosed with one or more oculomotor dysfunctions following their acute care phase and natural recovery period [7]. Of the sample population, 70 percent manifested nonstrabismic types of oculomotor deficiencies involving version, vergence, and accommodation. Such deficits could adversely affect reading and other nearwork ADLs [8]. Identifying these abnormalities and rehabilitating them are essential in improving reading ability and overall quality of life [8]. In this article, only the oculomotor system subcomponent of vergence is considered.

Vergence refers to the disjunctive movement of the eyes used to track objects varying in depth over the range of one's binocular visual field [9]. The goal is to rapidly obtain and maintain fusion, or singleness, of the object of interest by placing the foveally bifixated object on corresponding retinal points within Panum's fusional area [10]. Furthermore, the vergence system acts in synchrony and precision with the versional system to track objects laterally in one's visual space accurately and singly, with the accommodative system continuously activated to maintain target clarity [10].

There are several separate subsystems believed to be involved in the neural control of vergence [11]. While the midbrain comprises the majority of neurons [12], evidence for the existence of neurons that also discharge during vergence have been located in the pons [13–14], cerebellum [15], and some areas of the cerebral cortex, such as the frontal eye field [16], parietal lobe [17–18], middle temporal [19] and medial superior temporal visual areas [20], and primary visual cortex [21]. Since the vergence neural pathway is extensive, any injury to the multitude of related brain and contiguous structures may adversely affect the vergence system.

REVIEW OF VERGENCE DYSFUNCTIONS IN TRAUMATIC BRAIN INJURY

Clinical Studies

Retrospective Studies

Five retrospective studies have assessed the prevalence of oculomotor abnormalities in patients with mTBI, both in a civilian clinic population and in Department of

Veterans Affairs and military populations [7,22–25]. The results are remarkably similar across these populations, in which the etiology of the TBI included both blast and non-blast injuries. Vergence dysfunctions ranged from 24 to 48 percent. While convergence insufficiency (CI) was the main clinical vergence dysfunction (42.5%), other vergence deficits that were also found with a relatively high frequency included binocular instability (10.0%), convergence excess (2.5%), basic exophoria (2.5%), and divergence insufficiency (<2.0%) [7]. These general findings have been confirmed in four recent related investigations [26–29].

Clinical Studies Involving Nonstrabismic Vergence Dysfunctions

One of the earliest formal studies on the presence of binocular vision abnormalities following TBI was by Cross in 1945 [30]. Observations were made from several hundred cases examined at a military hospital. Convergence dysfunction was found to be one of the most common oculomotor anomalies. General body fatigue following TBI was presumed to be the cause of reported "ocular muscle fatigue," thus resulting in "defective convergence" in these individuals [30–31].

A number of more recent studies conducted in clinic populations have evaluated vergence function following TBI [32–39]. These studies have also found a range of vergence dysfunctions, including CI, reduced fusional ranges, and increased near exophoria, with percentages ranging from 25 to 75 percent.

Laboratory Investigations

An early study by Ron et al. objectively recorded vergence eye movements to a constant-velocity ramp stimulus, in which 28 patients with unspecified categories of TBI binocularly tracked a small target at near that moved continuously in depth from 30 to 5 cm along their midline [40]. Abnormal dynamic vergence responses were found in 71 percent of patients.

More recently, a wide range of static and dynamic vergence parameters were tested in 21 visually symptomatic adult patients with mTBI (mean ± 1 standard error of mean [SEM] age: 45.7 ± 3.1 yr), as related to nearwork, by the State University of New York (SUNY) acquired TBI research group [41]. Five static parameters were found to be significantly different and abnormal between the mTBI and the visually nondisabled groups: near point of convergence (NPC) break and recovery values were

receded, positive fusional vergence (PFV) break and recovery values were reduced, and the stereoacuity threshold was elevated (presumably related to inaccurate vergence) in the group with mTBI [10]. While the transient response amplitudes for convergence and divergence did not differ significantly between the nondisabled subjects and those with mTBI, because they were already normal at baseline, all of the dynamic parameters (i.e., peak velocity, time constant, and latency) were significantly different ($p < 0.05$) between the two groups for both convergence and divergence. Responses were all slowed, delayed, and more variable in the group with mTBI than the nondisabled group.

Lastly, in a recent pilot study, objective recordings of vergence were obtained in two young adults with self-reported mTBI and nearwork symptoms [42]. Vergence dynamics were markedly slowed (i.e., reduced peak velocity) for convergence but not for divergence, as has been found earlier in larger populations [42].

OVERVIEW OF OCULOMOTOR REHABILITATION IN TRAUMATIC BRAIN INJURY

Several clinical case studies and a few population studies have evaluated the effect of oculomotor rehabilitation (OR) in mTBI. One of the earliest studies involved with the treatment of vergence and accommodative disorders was conducted by Chandler in a hospital-based setting in a series of World War II-related TBI cases ($n = 33$) [43]. OR (unspecified, but presumably “orthoptic” fusional training) commenced anywhere from 3 wk to 5 yr postinjury. While 73 percent of the patients treated were either fully remediated or markedly improved, 12 percent failed to improve and only 6 percent exhibited spontaneous recovery (from 3 d to 2 wk postinjury). These results are consistent with later studies [44–48]. Evidence to support the fact that carefully programmed OR remediates binocular vision anomalies in those with mTBI also comes from several clinical population studies [38–39,49]. In each study, reading difficulty was one of the most common symptoms.

From these studies, there is abundant evidence from the literature in both laboratory-based and clinically based studies supporting the notion that targeted, specific, programmed OR procedures, which all incorporate the principle of motor learning [50–51], can remediate patients with

a range of binocular vision disorders as a consequence of mTBI. Symptoms were ameliorated concurrent with improvement or normalization of clinical signs. This is important information because improved oculomotor abilities and related visual-perceptual skills can hasten progress in the patient’s other rehabilitative programs [52–53]. This includes cognitive therapy, for example, which requires complex visual saccadic scanning and fine detail discrimination.

The purpose of the current investigation was to evaluate comprehensively clinically and laboratory-based vergence parameters in individuals with mTBI reporting nearwork-related symptoms of an oculomotor nature before and after oculomotor training (OMT) performed in the clinic, without a home-based component. The OMT involved all three main oculomotor subsystems: vergence, accommodation, and version. The measures were also compared after placebo (P) training. For the purpose of the present article, only the oculomotor subsystem of vergence is considered.

METHODS

Subjects

Twelve subjects (8 females and 4 males) between the ages of 23 and 33 yr (mean \pm standard deviation: 29 ± 3 yr) participated in the study (see [Appendix 1](#) [available online only] for demographics). The training effects for the study were hypothesized to be moderate to large based on our earlier related laboratory studies [8,54–55], as well as the extensive clinical experience of the second author (K.J.C.). Sample size was calculated using a power analysis program (G*Power 3; Institut für Experimentelle Psychologie, Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany) at an alpha level of 0.05, with a power set at 0.80 using two key parameters of vergence (i.e., NPC and peak velocity). All subjects had documented mTBI, with injury onset of greater than 1 yr (1–10 yr postinjury) to avoid possible contamination from the natural recovery process [56]. All manifested several nearwork-related symptoms (e.g., intermittent diplopia) and at least one clinical sign of vergence dysfunction (e.g., receded NPC) of an oculomotor nature. All had stable general health. None had a significant cognitive dysfunction. Subjects were identified by their university-based healthcare provider and were recruited from the Raymond J. Greenwald Vision Rehabilitation

Center at the SUNY College of Optometry University Optometric Center of New York. Subjects received a comprehensive vision examination prior to participating in the experiment, which included a detailed refractive, oculomotor, and ocular health assessment.

Study Design

We conducted a crossover, interventional experimental design of a single-blind nature (for the subject) (**Figure 1**). In this design, each subject acted as his or her own control, thus negating undesirable intersubject variability. Each subject received both OMT (treatment A) and P training (treatment B). During phase 1, every odd-numbered subject first received treatment A, every even-numbered subject first received treatment B, and vice versa during phase 2. This interventional study had a duration of 15 wk. It consisted of 12 wk of the two treatment phases, 6 wk each phase separated by 1 wk, for a total of 9 h of OMT and 9 h of P training. In addition, there was a 3 wk measurement period: 1 wk before phase 1 treatment, 1 wk after phase 1 treatment, and 1 wk after phase 2 treatment. During these training and measurement periods, subjects did not perform any other OR to avoid contamination of test results.

The study consisted of the following phases:

1. Week 1: Initial baseline measures—all evaluative procedures (described later) were recorded over two separate test sessions (each session lasting for up to 1.5 h, including rest periods to prevent fatigue), each separated by at least 2 d.
2. Weeks 2–7: Phase 1 treatment—6 wk of either OMT or P training. Subjects received two training sessions per

week. Each session was 60 min in duration, involving 45 min of actual training with the remainder of time consisting of short and interspersed rest periods for the subject. Total training time was 9 h over the 6 wk.

3. Week 8: Repeat baseline measures—same as step 1.
4. Weeks 9–14: Phase 2 treatment—same as step 2.
5. Week 15: Repeat baseline measures—same as step 1.

Evaluative Procedures

Several general areas of testing were performed; these included clinical and laboratory vergence measures, as well as visual attention and near-vision symptoms. All clinical measures were assessed using standardized clinical techniques [57]. All laboratory-based objective measures were performed using commercially available instrumentation with well-established test protocols developed in our laboratory for version [54], accommodation [58], and vergence [41]. All measures were noninvasive and were recorded with the subject's habitual distance correction in place. Order of testing was randomized over the 2 d of measurements.

1. Clinical measures: Selected binocular vision-related parameters were tested with randomization under standard clinical room illumination (80 Lux). They included NPC break and recovery, horizontal near phoria using the von Graefe prism dissociation method, horizontal near PFV and negative fusional vergence (NFG) ranges, vergence prism facility (with 12 prism diopter [Δ] base-out [BO] and 3 Δ base-in [BI] prism flippers), and stereoaquity using the Titmus stereo test.
2. Laboratory-based objective measures: Vergence dynamics to symmetric step vergence stimuli was recorded using the Power Refractor II (PRII) (Plusoptix Inc; Atlanta, Georgia) based on the principle of infrared videography and dynamic retinoscopy, with a sampling rate of 12.5 Hz (resolution: <0.9°) for binocular recording, as described elsewhere [41]. This sampling rate exceeds the Nyquist criterion [59]. Targets comprised the contiguous red and green fixation light-emitting diodes (LEDs) (angular size: 0.28°) located on the measuring head of the PRII at 1 m and a white LED (angular size: 0.86°) placed at 0.3 m, both aligned along the midline. Mean response amplitude, peak velocity, time constant, and steady-state (SS) response variability were calculated separately for both convergence and divergence.
3. Subjective visual attention test: A subjective correlate of global visual attention was assessed using the Visual

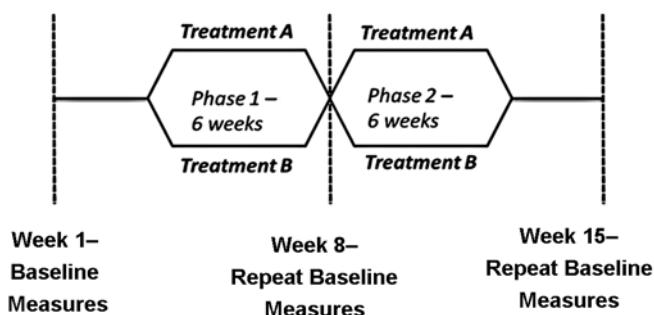


Figure 1.

Illustration of crossover interventional experimental design and treatment phases. Adapted from Thiagarajan [87].

Search and Attention Test (VSAT). It involves a search (for a letter or a symbol) and cancellation (cross-out) task that was developed by Trencerry et al. [60]. The VSAT was performed binocularly at the subject's habitual nearwork distance. Percentile scores were calculated from the age-matched normative table for the two test sheets.

4. Symptom scale: Individual symptoms related to near-work were rated by the subjects using the Convergence Insufficiency Symptom Survey (CISS) [61]. It is composed of a 15-item questionnaire probing reading-related symptoms (e.g., intermittent diplopia). The severity of symptoms is scaled from 0 to 4, i.e., from least symptomatic to most symptomatic. The total score was compared before and after each of the two training phases. A reduction in overall score of ≥ 10 was considered to reflect a significant reduction of symptoms. A score of ≤ 16 was considered to represent being relatively asymptomatic.

Treatment Protocol

Treatment A: Oculomotor Training

OMT was performed along the midline at 0.4 m, two sessions per week, for a total of 6 wk. OMT was performed with constant verbal and visual feedback, motivation, and repetition and involved active participation of the subject to maximize attention. At a session, each oculomotor component (version, vergence, and accommodation) was trained for 15 min, interspersed with 5 min rest periods. Each session lasted for 1 h, with 45 min of training and 15 min of rest periods, for a total of 9 h of training over the 6 wk OMT phase, 3 h for each oculomotor subsystem. For the purpose of the present article, however, only the vergence training and related results are discussed (**Table 1**).

For step vergence amplitude training, BO and BI prisms were used. The basic principle behind the training was to maintain the accommodative demand constant at 0.4 m (2.5 D), while increasing the vergence demand [57,62]. The fusional targets were composed of pictures, symbols, numbers, letters, tumbling E, and colors displayed on a computer screen at 0.4 m. As treatment progressed and the subject demonstrated improvement, task difficulty was increased by reducing target size (from 10° to 2°) and manually increasing the vergence demand prismatically. The total amount of prism depended on the subject's task performance level. After introducing each BO prism, subjects were instructed to fuse the target as rapidly

Table 1.
Training protocol for vergence.

Stimulus	Stimulus Parameter	Training Period Duration (min)	Total Training Duration (min)
Disparity	Step Amplitude (BO/BI)	7	15
	Step Facility (BO/BI)	5	
	Ramp	3	
No Disparity	Placebo-Step	10	15
	Placebo-Ramp	5	

BI = base-in, BO = base-out.

as possible. This trained the fast vergence mechanism [63]. The fused percept was then maintained for 15 to 20 s. This sustained viewing trained the slow vergence mechanism that maintained the vergence response [63]. Such response maintenance reflects the vergence adaptation mechanism [63–64]. BO training was terminated at the point at which subjects could no longer fuse (and/or focus) with their maximum effort. This was repeated for BI prisms, which stimulated relative divergence. The order of BO and BI training at each session was randomized.

For step vergence facility training [62], combinations of BO and BI prism flippers (3ΔBO/1ΔBI, 6ΔBO/2ΔBI, 9ΔBO/3ΔBI, and 12ΔBO/3ΔBI) were used while maintaining accommodation constant at 0.4 m (2.5 D). The fusional targets were similar to those used in the previously mentioned amplitude training. Based on the subject's initial ability to fuse, the magnitude of prism flipper was chosen. Subjects bifixated targets on a computer screen, and they were instructed to fuse and focus as rapidly as possible and to achieve the maximum number of cycles possible. As the treatment progressed and the subject demonstrated improvement, task difficulty was increased by increasing the prism flipper magnitude and by reducing target size (from 10° to 2°).

For ramp vergence training, subjects binocularly tracked an isolated, high-contrast (>90%), Snellen 20/30 letter controlled by an XY plotter and function generator moving continuously over a range of 0.5 to 0.2 m at the rate of 0.1 to 1.0 Hz. Task difficulty was increased by tracking at closer distances, with the combination of increased speed. Subjects were instructed to maintain the target clear and single.

Treatment B: Placebo Training

P training was performed as described previously for OMT. P training did not involve any disparity stimulation,

because this is the primary drive for the vergence system [10]. For the P-step, binocular and monocular plano-powered loose prism and prism flippers and/or monocular vertical prism (0.5 or 1 ΔD) flippers were used as the P training analog to OMT. Training was performed both monocularly (5 min) and binocularly (5 min). For the P-ramp, subjects tracked a difference of Gaussian (0.2 cycles/°) target through a 0.5 mm pinhole monocularly for 5 min (2.5 min each eye) in an otherwise darkened room, which did not provide any disparity (or blur or accommodative vergence) drive [10].

Data Acquisition and Analyses for Objective Recordings

The recorded video files were saved to the PRII hard drive and converted into .txt files. They were then transferred into Excel (Microsoft; Redmond, Washington) for detailed analysis. Three artifact-free (free of blinks and/or saccades) convergence and three divergence responses were selected for analysis from the right eye position traces for each subject from a sample of seven to eight responses in each direction. The middle three responses were used for analysis, and the initial and final responses were omitted to avoid possible learning and fatigue effects, respectively [41]. An exponential decay function was fit to the traces, and the response amplitudes and time constants were obtained using GraphPad Prism (GraphPad Software Inc; La Jolla, California). The peak velocities were derived from first-order differentiation of the exponential equation. The SS response variability was calculated from the standard deviation of the measured time window (~5 s) of response after SS was attained. The goodness of fit was assessed from the r^2 values of each fitted response. The mean r^2 value for both increasing and decreasing steps was always >0.8 for each subject, thus demonstrating a good fit. The mean amplitude, time constant, and peak velocity of the responses at baseline, post-OMT, and post-P training were compared statistically using GraphPad Prism at $p \leq 0.05$.

STATISTICAL ANALYSES

Combined Group

The key objective of the study was to evaluate the effect of OMT in individuals with mTBI and oculomotor-based near-vision symptoms. Therefore, the main analyses included a comparison of baseline measures before and after OMT using paired two-tailed t -tests. Data from all 12 subjects were analyzed and presented as the “com-

bined group” results. For those subjects who received OMT first, baseline measures from week 1 (baseline) and baseline measures from week 8 (post-OMT) were used for the analyses. For those subjects who received P training first, baseline measures from week 1 (baseline) and baseline measures from week 15 (post-OMT) were used for analyses. For subgroup analyses, a repeated-measures, one-way analysis of variance and Tukey post hoc analyses were performed for comparisons between baseline, OMT, and P training. In addition, correlations between relevant objective and subjective parameters were performed using linear regression.

Subgroups

See [Appendix 2](#) (available online only) for detailed subgroup analyses.

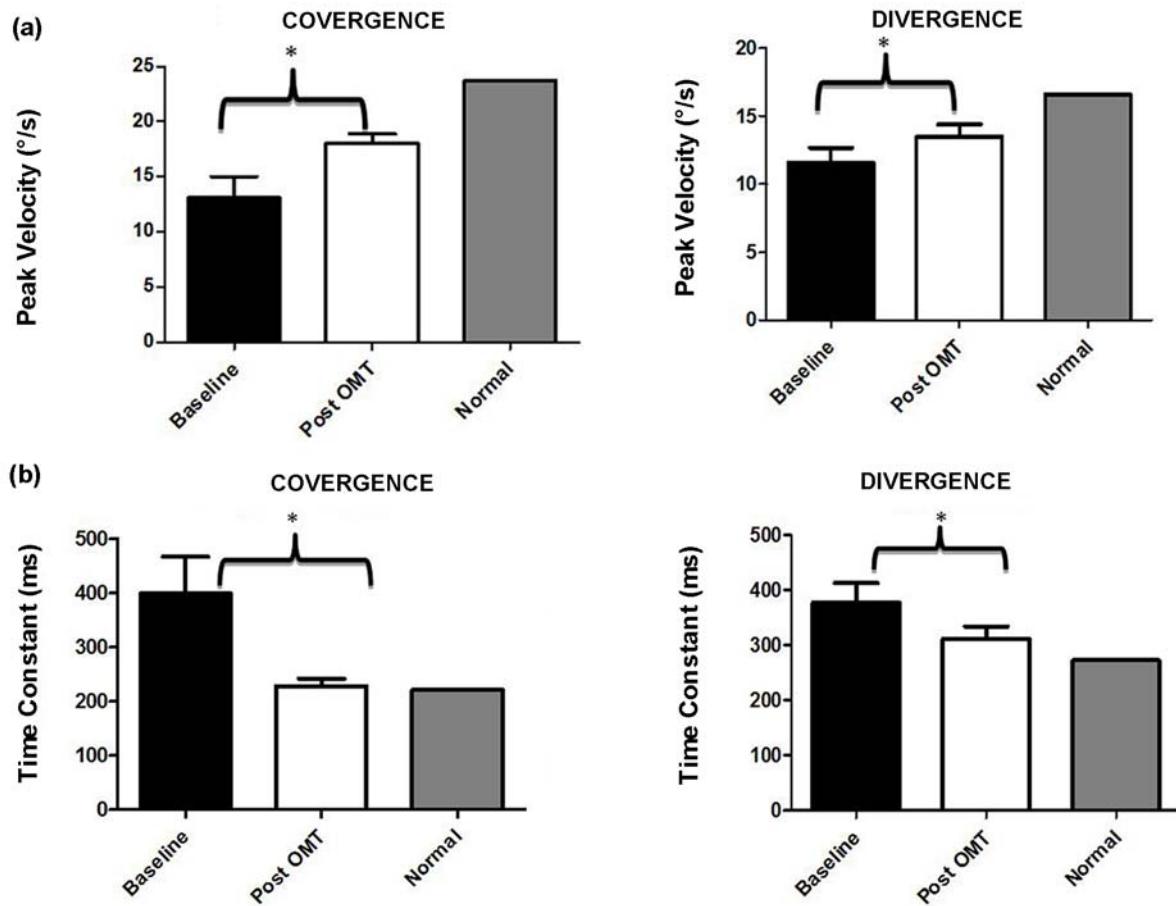
RESULTS (COMBINED GROUP ANALYSIS)

Laboratory-Based Objective Measures

The dynamic trajectories of the symmetric vergence responses from the right eye were fit using an exponential, one-phase decay function. There was a significant increase in peak velocity for both convergence ($t(11) = 3.08; p = 0.01$) and divergence ($t(11) = 3.96; p = 0.01$) following OMT, but it did not normalize ([Figure 2\(a\)](#)). There was a significant decrease in time constant for both convergence ($t(11) = 2.77; p = 0.01$) and divergence ($t(11) = 3.65; p = 0.01$) after OMT ([Figure 2\(b\)](#)). While the time constant normalized for convergence, it did not for divergence. [Figure 3](#) shows the exponential fit to vergence responses in a typical subject with mTBI. Faster convergence and divergence responses are evident following OMT. Convergence SS response variability reduced significantly ($t(11) = 2.28; p = 0.04$) after OMT, but it did not for divergence ($t(11) = 0.62; p = 0.54$). There was no significant difference in response amplitudes for either convergence ($t(11) = 0.80; p = 0.43$) or divergence ($t(11) = 0.41; p = 0.99$), because they were already accurate at baseline. See [Table 2](#) for group mean (± 1 SEM) dynamic values at baseline and post-OMT. Of the eight parameters that were abnormal at baseline, six (75%) improved significantly following OMT. The remaining two parameters were already normal at baseline.

Clinically Based Subjective Measures

Of the nine clinical parameters assessed, five were already normal at baseline, and four were found to be

**Figure 2.**

(a) Peak velocity for convergence and divergence before and after oculomotor training (OMT) in comparison with mean normal value for this response amplitude derived from Yuan et al. [75]. (b) Time constant for convergence and divergence before and after OMT in comparison with mean normal value derived from Ciuffreda et al. [48]. Error bar indicates ± 1 standard error of mean. *Significantly different.

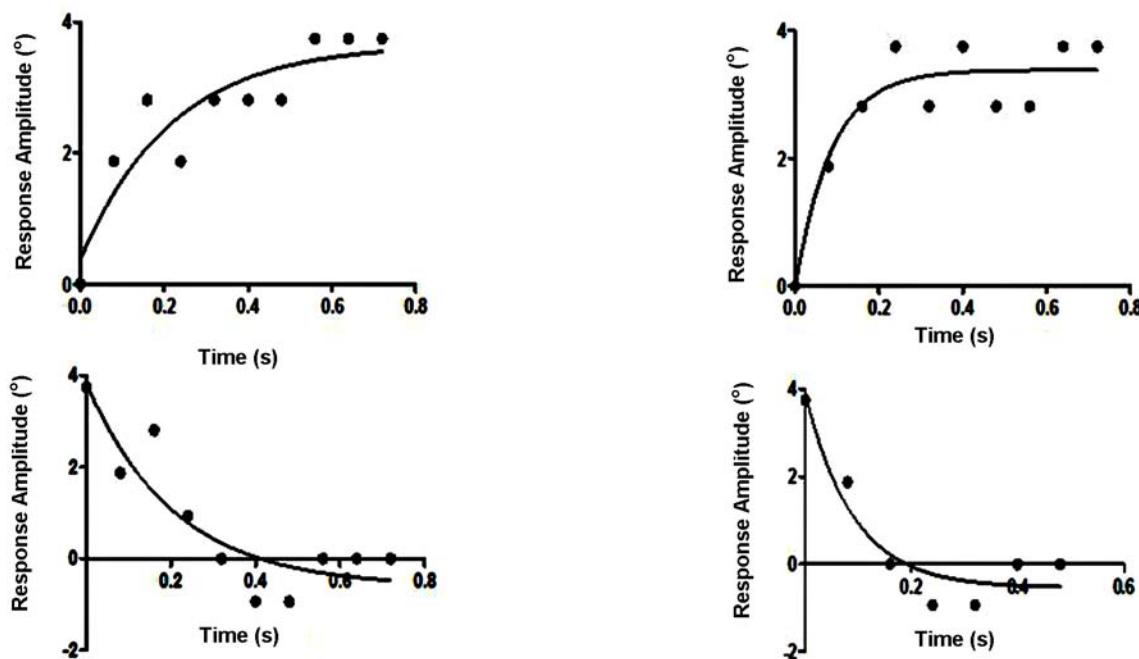
abnormal. All four abnormal parameters (100%) improved significantly following OMT. There was a significant decrease (i.e., improvement) in both the NPC break ($t(11) = 4.07; p = 0.01$) and NPC recovery ($t(11) = 3.64; p = 0.01$) after OMT, but they did not normalize (**Figure 4(a)**). In addition, this increase in maximum vergence amplitude (NPC break) was significantly correlated ($p < 0.05$) with reduction in symptoms ($r = 0.57$), as well as with improved visual attention ($r = 0.40$). Both the PFV break ($t(11) = 2.80; p = 0.01$) and PFV recovery ($t(11) = 4.71; p = 0.01$) values significantly increased with OMT. Prism vergence facility ($t(11) = 4.22; p = 0.01$) (**Figure 4(b)**) and stereoacuity ($t(11) = 2.34; p = 0.03$) also improved significantly following OMT. The NFV break increased significantly ($t(11) = 3.40; p =$

0.01) and normalized, while the NFV recovery exhibited a predicted trend ($t(11) = 2.04; p = 0.06$). There was no significant change in the horizontal near phoria value ($t(11) = 0.49; p = 0.62$), which ranged from 14 exophoria to 1 esophoria in the group. See **Table 3** for the group mean (± 1 SEM) values at baseline and post-OMT.

There was no statistically significant effect ($p > 0.05$) of the P training on any of the vergence parameters tested. See **Appendix 2** (available online only) for details.

Other Subjective Tests

The CISS total score significantly reduced ($t(11) = 3.69; p = 0.01$) from a mean value of 37 ± 4 to 28 ± 3 following OMT. This quantitatively indicated a reduction in nearvision-related symptoms following OMT.

**Figure 3.**

Horizontal eye position as function of time. Exponential fit of step vergence dynamic trajectory from right eye before (left column) and after (right column) oculomotor training for convergence (top row) and divergence (bottom row) in typical subject with mild traumatic brain injury.

Table 2.

Mean ± 1 standard error of mean laboratory-based objective parameters of symmetric vergence before (baseline) and after oculomotor training (post-OMT).

Dynamic Parameter	Baseline	Post-OMT	p-Value
C: Peak Velocity (°/s)	13.0 ± 1.9	18.0 ± 0.9	0.01*
D: Peak Velocity (°/s)	11.6 ± 1.1	13.5 ± 0.8	<0.01*
C: Time Constant (ms)	399 ± 68	228 ± 14	0.01*
D: Time Constant (ms)	378 ± 35	312 ± 22	<0.01*
C: SS Variability (°)	0.90 ± 0.07	0.75 ± 0.04	0.04*
D: SS Variability (°)	0.81 ± 0.05	0.78 ± 0.02	0.54
C: Response Amplitude (°)	$3.93 \pm 0.07^{\dagger}$	3.96 ± 0.08	0.43
D: Response Amplitude (°)	$3.93 \pm 0.06^{\dagger}$	3.93 ± 0.08	1.00

*Statistically significant.

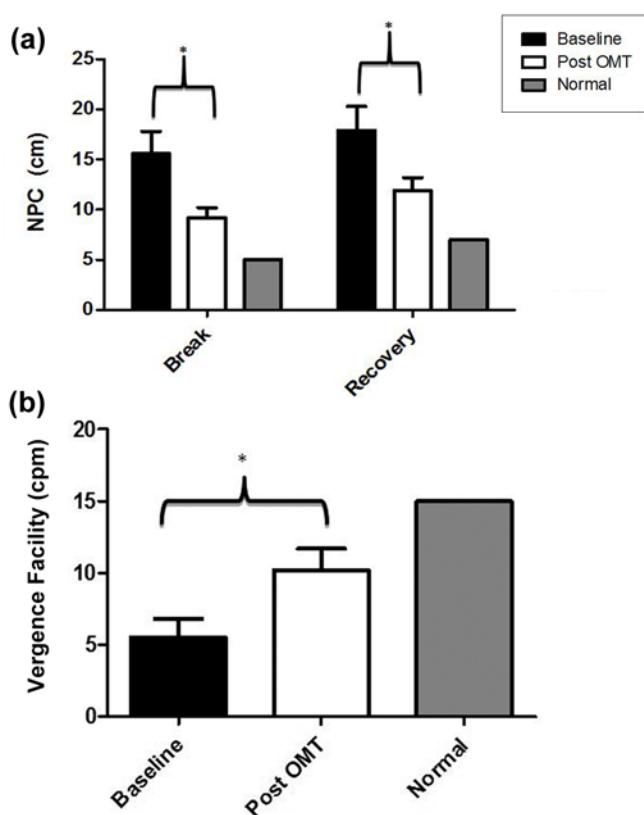
†Already normal at baseline.

C = convergence, D = divergence, SS = steady-state.

With respect to visual attention at baseline, the group mean VSAT percentiles increased significantly ($t(11) = 4.43; p = 0.01$) from the 32nd (± 9) to the 50th (± 10) percentile following OMT, with increases in 10 of the 12 (80%) subjects. This indicated quantitatively increased visual attentional aspects concurrent with OMT.

DISCUSSION

The primary aim of the present investigation was to evaluate a range of objective laboratory and subjective clinical measures of vergence before and after vergence-based OMT in individuals who reported nearwork-related

**Figure 4.**

(a) Mean near point of convergence (NPC) break and recovery values before and after oculomotor training (OMT) as compared with mean normal value derived from Manas [71]. (b) Mean vergence facility before and after OMT in mild traumatic brain injury as compared with mean normal value derived from Manas [71]. Error bar indicates ± 1 standard error of mean.

*Significantly different.

symptoms of an oculomotor nature following their mTBI. With only 3 h of total vergence training distributed over 6 wk, significant ($p < 0.05$) improvements were found in the vast majority (>80%) of the key laboratory and clinical aspects of vergence that were abnormal at baseline. The results were also compared with an equal dosage and distribution of P training. None of the vergence measures were found to have a significant group effect from the P training ($p > 0.05$).

Although most of the initially abnormal parameters significantly improved with OMT, many did not normalize. This may suggest that the OMT should be increased, perhaps twofold or greater, to obtain a yet more robust

result, assuming that the underlying neurology is sufficiently intact to yield a normalization. This critical area needs to be explored in the future. Lastly, as discussed for dynamic OMT aspects, the question remains whether additional hours of training would yield normalization of all static vergence parameters. Future studies in this critical area are needed.

Training Effect on Vergence Dynamics

At baseline, both convergence and divergence eye movements consistently demonstrated slowed dynamic trajectories in all subjects. This was evident from the reduced peak velocity along with the correlated increased time constant values. The group mean peak velocity in the population with mTBI was reduced by ~45 percent for convergence and ~25 percent for divergence [65–66]. The slowed but accurate responses suggest the presence of normal visual feedback with respect to disparity detection and processing. This is consistent with both laboratory and modeling findings, suggesting the dual-mode control of vergence [67]. That is, the initial response component (i.e., the first 200 ms) is preprogrammed (i.e., open-loop response) for the estimated amplitude of the step disparity input, followed by completion of the movement over the next several hundred milliseconds via visual feedback control (i.e., closed-loop response), with the overall response being completed in approximately 800 to 1,000 ms. These findings suggest that the slowed but accurate responses were primarily the result of improvement in the pulse subcomponent of the neural signal and not caused by its step subcomponent.

Following OMT, there was a significant increase in peak velocity by ~40 percent for convergence and ~15 percent for divergence from their mean baseline value. Concomitantly, the time constant for both convergence and divergence exhibited correlated and proportional decreases, as expected due to their inverse interrelation.

The prism flipper facility rate is the clinical analog for the overall laboratory-based vergence response incorporating and combining all dynamic parameters (i.e., peak velocity, time constant, and latency) into a global, validated metric [62]. Thus, peak velocity and prism flipper rate were found to correlate significantly with each other both before and after the OMT. At baseline, the mean vergence facility rate was ~65 percent less than the mean clinic norm [62]. With OMT, subjects could now fuse both the BO and BI prisms rapidly, with a large and significant twofold increase in facility rate, but it did not normalize.

Table 3.Mean \pm 1 standard error of mean clinically based parameters of vergence before (baseline) and after oculomotor training (post-OMT).

Clinical Parameter	Baseline	Post-OMT	p-Value
NPC Break (cm)	15.6 \pm 2.3	9.2 \pm 1.0	<0.01*
NPC Recovery (cm)	17.9 \pm 2.5	11.9 \pm 1.3	<0.01*
PFV Break (Δ)	22.0 \pm 1.8 [†]	27.0 \pm 1.6	0.01*
PFV Recovery (Δ)	13.0 \pm 1.3 [†]	21.0 \pm 1.7	<0.01*
NFV Break (Δ)	16.5 \pm 1.6	19.0 \pm 1.5	<0.01*
NFV Recovery (Δ)	10.5 \pm 1.2 [†]	12.3 \pm 1.1	0.06
Vergence Facility (cpm)	5.5 \pm 1.3	10.2 \pm 1.5	<0.01*
Horizontal Near Phoria (Δ)	5.8 \pm 1.0 (exo) [†]	6.1 \pm 0.9 (exo)	0.62
Stereoacuity (arc sec)	26.2 \pm 1.5 [†]	22.9 \pm 1.1	0.03*
CISS (score)	37 \pm 4	28 \pm 3	<0.01*
VSAT (%)	32 \pm 9	50 \pm 10	<0.01*

*Statistically significant.

[†]Already normal at baseline.

Δ = prism diopter, CISS = Convergence Insufficiency Symptom Survey, exo = exophoria, NFV = negative fusional vergence, NPC = near point of convergence, PFV = positive fusional vergence, VSAT = Visual Search and Attention Test.

In the present study, the SS response was assessed for \sim 5 s. Within this measured window of time, the SS variability for convergence decreased significantly following OMT as assessed at 30 cm. This suggests improved convergence sustainability involving the slow vergence mechanism [63]. Our previous study in this area [41] found abnormal, reduced vergence adaptation in those with mTBI, which is also typically found in those without mTBI but with vergence-related dysfunction and correlated symptoms [68]. In contrast, the SS variability did not change markedly for divergence at the 1-m test distance. This finding may not be surprising given the fact that the OMT was performed at the conventional near reading distance of 40 cm. This suggests lack of generalization of the rehabilitation effects (i.e., oculomotor learning) to the overall vergence system. In the future, vergence training should also be conducted at different distances and gaze directions to attain a more generalizable improvement in vergence responsivity.

Training Effect on Static Measures of Vergence

The NPC is the main static diagnostic measure used in the clinic for assessment of vergence dysfunctions [62]. At baseline, the subjects with mTBI demonstrated markedly receded NPC components (break and recovery), thus suggesting poor maximal convergence amplitude fusional ability. Following OMT, the NPC amplitude and recovery improved significantly but did not normalize.

The relative vergence amplitude increased in both the convergent and divergent directions following OMT. This was evident from the increased PFV and NFV break val-

ues. While the PFV recovery value significantly improved following OMT, it did not for the NFV recovery value. The relative vergence system has several response nonlinearities (e.g., amplitude, dynamics) between PFV and NFV [62], and this may reflect one such difference [66]. This is consistent with the fact that training relative convergence (PFV) is easier than relative divergence (NFV) [69]. It is also consistent with neurophysiological evidence demonstrating more convergence-related cells present than divergence-related cells [15].

The overall improvement in convergence ability was also reflected in the improved near stereoacuity with OMT. Presumably, this is caused by improvement in vergence response accuracy and stability, which would reduce the mean fixation disparity vergence error at near, hence improving stereoacuity [10]. This is consistent with the recent finding that increased fixation disparity was significantly correlated with reduced stereoacuity at near in individuals with mTBI [41].

However, OMT did not seem to have an effect on the near horizontal phoria. In the nonadapted state of vergence, this value reflects the horizontal position of eyes in the absence of fusional vergence [70]. This value would be expected to change only if the cross-link ratio (response accommodative convergence/accommodation) changed [71]. However, past studies have reported constancy of this cross-link following vergence training in both visually nondisabled subjects [64,72] and in symptomatic individuals manifesting binocular vision dysfunction [73].

From the present findings, as well as from the previous studies that assessed objective and clinical measures of

vergence, it appears that the laboratory-based peak velocity and clinically based prism flipper facility, along with NPC, are key diagnostic measures in the population with mTBI. This is consistent with recent suggestions in the literature based on the SUNY research group findings [41,74].

Neurophysiological Implications

Although several areas of the brain have been identified in the control of vergence, the midbrain houses the majority of vergence-related neurons [11]. The motoneuronal controller of vergence has been found to be somewhat similar to saccades, because the final neural signal consists of a small and broad pulse combined with a step [75–76]. The pulse signal, which is produced by the midbrain vergence “burst cells” that fire in relation to vergence velocity, is responsible for rapidly displacing the eyes in a time-optimal manner to a new binocularly fixated target position. In contrast, the step signal, which is produced by the vergence tonic cells that fire in relation to vergence angle, maintains the SS eye position (i.e., vergence angle) on the binocularly fixated target accurately [77]. A neural integrator (i.e., nucleus reticularis tegmenti pontis) [78–79] has been proposed to process the velocity signal to a step signal. Then, the combined signal is sent via the oculomotor neurons to innervate the extraocular muscles to make an appropriate vergence eye movement [11].

Based on the results of the present study at baseline, and earlier studies [41–42], the primary neural deficit in the patient with mTBI is believed to be the pulse. This is reflected in the consistently slowed dynamics (e.g., reduced peak velocity and increased time constant) for both convergence and divergence in the present study prior to OMT, which can be accounted for by a reduction in pulse height. Thus, the overall time course of the vergence dynamic trajectory was slowed. Since the appropriate vergence amplitude was eventually attained both before and after OMT, this suggests that the step component had the appropriate mean height. However, the subsequent vergence SS level exhibited increased variability, which suggests that the presence of increased neural noise could produce a more variable step signal. Tonic vergence cells constantly fire to maintain this SS level. The increased SS variability could reflect a higher degree of variability in the neural firing of such cells. Following OMT, the increased peak velocity can be attributed to an increase in pulse height (presumably because of the increased firing rate), thus resulting in faster motor responsivity to attain the final SS position. Following

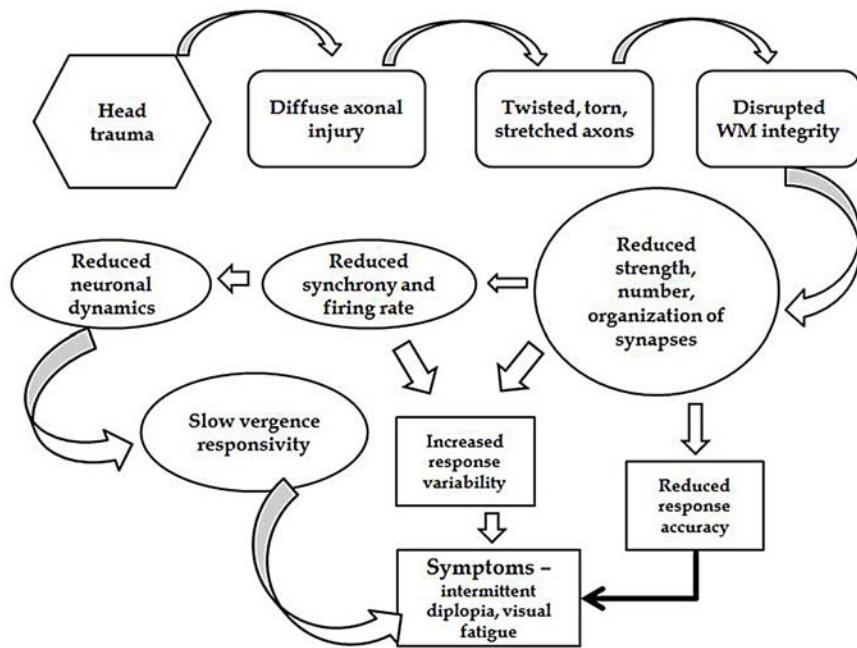
OMT, the reduced SS variability during convergence could be attributed to reduced step gain variability as a result of normalization of tonic cells firing.

Mechanisms of Neuroplasticity and Oculomotor Learning

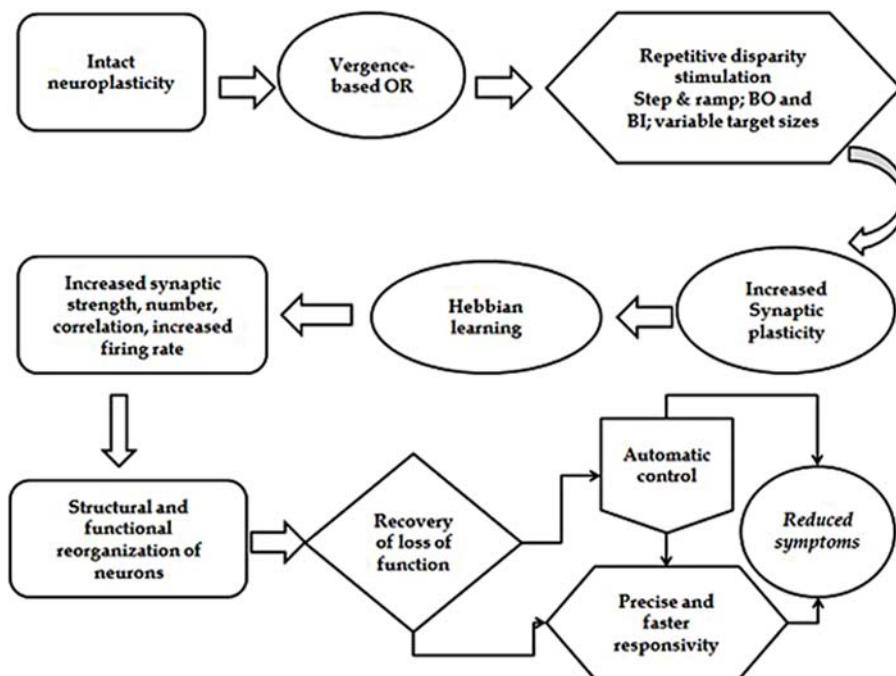
Under normal circumstances, repeated synaptic stimulation, along with its coincident activation, results in an increased synaptic strength and memory storage [80–82]. This experience-dependent neuroplasticity is composed of biochemical-, cellular-, physiological-, and structural-level changes [83]. Recovery following an insult to the brain has been categorized as “spontaneous reorganization” (or natural recovery) and “training-induced recovery” [56]. The former occurs immediately following injury. It is believed to involve restoration of neurotransmission in the adjacent spared area and regions distant from the injury location. This natural recovery period following TBI occurs over the first 6 to 9 mo [84]. However, training-induced recovery appears to be relatively independent of the amount of time elapsed after the injury. Significant oculomotor improvements can occur even 5 to 10 yr after the first injury [8]. This involves functional recovery via a “relearning” process. Remapping and reconfiguration of neural circuits both within and across relevant regions play a significant role in the recovery process [83].

Following TBI, the decreased vergence response peak velocity may be attributed to diffuse axonal injury. The compromised white matter integrity causes slowed conduction of nerve impulses [85–86], thus resulting in an overall slowed response (e.g., slowed vergence). In addition, the decreased number of synapses, reduced firing rate, reduced neural synchrony, and lack of correlation within and across the specific brain regions cause loss of automaticity and an overall reduction in the system’s maximum amplitude (e.g., NPC) [42]. **Figure 5** shows the schematic representation of the proposed neurological mechanisms involved based on the aforementioned laboratory findings.

OMT acts as a relearning process, in which the system being trained or conditioned regains its automaticity through repetition, which then becomes preprogrammed with much practice. In the present study, an overall improvement in oculomotor behavior was observed in all individuals with mTBI. It is believed to be a consequence of “oculomotor learning” involving the relearning processes described earlier [83]. **Figure 6** shows the schematic representation of the proposed mechanisms of OR based on

**Figure 5.**

Proposed neural mechanisms of traumatic brain injury causing vergence dysfunction. WM = white matter.

**Figure 6.**

Proposed underlying mechanisms of vergence-based oculomotor rehabilitation (OR). BI = base-in, BO = base-out.

the aforementioned laboratory findings. A combination of repeated stimulation with various amounts and types of disparity (crossed and uncrossed), increasing task-level difficulty, active participation of the subjects, increased attention, presence of visual and verbal feedback, and high motivation of the subjects to perform the task over the 6 wk training period resulted in a significant OMT effect. These ideas are further supported by a recent study [42] that evaluated the neurological changes using the functional magnetic resonance imaging technique in two individuals with mTBI before and after intensive vergence-based OMT. Their results showed increased amount of voxels and correlation within specific regions of interest (brain stem, cerebellum, frontal eye fields, and supplementary eye fields) following a total of 18 h of clinically based and laboratory-based vergence OR, similar in nature to that conducted in the present study. Their results also correlated with increased vergence peak velocity, as found in the present study. The increased convergence peak velocity was found to correlate with an increase in amount of active voxels and correlation within the brain stem, cerebellum, and frontal lobe regions. While the NPC was correlated with the brain stem activity, the PFV amplitude was correlated with frontal, parietal, and cerebellar regions. Increased cortical activity was suggested to be due to “neural recruitment” in the previously specified regions, and the correlation was attributed to “improved synchronization” of the involved subsystems vergence neurons [42]. These findings provide further direct neurological support for the proposed neurological process involved in our OMT (**Figures 5–6**).

CONCLUSIONS

Vergence-based OR was effective in individuals with mTBI who reported nearwork-related symptoms. Overall improvement in nearly all of the critical, abnormal measures of vergence was observed both objectively and clinically. Improved vergence motor control was attributed to residual neural visual system plasticity and oculomotor learning effects in these individuals. Concurrently, nearwork-related symptoms reduced, and visual attention improved.

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Author Contributions:

Study concept and design: P. Thiagarajan, K. J. Ciuffreda.

Acquisition of data: P. Thiagarajan.

Analysis and interpretation of data: P. Thiagarajan, K. J. Ciuffreda.

Drafting of manuscript: P. Thiagarajan.

Critical revision of manuscript for important intellectual content: P. Thiagarajan, K. J. Ciuffreda.

Statistical analysis: P. Thiagarajan.

Obtained funding: K. J. Ciuffreda.

Administrative, technical, or material support: K. J. Ciuffreda.

Study supervision: K. J. Ciuffreda.

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Participant Follow-Up: We do not plan to inform participants of the publication of this study. However, they have been encouraged to check PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) for study publications.

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ORIGINAL ARTICLE

Versional eye tracking in mild traumatic brain injury (mTBI): Effects of oculomotor training (OMT)

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Abstract

Objective: To evaluate a range of objective measures of versional eye movements before and after oculomotor training (OMT) in individuals with mTBI. The results were compared with placebo (P) training.

Methods: Twelve individuals with mTBI (mean age = 29 ± 3 years) having oculomotor-based near-vision symptoms participated in the study. Versional eye movements were recorded objectively before and after OMT (fixation, predictable saccades, simulated reading) and P training (6 weeks each, two sessions/week, 45 minutes/session).

Results: Following OMT, there was a significant ($p < 0.05$) reduction in the horizontal fixational error. Saccadic gain increased both horizontally and vertically ($p < 0.05$). The saccade ratio for the simulated reading, multiple-line paradigm reduced significantly ($p < 0.05$). None of the measures changed significantly following the P training.

Conclusions: The versional-based OMT had a significant, positive effect on most aspects of versional tracking. These findings are suggestive of improved rhythmicity, accuracy and sequencing of saccades following OMT in mTBI as a result of oculomotor learning.

Keywords

Neuroplasticity, oculomotor coordination, oculomotor training, traumatic brain injury, versional eye movement disorders, vision therapy

History

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Introduction

Oculomotor scanning of objects in one's visual world across different directions of gaze at a fixed distance is controlled by the versional eye movement system [1, 2]. It includes the fixational, saccadic, pursuit, optokinetic and vestibular sub-systems. These sub-systems act in a co-ordinated manner to stabilize the visual scene onto the high-resolution fovea. Of these versional sub-systems, the present paper focuses on the fixational and saccadic eye movement aspects. While the saccadic sub-system guides foveation to a new target initially positioned at an eccentric retinal location, the fixational sub-system stabilizes this new target on the fovea. Both act synchronously and in a time-optimal manner for effective visual scanning and registration of localized objects.

Numerous cortical and sub-cortical sites are involved in the generation and execution of saccades, as well as the maintenance of visual fixation [2]. Extensiveness of these neural networks makes them highly vulnerable to the diffuse and pervasive brain injury caused by the typical coup–contre-coup head trauma [3]. Moreover, the consequent saccadic and fixational abnormalities will likely adversely affect overall reading eye movements and the reading process itself [1], as reading predominantly consists of the continuous sequencing of saccades and intervening fixational pauses along the line of text.

Objective assessment of versional eye movements in TBI

Saccadic latency (i.e. time from stimulus change to saccadic onset) is one of the most commonly assessed oculomotor parameters following head trauma. An early study in this area was conducted by Ron et al. [4]. Their patient population ($n = 28$) included individuals with non-categorized diffuse brain injury only, diffuse brain damage with brain stem lesions and those who had craniotomy only. Twelve exhibited a mean increase in saccadic latency of ~ 270 milliseconds vs ~ 180 milliseconds in normals [1]. Time elapsed between the brain injury and the measurements was not specified. Later, Ron [5] reported similarly increased latency (mean = 329 milliseconds) in four out of 10 patients, 2–4 months following injury, which normalized over the subsequent 7 months. These findings are supported by more recent results from Pearson et al. [6], who tested 12 collegiate boxers 12 hours before and 7 minutes after three rounds (each 2 minutes) of a competitive bout. Nine (75%) had abnormally increased latency (by 20–40 milliseconds) as compared to their pre-fight baseline value. When they were re-tested 3, 7 and 12 days later, latency progressively reduced and returned to the pre-fight baseline value, thus indicating a relatively rapid natural recovery process in these young adults, as well as lack of any delay in all subjects tested. Several other studies have found normalcy of saccadic latency 1 week to 1 year following head trauma [7–9], thus again suggesting relatively rapid neural repair.

Saccadic gain (i.e. ratio of the first saccade amplitude to the step target amplitude) has also been frequently assessed

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in head trauma. A preliminary report detailed above by Ron et al. [4] revealed that nine of the 28 patients executed either abnormal hypometric or hypermetric saccades (gain values not specified). Furthermore, seven could not voluntarily execute a saccade to a change in target position for 5, 10 or 15° step displacements. Later, Ron [5] reported abnormally-low, mean saccadic gain (0.6) in five out of 10 patients with TBI. Fifty per cent executed abnormal multiple saccades, with this pattern found to normalize in 3–9 months. In contrast, Heitger et al. [10] reported normal gain (0.97) for horizontal, reflexive saccades in 30 individuals 10 days following mild closed-head injury (CHI). A recent, more comprehensive study by Heitger et al. [8] evaluated the effect of post-concussion syndrome (PCS) on a range of saccadic parameters. Six months following injury, normal mean saccadic gain was found in the 36 individuals having mild CHI with PCS (0.95), similar to that found in those 36 without PCS (0.96), with this being similar to that found by Kraus et al. [11]. One case report found reduced gain for vertical saccades in a patient with mTBI assessed more than 1 year post-injury [12]. They reported a gain value of 0.80 for upward saccades and 0.74 for downward saccades, with normal gain (~1.0) for horizontal saccades. While the above recent studies [8, 10–12] included only mild TBI patients, Ron's older studies [4, 5] did not classify their subjects. This difference in populations tested could contribute to the disparity in gain findings in the various studies. Thus, the results in this area are equivocal.

Normal *peak velocity* for visually-guided, reflexive saccades has been found in the TBI population over post-injury times from 10 days to 1 year [8, 10–12]. All saccades followed the normal main-sequence relationship [13]; that is, the peak velocity increased predictably and appropriately with increase in saccade amplitude. Peak velocity also seems to be unaffected following mild TBI, even when tested only a week following injury [7]. This suggests that brain areas controlling saccadic peak velocity are either spared or have an extremely rapid repair process, similar to that found for saccadic gain.

While basic saccadic parameters have been extensively studied using different experimental paradigms, *saccades during reading* have not, despite the fact that 'difficulty with reading' is the most common symptom (~90%) in TBI [14–18]. This is to be expected, as at least 50% of the visually-symptomatic mTBI population has saccadic tracking abnormalities [14]. Using simulated reading paradigms, Ciuffreda et al. [19] found that all nine individuals tested with mTBI executed an excessive number of saccades for a given number of target step displacements. This was evident from their calculated 'saccade ratio' (i.e. number of saccades executed/number of target displacements) [20]. This ratio was calculated for their single line (2.6) and multiple-line (1.4) simulated reading paradigms, where a ratio close to 1.0 is considered normal (i.e. one saccade per target step displacement). This increased saccade ratio is in agreement with the multiple, excessive saccades found by Ron et al. [4] in six out of 10 individuals with TBI, which normalized 4–9 months later. In addition, the clinically-based Visagraph system, which is a common clinical test for the objective assessment of reading and oculomotor-based reading-related parameters [21], indicated a reduced reading rate (mean 183 wpm), as

well as an increased number of fixations (mean 122) and regressions (mean 24), from the norm for grade-10 reading material in these nine adult individuals with mTBI [19]. This result was consistent with the finding of Kapoor et al. [12], who reported similarly abnormal Visagraphic reading eye movement findings in one patient with mTBI.

In contrast, fixational eye movements in mTBI has been the least studied area. Objective recordings in one case study [12] demonstrated increased binocular fixational errors along the horizontal, vertical and radial directions measured in five different gaze positions: central, ±10° horizontally and ±10° vertically 10 years post-injury. Mean error across all five positions of gaze along the horizontal, vertical and radial directions was 0.38, 0.46 and 0.26°, respectively. Similarly abnormal results were also found in a group of nine patients with mTBI when tested 1 year or more following their injury [22]. The mean horizontal, vertical and radial fixational errors were found to be ~0.5°, 0.7° and 0.75°, respectively.

Oculomotor training of versional eye movements in mTBI

While numerous studies have been conducted to diagnose oculomotor disorders in mTBI, relatively few have evaluated the effect of OMT on fixation and saccades. The first report was by Ron et al. [4] and Ron [5], in which six patients were trained for 7–15 weeks, 5 days a week, two sessions a day, 30–40 minutes each session. Mean saccadic gain increased from 0.6 to 0.8, but it did not normalize. Saccadic gain increased more rapidly and to a greater extent in those patients who received formal OMT when compared to those who simply were allowed to have natural recovery with no formal training aspect. This positive effect of the OMT persisted at the 2-month follow-up. While Ron's [5] study did not specify the training protocol used, a clearly-defined and detailed laboratory-based protocol for OMT in TBI was first proposed by Han et al. [20]. They used either normal visual (V) feedback alone or combined normal visual + oculomotor auditory (V+A) feedback to train fixation, saccades, pursuit and simulated reading; that is, with the latter approach, the patients continuously 'heard' their eye movements and related errors. Using this protocol, Ciuffreda et al. [19] trained nine patients with mTBI over an 8 week period, two sessions per week, for a total of 9.6 hours. Each session lasted for 36 minutes of total training for 8 weeks: 4 weeks using V feedback alone and 4 weeks using V+A feedback, in a counterbalanced manner. A significant reduction in the saccade ratio for both the single-line (from 2.6 to 1.95) and multiple-line (from 1.38 to 1.11) simulated reading paradigms was found. Thus, the results demonstrated an overall improvement in basic saccadic tracking following OMT. Similarly, in a case report, fixational error along the horizontal (0.38 to 0.25°), vertical (0.46 to 0.28°) and radial (0.26 to 0.17°) directions reduced by 30–40% with OMT in a patient with mTBI [12]. In the same subject, low vertical saccadic gain (for ±5 and ±10° predictable stimuli) was found at baseline, which increased significantly following training. Upward vertical saccadic gain increased from 0.8 to 0.9, and downward vertical saccadic gain increased from 0.74 to 1.04. Similarly, following 2.4 hours of fixational training, Ciuffreda

et al. [22] reported marked percentage reduction in fixational error along the horizontal (30%), vertical (57%) and radial (47%) directions in all nine patients with mTBI.

While the above investigations demonstrated improved versional tracking in mTBI with OMT, there were some limitations. First, they did not include a placebo training programme. Second, none trained all three oculomotor subsystems, which are directly related to reading (i.e. version, accommodation and vergence). Hence, the purpose of the current investigation was to evaluate basic versional tracking involving fixation and visually-guided saccades in individuals with mTBI before and after laboratory-based OMT, all purposely conducted *without* a home-based component to control compliance. Although the training involved all three main oculomotor sub-systems, namely vergence, accommodation and version, for the purpose for the present paper *only* the oculomotor sub-system of version is discussed. The measures were also compared after an equal dose of placebo (P) training. It is hypothesized that, while OMT would significantly improve fixation stability and saccadic accuracy, placebo training would not have a significant impact on any of the parameters.

Methods

Subjects

Twelve individuals between the ages of 23–33 years (mean age = 29 ± 3 years) with medically documented mTBI and all having a mild brain injury onset of greater than 1 year (1–10 years post-insult) participated in the study. This sample size was calculated using a power analysis program (G-Power software) at an alpha level of 0.05, with the power set at 0.80 based on two key parameters of version (i.e. saccadic gain and saccadic peak velocity). Subjects were identified by their university-based healthcare provider and were recruited from the Raymond J. Greenwald Vision Rehabilitation Center (RJGVRC) at the State University of New York (SUNY), State College of Optometry, University Optometric Center, New York City. Each received a comprehensive optometric vision examination prior to participating in the experiment, which included refractive, oculomotor and ocular health assessment. The study was approved by the SUNY Institutional Review Board (IRB) and the US Army Department of Defense (DoD) IRB. Written informed consent was obtained prior to participation. All exhibited at least one clinical symptom (e.g. skipping lines while reading, re-reading) and one clinical sign (e.g. reduced reading rate with objective Visagraph testing) of a non-strabismic oculomotor nature related to impaired reading.

Study design

A cross-over, interventional experimental design of a single-blinded nature (for the subject) was used [23]. Each subject received oculomotor training (OMT) (Treatment A), as well as placebo training (P) (Treatment B). During phase 1, every odd-numbered subject first received Treatment A and every even-numbered subject first received Treatment B and vice-versa during phase 2. This was a study of 15 weeks duration. It consisted of 12 weeks of the two treatment phases, 6 weeks

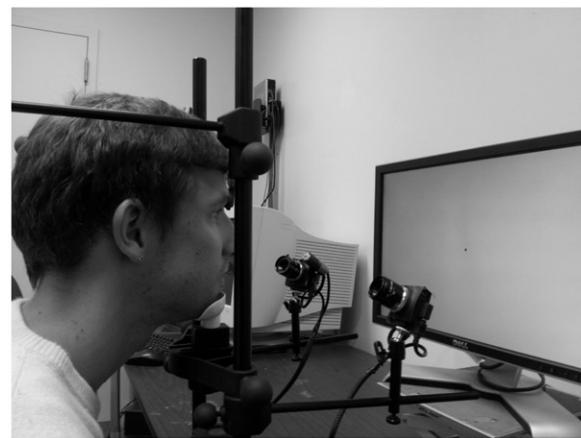


Figure 1. Arrington eye movement recording cameras arranged for versional eye movement recording.

each phase, separated by a week, for a total of 9 hours of OMT and 9 hours of P training. In addition, there was a 3 week measurement period: 1 week before phase 1 treatment, 1 week after phase 1 treatment and 1 week following phase 2 treatment. During these testing and training periods, subjects did not perform any other OMT to avoid contamination of test results.

Instrumentation

Basic binocular horizontal and vertical versional eye movements were recorded objectively using the Arrington eye movement recording system (Figure 1), which is a table mounted, infrared, binocular camera system with a 220 Hz sampling rate and 0.01° resolution [24]. This sampling rate satisfies the Nyquist criterion for high fidelity dynamic recordings [25]. A 12-point calibration was performed at each test session to assure response linearity, as well as after any rest period. Computer-controlled test stimuli were comprised of a 1° bright square target, which was displayed on a high-resolution computer monitor at a 40 cm test distance along the midline. Subjects were instructed to fixate the centre of the target. These test stimuli and paradigms were developed in the laboratory [20]. Subjects binocularly fixated/executed saccades based on the parameter tested.

Assessment protocol

The following parameters were assessed in random order:

- Binocular central fixation: The target was presented at the centre of the computer screen for 20 seconds along the subject's midline. Horizontal and vertical eye position was continuously recorded and calculated. See Table I for stimulus parameters.
- Saccadic gain: This was calculated using predictable horizontal and vertical saccadic stimuli. See Table I for stimulus parameters.
- Saccadic latency: This was calculated using random horizontal and vertical saccadic stimuli. See Table II for stimulus parameters.
- Saccade ratio: This was calculated using the simulated reading single line (SRSL) and simulated reading multiple lines (SRML) stimuli. See Table III for stimulus parameters.

Treatment protocol

Phase 1 and phase 2 treatment phases

Treatment A—OMT procedures. The OMT was performed along the midline at 40 cm, two sessions per week, for a total of 6 weeks. Training was performed with constant verbal and visual feedback, motivation, repetition and active participation of the subject. At every session, each oculomotor component (version, vergence and accommodation) was

Table I. Stimulus parameters for predictable saccade testing paradigm.

Stimulus	Amplitude (degrees)	Frequency (steps/second)	Test period duration (seconds)
Predictable horizontal saccades	± 2.5 ± 5	0.33	54
Predictable vertical saccades	± 2.5 ± 5	0.33	54

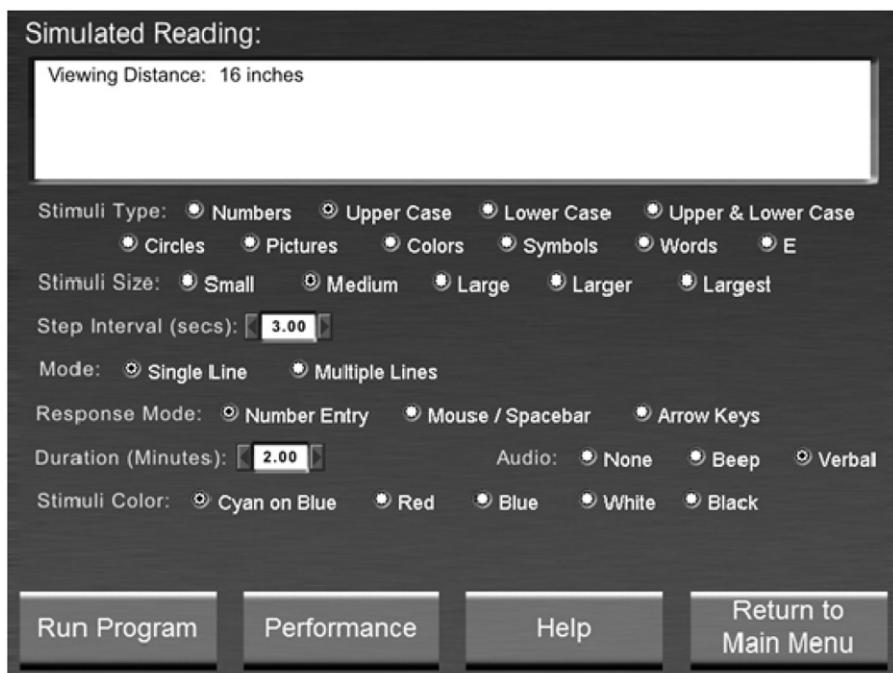
Table II. Stimulus parameters for random saccade testing paradigm.

Stimulus	Amplitude (degrees)	Frequency (steps/second)	Test period duration (seconds)
Random horizontal saccades	1/2/3	0.33/0.5/1	50
Random vertical saccades	1/2/3	0.33/0.5/1	50

Table III. Stimulus parameters for simulated reading testing paradigm.

Stimulus	Total amplitude (degrees)	Target amplitude (degrees)	Frequency (steps/second)	Test period duration (seconds)
Full-screen multiple-line simulated reading	± 10	1/2/3	0.5	220
Single-line simulated reading	± 5	2.5	0.5	50

Figure 2. Sample interface screen of COR program for simulated reading training.



trained for 15 minutes, interspersed with 5-minute rest periods. Each session lasted for 1-hour, with 45 minutes of training and 15 minutes of rest periods, with a total of 9 hours of training over the 6 week OMT phase, 3 hours for each oculomotor sub-system [23]. For the purpose of the present paper, only version alone is discussed.

Version (fixation, predictable saccades and simulated reading) was trained via the computerized oculomotor rehabilitation (COR) software developed in the laboratory using a rapid serial visual presentation (RSVP) paradigm [26] to maintain visual attention under binocular viewing conditions. With the RSVP paradigm, the subject must track all targets presented while recalling the number of times a pre-selected target appeared. Figure 2 presents the sample COR interface screen for training simulated reading. Targets in the form of pictures, numbers, symbols, letters, colour patches, etc., of varying sizes could be presented rapidly for different presentation times, along with blank intervals. Subjects either fixated a stationary target or executed saccades to track the target. At the commencement of each training component, a sample pre-selected target (e.g. picture) was first presented to the subject. Then, while maintaining either binocular fixation and/or saccadic tracking of the different possible targets, the subject was asked to count the number of times the sample target appeared during the stipulated training duration to maintain a high level of attention. The subject's response was compared with the actual number of presentations (provided by the software) to assess accuracy. Subjects were constantly motivated to achieve the maximum number of correct responses. Verbal feedback regarding a subject's performance was also provided by the software in the form of a female voice. See Table IV for the versional training stimuli.

Treatment B—Analogous P training procedures. Similar to the OMT, P training was performed along the midline at 40 cm, two sessions per week, for a total of 6 weeks, as described above for OMT [23].

Table IV. Stimulus parameters for versional training protocol.

Stimulus	Stimulus parameter	Training period duration (seconds)	Total training duration (seconds)
Fixation	Central (midline)	60	300
	Left (10°)	60	
	Right (10°)	60	
	Up (10°)	60	
	Down (10°)	60	
Predictable saccades	Horizontal ($\pm 5^\circ$)	50	300
	Horizontal ($\pm 10^\circ$)	50	
	Vertical ($\pm 5^\circ$)	50	
	Vertical ($\pm 10^\circ$)	50	
Simulated reading (repeated twice)	Full-screen	75	300
	Single-line	75	
	Full-screen	75	
	Single-line	75	

Fixation P training (5 minutes) purposely involved no formal, programmed and repetitive feedback-related central fixation task *per se* [27]. Subjects bifixated the estimated centre of the contourless blank computer screen at a 40 cm distance for 2 seconds before two targets (1 inch square picture/symbol/letter) were presented for 100 milliseconds, $\pm 10^\circ$ either horizontally or vertically with respect to the presumed/estimated fixation point. The subject attempted to identify the targets. Hence, no foveally-based visual feedback related to positional error was provided, as was the case with the OMT. The peripheral target presentation time (100 ms) was purposely shorter than the mean population saccadic latency (~ 180 ms) [1].

Saccade P training involved completion of perceptual puzzle blocks (5 minutes) with no formal, programmed and repetitive fixation or saccades *per se*. It involved the execution of intermittent and random saccades interspersed with random fixational pauses that would not be effective in training the saccadic system [27]. Subjects completed the puzzle by arranging the individual puzzle blocks into an appropriate pattern, both monocularly and binocularly.

Simulated reading P training consisted of a visual concentration task (5 minutes). This involved no formal, programmed and repetitive fixation or saccades *per se*. It rather involved the execution of intermittent and random saccades interspersed with fixational pauses that are not effective in training the reading eye movement system [28]. The subject viewed and randomly scanned with saccades an array (varying from 3×3 to 5×5) of pairs of pictures for a 10-second period. Then, the pictures were extinguished, and the subject was requested to recall the location of a specific picture.

Data acquisition and analyses

The output of the Arrington eye movement system was comprised of a DAT file spreadsheet, which was then converted into comma separated values (CSV) for detailed analyses. The output of the software was analysed from the right eye using a C++ program. For the saccadic ratio, any saccade greater than or equal to 0.25° in amplitude was included for both the SRML and SRSL analyses. For binocular midline fixation, blink artifacts and positional

errors greater than 2 SD from the mean were removed and horizontal and vertical standard deviations were calculated from the mean eye position. For each subject, saccadic gain and peak velocity were averaged from 10 artifact-free (e.g. no blink), high quality responses for each stimulus amplitude, both horizontally and vertically. Saccadic latency for each subject was averaged from a minimum of 20 responses.

Statistical analyses

Combined group

The primary objective of the study was to evaluate the effect of the OMT on oculomotor-based, near-vision symptoms and oculomotor control in mTBI. Therefore, the main analyses included a comparison of baseline measures before and after the OMT using paired, two-tailed *t*-tests. Data from all 12 subjects were analysed and presented as the ‘combined group’ results. For subjects who received OMT first, baseline measures from week 1 (baseline) and baseline measures from week 8 (post-OMT) were used for the analyses. For those subjects who received P training first, baseline measures from week 1 (baseline) and baseline measures from week 15 (post-OMT) were used for the analyses. For the sub-group analyses, a repeated-measures, one-way ANOVA and Tukey’s post-hoc analyses were performed for comparisons between baseline, OMT and P training.

Sub-groups

See the Appendix for detailed sub-group analyses.

Results

Combined group analysis ($n = 12$)

Versional parameters assessed at baseline and following the OMT (post-OMT) were statistically compared. See Table V for mean values of versional parameters before and after the OMT. Six of the seven (86%) parameters that were abnormal at baseline significantly improved following OMT.

Figure 3 presents a 2-dimensional, fixational plot from a typical individual with mTBI before and after the OMT. The fixational error reduced in both the horizontal and vertical dimensions by $\sim 35\%$ following the OMT. For the group, the mean horizontal standard deviation (i.e. variability or positional error) for binocular central fixation also reduced significantly ($t[11] = 2.54$, $p = 0.02$). However, the group mean vertical standard deviation for binocular central fixation did not reduce significantly ($t[11] = 1.26$, $p = 0.23$).

Figures 4(a) and (b) present unedited traces of horizontal saccadic eye movements before and after the OMT, respectively, for the simulated-reading, multiple-line (SRML) paradigm from a typical subject with mTBI. A ratio of 1.0 would indicate perfect saccadic tracking; that is, every target step displacement would be tracked by a single, accurate saccade. Following OMT, there was a marked reduction in the number of progressive and regressive saccades (see Table V), as well as a decreased number of blinks. The group mean saccade ratio for the SRML paradigm reduced significantly ($t[11] = 3.83$, $p = 0.002$) with OMT, thus demonstrating improvement in sequential saccadic tracking. However, the

Table V. Mean (± 1 SEM) laboratory-based parameters of version before (baseline) and after OMT (post-OMT).

Dynamic parameter	Baseline	Post-OMT	Significant	p Value
Fix – H – deviation (degrees)	0.4 (0.04)	0.26 (0.03)	yes	0.02
Fix – V – deviation (degrees)	0.42 (0.11)	0.27 (0.04)	no	0.23
SRML ratio	2.1 (0.2)	1.7 (0.2)	yes	<0.01
SRSR ratio	2.7 (0.3)	2.2 (0.4)	no	0.06
Saccadic latency – H (milliseconds)	192 (5.5)*	188 (6.5)	no	0.12
Saccadic latency – V (milliseconds)	193 (6.7)*	198 (8.2)	no	0.30
Saccadic gain – $\pm 2.5^\circ$ H	0.72 (0.02)	0.83 (0.05)	yes	0.03
Saccadic gain – $\pm 5^\circ$ H	0.8 (0.04)	0.85 (0.04)	yes	0.05
Saccadic gain – $\pm 2.5^\circ$ V	0.84 (0.02)	0.91 (0.01)	yes	<0.01
Saccadic gain – $\pm 5^\circ$ V	0.88 (0.02)*	0.91 (0.01)	no	0.18
Saccadic peak velocity – $\pm 2.5^\circ$ H (degrees/second)	174 (8)*	202 (12)	yes	0.03
Saccadic peak velocity – $\pm 5^\circ$ H (degrees/second)	273 (17)*	299 (14)	no	0.15
Saccadic peak velocity – $\pm 2.5^\circ$ V (degrees/second)	199 (8)*	217 (7)	no	0.06
Saccadic peak velocity – $\pm 5^\circ$ V (degrees/second)	306 (13)*	322 (11)	no	0.15

Fix, binocular fixation; H, horizontal; V, vertical; SRML, simulated reading multiple lines; SRSR, simulated reading single line. Italicized = statistically significant. *Normal at baseline.

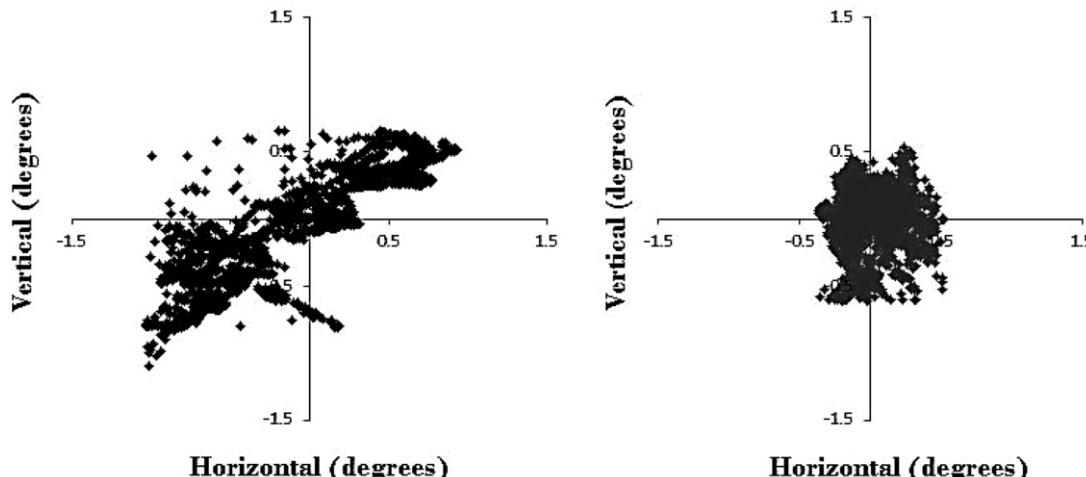


Figure 3. Two-dimensional plot of binocular central fixation before (left) and after (right) OMT in a typical individual with mTBI. Data presented from the right eye.

mean saccade ratio for the simulated reading single line (SRSR) paradigm did not ($t[11] = 2.06, p = 0.06$), but it demonstrated a decreasing trend suggestive of improvement.

There were several important findings with regard to the basic horizontal and vertical saccadic findings. See Table V for the before and after OMT results. First, all saccades over the range executed ($\sim 3\text{--}9^\circ$) exhibited a normal peak velocity-amplitude relationship, both before and after the OMT (Figures 5(a) and (b)). That is, they followed the normal ‘main sequence’ response profile [13], thus indicating a normal neurological pulse-step controller signal. While there was a small but statistically significant ($t[11] = 2.35, p = 0.03$) increase in peak velocity for the $\pm 2.5^\circ$ horizontal saccades after training, the values remained within the high normal range on the main sequence distribution for that specific amplitude. Second, saccadic gain significantly increased in three of the four test conditions following OMT. That is, it increased significantly for the $\pm 2.5^\circ$ predictable stimulus in both the horizontal ($t[11] = 2.4, p = 0.03$) and vertical ($t[11] = 3.54, p = 0.004$) directions and for the $\pm 5^\circ$ predictable stimulus horizontally ($t[11] = 2.16, p = 0.05$). For the $\pm 5^\circ$ vertical saccades, the gain was almost normal (0.88) at baseline and, hence, no

change ($t[11] = 1.41, p = 0.18$) was expected. Accordingly, the reduced amplitude of the primary saccade before training increased after training, with a concurrent increase in its peak velocity per the main sequence neurological constraint [13]. An example is shown in Figure 6. Third, saccadic latency did not change with OMT for either horizontal ($t[11] = 1.65, p = 0.12$) or vertical ($t[11] = 1.06, p = 0.30$) random saccades, as it was already normal at baseline.

Sub-group analysis

There was no statistically significant effect ($p > 0.05$) of P training on any of the versional parameters tested.

Discussion

The primary hypothesis of the present study was that versional OMT would improve objectively-assessed aspects of fixation, saccades and simulated reading in mTBI via motor learning, whereas the P training would not. With only 3 hours of versional training distributed over 6 weeks, marked and significant improvements were found (see Thiagarajan [23] for more details). Furthermore, a significant reduction in nearvision-related symptoms and increased visual attention,

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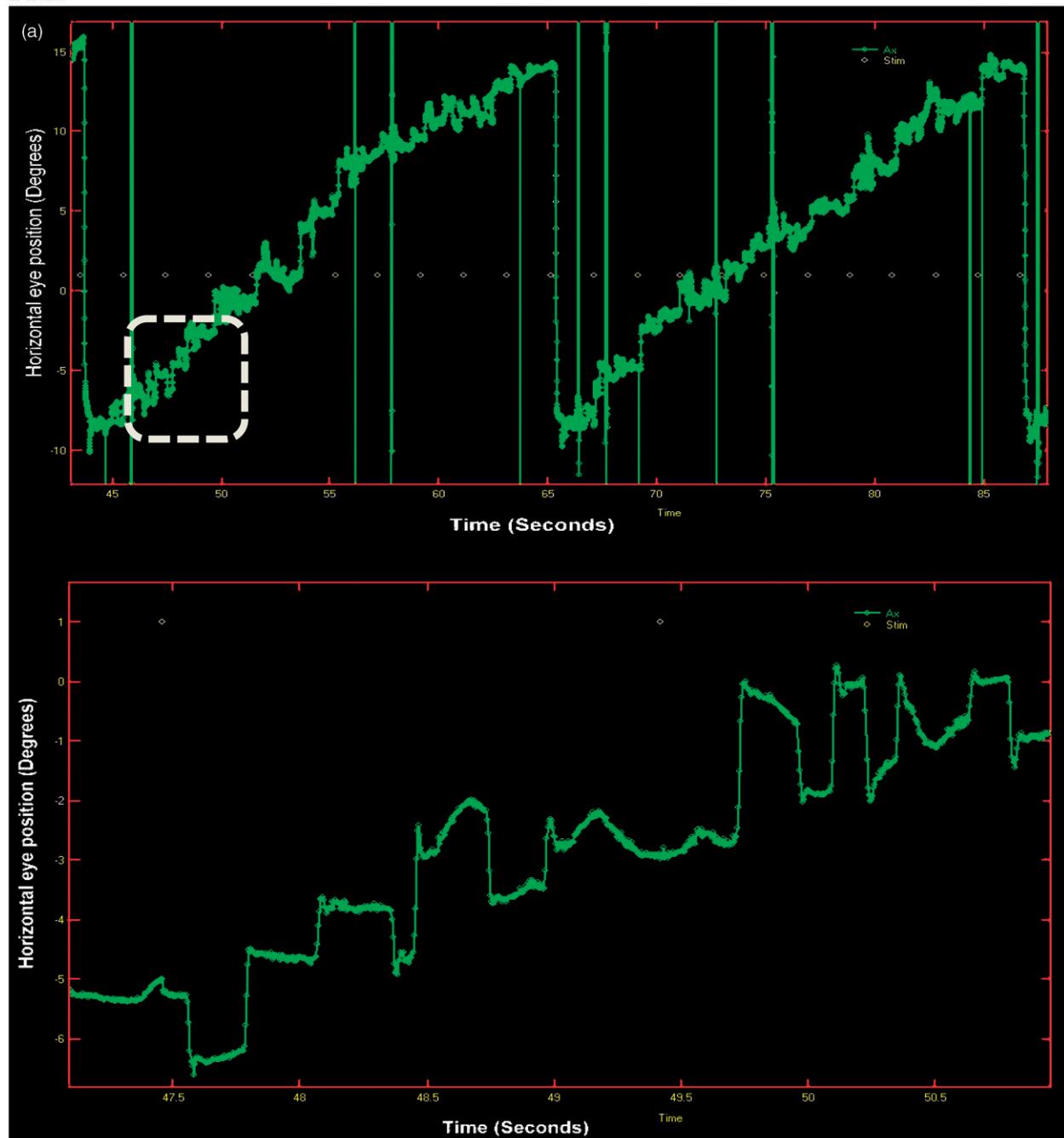


Figure 4. Horizontal eye position (degrees) as a function of time (seconds). (a) Unedited sample eye movement trace from SRML paradigm BEFORE OMT. (b) Sample eye movement trace from SRML paradigm AFTER OMT. Upward = left-to-right saccade and downward = right-to-left saccade. Large deflections represent blinks. Upper trace: a sample of two lines from the entire recording. Lower trace: Magnified view of piece of trace as marked with white-dotted line in the upper trace. This shows an increased number of progressive and regressive saccades that are not correlated with stimulus change (small open circles) and a decreased number of progressive and regressive saccades almost in conjunction with stimulus change. Green trace, Ax – horizontal eye position; small yellow open circles (stim) = stimulus onset. PRE = before and POST = after training.

with an overall improvement in the reading ability, was documented [23]. While the OMT had a significant effect on many aspects of version, the P training did not have an effect on any parameter, which was consistent with this hypothesis.

Binocular fixation

At baseline, both the mean horizontal and vertical fixational errors were similar in magnitude (0.4°). This is $\sim 60\%$ and 80% greater than found in five normal individuals (mean age

31 years) along horizontal and vertical directions, respectively, in the laboratory control group [23]. This is also similar to literature values [1]. With training, the fixational error reduced in both the horizontal and vertical directions by $\sim 35\%$, thus demonstrating improved fixational stability and accuracy. While the fixational error normalized horizontally, it nearly did so vertically. The increased inter-subject variability along the vertical meridian resulted in absence of statistical significance, despite a similar percentage of error reduction. The present results confirmed the findings of

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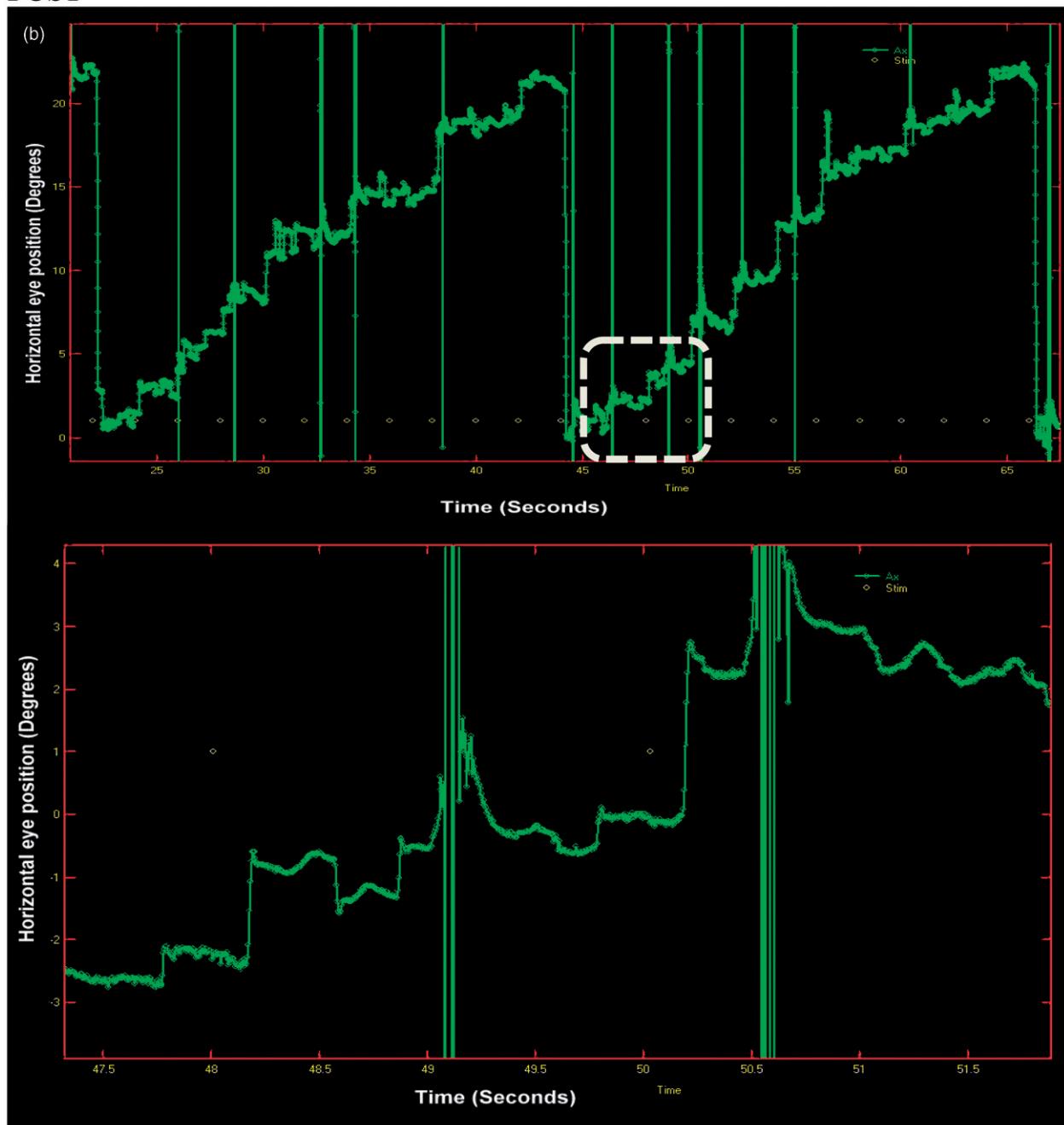


Figure 4. Continued.

Kapoor et al. [12], as well as Ciuffreda et al. [22], who reported similar and significant improvement in fixation along the horizontal, vertical and radial directions at five different gaze positions in nine subjects with mTBI following 8 weeks of versional-only OMT (9.6 hours total).

There are two likely reasons for the improved fixational ability following OMT. First, improved fixational ability following the OMT is presumed to have resulted from underlying neuroplasticity-induced, oculomotor learning [27, 29]. Second, although the present study did not involve direct attentional training, a component of visual attention is always embedded in OMT [27, 30], which in turn would likely also contribute to the improved fixation. It is also possible that the

improvement in binocular fixation at the near 40 cm test distance in the present study could be attributed to the vergence and accommodative training that was performed concurrently [23, 31]. However, correlations of the horizontal and vertical fixational errors with both maximum convergence amplitude (NPC break) and maximum binocular accommodative amplitude (AA), which were two key parameters, were not significant. This suggested versional fixational improvement being independent from the other two oculomotor sub-systems, at least with respect to their maximum response amplitudes. Similar findings in the earlier studies with versional training only are consistent with this notion [12, 19, 22].

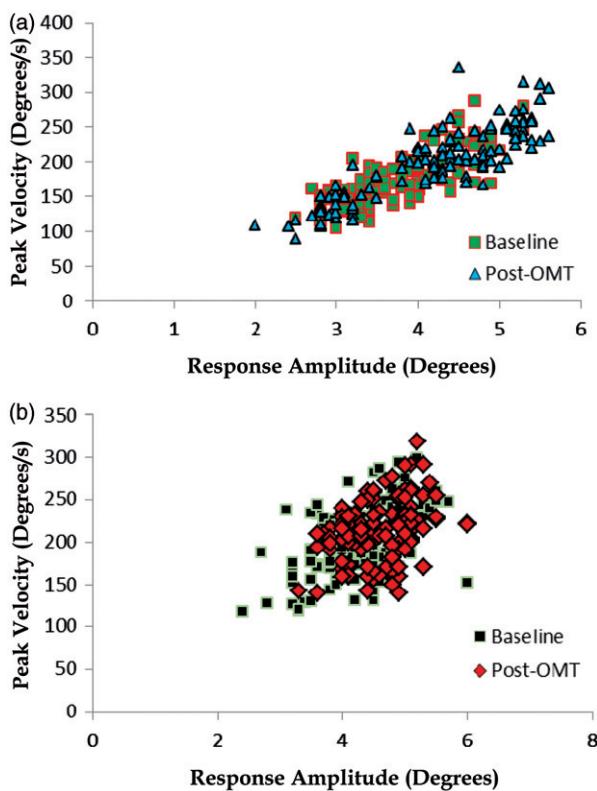


Figure 5. Main sequence plot for saccades found during the $\pm 2.5^\circ$ (a) horizontal and (b) vertical stimulus amplitude condition (5° step) before (baseline) and after (post-OMT) OMT.

Saccadic tracking

Saccadic eye movements revealed several interesting results. First, normal saccadic latency for unpredictable saccades both before and after the OMT was found. This demonstrates absence of a visual processing delay. Furthermore, it suggests that the neural sites related to visual processing were either spared or manifested rapid neural repair. Second, and similarly, all predictable saccades assessed both before and after the OMT followed the normal main sequence relationship [13, 32]. That is, they exhibited normal amplitude-matched peak velocities. This too suggests either sparing of, or rapid neural repair to the underlying neural substrates. Furthermore, it suggests normal pulse-step matched, neurological controller signals driving the saccadic system. These two findings are in agreement with those of Heitger et al. [7, 8, 10]. Third, similar to normals, the primary (i.e. initial) saccades exhibited hypometria, that is static undershooting [1], followed by one (or more) corrective saccades to acquire the target foveally. However, the magnitude of the hypometria was abnormally large (i.e. reflecting low saccadic gain), which increased following the OMT. This suggests the presence of considerable oculomotor-based, visual system plasticity. These saccadic gain findings, as well as those of Ron et al. [4] and Ron [5], are not in agreement with others [7–12]. A possible reason for these discrepancies may be ill-defined subject categorization of the individuals tested having TBI. Thus, the area of saccadic gain in mTBI remains equivocal, and this requires further careful investigation with a large and well-defined population.

Simulated reading

Since target position progressively changed stepwise, and at a given time only one target appeared on the screen, subjects were conditioned to suppress any attempt at executing regressive saccades during the simulated reading [33]. A saccade ratio of 1.0 is ideal and, hence, the goal of such training. At baseline, subjects executed at least *twice* the ideal number of saccades for both the single-line (SL) and multiple-line (ML) paradigms. This finding is consistent, in part, with the general results of Ron et al. [4]. Unlike the present study, however, Ron (1981) found accurate saccadic tracking 3–9 months after brain injury. The saccade ratio for the SL paradigm was greater than that found for the ML paradigm, both before and after the OMT. This result agrees with the case study report by Kapoor et al. [12], as well as Ciuffreda et al. [34]. While target change in the SL paradigm was predictable both spatially and temporally, it was only predictable temporally in the ML paradigm. Since prediction has been associated with an increased number of large, extraneous and inaccurate saccades [1], the higher saccade ratio found in the SL paradigm testing may not be unexpected. Following OMT, however, the saccade ratio in both paradigms reduced by $\sim 20\%$, although it did not normalize. While this reduction was statistically significant for ML, it was nearly so for SL. Regressions reduced by at least 50–60% from baseline, and progressions reduced by $\sim 35\%$. This percentage reduction is consistent with that reported by Ciuffreda et al. [34]; however, it is less than the value (40% for ML and 50% for SL) reported by Kapoor et al. [12] in one patient with mTBI. Additional training may be needed to result in normalization of the saccade ratio. Reduction in the saccade ratio demonstrates improved accuracy, rhythmicity and more precise gain control of the saccadic system following training, all being critical aspects for normal reading [28, 34].

Since reading eye movements involve sequences of saccades interspersed with fixational pauses, could individuals with mTBI have abnormal *sequencing* of saccades? The literature provides evidence for increased positional and directional errors in those with mTBI during memory-guided sequencing saccades [10, 35], in which subjects practiced saccade sequences in the light and then were requested to repeat them in the dark. Brain regions, such as supplementary eye field (SEF), supplementary motor area (SMA), parietal eye field (PEF), posterior parietal cortex (PPC), frontal eye field (FEF) and dorsolateral prefrontal cortex (DLPFC) have been reported to be involved in spatial inaccuracy and response errors [36]. However, no such study has been performed to assess saccadic accuracy during reading eye movements. While the present study, as well as the past case report [12] and population study [34], measured the saccade ratio, saccadic accuracy *per se* was not directly assessed but rather inferred. Such information would provide additional insight into the eye movement anomalies during reading in this population, and it deserves future investigation.

If multiple saccades were caused in part by attentional deficits, which is common in this population [37, 38], the frontal lobe might be involved. While memory-guided sequences have been evaluated in mTBI, and the areas

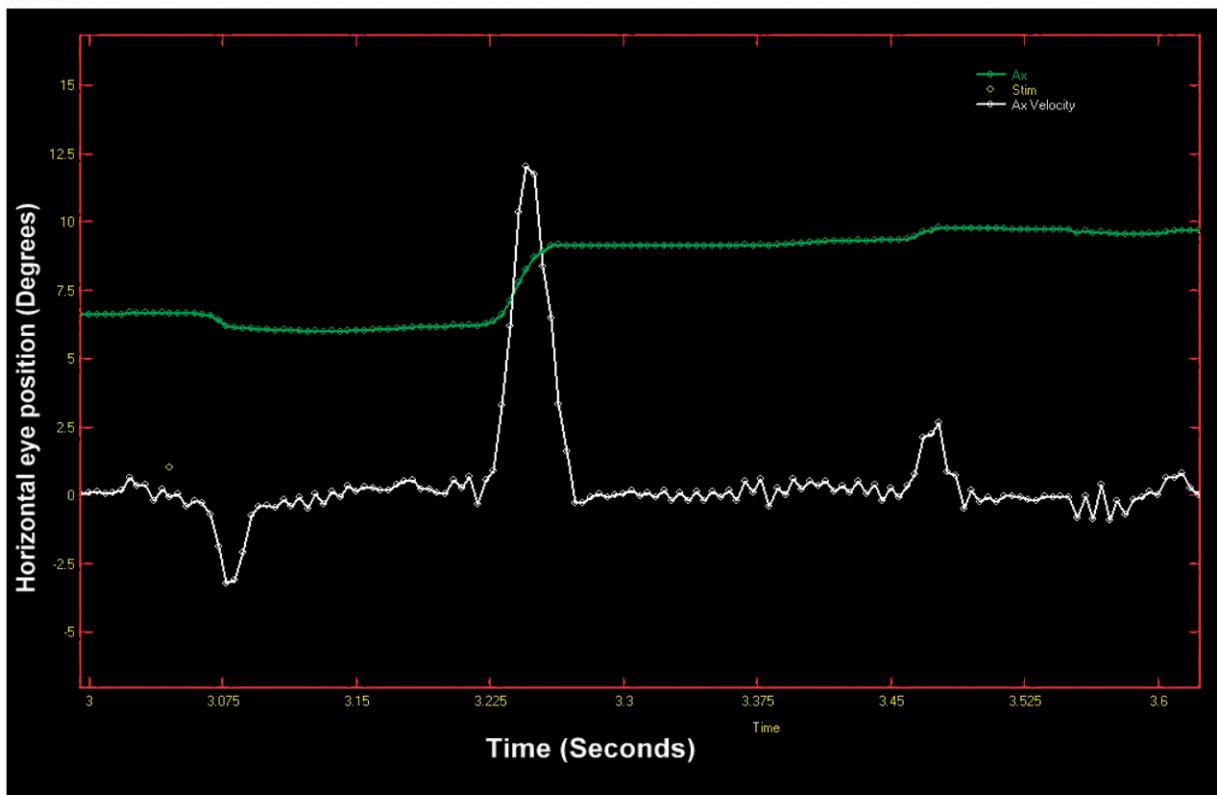
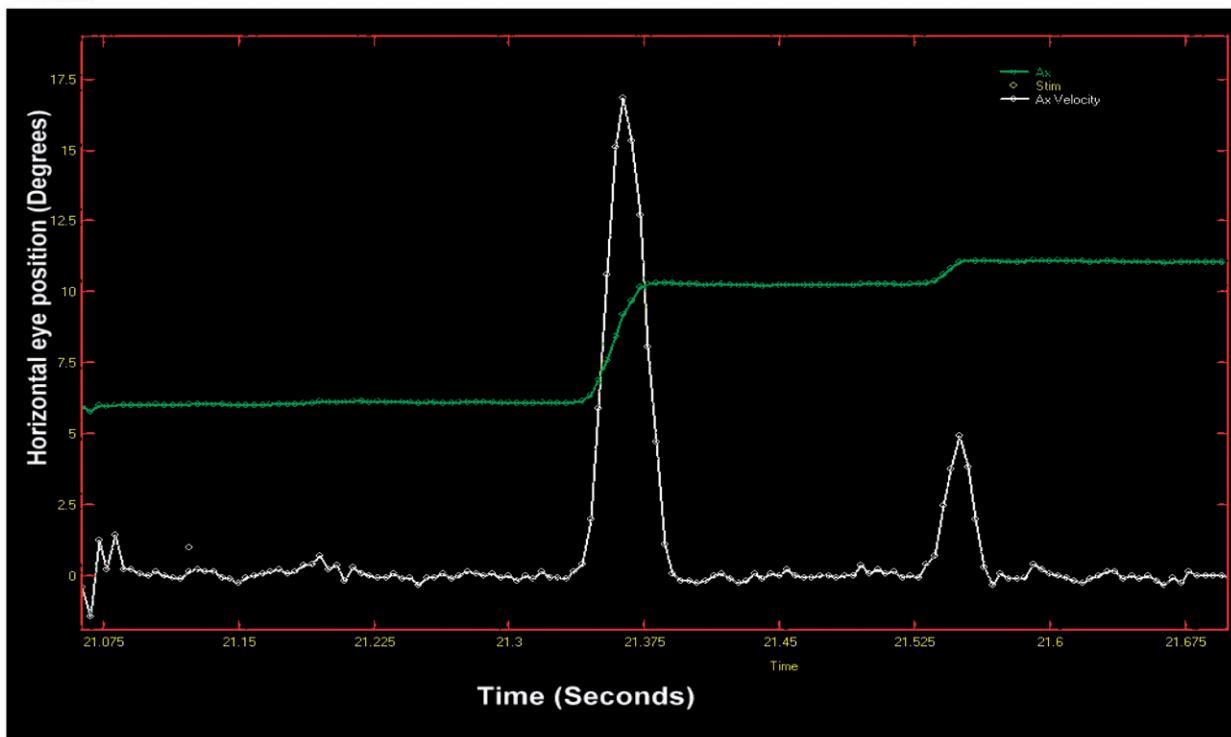
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Figure 6. A sample saccade trace for $\pm 2.5^\circ$ predictable horizontal stimulus (5° step) before (upper trace) and after (lower trace) OMT. Upward deflection = left-to-right saccade. Ax – right eye horizontal position; stim = stimulus onset; Ax velocity – right eye horizontal velocity. Green trace, Ax – horizontal eye position; small yellow open circles (stim) = stimulus onset. Increased saccadic gain with correlated peak velocity value is evident from the post-training trace. PRE = before and POST = after training. In each panel, top trace is eye position, and bottom trace is eye velocity.

SMA [39] and PPC [40] were found to be involved, detailed testing of saccadic sequencing *per se* as related to reading has not been assessed. Evaluation of reading eye movements, in conjunction with fMRI techniques, would provide critical

information on those brain areas activated during reading. A spectrum of brain regions are involved in text comprehension, such as lateral prefrontal cortex, Wernicke's area, dorsomedial prefrontal cortex, anterior temporal lobes, posterior

cingulate cortex, etc. [41]. Testing eye movements during actual simulated reading without a cognitive component, as done in the present study, provides information on the influence of these basic eye movements on overall reading ability in the absence of any contextual and linguistic factors.

Possible neuroanatomical regions involved

The neural network for visual fixation and saccadic control is extensive [2]. It involves the parietal and frontal cortices, thalamus, basal ganglia, superior colliculus (SC), brain stem reticular formation and cerebellum. Based on the biomechanical nature of mTBI (e.g. coup–contrecoup), there is increased possibility for a more diffuse type of brain injury in these individuals, although diffuse tensor imaging (DTI) data are not readily available. A global form of injury, such as in mTBI, might affect multiple regions associated with versional oculomotor control, execution, initiation and generation.

Increased fixational error in the present study suggests involvement of the SC and the pons, since motor aspects of steady fixation are predominantly controlled by the tonic firing rate of SC fixation neurons (FNs) and omnipause neurons (OPNs) of the pons to prevent the occurrence of extraneous saccades [42]. In addition to the aforementioned fixation-related neurons in the SC and pons, several other regions of the brain have been found to modulate activity during active fixation. Cells in area 7a of the posterior parietal cortex (PPC), dorsomedial frontal cortex [43], frontal eye fields (FEF) [44] and basal ganglia [45, 46] have been found to increase their activity during fixation. However, the precise contribution of these areas during active fixation has not been identified. Unstable fixation found at baseline in the present study could be attributed to the reduced number and/or discharge rate of the fixation-related neurons in the above-mentioned neurological sites that were presumably compromised following the TBI.

While the higher-level cortical processes involving the areas of V1, V2, lateral intraparietal (LIP), FEF, supplementary eye fields (SEF) dorsolateral prefrontal cortex (DLPFC) and medial eye fields (MEF) control target localization and calculation of the required eye position change, lower level midbrain and cerebellar areas controlling the actual saccade signal generation may be involved [2]. The caudal region of the superior colliculus (SC) plays an important role in target selection and saccade initiation [2]. Neurons from the SC project to the brainstem premotor burst neurons either directly or via NRTP of the pons, which in turn projects to the cerebellum and to the brainstem. The SC receives input from all cortical areas directly from the parietal eye field (PEF) and from the frontal regions (FEF, SEF, DLPFC) either directly or indirectly through the basal ganglia [2]. In addition to projecting to the SC, the cortical eye fields also project to the cerebellum via the medial NRTP of the pons. The caudal portion of the NRTP, which receives input from the SC, has been shown to consist of neurons that encode the size and direction of saccades similar to the collicular burst neurons. Since saccadic gain was low in the present study, structures involved in positional error calculation and saccade size estimation, such as the LIP, FEF, MEF and NRTP, might be

compromised following a typical coup–contrecoup insult involving axonal injury.

Although both the PEF and FEF are involved in saccadic initiation, the former has been suggested to be predominantly involved in the sensory-motor transformation and control of visually-guided, reflexive saccadic initiation [47]. Given the fact that an mTBI would likely cause diffuse axonal damage, reaction time measurement reflects WM integrity indirectly. Normal latency of saccades suggests an intact PEF area.

The final neural signal for the saccade is a pulse-step [2, 13]. While the pulse, generated by the burst neurons, displaces the eyes against the orbital viscous forces, the step, generated by the omnipause neurons, maintains the eyes on the target against the elastic restoring forces of the orbit. Burst neurons are primarily located in the brainstem area; for horizontal saccades in the PPRF of the caudal pons, while for vertical and oblique saccades in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). The critical regions of the cerebellum that are involved in saccade programming are the Purkinje cells of the dorsal vermis, which provides input to the caudal fastigial nucleus. They both are involved in controlling the pulse portion of the saccade. In addition, the flocculus and paraflocculus regions of the cerebellum control the pulse-step match. The cerebellum also receives feedback from the brainstem to terminate the on-going saccade, once foveated. Thus, the cerebellum acts as a ‘calibrator’ organ for controlling saccadic accuracy with respect to both amplitude and direction [2, 48]. Since there was no evidence of a pulse-step saccadic controller mismatch for both horizontal and vertical saccades in the present study, the cerebellum is likely relatively intact [2]. This notion is consistent with the finding of Heitger et al. [7, 10], who suggested that the cerebellum and the occipital areas are less affected in mTBI.

All saccades in the present study followed the main-sequence relationship having normal amplitude-matched peak velocity [13]. Peak velocity is primarily controlled by the brainstem burst neurons involving the pons. The normal peak velocity findings suggest that this area is either not compromised or has undergone very rapid neural repair in the mTBI population. While saccadic peak velocity was found to be normal, in contrast, peak velocity for both vergence and accommodation were found to be significantly reduced in the same group of subjects tested during the same time frame [23, 31, 49]. This suggests that the mTBI predominantly affected the midbrain area, thus sparing deeper brainstem areas in this population.

Oculomotor rehabilitation and neuroplasticity

All improvements found in the present study could be attributed to motor relearning [27, 29]. The significant improvement in overall eye movements following the OMT confirmed the presence of preserved mechanisms of neuroplasticity, even in the compromised adult human brain following an mTBI. Structural changes, such as increased synaptic number and strength, increased axonal/dendritic arborization, etc., have been demonstrated to be markers of neuroplasticity resulting in functional and behavioural changes [50]. Such remapping and reorientation of neural

networks in multiple brain areas that control fixation and saccades are believed to have caused the oculomotor behavioural changes observed in the present study. Repeated stimulation of programmed, systematic, sequential target displacements during training over 6 weeks resulted in improved sequencing, accuracy and rhythmicity of the saccadic eye movements.

Future directions

Evaluation of the persistence of the treatment effects is critical to plan for future vision rehabilitation protocols. Although the 6-weeks of OMT had statistically significant positive effects, oculomotor control did not normalize in many cases. This suggests the need for additional training, such as double or triple the treatment duration used in the present study, assuming that the brain is not too compromised to respond to this additional therapy: that is, it may be too damaged to do so and may never fully normalize in all respects. Follow-up at the 3rd and 6th months is on-going. Results from the follow-up will be used to develop the optimal treatment duration, strategy and perhaps include the need for 'booster' therapies to maintain the effect over the long-term (i.e. years). Lastly, neuroimaging should be performed to determine those neural sites activated by the OMT.

Conclusions

Oculomotor rehabilitation had a significant, positive impact on most parameters of version that were abnormal at baseline. Saccadic eye movement tracking improved markedly, thus demonstrating improved accuracy and rhythmicity. Similarly, binocular fixation became more accurate. The significant treatment effect in the mTBI population is suggestive of an intact neuroplasticity mechanism aiding oculomotor learning.

Declaration of interest

This project was funded by the US Army, DoD, Awards #: W81XWH-10-1-1041; W81XWH-12-1-0240 (PI: Dr. Ciuffreda). The authors report no conflicts of interest.

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Appendix

Sub-groups analyses

Odd group

There were seven subjects in this group who received OMT (Treatment A) during Phase 1 and P training (Treatment B) during Phase 2. Out of the seven subjects, two (BR03 and AK11) completed Phase 1, but withdrew from the study during Phase 2 training due to their lack of availability. Another subject (DB07) completed both phases of training, but suffered a second head injury during post-training measures (week 15); hence, evaluative procedures (repeat baseline measures) could only be performed partially in this subject. However, data from all seven subjects were analysed for baseline vs post-OMT for comparison. For comparisons involving baseline, post-OMT and post-P training, data from four subjects that completed both phases of training including post-training measures, along with available data from DB07, were analysed.

Even group

There were five subjects in this group who received P training (Treatment B) during Phase 1 and OMT during Phase 2. All completed both phases of training and post-training measures. Data from all five subjects were analysed for comparing baseline vs post-OMT, as well as comparisons involving baseline, post-P and post-OMT training.

Sub-group results

Odd group (n = 5), order of treatment: A–B

Objective versional parameters measured at baseline, then following the OMT (post-OMT) and later following the P training (post-P) were

Table AI. Mean (± 1 SEM) parameters of version before (baseline), after OMT (post-OMT) and following P training (Post-P) in the ODD group.

Parameter	Baseline	Post-OMT	Post-P
Fix – H – deviation (degrees)	0.39 (0.04)	0.20 (0.02)	0.25 (0.02)
Fix – V – deviation (degrees)	0.32 (0.02)	0.27 (0.05)	0.21 (0.05)
SRML ratio	2.5 (0.4)	2.1 (0.4)	2.4 (0.2)
SRSL ratio	3.7 (0.5)	3.1 (0.8)	3.3 (0.9)
Saccadic latency – H (milliseconds)	192 (4)	187 (8)	187 (9)
Saccadic latency – V (milliseconds)	190 (11)	198 (19)	203 (12)
Saccadic gain – $\pm 2.5^\circ$ H	0.74 (0.05)	0.78 (0.09)	0.77 (0.05)
Saccadic peak velocity – $\pm 2.5^\circ$ H (degrees/second)	176 (13)	185 (21)	191 (19)
Saccadic gain – $\pm 2.5^\circ$ V	0.89 (0.01)	0.92 (0.02)	0.90 (0.03)
Saccadic peak velocity – $\pm 2.5^\circ$ V (degrees/second)	204 (15)	205 (13)	215 (16)
Saccadic gain – $\pm 5^\circ$ H	0.83 (0.07)	0.84 (0.05)	0.79 (0.06)
Saccadic peak velocity – $\pm 5^\circ$ H (degrees/second)	296 (26)	271 (18)	274 (22)
Saccadic gain – $\pm 5^\circ$ V	0.88 (0.03)	0.88 (0.03)	0.87 (0.04)
Saccadic peak velocity – $\pm 5^\circ$ V (degrees/second)	307 (10)	308 (20)	302 (20)

Fix, binocular fixation; H, horizontal; V, vertical; SRML, simulated reading multiple lines; SRSL, simulated reading single line.

Table AII. Mean (± 1 SEM) parameters of version before (baseline), after P training (Post-P) and following OMT (post-OMT) in the EVEN group.

Parameter	Baseline	Post-P	Post-OMT
Fix – H – deviation (degrees)	0.46 (0.07)	0.30 (0.05)	0.33 (0.06)
Fix – V – deviation (degrees)	0.60 (0.25)	0.29 (10)	0.30 (0.09)
SRML ratio	1.6 (0.3)	1.6 (0.3)	1.3 (0.1)
SRSR ratio	2.0 (0.3)	1.5 (0.2)	1.4 (0.1)
Saccadic latency – H (milliseconds)	192 (14)	194 (14)	186 (14)
Saccadic latency – V (milliseconds)	194 (13)	198 (13)	199 (10)
Saccadic gain – $\pm 2.5^\circ$ H	0.71 (0.03)	0.72 (0.05)	0.88 (0.03)
Saccadic peak velocity – $\pm 2.5^\circ$ H (degrees/second)	167 (9)	167 (73)	214 (7)
Saccadic gain – $\pm 2.5^\circ$ V	0.80 (0.03)	0.78 (0.01)	0.92 (0.01)
Saccadic peak velocity – $\pm 2.5^\circ$ V (degrees/second)	187 (9)	186 (14)	230 (8)
Saccadic gain – $\pm 5^\circ$ H	0.78 (0.04)	0.78 (0.05)	0.89 (0.05)
Saccadic peak velocity – $\pm 5^\circ$ H (degrees/second)	250 (24)	241 (22)	329 (5)
Saccadic gain – $\pm 5^\circ$ V	0.88 (0.04)	0.83 (0.01)	0.94 (0.02)
Saccadic peak velocity – $\pm 5^\circ$ V (degrees/second)	295 (21)	274 (20)	322 (20)

Fix, binocular fixation; H, horizontal; V, vertical; SRML, simulated reading multiple lines; SRSR, simulated reading single line.

compared using one-way, repeated-measures ANOVA; post-hoc analyses were performed using Tukey's multiple comparison tests (Table AI). The mean horizontal deviation of binocular fixation reduced significantly ($F[2,14] = 13.04, p = 0.003$) after training. Post-hoc analysis revealed a significant difference between baseline and post-OMT and also between baseline and post-P, thus showing a positive effect of OMT ($p < 0.05$). However, there was no difference ($p > 0.05$) between post-OMT and post-P values, thus showing no effect of P training. None of the other versional parameters exhibited any significant differences ($p > 0.05$) in this group.

Even group (n = 5), order of treatment: B–A

Objective versional parameters measured at baseline, then following the P training (post-P) and later following the OMT (post-OMT) were

compared using a one-way, repeated-measures ANOVA; post-hoc analyses were performed using Tukey's multiple comparison tests (Table AII). Horizontal saccadic gain was found to be significantly increased for both the $\pm 2.5^\circ$ ($F[2,14] = 10.78, p = 0.005$) and the $\pm 5^\circ$ ($F[2,14] = 5.15, p = 0.03$) predictable stimuli. Correlated peak velocity was found to be significantly increased for both the $\pm 2.5^\circ$ ($F[2,14] = 7.61, p = 0.01$) and $\pm 5^\circ$ ($F[2,14] = 13.03, p = 0.003$) predictable horizontal stimuli following training. However, for predictable vertical saccades, saccadic gain ($F[2,14] = 12.32, p = 0.003$) and peak velocity ($F[2,14] = 17.80, p = 0.001$) increased significantly for the $\pm 2.5^\circ$ stimulus only following OMT. A post-hoc analysis for all of the above parameters revealed a significant difference between baseline and post-OMT and also between post-P and post-OMT, thus showing a positive effect of OMT ($p < 0.05$). None of the other versional parameters exhibited a significant difference after the OMT ($p > 0.05$).

Effect of oculomotor rehabilitation on accommodative responsiveness in mild traumatic brain injury

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Abstract—Accommodative dysfunction is a common oculomotor sequelae of mild traumatic brain injury (mTBI). This study evaluated a range of dynamic (objective) and static (subjective) measures of accommodation in 12 nonstrabismic individuals with mTBI and near vision-related symptoms before and after oculomotor training (OMT) and placebo (P) training (6 wk, two sessions per week, 3 h of training each). Following OMT, the dynamics of accommodation improved markedly. Clinically, there was a significant increase in the maximum accommodative amplitude both monocularly and binocularly. In addition, the near vision symptoms reduced along with improved visual attention. None of the measures were found to change significantly following P training. These results provide evidence for a significant positive effect of the accommodatively based OMT on accommodative responsivity. Such improvement is suggestive of oculomotor learning, demonstrating considerable residual brain-visual system plasticity in the adult compromised brain.

Key words: accommodation, accommodative dysfunction, accommodative training, acquired brain injury, mild traumatic brain injury, neuroplasticity, oculomotor learning, oculomotor rehabilitation, traumatic brain injury, vision rehabilitation.

INTRODUCTION

Accommodation is the process whereby the crystalline lens changes its dioptric power to focus precisely and maintain the object of interest at the high-resolution fovea [1]. It is a complex neurological control process involving optical, sensory, motor, perceptual, cognitive,

pharmacological, and biomechanical aspects. The accommodative system has four components [2–4]: blur-driven, or “reflex” accommodation; vergence accommodation; proximal accommodation; and tonic accommodation. These four components, along with modulation from the pupil, interact nonlinearly to produce the overall dynamic and static accommodative response profile, with disparity and blur being the two primary drives under normal binocular-viewing conditions in visually normal individuals [1,4–6].

Based on neurophysiological and anatomical experiments, the neural network of accommodation is quite extensive. Its pathway involves the following primary structures: retinal cones, optic nerve, lateral geniculate

Abbreviations: AA = amplitude of accommodation, AE = accommodative excess, AI = accommodative insufficiency, AS/R = accommodative stimulus/response, CISS = Convergence Insufficiency Symptom Survey, cpm = cycles per minute, D = diopter, DoD = Department of Defense, FEF = frontal eye field, MRI = magnetic resonance imaging, mTBI = mild traumatic brain injury, NPA = near point of accommodation, NRA = negative relative accommodation, OD = right eye, OMT = oculomotor training, OS = left eye, P = placebo, pons = pontis, PRA = positive relative accommodation, SEM = standard error of mean, SD = standard deviation, SS = steady-state, SUNY = State University of New York, TBI = traumatic brain injury, VSAT = Visual Search and Attention Test.

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nucleus, occipital lobe, posterior parietal cortex, frontal eye field (FEF), and the FEF sending projections via the internal capsule to the main oculomotor nucleus, as well as the parasympathetic accessory oculomotor nucleus (i.e., Edinger-Westphal nucleus) [1,7–9]. In addition, the rostral superior colliculus projects to the Edinger-Westphal nucleus via the primary, shorter route through the pretectum and also through a secondary, longer route through the nucleus reticularis tegmenti pontis (pons), cerebellar cortex, and cerebellar nuclei. In addition, the cerebellum has been demonstrated to act as a gain “calibrator” to optimize and maintain response accuracy, as well as to facilitate predictive tracking. Since the accommodative neural pathway is quite extensive, any injury to the multitude of brain and contiguous structures may adversely affect the accommodative system. Commonly associated with the rotational acceleration of the head, injuries involving the highly susceptible midbrain area, which houses accommodation-related neurons, could result in an accommodative dysfunction [10].

It is well established that due to the coup-contrecoup nature, and overall complexity and pervasiveness of a brain insult, traumatic brain injury (TBI) frequently results in a myriad of visual disturbances, including accommodative abnormalities [11–14]. However, there is a relative paucity of research that has investigated and confirmed the effect of TBI on accommodative function, especially in a comprehensive and objective manner. There were also study limitations in past studies [10–11,14–17].

Past studies have reported on three main categories of accommodative abnormality in the adult population with TBI. They are (1) accommodative insufficiency (AI), the most common finding; (2) accommodative excess (AE) or pseudomyopia; and (3) dynamic accommodative infacility. Accommodative function is usually defined and determined by the clinically assessed maximum amplitude of accommodation (AA). When this measure is significantly lower than the age-matched normal value [18], it is referred to as AI. Based on this criterion, 10 to 33 percent of the population with mild TBI (mTBI) was diagnosed with AI [10,15–17]. This has been confirmed in other studies [10,19–20].

In contrast to AI, AE has also been reported in patients with mTBI, but generally with less frequency [11]. In a sample of 161 patients with mTBI, 19 percent exhibited accommodatively based pseudomyopia [19]. In a recent retrospective study of 160 patients with mTBI, approximately 4 percent were clinically diagnosed with

AE [10]. There have also been several case studies reporting the rare but significant and related development of persistent bilateral accommodative spasm in individuals with TBI [21–23]. Since these studies showed accommodative spasm bilaterally, it was suggestive of a central defect. Magnetic resonance imaging (MRI) findings of one patient showed lesions involving subcortical white matter consisting of left temporal lobe areas, periventricular region, cerebellar vermis, and dorsal pons, all of which are areas involved in accommodation. However, no lesions were detected in the midbrain [22].

The least studied accommodative deficit in TBI has been dynamic accommodative infacility. This is diagnosed when a patient exhibits a slowed accommodative response (i.e., reduced peak velocity) to a change in dioptric lens power or target distance, which can occur alone or in conjunction with either AI or AE [11]. The aforementioned retrospective study also found that approximately 4 percent of the 160 patients with mTBI were diagnosed with accommodative infacility [10]. This has also been reported in a recent case series in three patients with mTBI [24].

While many clinically based studies have evaluated accommodative function following TBI, as described previously, only one laboratory prospective study employed an objective assessment [14]. A range of dynamic and static parameters of accommodation were evaluated in 12 individuals with mTBI (mean age: 31 yr; 6 mo to 13 yr following TBI) and near vision symptoms (e.g., intermittent blur). All parameters were compared with 10 visually normal, age-matched individuals (mean age: 27 yr). Accommodative dynamics to a 2 diopter (D) step (2 D ↔ 4 D) accommodative stimulus measured using the WAM 5500 autorefractor (Grand Seiko; Hiroshima, Japan) revealed significantly decreased peak velocity for both increasing and decreasing steps of accommodation in the group with mTBI when compared with the normal group. This reduced peak velocity (~35% less) was associated with a significantly prolonged response time and a correlated increase in time constant for both increasing and decreasing steps of accommodation in the group with mTBI when compared with the normal group. No difference was observed in the accommodative response magnitude and steady-state (SS) response variability between the two groups. The global clinical analog of the laboratory-tested accommodative dynamics was assessed using accommodative flipper facility. Reduced accommodative facility was not found, despite the laboratory-based measures that revealed slowed dynamics in the group with mTBI. This discrepancy could be due to the power of the lens flipper

used. Powers of ± 2.00 D are the clinic norm for testing accommodative facility [25]; in contrast, Green et al. used lower-powered ± 1.00 D flipper lenses, because their subjects had a relatively wide age range (18–40 yr) [14]. With repeated testing, the group with mTBI exhibited a significantly reduced flipper rate, suggestive of accommodative fatigue. In addition, several static aspects of accommodation were assessed in their study, which were significantly reduced in the group with mTBI as compared with the normal group. AA was reduced by ~ 1.5 D under both monocular (6.5 D) and binocular (7.1 D) viewing conditions in comparison with Duane's mean age-matched value (8–9 D) [18]. Of the subjects, 50 percent exhibited reduced values for relative accommodation (positive relative accommodation [PRA] and negative relative accommodation [NRA]) and 50 percent had an abnormal accommodative convergence to accommodation ratio. Hence, subjects with mTBI in general exhibited slowed dynamics and overall reduced accommodative ability over a range of parameters.

There is a total lack of data on accommodatively based oculomotor training (OMT) in mTBI. While many clinical studies and case reports evaluated accommodative dysfunction diagnostically, therapeutic efficacy was not assessed comprehensively, although the findings were positive [24–25]. Based on the previously mentioned studies, it is clear that individuals with mTBI experience a wide spectrum of accommodative deficiencies that impinge and adversely affect their near work abilities and produce disturbing symptoms that reduce their overall quality of life. Thus, abundant evidence in the clinical vision literature supports the notion that targeted, specific, and repetitive programmed vision therapy procedures (i.e., motor learning) can remediate patients with accommodative and binocular vision disorders as a consequence of mTBI [25]. While evidence from clinical studies exists on the efficacy of accommodative training in the population with TBI [24–25], there is a total lack of data on laboratory-based objective recordings of accommodation in these individuals following OMT. Moreover, no study evaluated the effect of comprehensive oculomotor rehabilitation (involving vergence, version, and accommodation) on objective (dynamic/laboratory) and subjective (clinical/static/symptom-rating scale/subjective attention) measures of oculomotor and related parameters and their possible interactions.

Thus, the purpose of the current investigation was to evaluate the effect of accommodative training on key clinical and laboratory parameters in individuals with mTBI reporting near work symptoms before and after

OMT performed in the clinic, purposely without a home-based component to assure consistency and control of the training. The training involved all three main oculomotor subsystems: vergence, accommodation, and version. All measures were compared after placebo (P) training. For the purpose of the present article, only the oculomotor subsystem of accommodation is considered.

METHODS

Subjects

Twelve adult subjects (8 females, 4 males) between the ages of 23 and 33 yr (mean \pm standard deviation [SD]: 29 ± 3 yr) with documented mTBI, having an injury onset of >1 yr (1–10 yr postinjury) to avoid possible contamination from the natural recovery process [26], participated in the study. See **Table 1** for demographics. They all manifested several near work-related symptoms and at least one clinical sign reflecting accommodative dysfunction (e.g., reduced near point of accommodation [NPA] or reduced facility). All had stable general health and absence of any significant cognitive dysfunction. Sample size was calculated using a power analysis program (G*Power, Heinrich-Heine-Universität Düsseldorf; Düsseldorf, Germany) at an alpha level of 0.05 with a power set at 0.80 using two key parameters of accommodation (i.e., NPA and accommodative facility). Subjects were identified by their university-based healthcare provider and were recruited from the Raymond J. Greenwald Vision Rehabilitation Center at the State University of New York (SUNY) College of Optometry, University Optometric Center of New York. Each subject received a comprehensive vision examination at the Raymond J. Greenwald Vision Rehabilitation Center prior to participating in the experiment. The vision examination included detailed refractive, binocular/oculomotor, and ocular health assessment.

Study Design

A crossover, interventional experimental design of a single-blind nature (for the subject) was used. In this design, each subject acted as his or her own control, thus negating undesirable intersubject variability. Each subject received OMT (treatment A) and P training (treatment B). During phase 1, every odd-numbered subject first received treatment A and every even-numbered subject first received treatment B, and vice-versa during phase 2. This was an interventional study of 15 wk duration. It consisted of

Table 1.

Demographics of population with mild traumatic brain injury (mTBI).

Patient	Age (yr)	Age at mTBI (yr)	Etiology of mTBI	Visual Symptoms/Complaints
JM01	25	23	Head hit against metal rod	Slow reading, skipping lines.
TB02	27	22	Head hit with baseball bat	Intermittent diplopia, poor concentration, intermittent blur at near.
BR03	30	27	Assault	Eye strain, difficulty reading, poor focusing ability.
CR04	31	25	MVA	Eye strain, headache.
EK05	25	22	MVA	Difficulty performing computer work, eye strain.
KO06	24	22	Fall	Difficulty performing ophthalmoscopy, eye strain.
DB07	29	27	MVA	Intermittent blur, intermittent diplopia, difficulty reading, skipping lines, visual motion sensitivity.
AN08	28	27	Fall	Headache, near vision blur, intermittent diplopia.
DJ09	33	31	MVA	Blurry vision, intermittent diplopia, difficulty reading, peripheral visual motion sensitivity.
SR10	29	25	MVA	Headache, intermittent diplopia at near, trouble focusing at near, dry eye, hyperacusis, photosensitivity, eye strain.
AK11	33	31	Assault	Difficulty shifting focus, blur at near, loss of place while reading, visual fatigue, headache, nausea, loss of balance.
NM12	31	25	Fall	Intermittent diplopia, imbalance, difficulty reading.

MVA = motor vehicle accident.

12 wk of the two treatment phases, 6 wk each phase, separated by 1 wk, for a total of 9 h of OMT and 9 h of P training, 3 h for each oculomotor system (accommodation, vergence, and version). In addition, there was a 3 wk measurement period: 1 wk before phase 1 treatment, 1 wk after phase 1 treatment, and 1 wk after phase 2 treatment. During these testing and training periods, subjects did not perform any other oculomotor-based vision rehabilitation to avoid contamination of test results [27].

The study consisted of the following phases:

1. Week 1: Initial baseline measures. All evaluative procedures (described later) were recorded over two separate test sessions (each session lasting up to 1.5 h, including rest periods to prevent fatigue), each separated by at least 2 d.
2. Weeks 2–7: Phase 1 treatment. Six weeks of either OMT or P training. Subjects received two training sessions per week. Each session was 60 min in duration, involving 45 min of actual training with the remainder of the time consisting of short interspersed rest periods for the subject. Total training time was 9 h.
3. Week 8: Repeat baseline measures. Same as week 1.
4. Weeks 9–14: Phase 2 treatment. Six weeks of either OMT or P training (same as phase 1).
5. Week 15: Repeat baseline measures. Same as week 1.

Evaluative Procedures

The evaluative procedures included the clinically based subjective, laboratory-based objective, and subjective visual attention testing and a near vision symptom-related scale questionnaire. All clinical parameters were measured using standardized clinical techniques [28]. All laboratory-based objective measures were performed using commercially available instrumentation with well-established test protocols for version, accommodation, and vergence [14,29–30]. All measures were noninvasive and recorded with the subject's habitual distance refractive correction in place. The order of testing was randomized over the 2 d of measurements. For the purpose of this article, accommodative measures alone are described.

Clinical Measures

Several study-related, near vision-specific, selected binocular vision-related tests and related parameters were assessed under standard clinical room illumination (80 Lux). Testing sequence was randomized. It included NPA, NRA, PRA, and accommodative facility (using ± 2.00 D flipper lenses). In addition, the WAM 5500 autorefractor was used to assess the accommodative stimulus/response (AS/R) function [1,14] to a high-contrast reduced Snellen chart stimuli monocularly in the right eye (OD); the left eye (OS) was fully occluded with a black eye patch. Subjects were instructed to focus on the 20/30 line. For

each stimulus/viewing condition, five measurements were obtained, and the average spherical equivalent (sphere + 1/2 cylinder value) was determined. The slope of the linear regression fit using stimuli and responses at each dioptric level provided the closed-loop accommodative gain value [31].

Laboratory Measures

First-order accommodative dynamics to 2 D increasing and decreasing step responses were obtained using the commercially available WAM 5500 objective, infrared, open-field autorefractor with a reported resolution of 0.01 D and approximately 5 Hz sampling rate [14]. This sampling rate is sufficient for acquiring valid accommodative dynamic responses based on the Nyquist criterion [32]. Subjects monocularly viewed a line of high-contrast 20/30 Snellen letters having a luminance of 36 cd/m² positioned at 2 D that were on a white background and a high-contrast 20/60 word with a luminance of 36 cd/m² at 4 D on a transparent background. The WAM 5500 autorefractor was aligned with the OD, as well as with both accommodative stimuli. Subjects received two or more practice trials before the actual testing. When instructed, the subject changed focus between the stimuli for 15 to 20 responses. Mean response amplitude (magnitude of response change), peak velocity (a point during the dynamic trajectory at which maximum change in response amplitude occurs over a specific time interval), time constant (the time for the exponential response to attain 63% of the final amplitude), SS response level (final SS response amplitude), and SS response variability (SD of the SS response level within the measured window of time) were calculated for both increasing and decreasing steps obtained from the OD [14].

Subjective Visual Attention Test

A subjective correlate of visual attention was assessed using the Visual Search and Attention Test (VSAT). It involves a search (for a letter or a symbol) and cancellation (cross-out) task that was developed by Trenerry et al. [33]. It assesses global sustained visual attention while scanning to search for selected letters or symbols. Test-retest reliability for the VSAT was 0.95. Calculated sensitivity and specificity were 0.88 and 0.86, respectively. The test was performed binocularly at the subject's habitual near work distance with correction. Following two practice trials, the actual test trial was performed. Percentile scores were calculated from the age-

matched normative table for the two test sheets. This test is frequently used in the clinical optometric [34], medical [35], and neuropsychological domains [36].

Symptom Scale

Individual symptoms related to near work were rated by the subjects using the Convergence Insufficiency Symptom Survey (CISS), whose sensitivity (0.978) and specificity (0.87) have been already demonstrated [37]. The test-retest reliability was found to be 0.88. It is comprised of a 15-item questionnaire probing near reading-related symptoms, such as intermittent blur, diplopia, headache, skipping lines, and loss of concentration. The severity of symptoms is scaled from 0 to 4, i.e., from least symptomatic to most symptomatic. The total score was compared before and after each of the two training phases. A reduction in overall score of 10 or more was considered to reflect a significant reduction of symptoms. A score of 0 indicates being absolutely symptom-free, and a score of 60 represents maximal symptomatology. A score of 16 or lower is considered to represent being relatively asymptomatic.

Treatment Protocol

Treatment A: Oculomotor Training

The OMT was performed along the midline at 0.4 m, two sessions per week, for a total of 6 wk. Training was performed with constant verbal and visual feedback, motivation, repetition, and active participation of the subject to maximize attention. For the purpose of the present article, however, only the accommodative training and related results are discussed. See **Table 2** for the accommodative training protocol.

For step AA training, various magnitudes of positive and negative spherical lenses were used. The basic principle behind the training was to maintain the target vergence demand constant at 0.4 m (2.5 MA) and increase the accommodative demand [38]. The accommodative targets were texts of various sizes ranging from 20/60 to 20/20 presented on a computer screen at 0.4 m. As the treatment

Table 2.
Training protocol for accommodation.

Stimulus Parameter	Training Period Duration (min)	Total Training Duration (min)
Step Amplitude Right Eye ± Lenses	5	15
Step Amplitude Left Eye ± Lenses	5	
Step Facility (binocularly) ± Lenses	5	

progressed and the subject demonstrated improvement, the level of task difficulty was increased by reducing target size and increasing lens power. While the subjects monocularly fixated the target, lenses were introduced manually at 0.5 D increments in front of the eye. After introducing each lens, subjects were instructed to focus the text as rapidly as possible. The focused text was maintained for 15 to 20 s to train sustaining ability. Hence, the goal of the training was not only to achieve rapid focus but also to maintain the accommodative response with accuracy and comfort. Such response maintenance would reflect the accommodative adaptation mechanism [39]. Accommodation training with minus lenses to increase the accommodative response was terminated at the point at which subjects could no longer focus with their maximum effort. This was repeated with positive lenses to reduce the accommodative response. The order of positive and negative lens training, as well as the eye trained at each session, was randomized.

For step accommodative facility training, combinations of plus and minus lens flippers (± 0.50 , ± 0.75 , ± 1.00 , ± 1.50 , and ± 2.00 D) were used while maintaining vergence constant at 0.4 m (2.5 MA). The accommodative targets were similar to those used in the amplitude training described previously. Based on the subject's ability to focus, the magnitude of the lens flipper power was chosen—the poorer the ability, the lower the initial lens power. Subjects bifixated targets on a computer screen and were instructed to fuse and focus as rapidly as possible and to achieve the maximum number of lens flipper cycles possible.

Treatment B: Placebo Training

Similar to OMT, P training was performed along the midline at 0.4 m, two sessions per week, for a total of 6 wk [27]. For the purpose of the present article, only the accommodative training and related results are discussed.

The P training did not involve any blur stimulation, because this is the primary drive for the accommodative system [1]. Plano powered/colored accommodative flipper step training was the P analog of the oculomotor accommodative flipper step training. This P training involved repetitive and systematic alternation of the flippers every 15 to 20 s monocularly and binocularly, without any spherical lens power changes (i.e., plano/colored lenses), while the subjects either read a text paragraph or watched a cartoon movie at 0.4 m on a computer screen, similar to that performed for OMT.

Data Acquisition and Analyses for Objective Recordings

The recorded files were saved as .csv files by the WAM 5500 autorefractor software. They were then transferred into Excel (Microsoft Corporation; Redmond, Washington) for detailed analyses. Three artifact-free (e.g., blink-free) increasing and three artifact-free decreasing accommodative responses were selected for analysis from the OD traces for each subject. There were approximately 7 to 10 increasing and 7 to 10 decreasing responses in total for each subject. Blinks were identified by 200 to 300 ms large deflections in the recordings and were discarded in the analysis. The middle three blink-free responses were used for analysis. An exponential decay function was fit to the dynamic trajectory, and the response amplitudes and time constants were obtained using GraphPad Prism software (GraphPad Software Inc; La Jolla, California). The goodness of fit was assessed from the r^2 values of each individual response fit. The mean r^2 value for both increasing and decreasing steps was greater than 0.8 for each subject. The peak velocities were derived from first-order differentiation of the exponential equation. The mean amplitude, time constant, peak velocity, mean SS response level, and SS response variability of the responses at baseline, post OMT, and post P training were compared statistically using GraphPad Prism software. For each subject, the mean for each parameter was calculated, then the overall group mean was computed [14].

STATISTICAL ANALYSES

Combined Group

The key objective of the study was to evaluate the effect of OMT in individuals with mTBI and oculomotor-based near vision symptoms. The main analyses included a comparison of baseline measures before and after OMT using paired two-tailed *t*-tests. Data from all 12 subjects were analyzed and presented as the combined group results. For subjects who received OMT first, baseline measures from week 1 (baseline) and baseline measures from week 8 (post OMT) were used for the analyses. For those subjects who received P training first, baseline measures from week 1 (baseline) and baseline measures from week 15 (post OMT) were used for analyses. For subgroup analyses, a repeated-measures, one-way analysis of variance and Tukey post hoc analyses were performed for comparisons between baseline, OMT, and P training. Correlations between relevant objective and subjective parameters were performed using linear regression. Furthermore, the effect

size was calculated using the G*Power software for the key parameters, which included binocular AA, binocular accommodative facility, and peak velocity for increasing step accommodation. Values greater than 0.5 were considered as having large effects of treatment.

Subgroup

See [Appendix](#) (available online only) for detailed subgroup analyses.

RESULTS

Combined Group Analysis

Laboratory-Based Objective Measures

The dynamic trajectories of the monocular step accommodative responses were fit using an exponential, one-phase decay function [14]. The dynamic parameters derived from the fit were compared before (baseline) and after completion of OMT (post OMT). There was a significant increase (~30%) in peak velocity for both increasing ($t(11) = 3.61, p = 0.01$, effect size = 0.6) and decreasing ($t(11) = 3.65, p = 0.01$) steps of accommodation following OMT (**Figure 1**). Concomitantly, there was a significant (and predicted) decrease (~40%) in the related time constant for both increasing ($t(11) = 4.17, p = 0.01$) and decreasing ($t(11) = 4.7, p = 0.01$) steps of accommodation (**Figure 2**). **Figure 3** presents unedited accommodative 2 D, objective step response traces in a typical subject with mTBI before and after OMT. Slowed dynamic trajectories were evident before training (see arrows) at baseline, which became significantly more rapid following OMT. This positive training effect is evident in **Figure 4**, which presents samples of the exponential fit of increasing and decreasing step accommodative response before and after OMT in the same subject. Faster motor responses were evident. See **Table 3** for the group mean (± 1 standard error of mean [SEM]) values at baseline and post OMT. All four of the initially abnormal parameters improved significantly following OMT, although they did not normalize.

The other dynamic parameters did not change following OMT. This is attributed to the parameters already being normal at baseline; hence, no positive effect was anticipated. There was no significant difference in the response amplitudes for either increasing ($t(11) = 0.43, p = 0.67$) or decreasing ($t(11) = 0.75, p = 0.46$) steps of

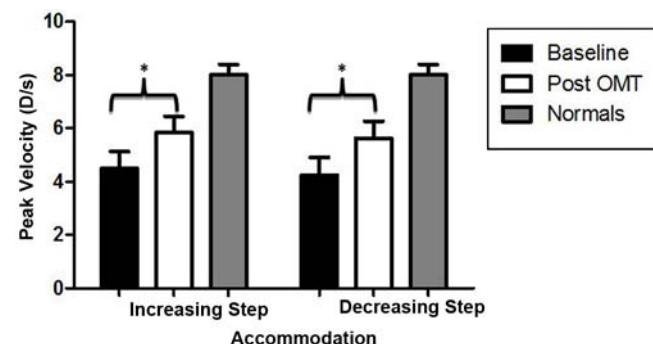


Figure 1.

Group mean peak velocity of accommodation before (baseline) and after oculomotor training (post OMT) in mild traumatic brain injury in comparison with normal. Error bars indicate ± 1 standard error of mean. *Significantly increased from baseline. D = diopter.

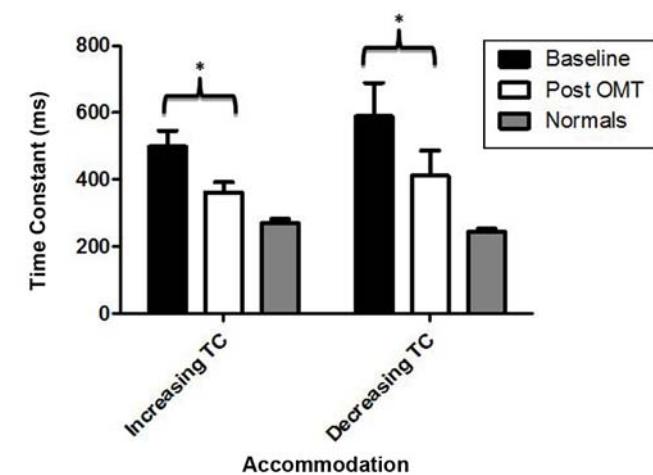


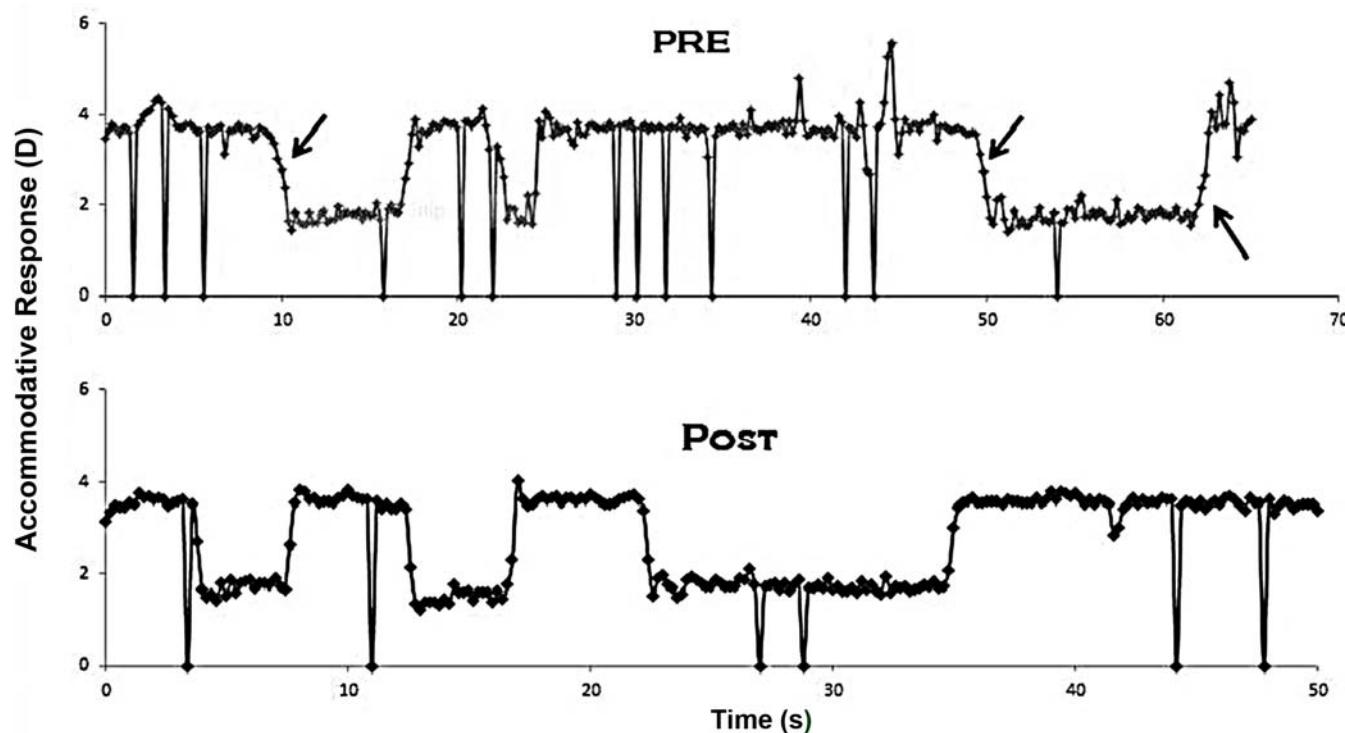
Figure 2.

Group mean time constant (TC) for accommodation before (baseline) and after oculomotor training (post OMT) in mild traumatic brain injury in comparison with normal. Error bars indicate ± 1 standard error of mean. *Significantly decreased from baseline.

accommodation. Both the SS response dioptric level and the SS response variability did not differ significantly for either increasing ($t(11) = 0.55, p = 0.59$, and $t(11) = 1.31, p = 0.21$, respectively) or decreasing ($t(11) = 0.61, p = 0.54$, and $t(11) = 0.34, p = 0.74$, respectively) steps of accommodation after training.

Clinically Based Subjective Measures

All clinic parameters related to accommodation were compared before (baseline) and after OMT (post OMT). See **Table 4** for mean (± 1 SEM) values at baseline and post

**Figure 3.**

Monocular accommodative responses as function of time. Unedited two-dimensional step accommodative traces in typical subject with mild traumatic brain injury before (pre) and after (post) oculomotor training. Large deflections represent blinks. Arrows denote slowed dynamic trajectory. D = diopter.

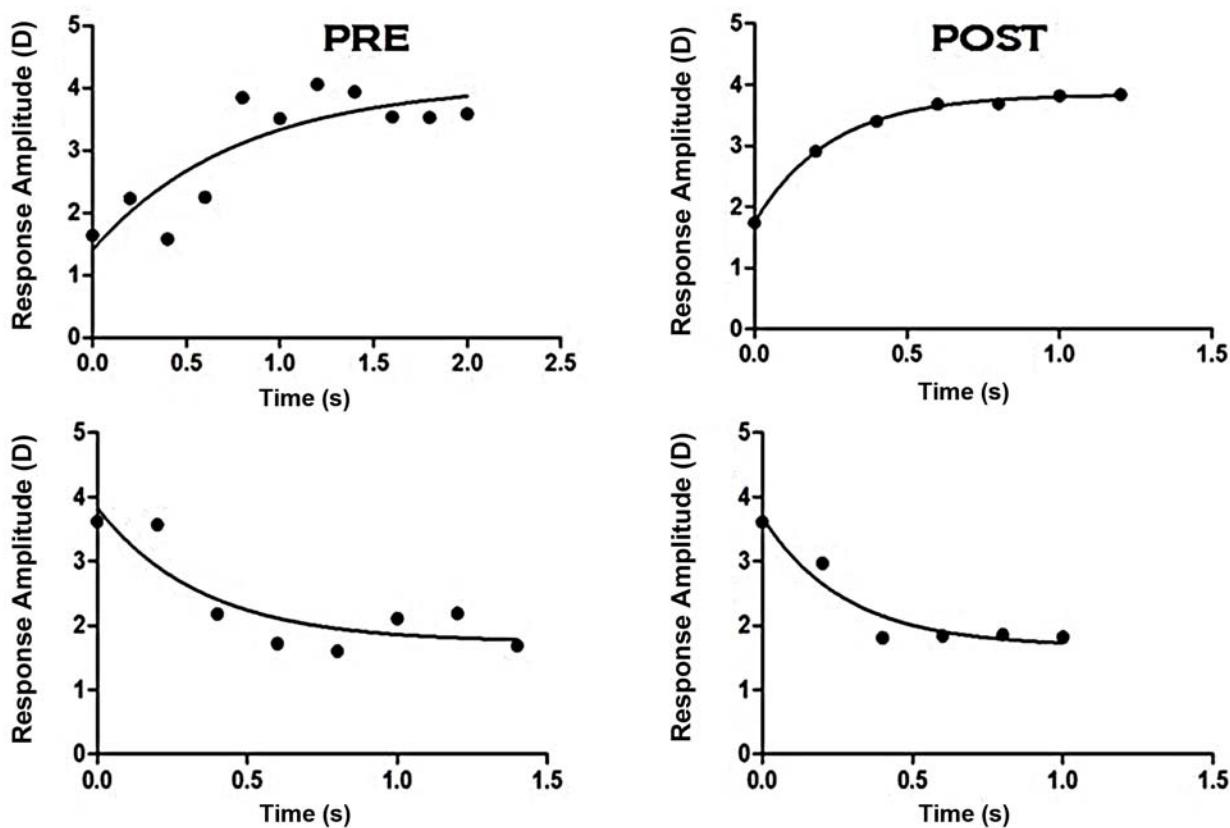
OMT. All six of the parameters that were abnormal at baseline improved significantly with OMT. There was a large and significant ($\sim 220\%$) increase in lens flipper accommodative facility both monocularly (OD: $t(11) = 6.24, p \leq 0.001$, and OS: $t(11) = 5.84, p = 0.01$) and binocularly ($t(11) = 4.87, p = 0.01$, effect size = 1.1) following OMT (Figure 5), and it normalized. Similarly, AA increased ($\sim 30\%$) significantly both monocularly (OD: $t(11) = 3.68, p = 0.01$, and OS: $t(11) = 4.07, p = 0.01$) and binocularly ($t(11) = 4.41, p = 0.01$, effect size = 1.1) with OMT (Figure 6), and it nearly normalized. The accommodative gain did not change significantly ($F(2,94) = 0.26, p = 0.76$) with OMT. Similarly, there was no significant difference in either the PRA ($t(11) = 1.35, p = 0.20$) or NRA ($t(11) = 1.38, p = 0.19$) values following OMT. However, the accommodative gain, NRA, and PRA values were already normal at baseline; hence, no positive training effect was anticipated.

Other Subjective Tests

The CISS total score significantly reduced ($t(11) = 3.69, p < 0.01$) from a mean value of 37 ± 4 to 28 ± 3 fol-

lowing OMT. This indicated a reduction in near vision-related symptoms following OMT. In addition, the increases in AA following training were also significantly correlated with reduction in symptoms, as evident from the decreased CISS score (Figure 7).

With respect to visual attention at baseline, and based on the age-matched norms, 4 of the 12 subjects were abnormal by scoring below the 2nd percentile [33]. In addition, one subject had borderline abnormality, and the remaining seven subjects scored in the normal range. Following OMT, however, the percentile scores for 10 of the 12 subjects (80%) increased. The group mean VSAT percentiles increased significantly ($t(11) = 4.43, p < 0.01$) from the 32nd (± 9) to the 50th (± 10) percentile following OMT. This indicated increased visual attentional aspects concurrent with OMT. However, the mean baseline value was already normal in the present study population. Lastly, the improved subjective attention based on the increased VSAT percentile correlated significantly with the increased AA following OMT (Figure 8).

**Figure 4.**

Accommodative dynamic trajectory as function of time. Exponential fit of two-dimensional step accommodative dynamic trajectory before (left column) and after (right column) oculomotor training for increasing (top row) and decreasing (bottom row) step accommodation in typical subject with mild traumatic brain injury. D = diopter.

Subgroup Analysis

There was no statistically significant effect ($p > 0.05$) of P training on any accommodative parameters tested both clinically and laboratory-wise. See [Appendix](#) (available online only) for details.

DISCUSSION

The present study evaluated a wide range of dynamic and static measures of accommodation before and after accommodatively based OMT in individuals with mTBI who reported near work-related symptoms of an oculomotor nature following head trauma. With only 3 h of direct accommodative training per se distributed over 6 wk, marked improvements were found in several key dynamic and static behaviors of accommodation that were abnormal at baseline. Of the 10 laboratory parame-

ters assessed, 4 were found to be abnormal at baseline, and all 4 improved significantly with OMT. Similarly, of the nine clinical parameters assessed, six were found to be abnormal at baseline, and all six improved significantly with OMT. Thus, the improvement rate was 100 percent. Such a high percentage of individuals with mTBI showing significant improvement in accommodation is remarkable given their ages and compromised brains. The results were also compared with an equal dosage of P training. None (0%) of the accommodative parameters were found to have a significant effect from the P training.

Training Effect on Accommodative Dynamics

At baseline, the dynamic trajectory for both increasing and decreasing steps of accommodation exhibited slowed responsivity. This was evident from the reduced peak velocities along with the correlated increased time

Table 3.

Mean \pm 1 standard error of mean values of laboratory-based objective parameters for monocular steps of accommodation before (baseline) and after oculomotor training (post OMT).

Dynamic Parameter	Baseline	Post OMT	p-Value
Peak Velocity (D/s)			
Increasing Step	4.5 \pm 0.6	5.8 \pm 0.6	<0.01*
Decreasing Step	4.2 \pm 0.7	5.6 \pm 0.6	<0.01*
Time Constant (ms)			
Increasing Step	499 \pm 47	362 \pm 31	<0.01*
Decreasing Step	589 \pm 99	412 \pm 75	<0.01*
Steady-State Response Level (D)			
Increasing Step	3.42 \pm 0.10 [†]	3.46 \pm 0.10	0.59
Decreasing Step	1.74 \pm 0.08 [†]	1.79 \pm 0.07	0.54
Steady-State Variability (D)			
Increasing Step	0.14 \pm 0.02 [†]	0.11 \pm 0.01	0.21
Decreasing Step	0.11 \pm 0.01 [†]	0.10 \pm 0.01	0.74
Response Amplitude (D)			
Increasing Step	1.94 \pm 0.13 [†]	1.91 \pm 0.08	0.67
Decreasing Step	1.88 \pm 0.10 [†]	1.83 \pm 0.08	0.46

*Statistically significant.

[†]Normal at baseline.

D = diopter.

Table 4.

Mean \pm 1 standard error of mean clinically based subjective parameters of accommodation before (baseline) and after oculomotor training (post OMT).

Clinical Parameter	Baseline	Post OMT	p-Value
Amplitude of Accommodation (D)			
OD	6.2 \pm 0.6	7.9 \pm 0.5	<0.01*
OS	5.9 \pm 0.6	7.9 \pm 0.5	<0.01*
OU	6.9 \pm 0.6	8.8 \pm 0.5	<0.01*
Accommodative Facility (cpm)			
OD	5 \pm 1.0	11 \pm 2.0	<0.01*
OS	5 \pm 1.0	11 \pm 2.0	<0.01*
OU	5 \pm 1.5	11 \pm 2.0	<0.01*
Positive Relative Accommodation (D)	2.5 \pm 0.4 [†]	3.1 \pm 0.3	0.20
Negative Relative Accommodation (D)	2.1 \pm 0.2 [†]	2.3 \pm 0.1	0.19
Accommodative Gain	0.86 \pm 0.13 [†]	0.88 \pm 0.10	0.76

*Statistically significant.

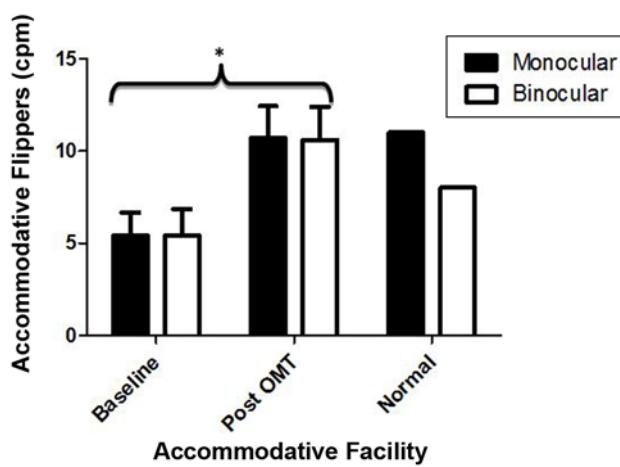
[†]Normal at baseline.

cpm = cycles per minute, D = diopter, OD = right eye, OS = left eye, OU = both eyes.

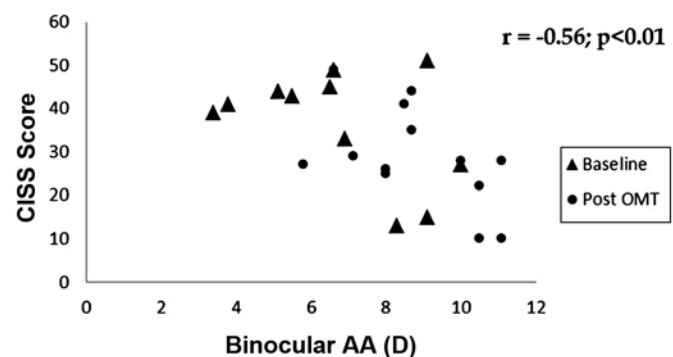
constant values. The group mean peak velocity (\sim 4.4 D/s) at baseline was \sim 40 percent less than that found in normal individuals (8 D/s) for the same stimulus amplitude (i.e., 2 D) [14,40–41] for both increasing and decreasing steps of accommodation. Following OMT, there was a significant increase in peak velocity by \sim 30 percent from the baseline value for both increasing and decreasing steps of accommodation, although peak velocity did not normalize (Figure 1). Subjects now attained their SS response level more rapidly. Concomitantly, the time constant exhibited

a correlated significant decrease (Figure 2). These two dynamic parameter changes were correlated for both increasing and decreasing steps of accommodation, as one might expect due to their inverse nature [1].

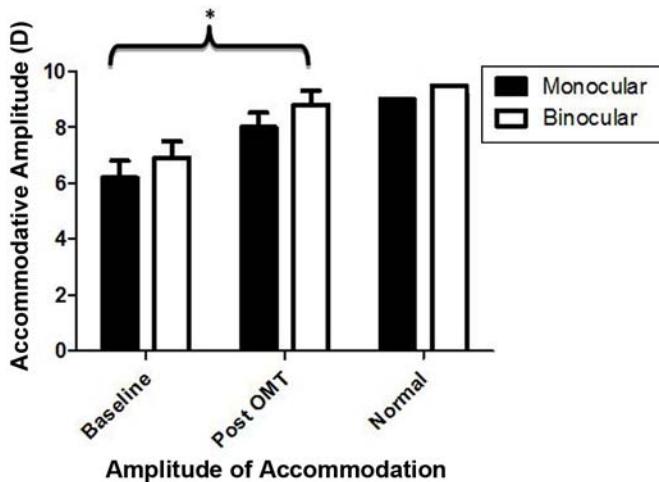
The lens flipper facility rate is the clinical analog for the overall laboratory-based response, thus incorporating and effectively combining all dynamic parameters (i.e., peak velocity, time constant, and latency) into a single, global, validated metric [38,42]. Based on the mean normative values [43] for monocular (11 cycles per minute [cpm]) and

**Figure 5.**

Group mean accommodative facility before (baseline) and after oculomotor training (post OMT) in mild traumatic brain injury in comparison with expected clinic norm for monocular and binocular accommodative facility. Error bars indicate +1 standard error of mean. *Significantly increased from baseline. cpm = cycles per minute.

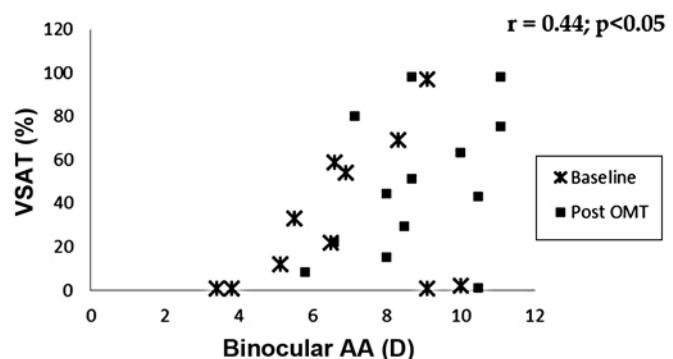
**Figure 7.**

Correlation of Convergence Insufficiency Symptom Survey (CISS) score and binocular amplitude of accommodation (AA) showing significant decrease in CISS score with significant increase in AA. D = diopter, OMT = oculomotor training.

**Figure 6.**

Group mean amplitude of accommodation before (baseline) and after oculomotor training (post OMT) training in mild traumatic brain injury in comparison with Duane's age-matched normal values for monocular and binocular accommodation [18]. Error bars indicate +1 standard error of mean. *Significantly increased from baseline. D = diopter.

binocular (8 cpm) accommodative facility values at baseline, the rates were found to be ~40 percent less in individuals with mTBI. Following OMT, subjects could perform the

**Figure 8.**

Correlation of Visual Search and Attention Test (VSAT) percentile and binocular amplitude of accommodation (AA) showing significant increase in VSAT percentile with significant increase in AA. D = diopter, OMT = oculomotor training.

task (± 2.00 D lens flipper) more rapidly, with a large and significant twofold increase in the facility rates both monocularly and binocularly. The accommodative facility rates normalized following training (Figure 5).

Both before and after OMT, the accommodative response amplitudes for increasing and decreasing steps of accommodation were accurate (i.e., within the estimated depth of focus) but significantly slower before OMT. This finding of accuracy suggested the presence of normal visual feedback with respect to blur detection and processing [31]. This was confirmed from the normal accommodative (closed-loop) gain values found in these individuals

as measured from the AS/R function [44]. The mean SS response level and SS variability values were within normal limits at baseline, and they did not change with OMT for either increasing or decreasing steps of accommodation. Since the response amplitudes remained unaltered with training, the observed changes in dynamic responsivity can be attributed to an increase in the pulse and not the step neural signal [45–46] (discussed later).

Training Effect on Static Measures of Accommodation

The NPA (i.e., AA) is the main static diagnostic parameter used in the clinic for assessment of accommodative dysfunctions. It denotes the maximum accommodation that can be exerted by the ciliary muscle on the crystalline lens. It is one of the most frequently found abnormal accommodative parameters in mTBI [10,13–14,25,47]. While a reduced monocular AA is attributed solely to an accommodative disorder, a reduced binocular AA may be due to a combination of both accommodative (i.e., blur-driven accommodation) and vergence (i.e., disparity-driven accommodation) dysfunction [38]. Based on Duane's age-matched data for AA [18], individuals with mTBI in the present study exhibited reduced amplitudes at baseline both monocularly and binocularly, on average by 33 and 28 percent, respectively. Following OMT, the AA increased significantly by ~28 percent from baseline value under both monocular and binocular conditions. While subjects attained 89 percent of the expected norm monocularly, it completely normalized binocularly (93%) (**Figure 6**). Thus, the improvements demonstrate a large increase in the magnitude of the patient with mTBI's maximum accommodative ability. Neurophysiologically, one may speculate that this improvement in maximum amplitude reflects an increase in neuronal firing (through recruitment) and/or better synchronization of the accommodatively based midbrain and related neurons [48–49]. A recent pilot study has shown increased activity in the brain stem area following improved convergence amplitude subsequent to vergence training assessed using the functional MRI technique [49]. We speculate a similar neurophysiological underpinning for the improved AA, because accommodation and vergence share strong cross-coupling. In addition, an increase in AA was also significantly correlated with reduction in symptoms, as evident from the decreased CISS score (**Figure 7**), as well as improved subjective attention from the increased VSAT percentile scores (**Figure 8**).

The training did not have an effect on the relative AAs (NRA and PRA). Under the noncongruent test con-

dition [50], where vergence was maintained constant at 0.4 m and the accommodative demand was systematically altered using minus and plus lenses, the relative AAs were found to be normal at baseline; hence, no changes with training were expected.

In Relation to Previous Literature

The present study results provide the first objectively based data demonstrating the positive effect of OMT on accommodative responsivity in individuals with mTBI. Reduction of accommodative responsivity (e.g., decreased peak velocity) found at baseline in the present study was consistent with the findings of Green et al., who reported similarly slowed dynamic behavior for both increasing and decreasing steps of accommodation in individuals with mTBI [14]. The normal response amplitudes and SS response variability found in the present study were also consistent with their findings. In contrast, the reduced lens flipper facility rates (monocular and binocular) found in the present study at baseline were not reported in the previous prospective study in the population with mTBI [14]. They did not find a significant difference between the normal and mTBI groups. However, Green et al. used ± 1.00 D flipper lens to test accommodative facility [14], while the present study used a much higher dioptric demand level of ± 2.00 D flipper lens, which is the clinical norm to diagnose accommodative dysfunctions [38]. It is therefore important for clinicians to use ± 2.00 D flipper lens to assess accommodative infacility, which can be left undiagnosed when tested with such low-powered lenses, or perhaps use age-based lens flipper norms [38]. To support the present study findings, Ciuffreda et al. found accommodative infacility in the population with mTBI retrospectively (~4%) using the ± 2.00 D lens flipper [10].

Several of the static accommodative findings assessed at baseline were consistent with some earlier clinical reports [10,15–17,19]. As discussed in the “Introduction” section, the most common finding was AI. Although infrequently reported, a few studies have reported AE (or spasm) [21–23]. The present study did not find such accommodative behavior in the individuals evaluated, likely due to its extreme rarity.

While the maximum AA was markedly reduced at baseline, gain of the accommodative system was normal within the tested range (2–5 D), both before and after training, as deduced by the slope of the AS/R function, which directly reflects the system's closed-loop gain [31,44]. This finding confirms Green et al. [14], who

reported similar normal gain values in subjects with mTBI (0.8) and normal subjects (0.87). Training expanded the upper level of the linear and nonlinear zones of accommodation of the AS/R function [1,10], as evident from the increased AA. While similar gain values were obtained within the measured linear range (2–5 D), the OMT extended the zone of the focusable region beyond 5 D. Increase in the AA by ~2 D subsequent to the OMT confirmed the retrospective clinical findings of Ciuffreda et al. [25] and the clinical cases by Scheiman and Gallaway that also found improvement in AA following OMT [24].

From the present findings as well as from previous studies that assessed dynamic and static parameters of accommodation, it is apparent that the dynamic laboratory-based peak velocity and the clinically based dynamic lens flipper facility, along with the static clinically based AA, are the key parameters in the population with mTBI to diagnose accommodative dysfunctions [10,14–17,47]. While such a finding is also possible in other non-mTBI-based accommodative dysfunctions (i.e., AI), detailed case history will specify the etiology of the anomaly. Although treating the population with mTBI for accommodative and/or binocular vision disorders using conventional OMT procedures might be challenging given the complexity of more general factors [51], such as fatigue, chronic headache, memory deficits, and physical ailments, as well as other non-oculomotor-based vision problems, such as visual field defects and photosensitivity, a considerable degree of oculomotor-based treatment effect has been reported in this population, as described previously. Improvement in the critical parameters of accommodation, such as AA, along with significant reduction in the near vision-related symptoms, is suggestive of considerable and pervasive treatment effect in individuals with mTBI. The findings of the present investigation, along with the aforementioned studies, support the notion that targeted, specific, repetitive, programmed therapy procedures can remediate via oculomotor learning (discussed later) a range of accommodative and binocular vision disorders occurring as a consequence of the mTBI. Symptoms were ameliorated along with concurrent normalization of clinical signs, as well as subjective visual attention, in the present study.

Neurophysiological Implications

The neural control mechanism of accommodation has been postulated to be similar to the saccadic [52] and vergence [53] systems. The final neural signal for accom-

modation is proposed to consist of a small pulse/phasic signal and a step/tonic signal [45–46]. While the pulse controls the velocity of the accommodative response, the step controls the final accommodative SS response level. While height of the pulse signal determines the peak velocity, height of the step signal determines the final SS dioptric level. Evidence from nonhuman primate studies suggests that although the midbrain (e.g., supra oculomotor area) houses a majority of near response neurons, several other areas, such as FEF, cerebellar nucleus, and pons, to name a few, consist of neurons that also fire during accommodation [48,54]. Cells in these areas contain both phasic and tonic cells that fire in relation to velocity and position, respectively.

Based on the results of the present investigation at baseline and earlier studies [14], the primary neural deficit in the patient with mTBI is believed to be the pulse component. This can account for the reduced peak velocity and related increased time constant at baseline. Reduction in pulse height is speculated to be derived from a combination of decreased firing rate of the phasic (burst) cells and a reduced number of phasic cells, possibly resulting from shearing of axons following TBI. Since the appropriate accommodative response level was eventually attained, this suggests that the step component had the appropriate mean height. Following OMT, one may speculate that the increase in peak velocity was because of an increase in pulse height (presumably because of the increased firing rate) as a result of oculomotor learning and neuroplasticity (discussed later), thus resulting in faster motor responsiveness to attain the final SS position. Unlike vergence [49], there is no study in the literature that monitored cortical activity related to accommodative training in humans with mTBI. Although vergence training alone [49] can indirectly influence and possibly train accommodation indirectly via the vergence-accommodation cross-link [55–56], a discrete neuroimaging study involving accommodation only before and after OMT is critical in humans.

Neuroplasticity and Oculomotor Learning Effects

Basic learning is comprised of repeated stimulation of a particular task, which initially comprises a trial-and-error mechanism and eventually becomes an associated learning process. This automaticity is achieved through increase in synaptic number and strength, and it is referred to as Hebbian learning [57–59]. The process of learning a new task not only involves functional and behavioral changes due to repeated practice, but it also

includes a spectrum of underlying mechanisms, such as biochemical and cellular changes, as well as structural changes including increased synapse number, firing rate, increased axonal/dendritic arborization, etc. [58]. While neuroplasticity in response to an external stimulus is common in a normal brain, these mechanisms have also been identified in the relearning process following an insult to the brain [58]. It is central to the recovery process independent of the time duration elapsed after the injury. Regaining functional loss following TBI could be either through a natural recovery process, where neurotransmission is restored in the adjacent spared location, or through retraining. Retraining involves functional recovery through relearning a particular task that was compromised following an injury, and thus forms the basis for any type of neurorehabilitation. This is achieved through restoring activity in spared brain areas within the affected region that were inactive due to disuse, and now through recruiting new regions remote from the injury site that have similar functional abilities but did not contribute predominantly before the injury.

With regard to the present study, following TBI, a global type of injury resulting in a diffuse axonal injury could compromise white matter integrity [60], thus resulting in slowed responsivity (e.g., slowed accommodation). The presumed decreased number of synapses, reduced firing rate, reduced synchrony, and/or lack of correlation within and across the specific brain regions may cause loss of automaticity, and hence an overall reduction in the system's maximum amplitude (e.g., NPA), as found at baseline [27]. Accommodatively based vision rehabilitation acts to regain accommodative function through repeated stimulation with different magnitudes of blur over a period of time (e.g., several weeks). A combination of repeated stimulation with these various amounts and types of blur (negative and positive), increasing task level difficulty (e.g., progressively reducing target size), active participation of the subjects with high attention, presence of visual and verbal feedback, sensitized visual feedback related to the blur (i.e., perceptual learning) [61], and high motivation of the subjects to perform the task over the training period resulted in a significant OMT effect and relearning process.

Study Limitations

The study had some potential limitations. First, accommodative ramp (i.e., slow constant velocity) responses were not evaluated. This should be performed to assess both of these key control aspects of accommo-

dation, per models of the vergence system [62]. Second, due to technical constraints, latency for accommodation was not assessed in the present study. This information would have provided insight regarding possible sensory information processing delays, especially given the fact that blunt trauma affects brain areas diffusely. Last, evaluation of accommodative dynamics under binocular viewing conditions would provide additional insight into the influence of vergence and its training on the overall accommodative dynamic behavior.

Future Directions

The present study evaluated the global aspects of OMT on several critical parameters of accommodation, along with vergence and version. There is a paucity of data on the neurological correlates of OMT that results in functional changes. Hence, functional and structural brain imaging studies are critical to assess for correlation with the behavioral changes, and then to use this information to plan for future targeted treatment accordingly. Persistence of the treatment effect is still an ongoing evaluation. All subjects are being reevaluated at 3 and 6 mo after the completion of training, and this will be the topic of a future publication. Based on the results from these follow-up studies, future therapies will be planned to improve and retain their oculomotor function and reduce symptoms even further. While it might be challenging to restore complete normalcy in these individuals, the current level of improvement attained was appreciated by the subjects. Future studies should be conducted to assess whether additional OMT would result in greater levels of normalcy or whether the possibility is limited by the underlying neural damage to the brain. Long-term training distributed over 6 to 12 mo intervals may be necessary to maintain the initial improvements (booster therapies). Last, investigations should be extended in a larger sample size and more diverse group (e.g., moderate TBI) to generalize the treatment effects, and longer follow-up (1–5 yr) may be necessary.

CONCLUSIONS

Oculomotor rehabilitation was effective in individuals with mTBI who reported near work-related symptoms of an oculomotor basis. An overall improvement in nearly all of the critical, abnormal parameters of accommodation was observed both objectively and subjectively following OMT. Improved oculomotor behavior was

attributed to effective oculomotor learning effects in these individuals.

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Analysis and interpretation of data: P. Thiagarajan, K. J. Ciuffreda.

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Oculomotor neurorehabilitation for reading in mild traumatic brain injury (mTBI): An integrative approach

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Abstract.

BACKGROUND: Considering the extensive neural network of the oculomotor subsystems, traumatic brain injury (TBI) could affect oculomotor control and related reading dysfunction.

OBJECTIVE: To evaluate comprehensively the effect of oculomotor-based vision rehabilitation (OBVR) in individuals with mTBI.

METHODS: Twelve subjects with mTBI participated in a cross-over, interventional study involving oculomotor training (OMT) and sham training (ST). Each training was performed for 6 weeks, 2 sessions a week. During each training session, all three oculomotor subsystems (vergence/accommodation/version) were trained in a randomized order across sessions. All laboratory and clinical parameters were determined before and after OMT and ST. In addition, nearvision-related symptoms using the Convergence Insufficiency Symptom Survey (CISS) scale and subjective visual attention using the Visual Search and Attention Test (VSAT) were assessed.

RESULTS: Following the OMT, over 80% of the abnormal parameters significantly improved. Reading rate, along with the amplitudes of vergence and accommodation, improved markedly. Saccadic eye movements demonstrated enhanced rhythmicity and accuracy. The improved reading-related oculomotor behavior was reflected in reduced symptoms and increased visual attention. None of the parameters changed with ST.

CONCLUSIONS: OBVR had a strong positive effect on oculomotor control, reading rate, and overall reading ability. This oculomotor learning effect suggests considerable residual neuroplasticity following mTBI.

Keywords: Traumatic brain injury, mTBI, reading dysfunction, oculomotor deficiency, nearvision symptoms, oculomotor rehabilitation, neuroplasticity, oculomotor learning, eye movements

1. Background

1.1. Reading: Basic concepts

Reading is a complex task that requires precise coordination of one's versional eye movements (especially saccades), synchrony between ocular accommodation and vergence, and maintained higher-level visual

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attentional aspects associated with text processing in conjunction with concurrently accurate comprehension. All of the above must be performed in an efficient manner to gain optimal benefits (Ciuffreda, 1994; Ciuffreda & Tannen, 1995).

Normal reading is comprised of precise, rhythmical, and automatically-executed sequences of saccadic eye movements interspersed with brief fixational pauses (Taylor, 1966; Ciuffreda & Tannen, 1995; Reichle & Raynor, 2002; Ciuffreda et al., 2005, 2006). The reading-related saccadic eye movements, typically being 1–3 degrees in amplitude and 30–60 msec in duration, progressively shift the eyes from left-to-right across the line of print. These saccadic shifts are interspersed with brief oculomotor fixational pauses of approximately 250 msec duration to allow for the initial text processing (~75 msec), followed by oculomotor positional programming (~175 msec) of the subsequent saccade to the next word along with attentional allocation (Ciuffreda & Tannen, 1995; Abrams & Zuber, 1972; Reichle & Rayner, 2002). At times, the saccadic eye movements are regressive in nature, wherein the eyes either shift back briefly to a previously fixated word for informational confirmation or simply return to the beginning of the next line of text (i.e., return-sweep saccade). In addition, during each saccadic eye movement itself, there is a very small (<0.10 deg) dynamic alteration in the binocular vergence angle (i.e., dynamic fixation disparity), which must be corrected rapidly upon bifixation of the subsequent word (Clark, 1935; Taylor, 1966; Ciuffreda & Tannen, 1995). Hence, continuous small but highly accurate vergence adjustments are necessary to attain and maintain rapidly and fully, precise binocular alignment, and thus prevent either diplopia or partially overlapping images from intermittently occurring (Ciuffreda et al., 1996). Lastly, clarity of the text is critical for efficient visual information processing (Green et al., 2010, a,b), and hence the accommodative subsystem must function in a time-optimal manner to obtain and maintain an accurate focusing response. Thus, the version, vergence, and accommodative functions are essential for efficient oculomotor control during reading under a variety of naturalistic conditions. Furthermore, they must function in an *interactive* and *integrated* manner with precise *synchronization* for optimal reading performance to occur (Taylor, 1966; Ciuffreda & Tannen, 1995). In addition, this must be accomplished for a sustained period of time with a high level of attention, comprehension, and visual comfort (Taylor, 1966; Ciuffreda & Tannen, 1995).

1.2. Investigations on reading in brain injury: Diagnosis

Reading dysfunction is a major problem, and hence symptom, in individuals with mTBI (Ciuffreda et al., 2006, 2007; Goodrich et al., 2007, 2013; Lew et al., 2007; Brahm et al., 2009; Stelmack et al., 2009; Capó-Aponte et al., 2012; Bulson et al., 2012). A major source of this reading problem is *oculomotor-based* (Ciuffreda et al., 2005, 2006, 2007). Any failure in one or more of these oculomotor systems will likely result in problematic reading, especially as these three subsystems are interactive and integrative in nature (e.g., an accommodative problem will also impact on vergence via accommodative vergence) (Ciuffreda & Kenyon, 1983).

Based on earlier investigations, it was estimated that the majority (>60%) of individuals with mTBI manifest a range of oculomotor abnormalities (Baker & Epstein, 1991; Suchoff et al., 1999; Ciuffreda et al., 2007). Of particular interest is a recently completed retrospective study in a civilian clinic, in which Ciuffreda et al. (2007) found that 90% of the visually-symptomatic, adult, mTBI group sampled ($n = 160$) exhibited some form of oculomotor dysfunction, when investigated comprehensively and in detail clinically. This is consistent with five recent reports from VA hospitals, in which many of the mTBI patients were warfighters (Goodrich et al., 2007, 2013; Lew et al., 2007; Brahm et al., 2009; Stelmack et al., 2009). Most relevant was the very high frequency of saccadic inaccuracy (i.e., saccadic dysmetria), convergence insufficiency, and accommodative insufficiency uncovered in each study. These basic oculomotor anomalies transfer to one's naturalistic setting to affect adversely both sensory and motor-based aspects of the reading process (Taylor, 1966; Ciuffreda & Tannen, 1995; Ciuffreda, 1994; Han et al., 2004; Ciuffreda et al., 2005, 2006), and in turn text processing and comprehension (Solan et al., 2003), as well as desynchronize the attentional aspect and its spatial allocation (Posner, 1980).

In addition, general attentional and more specifically visual attentional deficits are frequently present in individuals with TBI (Mateer & Mapou, 1996; Nag & Rao, 1999; Park & Ingles, 2001; Hibbard et al., 2001; Bonnelle et al., 2011; Kim et al., 2012). Traditionally, attention has been broadly categorized as follows (Pashler, 1998): *selective attention*, which involves the selection of relevant stimuli with disregard for irrelevant distracting or competing ones; and, *divided attention*, which involves the simultaneous monitoring of, and

response to, more than one relevant sensory stimulus. Both types are important to be normally functioning for successful completion of one's activities of daily living (ADL), including reading. This is evidenced in a current model of reading (E-Z Reader) (Reichle & Rayner, 2002), which incorporates two primary components: the *oculomotor* loop, which is activated once the fixated word is recognized to subsequently saccade to the next word of text; and, the *attentional* loop, which is activated following lexical completion and attention (but not gaze), is shifted to the next word of text per Posner's attentional spotlight hypothesis (Posner, 1980). A significant component of our basic tracking and reading-related oculomotor training involves, by its very nature, aspects of both sustained selective and divided attention. That is, visual attention *per se* is a significant underlying component in the overall oculomotor training process (Ciuffreda, 2002). This notion is consistent with the findings of Solan (Solan et al., 2003), in which both oculomotor and attentional training impacted positively on reading ability.

1.3. Oculomotor rehabilitation for reading in TBI

The area of reading in mTBI has been addressed using objective recording techniques in a series of studies, including its remediation, but using *version only* training protocols (fixation, saccade, simulated reading, and pursuit) (Han et al., 2004; Kapoor et al., 2004; Ciuffreda et al., 2005, 2006). Briefly, the results of these four investigations demonstrated large, consistent, and statistically significant improvements in all subjective aspects and many objective oculomotor aspects of reading in the mTBI group following a total of 9.6 hours of laboratory-based, versional eye movement training distributed over an 8-week period. First, all individuals ($n=9$) reported significant increases in overall reading ease and ability, with subjectively-based increased attentional aspects transferring to their other vocational and avocational task domains. Of these, 55% demonstrated an increase in reading rate of 10–30%. Second, there were marked objective improvements in saccadic tracking ability during simulated reading (i.e., they executed fewer saccades). Third, there were objectively-based improvements in many of the reading eye movement parameters for the Visagraph grade 10, adult-level paragraphs, especially with respect to reduction of the number of progressive saccades executed, which is a major limiting factor in reading speed (Taylor, 1966; Ciuffreda & Tannen, 1995; Ciuffreda

et al., 1996). However, there were study limitations: (1) relatively small sample sizes, (2) lack of a vergence eye movement testing and training component, (3) lack of an accommodative testing and training component, (4) lack of a validated method to assess critical aspects of visual attention and (5) lack of a validated questionnaire to assess the oculomotor training effects on reading ability and quality of life.

Thus, the purpose of the present investigation was to perform oculomotor training (OMT) in adults with mTBI with the aforementioned past study limitations in mind. There were two critical questions: (1) Can OMT improve reading rate in this population, and (2) what oculomotor parameters correlated with the improved reading rate and related factors?

2. Methods

2.1. Subjects

Twelve subjects between the ages of 23 and 33 years (mean age: 29 [± 3] years) with documented mTBI, and having a brain injury onset of greater than 1 year (1–10 years post-insult), participated in the study. Only younger, non-presbyopic individuals participated in the study to assure that sufficient accommodation was present for our testing. The training effects for the study were hypothesized to be moderate to large based on our earlier related laboratory studies as well as extensive clinical experience. Thus, this sample size was calculated using a power analysis program (G-Power software) at an alpha level of 0.05, with a power set at 0.80 using key parameters of vergence (i.e., near point of convergence, NPC) and accommodation (i.e., near point of accommodation, NPA). Inclusion and exclusion criteria are presented in Table 1. Subjects were identified by their university-based health care provider and were recruited from the Raymond J. Greenwald Vision Rehabilitation Center at the State University of New York (SUNY), State College of Optometry, Optometric Center of New York (OCNY), New York City. All were referred from local hospitals with detailed medical records regarding their diagnosis. Each subject received a comprehensive vision examination in the Raymond J. Greenwald Vision Rehabilitation Center prior to participating in the experiment. The vision examination included detailed refractive, oculomotor, and ocular health assessment. The study was approved by the SUNY Institutional Review Board (IRB) and the US Army Department of Defense (DoD) IRB. Written

Table 1
Inclusion and exclusion criteria for study subjects

Inclusion criteria	TBI onset at least one year post-incident to ensure that any subsequent changes during training are not secondary to their natural neurological recovery function period (~6–9 months) Exhibit at least one symptom (e.g., skipping lines while reading, blur, diplopia, etc.) and one clinical sign (e.g., receded near point of convergence) of a non-strabismic oculomotor dysfunction related to impaired sustained reading Intact cognitive ability to perform the required tasks for the study Stable systemic health
Exclusion criteria	Persons over the age of 40 years, as they typically will not have sufficient accommodation to measure reliably Best corrected visual acuity poorer than 20/30 in either eye Constant strabismus, amblyopia, or ocular disease in either eye Medications that alter oculomotor function and/or attentional state

Table 2
Stimulus parameters for objective evaluation of simulated reading with saccadic tracking (Han et al., 2004)

Stimulus	Total amplitude (degrees)	Target amplitude (degrees)	Frequency	Test period duration (seconds)
Full-screen Simulated Reading Multiple-Line (SRML)	±10 horizontally	1, 2, or 3 randomly	Every 2 seconds	220
Simulated Reading Single-Line (SRLS)	±5 horizontally	2.5	Every 2 seconds	50

informed consent was obtained from all subjects prior to their participation.

2.2. Study design

A cross-over, interventional experimental design of a single-blinded nature (for the subject) was used. In essence, in such a design (Hatch, 1988), each subject acts as their own control, thus negating undesirable intersubject variability. In addition, each subject received the OMT, as well as ST. During phase 1, every odd-numbered subject first received OMT, and every even-numbered subject first received ST, and vice-versa during phase 2. This was an intervention study of 15 weeks duration. It consisted of 12 weeks of the 2 treatment phases, 6 weeks each phase, separated by a week, for a total of 9 hours of OMT and 9 hours of ST. In addition, there were 3, one-week measurement periods: one week before phase 1 treatment, one week after phase 1 treatment, and one week following phase 2 treatment. During these testing and training periods, subjects did not perform any other oculomotor-based vision rehabilitation to avoid contamination of test results. All testing and training of the subjects was performed by the first author, who is an optometrist with experience in oculomotor rehabilitation.

The study consisted of the following phases:

- Week 1 – *Initial baseline measures* - All “Evaluative Procedures” (described later) were recorded over two separate test sessions (each session lasting for up to 1.5 hours, including rest peri-

ods to prevent fatigue) separated by at least two days.

- Weeks 2–7 - *Phase 1 treatment* – 6 weeks of either the OMT or ST. Subjects received 2 training sessions per week. Each session was 60 minutes in duration, involving 45 minutes of actual training with the remainder of time consisting of short and interspersed rest periods for the subject. Total training time of 9 hours.
- Week 8 – *Repeat baseline measures* - All “Evaluative Procedures” were repeated over two separate test sessions (each session lasting for up to 1.5 hours including rest periods to prevent fatigue) separated by at least two days.
- Weeks 9–14 – *Phase 2 treatment* - 6 weeks of either the OMT or the ST. The subjects received 2 training sessions per week. Each session was 60 minutes in duration, involving 45 minutes of actual training with the remainder of time consisting of short and interspersed rest periods for the subject. Total training time of 9 hours.
- Week 15 – *Repeat baseline measures* - All “Evaluative Procedures” were repeated over two separate test sessions (each session lasting for up to 1.5 hours including rest periods to prevent fatigue) separated by at least two days.

2.3. Evaluative procedures

A range of clinically-based subjective and laboratory-based objective measures, along with subjective visual attention and near vision symptoms,

were assessed (Thiagarajan, 2012; Thiagarajan & Ciuffreda, in press). All clinical parameters were measured using conventional standardized clinical techniques (Borish, 2006). All laboratory-based objective measures were performed using commercially-available instrumentation with well-established test protocols (Han et al., 2004; Green et al., 2010b; Szymanowicz et al., 2012, for version, accommodation, and vergence, respectively). All measures were non-invasive and were recorded with their habitual distance correction in place. Order of testing was randomized over the 2 days of measurements. See Thiagarajan (2012) for details of the parameters assessed. For the purpose of the present paper, the primary oculomotor parameters (clinical and laboratory-based), as well as nearvision symptoms and visual attentional aspects, involved in reading ability will be considered.

2.3.1. Clinical parameters

This included the near point of convergence (NPC), near point of accommodation (NPA) using the push-up method, and reading eye movements. While the NPC and NPA were recorded using standardized clinical procedures (Borish, 2006), reading eye movements were recorded using the Visagraph objective eye movement recording system as described below.

Reading eye movements (horizontal position of both eyes) to standardized text paragraphs (grade-10 level equivalent) were recorded using the Visagraph reading eye movement system (Taylor Associates, Huntington, NY). It consists of an infrared, limbal-reflection eye movement recording system, which has become a standard clinical test in optometry (Ciuffreda & Tannen, 1995), to assess oculomotor-based reading dysfunctions objectively (Ciuffreda et al., 2003). The system has a resolution of $<1^\circ$, a sampling rate of 50 Hz, and a linear range of at least $\pm 10^\circ$. This sampling rate is sufficient for appropriate saccadic detection during reading (Ciuffreda & Tannen, 1995). Subjects wore test goggles incorporating the infra-red sensors and emitters. They read silently the standardized 100-word text binocularly at their habitual reading distance in primary position. Following two practice paragraphs at level 10 to assure the attainment of a stable baseline (Ciuffreda et al., 2003; Griffin & Grisham, 2002), each subject then silently read a new level 10-paragraph at each test session, and they then answered 10 yes/no questions related to details of the paragraph to assess for adequate comprehension ($\geq 70\%$) (Taylor, 1966). Subjects were instructed to read the paragraphs using their normal reading strategy, and furthermore to pay

attention to text details, as they were tested for comprehension at the end of reading, but not to reread. The following selected conventional reading eye movement parameters (Taylor, 1966) were compared both within and between subgroups before and after training: reading rate in words per minute (wpm), number of progressive saccades as fixations/100 words, number of regressive saccades as regressions/100 words, comprehension in percentage calculated from the number of correct answers, fixation duration in seconds, and grade-level efficiency based on a weighted average of the aforementioned parameters. The Visagraph software automatically calculated the values for each parameter.

2.3.2. Laboratory parameters

Binocular horizontal versional eye movements were recorded objectively using the Arrington eye movement recording system, which is a table-mounted, infrared, binocular camera system having a 220 Hz sampling rate and 0.01° resolution, with a linearity of $\pm 44^\circ$ horizontally (Chiu & Yantis, 2009). Its sampling rate satisfies the Nyquist criterion (Khan, 2005). A 12-point calibration was performed at each test session to assure response linearity across the tested field, as well as after any rest period during which the subject removed their head from the headrest/chinrest assembly. The computer-controlled test stimuli were comprised of a 1° bright square target displayed on a high-resolution computer monitor at a 40 cm test distance, with the target either remaining stationary at a given screen position for a specified period of time or being displaced step-wise horizontally. Subjects were instructed to fixate the center of the target. These test stimuli and paradigms were developed in our laboratory over the past decade (Han et al., 2004). Subjects either binocularly fixated or executed saccades based on the laboratory parameter tested (Thiagarajan, 2012). A range of basic versional parameters (e.g., saccadic latency, saccade ratio, amplitude, peak velocity, horizontal and vertical fixation) were measured. For the purpose of the present paper, the parameter of *saccade ratio* alone is described as related to reading (Han et al., 2004; Kapoor et al., 2004; Ciuffreda et al., 2006).

The *saccade ratio* is defined as the number of tracking saccades executed divided by the number of test target step displacements; a ratio of 1.0 indicating one saccade for each target step displacement would be optimal (Han et al., 2004). This was calculated using a simulated reading single line (SRSL) ($\pm 5^\circ$ horizontal range) and a simulated reading multiple line (SRML)

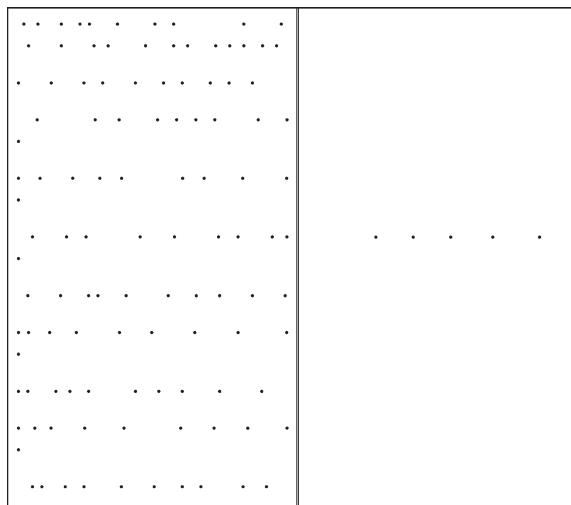


Fig. 1. Full-screen multiple lines stimulus pattern for simulated reading (left). Single-line stimulus pattern for simulated reading (right). In both cases, at any given time, only an isolated, single 1° square target appeared on the screen at the positions shown by the dots that the subject tracked with saccades.

($\pm 10^\circ$ horizontal range) paradigms (Fig. 1). While the former paradigm consisted of both spatially and temporally predictable stimulus changes (2.5° steps, every 2 seconds), the latter paradigm consisted of a spatially randomized (1, 2, or 3 degree steps) and temporally predictable (every 2 seconds) stimulus. For SRML, the

subject followed the single square 1° target as it randomly moved across the screen to simulate reading a paragraph of text. For SRLS, the subject followed the same target as it predictably moved across the center of the screen in a repeated pattern. See Table 3 for related stimulus parameters. While the SRLS simulated reading on a single line repetitively to develop accuracy and automaticity, the SRML simulated reading of a 10-lined text paragraph to develop accuracy and global visual scanning ability during reading. However, considering the test target used (e.g., a black square), both paradigms tested pure saccadic tracking in the absence of any cognitive component (e.g., word recognition or text comprehension). Subjects were instructed to execute saccades that were as accurate as possible as the target was displaced laterally on the screen, while fixating the target center once it was foveally acquired. The total number of saccades executed by the subject was determined off-line manually on the high resolution display monitor. Any saccade greater than or equal to 0.25 degrees in amplitude was counted as a saccade for both the SRML and SRLS paradigms.

2.3.3. Subjective visual attention test

A subjective correlate of visual attention was assessed using the Visual Search and Attention Test (VSAT). It involves a visual search (for a letter or a symbol) and cancellation (cross-out) task that was

Table 3
Stimuli for oculomotor training protocol

Stimulus	Stimulus parameter	Training period duration (seconds)	Total training duration (minutes)
Version			
Fixation	Central (midline)	60	5
	Left (10 degrees)	60	
	Right (10 degrees)	60	
	Up (10 degrees)	60	
	Down (10 degrees)	60	
Predictable Saccades	Horizontal (± 5 degrees)	50	5
	Horizontal (± 10 degrees)	50	
	Vertical (± 5 degrees)	50	
	Vertical (± 10 degrees)	50	
Simulated Reading (repeated twice)	Full-screen	75	5
	Single-line	75	
	Full-screen	75	
	Single-line	75	
Vergence			
	Step amplitude (BO/BI)	7	15
	Step facility (BO/BI)	5	
	Ramp	3	
Accommodation			
	Step amplitude right eye plus/minus lenses	5	15
	Step amplitude left eye plus/minus lenses	5	
	Step facility	5	

developed by Treanerry et al. (1989). It assesses global sustained visual attention, while scanning to search for selected letters/symbols. Test-retest reliability for the VSAT was found to be 0.95, using the Pearson product-moment correlation. Calculated sensitivity and specificity were 0.88 and 0.86, respectively (Treanerry et al., 1989). The test was performed binocularly at the subject's habitual near work distance.

2.3.4. Symptom scale

Individual symptoms related to near-work were rated by the subjects using the Convergence Insufficiency Symptom Survey (CISS), whose sensitivity (0.98) and specificity (0.87) have been demonstrated to be high (Rouse et al., 2004). The test-retest reliability was found to be 0.88. It is comprised of a 15-item questionnaire specifically probing reading-related symptoms, such as intermittent blur, diplopia, headache, skipping lines, losing concentration, etc. Severity of symptoms is scaled from 0 to 4, i.e., from least symptomatic to most symptomatic. The total score was compared before and after the 2 training phases. A reduction in overall score

of 10 or more was considered to reflect a significant reduction of symptoms. A score of zero would indicate being absolutely symptom-free, and a score of 60 would represent maximal symptomatology.

3. Treatment protocol

3.1. Phase 1 and phase 2 treatment phases

3.1.1. OMT procedures

This oculomotor rehabilitation was performed along the midline at 40 cm, 2 sessions per week, for a total of 6 weeks. Training was performed with constant verbal and visual feedback, motivation, repetition, and maintained attention by involving active participation of the subject (Ciuffreda, 2002). At each session, each oculomotor component (version, vergence, and accommodation) was trained for 15 minutes, interspersed with 5 minute rest periods. Each session lasted for 1-hour, with 45 minutes of total training and 15 minutes of rest periods, for a total of 9 hours of training over the 6 week period (Fig. 2).

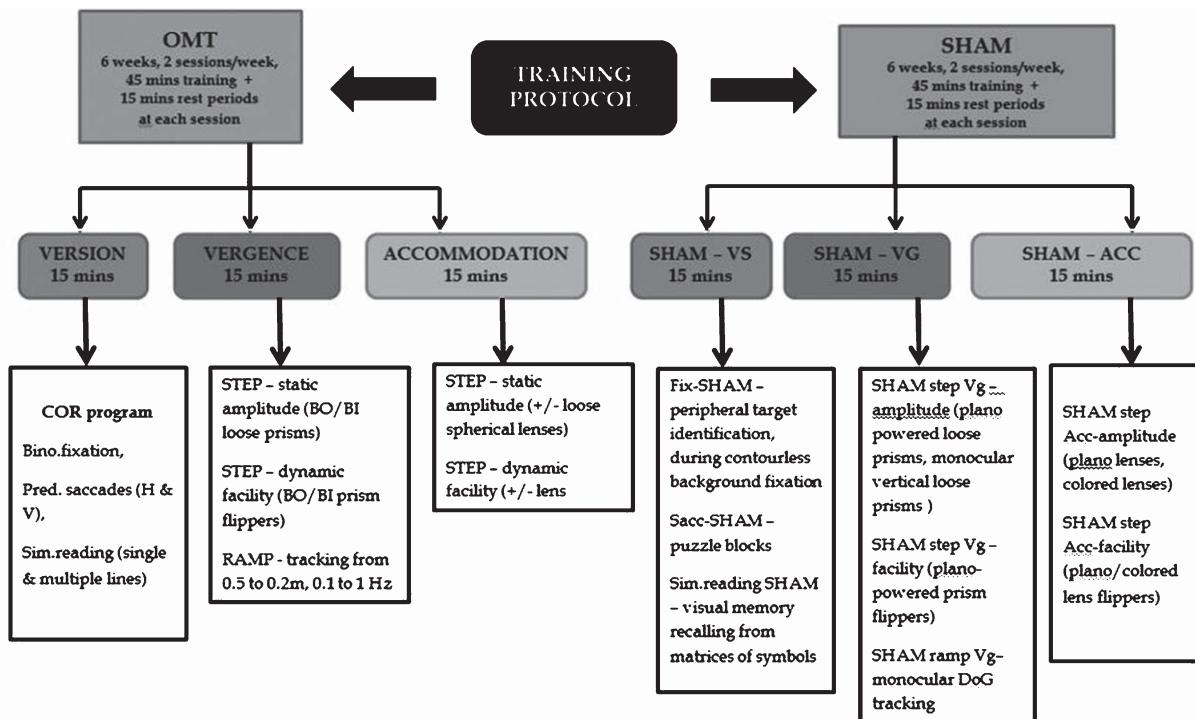


Fig. 2. Overview of oculomotor training (OMT) and sham training (ST) protocols, see text for details. VS = version; VG = vergence; ACC = accommodation; COR = computerized oculomotor rehabilitation; Bino = binocular; Pred. = predictable; Sim. = simulated; BO = base-out; BI = base-in; Fix. = fixation; DoG = difference of Gaussian.

3.1.1.1. Version. Version (fixation, predictable saccades, and simulated reading) was trained via the computerized oculomotor rehabilitation (COR) software developed in our laboratory (Thiagarajan, 2012) using a rapid-serial visual presentation (RSVP) paradigm (Xu et al., 2009) with binocular viewing. The COR program allows for training of versional, vergence, and accommodation. For version, it can train fixation, saccades, pursuit, vestibular (VOR), and simulated reading by appropriate target selection. Targets can be altered with respect to size, color, detail, test duration, etc. For vergence and accommodation, the same versional target selection is used, but the changes in vergence and accommodative demand levels are introduced manually by the experimenter. Targets in the form of pictures, numbers, symbols, letters, color patches, etc., of varying sizes were presented rapidly for different presentation times. Subjects either fixated a stationary target to train fixation or executed saccades to track the target to train predictable saccades. At the beginning of each training component, a sample target (e.g., picture) was presented to the subject. While maintaining either binocular fixation or tracking of the target, the subject was instructed to count the number of times the sample target appeared in the array of possible targets presented during the stipulated training duration (i.e., RSVP). Subjects were constantly motivated to achieve the maximum number of correct responses. The subject's numerical response was compared with the actual number of presentations (provided by the software). Verbal feedback related to subject's performance was also given by the software in the form of a female voice. See Table 3 for the versional training stimuli.

3.1.1.2. Vergence. Similar to version, at each training session, horizontal vergence was trained for 15 minutes. While rapid step vergence was trained for 12 minutes, slow ramp vergence was trained for 3 minutes (Hung et al., 1986). During the step tracking, both amplitude (7 minutes) and facility (5 minutes) were trained to attain both response accuracy and speed (Scheiman & Wick, 2008), respectively. See Table 3 for the vergence training protocol.

For step vergence amplitude training, base-out and base-in (BO/BI) prisms were used. The fusional targets were comprised of pictures, symbols, numbers, letters, tumbling E, and colors displayed on a computer screen at 40 cm. While the subjects bifixated the target, loose prisms were introduced manually by the experimenter in 2 prism diopter (pd) increments either in front of one eye or divided equally between the two

eyes. The total amount of prism was determined by the subject's task performance level. After introducing each BO/BI prism, subjects were instructed to fuse the target as rapidly as possible and sustain single/fused vision for 15–20 seconds. For step vergence facility training, combinations of BO/BI prism flippers (3Δ BO/ 1Δ BI, 6Δ BO/ 2Δ BI, 9Δ BO/ 3Δ BI, and 12Δ BO/ 3Δ BI) were used, while maintaining the accommodative stimulus constant at 0.4 m (2.5D). Based on the subjects' ability to fuse the target, the magnitude of prism flipper was chosen. Subjects bifixated targets displayed on a computer screen and were instructed to fuse and focus as rapidly as possible and to achieve the maximum numbers of cycles of prismatic stimulus change as possible.

For ramp vergence training, subjects binocularly tracked a 20/30 letter on an X-Y plotter in free space over a range of 0.5 m to 0.2 m at the rate of 0.1 to 1 Hz. Task difficulty was increased as performance improved by tracking at closer distances in combination with increased target speed.

3.1.1.3. Accommodation. At each training session, accommodation was trained for 15 minutes. Step accommodative amplitude was trained for 10 minutes (5 minutes each eye), binocular step accommodative facility was trained for 5 minutes (Hung & Ciuffreda, 1988). See Table 3 for the accommodative training protocol.

For step accommodative amplitude training, positive and negative spherical lenses were used. The accommodative targets were comprised of texts of various sizes ranging from 20/60 to 20/20 displayed on a computer screen at 40 cm. While the subjects monocularly fixated the target, lenses were introduced manually at 0.5D increments in front of the eye. The lens magnitude was selected based on the subject's task performance level. After introducing each lens (positive/negative), subjects were instructed to focus the text as rapidly as possible and to sustain clarity of vision for 15–20 seconds. For step accommodative facility training, combinations of \pm lens flippers (± 0.5 , ± 0.75 , ± 1.00 , ± 1.50 , and ± 2.00 D) were used, while maintaining the vergence stimulus demand constant at 0.4 m (2.5MA) (Scheiman & Wick, 2008). Subjects bifixated targets displayed on a computer screen and were instructed to fuse and focus as rapidly as possible and to achieve the maximum number of cycles possible.

3.1.2. Analogous ST procedures

Similar to the OMT, ST was performed along the midline at 40 cm, 2 sessions per week, for a total of 6 weeks (Thiagarajan, 2012). Again, training was

performed with constant verbal feedback, motivation, repetition, and involving active participation of the subject to maintain attentional awareness (Ciuffreda, 2002). At each session (lasting for 1 hour), the sham analogue of version, vergence, and accommodation training was performed for a total of 45 minutes with interspersed rest periods for 15 minutes, for a total of 9 hours of training over the 6 week treatment phase. For version, there was no formal, programmed, and repetitive fixation (with foveal feedback) or saccades per se. It rather involved intermittent and random saccades interspersed with random fixational pauses that would not be effective in training the versional system (Ciuffreda, 2002). Similarly, vergence sham did not involve any disparity stimulation, and accommodative sham did not involve any blur stimulation, as these are the primary drives to the respective systems (Ciuffreda, 1992, 2002; Hung et al., 1996).

3.1.2.1. SHAM version. For fixation ST, subjects bifixated the estimated center of a contourless blank computer screen at a 40 cm distance for 2 seconds before two targets (1 inch square picture/symbol/letter) were presented for 100 msec on either one or both sides (± 10 degrees either horizontally or vertically) of the estimated fixation point. The subject attempted to identify the two peripheral targets presented. Peripheral target presentation time (100 ms) was shorter than the mean saccadic latency (~ 200 ms) (Ciuffreda & Tannen, 1995) to prevent target foveation. *Saccade sham* involved completion of perceptual puzzle blocks, in which subjects completed the puzzle by arranging individual puzzle blocks into an appropriate pattern both monocularly and binocularly. Visual concentration was the sham analogue of the *simulated reading* training. The subject viewed and randomly scanned with saccades an array (varying from 3×3 to 5×5) of pairs of pictures for a 10-second period. Then, the pictures were removed, and the subject was requested to recall by visual memory the location of a specific picture in the array.

3.1.2.2. Sham vergence. For sham-step stimuli, binocular or monocular plano-powered loose prisms, prism flippers, and/or monocular vertical prism (0.5 or 1pd) flippers were used. The targets were comprised of pictures, a vertical column of letters/numbers of varying sizes, and a cartoon movie displayed on a computer screen at 40 cm. The training was comprised of repetitive and systematic manual alternation of the flippers/prisms every 15–20 seconds, but without

any actual prismatic power changes horizontally, while bifixating static targets or watching a cartoon movie. For sham-ramp stimuli, subjects tracked a difference of Gaussian (0.2cycles/degree) target through a 0.5 mm pinhole monocularly for 5 minutes (2.5 minutes each eye) in an otherwise dark room (Ciuffreda, 1992). This target does not have any blur or disparity stimulation when viewed monocularly (Kotulak & Schor, 1987).

3.1.2.3. Sham accommodation. This ST involved repetitive and systematic manual alternation of the lens flippers, monocularly and binocularly, but without any spherical lens power changes (i.e., plano/colored lenses). Subjects read a text paragraph or watched a cartoon movie at 40 cm on a computer screen, similar to that performed for the OMT.

4. Results

Figure 3 presents the group mean findings related to reading rate before and after the OMT, with comparison to the grade-level normative data of Taylor (1966). There was a significant 25% increase in reading rate following the OMT. It increased from 142 to 177 words per minute, with it closely approaching the lower normal limit (Taylor, 1966). However, it did not normalize.

Table 4 presents the key group mean Visagraphic oculomotor-based parameters, including reading rate as described above. Grade-level efficiency significantly

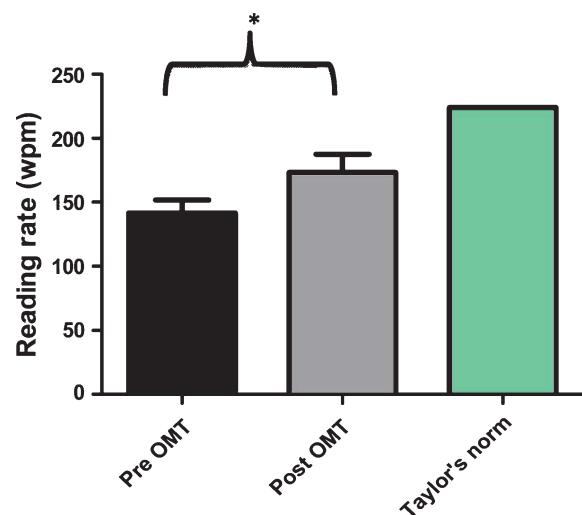


Fig. 3. Mean reading rate before (Pre-OMT) and after (Post-OMT) in mTBI compared to Taylor's norm. Error bar indicates $\pm 1\text{SEM}$; * = statistically significant.

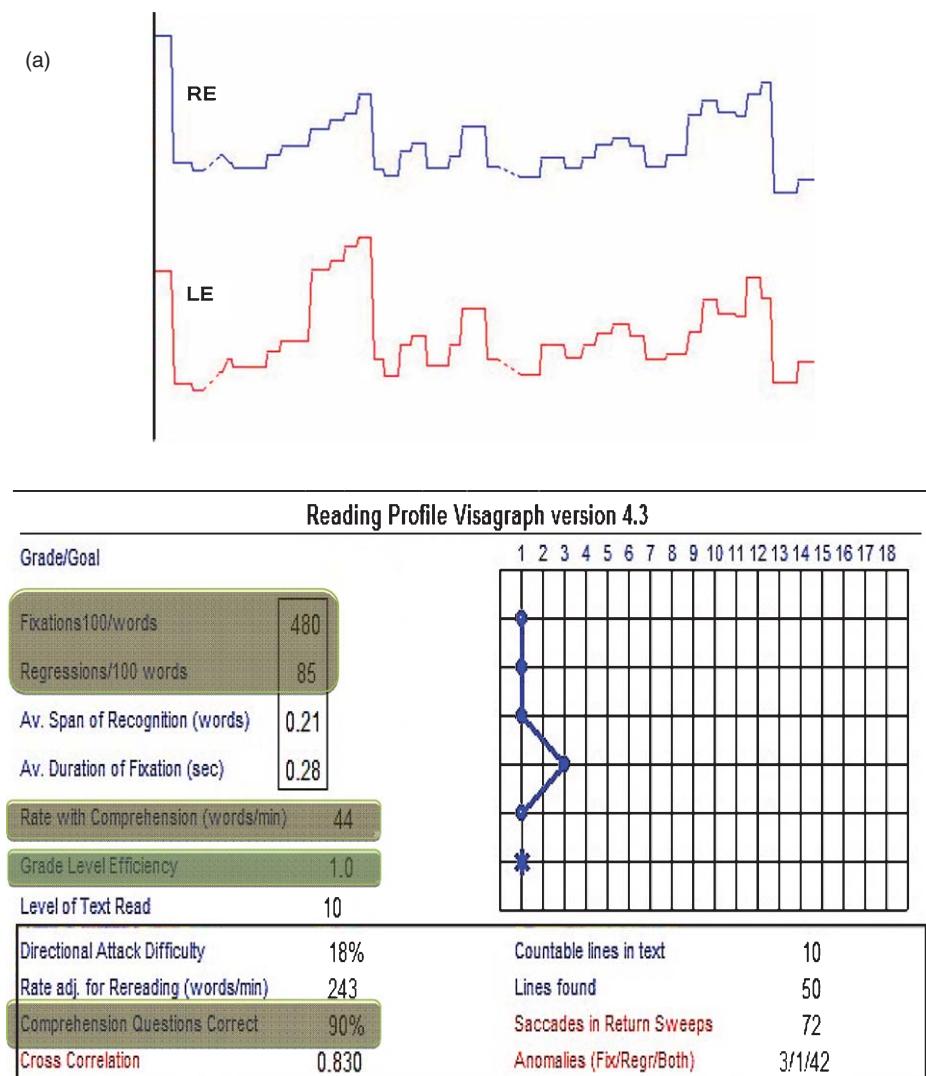


Fig. 4(a). Visagraph output in a mTBI subject at baseline who showed the best post-OMT Visagraph-based reading gains: Top - Horizontal eye position as a function of time (8 seconds data); RE = right eye; LE = left eye; Upward inflection = progressive saccade; downward inflection = regressive saccade. Bottom – On the left = Various Visagraph parameters assessed for grade-10 reading material; Graph plot on the right = Taylor's grade level efficiency (from 1–18; >12 is normal), showing a level of 1.0 (star) in this subject before OMT. Relevant parameters are highlighted.

increased following the OMT by over 2 grade levels, which is considered to be clinically significant (Ciuffreda et al., 2003). Similarly, the number of fixations per 100 words (i.e., number of progressive saccades) reduced significantly. However, neither parameter normalized. The number of regressions per 100 words decreased by 23% in the predicted direction, but this large change was not statistically significant, presumably due to the relatively large inter-subject variability found. Lastly, the comprehension level did not change significantly, as it was already normal at baseline ($\geq 70\%$) (Taylor, 1966).

With regard to the saccade ratio, there was a marked reduction in the number of progressive and regressive saccades, following the OMT. The group mean saccade ratio for the SRML paradigm reduced significantly ($p < 0.05$) from a mean value of 2.1 to 1.7 ($\sim 20\%$), thus demonstrating improvement in pure sequential saccadic tracking ability. With respect to the simulated reading single line (SRSL) ratio, it reduced from 2.7 to 2.2 ($\sim 20\%$), but this change was not statistically significant, presumably due to the relatively large inter-subject variability found. However, its decreasing trend is suggestive of improvement. Neither

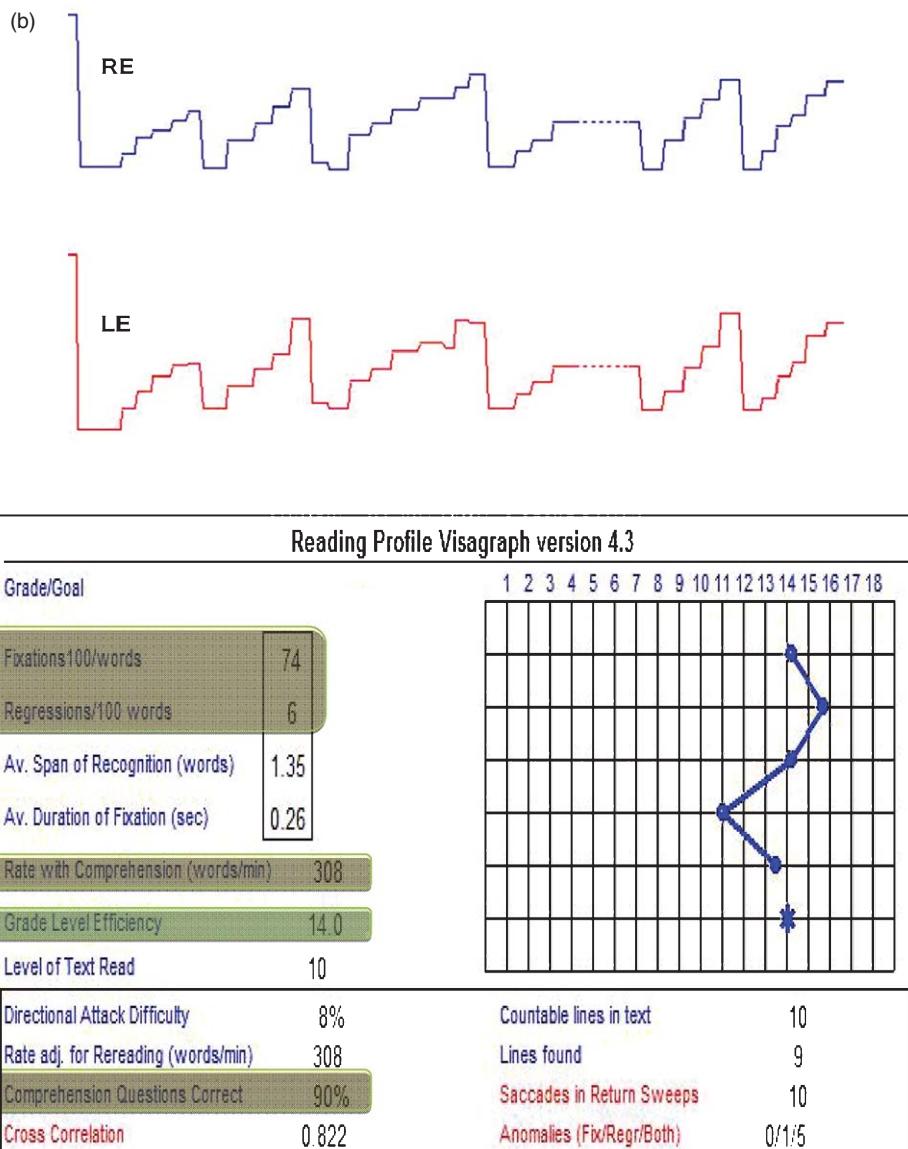


Fig. 4(b). Visagraph output in the same mTBI subject after OMT: Top - Horizontal eye position as a function of time (8 seconds data); RE = right eye; LE = left eye; Upward inflection = progressive saccade; downward inflection = regressive saccade. Bottom – On the left = Various Visagraph parameters assessed for grade-10 reading material; Graph plot on the right = Taylor's grade level efficiency (from 1–18; >12 is normal, based on weighted average of the reading parameters), showing a level of 14.0 (star) in this subject. Relevant parameters are highlighted.

saccade ratio correlated with the increase in reading rate (Table 5).

Figure 4a and b present Visagraphic reading eye movement traces before and after OMT, along with the related tabular reading-related analysis (see highlighted areas), in the subject who demonstrated the most dramatic improvements. Notably, reading rate increased from 44 to 308 words per minute, and hence it normalized (Taylor, 1966). Related to this, grade-level

efficiency increased markedly, and it normalized going from grade 1 to grade 14 (college level), with a high comprehension level present at each test phase (90%). The global reading eye movement pattern became more regular and “staircase-like” following the OMT, a desirable profile (Taylor, 1966; Ciuffreda & Tannen, 1995).

The change in reading rate with OMT was also significantly correlated with two key clinical parameters, which are typically abnormal at baseline

Table 4

Mean ($\pm 1\text{SEM}$) Visagraph parameters of reading eye movements before (baseline) and after oculomotor training (post-OMT) for grade-10 level text. wpm- words per minute; fixations/100 words – number of progressive saccades; regressions/100 words – number of regressive saccades. BOLD, italicized = statistically significant. * - normal at baseline

Visagraph parameter	Baseline	Post-OMT	Significant	p value
Reading rate (wpm)	142 (10)	177 (14)	yes	<0.01
Comprehension (%)	81 (4)*	85 (3)	no	0.31
Fixations/100 words	164 (10)	135 (11)	yes	0.02
Regressions/100 words	30 (3)	23 (4)	no	0.11
Fixation duration (sec)	0.27 (0.008)*	0.27 (0.10)	no	0.91
Grade level efficiency	4.1 (0.7)	6.3 (1.2)	yes	0.01

Table 5

Correlation of critical oculomotor parameters for reading

Correlated parameters	R value	Significant	p value
SRML ratio vs. reading rate	0.13	No	0.52
SRSR ratio vs. reading rate	0.27	No	0.19
Binocular accommodative amplitude vs. reading rate	0.43	Yes	0.03
NPC break vs. reading rate	-0.51	Yes	0.01
Binocular accommodative facility vs. reading rate	0.23	No	0.26
Vergence facility vs. reading rate	0.31	No	0.14
Reading rate vs. CISS score	-0.37	Yes	0.03
Reading rate vs. VSAT percentile	0.35	Yes	0.04

(i.e., prior to any OMT) in individuals with mTBI (Green et al., 2010b; Szymanowicz et al., 2012; Thiagarajan, 2012; Ciuffreda et al., 2007) (see Table 5). Binocular accommodative amplitude (i.e., the maximum accommodative amplitude), which increased significantly and normalized following OMT, significantly correlated with reading rate. Similarly, the near point of convergence (i.e., the maximum convergence amplitude), which increased significantly following OMT but did not normalize, significantly correlated with reading rate (Thiagarajan, 2012).

The change in reading rate also significantly correlated with two key non-oculomotor-based, but related, visual parameters (Table 5). Nearwork symptoms significantly decreased, and visual attention significantly increased, with increase in reading rate following OMT.

This aforementioned change in reading rate did not significantly correlate with two key clinical dynamic parameters, which are frequently abnormal at baseline

in mTBI (Green et al., 2010b; Szymanowicz et al., 2012; Ciuffreda et al., 2007). These were lens facility and prism facility (Table 5).

Lastly, and of considerable interest and importance, was the frequency of occurrence of an abnormality in one or more of the three oculomotor subsystems based on dual categorization, namely clinically-based and laboratory-based parameters. The summarized findings are presented in Table 6 for each of the 12 subjects at baseline. For each subject, there are 6 possible categories of oculomotor abnormalities across the three oculomotor subsystems tested (2 for each, i.e., clinical and laboratory). If all subjects exhibited an abnormality for all three subsystems for both the clinical and laboratory-based parameters, there would be 72 boxes checked in Table 6. First, across subjects, 60 out of the 72 possible boxes were checked as “abnormal” (84%). Second, 11 of the 12 subjects (92%) had at least one of the categorized parameters (clinical/laboratory) abnormal for all three subsystems. Only one subject (CR04) demonstrated abnormality in two systems (version and vergence). Accommodation was found to be normal in this subject. Third, no subject had an oculomotor abnormality in only one oculomotor subsystem. Lastly, the greatest number of abnormalities was found in the versional system and the least number in the accommodative subsystem.

In contrast to that found for the OMT, the ST did not have a significant effect on *any* parameters assessed (Thiagarajan, 2012). In the odd group of subjects who performed oculomotor training first, there was no significant difference ($p > 0.05$) between post-OMT and post-ST measures, thus showing no effect of the ST. Similarly, in the even group of subjects who performed ST first, there was no significant difference ($p > 0.05$) between baseline and post-sham measures, again thus showing no effect of the ST.

5. Discussion

Reading constitutes one of the most important activities of daily living (ADLs) (Ciuffreda et al., 2006). As mentioned in the Introduction, efficient reading requires the precise coordination of both the lower-level, oculomotor (version, accommodation, and vergence) and the higher-level, non-oculomotor (e.g., attention, linguistic, cognitive, memory) processes (Reichle & Rayner, 2002). Since TBI produces a diffuse/global kind of brain injury (e.g., coup-contrecoup) (Suchoff et al., 2001; Greve et al., 2009), deficits in either the oculo-

Table 6
Baseline abnormal oculomotor subsystems. Symbols: ✓ = presence of abnormality; grey filled box = absence of abnormality

	VERGENCE		ACCOMMODATION		VERSION	
	Clinical	Lab	Clinical	Lab	Clinical	Lab
JM01		✓		✓	✓	✓
TB02	✓	✓	✓		✓	✓
BR03	✓	✓	✓		✓	✓
CR04		✓			✓	✓
EK05	✓		✓	✓	✓	✓
KO06	✓	✓		✓	✓	✓
DB07	✓	✓	✓	✓	✓	✓
AN08	✓	✓	✓	✓	✓	
DJ09	✓	✓	✓	✓	✓	✓
SR10	✓	✓	✓	✓	✓	✓
AK11	✓	✓	✓	✓	✓	✓
NM12	✓		✓	✓	✓	

motor and/or non-oculomotor systems could adversely affect reading. If an individual cannot read efficiently with comfort for a sustained period of time, their ability to perform many routine ADLs (e.g., computer work), as well as one's overall quality of life (QOL), will likely be compromised (Ciuffreda et al., 2006).

Following head trauma, the diffuse axonal injury (DAI) causes the axons to stretch, twist, and tear, which results in overall disrupted white matter (WM) integrity (Greve et al., 2009). As a consequence, the strength, number, and organization of the neuronal synapses are reduced, thus causing the neuronal synchrony and firing rate to be compromised (Warraich & Kleim, 2010). These structural changes along the affected neural pathways are reflected in the functional abnormality as a response that is *inaccurate, variable, and slowed*. In particular, the "automaticity" or "reflexive nature" of a particular function is lost, and hence the affected individual cannot respond in a time-optimal manner. Thus, an individual whose functional automaticity is compromised will need to constantly exert considerable effort simply to perform this necessary but *lower-level* actions (e.g., basic saccadic oculomotor control), which in turn will adversely impact upon and compromise higher-level aspects, such as comprehension, sustained

attention, and short-term visual memory, as well as visual comfort.

One of the main motor systems that is commonly affected subsequent to a TBI is the oculomotor system (Ciuffreda et al., 2007; Capó-Aponte et al., 2012). Considering the vulnerability of the brain stem structures (Greve et al., 2009) that primarily house neurons related to accommodation, vergence, and version, the frequency of disorders in one or more of these three subsystems is not surprising (Ciuffreda et al., 2007). Since reading involves synchrony within and between each of these three oculomotor subsystems and their related aspects, it is not surprising that "*difficulty with reading*" is the primary symptom in individuals with TBI (Ciuffreda et al., 2007; Goodrich et al., 2007, 2013; Lew et al., 2007; Brahm et al., 2009; Stelmack et al., 2009). A combination of intermittent blur/diplopia due to accommodative and/or vergence dysfunctions, and skipping words/lines and loss of place due to a saccadic dysfunction, would adversely affect reading. More importantly, higher level attentional aspects, of necessity, would now be allocated to perform basic oculomotor functions during reading (e.g., intermittently focusing/fusing the words), thus resulting in compromised comprehension. However, individu-

als with oculomotor abnormalities may modulate their reading speed and frequently reread to attain an acceptable level of comprehension (Ciuffreda & Tannen, 1995). All of the above would significantly reduce reading speed and impact adversely on overall reading efficiency, thus producing nearvision symptoms.

In the present study, reading eye movements recorded using the Visagraph system revealed several interesting results. Taylor's normative data (Taylor, 1966) show that the expected average adult values to be 224 wpm for reading rate, 101 fixations per 100 words, 19 regressions per 100 words, and grade-level efficiency to be 14. However, those with mTBI in the present study demonstrated significantly reduced reading rate, an increased number of fixations/100 words, a higher number of regressions/100 words, and decreased grade-level efficiency. An excessive (i.e., unwanted) number of saccades, both progressive and regressive in nature, are the main determinants of slow reading (Ciuffreda & Tannen, 1995). The more saccades that are executed, the slower the reading rate based on sampled-data theory alone (Stark, 1968); that is, after a saccade is completed, the refractory period for initiation of the next saccade is approximately 180 msec. The present finding of an increased number of unwanted/unnecessary, inaccurate saccades is consistent with that of the significantly elevated saccade ratio found in these subjects. However, the fixation durations were within normal limits, and thus did not contribute to the reduced reading rate of the subjects (Table 3).

Following training, there was a significant 25% improvement in reading rate. Figure 3 shows reading rate values before and after training in comparison to Taylor's age-normed values. This reading rate increase was also significantly correlated with the reduction in CISS score, along with the increase in VSAT percentile, thus suggesting concurrently improved subjectively-based visual comfort and visual attention, respectively, in the process. In addition, the number of fixations/100 words reduced by 18%, thus demonstrating a reduced number of excessive and unnecessary saccades after the training. The simulated reading training protocol was purposely designed, so that subjects could not make a "regression", by extinguishing the previous target when the new target appeared. While this reduces the number of purely oculomotor-based regressive saccades, however, it might not reduce regressions made to reconfirm a particular text component during actual reading. In the present study, the number of regressions/100 words decreased by 23% in the predicted direction following the training. However, it was not significant due

to the relatively large intersubject variability. As far as comprehension was concerned, it was normal at baseline, and hence no large change was expected following the training. Since comprehension did not change after the training, it suggests that the increased reading rate was primarily oculomotor-based, and an effect of OMT training. Based on the present results, it is clear that the oculomotor-based training had a significant positive effect on reading rate and related aspects.

The correlational analyses provided several important insights into the OMT effects and their functional significance (Table 5). First, improvement in reading rate was correlated with two key clinical, *amplitude-based, static* oculomotor parameters: the maximum amplitude of accommodation and the maximum amplitude of convergence, following OMT. In contrast, reading rate was not correlated with two key clinical, *facility-based, dynamic* oculomotor parameters: lens facility and prism facility, following OMT. There is a logic to these findings. Reading requires a sustained level of accommodation and convergence, as the reading material is maintained at a relatively constant near distance for prolonged periods of time. This suggests that a considerable amount of both accommodation and vergence must be exerted, as well as be maintained "in reserve" to allow for sustained and comfortable reading and nearwork in general, as has been hypothesized for the relationship between "accommodative reserve" and the onset of symptomatic presbyopia (Rabbets, 2007). That is, according to this notion, the maximum amplitude of accommodation should be at least twice the near dioptric demand for sustained and comfortable nearwork. Second, there were correlations between reading rate, and both the CISS and VSAT score changes, following OMT. It is not surprising that the reading rate would increase, once the three oculomotor subsystems were significantly remediated, as the presumption was that all/most of the reading problems at baseline (i.e., pre-OMT) had a primary oculomotor basis in the sample population (Ciuffreda et al., 2007; Capó-Aponte et al., 2012). Thus, following the OMT, there was presumably less effort allocated to the low-level oculomotor-based reading components. Related to this was the significant increase in visual attention with OMT, as well as its correlation with the training-related increase in reading rate. This finding suggests that overall attention could now be directed to the task of comprehending the text rather than to the low-level control oculomotor aspects. Furthermore, it has been established that the task of oculomotor remediation per se has embedded into it an underly-

ing attentional training component (Solan et al., 2003; Ciuffreda, 2002). That is, with the associated high level of attention and continuous task demands (e.g., keeping the target in focus at all times) and related visual feedback involving the concept of “perceptual learning” (Ciuffreda, 2002) in the training process, visual attention was heightened and improved. This was demonstrated several years ago by Ciuffreda et al. (2006), in which the training of basic versional eye movements and simulated reading resulted in marked improvement of the attentional state under a variety of environmental conditions (e.g., quiet versus noisy room) in individuals with mTBI using a simple rating-scale questionnaire.

The lack of correlation of reading rate with the saccade ratio is interesting. An improvement in basic saccadic tracking ability, as evident from the reduction in saccade ratio, was expected to correlate with the increased reading rate. However, the present study results revealed lack of correlation with either the single-line or multiple-line saccade ratios. Although improved tracking ability was reflected in the reduction of fixation/100 words and regressions, the finding could be attributed to the individual subject variability. The reduction in saccade ratio was smaller than the magnitude reported by Ciuffreda et al. (2006), although the baseline ratios reported in their study were larger than in the current study, and thus there was more room for a significant improvement to occur.

Neurophysiologically, the observed changes in oculomotor behavior could be attributed to residual oculomotor/visual neuroplasticity in the present subjects. This training-induced recovery process involves functional recovery via a “relearning” process (Chen et al., 2010; Munoz-Cespedes et al., 2001). Vision rehabilitation acts as a critical part of the relearning process, in which the trained system gains its accuracy and automaticity through feedback and repetition. With regard to the results of the present study, an overall improvement in the oculomotor behavior was observed in all 12 individuals with mTBI to some degree, and it is a consequence of “oculomotor learning” (Abernathy et al., 1997; Ciuffreda, 2002). A combination of repeated stimulation with various amounts and types of blur (via negative and positive lens), horizontal disparity (crossed and uncrossed), target step displacements (horizontal and vertical), etc., as well as increasing task level difficulty (e.g., progressively reducing target size), active participation of the subjects, heightened attentional state, presence of visual and verbal feedback, and high motivation of the subjects to perform

the task over the 6 week training period resulted in a significant oculomotor training effects (Ciuffreda, 2002). This marked functional improvement shows great promise for future rehabilitation in these and other such individuals. Based on the existing knowledge of oculomotor control neurology (Leigh & Zee, 2006), it is difficult to definitely state what specific areas of the brain have regained activity, since the brain utilizes different strategies (restoration/recruitment/retraining) to recover from the functional loss (Warraich & Kleim, 2010). Functional neuroimaging studies are thus necessary to assess for correlation with these relearned oculomotor behavioral changes. To date, there is only one pilot study (Alvarez et al., 2010) that evaluated brain activity changes in 2 individuals with mTBI associated with oculomotor rehabilitation involving solely the vergence subsystem. Their fMRI results showed increased amount of voxels and correlation within several regions of interest (ROI) (i.e., brain stem, cerebellum, FEF, and SEF) following a total of 18 hours of both clinically-based and laboratory-based *vergence only* rehabilitation. While increased cortical activity was attributed to neural recruitment, increased correlation was attributed to improved synchronization of the involved subsystem’s population of neurons. Similar future studies are required to evaluate the neural correlates of oculomotor rehabilitation and improved function in individuals with mTBI.

Related to the above notion of residual brain neuroplasticity was the finding that the vast majority of the oculomotor parameters significantly improved/increased following the OMT, but many did not normalize except for the accommodative facility rate (Thiagarajan, 2012). Perhaps increasing the oculomotor rehabilitative time by two-fold or more would have resulted in an even more positive outcome: that is, a greater number of parameters that were abnormal at baseline would have both increased significantly and normalized. This remains to be tested. The present study is on-going, and the study individuals are being followed-up at 3 and 6-month intervals. Results from this follow-up investigation will be used for planning more efficient and targeted future vision therapies (both active and maintenance). However, there may be an alternative explanation given the global and pervasive damage to the brain (e.g., coup-contrecoup): complete restoration of oculomotor control may be beyond the scope and ability of such a damaged brain. This notion warrants future investigation via anatomical, physiological, and brain imaging studies in individuals with TBI before and after such remediation.

Although the present investigation was intended to be relatively comprehensive, there were some study limitations. First, it was primarily restricted to those with mTBI. Investigation of the oculomotor system in moderate TBI with respect to baseline dysfunctions and their remediation would add considerably to our knowledge in this area, especially with respect to oculomotor/visual system plasticity in a more damaged brain. Second, due to our experimental crossover design and related practical aspects, only 9 hours of true training could be performed. Future studies on remediation should be conducted to determine how effective longer training durations might be. And, third, long-term follow-up was not performed. Follow-up should be at least one year, at 3 month intervals, and then perhaps as long as 4 additional years with full testing occurring annually.

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Declaration of interest

Authors have no direct or indirect affiliation with any organization with a financial interest in the subject matter or materials discussed in the manuscript.

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Functional activity within the frontal eye fields, posterior parietal cortex, and cerebellar vermis significantly correlates to symmetrical vergence peak velocity: an ROI-based, fMRI study of vergence training

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Convergence insufficiency (CI) is a prevalent binocular vision disorder with symptoms that include double/blurred vision, eyestrain, and headaches when engaged in reading or other near work. Randomized clinical trials support that Office-Based Vergence and Accommodative Therapy with home reinforcement leads to a sustained reduction in patient symptoms. However, the underlying neurophysiological basis for treatment is unknown. Functional activity and vergence eye movements were quantified from seven binocularly normal controls (BNC) and four CI patients before and after 18 h of vergence training. An fMRI conventional block design of sustained fixation vs. vergence eye movements stimulated activity in the frontal eye fields (FEF), the posterior parietal cortex (PPC), and the cerebellar vermis (CV). Comparing the CI patients' baseline measurements to the post-vergence training data sets with a paired *t*-test revealed the following: (1) the percent change in the BOLD signal in the FEF, PPC, and CV significantly increased ($p < 0.02$), (2) the peak velocity from 4° symmetrical convergence step responses increased ($p < 0.01$) and (3) patient symptoms assessed using the CI Symptom Survey (CISS) improved ($p < 0.05$). CI patient measurements after vergence training were more similar to levels observed within BNC. A regression analysis revealed the peak velocity from BNC and CI subjects before and after vergence training was significantly correlated to the percent BOLD signal change within the FEF, PPC, and CV ($r = 0.6$; $p < 0.05$). Results have clinical implications for understanding the behavioral and neurophysiological changes after vergence training in patients with CI, which may lead to the sustained reduction in visual symptoms.

Keywords: vergence, frontal eye fields, posterior parietal cortex, cerebellar vermis, vision therapy, vergence training, convergence insufficiency, Convergence Insufficiency Symptom Survey

INTRODUCTION

Throughout the day, the visual system mediates vergence eye movements to acquire visual information located at different spatial depths from the retina using the medial and lateral recti muscles. The inward rotation of the eyes is known as convergence. Convergence insufficiency (CI), a prevalent binocular vision disorder in adults (Porcar and Martinez-Palomera, 1997) and children (Rouse et al., 1999), is typically characterized by reduced fusional convergence amplitude, receded near point of convergence (NPC), greater exophoria at near than at far and visual symptoms. The visual symptoms commonly experienced by CI patients include the following: double/blurred vision, eyestrain, and headaches when engaged in reading or other near work, thus interfering with activities of daily living (Scheiman et al., 2011; Lee et al., 2014). Exophoria is the outward deviation of the eye when binocular fusion is disrupted (i.e., one eye is occluded while the other eye is fixating on a target). Scheiman and others hypothesize that CI patients are symptomatic because

of the excessive convergence needed to compensate for a larger exophoria at near (40 cm) compared to far (6 m) (Cooper et al., 1998; Scheiman and Wick, 2008; Scheiman et al., 2011; Cooper and Jamal, 2012). Double vision is a common symptom of CI patients which could be explained by a reduced speed of convergence eye movements. Thus, their convergence responses require more time to attain fusion leading to double vision. Several investigations also report that vergence peak velocities elicited from abrupt changes in disparity are reduced in those with CI compared to binocularly normal controls (BNC) and improves to levels more similar to controls after repetitive vergence training (Van Leeuwen et al., 1999; Alvarez et al., 2010b; Thiagarajan et al., 2011; Alvarez and Kim, 2013).

Randomized clinical trials report that Office-Based Vergence and Accommodative Therapy with home reinforcement (OBVAT) reduces the visual symptoms in CI patients (Scheiman et al., 2009, 2011). The reduction of visual symptoms is sustained 1 year post-therapy in most subjects (CITT, 2009). Clinicians commonly

prescribe vergence training (also known as vision therapy, vision rehabilitation, or orthoptic exercises) to reduce visual symptoms (Scheiman et al., 2011; Cooper and Jamal, 2012). However, the true neural mechanism by which vergence training leads to a reduction in visual symptoms is currently unknown (Scheiman et al., 2011).

There are many single cell and lesion studies on primates, as well as human case reports and fMRI studies that form the basis of our understanding of the neural substrates used to mediate a convergence response. Studies on primates report that the convergence circuit does involve cortical areas within the posterior parietal cortex (PPC) where cells have been identified that have a preferred direction for targets closer or farther away (Gnadt and Mays, 1995; Sakata et al., 1999; Taira et al., 2000; Genovesio and Ferraina, 2004). Single cell recordings from primates reveal a distinct area within the frontal eye fields (FEF) that is allocated for step convergence responses and is located more anterior compared to the cells responsible for generating saccadic responses (Gamlin and Yoon, 2000). Our team reports differentiation within FEF between saccadic and step convergence responses using fMRI (Alvarez et al., 2010a; Alkan et al., 2011a). Other investigators support that smooth convergence tracking is also encoded within FEF using single cell recording from primates (Kurkin et al., 2003; Akao et al., 2005) and using fMRI (Petit and Haxby, 1999). Many studies support the cerebellum is active during convergence responses (Miles et al., 1980; Gamlin and Clarke, 1995; Zhang and Gamlin, 1998; Gamlin, 2002; Takagi et al., 2003; Nitta et al., 2008a,b). In addition, lesions to the cerebellar vermis (CV) VI/VII in primates (Takagi et al., 2003) and humans (Sander et al., 2009) result in a convergence dysfunction. Many single cell studies also show neural activity within the midbrain (Mays et al., 1986; Zhang et al., 1991, 1992). In summary, the PPC, FEF, cerebellum, and midbrain are utilized to generate a convergence response.

Functional imaging investigations non-invasively quantify the metabolic demand generated through an experimental task by studying the blood oxygen level dependent (BOLD) response. For this study, we will measure the paramagnetic properties of blood during sustained fixation compared to active vergence eye tracking. The portions of the brain that are more metabolically active during vergence eye tracking will be assumed to be responsible for generating a vergence response. Functional imaging signals from the cerebrum and cerebellum are easier to obtain compared to signals within the brainstem. The brainstem is more susceptible to breathing and swallowing motion artifacts compared the cerebrum and cerebellum and hence is beyond the scope of this present study. Vergence training leads to a sustained reduction in symptoms suggesting neuroplasticity. Based upon the aforementioned studies about the neurophysiology of the vergence circuit, this investigation analyzed the PPC, FEF, and CV before and after vergence training in patients with CI compared to BNC. BNC did not participate in vergence training since they did not have visual symptoms. This research takes a critical step in understanding the neural basis of how vergence training leads to a sustained reduction of vision symptoms in patients with CI. Such knowledge may ultimately lead to new vergence training protocols to further improve vision function.

This study investigated convergence responses and functional activity of the vergence neural substrates before and after repetitive vergence training in symptomatic CI patients compared to BNC subjects. The following hypotheses were tested. First, reduced convergence peak velocity elicited from symmetrical convergence step stimuli and reduced functional activity within the FEF, PPC, and CV would be observed in those with CI before repetitive vergence training compared to BNC subjects. Second, after repetitive vergence training, the peak velocity of symmetrical convergence step responses would increase along with the percent change in functional activity of the vergence neural substrates from CI patients compared to their baseline measurements. Third, the peak velocity of convergence responses would significantly correlate to the functional activity of the FEF, PPC, and CV neural substrates quantified as the BOLD percent signal change.

MATERIALS AND METHODS

SUBJECTS AND VISION PARAMETERS

Four CI (four females) and seven BNC subjects (three females) participated in this study. CI was diagnosed by an optometrist using methods described in our prior study, which included a receded NPC and reduced positive fusional amplitudes (Alvarez et al., 2010b). The diagnosis criteria comply with conventional clinical methods (Cooper et al., 1998). At the beginning of the study, the CI subjects had the following parameters denoted as the average with one standard deviation: near point convergence of 13.4 ± 5.6 cm, positive [base out (BO)] vergence amplitude of $14 \pm 4.5\Delta$, and a dissociated near (measured at 40 cm from midline) phoria of $9.0 \pm 1.4\Delta$ exophoria. NPC was assessed by measuring the distance from the orbit to the location where a high acuity target was perceived as diplopia along the subject's midline (Von Noorden and Campos, 2002). Stereopsis was assessed by the Randot Stereopsis Test (Bernell Corp., South Bend, IN, USA). Normal binocular vision was defined as having a NPC of less than 8 cm. The inclusion criteria were as follows: normal stereopsis, no ocular surgeries and corrected to normal acuity. In addition, if an eye spectacle prescription was required then subjects who required a prescription greater than 2D or less than -3D were excluded to reduce potential confounding variables. All subjects had a stereopsis of ≤ 50 s of arc. Three of the CI and five of the BNC did not need spectacles to read clearly at near. All subjects had no history of brain disorders and were between the ages of 18 and 35 years. All subjects signed written informed consent forms approved by the University of Medicine and Dentistry of New Jersey (UMDNJ) and New Jersey Institute of Technology (NJIT) Institution Review Boards (IRB) in accordance with the Declaration of Helsinki.

CONVERGENCE INSUFFICIENCY SUBJECT SYMPTOMS

Symptoms were quantified using the Convergence Insufficiency Symptom Survey (CISS), which contains 15 questions (CITT, 2008). All questions were in regard to the subject's ability to read or perform near work. Each symptom was scored between zero and four where zero represents the symptom never occurs and four represents the symptom occurs very often. A prior investigation compared visual symptoms to the clinical diagnosis of

CI defined as an exophoria at near at least 4Δ greater than at far, failure of Sheard's criteria or a minimum normal positive fusional vergence (break $< 15\Delta$), and a receded (≥ 6 cm) NPC (Rouse et al., 2004). The responses of CISS were summed where a score of 21 or higher had a sensitivity of 98% and specificity of 87% using the aforementioned diagnostic criteria of CI in young adults between the ages of 18 and 35 years of age (Rouse et al., 2004). Hence, the CISS symptom survey was used within this present investigation to assess visual symptoms of the CI and BNC subjects who participated in this study.

OVERALL EXPERIMENTAL PROTOCOL GOALS

The CI subjects participated in 18 h of vergence training as described below. The CI data were compared to BNC data where BNC subjects did not participate in vergence training since they did not have visual symptoms. The primary measurements compared were the peak velocity from convergence step responses and the percent change in the BOLD signal within the FEF, PPC, and CV. Secondary measurements included the NPC, positive fusional range, near dissociated phoria and the CISS score. A group level analysis compared the following: (1) the BNC data to the CI baseline data and (2) the CI pre and post-vergence training measurements.

VERGENCE TRAINING PROTOCOL FOR CONVERGENCE INSUFFICIENCY SUBJECTS

Repetitive vergence training was designed to provoke changes in the neural substrates (FEF, PPC, and CV) that stimulate vergence ocular motor responses. The CI subjects participated in a total of 18 h of vergence training, 6 h at home, and 12 h in the laboratory. Home training was monitored by having each CI subject record the amount of time spent on training and entailed two 10-min sessions (morning and evening) 3 days per week for 6 weeks. Laboratory training was composed of 1-h sessions, twice per week for 6 weeks. Within a single day, a subject participated in either laboratory or home training but not both.

For the laboratory step training, 2, 4, and 6° disparity convergence steps and 4° disparity divergence steps within the range of a 2° vergence angle to 8° vergence angle were presented after a randomized delay of 0.5–2.0 s. The randomized delay reduces anticipatory cues that are known to alter the latency and peak velocity of vergence responses (Alvarez et al., 2002, 2005, 2010a; Kumar et al., 2002a,b). The ramp training consisted of 1 and $2^\circ/\text{s}$ ramps starting at an initial vergence angle of 2° producing a convergence ramp response to the vergence angle of 8° and then stimulating a divergence ramp response to a vergence angle of 2° . The laboratory and home training consisted of step and ramp stimuli similar to methods used clinically (Griffin, 1988; Scheiman and Wick, 2008).

EYE MOVEMENT ACQUISITION AND ANALYSIS

Eye movements were recorded using a Skalar Iris (model 6500, Delft, Netherlands) infrared ($\lambda = 950$ nm) limbus tracking system. The manufacturer reports that the linear range of the system was $\pm 25^\circ$ where all responses of this study were within the linear range of the device. Prior research confirms a high degree of linearity, within 3% between 5° horizontally for this system

(Horng et al., 1998). A 12-bit acquisition hardware card (National Instruments 6024 E series, Austin, TX, USA) digitized the individual left-eye and right-eye movements with a sampling rate of 200 Hz. The visual stimuli utilized green light emitting diodes (LEDs) (Stanley model MU07 part 5101, London, OH, USA) 2 mm wide by 25 mm in height with a wavelength of 555 nm. Subjects were situated in a head and chin rest assembly to reduce any influence from the vestibular system (Khojasteh and Galiana, 2007). The subject initiated each experimental trial by pressing a button, which allowed the subject to blink between experimental trials. Potential subject fatigue was also reduced by allowing the subject to initiate the experimental trial (Yuan and Semmlow, 2000).

A custom MATLAB™ (Waltham, MA, USA) program was used for all eye movement analyses. Left-eye and right-eye movement data were converted from voltage values into degrees using the individual calibration data. Eye movements were calibrated using 2° , 4° , 6° , and 8° vergence angles. Vergence was calculated as the difference between the right-eye and the left-eye position to yield a net vergence response. Convergence responses were plotted as positive. Blinks were easily identified based upon manual inspection of the left-eye and right-eye movement response. Responses with blinks at any point during the movement were omitted (up to 2.1% of the data depending upon the subject). Only convergence responses were analyzed since convergence responses were reported to have reduced peak velocities in CI subjects compared to BNC (Alvarez et al., 2010b).

Peak velocity generated from a 4° symmetrical convergence step stimulus was a primary measurement within this study. Velocity was computed by taking the derivative of the position response using a two-point central difference algorithm (Bahill et al., 1982). Each individual left-eye and right-eye convergence movement response was manually inspected for the presence of a saccade, which was easily identified because saccade velocities are an order of magnitude greater than vergence. A phase plot (vergence velocity as a function of vergence amplitude) for the left-eye and the right-eye movement was used to determine whether the saccades obscured the peak velocity of the vergence response to the symmetrical stimulus. Only when saccades obstructed the convergence peak velocity was the response omitted from the peak velocity analysis, which occurred in less than 10% of the responses depending on the subject as shown in our prior investigations (Alvarez et al., 1998; Lee et al., 2008; Kim and Alvarez, 2012). The peak velocity of the combined vergence response was quantified as the maximum value.

IMAGING INSTRUMENTATION AND ACQUISITION

A 3-Tesla Siemens Allegra Magnetron MRI Scanner with a standard single channel head coil (Erlangen, Germany) was used to perform the fMRI scans during the experimental tasks. The fMRI imaging parameters used during the acquisition included: repetition (TR) = 2000 ms, echo time (TE) = 27 ms, matrix size = 64×64 , field of view (FOV) = 220 mm, and flip angle = 90° . A total of 32 slices were collected (axial orientation) with a slice thickness of 5 mm. The voxel resolution was $3.4 \times 3.4 \times 5.0$ mm. High resolution anatomical volumes acquired using a magnetization-prepared rapid acquisition with

gradient echo (MPRAGE) were collected after all functional tasks. The MPRAGE imaging parameters included the following attributes: $TR = 7.2$ ms, $TE = 4.38$ ms, $T1 = 900$ ms, flip angle = 8° , matrix size = 256×256 with a total of 80 acquired slices. The voxel resolution was $0.9 \times 0.9 \times 2.0$ mm. Subjects were instructed to limit head motion and foam padding was used to facilitate the restriction of physical movement. All subjects were positioned supine on the gantry of the scanner with their heads situated along the midline of the coil.

FUNCTIONAL MRI VISUAL STIMULUS EXPERIMENTAL DESIGN

The visual stimulus (see **Figure 1A**) was carefully aligned with the subject's midline to stimulate symmetrical vergence eye movements to test the hypotheses of this study. Subjects could see the targets with the aid of a mirror. Visual stimuli were a set of non-ferrous LED targets that formed a line 5 cm in height by 2 mm in width secured with polyvinyl chloride (PVC) tubing. The LED stimulus targets were located at the following three full vergence angle demands: 2, 3, and 4° . The target positions were chosen because smaller vergence movements have been shown to elicit fewer saccadic responses compared to larger vergence movements (Coubard and Kapoula, 2008; Semmlow et al., 2008, 2009; Chen et al., 2010).

The experiment utilized a conventional block design of sustained fixation for the "off" stimulus compared to vergence eye movements for the "on" stimulus as shown in **Figure 1B**. Anticipatory cues are known to decrease the latency and increase peak velocity of convergence responses (Alvarez et al., 2002, 2005, 2010a; Kumar et al., 2002a,b). Hence, to reduce anticipatory or predictive cues, this experiment utilized a series of vergence eye movements where each target was illuminated for a random duration between 3 and 5 s. LED targets were never simultaneously

illuminated. The eye movement sequence illuminated one of the following three stimuli: the near (4°), middle (3°), or far (2°) target where the subject could not anticipate when the next target would illuminate or which of the three targets would be illuminated. Each phase lasted 20 s and was repeated for 3.5 cycles. Hence, the total experiment time was 2 min 20 s. The experiment was repeated three times per subject.

IMAGING ANALYSIS

Image preprocessing

The AFNI (Cox, 1996) and FSL (Jenkinson and Smith, 2001; Jenkinson et al., 2002) software suites were used to process and analyze the raw data retrieved from the MRI scanner. The first five images of each trial dataset were removed to mitigate the effect of transient scanner artifact (Biswal et al., 2010).

The AFNI motion correction utilizes the application of a six-parameter, rigid-body, least-squares alignment routine. Three parameters calculate the amount (mm) of movement within each plane (anterior to posterior, right to left, and inferior to superior) and three parameters calculate the amount of rotation ($^\circ$) between planes (yaw, pitch, and roll). These six motion regressors are used within the linear regression model to minimize motion effects of the acquired BOLD signal. A detailed motion analysis of all subjects using a frame displacement method which calculates the absolute value of movement was conducted (Satterthwaite et al., 2013). The average frame displacements with one standard deviation for the degree of rotation were $0.18 \pm 0.07^\circ$, $0.16 \pm 0.09^\circ$, and $0.20 \pm 0.08^\circ$ for yaw, pitch, and roll, respectively. The average frame displacement analyzing all subjects within each plane, with one standard deviation, were 0.36 ± 0.13 mm, 0.42 ± 0.11 mm, and 0.37 ± 0.08 mm for the anterior to posterior, left to right, and inferior to superior planes, respectively. No

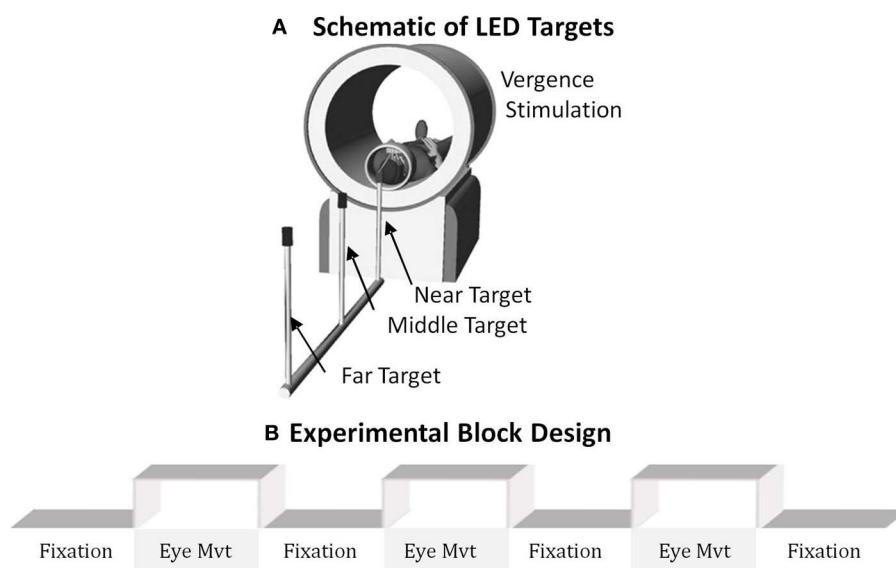


FIGURE 1 | (A) Schematic of the LED targets showing visual stimuli. **(B)** The experimental block design was composed of sustained fixation (denoted as Fixation) and vergence eye movements

(denoted as Eye Mvt). This experimental block design modulated functional activity of the BOLD signal within the vergence neural substrates.

significant differences in motion artifacts were observed between the post and pre-vergence training data sets of the CI patients assessed using a paired *t*-test ($p > 0.9$). No significant difference in head motion was observed between the two groups (CI compared to BNC) ($p > 0.9$). Hence, head motion was not considered problematic within this dataset.

The CompCor data-driven method was used to further reduce effects of noises in the BOLD signal, as described below (Behzadi et al., 2007). FSL's BET (Brain Extraction Tool) (Smith, 2002) function removed non-brain tissue from the anatomical image dataset. FSL's FAST (FMRIBs Automated Segmentation Tool) (Zhang et al., 2001) stratifies the skull-stripped anatomical dataset into three different segments. The whole brain probability maps of CSF, WM, or gray matter (GM) were derived. The segmented anatomical CSF and WM probability images were transformed into functional space using FSL's FLIRT function (Beckmann and Smith, 2004, 2005). To create CSF and WM regressors, all voxels of the CSF and WM probability images were first thresholded using levels of 99 and 97% probability, respectively. Time-series from all the voxels surviving the threshold were extracted. The probability levels of this study are more conservative compared to those used previously, which used a threshold level of 80% (Biswal et al., 2010). Then, the first five principle components relating to CSF and WM time-series were calculated. FSL's FEAT command was used to perform the voxel-wise linear regression analysis on all datasets using the 16 aforementioned regressors (six motion parameters, five principle components of CSF, and five principle components of WM). The residuals of the regressed datasets (removal of the 16 artifacts) were then filtered in AFNI using a band pass filter [full width at half maximum (FWHM) Gaussian filter with cut off frequencies of 0.01 and 0.15 Hz]. The band pass filter was used to remove DC offset and high frequency signals that were probably not neuro-physiological in nature. Following band-pass filtering, a general linear model (GLM) analysis was performed to derive functionally active regions during the task.

General linear model

A GLM using a reference time series representation of the block design experimental stimulus convolved with the hemodynamic response function (HRF) was used. Correlation maps were created using a threshold of $r \geq 0.4$ ($p < 0.05$) to show active brain regions. Mask identification was facilitated by observing the active brain regions coupled with the anatomical locations described above for the FEF, PPC, and CV. Broca's region was the control region of interest (ROI) and was identified strictly using anatomical markers. Since the datasets were not transformed into a standardized space such as the Montreal Neurological Institute (MNI) space, some variance was also observed for the mask of Broca's region. Broca's region served as a control ROI (unrelated to the hypotheses of this study). Language was not manipulated within the experimental protocol. Prior investigations show Broca's region was stimulated during experiments that study language (Geschwind, 1970; Kim et al., 1997) but is not stimulated within vergence eye movement experiments (Alkan et al., 2011a,b).

Cortical and subcortical regions of interest (ROIs) within the fMRI experiment

The ROIs were defined using anatomical markers coupled with a model-driven method to identify functional activity near the anatomical markers. Neurophysiology studies on primates support the following ROIs are involved in vergence eye movements: FEF, PPC, and CV (Gamlin et al., 1996; Gamlin and Yoon, 2000). This experiment sought to stimulate the cortical and cerebellar regions required to mediate vergence eye movements.

The following ROIs were drawn in native space using anatomical markers and functional activity derived using a GLM: FEF, PPC, and CV. The bilateral FEFs were defined as the area within the intersection between the precentral sulcus and superior frontal sulcus. The PPC was around the intraparietal sulcus as shown in **Figure 2**. The CV regions VI and VII were defined on the mid-sagittal plane. Broca's region served as a control ROI because it was not stimulated in prior fMRI vergence studies (Alvarez et al., 2010a; Alkan et al., 2011a,b). The mask for Broca's region was created using only anatomical markers that are defined near the inferior frontal gyrus anterior to the motor strip as shown in **Figure 2**. **Figure 2** depicts the ROIs within a series of axial slices. The average with one standard deviation for the masks studied (measured in mm³) were 880 ± 118 , 901 ± 126 , 1430 ± 275 , 1194 ± 382 , 1006 ± 131 , 499 ± 58 , 541 ± 47 for the FEF-L, FEF-R, PPC-L, PPC-R, CV, Broca-L, and Broca-R, respectively. The average and one standard deviation of each ROI are shown in **Figure 2** using an MNI template. As **Figure 2** shows, none of the masks overlap to avoid any partial volume effects. The centroid of the mask listed as left (positive) or right (negative), anterior (positive) or posterior (negative), and superior (positive) or inferior (negative) are (30, 12, 42), (-30, 12, 42), (52, 10, 12), (-52, 10, 12), (-2, -74, -28), (26, -54, 48), and (-26, -54, 48) for the FEF-L, FEF-R, PPC-L, PPC-R, CV, Broca-L, and Broca-R, respectively.

Analysis of percent change of BOLD signal to quantify functional activity

All data were kept in native space (i.e., data were not transformed into Talairach and Tournoux or MNI space) to avoid any warping artifacts. The time series located within the vicinity of the anatomical markers, which had a Pearson correlation coefficient of $r \geq 0.4$ ($p < 0.05$) with the hemodynamic model described above, were pooled. While the percent signal change will be threshold dependent, this study is longitudinal comparing the data after vergence training to the baseline measurements before vergence training for the CI subjects. Since the threshold used is the same for both pre and post-vergence training analysis, we assume that any potential differences observed within the data sets are mostly due to vergence training. The BOLD percent signal change for each ROI per subject comparing elevated activation observed during the vergence task to the baseline of sustained fixation was computed from the time series. The individual-subject percent signal change values were pooled to conduct the group-level statistics described below.

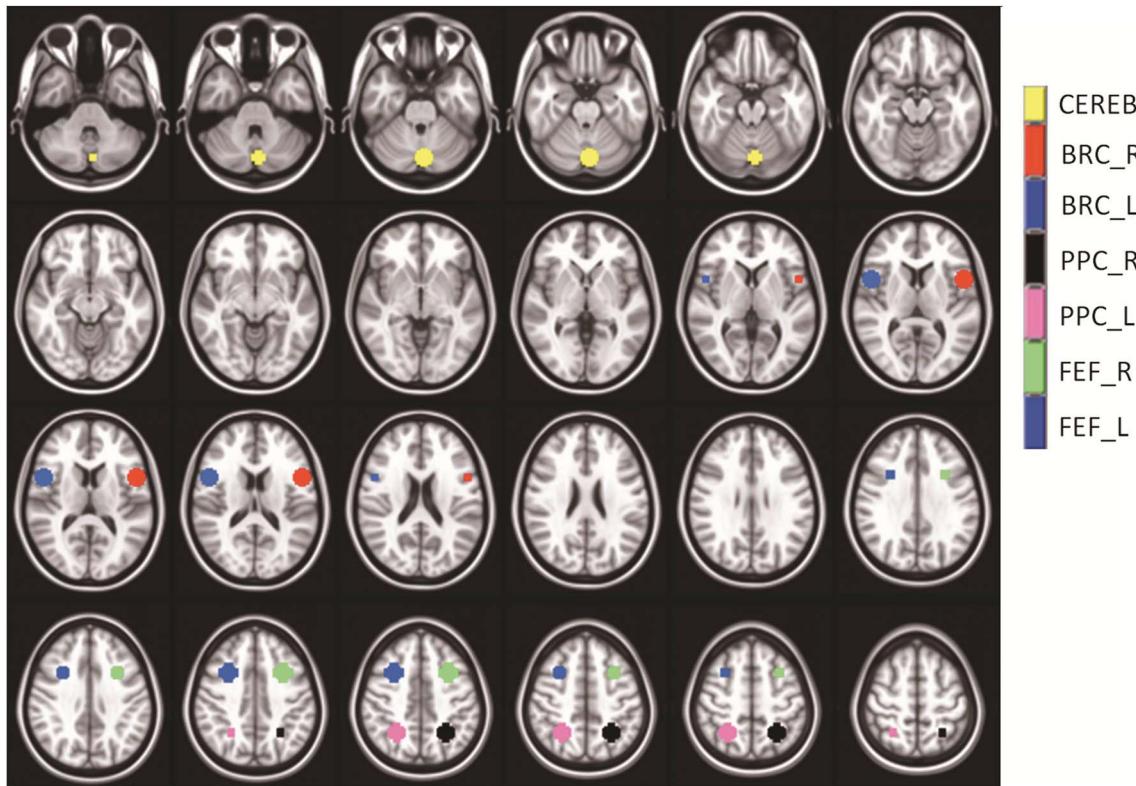


FIGURE 2 | Series of axial images showing the average masks with one standard deviation used within the analysis. The cerebellar vermis (yellow), Broca-Right (red), Broca-Left (dark blue), Posterior Parietal Cortex-Right (black), Posterior Parietal Cortex-Left

(pink), Frontal Eye Field-Right (green), and Frontal Eye Field-Left (medium blue) are shown. The masks did not overlap. Broca's Region served as a control ROI to study the variability within a non-stimulated ROI.

STATISTICAL ANALYSES

The subject data were stratified into the following three groups: BNC, CI subjects before vergence training, and CI subjects after vergence training. An unpaired *t*-test was used to determine whether significant differences were observed between BNC and CI subjects before vergence training when analyzing (1) the peak velocity of convergence responses stimulated from 4° symmetrical convergence step stimuli and (2) the percent signal change of the BOLD fMRI signal within an ROI. A paired *t*-test determined whether the CI subjects exhibited significant changes comparing the pre and post vergence training measurements for the following parameters: (1) peak velocity of convergence responses stimulated from 4° symmetrical convergence steps, (2) percent signal change of the fMRI BOLD signal within an ROI, (3) CISS score, (4) NPC, (5) positive vergence amplitude ranges, and (6) near dissociated phoria. A linear regression analysis was conducted between the peak velocity of convergence responses stimulated from 4° symmetrical convergence steps and the BOLD percent signal change for the following ROIs: FEF, PPC, CV and Broca's region. Statistics were calculated using NCSS2004 (Kaysville, UT, USA). Significance was defined as a *p*-value < 0.05. Bonferroni correction for multiple parameters was not applied because of the limited number of subjects within the study. Figures were generated using MATLAB (Mathworks, MA).

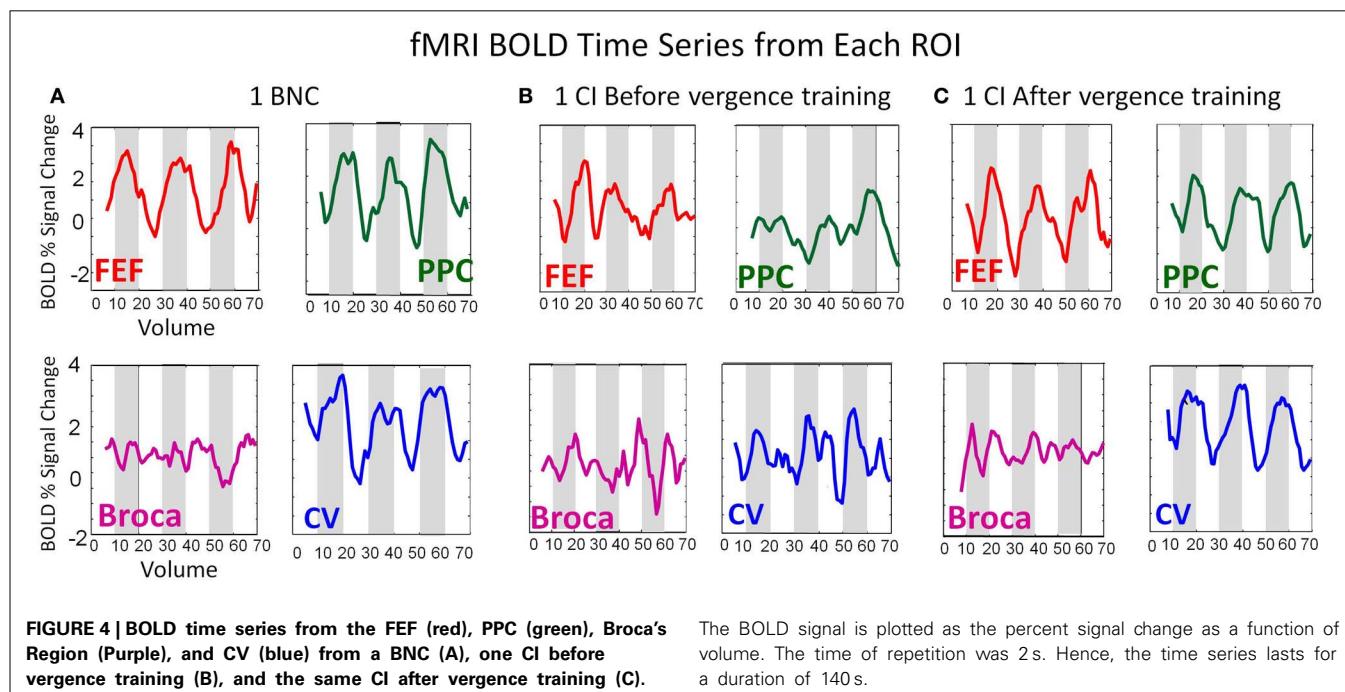
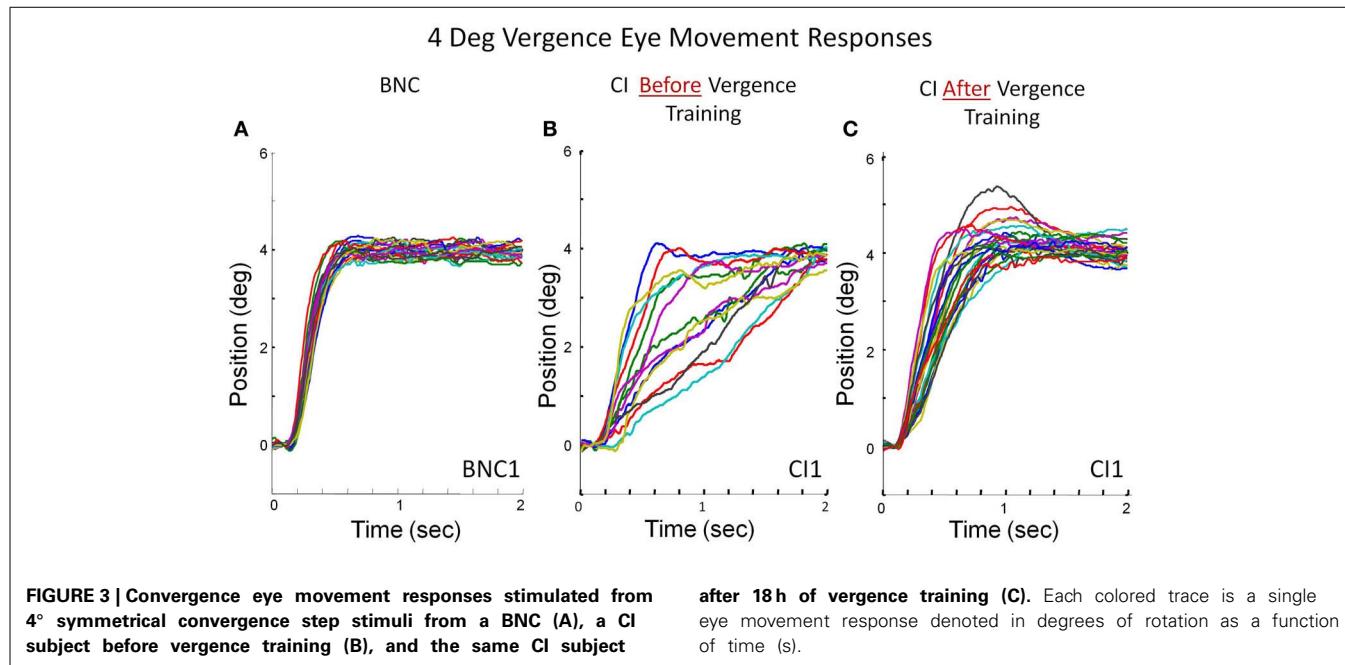
RESULTS

CONVERGENCE EYE MOVEMENTS FROM SYMMETRICAL CONVERGENCE STEP STIMULI

Peak convergence velocity was one of the primary measurements within this study. Figure 3 plots multiple eye movements. Each colored line in Figure 3 is a convergence eye movement response evoked from a symmetrical 4° convergence step stimulus. Figure 3A is convergence responses from a BNC. The BNC subject attains fusion of the new target within the first half second. Figures 3B,C are from the same CI subject before and after vergence training, respectively. The CI subject before vergence training has more variability between responses compared to the BNC and can take up to 2 s to fuse the new target. After vergence training, the CI subject's responses are still slower than the BNC (comparing Figures 3A,C), but considerably faster than the subject's baseline responses (Figure 3B).

TIME-SERIES OF THE BOLD SIGNAL FROM THE ROIs STUDIED

Figure 4 shows data from two subjects, one BNC (Figure 4A), one CI subject before vergence training (Figure 4B), and the same CI subject after vergence training (Figure 4C). Figure 4 shows the average time series from the FEF-L (red lines), PPC-L (green lines), Broca-L (purple lines), and CV (blue shows data from two subjects, one e lines). Figure 4 plots the BOLD percent signal



change as a function of volumes collected (70 volumes equating to 140 s in duration). The BNC shows an FEF time series which is more correlated ($r = 0.66$; $p < 0.001$) with the experimental block design (white and gray boxes for the 3.5 cycles of the experiment) compared to the CI subject before vergence training ($r = 0.33$; $p < 0.01$). After vergence training, this subject's FEF correlation with the block design increases ($r = 0.73$; $p < 0.001$). Similar trends are observed for the PPC and the CV. As expected, the time series from Broca's region (control ROI to study variability of a non-stimulated region) does not correlate with the

experimental block design for the BNC and the CI before or after vergence training ($r = 0.15 \pm 0.05$; $p > 0.1$).

GROUP-LEVEL ANALYSES

The peak velocities elicited from 4° symmetrical convergence steps were averaged for the seven BNC and the four CI subjects before and after repetitive vergence training. **Figure 5A** plots the average (bar) with one standard deviation (error bar) of the peak velocity (°/s) from CI subjects before vergence training (blue bar), the same CI subjects after vergence training (red bar), and from

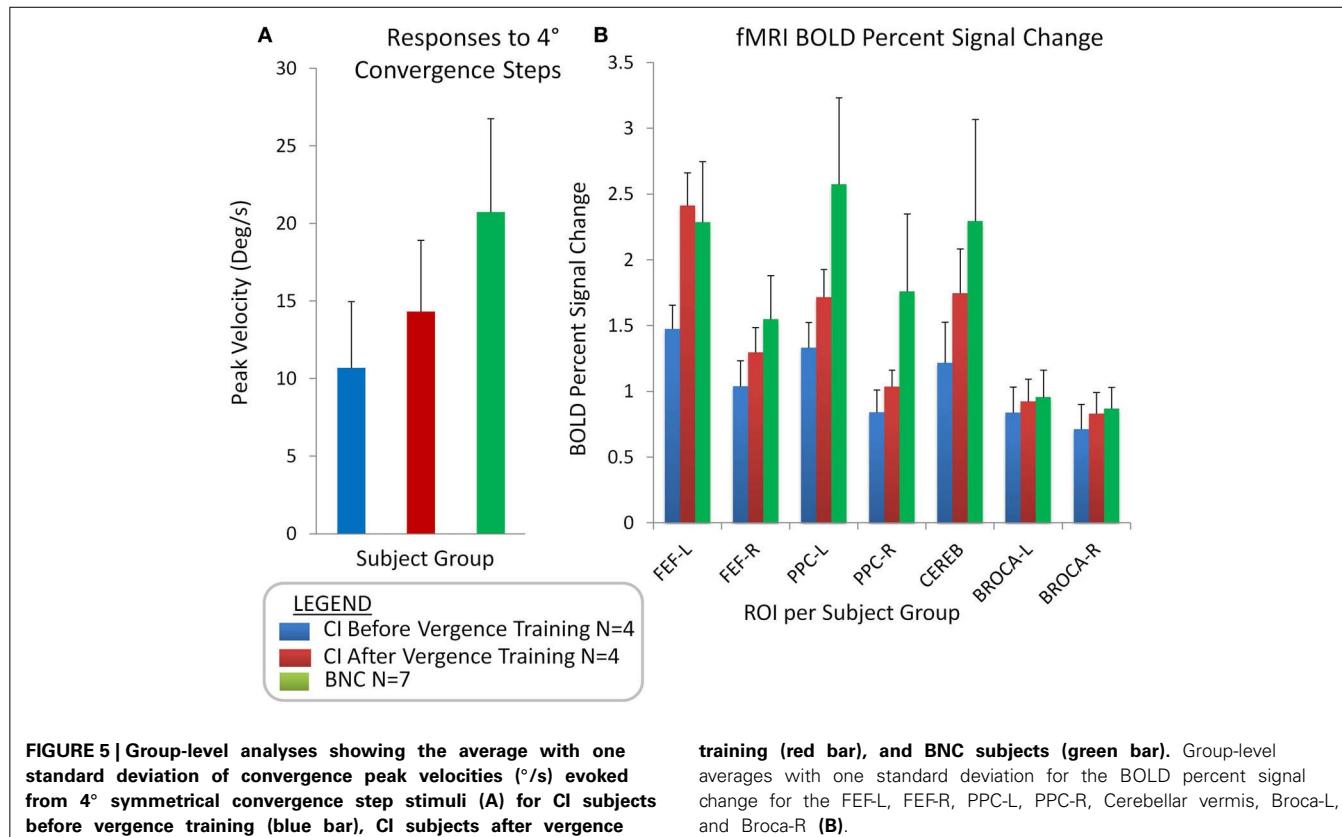


FIGURE 5 | Group-level analyses showing the average with one standard deviation of convergence peak velocities ($^{\circ}/\text{s}$) evoked from 4° symmetrical convergence step stimuli (A) for CI subjects before vergence training (blue bar), CI subjects after vergence

training (red bar), and BNC subjects (green bar). Group-level averages with one standard deviation for the BOLD percent signal change for the FEF-L, FEF-R, PPC-L, PPC-R, Cerebellar vermis, Broca-L, and Broca-R (B).

BNC subjects (green bar). When comparing the BNC group with the CI before vergence training group, an unpaired *t*-test revealed that significant differences were observed ($T = 2.92$; $p < 0.02$). The CI subjects had significantly slower peak velocities evoked from 4° symmetrical convergence steps compared to BNC subjects. The CI subjects also exhibited significant changes in peak velocities to symmetrical 4° convergence steps when comparing the responses after vergence training to the baseline before vergence training responses, when using a paired *t*-test ($T = 6.93$; $p < 0.02$).

Figure 5B shows the average with one standard deviation for the group-level analysis of the percent change in the BOLD signal per ROI for the following groups: CI subjects before vergence training (blue bar), CI subjects after vergence training (red bar), and BNCs (green bar). When comparing the BNC to the CI data before vergence training using an unpaired *t*-test, significant differences were observed within the FEF, PPC, and CV ($t > 2.3$; $p < 0.05$). No significant differences were observed within Broca's region between the BNC and either the before or after vergence training CI datasets ($t > 1.1$; $p > 0.3$). A paired *t*-test showed the percent change in the BOLD signal in the FEF, PPC, and CV of the four CI subjects who participated in vergence training were significantly greater after training compared to the baseline values ($t > 2.6$; $p < 0.001$). No statistical difference was observed in Broca's region ($t = 1.2$; $p > 0.3$) when comparing the baseline and after vergence training data.

A linear regression analysis was conducted of the average convergence peak velocity evoked from 4° symmetrical convergence

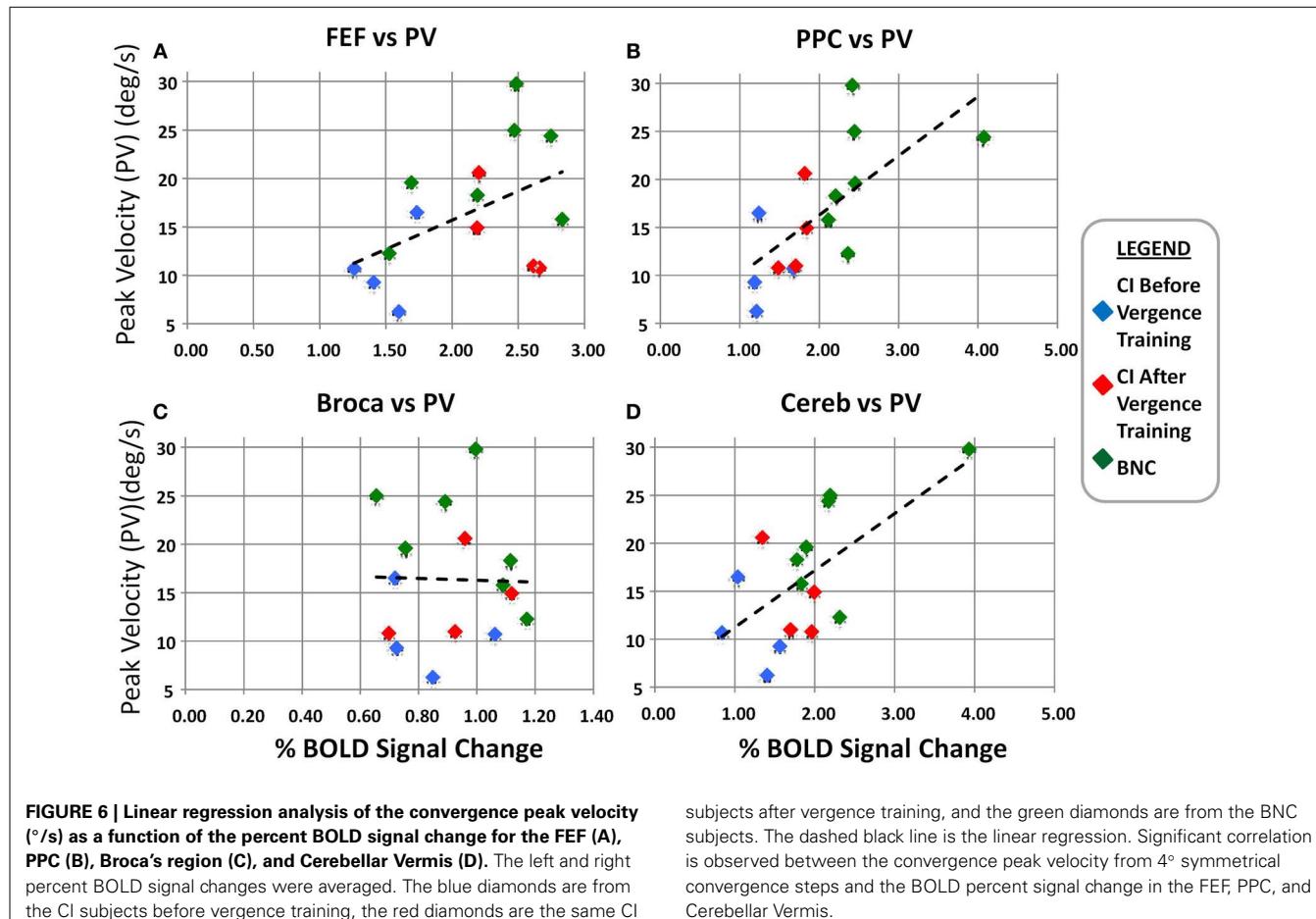
steps as a function of the BOLD percent signal change for the FEF (Figure 6A), PPC (Figure 6B), Broca's Region (Figure 6C), and CV (Figure 6D). The left and right ROIs were averaged for Figure 6. A regression analysis revealed the convergence peak velocity of 4° symmetrical convergence steps from BNC and CI patients before and after vergence training was significantly correlated to the percent BOLD signal change within the FEF ($r = 0.5$; $p < 0.05$), PPC ($r = 0.7$; $p < 0.01$), and CV ($r = 0.6$; $p < 0.01$). Conversely, convergence peak velocity of 4° symmetrical convergence steps from BNC and CI patients before and after vergence training was not significantly correlated to the percent BOLD signal change within Broca's regions, which was the control ROI ($r = -0.0059$; $p > 0.98$).

CLINICAL VISION PARAMETERS

A paired *t*-test revealed a significant difference comparing the baseline (before vergence training) parameters and the after vergence training parameters for the following measurements: the NPC ($t = 4.9$; $p = 0.04$), BO positive fusional vergence range ($t = 9.5$; $p = 0.01$), near dissociated phoria ($t = 11$; $p = 0.008$), and CISS ($t = 3.6$; $p = 0.05$). All significant changes are improvements to each parameter studied.

DISCUSSION

The data support the hypotheses that were tested. Reduced convergence peak velocity from convergence step stimuli and functional activity within the FEF, PPC, and CV were observed in



those with CI before repetitive vergence training compared to BNC subjects. Both convergence peak velocity and functional activity significantly improved after vergence training in the CI subjects when comparing the pre and post-vergence training measurements. The average peak velocity of convergence responses was significantly correlated to the BOLD percent signal change within the functional activity of the FEF, PPC, and CV neural substrates. The results of this study will be compared to those in the literature.

CLINICAL IMPLICATIONS OF LONG-TERM ADAPTATION EVOKED THROUGH VERTGENCE TRAINING

Understanding the relationship between the functional activity within the FEF, PPC, and CV and convergence eye movement responses has both basic science and clinical applications. Although the majority of humans perform vergence movements with ease, the dysfunction known as CI is reported to be present within 4.2–7.7% of the population (Hokoda, 1985; Scheiman et al., 1996; Porcar and Martinez-Palomera, 1997; Rouse et al., 1998, 1999). CI is an eye co-ordination and alignment problem, which can result in visual symptoms when engaged in reading or performing other near work (Scheiman et al., 2011).

The randomized clinical trial, the Convergence Insufficiency Treatment Trial (CITT), showed that OBVAT was successful in 73% of children, resulting in significantly improved symptoms,

subjects after vergence training, and the green diamonds are from the BNC subjects. The dashed black line is the linear regression. Significant correlation is observed between the convergence peak velocity from 4° symmetrical convergence steps and the BOLD percent signal change in the FEF, PPC, and Cerebellar Vermis.

NPC and positive vergence amplitude (Scheiman et al., 2009). Clinical signs and symptoms were sustained 1 year post-therapy for most subjects (CITT, 2009). OBVAT is composed of symmetrical, horizontal convergence movements. Hence, although the stimulus used within this current study may not occur often in natural viewing conditions, it is the basis of therapeutic interventions to treat patients with CI (Cooper et al., 1998; Scheiman and Wick, 2008; Scheiman et al., 2011).

The Dual-Mode model of vergence describes vergence as a two component system composed of a fusion initiating and a fusion sustaining component (Hung et al., 1986; Lee et al., 2012). The transient fusion initiating component is modeled as a pre-programmed control system mainly contributing to the vergence system's speed but is not necessarily very accurate. The fusion sustaining component is feedback controlled and facilitates the accuracy of the vergence system. The present data suggest that the fusion initiating component, which mainly contributes to the vergence peak velocity, is modified after vergence training. The CI subjects had reduced peak velocity before training, which increased after training. The results of this study suggest that vergence training protocols may concentrate on the stimulation of the preprogrammed portion of vergence system.

Investigations identifying the neural substrates responsible for vergence oculomotor learning are scarce. Several saccade oculomotor studies suggest the oculomotor vermis is responsible

for oculomotor learning within the saccadic system (Iwamoto and Kaku, 2010; Prsa and Thier, 2011). Evidence also suggests that the FEF can be modified through adaptation when studying saccades (Lee et al., 2011). This present study provides a critical step in understanding the brain-behavior relationship of how vergence training is inducing changes to the functional activity within the FEF, PPC, and CV, which in part mediates convergence oculomotor responses. Future research can study neurological differences between various vergence training protocols to determine how changes within neural substrates facilitate an improvement in visual comfort while performing near work such as reading. Such knowledge could ultimately lead to an improvement in vergence training protocols.

BOLD PERCENT SIGNAL CHANGE IN RELATION TO OTHER BODIES OF LITERATURE

Non-human primate single cell electrophysiology studies have investigated the influence of disparity in the FEF using symmetrical step stimuli (Gamlin and Yoon, 2000), near and far targets (Ferraina et al., 2000), and smooth sinusoidal tracking stimuli (Fukushima et al., 2002; Akao et al., 2005). The FEF and PPC have also been shown to be involved in predictive oculomotor learning (Tseng et al., 2013). The PPC encodes for different binocular distances defined by different vergence angles studying primates using single cell recordings (Genovesio and Ferraina, 2004; Ferraina et al., 2009; Breveglieri et al., 2012) and humans using transcranial magnetic stimulation (Kapoula et al., 2001, 2004, 2005; Yang and Kapoula, 2004) and fMRI (Quinlan and Culham, 2007; Alvarez et al., 2010a; Alkan et al., 2011a,b). Primate single cell studies have also shown that the CV is used to mediate a vergence response (Gamlin et al., 1996; Nitta et al., 2008a,b). Patients, particularly those with lesions to the cerebellar vermal regions, exhibit a decrease in slow tracking vergence (Sander et al., 2009).

This present study further confirms that the FEF, PPC, and CV are metabolically active during a vergence task. The novelty of this study's results is that the functional activity of the FEF, PPC and CV are: (1) reduced in CI subjects at baseline compared to BNC subjects, (2) significantly increased after 18 h of vergence training to levels more similar to those exhibited by the BNC subjects, and (3) significantly correlated to the convergence peak velocity elicited from 4° symmetrical convergence stimuli. The results support the hypothesis that subjects with CI have reduced functional activity within the vergence neural substrates and reduced peak velocity of convergence responses compared to BNC. Results further support that after vergence training; the functional activity improves to levels more similar to those observed in BNC subjects.

STUDY LIMITATIONS AND FUTURE DIRECTIONS

The reduced strength in fMRI activity and convergence peak velocity measurements observed from CI subjects compared to BNC is recommended for investigation in a masked randomized clinical trial where both CI and BNC participate in vergence training. Such a study could determine whether these differences between BNC and CI subjects generalize in a larger population and hence may, in part, explain asthenopia in CI patients.

The techniques used within the present study could also be applied to study the brain-behavior relationships of other oculomotor and vision dysfunctions. For example, Bucci and colleagues studied vergence insufficiency patients whose symptoms included headache and vertigo before and after orthoptic vergence training (Bucci et al., 2004, 2006a,b, 2011; Jainta et al., 2011). The techniques presented here could be used to better understand the mechanisms underlying vergence training for those with other visual and vestibular dysfunctions.

CONCLUSIONS

The data collected within this study support that CI subjects have significantly reduced convergence peak velocity to 4° symmetrical convergence steps and BOLD percent signal change within the FEF, PPC, and CV compared to BNC subjects. Both convergence peak velocity and BOLD percent signal changes within the FEF, PPC, and CV significantly improved post-vergence training in CI subjects compared to their baseline measurements. The convergence peak velocity was significantly correlated to the BOLD percent signal change in the FEF, PPC, and CV. Results suggest that repetitive vergence training leads to an increase in the functional activity of the FEF, PPC, and CV which may in part lead to the increase in convergence peak velocity to symmetrical step stimuli.

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Role of Primary Care Optometrists in the Assessment and Management of Patients with Traumatic Brain Injuries in Canada

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Introduction

Traumatic brain injury (TBI) results from a strong blow or jolt to the head that disrupts the normal function of the brain.¹ The severity of a TBI can range from mild to severe, depending on the patient's mental status, consciousness level and amnesia following the injury. The annual incidence of TBI in North America and Europe is conservatively estimated to be approximately 600/100,000.^{2,3} This translates to at least 200,000 TBI cases in Canada every year. According to the Centers for Disease Control and Prevention, and the Canadian Institute for Health Information, the leading cause of TBIs that result in hospital admission is falls (35%-45%), followed by motor vehicle accidents (17%-36%), collision-related events (struck by or against) (10-17%) and assaults (9-10%).^{4,5} Head injuries are more common in the 0- to 19-year age group, followed by those who are aged 60+. Males are more highly represented in every age group than females. However, it should be noted that the demographics of patients who present in an optometrist's office may differ from those based on hospital admissions.

TBIs are classified by the duration of loss of consciousness and post-traumatic amnesia, along with the results of brain imaging (Table 1).^{6,7} Not all of these signs need to be present. Menon et al. stated that TBI can be diagnosed when there is alteration in brain function defined by any one of the following signs: a period of loss or decreased consciousness, any loss of memory for events immediately before or after the injury, neurologic deficits (weakness, loss of balance, change in vision, dyspraxia paresis/paralysis, sensory loss, aphasia, etc.), and any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.).⁸

Common phenomena following a TBI include decreased attention, concentration and processing speed, memory problems, confusion, irritability, depression and anxiety. Physical consequences can include headaches, fatigue, dizziness and nausea, balance difficulties, visual disturbance and sleep disruption.¹ In cases of moderate to severe TBI, patients may also experience decreased executive function, increased confusion, depression, anxiety, lack of impulse control, chronic pain and severe physical consequences.⁶ Visual symptoms are observed in 75% of TBI cases.⁹ These symptoms can be caused by decreased visual function, disorders of the binocular vision system, changes in ocular health and higher-order processing disorders, which are discussed further below. Due to the broad spectrum of visual symptoms that may occur following TBIs, it is important for the primary care optometrist to be familiar with the testing and management of patients with a history of traumatic brain injury.

Table 1: TBI Classification System^{6,7}

Characteristic	Mild TBI	Moderate TBI	Severe TBI
Loss of consciousness (LOC)	0 to 30 mins	0.5 to 24 h	>24 h
Post-traumatic amnesia (PTA)	0-1 days	1-7 days	>7 days
Brain-imaging results	Normal	Abnormal	Abnormal

EVALUATION

A thorough ocular-visual assessment (OVA) should be performed for all patients following a TBI. Testing includes a detailed case history, refraction, routine binocular vision and accommodation assessment, automated visual fields and ocular health assessment with dilated fundus evaluation. Additional in-depth testing of some systems should be included in the OVA for patients with a suspected or diagnosed TBI. This includes complementary assessments of the accommodative, vergence and oculomotor systems, and may include visual information-processing testing and visual-midline shift assessment.

The TBI population is also susceptible to cognitive and/or memory impairments, and special consideration should be given when considering the speed and duration of testing. Patients with TBI frequently require more time to process questions and commands. Therefore, objective measurements are preferred, as they will often provide more reliable results.¹⁰ The results of clinical testing should include any reported dizziness, headaches, nausea, or photophobia. If necessary, it may be beneficial to separate the vision examination into two or more appointments.

Case history

A thorough review of visual symptoms should be conducted, which can be facilitated by a symptom checklist completed by the patient prior to the appointment.¹¹ Case history should include details of the TBI incident and associated injuries. It is useful to review the patient's current and previous rehabilitation services and the progress of their therapy (occupational therapy, physiotherapy, etc.). Patient goals and needs should also be assessed, including their occupational and vocational visual demands, computer use, driving, mobility and reading. Optometrists should remember to record previous ocular conditions and general health (pre- and post-TBI), to differentiate between new and pre-existing conditions.

Visual acuity and refraction

Visual acuity itself is less often affected by TBI, and therefore traditional methods (i.e. Snellen) can be used to assess visual acuity in TBI patients. If a patient has cognitive or communication impairments, modified charts such as a Tumbling E or Broken Wheel test may provide more valid results.¹¹

When the optometrist performs a refraction, objective measurements such as retinoscopy should be considered for all patients since it may be difficult to elicit reliable subjective responses. Automated refractors can also be considered for photophobic patients. Although TBIs may not directly change a patient's refractive error, this population may become more sensitive to small prescription changes or uncorrected refractive errors. Special consideration should be given to latent or uncorrected hyperopic patients, who may become symptomatic following a TBI.¹² Progressive addition lenses are not recommended due to peripheral distortions.

Ocular health

A thorough slit lamp examination is performed to assess the ocular health of TBI patients, including a dilated fundus evaluation. Ocular health disorders following TBI can affect the anterior or posterior segments and may include angle recession, dry eye, intraocular hemorrhage or embolisms and papilledema.¹³⁻¹⁷ An in-depth assessment of the cranial nerves, pupils and optic nerves should also be performed. Appropriate treatment should be made for the management of these conditions or referral when indicated, such as to the family physician, ophthalmologist, neuro-ophthalmologist, neurologist, etc.

Visual field

Visual field defects may occur through trauma to the optic nerve, chiasm, optic radiations, or occipital cortex.¹⁵⁻¹⁷ Subtle visual field defects may not be detected by confrontation visual field.¹⁸ Automated perimetry is better suited for de-

tecting mild neurological defects and for monitoring changes over time.¹⁸ Screening for visual neglect should also be considered for TBI patients.¹⁹⁻²¹ Tests for spatial inattention (neglect) include line bisection and the clock drawing test.²²

Once appropriate investigation into the visual defect has been completed, treatment therapies are typically aimed at increasing the awareness of the affected field and the development of compensatory techniques. This can be achieved via field-enhancing prisms such as sector prisms, or Peli prisms.^{23,24} These prisms are aimed at bringing the image of the affected field into view to provide the patient with information about their periphery. Compensatory functional and rehabilitative techniques can also be taught to patients, such as field scanning, and visuomotor, behavioural and reading techniques.^{24,25}

Visual midline shift

Visual midline shift syndrome (VMSS) has been defined as a sense of shifted egocenter and has been reported after brain injuries.²⁶ It is often associated with, and indeed, may result from, neglect and/or hemianopia, although the exact association has not been documented. These alterations in the perceived midline can create changes in balance and posture. Healthcare professionals who typically address gait and balance include physiotherapists and occupational therapists.²⁶

Standardized assessment procedures have not been developed for visual midline shift testing. Current techniques include the subjective alignment of a wand at the midline, eye-hand coordination tests, observation of gait, as well as emerging devices to more accurately quantify the deviation and egocenter.²⁶ Padula and Argyris stated that a horizontal shift in midline may result in a lateral lean away from the affected visual space, and a possible drift left or right when walking. A vertical shift may result in tilting the body forward or backward (posterior/anterior).²⁷

Although further research in this field is needed, practitioners have reported success with the use of compensatory yoked prisms.²⁶ For assessment, prism lenses are initially placed with the base in the direction opposite the perceived shift in midline, aiming to realign the patient's egocenter. Testing is then repeated with different lenses in place. These trials are usually completed with yoked prisms under 10-12 prism diopters. Spatial localization therapies have also been used to enhance eye-hand coordination. A second approach is prism adaptation, in which localization training is undertaken with prisms in place, with the base contralateral to the direction of the shift. Typically, a higher power of prism is used (17 prism diopters). When the prisms are removed, pointing becomes more central, which can last up to 3.5 years.²⁸

Accommodation

Accommodative dysfunctions are present in approximately 40% of TBI patients,^{29,30} and include accommodative insufficiency, accommodative infacility, or accommodative spasms (which may induce pseudo-myopia).³¹ Accommodative testing should include the assessment of accommodative amplitudes (push-up to blur, or pull away to clear), accommodative accuracy (Monocular Estimation Method, cross cylinder evaluation, or Nott's modified dynamic retinoscopy) and accommodative facility (monocular and binocular).¹⁰

Management of accommodative disorders may include reading glasses with increased plus at near,¹⁰ or vision rehabilitation exercises.^{10,32,33} In non-presbyopic patients, vision exercises are usually recommended as the initial treatment and may include accommodative rock using lenses or different distances, as well as accommodative push-up techniques. There is some evidence that 87-100% of patients with accommodative dysfunctions show improvements with vision therapy.³³

Binocular vision

Vergence dysfunctions are one of the most common disorders following TBI, and are seen in approximately 50% of patients.^{9,29,34} Common disorders include convergence insufficiency (36%), binocular instability (restricted vergence ranges) (10%), basic esophoria (18% of patients with cerebrovascular accidents) and strabismus (e.g., intermittent exotropia, cranial nerve palsy) (7-25%).^{9,29,34}

Binocular vision testing should include routine and additional testing, including ocular alignment at distance and near (cover test, Maddox rod, phoria, associated phoria), motor fusion (vergence ranges, near point of convergence, vergence facility with 3BI/12BO prism jumps), sensory fusion (stereoscopy and fusion) and ocular motilities.¹²

Management of vergence disorders may include lenses, correcting prism, or vision therapy exercises.^{12,33,35} Vision therapy is usually recommended as the initial treatment for convergence insufficiency, while plus lenses should initially be considered for convergence excess. In-office binocular vision training has been used to successfully treat > 75% of TBI patients with convergence insufficiency.^{33,35} These therapies include Brock string, pencil push-ups, prism jumps, or instruments such as the Aperture Rule, cheirosopes, vectograms and tranaglyphs, often in combination.

Oculomotor

Fixation, pursuits and saccades are affected in approximately 20% of TBI patients.³⁶ Test procedures that involve oculomotor function include the Developmental Eye Movement Test, King Devick Test, Visagraph/ReadAlyzer goggles with infra-red sensors and the NSUCO (Northeastern State University College of Optometry) and SCCO (Southern California College of Optometry) oculomotor tests.¹²

Treatment is aimed at training each of these individual skills. There is some evidence that oculomotor therapies are successful in improving these skills, especially with reading.^{12,33,37} Although training techniques for oculomotor skills have not been extensively researched, therapies can include letter-tracking workbooks, oculomotor pursuit exercises, Brock string fixations, flashlight tag and computerized programs (i.e., Home Therapy System [HTS]) or other computer-aided vision therapy software).

Photophobia

Following a TBI, patients commonly report photophobia and increased sensitivity to glare.³⁸ Despite its prevalence, photophobia remains poorly understood and is difficult to assess and treat. Ongoing research in this field is performed to better understand the underlying mechanisms. Various theories have attributed photophobia to migraines following TBI, damage to the pain-sensitive intracranial structure and deficits in dark adaptation.³⁸⁻⁴⁰

For TBI patients, the case history should include questions about increased sensitivity to glare, sunlight, computers and screens.⁴¹ Careful pupil testing should be performed, although this will often yield normal results. Dry eye or headaches should also be investigated, as these conditions may exacerbate photophobia symptoms.³⁸ All underlying disease should be appropriately treated.

Although no major studies have been conducted on the management of photophobia symptoms, current treatment options include tinted lenses, overlays, and polarized, photochromic or fit-over sunglasses.⁴¹ These options are mostly selected subjectively, but often provide relief to patients and improve their visual comfort. However, there is some evidence that no tint, lighter tints or decreasing the tint over time encourages a decrease in photosensitivity with time.⁴²

MULTIDISCIPLINARY APPROACH

It is not uncommon for TBI patients to have comorbid health conditions. A multidisciplinary approach is always recommended when managing these patients. Interprofessional collaboration with other health care providers allows improved patient care through regular progress reports and communications. In addition to optometrists and ophthalmologists, other specialists who are often involved in the care of TBI patients include medical doctors, neurologists, physiotherapists, occupational therapists, audiologists, vestibular therapists, physical therapists and chiropractors. It is recommended that optometrists develop a good relationship with other providers to ensure optimal patient care. Allied healthcare providers should be provided with a report detailing the oculo-visual findings and recommendations for mutual patients.

CONCLUSION

As discussed, visual symptoms are very common following TBI. These patients benefit from a thorough optometric evaluation to identify and manage any underlying vision condition. Treatments may include tinted lenses and overlays, corrective and prismatic lenses, and vision therapy and rehabilitation. Addressing the visual needs of patients with TBI can reduce their symptoms, improve their quality of life and help them return to work and daily living. ●

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Randomized Clinical Trial of Treatments for Symptomatic Convergence Insufficiency in Children

*Convergence Insufficiency Treatment Trial Study Group**

Objective: To compare home-based pencil push-ups (HBPP), home-based computer vergence/accommodative therapy and pencil push-ups (HBCVAT+), office-based vergence/accommodative therapy with home reinforcement (OBVAT), and office-based placebo therapy with home reinforcement (OBPT) as treatments for symptomatic convergence insufficiency.

Methods: In a randomized clinical trial, 221 children aged 9 to 17 years with symptomatic convergence insufficiency were assigned to 1 of 4 treatments.

Main Outcome Measures: Convergence Insufficiency Symptom Survey score after 12 weeks of treatment. Secondary outcomes were near point of convergence and positive fusional vergence at near.

Results: After 12 weeks of treatment, the OBVAT group's mean Convergence Insufficiency Symptom Survey score (15.1) was statistically significantly lower than those of 21.3, 24.7, and 21.9 in the HBCVAT+, HBPP, and OBPT groups, respectively ($P < .001$). The OBVAT group also

demonstrated a significantly improved near point of convergence and positive fusional vergence at near compared with the other groups ($P \leq .005$ for all comparisons). A successful or improved outcome was found in 73%, 43%, 33%, and 35% of patients in the OBVAT, HBPP, HBCVAT+, and OBPT groups, respectively.

Conclusions: Twelve weeks of OBVAT results in a significantly greater improvement in symptoms and clinical measures of near point of convergence and positive fusional vergence and a greater percentage of patients reaching the predetermined criteria of success compared with HBPP, HBCVAT+, and OBPT.

Application to Clinical Practice: Office-based vergence accommodative therapy is an effective treatment for children with symptomatic convergence insufficiency.

Trial Registration: clinicaltrials.gov Identifier: NCT00338611

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CONVERGENCE INSUFFICIENCY (CI) is a common binocular vision disorder¹⁻⁴ that is often associated with a variety of symptoms, including eyestrain, headaches, blurred vision, diplopia, sleepiness, difficulty concentrating, movement of print while reading, and loss of comprehension after short periods of reading or performing close activities.⁵⁻¹³ Various treatments^{10,14-23} are commonly prescribed, including passive treatment with base-in prism

**For editorial comment
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reading glasses and active treatment, such as home-based therapy using pencil push-ups (HBPP) alone, home-based therapy using pencil push-ups plus other therapy techniques, office-based vision therapy, and orthoptics. Consensus regarding the most

effective treatment is lacking and there are considerable differences among treatments in time and cost. Recent studies that surveyed the ophthalmic community suggest that HBPP is the most commonly prescribed treatment by both ophthalmologists and optometrists for young patients with symptomatic CI.²⁴⁻²⁶

Active therapies for the treatment of symptomatic CI typically involve the purposeful, controlled manipulation of target blur, vergence demand, and/or target proximity with the aim of normalizing the accommodative and vergence systems and their mutual interactions.²⁷ The various active treatment approaches for CI differ in their (1) ability to control and manipulate stimulus parameters (eg, vergence and accommodative demand), (2) dosage, (3) mode of administration, and (4) use of motor learning theory and patient feedback. It is unknown, however, whether these differences affect the outcome of treatment.

*The Authors/Writing Committee are listed at the end of this article. Group Information: The members of the Convergence Insufficiency Treatment Trial Study Group are listed on page 1347.

Until recently, there has been a scarcity of rigorously performed scientific studies that document the effectiveness of treatments for CI. In preparation for our randomized clinical trial, the Convergence Insufficiency Treatment Trial (CITT) Study Group completed 2 pilot studies that were placebo-controlled, randomized trials investigating the effectiveness of passive and active treatments for symptomatic CI in children.^{28,29} In the trial that evaluated the effectiveness of base-in prism reading glasses prescribed according to Sheard's criterion (convergence amplitudes less than twice the near phoria),³⁰ prism glasses were found to be no more effective than placebo reading glasses.²⁸ The other randomized trial that compared the effectiveness of HBPP, office-based vision therapy/orthoptics, and office-based placebo vision therapy/orthoptics found office-based vision therapy/orthoptics to be more effective than pencil push-ups or placebo therapy in improving both the signs and symptoms associated with CI.²⁹ A limitation of the latter study was a 19% (9 of 47) loss to follow-up before treatment completion. In addition, it was suggested that a more intensive home-based vision therapy/orthoptics regimen should have been included as a treatment arm.³¹

The purpose of this randomized clinical trial was to further evaluate the commonly used active treatments for CI. We compared the effectiveness of 12 weeks of treatment using HBPP, home-based computer vergence/accommodative therapy and pencil push-ups (HBCVAT+), office-based vergence/accommodative therapy with home reinforcement (OBVAT), and office-based placebo therapy (OBPT) in improving symptoms and signs associated with symptomatic CI in children.

METHODS

We followed the tenets of the Declaration of Helsinki throughout the study. The institutional review boards of all participating centers approved the protocol and informed consent forms. The parent or guardian (subsequently referred to as *parent*) of each study patient gave written informed consent and each patient assented to participation. There was an initial consent process for performing an eligibility examination followed by a second consent for the enrollment and randomization of eligible patients into the trial. Health Insurance Portability and Accountability Act authorization was obtained from parents. Study oversight was provided by an independent data and safety monitoring committee.

PATIENT SELECTION

Major eligibility criteria for the trial was being aged 9 to 17 years and having exodeviation at near of at least 4 prism diopters (Δ) greater than at far, a receded near point of convergence (NPC) break (≥ 6 cm), insufficient positive fusional vergence at near (PFV) (convergence amplitudes) (ie, failing Sheard's criterion [PFV less than twice the near phoria]³⁰ or minimum PFV of $\leq 15\Delta$ base-out blur or break), and a CI Symptom Survey (CISS) score of 16 or greater. Because patients with symptomatic CI often have an associated accommodative insufficiency,¹² patients with symptomatic CI associated with accommodative insufficiency were included in the study. However, children with monocular accommodative amplitudes of less than 5 diopters (D) were excluded because the severity of their accommodative insufficiency may indicate an organic etiology. The eTable

provides a complete listing of eligibility and exclusion criteria (available at <http://www.archophthalmol.com>).

A refractive correction was prescribed for patients if they had a significant refractive error or a significant change in refractive correction. A significant refractive error or change was defined as 1.50 D or greater of hyperopia, 0.50 D or greater of myopia, 0.75 D or greater of astigmatism, 0.75 D or greater of anisometropia in spherical equivalent, or 1.50 D or greater of anisometropia in any meridian (based on cycloplegic refraction). For hyperopes, the investigator could reduce the prescription by up to 1.25 D. For myopia, full correction was required. After wearing the glasses for at least 2 weeks, eligibility testing was repeated to determine if the patient still met the eligibility criteria. Thus, the CISS and eligibility testing were always performed with appropriate refractive correction in place.

EXAMINATION PROCEDURES

Eligibility testing included administration of the CISS to identify whether the child was symptomatic.^{12,13,32,33} Other eligibility tests included best-corrected visual acuity at distance and near, a sensorimotor examination (cover testing at distance and near, NPC, and positive and negative fusional vergence at near [fusional convergence and divergence amplitudes]), near stereoacuity, monocular accommodative amplitude, monocular accommodative facility (the ability to quickly achieve clear vision while alternately viewing 20/30 print through +2 D and -2 D lenses), a cycloplegic refraction, and an ocular health evaluation. Convergence Insufficiency Treatment Trial-trained and -certified ophthalmologists or optometrists performed all testing using a previously described standardized protocol.³⁴ Eligible patients who consented to participate were enrolled in the study, and the measures taken at their eligibility examination were used as the study baseline measures.

RANDOMIZATION

Using a permuted block design, we randomly assigned eligible patients who consented to participate with equal probability to HBPP, HBCVAT+, OBVAT, or OBPT. Randomization was achieved using a secure Web site created and managed by the data coordinating center. To ensure approximately equal numbers of patients in each treatment arm by site, randomization was stratified by clinical site.

TREATMENT PROTOCOLS

The therapy regimens each lasted 12 weeks. Patients were taught their assigned therapy procedures by CITT-trained and -certified therapists. Therapists were either optometrists, vision therapists, or orthoptists with at least 1 year of experience; most optometrists were residency-trained. Patients were required to demonstrate their understanding and ability to perform home therapy procedures in the office before the therapies were prescribed for home. Instructional handouts were also provided for the home treatment procedures. Patients in all groups maintained a home therapy log and recorded their performances for each home therapy session. Monthly office visits were scheduled for those assigned to the 2 home-based therapy groups. At these visits, the therapists answered questions, reviewed home therapy procedures, and estimated adherence (compliance). In addition, the therapist contacted the patients by telephone on a weekly basis, during which time the home therapy procedures and home logs were reviewed and attempts were made to motivate the patients to adhere to treatment. Those assigned to office-based therapy groups were scheduled for weekly office therapy visits.

All treatments included time for instruction, feedback, review of the home log, and discussion about adherence. For the office-based groups, this all occurred during the weekly office visits. For the home-based groups, these interactions occurred every 4 weeks in the office and weekly via a telephone call with the therapist. The total treatment time for each group included the time spent in therapy at home or in the office plus the contact with the therapist via the weekly phone calls (for the home-based therapy groups).

HOME-BASED PENCIL PUSH-UPS

The pencil push-ups procedure involved using a pencil with 20/60 reduced Snellen letters and a white index card placed in the background to provide a suppression check by using physiological diplopia awareness. The goal of the procedure was to move the pencil to within 2 to 3 cm of the brow, just above the nose on each push-up while trying to keep the target single and clear. Patients were instructed to perform the pencil push-ups procedure 15 minutes per day, 5 days per week. They maintained home therapy logs, recording the closest distance that they could maintain fusion after each 5 minutes of therapy.

HOME-BASED COMPUTER VERGENCE/ACCOMMODATIVE THERAPY AND PENCIL PUSH-UPS

Patients in this group were taught to perform the pencil push-up procedure as well as procedures on the Home Therapy System/Computerized Vergence System (HTS/CVS) computer software system (Computer Orthoptics, Gold Canyon, Arizona). Using this program, they performed fusional vergence and accommodative therapy procedures, including vergence base-in, vergence base-out, autoslide vergence, and jump ductions vergence programs using random-dot stereopsis targets. The accommodative rock program was used for accommodative therapy. Much like a clinician would do at each follow-up visit, this computer program automatically modified the therapy program after each session based on the patient's performance. Patients were instructed to do pencil push-ups 5 minutes per day, 5 days per week, and the HTS software program for 15 minutes per day, 5 days per week, and to save their data on a disk provided by the study and to bring the disk to each follow-up visit.

OFFICE-BASED VERGENCE/ACCOMMODATIVE THERAPY WITH HOME REINFORCEMENT

The OBVAT group received a weekly 60-minute in-office therapy visit with additional prescribed procedures to be performed at home for 15 minutes a day, 5 days per week. The therapy procedures are described in detail elsewhere²⁹ and those performed during the weekly OBVAT sessions are shown in the eFigure. At each office-based therapy session, the patient performed 4 to 5 procedures with constant supervision and guidance from the therapist. There were no diagnostic tests performed during these sessions. The therapist followed a detailed and specific protocol from the CITT manual of procedures (<http://optometry.osu.edu/research/CITT/4363.cfm>); this document describes each procedure, amount of time procedure was performed, expected performance, and criteria for ending the procedure and advancing to a more difficult level.

OFFICE-BASED PLACEBO THERAPY

Patients in the OBPT group received therapy during a weekly 60-minute office visit and were prescribed procedures to be performed at home for 15 minutes per day, 5 days per week. The

placebo therapy program consisted of 16 in-office therapy procedures and 4 home therapy procedures, which were designed to look like real vergence/accommodative therapy procedures yet not to stimulate vergence, accommodation, or fine saccadic eye movement skills beyond normal daily visual activities. The therapist followed a detailed protocol from the CITT manual of procedures. Five procedures were performed during each office therapy visit and 2 procedures were assigned for home therapy each week. Placebo procedures included traditional vergence/accommodative therapy procedures modified to be monocular rather than binocular; binocular procedures performed at 0 vergence disparity; and testing procedures that did not require significant demand on the vergence, accommodative, or fine saccadic eye movement systems. For example, in 1 placebo procedure, the patient wore the appropriate filter glasses and performed vergence therapy at 0 vergence demand on the Computer Orthopter (Computer Orthoptics). Some procedures were designed to have increasing levels of difficulty. As in real therapy, patients frequently wore filter glasses and were told that the glasses ensured that both eyes were being used together. Objectives and goals were established for each placebo procedure to simulate real therapy. For motivational purposes, the therapist told the patient the objective of each procedure before beginning the technique.

MASKING OF THERAPISTS AND PATIENTS

Because experienced therapists provided the treatments, it was not feasible to mask them to patients' assigned treatment. However, each therapist followed a well-defined protocol for all treatments and was instructed to interact in an identical fashion with all patients. Although patients were obviously aware of whether they were assigned to office- or home-based therapy, those receiving office-based treatment were masked regarding whether they were assigned to vergence/accommodative or placebo therapy.

To determine the effectiveness of masking, patients assigned to either of the 2 office-based treatments were asked at the completion of their treatment whether they thought they were randomized into the active or placebo treatment. To assess examiner masking, examiners were asked if they thought they could identify the patient's treatment assignment at the completion of each masked examination. In addition, at the completion of the 12-week outcome examination, examiners were asked to guess the patient's group assignment and to report a level of confidence in the response.

FOLLOW-UP EXAMINATIONS

Protocol-specified follow-up visits were conducted after 4 and 8 weeks of treatment. The primary outcome assessment was made at the visit following the 12th week of treatment. At these follow-up visits, an examiner who was masked to the patient's treatment group administered the CISS and a sensorimotor examination that included cover testing at distance and near, NPC, PFV, accommodative amplitude, and accommodative facility testing. After the clinical testing was completed, the CISS was readministered.

TREATMENT ADHERENCE DATA

To assess adherence with home-based therapy, at each masked examination the therapist was asked, "What percent (0%, 1%-24%, 25%-49%, 50%-74%, 75%-99%, or 100%) of the time do you feel the patient adhered to the home protocol?" The therapists' estimate was based on a review of the home log, electronic data from the computer therapy program, and a discussion with the patient about home therapy. Thus, this estimate was primarily based on patient reports. The response options of 0%, 1% to 24%,

Clinician instructions: Read the following subject instructions and then each item exactly as written. If subject responds with "yes," please qualify with frequency choices.

Do not give examples.

Subject instructions: Please answer the following questions about how your eyes feel when reading or doing close work.

		Never	(Not Very Often) Infrequently	Sometimes	Fairly Often	Always
1.	Do your eyes feel tired when reading or doing close work?					
2.	Do your eyes feel uncomfortable when reading or doing close work?					
3.	Do you have headaches when reading or doing close work?					
4.	Do you feel sleepy when reading or doing close work?					
5.	Do you lose concentration when reading or doing close work?					
6.	Do you have trouble remembering what you have read?					
7.	Do you have double vision when reading or doing close work?					
8.	Do you see the words move, jump, swim or appear to float on the page when reading or doing close work?					
9.	Do you feel like you read slowly?					
10.	Do your eyes ever hurt when reading or doing close work?					
11.	Do your eyes ever feel sore when reading or doing close work?					
12.	Do you feel a "pulling" feeling around your eyes when reading or doing close work?					
13.	Do you notice the words blurring or coming in and out of focus when reading or doing close work?					
14.	Do you lose your place while reading or doing close work?					
15.	Do you have to reread the same line of words when reading?					
		_x0	_x1	_x2	_x3	_x4

Total Score: _____

Figure 1. Convergence Insufficiency Symptom Survey.

25% to 49%, and 50% to 74% were combined into 1 category (0%-74%) for data analysis because only 16% of patients were categorized into the response options below 75%.

MAINTENANCE THERAPY

Patients who demonstrated sufficient improvement on the CISS at the 12-week outcome visit were considered asymptomatic (CISS score <16) and were prescribed maintenance therapy of 15 minutes per week using home therapy procedures specific to the patient's assigned treatment group. Patients not demonstrating sufficient improvement on the CISS, and thus considered symptomatic (CISS score ≥ 16), were referred to a non-CITT eye care provider to receive alternative treatment for their CI.

OUTCOME MEASURES

Patients with CI who seek treatment usually do so because they are symptomatic (or perceived to be by their parents), and successful treatment should result in a lessening or abatement of symptoms. Thus, we used symptom level (as measured by the CISS) as the primary outcome measure (**Figure 1**). The questionnaire consisted of 15 items that were read aloud to the child by the examiner. The examiner read the questions while the child looked at a card with 5 answer options and was instructed to choose 1 of those possible answers (never, infrequently, sometimes, fairly often, or always). Each response was scored on a scale of 0 to 4, with 4 representing the highest frequency of symptom occurrence (ie, always). The 15 items were summed to obtain the total CISS score. The lowest possible score (least symptomatic) was 0 and the highest was 60 (most symptomatic). Based on our previous work,^{13,32} a CISS score of less than 16 is considered asymptomatic and a decrease of at least 10 or more points is considered improved.

The goal of treatment for CI is not only to eliminate patient symptoms, but also to improve the patient's convergence ability.

Thus, we used NPC and PFV as secondary outcome measures. A normal NPC was defined as less than 6 cm and an improved NPC was defined as an improvement (decrease) in NPC of 4 cm or more from baseline to the 12-week outcome examination. To be classified as having normal PFV, a patient had to pass Sheard's criterion (ie, PFV blur or if no blur, then break value at least twice the near phoria magnitude) and have a PFV blur/break of more than 15Δ . Improvement in PFV was defined as an increase of 10Δ or more from baseline to the 12-week outcome examination.

To evaluate each treatment's ability to improve both signs and symptoms, we also developed a composite outcome classification that considered the change in all 3 outcome measures from baseline to the 12-week examination. A successful outcome was a score of less than 16 on the CISS, a normal NPC (<6 cm), and a normal PFV ($>15\Delta$ and passing the Sheard's criterion). Improved was defined as a score of less than 16 or a 10-point decrease in the CISS score, and at least 1 of the following: normal NPC, an improvement in NPC of more than 4 cm, normal PFV, or an increase in PFV of more than 10Δ . Patients who did not meet the criteria for successful treatment or improved outcome were considered nonresponders.

STATISTICAL ANALYSIS

All sample size calculations were performed using PASS 2000 software³⁵ and assuming a 2-sided test with 90% power. For a given outcome measure, the common standard deviation (SD) obtained from the CITT pilot study²⁹ was used as an estimate of variability. To control for multiple comparisons (4 groups, with 2 compared at a time [6 pair-wise comparisons]), the α level used for determining sample size was set at 0.0083 (0.05/6).

The CITT was powered to reject the null hypothesis of no difference between groups, assuming that the true population differences between groups are 10 points on the CISS, 4 cm in NPC, and 10Δ in PFV. These differences were based on clinician expert opinion and the repeatability of each measure.^{13,36}

Table 1. CITT Population Demographics and Clinical Measures at Baseline

Characteristic	Mean (SD) by Therapy Group			
	HBPP (n=54)	HBCVAT+ (n=53)	OBVAT (n=60)	OBPT (n=54)
Age, y	11.9 (2.2)	11.6 (2.3)	12.0 (2.6)	11.8 (2.2)
Convergence Insufficiency Symptom Survey score	27.8 (7.6)	31.7 (9.1)	30.2 (9.8)	29.8 (8.9)
Near point of convergence, cm	14.7 (8.4)	14.4 (7.5)	13.4 (6.6)	14.4 (7.8)
Positive fusional vergence blur/break, Δ	11.3 (4.0)	10.5 (4.2)	11.0 (4.2)	11.0 (3.1)
Negative fusional vergence blur/break, Δ	13.0 (5.5)	11.3 (4.3)	10.4 (4.9)	10.2 (3.3)
Monocular accommodative amplitude, D	10.1 (3.8)	10.0 (4.5)	10.0 (4.0)	9.4 (2.9)
Accommodative insufficiency, ^a No. (%)	27 (50)	30 (57)	36 (60)	28 (52)
Monocular accommodative facility, cycles/min	6.9 (4.2)	5.7 (4.3)	6.5 (4.4)	6.8 (4.8)
Near phoria, Δ	9.9 exo (5.0)	9.4 exo (4.5)	8.8 exo (3.7)	9.0 exo (4.5)
Distance phoria, Δ	2.4 exo (3.4)	2.0 exo (3.0)	1.7 exo (2.2)	1.8 exo (2.5)
Spherical equivalent refractive error, right eye, D	-0.34 (1.5)	0.08 (1.5)	-0.20 (1.3)	0.15 (1.5)
Female sex, No. (%)	27 (50)	31 (58)	41 (68)	32 (59)
Race/ethnicity, No. (%)				
American Indian/Alaskan Native	0	3 (6)	2 (3)	5 (9)
Asian/Pacific Islander	2 (4)	0	2 (3)	0
Black	18 (34)	12 (23)	15 (25)	20 (37)
White	30 (57)	30 (57)	35 (59)	25 (46)
Other	3 (6)	8 (15)	5 (8)	4 (7)
Hispanic ethnicity, No. (%)	12 (22)	23 (45)	24 (41)	16 (30)
Attention-deficit/hyperactivity disorder, parent report, No. (%)				
Yes	6 (11)	9 (17)	7 (12)	12 (22)
No	45 (83)	42 (79)	51 (85)	40 (74)
Missing	3 (6)	2 (4)	2 (3)	2 (4)
Glasses wearers, No. (%)	24 (44)	16 (30)	16 (27)	20 (37)
Medication use, No. (%)				
Reporting use	5 (9)	15 (28)	14 (23)	21 (39)
Psychotropic medications ^b	2 (40)	4 (27)	3 (21)	6 (29)
Pulmonary medications ^b	2 (40)	5 (33)	2 (14)	10 (48)
Allergy medications ^b	1 (20)	6 (40)	4 (29)	11 (52)

Abbreviations: CITT, Convergence Insufficiency Treatment Trial; D, diopters; exo, exophoria; HBCVAT+, home-based computer vergence/accommodative therapy and pencil push-ups; HBPP, home-based pencil push-up therapy; OBPT, office-based placebo therapy with home reinforcement; OBVAT, office-based vergence/accommodative therapy with home reinforcement; Δ , prism diopter.

^aDefined as having a monocular accommodative amplitude less than Hoffstetter's minimum accommodative amplitude criteria minus 2.0 D.

^bAmong those who reported medication use.

The sample size of 52 children per group was based on the required sample size for the 3 outcome variables and adjusted for a 10% loss to follow-up.

All data analyses were performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina). All analyses followed the intention-to-treat principle. The mean of the 2 measures of the CISS score and the 3 measures of both the NPC and PFV obtained at each study visit were used for analyses. Positive fusional vergence at near was obtained from the base-out to blur measure if present; otherwise, base-out to break was used.

As planned a priori, a 4-group by 3-period repeated-measures analysis of covariance (ANCOVA) was used to compare the treatment groups at week 12. Using data from both the 4-and 8-week visits maximizes the degrees of freedom, thus ensuring the most appropriate estimate of the mean square error used in group mean comparisons. The baseline value of the outcome measure was used as a covariate because our initial pilot data showed a strong correlation between baseline and all subsequent values. In addition, all clinical and demographic variables collected at baseline were examined as potential confounders of the true relationship between a particular outcome measure and treatment group. For these analyses, the α level for inclusion in the final ANCOVA model was set at 0.10. If the final ANCOVA model indicated a significant group effect or group \times time interaction, Tukey's method of adjustment for multiple pairwise group comparisons was used to hold the overall error rate at $\alpha=0.05$. The mean square error from

the ANCOVA model was also used to construct 95% confidence intervals for the mean difference between groups.

A χ^2 test was used to compare the percentage of patients in each group who were classified as having successful or improved outcomes or as a nonresponder. Post hoc pairwise group comparisons of the percentage in each classification were achieved using logistic regression models. The baseline value of each outcome measure was included in the regression model. An unweighted κ statistic and the 95% confidence interval were used to assess the agreement between the examiner's guess and the patient's actual group assignment.

RESULTS

ENROLLMENT

Between July 2005 and October 2006, 221 patients were enrolled in the study. The number of patients enrolled at the 9 sites ranged from 14 to 35 (median, 25). The mean age of the patients was 11.8 years (SD, 2.3 years); 59% were female, 55% were white, 30% were African American, and 34% were Hispanic. At baseline, the mean (SD) clinical findings were 2Δ (2.8Δ) exodeviation at distance; 9.3Δ (4.4Δ) exodeviation at near; NPC break/recovery of 14.2 (7.5) cm/ 17.9 (8.2) cm; and PFV break/recovery at near of 12.7 (4.6Δ)/ 8.8 (4.5Δ). **Table 1**

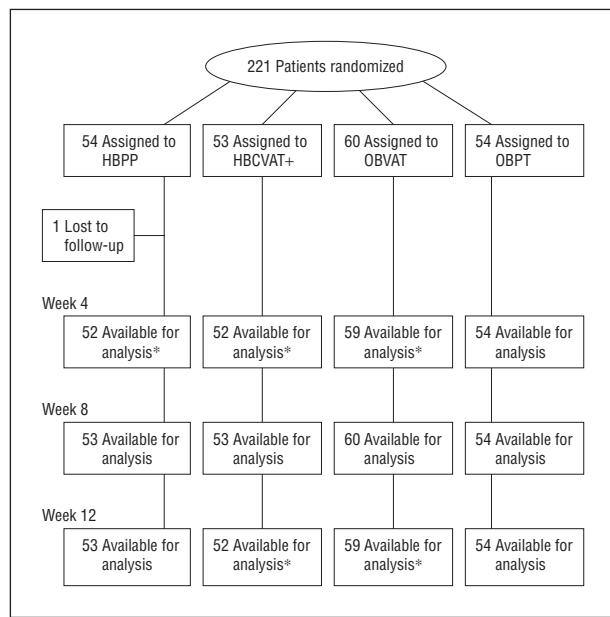


Figure 2. Flowchart of the randomized, clinical Convergence Insufficiency Treatment Trial. HBCVAT+ indicates home-based computer vergence/accommodative therapy and pencil push-ups; HBPP, home-based pencil push-up therapy; OBPT, office-based placebo therapy with home reinforcement; and OBVAT, office-based vergence/accommodative therapy with home reinforcement. *One missed visit.

provides the study population demographics and pertinent clinical measures at baseline by treatment group. While children with constant strabismus were excluded, patients with intermittent exotropia were eligible for the study and a small number (4-7 patients) were randomized to each treatment group. Although there was an imbalance at baseline in medication used among the 4 groups (highest in the OBPT group), only psychotropic medications had potential effects on accommodation, and the groups were balanced for these medications. Based on initial bivariate analyses, no confounders were identified for inclusion in the ANCOVA model for any of the 3 outcome measures.

PATIENT FOLLOW-UP

Of the 221 patients who entered the trial, 218 (99%) completed the 12-week outcome examination (**Figure 2**). Less than 2% of all study visits through week 12 were missed. The highest percentage of missed visits occurred in the OBPT group (18 of 648 visits [2.8%]). Of the 720 study visits scheduled in the OBVAT group, only 17 were missed (2.4%). In both of the home-based treatment groups, the percentage of visits missed was less than 1.5% (1.3% of 639 visits in the HBPP group and 1.4% of 636 visits in the HBCVAT+ group).

TREATMENT ADHERENCE DATA

At 12 weeks, the percentage of CITT patients rated by therapists as compliant with the home therapy protocol at least 75% of the time was 67.3% in the HBCVAT+ group, 84.9% in the HBPP group, 87% in the OBPT group, and 91.4% in the OBVAT group (**Table 2**). Accounting

Table 2. Patients Rated by Therapist as Compliant With Home Therapy Protocol at Least 75% of the Time

Week	Patients by Therapy, No. (%)			
	HBPP	HBCVAT+	OBVAT	OBPT
4	48 (92.3)	37 (69.8)	54 (94.7)	52 (98.1)
8	45 (84.9)	35 (66.0)	55 (91.7)	50 (96.1)
12	45 (84.9)	35 (67.3)	53 (91.4)	47 (87.0)

Abbreviations: HBCVAT+, home-based computer vergence/accommodative therapy and pencil push-ups; HBPP, home-based pencil push-up therapy; OBPT, office-based placebo therapy; OBVAT, office-based vergence/accommodative therapy with home reinforcement.

for the observed differences in estimated adherence did not affect the results of the treatment group comparisons for symptom score, NPC, or PFV (data not shown).

MASKING

Eighty-five percent of the patients assigned to placebo therapy and 93% of those assigned to vergence/accommodative therapy believed that they had been assigned to the active therapy group. None of the examiners felt that they could identify the patients' group assignment at the 4- or 8-week masked examinations, and only 1 examiner felt that he could identify the group assignment at outcome. One-third of the examiners responded that their patient was assigned to the OBVAT group, 24% responded that he/she was assigned to HBCVAT+, 21% said their patient was assigned to HBPP, and 21% said their patient was assigned to the OBPT group. Examiners, when asked to guess, were correct in identifying the patient's group assignment only 34% of the time, which is less than is expected by chance (ie, 50% correct vs incorrect, $P < .001$). There was low agreement between the actual group assignment and the examiner's guess of assigned treatment group ($\kappa = 0.11$, 95% confidence interval, 0.04-0.20).

PRIMARY OUTCOME MEASURE

Figure 3 displays the cumulative distribution plots of the mean symptom level for the 4 treatment groups at baseline and after 12 weeks of treatment. At the 12-week outcome examination, patients assigned to the OBVAT group reported a significantly lower mean symptom level compared with patients in the 3 other treatment groups (**Table 3**). The mean CISS score at 12 weeks in patients in the OBVAT group was 6.8 points lower than that in patients assigned to OBPT (95% confidence interval, 3.4-10.3; $P < .001$). A mean difference of 7.9 points was found between the OBVAT and HBPP groups (95% confidence interval, 4.4-11.4; $P < .001$). The largest difference in mean symptom level was 8.4 points (95% confidence interval, 4.9-11.9; $P < .001$), observed between the OBVAT and HBCVAT+ groups. No significant differences were observed among the HBPP, HBCVAT+, and OBPT groups (pairwise $P \geq .38$ for all).

As seen in **Table 4**, the percentage of patients in each group who were considered asymptomatic (ie, CISS score

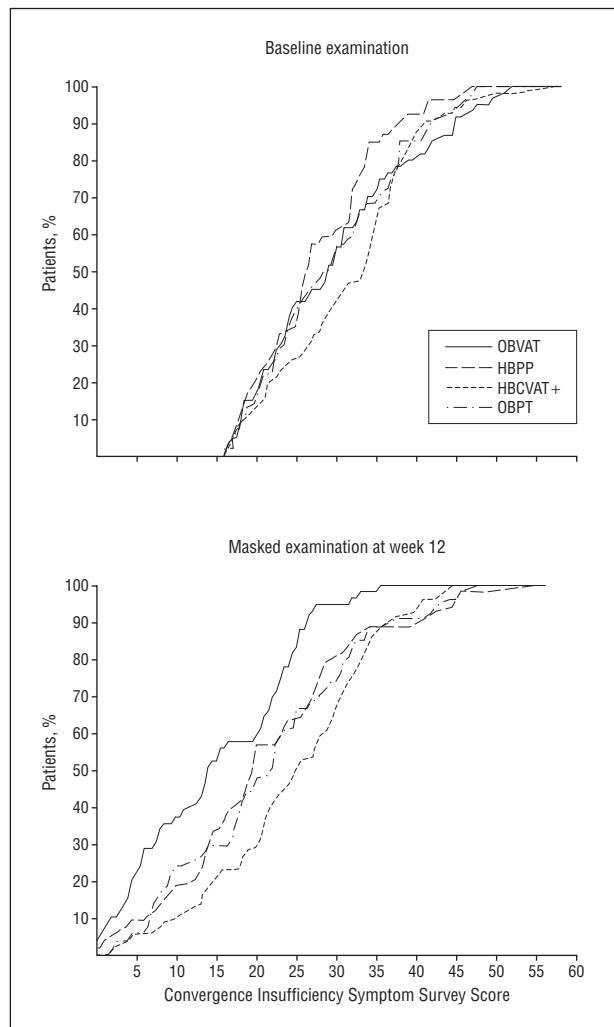


Figure 3. Cumulative distribution of Convergence Insufficiency Symptom Survey scores collected during the eligibility examination and at the masked examination at week 12. HBCVAT+ indicates home-based computer vergence/accommodative therapy and pencil push-ups; HBPP, home-based pencil push-up therapy; OBPT, office-based placebo therapy with home reinforcement; and OBVAT, office-based vergence/accommodative therapy with home reinforcement.

<16) or improved (ie, change in score of ≥ 10 points at the outcome examination) was significantly higher in the OBVAT group compared with the other treatment groups (HBPP, $P=.013$; HBCVAT+, $P<.001$; OBPT, $P=.004$). There was no significant difference in the percentage of patients considered asymptomatic or improved between the OBPT group and the 2 home-based groups (pairwise $P>.60$ for all).

We also used an alternate definition of success in which patients who achieved a symptom score of less than 16 were only considered to have had successful treatment if improvement was 10 or more points (Table 4). This eliminated the chance that patients with CISS scores that just met the eligibility criterion (≥ 16) would be classified as achieving successful treatment when the change in the CISS score was within the normal variability of the survey. Sixty-six percent of patients in the OBVAT group met this criterion, which was significantly greater than that observed in any of the other treatment groups (38% in HBPP, $P=.003$;

33% in HBCVAT+, $P<.001$; 35% in OBPT, $P=.001$); there were no statistical differences among the latter 3 treatment groups (pairwise $P>.50$ for all).

SECONDARY OUTCOME MEASURES

NPC Break

Figure 4 displays the cumulative distribution plots of the mean NPC break for the 4 treatment groups at baseline and after 12 weeks of treatment. At the outcome visit, the mean NPC was significantly improved in the OBVAT group compared with the other 3 groups (pairwise $P\leq .005$ for all) (Table 3). While the mean NPC of both home-based groups measured significantly closer than that of the OBPT group (pairwise $P\leq .01$ for all), there were no statistically significant differences between the 2 home-based therapy groups ($P=.33$).

The percentage of patients who had normal (break <6 cm) or improved (decrease of ≥ 4 cm) NPC at the 12-week outcome examination was significantly greater in the OBVAT group compared with the other treatment groups (HBPP, $P=.008$; HBCVAT+, $P=.006$; OBPT, $P<.001$) (Table 4). There were slightly more patients with a normal or improved NPC in both the HBPP and HBCVAT+ groups compared with the OBPT group; however, the difference was not statistically significant ($P=.06$ and $.07$, respectively). There was no significant difference between the 2 home-based groups ($P=.93$).

We also used an alternate definition of successful treatment in which patients who achieved a normal NPC were only considered to have had a successful treatment if improvement was greater than 4 cm (Table 4). Eighty-seven percent of patients in the OBVAT group achieved this criterion, a significantly higher percentage than that found in any of the other treatment groups (71% in HBCVAT+, $P=.023$; 64% in HBPP, $P=.002$; and 54% in OBPT group, $P<.001$). There was also a significant difference between the HBCVAT+ and the OBPT groups ($P=.032$); no differences were found between the HBPP group and either the HBCVAT+ ($P=.37$) or OBPT ($P=.20$) groups. This conservative estimate would not include some patients who would be considered to have had clinically successful treatment (eg, a 7 cm NPC at baseline, which improves to 3.5 cm).

PFV at Near

Figure 5 displays the cumulative distribution plots of the mean PFV at near for the 4 treatment groups at baseline and after 12 weeks of treatment. At the outcome examination, the mean PFV for patients in the OBVAT group was significantly greater than all other groups (pairwise $P<.001$ for all). The mean PFV in the HBCVAT+ group was significantly better (higher) than in the HBPP ($P=.037$) and OBPT ($P=.008$) groups. There was no significant difference in response in the HBPP and OBPT groups ($P=.57$).

As seen in Table 4, the percentage of patients with normal or improved PFV at the outcome examination was significantly higher in the OBVAT group compared with all other treatment groups (HBPP, $P=.002$; HBCVAT+, $P=.007$;

Table 3. Means and 95% Confidence Intervals for Each Outcome by Treatment Group and Time

Outcome	Mean (95% Confidence Interval)			
	HBPP	HBCVAT+	OBVAT	OBPT
CISS score				
Baseline	27.8 (25.8 to 29.8)	31.7 (29.3 to 34.1)	30.2 (27.7 to 32.7)	29.8 (27.4 to 32.2)
Week 12				
Unadjusted	21.3 (18.0 to 24.6)	24.7 (21.9 to 27.5)	15.1 (12.6 to 17.6)	21.9 (18.8 to 25.0)
Adjusted ^a	22.9 (20.4 to 25.5)	23.5 (20.9 to 26.0)	15.0 (12.6 to 17.4)	21.9 (19.3 to 24.4)
Total change ^a	-7.1 (-9.6 to -4.5)	-6.0 (-8.6 to -3.4)	-14.8 (-17.2 to -12.4)	-7.8 (-10.4 to -5.3)
NPC break, cm				
Baseline	14.7 (12.5 to 16.9)	14.4 (12.4 to 16.4)	13.3 (11.6 to 15.0)	14.4 (12.3 to 16.5)
Week 12				
Unadjusted	8.0 (6.1 to 9.9)	6.8 (5.2 to 8.4)	3.5 (3.0 to 4.0)	10.3 (8.4 to 12.2)
Adjusted ^a	7.8 (6.4 to 9.2)	6.8 (5.4 to 8.2)	4.0 (2.7 to 5.3)	10.3 (8.9 to 11.6)
Total change ^a	-6.4 (-7.8 to -5.0)	-7.5 (-8.9 to -6.1)	-10.4 (-11.7 to -9.0)	-3.9 (-5.3 to -2.5)
PFV blur or break, Δ ^b				
Baseline	11.3 (10.2 to 12.4)	10.5 (9.4 to 11.6)	11.0 (9.9 to 12.1)	11.0 (10.2 to 11.8)
Week 12				
Unadjusted	19.1 (16.8 to 21.4)	22.8 (19.8 to 25.8)	30.7 (27.5 to 33.9)	17.8 (15.5 to 20.1)
Adjusted ^a	18.9 (16.2 to 21.6)	23.0 (20.3 to 25.7)	30.5 (28.0 to 33.1)	17.8 (15.2 to 20.5)
Total change ^a	7.9 (5.2 to 10.6)	12.0 (9.3 to 14.8)	19.7 (17.1 to 22.3)	6.9 (4.2 to 9.5)

Abbreviations: CISS, Convergence Insufficiency Symptom Survey; HBPP, home-based pencil push-up therapy; HBCVAT+, home-based computer vergence/accommodative therapy and pencil push-ups; NPC, near point of convergence; OBPT, office-based placebo therapy with home; OBVAT, office-based vergence/accommodative therapy with home reinforcement; PFV, positive fusional vergence; Δ, prism diopter.

^aAdjusted for measurement obtained at the baseline examination.

^bThe blur finding was used, but if the patient did not report a blur, the break finding was used.

OBPT, $P < .001$). There were no significant differences in the percentage of patients with normal or improved PFV in the latter 3 treatment groups (pairwise $P > .10$ for all).

As with CISS score and NPC break, an alternate definition of success was used in which patients who achieved a normal PFV were only considered to have had a successful treatment outcome if improvement was greater than 10Δ (Table 4). Seventy-three percent of patients in the OBVAT group achieved this criterion, a significantly higher percentage than that in any of the other treatment groups (52% in the HBCVAT+ group, $P = .02$; 40% in the HBPP group, $P < .001$; and 26% in the OBPT group, $P < .001$). There was also a significant difference between the HBCVAT+ and OBPT groups ($P = .007$); however, no other significant differences were detected ($P > .10$ for all). Again, this conservative estimate would not include some patients who would be considered clinically successful (eg, 10Δ exophoria at near with a PFV at near of 16Δ at baseline, which improves to 25Δ).

Successful, Improved, and Nonresponder Criteria

Using the composite outcome classification, which combines symptoms, NPC, and PFV, the proportion of patients found to have had successful treatment or improved outcome in the OBVAT group was significantly greater than that in any of the other groups ($P < .002$ for all). While nearly three-quarters of patients in the OBVAT group (73%) had either successful or improved outcomes, less than half the patients in the HBPP group (43%), one-third of the patients in the HBCVAT+ group (33%), and just more than one-third in the placebo group (35%) were similarly classified.

Secondary Measures Combined

Previous studies have assessed treatment effectiveness by evaluating whether improvements occurred in both NPC and PFV. Seventy-three percent, 40%, 37%, and 22% of patients in the OBVAT, HBPP, HBCVAT+, and OBPT groups, respectively, achieved both a normal NPC and PFV. The percentage of patients who achieved both a normal NPC and a normal PFV was significantly higher in the OBVAT group compared with the other treatment groups ($P < .001$ for each pairwise comparison). No other group differences were significant ($P > .11$ for each pairwise comparison).

Attention-Deficit/Hyperactivity Disorder

Children with parent-reported attention-deficit/hyperactivity disorder (ADHD) scored higher on the CISS at baseline than children without parent-reported ADHD, and there were slight differences in the distribution of these children among treatment groups at baseline. However, ADHD was not a confounder and did not affect the mean treatment differences among the groups. There was also no interaction between ADHD and treatment ($P = .93$). We examined the 3-way interaction between ADHD, treatment, and time and found no significant effect ($P = .26$).

ADVERSE EVENTS

Six adverse events that included eyes or vision were reported. All were unexpected and further evaluations determined that none of the events were serious or related to the study treatment.

Table 4. Improvement in Signs and Symptoms of Convergence Insufficiency by Therapy Group

Treatment Group	Patients, No.	CISS			
		% of Patients			
		Score ≥16 but Improved by ≥10	Score <16 but Improved by <10	Score <16 and Improved by ≥10	Score <16 and/or Improved by ≥10
HBPP	53	13.2	9.4	24.5	47.1
HBCVAT+	52	15.4	5.8	17.3	38.5
OBVAT	59	17.0	6.8	49.2	72.9
OBPT	54	13.0	7.4	22.2	42.6

Treatment Group	Patients, No.	NPC Break ^a			
		% of Patients			
		Receded NPC but Improved by ≥4 cm	Normal NPC but Improved by <4 cm	Normal NPC and Improved by ≥4 cm	Normal NPC and/or Improved by ≥4 cm
HBPP	53	28.3	13.2	35.9	77.4
HBCVAT+	52	23.1	5.8	48.1	77.0
OBVAT	59	8.5	8.5	78.0	95.0
OBPT	54	33.3	5.6	20.4	59.3

Treatment Group	Patients, No.	PFV ^b			
		% of Patients			
		Insufficient PFV but Improved by >10Δ	Normal PFV but Improved by ≤10Δ	Normal PFV and Improved by >10Δ	Normal PFV and/or Improved by >10Δ
HBPP	53	9.4	17.0	30.2	56.6
HBCVAT+	52	7.7	7.7	44.2	59.6
OBVAT	59	3.4	10.2	69.5	83.1
OBPT	54	1.9	18.5	24.1	44.5

Abbreviations: CISS, Convergence Insufficiency Symptom Survey; HBPP, home-based pencil push-up therapy; HBCVAT+, home-based computer vergence/accommodative therapy and pencil push-ups; NPC, near point of convergence; OBPT, office-based placebo therapy with home; OBVAT, office-based vergence/accommodative therapy with home reinforcement; PFV, positive fusional vergence; Δ, prism diopter.

^aNormal is defined as NPC less than 6 cm; improved is defined as a decrease in NPC of 4 cm or more; receded is defined as NPC 6 cm or greater.

^bNormal is defined as PFV greater than 15Δ and meeting Sheard's criterion; improved is defined as an increase in PFV of more than 10Δ; insufficient is defined as PFV of 15Δ or less or failing Sheard's criterion.

COMMENT

We compared the effectiveness of 3 active vision therapy approaches in 221 children with symptomatic CI. Office-based vergence/accommodative therapy with home reinforcement was significantly more effective than HBPP, HBCVAT+, and OBPT in improving both the symptoms and clinical signs associated with symptomatic CI. Although symptoms did improve in the 2 home-based therapies, these treatments were no more effective in improving symptoms than office-based placebo therapy.

We established 4 criteria, a priori, to determine the clinical relevance of the data from this study: (1) the score differences on the CISS between treatment groups at outcome, (2) the proportion of children who achieved a normal or improved symptom score on the CISS at outcome, (3) the change in secondary outcome measures, NPC, and PFV (convergence amplitudes) at outcome, and (4) the proportion of patients classified as having had successful or improved outcomes when using the compos-

ite outcome classification (combining the treatment effects of all 3 outcome measures).

The first criterion, the treatment group difference in the CISS score at outcome, was difficult to establish a priori. Our survey instrument had not been incorporated into clinical practice, and, consequently, the magnitude of the difference between 2 treatment regimens that indicated clinical relevance had not been established. Based on the group mean differences found for the CISS in our previous pilot study,²⁹ the CITT was designed to have 90% power to reject the null hypothesis of no group mean differences if the true population difference between groups in the CISS score was 10 points. This difference of 10 points, along with data on the variability in CISS scores obtained from 3 separate randomized trials conducted by the CITT Study Group, translates into an effect size of greater than 1 SD.

In the present study, we did not find a difference in group means of 10 or more points on the CISS. Instead, we found statistically significant group differences that ranged from 7 to 8.5 points between the OBVAT group

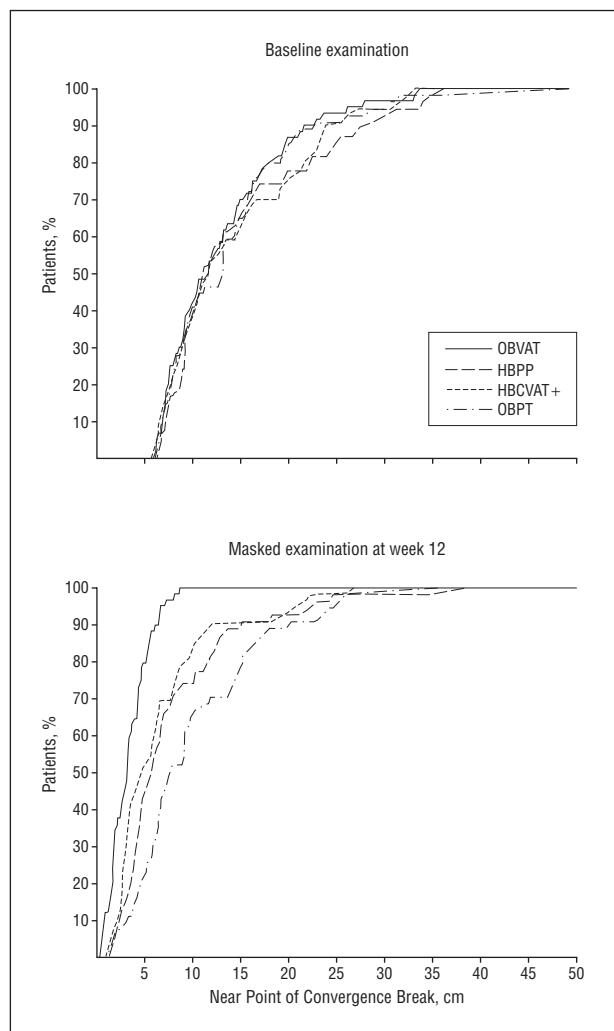


Figure 4. Cumulative distribution of near point of convergence data collected during the eligibility examination and at the masked examination at week 12. HBCVAT + indicates home-based computer vergence/accommodative therapy and pencil push-ups; HBPP, home-based pencil push-up therapy; OBPT, office-based placebo therapy with home reinforcement; and OBVAT, office-based vergence/accommodative therapy with home reinforcement.

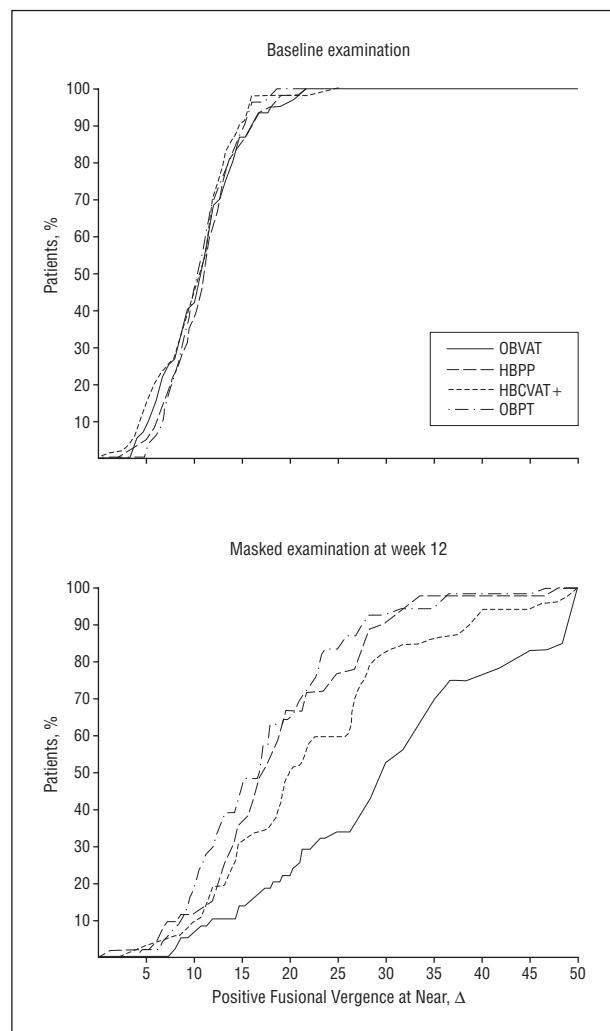


Figure 5. Cumulative distribution of positive fusional vergence data collected during the eligibility examination and at the masked examination at week 12. HBCVAT + indicates home-based computer vergence/accommodative therapy and pencil push-ups; HBPP, home-based pencil push-up therapy; OBPT, office-based placebo therapy with home reinforcement; OBVAT, office-based vergence/accommodative therapy with home reinforcement; and Δ , prism diopter.

and each of the other 3 treatment groups. This translates to an effect size that ranges from 0.77 to 0.94 SD. Using Cohen's³⁷ guidelines for interpretation of effect size (0.2 is small, 0.5 is medium, 0.8 is large), the group differences we found are considered large. Sloan et al³⁸ contend that an effect size of 0.5 is a conservative estimate of a clinically meaningful difference that is scientifically supportable and unlikely to be one that can be disregarded. Thus, group differences observed in this study are considered clinically meaningful, though they are less than the a priori estimate of a 10 or more points change between groups. Looking retrospectively and reviewing the literature on effect size, the 10-point difference was a significant overestimate of the potential treatment effect. Further study and refinement of the CISS will help clarify the issue.

The second criterion used to assess clinical relevance was whether there were differences among treatment groups in patients' ability to achieve a normal or improved symp-

tom level on the CISS. After treatment, 73% of patients assigned to OBVAT met this criterion, in contrast to 47% assigned to HBPP, 39% assigned to HBCVAT+, and 43% assigned to OBPT. Changing the criterion to require that patients achieved both a score of less than 16 and a change of 10 or more points on the CISS resulted in lower success rates for all groups, but the differences among treatment groups remained the same.

The third criterion used was an evaluation of the secondary outcome measures, NPC and PFV (convergence amplitudes), as they are often used clinically to determine treatment success for CI. The proportion of patients who achieved a clinically normal level for both measures was 73% in the OBVAT group compared with no more than 40% in each of the other 3 treatment groups.

The fourth a priori criterion for determining clinical significance was the proportion of patients classified as having successful or improved outcomes when

using the composite outcome classification (combining the treatment effects of all 3 outcomes). A significantly higher proportion of children assigned to OBVAT (73%) compared with the 3 other treatment groups was classified as having successful treatment or improved outcome. No significant differences were observed between the 2 home-based groups and the placebo therapy group. Thus, based on the analysis of all 4 a priori criteria, we conclude that there are both statistically significant and clinically meaningful differences between the groups.

The results of this large, randomized clinical trial are similar to those from the only previous randomized trial of vision therapy/orthoptics for CI in children²⁹ in which 3 treatment groups were studied: HBPP, office-based vision therapy/orthoptics, and OBPT. In that pilot study, only the OBVAT group experienced a significant improvement in symptoms, NPC, and PFV.

The current study was not designed to show the maximal possible improvement with treatment. Longer treatment may have resulted in additional changes in signs and symptoms. Office-based vergence/accommodative therapy programs for CI often include 12 to 24 office visits.¹⁹⁻²¹ Our 12-week treatment program was based on the assumption that this represented the maximum length of time that a symptomatic patient who was not improving would stay on the assigned treatment. Because our 12-week treatment program is at the low end of the range of time recommended for office-based CI therapy, it is possible that OBVAT might have been effective in more patients had the treatment program been longer. Likewise, a longer treatment program may have resulted in additional improvements by those assigned to the home-based treatment groups. It is also possible that using more home-based therapy procedures or prescribing longer periods of daily home-based therapy may have produced different results. Answers to these questions will have to await further study.

While a placebo effect could be associated with any of the 4 treatments owing to the patient's expectation that the treatment would be effective, office-based therapy might be more susceptible to this effect owing to the enthusiasm, caring, and compassion of a therapist who spends 60 minutes per week with the patient.³⁹ However, this is the second randomized trial of OBVAT that was designed to control for the effect of the therapist as a placebo⁴⁰; placebo therapy was designed to simulate bona fide therapy procedures and therapists were trained to behave identically for patients in both of the office-based therapy groups. The data reported herein confirm that we were successful in achieving this objective, as 85% of the patients assigned to OBPT believed they had been assigned to the actual OBVAT group. This compares well with our previous pilot study in which 90% of the patients assigned to placebo therapy believed they had been assigned to actual therapy.²⁹ A no treatment group was not included; therefore, it is not known whether any improvements were due to regression to the mean or natural history of the disease. However, this should have affected all treatment groups similarly because there were no statistically significant or clinically relevant differences in any primary or secondary outcome measure

among the treatment groups at baseline. Therefore, the observed differences in effectiveness between the OBVAT and placebo therapy groups are most likely attributable to treatment effect.

The OBVAT used in this study represents a typical approach used in clinical practice.²¹ We conclude that this specific therapy protocol was successful in this study and should be applicable to children with similar clinical findings. A better understanding of which procedures were most effective will require additional research.

While this study was not designed to determine which factors within a particular group contributed to the outcome, the procedures that comprise the OBVAT provide therapists with the greatest ability to control and manipulate stimulus parameters (eg, vergence amplitude and accommodative demand) and to incorporate motor learning theory (eg, modeling and demonstration, transfer of training, patient feedback). The weekly visits with the therapist during OBVAT also permit the inclusion of a variety of procedures that stress convergence and accommodative abilities not typically addressed in home therapy programs. There were also differences among the treatment groups in time spent performing therapy and interacting with the therapist. The 2 office-based groups had a mean prescribed therapy time of 135 minutes per week; the HBCVAT+ group averaged 115 minutes; and the HBPP group averaged 90 minutes, which included weekly telephone calls with the therapist. However, this study was not designed to equalize time spent performing therapy and/or interacting with a therapist; rather, it was designed as an effectiveness study to evaluate 3 clinical treatments typically provided in clinical practice. It is possible that the difference in treatment effect found in this study could be related to the OBVAT group having been prescribed more minutes of therapy per day than the home-based groups. However, having a patient perform a greater amount of daily home-based therapy, particularly pencil push-ups, is likely impractical.

There are limited data in the literature that suggest there is a relationship between CI and ADHD.^{41,42} Although we asked parents whether their child had ADHD (ie, parental report), this study was not designed to assess this relationship and was not powered for such subgroup analyses, nor was the diagnosis of ADHD definitive. However, investigation of this possible association is of interest and merits additional research.

We could not identify any other sources of bias or confounding factors to explain our findings. Accounting for slight differences in the distribution of baseline factors between groups in the analyses did not alter the interpretation of the results. The follow-up visit rate was excellent and almost identical in all 4 groups. The investigators performing the 4-, 8-, and 12-week examinations were masked to the treatment group, and the patients in the 2 office-based treatment groups were effectively masked as well. We did have slight differences in adherence among the groups, however, and accounting for these differences in estimated adherence did not affect the results of the treatment group comparisons for the CISS

Clinical Sites

Sites are listed in order of the number of patients enrolled in the study, with the number of patients in parentheses after the site name and location. Personnel are listed as PI for principal investigator, SC for site coordinator, E for examiner, and VT for vision therapist.

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State University of New York College of Optometry, New York, New York (28): Dr Cooper (PI); Audra Steiner, OD (E, Co-PI); Marta Brunelli (VT); Stacy Friedman, OD (VT); Steven Ritter, OD (E); Lily Zhu, OD (E); Lyndon Wong, OD (E); Ida Chung, OD (E); and Kaity Colon (SC).

University of Alabama at Birmingham School of Optometry, Birmingham (28): Dr Hopkins (PI); Marcela Frazier, OD, MPH (E); Janene Sims, OD (E); Marsha Swanson, OD (E); Katherine Weise, OD, MBA (E); Adrienne Broadfoot, MS, OTR/L (VT, SC); Michelle Anderson, OD (VT); and Catherine Baldwin (SC).

Nova Southeastern University, Ft Lauderdale, Florida (27): Dr Coulter (PI); Deborah Amster, OD (E); Gregory Fecho, OD (E); Tanya Mahaphon, OD (E); Jacqueline Rodena, OD (E); Mary Bartuccio, OD (VT); Yin Tea, OD (VT); and Annette Bade, OD (SC).

Pennsylvania College of Optometry, Philadelphia (25): Dr Gallaway (PI); Brandy Sombordi, OD (E); Mark Boas, OD (VT); Tomohiko Yamada, OD (VT); Ryan Langan (SC), Ruth Shoge, OD (E); and Lily Zhu, OD (E).

The Ohio State University College of Optometry, Columbus (24): Dr Kulp (PI); Michelle Buckland, OD (E); Michael Earley, OD, PhD (E); Gina Gabriel, OD, MS (E); Aaron Zimmerman, OD (E); Kathleen Reuter, OD (VT); Andrew Toole, OD, MS (VT); Molly Biddle, MEd (SC); and Nancy Stevens, MS, RD, LD (SC).

Southern California College of Optometry, Fullerton (23): Dr Cotter (PI); Eric Borsting, OD, MS (E); Dr Rouse (E); Carmen Barnhardt, OD, MS (VT); Raymond Chu, OD, MS (VT); Susan Parker (SC); Rebecca Bridgeford (SC); Jamie Morris (SC); and Javier Villalobos (SC).

University of California–San Diego Ratner Children’s Eye Center, San Diego (17): Dr Granet (PI); Lara Hustana, OD (E); Shira Robbins, MD (E); Erica Castro (VT); and Cintia Gomi, MD (SC).

Mayo Clinic, Rochester, Minnesota (14): Dr Mohney (PI); Jonathan Holmes, MD (E); Melissa Rice, OD (VT); Virginia Karlsson, BS, CO (VT); Becky Nielsen (SC); Jan Sease, COMT, BS (SC); and Tracee Shevlin (SC).

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CITT Data Coordinating Center

Ms Mitchell (PI); Tracy Kitts (project coordinator); Melanie Bacher (programmer); Linda Barrett (data entry); Loraine Sinnott, PhD (biostatistician); Kelly Watson (student worker); and Pam Wessel (office associate).

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Dr Redford; and Paivi Miskala, PhD.

CITT Executive Committee

Dr Scheiman; Ms Mitchell; Dr Cotter; Dr Hertle; Dr Kulp; Dr Redford; and Dr Rouse.

Data and Safety Monitoring Committee

Marie Diener-West, PhD (chair); Rev Andrew Costello, CSsR; William V. Good, MD; Ron D. Hays, PhD; Argye Hillis, PhD (through March 2006); and Ruth Manny, OD, PhD.

score, NPC, or PFV. The placebo effect was accounted for by incorporating the OBPT group.

When translating these study results into clinical practice, it is important to recognize that they can only be applied to children with symptomatic CI who are aged 9 to 17 years. Adults with symptomatic CI may respond differently, as suggested by our pilot study.⁴³ Our findings indicate that the specific form of vision therapy/orthoptics we used, OBVAT with home reinforcement, is the most effective of the treatments we studied in this trial, with about 75% of patients achieving normalization of or improvement in symptoms and signs within 12 weeks.

With regards to home-based therapy, it is important to note that the data reported in this study for the HBPP

group were derived from a therapy program designed with considerably closer follow-up than is typical in clinical practice. Patients were called on a weekly basis by a therapist, completed a home log, and returned for office visits every fourth week. It is possible that this treatment would be less effective if prescribed according to usual clinical practice, which does not include weekly telephone calls from a therapist and often has less frequent follow-up. The results of the CITT pilot study, in which the HBPP group did not receive weekly phone calls, provide some support for this hypothesis, as none of the 11 patients were classified as having successful or improved outcomes.²⁹

It is easy to understand the clinical popularity of home-based treatment because of its simplicity and

cost-effectiveness. Both HBPP and HBCVAT+ can be taught to patients in a short time and require fewer follow-up visits than office-based therapy (4 visits for home-based treatments compared with 12 visits for office-based treatment). While our study was not designed to conduct a cost-utility analysis, this is worthwhile to explore in future research.

There are a number of interesting clinical questions that cannot be answered at this time. It is possible that there may be psychological effects from the interaction between the therapist and the patient that could affect the office-based and home-based treatment groups' results differentially (if these effects were present, and if they were dependent on patient-therapist contact time). In this study, we did not have a placebo home-based therapy group and thus, do not know whether the changes found in the 2 home-based groups are due to a real or placebo treatment effect. It is possible that different protocols that more closely monitor and encourage adherence would affect the outcomes. For the OBVAT regimen, we do not know which procedures were most effective or whether the treatment protocol can be modified to make it more effective. This includes understanding the nature of the synergistic role of the active home treatment component as well as the therapist interaction. It is also not known whether the treatment effect will be sustained over time. Therefore, a conclusion about the long-term benefit of treatment must await the results of the 12-month follow-up study we are conducting.

CONCLUSIONS

This large-scale multi-center, randomized clinical trial of treatments for children with symptomatic CI demonstrates that a 12-week regimen of OBVAT with home reinforcement is more effective than a 12-week program of HBPP or HBCVAT+ in improving symptoms and signs associated with CI.

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Additional Information: The eTable and eFigure are available at <http://www.archophthalmol.com>.

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The Wilcoxon Signed Rank Test for Paired Comparisons of Clustered Data

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SUMMARY. The Wilcoxon signed rank test is a frequently used nonparametric test for paired data (e.g., consisting of pre- and posttreatment measurements) based on independent units of analysis. This test cannot be used for paired comparisons arising from clustered data (e.g., if paired comparisons are available for each of two eyes of an individual). To incorporate clustering, a generalization of the randomization test formulation for the signed rank test is proposed, where the unit of randomization is at the cluster level (e.g., person), while the individual paired units of analysis are at the subunit within cluster level (e.g., eye within person). An adjusted variance estimate of the signed rank test statistic is then derived, which can be used for either balanced (same number of subunits per cluster) or unbalanced (different number of subunits per cluster) data, with an exchangeable correlation structure, with or without tied values. The resulting test statistic is shown to be asymptotically normal as the number of clusters becomes large, if the cluster size is bounded. Simulation studies are performed based on simulating correlated ranked data from a signed log-normal distribution. These studies indicate appropriate type I error for data sets with ≥ 20 clusters and a superior power profile compared with either the ordinary signed rank test based on the average cluster difference score or the multivariate signed rank test of Puri and Sen (1971, *Nonparametric Methods in Multivariate Analysis*, New York: John Wiley). Finally, the methods are illustrated with two data sets, (i) an ophthalmologic data set involving a comparison of electroretinogram (ERG) data in retinitis pigmentosa (RP) patients before and after undergoing an experimental surgical procedure, and (ii) a nutritional data set based on a randomized prospective study of nutritional supplements in RP patients where vitamin E intake outside of study capsules is compared before and after randomization to monitor compliance with nutritional protocols.

KEY WORDS: Clustered data; Nonparametric tests; Ophthalmologic data; Paired data.

1. Introduction

Clustered data are often found in studies of eyes, ears, knees, teeth, and coronary arteries as well as in family studies. It is customary in ophthalmologic studies to record data on responses for individual eyes. The responses may either be continuous (such as visual field area), binary (e.g., presence or absence of cataract), or ordinal (e.g., diabetic retinopathy grade or lens opacity grade). Regardless of the type of data, responses for individual eyes of the same subject are usually highly correlated. For example, in an ophthalmologic clinical trial with a parallel design, subjects are randomized to different treatments and each subject might provide a paired difference score (e.g., posttreatment score minus pretreatment score) for each of two eyes. If the eye is the unit of analysis, then standard methods of analysis are inappropriate because they assume independence of sampling units. Alternatives to standard methods that incorporate clustering effects have been well studied for continuous and binary outcome variables (Rosner, 1984; Liang and Zeger, 1986). However, only a small amount of literature exists for incorporating cluster-

ing effects for nonparametric tests. Rosner and Grove (1999) discussed the incorporation of clustering effects for the Mann-Whitney U test. A corrected variance estimate was obtained based on four estimated correlation parameters. This test procedure was shown to have appropriate size in balanced designs with as few as 20 clusters per group. Rosner, Glynn, and Lee (2003) have presented a large sample randomization test for the clustered Wilcoxon rank sum test that generalizes Rosner and Grove (1999) by allowing the average rank to differ by cluster size and to allow for control of covariates while performing the Wilcoxon rank sum test. Lee and Rosner (2001) have incorporated clustering effects for the Mann-Whitney U statistic in the analysis of correlated ROC curve data arising from multiple readers evaluating the same slides.

In this article, we present a randomization distribution representation of the signed rank test statistic that is extended to the clustered data setting, thus allowing one to easily obtain variance estimates for the Wilcoxon signed rank test that are corrected for clustering effects. In Section 2, we present the test statistic, derive a formula for the estimated variance of

the signed rank test statistic that is corrected for clustering, and present the large sample results. In Section 3, we conduct simulation studies exploring the validity of the large sample test in finite samples and comparing it to other nonparametric approaches to the analyses of paired data. In Section 4, we present two examples using the signed rank statistic based on (i) a study of the ocular effects of a surgical intervention for retinitis pigmentosa (RP) patients, and (ii) a study comparing dietary vitamin E intake before and after randomization in a clinical trial investigating the effect of nutritional supplementation on the course of disease in RP patients.

2. Methods

We let X_{ij} (Y_{ij}) denote the baseline (follow-up) score for the j th subunit in the i th cluster (subject) and define $Z_{ij} = Y_{ij} - X_{ij}$, $j = 1, \dots, g_i$; $i = 1, \dots, m$. We assume an exchangeable correlation structure, such that conditional within any cluster i , the difference scores $\{Z_{i1}, \dots, Z_{ig_i}\}$ are independent and identically distributed, $i = 1, \dots, m$. We wish to test the hypothesis H_0 : the difference score Z is symmetric about 0 versus H_1 : Z is symmetric about γ , for some $\gamma \neq 0$. We define $\theta_{ij} = F(|Z_{ij}|)$, where

$$F(v) = \Pr(|Z| \leq v), \quad v > 0, \quad (1)$$

is the c.d.f. of $|Z|$. Then $|Z_{ij}|$ is the (random) θ_{ij}^{th} percentile of F , $j = 1, \dots, g_i$; $i = 1, \dots, m$. We rank $|Z_{ij}|$ over the total of $G = \sum_{i=1}^m g_i$ subunits from the m clusters and let S_{ij} = signed rank of the j th subunit in the i th cluster, given by $S_{ij} = R_{ij}V_{ij}$, where R_{ij} = rank of $|Z_{ij}|$ within the total data set of G subunits over m clusters, and $V_{ij} = \text{sign}(Z_{ij})$. Note that under H_0 , V_{ij} and θ_{ij} are independent random variables (Randles and Wolfe, 1979).

2.1 Balanced Design

We first consider the case of a balanced design (i.e., each cluster has the same number of subunits, g). The clustered Wilcoxon signed rank statistic is then defined by

$$T_c^{(\text{obs})} = \sum_{i=1}^m S_{i+} \equiv \sum_{i=1}^m \sum_{j=1}^g R_{ij}V_{ij}, \quad (2)$$

where $S_{i+} = \sum_{j=1}^g S_{ij}$ and we only consider nonzero Z_{ij} in the computation of signed ranks.

We assume a design where each subunit j within a cluster (subject) i has a score assessed at baseline (X_{ij}) when they do not receive treatment and another score at follow-up (Y_{ij}) after they receive treatment, $j = 1, \dots, g$. Thus, for the purpose of defining the randomization distribution of Z_{ij} , the unit of randomization is the cluster (i), while the unit of analysis is the subunit (j) within the cluster (i). This implies that if $\delta_1, \dots, \delta_m$ are i.i.d. random variables each taking on the values +1 and -1 with probability 1/2, then the randomization distribution corresponding to $T_c^{(\text{obs})}$ is given by the distribution of T_c conditional upon S_{1+}, \dots, S_{m+} , where

$$T_c = \sum_{i=1}^m \delta_i S_{i+}. \quad (3)$$

If m is small, we can evaluate the significance of $T_c^{(\text{obs})}$ by enumerating the 2^m realizations of T_c and computing the two-

tailed p -value by $p = 2 \times \min\{\Pr(T_c \geq T_c^{(\text{obs})}), \Pr(T_c \leq T_c^{(\text{obs})})\}$, 0.5}. Otherwise, we can consider a large sample approach, where $\text{Var}(\delta_i) = 1$, $i = 1, \dots, m$ and

$$\text{Var}(T_c) = \sum_{i=1}^m S_{i+}^2. \quad (4)$$

Note that because the sum of squares of subunit-specific signed ranks over all clusters is fixed, under H_0 , decreased within-cluster variation in subunit-specific ranks (i.e., higher intracluster correlation) will result in a higher $\text{Var}(T_c)$. We prove that T_c is asymptotically normal as $m \rightarrow \infty$ if $1 < g < \infty$. This large sample result holds either when the Z_{ij} come from an underlying continuous distribution with no ties, or when the Z_{ij} come from an underlying discrete (or grouped continuous) distribution with tied values (see *Biometrics* website for proofs). Thus, we use the large sample test statistic

$$W_c = T_c \left/ \left(\sum_{i=1}^m S_{i+}^2 \right)^{1/2} \right. \sim N(0, 1) \quad \text{under } H_0. \quad (5)$$

The asymptotic two-tailed p -value equals $2 \times \{1 - \Phi(|W_c|)\}$, where Φ is the standard normal c.d.f.

Another possible approach in the case of a *balanced design with distinguishable components* is to use a multivariate signed rank test (Puri and Sen, 1971). Suppose we denote the ordinary signed rank statistic for the j th component by $T_j^{(\text{obs})}$, $j = 1, \dots, g$ and the vector of signed rank statistics by $\mathbf{T}^{(\text{obs})} = (T_1^{(\text{obs})}, \dots, T_g^{(\text{obs})})$, where $T_j^{(\text{obs})} = \sum_{i=1}^m R_i^{(j)} \text{sign}(Z_{ij})$, $j = 1, \dots, g$, and $R_i^{(j)} = 0.5 + \sum_{l=1}^m U(|Z_{ij}| - |Z_{lj}|)$, where $U(a) = 1$ if $a > 0$, $U(a) = 1/2$ if $a = 0$, and $U(a) = 0$ otherwise. The randomization distribution corresponding to $\mathbf{T}^{(\text{obs})}$ is given by the distribution of $\mathbf{T} = (T_1, \dots, T_g)$ conditional on $\{R_i^{(j)}, i = 1, \dots, m; j = 1, \dots, g\}$ where $T_j = \sum_{i=1}^m \delta_i R_i^{(j)} \text{sign}(Z_{ij})$, $j = 1, \dots, g$ and $\delta_1, \dots, \delta_m$ are i.i.d. random variables each taking on the values +1 and -1 with probability 1/2. The multivariate signed rank test statistic W_m corresponding to \mathbf{T} is

$$W_m = \mathbf{T} \mathbf{U}^{-1} \mathbf{T}' / m \quad (6)$$

where the matrix \mathbf{U} is defined by $U_{jj} = \sum_{i=1}^m [R_i^{(j)}]^2 / m$, $j = 1, \dots, g$, and $U_{jk} = \sum_{i=1}^m R_i^{(j)} R_i^{(k)} \text{sign}(Z_{ij}) \text{sign}(Z_{ik}) / m$; $j \neq k = 1, \dots, g$.

It is shown in Puri and Sen (1971), Theorem 4.4.2, that W_m converges in law to a χ_g^2 distribution as $m \rightarrow \infty$.

2.2 Unbalanced Designs

We now consider the case of an arbitrary number of subunits per cluster (g_i). In the case of an unbalanced design, the signed rank statistic in (2) can also be written in the form

$$T_c^{(\text{obs})} = \sum_{i=1}^m g_i \bar{S}_i, \quad \text{where } \bar{S}_i = S_{i+} / g_i.$$

However, in the unbalanced setting, our simulations in Table 1 show that it may be more efficient to consider a possible alternative stratified statistic given by

Table 1

Simulation study—estimated type I error, and power of clustered Wilcoxon signed rank statistic, ordinary signed rank statistic, and multivariate signed rank statistic, 4000 replications per cell

Design ^a	m ₂ ^b	m ₄	m ₈	ρ	T _c				T			
					0.05	0.2	0.5	0.8	0.05	0.2	0.5	0.8
1	20	0	0	$\hat{\alpha}^c$	0.045	0.043	0.047	0.054	0.051	0.046	0.046	0.051
				Power ^d	0.407	0.367	0.304	0.267	0.407	0.359	0.299	0.260
1M ^e	20	0	0	$\hat{\alpha}$	0.043	0.043	0.044	0.044				
				Power	0.288	0.259	0.221	0.182				
2	0	20	0	$\hat{\alpha}$	0.041	0.045	0.046	0.048	0.046	0.042	0.045	0.045
				Power	0.645	0.505	0.357	0.277	0.632	0.501	0.351	0.272
3	0	0	20	$\hat{\alpha}$	0.048	0.048	0.046	0.046	0.048	0.048	0.046	0.046
				Power	0.868	0.639	0.391	0.282	0.847	0.624	0.375	0.275
4 ^f	10	10	0	$\hat{\alpha}$	0.044	0.044	0.050	0.048	0.047	0.048	0.053	0.049
				Power	0.523	0.431	0.324	0.263	0.512	0.429	0.320	0.261
4U	10	10	0	$\hat{\alpha}$	0.043	0.044	0.047	0.049				
				Power	0.524	0.425	0.308	0.248				
5	10	0	10	$\hat{\alpha}$	0.044	0.046	0.048	0.053	0.046	0.046	0.049	0.051
				Power	0.679	0.511	0.358	0.277	0.606	0.479	0.344	0.269
5U	10	0	10	$\hat{\alpha}$	0.042	0.044	0.048	0.049				
				Power	0.665	0.470	0.288	0.208				
6	20	0	0	$\hat{\alpha}$	0.045	0.045	0.047	0.046	0.044	0.046	0.046	0.054
				Power	0.388	0.351	0.300	0.256	0.380	0.342	0.297	0.255
7	20	0	0	$\hat{\alpha}$	0.041	0.043	0.047	0.055	0.047	0.046	0.047	0.051
				Power	0.402	0.361	0.302	0.263	0.394	0.354	0.296	0.261

^aDesigns 1–5 are based on continuous data with no ties; Design 6 is based on grouped data with many tied values (see text); Design 7 is based on nonexchangeable data (see text).

^bm₂ is the number of clusters with two paired difference scores; m₄, m₈ are defined similarly.

^cNominal $\alpha = 0.05$.

^dAnalyses from Designs 1–6 based on $H_{ij}^* = \text{sign}(H_{ij})\exp(|H_{ij}|)$, where $H_{ij} = T_i + e_{ij}$, $T_i \sim N(\delta, \rho)$, $e_{ij} \sim N(0, 1 - \rho)$, i = cluster, j = subunit, where $\delta = 0$ for the type I error analyses and $\delta = 0.3$ for the power analyses; see text for specification of Design 7.

^eThe data from Design 1 were reanalyzed in Design 1M using the multivariate signed rank test.

^fDesigns 4 and 5 were analyzed using the weighted clustered signed rank statistic, $T_{c,s}$; the same data were used in Designs 4U and 5U, but were reanalyzed using the unweighted clustered signed rank statistic, T_c .

$$T_{c,s}^{(\text{obs})} = \sum_{i=1}^m w_i \bar{S}_i, \quad (7)$$

where $w_i = 1/\text{Var}(\bar{S}_i)$ under H_0 . The randomization distribution corresponding to $T_{c,s}^{(\text{obs})}$ is given by the distribution of $T_{c,s}$ conditional upon $\bar{S}_1, \dots, \bar{S}_m$, where

$$T_{c,s} = \sum_{i=1}^m \delta_i w_i \bar{S}_i. \quad (8)$$

To derive w_i , we note that

$$\text{Var}(\bar{S}_i) = \text{Var}(S_{ij})[1 + (g_i - 1)\rho_s]/g_i, \quad (9)$$

where the intraclass correlation coefficient $\rho_s = \text{Corr}(S_{ij}, S_{il})$. We can estimate $\text{Var}(S_{ij})$ by $\sum_{i=1}^m \sum_{j=1}^{g_i} (S_{ij} - \bar{S}_i)^2/(G - 1)$. Also, we can estimate ρ_s by the intraclass correlation coefficient given by $\hat{\rho}_s = \max[\hat{\sigma}_A^2/(\hat{\sigma}_A^2 + \hat{\sigma}^2), 0]$, where $\hat{\sigma}^2 = \sum_{i=1}^m \sum_{j=1}^{g_i} (S_{ij} - \bar{S}_i)^2/(G - m)$, $\hat{\sigma}_A^2 = \max[\{\sum_{i=1}^m g_i (\bar{S}_i - \bar{\bar{S}})^2 / (m - 1) - \hat{\sigma}^2\}/g_0, 0]$, and $g_0 = [\sum_{i=1}^m g_i - \sum_{i=1}^m g_i^2 / \sum_{i=1}^m g_i] / (m - 1)$. Because $\hat{\rho}_s$ is known to be negatively biased in finite samples (Donner, 1986), we instead use the estimator of Olkin and Pratt (1958) given by

$$\hat{\rho}_{s,\text{cor}} = \hat{\rho}_s \left(1 + \frac{1 - \hat{\rho}_s^2}{m - 5/2} \right)$$

to estimate ρ_s . Thus, because $\text{Var}(\delta_i) = 1$, $i = 1, \dots, m$ we have

$$\text{Var}(T_{c,s}) = \sum_{i=1}^m w_i^2 \bar{S}_i^2. \quad (10)$$

We prove that $T_{c,s}$ is asymptotically normal as $m \rightarrow \infty$ if $1 < g_{\max} = \max_{i=1, \dots, m} g_i < \infty$ and if $\lim_{m \rightarrow \infty} m_g/m \rightarrow \xi_g$, where $0 \leq \xi_g \leq 1$, and $m_g =$ number of clusters with g subunits, $g = 1, \dots, g_{\max}$ (see *Biometrics* website for proof). Hence, we have the large sample test statistic

$$W_{c,s} = T_{c,s} \left/ \left(\sum_{i=1}^m \hat{w}_i^2 \bar{S}_i^2 \right)^{1/2} \right. \sim N(0, 1) \text{ under } H_0, \quad (11)$$

where $\hat{w}_i = g_i / [\widehat{\text{Var}}(S_{ij})\{1 + (g_i - 1)\hat{\rho}_{s,\text{cor}}\}]$.

The asymptotic two-tailed p-value equals $2 \times \{1 - \Phi(|W_{c,s}|)\}$. Note that (a) if $\hat{\rho}_{s,\text{cor}} = 0$, then \hat{w}_i is proportional to g_i ; (b) if $\hat{\rho}_{s,\text{cor}} = 1$, then $\hat{w}_i = 1/\widehat{\text{Var}}(S_{ij})$ for all $i = 1, \dots, m$; (c) if $g_i = g$ for all $i = 1, \dots, m$, then $\hat{w}_i = g / [\widehat{\text{Var}}(S_{ij})\{1 + (g - 1)\hat{\rho}_{s,\text{cor}}\}]$, which is the same for all $i = 1, \dots, m$. Under (c), $W_{c,s} = W_c$.

3. Simulation Study

The random variables T_c in (3) and $T_{c,s}$ in (8) are asymptotically normal as the number of clusters gets large.

Furthermore, the multivariate signed rank statistic W_m is asymptotically χ_g^2 if we have a balanced design with cluster size g . In this section, we present simulations to study the finite sample properties of these random variables.

There are three principal questions we wish to answer with our simulation studies. First, in finite samples how valid are the asymptotic properties of T_c , $T_{c,s}$, and W_m ? Second, what is the comparative power of the clustered Wilcoxon signed rank test versus either the ordinary signed rank test based on the average difference score over all replicates or the multivariate signed rank test? Third, what is the magnitude of inflation of type I error when clustering is present, if the standard signed rank test is used and the clustering is ignored?

3.1 Type I Error

To assess type I error of the test procedure in finite samples for a given number of clusters m and intraclass correlation ρ , we generate $H_{ij} = h_i + e_{ij}$, $h_i \sim N(0, \rho)$, and $e_{ij} \sim N(0, 1 - \rho)$, where $i = 1, \dots, m$; $j = 1, \dots, g_i$. It follows that $\text{Corr}(H_{ij_1}, H_{ij_2}) = \rho$. We then compute $H_{ij}^* = \text{sign}(H_{ij})\exp(|H_{ij}|)$ and refer to this distribution as the clustered signed log-normal distribution. This distribution is symmetric about zero, but has longer tails than a standard normal distribution. Thus, H_{ij}^* represents a paired difference score, where $H_{ij_1}^*$, $H_{ij_2}^*$ will in general be correlated for two subunits within the same cluster. For balanced designs (Table 1, Designs 1–3 and 6), we then computed the clustered signed rank statistic $T_c^{(\text{obs})}$ from (2) based on H_{ij}^* , its associated variance $\text{Var}(T_c)$ from (4), the test statistic W_c from (5), and the multivariate signed rank statistic W_m from (6) (Table 1, Design 1M).

For unbalanced designs (Table 1, Designs 4 and 5), we computed $T_{c,s}^{(\text{obs})}$, $\text{Var}(T_{c,s})$, and $W_{c,s}$ from (7), (10), and (11), respectively. We also computed $T_c^{(\text{obs})}$ by setting $w_i = g_i$ to assess the impact of weighting on the properties of the test statistic in unbalanced designs (Table 1, Designs 4U and 5U). For both balanced and unbalanced designs, we compared these tests with the ordinary signed rank test based on \bar{H}_i^* . We repeated each simulation 4000 times for each design (see Table 1) and each of four values of $\rho = 0.05, 0.2, 0.5$, and 0.8.

For each design and value of ρ , we computed the empirical type I error $\hat{\alpha}$ = empirical proportion of test statistics T_c which exceed the nominal critical value 1.96 (at a 5% significance level). Designs 1–3 are balanced designs with 20 clusters and $g = 2, 4$, and 8 subunits per cluster, denoted by $m_2 = 20$, $m_4 = 20$, and $m_8 = 20$, respectively. Design 4 (10 clusters of size 2, 10 clusters of size 4) and Design 5 (10 clusters of size 2, 10 clusters of size 8) are unbalanced designs. In Design 6, we relaxed the continuous data assumption, by creating balanced data from a continuous distribution as in Design 1 above with 20 clusters and two subunits per cluster, but then grouping the data into six groups determined by five percentiles of the standard normal distribution given by $-0.84, -0.25, 0, 0.25$, and 0.84 , which correspond to the 20th, 40th, 50th, 60th, and 80th percentiles of an $N(0, 1)$ distribution. The values used in the analysis were the median values from an $N(0, 1)$ distribution within each of the subgroups defined by the H_{ij} . Thus, we created grouped continuous data with six groups from the original 40 data points thereby creating a data set with many tied values.

Finally, in Design 7, to assess the impact of the exchangeability assumption, we used a similar design to Design 1, but set $H_{i1} = h_i + e_{i1}$ and $H_{i2} = (2)^{\frac{1}{2}}(h_i + e_{i2})$, $i = 1, \dots, 20$, where $h_i \sim N(0, \rho)$ and $e_{ij} \sim N(0, 1 - \rho)$ and then computed H_{ij}^* as given above. This preserves the symmetry and correlation structure of Design 1 under H_0 , but observations with large absolute values will tend to occur more often in H_{i2} (e.g., the left eye) than H_{i1} (e.g., the right eye). Note that the multivariate signed rank test is the same for Designs 1 and 7 because component-specific ranks are the same. Hence, the results for Design 1M also hold for Design 7 (see Table 1).

3.2 Power

To assess power, in Designs 1–6 we let $H_{ij} = h_i + 0.3 + e_{ij}$, where $h_i \sim N(0, \rho)$, $e_{ij} \sim N(0, 1 - \rho)$; in Design 7, we let $H_{i1} = h_i + 0.3 + e_{i1}$, $H_{i2} = (2)^{\frac{1}{2}}(h_i + 0.3 + e_{i2})$. For all designs we then computed H_{ij}^* as defined above.

The range of estimated type I errors for the clustered signed rank test is from 0.041 to 0.055 (mean = 0.047). For the ordinary signed rank test based on cluster means of paired difference scores, the range of estimated type I errors is from 0.042 to 0.054 (mean = 0.048). For the multivariate signed rank test (Design 1M), the range of estimated type I errors is from 0.043 to 0.044 (mean = 0.044). Thus, the asymptotic type I error for each procedure is appropriate for data sets with ≥ 20 clusters.

Regarding power for each design, the power decreased as the intraclass correlation ρ increased. Furthermore, as expected, for Designs 1–3 the power increased as the number of subunits per cluster increased. Power for the unbalanced designs (i.e., Designs 4, 5) was generally intermediate between the corresponding balanced designs (i.e., Designs [1, 2] and Designs [1, 3], respectively). Also, the power based on grouped data (Design 6) was slightly lower than the power for the comparable continuous data design (Design 1). For all balanced designs, power for the clustered Wilcoxon signed rank procedure tended to be slightly higher than for the ordinary signed rank procedure. Furthermore, power for the clustered Wilcoxon signed rank statistic (Design 1) was substantially higher than for the multivariate signed rank test (Design 1M). Similar results were also obtained for Designs 2 and 3 (data not shown). For unbalanced designs with low intraclass correlation, the weighted clustered signed rank statistic had considerably more power than the ordinary signed rank statistic (e.g., Design 5, $\rho = 0.05$; clustered signed rank test, power = 0.679; ordinary signed rank test, power = 0.606). Furthermore, for unbalanced designs with high intraclass correlation, the weighted clustered Wilcoxon signed rank statistic ($T_{c,s}$) had more power than the corresponding unweighted statistic (T_c) (Designs 4U, 5U) justifying the appropriateness of weighting according to the level of intraclass correlation. Finally, in Design 7, the impact of nonexchangeability was minimal for all three procedures considered compared with Design 1 with the clustered signed rank procedure retaining a superior power profile.

3.3 Impact of Clustering on Type I Error

Another issue that we investigated is the impact of clustering on the type I error of the standard signed rank procedure

Table 2
Simulation study—estimated type I error and variance of ordinary Wilcoxon signed rank test in the presence of clustering, nominal $\alpha = 0.05$, 4000 replications per cell

m		ρ			
		0	0.2	0.5	0.8
10	$\hat{\alpha}^a$	0.043 ^b \pm 0.003	0.098 ^b \pm 0.005	0.165 ^b \pm 0.006	0.228 ^b \pm 0.007
	C^c	1.00	1.38	1.96	2.57
20	$\hat{\alpha}$	0.049 \pm 0.003	0.097 ^b \pm 0.005	0.167 ^b \pm 0.006	0.227 ^b \pm 0.007
	C	1.00	1.38	1.97	2.60
50	$\hat{\alpha}$	0.050 \pm 0.003	0.096 ^b \pm 0.005	0.155 ^b \pm 0.006	0.216 ^b \pm 0.007
	C	1.00	1.37	1.94	2.54
100	$\hat{\alpha}$	0.056 \pm 0.004	0.099 ^b \pm 0.005	0.157 ^b \pm 0.006	0.215 ^b \pm 0.006
	C	1.00	1.39	1.94	2.51

^aEstimated type I error \pm SE.

^bSignificantly different from $\alpha = 0.05$ ($p < 0.05$).

^c $C = \{\sum_{i=1}^{4000} (T_i - \bar{T})^2 / 3999\} / \{G(G+1)(2G+1)/24\}$; C = design effect when $\rho > 0$, $C = 1.0$ when $\rho = 0$.

(Wilcoxon, 1945; Woolson, 1998). For this purpose, we simulated data as in Table 1 for each combination of the number of clusters $m = 10, 20, 50, 100$, and $\rho = 0, 0.2, 0.5$, and 0.8 with $g = 3$ subunits per cluster, but analyzed the data as if all observations were independent using the standard signed rank test (i.e., $\rho = 0$). For each simulation, we computed the empirical type I error and the C statistic, which equals the ratio of the empirical variance divided by the theoretical variance estimate based on the signed rank test. The results are given in Table 2.

We see that in the absence of clustering ($\rho = 0$), the type I error ranges from 0.043 to 0.056 and the C statistic is 1.0. However, in the presence of clustering ($\rho > 0$), the type I error ranges from 0.09 to 0.10 for $\rho = 0.2$, from 0.15 to 0.17 for $\rho = 0.5$, and from 0.21 to 0.23 for $\rho = 0.8$. The corresponding C statistics range from 1.3 to 1.4 for $\rho = 0.2$, from 1.9 to 2.0 for $\rho = 0.5$, and from 2.5 to 2.6 for $\rho = 0.8$. Thus, the clustering has a substantial impact on the type I error and variance estimate which invalidates the use of the standard Wilcoxon signed rank test even if the intraclass correlation is as low as 0.2.

4. Examples

4.1 Results of a Surgical Intervention on Retinal Function of RP Patients

We apply the methods in this article to data from patients with RP who voluntarily underwent a nonrandomized nonmasked intervention in Cuba that consisted of a surgical intervention whose intent was to increase blood flow to the degenerating retina. In addition, patients had electrical stimulation applied to various parts of their body for 4 days and had their blood drawn, ozonated, and reintroduced intravenously on multiple days during the period. Because some patients reported improvement in vision, the present study was undertaken where 10 RP patients who were planning to participate in the Cuba protocol, volunteered to be examined at the Berman Gund Laboratory, Massachusetts Eye and Ear Infirmary, both 3 months before and 3–5 months after the Cuba intervention. A more complete description of the study protocol is given in Berson et al. (1996). Here we present the

electroretinogram (ERG) data before and after the intervention. The ERG amplitude is a measure of retinal function with an average amplitude in normal subjects of about 50 μ V; in RP patients, the amplitude declines over time and is usually $<10 \mu$ V and sometimes $<1 \mu$ V, the latter of which is often accompanied by legal blindness. Because the distribution of ERG is almost always positively skewed, the data are usually represented in the log_e scale (see Table 3).

A signed rank test is reasonable here due to the possible skewness and the small sample size. One might perform this analysis by averaging paired difference scores (i.e., after intervention score minus before intervention score) over both eyes and using the ordinary signed rank test based on the person as the unit of analysis. This yields an exact two-sided randomization test p -value of 0.014. Because outlying values may have an undue influence on the cluster averages resulting in a possible loss of power, we also conducted the analysis using the clustered signed rank test based on the eye as the unit of analysis. Because the design was balanced and the number of clusters was small, we generated the exact randomization distribution based on (3), which consists of $2^{10} = 1024$ possible outcomes. The observed value of T_c was -141. From the randomization distribution, the exact p -value equals $2 \times \Pr(T_c \leq -141) = 2(3/1024) = 0.006$. In addition, we performed the exact multivariate signed rank test based on W_m in (6) over the 2^{10} possible outcomes (Puri and Sen, 1971) and obtained an exact p -value = 0.029. Thus, ERG amplitude significantly declined after the intervention. Unfortunately, there was not an untreated control group for comparison purposes. Nevertheless, the results indicate that after taking the clustering effects into account, the Cuba intervention did not stabilize or improve the retinal function of these patients as was hoped.

4.2 Compliance with Dietary Intake in a Clinical Trial of Nutritional Supplements in Patients with RP

A randomized 2×2 factorial double-blind clinical trial was previously performed among 601 patients with RP (Berson et al., 1993). Patients were randomized to receive either 15,000 IU or 75 IU of vitamin A daily and to receive either 400 IU or 3 IU of vitamin E daily in a factorial design. The trace doses of each of these supplements (75 IU daily of vitamin A and

Table 3
ERG 30-Hz amplitude in patients with RP over 6 to 8 months before and after an intervention in Cuba

Patient	Eye ^a	ERG 30-Hz amplitude (μV) before intervention	ERG 30-Hz amplitude (μV) after intervention	Change score ^b	Signed rank for each eye (S_{ij})	Mean change score ^c	Signed rank of mean change score over both eyes (S_i)	Multivariate signed rank test
1	R	9.80	7.60	-0.254	-13.5	-0.238	-8	
	L	8.12	6.50	-0.223	-9.0			
2	R	2.03	2.00	-0.015	-1.0	-0.085	-3	
	L	2.45	2.10	-0.154	-2.5			
3	R	1.12	0.91	-0.208	-8.0	-0.215	-6	
	L	1.05	0.84	-0.223	-10.0			
4	R	6.50	5.32	-0.200	-6.0	-0.227	-7	
	L	6.86	5.32	-0.254	-13.5			
5	R	0.11	0.13	+0.167	+4.0	-0.037	-1	
	L	0.14	0.11	-0.241	-11.5			
6	R	0.31	0.24	-0.256	-15.0	+0.090	+4	
	L	0.11	0.17	+0.435	+19.0			
7	R	0.25	0.14	-0.580	-20.0	-0.376	-10	
	L	0.19	0.16	-0.172	-5.0			
8	R	0.13	0.09	-0.368	-18.0	-0.365	-9	
	L	0.23	0.16	-0.363	-17.0			
9	R	1.47	1.26	-0.154	-2.5	-0.179	-5	
	L	1.89	1.54	-0.205	-7.0			
10	R	0.11	0.14	+0.241	11.5	-0.048	-2	
	L	0.07	0.05	-0.336	-16.0			
T exact randomization test					-141.0			
p-value (2-tail)					0.006	-47	0.014	0.029

^aR = right eye, L = left eye.

^bChange score = $\ln(\text{ERG 30-Hz amplitude } (\mu V) \text{ after intervention}) - \ln(\text{ERG 30-Hz amplitude } (\mu V) \text{ before intervention})$.

^cMean change score = {change score^b (R) + change score^b (L)}/2.

3 IU daily of vitamin E, respectively) were considered too low to have any physiologic significance. The patients were followed each year up to a maximum of 6 years. However, due to staggered enrollment and missed visits the actual number of follow-up visits ranged from one to six with most patients having four to six follow-up visits. There was one patient with no follow-up data. In addition, there were 20 patients with invalid or missing dietary data either at baseline ($N = 11$) or at all follow-up visits ($N = 9$). Thus, this left 580 patients available for analysis.

The outcome variable for the study was the rate of decline of ERG 30-Hz amplitude over time, a measure of the electrical activity in the retina. Because this was a study of nutritional supplements, the patients were told not to take single vitamin E supplements (e.g., vitamin E pills) and were instructed to maintain a diet during follow up that was similar to the baseline diet. Thus, to monitor compliance with these instructions, we compared vitamin E intake (from diet and vitamin E pills outside the study) at each follow-up visit with vitamin E intake at the baseline visit using a food frequency questionnaire (FFQ). Specifically, we computed the difference scores $d_{ij} = E_{ij} - E_{i0}$, $j = 1, \dots, 6$, where E_{ij} = vitamin E intake at the j th follow-up visit and E_{i0} = vitamin E intake at baseline and tested the hypothesis $H_0 : d_{ij}$ is symmetric about 0 versus $H_1 : d_{ij}$ is symmetric about γ for some $\gamma \neq 0$.

The distribution of vitamin E intake is highly variable for some individuals due to variation in food intake, sporadic multivitamin intake, and occasional proscribed single vitamin E intake at some, but not necessarily all visits. A sample of the

data from 15 patients in one treatment group is shown in Table 4.

Due to the grossly nonnormal distribution of the difference scores, a signed rank test is indicated to test the above hypothesis. However, due to the correlated paired difference scores for the same subject over time and the variable number of follow-up visits per subject, the weighted clustered signed rank test for unbalanced designs based on (11) was used. The results both for each treatment group and overall are shown in Table 5.

The results indicate a slight decline in vitamin E intake after baseline. However, there was no significant change in vitamin E intake over the course of the study within each treatment group, but a borderline significant effect when all treatment groups are combined ($p = 0.052$). Furthermore, we can describe the degree of clustering in terms of the intraclass correlation ($\hat{\rho}_{s,cor}$). We see that the intraclass correlation ranges from 0.486 to 0.560 over the four treatment groups indicating substantial clustering of the follow-up visit-specific difference scores within an individual. Thus, the clustered signed rank test is very appropriate for these data.

5. Discussion

We have considered the problem of incorporating clustering effects for the Wilcoxon signed rank test when the sub-units within a cluster are exchangeable for either balanced or unbalanced designs. Our test procedure is based on a randomization test approach where the unit of randomization is the cluster, while the unit of analysis is the paired

Table 4
Sample of vitamin E intake (IU per day) from 15 patients in the RP clinical trial

Subject	Baseline	Visit					
		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
1	5.9	3.8	9.8	6.2	6.6	4.9	5.0
2	6.5	7.1	7.7	7.0	7.0	7.2	6.4
3	7.1	6.8	5.8	4.6	6.6	5.9	3.7
4	4.5	3.7	6.4	3.2	3.1	4.9	3.2
5	8.2	7.6	7.3	5.0	11.1	—	—
6	7.0	9.8	5.4	7.0	7.9	208.6	113.3
7	155.8	158.0	157.4	6.0	5.9	6.8	6.0
8	5.6	11.6	7.1	8.6	6.4	—	9.4
9	5.3	7.4	6.5	6.1	5.0	6.4	—
10	5.9	6.1	9.3	7.9	9.6	8.6	—
11	5.9	5.1	3.8	4.3	7.4	5.3	—
12	6.4	12.0	7.0	12.7	7.9	5.9	—
13	5.1	5.4	4.2	5.4	7.2	4.2	—
14	5.6	4.0	7.5	6.2	9.7	7.5	—
15	7.5	10.9	12.2	11.8	9.9	—	—

difference score for the subunit within the cluster. Both a large sample and a small sample approach were considered. We tested the validity of the large sample test in finite samples using simulation studies. Based on the simulation studies, the large sample approach was shown to yield appropriate type I errors and variance estimates when the number of clusters is ≥ 20 for either balanced or unbalanced data both in the presence or absence of ties. However, ignoring the clustering, even for intraclass correlations as low as 0.2, resulted in invalid type I errors and variance estimates that were too low.

5.1 Comparison with the Multivariate Signed Rank Test

Our simulations show that the clustered signed rank test appeared to provide more power in balanced designs than traditional multivariate signed rank methods where the vector of component-specific signed rank statistics (all of which must be nonzero) is treated as an outcome variable (Puri and Sen, 1971). Also, traditional multivariate methods cannot be used either in unbalanced designs or in balanced designs, where the subunits within a cluster are not distinguishable (e.g., family data) and one wishes to compute ranks over all subunits over all clusters rather than for specific components of the vector of outcomes. Furthermore, the clustered Wilcoxon signed

rank test had appropriate type I error and higher power than the multivariate signed rank test even in the setting of nonexchangeable clustered designs.

5.2 Comparison with the Ordinary Signed Rank Test

Another possible approach is to average paired difference scores within a cluster (e.g., average posttreatment minus pre-treatment score over two eyes of an individual) and perform the Wilcoxon signed rank test based on the averages using the cluster as the unit of analysis. For balanced data, this may result in a slight loss of power if the number of subunits per cluster is large and/or if the intraclass correlation is low. For unbalanced data, this method treats each average cluster difference score as identically distributed while cluster averages would be expected to have a lower variance as the number of cluster members increases. Indeed, in our simulation studies, the clustered signed rank test was shown to have substantially more power than the ordinary signed rank test based on cluster means in unbalanced designs when the intraclass correlation was low. Furthermore, averaging of nonzero subunit difference scores may result in a zero average cluster difference score, thus obviating the use of this cluster with the usual implementation of the Wilcoxon signed rank test, where zero scores are excluded.

Table 5
Analysis of vitamin E change scores by treatment group using the clustered Wilcoxon signed rank test^a

Treatment group	Vitamin A (IU/day)	Vitamin E (IU/day)	$W_{c,s}$	p-value	$\hat{\rho}_{s,cor}$	Number of subjects (m)	Number of visits (G)
1	15,000	3	-0.446	0.66	0.537	142	748
2	75	400	-1.355	0.18	0.486	153	790
3	15,000	400	-0.455	0.65	0.517	143	730
4	75	3	-1.598	0.11	0.560	142	724
Overall			-1.944	0.052	0.522	580	2992

^aThe units of analysis are the paired difference scores reflected in the change in vitamin E intake from baseline to each respective follow-up visit.

The average paired difference score approach is also presented in Donner and Klar (2000), where, for example, a pair of classrooms in the same school (j) may be randomized with one classroom (classroom A) receiving active treatment and the other classroom (classroom B) receiving placebo treatment. The mean difference score $\bar{Y}_{Aj} - \bar{Y}_{Bj}$ is computed for each school and the signed rank test is computed using the school as the unit of analysis. Note that it is not possible to compute difference scores for individual cluster members (i.e., children) because a child receives only one treatment. In the ophthalmologic setting presented in this article, the right eye score before and the right eye score after represent matched subunits, and this matching enables one to compute ranks for difference scores of individual cluster members (i.e., eyes). Another advantage of the proposed method is that the large sample procedures in this article are very trivial computationally, can be easily implemented with standard software (e.g., SAS PROC RANK), and are appropriate for balanced or unbalanced exchangeable data, both in the presence or absence of ties. SAS macros to implement the methods in this article are available on the *Biometrics* website (<http://www.tibs.org/biometrics>).

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APPENDIX

Visit the official website of *Biometrics* at <http://www.tibs.org/biometrics>.

Change in convergence and accommodation after two weeks of eye exercises in typical young adults

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BACKGROUND

Although eye exercises appear to help heterophoria, convergence insufficiency, and intermittent strabismus, results can be confounded by placebo, practice, and encouragement effects. This study assessed objective changes in vergence and accommodation responses in naive young adults after a 2-week period of eye exercises under controlled conditions to determine the extent to which treatment effects occur over other factors.

METHODS

Asymptomatic young adults were randomly assigned to one of two no-treatment (control) groups or to one of six eye exercise groups: accommodation, vergence, both, convergence in excess of accommodation, accommodation in excess of convergence, and placebo. Subjects were tested and retested under identical conditions, except for the second control group, who were additionally encouraged. Objective accommodation and vergence were assessed to a range of targets moving in depth containing combinations of blur, disparity, and proximity/looming cues.

RESULTS

A total of 156 subjects were included. Response gain improved more for less naturalistic targets where more improvement was possible. Convergence exercises improved vergence for near across all targets ($P = 0.035$). Mean accommodation changed similarly but nonsignificantly. No other treatment group differed significantly from the nonencouraged control group, whereas encouraging effort produced significantly increased vergence ($P = 0.004$) and accommodation ($P = 0.005$) gains in the second control group.

CONCLUSIONS

True treatment effects were small, significantly better only after vergence exercises to a nonaccommodative target, and rarely related to the response they were designed to improve. Exercising accommodation without convergence made no difference to accommodation to cues containing detail. Additional effort improved objective responses the most. (J AAPOS 2014;18:162-168)



Orthoptic exercises for convergence insufficiency, heterophoria, and intermittent strabismus have been in use for over 70 years.¹ They may involve intensive, clinic-based vision training or simpler, home-based, exercises. Orthoptists have generally adopted less intensive methods over the decades, while “vision therapy” textbooks and some branches of optometry continue to support intensive therapy.² The lack of strong evidence was identified by the Convergence Insufficiency Treatment Trial (CITT) Group in designing a large multicenter trial³ comparing the effects of different treatment regimens on

convergence insufficiency, a condition where most professionals agree that exercises are effective. Studies clearly suggest that children receiving office-based therapy had the best outcome⁴⁻¹⁰ compared to home-based methods; however, despite great efforts in the study design, true treatment effects and particularly the added benefit of therapist encouragement on simple exercises, could have accounted for apparent additional improvements in patients receiving intensive office therapy. Recently, Fray¹¹ has remarked on the many uncertainties and inconsistencies concerning the effects of different testing methods and instruction sets among clinicians as well as the level of alertness in participants.

Research concentrates on relief of symptoms,^{3,12} but symptomatic improvement could also be due to placebo effects, without changes in ocular responses. It is therefore unclear how exercises influence *objective* changes in accommodation and convergence. Some evidence suggests that accommodation and proximity responses are less susceptible to training than convergence^{13,14} and that vergence change may mediate accommodation change.¹⁵ It is unknown whether accommodation exercises improve only accommodation, convergence via the accommodative convergence/accommodation (AC/A) linkage, or neither, and whether exercises that stress vergence in excess of accommodation (or vice versa) are more effective than those

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that stress them in their natural relationship, or than those that only stress one system.

This study aimed to assess objective changes produced by short courses of different exercises, with particular attention to the relative influence of practice, placebo, and encouragement effects, which are not well researched, even in normal populations.¹⁵⁻¹⁸ In view of the paucity of normative data by which to judge the CITT and other vision therapy studies, we performed a baseline study on typical young adults. Our previous work¹⁹ found that disparity drives the majority of convergence and accommodation. Accordingly, we expected that exercises based on enhancing the response to disparity would be more effective than those based on blur resolution. We also have evidence that hypo-accommodation is common for naturalistic targets if clarity is not stressed; thus we predicted that exercises stressing the importance of clarity might improve accommodation.¹⁹

Methods

This study adhered to the Declaration of Helsinki, and no objections were raised by the University of Reading Research Ethics Committee. Full methodological details are provided in e-Supplement 1 (available online at jaapos.org) and summarized below.

Participants were recruited from university students 18–25 years of age who considered themselves to have “normal” eyes, aside from spectacles < ±4.00 D. None had a history of past ocular treatment or had taken part in prior vision research. Volunteers were excluded if they had significant ocular symptoms (≥ 16 on an adjusted CISS questionnaire⁷) and if orthoptic examination revealed any abnormality, such as manifest strabismus, exophoria $> 6^\Delta$ or esophoria $> 1^\Delta$, any vertical deviation, convergence poorer than to 8 cm, or a low fusion range ($< 25^\Delta$ base-out and 10^Δ base-in for near). Participants were informed that we were investigating how different types of eye exercises affected focusing in comparison to practice/repetition effects. They were not told that we were also investigating placebo treatment and effort effects.

Two testing sessions were carried out 10–18 days apart, with 98% of tests exactly 2 weeks apart and at the same time of day. Testing was carried out wearing any current refractive correction (glasses or contact lenses). At both visits, participants were tested by the same researcher, who was masked to the treatment group allocation, except for those in the effort group, who were given extra encouragement, so masking was not possible. Scoring of laboratory data was carried out masked to participant identity and treatment group allocation.

Remote Haploscopic Photorefractor

The examination method has been described in detail elsewhere.¹⁹ Briefly, all participants watched the target being presented on a video monitor via a two-mirror optical system, while a PlusoptixXS04 PowerRefII photorefractor (Plusoptix GmbH, Nuremberg, Germany) collected simultaneous eye position and refraction measurements (Figure 1).

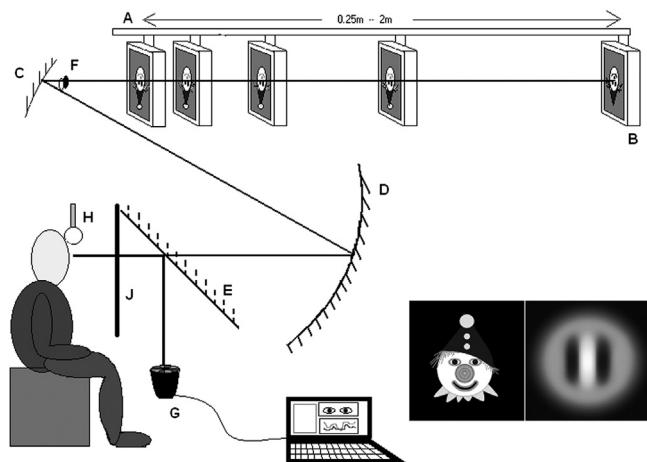


FIG 1. The remote haploscopic videorefractor. The two targets (brightly colored clown target or Gabor image were designed to maximize or minimize blur cues, respectively). *A*, motorized beam. *B*, target monitor, moving between fixation distances. *C*, upper concave mirror. *D*, lower concave mirror. *E*, “hot” mirror. *F*, image of subject’s eye, where occlusion takes place. *G*, Plusoptix S04 PowerRef II. *H*, headrest. *J*, black cloth screen, which can be raised to occlude the target when required.

Table 1. Target cue conditions. Target presented in the different cue conditions: *b*, blur present in cue; *d*, disparity present; *p*, proximity/looming present; *o*, minimal cue condition

Stimulus	Target		
	Disparity	Blur	Proximity
Blur + proximal + disparity (bdp)	Both eyes open	Clown	Unscaled
B removed (dp)	Both eyes open	Gabor	Unscaled
D removed (bp)	Occluded	Clown	Unscaled
P removed (bd)	Both eyes open	Clown	Scaled
B only (b)	Occluded	Clown	Scaled
D only (d)	Both eyes open	Gabor	Scaled
P only (p)	Occluded	Gabor	Unscaled
None (o)	Occluded	Gabor	Scaled

We could manipulate blur (B) by using a detailed clown cartoon or a blurry Gabor patch target to present or minimize detail cues. Disparity cues (D) were available by allowing binocular fixation, or could be prevented by occluding half of the upper mirror. Proximity/looming (P) cues were available if the participant watched the same target moving between fixation distances, or could be minimized by screening the monitor as it moved and scaling the target so that it subtended the same visual angle at each position. Thus 8 different target conditions representing all combinations of presence or absence of these cues were possible (Table 1). All other aspects of the data collection and testing paradigm were identical.

Instructions were minimal so that we could assess responses in as naturalistic manner as possible. In the all-cue, naturalistic (BDP) condition many asymptomatic participants would be expected to show excellent responses, with little room for improvement (a ceiling effect), at least for vergence. But as cues were

Table 2. Exercise regimens carried out three times a day for five minutes

Group	Skill manipulated	Target	Exercise	Subject end point
Blur	Accommodation only; blur independent of disparity	Detailed	Monocular push-ups Monocular near /distance “jump” accommodation Monocular accommodation facility (+2/-2D [near], 0/-2D [distance] lens flippers)	Blur
Both	Accommodation and convergence in normal relationship	Detailed	Binocular push-ups Binocular “jump” vergence/accommodation Near/distance physiological diplopia	Blur or diplopia
Disparity	Vergence independent of accommodation	Gabor image	Binocular push-ups Binocular “jump” vergence Near & distance vergence facility (12 ^A BO/4 ^A BI prism flippers)	Diplopia
Conv+	Convergence in excess of accommodation	Detailed	Binocular push-ups (+2.0 D or 12 ^A BO) Binocular near accommodation facility(0/+2.0 D)	Blur or diplopia
Accom+	Accommodation in excess of convergence	Detailed	Binocular near & distance vergence facility (0/12 ^A BO) Binocular push-ups (-2.0 D or 12 ^A BI) Binocular near and distance accommodation facility (0/-2.0 D)	Blur or diplopia
Motion (placebo)	Attention, motion detection, proprioception	Visual illusions; physical objects	“Snakes illusion”: max/ min moving Necker cube: perceptual shift Yoked prisms: visually directed reach with / without prisms	
Nil Effort	Practice, test-retest Tester, instruction set, effort		None None	

removed, we expected to be able to detect more changes in the reduced accommodation and vergence responses that these “im-poverished” targets typically produce, and that these responses might be specific to the exercise regime. We wanted to determine whether an exercise targeting just blur or just disparity helped responses to accommodation or vergence differentially or overall. On each visit measurements were repeated twice in a counterbalanced order, with an orthoptic testing session between the measurement periods.

Accommodation response in diopters and vergence in meter angles were calculated from the raw data, corrected for measured angle lambda, interpupillary distances and any spectacle magnification.

Exercises

After the initial testing session, each participant was randomly allocated to one of 8 experimental groups by a second researcher masked to test results (Table 2). If exercises were given they were to be done 3 times daily for 5 minutes.

Orthoptic exercises were administered specifically to target: (1) blur, that is, blur awareness and accommodation but not disparity awareness or vergence; (2) both, or use of maximal vergence and blur awareness in a balanced (naturalistic) relationship; (3) disparity, that is, vergence and disparity awareness independent of blur/clarity; (4) “conv+,” that is, convergence in excess of accommodation (positive relative convergence or negative relative accommodation); (5) “accom+,” that is, accommodation in excess of convergence (positive relative accommodation or negative relative vergence); or (6) motion, or placebo “treatments” that did not exercise the vergence or accommodation systems, involving atten-

tion, motion detection, and proprioception. There were two no-treatment groups: (7) “nil,” to assess practice and repetition effects; and (8) “effort,” a no-exercise group that at the second testing session was exhorted to maximum effort.

Participants in each group were told what their exercises were for, shown how to do them, and asked to demonstrate to the researcher what they had been taught. The importance of honesty in reporting missed exercise sessions was stressed and diaries and cell phone alarms were used to aid adherence to the protocol.

Analysis

Data analysis was carried out using Excel and SPSS version 18 (SPSS, Chicago, IL). Three-way mixed ANOVA was performed with cue (8 levels) and response (vergence or accommodation) as within-groups factors and treatment group (8 levels) as a between-groups factor. Post hoc testing used two-way ANOVA and *t* tests with appropriate correction for multiple comparisons. In view of the multiple measures we obtained, in this paper we report the change in calculated convergence and accommodation response gain between first and second testing sessions as well as responses in meter angles and diopters at 33 cm, which was the fixation distance where most changes were found. A gain of 1.0, and 3 meter angles of convergence and 3.0 D of accommodation at 33 cm, indicate appropriate responses to target distance.

Results

Data from 156 participants were analyzed, and each group included 17-21 participants; 14 additional participants were excluded because they showed evidence of mild convergence insufficiency according to the strict CITT

criteria,⁴ despite denying any symptoms, and a further 2 were excluded because lid or eyelash configuration prevented collection of photorefraction data. Two participants who admitted by email that they had not done any exercises were re-allocated to one of the no-treatment groups without breaking the masking of the tester to group allocation.

Informal examination of exercise diary sheets showed no systematic differences between groups, although some individuals had been more assiduous in completing them than others. As objective confirmation of adherence to the regimes could not be further verified, we were unable to analyze this further.

There were no statistically significant differences in range of refractive errors, heterophoria or initial fusion ranges between the 8 groups. Reduced gain (flatter stimulus/response slope) can be due to poor response for near or overresponse in the distance (or both). To investigate this, we analyzed the responses at 33 cm and 2 m. No differences at 2 m approached significance ($P > 0.4$ in all comparisons); thus the changes in gain represent alterations in responses to the closer targets.

Figure 2 illustrates that most improvements in gain occurred for targets containing fewer cues. The majority of the participants performed near optimally (at ceiling) to the all-cue BDP condition even before exercises, with a mean vergence gain of 1.00 ($\pm 95\% \text{ CI}, 0.04$) and vergence response of 3.01 meter angles at 33 cm. There was concurrent accommodative lag of 0.73 D at 33 cm, with mean accommodative gain of 0.75 ($\pm 95\% \text{ CI}, 0.05$). Before treatment, mean vergence and accommodation gains were reduced to all other targets. Therefore, the gains in response to these targets had more potential to improve with exercise.

A three-way mixed ANOVA of the within-subjects improvements showed significant differences between groups ($F[7,148] = 3.29, P = 0.003$) as well as the differences between cues which we typically find in all our studies ($F[7,148] = 4.75, P = 0.0002$), and a significant cue \times group \times response interaction ($F[49,148] = 1.4, P = 0.04$). Post hoc testing showed that, averaged across all the cues, both vergence and accommodation gain improved ($F[5,115] = 3.94, P = 0.002$) and ($F[5,115] = 3.42, P = 0.006$) and were not significantly different from each other (paired t test [155] = 0.53, $P = 0.5$). There was wider variance in accommodation change, reflecting the more variable accommodation responses overall (between visits and between and within individuals). **Figure 3** shows mean improvement in convergence and accommodation gain averaged across all the cues in the different treatment groups.

The small improvements in the nil group (practice/repetition effect) were then used as the baseline by which to judge the additional effects of treatment or effort.

Only the disparity and effort groups showed statistically significant differences from the nil group. The disparity group vergence gain ($t[37] = 2.19, P = 0.035$) improved,

but although the mean improvement in accommodation gain was similar, accommodation increases (particularly in the nil group) showed more variance and so differences did not reach significance ($t[37] = 1.20, P = 0.24$). Disparity exercises improved vergence responses by an average across cues of 0.35 meter angles (12%) and accommodation by 0.27 D (9%) at 33 cm.

The no-treatment effort group showed the greatest improvement in both vergence and accommodation ($t[38] = 3.10, P = 0.004$ for vergence, and $t[38] = 2.95, P = 0.005$ for accommodation). Mean vergence across all cues improved by 0.34 meter angles (11%) and accommodation by 0.46 D (15% of the total demanded by the target) at 33 cm, with the most effect seen for the more impoverished targets where responses were poorer at first.

Figure 4 illustrates the actual changes in vergence (in meter angles) and accommodation (in diopters) at 33 cm for each group and each cue, which may be of more practical significance to clinicians.

Although improvement in overall responses across cues were statistically significant, when broken down by cue, clear patterns were less evident. Disparity exercises improved vergence in the BD ($P = 0.02$) and DP ($P = 0.03$) conditions and marginally in the D condition ($P = 0.06$), that is, when disparity cues were available to be responded to, whereas they improved accommodation only in the BP condition ($P = 0.049$), when they were not available.

Accommodation exercises (the blur group, when participants had been specifically told to concentrate on clearing images for the past two weeks), did not result in mean accommodation for near improving at all (-0.004 D or -0.1%), with no significant differences between accommodation to the targets where detail was available (BDP, BD, BP, B) and those where it was not (DP, D, P, O). If accommodation exercises are effective we expected to find greatest effect from the blur group in the blur-only B condition (where responses are also typically poor, so with good potential for improvement) but accommodation to this target remained poor (gain improved by only 0.04 to 0.58 and accommodation at 33 cm improved only 0.17 D, remaining poor at 1.6 D). Effort alone, however, improved accommodation gain to this target by 0.21 to 0.57 and accommodation at 33 cm improved by 0.5 to 1.8 D.

When the effort group was compared to the nil group, there were improvements in gain across all cues, and these were most marked in the more impoverished targets, and more for accommodation than vergence (**Figure 4**), but after correction for multiple comparisons the only individually significant differences were for vergence in the BDP condition ($P = .02$), where 8 of the 21 participants (38%) overconverged by more than 10% and for accommodation gain in the BP ($P = 0.001$) and O ($P = 0.04$) conditions.

Although exercises stressing more convergence than accommodation (positive relative vergence/ negative relative accommodation) would be expected to lead to better convergence gain and responses for near than for

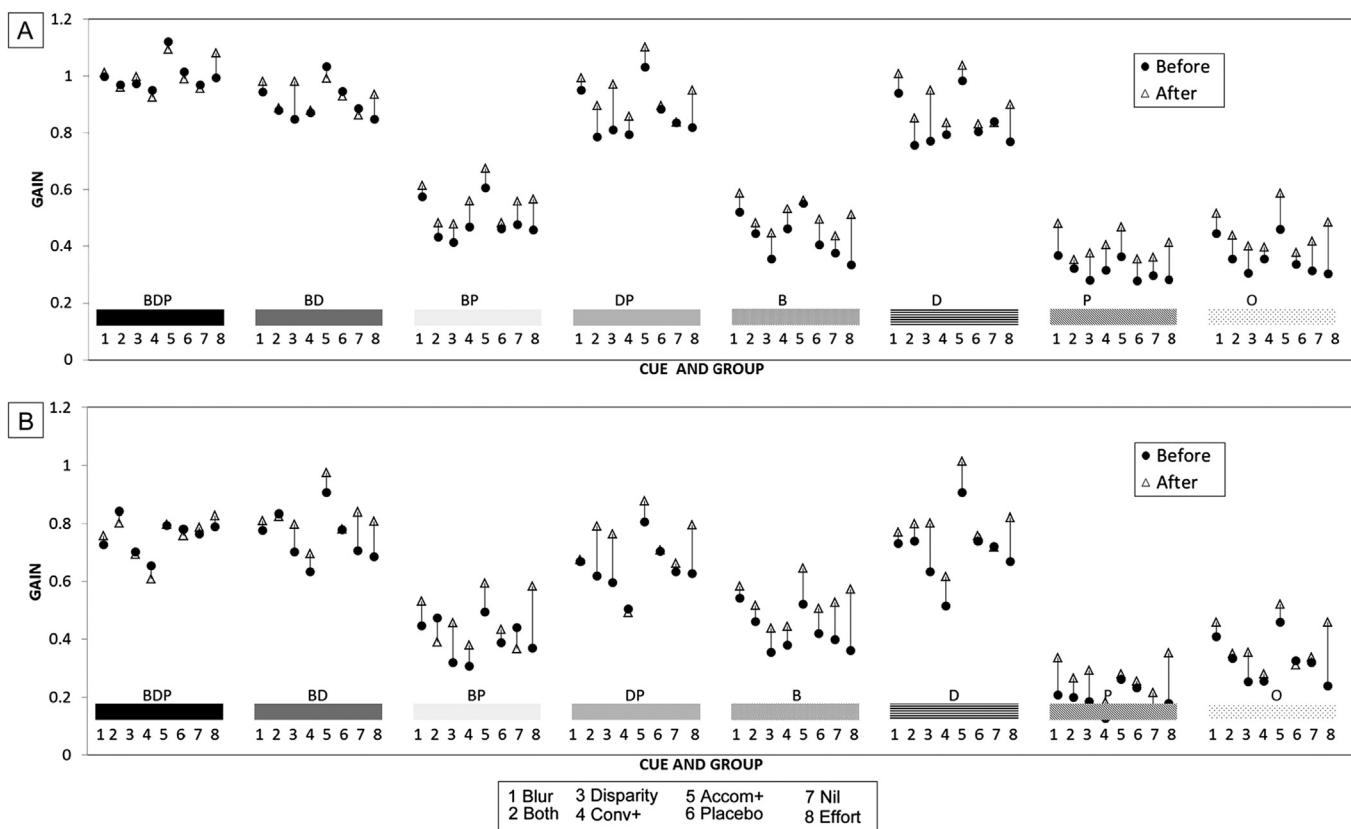


FIG 2. Response gain changes. Change in mean response gain according to cue condition (shaded sections on x-axis) and exercise group (lower text on x-axis) within cue condition A gain of 1.0 indicates perfect performance for target demand. *A*, Vergence gain change. In all cases above, reduced gain is due to underperformance for near. *B*, Accommodation gain change. *B*, blur available; *D*, disparity available; *P*, proximity/looming available; *O*, minimal cue condition.

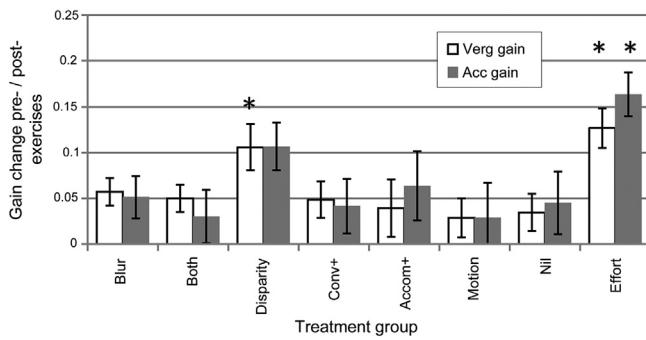


FIG 3. Mean improvement in gain across all cue conditions for the different treatment groups. Error bars denote standard error of the mean. An improvement in gain of 0.1 denotes approximately 0.3 D or 0.3 meter angles at 33 cm (approximately 2^{Δ} for an interpupillary distance of 6 cm). Asterisks denote significant differences from the nil (no treatment) group.

accommodation, and exercises stressing accommodation more than convergence (positive relative accommodation or negative relative vergence) would be expected to have the opposite effect, neither strategy made any significant

difference over the no treatment (nil) group. Although Figure 4 suggests small changes in the predicted directions, none approached statistical significance.

Discussion

This study investigated medium-term changes in naturalistic responses produced by 2 weeks of different types of exercises on objective measures of convergence and accommodation in typical young adults rather than on symptoms or clinical measures. It provides a normal dataset by which similar changes in patient groups can be judged.

While exercises appear effective, any good therapy uses motivational, effort, practice, and placebo effects that are difficult to quantify. It is important that health economists, patients, and parents accessing treatment recognize, understand, and identify the relative contribution of these factors. For example, the CITT trials⁴ showed that 35% of patients improved with office-based placebo therapy, indicating that placebo and encouragement effects were significant. The additional advantage that the CITT found of in-office therapy could be due to the additive effects of patients being taught the importance of effort in addition

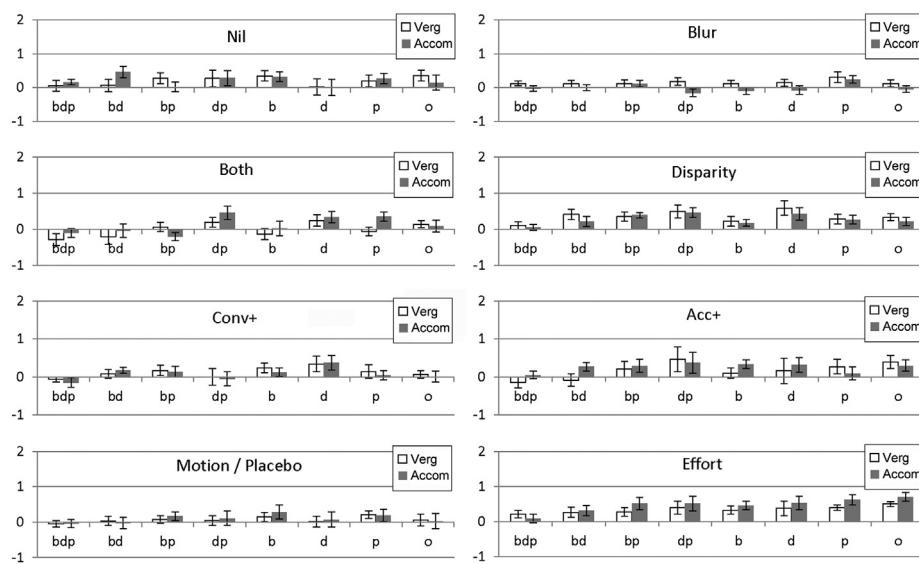


FIG 4. Change in responses at 33 cm after treatment. Convergence in meter angles (1 = approximately 6^{Δ} for average adults); accommodation in diopters. Stimulus: *bdp*, blur + proximal + disparity; *bd*, proximal removed; *bp*, disparity removed; *dp*, blur removed; *b*, blur only; *d*, disparity only; *p*, proximal only; *o*, none.

to the eye exercises themselves rather than the intrinsic superiority of the more specific or intensive therapeutic techniques. In our study, simple vergence exercises, independent of accommodation, were the most effective therapy; more complex manipulations of vergence and accommodation were less effective.

Unsurprisingly, the greatest treatment effects of vergence practice were found for the BD, DP, and D targets where disparity was available. These targets used reduced cues that produce reduced responses, and therefore, improvement was still possible. Mean accommodation improved as much as vergence with these exercises, and the failure to find statistical significance may be because there was more variability and slightly higher accommodation in the second visit, particularly for the control group.

Any treatment effect of concentrating on resolving blur was very small, if any. The largest improvement was found for the blurred P and O targets, so even when detail was available in any cue using the clown target (BDP, BD, BP, B), practicing and concentrating on clearing images made no difference to naturalistic responses to this detailed target. Blur exercises, placebo exercises, and no treatment had very similar effects.

The conv+ and accom+ and the both groups, all stressing concentration on clarity and single vision, did not produce better, or as good, responses as found in the disparity group, where clearing the target had been impossible. In our lab we repeatedly find that disparity is by far the strongest driver of responses. Thus finding that disparity exercises were the most effective was not surprising; however, it is unclear why stressing fusion independent of accommodation is better than exercising clarity and fusion. Although some exercises were possibly less demanding or less realistic than others,

we attempted to devise exercises demanding a similar amount of effort.

Even in this asymptomatic, typical, young adult population, where vergence in the most naturalistic condition was good (near ceiling), we still produced treatment effects, but they were small and often not very different from those found by just repeating the same tests on a second occasion. Effects in patient groups might of course differ, but this study provides a baseline with which to compare them. In clinical groups, where values are outside normal ranges, treatment-induced changes are likely to be greater. It is also possible that our treatment period was too short for changes in naturalistic behavior to be detected or that children might behave differently from adults.

We were not able to prove that participants had complied with the exercises, but there appeared to be no systematic between-group differences. Study participants were mostly science undergraduates, who would presumably appreciate the value of both obtaining and providing accurate data. They were told that we could still use their data if they had not practiced, as long as we knew before the second testing session. We also said that we expected that the laboratory data would tell us if they had cheated, although we were less confident that this would be the case.

The test-retest variability of the no-treatment control group (particularly for accommodation) may have hidden subtle effects. All groups except this nil group were encouraged to use some element of effort or attention either while doing exercises or during second testing, so might have been more consistent in their change in responses, as the overall patterns suggest (Figure 4), while the nil group received no instruction. Levels of effort on the second visit

in the nil control group could have varied more due to familiarity (less effort) or practice (more effort), respectively. Adler and colleagues¹⁸ found considerable inter-tester and within-subject accommodative variability, presumably tapping in to similar effects, in primary school children.

It is clear that the greatest influence in changing responses to an approaching target is how the participant was instructed and the amount of effort they exerted. This effect was more noticeable when there was more room for improvement for reduced-cue targets where habitual responses were poorer. Many individuals seemed happy to leave images blurred unless told to try to clear them. While this may not surprise those who deliver any form of therapy, if a specific exercise is to be assessed for effectiveness, then instructions and levels of effort expected should be identical before and after treatment. It may also be important that levels of alertness be assessed. Fray¹¹ has reported similar effects of encouragement in the testing of convergence amplitudes and found that lower levels of alertness affected fusion ranges. The additional benefit of in-office vision therapy is likely to be due to the patient getting more encouragement and reinforcement to try harder. Any claims for specific treatment effects must be considered in relation to this. In view of the importance of effort in comparison to true treatment effects of different exercises and the costs in terms of professional time, loss of schooling, and many office visits of a long course of in-office vision therapy, maximizing motivation and feedback strategies for less costly home exercises seems desirable.

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