Objective Assessment of Visual Dysfunction in the Acquired Brain Injury (ABI) Population Using the Visual-Evoked Potential (VEP)

Submitted by

Naveen Kumar Yadav

DISSERTATION

In partial satisfaction of the requirements for the degree of

Doctor of Philosophy
in
Vision Science

State University of New York
State College of Optometry

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Overall Dissertation Abstract

Purpose: To assess quantitatively and objectively selected visual dysfunctions in patients with mild traumatic brain injury (mTBI) (i.e., increased abnormal visual motion sensitivity (VMS), attentional deficits) and stroke (i.e., hemianopic visual field defects) by using empirically-derived, optimized pattern visual evoked potential (VEP) parameters derived from our laboratory. Furthermore, the goal was to develop simple and reliable clinical VEP protocols to assess the aforementioned visual dysfunctions in acquired brain injury.

Methods: Four experiments were performed binocularly with full refractive correction using an objective, pattern VEP technique. Experiments #1-3 included both visually-normal (VN) adults and adults with mTBI, all ages 18-70 years. Experiment #4 included adult patients with stroke and hemianopic visual field defects, all ages 18-70 years. The following tests and stimulus conditions were used in Experiments #1-4: Experiment #1 – central field VEP with 10, 20, and 40 min arc check sizes at low (20%) and high (85%) contrast levels; Experiment #2 – central field VEP (baseline), binasal occlusion only (BNO), base-in prism (BI) only (4 pd total), and BNO with 4 pd BI; Experiment #3 – central field VEP (eyes open (EO), baseline), eyes-closed (EC, "relaxed"), and eyes-closed number counting (ECNC, "increased attentional state"); Experiment #4 – central field VEP, intact hemi-field only, and hemianopic field only.

Results: The followings results were found: Experiment #1 – The 20 min arc check size provided the largest VEP amplitude and normative latency values at both contrast levels in both the VN and mTBI groups. These optimal parameters were then used to measure

VEP responses in Experiments #2-4. Experiment #2 – With BNO alone, the VEP amplitude was larger in individuals with mTBI (90%) and smaller in the VN (100%) groups, as compared to other two test conditions and baseline. In addition, with BNO only, those with mTBI demonstrated improvement in their visual impressions and in performing specific sensorimotor tasks. Experiment #3 – Objectively-based alpha attenuation ratio (AR = EC ÷ EO, ECNC ÷ EC) was able to detect, assess, and differentiate between mTBI with versus without an attentional deficits, as well as between VNs. These objective AR findings were correlated with the subjective Adult ADHD Self-Report Scale (ASRS) questionnaire scores. Experiment #4 – The group and individual VEP findings showed that the central field and the intact hemi-field VEP amplitudes were larger than found in the hemianopic field. Moreover, these objective findings were correlated with the subjective clinical perimetric results.

Conclusions: The optimized VEP parameters provided quantitative, rapid, reliable, and repeatable responsivity in all experiments. These findings demonstrated that the conventional pattern VEP could be beneficial for researchers in general, as well as clinicians to differentiate between mTBI versus the VN group with a high probability, and also between mTBI with versus without an attentional deficit. In addition, the VEP could be used clinically to detect and assess hemianopic visual field defects in patients with stroke. Based on these findings, the VEP has the potential to be used as an objective visual system biomarker for the diagnosis of mTBI/concussion, and also as an objective adjunct clinical tool to detect visual field defects in patients with stroke.

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Dedication

This thesis is dedicated to my loving parents and my family members whose constant support and encouragement helped me in this endeavor.

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1. Dissertation Preamble

1.1 Introduction

1.1.1 Overview: *Acquired Brain Injury (ABI): Traumatic Brain Injury (TBI) and Cerebral Vascular Accident (CVA)/Stroke*

Traumatic Brain Injury (TBI)

Traumatic brain injury (TBI) is a major medical, economic, and public health problem in the United States (Suchoff et al., 2001; Okie, 2005). Approximately 1.7 million people suffer from a TBI every year. It is one of the main causes of death and disability in the United States (Faul et al., 2010). TBI is categorized as mild, moderate, and severe. Approximately 70-80% of TBI is of the mild variety, and therefore most research has focused on it. The prevalence of TBI has increased in recent years due to the past Iraq/Afghanistan wars (Warden, 2006), as well as greater recognition of sports-related concussions (e.g., football) (Guskiewicz et al., 2005) and perhaps related neurodegenerative disorders (e.g., Alzheimer's, Parkinson's) (Daneshvar et al., 2011).

Mechanisms of injury in TBI

The United States Centers for Disease Control and Prevention developed the "Guidelines for Surveillance of Central Nervous System Injury", which defined TBI "as an event involving an injury to the head (brain) due to blunt or penetrating trauma" (Marr and Coronado, 2002). On the basis of its underlying mechanisms, TBI can be categorized

into primary and secondary injuries (Werner and Engelhard, 2007; Greve and Zink, 2009).

Primary Injury

The *primary* injury is caused by the initial mechanically-based, coup-countrecoup event within the cranium, which involves rapid and powerful acceleration, deceleration, and rotational forces (Figure 1). These primary injuries mainly cause diffuse axonal injury (DAI), shearing, torque effects, etc. (Thibault and Gennareli, 1990; Mendez et al., 2005). These axons are responsible for transmission of neural information between different cortical areas. Therefore, DAI causes disruption in neural information transmission, which is responsible for slowing and delays in cortical processing, including vision (Hurley et al., 2004).

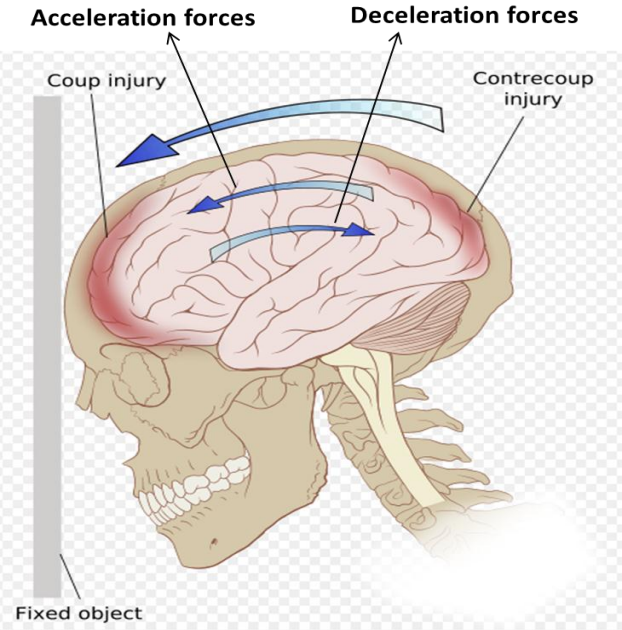


Figure 1: Mechanism of traumatic brain injury (TBI) (image is taken from http://en.wikipedia.org/wiki/Coup_contrecoup_injury; Accessed on May 22nd, 2014).

Secondary Injury

In comparison, the *secondary* injury occurs due to the subsequent biomolecular, biochemical, and physiological changes in the underlying brain tissues over the next days, weeks, and months caused by the primary injury. It adversely impacts on calcium homeostasis and produces oxygen deficiency, both of which are responsible for causing cell death (Werner and Engelhard, 2007; Greve and Zink, 2009). Most individuals with TBI recover to some degree, especially those with mild traumatic brain injury (mTBI) (i.e., within 6-9 months) (Nakamura et al., 2001). Severity of these secondary injuries are correlated with the recovery (Werner and Engelhard, 2007; Greve and Zink, 2009).

TBI cannot be detected by most conventional neuroimaging techniques such as computerized tomography (CT), magnetic resonance imaging (MRI), especially in the mild types. TBI causes damage to the white matter (WM) tracts, which are very small in dimension (~20-30 microns). Therefore, it is not detected by typical clinical imaging techniques (i.e., CT and MRI). Researchers have developed a newer neuroimaging technique to assess damage of these WM tracts. This technique is called diffusion tensor imaging (DTI) (Alexander et al., 2007; Bigler, 2011). DTI is a non-invasive, high resolution MRI-based technique which involves the principle of “anisotropic diffusion” (Alexander et al., 2007). It is found to be successful in detecting and assessing structural integrity of WM tracts after TBI. Therefore, DTI is one of the best neuroimaging techniques to use in those with mTBI, as compared to CT and MRI, and is slowly becoming more available in hospitals.

Types of impairment in the TBI population

Due to its global and pervasive nature, TBI will result in a constellation of adverse effects of a sensory, motor, perceptual, linguistic, cognitive, attentional, and/or behavioral nature (Ciuffreda et al., 2009; Ciuffreda and Ludlam, 2011a,b) (Figure 2). Most of the cranial nerves are involved in vision and related visual functions (i.e., CN II, III, IV, V, VI, VII, VIII, and XI), as well as at least 30 distinct cortical areas of the brain (Helvie, 2011). For example, CN V is involved in the blink reflex (Kazem and Behzad, 2006), and CN VI is involved in oculomotor control (Ciuffreda and Tannen, 1995). Therefore, it is not surprising that adverse visual consequences frequently occur following a TBI (e.g., oculomotor problems, visual-field defects, attentional deficits, and increased visual motion sensitivity) (Kapoor and Ciuffreda, 2002; Helvie, 2011; Ciuffreda and Ludlam, 2011a,b; Ciuffreda et al., 2011). Presence of such visual deficits will have an adverse effect on many general activities of daily living (ADLs). Presence of current/residual visual deficits will also have an adverse impact on the individual's vocational and avocational goals, as well as rehabilitative progress (Reding and Potes, 1988).

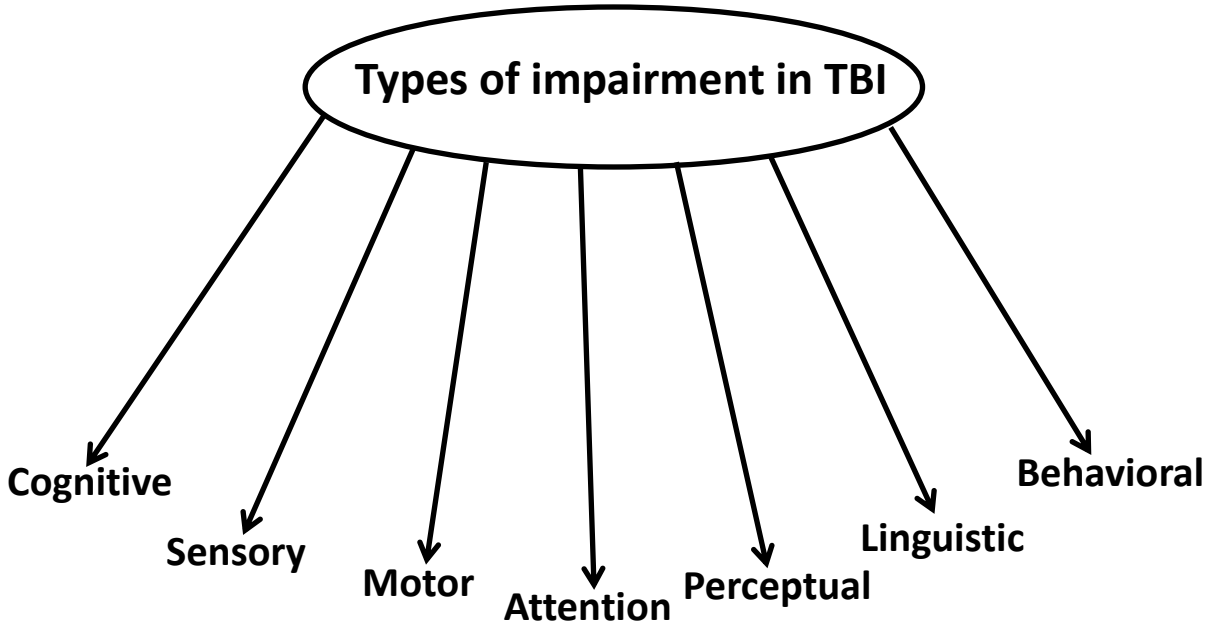


Figure 2: Constellation of general deficits in TBI.

Cerebral Vascular Accident (Stroke)

Stroke is one of the leading causes of death and disability in the US adult population (Feigin, 2005). The World Health Organization (WHO) defines stroke as a "rapidly developing sign of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" (Aho et al., 1980). Hypertension, diabetes, high cholesterol, smoking, and atrial fibrillation are the common risk factors responsible for stroke (Donnan et al., 2008).

Mechanism of Stroke

Stroke can either be ischemic (83%) or hemorrhagic (17%) (Goldstein et al., 2011). The former is caused either by blockage of a blood vessel via arterial embolism or by cerebral hypoperfusion. In contrast, the latter is due to bleeding of blood vessels of the brain. Both ischemic and hemorrhagic stroke are responsible for insufficient supply of oxygen (i.e., anoxia) via blood vessels to the affected cells of the brain. This oxygen deficiency causes death of underlying brain tissues. Stroke causes more localized damage, as compared to mTBI. In contrast to mTBI, stroke can be readily diagnosed by conventional clinical neuroimaging techniques, such as CT and MRI.

Types of impairment in the CVA population

Stroke causes visual dysfunctions of various sorts (Hibbard et al., 2001; Kapoor and Ciuffreda, 2002). Hemianopic visual field defects, with or without visual neglect, are common visual sequelae to a stroke (Suchoff et al., 2001; Suchoff et al., 2008; Suter and Harvey, 2011). Hemianopia is defined as a physiologically-based phenomenon which involves loss of one-half of the lateral visual-field and for which the individual is fully "aware" of its existence. In contrast, visual neglect is defined as a perceptually-based phenomenon in which the individual is "unaware" of the loss of one half of their lateral visual-field (Suter and Harvey, 2011). Hemianopia will adversely affect one's activities of daily living (ADLs), and also one's vocational and avocational goals (Suter and Harvey, 2011). Stroke patients have fixational eye movement, attentional, and cognitive deficits, and therefore conventional perimetry may not be an ideal technique to assess for common visual-field defects (e.g., hemianopia). Therefore, the VEP is a logical and

reliable technique to detect and assess these visual field defects in stroke patients. It is an objective, fast, and repeatable method. Furthermore, the VEP technique does not require prolonged attention and highly accurate fixation, as compared to subjective clinical perimetry.

1.1.2 Overview: *Visual Evoked Potentials (VEP)*

The VEP technique is an objective, rapid, reliable, repeatable, and non-invasive method to assess the functionality and integrity of the retinal and early-afferent visuo-cortical pathways (Odom et al., 2010; Ridder and Rouse, 2007; Yadav et al., 2012). It has been used clinically since at least 1970 (e.g., Ludlam et al., 1970). In addition, the patient's global real-time information can be assessed (i.e., VEP amplitude and latency as the time-averaged responses dynamically summate) for each specific stimulus pattern. The VEP technique has also been used to investigate integrity of the visual pathways in the ABI population (described later in detail).

The pattern VEP has two response components, one is the N75, and the other is the P100 (Figure 3) (other VEPs use other names for the peaks). The former reflects the negative peak occurring approximately 75 msec after stimulus onset, whereas the later reflects the positive peak occurring approximately 100 msec after stimulus onset. The N75-P100 (peak-to-trough) difference represents the VEP amplitude. The VEP latency is defined "as the time from the stimulus onset to the largest amplitude of a positive (P100) and/or negative peak (N75)" (Odom et al., 2010). In the present research, the P100 value was used as the latency.

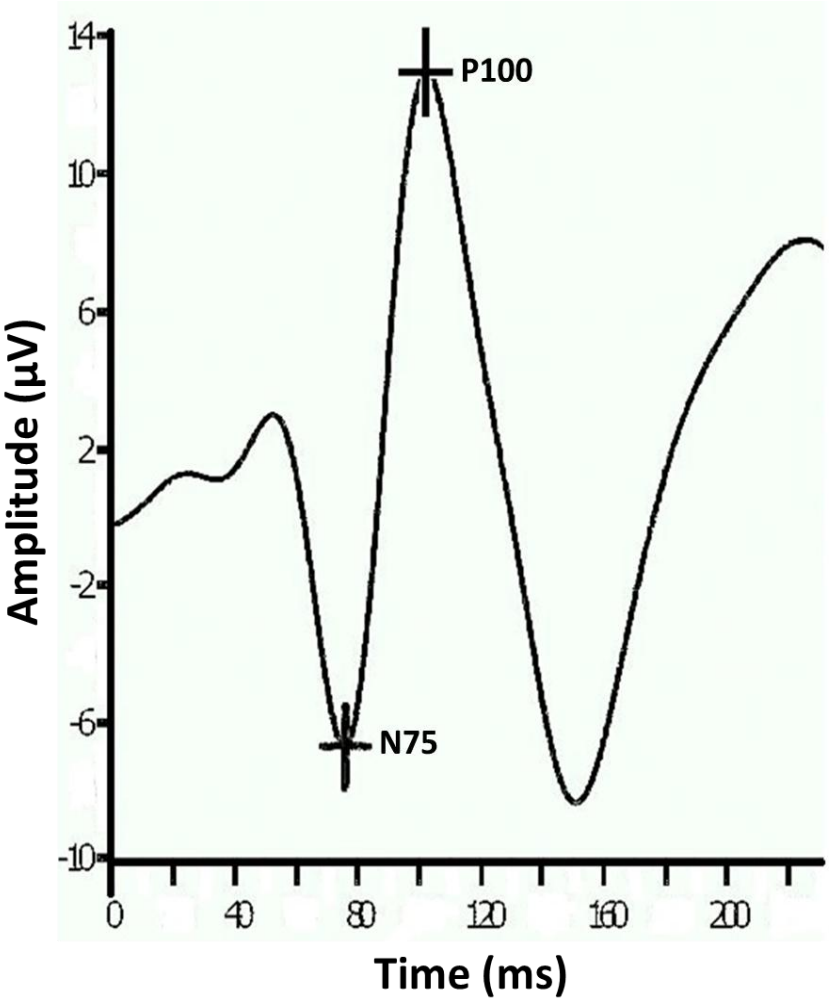


Figure 3: Typical pattern VEP waveform showing negative trough (N75) and positive peak (P100).

1.1.3 Dissertation Experiments

This Ph.D. dissertation is comprised of 4 experiments. In each case, a brief explanation of the study is first presented followed by related background information.

1.1.3.1 ***Experiment #1:*** The hypothesis is that specific stimulus parameters will optimize the VEP response in each population. The primary purpose of this experiment was to optimize selected VEP parameters to assess electrophysiologically, and thus objectively, specific aspects of cortically-based visual dysfunction in mild traumatic brain injury (mTBI). In addition, the findings in the visually-normal group regarding these two parameters (i.e., check size and contrast) were equivocal. These parameters have never been explored to this extent in mTBI, as well as in the visually-normal population. The findings of the experiment served as baseline data, as well as provided evidence of the more sensitive parameters to be used in the three subsequent experiments (#2-4).

Experiment #1 included the assessment of the following parameters:

I. **Check size (128X128, 64X64, and 32X32 equivalent to 10, 20, and 40 min arc, respectively)**
II. **Contrast (20 and 85%)**

Visual Evoked Potential (VEP) investigations in TBI

Electrocephalography (EEG) was the first clinical diagnostic technique to assess brain dysfunction caused by TBI (Jasper et al., 1940; Williams, 1941). The EEG technique includes quantitative EEG (qEEG), event-related potentials (ERPs), evoked potentials (EP), magnetocephalography (MEG), and auditory-evoked potentials (AEP). However, in the present study, the more conventional pattern-reversal VEP technique was used to assess specific aspects of visual dysfunction in the TBI population. Selected papers are reviewed briefly, which used the clinical VEP method in this population.

Papathansopoulos et al., (1994) – This research group used the pattern VEP technique in 50 mTBI patients and 20 control subjects. The following stimulus parameters were used: central full-field checkerboard pattern (14H X 10V degrees), 52 min arc check size, luminance = 190 cd/m^2, and temporal frequency = 1.9 Hz. The results showed that the VEP amplitude and P100 latency were normal in the mTBI patients tested on day 30, i.e., right eye amplitude = 10.08 µV (SD = 4.86), and latency =99.95 ms (SD = 4.79); left eye amplitude = 10.38 µV (SD = 5.21), and latency =98.78 ms (SD = 4.42), after their initial injury, as compared to day 1, i.e., right eye amplitude = 8.26 µV (SD = 4.75), and latency = 102.02 ms (SD = 6.27); left eye amplitude = 8.2 µV (SD = 4.03), and latency = 100.41 ms (SD = 5.56), where abnormalities were evident. This suggested rapid cortical recovery and normalization.

Freed and Hellerstein (1997) – They used the VEP method in two mTBI groups to define and quantify globally any cortically-based visual dysfunction. In addition, the

effect of vision rehabilitation on the VEP amplitude and latency were also assessed. *Group 1* consisted of 18 mTBI patients who received comprehensive optometric vision rehabilitation: prescription of lenses either refractive or prisms (compensatory or yoked), partial occlusion, and oculomotor and fusion-based vision therapy. *Group 2* was comprised of 32 age-matched mTBI control patients, who did not receive any type of vision rehabilitation. The following stimulus parameters were used: central circular full-field checkerboard pattern (diameter = 14 degree), 56 min arc check size, and temporal frequency = 1.88 Hz. Contrast was not specified, but presumed to be high. The results showed that 71% of the former and 81% of the latter group had abnormal VEP waveforms, respectively. The VEP waveform was considered abnormal if the P100 latency was increased by 15% or more and/or the amplitude was decreased by 50% or more, averaged over three trials, as compared to their normative data. After the vision rehabilitation, only 38% of those with mTBI had an abnormal waveform in group 1. In contrast, in the non-treated group 2, 78% still had an abnormal waveform. Thus, the clinical VEP method revealed cortically-based, objective response abnormalities that normalized in the majority of cases after conventional vision rehabilitation therapy (i.e., optometric vision therapy). These findings suggest perceptual and motor training-related visual system plasticity effects (Ciuffreda, 2002), even at this very early stage of the damaged brain.

Gaetz and Weinberg, (2000) – These researchers used the pattern VEP in 43 individuals with mTBI and in 43 normals. Both groups were divided by age, namely a younger group (18-34 years) and an older group (35-61 years). The VEP was performed

in the former group 20-51 months post-injury, and in the latter group 1-53 months post-injury. The following stimulus parameters were used: central full-field checkerboard pattern (40H X 24V degrees), 31.05 min arc check size, and temporal frequency = 3 Hz with unspecified contrast. The latency was found to be delayed by 33% of the individuals with mTBI in both groups, as compared to the two normal age groups. The VEP amplitude was not assessed. They suggested that the pattern VEP was a useful technique for objectively assessing global cortical visual dysfunction in the mTBI population, especially the presence of early delayed visual processing.

Lachapelle et al., (2004) – This group assessed the VEP using a "texture segregation" protocol. They used stationary complex and simple diagonal test patterns, as well as simple and complex coherent motion patterns. 13 TBI (5 mild, 5 moderate, and 3 severe) and 13 control subjects were tested. The more complex "texture segregation" patterns were found to be more sensitive in detecting cortically-based visual dysfunction in the TBI patients. Thus, this unique stimulus may prove in the future to be a more provocative and useful approach.

Studies in the visually-normal population

The following studies assessed the effect of check size and contrast on the VEP response in the visually-normal population:

Ristanović and Hajduković (1981) - They measured the VEP response in 11 visually-normal adults. They used a wide range of check sizes (11.4 to 121.1 min arc) at

100% contrast. They found that the VEP amplitude varied non-monotonically over a range of check sizes, with a maximum VEP response at 60.8 min arc. In addition, the latency decreased exponentially with increase in check size (i.e., from 11.4 to 121.1 min arc). Furthermore, Török et al. (1992) also found decreased latency with increasing check size.

Kurita-Tashima et al., (1991) – They assessed the effect of check size in 11 visually-normal adults. They also used a wide range of check sizes from 10 to 90 min arc at 90% contrast. However, they did not find any significant effects on the VEP responses. Furthermore, they found a curvilinear relation between the P100 latency and the different check sizes, with minimal latency between 22.5 to 50 min arc.

Sokol et al. (1983) – They tested 2 visually-normal, adult subjects and assessed the effect of contrast on the VEP amplitude. However, latency was not tested. They used both low (i.e., 30%) and high (i.e., 85%) contrast conditions, with check sizes ranging from 7.5-240 min arc, with modulation at three different temporal frequencies (i.e., 0.94, 3.75, and 7.5 Hz). The results revealed that the VEP amplitude was maximum at the 15 min arc check size, at both low and high contrast levels, at a temporal frequency of 0.94 Hz. The result at this particular temporal frequency is relevant to the present study, which used 1 Hz.

However, in none of the above studies was the goal to optimize VEP parameters (i.e., check size and contrast) to maximize responsivity. Furthermore, none of the aforementioned studies assessed the effect of a wide range of check sizes and contrasts on

the VEP amplitude and latency in the mTBI population in a detailed and quantitative manner.

Thus, the purpose of the present study was to assess the effect of different check sizes and contrast levels on the VEP amplitude and latency in visually-normal, as well as in individuals with mTBI. Furthermore, this information will also help us to develop a VEP protocol which is rapid, high yield, and targeted for both visually-normal individuals and in those with mTBI.

1.1.3.2 ***Experiment #2:*** The hypothesis is that there will be an increase in the VEP amplitude with binasal occlusion (BNO), as well as with the BNO combined with small amounts of base-in (BI) prisms, in the mTBI population manifesting symptomatic visual motion sensitivity (VMS). Latency will likely remain the same (based on our pilot study, i.e., Ciuffreda et al., 2013). The BNO may act to reduce peripheral motion inhibition related to their abnormal VMS, whereas the BI prism may act to reduce the vergence error and thus allow for more accurate stimulation of corresponding retinal points (CRPs).

Experiment #2 will include the following test conditions:

I. **Central full-field VEP (baseline)**
II. **Binasal occlusion (BNO) only**
III. **Base-in prism only (4 pd total)**
IV. **BNO with base-in prism (4 pd total)**
V. **Repeatability of I-IV above**

Binasal Occlusion

Binasal occlusion (BNO) has been used clinically since at least 1950 in optometry for the treatment of strabismus. Jaques (1950) used BNO, which he called the "half-cover" technique, to treat constant unilateral strabismus. He suggested that the BNO was able to remove the cortically-based visual inhibition and suppression caused by the constant strabismus, presumably by forcing ocular alignment and foveation. The BNO

functioned to force divergence in esotropes. This helped strabismic individuals regain their binocularity (i.e., motor fusion), at least to some degree if successful.

Currently, BNO is also used by some optometric practitioners involved in brain injury. BNO can be accomplished by using strips of translucent scotch tape, heavily-layered transparent nail polish, and/or opaque electrical tape placed either on the front or the back surface of the spectacle lenses nasal to the pupillary-limbal margin (Figure 4). The BNO should be oriented either vertically, or more beneficially tilted 15° superiorly-temporalward to allow for convergence at near to be unobstructed. Lastly, some have used bitemporal occlusion in TBI (Padula and Shapiro, 1988), but this may restrict too much of the peripheral visual-field with possible resultant safety issues during ambulation.

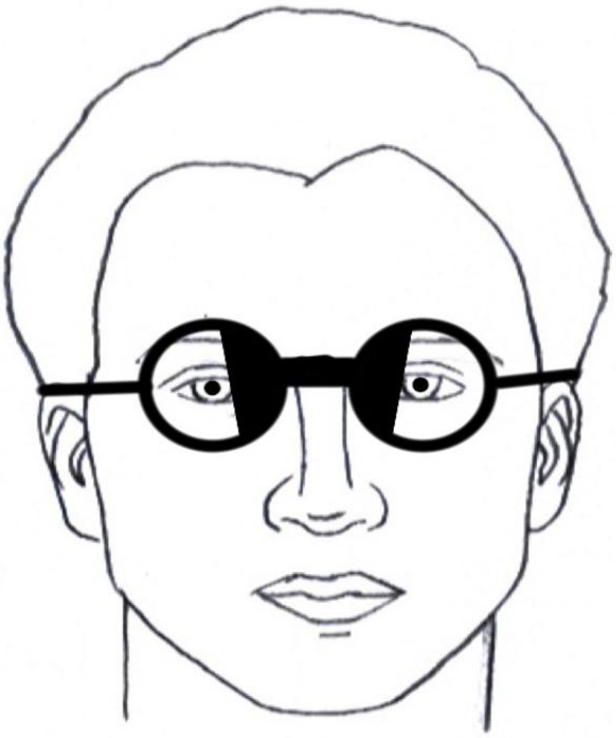


Figure 4: Schematic representation of binasal occluders on a subject.

Numerous studies have confirmed that many individuals with TBI suffer from a constellation of abnormal visual functions, including accommodative insufficiency (AI), convergence insufficiency (CI), headaches, diplopia, attentional deficits, vestibular problems, reading problems, versional eye movement problems, photosensitivity, and abnormal visual motion sensitivity (e.g., Ciuffreda, 1999; Suter and Harvey, 2011; Ciuffreda et al., 2013). It is the last symptom that is the focus of the present study.

There are a paucity of experimental studies dealing with BNO in TBI, especially with respect to abnormal VMS. Proctor (2009) reported a clinical case study in which the

mTBI patient had a primary complaint of “dizziness due to moving objects”. All neurological testing, which included repeated magnetic resonance imaging (MRI), was within normal limits. The patient had an abnormal exophoria of 6 prism diopters (pd) at distance and 8 at near. Base-in prism (3 pd BI each eye), in conjunction with office and home-based optometric vision therapy (i.e., vision rehabilitation), was prescribed for six weeks to reduce the exophoria and other oculomotor problems, as well as to improve peripheral awareness and fusion. BNO was then introduced after 3 months. The patient had a very positive response. He was very comfortable visually. He was able to walk more comfortably and confidently in the hallway, perhaps due to a reduction in the abnormal VMS resulting from occlusion of parts of the disturbing peripheral visual-field motion (e.g., Gibsonian optic flow) (Gibson, 1950).

There are two studies directly relevant to the question of VEP and BNO in TBI. Details are below.

Padula et al., (1994) - They assessed the effect of BNO, in conjunction with base-in prisms (2 pd BI each eye), on the visual-evoked potential (VEP) amplitude in both visually-normal and in unspecified TBI subjects in a hospital setting. The results were quite convincing, as they demonstrated *objectively* for the first time the positive effect of BNO in patients with TBI, along with correlated reduction of vergence-related symptoms in some. Details of the study were as follows: 10 visually-normal, and 10 hospital-based individuals with TBI, were assessed binocularly using the pattern VEP (check size = 30 minutes of arc, temporal frequency = 0.95 Hz). They assessed the VEP amplitude under 2 conditions; 1) central full-field VEP, and 2) central full-field VEP with BNO *and* 2 pd of base-in prism over each eye. The results revealed that there was a modest but consistent,

and statistically significant, increase in the VEP amplitude in 8 of the 10 individuals with TBI for condition 2 versus condition 1 (6.35 µV to 7.99 µV). The amplitude remained the same in the other 2 subjects. In contrast, in the normals for the same test conditions, the VEP amplitude decreased in 6 (15.39 µV to 14.42 µV), increased in 2 (8.93 µV to 9.81 µV), and remained the same in 2, thus suggesting a random "noise" phenomenon. The Padula et al. (1994) results confirmed that BNO, with a small amount of base-in prism, increased visuo-cortical activity in individuals with TBI, along with correlated reduction in symptoms in some. However, the *separate* effects of the BNO and BI prisms were not assessed.

Ciuffreda et al., (2013) - They assessed the effect of BNO *only*, on the visual-evoked potential (VEP) amplitude and latency, in both VN individuals and in those with mTBI. All with mTBI had the symptom of increased VMS. Details of the study were as follows: 10 VN adults, and 10 adult individuals with mTBI and VMS, were assessed binocularly with full refractive correction using the clinical pattern VEP (check size = 20 min arc, temporal frequency = 1 Hz, luminance = 74 cd/m^2, test distance = 1m). The VEP responses were analyzed under 2 test conditions; 1) central full-field VEP (17°H X 15°V) as the baseline condition, and 2) central full-field VEP with BNO over each eye. The results showed a significant increase in the mean VEP amplitude in *all* 10 individuals with mTBI and VMS for condition 2 versus the baseline condition 1 (i.e., 19.15 µV to 21.32 µV). In contrast, for the same test conditions, the mean VEP amplitude significantly decreased in *all* 10 VN individuals (i.e., 21.60 µV to 17.37 µV) relative to baseline. In both groups, latency was found to be normal with no significant change found under any test condition. In addition, the VEP findings were repeatable in both

groups. Lastly, the mTBI patient's self-reported visuomotor activities improved with BNO (e.g., grasping for a near object, walking in a long hallway), along with reduction in VMS symptoms, especially during ambulation: they felt more confident, comfortable, and experienced less "visual noise" in their peripheral visual field. This study demonstrated even stronger findings at the visuo-cortical level, as compared to the Padula et al. (1994) study, with regard to the use of BNO alone in individuals with mTBI and VMS.

The mechanism and neurophysiology for improving visual function and reducing symptoms by using BNO is not well understood. Gallop (1998) proposed that the BNO occluded the binocular nasal field and helped in maintaining "binocular integration" in some unclear and unspecified manner. The binocular interactive ability was speculated to become "inefficient" after the neurological insult. Gallop (1998) also proposed that BNO helped in providing a stable visual perception of the environment, with the tape borders acting as vertical reference points in visual space for these dizzy and visually-disorientated individuals. Similarly, Padula et al. (1994) suggested that the increase in VEP amplitude with BNO in individuals with TBI might be due to providing a vertical visual frame of reference for orientation, as well as an increase in "functionality of binocular cortical cells" by incorporation of the prisms. Their proposed mechanisms remain somewhat vague and non-specific.

More recently, Ciuffreda et al., (2013) proposed that mTBI patients habitually attempted to suppress, at least partially, visual information in the near retinal periphery to reduce the abnormal VMS in those regions. With addition of the BNO in mTBI, such regional suppression would now be rendered unnecessary. This leads to the spread of

reduced inhibition effectively producing enhanced central visual field responsivity. In contrast, in the visually-normal individuals, it may produce reduction of normal neuronal excitation activity over the same spatial regions, thus effectively decreasing central visual field responsivity. However, the phenomenon of BNO still needs to be addressed, with disambiguation of the BNO and BI prism effects, as used by Padula et al., (1994).

Thus, the purpose of the present study was to assess quantitatively the effect, and relative contribution, of binasal occlusion (BNO) and base-in prisms (BI) on visually-evoked potential (VEP) responsivity in those having mild traumatic brain injury (mTBI) *and* the symptom of visual motion sensitivity (VMS), as well as in asymptomatic visually-normal individuals.

1.1.3.3 ***Experiment #3:*** The hypothesis is that the VEP will be able to detect and assess objectively attentional deficits in the mTBI population using modulation of its alpha frequency (8-13 Hz) band, which is related to the attentional state. Thus, different stimulus conditions will be used to modulate the attentional state, and in turn alpha responsivity, as quantified via power spectrum analysis.

Experiment #3 will include the following test conditions:

I. **VEP [baseline, "eyes open (EO)"]**
II. **"Eyes-closed (EC)" ("relaxed", reduced attentional state)**
III. **"Eyes-closed number counting (ECNC)" (increased attentional demand)**
IV. **Repeatability of I-III above**

As mentioned earlier, TBI causes an adverse effect on both general and visual attention (Whyte et al., 1998; Daffner et al., 2000; Suter and Harvey, 2011). Attention is processed by different cortical (i.e., visual cortex, frontal, and parietal lobes) and subcortical (i.e., thalamus) areas of the brain (Chen et al. 2008; Helvie, 2011). Kastner and Ungerleider (2000) indicated that the mechanism of attentional processing is initiated in the visual cortex before being transmitted to higher cortical areas. Therefore, assessing visual attention at the visual cortex area using the VEP method may provide early information about the attentional state in humans.

This topic goes back nearly 100 years, with wide gaps. Berger (1929) was the first to investigate the alpha band (8-13 Hz) electrophysiologically in the human. Klimesch

(1999) also found that the alpha band (8-13 Hz) was related to human thalamo-cortical attention. It has been confirmed that the high alpha band power (μV^2) is related to synchronous neuronal activity. In contrast, lower alpha band power (μV^2) is related to asynchronous neuronal activity (Klimesch, 1999) (see Figure 8). Studies have demonstrated that alpha band activity was correlated with different human attentional states, i.e., the eyes-closed versus eyes-open conditions (Gomarus et al., 2009), visual imagery (Lauria, 1966), and visual attention (Ludlam, 1979). These studies suggested that modulation of neuronal activity occurs due to these different attentional states that produce changes in the alpha band power. Attenuation of the alpha band magnitude occurs from the eyes-closed to the eyes-open condition (Legewie et al., 1969), which is a normal phenomenon: *inability to suppress alpha suggests an attentional deficit*. Therefore, measuring alpha band neuronal activity may provide a way to assess the attentional state of an individual rapidly and objectively. Kirschfeld (2008), and Hale et al. (2009), also demonstrated that alpha band activity was related to attention using the EEG technique.

Most of the studies focused on assessing attention in higher cortical areas, i.e., parietal and temporal lobes (Bernal et al., 1992). However, some have focused on the primary visual cortex. Thus, these are the following studies most relevant to the present study.

Fuller (1978) – Fuller (1978) measured visual attention using the EEG method at a frequency band of 0.5-30 Hz in 10 children with learning disability (LD) and 11 normal, age-matched children. The alpha band power was extracted from the overall EEG band, and then power spectrum analysis was used to quantify the response and its frequency

subcomponents. First, alpha power was recorded with the eyes-closed (i.e., relaxed state) for 5 minutes, so that any remaining visually-based attentional aspects dissipated. Then, a cognitive demand was added to the eyes-closed condition, that is the subjects performed simple addition, recall of common objects, and a word problem task, all during which alpha was recorded. Fuller (1978) then calculated the alpha attenuation ratio (AR) between the average alpha power measured during the cognitively-demanding eyes-closed condition to the average alpha power measured during the eyes-closed condition. An attenuation ratio of <1.00 suggested an ability to suppress alpha activity during the cognitively-demanding, eyes-closed condition, as expected to be the case for those with normal attention. Fuller (1978) found that 81% of the normal children had an average AR of 0.91. In comparison, 80% of the LD children had an average AR of 1.01, which suggested an attentional deficit.

Ludlam (1979) – Similar results were found by William Ludlam (1979). The VEP method was used to assess two children with reading disability. They measured alpha band (8-13 Hz) attenuation ability before and after vision therapy under two conditions. In the first condition, their eyes were closed, and in the second condition, the children performed a reading task. The results revealed that both of the learning-disabled children were unable to attenuate alpha during the reading task, as would be expected in normal children. This suggested that they had a visual-attentional deficit. They then underwent vision therapy (i.e., home- and office-based oculomotor training) to improve their reading ability, which likely indirectly improved their overall general and visual attention (Ciuffreda, 2002; Solan et al., 2003; Yadav et al., 2014). After the vision therapy, they

were now able to attenuate their alpha activity. This suggested improvement in attention, which appeared to be related to the correlated improvement in reading.

Willeford et al., (2013a) – Recently, Willeford et al. (2013a) used the above ideas to detect and assess objectively normal human attention. The Willeford et al. (2013a) results obtained in our laboratory serve as the normative data base for the present study. In the Willeford et al. (2013a) investigation, two different attenuation ratios (ARs) were calculated: the first was between the average alpha band power during the eyes-closed "relaxed" attentional condition (EC) and the average alpha band power during the eyes-open condition (EO); and, the second was between the average alpha band power during the eyes-closed number counting condition (ECNC) and the average alpha band power during the eyes-closed "relaxed" attentional condition (EC). The EC ÷ EO AR was found to correlate with a standard subjective clinical visual attention test, namely the Visual Search and Attention Test (VSAT) (Willeford et al., 2013a). In addition, Willeford et al. (2013a) found the following: (1) an AR (EC ÷ EO) = 2 or greater suggested presence of normal attention; (2) the AR at 10 Hz was significantly correlated with the VSAT percentile score; and, (3) the second alpha AR (ECNC ÷ EC) = <1 was similar to Fuller's (1978) normative value. Therefore, the results of the Willeford et al. (2013a) study suggested that the VEP alpha band component provided an objective correlate of human attention in normal individuals.

None of the above studies used the VEP method in the mTBI adult population to detect and assess attention. Therefore, the current study was performed in the mTBI population to investigate attention objectively. The objective results were also correlated with two subjective attention tests, i.e., the Visual Search Attention Test (VSAT) and the

Adult ADHD Self-Report Scale (ASRS). The purpose of the proposed experiment is to develop a ratio between the eyes-open and eyes-closed conditions, and also between the eyes-closed number counting and eyes-closed, which would relate to attenuation ability that could be reliably used as a barometer of attentional state and its normalcy. These objectively-based ratios should help the clinician diagnose attentional problems in mTBI, and furthermore may be used to assess the effect of visual/attentional intervention, along with the subjective test analogs.

1.1.3.4 ***Experiment #4:*** The hypothesis is that the VEP will be able to detect and assess objectively hemianopic visual field defects in individuals with stroke. Furthermore, it may also be able to detect hemianopia in stroke patients with more subtle stimuli, such as low contrast and low luminance patterns.

Experiment #4 will include the following test conditions:

I. **Central field [high contrast (HC) and high luminance (HL); low contrast (LC) and high luminance (HL); low luminance (LL) and high contrast (HC)]**
II. **Intact hemi-field only (HC/HL, LC/HL, LL/HC)**
III. **Hemianopic field only (HC/HL, LC/HL, LL/HC)**

There are a paucity of relevant studies which have used the VEP method to assess hemianopia in stroke patients.

Viggiano et al., (1995) – These researchers studied 10 individuals with stroke having left-field hemianopia and visual neglect, 11 individuals with stroke having left-field hemianopia only, and 6 visually-normal subjects. In their first experiment, they used 5 different check sizes (i.e., 12, 14, 36, 48, and 72 min arc) with a common temporal frequency of 4.76 Hz. In their second experiment, they used 6 different temporal frequencies (i.e., 1.96, 3.03, 4.76, 6.66, 8.33, and 16.66 Hz) with a common check size of 48 min arc. Contrast was 87%, and luminance was 120 cd/m^2. A circular checkerboard stimulus (radius = 7.5 degrees) was presented both centrally and peripherally (8.5 degrees laterally). For both the central and peripheral stimulus, there were no significant

differences in amplitude between hemianopes with versus without visual neglect. They suggested that the phenomenon of visual neglect was due to damage to the higher-level cortical areas, and not to early primary cortical areas (V1). However, they did not assess latency, which could have provided additional information regarding any delay in visual processing in these patients.

Spinelli et al., (1994) – They used the steady-state VEP in 16 right-brain-injured, hemianopic stroke patients (i.e., 9 with left-visual field neglect, 7 patients without neglect), and 16 visually-normal subjects. Vertical sinusoidal gratings (field size = 12.8H X 32.8V degrees) of 0.56 cycles per degree were used. They modulated at temporal frequencies ranging from 4-11Hz. Contrast was 32%, and luminance was 150 cd/m^2. They assessed both VEP amplitude and latency. There was no significant effect on either the VEP amplitude or latency for either the neglected or normal hemifield. Similar results were found in hemianopic patients without neglect, as well as in visually-normal subjects. However, they did find that the amplitude was slightly lower at higher temporal frequencies (e.g., 8 Hz) in those with a neglected left visual field as compared to their normal right visual field. In addition, they found markedly delayed latencies of ~30-40 ms with increase in temporal frequency in patients with visual neglect, as compared to those without neglect. This study revealed that patients with visual neglect had slowed visual processing in the visually-neglected field only, at least under specific stimulus conditions in V1 per the VEP responsivity.

Angelelli et al. (1996) - They measured steady-state VEP responses in 19 right brain-damaged (RBD) patients with left-sided hemianopia and visual neglect. They had two

controls groups: 15 left brain-damaged (LBD) patients and 12 right brain-damaged (RBD) patients, all with hemianopia but without visual neglect. They used vertical sinusoidal gratings (field size = 6H X 16V degrees) of 0.56 cycles per degree. The gratings were modulated at 10 temporal frequencies ranging from 4-10.5 Hz, with a central fixation target present. Contrast was 32%, and luminance was 150 cd/m^2. They assessed both amplitude and latency. Stimuli were presented either in the right (RVF) or left visual field (LVF). The results revealed that the mean VEP latency was significantly delayed by ~25 msec in the neglected LVF, as compared to their normal RVF, in those with RBD. In contrast, there was no significant difference in latency in either the right or left hemifield in the RBD and LBD groups without visual neglect. The VEP amplitudes were reduced in the hemianopic visual field in the RBD patient, with and without visual neglect. However, the amplitudes were similar in both hemianopic fields in the LBD group. These findings demonstrated that both visual-neglect and hemianopia could be detected, even at the V1 level.

Based on the aforementioned studies, the results remain equivocal. Therefore, the purpose of the present study was to determine if the VEP technique could be used to detect and assess hemianopic visual field defects objectively, repeatably, and reliably in individuals with stroke.

1.2 Methods

Subjects

Experiment #1-3 included both visually-normal (VN) adults and adults with mTBI, ages 18-70 years: Experiment #1 (19 VN and 16 mTBI), Experiment #2 (20 VN and 15 mTBI), and Experiment #3 (18 VN from Willeford et al, (2013a) and 16 mTBI: 11 with a self-reported attentional deficit, and 5 without). In contrast, 5 adults with stroke and hemianopia (ages 18-70 years) participated in Experiment #4. All individuals with ABI had their brain insult at least 6-9 months before testing to preclude changes attributed to natural recovery (Nakamura et al., 2001). The following criteria were used for the diagnosis of mTBI (Kay et al., 1993): 1) loss of consciousness for less than 30 minutes or an altered state of consciousness for up to 24 hours, 2) 13 or greater score on the Glasgow coma scale (GCS), and 3) post-traumatic amnesia (PTA) lasting less than 24 hours. All subjects had corrected visual acuity of 20/20 or better in each eye at both distance and near. Exclusion criteria for ABI included a history of seizures, constant strabismus, and amblyopia, as well as any type of ocular, systemic, or degenerative neurological disease. All subjects were recruited from the Raymond J. Greenwald Rehabilitation Center at the State University of New York (SUNY), State College of Optometry, as well as outside clinics and hospitals. The visually-normal subjects were recruited from its student body and faculty at the college. The study was approved by the Institutional Review Board (IRB) at the SUNY, State College of Optometry. Written informed consent was obtained from all subjects.

Apparatus

The DIOPSYS^{TM} NOVA-TR system (Diopsys, Inc., Pine Brook, New Jersey, USA) was used to generate a checkerboard pattern stimulus and analyze the VEP data (Figure 5). It consisted of a test monitor for stimulus presentation and a display monitor for on-line viewing of the responses by the experimenter, as well as a computer for stimulus generation and graphical display. This system is available commercially and has been approved by the FDA. It has been used in several pediatric clinics, as well as adult medical and optometric practices (Tello et al., 2010), and for the last 4 years in our laboratory (Yadav et al., 2012; Willeford et al., 2013a,b; Ciuffreda et al., 2013; Yadav and Ciuffreda 2013; Yadav et al., 2014). The stimulus was presented on the 17" LCD display monitor with a refresh rate of 75 Hz. Three Grass (Grass Technologies, Astro-Med, Inc., West Warwick, RI, USA) gold cup electrodes of 1 cm in diameter (one active, one reference, and one ground) were used for the recordings.

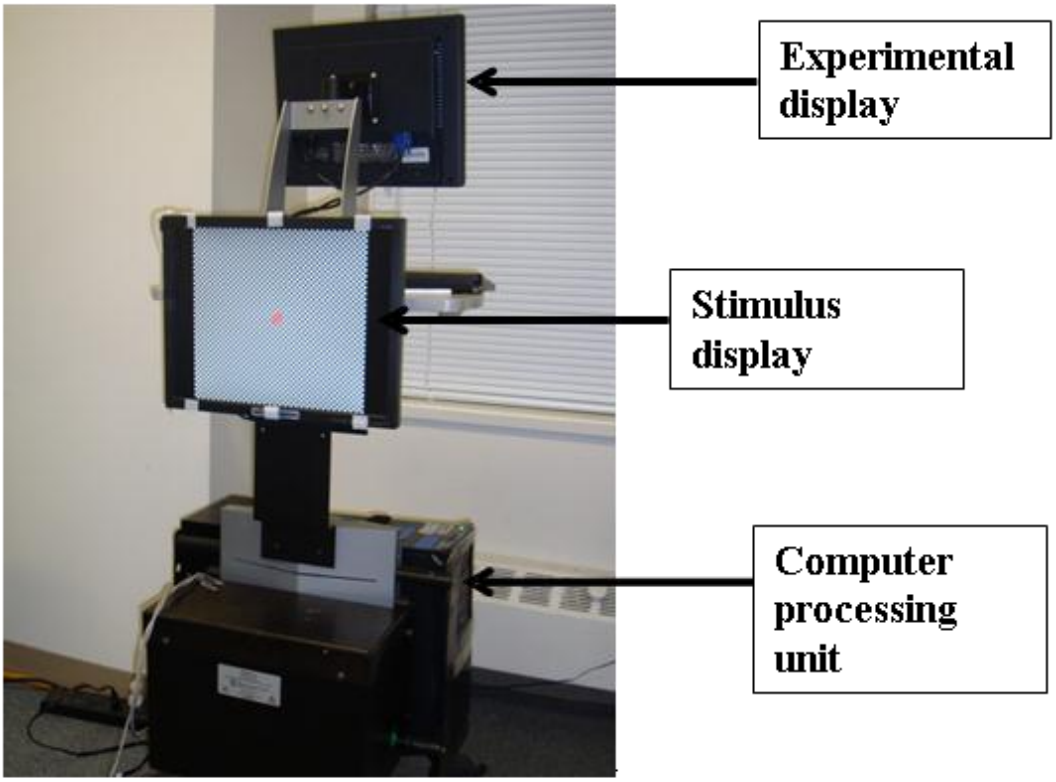


Figure 5: The DIOPSYS™ NOVA-TR VEP system (Diopsys, Inc., Pine Brook, New Jersey, USA). Not shown is the headrest/chinrest assembly used for subject stability and constancy of test distance positioned 1 meter away.

Procedures

Electrode Placement

The VEP amplitude and latency were recorded over the primary visual cortex (V1). The electrode placement was slightly modified from the International 10/20 system (American Clinical Neurophysiology Society, 2006), as suggested by the manufacturer to

reduce test preparation time in clinical populations. After thorough cleaning of the scalp with alcohol wipes, the central active channel electrode was placed at the Oz position which is 2.5 cm above the inion, the reference electrode was placed at the Fz position which is approximately 10% of the distance from the nasion to inion, and the ground electrode was placed at the Fp2 position which is on the right side of the forehead (Figure 6). A head-band was used to maintain the electrodes firmly positioned on the scalp.

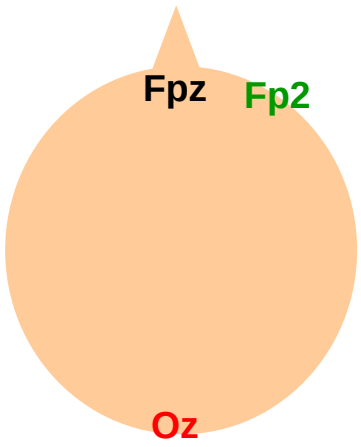


Figure 6: Position of three recording electrodes on the subject's scalp – Oz (active electrode), Fpz (reference electrode), and Fp2 (ground electrode).

Recordings

Each electrode had an impedance of ≤5K ohms, per the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) (Odom et al., 2010). An amplification factor of 10K was used to increase the analog signals. A bandpass filter (0.5-100 Hz) was used to filter any noise. Sampling frequency was 1024 Hz. An artifact detector was used to eliminate artifacts in the EEG signals produced by

such factors as blinks and saccadic gaze shifts. Furthermore, based on our experience with this system, up to 5 artifacts were allowed to be present before rejecting any record; based on our extensive experience with this system, more than 5 artifacts typically produced noise and increase variability in the response profile, with such records rejected for use. In addition, an artifact rejection algorithm was used in the DIOPSYS system to assess the digitized response. This algorithm checks the sampled data to ascertain if the maximum amplitude has been maintained over consecutive samples during the trial.

Following electrode placement, the subjects were requested to gaze carefully at the central fixation target (0.25 degree radius) on the monitor positioned at eye level along the midline. The VEP measurements were obtained binocularly with refractive correction in place. Testing was performed in a darkened room (38 lux) with natural pupils. Subjects were provided 5 minute rest periods between the different test conditions, as needed.

General data analysis

Data analyses and graphical displays were done using either GraphPad Prism 5.04 software or Statistica 7 software. Statistical tests included the t-test, Pearson correlation, and ANOVA (see specific experiments for more details and the exact tests used). Initially, a $p \leq 0.05$ was specified to determine which parameters and conditions were statistically significant. Then, for those that were significant, the exact p-values were specified in the text. Given all of the test conditions and test parameters used in each study, it is possible that some of the statistically significant results were based on chance

alone. However, in the majority of conditions/parameters, the exact p-values were considerably *less* than $p = 0.05$ (e.g., $p = 0.001$), and thus in the majority of cases the probability of a Type I error (rejecting the null hypothesis when it is true) was very low.

The above described apparatus, electrode placement, and procedures were used for all the four experiments. However, the stimulus and tests conditions were different for each experiment, as described below.

1.2.1 ***Experiment #1:*** The effect of different check size and contrast parameters on the VEP amplitude and latency were assessed for response optimization. There were the following 6 stimulus conditions (3 check sizes X 2 contrast levels). Five trials were performed for each test condition:

I. **Check size** (128X128, 64X64, and 32X32 equivalent to 10, 20, and 40 min arc, respectively)

II. **Contrast (20 and 85%) –** Low and high contrast levels was used.

A standard central full-field (17 H X 15 V degrees) checkerboard pattern comprised of black-and-white checks with three different check sizes was used. It was presented binocularly at low and high Michelson contrast levels. Mean luminance was 74 cd/m^2. Test distance was 1 m. A temporal frequency of 1 Hz (two reversals per second) was used for modulating the checkerboard pattern.

The optimized, most sensitive, and most reliable VEP parameters (i.e., check size and contrast) from Experiment #1 were then used for Experiments #2, 3, and 4.

Data Analysis

An average of five trials for each of the 6 test conditions for each subject was performed initially. Then, for each condition and subject, the trial for which the response exceeded 1SD from the mean was deleted to remove the outlier, and the mean and SD for the 4 remaining trials were calculated and used for the individual subject and subsequent group analysis. Furthermore, if the outlier was within 1 SD, then the most deviant trial response was deleted. Repeated-measures, two-way and three-way ANOVAs were performed on the two groups and two mTBI subgroups (asymptomatic and symptomatic), respectively, using STATISTICA 7 software. GraphPad Prism 5 software was also used for the data and graphical analysis

1.2.2 *Experiment #2*: The effect of binasal occlusion (BNO) alone, BI prism alone, or BNO in combination with the BI prism, on the VEP amplitude and latency in the mTBI and visually-normal populations, were assessed using the following 4 different stimulus conditions. Five trials were performed for each test condition:

I. **Central full-field VEP (baseline)** – A standard central full-field (17°H X 15°V), black-and-white checkerboard pattern (64 X 64 equivalent to 20 min arc check size, test distance = 1 m, temporal frequency = 1 Hz, luminance = 74 cd/m^2, and contrast = 85%) was used. These VEP responses were used as a baseline for comparison with the subsequent three experimental test conditions.

II. **Central full-field VEP with binasal occlusion (BNO)** – The VEP responses were assessed with the BNO alone. Before measuring the VEP responses, the binasal occluders were adjusted in an ophthalmic trial frame, so that the subject was able to see the entire checkerboard pattern both monocularly and binocularly. A 5.7°H x 15°V region of space 5.5° lateral to the edge of the test stimulus on either side of the horizontal extent of the screen was occluded by the binasal occluders (Figure 7).

III. **Central full-field VEP with base-in (BI) prisms** – The VEP responses were assessed with 2 pd BI prisms in front of each eye (4 BI prism diopters total).

IV. **Central full-field VEP with the combination of the binasal occluders (BNO) and BI prisms** – The VEP responses were assessed with a

combination of the BNO and the 2 pd BI prisms before each eye. The binasal occluders were placed in the trial frame as described in condition 2 (i.e., for BNO only). The BI prisms were also added in the ophthalmic trial frame.

In addition, repeatability of the above 4 experimental test conditions was performed on two different days in two subjects in each group.

Subjective Testing

Subjective testing was performed in each group to assess their visual perception and visuomotor performance. Three subjective viewing conditions were performed, as described below (A-C). It was accomplished with the same four test conditions as used for the VEP measurements: baseline, BNO, BI prisms, and the combination of BNO plus BI prisms (details will be presented in Paper #2).

(A) Simple viewing task

(B) Grasping task

(C) Walking task

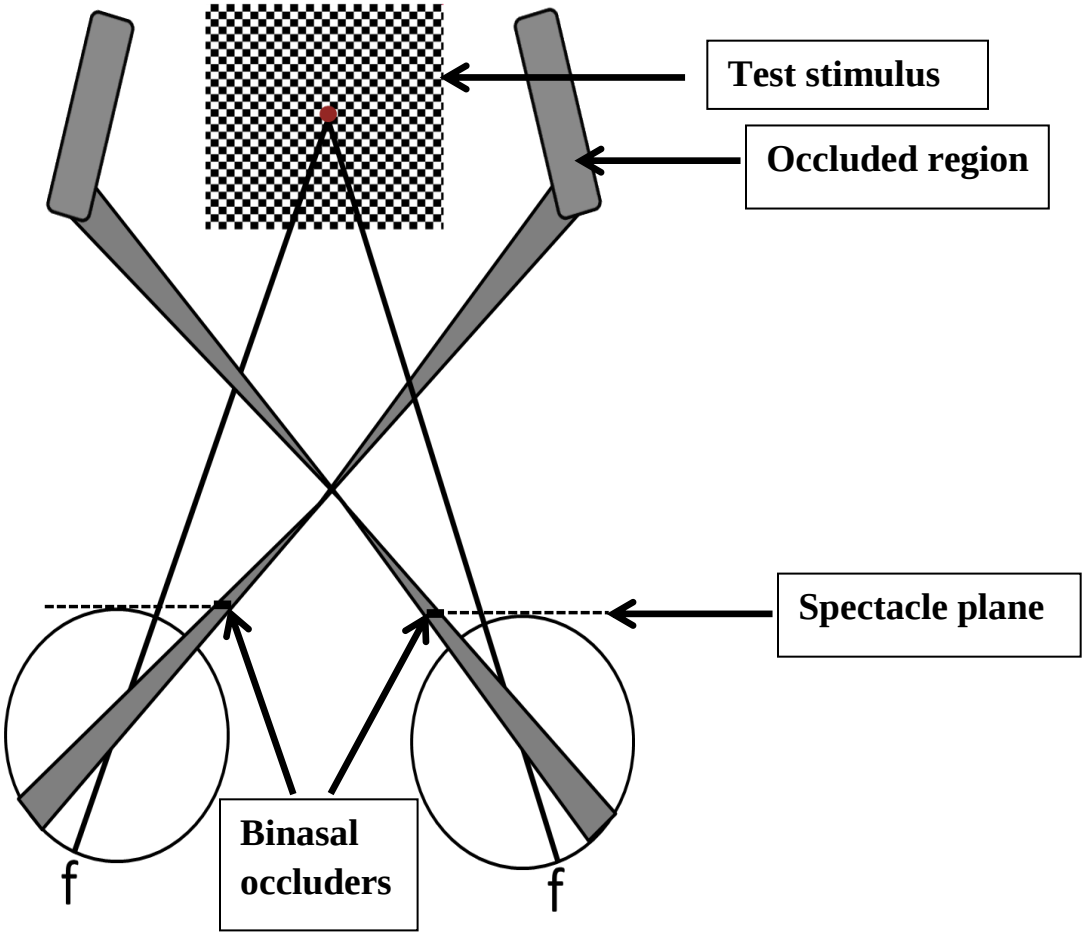


Figure 7: Representation of binocular visual-field with binasal occluders during the VEP recording. Not drawn to scale. f = fovea

Data Analysis

An average of the five trials for each of the 4 test conditions for each subject was initially calculated. Then, the trial for which the VEP response exceeded 1SD from the mean was deleted to remove the outlier; in the case where all 5 trials value were within 1 SD, the most deviant response was deleted. The mean and SD for the 4 remaining trials were calculated and used for analysis of the group mean VEP amplitude and latency.

Furthermore, for the subjective rating scale, the mean and standard deviation for each test condition was calculated and analyzed for each group. A one-way, repeated-measures ANOVA was performed on each group using GraphPad Prism 5 software. Graphical displays were prepared with the same software.

In addition, VEP repeatability was assessed in two subjects in both groups. The same test conditions were repeated three weeks apart. The coefficient of variation (CV = standard deviation ÷ mean) was calculated to assess for repeatability of the VEP responses. The CV value can range from 0.00 to 1.00 (Abdi, 2010). This value represents the intra-individual variability: the smaller the value, the less the variability, and the better the repeatability.

1.2.3 ***Experiment #3*****:** The following three test conditions were used to measure the VEP responses, as well as to modulate the attentional state to assess the alpha power responses. Five trials for each of the three test conditions were performed. Test duration of each trial was 20 seconds. These protocols have been tested fully by our laboratory in visually-normal individuals (Willeford et al., 2013a,b):

I. **VEP [baseline, "eyes open (EO)"] –** Conventional VEP test stimulus was employed (17° H x 15° V, 64 x 64 checkerboard pattern equivalent to 20 min arc check size at 1 meter distance, 85% contrast, 74 cd/m^2 luminance, 1 Hz temporal frequency, binocular viewing with spectacle correction). During this condition, both the VEP and the alpha (8-13 Hz) responses were measured. This test condition was always performed first to assure VEP response normalcy. It was the baseline comparison condition, in which the alpha power is predicted to be markedly reduced due to the occurrence of visual "damping", or "attenuation" (Figure 8).

II. **"Eyes-closed (EC)" ("relaxed", reduced attentional state) –** Subjects were instructed to sit comfortably in the chair and close their eyes. Then, they were asked to relax, and "clear their mind", for 2 minutes before starting the trials. It was important to attain a reduced attentional state, which would allow for maximum alpha (8-13 Hz) power responsivity (Fuller, 1978; Willeford et al., 2013a,b). They were also instructed to imagine "gazing" straight ahead where the central fixation target was originally presented, and also not to move their eyes during test, to avoid any artifacts caused by saccadic eye movements. In

this condition, an increase in alpha power is predicted, as compared to both the EO and the ECNC conditions (Fuller, 1978; Willeford et al., 2013a) (Figure 8).

III. **"Eyes-closed number counting (ECNC)" (increased attentional demand)** – Subjects were instructed to again close their eyes, as in condition 2 (EC). However, they were now instructed to perform a mental arithmetic task (Fuller, 1978; Willeford et al., 2013a). Subjects were asked to count silently backwards in steps of seven, starting from 100, 96, 94, 92, and 90 for each of the five test trials, respectively (Smith, 1967; Willeford et al., 2013a). Different numerical starting positions were used to prevent memorization of the reverse order number sequences. This cognitive task is expected to increase the attentional demand with the eyes closed. The alpha (8-13 Hz) power was assessed. Attenuation of alpha power was expected, as compared to the EC condition.

In addition, repeatability was assessed for each test condition. This was performed in four individuals with mTBI tested on two different days, two with and two without an attentional deficit.

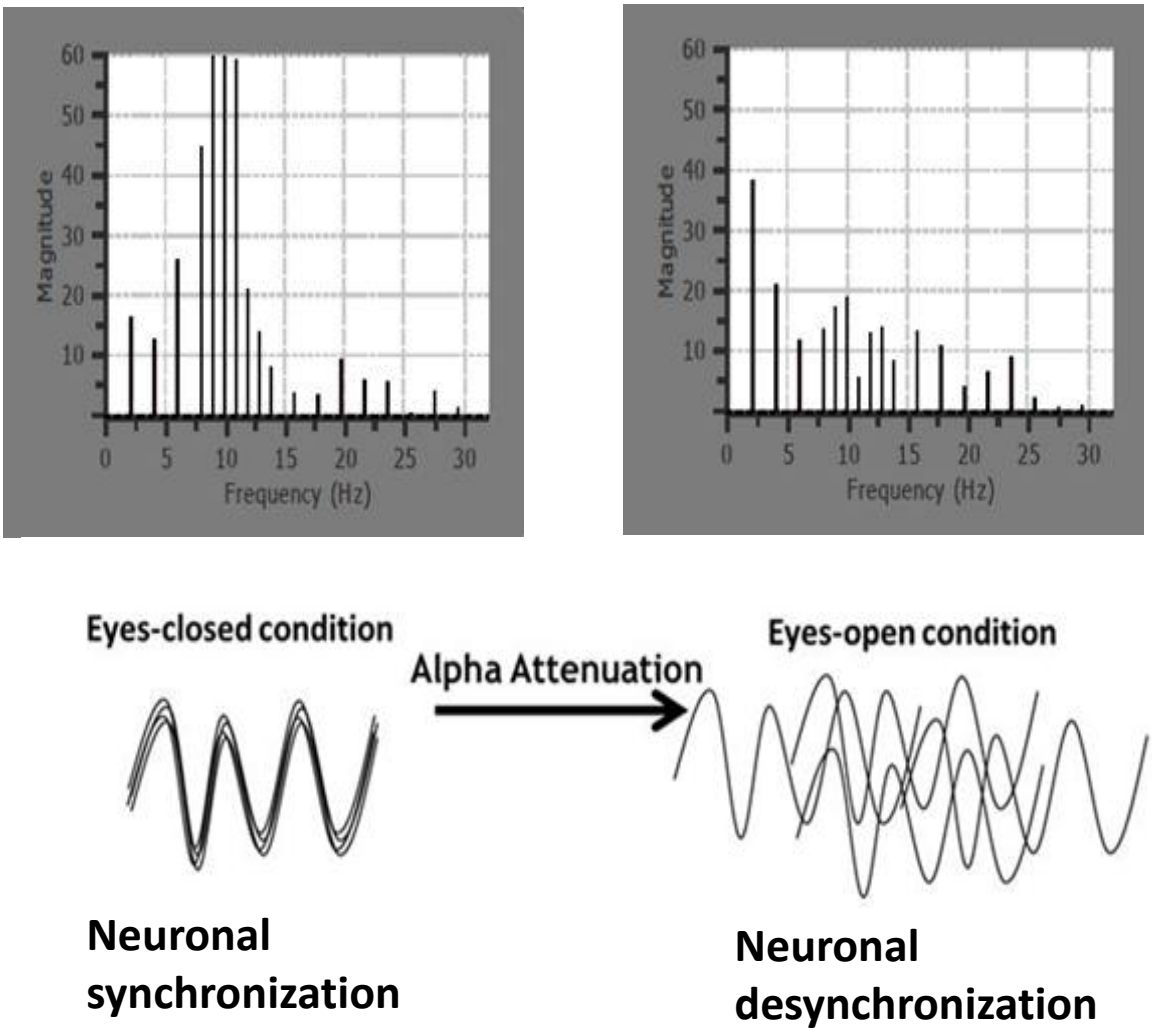


Figure 8: Representation of power spectrum and alpha attenuation for the "eyes closed" and "eyes open" conditions.

Subjective Testing

The following two subjective tests were performed to assess attention:

1. **Adult ADHD Self-Report Scale (ASRS) -** The Adult ADHD Self-Report Scale (ASRS) questionnaire was used as a screening tool to assess for an attentional deficit in those with mTBI (Kessler et al., 2005). The World

Health Organization (WHO) developed this test to screen adults for attention-deficit/hyperactivity disorder. It is comprised of 18 questions divided into 2 parts, with 9 questions per part. Part A and Part B questions were related to inattention and hyperactivity/impulsivity, respectively. However, in the present study, only the Part A questionnaire scores were used related to attention (details are presented in Paper #3).

2. **Visual Search and Attention Test (VSAT) -** A second subjective attention test was performed in each individual with mTBI, namely the Visual Search and Attention Test, or VSAT (© Psychological Assessment Resources, Inc). It is used in many optometric clinics and psychological practices (Trenerry, 1989) (details are presented in Paper #3).

Alpha Attenuation Ratio (AR)

The alpha AR is related to the human attentional state. Two different alpha attenuation ratios (ARs) were calculated. The first was the alpha power (μV^2) measured during the "eyes-closed (EC)" condition divided by the alpha power measured during the "eyes-open (EO)" condition. The second alpha AR was calculated as the alpha power (μV^2) measured during the "eyes-closed number counting (ECNC)" condition divided by the alpha power measured during the "eyes-closed (EC)" condition.

Data Analysis

Several types of data analyses were performed. Five trials per test condition were done, and the average was used in the data analysis; no data were deleted, so that the effects across frequencies were constant. First, the group mean VEP amplitude and latency were assessed. Second, the group mean of each alpha AR (i.e., EC ÷ EO and ECNC ÷ EO) at *each* individual alpha frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) was assessed, as well as the *combined* mean of each alpha AR (i.e., EC ÷ EO and ECNC ÷ EO) across all frequencies (i.e., 8-13 Hz). A one-way, repeated-measures ANOVA was used to assess the group data. In addition, two correlations were performed: between each subject's ASRS Part A scores and their alpha ARs, and between each subject's VSAT percentile score and their alpha ARs. Lastly, the coefficient of variation (CV = standard deviation ÷ mean) of the alpha wave responses was calculated to assess repeatability. The CV value can range from 0.00 to 1.00 (Abdi, 2010). This value represents the intra-individual variability: the smaller the value, the less the variability, and the better the repeatability. GraphPad Prism 5 software was used to perform the analyses. Lastly, the data were segregated into those with versus without a self-reported attention deficit, as well as combined, for specific subgroup and group analyses.

1.2.4 ***Experiment #4:*** The VEP amplitude and latency were assessed for the following three experimental test conditions (See Figure 9):

I. **Central field [high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), low luminance (LL) and high contrast (HC)] –** A standard, central, checkerboard pattern (17H X 15V degrees, 20 min arc check size at 1 meter, 20 second test duration, temporal frequency 1 Hz) was used as the baseline comparison stimulus. A checkerboard pattern with both low and high contrast levels (i.e., 20 and 85%), and also with both low and high luminance levels (i.e., 7.4 and 74 cd/m^2), was presented for all 3 stimulus combinations as described above.

II. **Intact hemi-field only (HC/HL, LC/HL, LL/HC) –** The checkerboard pattern was presented only to the intact visual-field (8.5H X 7.5V degrees) with the contrast and luminance levels as described in #1 test condition. The other half of the visual field (i.e., the hemianopic field) was presented with a blank, non-patterned stimulus field (luminance 1.27 cd/m^2) (Yadav et al., 2012).

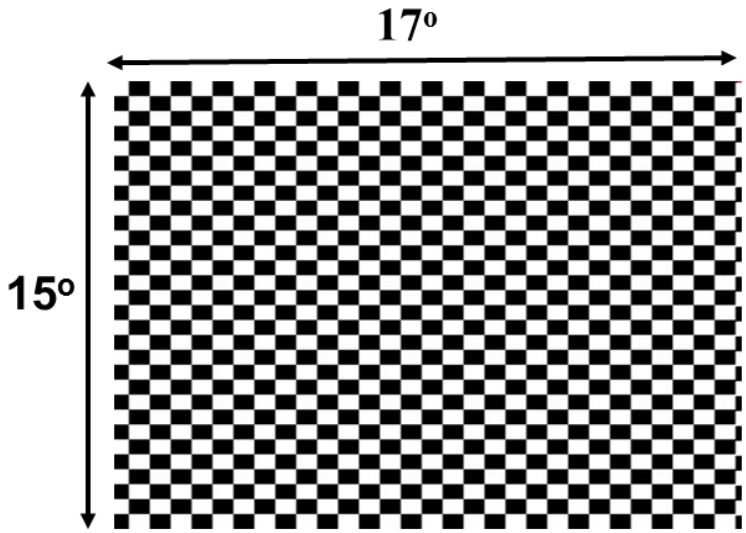
III. **Hemianopic field only (HC/HL, LC/HL, LL/HC) –** The checkerboard pattern was again presented only to the hemianopic field (8.5H X 7.5V degrees) with the contrast and luminance levels as mentioned above in #1 test condition. The other half of the visual-field (i.e., intact hemi-field)

was presented with a blank, non-patterned stimulus field (luminance 1.27 cd/m^2) (Yadav et al., 2012).

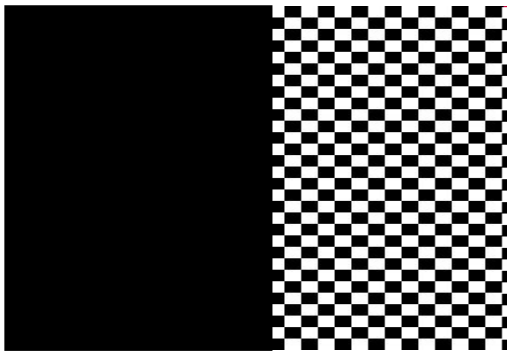
Data Analysis

An average of the three trials for each of the three visual field test conditions (i.e., complete, intact, and hemianopic) and three stimulus combinations (i.e., HC/HL, LC/HL, LL/HC) were initially calculated for each subject. Then, for each subject, the trial for which the VEP response exceeded 1SD from the mean was deleted to remove this outlier; and, in the case where all 3 trial values were within 1 SD, the most deviant trial response value was deleted. The mean and SD for the 2 remaining trials were calculated and used for analysis of the group mean VEP amplitude and latency. A one-way, repeated-measures ANOVA was performed on each condition using GraphPad Prism 5 software. Furthermore, due to the small sample size, the data analysis was also performed for each subject, along with additional information, such as their conventional clinical perimetric findings (Figure 10) except for subject #1.

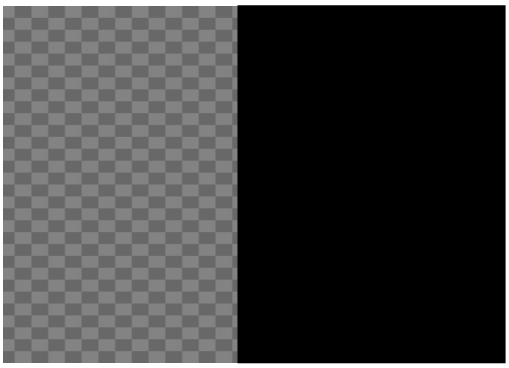
VEP repeatability was assessed in subject #5. The same test conditions were repeated one week later. The coefficient of variation (CV = standard deviation ÷ mean) was calculated to assess for repeatability of the VEP responses. It can range from 0.00 to 1.00 (Abdi, 2010). This value represents the intra-individual variability: the smaller the value, the less the variability, and the better the repeatability.



(A)



(B)



(C)

Figure 9: Test stimulus configurations. (A) Central, VEP checkerboard pattern showing high contrast and high luminance conditions, (B) Hemianopic visual-field test stimulus for high contrast and high luminance condition, and (C) Hemianopic visual-field test stimulus for low contrast and high luminance condition. All not drawn to scale.

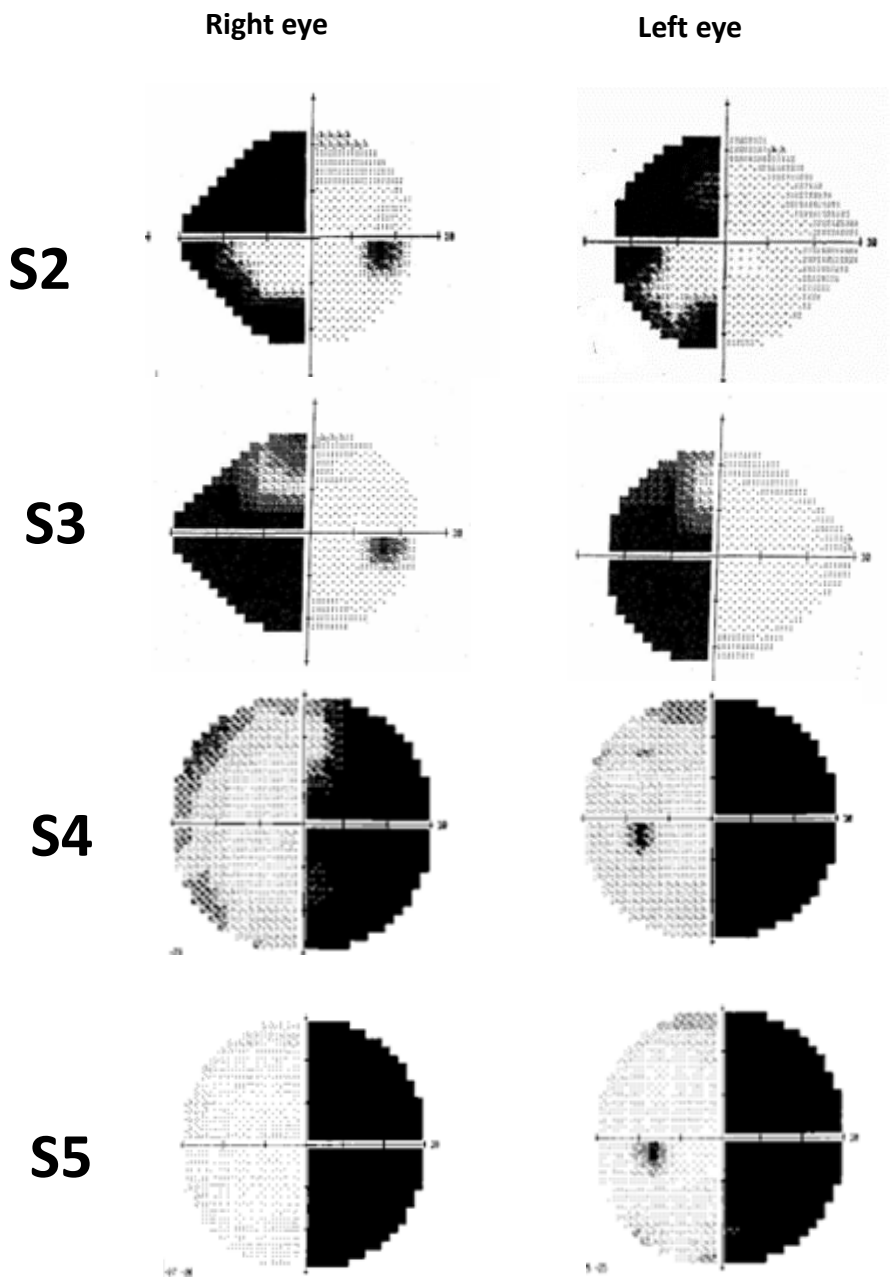


Figure 10: Conventional visual fields of subjects #2-5 using the central 24-2 threshold test (Humphery Visual System, CARL ZEISS MEDITECH).

1.3 Results

1.3.1 *Experiment #1*

Amplitude

Visually-normal

A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. The results revealed a significant effect of check size ($p = 0.0002$) and contrast ($p = 0.0001$) on the VEP amplitude in the visually-normal group (Figure 11A). The relevant post-hoc Tukey test results showed that at both the high and low contrast, the response amplitude for the 20 min arc check size was significantly larger than that found for the 40 min arc check size ($p = 0.0001$).

mTBI

A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. The results revealed a significant effect of check size ($p = 0.0001$) and contrast ($p = 0.0002$) on the VEP amplitude in the mTBI group (Figure 11B). The relevant post-hoc Tukey test results showed that at high contrast, the response amplitude for the 20 min arc check size was significantly larger than that found for the 40 min arc ($p = 0.0001$) check size; however, this relation was not found at low contrast ($p > 0.05$).

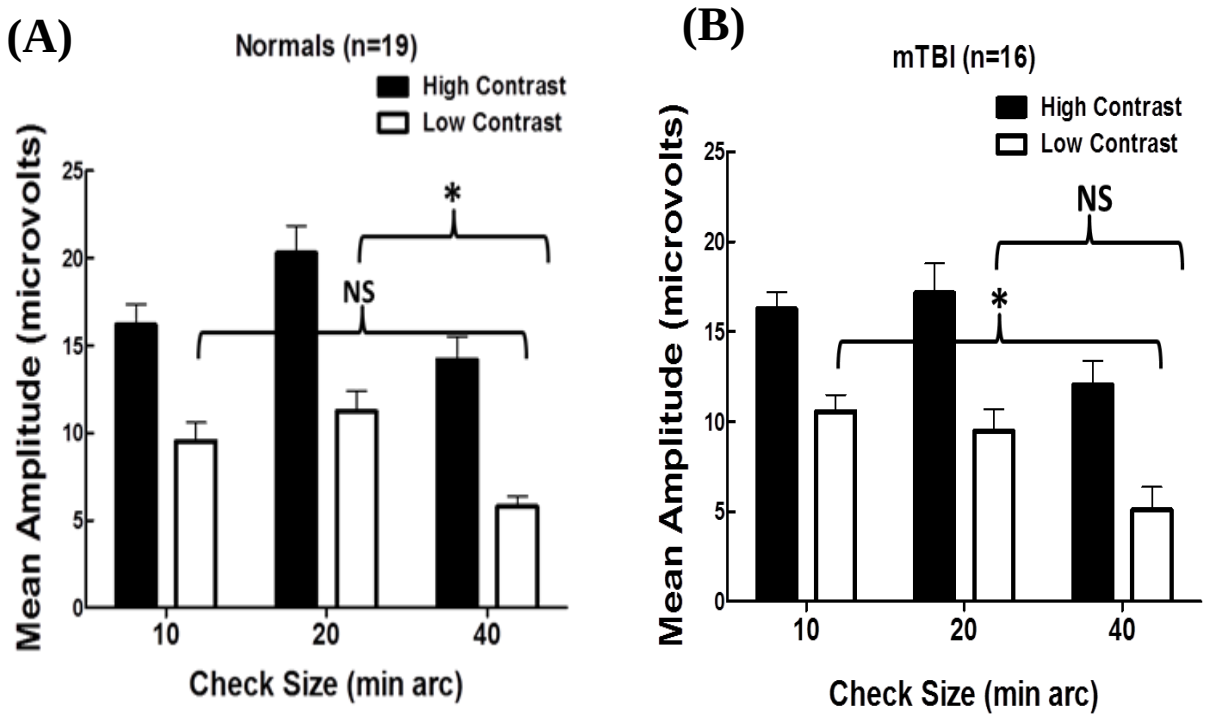


Figure 11: Mean VEP amplitude as a function of check size for both the low and high contrast levels. Plotted is the mean +1 SEM. (A) visually-normal, (B) mTBI. * = significant post-hoc comparison, NS = non-significant post-hoc comparison.

Comparisons were made between the visually-normal subjects and individuals with mTBI. These were the following two differences found between two groups: first, in the visually-normal group at low contrast, the 20 min arc check size response amplitude was significantly larger ($p = 0.0001$) as compared to the 40 min arc check size. But this difference was not found in the mTBI group ($p > 0.05$). Second, in the mTBI group at low contrast, the 10 min arc check size response amplitude was significantly larger ($p = 0.0001$) as compared to the 40 min arc. However, this relation was not found in the visually-normal group ($p > 0.05$).

Latency

Visually-normal

A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. The results revealed a significant effect of check size ($p = 0.0001$) and contrast ($p = 0.0002$) on the VEP latency in the visually-normal group (Figure 12A). There were several relevant post-hoc Tukey test comparisons: first, at high contrast, the 10 min arc check size response latency was significantly longer, as compared to either the 20 or 40 min arc check size values ($p = 0.0001$). In addition, at high contrast, the 10 min arc check size latency was also significantly longer, as compared to either the 10 or 40 min arc check sizes at low contrast ($p = 0.0002$). Second, at low contrast, the 10 min arc check size response latency was significantly longer, as compared to either the 20 or 40 min arc check size latency values at both low and high contrast ($p = 0.0001$). Furthermore, the VEP response latency decreased significantly and exponentially with increase in check size at both low ($p = 0.001$), $r = +0.895$) and high ($p = 0.002$, $r = +0.861$) contrast.

mTBI

A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. The results revealed a significant effect of check size ($p = 0.0001$) and contrast ($p = 0.0001$) on the VEP latency in the mTBI group (Figure 12B). There were several relevant post-hoc Tukey test comparisons: first, at high contrast, the 10 min arc check size response latency was significantly longer as compared to the 40 min arc check size ($p = 0.0002$). Second, at low contrast, the 10 min arc check

size latency was significantly longer, as compared to either the 20 or 40 min arc check size values at both low and high contrast (p = 0.0001). In addition, at low contrast, latency for the 10 min arc check size was also significantly longer as compared to the 10 min arc check sizes at high contrast (p = 0.0002). Furthermore, the VEP latency decreased significantly and exponentially with increase in check sizes at both low (p = 0.001, r = +0.830) and high (p = 0.001, r = +0.833) contrast.

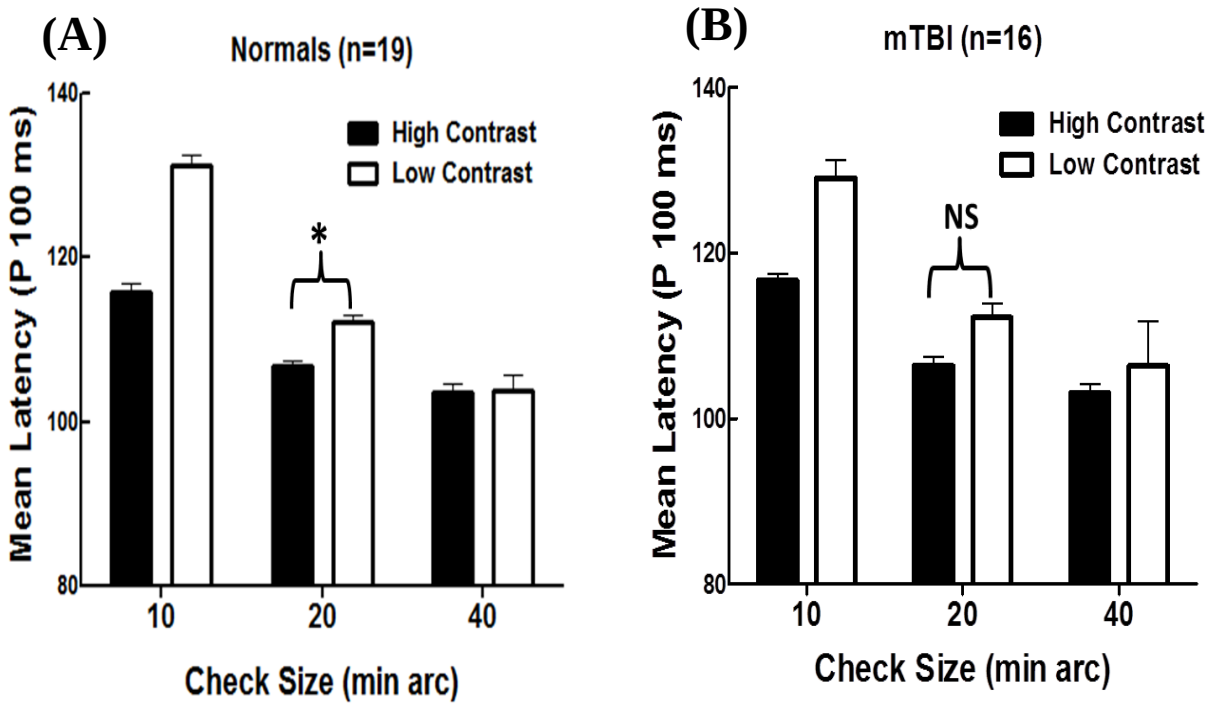


Figure 12: Mean VEP latency (P100) as a function of check size for both the low and high contrast levels. Plotted is the mean +1 SEM. (A) visually-normal, (B) mTBI. * = significant post-hoc comparison, NS = non-significant post-hoc comparison.

Comparisons were made between the visually-normal subjects and those with mTBI. In the visually-normal group, at low contrast, the 20 min arc check size response latency was significantly longer, as compared to the latency at high contrast ($p = 0.0001$). In contrast, this relation was not found in the mTBI group ($p > 0.05$).

mTBI *(symptomatic vs asymptomatic)*

Amplitude

A repeated-measures, three-way ANOVA was performed on the group mean amplitude for the factors of subgroup (i.e., asymptomatic = 4 versus symptomatic = 12), check size, and contrast. The results revealed a significant effect of subgroup ($p = 0.002$), check size $p = 0.001$), and contrast ($p = 0.001$) on the VEP amplitude (Figure 13A). The post-hoc Tukey test results showed that at high contrast, the mean amplitude value for the 20 min arc check size for the asymptomatic group was significantly larger, as compared to the symptomatic group at the other check sizes ($p = 0.0001$) and contrast levels ($p = 0.0002$).

Latency

A repeated-measures, three-way ANOVA was performed on the group mean latency for the factors of subgroup (i.e., asymptomatic = 4 versus symptomatic = 12), check size, and contrast. The results revealed a significant effect of check size ($p = 0.0002$) and contrast ($p = 0.0001$), but not subgroup ($p > 0.05$) on the VEP latency (Figure 13B). The following relevant post-hoc Tukey test comparisons for the factors of

check size and contrast were found: first, at low contrast, the 10 min arc check size response latency for the asymptomatic group was significantly longer, as compared to the 40 min arc check size at high contrast (p = 0.003). Second, at low contrast, the 10 min arc check size response latency for the symptomatic group was significantly longer, as compared to the 20 and 40 min arc check size values at both the low and high contrast (p = 0.0001).

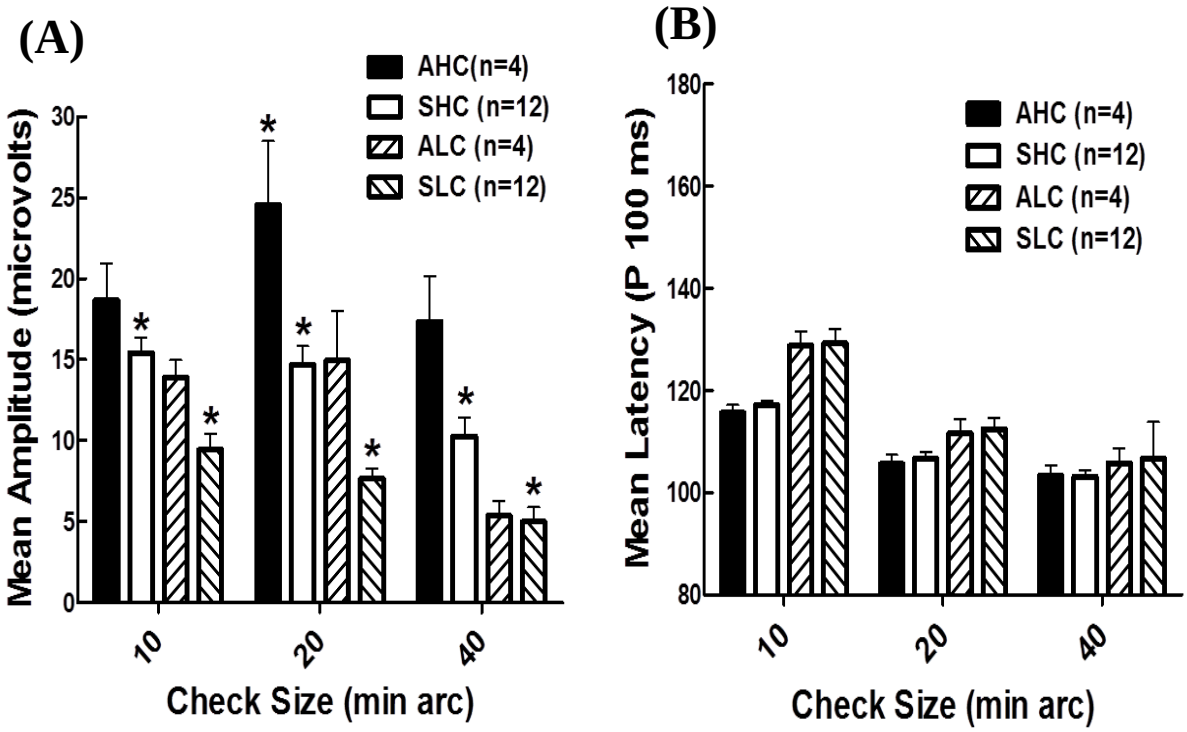


Figure 13: (A) The VEP amplitude as a function of check size at both the low and high contrast levels for the asymptomatic and symptomatic groups. Plotted is the mean +1 SEM. * = significant post-hoc comparisons, (B) The VEP latency (P100) as a function of check size at both low and high contrast levels for the asymptomatic and symptomatic groups. Plotted is the mean +1 SEM. AHC = asymptomatic high contrast; SHC = symptomatic high contrast; ALC = asymptomatic low contrast; and SLC = symptomatic low contrast

Correlation

For the mTBI subjects, at the three check sizes and two contrasts, correlations were performed between time since their most recent brain injury and the VEP amplitude and latency. It was found to be significant only for the 20 min arc check size amplitude at low contrast ($r = +0.586$, $p = 0.01$).

1.3.2 *Experiment #2*

Amplitude

Visually-normal

A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. The results revealed a significant effect of test condition on the mean VEP amplitude ($p = 0.0001$) in the visually-normal group (Figure 14A). The post-hoc Tukey test results showed the following two significant comparisons ($p < 0.05$): first, the amplitude for the BNO (17.08 ±1.65 µV) ($p = 0.001$) and for the combination of BNO plus BI prism (18.13 ±1.66 µV) ($p = 0.002$) conditions were significantly *decreased*, as compared to the baseline condition (20.79 ±1.78 µV). Second, the amplitude for the BNO ($p = 0.001$) and for the combination of BNO plus BI prism ($p = 0.02$) conditions were also significantly *decreased*, as compared to the BI prism condition (20.62 ±1.71 µV).

mTBI

A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. The results revealed a significant effect of test condition on the mean VEP amplitude ($p = 0.01$) in the mTBI group (Figure 14B). The post-hoc Tukey test results showed the following two significant comparisons: first, the amplitude for the BNO condition (23.19 ±2.13 µV) ($p = 0.02$) was significantly *increased*, as compared to the baseline condition (20.89 ±2.14 µV), but not for the BNO plus BI prism condition (21.98 ±2.36 µV) ($p > 0.05$). Second, the amplitude for the BNO condition ($p = 0.03$) was

significantly *increased*, as compared to the BI prism condition (21 ±2.32 μV), but not for the BNO plus BI prisms condition ($p > 0.05$).

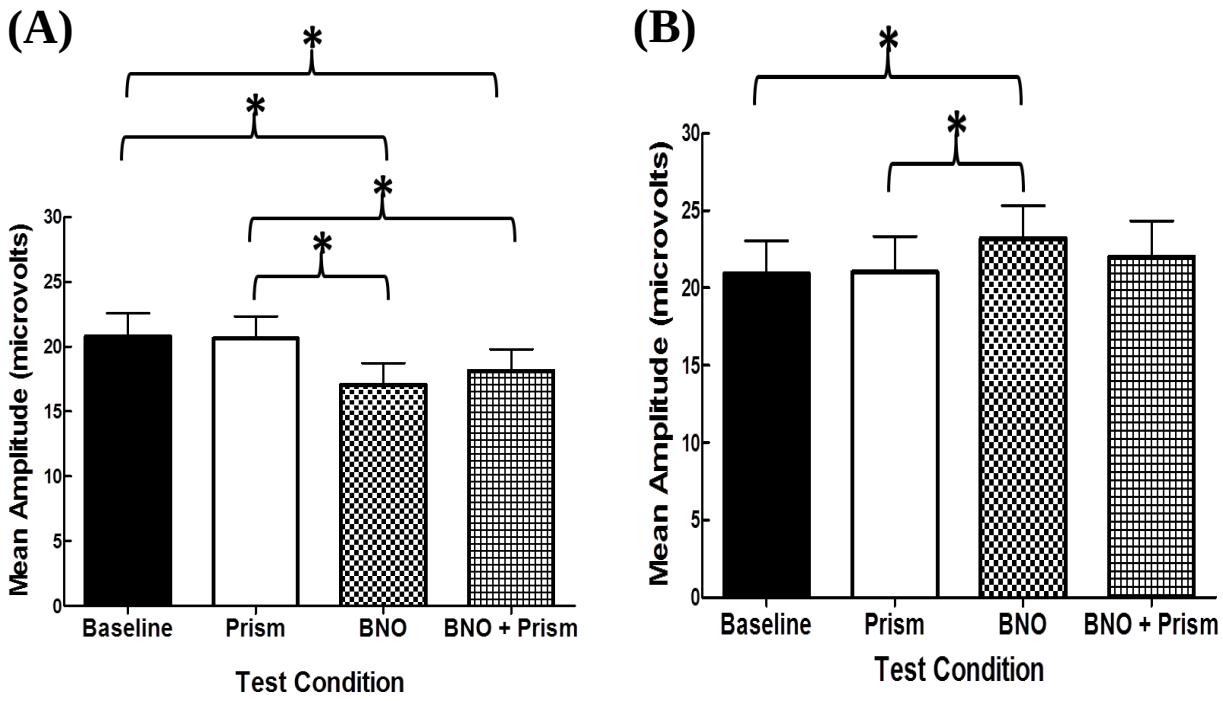


Figure 14: Group mean VEP amplitude for the four test conditions (baseline, prism, BNO, and BNO plus prism). Plotted is the mean +1 SEM. (A) visually-normal, (B) mTBI. Brackets with an asterisk (*) represent significant differences ($p < 0.05$).

Therefore, in both the groups, *only* the BNO alone condition revealed significant, but *opposite*, directional effects with respect to the baseline VEP amplitude.

Latency

Visually-normal

A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. The results revealed a significant effect of test condition on the mean VEP latency ($p = 0.0001$) in the visually-normal group (Figure 15A). The post-hoc Tukey test results showed the following two significant comparisons: first, the latency responses for the BI prism (106 ±0.57 ms) ($p = 0.01$), BNO (106 ±0.74 ms) ($p = 0.02$), and BNO plus BI prism conditions (107 ±0.62 ms) ($p = 0.001$), were each significantly increased, as compared to the baseline condition (105 ±0.57 ms). Second, latency values for the BNO plus BI prism combination ($p = 0.02$) were found to be significantly increased, as compared to the BI prism condition. However, latency values were all within normal limits for our laboratory (Yadav et al., 2012, Willeford et al., 2013a,b; Yadav et al., 2013), with the largest increase being 2 ms.

mTBI

A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. The results revealed a significant effect of test condition on the mean VEP latency ($p = 0.0001$) in the mTBI group (Figure 15B). The post-hoc Tukey test results showed the following significant comparisons: the latency responses for the BI prism (109 ±1.35 ms) ($p = 0.01$), BNO (109 ±1.48 ms) ($p = 0.001$), and BNO plus BI prism conditions (109 ±1.51 ms) ($p = 0.002$) were found to be significantly increased, as compared to the baseline condition (107 ±1.43 ms). However, all values were within

normal limits for our laboratory (Ciuffreda et al., 2013; Yadav and Ciuffreda, 2013; Yadav et al., 2014), with the largest difference being 2 ms.

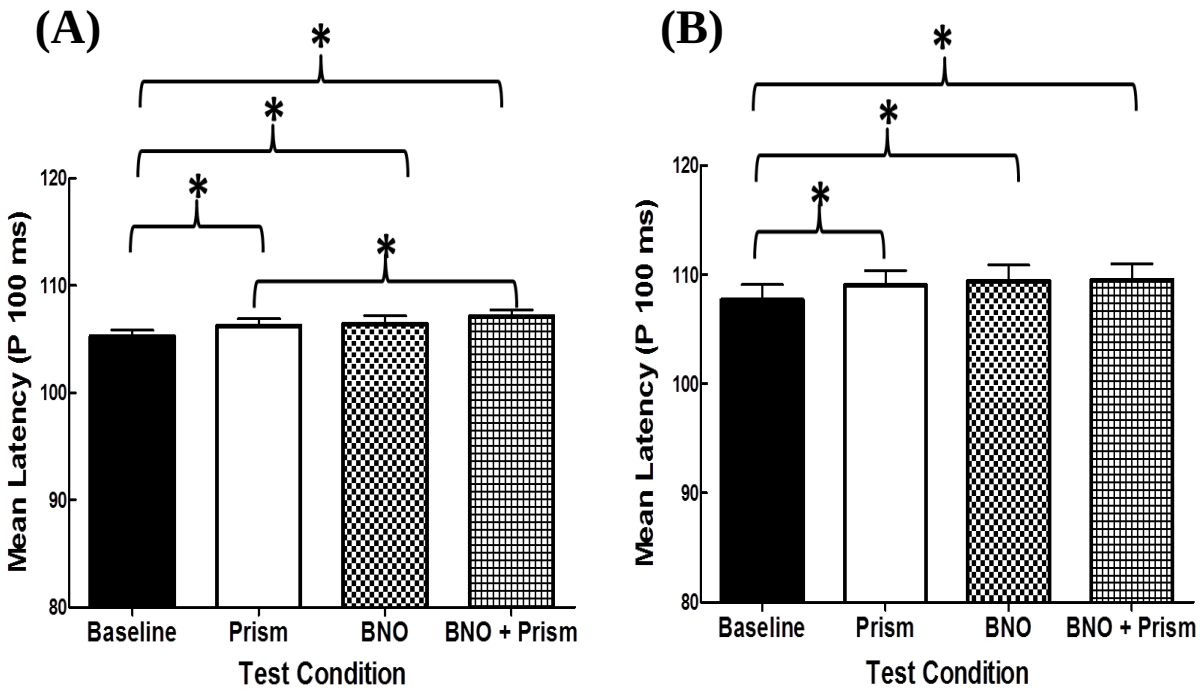


Figure 15: Group mean VEP latency (P100) for the four test conditions (baseline, prism, BNO, and BNO plus prism). Plotted is the mean +1 SEM. (A) visually-normal, (B) mTBI. Brackets with an asterisk (*) represent significant differences (p < 0.05).

Therefore, in both groups, the mean latency increased by no more than 2 ms, but it was still within normal limits for all 3 test conditions, with respect to their respective baseline values.

Percentage difference in mean VEP amplitude

Visually-normal

The percentage difference in mean amplitude for each visually-normal subject for each condition with respect to their mean baseline values are presented in Figure 16A. The percentage difference in the BI prism condition increased in 10 visually-normal subjects and decreased in the other 10 (range from -18.22 to 18.41%). In contrast, the percentage difference in the BNO condition decreased in *all* 20 visually-normal subjects (range from -49.88 to -3.15%). Lastly, the percentage difference in the BNO plus BI prism condition increased in 3 visually-normal subjects and decreased in the remaining 17 (range from -39.49 to -4.91%).

mTBI

The percentage difference in mean amplitude for each mTBI subject for each condition with respect to their mean baseline values are presented in Figure 16B. The percentage difference in the BI prism condition increased in 8 mTBI subjects and decreased in the other 7 (range from -18.80 to 22.71%). In contrast, in the BNO condition, it increased in 13 mTBI subjects and decreased in the remaining 2 (range from -9.72 to 40.6%). Lastly, the percentage difference in the BNO plus BI prism condition increased in 7 subjects and decreased in the other 8 (range from -19.39 to 92.27%).

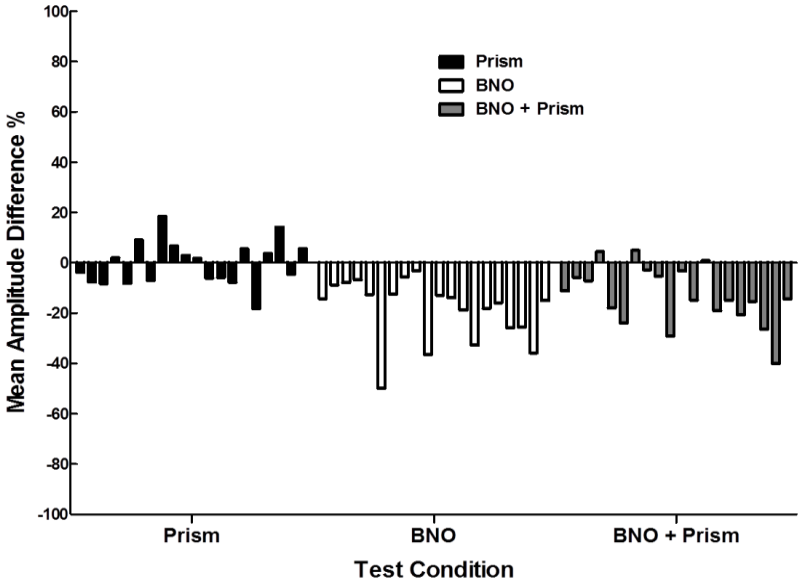


Figure 16A: Visually-normal, percentage amplitude differences for the three test conditions relative to the baseline value for each subject. Negative values indicate a decrease, and positive values indicate an increase, in amplitude.

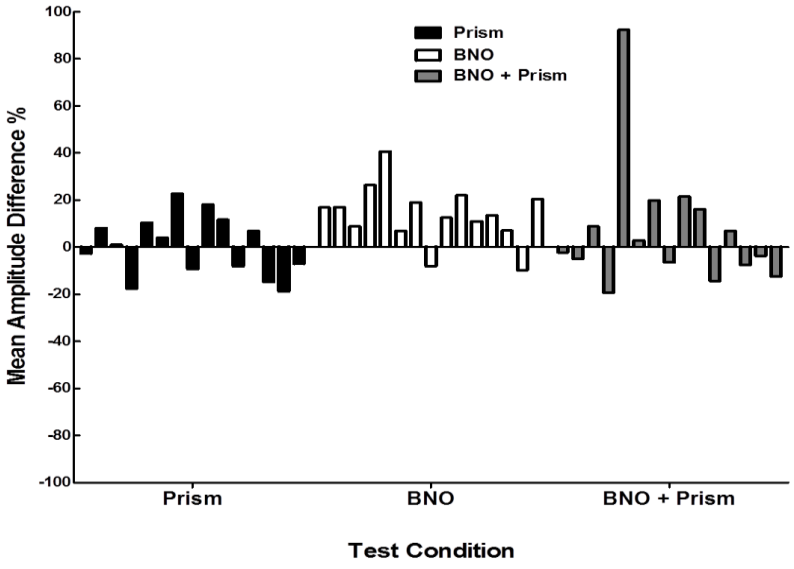


Figure 16B: mTBI, percentage amplitude differences for the three test conditions relative to the baseline value for each subject. Negative values indicate a decrease, and positive values indicate an increase, in amplitude.

Repeatability using the coefficient of variation (CV)

Repeatability was performed in 2 visually-normal and in 2 mTBI subjects after a period of 3 weeks with respect to both amplitude and latency. The coefficient of variation (CV) analysis was used (Table 1a and 1b). CV values were found to be very small for both parameters for all test conditions and groups. It ranged from 0 to 0.07, thus suggesting excellent repeatability.

Table 1a: Repeatability results for the VEP amplitude and latency in the visually-normal subjects. CV = coefficient of variation.

Amplitude			Latency		
Test condition	**Subject 1 CV**	**Subject 2 CV**	**Test condition**	**Subject 1 CV**	**Subject 2 CV**
Baseline	0.02	0.01	Baseline	0.009	0.008
Prism	0.05	0.06	Prism	0.006	0.006
BNO	0.05	0.02	BNO	0.004	0.006
BNO + Prism	0.03	0.07	BNO + Prism	0.014	0.004

Table 1b: Repeatability results for the VEP amplitude and latency in the mTBI subjects. CV = coefficient of variation.

Amplitude			Latency		
Test condition	**Subject 1 CV**	**Subject 2 CV**	**Test condition**	**Subject 1 CV**	**Subject 2 CV**
Baseline	0.03	0.03	Baseline	0	0.003
Prism	0.01	0.07	Prism	0.006	0.004
BNO	0.02	0.02	BNO	0.01	0.01
BNO + Prism	0.03	0.03	BNO + Prism	0.01	0.009

Subjective testing

The following are the results for the three subjective viewing conditions (A-C):

(A) Simple viewing task

Visually-normal

None of the visually-normal subjects experienced any perceptual effects for any of the three visual stimuli (i.e., patternless wall, stationary checkerboard pattern, and flickering checkerboard) under the four test conditions (i.e., baseline, BI prism, BNO, and BNO plus BI prism) (Figure 17A). Thus, mean rating score in the visually-normal group in all cases was 1.00 (SEM = 0).

mTBI

The group mean, perceptually-based rating scores in individuals with mTBI are presented in Figure 17B for the three visual stimuli and four test conditions, as specified above.

A repeated-measures, one-way ANOVA was performed on the group mean rating score for the factor of test condition for the patternless wall visual stimulus. The results revealed lack of a significant effect of test condition on the mean rating scores ($p > 0.05$). None of the mTBI subjects experienced any difficulty viewing the patternless wall under any of the four test conditions. All mTBI subjects perceived the wall to be flat. In addition, they were able to judge its distance readily, and none perceived any apparent motion.

A repeated-measures, one-way ANOVA was performed on the group mean rating score for the factor of test condition for the stationary, checkerboard pattern visual stimulus. The results revealed a significant effect of test condition on the mean rating scores ($p = 0.0001$). The post-hoc Tukey test results showed that the mean rating score for the BNO (1.33 ±0.12) ($p = 0.001$) and the BNO plus BI prism conditions (1.80 ±0.17) ($p = 0.02$) were each significantly decreased, as compared to the baseline value (2.8 ±0.24). Furthermore, the mean rating score for the BNO condition ($p = 0.03$) was found to be significantly decreased, as compared to the BI prism condition (2.26 ±0.24). In addition, with the BNO condition, the majority of mTBI subjects (13 out of 15) did not perceive any apparent motion of the stationary checkerboard stimulus (1.33 ±0.12), with repect to the other three test conditions. Therefore, their impressions regarding apparent motion of the stationary stimulus depended on test condition.

Lastly, a repeated-measures, one-way ANOVA was performed on the group mean rating score for the factor of test condition for the flickering, checkerboard pattern visual stimulus. The results revealed a significant effect of test condition on the mean rating scores ($p = 0.0001$). The post-hoc Tukey test results revealed that the mean rating score for the BNO (1.67 ±0.21) ($p = 0.01$) and BNO plus BI prism conditions (2.26 ±0.24) ($p = 0.02$) were each significantly decreased, as compared to the baseline value (3.13 ±0.33). Furthermore, the mean rating score for the BNO condition ($p = 0.02$) was significantly decreased, as compared to the BI prism condition (2.60 ±0.24). All mTBI subjects perceived significantly less flicker with the BNO, with respect to the other three test conditions.

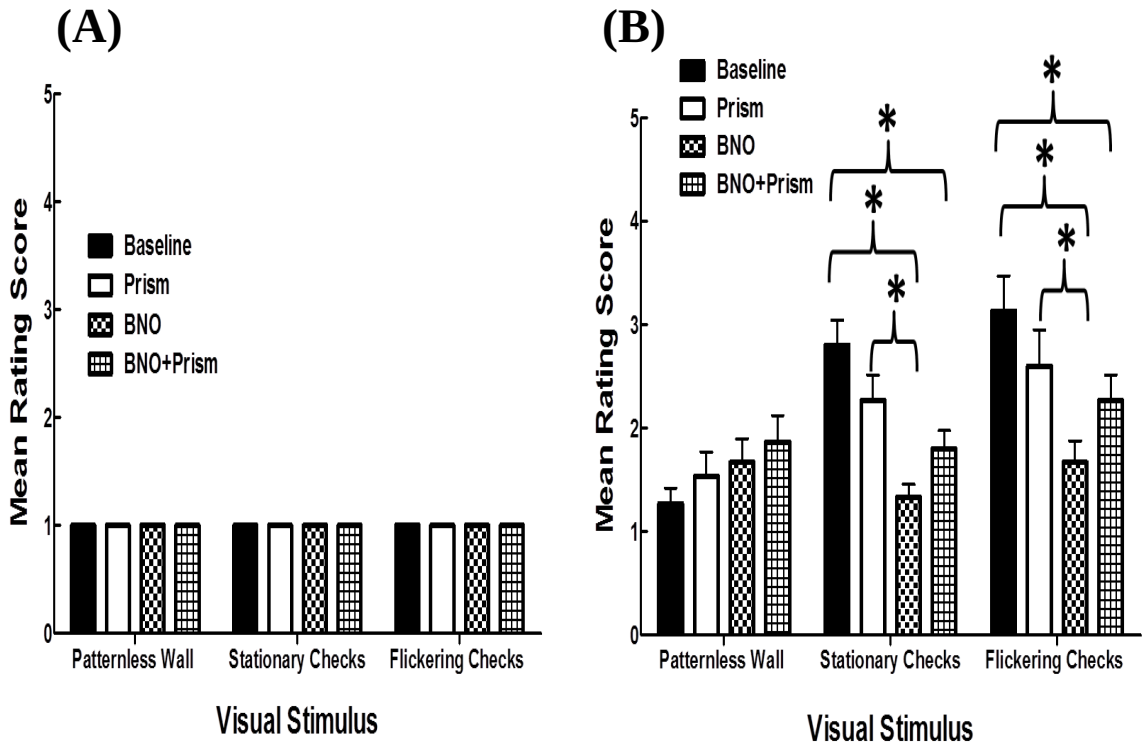


Figure 17: The group mean rating scores for each of the three visual stimuli for the four test conditions. (A) visually-normal, (B) mTBI. Brackets with an asterisk (*) represent significant differences ($p < 0.05$).

(B) Grasping task: The subjective responses in the mTBI group for the grasping task are presented in Table 2a for the four test conditions. This task was found to be easier in those subjects who did not report a baseline distance perception problem, as compared to those that did. In contrast, visually-normal individuals did not experience any difficulty in performing this task.

Table 2a: Perceptually-based, subjective responses for the grasping task in the mTBI group.

mTBI subjects (n=15)	Subjective responses
10 with no distance perception problem	Easy to grasp an object under all test conditions
5 with distance perception problem	**With Baseline, Prism**, **and BNO+P** – difficult to judge distance, slow in grasping **With BNO alone** – able to judge distance better and easier to grasp objects

(C) Walking task: The subjective responses in the mTBI group for the walking task are presented in Table 2b for the four test conditions. Thirteen of the 15 subjects were found to respond positively with the BNO; that is, they reported being more comfortable, stable, and confident, and perceiving less "visual noise", as compared to the other test conditions. In contrast, visually-normal individuals did not experience any difficulty in performing this task.

Table 2b: Perceptually-based, subjective responses for the walking task in the mTBI group.

mTBI subjects (n=15)	Subjective responses
11	most comfortable and most stable walking with the BNO alone
2	most comfortable and most stable, as well as confident, walking with the BNO alone
1	most comfortable, most stable, brain feels “relaxed”, reduced attention to peripheral motion/noise, can “control” surrounding visual information to prevent a sensory overload
2	uncomfortable walking either with BNO or BNO+Prism, BNO blocked their field-of-view, provided a sense of visual discomfort and annoyance

1.3.3 *Experiment #3*

VEP analysis

The group mean VEP amplitude (19.20 µV, SEM = ±2.38) and latency (108.86 ms, SEM = ±1.84) values were found to be within normal limits for our laboratory (Ciuffreda et al., 2013; Yadav and Ciuffreda, 2013; Yadav et al., 2014). This testing was performed to confirm VEP response normalcy before assessing the attentionally-related alpha power.

Power spectrum analysis

mTBI with an attention deficit (n=11)

A one-way ANOVA was performed for the factor of power for each alpha frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) across all 3 tests conditions. The results revealed no significant effect of power on the alpha band frequency ($p > 0.05$) (Figure 18A).

A one-way ANOVA for each alpha frequency comparing between conditions 1, 2, and 3 was performed. The results revealed a significant difference between conditions ($p = 0.02$). However, it was only significant for the 11 Hz alpha frequency. The post-hoc Tukey test results at 11 Hz showed that the EO condition power (μV^2) value was significantly reduced, as compared to the ECNC condition ($p = 0.01$).

mTBI without an attention deficit (n=5)

A one-way ANOVA was performed for the factor of power for each alpha frequency across all 3 test conditions. The results revealed a significant effect of power

on the alpha band frequency ($p = 0.01$) (Figure 18B). The post-hoc Tukey test results showed that at 10 Hz ($p = 0.01$) and 11 Hz ($p = 0.02$) the power (μV^2) values were significantly larger, as compared to 13 Hz. No other comparisons were found to be significant ($p > 0.05$).

A one-way ANOVA for each alpha frequency comparing conditions 1, 2, and 3 was performed. The one-way ANOVA found significant differences between conditions per the following alpha frequencies:

9 Hz: There were significant differences between conditions ($p = 0.03$). The post-hoc Tukey test results revealed that the EO condition ($p = 0.01$) power (μV^2) value was significantly less, as compared to the EC condition. No other comparisons were found to be significant ($p > 0.05$).

10 Hz: There were significant differences between conditions ($p = 0.003$). The post-hoc Tukey test results revealed that the EO ($p = 0.001$) and ECNC conditions ($p = 0.01$) power (μV^2) values were significantly less, as compared to the EC condition. No other comparisons were found to be significant ($p > 0.05$).

11 Hz: There were significant differences between conditions (0.008). The post-hoc Tukey test results revealed that the EO condition power (μV^2) value was significantly less, as compared to the EC ($p = 0.01$) and the ECNC conditions ($p = 0.02$). No other comparisons were found to be significant ($p > 0.05$).

12 Hz: There were significant differences between conditions (0.003). The post-hoc Tukey test results revealed that the EO condition power (μV^2) value was significantly less, as compared to the EC ($p = 0.02$) and the ECNC conditions ($p = 0.01$). No other comparisons were found to be significant ($p > 0.05$).

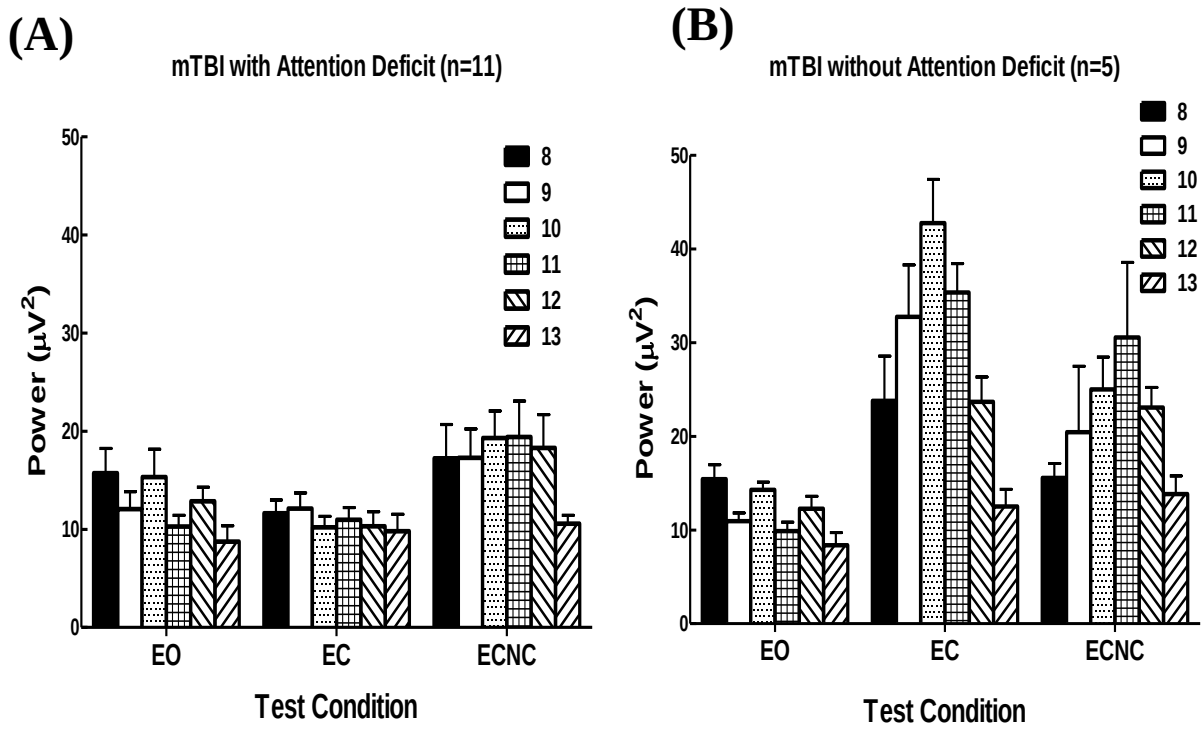


Figure 18: The group mean power spectrum value (μV^2) at each alpha band frequency (8-13 Hz) for the 3 test conditions. Plotted is the mean +1 SEM. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit. Symbols: EO = eyes-open, EC = eyes-closed, and ECNC = eyes-closed number counting.

Alpha Attenuation Ratio (AR): Individual alpha frequencies

Eyes-closed ÷ Eyes-open (EC ÷ EO)

The group mean AR for *each* alpha frequency for individuals with mTBI and an attentional deficit is presented in Figure 19A. The mean AR at each alpha frequency was found to be lower, as compared to the normative AR value of ≥2:00 (Willeford et al., 2013a,b), with a range from 0.806 to 1.36. A one-way, repeated-measures ANOVA was

performed for the factor of AR at each alpha frequency. The results revealed a significant effect of AR on the alpha frequencies ($p = 0.01$). The post-hoc Tukey test results showed that the AR at 10 Hz was significantly lower than the AR at 13 Hz ($p = 0.01$). No other comparisons were found to be significant ($p > 0.05$).

The group mean AR for *each* alpha frequency for individuals with mTBI but without an attention deficit is presented in Figure 19B. The mean AR at 9, 10, 11, and 12 Hz was ≥2:00, which was normal (Willeford et al., 2013a,b), with a range from 1.59 to 3.92. A one-way, repeated-measures ANOVA was performed for the factor of AR at each alpha frequency. The results revealed a significant effect of AR on the alpha frequencies ($p = 0.006$). The post-hoc Tukey test results revealed that AR at 8 Hz ($p = 0.01$) and 13 Hz ($p = 0.02$) were significantly lower than the AR at 11 Hz ($p < 0.05$).

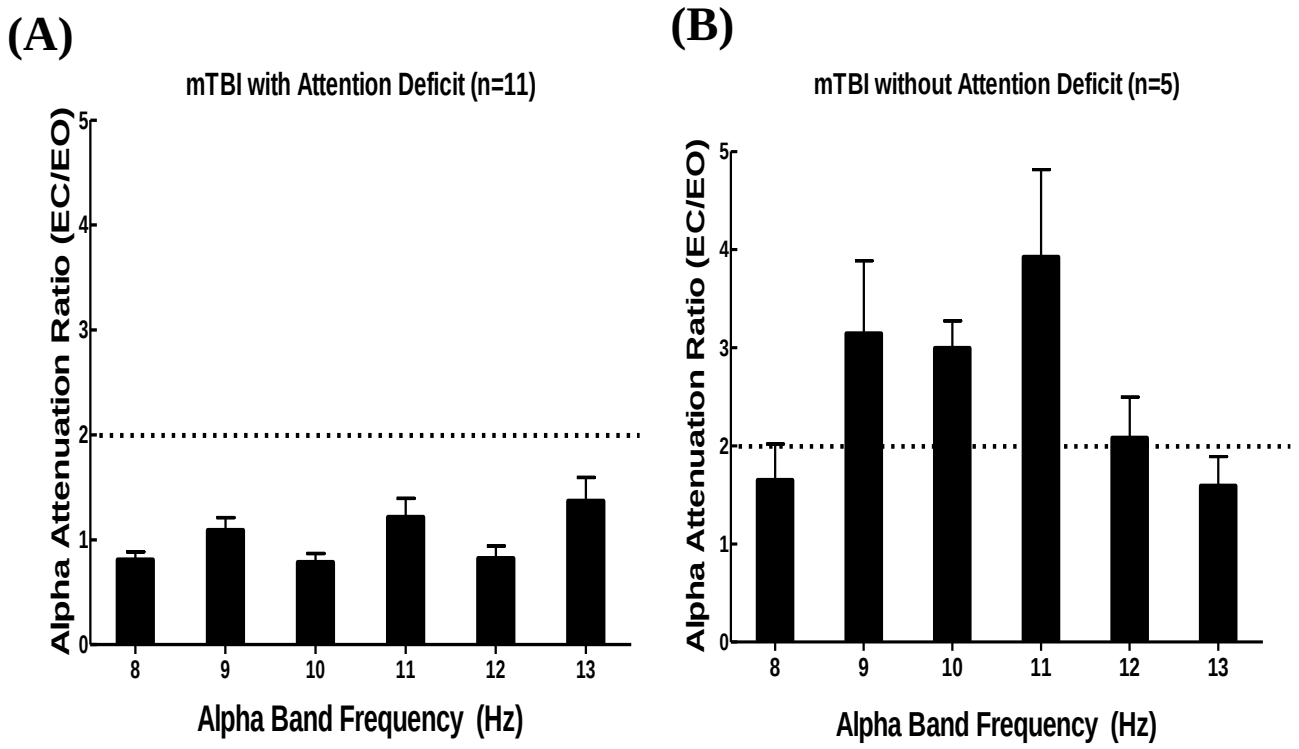


Figure 19: The group mean alpha attenuation ratio (AR) (EC ÷ EO) for each alpha frequency. Plotted is the mean +1SEM. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit.

Eyes-closed Number Counting ÷ Eyes-closed (ECNC ÷ EC)

The group mean AR for *each* alpha frequency for individuals with mTBI and an attentional deficit is presented in Figure 20A. The mean AR at each alpha frequency was higher, as compared to the normative AR value of <1.00 (Fuller, 1978; Willeford et al., 2013a), with a range from 1.27 to 2.24. A one-way, repeated-measures ANOVA was performed for the factor of AR at each alpha frequency. The results revealed no significant effect of AR on the alpha frequencies ($p > 0.05$).

The group mean AR for *each* alpha frequency for individuals with mTBI but without an attentional deficit is presented in Figure 20B. The mean AR at 8, 9, 10, 11, and 12 Hz was <1.00, which was normal (Fuller, 1978; Willeford et al., 2013a), with a range from 0.59 to 1.10. A one-way, repeated-measures ANOVA was performed for the factor of AR at each alpha frequency. The results revealed a significant effect of AR on the alpha frequencies ($p = 0.02$). The post-hoc Tukey test results revealed that the AR at 10 Hz was significantly lower than the AR at 13 Hz ($p = 0.01$). No other comparisons were found to be significant ($p > 0.05$).

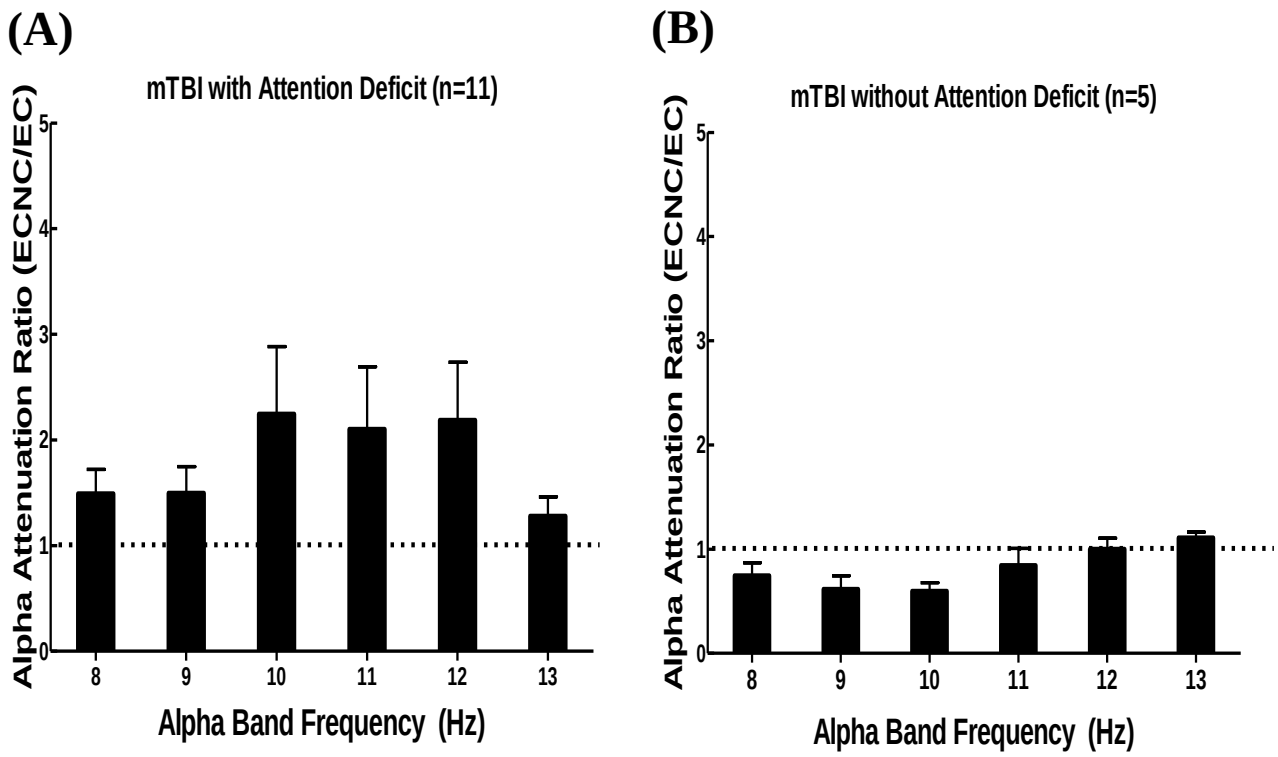


Figure 20: The group mean alpha attenuation ratio (AR) (ECNC ÷ EC) for each alpha frequency. Plotted is the mean +1SEM. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit.

Alpha Attenuation Ratio (AR): combined across the alpha frequency band (i.e., from 8-13 Hz)

Eyes-closed ÷ Eyes-open (EC ÷ EO)

The AR combined across the alpha frequency band for each individual with mTBI and an attentional deficit is presented in Figure 21A. The combined AR was 1.01 (SEM = 0.07) with a range from 0.62 to 1.33. It was lower than the mean normative AR value of ≥2:00 (Willeford et al., 2013a,b).

The AR combined across the alpha frequency band for each individual with mTBI but without an attentional deficit is presented in Figure 21B. The combined AR was 2.19 (SEM = 0.03) with a range from 2.07 to 2.18. It was ≥2:00, which was normal (Willeford et al., 2013a,b).

An unpaired, two-tailed, t-test was performed between subgroups for the AR combined across the alpha frequency band. It was found to be significantly higher in the mTBI without an attentional deficit ($p = 0.0001$).

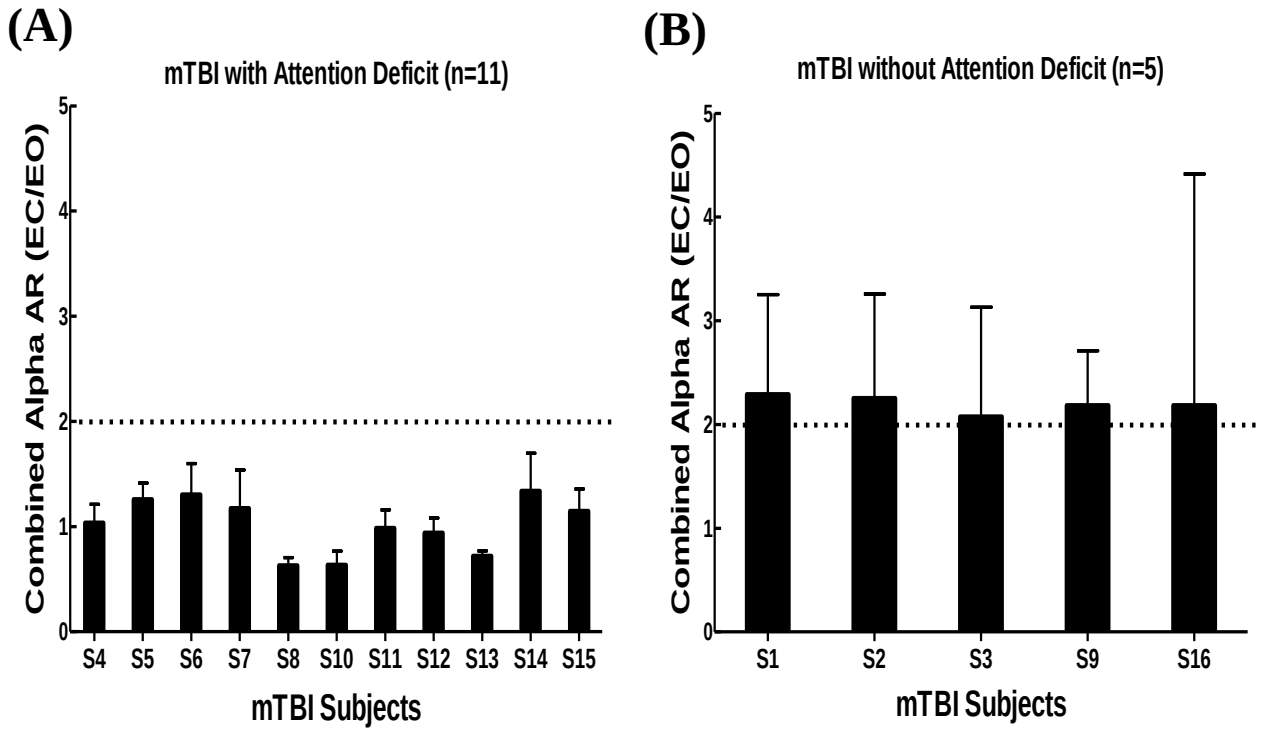


Figure 21: The attenuation ratio (AR) (EC ÷ EO) combined across the alpha frequency band (8-13 Hz). Plotted is the mean +1SD. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit.

Eyes-closed Number Counting ÷ Eyes-closed (ECNC ÷ EC)

The AR combined across the alpha frequency band for each individual with mTBI and an attentional deficit is presented in Figure 22A. The combined AR was 1.79 (SEM = 0.96) with a range from 0.86 to 4.33. It was higher (except subjects #12 and 13) than the normative AR value of <1.00 (Fuller, 1978; Willeford et al., 2013a). However, in these two subjects, the error bars (+SD) crossed into the abnormal range.

The AR combined across the alpha frequency band for each individual with mTBI but without an attentional deficit is presented in Figure 22B. The combined AR was

0.806 (SEM = 0.02) with a range from 0.71 to 0.86. It was <1.00, which was normal (Fuller, 1978; Willeford et al., 2013a).

An unpaired, two-tailed, t-test was performed between subgroups for the AR combined across the alpha frequency band. It was found to be significantly smaller in mTBI without an attentional deficit (p = 0.04).

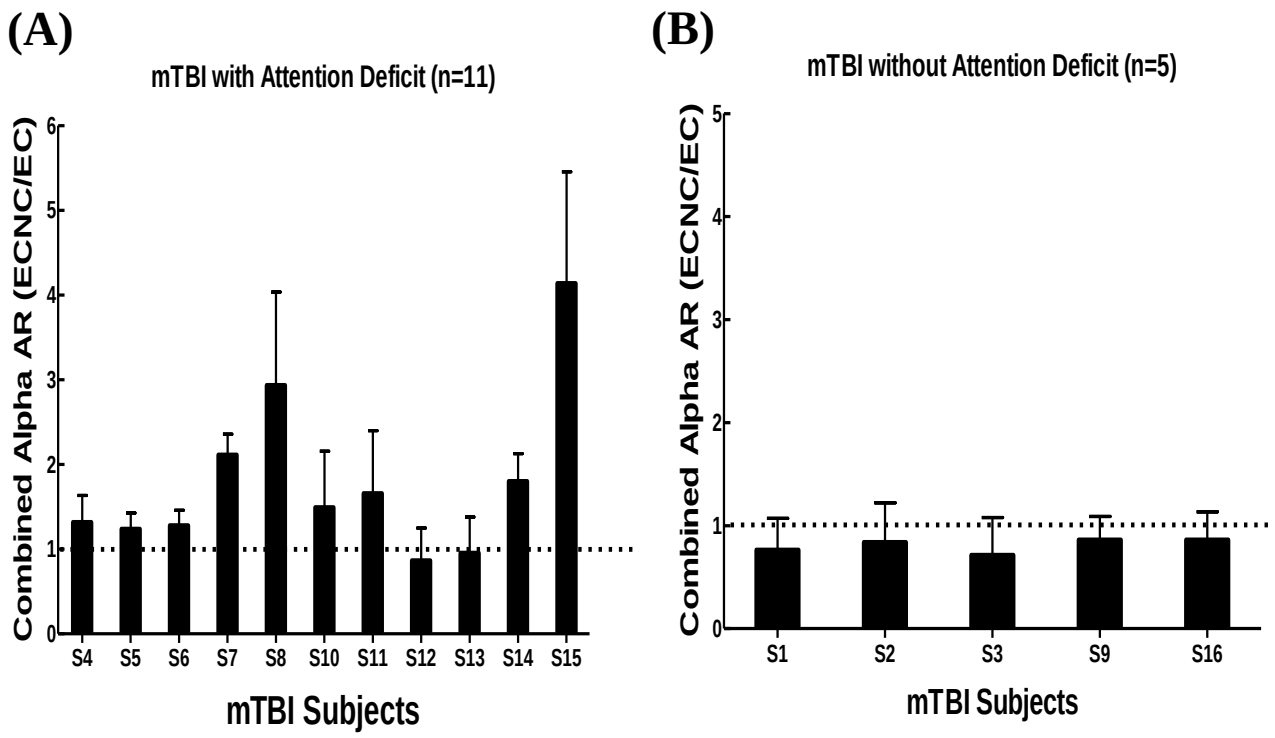


Figure 22: The attenuation ratio (AR) (ECNC ÷ EO) combined across the alpha frequency band (8-13 Hz). Plotted is the mean +1SD. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit.

Adult ADHD Self-Report Scale (ASRS)

The Part A questionnaire scores for the ASRS test for each subject are presented in Table 3. If the scores were in a range from 0-16, 17-23, and 24 or greater, the subject was unlikely, likely, and highly likely to manifest an attentional deficit, respectively. In mTBI with a self-reported attentional deficit *(n=11)*, the mean score was 22.81 (SEM = 0.97), with a range from 17 to 28. In contrast, in mTBI without a self-reported attentional deficit *(n=5)*, the mean score was 12.4 (SEM = 1.36), with a range from 8 to16. An unpaired, two-tailed, t-test was performed between subgroups per the ASRS score. It was significantly higher in those having mTBI and an attentional deficit ($p = 0.0003$).

Visual Search and Attention Test (VSAT)

The VSAT percentile scores for each subject are presented in Table 3. In mTBI with a self-reported attentional deficit *(n=11)*, the mean VSAT percentile score was 54.72 (SEM = 10.95) with a range from 1 to 93. In contrast, the mTBI without a self-reported attentional deficit *(n=5)*, the mean VSAT percentile score was 68.8 (SEM = 14.54), with a range from 12 to 95. Subjects S10 and S9 had borderline 6th and 12th percentile scores, respectively, and subject S12 had an abnormal 1st percentile score. The unpaired, two-tailed, t-test was performed between subgroups per the VSAT percentile scores. No significant difference was found ($p > 0.05$).

Table 3: Attentional Adult ADHD Self-Report Scale (ASRS) Part A and Visual Search and Attention Test (VSAT) score for each individual with mTBI.

Subjects	ASRS Part A Questionnaire Score	VSAT Percentile Score
S1	13	81
S2	11	77
S3	16	95
S4	21	93
S5	25	90
S6	28	75
S7	20	31
S8	17	93
S9	14	12
S10	22	6
S11	26	87
S12	25	1
S13	25	65
S14	20	15
S15	22	46
S16	8	79

Bold, italics subjects (***S***) represent those with a self-reported visual attentional deficit.

Correlations

Correlation analysis was performed between the different parameters for all individuals with mTBI (n=16). The following correlations were significant: first, the correlation between AR for the EC ÷ EO condition and the ASRS score at most alpha frequencies were found to be significant: 8 ($p = 0.01$), 9 ($p = 0.001$), 10 ($p = 0.0001$), 11 ($p = 0.0006$), and 12 ($p = 0.005$) Hz ($r = +0.62$ to $+0.83$,), with it highest at 9, 10, and 11 Hz ($r = +0.73$ to $+0.83$). Second, correlation was also found to be significant between the AR for the EC ÷ EO condition combined across the alpha frequency band and the ASRS scores ($r = 0.76$; $p = 0.006$). Lastly, correlation between the AR for the ECNC ÷ EC condition and the ASRS score at each alpha frequency was significant, but only at 8 Hz ($r = 0.53$, $p = 0.03$). There were no significant correlations with VSAT scores ($p > 0.05$).

Repeatability

Repeatability was performed in 2 individuals with, and 2 individuals without, an attentional deficit after a period of 2 weeks with respect to power spectrum values across all 3 conditions for each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz), amplitude, and latency. The coefficient of variation (CV) analysis was used. CV values across all parameters were typically found to be extremely small (median = 0.09, range = 0.003 to 0.58) in the subgroups, and thus suggesting excellent repeatability.

1.3.4 *Experiment #4*

Group Data

Amplitude

The group mean VEP amplitude for the central, intact, and hemianopic visual fields for the three stimulus combinations (i.e., HC/HL, LC/HL, and LL/HC) are presented in Figure 23A. A one-way ANOVA for the factor of visual field at HC/HL was found to be significant ($p = 0.02$). The post-hoc Tukey test results revealed that the amplitudes for the central ($p = 0.01$) and intact fields ($p = 0.02$) were significantly larger, as compared to the hemianopic field. A one-way ANOVA for the factor of visual field at LC/HL was found to be significant ($p = 0.02$). The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger, as compared to the hemianopic field ($p = 0.01$). A one-way ANOVA for the factor of visual field at LL/HC was also found to be significant ($p = 0.03$). The post-hoc Tukey test results revealed that the amplitudes for the central ($p = 0.01$) and intact fields ($p = 0.02$) were significantly larger, as compared to the hemianopic field.

Latency

The group mean VEP latency (P 100 ms) for the central, intact, and hemianopic visual fields for the three stimulus combinations are presented in Figure 23B. A one-way ANOVA for the factor of visual field for each of the three stimulus combinations was not found to be significant ($p > 0.05$). This may be due to either the small sample size or the increased variability found in their hemianopic field.

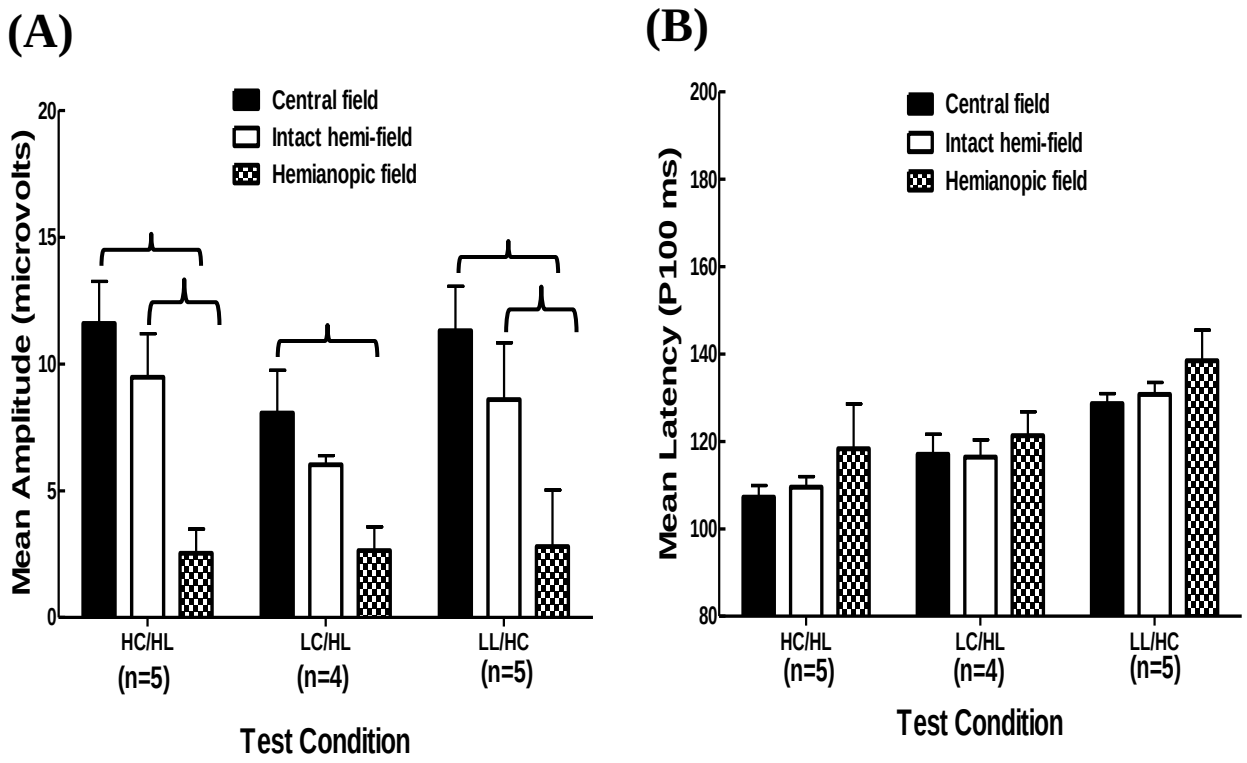


Figure 23: Group mean VEP responses for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). Plotted is the mean +1SEM. (A) Amplitude (microvolts) (B) Latency (ms). Brackets indicate statistically significant comparisons ($p < 0.05$).

Individual Subject Data

The same analyses were performed on the VEP amplitude and latency data for each subject. The results were similar to the group findings. See Figures 24A and B for a representative subject. Details for each subject are presented in Paper #4. Sample VEP

waveforms for one subject for the 3 conditions (i.e., central field, intact hemi-field, and hemianopic field) are presented in Figure 25 A, B, and C.

Repeatability

Repeatability results for subject #5 are presented in Figure 24A and B for amplitude and latency, respectively. Repeatability was assessed after a period of 1 week. The CV (median, range) across the three visual fields and three stimulus combinations were: amplitude (median = 0.05, range = 0.02 to 0.80) and latency (median = 0.01, range = 0.0002 to 0.019), thus suggesting repeatability.

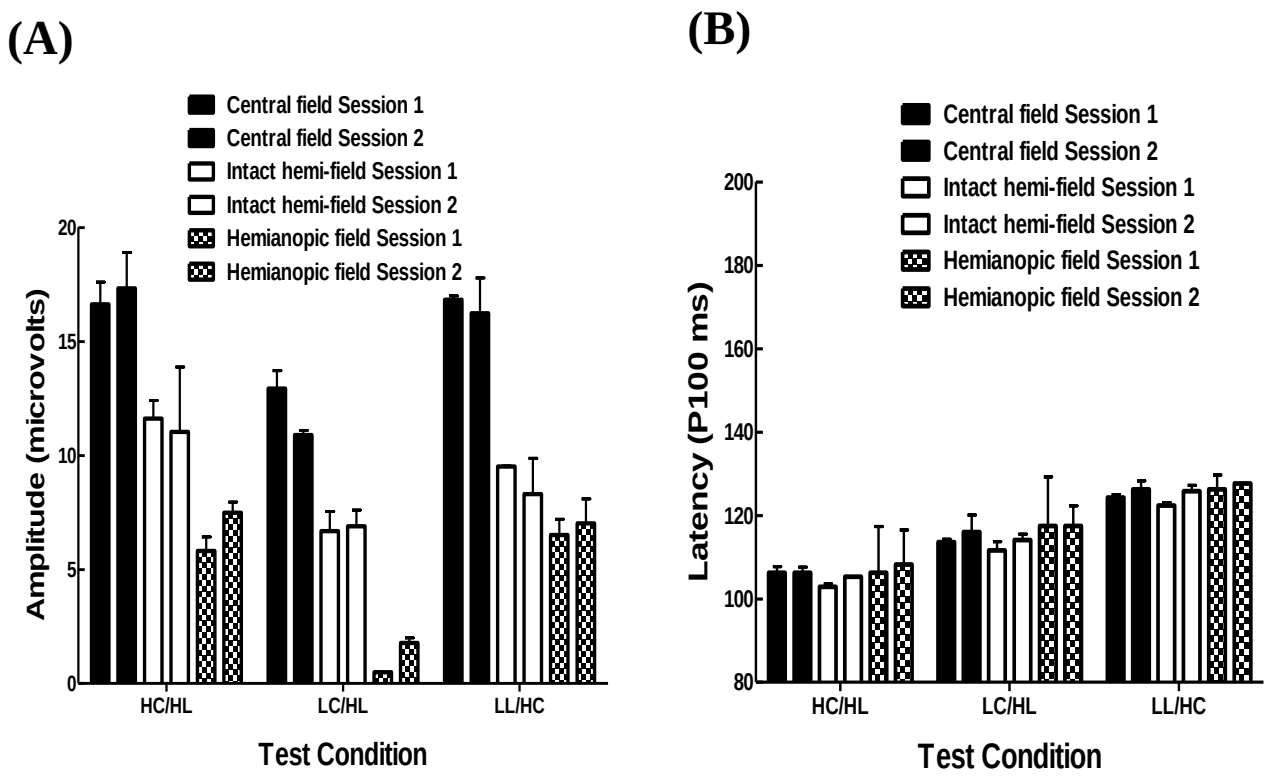


Figure 24: **Repeatability assessment. Mean VEP responses of subject #5 for session 1 and 2 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). Plotted is the mean +1SD. (A) Amplitude (microvolts) (B) Latency (ms).**

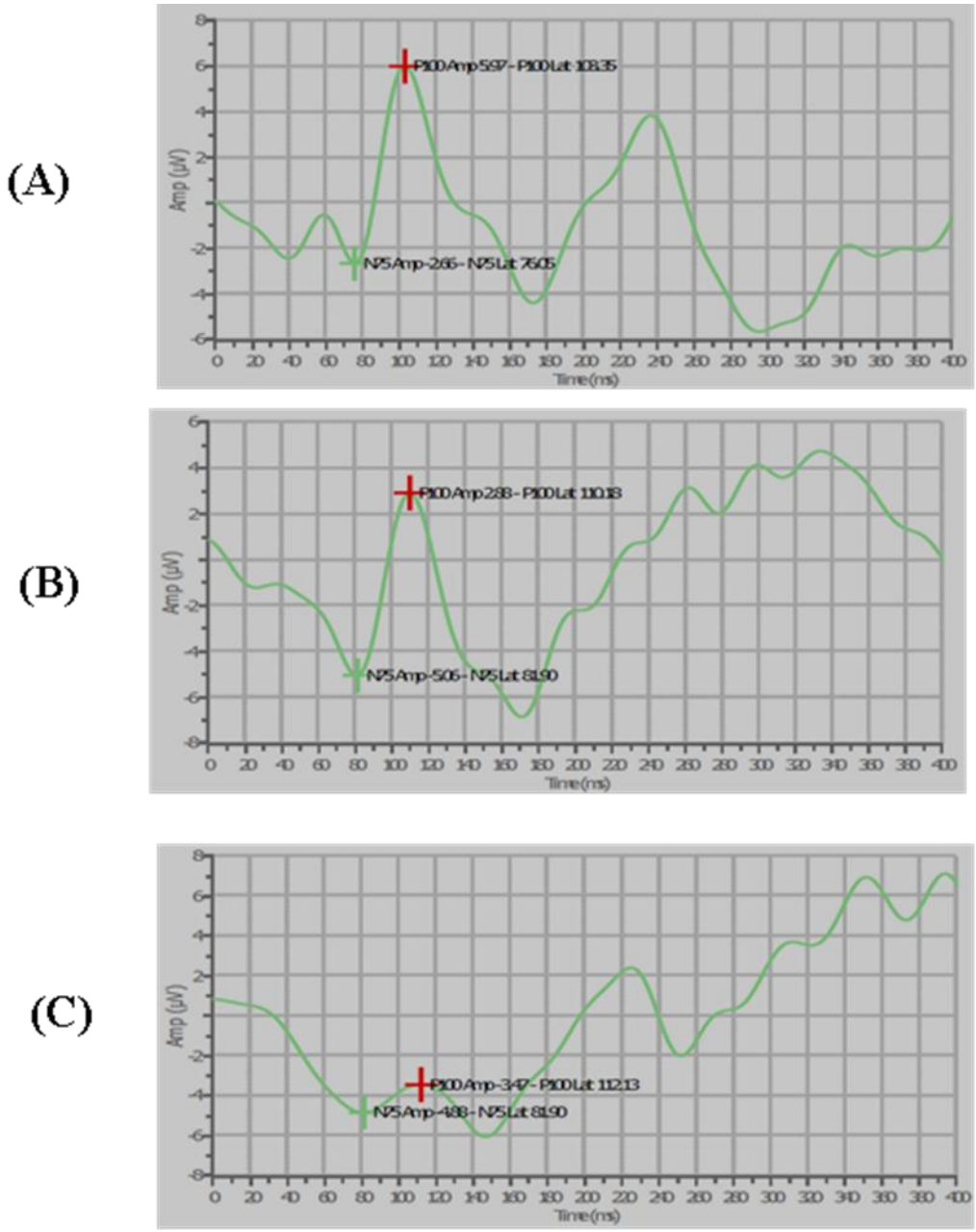


Figure 25: VEP waveforms for a hemianopic subject: (A) central field, (B) intact hemi-field, and (C) hemianopic field. The green "plus sign" represents the cursor for N75, and the red "plus sign" represents the cursor for P100.

1.4 Discussion

1.4.1 *Experiment #1*

The findings of the present study resulted in the desired optimized VEP parameters (i.e., check size and contrast) for both the visually-normal and mTBI populations. These optimal parameters provided reliable and maximal VEP responsivity in both groups. Furthermore, the VEP responses elicited with these two VEP test parameters were helpful in understanding the differential neuronal visual processing as related to the parvocellular (P) and magnocellular (M) pathways at the retinal and visuo-cortical levels in both groups. These optimized parameters were also able to differentiate between two mTBI subgroups (asymptomatic versus symptomatic). Lastly, the optimal parameters provided a significant correlation between time since their last brain injury and the VEP response.

Results in the visually-normal group showed that the VEP amplitude and latency were significantly affected by stimulus check size and contrast. The 20 min arc check size provided the largest VEP amplitude *and* normative latency values at both contrast levels. None of the other check size/contrast combinations provided similarly large, normal, and consistent VEP findings.

This was the first study to assess specifically the effect of different check sizes and contrast levels on VEP responsivity in individuals with mTBI. The findings of the present study demonstrated that the VEP responses were significantly affected by these two stimulus parameters. The 20 min arc check size provided the largest VEP amplitudes and normative latency values at both contrast levels. None of the other check

size/contrast combination provided similarly large and consistent findings. Furthermore, and quite fortunately, these optimal check size and contrast parameters are the *same* as that found in the visually-normal group. Therefore, these findings provided a *common*, targeted, objective protocol which makes clinical VEP testing more simplified in these two populations.

Neurophysiological mechanisms (visually-normal and mTBI)

What might be the possible underlying neurophysiological mechanisms that may be able to explain these optimized VEP responses in both groups? Stimulus check size was increased by a factor of two (i.e., 10, 20, and 40 min arc) in the present study. Based on the Osterberg (1935), and Curcio et al. (1990), quantitative information regarding human retinal topography, the 10 min arc check size should only be resolvable by the receptive field (RF) of foveal cones, but not by the cones across the whole tested retinal eccentricity (i.e., approximately 8 degrees radius). In contrast, the 20 min arc check size would be optimally resolvable by the RF of both foveal and near peripheral cones. Related to the above, Yadav et al. (2012), and Meredith and Celesia (1982), demonstrated that the VEP response was derived from the cumulative responses of cones across the retina, and not primarily from foveal cones only. These results suggest that the 20 min arc check size was able to stimulate a maximal number of cones across the tested field. Therefore, the 20 min arc check size was also able to stimulate the maximum number of retinal ganglion cells. Retinal ganglion cells transmit this information to both the parvocellular and magnocellular layers of the lateral geniculate nucleus (LGN). The LGN

transfers this information to the primary visual cortex (V1), where it produces maximal stimulation of the RF of cortical neurons at the V1 level. This result in an increase in neuronal activity at the visuo-cortical level, and thus produces larger VEP amplitude together with normative latency. Furthermore, the VEP aplitude not only depends on the response level of individual cells but also the overall number of cells responding in V1 and the extrastriate cortex. Another factor is the phase of the cells. The response will be greater if the individual cells responses are in phase and they sum to produce a larger response. These factors play a role in determining why a 20 min arc check size produces the largest amplitude. Individual cones may have less of an effect.

Proposed VEP protocol

Based on the present study findings, it is proposed that the following protocol be used clinically to quantify VEP responses optimally in both the visually-normal and mTBI groups:

- **Check size** – 20 min arc
- **Contrast –** Low contrast (20%) and high contrast (85%)
- **Luminance –** 74 cd/m^2
- **Trial duration –** 20 seconds (45 seconds if variability is high) (Willeford et al., 2013b).

- **Number of trials –** 3-5 trials (Ciuffreda et al., 2013; Willeford et al., 2013a,b) should be performed at each stimulus conditions. In addition, one outlier out of the 3-5 trials should be removed, and then the mean of the remaining 2-4 trials should be representative of the overall mean VEP response.

The proposed clinical protocol should be helpful for the clinicians in reducing the VEP test time. This would help to prevent fatigue effects and maintain visual attention during the VEP testing. It would eventually help in reducing VEP response variability, and thus yield more repeatable, reliable measurements. In addition, two individuals with mTBI (~13%) were found to have delayed latency relative to the upper range found in normals at the lower contrast (20%).

Neurophysiological differences (visually-normal and mTBI)

There were two important differences in VEP responsivity found between two groups for the different check sizes and contrasts. First, at low contrast, the response amplitudes were dissimilar between the two groups; however, they were similar at high contrast. Second, for the 20 min arc check size, latencies were found to be different. These neurophysiological differences might be attributed to magnocelluar pathway deficits (Chang et al., 2007; Patel et al., 2011; Ciuffreda et al., 2013) and diffuse axonal injury (DAI) (Thiabault and Gennareli, 1990; Mendez et al., 2005) in individuals with mTBI, as compared to the visually-normal group. They may also be helpful in the objective, differential diagnosis between the two subgroups.

Clinical implications

These optimized VEP parameters have several important clinical implications. First, and most importantly, they provide a clinical VEP protocol which is simple, rapid, high yield, and targeted for the mTBI population. Both clinicians and researchers could use the suggested VEP protocol to obtain a comparable normative data base for direct comparison in individuals with mTBI, as the proposed VEP protocol was found to be the same for both groups. This protocol would be helpful in the *differential diagnosis* between visually-normal individuals and those suspected of having concussion/mTBI, especially in the cognitively-impaired patients or in individuals with vague visual symptoms. Second, the proposed VEP protocol is also helpful in the assessment of the basic axonal integrity of the P and M pathways at both the retinal and visuo-cortical levels. Third, it is well-known that mTBI patients fatigue quickly during testing (Ciuffreda 2011 a,b). Therefore, this objective VEP protocol makes clinical testing more rapid and targeted in assessing for potential visual abnormalities at the visuo-cortical level. Fourth, and lastly, this protocol could be used to measure baseline VEP responses in both warfighters and sportsmen before their deployment in the battle-field and sports-field, respectively, as these two populations are highly vulnerable to concussion/mTBI (Warden, 2006; Guskiewickz et al., 2005). These baseline responses would later be compared when they show signs and/or symptoms of possible post-concussive syndrome. This information would help clinicians by providing an objectively-based diagnosis for the presence of a concussion/mTBI, in addition to the traditional clinical assessment of these patients.

Conclusions

The current findings provide an optimal VEP testing protocol for both normals and those with mTBI. In both groups, the 20 min arc check size at both low (20%) and high (85%) contrast levels provided the largest VEP amplitude, in conjunction with normal latency values. The proposed protocol is rapid, high yield, and targeted for each diagnostic group. The suggested VEP protocol would be beneficial in assessing the functionality and integrity of the visuo-cortical pathway in the mTBI group, especially the magnocellular pathway.

1.4.2 *Experiment #2*

The findings of the present study clearly demonstrated that the BNO *alone* provided consistent and significant increases in the VEP amplitude in almost all (~90%) individuals with mTBI *and* increased VMS, as compared to the other 2 test conditions and baseline. The present study confirmed and extended the earlier results of Ciuffreda et al. (2013), which showed that with BNO alone, 100% of their mTBI population with VMS exhibited a significant increase in VEP amplitude as compared to baseline. Most importantly, and a key new result, the current findings were able to disambiguate the interactive effects of the BNO and BI prism on VEP responsivity in both the mTBI and visually-normal groups. With BNO alone, VEP amplitude responses were larger in the mTBI group and smaller in the visually-normal group, as compared to the BI prisms, either alone or in combination with the BNO. These BNO-VEP findings were found to be repeatable and reliable in both groups. Thus, the BNO alone condition was able to differentiate between the two diagnostic groups at a high probability level.

With BNO only, the objective VEP results were found to be correlated with the individual's visual impressions and sensorimotor performance, as compared to the other test conditions. BNO alone revealed the most consistent improvements in their visual perceptions and in performing the specific sensorimotor tasks in those with mTBI and VMS. They also perceived less flickering of the VEP checkerboard stimulus with the BNO. Furthermore, the sensorimotor task was reported to be easier to perform with BNO alone. In addition, walking in the long hallway was found to be most comfortable, and performed with more confidence, with the BNO only. Lastly, reduction of VMS symptoms was reported with the BNO condition only.

Possible underlying neurophysiological mechanisms

Ciuffreda et al., (2013) proposed two possible, primary underlying neurophysiological mechanisms to explain VEP responsivity with BNO alone in individuals with mTBI. The first mechanism incorporated the notion of "spread of suppression" (described in the Introduction), and the second involved a "faulty" neural filtering mechanism. The later mechanism suggested that the individuals with mTBI and VMS might not be able to filter unwanted and bothersome peripheral visual motion information from entering their visual processing stream (Hillyard et al., 1998). Therefore, they may have a relatively low, signal-to-noise ratio (S/N) for the incoming and bothersome visual information, which was presumably averaged across the visual field. With introduction of the BNO, however, less of the irrelevant visual information would be present. This filtering phenomenon would produce enhancement in the global neural S/N ratio, which would in turn increase the VEP amplitude. The present results are consistent with either mechanism, or both in combination. However, a third possible mechanism was also proposed. This involved visual attention. BNO likely reduces some of the irrelevant and distracting peripheral visual motion information from the occluded bitemporal retinal regions. Therefore, it is speculated to cause attentional weighting to be shifted back to the central visual field to some extent, and thus produces an increase in the VEP amplitude in the mTBI population. Moreover, increased visual attention has been confirmed to increase the VEP amplitude in those with mTBI (Yadav et al., 2014).

Clinical implications

The findings of the present study have several clinical implications. First, and most importantly, the current study *for the first time* was able to assess objectively and quantitatively the effect, and relative contribution, of the BNO and BI prisms on VEP responsivity in mTBI and in the visually-normals. Furthermore, BNO alone had a high probability of differentially diagnosing the individuals with mTBI and VMS from the visually-normal group. With BNO only, ~90% of those with mTBI demonstrated an increase in VEP amplitude, as compared to the visually-normals. Thus, the BNO-VEP test has the potential to be used clinically as an objective, visual system *biomarker* for the diagnosis of mTBI/concussion. In these individuals with mTBI and VMS, the mean difference between the BNO only condition and baseline was approximately 2.6 µV, with a noise level of 1.5 µV per our laboratory test conditions. However, some subjects had a BNO-baseline difference of up to 6 µV. Thus, based on the VEP alone, most of the results in each subject were positive for the BNO. *However*, none would be prescribed the BNO based on the VEP alone. They would have to exhibit positive visual perceptual and motor responses; that is, they would have to exhibit more stable gait, feel more comfortable in walking, and having improved visual scanning. In one case, the subject remarked on perceiving less "visual noise" with the BNO, in conjunction with improvement in ambulation. Second, with BNO alone, the objective findings in those with mTBI and VMS were consistent with their reported improvements in visual perception. Third, and lastly, with the BNO alone, the VEP findings in individuals with mTBI were in agreement with improvements in performing the sensorimotor tasks (e.g., grasping an object, walking in long hallway). This should translate to their natural

environment. The BNO alone improved visual function at the primary cortical level (V1), and also apparently at the higher cortical levels (e.g., V5/MT) related to motion-based visual perception per their subjective impressions. Lastly, these BNO-VEP findings should prove helpful to the clinician when considering the prescription of BNO to those with mTBI and VMS.

Conclusions

With BNO only, individuals with mTBI and VMS demonstrated significant, consistent, and repeatable increases in VEP amplitude, as compared to other test conditions. Furthermore, with BNO condition only, the VEP objective findings were correlated with improvements in their subjective visual perception and performance in sensorimotor tasks. Lastly, and most importantly, the BNO-VEP test can now be used clinically in the objectively-based, differential diagnosis of suspected individuals with mTBI and VMS from visually-normal individuals, with a very high degree of probability (>90%). Therefore, it may prove to be an objective visual system biomarker for the presence of an mTBI/concussion.

1.4.3 *Experiment #3*

The present study revealed *for the first time* that the VEP technique could be used to detect and assess objectively an attentional deficit in the mTBI population with high probability. Furthermore, this objective technique was also able to differentiate between those having mTBIwith versus those without an attentional deficit. More specifically, the attenuation ratios (AR) (i.e., EC ÷ EO and ECNC ÷ EC) value at each alpha band frequency was used to make this discrimination. In addition, the present results confirmed that an attentional deficit could be assessed and detected as early as the primary visual cortex (V1). Lastly, the objective alpha AR values were significantly correlated with the subjective ASRS attention questionnaire scores.

The findings of the current study confirmed, clarified, and extended the results of previous studies (Willeford et al., 2013a,b; Yadav et al., 2014). First, it extended the results of Willeford et al. (2013a,b), who predicted that individuals with mTBI and an attentional deficit would manifest an abnormal AR, as found in the present study. Furthermore, 3 individual alpha band frequencies in the current study (i.e., 9, 10, and 11 Hz) exhibited highly repeatable and reliable information regarding the attentional state in the individuals with mTBI. These same 3 alpha band frequencies were also found to provide consistent attentional information in the visually-normal adult population (Willeford et al., 2013a,b). Therefore, these specific alpha band frequencies are important test parameters in both populations. Second, the present findings were also in agreement with the recent Yadav et al., (2014) results. They found an abnormal EC ÷ EO AR for both the individual and combined alpha frequencies before oculomotor vision rehabilitation (OVR) in individuals with mTBI. More interestingly and importantly, the

AR significantly increased following oculomotor vision rehabilitation (OVR). These findings suggested associated enhanced attention following the OVR. Lastly, these results demonstrated that attentional processing occurs as early as the V1 in both the mTBI and visually-normal populations before being transmitted to higher cortical areas (e.g., parietal, temporal) for further processing (Somers et al., 1999; Kastner and Ungerleider, 2002).

Alpha attenuation ratio (AR)

The present results revealed that the mean EC ÷ EO AR was found to be abnormal (i.e., ≤2) at each alpha band frequency in individuals with mTBI *and* having an attentional deficit. In contrast, it was found to be within normal limits (i.e., ≥2) at the 9, 10, 11, and 12 Hz alpha frequencies in those with mTBI, but *without* an attentional deficit. In addition, the results were found to be similar when the EC ÷ EO AR was combined across the alpha frequency band (8-13 Hz) in both of these mTBI sub-groups.

The mean ECNC ÷ EC AR was also abnormal (i.e., >1) at each alpha band frequency in mTBI with an attentional deficit. In contrast, it was found to be within normal limits (i.e., <1) at the 8, 9, 10, and 11 Hz alpha frequencies in those with mTBI, but without an attentional deficit. Moreover, the results were found to be similar when the ECNC ÷ EC AR was combined across the alpha frequency band (8-13 Hz) in both of these mTBI sub-groups. Thus, the AR (EC ÷ EO and ECNC ÷ EC) findings were able to detect, assess, and differentiate the attentional state in individuals with mTBI, and

furthermore, the ARs were also able to differentiate between mTBI with and without an attentional deficit.

Subjective attention tests (ASRS versus VSAT)

Similar to the VEP findings, the subjective ASRS questionnaire was found to be reliable in differentiating between mTBI with versus without an attentional deficit. The ASRS scores were in the abnormal range (17 to 28) for all those with mTBI and an attentional deficit (n=11). In contrast, it was within the normal range (8 to 16) for all individuals with mTBI, but without an attentional deficit (n=5). This provided evidence that the ASRS questionnaire was a sensitive subjective test in assessing the attentional state in the mTBI population. However, the VSAT was not found to be a good indicator, and moreover it was not able to differentiate between the two mTBI sub-groups.

Correlation between objective and subjective findings

The above subjective ASRS questionnaire scores were also significantly correlated with both the individual and combined AR values. However, the AR was not found to be correlated with the VSAT percentile scores. Therefore, these findings also demonstrated that the subjective ASRS questionnaire is a more sensitive indicator of attention, as compared to the VSAT test.

Neurophysiological mechanisms

What might be the possible underlying neurophysiological mechanisms related to these VEP attentional findings? Klimesch(1999), and others (Pfurtscheller and Lopes da Silva, 1999; Rihns et al., 2007), suggested that during the EC "relaxed" attentional state, synchronous neuronal activity occurs in individuals with normal attention. This was likely due to oscillation of a large number of neurons having the same phase and frequency. These synchronous oscillations are responsible for the resultant increase in alpha band power. This oscillatory activity is assumed to "block" information processing from occurring. In contrast, it was proposed that in those individuals with mTBI and an attentional deficit, asynchronous activity occurs during the EC ("relaxed") attentional state, and thus those with an attentional deficit cannot "block" this information processing from occurring. The asynchronous neuronal activity would cause attenuation, or damping, of the alpha band power via a signal cancellation process (Hansen, 2001).

The opposite is believed to occur in the EO condition. In individuals with normal attention, *a*synchronous neuronal activity is believed to occur during the EO condition, whereas synchronous neural activity is believed to occur during the ECNC condition. This asynchrony during the former condition is believed to be due to oscillation of a large number of neurons with different phases and frequencies, which occurs due to processing of the more visually-based and cognitively-demanding information. This asynchrony causes attenuation of the alpha band power, again via signal cancellation (Hansen, 2001). In individuals with mTBI and an attentional deficit, *a*synchronous activity occurs during all three conditions, and thus presence of relative attenuation. The findings of the present

study are also consistent with the proposed mechanism of Klimesch(1999), and others (Pfurtscheller and Lopes da Silva, 1999; Rihns et al., 2007).

Proposed clinical VEP attentional test protocol

Based on the findings of the present study and others conducted in our laboratory (Willeford et al., 2013a,b; Yadav et al., 2014), the following clinical VEP attentional test protocol is proposed for use in individuals with mTBI and a possible attentional deficit:

1. **Case history –** A detailed case history should be taken regarding visual and general attention.

2. **Subjective test** –The Adult ADHD Self-Report Scale (ASRS) Part A questionnaire should be used as a screening tool to assess for presence of an attentional deficit.

3. **Objective test** – The following two VEP test conditions should be performed to assess for VEP normalcy, as well as to quantify the alpha band power and AR parameter:

   A. Eyes open (EO)

   B. Eyes-closed (EC)

   Number of trials – 5 trials (each 20 seconds) should be performed for each test condition and averaged.

Quantification of the EC ÷ EO AR should be performed. This proposed VEP attentional protocol may prove to be beneficial to clinicians for assessing and detecting attention objectively, rapidly, reliably, and quantitatively.

Clinical implications

The present findings have several important clinical implications. First, the alpha AR parameter was found to be related to one's attentional state and attenuation ability. Therefore, it could reliably be used as a clinical barometer to assess attention. The quantitative VEP-based AR should be correlated with the patient's subjective ASRS Part A questionnaire scores. This would help the clinician make a more reliable diagnosis related to the patient's attentional state. Second, the proposed objective VEP protocol might be extended to assess and detect attention in other vulnerable populations, such as cognitively-impaired individuals, non-verbal patients, and pediatric patients with attention deficit hyperactivity disorder (ADHD). Lastly, the objectively proposed testing may also be useful for clinicians to evaluate the effect of a visual intervention (Ciuffreda, 2002; Solan et al., 2003; Yadav et al., 2014), which incorporates an attentional component.

Conclusions

This is the *first* study to demonstrate that the clinical VEP technique could be used to detect and assess an attentional deficit at the V1 cortical level in the mTBI population. It was achieved by modulating the attentional state and quantifying the

outcome via the AR power spectrum analysis. The AR was found to be able to detect, assess, and differentiate between those having mTBI with versus without an attentional deficit. Furthermore, these objective findings were in agreement with the subjective ASRS scores. Lastly, this objective test protocol should now be extended to other "special" populations having attentional problems.

1.4.4 *Experiment #4*

The findings of the present study confirmed and extended the results of previous studies demonstrating that the VEP technique could be used to detect and assess for the presence of hemianopia in patients with stroke (Yadav et al., 2012; Angelelli et al., 1996). Yadav et al. (2012) simulated 4 different types of absolute visual-field defects (i.e., circular, annular, hemi-field, and quadrant) in the visually-normal population. They were able to detect objectively and assess reliably and repeatably all of the aforementioned visual field defect types using the pattern VEP technique. Furthermore, they predicted that the clinical pattern VEP approach would be able to detect and assess absolute hemifield defects in clinical patients with stroke, which the present pilot study confirmed. These findings were also in agreement with Angelelli et al., (1996). The findings of the current study also revealed that visual field loss in stroke patients could be rapidly and reliably detected *as early as* the primary visual cortex (V1), which agreed with Angelelli et al., (1996). Lastly, these objective VEP visual field results typically correlated with the subjective clinical perimetric findings.

The present study demonstrated *for the first time* that more subtle stimuli, such as the LC/HL and LL/HC patterns, are particularly sensitive in the detection of hemifield loss in stroke patients. Both the group and individual results showed that all three stimulus combinations (i.e., HC/HL, LC/HL, LL/HC) were effective. However, the HC/HL and LL/HC stimulus combinations provided more reliable amplitude findings, which were consistent with the clinical visual field findings, as compared to the LC/HL combination (see Figure 9C). Therefore, these two stimulus configurations may be most

clinically useful in detecting visual field loss in patients with stroke, especially in those patients with variable visual field test findings and/or cognitive dysfunction.

Proposed VEP hemianopic visual-field test protocol

Based on the findings of the present study and another conducted in our laboratory (Yadav et al., 2012), the following clinical VEP visual-field test protocol is proposed in patients with stroke and hemianopia:

I. **Central field (HC/HL)**
II. **Intact hemi-field only (HC/HL)**
III. **Hemianopic field only (HC/HL)**

Number of trials – 3 trials (each 20 seconds) should be performed for each test condition. Additional trials (e.g., 5) could also be performed, if required, for more consistent VEP responses. In addition, longer trial durations (e.g., 45 seconds) may prove to be useful for assessment of residual field functionality in those thought to have incomplete hemianopia, or when increased response variability is evident.

Clinical implications

The findings of the present study have several important clinical implications. First, the objective VEP technique may be used as an adjunct to subjective conventional clinical visual field testing to detect, assess, and confirm the presence of hemianopic

visual field defects in stroke patients. Due to the objective, rapid, and repeatable nature of the VEP technique, it would be especially helpful in non-verbal and cognitively-impaired individuals with stroke, as these individuals may not be able to understand the instructions and/or respond reliably to subjective clinical visual-field testing. Therefore, the VEP seems to be an ideal technique to detect hemianopic field defects in these patients. This technique could also be used to assess the effect of any visual intervention (e.g., eye movement visual scanning training) provided to these patients with stroke, as has been demonstrated in mTBI (Freed and Hellerstein, 1997; Yadav et al., 2014)

Conclusion

The clinical pattern VEP technique was found to be beneficial in detecting and assessing hemianopic field defects in patients with stroke. These quantitative and objective visual-field findings were repeatable and reliable. Furthermore, these objective findings typically agreed with the patient's subjective clinical perimetric results. Thus, the pattern VEP has the potential to be an important, adjunct objective technique to test for the presence of visual-field defects in these patients.

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Paper #1

Optimization of the Pattern Visual Evoked Potential (VEP) in the Visually-Normal and Mild Traumatic Brain Injury (mTBI) Populations

Yadav NK, Ciuffreda KJ. Optimization of the pattern visual evoked potential (VEP) in the visually-normal and mild traumatic brain injury (mTBI) populations. Brain Injury 2013; 27:1631-1642. (Published)

Abstract

Primary objective: The purpose of this study was to assess the effect of check size (CS) and contrast (C) on VEP amplitude and latency in visually-normal (VN) and in mild traumatic brain injury (mTBI) adults to develop an optimized test protocol in each group.

Research design and methods: Subjects were comprised of VN (n=19) and individuals with mTBI (n=16). Full-field, pattern VEP testing was employed with three different CSs (10, 20 and 40 min arc) and at two C levels (20 and 85%).

Results: There was a significant effect of CS and C on the VEP amplitude and latency in both groups. The 20 min arc CS at both contrast levels produced the largest VEP amplitude, in conjunction with normative latency values, in both populations. There was a significant differential effect of CS and C on VEP responses in the visually symptomatic versus asymptomatic mTBI subgroups. A significant correlation was found between time since their most recent brain injury and VEP amplitude for the 20 min arc CS at low contrast.

Conclusions: Use of the 20 min arc CS at both contrast levels represents an optimized clinical VEP test protocol in both the VN and mTBI groups. This protocol is rapid, high yield, and targeted for each diagnostic group.

Key words: check size, contrast, protocol, optimization, visual-evoked potential (VEP), VEP amplitude, VEP latency, mild traumatic brain injury (mTBI)

Introduction

Overview of the visual-evoked potential (VEP)

The visual-evoked potential (VEP) refers to an electrical signal generated over the primary visual cortex (V1) in response to a time-locked visual stimulus. The VEP is an objective, rapid, repeatable, and non-invasive method to assess functionality and integrity of the retinal and early-afferent, visuo-cortical pathways [1, 2]. It has been used clinically since at least 1970 [3]. Due to its objective nature, this technique has proven to be beneficial for special populations (e.g., infants and young children, non-verbal patients, cognitively-challenged patients) [1, 4-7]. It is also helpful in assessing the progression of many ocular and neurological disease conditions (e.g., glaucoma, multiple sclerosis) [8-10].

The VEP has two primary response components, one is the negative N75, and the other is the positive P100 (Figure 1). The VEP amplitude is defined as the voltage difference between N75, the trough of its negative most component occurring at t ≅75 msec, and the P100, the peak of its positive most component occurring at t ≅100 msec. The latency is defined by the exact time of the P100 peak. Many electrophysiological and fMRI studies have provided evidence that the negative N75 waveform response component is generated in the primary visual cortex (V1) [11-14]. However, there is still controversy regarding the precise site of neural generation of the positive P100 waveform response. Some studies have shown that it is generated in V1 [12,13,15], whereas others have suggested its generation to be in extrastriate cortical areas (i.e., V3, V5/MT) [14, 16-18].

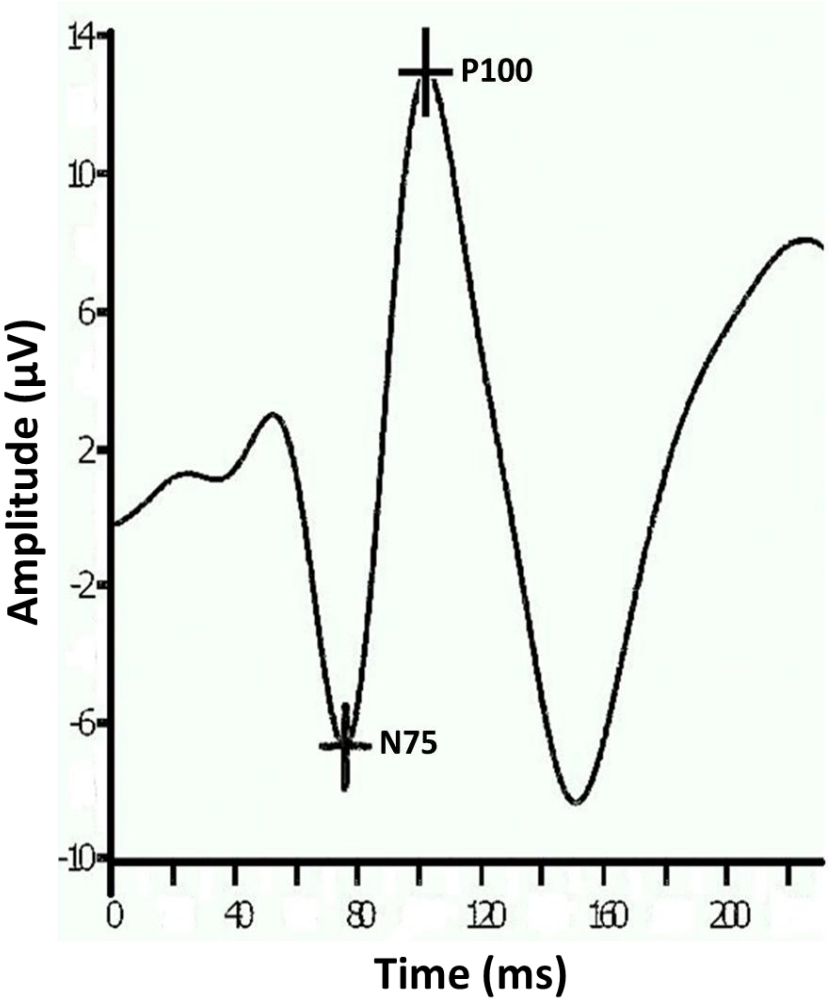

Figure 1: Typical pattern VEP waveform showing negative trough (N75) and positive peak (P100).

Optimization of the VEP stimulus parameters is important to provide rapid and repeatable responses containing high information content. Quick and reliable test conditions are especially necessary for those clinical populations having a short visual-attention span and/or fixational eye movement problems (e.g., younger children, mild traumatic brain injury (mTBI), stroke) [19-24]. Critical parameters include check size,

contrast, luminance, and temporal frequency [1]. Two parameters with particular physiological and clinical importance are check size and contrast, the main focus of the present paper, which are subsequently reviewed and discussed in detail. These two parameters are significant in assessing visual-pathway dysfunction (i.e., the magno- and parvocellular pathways) in many retinal and neurological disease conditions (e.g., glaucoma, retinitis pigmentosa (RP), amblyopia, multiple sclerosis (MS), visual-pathway tumors) [10, 25-27]. Optimal check size and contrast would provide maximal responsivity in visually-normal individuals, but likely an abnormal VEP response (i.e., reduced amplitude and/or delayed latency) in many ophthalmic clinical conditions, even at the earliest stages of the disease process, hence its diagnostic usefulness.

Studies in the visually-normal population

In the visually-normal population, studies have been performed to assess the effect of check size and contrast on the VEP amplitude and latency [26, 28-31]. However, the results were equivocal.

The following relevant studies assessed the effect of check size on the VEP response. Ristanović and Hajduković [28] measured the VEP response in 11 visually-normal, adult subjects. They used a wide range of check sizes (11.4 to 121.1 min arc), as compared to other studies, at 100% contrast. Their results revealed that the VEP amplitude varied non-monotonically over a range of check sizes, with a maximum response at 60.8 min arc. In addition, the VEP latency decreased exponentially with increase in check size (i.e., from 11.4 to 121.1 min arc). Török et al. [29] also found

decreased latency with increasing check size. In contrast, Kurita-Tashima et al. [30] assessed the effect of check size in 11 visually-normal, adult subjects. Check sizes ranged from 10 to 90 min arc at 90% contrast. They did not find any significant effects. Furthermore, a curvilinear relation was found between the P100 latency and the different check sizes, with minimal latency between 22.5 to 50 min arc.

Regarding contrast, there is only one primary and relevant study. Sokol et al. [31] tested 2 visually-normal, adult subjects. They assessed the effect of contrast on the VEP amplitude; latency was *not* assessed. They used both low (i.e., 30%) and high (i.e., 85%) contrast conditions, with check sizes ranging from 7.5-240 min arc, with modulation at three different temporal frequencies (i.e., 0.94, 3.75, and 7.5 Hz). They found that the VEP amplitude was maximum at the 15 min arc check size, at both contrast levels, at a temporal frequency of 0.94 Hz. The result at this temporal frequency is particularly relevant to the present study, which used 1 Hz.

The neurophysiological mechanisms linked to the effects of these parameters on VEP responsivity have only been discussed in detail by Oishi et al. [26], and by Ristanović and Hajduković [28]. The former believed that VEP activity primarily was derived from stimulation of the central fovea by use of optimally-sized, patterned stimuli. The human fovea has the highest cone density as compared to the extra-foveal regions [32]. Foveal cones have the highest resolution due to their smaller receptive fields and intercone spacing as compared to other retinal regions [33]. Therefore, an optimal check size is able to stimulate the maximum number of foveal cones, hence with a resultant large VEP amplitude and normative latency. Oishi et al [26] provided similar arguments. However, a recent study performed by Yadav et al. [2] confirmed that ~80% of the VEP

response was due to stimulation of the *cumulative* cone across the entire region of retina, tested [17˚H and 15˚V] and only ~20% of the response was due to stimulation of the central foveal cones (~0.5 degrees radius) per se. This will be discussed later in detail.

However, in none of the aforementioned studies was the goal to optimize VEP parameters (i.e., check size and contrast) to maximize responsivity. Thus, a primary goal of the current study was to develop a rapid, optimal, targeted protocol in visually-normal individuals, as well as in those with mTBI.

Studies in mild traumatic brain injury (mTBI)

Currently, in the United States, traumatic brain injury (TBI) is one of the major health care concerns [34, 35]. The prevalence of TBI has increased in recent years due to the past Iraq/Afghanistan wars [36], as well as greater recognition of sports-related concussions [37]. Since ~70-80% of TBI is of the "mild" variety, most research has been conducted in that population [38, 39]. Given that the majority of cranial nerves are involved in vision (i.e., 7 out of 12), and 30-40 cortical areas of the brain are involved in vision [40], it is not surprising that the visual system frequently loses a wide range of functionality subsequent to an mTBI (e.g., oculomotor problems, visual-field defects, visual-attention deficits, and increased motion sensitivity) [40-42].

To diagnose objectively the aforementioned visual dysfunctions in the mTBI population, researchers have used the VEP to assess brain damage occurring in the early afferent visual pathway [43-45]. Due to its objective and non-invasive nature, it is advantageous to use the VEP technique in these individuals, who frequently cannot

attend for an extended period of time, as mentioned earlier. The VEP method is capable of circumventing many of these potential problems.

Currently, there are no studies in mTBI which specifically assessed optimization of check size and contrast on the VEP amplitude and latency. However, there are some studies which have used the pattern VEP technique in this population with findings relevant to the current investigation. For example, Papanthansopoulos et al. [43] assessed the VEP amplitude and latency in the mTBI (n = 50) population on day 1 and day 30 post-injury, and they compared these results with normal controls (n = 20). They used 52 min arc check sizes at 90% contrast, with a very high luminance of 190 cd/m^2. They found that the VEP responses normalized 30 days post-injury as compared to day 1; at day 1, they found reduced amplitude (~20%) with delayed latency (~2-4 ms), on day 30, both parameters normalized. This suggests relatively rapid, natural, visual-cortical recovery. Later, Gaetz and Weinberg [44] used the VEP in 20 individuals with mTBI, and in 43 normal controls. Both groups were stratified by age, namely 18-34 years and 35-61 years. The VEP was performed in the younger mTBI group 20-51 months post-injury, and in the older group 1-53 months post-injury. They used a 31.05 min arc check size, with unspecified contrast. They found that latency was delayed in 33% of these individuals in both age groups, as compared to the two normal age groups. This suggested the presence of early delayed, visual processing in the mTBI group across ages. However, the VEP amplitude was not assessed in this study. Both studies were able to assess visual dysfunction in mTBI patients by using the VEP, but the results were equivocal and incomplete.

The VEP has also been used to monitor therapeutive progress in mTBI. Freed and Hellerstein [45] used this method to assess the effect of vision rehabilitation in individuals with mTBI and visual dysfunctions. They tested 2 groups of adult subjects. *Group 1* consisted of 18 mTBI patients (mean age = ~32.5 years), who received the rehabilitation which included: prescription of lenses either refractive or compensatory, prisms (compensatory or yoked), partial occlusion, and oculomotor/fusion-based therapy. *Group 2* was comprised of 32 age-matched mTBI control patients (mean age = ~32 years), who did not receive any type of vision rehabilitation, and in effect served as mTBI controls. The VEP was performed in group 1, on average ~1.7 years post-injury, and in group 2, on average ~1.35 years post injury. They used a 56 min arc check size, with unspecified contrast. The results showed that 71% of the former, and 81% of the latter, exhibited an "abnormal" VEP waveform at baseline. The VEP waveform was considered abnormal if the P100 latency was increased by 15% or more and/or the amplitude was decreased by 50% or more, over three trials, as compared to their normative data. After the vision rehabilitation, only 38% of those in group 1 manifested a residual abnormal waveform. In contrast, in the non-treated group 2, 78% still had an abnormal waveform, with this suggesting a considerable lack of natural recovery. Thus, the clinical VEP method revealed cortically-based, objective responses that normalized in the majority of cases after the vision rehabilitation, which could not be attributed to any natural recovery process [41]. This finding suggests perceptual and motor training-related visual system plasticity effects, even at this very early visual processing stage of the damaged adult brain [46].

Currently, the VEP is primarily used in the clinic for diagnostic purposes, for example in multiple sclerosis (MS) and glaucoma, as mentioned earlier [8-10]. Clearly, the pattern VEP method could be readily used as a clinical tool to assess visual dysfunction and its remediation in the mTBI population objectively. However, these past studies used a limited number of the VEP parameters, which were not necessarily optimized, but that was not their intent.

Thus, the purpose of the present investigation was to assess the effect of different check sizes and contrast levels on the VEP amplitude and latency in visually-normals, as well as in individuals with mTBI. With the above in mind, the goal was to optimize these VEP test parameters in the mTBI population to improve their diagnostic capability, and for assessment of therapeutic efficacy, in the future. These optimized check size and contrast parameters would be most sensitive to the presence of any brain damage in the early visual pathways, and thus would be helpful in assessing their visually-related symptoms objectively. In addition, this information would also help to develop a VEP protocol which is rapid, high yield, and targeted for both visually-normal individuals and in those with mTBI.

Methods

Subjects

Sixteen individuals with mTBI participated in the study based on the medical records sent from the referring institutions/clinics. They had a mean age of 27.3 ±5.6 years, with a range from 24 to 42 years. Their mTBI resulted from either a motor vehicle accident, fall, assault, or sports-related injury within a time period of 6 months to 10 years prior to the VEP testing (See Appendix 1), with an average time since brain injury of 5.6 (±0.75) years. The following criteria were used for the diagnosis of mTBI [47]: 1) loss of consciousness for less than 30 minutes or an altered state of consciousness, 2) 13 or greater score on the Glasgow Coma Scale (GCS), and 3) post-traumatic amnesia (PTA) lasting less than 24 hours. They each had a comprehensive vision examination in the Raymond J. Greenwald Center, SUNY/State College of Optometry clinic prior to participating in the study, which included assessment of refractive, binocular/oculomotor, and ocular health status. All subjects had corrected visual acuity of 20/20 or better in each eye at both distance and near. Exclusion criteria included a history of seizures, being wheel-chair bound, moderate cognitive dysfunction, strabismus, and amblyopia, as well as any type of comorbid ocular, systemic, or degenerative neurological disease. They were further sub-grouped into symptomatic and asymptomatic on the basis of having any residual visual symptoms (e.g., reading problems, visual attention dysfunction) at the time of the VEP testing.

Nineteen visually-normal, asymptomatic individuals participated in this study. They had a mean age of 26.8 ±5.1 years, with a range from 24 to 38 years. Ages of the

visually-normal subjects were statistically similar to that of the mTBI group [$t(32) = 0.26$, $p = 0.79$]. They also received a comprehensive vision examination prior to testing, as described above for those with mTBI. All had corrected visual acuity of 20/20 or better in each eye at both distance and near. Exclusion criteria for the visually-normal group included a history of seizures, concussion/head trauma, stroke, strabismus, and amblyopia, as well as any type of ocular, systemic, or neurological disease. They were similarly assessed for visual symptoms.

All subjects were recruited from State University of New York (SUNY), State College of Optometry. Individuals with mTBI were recruited from the Raymond J. Greenwald Rehabilitation Center at the State University of New York (SUNY), State College of Optometry. The visually-normal subjects were recruited from its student, staff, and faculty body at the college. The study was approved by the Institutional Review Board (IRB) at the SUNY, State College of Optometry. Written informed consent was obtained from all subjects.

Apparatus

The DIOPSYS™ NOVA-TR system (Diopsys, Inc., Pine Brook, New Jersey, USA) was used to generate the stimulus and analyze the VEP responses (Figure 2). A single computer processing unit controlled the entire system. This system had a 17" LCD stimulus test monitor with a refresh rate of 75 Hz. It was used for presentation of the test stimuli. The system also had a real-time response monitor, which was used by the experimenter for on-line viewing and graphical display of the averaged VEP responses.

The DIOPSYS system has been approved by the FDA for use in clinic patients. It has been used in many medical and optometric practices [48], and for the past three years, it has been used extensively in our laboratory [2, 49-51].

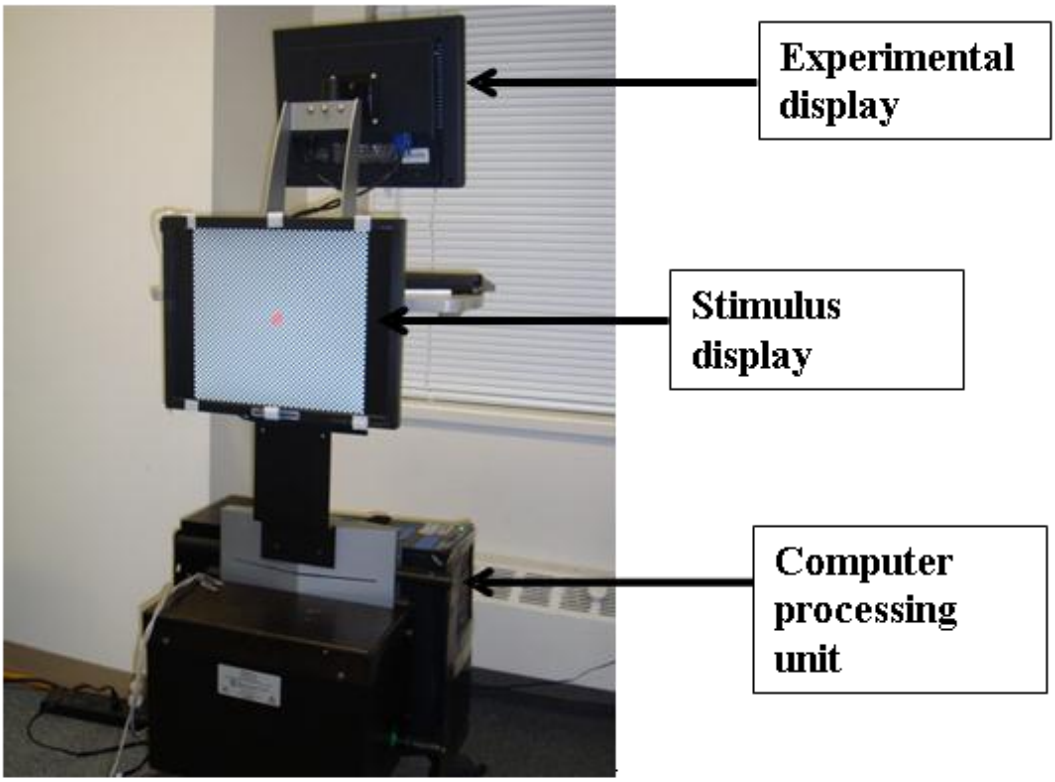

Figure 2: The Diopsys® NOVA-TR VEP system (Diopsys, Inc., Pine Brook, New Jersey, USA). Not shown is the headrest/chinrest assembly positioned 1 meter away from the stimulus display for subject stability and constancy of test distance.

Stimulus

A standard full-field (17 H X15 V degrees) checkerboard pattern comprised of black-and-white checks with three different check sizes (i.e., 128X128, 64X64, and 32X32 equivalent to 10, 20, and 40 min arc, respectively) was used. They were presented binocularly at low (i.e., 20%) and high (i.e., 85%) Michelson contrast levels (Figure 3a and 3b). Mean luminance was 74 cd/m^2, which is standard for this system. Test distance was 1 m. The VEP amplitude and latency were assessed in both groups for each of the six stimulus conditions (i.e., 3 check sizes X 2 contrast levels). A temporal frequency of 1 Hz (two reversals per second) was used for modulating the checkerboard pattern, which is standard for this system. A darkened room (38 lux) was used for the VEP testing, which was performed with natural pupils. A small (0.25 deg radius), red, rotating central fixation target was used to maintain visual fixation and visual attention, per the manufacturer's software.

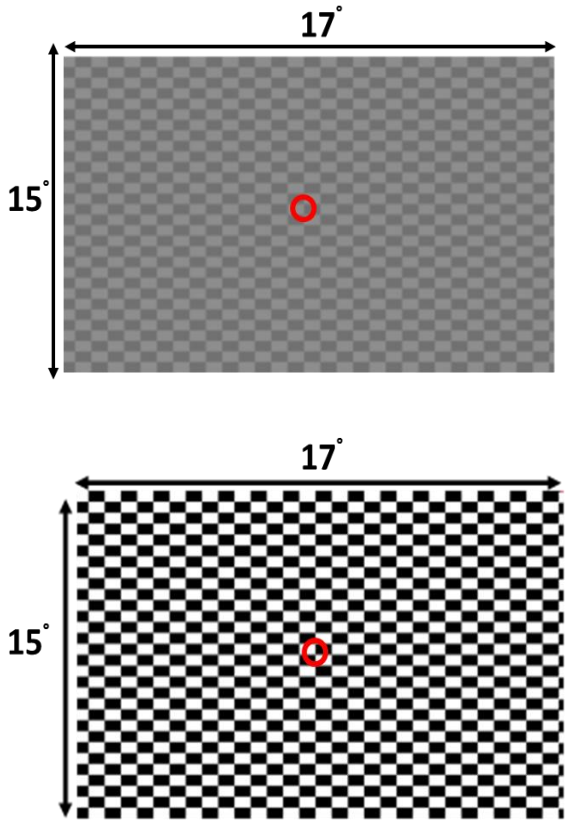

Figure 3: Standard full-field black-and-white checkerboard stimulus. (a) low contrast, (b) high contrast. Not drawn to scale.

Procedures

Electrode Placement

The average VEP responses were recorded from over the primary visual cortex (V1) by a central active electrode. Three Grass (Grass Technologies, Astro-Med, Inc., West Warwick, RI, USA) gold cup electrodes, each 1 cm in diameter, were used for the recordings. The electrode placement was simplified from the International 10/20 system [52], per the manufacturer's instructions. This electrode placement was used to reduce

test preparation time in clinical populations. The scalp was cleaned with alcohol wipes, followed by an abrasive gel, to provide excellent electrical contact. Then, the central active channel electrode was positioned at the Oz position, which was 2.5 cm above the inion. The reference electrode was placed at the Fz position, which was approximately 10% of the distance from the nasion to the inion. Finally, the ground electrode was placed at the Fp2 position, which was on the right side of the forehead. All electrodes were attached with the conductive paste, which was used to provide an excellent electrical contact, as well as to maintain the electrodes in place. Furthermore, the electrodes were held firmly in place by an elastic headband.

Recordings

The following procedure was used for recording the VEP responses. Firstly, the subjects placed their head within the headrest/chinrest assembly, which was used for stability during the recordings. Secondly, the stimulus monitor was aligned along the subject's midline at eye level. Lastly, before presenting the stimulus, the individuals were instructed by the experimenter to gaze carefully, with minimal blinks, at the central red rotating fixation target on the test monitor when the stimulus was presented. In addition, subjects wore either their distance spectacle or contact lens prescription during all testing. Five trials for each of the 6 test conditions were performed, with test conditions being counterbalanced. Test duration was 20 seconds for each trial [51]. Subjects were provided a 5 minute rest period between each test condition to prevent fatigue effects.

Standardized electronic parameters were used to reduce the noise level and to attain enhanced EEG signals. Impedance of the electrodes was maintained at <5K ohms, per the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) [1]. To increase the analog signals, an amplification factor of 10K was used. In addition, a bandpass filter (0.5-100 Hz) was used to remove any noise. Sampling frequency was 1024 Hz. Lastly, to eliminate further any artifacts/noise in the EEG signals, an artifact detector was integrated into the manufacturer's software. Artifacts were typically produced by such factors as full blinks and saccadic eye movements. Based on three years of experience with this DIOPSYS system, more than 5 artifacts is considered to produce excessive noise and variability in a particular trial. This occurred in no more than 5% of the present trials, which were rejected and not included in the analysis.

Data Analysis

An average of the five trials for each of the 6 test conditions for each subject was performed initially. Then, for each condition and subject, the trial for which the response exceeded 1SD from the mean was deleted to remove an outlier, and the mean and SD for the 4 remaining trials were calculated and used for the individual subject and subsequent group analysis. If the outlier were within 1 SD, then the most deviant trial response was deleted. Repeated-measures, two-way and three-way ANOVAs were performed on the two groups and two mTBI subgroups (asymptomatic and symptomatic), respectively, using STATISTICA 7 software.

Results

Normal and mTBI

Amplitude

The group mean, visually-normal amplitude values are presented in Figure 4a. A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. There was a significant effect of check size [$F(2, 2) = 11.7$, $p < 0.05$] and contrast [$F(1, 2) = 68.9$, $p < 0.05$] on the VEP amplitude. The post-hoc Tukey test results showed several significant comparisons, with the following relevant ones. At both high and low contrast, the response amplitude for the 20 min arc check size was significantly larger than that found for the 40 min arc check size ($p < 0.05$).

The group mean, mTBI amplitude values are presented in Figure 4b. A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. There was a significant effect of check size [$F(2, 2) = 11.3$, $p < 0.05$] and contrast [$F(1, 2) = 50.8$, $p < 0.05$] on the VEP amplitude. The post-hoc Tukey test results showed several significant comparisons, with the following relevant ones. At high contrast, the response amplitude for the 20 min arc check size was significantly larger than that found for the 40 min arc ($p < 0.05$) check size; however, this difference was not found at low contrast ($p > 0.05$).

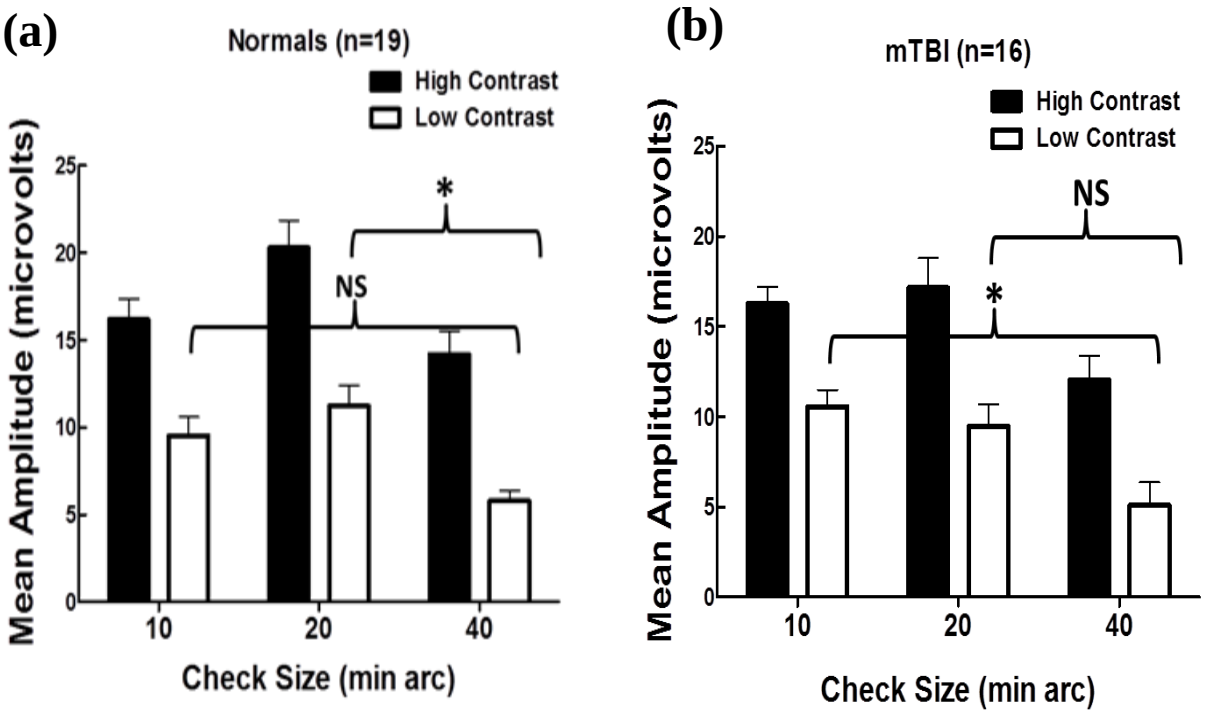

Figure 4: Mean VEP amplitude as a function of check size for both contrast levels. Plotted is the mean +1 SEM. (a) visually-normal, (b) mTBI. * = significant post-hoc comparison, NS = non-significant post-hoc comparison.

Comparisons were also made between the visually-normal subjects and those with mTBI. In the visually-normal group at low contrast, the response amplitude for the 20 min arc check size was significantly larger ($p < 0.05$) than that found for the 40 min arc check size. However, this specific check size amplitude comparison was not significantly different ($p > 0.05$) in the mTBI group. In the mTBI group at low contrast, the 10 min arc check size response amplitude was significantly larger ($p < 0.05$) than that found for the 40 min arc. This difference was not found in the visually-normal group ($p > 0.05$).

Latency

The group mean, visually-normal latency (P100) values are presented in Figure 5a. A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. There was a significant effect of check size [$F(2, 2) = 143$, $p < 0.05$] and contrast [$F(1, 2) = 51.2$, $p < 0.05$] on the VEP latency. The post-hoc Tukey test showed several significant comparisons, with the following relevant ones. First, at high contrast, the response latency for the 10 min arc check size was significantly longer than that found for either the 20 or 40 min arc check size values ($p < 0.05$) and, in addition, the 10 min arc check size at high contrast was also significantly longer than that found for either the 10 or 40 min arc check sizes at the low contrast ($p < 0.05$). Second, at low contrast, the response latency for the 10 min arc check size was significantly longer than that found for either the 20 or 40 min arc check size values at both low and high contrast ($p < 0.05$). Furthermore, the VEP latency decreased exponentially with increase in check size at both low ($r = +0.895$) and high ($r = +0.861$) contrast.

The group mean, mTBI latency values are presented in Figure 5b. A repeated-measures, two-way ANOVA was performed on the group mean for the factors of check size and contrast. There was a significant effect of check size [$F(2, 2) = 26.8$, $p < 0.05$] and contrast [$F(1, 2) = 11.5$, $p < 0.05$] on the VEP latency. The post-hoc Tukey test showed several significant comparisons, with the following relevant ones. First, at high contrast, the response latency for the 10 min arc check size was significantly longer than that found for the 40 min arc check size ($p < 0.05$). Second, at low contrast, the response latency for the 10 min arc check size was significantly longer than that found for either the 20 or 40 min arc check size values at both low and high contrast ($p < 0.05$). In

addition, the 10 min arc check size latency value at low contrast was also significantly longer than that found for the 10 min arc check sizes at high contrast ($p < 0.05$). Furthermore, the VEP latency decreased exponentially with increase in check sizes at both low ($r = +0.830$) and high ($r = +0.833$) contrast.

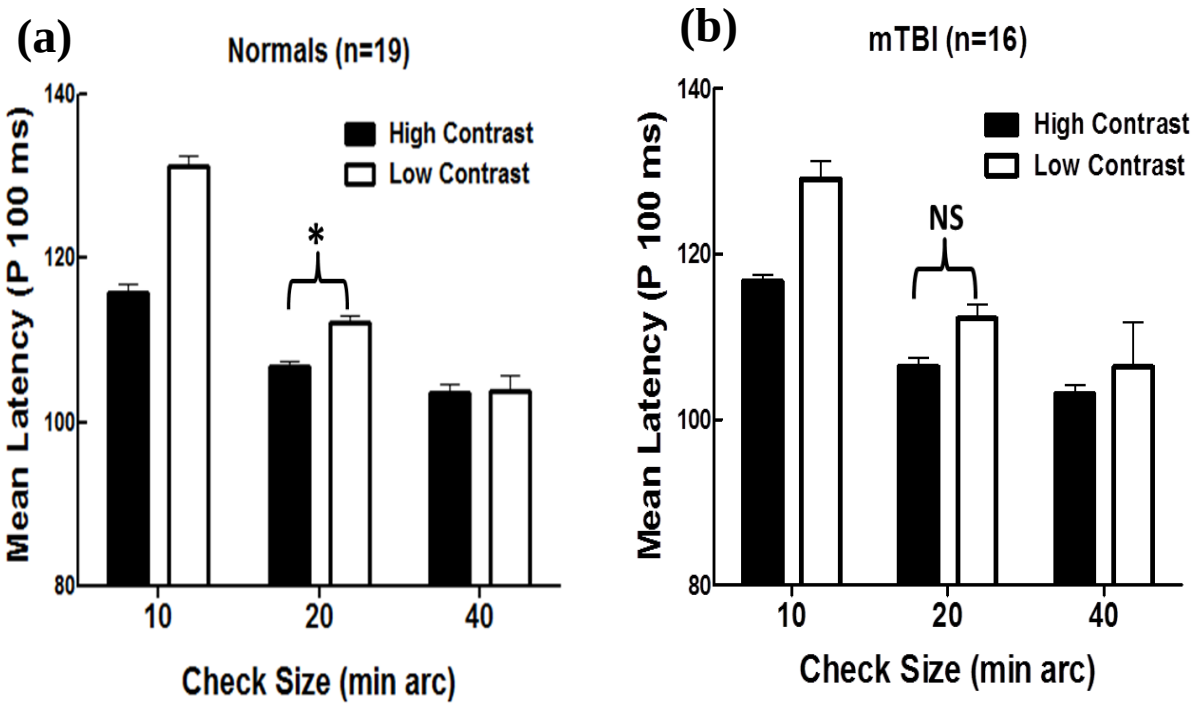

Figure 5: Mean VEP latency (P100) as a function of check size for both contrast levels. Plotted is the mean +1 SEM. (a) visually-normal, (b) mTBI. * = significant post-hoc comparison, NS = non-significant post-hoc comparison.

Comparisons were also made between the normal subjects and those with mTBI. For the 20 min arc check size, the response latency in the visually-normal group was

significantly longer at low contrast than that found for the latency at high contrast ($p < 0.05$). However, this difference was not found in the mTBI group ($p > 0.05$).

mTBI *(Symptomatic vs Asymptomatic)*

Amplitude

The asymptomatic (n=4) versus symptomatic (n=12) group mean amplitude values are presented in Figure 6a. A repeated-measures, three-way ANOVA was performed on the group mean for the factors of subgroup, check size, and contrast. There was a significant effect of subgroup [$F(1, 2) = 35$, $p < 0.05$], check size [$F(2, 2) = 16.2$, $p < 0.05$], and contrast [$F(1, 2) = 66.8$, $p < 0.05$] on the VEP amplitude. The post-hoc Tukey test showed several significant comparisons, with the following relevant one. At high contrast with the 20 min arc check size, the mean amplitude value for the asymptomatic group was significantly larger than that found for the symptomatic group at all check sizes ($p < 0.05$) and contrast levels ($p < 0.05$).

Latency

The asymptomatic (n=4) and symptomatic (n=12) group mean latency (P100) values are presented in Figure 6b. A repeated-measures, three-way ANOVA was performed for the factors of subgroup, check size, and contrast. There was a significant effect of check size [$F(2, 2) = 18.5$, $p < 0.05$] and contrast [$F(1, 2) = 8.1$, $p < 0.05$], but not subgroup [$F(1, 2) = 0.1$, $p > 0.05$], on the VEP latency. The post-hoc Tukey test results for the factors of check size and contrast revealed the following relevant

comparisons. First, for the 10 min arc check size at low contrast, the latency for the asymptomatic group was significantly longer than that found for the 40 min arc check size at high contrast ($p < 0.05$). Second, for the 10 min arc check size at low contrast, the latency for the symptomatic group was significantly longer than that found for the 20 and 40 min arc check size values at both the low and high contrast ($p < 0.05$).

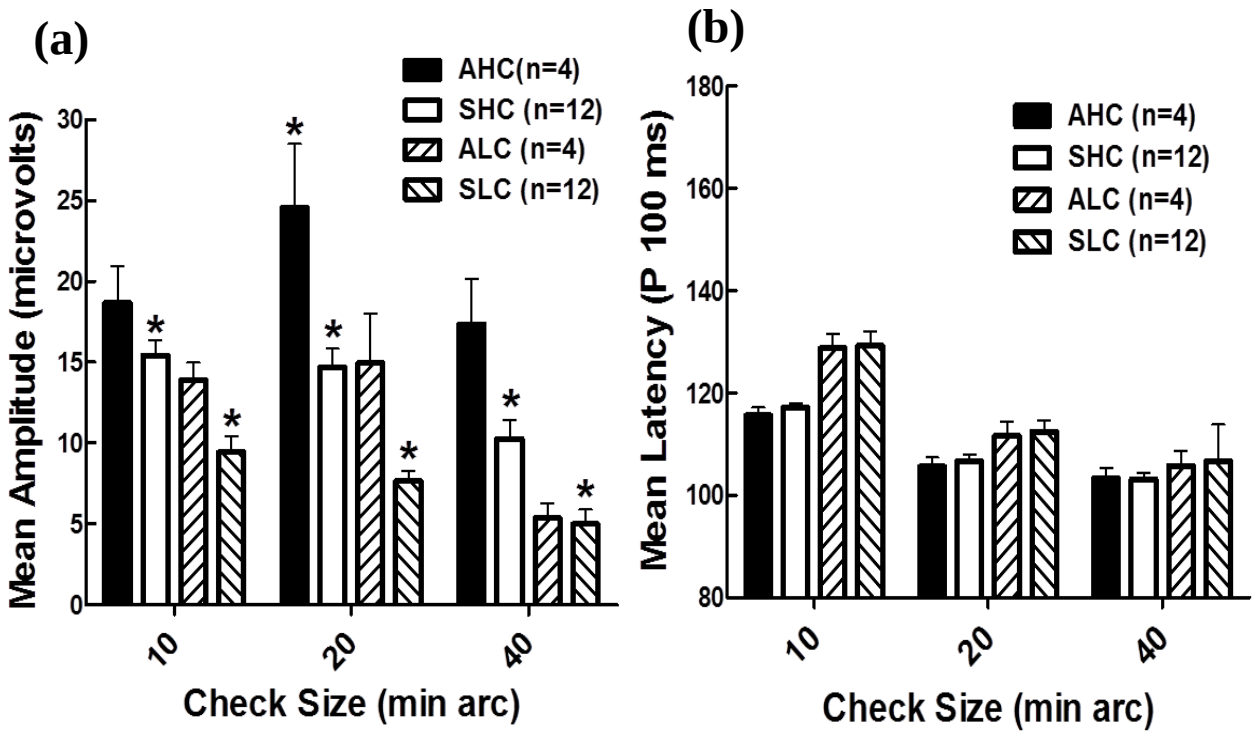

Figure 6: (a) The VEP amplitude as a function of check size at both contrast levels for the asymptomatic and symptomatic groups. Plotted is the mean +1 SEM. * = significant post-hoc comparisons, (b) The VEP latency (P100) as a function of check size at both contrast levels for the asymptomatic and symptomatic groups. Plotted is the mean +1 SEM. AHC = asymptomatic high contrast; SHC = symptomatic high contrast; ALC = asymptomatic low contrast; and SLC = symptomatic low contrast

Correlation

For the mTBI subjects, at the three check sizes and two contrasts, correlational analysis was performed between time since their most recent brain injury and the VEP amplitude and latency. It was found to be significant only for the 20 min arc check size amplitude at low contrast ($r = +0.586$, $p < 0.05$).

Discussion

The primary goal of the present study was to optimize two specific VEP test stimulus parameters with respect to responsivity, namely check size and contrast. This was performed in visually-normal individuals to obtain normative data, as well as in individuals with mTBI. While this study was not specifically performed to compare directly the effects of these parameters between the two groups, the comparative outcomes of this study are beneficial and insightful in assessing their neurophysiologically-based differences, as discussed later.

The test stimuli used are able to assess differentially the integrity of the paravocellular (P) and magnocellular (M) pathways. It is well-known that the P pathway is mainly responsible for processing visual stimuli related to high contrast, color, high spatial frequency, and low temporal frequency [53, 54]. Furthermore, it is well established that the M pathway is mainly responsible for processing visual stimuli related to low contrast, motion, low spatial frequency, and high temporal frequency [53, 54]. Thus, the VEP responses elicited with the present two test parameters are helpful in understanding the differential neuronal visual processing as related to the P and M pathways at the retinal and visuo-cortical levels within and across both groups, as will also be discussed later.

Furthermore, the present study assessed the effect of these two test parameters in the mTBI subgroups of visually-symptomatic versus visually-asymptomatic individuals. It is clinically important to differentiate between these two subgroups by using objectively-based optimized parameters, for both confirmation and extension into the

subjectively-based symptomatology and its clinical ramifications. Thus, while the ultimate goal of this study was to develop an optimal and targeted VEP protocol in both the visually-normal and mTBI groups, it also provided additional clinical insight into group and subgroup similarities and differences.

Optimization in normals

Results in the visually-normal group revealed that the VEP amplitude and latency were significantly affected by stimulus check size and contrast. The 20 min arc check size provided the largest VEP amplitude, in conjunction with normative latency values, at both contrast levels. No other check size/contrast combination provided similarly large, normal, and consistent findings.

Previous studies performed in visually-normal individuals also assessed the effect of check size and contrast on the VEP response (as described in the Introduction section) [26, 28-31]. However, the test protocols were not as extensive as that used in the present study, and furthermore, the results were equivocal. In addition, the primary goal of these earlier researchers was *not* optimization per se of the VEP test stimulus parameters. The latency responses measured in the present study are similar to that found in some previous investigations, i.e., the VEP latency decreased exponentially with increase in check sizes at both contrast levels [28, 29]. Lastly, the earlier studies never explicitly explained and/or speculated in detail on the possible neurophysiological mechanism(s) related to their findings. The present study was able to accomplish all of the above goals by optimizing the VEP test stimulus parameters in a group of visually-normal

individuals, as well as in a group of individuals with mTBI (see later Discussion), and in addition provide some ideas as to the possible underlying visual neurology.

Optimization in mTBI

This is the first study to assess specifically the effect of different check sizes and contrasts on the VEP amplitude and latency in individuals with mTBI. The results indicated that the VEP responses were significantly affected by variation in these two parameters: at both contrasts, the 20 min arc check size provided the largest VEP amplitudes, along with normative latency values. No other check size/contrast combination provided similarly large and consistent findings and, quite conveniently, these optimal stimulus parameters are the same that found in the visually-normal group, as described earlier. Thus, this provides for a *common* targeted protocol, which makes clinical VEP testing simplified in these two clinical populations.

Previous studies in the mTBI population did not specifically quantify the effect of both parameters on VEP responsivity. Furthermore, they used only one check size and one contrast level to assess visual-dysfunction [43-45]. In addition, in one study, their primary goal was to evaluate pre/post-therapeutic visual dysfunction and not optimization of the VEP test stimulus parameters per se [45]. Lastly, none of these earlier studies discussed the possible underlying neurophysiological mechanisms in detail.

The present study was able to accomplish this goal by optimizing the VEP test stimulus parameters in individuals having mTBI. These optimized parameters provide more ideal/detailed information related to the abnormal visual conditions in mTBI, as

compared to the previous studies. Furthermore, it allows testing to be conducted in a more efficient and targeted manner.

Proposed protocol

Based on the results of the present study, it is suggested that the following protocol should be used clinically to quantify optimally VEP responses in both visually-normal and mTBI groups:

- **Check size** – 20 min arc
- **Contrast –** Low contrast (20%) and high contrast (85%)
- **Luminance –** 74 cd/m^2 [2,49-51]
- **Trial duration –** 20 seconds (45 seconds if variability is high) [51].
- **Number of trials –** 3-5 trials [49-51] should be performed at each stimulus conditions. In addition, one outlier out of the 3-5 trials should be removed, and then the mean of the remaining 2-4 trials should be representative of the overall mean VEP response.

The proposed protocol should help clinicians/practitioners by reducing VEP test time. This would help prevent fatigue effects and maintain attention, both of which would reduce response variability, and hence yield more repeatable measurements. This in turn would provide optimal VEP responsivity for improved diagnostic capabilities. Relevant visual problems found in mTBI (and TBI in general) that could be assisted with regard to

the diagnosis and prognosis via VEP include visual motion sensitivity [49, 55], visual-field deficits [2], and visual attention loss [51], as well as for assessment of the oculomotor vision rehabilitative effects in mTBI [49].

Neurophysiological mechanisms (normal and mTBI)

What might be the underlying neural substrate that could explain the optimized responses found in both groups? Osterberg [32], and Curcio et al. [33], provided details regarding human retinal topography. They reported that the fovea contained the greatest cone density, which ranged from 147,000/mm^2 [32] to 258,900/ mm^2 [33] across these studies, with a rapid and progressive decrease in cone number with increased retinal eccentricity. Cone spacing is minimal at the fovea, ranging from 2.1 to 2.8 µm, and increasing with retinal eccentricity [33]. Related to this is the fact that visual resolution is maximum at the fovea, and it too decreases with increased retinal eccentricity. Lastly, foveal cone on-type receptive field (RF) center sizes ranged from 4 to 9 min arc, also increasing to 60 to 90 min arc at 10 to 15 degrees from fovea [56]. Taken together, these findings may be helpful in uncovering the underlying mechanisms related to the present results, as described below.

Stimulus check size in the present study was increased by a factor of two (i.e., 10, 20, and 40 min arc). Therefore, based on the above information, the small 10 min arc check size should only be resolvable by the RF of foveal cones, but not by most of the cones across the whole retinal area tested (i.e., approximately 8 degrees of retinal eccentricity). In contrast, the 20 min arc check size would be optimally resolvable by the

RF of foveal cones, as well as those cones in the near retinal periphery. Moreover, Yadav et al. [2], and Meredith and Celesia [57], confirmed that the VEP was derived from the *cumulative* cone-mediated response, and that it was not predominantly a foveal cone response. This suggests that the 20 min arc check size was able to stimulate a maximal number of cones across the test field used in the present study. Similarly, and related to the above, the 20 min arc check size was able to stimulate the maximum number of retinal ganglion cells. Retinal ganglion cells then transmit this information to both the parvocellular and magnocellular layers of the lateral geniculate nucleus (LGN). The LGN layer projects this visual-information by the P and M pathways to layer 4 of the primary visual cortex (V1), where it produces maximal stimulation of the RF of cortical neurons at the V1 level. This enhanced neuronal activity at the visuo-cortical level is reflected by the increased VEP amplitude, in conjunction with normative latency. Lastly, modulation of stimulus contrast allows differentiation between the P and M pathways, which is important diagnostically in the mTBI population [53, 54].

Neurophysiological differences (normals and mTBI)

There were important differences in VEP responsivity found between the normal and mTBI groups for the different check sizes and contrasts. First, response amplitude was dissimilar at low contrast, but similar at high contrast, between the two groups. This is consistent with the fact that individuals with mTBI frequently exhibit magnocellular pathway deficits, with this pathway being responsible for visual processing of low contrast visual information at both the retinal and cortical levels. Several studies have

confirmed that TBI causes disruption to the magnocellular pathway, which may result in: elevated coherent motion thresholds [58], increased visual-motion sensitivity [49, 55], and slightly elevated and increased variability in critical flicker frequency threshold values [59, 60]. Therefore, a magnocellular pathway deficit in the mTBI population is likely to play a role at low contrast levels in providing differential subgroup VEP findings. Second, the latency results for the 20 min arc check size were also different between the two groups. This might be due to the relatively larger VEP variability found in the mTBI group (i.e., high contrast SEM = ±1.08 ms and low contrast SEM = ±1.78 ms) as compared to the visually-normal group (i.e., high contrast SEM = ±0.67 ms and low contrast SEM = ±0.89 ms). Increased response variability is one of the hallmarks of the mTBI population [60, 61]. This may be attributed to diffuse axonal injury (DAI), which is a primary injury in individuals with mTBI [62, 63]. DAI causes damage to the white matter (WM) tract, which is responsible for transmitting visual information across the cortical neurons and brain pathways [64,65]. Therefore, impairment to the WM may cause increased variability in the VEP latency in the mTBI group, in contrast to the visually-normal group, as found in the present study.

mTBI (asymptomatic vs symptomatic)

The VEP responses for the symptomatic versus asymptomatic mTBI subgroups were also differentially affected by check size and contrast. The 20 min arc check size provided objective, VEP-based, neurophysiological differentiation between the asymptomatic and symptomatic subgroups. Their residual, symptomatic visual deficits

appeared to be related to the reduced VEP amplitude in the later as compared to former group. It is likely a reflection of residual compromised axonal integrity. Interestingly, there was no effect on VEP latency, and hence the effect's relative subtlety. Amplitude rather than latency appears to be more sensitive indicator of these remaining, long-term, visual system abnormalities. This finding is beneficial to the clinician/practitioner, as they may now be able to discriminate *objectively* between asymptomatic and symptomatic patients in those cases in which such information is vague, or cognitive/verbal limitations preclude obtaining an accurate description. It may also be useful for those individuals suspected of malingering.

Correlation between time since their last brain injury and the VEP response

A significant correlation was found between the time since an individual's last brain injury and VEP amplitude for the 20 min arc check size, but *only* at low contrast. The mean VEP amplitude increased with longer post-injury times. This result suggests the presence of residual, long-term, natural cortical recovery in these patients, in particular in the magnocellular pathway. For example, the range of time since the last injury was from 6 months to 10 years, with a mean of 5.26 (SEM = ±0.84) years. In addition, this finding also supports the notion that the 20 min arc check size at low contrast is an optimal parameter to reveal more subtle visuo-cortical information in this population. However, this findings must be interpreted with caution, as testing was not performed longitudinally.

Clinical implications

These optimized VEP parameters have several important clinical implications. First, they provide a clinical VEP protocol that is simple, rapid, high yield, and targeted for mTBI population. Clinicians and researchers could use the proposed VEP protocol to develop a comparable normative data base for direct comparison with the mTBI population, as the proposed optimal protocol is exactly the same for both groups. This allows one to use an objective means (i.e., VEP) to assist in the differential diagnosis between visually-normal individuals and those suspected of having mild concussion/mTBI in the absence of clearly defined symptoms. Thus, this assessment can now be accomplished with a reasonable degree of certainty using the proposed comparative sub-protocol, namely the 20 min arc check size at both low and high contrast levels. Furthermore, it may be useful to be able to differentiate between asymptomatic and symptomatic patients objectively, as mentioned earlier. Second, the correlation found between time since last injury and VEP testing is insightful for a number of reasons. It suggests that the brain has very long-term neural repair processes. Additionally, it would be helpful for clinicians/researchers to estimate the exact natural, cortically-based recovery time period in individuals with mTBI. The proposed protocol is also important in the assessment of axonal integrity of the P and M pathways at both the retinal and visuo-cortical levels. Third, it is well-known that mTBI patients fatigue quickly during clinical testing [42, 66]. Therefore, this protocol makes clinical VEP testing more rapid and targeted in assessing visual abnormalities at the visuo-cortical level. Fourth, and lastly, this protocol could be used to record baseline VEP responses in both warfighters and sportsmen before their deployment in the battle-field and sports-field, respectively, as

these populations are highly susceptible to concussion/mTBI [36, 37]. VEP responses should be evaluated when they present with signs/symptoms of post-concussive syndrome, with comparison to their previous baseline responses. This would help clinicians by providing an objectively-based diagnosis for the presence of a concussion/mTBI. Thus, these optimized VEP parameters in the mTBI population are clinically promising in their diagnostic evaluation, and perhaps even in the objective assessment of a therapeutic intervention.

Conclusions

Our new findings provide an optimal testing protocol for both normals and those with mTBI. In both groups, the 20 min arc check size at both low and high contrast levels provided the *largest* VEP amplitude, along with *normal* latency values. In comparison, in both groups, the 10 min arc check size at both contrast levels provided *delayed/longer* latencies, *even though* the amplitude was similar to that of the 20 min arc check size. These results provided evidence that the 20 min arc check size at both contrasts would be the optimal parameter in both groups. In addition, these results provide an objective approach in the differential diagnosis of these two groups using specific sub-protocol.

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Appendix 1: Demographics of the individuals having mTBI.

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports /Fall	Visual symptoms
M1/25/M	7	• Soccer injury (two injuries within a week) • Altered state of consciousness (ASOC) for 24 hours	• Reading problems • Oculomotor problems • Photosensitive
M2/24/M	10	• Bicycle accident (hit head against wall)	• None
M3/26/F	0.7	• Hit back of head against sink and had loss of consciousness (LOC) for ~2-3 minutes	• Reading problems • Diplopia • Headaches
M4/24/F	6	• Tubing accident (water sports injury) and ASOC for 24 hours	• None
M5/24/M	10	• Soccer injury • ASOC for 1-2 minutes	• None

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall	Visual symptoms
M6/25/M	6	• Hit by iron rod on head	• Visual motion sensitivity (VMS)
M7/24/F	10	• Hit head during cheerleading and LOC for 10 seconds • ASOC for few hours	• Feels tired after watching any scene (e.g., TV) • Visual fatigue
M8/42/M	4	• Involved in 7-8 blast injuries • During sports (i.e., soccer, swimming) • LOC for 5-8 minutes	• Reading problems • Oculomotor problems • VMS • Visual-attention deficit • Visual fatigue
M9/25/F	10	• Head hit by "discus throw" during athletic meet • LOC for ~10-15 minutes	• None
M10/23/M	4 (second injury 6 months ago)	• Both soccer injuries • LOC for less than 10 seconds	• VMS • Photosensitive

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/ Fall	Visual symptoms
M11/28/F	5	• MVA • LOC for 10-15 minutes	• Reading problems • Oculomotor problems • VMS • Photosensitive • Visual-attention deficit
M12/28/F	2 (second injury 1 year ago)	• Hit by car 2 years ago, and hit by heavy table lamp 1 year ago • LOC for <15 minutes	• Reading problems • VMS • Visual-attention deficit • Vestibular problems • Migraine
M13/30/M	4 (second injury 3 years ago)	• First injury due to snow-boarding accident and second MVA • LOC for <15 minutes	• Reading problems • Oculomotor problems • VMS

Subject/Age/Gender	Years since first injury	Type of injury: MVA/Sports/ Fall	Visual Symptoms
M14/29/F	4	• MVA • LOC for 2-3 minutes • ASOC for 24 hours	• Oculomotor problems • VMS
M15/38/F	4	• MVA • LOC for 2-3 minutes • ASOC for 24 hours	• Reading problems • Oculomotor problems • VMS
M16/18/F	3	• MVA • LOC for 2-3 minutes • ASOC for 24 hours	• Reading problems • Oculomotor problems • VMS • Photosensitive

Paper #2

Effect of Binasal Occlusion (BNO) and Base-In Prisms on the Visual-Evoked Potential (VEP) in Mild Traumatic Brain Injury (mTBI)

Yadav NK, Ciuffreda KJ. (2014). Effect of binasal occlusion (BNO) and base-in prisms on the visual-evoked potential (VEP) in mild traumatic brain injury (mTBI). Brain Injury 2014. (In Press).

Abstract

Purpose: To assess quantitatively the effect, and relative contribution, of binasal occlusion (BNO) and base-in prisms (BI) on visually-evoked potential (VEP) responsivity in persons with mild traumatic brain injury (mTBI) and the symptom of visual motion sensitivity (VMS), as well as in visually-normal (VN) individuals.

Research design and methods: Subjects were comprised of 20 VN adults, and 15 adults with mTBI and VMS. There were 4 test conditions: 1) conventional pattern VEP, which served as the baseline comparison condition; 2) VEP with BNO alone; 3) VEP with 2 pd BI prisms before each eye; and 4) VEP with the above BNO and BI prism combination.

Results: In mTBI, the mean VEP amplitude *increased* significantly in *nearly all* subjects (~90%) with BNO alone. In contrast, in VN, it *decreased* significantly with BNO alone in *all* subjects (100%), as compared to the other test conditions. These objective findings were consistent with improvements in visual impressions and sensorimotor tasks in the group with mTBI. Latency remained within normal limits under all test conditions in both groups.

Conclusions: Only the BNO condition demonstrated significant, but opposite and consistent, directional effects on the VEP amplitude in both groups. The BNO-VEP test condition may be used clinically for the objectively-based, differential diagnosis of persons suspected of having mTBI and VMS from the VNs.

Key words: mild traumatic brain injury (mTBI), visual motion sensitivity (VMS), binasal occlusion (BNO), base-in prism, visual-evoked potential amplitude, visual-evoked potential latency, objective mTBI biomarker

Introduction

According to the Centers for Disease Control and Prevention (CDC), traumatic brain injury (TBI) is a major medical and public health problem in the United States [1, 2, 3]. Every year, approximately 1.7 million people suffer from a TBI, with approximately 70-80% of them being of the mild type (mTBI), also including "concussion" [4, 5]. The prevalence of TBI has increased in recent years due to the past Iraq/Afghanistan wars [6], as well as greater recognition of sports-related concussions (e.g., football, ice hockey) [7].

The CDC developed the "Guidelines for Surveillance of Central Nervous System Injury", which defined TBI "as an event involving an injury to the head (brain) due to blunt or penetrating trauma" [8]. On the basis of its underlying mechanisms, TBI can be categorized into having primary and secondary injuries [9, 10]. The *primary* injury refers to the immediate biomechanically-based aspect, which causes diffuse axonal injury (DAI), whereas the *secondary* injury refers to the subsequent physiological and biomolecular aspects that occur over the next days, weeks, and even months. Many persons with mTBI appear to recover to some degree [11]. Recovery is correlated with the severity of the secondary injury process [9, 10].

Due to its global and pervasive nature, a TBI will result in a constellation of adverse effects of a sensory, motor, perceptual, linguistic, cognitive, attentional, and/or behavioral nature [3, 12, 13]. More specifically, since 8 of the 12 cranial nerves are involved in vision (CN II, III, IV, V, VI, VII, VIII, and XI) [14], some directly such as CN II and some more indirectly such as CN XI. Furthermore, at least 30 distinct cortical areas of the brain are involved in vision and visual processing [14]. Thus, it is not

surprising that adverse visual consequences frequently occur following a TBI (e.g., oculomotor problems, visual-field defects, photosensitivity, and visual attention deficits) [12-17]. Presence of visual deficits will have an adverse effect on one's activities of daily living (ADLs). Furthermore, and quite importantly, any residual visual deficits will have an adverse impact on the individual's vocational and avocational goals, as well as rehabilitative progress [18].

One such common visual problem is increased visual motion sensitivity (VMS). This refers to the peripheral visual motion (e.g., Gibsonian optic flow) [19] present in the environment that will adversely impact some of the TBI population both physiologically and perceptually. Individuals with increased (i.e., abnormal) VMS frequently report nausea, unsteadiness, balance difficulties, vertigo, disorientation, and a sense of visual confusion/chaos [20, 21]. These symptoms have also been referred to as visual-vertigo syndrome, or 'supermarket syndrome', as visually-stimulating environments (e.g., crowded places, supermarkets) may provoke these symptoms [20, 21].

Clinically, the following three techniques have been used to reduce abnormal VMS in persons with TBI: (1) tinted spectacle and tinted contact lenses to reduce the luminous intensity of the disturbing visual-field/visual stimulus entering the eye [16], (2) "desensitization or habituation maneuvers", in which the doctor or therapist purposely induces visual motion into the patient's near and far peripheral visual field, either by using his/her hands or by slowly rotating an optokinetic drum [16], and (3) binasal occlusion (BNO) in which partial occluders are added to the spectacle lenses to suppress and/or inhibit the abnormal visual motion in the patient's peripheral visual field [22].

Currently, BNO is used by many neurorehabilitative optometrists [3, 23] and occupational/physical therapists [24] involved in brain injury. BNO refers to the partial occlusion of the visual field to reduce visual motion in the periphery [22, 25, 26, 27]. BNO can be accomplished by using strips of translucent scotch tape, heavily-layered transparent nail polish, and/or opaque electrical tape, placed either on the front or the back surface of the spectacle lenses, typically placed nasal to the pupillary-limbal margin (Figure 1a). The BNO can be oriented either vertically, or tilted 15° superiorly-temporalward. Clinically, the BNO is preferably tilted to provide an unobstructed view at distance, as well as at near with convergence. Lastly, some have used bitemporal occlusion in TBI [28], but this may restrict too much of the lateral peripheral visual-fields, with possible resultant safety issues during ambulation.

Figure 1a: Schematic representation of binasal occluders on a subject.

There are a paucity of experimental studies dealing with BNO in those with TBI, especially with respect to abnormal visual motion sensitivity. In the sole clinical case study [23], the patient with mTBI had a primary complaint of "dizziness due to moving objects". All neurological testing, which included repeated magnetic resonance imaging (MRI), was within normal limits. The patient had an abnormally-large exophoria of 6 prism diopters (pd) at distance and 8 pd at near. Base-in prisms (3 pd BI each eye), in conjunction with office and home optometric vision rehabilitation [12, 13, 16, 17], were

prescribed for six weeks to resolve this and other oculomotor problems. After 3 months, BNO was introduced. The patient's immediate reaction was very positive: he felt more comfortable visually. He was also able to ambulate more confidently in the hallway, with this likely being due to reduction in the abnormal visual motion resulting from occlusion of parts of the disturbing peripheral visual-field.

There are two studies directly relevant to the question of VEP and BNO in persons with TBI. The first study was performed by Padula et al., [25]. They assessed the effect of BNO, in conjunction with base-in (BI) prisms (2 pd each eye), on the visual-evoked potential (VEP) amplitude in both visually-normal (VN) individuals, as well as in patients with TBI, in a hospital setting. The results demonstrated *objectively*, for the first time, the positive effect of the BNO and BI prism combination in patients with TBI and oculomotor dysfunctions (e.g., convergence problems). Details of the study were as follows: 10 VN, and 10 hospital-based persons with TBI, were assessed binocularly with full refractive correction using the pattern VEP (check size = 30 min arc, temporal frequency = 0.95 Hz). They analyzed the VEP amplitude under 2 conditions; 1) full-field VEP as the baseline comparison condition, and 2) full-field VEP with the combination of BNO *and* 2 prism diopters (pd) of BI prism over each eye. The results revealed a modest but consistent, and statistically significant, increase in VEP amplitude in 8 of the 10 persons with TBI for condition 2 versus baseline condition 1 (6.35µV to 7.99 µV). The amplitude remained the same in the other 2 subjects with TBI. In contrast, for the same test conditions in the VN group, the VEP amplitude decreased in 6 (15.39 µV to 14.42 µV), increased in 2 (8.93 µV to 9.81 µV), and remained the same in 2, thus demonstrating lack of a consistent effect. The Padula et al. [25] results confirmed that

BNO, in conjunction with a small amount of base-in prism, increased visuo-cortical activity in most of the individuals tested having TBI, along with correlated reduction of vergence-related symptoms in some. However, the separate effects of the BNO and BI prisms were not assessed. The second study was performed by Ciuffreda et al. [22]. They assessed the effect of BNO *only*, on the visual-evoked potential (VEP) amplitude and latency, in both VN individuals and in those with mTBI. All persons with mTBI had the symptom of increased VMS. Details of the study were as follows: 10 VN, and 10 persons with mTBI and VMS, were assessed binocularly with full refractive correction using the pattern VEP (check size = 20 min arc, temporal frequency = 1 Hz, test distance = 1m). They analyzed the VEP responses under 2 conditions; 1) full-field VEP (17°H X 15°V) as the baseline comparison condition, and 2) full-field VEP with BNO over each eye. The results revealed a significant increase in the mean VEP amplitude in *all* 10 persons with mTBI and VMS for condition 2 versus baseline condition 1 (19.15 µV to 21.32 µV). In contrast, for the same test conditions, the mean VEP amplitude significantly decreased in *all* 10 VN individuals (21.60 µV to 17.37 µV) relative to baseline. In both groups, latency was normal with no significant change found under any condition. In addition, the VEP results were repeatable in both groups. Lastly, in those with mTBI, the self-reported visuomotor activities improved with BNO (e.g., grasping for a near object, ambulation in a long hallway), along with reduction in VMS symptoms, especially during ambulation: they felt more “confident” and experienced less “visual noise” in the peripheral visual field. This study provided even stronger results at the visuo-cortical level, as compared to the Padula et al. [25] study, with regard to the use of BNO in patients with mTBI and VMS.

The precise mechanism and related underlying neurophysiology for improving visual function and reducing symptoms with the incorporation of BNO in TBI has been of considerable interest. Several ideas have been advanced. Gallop [27] proposed that by partially occluding the temporal visual field of each eye with the BNO, "binocular integration" was improved in some unspecified manner. Normal binocular, interactive ability was believed to have become "inefficient" after the neurological insult. Gallop [27] also proposed that BNO provided perceptual stability of the visual world, with its taped borders on the spectacles acting as stable and veridical vertical reference lines in visual space for these visually-disorientated individuals. Similarly, Padula et al. [25] suggested that BNO in persons with TBI might provide a vertical-visual "frame of reference" that assisted spatial orientation. Furthermore, Padula et al. [25] believed that BNO improved central versus peripheral visual-field interactions, as well as increased "functionality of binocular cortical cells" by incorporation of the BI prisms, presumably by reducing the convergence demand and thereby decreasing the vergence error (i.e., fixation disparity) in their subjects, all of whom had poor convergence and increased exophoria at near. Lastly, Ciuffreda et al. [22] proposed two mechanisms in those with mTBI and VMS. The first was the concept of "spread of suppression", a well-documented cortically-based neurophysiological phenomenon present in normal [29, 30], as well as in abnormal [31], binocular vision. That is, when cortical suppression of specific stimuli takes place, it also spreads to adjacent areas. With respect to persons with mTBI and VMS, they would attempt to suppress this visual motion information habitually in the retinal periphery to reduce the abnormal VMS, that is, to reduce their peripheral visual motion overload. However, this process appears to be only partially

successful, as their symptom of VMS persists. With addition of the BNO, however, suppression in the occluded bitemporal regions is now rendered unnecessary. Thus, the related spread of suppression to adjacent retinal regions, including those areas directly stimulated by the VEP stimulus, is reduced. This now results in a relative spread of "disinhibition", and therefore the VEP amplitude is increased. The opposite was proposed in the VN group having normal excitation in their bitemporal retinas, hence resulting in reduction of the VEP amplitude with the BNO added. A second possible mechanism was based on the concept of having a 'faulty' filtering mechanism [32, 33] in TBI. That is, neural filtering of irrelevant peripheral visual motion information is a normal visual processing and visual attentional phenomenon. This is believed to be occur via the magnocellular pathway, which is involved in visual motion processing [34]. Persons with mTBI and VMS may not be able to filter/inhibit this unwanted and bothersome peripheral visual motion information from entering their visual processing stream. Thus, they would have a relatively low, mean signal-to-noise ratio (S/N) for the incoming visual information averaged across the visual field. With the addition of BNO, however, less of the irrelevant visual information would be entering the visual system simply based on bitemporal occlusion of parts of the problematic regions of the visual field. This in turn would increase the global neural S/N ratio, which would produce an increase in VEP amplitude. This is consistent with some patient's report of perceiving less "visual noise" during ambulation with BNO in our laboratory. It is also possible that both mechanisms may be involved in the process. In addition, the notion of providing a vertical frame-of-reference for spatial orientation purposes is also likely, as proposed by others [25, 27]. However, the physiological phenomenon underlying BNO still needs to be addressed,

with disambiguation of the possible BNO and BI prism interactive effects on VEP responsivity.

Thus, the purpose of the present study was to assess quantitatively the effect, and relative contribution, of binasal occlusion (BNO) and base-in prisms (BI) on visually-evoked potential (VEP) responsivity in those having mild traumatic brain injury (mTBI) and the symptom of visual motion sensitivity (VMS), as well as in visually-normal (VN) individuals.

Methods

Subjects

Twenty visually-normal, asymptomatic adults participated in the study. They constituted the control group. They had a mean age of 25.5 (SEM = ±0.61) years, with a range from 20 to 33 years. Each had a best corrected visual acuity of 20/20 monocularly and binocularly, at both distance and near. None had any binocular vision dysfunction (e.g., convergence insufficiency). Each received a comprehensive vision examination within the last year at the University Eye Center at the SUNY, State College of Optometry. None had a history of seizures, strabismus, amblyopia, or any type of ocular and neurological disease, nor were they taking any drugs or medications that would affect either their visual or attentional state. Subjects were recruited from its student, staff, and faculty body at the SUNY, State College of Optometry.

Fifteen adults with medically-documented mTBI and having the symptom of 'increased (i.e., abnormal) visual motion sensitivity (VMS)' based on their medical records participated in the study. They had a mean age of 35.2 (SEM = ±3.1) years, with a range from 25 to 65 years. Their brain injury resulted from either a motor vehicle accident (MVA) or sports-related injury, with the brain injury occurring from 1 to 27 years (mean = 7.2 years) prior to the VEP and subjective testing. See Appendix 1 for subject demographics. The following criteria were used for the diagnosis of mTBI [35]: 1) loss of consciousness for less than 30 minutes or an altered state of consciousness, 2) 13 or greater score on the Glasgow Coma Scale (GCS), and 3) post-traumatic amnesia (PTA) lasting less than 24 hours. Most were referred to the Raymond J. Greenwald

Rehabilitation Center (RJGRC)/Brain Injury Clinic at the SUNY, State College of Optometry 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, as well as from students and staff at the optometry college. Each had a best corrected visual acuity of 20/20 monocularly and binocularly, at both distance and near. Some (n = 7) had moderately large exophoria at near (mean = 7.14 pd; range = 6 to 8 pd), but all were essentially orthophoric at distance; none reported diplopia. Each had a comprehensive vision examination within the past year at the RJGRC/Brain Injury Clinic at the SUNY, State College of Optometry. None had a history of seizures, strabismus, amblyopia, cognitive dysfunction, or any type of ocular or neurological disease, nor were they taking any drugs or medications that would affect either their visual or attentional state.

The Institutional Review Board (IRB) at the SUNY, State College of Optometry approved this study. Each subject provided written informed consent.

Apparatus

The DIOPSYS™ NOVA-TR VEP system (Diopsys, Inc., Pine Brook, New Jersey, USA) was used to generate a black-and-white checkerboard stimulus and to analyze the VEP responses. The test stimulus was presented on a 17” LCD monitor with a refresh rate of 75 Hz. In addition, this system had a real-time response monitor. This was used by the experimenter for on-line viewing of the VEP responses, as well as to

observe any blinks and/or eye movements artifacts in the on-going traces during each trial. This system has been approved by the FDA for use in clinic patients. Many medical and optometric practices use the DIOPSYS VEP system, and for the last three years, it has been used extensively in our laboratory [36, 37, 38]. In addition, binasal occluders (BNO) were used, which were created by applying opaque, black tape onto the front surface of the two circular plano (zero diopter) trial lenses. The BNO were tilted 15° superiorly-temporalward in an ophthalmic trial frame over each eye to provide an unobstructed view of the VEP stimulus, both monocularly and binocularly (see Ciuffreda et al. [22] for details, and also the Introduction section). Furthermore, 2 pd BI prisms were placed over each eye (4 pd total) in the trial frame either alone or in combination with the BNO (as described below).

Stimulus

A standard full-field (17°H X 15°V), black-and-white checkerboard pattern (64 X 64 equivalent to 20 min arc check size at 1 meter), with a luminance of 74 cd/m^2 and contrast of 85%, was used. It was modulated at a temporal frequency of 1 Hz (2 reversals per seconds). In addition, a central red rotating (0.5° diameter) fixation target was presented in the center of the test stimulus per the manufacture's software. It was used to control binocular fixation and accommodation, as well as to maintain visual attention, during each trial.

The VEP amplitude and latency were assessed with binocular viewing and full refractive correction under the following four experimental conditions, with the last three conditions being counterbalanced to prevent any order effects:

- ***Condition 1:*** Full-field VEP (baseline) – The VEP responses measured during this test condition were used as a baseline for comparison with the subsequent three experimental conditions.

- ***Condition 2:*** Full-field VEP with binasal occlusion (BNO) – During this condition, the VEP responses were assessed with the BNO in place. Before commencing the VEP measurements, the binasal occluders were adjusted in an ophthalmic trial frame, so that the subject was able to see the entire checkerboard pattern both monocularly and binocularly. A 5.7°H x 15°V region of space 5.5° *lateral* to the edge of the test stimulus on either side of the horizontal extent of the screen was blocked by the binasal occluders (Figure 1b). Thus, no portion of the VEP stimulus was blocked by the BNO.

- ***Condition 3:*** Full-field VEP with base-in (BI) prisms – During this condition, the VEP responses were assessed with 2 BI prisms in front of each eye (4 BI prism total).

- ***Condition 4:*** Full-field VEP with the combination of the binasal occluders (BNO) and BI prisms – During this condition, the VEP responses were assessed with a combination of the BNO *and* the 2 BI prisms before each eye. The binasal occluders were placed in the trial frame as described in condition 2 (i.e., for BNO only). The BI prisms were also placed in the ophthalmic trial frame.

In addition, repeatability of the above 4 experimental conditions was performed on two different days in two subjects in each group.

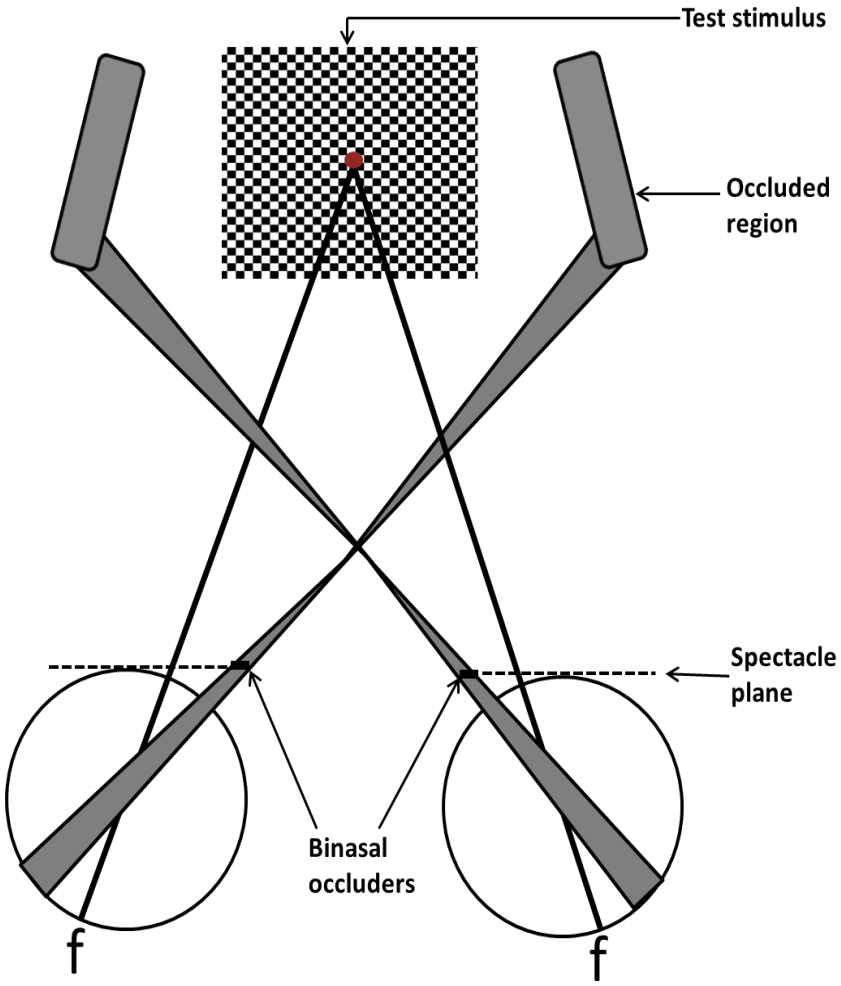

Figure 1b: Representation of binocular visual-field with binasal occluders in place, including the checkerboard visual stimulus. Not drawn to scale. f = fovea

Procedures

Electrode Placement

Three Grass gold-cup electrodes (Grass Technologies, Astro-Med, Inc., West Warwick, RI), each of 1 cm in diameter, were placed on the scalp to measure the VEP responses. The active electrode was placed at the Oz position, which was 2.5 cm above the inion. The primary visual cortex (V1) responses were measured by this Oz active electrode. The reference electrode was placed at the Fz position (i.e., approximately 10% of the distance from the nasion to the inion), and the ground electrode was placed at the Fp2 position (i.e., on the right side of the forehead). The electrode placement was modified from the International 10/20 system to reduce test preparation time in clinic patients, per the manufacturer's instructions [39]. Before applying the electrodes, the designated scalp region was cleaned with alcohol wipes and abrasive gel, and finally, all three electrodes were attached with the conductive paste. In addition, an elastic head band was used to hold the electrodes firmly in place.

Recordings

Impedance of all three electrodes was measured with a EIM105 electrode impedance meter (General Devices, Ridgefield, New Jersey). The impedance was maintained at <5 K ohm to achieve enhanced electroencephalographic (EEG) signals, per the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) [40]. In addition, standard electronic parameters were used to measure the VEP signals. An amplification factor of 10K was used to increase the analog signals. Furthermore, to remove electronic noise, a bandpass filter (0.5-100 Hz) was used.

Sampling frequency was 1024 Hz. Finally, an artifact detector was incorporated into the DIOPSYS™ system software to detect artifacts caused by blinks and/or eye movements.

Before commencing the VEP recording, each subject was asked to place their head within a chinrest/headrest assembly, which stabilized their head, as well as maintained a constant test distance. Subjects were instructed to fixate binocularly at the central red rotating circle during each trial with minimal blinking. Five trials for each of the 4 test conditions were performed. Test duration for each trial was 20 seconds [22]. To prevent fatigue during testing, subjects were provided with a 5 minute rest period between each test condition.

Subjective Testing

Subjective testing was performed in each group to assess their visual perception/visual impressions and visuomotor performance. There were three subjective viewing conditions, as described below (A-C). Each was performed with the same four test conditions as used for the VEP measurements: baseline, BNO, BI prisms, and the combination of BNO plus BI prisms.

(A) Simple viewing task: Subjects viewed each of the following three visual stimuli: 1) a patternless white wall, 2) a printed copy of a stationary, black-and-white checkerboard pattern similar to that used for the VEP testing, and 3) the black-and-white, alternating checkerboard pattern comprised of the actual DIOPSYS VEP test display. The following question was asked with regard to all three visual stimuli: “Is it visually bothersome in any way”? A continuous rating scale from 1

to 5 was used, with 1 signifying that the visual stimulus was not bothersome at all, and 5 signifying that the visual stimulus was very bothersome.

Each subject was also queried about their visual perception after viewing each condition, with the response being a simple "yes" or "no". The following specific questions were asked: (1) Patternless white wall – "Does the wall look flat or curved"? "Are you readily able to judge the distance of the wall"? "Do you perceive any motion"? (2) Printed copy of a stationary black-and-white VEP test checkerboard pattern – "Do you perceive any motion"? (3) Black-and-white, alternating DIOPSYS VEP test checkerboard display – "Does the display appear to flicker more or less as compared to baseline"?

(B) Grasping task: Subjects were asked to grasp/reach for a nearby object while seated at a table. A small, cylindrically-shaped object (2 cm in length and 0.25 cm in diameter) was placed on the table within the subject's reach at the following three distances and angles: 1) 40 cm along the subject's body midline, 2) 40 cm, 10 degrees to the right of the subject's body midline, and 3) 40 cm, 10 degrees to the left of the subject's body midline. Before starting the test, the examiner instructed the subject to close their eyes, and during that time the examiner placed the object at one of the three positions. After they opened their eyes, they were instructed to use their dominant hand to grasp the small object as rapidly and as accurately as possible. The following specific questions were asked: "Are you readily able to judge the distance of the object"? "Which of the four test conditions was easiest in grasping the object"?

(C) Walking task: Subjects were instructed to walk up and down the center of a long hallway (20 m long and 1.8 m wide) in their usual manner. The experimenter observed the subject's walking pattern to determine whether they veered away from center, and if so, by how much and in what direction. Lastly, each subject was queried regarding which of the four test conditions was most comfortable while walking, as well their visual perception of motion and any other sensations they experienced during the task.

Data Analysis

An average of the five VEP trials for each of the 4 test conditions for each subject was calculated. Then, the trial for which the VEP response exceeded 1SD from the mean was deleted to remove the outlier; in the case where all 5 trials value were within 1 SD, the most deviant response was deleted. The mean and SD for the 4 remaining trials were then calculated and used for analysis of the group mean VEP amplitude and latency. Furthermore, for the subjective rating scale, the mean and standard deviation for each test condition was calculated and analyzed for each group. A one-way, repeated-measures ANOVA was performed on each group using GraphPad Prism 5 software. Graphical displays were also prepared with the same software.

In addition, VEP repeatability was assessed in two subjects in both the visually-normal and mTBI groups. The same test conditions were repeated three weeks apart. The coefficient of variation (CV = standard deviation of the multiple sessions for each condition divided by the mean of these multiple sessions for each condition) was

calculated to assess for repeatability of the VEP responses [36, 37, 41, 42]. The CV value can range from 0.00 to 1.00 [41]. This value represents the intra-individual variability: the smaller the value, the less the variability, and the better the repeatability.

Results

Amplitude

Normals

The group mean, visually-normal amplitude values for the four test conditions (i.e., baseline, BI prism, BNO, and BNO plus BI prism) are presented in Figure 2a. A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. There was a significant effect of test condition on the VEP amplitude [$F(3,19) = 23.47$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the BNO condition (17.08 ±1.65 μV), and for the combination of BNO plus BI prism condition (18.13 ±1.66 μV), were each significantly *decreased* with respect to the baseline condition (20.79 ±1.78 μV). Furthermore, the amplitude for the BNO condition, and for the combination of BNO plus BI prism condition, were significantly *decreased* with respect to the BI prism condition (20.62 ±1.71 μV).

mTBI

The group mean, mTBI amplitude values for the four test conditions are presented in Figure 2b. A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. There was a significant effect of test condition on the VEP amplitude [$F(3,14) = 4.27$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the BNO condition (23.19 ±2.13 μV) was significantly *increased* with respect to the baseline condition (20.89 ±2.14 μV), but not for the BNO plus BI prism condition (21.98 ±2.36 μV). Furthermore, the amplitude for the BNO condition was

significantly *increased* with respect to the BI prism condition (21 ±2.32 μV), but not for the combination of the BNO plus BI prisms.

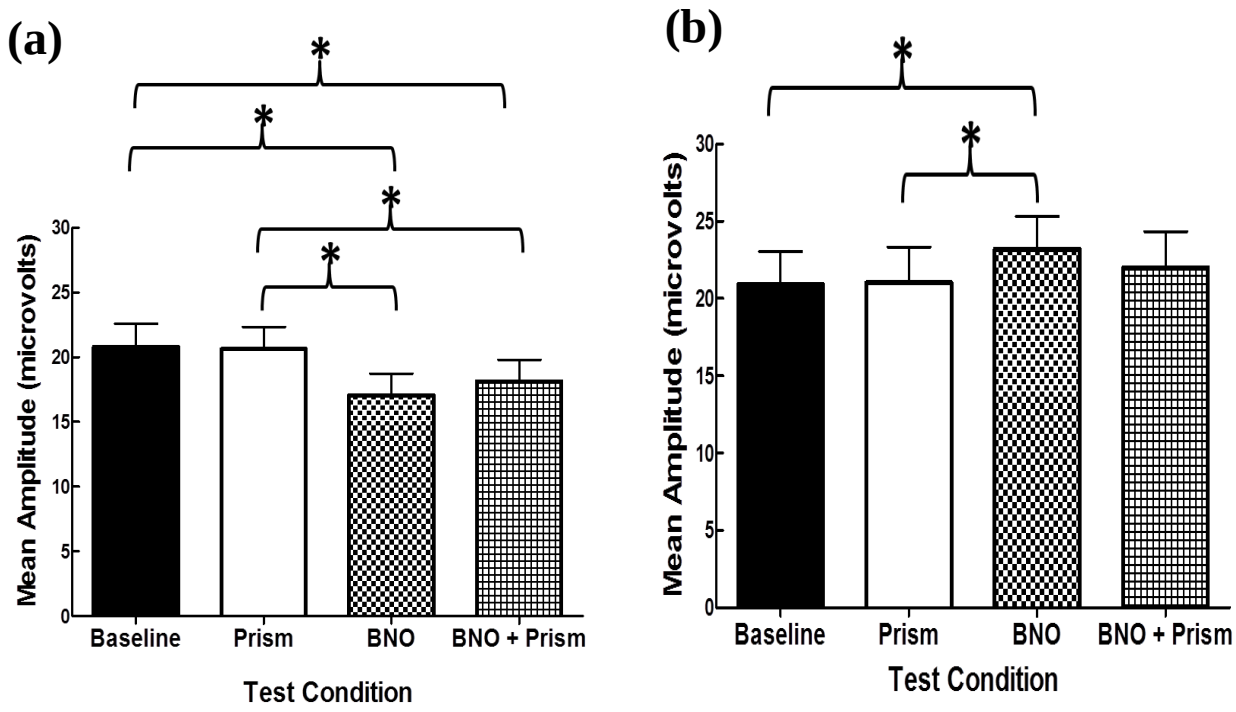

Figure 2: Group mean VEP amplitude for the four test conditions (baseline, prism, BNO, and BNO plus prism). Plotted is the mean +1 SEM. (a) visually-normal, (b) mTBI. Brackets with an asterisk (*) represent significant differences ($p < 0.05$).

Thus, in both the visually-normal and the mTBI groups, *only* the BNO condition demonstrated significant, but *opposite*, directional effects with respect to the baseline VEP amplitude.

Latency

Normals

The group mean, visually-normal latency (P100) values for the four test conditions are presented in Figure 3a. A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. There was a significant effect of test condition on the VEP latency [$F(3,19) = 11.12$, $p < 0.05$]. The post-hoc Tukey test results revealed that the latencies for the BI prism (106 ±0.57 ms), BNO (106 ±0.74 ms), and BNO plus BI prism conditions (107 ±0.62 ms), were each significantly increased with respect to the baseline condition (105 ±0.57 ms). However, they were all within normal limits for our laboratory [36, 37, 38], with the largest increase being 2 ms. Lastly, latency for the combination of the BNO plus BI prism condition was significantly increased with respect to the BI prism condition.

mTBI

The group mean, mTBI latency (P100) values for the four test conditions are presented in Figure 3b. A repeated-measures, one-way ANOVA was performed on the group mean for the factor of test condition. There was a significant effect of test condition on the VEP latency [$F(3,14) = 11.10$, $p < 0.05$]. The post-hoc Tukey test results revealed that the latencies for the BI prism (109 ±1.35 ms), BNO (109 ±1.48 ms), and BNO plus BI prism conditions (109 ±1.51 ms), were significantly increased with respect to the baseline condition (107 ±1.43 ms). However, they were all within normal limits for our laboratory [38], with the largest increase being 2 ms.

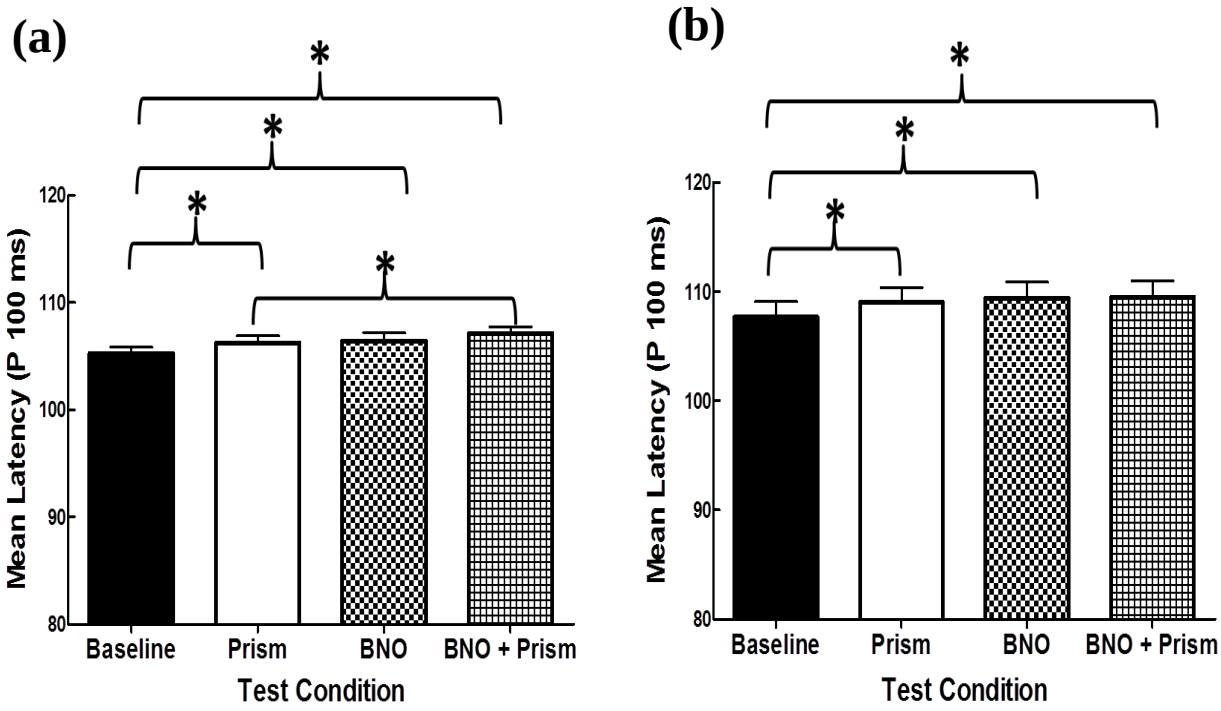

Figure 3: **Group mean VEP latency (P100) for the four test conditions (baseline, prism, BNO, and BNO plus prism). Plotted is the mean +1 SEM. (a) visually-normal, (b) mTBI. Brackets with an asterisk (*) represent significant differences ($p < 0.05$).**

Thus, in both the visually-normal and the mTBI groups, the group mean latency increased by no greater than 2 ms, but it was within normal limits, for all 3 test conditions, as compared to their respective baseline.

Percentage difference in mean VEP amplitude

Normals

The percentage difference in mean amplitude for each subject for each condition with respect to their respective mean baseline values are presented in Figure 4a. In the BI prism condition, this percentage difference increased in 10 subjects and decreased in the other 10 (range from -18.22 to 18.41%). In contrast, in the BNO condition, it decreased in *all* 20 subjects (range from -49.88 to -3.15%). Lastly, in the BNO plus BI prism condition, the percentage difference increased in 3 subjects and decreased in the remaining 17 (range from -39.49 to -4.91%).

mTBI

The percentage difference in mean amplitude for each subject for each condition with respect to their respective mean baseline values are presented in Figure 4b. In the BI prism condition, this percentage difference increased in 8 subjects and decreased in the other 7 (range from -18.80 to 22.71%). In the BNO condition, it increased in 13 subjects and decreased in the remaining 2 (range from -9.72 to 40.6%). Lastly, in the BNO plus BI prism condition, the percentage difference increased in 7 subjects and decreased in the other 8 (range from -19.39 to 92.27%).

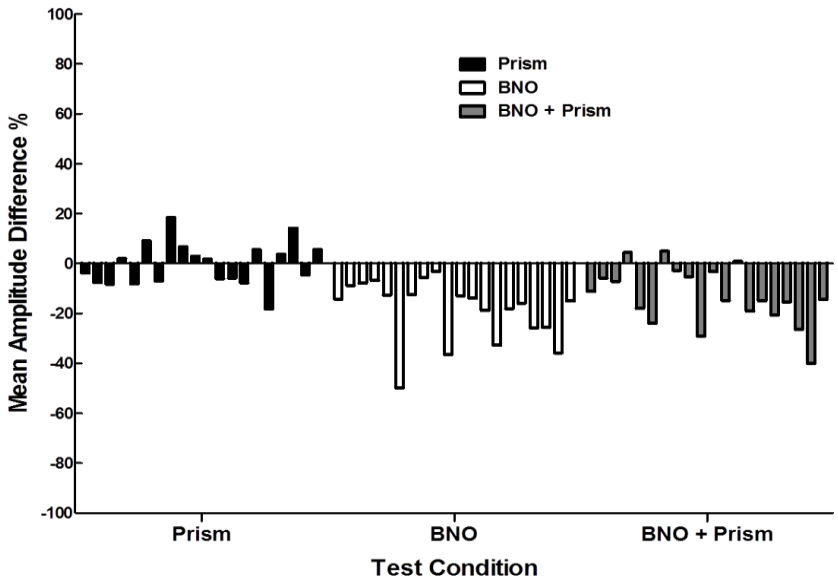

Figure 4a: Visually-normal, percentage amplitude differences for three test conditions relative to baseline values for each subject. Negative values indicate a decrease, and positive values indicate an increase, in amplitude.

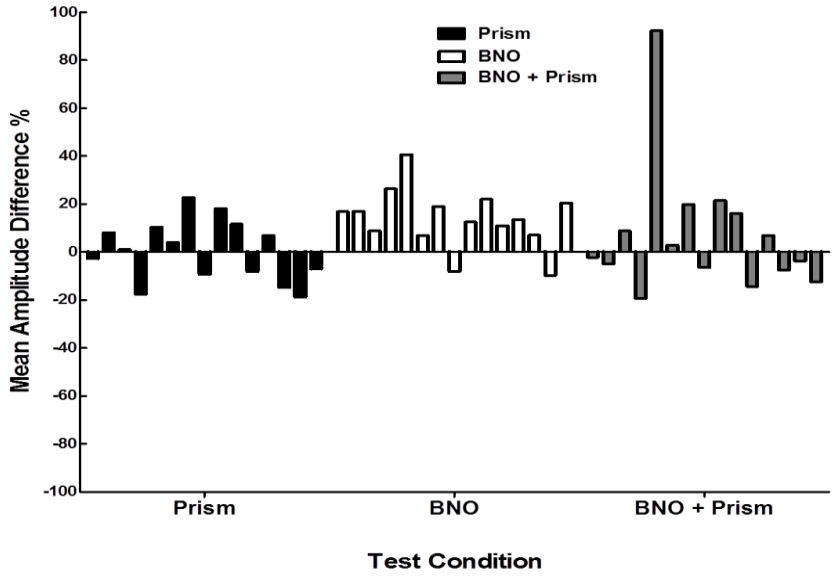

Figure 4b: mTBI, percentage amplitude differences for three test conditions relative to baseline values for each subject. Negative values indicate a decrease, and positive values indicate an increase, in amplitude.

Repeatability using the coefficient of variation (CV)

Repeatability was assessed after a period of 3 weeks in 2 subjects from each group with respect to both amplitude and latency using the coefficient of variation (CV) analysis (Table 1a and 1b). CV values for both parameters were extremely small for all test conditions and groups, thus suggesting excellent repeatability. Values ranged from 0 to 0.07.

Table 1a: Repeatability results for the VEP amplitude and latency in the VN subjects. CV = coefficient of variation

Amplitude			Latency		
Test condition	**Subject 1 CV**	**Subject 2 CV**	**Test condition**	**Subject 1 CV**	**Subject 2 CV**
Baseline	0.02	0.01	Baseline	0.009	0.008
Prism	0.05	0.06	Prism	0.006	0.006
BNO	0.05	0.02	BNO	0.004	0.006
BNO + Prism	0.03	0.07	BNO + Prism	0.014	0.004

Table 1b: Repeatability results for the VEP amplitude and latency in persons with mTBI. CV = coefficient of variation

Amplitude			Latency		
Test condition	**Subject 1 CV**	**Subject 2 CV**	**Test condition**	**Subject 1 CV**	**Subject 2 CV**
Baseline	0.03	0.03	Baseline	0	0.003
Prism	0.01	0.07	Prism	0.006	0.004
BNO	0.02	0.02	BNO	0.01	0.01
BNO + Prism	0.03	0.03	BNO + Prism	0.01	0.009

Subjective testing

The following are the results for the three subjective viewing conditions (A-C):

(A) Simple viewing task

Normals

The group mean, perceptually-based rating scores in the visually-normal subjects are presented in Figure 5a. None experienced any perceptual effects for any of the three visual stimuli (i.e., patternless wall, stationary checkerboard pattern, and flickering checkerboard) under the four test conditions (i.e., baseline, BI prism, BNO, and BNO plus BI prism). Therefore, the group mean rating score in all cases was 1.00 (SEM = 0).

mTBI

The group mean, perceptually-based rating scores in persons with mTBI are presented in Figure 5b for the three visual stimuli and four test conditions, as specified above.

A repeated-measures, one-way ANOVA was performed on the group mean rating score for the factor of test condition for the patternless wall visual stimulus. There was no significant effect of test condition on the mean rating scores [$F(3,14) = 1.45$, $p > 0.05$]. None experienced any difficulty viewing the patternless wall under any of the four test conditions. They all perceived the wall to be flat, were able to judge its distance readily, and did not perceive any apparent motion.

A repeated-measures, one-way ANOVA was performed on the group mean rating score for the factor of test condition for the stationary, checkerboard pattern visual stimulus. There was a significant effect of test condition on the mean rating scores [$F(3,14) = 11.87$, $p < 0.05$]. The post-hoc Tukey test results revealed that the mean rating score for the BNO (1.33 ±0.12) and the BNO plus BI prism (1.80 ±0.17) conditions were each significantly decreased with respect to the baseline value (2.8 ±0.24). Furthermore, the mean rating score for the BNO condition was significantly decreased with respect to the BI prism condition (2.26 ±0.24). In addition, with the BNO condition, the majority of subjects (13 out of 15) did not perceive any apparent motion for the stationary checkerboard stimulus (1.33 ±0.12), as compared to the other three test conditions. Thus, their sensation regarding apparent motion of the stationary stimulus depended on the test condition.

Lastly, a repeated-measures, one-way ANOVA was performed on the group mean rating score for the factor of test condition for the flickering, checkerboard pattern visual stimulus. There was a significant effect of test condition on the mean rating scores [$F(3,14) = 10.22$, $p < 0.05$]. The post-hoc Tukey test results revealed that the mean rating score for the BNO (1.67 ±0.21) and BNO plus BI prism (2.26 ±0.24) conditions were each significantly decreased with respect to the baseline value (3.13 ±0.33). Furthermore, the mean rating score for the BNO condition was significantly decreased with respect to the BI prism condition (2.60 ±0.24). All subjects perceived significantly less flicker with the BNO, as compared to the other three test conditions.

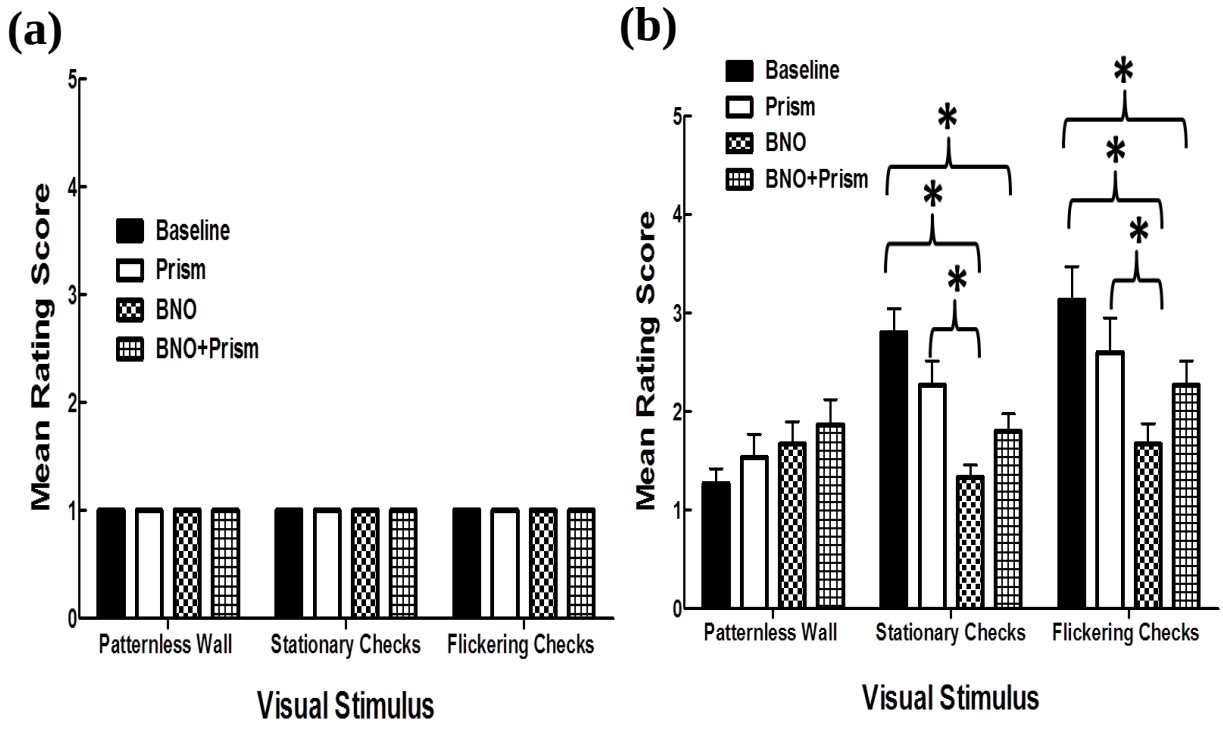

Figure 5: The group mean rating scores for each of the three visual stimuli for the four test conditions. (a) visually-normal, (b) mTBI. Brackets with an asterisk (*) represent significant differences ($p < 0.05$).

(B) Grasping task: The subjective responses in the mTBI group for the grasping task are presented in Table 2a for the four test conditions. This task was easier in those not reporting a baseline distance perception problem, as compared with those that did. In contrast, visually-normal individuals did not experience any difficulty with this task.

Table 2a: Perceptually-based, subjective responses for the grasping task in the mTBI group.

mTBI subjects (n=15)	Subjective responses
10 with no distance perception problem	Easy to grasp an object under all test conditions
5 with distance perception problem	**With Baseline, Prism**, **and BNO+P** – difficult to judge distance, slow in grasping **With BNO alone** – able to judge distance better and easier to grasp objects

(C) Walking task: The subjective responses in the mTBI group for the walking task are presented in Table 2b for the four test conditions. Thirteen of the 15 subjects responded positively with the BNO; that is, they reported being more comfortable, stable, and confident, and with less "visual noise", as compared to the other test conditions. In contrast, visually-normal individuals did not experience any difficulty with this task.

Table 2b: Perceptually-based, subjective responses for the walking task in the mTBI group.

mTBI subjects (n=15)	Subjective responses
11	most comfortable and most stable walking with the BNO alone
2	most comfortable and most stable, as well as confident, walking with the BNO alone
1	most comfortable, most stable, brain feels “relaxed”, reduced attention to peripheral motion/noise, can “control” surrounding visual information to prevent a sensory overload
2	uncomfortable walking either with BNO or BNO+Prism, BNO blocked their field-of-view, provided a sense of visual discomfort and annoyance

Discussion

The results of the present study demonstrated that the BNO condition *alone* produced consistent and significant increases in the VEP amplitude in nearly all (~90%) individuals having mTBI *and* increased VMS, relative to the other 2 test conditions and as compared to baseline. Furthermore, the present findings were able to disambiguate the interactive effects of the BNO and BI prism on VEP responsivity in those with mTBI. BNO alone produced consistently larger, repeatable, and reliable VEP amplitude responses, as compared to the BI prisms, either alone or in combination with the BNO. The present BNO findings were also consistent with the earlier results of Ciuffreda et al. [22]. They found that 100% of their mTBI patients with VMS (n=10) exhibited a significant increase in VEP amplitude with BNO alone, as compared to baseline, thus demonstrating a similarly robust effect as found in the current study. Therefore, the findings of both of the aforementioned studies clearly demonstrated that BNO alone was responsible for optimal enhancement in visuo-cortical responsivity in persons with mTBI having the symptom of VMS. Lastly, the objective findings of the present study correlated with the individual's visual impressions and sensorimotor performance found with BNO only, as compared to the other test conditions. Visual perception was more veridical, and sensorimotor performance was maximally improved, in the BNO condition.

With the BNO alone, persons with mTBI and VMS exhibited the greatest and most consistent improvements in their subjective visual perceptions and in performing the specified sensorimotor tasks, as compared to the other test conditions. For example, with respect to their visual perceptions, apparent motion of the stationary checkerboard

pattern was no longer observed, and less flickering was noticed. Furthermore, the actual VEP checkerboard stimulus appeared to be brighter and more sharply defined. Similarly, with respect to the sensorimotor tasks, grasping of a small, nearby object was reported to be easier, and walking in the long hallway was most comfortable, and done with more confidence, with the BNO condition. In addition, reduction in the symptom of VMS was reported with the BNO condition only. These improvements agree with the objective findings found with BNO alone, as compared with the other VEP test conditions.

The VEP amplitude findings of the present study in the mTBI population were more variable and less robust with the BI prisms alone, as well as with the combination of BNO *and* BI prisms, than found for the BNO condition alone. In both test conditions incorporating BI prisms, ~50% of the persons with mTBI exhibited an increase, and ~50% a decrease, in VEP amplitude as compared to the much higher percentage exhibiting a VEP amplitude increase for the BNO alone condition (~90%) in the present study. Furthermore, differences in the enhanced VEP responses with the BNO and BI prism combination were found between the present study and that of Padula et al. [25] (i.e., 50% versus 80%, respectively). There may be three reasons for this difference. First, Padula et al. [25] tested hospital-based patients, who were likely to include a combination of persons with mild *and* moderate TBI, and thus it was probably not a homogeneous subject pool. In contrast, the present study tested persons with mild TBI only in an out-patient clinic setting. Second, in the Padula et al. [25] study, it was not explicitly stated whether the patients had the key symptom of increased VMS, whereas all individuals in the present study were required to have this critical symptom. Third, and lastly, in the Padula et al. [25] study, all persons with TBI were exophoric at near, whereas in the

present study only ~50% were. BI prisms optically-assist convergence in those with exophoria at near [3]. Thus, Padula et al. [25] were likely to help all of their patients binocular vision-wise, thereby resulting in improved binocular function at near and enhanced VEP responsivity.

There were some differences found between the present investigation and two previous ones related to the effect of BI prism alone on the VEP amplitude and latency in the VN population [43, 44]. Firstly, with respect to *amplitude*, with the 2 pd BI prisms over each eye in the present study (n=20), no significant changes in mean VEP amplitude were found, as compared to the baseline value. In contrast, Heravian-Shandiz et al. [43] assessed VEP amplitude in 12 VN subjects with either 3 or 4 pd BI prisms over each eye, as well as the no-prism baseline condition. They found a small decrease in VEP amplitude (~2 μV) with each prism amount, as compared to baseline. However, they did not test with 2 pd BI prisms, as used in the present study. Similarly, Shushtarian and Norouzi [44] assessed the VEP amplitude in 50 VN subjects with 2, 4, 6, 8, and 10 pd BI prisms over each eye, as well as baseline. The VEP amplitude decreased by 0.8 μV with the 2 pd BI prisms, as compared to the mean baseline value, which represents a very small change. Secondly, with respect to *latency*, in the present study it increased (~2 ms) with the 2 pd BI prisms, as compared to the baseline value, but it was still within normal limits for our laboratory [36, 37, 38]. Similarly, Shushtarian and Norouzi [44] found a significant increase in the VEP latency (~3 ms) with 2 pd BI prisms over each eye, as compared to the mean baseline value, but again it was within normal limits for their laboratory. In contrast, Heravian-Shandiz et al. [43] did not find any significant change in VEP latency with either the 3 or 4 pd BI prisms over each eye. Both researchers [43, 44]

speculated that the BI prisms may have disrupted binocular function at the visuo-cortical level via an increase in the steady-state vergence error (i.e., fixation disparity) and related decrease in fusional ability, which may result in reduction in the VEP amplitude and/or increase in latency, as now precisely corresponding retinal points were not being stimulated optimally. However, neither study measured fixation disparity per se during the actual VEP testing, but rather assumed it to be present despite considerable differences in its measurement with respect to stimulus conditions and the related VEP test stimulus conditions. Therefore, the 2 pd BI prism results are equivocal in the visually-normal population. More control investigations (e.g., measuring the fixation disparity with BI prism during the actual VEP testing) are needed.

The present findings regarding VEP latency were of interest. In the mTBI group, the mean VEP latency significantly increased by ~2 ms for all 3 test conditions, as compared to baseline. Similar results were found in the VN individuals. However, this increase in latency was very small, and it was still within normal limits for our laboratory [36, 37, 38]. Possible reasons for this small increase are unclear. However, it may be due to the reason suggested earlier by Shushtarian and Norouzi [44] regarding disturbance of binocular function. Further careful studies are needed to clarify this issue.

Possible underlying neurophysiological mechanisms

Two possible underlying neural mechanisms were suggested and described in detail by Ciuffreda et al. [22] regarding VEP responsivity with BNO alone in persons with mTBI. They have also been described in detail earlier (see Introduction). These

included the “spread of suppression” and a “faulty” neural filtering mechanism. The present findings are consistent with either mechanism, or both in combination. However, a third mechanism may be possible related to visual attention. Assuming that the BNO reduces some of the irrelevant and distracting peripheral visual motion information from the occluded bitemporal retinal regions, then attentional weighting would be shifted back to the central visual field to some extent. Furthermore, it is well-established that visual attention can influence the VEP amplitude via the alpha-band (8-13 Hz) component contribution in both visually normal individuals [37] and in persons with mTBI [45]. Moreover, increased visual attention has been demonstrated to increase the VEP amplitude in persons with mTBI [45]. Therefore, with introduction of the BNO in those with mTBI and VMS, enhancement of the centrally-mediated visual attention is believed to occur, which in turn would increase the VEP amplitude. Further experiments are needed to address this important issue regarding the underlying neural mechanism for the positive BNO effect. Lastly, other possibilities have been proposed [25, 27] (see Introduction).

Clinical implications

There are several clinical implications based on the findings of the present study. Most importantly, for the first time, the present study was able to assess quantitatively the effect, and relative contribution, of the BNO and BI prisms on VEP responsivity in mTBI. Furthermore, BNO alone had a *high* probability of differentially diagnosing the persons with mTBI and VMS from the VN individual. With BNO alone, ~90% of those

with mTBI exhibited an increase in VEP amplitude, as compared to the VNs. Similarly, the Ciuffreda et al. [22] study found that 100% of their mTBI patients with VMS could be differentiated from the VNs with this simple and rapid VEP-BNO test condition; set-up and test time is approximately 10 minutes. Thus, the BNO-VEP test condition provided an *objective*, *non-invasive*, *rapid*, and *direct* response from the primary visual cortex (V1) for the diagnosis of mTBI/concussion. Thus, this test has the potential to be used as an objective, visual system biomarker for the diagnosis of mTBI/concussion. Second, with BNO alone, the VEP amplitude findings in those with mTBI and VMS were consistent with improvements in their visual impressions. That is, all patients (100%) observed less flickering of the VEP checkerboard stimulus, and ~90% no longer reported apparent motion of this stationary checkerboard stimulus. Third, and lastly, the objective findings were also in agreement with improvements in performing the sensorimotor tasks. That is, with BNO alone, all (100%) of the persons with mTBI and VMS, and with the report of having a "distance perception problem" [46], were able to grasp objects more easily and accurately. Furthermore, ~90% performed the walking task more comfortably and confidently, with a reduced sense of apparent visual motion of the surroundings walls. Therefore, the BNO alone appeared to improve visual function both at the primary cortical level, and also apparently at the higher cortical levels related to motion-based visual perception. Lastly, these VEP-BNO findings should be helpful to the clinician when considering the prescription of BNO to persons with mTBI and VMS.

Study limitations

There were three possible limitations to the present study. First, both the grasping and walking tasks were assessed qualitatively, but not quantitatively. Second, the walking task was performed in a quiet, relatively static visual environment rather than a noisy dynamic one, as found under many naturalistic conditions (e.g., walking across a crowded intersection). Third, changes in balance were not assessed, which could be performed in the future using objective, dynamic posturography [47].

Conclusions

With BNO alone, persons with mTBI and VMS demonstrated significant and consistent increases in VEP amplitude. In contrast, opposite directional effects were found in all of the VN cohort. The BNO condition alone was responsible for these consistent visuo-cortical changes, as compared to the other three test conditions. Furthermore, these objective findings were in agreement with improvements in both their visual impressions and performance of sensorimotor tasks. Finally, and most importantly, we believe that the BNO-VEP test may now be used clinically in the objectively-based, differential diagnosis of suspected persons having mTBI and VMS from VN individuals with a very high degree of probability (>90%). Thus, it may provide an objective visual system biomarker for the presence of an mTBI/concussion.

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Appendix 1: Demographics of the mTBI subjects.

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall	Visual symptoms
S1/26/F	2	• Hit back of head against sink • Loss of consciousness (LOC) for 2 minutes	• Visual motion sensitivity (VMS) • Reading problems • Visual-attention problems • Distance perception problems
S2/45/M	8	• Involved in 8 blast injuries • LOC for 5 minutes	• VMS • Reading problems • Visual-attention problems • Visual fatigue
S3/26/M	7	• Soccer injury (two injuries within a week) • Altered state of consciousness (ASOC) for < 30 minutes	• VMS • Reading problems • Photosensitive
S4/43/M	27	• Soccer injury • ASOC for < 30 minutes	• VMS

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall	Visual symptoms
S5/30/F	5	• Motor vehicle accident (MVA) • LOC for 10 minutes	• VMS • Reading problems • Photosensitive
S6/25/M	10	• Soccer injury • ASOC for < 30 minutes	• VMS
S7/39/F	4	• MVA • LOC for 2 minutes • ASOC for < 30 minutes	• VMS • Reading problems • Visual-attention problems
S8/29/F	2	• Hit by car 2 years ago, and hit by heavy table lamp 1 year ago • LOC for 15 minutes	• VMS • Reading problems • Distance perception problems • Vestibular problems • Migraine
S9/54/F	8	• Hit head on the ground • LOC for 2 minutes • ASOC for < 30 minutes	• VMS • Reading problems • Visual-attention problems • Photosensitive

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall	Visual symptoms
S10/30/F	1	• MVA • LOC for 3 minutes • ASOC for < 30 minutes	• VMS • Reading problems • Visual-attention problems • Photosensitive
S11/30/F	6	• Hit head during gymnastics • ASOC for < 30 minutes	• VMS • Reading problems
S12/29/F	13	• First injury due to snow-boarding accident, and second hit head on the ground 5 years ago • LOC for 3 minutes • ASOC for < 30 minutes	• VMS • Reading problems • Visual-attention problems • Distance perception problems

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall	Visual symptoms
S13/29/F	7	• First injury due to water boarding sports accident; during second and third hit head on the ground • LOC for 3 minutes • ASOC for < 30 minutes	• VMS • Reading problems • Visual-attention problems • Photosensitive • Distance perception problems
S14/30/F	1	• MVA • LOC for 5 minutes • ASOC for < 30 minutes	• VMS • Reading problems • Visual-attention problems • Photosensitive
S15/65/F	7	• Hit head on the ground 7, 3, and 1 years ago • LOC for 5 minutes • ASOC for < 30 minutes	• VMS • Reading problems • Visual-attention problems • Photosensitive • Distance perception problems

Paper #3

Objective Assessment of Attention in Mild Traumatic Brain Injury (mTBI) Using the Visual-Evoked Potential (VEP)

Yadav NK, Ciuffreda KJ. Objective assessment of attention in mild traumatic brain injury (mTBI) using the visual-evoked potential (VEP). Brain Injury. (Under Review).

Abstract

Purpose: To quantify attention objectively using the visual-evoked potential (VEP) in those having mild traumatic brain injury (mTBI) with versus without a self-reported attentional deficit.

Research design and methods: Subjects were comprised of 16 adults with mTBI: 11 with an attentional deficit, and 5 without. Three test conditions were used to modulate the attentional state to quantify objectively the VEP alpha band attenuation ratio (AR) related to attention: 1) pattern VEP; 2) eyes-closed; and 3) eyes-closed number counting. The AR was calculated for both the individual and combined alpha frequencies (8-13 Hz). The objective results were compared to two subjective tests of attention (i.e., VSAT and ASRS).

Results: The AR for both the individual and combined alpha frequencies was found to be abnormal in those with mTBI having an attentional deficit. In contrast, the AR was normal in those with mTBI but without having an attentional deficit. The AR was correlated with the ASRS, but not with the VSAT, test scores.

Conclusions: The objective and subjective tests were able to differentiate between those having mTBI with versus without an attentional deficit. This VEP protocol can be used in the clinic to detect and assess objectively and reliably an attentional deficit in the mTBI population.

Key words: mild traumatic brain injury (mTBI), visual-evoked potential (VEP), attention deficit, alpha band power, attenuation ratio (AR), primary visual cortex (V1)

Introduction

Traumatic brain injury (TBI) is a major medical and public health concern in the United States [1, 2]. Approximately 1.7 million people suffer from a TBI annually. The prevalence of TBI has increased in recent years due to the past Iraq/Afghanistan military encounters [3], as well as the greater appreciation of sports-related concussions [4] and possibly related neurodegenerative disorders (e.g., Alzheimer's, Parkinson's) [5]. Since ~70-80% of TBI is of the "mild" variety (i.e., mTBI), most research has focused in that direction [6, 7].

Mild traumatic brain injury (mTBI) occurs as a result of injury to the brain due to blunt or penetrating head trauma [8]. It produces widespread damage to the brain tissues due to the initial and immediate biomechanical effects (e.g., coup-countrecoup, shearing, etc.) [9], as well as the subsequent biomolecular/biochemical changes [10]. It causes diffuse axonal injury (DAI), which is responsible for slowed and delayed cortical information processing [11].

Due to its global nature, mTBI results in a constellation of adverse effects of a sensory, motor, perceptual, linguistic, cognitive, and/or behavioral nature [12, 13, 14]. Since the majority of cranial nerves (i.e., II, III, IV, V, VI, VII, VIII, and XI) are involved in vision, as well as at least 30-40 distinct cortical areas of the brain [15], it is not surprising that visual deficits frequently occur following mTBI (e.g., oculomotor problems, visual-field defects, photosensitivity, and increased visual motion sensitivity) [12, 16-19].

One of the most common visual sequelae of mTBI is an *attentional deficit* [14, 20-22]. Individuals with mTBI having attentional deficits typically report problems reading, and they manifest slowed visual information processing as well as distractibility [17, 18, 20, 23]. Thus, presence of an attentional deficit will likely have an adverse effect on many activities of daily living (ADLs), e.g., reading. Furthermore, it may have an adverse impact on the individual's vocational and avocational goals, as well as rehabilitative progress [24].

There is a long, but sparse, history of using objective techniques to assess human attention. Berger [25] was the first to investigate the *alpha band* (8-13 Hz) electrophysiologically in the human brain. Decades later, Klimesch [26] found that the alpha band was related to human thalamo-cortical attention. It has been confirmed that high levels of alpha power, which occur during the "relaxed", eyes-closed attentional state, are associated with *synchronous* neuronal cortical activity. In contrast, low levels of alpha power, which occur during visual stimulation and visual-attentional engagement with the eyes-open, are associated with *asynchronous* neuronal cortical activity [26]. This comparison is presented in Figure 1. More recent studies have demonstrated that the level of alpha band activity was correlated with different attentional states: eyes-closed versus eyes-open conditions [27-29], eyes closed with increased attentional demand versus eyes-closed [28, 30], visual imagery [31], and visual attention during reading [32]. These studies revealed that changes in neuronal activity occurred and were related to the different attentional states, thus producing predictable changes in the relative alpha band power contributions. Of particular importance is the following: attenuation of the alpha band amplitude occurs with the eyes-open as compared to the eyes-closed condition. This

is a normal phenomenon: in fact, *inability to attenuate or suppress alpha during the eyes-open condition suggests presence of an attentional deficit* [28-30, 32, 33]. Thus, assessing the alpha band neuronal activity provides a non-invasive and direct route to probe the attentional state of an individual *objectively*. More recent studies performed by Kirschfeld [34], and Hale et al. [35], using the EEG technique have also revealed that alpha band activity was related to one's attentional state.

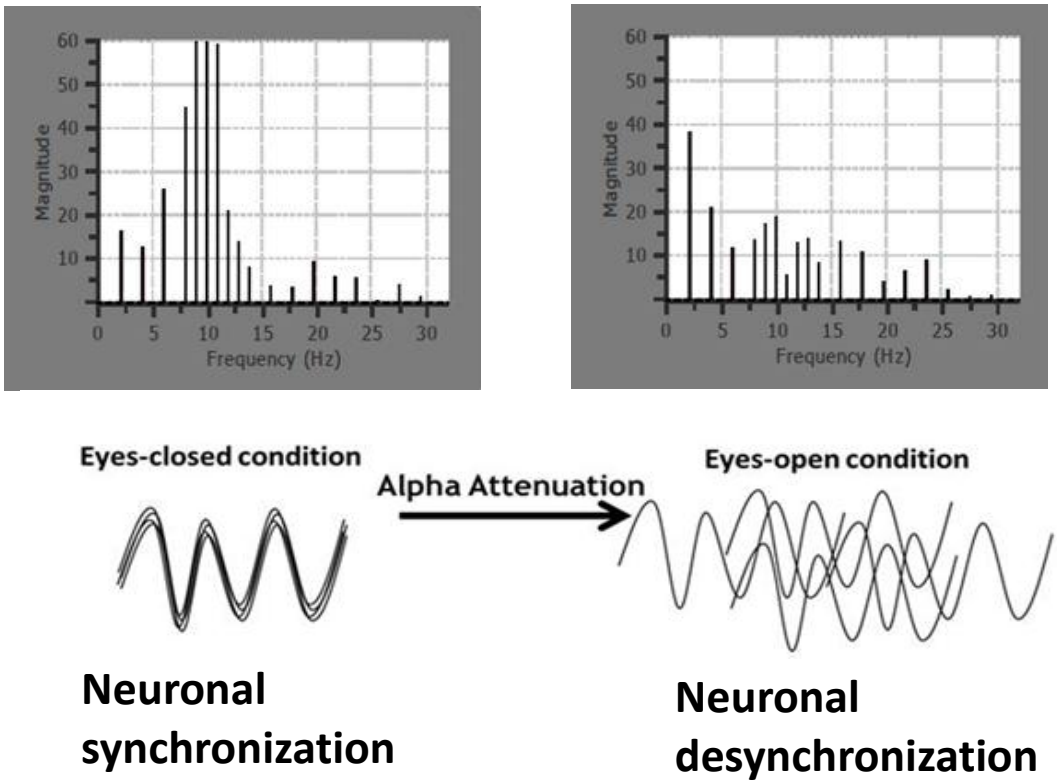

Figure 1: Alpha attenuation for eyes-closed to eyes-open condition. X and Y axis are representing the alpha band frequency (Hz) and power magnitude (μV^2), respectively.

Most studies have concentrated on assessing attention in higher cortical areas, i.e., the parietal and temporal lobes [36-38]. However, some researchers have measured attention directly from the visual cortex (V1) to assess for its early visual pathway patency. For example, Fuller [30] investigated visual attention using the EEG method at a frequency band of 0.5-30 Hz in 10 children with learning disability (LD). Their responses were compared with 11 normal, age-matched children. The alpha band was extracted from the overall EEG band, and then power spectrum analysis (described in the Methods section) was used to quantify the response and its subcomponents. First, alpha power was recorded with the eyes-closed in a relaxed state for 5 minutes, so that any residual visually-based attentional aspects were allowed to dissipate. Then, a cognitive demand was added to the eyes-closed condition, that is the subjects performed simple addition, recall of common objects, and a word problem task, all during which alpha brain wave activity was recorded. Fuller [30] calculated the alpha attenuation ratio (AR) between the average alpha power measured during the cognitively-demanding eyes-closed condition to the average alpha power measured during the eyes-closed "resting" condition. An attenuation ratio of <1.00 suggested an ability to suppress alpha activity during the cognitively-demanding, eyes-closed condition, as expected to be the case for those with normal attention. Fuller found that 81% of the normal, age-matched children had an average attenuation ratio of 0.91. In comparison, 80% of the LD children had an average attenuation ratio of 1.01. Thus, children with LD were not able to suppress their alpha activity as well during the cognitively-demanding, eyes-closed condition, as compared to the normal children. Similar results were found by Ludlam [32].

Recently, Willeford et al. [28] used the above ideas and improved VEP hardware/software technology to assess normal human attention. They confirmed and extended Fuller's earlier findings in 18 visually-normal, young-adults. The Willeford et al. [28] results obtained in our laboratory serve as the normative data base for the present study. In the Willeford et al [28] study, two different attenuation ratios (ARs) were calculated: the first was between the average alpha band power during the eyes-closed "relaxed" attentional condition (EC) and the average alpha band power during the eyes-open condition (EO); and, the second was between the average alpha band power during the eyes-closed number counting condition (ECNC) and the average alpha band power during the eyes-closed "relaxed" attentional condition (EC). The EC ÷ EO AR was found to correlate with a standard subjective clinical visual attention test, namely the Visual Search and Attention Test (VSAT) [28, 39]. In addition, Willeford et al. [28] found the following: (1) alpha attenuation ratio (AR) (EC ÷ EO) values of 2 or greater, which suggested presence of normal visual attention; (2) the objectively-based AR at 10 Hz was significantly correlated with the subjectively-derived VSAT percentile score; and (3) the second alpha AR (ECNC ÷ EC) was less than 1, which was similar to Fuller's [30] normative value. Lastly, the mean coefficient of variation (CV) values across all alpha wave frequencies, and across all subjects, ranged from 0.48 to 0.64, which was relatively low; this suggested repeatability of the alpha wave responses. Thus, the Willeford et al. [28, 29] studies demonstrated that the VEP alpha wave component provided an *objective* correlate of human attention, and furthermore significantly correlated with the subjective VSAT percentile score.

Lastly, Yadav et al. [40] quantitatively assessed the effect of oculomotor vision rehabilitation (OVR) [41] on the VEP responsivity and on attention in the mTBI population. Each individual (n=7) received 9 hours of OVR over a period of 6 weeks. It included training of all three oculomotor systems (i.e., version, vergence, and accommodation), with an embedded visual attentional training element [42, 43]. Following successful OVR: VEP amplitude increased, and its variability decreased; latency remained constant; the attentional AR (EC ÷ EO) increased at each alpha frequency and across frequencies; and the VSAT percentile score increased. These findings suggested that the OVR produced significant changes at the visuo-cortical level both with respect to vision and attention in this sample mTBI population. However, in this study, there was no attempt to use these objective and subjective techniques to detect and differentiate between those having mTBI with versus without an attentional deficit.

Thus, the purpose of the present experiment was to quantify attention objectively using the visual-evoked potential (VEP) in those having mild traumatic brain injury (mTBI) with versus without a self-reported attentional deficit. The hypothesis is that the VEP will be able to detect and assess objectively attentional deficits in the mTBI population. Those with mTBI and an attentional deficit are predicted to exhibit an inability to attenuate their alpha power during the EO and ECNC (i.e., increased attentional demand) conditions, as compared to the eyes-closed “relaxed” attentional state (EC). In contrast, those without an attentional deficit are predicted to exhibit attenuation ability.

Methods

Subjects

Sixteen individuals with medically-documented mTBI participated in this study: 11 with a self-reported attentional deficit (mean age = 38.0 years, SEM = 4.8 years), and 5 without (mean age = 29.8 years, SEM = 2.2 years). This attentional information was consistent with their clinical case history taken by a neuro-optometrist and a social worker in the college's brain injury clinic, as well as with other supporting medical and neuropsychological documentation. Brain injury resulted from either a motor vehicle accident (MVA), sports-related injury, fall, or an assault, all occurring 4 months to 13 years (mean = 5.4 years) prior to the VEP testing. See Appendix 1 for subject demographics. The following criteria were used for the diagnosis of mTBI [44]: 1) loss of consciousness for less than 30 minutes or an altered state of consciousness for up to 24 hours, 2) 13 or greater score on the Glasgow coma scale (GCS), and 3) post-traumatic amnesia (PTA) lasting less than 24 hours. Most were referred to the Raymond J. Greenwald Rehabilitation Center (RJGRC)/Brain Injury Clinic at the SUNY, State College of Optometry, 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. In addition, some were referred from students and staff at the college. Each had corrected visual acuity of 20/20 or better in each eye at both distance and near. Exclusion criteria included a history of seizures, constant strabismus, and amblyopia, as well as any

type of ocular, systemic, or neurological disease. The study was approved by the Institutional Review Board (IRB) at the SUNY, State College of Optometry. Written informed consent was obtained from all subjects.

Apparatus

The DIOPSYS™ NOVA-TR VEP system was used to assess both VEP responsivity (i.e., amplitude and latency) [19, 45, 46] and alpha band (8-13 Hz) power [28, 29, 40]. This system was used to generate an alternating checkerboard stimulus pattern, record the cortical responses, and analyze the data. It has two monitors, one to present the test stimuli to the subject, and a second for the experimenter to view the VEP and alpha responses online in real-time. In addition, artifact detection software was incorporated by the manufacturer to detect transients caused by blinks and/or saccadic eye movements. A custom-designed software program developed by the manufacturer was used to extract the alpha response information and process it quantitatively via power spectrum analysis [47]. Basically, with the power spectrum approach, at each frequency component of the response within the 8-13 Hz alpha wave signal embedded in the overall VEP frequency spectrum of 0.5-30 Hz, the signal magnitude is extracted and quantified (unit = μV^2 = microvolt^2 of the alpha band). The power at each frequency is plotted (see figure 1). This is an excellent way to extract and quantify the underlying frequency and amplitude aspects of a complex signal, and then relate the response amplitude to its specific bandwidth component contribution. The software has been used successfully in

our laboratory to measure human attention via alpha power responses in the visually-normal population [28, 29].

Procedures

VEP and alpha recordings

The VEP and alpha recordings were obtained by using three standard, gold cup electrodes (i.e., active, reference, and ground) (Grass Technologies, Astro-Med, Inc., West Warwick, RI, USA), each 1 cm in diameter [see 19, 28, 29, 40, 45, 46 for details]. The active, reference, and ground electrodes were placed at the Oz, Fz, and Fp2 scalp positions, respectively. The active electrode was used to measure the response over the primary visual cortex (V1). To reduce test preparation time in clinic patients, the electrode placement was slightly modified from the International 10/20 system (American Clinical Neurophysiology Society, 2006) [48]. Before attaching the electrodes, the designated scalp regions were cleaned with alcohol wipes and abrasive gel, and lastly, conductive paste was used to attach the electrodes. Furthermore, to maintain the electrodes firmly in place, an elastic head band was applied.

The following three test conditions were used to measure the VEP responses, as well as to modulate the attentional state to assess the alpha power responses. Five trials for each of the three test conditions were performed. Test duration of each trial was 20 seconds. These protocols have been tested fully by our laboratory in visually-normal individuals [28]:

1. **VEP [baseline, "eyes open (EO)"] –** Conventional VEP test stimulus was employed (17° H x 15° V, 64 x 64 checkerboard pattern equivalent to 20 min arc check size at 1 meter distance, 85% contrast, 74 cd/m^2 luminance, 1 Hz temporal frequency, binocular viewing with spectacle correction). Per the manufacture's software, a small (0.25 degree radius) red, rotating, annular fixation target was presented in the center of the test field to control fixation and accommodation, as well as to maintain visual attention. Subjects were instructed to fixate upon this small central target with minimal blinking to reduce any response artifacts. A chinrest/headrest assembly was used to reduce head movement and to maintain test distance. During this EO test condition, both the VEP and the alpha (8-13 Hz) power responses were measured. The EO condition was always performed first to assure VEP response normalcy. This was the baseline comparison condition, in which the alpha component is predicted to be markedly reduced due to the occurrence of visual "damping", or "attenuation", as described in the Introduction (Figure 1).

2. **"Eyes-closed (EC)" ("relaxed", reduced attentional state) –** Subjects were instructed to sit comfortably in the chair and close their eyes. Then, they were asked to relax, and "clear their mind", for 2 minutes before commencing the trials. This was the critical instruction to attain a reduced attentional state, which would allow for maximum alpha (8-13 Hz) power responsivity [28-30]. They were also instructed to imagine "gazing"

straight ahead where the central fixation target was presented, and not to move their eyes, to avoid any artifacts caused by saccadic eye movements. In this EC state, an increase in alpha power was predicted, as compared to both the EO and the ECNC conditions (Figure 1) [28, 30].

3. **"Eyes-closed number counting (ECNC)" (increased attentional demand) –** Subjects were instructed to close their eyes, as in condition 2 (EC). However, they were also instructed to perform a mental arithmetic task [30]. Subjects were initially asked to count silently backwards in steps of seven, starting from 100, 96, 94, 92, and 90 for each of the five trials, respectively [28, 49]. Different numerical starting positions prevented memorization of the reverse order number sequences. This cognitive task was added to increase the attentional demand with the eyes closed. The alpha (8-13 Hz) power was assessed. Attenuation of alpha power was expected, as compared to the EC condition.

In addition, repeatability was assessed for each test condition. This was performed in four individuals with mTBI tested on two different days, two with and two without an attentional deficit.

Adult ADHD Self-Report Scale (ASRS)

The Adult ADHD Self-Report Scale (ASRS) questionnaire was used as a screening tool to assess for an attentional deficit in those with mTBI [50]. This was developed by the World Health Organization (WHO) to screen adults for attention-deficit/hyperactivity disorder. Test-retest reliability for the ASRS was 0.87 [51]. Sensitivity and specificity were 56.3 and 98.3, respectively [50]. It is comprised of 18 questions divided into 2 parts, with 9 questions per part. Part A and Part B questions were related to inattention and hyperactivity/impulsivity, respectively. The subject is instructed to score each question based on "how they have felt and conducted themselves" over the past 6 months. Each question had a rating scale ranging from 0-4, with 0 signifying "never felt and conducted" to 4 signifying "very often felt and conducted". The Part A and Part B values are scored separately. If the score for either Part A or Part B is in a range from 0-16, 17-23, and 24 or greater, the subject was unlikely, likely, and highly likely to manifest an attentional and/or hyperactivity disorder, respectively. *However, in the present study, only the Part A questionnaire scores were used related to attention* (Appendix 2).

Visual Search and Attention Test (VSAT)

A second subjective visual attention test was performed in each individual with mTBI, namely the Visual Search and Attention Test, or VSAT (© Psychological Assessment Resources, Inc) (Appendix 3). It is used in many optometric clinics and psychological practices [28, 39]. Test-retest reliability for the VSAT was 0.95 [39].

Sensitivity and specificity were 0.88 and 0.86, respectively [39]. It incorporates a visual search and cancellation task (e.g., find a blue colour letter "H" and cross it out) that assesses the individual's global, sustained attention [39]. This test was performed binocularly at the individuals habitual near working distance, with refractive correction in place, in a quiet room per manual instructions. Following the two practice trials, the two test trials were performed. The subject was instructed to execute each trial in sixty seconds, and to do so as rapidly and accurately as possible. An average of the two test trials was used to calculate the mean VSAT percentile score for each subject. These percentile scores were compared with the age-matched normative table provided in the VSAT manual.

Alpha Attenuation Ratio (AR)

The alpha AR is related to the human attentional state [28-30, 40]. Two different alpha attenuation ratios (ARs) were calculated, as described in detailed earlier based on prior studies. The first was the alpha power (μV^2) measured during the "eyes-closed (EC)" condition divided by the alpha power measured during the "eyes-open (EO)" condition [28, 29]. Willeford et al., [28, 29] found that an AR (EC ÷ EO) of 2.0 or greater suggested the presence of normal visual attenuation. That is, there was considerable and normally-expected attenuation/suppression of the alpha activity in the "eyes-open" condition as compared to the "eyes closed" test condition. The second alpha AR was calculated as the alpha power (μV^2) measured during the "eyes-closed number counting (ECNC)" condition divided by the alpha power measured during the "eyes-closed (EC)"

condition [28, 30]. Fuller [30] was the first to find, and Willeford et al. [28] confirmed and extended, that an AR (ECNC ÷ EC) of <1.00 suggested the presence of normal attenuation. That is, there was considerable and normally-expected suppression of the alpha activity in the "eyes-closed number counting (ECNC)" condition as compared to the "eyes closed (EC)" test condition.

Data Analysis

Several types of data analyses were performed. Five trials per test condition were done, and the average was used in the data analysis; no data were deleted, so that the effects across frequencies were constant. First, the group mean VEP amplitude and latency were assessed. Second, the group mean of each alpha AR (i.e., EC ÷ EO and ECNC ÷ EO) at *each* individual alpha frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) was assessed, as well as the *combined* mean of each alpha AR (i.e., EC ÷ EO and ECNC ÷ EO) across all frequencies (i.e., 8-13 Hz). A one-way, repeated-measures ANOVA was used to assess the group data. In addition, two correlations were performed: between each subject's ASRS Part A scores and their alpha ARs, and between each subject's VSAT percentile score and their alpha ARs. Lastly, the coefficient of variation (CV = standard deviation ÷ mean) of the alpha wave responses was calculated to assess repeatability [28, 29, 45, 52]. GraphPad Prism 5 software was used to perform the analyses. Lastly, the data were segregated into those with versus without a self-reported attention deficit, as well as combined, for specific subgroup and group analyses.

Results

VEP analysis: group data (n=16)

The group mean VEP amplitude and latency (P100) were analyzed. The group mean amplitude was 19.20 µV (SEM = ±2.38). The group mean latency was 108.86 ms (SEM = ±1.84). These amplitude and latency values were within normal limits for our laboratory [19, 40, 46]. This information was evaluated to confirm VEP response normalcy before assessing the attentionally-related alpha band component.

Power spectrum analysis

mTBI with an attention deficit (n=11)

The group mean power spectrum value at each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) across the 3 test conditions for individuals with mTBI and an attentional deficit are presented in Figure 2A. A one-way ANOVA was performed for the factor of power for each alpha frequency across all 3 tests conditions. There was no significant effect of power on the alpha band frequency [$F(5, 60) = 1.12$, $p > 0.05$].

The group mean results were analyzed using a one-way ANOVA for each alpha frequency comparing between conditions 1, 2, and 3. A significant difference between conditions was only found for the 11 Hz alpha frequency [$F(2, 30) = 4.04$, $p < 0.05$]. At 11 Hz, the post-hoc Tukey test results revealed that the power (μV^2) value for the EO condition was significantly reduced with respect to the ECNC condition ($p < 0.05$).

mTBI without an attention deficit (n=5)

The group mean power spectrum value at each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) across the 3 test conditions for individuals with mTBI but without an attentional deficit are presented in Figure 2B. A one-way ANOVA was performed for the factor of power for each alpha frequency across all 3 test conditions. There was a significant effect of power on the alpha band frequency [$F(5, 60) = 1.12$, $p < 0.05$]. The post-hoc Tukey test results revealed that the power (μV^2) value at 10 and 11 Hz was significantly larger than at 13 Hz ($p < 0.05$). No other comparisons were significant ($p > 0.05$).

The group mean results were analyzed using a one-way ANOVA for each alpha frequency comparing conditions 1, 2, and 3. The one-way ANOVA found significant differences between conditions per the following alpha frequencies:

9 Hz: There were significant differences between conditions [$F(2, 12) = 4.43$, $p < 0.05$]. The post-hoc Tukey test results revealed that the power (μV^2) value for the EO condition was significantly less than the EC condition ($p < 0.05$). No other comparisons were significant ($p > 0.05$).

10 Hz: There were significant differences between conditions [$F(2, 12) = 17.87$, $p < 0.05$]. The post-hoc Tukey test results revealed that the power (μV^2) value for the EO and ECNC conditions were significantly less than for the EC condition ($p < 0.05$). No other comparisons were significant ($p > 0.05$).

11 Hz: There were significant differences between conditions [$F(2, 12) = 7.35$, $p < 0.05$]. The post-hoc Tukey test results revealed that the power (μV^2) value for the EO

condition was significantly less than for the EC and the ECNC conditions ($p < 0.05$). No other comparisons were significant ($p > 0.05$).

12 Hz: There were significant differences between conditions [$F(2, 12) = 9.24$, $p < 0.05$]. The post-hoc Tukey test results revealed that the power (μV^2) value for the EO condition was significantly less than for the EC and the ECNC conditions ($p < 0.05$). No other comparisons were significant ($p > 0.05$).

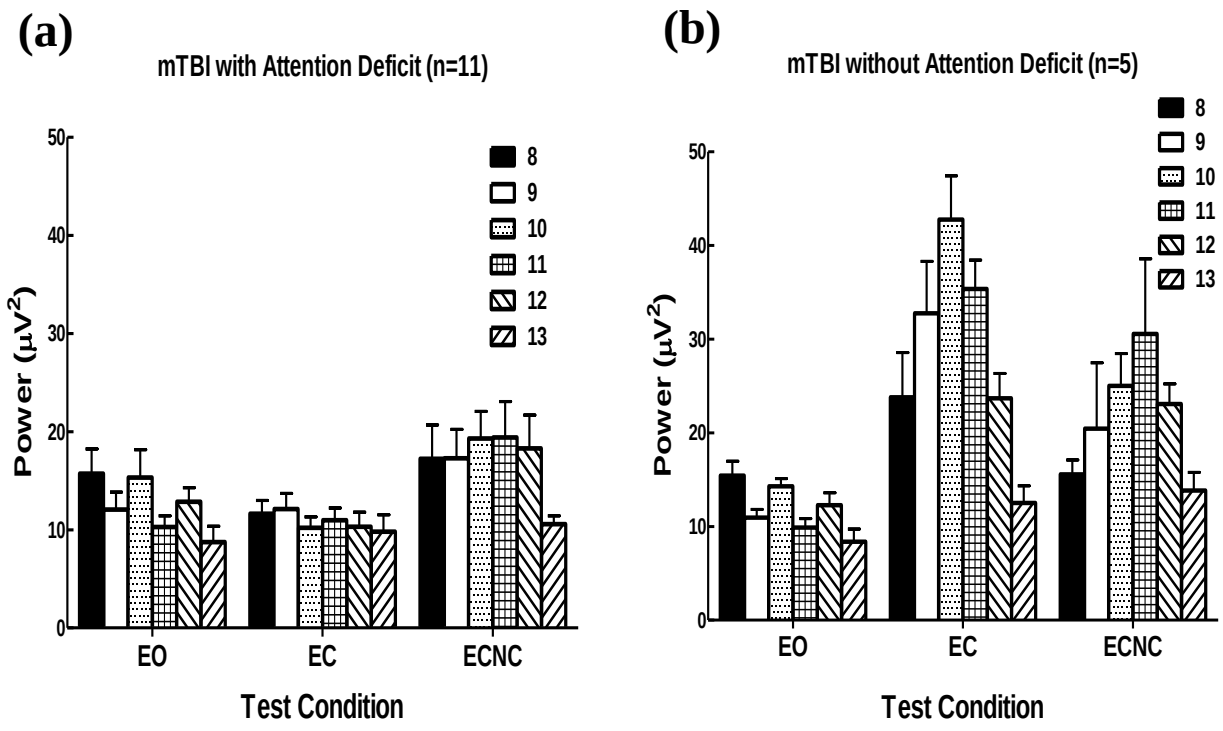

Figure 2: The group mean power spectrum value (μV^2) at each alpha band frequency (8-13 Hz) for the 3 test conditions. Plotted is the mean +1 SEM. (a) Individuals with mTBI and an attention deficit, (b) Individuals with mTBI without an attention deficit. Symbols: EO = eyes-open, EC = eyes-closed, and ECNC = eyes-closed number counting.

Alpha Attenuation Ratio (AR): Individual alpha frequencies

Eyes-closed ÷ Eyes-open (EC ÷ EO)

The group mean AR for *each* alpha frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for individuals with mTBI and an attentional deficit is presented in Figure 3A. The mean AR at each alpha frequency was lower than the normative AR value of ≥2.00 [28, 29]. The mean alpha AR ranged from 0.806 to 1.36. A one-way, repeated-measures ANOVA was performed for the factor of AR at each alpha frequency. There was a significant effect of AR on the alpha frequencies [$F(5, 10) = 3.36$, $p < 0.05$]. The post-hoc Tukey test results revealed that the AR at 10 Hz was significantly lower than the AR at 13 Hz ($p < 0.05$). No other comparisons were significant ($p > 0.05$).

The group mean AR for *each* alpha frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for individuals with mTBI but without an attention deficit is presented in Figure 3B. The mean AR at 9, 10, 11, and 12 Hz was ≥2.00, which was normal [28, 29]. The mean alpha AR ranged from 1.59 to 3.92. A one-way, repeated-measures ANOVA was performed for the factor of AR at each alpha frequency. There was a significant effect of AR on the alpha frequencies [$F(5, 4) = 4.46$, $p < 0.05$]. The post-hoc Tukey test results revealed that AR at 8 and 13 Hz was significantly lower than the AR at 11 Hz ($p < 0.05$).

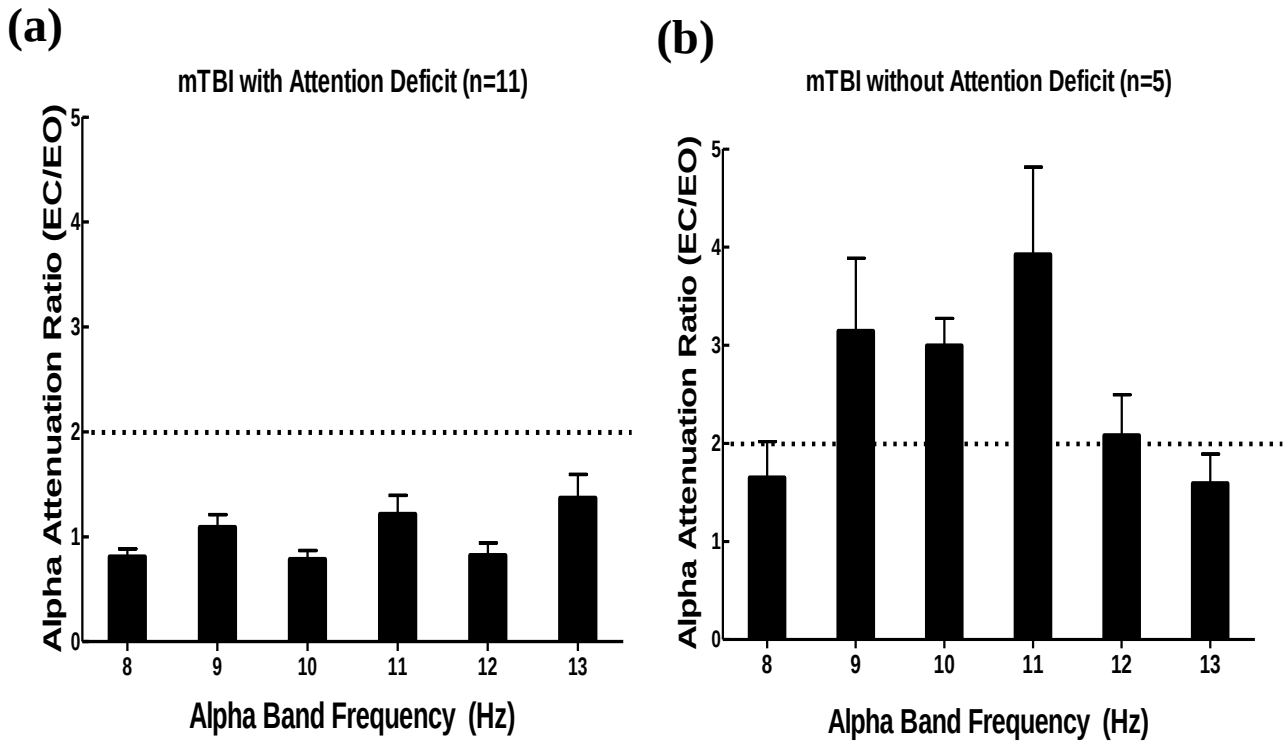

Figure 3: The group mean alpha attenuation ratio (AR) (EC ÷ EO) for each alpha frequency. Plotted is the mean +1SEM. (a) Individuals with mTBI and an attention deficit, (b) Individuals with mTBI without an attention deficit.

Eyes-closed Number Counting ÷ Eyes-closed (ECNC ÷ EC)

The group mean AR for *each* alpha frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for individuals with mTBI and an attentional deficit is presented in Figure 4A. The mean AR at each alpha frequency was higher than the normative AR value of <1.00 [28, 30]. The mean alpha AR ranged from 1.27 to 2.24. A one-way, repeated-measures ANOVA was performed for the factor of AR at each alpha frequency. There was no significant effect of AR on the alpha frequencies [$F(5, 10) = 1.28$, $p > 0.05$].

The group mean AR for *each* alpha frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for individuals with mTBI but without an attentional deficit is presented in Figure 4B. The mean AR at 8, 9, 10, 11, and 12 Hz was <1.00, which was normal [28, 30]. The mean alpha AR ranged from 0.59 to 1.10. A one-way, repeated-measures ANOVA was performed for the factor of AR at each alpha frequency. There was a significant effect of AR on the alpha frequencies [$F(5, 4) = 2.92$, $p < 0.05$]. The post-hoc Tukey test results revealed that the AR at 10 Hz was significantly lower than the AR at 13 Hz ($p < 0.05$). No other comparisons were significant ($p > 0.05$).

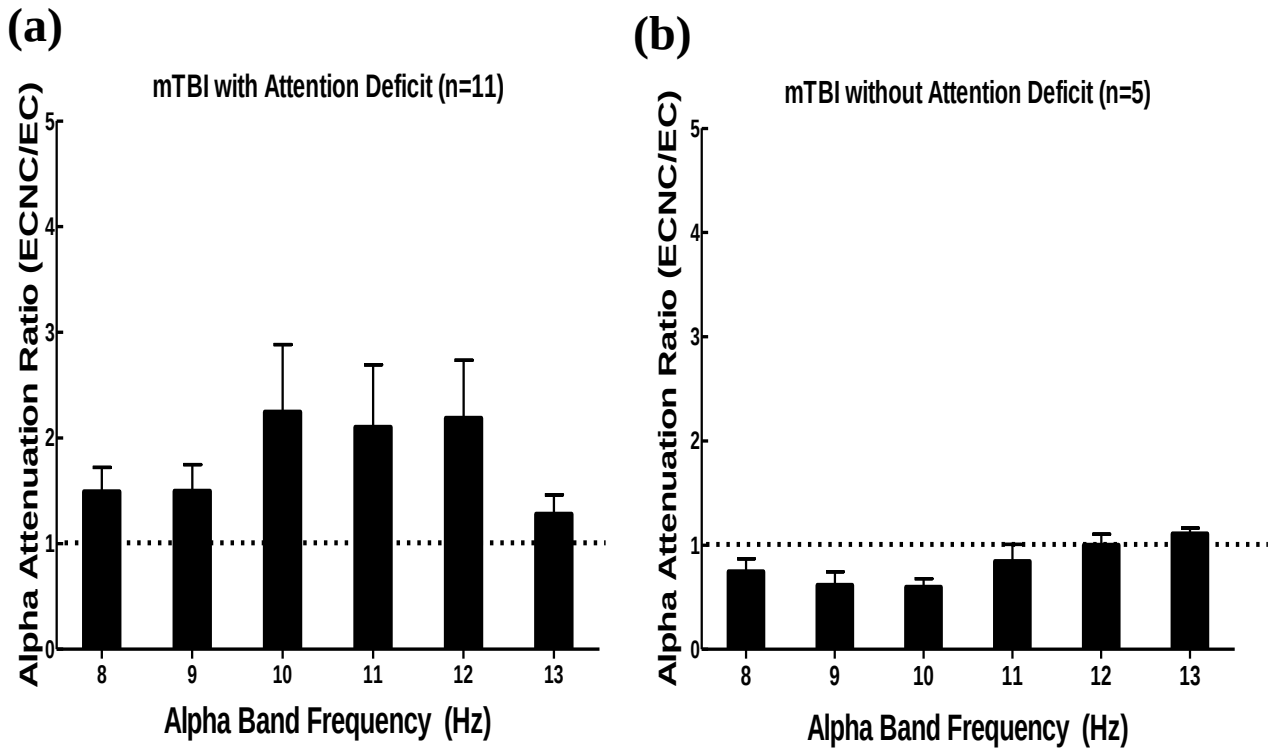

Figure 4: The group mean alpha attenuation ratio (AR) (ECNC ÷ EC) for each alpha frequency. Plotted is the mean +1SEM. (a) Individuals with mTBI and an attention deficit, (b) Individuals with mTBI without an attention deficit.

Alpha Attenuation Ratio (AR): combined across the alpha frequency band (8-13 Hz)

Eyes-closed ÷ Eyes-open (EC ÷ EO)

The AR combined across the alpha frequency band (i.e., from 8-13 Hz) for each individual with mTBI and an attentional deficit is presented in Figure 5A. The AR combined across the alpha frequency band for each individual was lower than the mean normative AR value of ≥2.00 [28, 29]. The group mean AR combined across the alpha frequency band was 1.01 (SEM = 0.07) with a range from 0.62 to 1.33.

The AR combined across the alpha frequency band (i.e., from 8-13 Hz) for each individual with mTBI but without an attentional deficit is presented in Figure 5B. The AR combined across the alpha frequency band for each individual was ≥2.00, which was normal [28, 29]. The group mean AR combined across the alpha frequency band was 2.19 (SEM = 0.03) with a range from 2.07 to 2.18.

An unpaired, two-tailed, t-test was performed between those having mTBI with versus without an attentional deficit for the AR combined across the alpha frequency band. The results revealed a significant difference [$t(14) = 9.78$, $p < 0.05$]. It was higher in the mTBI subgroup without an attention deficit.

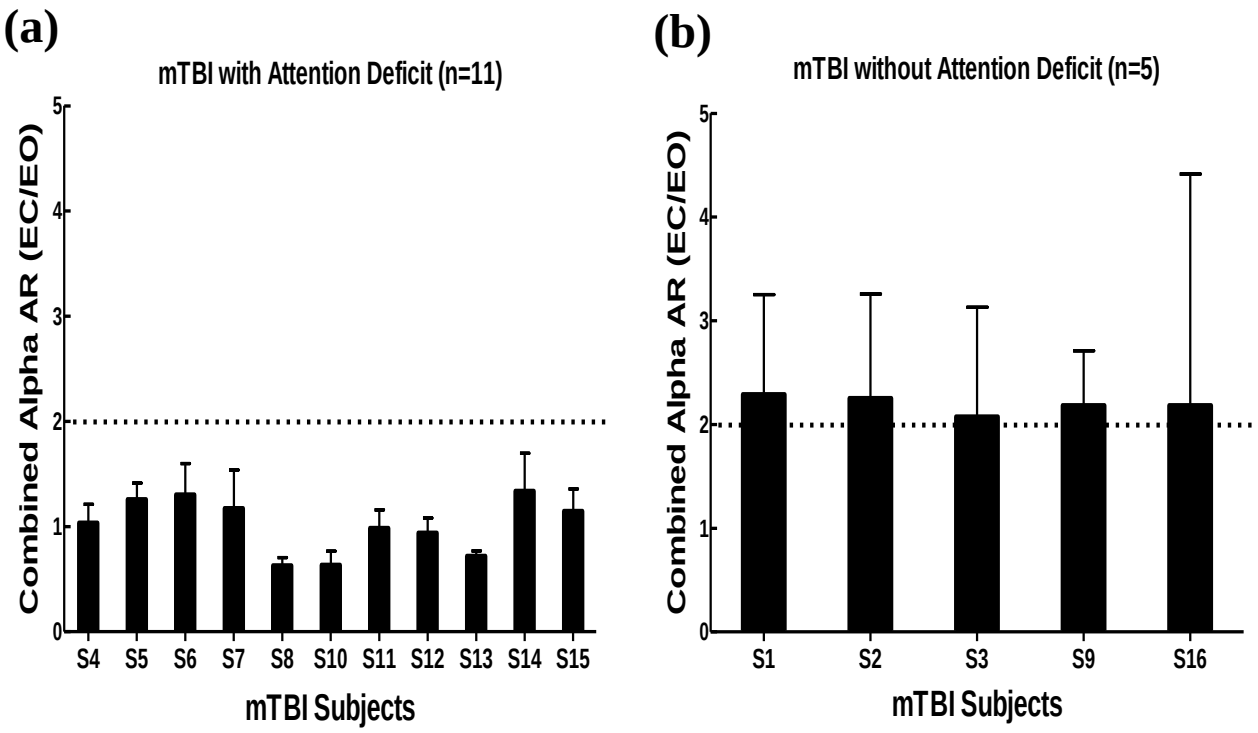

Figure 5: The attenuation ratio (AR) (EC ÷ EO) combined across the alpha frequency band (8-13 Hz). Plotted is the mean +1SD. (a) Individuals with mTBI and an attention deficit, (b) Individuals with mTBI without an attention deficit.

Eyes-closed Number Counting ÷ Eyes-closed (ECNC ÷ EC)

The AR combined across the alpha frequency band (i.e., from 8-13 Hz) for each individual with mTBI and an attentional deficit is presented in Figure 6A. The AR combined across the alpha frequency band for most individuals (except subjects #12 and 13) was higher than the normative AR value of <1.00 [28, 30]. However, in these two subjects, the error bars (+SD) crossed into the normal range. The group mean AR combined across the alpha frequency band was 1.79 (SEM = 0.96) with a range from 0.86 to 4.33.

The AR combined across the alpha frequency band (i.e., from 8-13 Hz) for each individual with mTBI but without an attentional deficit is presented in Figure 6B. The AR combined across the alpha frequency band for each individual was <1.00, which was normal [28, 30]. The group mean AR combined across the alpha frequency band was 0.806 (SEM = 0.02) with a range from 0.71 to 0.86.

An unpaired, two-tailed, t-test was performed between those having mTBI with versus without an attentional deficit for the AR combined across the alpha frequency band. The results revealed a significant difference [$t(14) = 2.24$, $p < 0.05$]. It was smaller in mTBI without an attentional deficit.

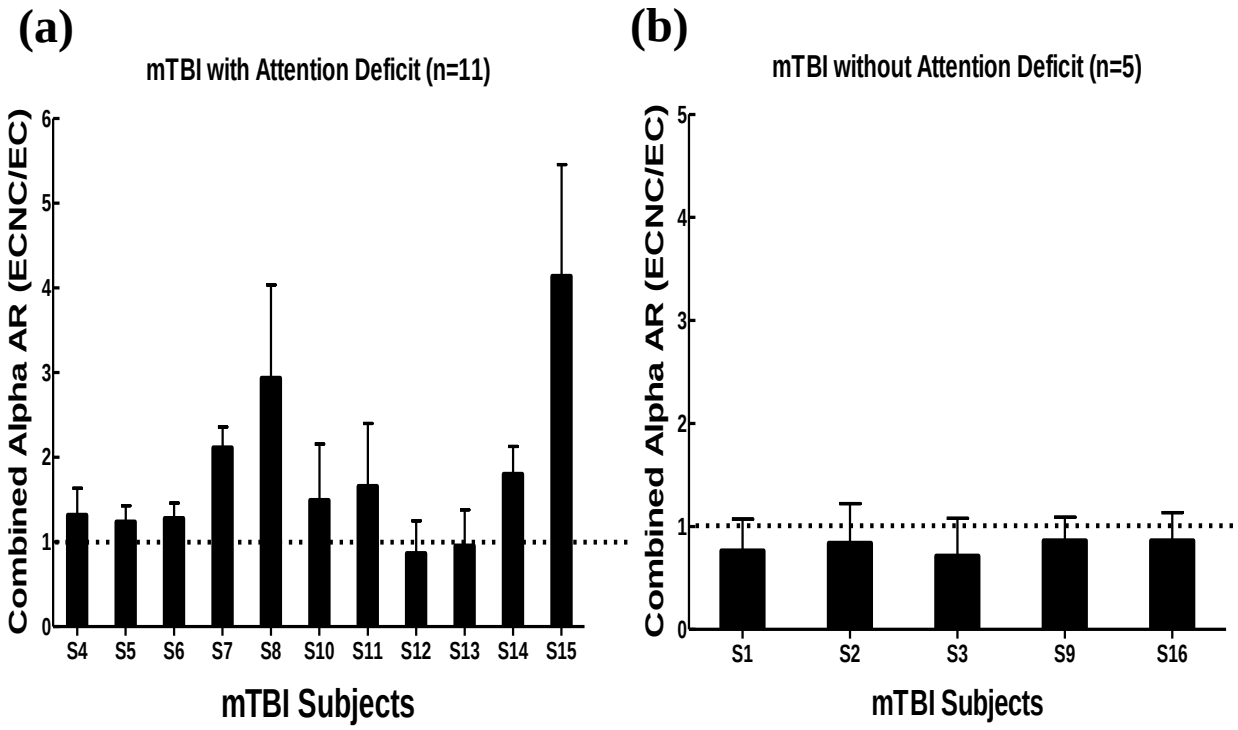

Figure 6: The attenuation ratio (AR) (ECNC ÷ EO) combined across the alpha frequency band (8-13 Hz). Plotted is the mean +1SD. (a) Individuals with mTBI and an attention deficit, (b) Individuals with mTBI without an attention deficit.

Adult ADHD Self-Report Scale (ASRS)

The Part A questionnaire scores for the ASRS test, which were related to attention for each subject, are presented in Table 1. As mentioned earlier, if the scores were in a range from 0-16, 17-23, and 24 or greater, the subject was unlikely, likely, and highly likely to manifest an attentional deficit, respectively. The mean score in those having mTBI with a self-reported attentional deficit *(n=11)* was 22.81 (SEM = 0.97), with a range from 17 to 28. In contrast, the mean score in those having mTBI without a self-reported attentional deficit *(n=5)* was 12.4 (SEM = 1.36), with a range from 8 to16. An unpaired, two-tailed, t-test was performed between those having mTBI with versus without an attentional deficit per the ASRS score. There was a significant difference [$t(14) = 6.04$, $p < 0.05$]. It was higher in those having mTBI with an attentional deficit.

Visual Search and Attention Test (VSAT)

The VSAT percentile scores for each subject are presented in Table 1. The mean VSAT percentile score in those having mTBI with a self-reported attentional deficit *(n=11)* was 54.72 (SEM = 10.95) with a range from 1 to 93. The mean score in those having mTBI but without a self-reported attentional deficit *(n=5)* was 68.8 (SEM = 14.54) with a range from 12 to 95. Subjects S10 and S9 had borderline 6th and 12th percentile scores, respectively. Subject S12 had a frank abnormal 1st percentile score. The unpaired, two-tailed, t-test was performed between those having mTBI with versus

without an attentional deficit per the VSAT percentile scores. There was no significant difference [$t(14) = 0.73$, $p > 0.05$].

Table 1: Attentional Adult ADHD Self-Report Scale (ASRS) Part A and Visual Search and Attention Test (VSAT) score for each mTBI subject.

Subjects	ASRS Part A Questionnaire Score	VSAT Percentile Score
S1	13	81
S2	11	77
S3	16	95
S4	21	93
S5	25	90
S6	28	75
S7	20	31
S8	17	93
S9	14	12
S10	22	6
S11	26	87
S12	25	1
S13	25	65
S14	20	15
S15	22	46
S16	8	79

Bold, italics subjects (***S***) represent those with a self-reported visual attentional deficit.

Correlations

Linear regression analysis was used to assess all of the correlations between the different parameters for all individuals with mTBI (n=16), as described below.

Alpha AR versus Adult ADHD Self-Report Scale (ASRS) score

Correlation between the AR for the EC ÷ EO condition and the ASRS score at each alpha frequency was performed. There were significant correlations at 8, 9, 10, 11, and 12 Hz ($r = +0.62$ to $+0.83$, $p < 0.05$), being highest at 9, 10, and 11 Hz ($r = +0.73$ to $+0.83$). Similarly, a significant correlation was found between the AR for the EC ÷ EO condition combined across the alpha frequency band and the ASRS scores ($r = 0.76$; $p < 0.05$).

Correlation between the AR for the ECNC ÷ EO condition and the ASRS score at each alpha frequency was quantified. There was a significant correlation only at 8 Hz ($r = 0.53$, $p < 0.05$). A significant correlation was not found between the AR for the ECNC ÷ EC condition combined across the alpha frequency band and the ASRS scores ($p > 0.05$).

Alpha AR versus VSAT percentile score

Correlation between the AR for the EC ÷ EO condition and the VSAT percentile scores at each alpha frequency, as well as across the alpha frequency band, was quantified. No significant correlations were found ($p > 0.05$).

Correlation between the AR for the ECNC ÷ EC condition and the VSAT percentile scores at each alpha frequency, as well as across the alpha frequency band, was quantified. No significant correlations were not found ($p > 0.05$).

Repeatability

Repeatability was assessed after a period of 2 weeks in 2 individuals with, and 2 individuals without, an attentional deficit with respect to power spectrum values across all 3 conditions for each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz), amplitude, and latency. The coefficient of variation (CV) analysis was used. CV values across all parameters were extremely small in both groups. The median value was 0.09, with a range from 0.003 to 0.58.

Discussion

The present investigation demonstrated for the first time that the VEP could be used to detect and assess objectively for an attentional deficit in the mTBI population, and furthermore differentiate between those having mTBI with versus those without an attentional deficit. The attentional deficit could be detected as early as the primary visual cortex (V1). More specifically, the attenuation ratio (AR) (i.e., EC ÷ EO and ECNC ÷ EC) at each alpha band frequency was able to differentiate objectively between those with versus without an attentional deficit. Similar results were also found when the AR was combined across the alpha frequency band (8-13 Hz). Lastly, the objective VEP alpha frequency findings were significantly correlated with the subjective ASRS neuropsychological attention questionnaire scores.

The findings of the current study confirmed, clarified, and extended the results of previous studies [28, 29, 40, 53, 54]. First, the present findings extended the results of Willeford et al. [28, 29], who predicted that individuals with mTBI and an attentional deficit would manifest an abnormal AR, as found in the present study. In addition, in the current investigation, 3 individual alpha band frequencies (i.e., 9, 10, and 11 Hz) provided highly reliable information regarding the attentional state in the mTBI population. The same alpha band frequencies were found to provide highly reliable attentional information in the visually-normal adult population [28, 29]. Thus, these specific frequencies were high-yield parameters in both populations. Second, the present study results were in agreement with the recent Yadav et al. [40] study. They found an abnormal EC ÷ EO AR at both the individual and combined alpha frequencies before oculomotor vision rehabilitation (OVR) in a sample mTBI population. Following

successful OVR, however, the AR significantly increased, thus reflecting concomitant increased and enhanced attention. This confirms the speculation of many that embedded in all OVR is attentional training [42, 43]: one must be able to attend to and detect progressively smaller changes in magnitude of target blur, disparity, and displacement as part of the oculomotor rehabilitative training process. Lastly, the present study suggests that the processing of attention occurs as early as the primary visual cortex (V1) in the mTBI population, as well as in the visually-normal population [28, 29], with this information later being transmitted to higher cortical areas (e.g., parietal, temporal) for further processing, as suggested by Somers et al. [53] and Kastner and Ungerleider [54].

Alpha attenuation ratio (AR)

The present findings support our proposed hypothesis: individuals with mTBI and an attentional deficit were unable to attenuate alpha band power during the EO and ECNC conditions, as compared to the EC condition. No significant differences were found across these 3 conditions. In contrast, those with mTBI but without an attentional deficit did. Furthermore, the mean EC ÷ EO AR was found to be abnormal (i.e., ≤2) at each alpha band frequency in those with an attentional deficit. In contrast, it was within normal limits (i.e., ≥2) at the 9, 10, 11, and 12 Hz alpha frequencies in individuals without an attentional deficit. Similar results were found when the EC ÷ EO AR was combined across the alpha frequency band (8-13 Hz) in both mTBI sub-groups.

The mean ECNC ÷ EC AR was also found to be abnormal (i.e., >1) at each alpha band frequency in those with an attentional deficit. In contrast, it was within normal

limits (i.e., <1) at the 8, 9, 10, and 11 Hz alpha frequencies in those individuals without an attentional deficit. Similar findings were found when the ECNC ÷ EC AR was combined across the alpha frequency band (8-13 Hz) in both mTBI sub-groups. Therefore, these findings clearly demonstrate that the VEP could be used as an objective, rapid, and repeatable technique to detect and assess the attentional state in those with mTBI.

Subjective attention tests (ASRS versus VSAT)

The ASRS questionnaire was found to be valuable in differentiating between those with versus without an attentional deficit in the mTBI population. The ASRS questionnaire scores for *all* individuals with mTBI having a self-reported attentional deficit (n=11) were in the abnormal range (17 to 28). Moreover, the ASRS scores for *all* individuals with mTBI but without having a self-reported attentional deficit (n=5) were in the normal range (8 to 16). This suggests that the ASRS questionnaire was an excellent predictor for detecting an attentional deficit in the mTBI population (100%). In contrast, the VSAT was not a good predictor (18%), and furthermore the VSAT percentile scores were not able to differentiate these two mTBI sub-groups regarding presence of an attentional deficit.

Correlation between objective and subjective findings

The aforementioned objective findings were in agreement with the subjective ASRS questionnaire scores. These scores were significantly correlated with the EC ÷ EO AR at each of the individual alpha band frequencies (except for 13 Hz). In contrast, the ASRS score was only significantly correlated with the ECNC ÷ EC AR at the 8 Hz alpha band frequency. Similarly, a correlation was found when the EC ÷ EO AR was combined across the alpha band frequencies (8-13 Hz); however, again there was no correlation with the ECNC ÷ EC AR. Taken together, these findings suggest that the EC ÷ EO AR was a much more robust and sensitive indicator for detection of an attentional deficit in this population as compared with the ECNC ÷ EC AR. Lastly, these correlations suggest that the VEP findings at the V1 level were related to responses at higher cortical levels, as the subjective responses likely involve higher cortical attentional areas (e.g., frontal) [55].

In contrast, the objective VEP alpha frequency findings were not correlated with the VSAT percentile scores. The present VSAT results were not in agreement with that of Willeford et al. [28]; however, their test population was visually-normal and not mTBI. Another possible reason for this difference might be due to larger spread of AR values in their visually-normal population, as compared to the present mTBI population, which would yield more likelihood for obtaining a significant correlation [56].

Neurophysiological mechanism

A possible neurophysiological mechanism underlying these findings is based on the concept of synchronous versus asynchronous neuronal activity. Such activity occurs at the primary visual cortex (V1) level during modulation of one's attentional state (e.g., eyes-closed versus eyes-open condition).

What might occur during the EC relaxed/low attentional demand condition? Klimesch [26], and others [57, 58], suggested that in individuals with normal attention, synchronous neuronal activity occurs. This was presumably due to oscillation of a large number of neurons having the same phase and frequency. These synchronous oscillations can be appreciated quantitatively as reflective of increased alpha band power. This oscillatory activity is believed to "block" information processing from occurring. In contrast, it was suggested that in those individuals with mTBI and an attentional deficit, *a*synchronous activity occurs during the EC ("relaxed") attentional state, and thus these individuals cannot "block" information processing from occuring. The asynchronous neuronal activity would cause attenuation, or suppression/damping, of the alpha band power via signal cancellation [59].

The opposite is believed to occur in the EO condition. In individuals with normal attention, *a*synchronous neuronal activity is believed to occur during the EO condition, whereas synchronous neural activity is believed to occur during the ECNC condition. This asynchrony during the former condition is believed to be due to oscillation of a large number of neurons with different phases and frequencies, which occurs due to processing of the more visually-based and cognitively-demanding information. This asynchrony

causes attenuation of the alpha band power, again via signal cancellation [59]. In individuals with mTBI and an attentional deficit, *a*synchronous activity occurs during all three conditions, and thus presence of relative attenuation. The findings of the present study are consistent with the proposed mechanism of Klimesch [26], and others [57, 58].

Proposed VEP attentional test protocol

Based on the results of the present study and others conducted in our laboratory [28, 29, 40], the following attentional test protocol is proposed for clinic use in the mTBI population:

4. **Case history –** A detailed case history should be taken regarding attention.

5. **Subjective test** –The Adult ADHD Self-Report Scale (ASRS) Part A questionnaire should be used as a screening tool to assess for presence of an attentional deficit.

6. **Objective test** – The following two VEP test conditions should be performed to assess for VEP normalcy, as well as to quantify the alpha band power and AR parameter:

   C. Eyes open (EO)

   D. Eyes-closed (EC)

   Number of trials – 5 trials (each 20 seconds) should be performed for each test condition and averaged.

Quantification of the EC ÷ EO AR should be performed. If the AR is ≥2, mainly at the 9, 10, and 11 Hz high-yield alpha band frequencies, this would suggest normal attention; if not, it would suggest presence of an attentional deficit. If the subjective and objective test results agree, and are consistent with the case history findings, the patient would likely have an attentional deficit. This proposed VEP attentional protocol may prove helpful to clinicians in assessing attention objectively, rapidly, reliably, and quantitatively.

Clinical implications

There are several important clinical implications based on the findings of the present study. First, the AR parameter was related to attentional state and attenuation ability. Thus, it may be reliably used as a *clinical barometer* of the overall attentional state. The objectively-based AR should be compared with the patient's subjective ASRS Part A scores. This would help the clinician make a more accurate diagnosis regarding a patient's attentional state. Second, due to its objective nature, the VEP protocol may be extended to assess attention in cognitively-impaired individuals [60] and non-verbal patients [61], as well as pediatric patients with attention deficit hyperactivity disorder (ADHD) [62]. Lastly, the proposed testing would also allow clinicians to evaluate objectively the effect of a visual intervention incorporating an attentional component [40].

Study limitations

There were two possible study limitations. First, sample size was relatively small. However, the effect was robust (100%). Second, this study included only those with mTBI. It should be extended to those with moderate and severe TBI.

Conclusions

This is the first time the clinical VEP technique has been used to detect and assess attentional deficit at the V1 cortical level in the mTBI population. It was accomplished by modulating the attentional state and quantifying the outcome via the AR power spectrum analysis parameter. The AR was found to be able to detect and differentiate between mTBI with versus without an attentional deficit. Furthermore, these objective findings were in agreement with the subjective Part A ASRS scores. This test protocol should be extended to other “special” populations having attentional problems.

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Appendix 1: Demographics of the mTBI subjects.

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall/Assault	Visual symptoms
S1/30/F	5	• Motor vehicle accident (MVA) • Loss of consciousness (LOC) for 10 minutes	• Visual motion sensitivity (VMS) • Reading problems • Photosensitivity
S2/38/F	6	• Hit head during gymnastics • Altered state of consciousness (ASOC) for < 30 minutes	• VMS • Reading problems
S3/26/M	7	• Soccer injury (two injuries within a week) • ASOC for < 30 minutes	• VMS • Reading problems • Photosensitivity
S4/45/M	8	• Involved in 8 military blast injuries • LOC for 5 minutes	• Visual-attention deficit • VMS • Reading problems • Visual fatigue
S5/24/F	6	• Soccer injury • LOC for 10 minutes • ASOC for < 24 hours	• Visual-attention deficit

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall/Assault	Visual symptoms
S6/29/F	13	• First injury due to snow-boarding accident, and second hit head on the ground 5 years ago • LOC for 3 minutes • ASOC for < 30 minutes	• Visual-attention deficit • VMS • Reading problems • Distance perception problems
S7/54/F	8	• Hit head on the ground • LOC for 2 minutes • ASOC for < 30 minutes	• Visual-attention deficit • VMS • Reading problems • Photosensitivity
S8/39/F	4	• MVA • LOC for 2 minutes • ASOC for < 30 minutes	• Visual-attention deficit • VMS • Reading problems
S9/29/F	2	• Hit by car 2 years ago, and hit by heavy table lamp 1 year ago • LOC for 15 minutes	• VMS • Reading problems • Distance perception problems • Vestibular problems • Migraine

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall/Assault	Visual symptoms
S10/63/F	7	• Iron bookcase fall on her head • LOC for 10 minutes • ASOC for < 24 hours	• Visual-attention deficit • VMS • Reading problems • Photosensitivity
S11/25/F	7	• First injury due to water boarding sports accident; during second and third hit head on the ground • LOC for 3 minutes • ASOC for < 30 minutes	• Visual-attention deficit • VMS • Reading problems • Photosensitivity • Distance perception problems
S12/26/F	1	• MVA • LOC for 5 minutes • ASOC for < 30 minutes	• Visual-attention deficit • VMS • Reading problems • Photosensitivity
S13/65/F	7	• Hit head on the ground 7, 3, and 1.5 years ago • LOC for 5 minutes • ASOC for < 30 minutes	• Visual-attention deficit • VMS • Reading problems • Photosensitivity • Distance perception problems

Subject/Age (years)/Gender	Years since first injury	Type of injury: MVA/Sports/Fall/Assault	Visual symptoms
S14/26/F	2	• Hit back of head against sink • LOC for 2 minutes	• Visual-attention deficit • VMS • Reading problems • Distance perception problems
S15/23/F	0.4	• Hit head on the ground • LOC for 5 minutes • ASOC for < 45 minutes	• Visual-attention deficit • VMS • Photosensitivity
S16/26/M	3	• Assaulted on head • LOC for < 30 minutes • ASOC for < 24 hours	• Photosensitivity

Appendix 2: Adult ADHD Self-Report Scale (ASRS) attention related Part A questionnaire.

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, circle the correct number that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.	Never	Rarely	Sometimes	Often	Very Often	Score
1. How often do you make careless mistakes when you have to work on a boring or difficult project?	0	1	2	3	4	
2. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?	0	1	2	3	4	
3. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?	0	1	2	3	4	
4. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?	0	1	2	3	4	
5. How often do you have difficulty getting things in order when you have to do a task that requires organization?	0	1	2	3	4	
6. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?	0	1	2	3	4	
7. How often do you misplace or have difficulty finding things at home or at work?	0	1	2	3	4	
8. How often are you distracted by activity or noise around you?	0	1	2	3	4	
9. How often do you have problems remembering appointments or obligations?	0	1	2	3	4	
					Part A – Total	

Appendix 3: Visual Search and Attention Test (VSAT).

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Paper #4

Assessing Hemianopia Objectively in Stroke Patients Using the VEP Technique: A Pilot Study

Yadav NK, Ciuffreda KJ. Assessing hemianopia objectively in stroke patients using the VEP technique: A pilot study. (Under Review).

Abstract

Purpose: To detect and assess hemianopic visual field defects objectively in individuals with stroke using the pattern visual evoked potential (VEP) technique.

Methods: Subjects were comprised of 5 adults with documented hemianopic visual field defects: three with complete right hemianopia, one with complete left hemianopia, and one with incomplete left hemianopia. Three test conditions were assessed binocularly with refractive correction to determine VEP responsivity: 1) central field, 2) intact hemi-field, and 3) hemianopic field. The following stimulus combinations were used: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC).

Results: The group and individuals findings revealed that the central field and the intact hemi-field VEP amplitudes were significantly larger than found in the hemianopic field ($p < 0.05$). However, latency values were similar ($p > 0.05$). Furthermore, the HC/HL and LL/HC stimulus conditions were found to be somewhat more effective and reliable, as compared to the LC/HL condition. Lastly, these objective findings were typically consistent with the subjective clinical perimetric results.

Conclusions: These pilot findings provide evidence that the pattern VEP has the potential to be used rapidly and reliably to detect for the presence of hemianopic visual field defects in stroke patients. The VEP technique would be beneficial for clinicians in confirming the presence of a hemianopic field defect, especially when the clinical perimetric findings are variable and inconsistent.

Key words: visual-evoked potential (VEP), stroke, hemianopia, visual-field, acquired brain injury, vision

Introduction

Stroke is one of the leading causes of death and disability in the adult population of the United States [1]. Common risk factors include hypertension, diabetes, high cholesterol levels, smoking, and atrial fibrillation [2].

Stroke can either be ischemic or hemorrhagic. According to the American Stroke Association, 83% of strokes are ischemic, and 17% are hemorrhagic [3].

Stroke produces an insufficient supply of oxygen (i.e., anoxia) via the blood circulation to the affected brain cells. This oxygen deprivation causes insult and frequently death to the underlying brain tissues, with resulting impairment of its neurological control function.

Stroke frequently results in impaired visual functioning to a constellation of areas [4, 5]. Visual-field defects (e.g., hemianopia), at times with visual neglect, are common visual sequelae to a stroke, or CVA (i.e., cerebrovascular accident) [6, 7]. Hemianopia refers to a physiologically-based phenomenon involving loss of one-half of the lateral visual-field and for which the individual is fully aware of its absence. In contrast, visual neglect refers to a perceptually-based phenomenon in which the individual is "unaware" of the loss of one half of their lateral visual-field [8]. Hemianopia and visual neglect can be present together, or independently. Hemianopia will adversely affect one's activities of daily living (ADLs), as well as have an adverse impact on one's vocational and avocational goals, and rehabilitative progress [9].

Since stroke patients with hemianopia frequently have fixational eye movement, attentional, and/or cognitive deficits, clinical visual field perimetry may not always be an optimal method to investigate for the presence of hemianopia [10, 11]. The VEP is a logical adjunct technique to assess for hemianopia in the CVA population. It is an

objective, rapid, and repeatable method [11, 12]. Furthermore, it circumvents, or at least minimizes, many of the inherent problems associated with clinical visual field testing. In addition, the VEP method does not demand prolonged attention or highly accurate fixation, as compared to conventional perimetry, especially over a relatively long test duration (i.e., 5 minutes or more for perimetry versus 20 seconds for VEP).

There are a paucity of relevant studies which have used the VEP method to assess hemianopia in CVA patients. The results are equivocal, as described below.

Viggiano et al. [13] studied 10 individuals with CVA having left-field hemianopia and visual neglect, 11 individuals with CVA having left-field hemianopia only, and 6 visually-normal subjects. In the first experiment, they used different check sizes (12, 14, 36, 48, and 72 min arc) with a constant temporal frequency of 4.76 Hz. In the second experiment, they used different temporal frequencies (1.96, 3.03, 4.76, 6.66, 8.33, and 16.66 Hz) with a constant check size of 48 min arc. Contrast was 87%, and luminance was 120 cd/m^2. The circular checkerboard stimulus (radius = 7.5 degrees) was presented both centrally and peripherally (8.5 degrees laterally). For both the central and peripheral stimulus, there were no significant differences in the VEP amplitude between those hemianopes with versus without visual neglect. They speculated that the phenomenon of visual neglect was the result of damage to higher-level cortical areas, and not to early primary cortical areas encompassed by the underlying VEP signal region. However, they did not investigate latency, which may provide additional information regarding any delay in visual processing in these patients, as latency is typically slowed based on other test findings [14].

Similarly, Spinelli et al. [15] used the steady-state VEP in 16 right-brain-injured, hemianopic stroke patients (i.e., 9 with left-visual field neglect, 7 without neglect), and 16 visually-normal subjects. Vertical sinusoidal gratings of 0.56 cycles per degree were used with a field size of 12.8H X 32.8V degrees. They were sinusoidally-reversed at temporal frequencies ranging from 4-11Hz. Contrast was 32%, and luminance was 150 cd/m^2. They assessed both VEP amplitude and latency. There was no significant effect on either parameter in the neglected and normal hemifields. The same was true in hemianopic patients without neglect, as well as in the visually-normal subjects. However, they did find that the VEP amplitude was slightly lower at higher temporal frequencies (e.g., 8 Hz) in those with a neglected left-visual field as compared to their normal right-visual field. Furthermore, with increase in temporal frequency, they found markedly delayed latencies of ~30-40 ms in patients with visual neglect, as compared to those without neglect. This study demonstrated that individuals with visual neglect exhibited slowed visual processing in the visually-neglected field only, at least under highly specific stimulus conditions, in the primary visual cortex.

In contrast, Angelelli et al. [16] measured steady-state VEP responses in 19 right brain-damaged (RBD) patients with left-sided hemianopia and visual neglect. They also had two controls groups: 15 left brain-damaged (LBD) patients and 12 right brain-damaged (RBD) patients, all with hemianopia but without visual neglect. They used vertical sinusoidal gratings of 0.56 cycles per degree with a central field size of 6H X 16V degrees. The gratings were sinusoidally-reversed at 10 temporal frequencies ranging from 4-10.5 Hz, with a central fixation target present. Contrast was 32%, and luminance was 150 cd/m^2. They assessed both amplitude and latency. Stimuli were presented either

in the right (RVF) or left (LVF) visual field. They too found that the mean latency was significantly delayed by approximately 25 ms in the neglected LVF, as compared to the normal RVF, in those with RBD. In contrast, there was no significant difference in latency in either the right or left hemifield in the RBD and LBD groups who did not have neglect. The VEP amplitudes were reduced in the hemianopic hemified in the RBD patients, with or without neglect. However, the VEP amplitudes were similar in both hemifields in the LBD group. These results suggested that both visual-neglect and hemianopia could be detected, *even at* the level of the primary visual cortex (V1). These findings supported the notion that the VEP can be used clinically to detect and assess hemianopia and/or visual neglect in individuals with CVA.

Based on the above 3 studies, the results are equivocal. Viggiano et al., [13] (1995), and Spinelli et al. [15], showed that the VEP could not differentiate between the hemianopic and intact visual field, which is surprising. In contrast, Angelelli et al. [16] found that it could. Furthermore, none of the studies used either low luminance and/or low contrast stimuli to assess hemianopia, which might be more sensitive to elicit its presence. Therefore, this area deserves to be explored, which might reveal more subtle differences early in the afferent visual pathway.

Thus, the purpose of the present pilot study was to determine if the VEP technique could be used to detect and assess hemianopia objectively and reliably in individuals with CVA/stroke. More specifically, the hypothesis is that the VEP approach will be able to detect and assess hemianopia objectively in individuals with stroke using more subtle stimuli, such as low contrast and low luminance patterns, which has never been tested before in this population.

Methods

Subjects

Five individuals with CVA/stroke and hemianopia (mean age = 46.6 years, age range = 29 to 62 years) participated in this study: three with complete right hemianopia, one with complete left hemianopia, and one with incomplete left hemianopia. None had visual neglect. See Appendix 1 for subject demographics. They were referred with full medical documentation to the Raymond J. Greenwald Rehabilitation Center (RJGRC)/Brain Injury Clinic at the SUNY, State College of Optometry 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. All had corrected visual acuity of 20/20 or better in each eye at both distance and near. Exclusion criteria included a history of seizures, constant strabismus, and amblyopia, as well as any type of ocular, neurological, and/or systemic disease. The study was approved by the Institutional Review Board (IRB) at the SUNY, State College of Optometry. Each subject provided written informed consent.

Apparatus

The Diopsys™ NOVA-TR system (Diopsys, Inc., Pine Brook, New Jersey, USA) was used to generate a checkerboard pattern stimulus and analyze the VEP data. Three

Grass gold-cup electrodes (Grass Technologies, Astro-Med, Inc., West Warwick, RI), each of 1 cm in diameter, were placed on the scalp to measure the VEP responses. Details have been provided elsewhere [11].

Stimulus

The VEP amplitude and latency were assessed with binocular viewing and full refractive correction in place under the following three experimental conditions (See Figure 1). Three trials for each test condition were performed:

1. **Central field [high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), low luminance (LL) and high contrast (HC)] –** A standard, central, checkerboard pattern (17H X 15V degrees, 20 min arc check size at 1 meter, 20 second test duration, temporal frequency 1 Hz) with a central fixation (0.5° diameter) target was used as the baseline comparison stimulus. A checkerboard pattern with either low or high contrast levels (i.e., 20 and 85%), and with either low or high luminance levels (i.e., 7.4 and 74 cd/m^2), was presented for all 3 stimulus combinations as described above.

2. **Intact hemi-field only (HC/HL, LC/HL, LL/HC) –** In this condition, the checkerboard pattern was presented only to the intact hemianopic visual-field (8.5H X 7.5V degrees) with the contrast and luminance levels as described in #1 above. The other half of the visual field (i.e., the

hemianopic field) was presented with a blank, non-patterned stimulus field (luminance 1.27 cd/m^2) as used in an earlier study by us [11].

3. **Hemianopic field only (HC/HL, LC/HL, LL/HC) –** In this condition, the checkerboard pattern was presented only to the hemianopic field (8.5H X 7.5V degrees) with the contrast and luminance levels as mentioned above in #1. The other half of the visual-field (i.e., intact) was presented with a blank, non-patterned stimulus field (luminance 1.27 cd/m^2), as used in an earlier study by us [11].

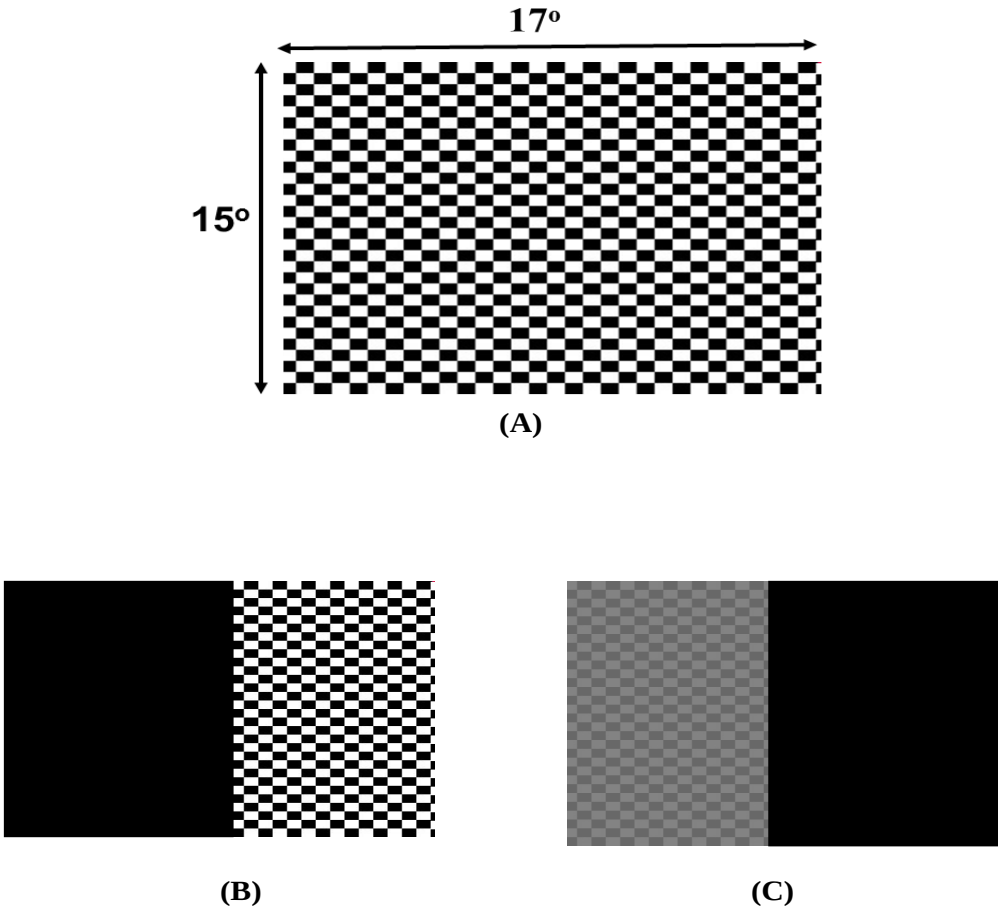

Figure 1: Test stimulus configurations. (A) Central, VEP checkerboard pattern showing high contrast and high luminance conditions, (B) Hemianopic visual-field test stimulus for high contrast and high luminance condition, and (C) Hemianopic visual-field test stimulus for low contrast and high luminance condition. All not drawn to scale.

Data Analysis

An average of the three trials for each of the three visual field test conditions (i.e., completes, intact, and hemianopic) and three stimulus combinations (i.e., HC/HL,

LC/HL, LL/HC) was initially calculated for each subject. Then, for each subject, the trial for which the VEP response exceeded 1SD from the mean was deleted to remove this outlier; and, in the case where all 3 trial values were within 1 SD, the most deviant trial response value was deleted. The mean and SD for the 2 remaining trials were calculated and used for analysis of the group mean VEP amplitude and latency. A one-way, repeated-measures ANOVA was performed on each condition using GraphPad Prism 5.04 software. Graphical displays were also prepared with the same software. In addition, due to the small sample size, the results for each subject were analyzed and presented, along with additional information such as their conventional clinical perimetric findings, except for subject #1 (Figure 2).

VEP repeatability was assessed in subject #5. The same test conditions were repeated one week later. The coefficient of variation (CV = standard deviation of the multiple sessions for each condition divided by the mean of these multiple sessions for each condition) was calculated to assess for repeatability of the VEP responses [11, 17-19]. The CV value can range from 0.00 to 1.00 [19]. This value represents the intra-individual variability: the smaller the value, the less the variability, and the better the repeatability.

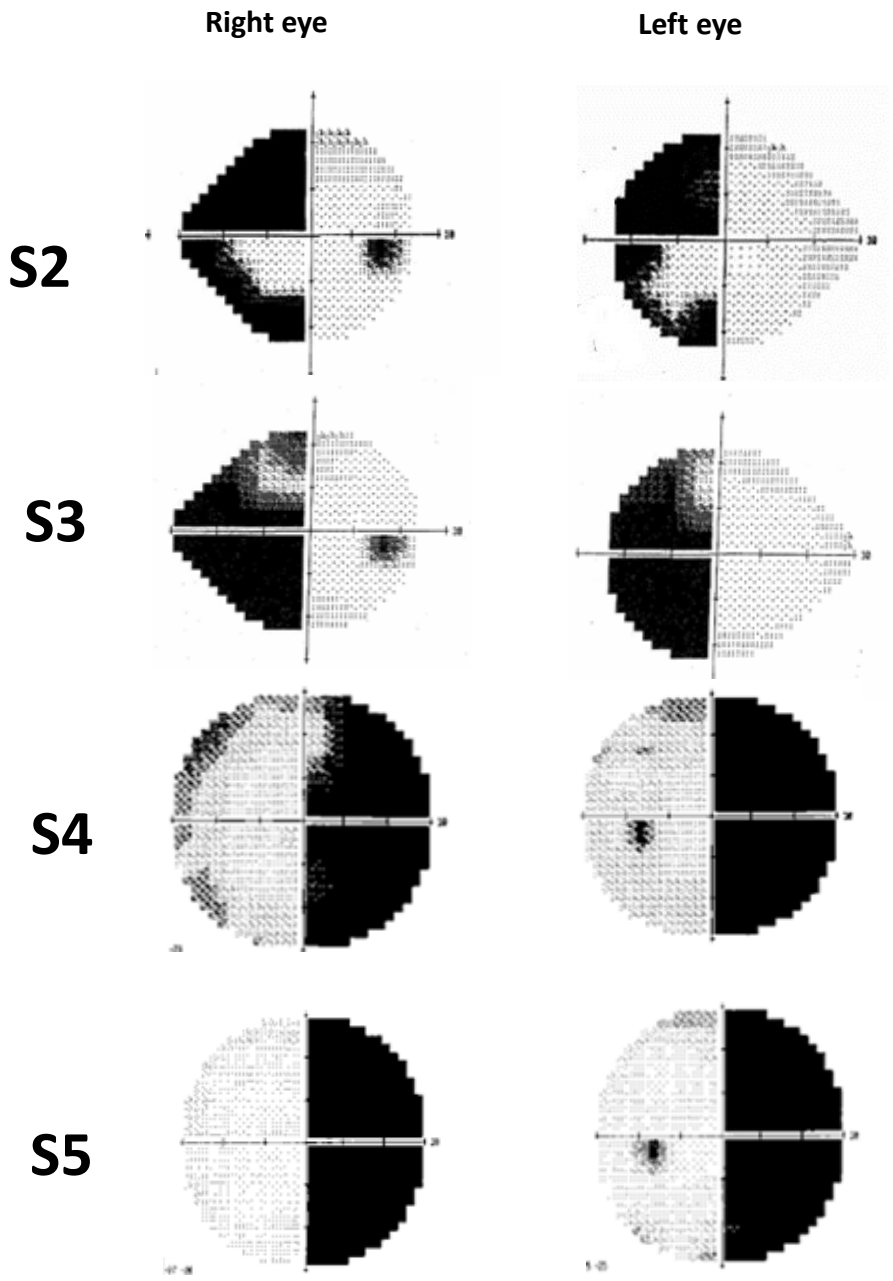

Figure 2: Conventional visual fields of subjects #2-5 using the central 24-2 threshold test (Humphery Visual System, CARL ZEISS MEDITECH).

Results

Group Data

Amplitude

Figure 3A presents the group mean VEP amplitude for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). A one-way ANOVA for the factor of visual field at HC/HL was significant [$F(2, 12) = 10.18$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$). A one-way ANOVA for the factor of visual field at LC/HL was significant [$F(2, 9) = 5.88$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger than for the hemianopic field. A one-way ANOVA for the factor of visual field at LL/HC was significant [$F(2, 12) = 10.18$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$).

Latency

Figure 3B presents the group mean VEP latency (P 100 ms) for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field for each of the three stimulus combinations was not significant ($p > 0.05$).

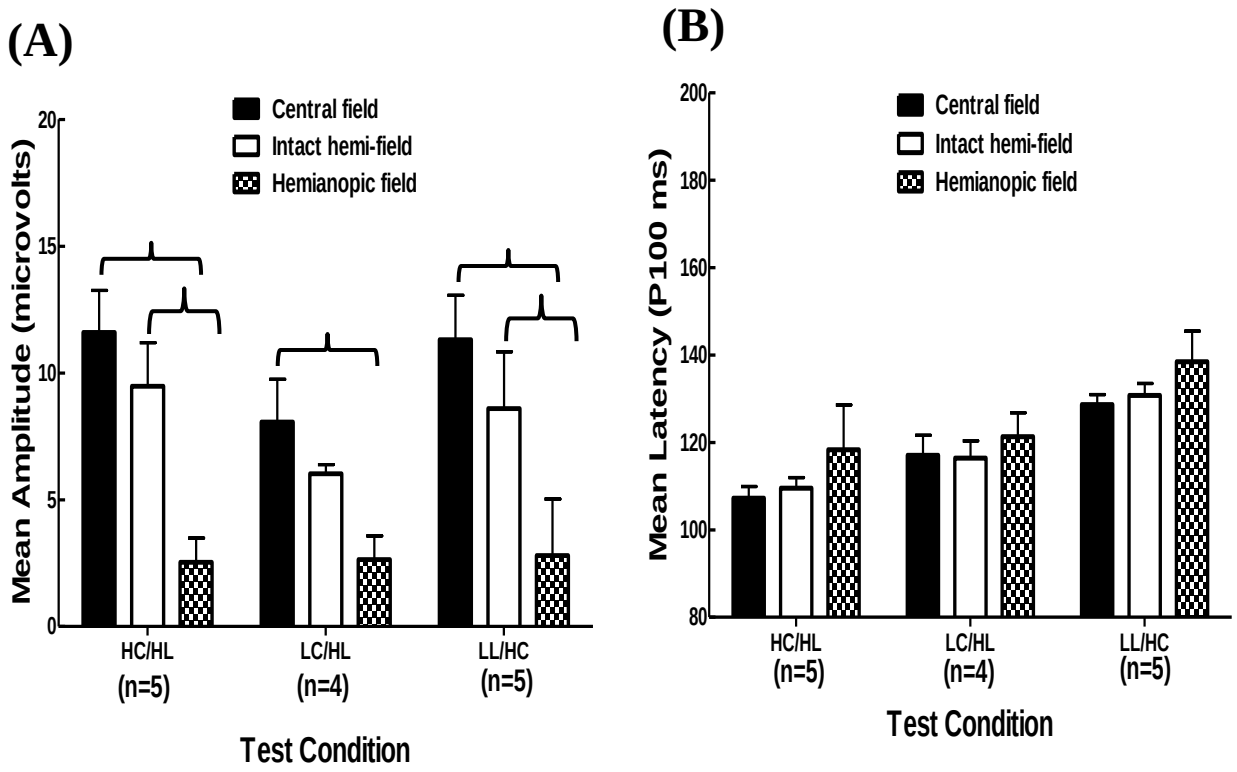

Figure 3: Group mean VEP responses for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). Plotted is the mean +1SEM. (A) Amplitude (microvolts) (B) Latency (ms). Brackets indicate statistically significant comparisons ($p < 0.05$).

Individual Subject Data

Subject #1

Amplitude

Figure 4A presents the mean VEP amplitude of subject #1 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field at HC/HL was significant [$F(2, 3) = 43.45$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$). A one-way ANOVA for the factor of visual field for LC/HL was not significant [$F(2, 3) = 7.48$, $p > 0.05$]. A one-way ANOVA for the factor of visual field at LL/HC was significant [$F(2, 3) = 40.43$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$).

Latency

Figure 4B presents the mean VEP latency (P 100 ms) of subject #1 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field at HC/HL was not significant [$F(2, 3) = 9.05$, $p > 0.05$]. A one-way ANOVA for the factor of visual field at LC/HL was significant [$F(2, 3) = 16.47$, $p < 0.05$]. The post-hoc Tukey test results revealed that the latency for the hemianopic field was significantly longer than

for the intact hemi-field ($p < 0.05$). A one-way ANOVA for the factor of visual field at LL/HC was not significant [$F(2, 3) = 10.74$, $p > 0.05$].

Visual field

The visual field plot was unavailable in his current medical records. However, according to his earlier clinical records which incorporated visual field testing, and current clinical confrontation testing, S1 had a complete right hemianopia.

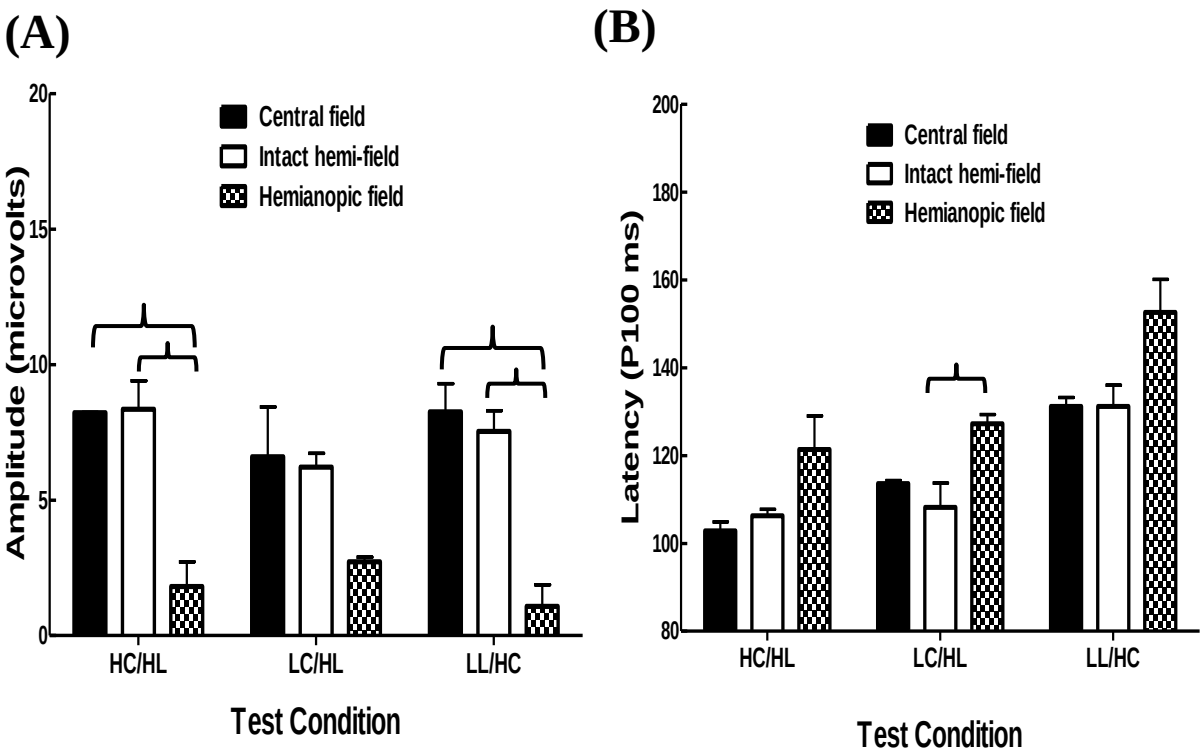

Figure 4: Mean VEP responses of subject #1 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). Plotted is the mean +1SD. (A) Amplitude (microvolts) (B) Latency (ms). Brackets indicate statistically significant comparisons ($p < 0.05$).

Subject #2

Amplitude

Figure 5A presents the mean VEP amplitude of subject #2 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field at HC/HL was significant [$F(2, 3) = 14.52$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger than either the intact or hemianopic fields ($p < 0.05$). A one-way ANOVA for the factor of visual field at LC/HL was not significant [$F(2, 3) = 0.018$, $p > 0.05$]. A one-way ANOVA for the factor of visual field at LL/HC was significant [$F(2, 3) = 15.11$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger than for the hemianopic field ($p < 0.05$).

Latency

Figure 5B presents the mean VEP latency (P 100 ms) of subject #2 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field for each of the three stimulus combinations was not significant ($p > 0.05$).

Visual field

Visual field findings for subject #2 (S2) are presented in Figure 2. She had a left incomplete hemianopia.

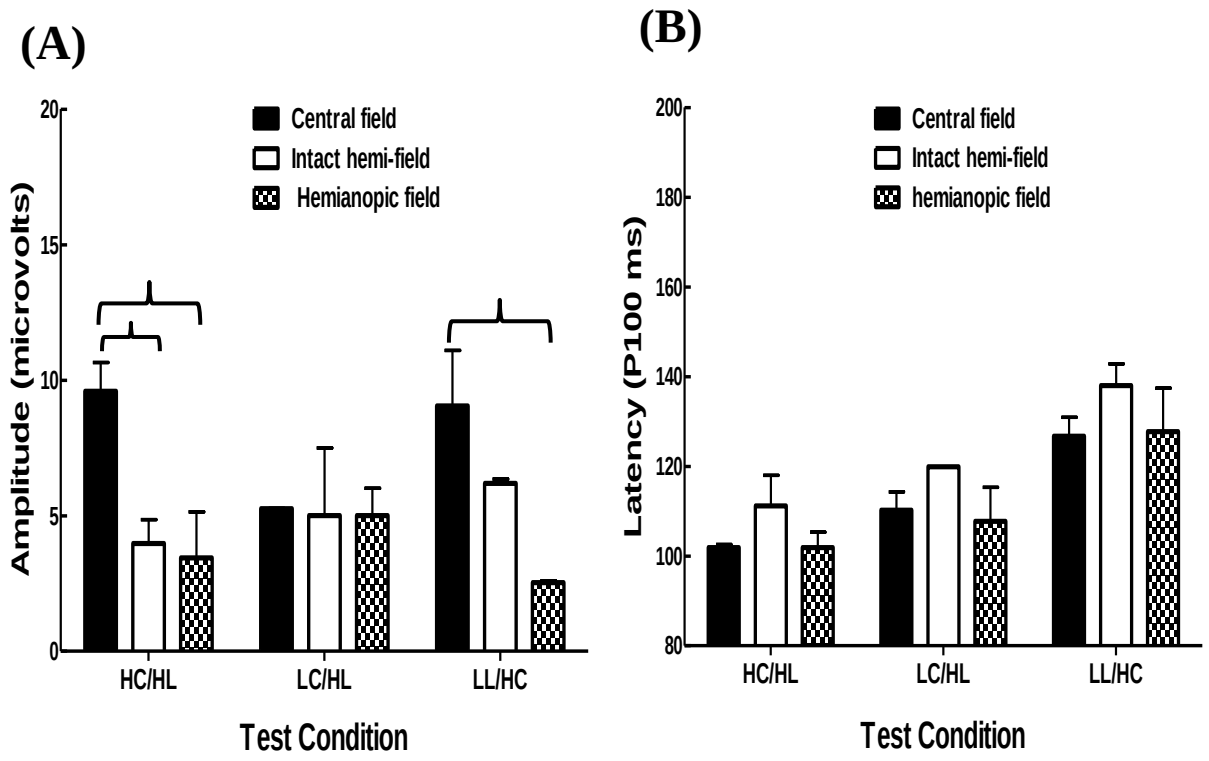

Figure 5: Mean VEP responses of subject #2 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). Plotted is the mean +1SD. (A) Amplitude (microvolts) (B) Latency (ms). Brackets indicate statistically significant comparisons ($p < 0.05$).

Subject #3

Amplitude

Figure 6A presents the mean VEP amplitude of subject #3 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL and

LL/HC; LC/HL was not tested due to subject fatigue. A one-way ANOVA for the factor of visual field at HC/HL was significant [$F(2, 3) = 577$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$). A one-way ANOVA for the factor of visual field at LL/HC was significant [$F(2, 3) = 97.19$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$).

Latency

Figure 6B presents the mean VEP latency (P 100 ms) of subject #3 for the central, intact, and hemianopic visual fields for the following two stimulus combinations: HC/HL and LL/HC.; the LC/HL was not tested. A one-way ANOVA for the factor of visual field at HC/HL was not significant [$F(2, 3) = 4.44$, $p > 0.05$]. A one-way ANOVA for the factor of visual field at LL/HC was significant [$F(2, 3) = 22.61$, $p < 0.05$]. The post-hoc Tukey test results revealed that the latency for the intact and hemianopic fields was significantly longer than for the central field ($p < 0.05$).

Visual field

Visual field findings for subject #3 (S3) are presented in Figure 2. She had a complete left hemianopia.

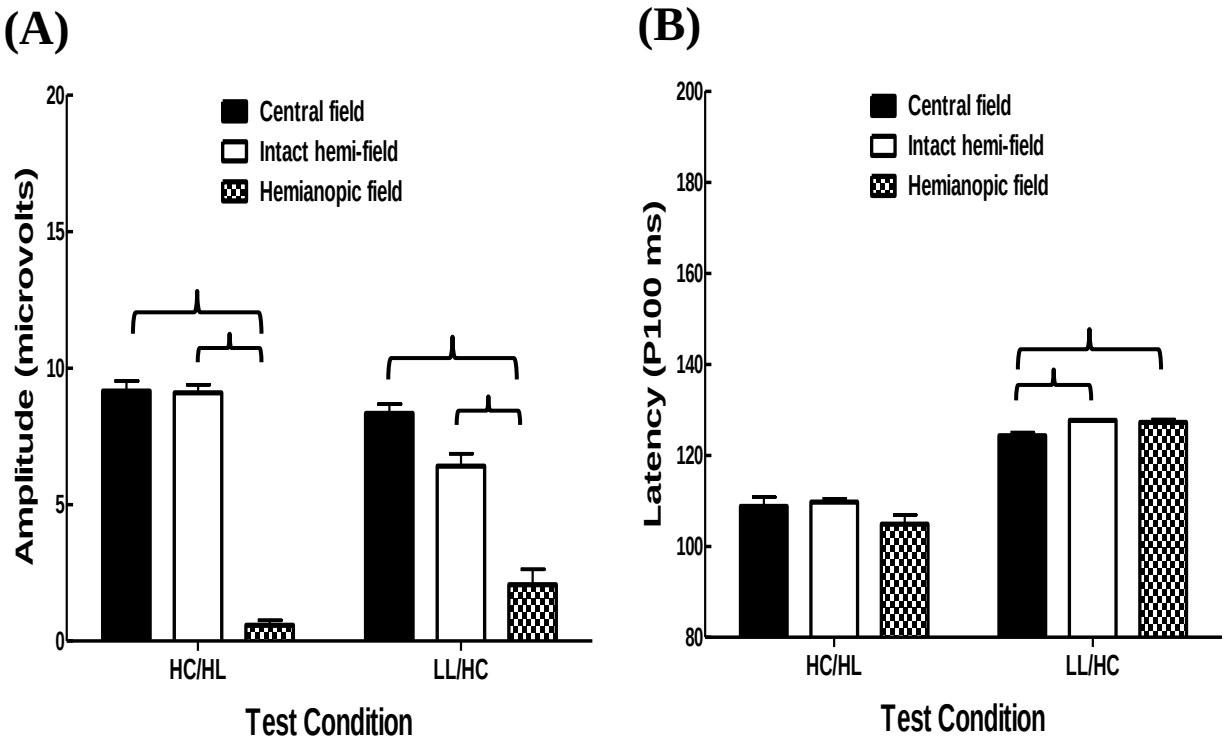

Figure 6: Mean VEP responses of subject #3 for the central, intact, and hemianopic visual fields for the following two stimulus combinations: high contrast (HC) and high luminance (HL) and low luminance (LL) and high contrast (HC). Plotted is the mean +1SD. (A) Amplitude (microvolts) (B) Latency (ms). Brackets indicate statistically significant comparisons ($p < 0.05$).

Subject #4

Amplitude

Figure 7A presents the mean VEP amplitude of subject #4 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field at HC/HL was

significant [$F(2, 3) = 79.43$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$). A one-way ANOVA for the factor of visual field at LC/HL was significant [$F(2, 3) = 11.64$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger than for the hemianopic field ($p < 0.05$). A one-way ANOVA for the factor of visual field at LL/HC was significant [$F(2, 3) = 445$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitudes for the central and intact fields were significantly larger than for the hemianopic field ($p < 0.05$).

Latency

Figure 7B presents the mean VEP latency (P 100 ms) of subject #4 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field at HC/HL was significant [$F(2, 3) = 146$, $p < 0.05$]. The post-hoc Tukey test results revealed that the latency for the hemianopic field was significantly longer than for either the central or intact fields ($p < 0.05$). A one-way ANOVA for the factor of visual field at LC/HL was not significant [$F(2, 3) = 0.41$, $p > 0.05$]. A one-way ANOVA for the factor of visual field at LL/HC was also not significant [$F(2, 3) = 1.19$, $p > 0.05$].

Visual field

Visual field findings for subject #4 (S4) are presented in Figure 2. She had a complete right hemianopia.

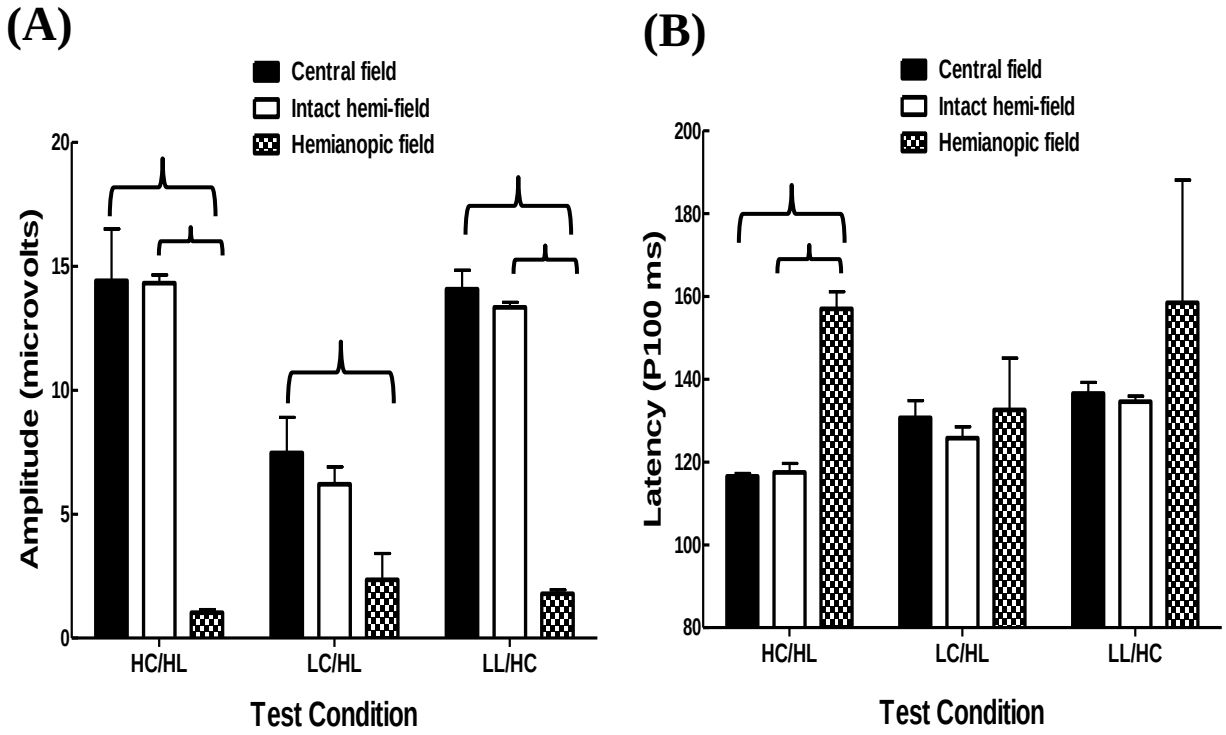

Figure 7: Mean VEP responses of subject #4 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). Plotted is the mean +1SD. (A) Amplitude (microvolts) (B) Latency (ms). Brackets indicate statistically significant comparisons ($p < 0.05$).

Subject #5

Amplitude

Figure 8A presents the mean VEP amplitude of subject #5 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field at HC/HL was

significant [$F(2, 3) = 89.06$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger than for either the intact or hemianopic fields ($p < 0.05$). In addition, the amplitude of the intact hemi-field was significantly larger than for the hemianopic field ($p < 0.05$). A one-way ANOVA for the factor of visual field at LC/HL was significant [$F(2, 3) = 170$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger than for either the intact or hemianopic fields ($p < 0.05$). In addition, amplitude of the intact hemi-field was significantly larger than for the hemianopic field ($p < 0.05$). A one-way ANOVA for the factor of visual field at LL/HC was significant [$F(2, 3) = 333$, $p < 0.05$]. The post-hoc Tukey test results revealed that the amplitude for the central field was significantly larger than for either the intact or hemianopic fields ($p < 0.05$). In addition, the amplitude of the intact hemi-field was significantly larger than for the hemianopic field ($p < 0.05$).

Latency

Figure 8B presents the mean VEP latency (P 100 ms) of the subject #5 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: HC/HL, LC/HL, and LL/HC. A one-way ANOVA for the factor of visual field for each of the three stimulus combinations was not significant ($p > 0.05$).

Visual field

Visual field findings for subject #5 (S5) are presented in Figure 2. She had a complete right hemianopia.

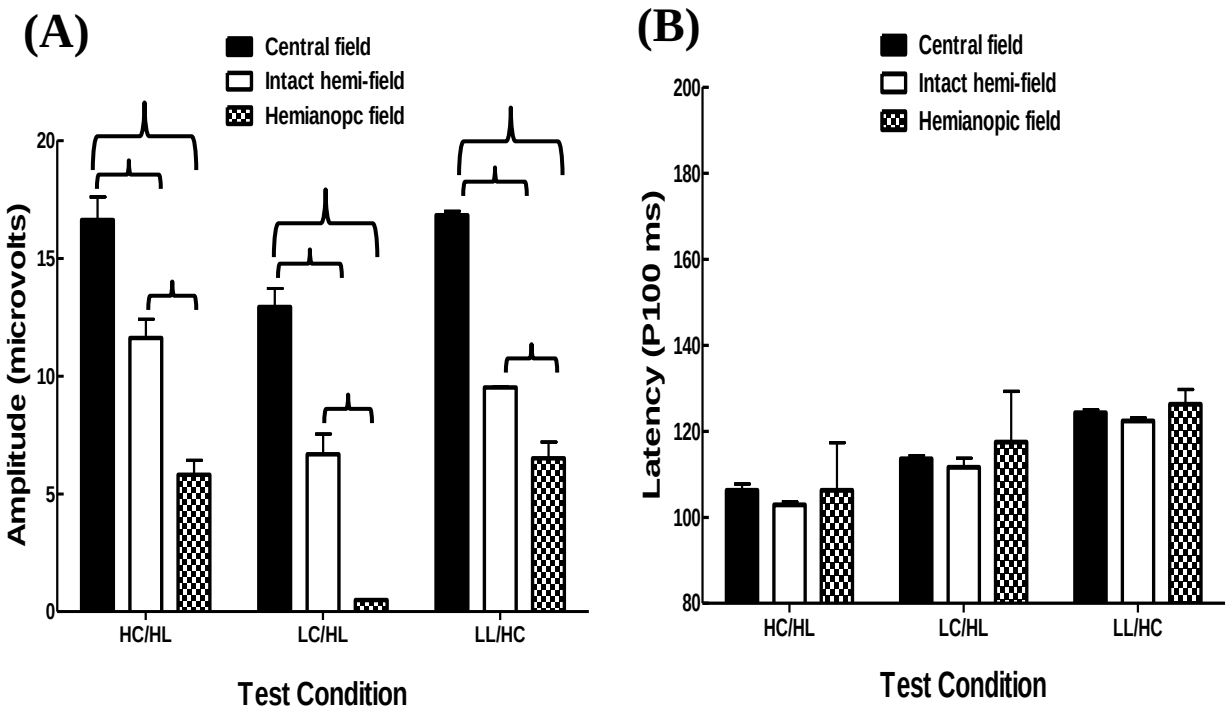

Figure 8: Mean VEP responses of subject #5 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC). Plotted is the mean +1SD. (A) Amplitude (microvolts) (B) Latency (ms). Brackets indicate statistically significant comparisons ($p < 0.05$).

Repeatability

Repeatability results for subject #5 are presented in Figure 9A and 9B for amplitude and latency, respectively. Repeatability was assessed after a period of 1 week. The CV (median, range) across the three visual field and three stimulus combinations were: amplitude (median = 0.05, range = 0.02 to 0.80) and latency (median = 0.01, range = 0.0002 to 0.019), thus suggesting repeatability.

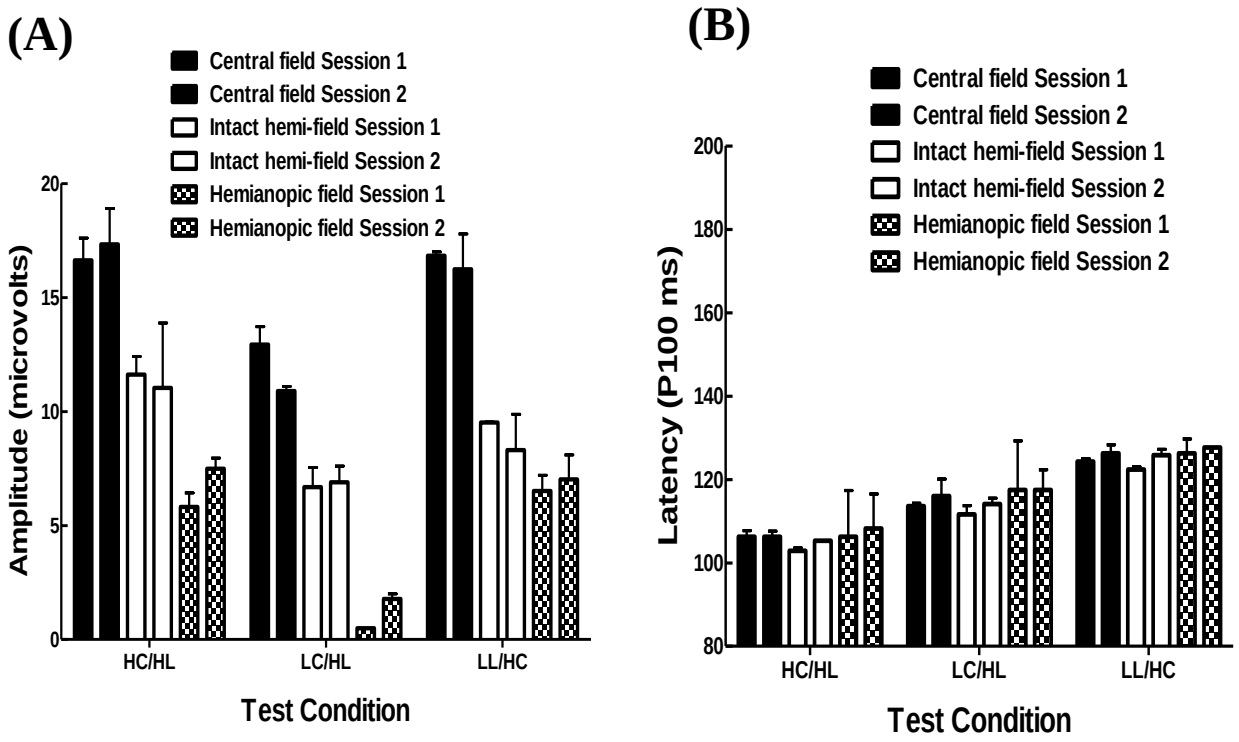

Figure 9: Repeatability assessment. Mean VEP responses of subject #5 for session 1 and 2 for the central, intact, and hemianopic visual fields for the following three stimulus combinations: high contrast (HC) and high luminance (HL), low contrast (LC) and high luminance (HL), and low luminance (LL) and high contrast (HC).Plotted is the mean +1SD. (A) Amplitude (microvolts) (B) Latency (ms).

Discussion

The findings of the present study confirmed and extended the results of previous studies demonstrating that the VEP technique could be used to detect for the presence of hemianopia in stroke patients [11, 16]. Yadav et al. [11] simulated circular, annular, hemi-field, and quadrant absolute visual-field defects in the visually-normal population. They were able to detect and assess reliably all of the aforementioned field defect types objectively using the pattern VEP approach. Furthermore, they predicted that the clinical VEP technique would be able to detect and assess actual hemifield defects in clinical patients with stroke, which the present pilot study confirmed. The present findings were also in agreement with Angelelli et al. [16]. They too were able to detect hemianopic defects in stroke patients using the VEP technique. The present study also provided additional evidence that visual field loss in stroke patients could be reliably detected as early as the primary visual cortex (V1), in agreement with Angelelli et al. [16]. Lastly, the objective VEP results typically corroborated the subjective clinical perimetric findings.

The present investigation demonstrated *for the first time* that more subtle stimuli, such as the LC/HL and LL/HC patterns, are particularly useful and highly sensitive in the detection of hemifield loss in stroke patients. Both the group and individual results revealed that all three stimulus combinations (i.e., HC/HL, LC/HL, LL/HC) were able to detect hemifield loss in the present small sample of individuals with stroke. However, the HC/HL and LL/HC stimulus combinations provided more reliable amplitude results, which were consistent with the clinical visual field findings, as compared to the LC/HL combination. Therefore, these two stimulus configurations may be most clinically

beneficial in detecting and assessing visual field loss in patients with stroke, especially in those with variable visual field test findings and/or cognitive dysfunction.

The VEP findings for subject 5 (S5) were of special interest. The conventional perimetric test performed 3 months subsequent to her stroke revealed that she had a complete, right, absolute hemianopia (Figure 5). However, the VEP results two years later in our laboratory did not correlate well with the earlier visual-field test findings. During the VEP testing, when the checkerboard pattern was presented to her right hemianopic field with the stimulus combination HC/HL, the amplitude was approximately 50% as large as that found for the intact hemi-field, and furthermore was well above the response "noise" level for our system (i.e., 1.5-2.0 μV) [11]. Moreover, when the amplitude of each hemifield was combined, it approximated the overall, combined central field response. This strongly suggested that her hemifield loss was not absolute as found earlier by the perimetry. Most interestingly, the VEP findings were consistent with her subjective impression during the VEP testing. The patient reported that she perceived a faint checkerboard pattern with soft edges in her right hemianopic field, similar to that also reported with the LL/HC pattern. Furthermore, it agreed with her visual perception in real-life situations, such as with faces. The discrepancy between the visual field and VEP findings might be due to natural cortical recovery or possibly due to improvement in visual attention after her visual scanning therapy that was prescribed during the first few months after the stroke. Unfortunately, due to subsequent unavailability to have her current visual-field tested, it was not possible to directly relate and explain the difference between the objective and subjective visual-field results.

Clinical implications

The pattern VEP technique should prove beneficial in individuals with stroke. This technique could be used as an adjunct to conventional clinical visual field testing to detect, assess, and confirm the presence of hemianopia. Due to its objective, rapid, and repeatable nature, the VEP should be especially useful in non-verbal and cognitively-impaired individuals with stroke, as they may not be able to understand the instructions and/or respond reliably to subjective clinical visual-field testing. Therefore, the VEP may be an ideal technique to detect hemianopic field defects in these patients, as it does not require any verbal or physical response (e.g., depressing a button) by the patient. The VEP could also be used to assess the effect of any visual intervention (e.g., eye movement visual scanning training) provided to these stroke patients, as has been performed in mild traumatic brain injury (mTBI) [20, 21]. In addition, the VEP could also be extended to the traumatic brain injury (TBI) and pediatric populations exhibiting visual-field defects. Thus, it has the potential to become another "tool" in the clinician's diagnostic and therapeutic armamentarium for a possible range of visual field abnormalities across a range of visual conditions.

Proposed VEP hemianopic visual-field test protocol

Based on the results of the present study and another conducted in our laboratory [11], the following abbreviated clinical VEP visual-field test protocol is proposed in patients with stroke and hemianopia:

IV. **Central field (HC/HL)**

V. **Intact hemi-field only (HC/HL)**

VI. **Hemianopic field only (HC/HL)**

Number of trials – 3 trials (each 20 seconds) should be performed for each test condition, the outlier should be deleted, and remaining two values averaged. Additional trials (e.g., 5) could be performed, if needed, for more consistent responsivity.

Study limitations

There were two possible study limitations. First, sample size was small. However, the effect was robust. Second, only individuals with stroke at the chronic stage were included, but none in either the acute or sub-acute stages were tested. In these earlier stages, any cognitive and/or attentional deficits may be more marked, and hence objective testing may prove to be even more beneficial.

Future directions

There are four possible future directions proposed. First, a similar study should be performed with a larger sample size, such as 30 or more. In addition, hemianopic stroke patients should be included, with and without visual neglect. The VEP might differentiate objectively between those hemianopes with versus without the visual neglect aspect, or just for detection of visual neglect alone. Second, as mentioned above, stroke patients at

the acute and sub-acute stages should also be tested to generalize and extend the present pilot findings. Third, smaller visual-field defects (e.g., quadranopsia) should be addressed with the VEP technique [11] and proposed protocol. Lastly, the effect of any visual intervention (e.g., eye movement training) provided to these patients should be assessed to demonstrate possible improvement objectively at the early cortical level [20, 21].

Conclusion

The clinical pattern VEP technique was found to be useful in detecting and assessing hemianopic field defects in patients with stroke in the present pilot study. These quantitative visual-field findings were found to be repeatable and reliable. In addition, these objective findings were typically in agreement with the patient's clinical perimetric results. Therefore, the pattern VEP has the potential to be an appropriate adjunct technique to test for the presence of visual-field defects in stroke patients.

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Appendix 1: Demographics of stroke patients.

Subject/Age (years)/Gender	Years since last stroke	Type of hemianopia	Visual symptoms
S1/47/M	23 years (stroke at 2 years of age due to arteriovenous malformation)	Right hemianopia	• Reading problems
S2/29/F	1 year	Left incomplete-hemianopia	• Reading problems • Migraines
S3/39/F	1 year	Left hemianopia	• Reading problems • Migraines • Photosensitivity • Visual motion sensitivity
S4/56/F	24 years	Right hemianopia	• Reading problems • Visual-attention deficit
S5/62/F	2 years (first stroke 25 years ago)	Right hemianopia	• Reading problems • Visual-attention deficit • Visual fatigue • Distance perception problem