Featured Article: VEP and Human Attention: Translation from Laboratory to Clinic

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ABSTRACT

The purpose is to review recent studies from our laboratory that used the visual-evoked potential (VEP) to assess attention in both the visually-normal (VN) and mild traumatic brain injury (mTBI) populations. The VEP (amplitude and latency), and attention-related alpha band responses, were assessed. The alpha responses were abnormal in those with mTBI. Furthermore, these values differentiated well between mTBI with versus without an attentional deficit. Following oculomotor vision rehabilitation, the alpha and VEP responses increased significantly. The VEP technique can be used reliably in both clinic and laboratory settings to detect attention objectively in both VN and mTBI populations.

INTRODUCTION

Traumatic brain injury (TBI) is a major health issue in the United States.[1] Approximately 1.7 million people suffer from a TBI annually. Mild traumatic brain injury (mTBI), the most common variety of TBI (~70-80%), occurs as a result of injury to the brain due to blunt or penetrating head insult.[2] It produces widespread damage to the underlying brain tissues. This occurs due to the initial and immediate biomechanical effects[3] (e.g., coup-countrecoup, shearing, etc.), as well as the subsequent adverse biomolecular/ biochemical changes that occur over the next days and weeks.[4,5] These effects produce diffuse axonal injury (DAI). The DAI is responsible for slowing and delaying cortical information processing.[6]

mTBI results in a constellation of adverse effects. These are of a sensory, motor, perceptual, linguistic, cognitive, attentional, and/or behavioral nature.[7-9] Most of the cranial nerves (i.e., II, III, IV, V, VI, VII, VIII, and XI) are involved in vision and visual processing in some way.[10] In addition, 30-40 distinct cortical areas of the brain receive and/or process visual information.[11] Thus, it is not surprising that a range of visual deficits frequently occur following mTBI.[7,8,12,13]

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Yadav N, Ciuffreda K, Willeford K, Thiagarajan P, Ludlam, D. Vep and human attention: translation from laboratory to clinic. Vision Dev & Rehab 2015;1(1):13-28

Keywords: attention, visual-evoked potential (VEP), mild traumatic brain injury (mTBI)

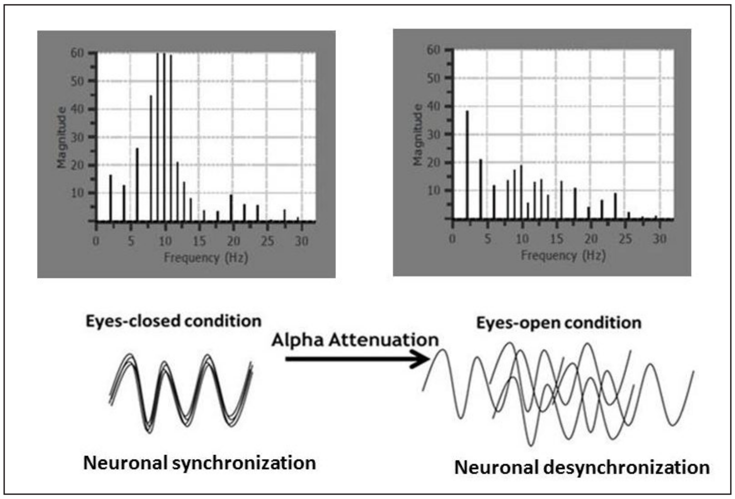

Figure 1: Alpha attenuation for the eyes-closed (neuronal synchronization) and the eyes-open (neuronal desynchronization) conditions. X and Y axes represent the alpha band frequency (Hz) and power magnitude (μV2), respectively.

One of the most common problems in mTBI is a presence of a *general/visual attentional deficit.*[8,14-16] Attentional deficits, both general and visual, occur in approximately 50-60% of the TBI population.[17,18] Symptoms include problems reading and slow visual information processing, as well as visual distractibility.[12-14,19] Thus, such a deficit will adversely effect activities of daily living (ADLs),[18] as well as rehabilitative progress.[20]

Different cortical (i.e., visual cortex, frontal, and parietal lobes) and subcortical (i.e., thalamus) areas of the brain are involved in general and visual attentional processing,[16,21] with visual attentional processing initiated in the primary visual cortex (V1).[22,23] Disruption to *any* of these regions following a concussion/ mTBI will likely cause an attentional deficit.[8,14-16] Therefore, using the visual evoked potential (VEP) technique to assess attention objectively and rapidly at the V1 level provides critical, as well as very early, information regarding the human attentional state.[24-28]

There is a long history of using objective techniques to assess human visual/general attention, with emphasis on the attentionally-related alpha band activity (8-13 Hz) of the electro-encephalograph (EEG). Berger[29] was the first to investigate the *alpha band* electrophysiologically in the human brain. More than one-half century later, Klimesch[30] suggested that human thalamo-cortical attention could be probed by assessing the alpha band. *High* alpha power occurs during the "relaxed", eyes-closed attentional state. It is associated with *synchronous* neuronal cortical activity. In contrast, *low* alpha power occurs during visual stimulation with the eyes-open. It is associated with *asynchronous* neuronal cortical activity[30] (See Figure 1). Most importantly, attenuation of the alpha band power occurs with the eyes-open versus eyes-closed condition: *inability to suppress alpha during the eyes-open condition suggests an attentional deficit.*[24-27,31] Thus, assessing alpha band neuronal activity provides a direct route to probe the attentional state of an individual *objectively.*

Two primary researchers have assessed visual/general attention directly from the visual cortex (V1). Fuller[24] investigated attention using the EEG method at a frequency band of 0.5-30 Hz in 10 children with learning disability (LD)/"minimally brain-damaged" (MBD). They were compared with 11 normal, age-matched children. The alpha band (i.e., 8-13 Hz) was extracted from the overall EEG band (0.5-30 Hz). Then, the mathematical technique of power spectrum analysis[32] (described in the Methods section) was applied to quantify the response. To prevent any residual visually-based attentional aspects from contaminating the responses, the alpha power was recorded with the eyes-closed in a relaxed state for 5 minutes prior to actual testing. Then, a cognitive demand was added to the eyes-closed condition; they performed simple addition, recall of common objects, and a word problem task during the subsequent testing. Fuller[24] derived and calculated the "alpha attenuation ratio". That is, the average alpha power measured during the cognitively-demanding eyes-closed condition was divided by the average alpha power measured during eyes-closed "resting" condition. He found that an attenuation ratio of <1.00 suggested an ability to dampen, or suppress, alpha activity during this more cognitively-demanding, eyes-

Table 1: Attentional Adult ADHD Self-Report Scale (ASRS) Part A and Visual Search and Attention Test (VSAT) score for each individual with mTBI in the Experiment #2.

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.

closed condition, as predicted to be the case for those with normal attention. Fuller[24] found that 81% of the normal children exhibited an average attenuation ratio of 0.91, whereas 80% of the LD/MBD children had an average attenuation ratio of 1.01. Thus, as compared to the normal children, those with LD/MBD were not able to suppress their alpha activity as well during the cognitively-demanding, eyes-closed condition. Similar results were found by Ludlam.[25] He used the VEP method to assess two children with clinically-diagnosed "reading disability". Alpha-band attenuational ability was assessed under two conditions before and after conventional, oculomotor-based, vision therapy. First, with the eyes closed, and second with the eyes open as they read from a book. Before therapy, neither child was able to attenuate alpha activity during the reading task, as would be the case in normal children without reading disability. This suggested the presence of an attentional deficit. Then, they underwent vision therapy to remediate their oculomotor-based reading deficit, which indirectly acts to improve general and visual attention.[33,34] After therapy, they were able to attenuate their alpha activity during reading. This suggested improvement in visual attention, which appeared to be related with an improvement in reading ability and basic oculomotor control.

The purpose of the present paper is to review recent studies from our laboratory on the topic of human attention as assessed objectively using the VEP approach. Three experiments will be reviewed, with details provided in the original references:

Experiment #1: Objective assessment of the human visual attentional state.[26]

Experiment #2: Objective assessment of attention in mild traumatic brain injury (mTBI) using the visual-evoked potential (VEP).[35]

Experiment #3: Effect of oculomotor vision rehabilitation on the visual-evoked potential and visual attention in mild traumatic brain injury (mTBI).[28]

METHODS

Subjects

Subjects participating in each experiment were as follows: *Experiment #1* included 18 visually-normal adults (mean = 24.0 years, SEM = 0.5 years); *Experiment #2* included 16 adults with mTBI, 11 with a self-reported attentional deficit[18] (mean age = 38.0 years, SEM = 4.8 years) and 5 without (mean age = 29.8 years, SEM = 2.2 years); and *Experiment #3* included 7 adults with mTBI (mean age = 29.5 years, SEM = 4.3 years), 4 with a self-reported attentional deficit (See Table 1 of Reference #28). The attentional information of the subjects was consistent with their clinical case history taken by an experienced neuro-optometrist and a social worker in the college's brain injury clinic, as well as with other supporting medical and neuropsychological documentation. All individuals with mTBI received their head injury at least nine months prior to testing, which exceeded the natural recovery period.[36] Visually-normal subjects were recruited from the student, faculty, and staff at the State University of New York (SUNY), State

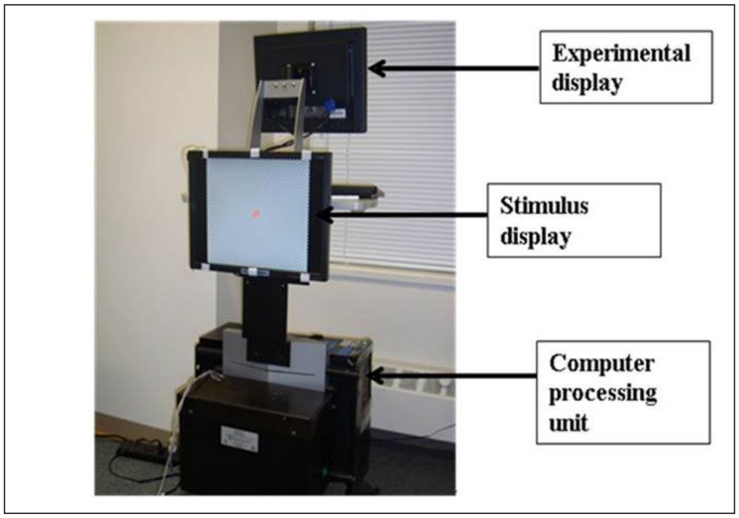

Figure 2: The DIOPSYSTM NOVA-TR system used for the VEP testing.

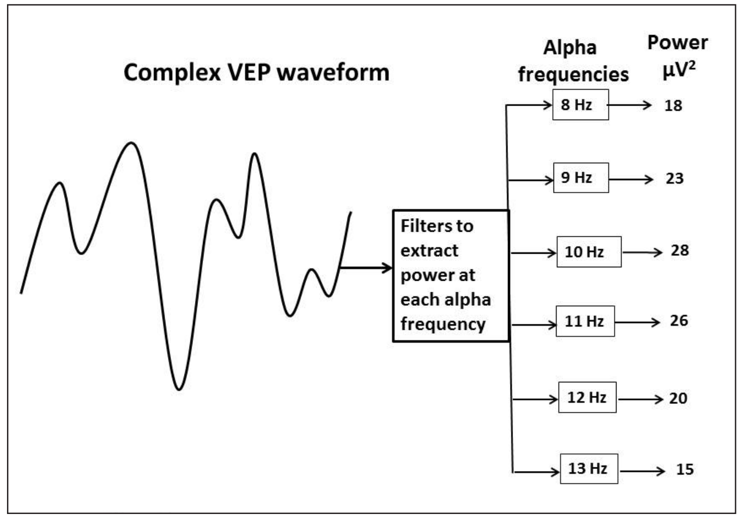

Figure 3: Extraction of the individual alpha power responses (8-13 Hz, μV2) (right) from the complex VEP waveform (left) using the mathematical techniques of Fourier analysis and power spectrum analysis.

College of Optometry. Individuals with mTBI were obtained from the Raymond J. Greenwald Rehabilitation Center (RJGRC)/Brain Injury Clinic at the SUNY, State College of Optometry with full medical documentation. Both visually-normal individuals and those with mTBI 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. These studies were approved by the Institutional Review Board (IRB) at the SUNY, State College of Optometry. All subjects provided written informed consent.

Apparatus

The DIOPSYSTM™ NOVA-TR VEP system (Diopsys. Inc., Pine Brook, NJ) was used for the experiments to measure VEP amplitude, latency, and alpha band power (Figure 2). This system generated an alternating, black-and-white checkerboard pattern stimulus. It recorded responses from the primary visual cortex (V1), which then analyzed/stored the real-time data. The system consists of a 17″ LCD stimulus test monitor with a refresh rate of 75 Hz, and a single computer processing unit which controls the entire VEP system. This system has been approved by the FDA, and it has been used in our laboratory for the last 4 years for a variety of VEP studies.[26-28,35,37] The Diopsys company developed a custom-designed software program to measure quantitatively the alpha power responses via power spectrum analysis (Dumermuth and Molinari, 1987).[32] The power spectrum analysis filters and extracts the power (unit = μV2) of each alpha single frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) that is embedded in the overall complex VEP response waveform using Fourier analysis[38] (Figure 3). It calculates the magnitude of the signal independently at each alpha frequency, and then provides a bar graphical display of the power at each frequency.

PROCEDURES

Vep and Alpha Recordings

The VEP and alpha recordings were assessed by using three standard GRASS (Grass Technologies, Astro-Med, Inc., West Warwick, RI) gold cup electrodes (i.e., active, reference, and ground), each of 1 cm diameter in size. The following attentional test conditions were performed to measure the VEP responses and to modulate the attentional state to assess the correlated alpha power responses:

1. Central VEP [baseline, "eyes open (EO)"] – The system's standard, conventional black-and-white, checkerboard, pattern reversal VEP test stimulus was employed (17° H x 15° V, 20 min arc check size at

1 meter distance, 85% contrast, 74 cd/m2 luminance, 1 Hz temporal frequency, 20 second trial duration, binocular viewing with spectacle correction, and a chinrest/headrest for stability). Subjects were instructed to gaze at the center of the display screen on a small target. This condition was performed to assess the VEP amplitude and latency, as well as the alpha (8-13 Hz) power responses. It was also conducted to assure VEP response normalcy. During this condition, it was predicted that the alpha power would be reduced if the normally-occurring, eyes-open, visual damping process were present[24,30] (Figure 1).

2. **"Eyes-closed (EC)" ("relaxed", reduced attentional state)** – Subjects were instructed to close their eyes, relax, and "clear their mind", for 2 minutes before starting the VEP trials. This was done to attain a relaxed attentional state, which would help them in attaining maximum alpha power.[24,26] During the trial, they were requested to imagine "looking" straight ahead where the central fixation target was originally presented during the initial eyes-open condition, with minimal saccadic eye movements to avoid artifacts in the recordings. During this condition, it was predicted that the alpha power would increase, as found in normal individuals,[24,30] as compared to both the EO and the ECNC (see below) conditions (Figure 1).

3. **"Eyes-closed number counting (ECNC)" (increased attentional demand)** – In this condition, subjects were requested to close their eyes, as they did in the above eyes-closed condition (#2). They were then instructed to perform a cognitive task (i.e., mental arithmetic).[24] This consisted of counting backwards silently, starting from 100, 96, 94, 92, and 90 for each trial, respectively.[39] Different numerical starting positions were used to prevent memorization. It was predicted that with the added cognitive task, the alpha power would be attenuated due to the increase in non-visual attentional demand, as compared to the eyes-closed condition.

Additionally, a passive rapid-serial visual presentation (RSVP) gazing task,[40] and two active RSVP tasks, were performed in Experiment #1 (details are provided in Willeford et al.[26] 2013[a]). The Willeford et al.[26] study found no significant differences in alpha power values for these three RSVP conditions, as compared to the EO condition. Therefore, only the EO, EC, and ECNC conditions were performed in the Experiment #2, and only the EO and EC conditions were performed in Experiment #3 before and after the oculomotor vision rehabilitation (OVR), as these were the most robust and consistent attentional test conditions.

SUBJECTIVE ATTENTIONAL TESTING

Visual Search and Attention Test (VSAT)

The Visual Search and Attention Test, or VSAT (© Psychological Assessment Resources, Inc.) involves a visual search and cancellation task, which assesses an individual's sustained attentional ability.[41] Sensitivity and specificity are 88 and 86, respectively, and test-retest reliability is 0.95. The subject was provided 60 seconds to complete each of two trials. The results of the two test trials were averaged to calculate the mean VSAT raw score for each subject. The raw score was then compared with the age-matched normative table to determine the VSAT percentile score. The VSAT abnormal scores include the 1st and 2nd percentile, with the 3rd through 16th percentiles being considered borderline abnormal. This test of attention was used in all three experiments.

Adult ADHD Self-Report Scale (ASRS)

The Adult ADHD Self-Report Scale (ASRS) questionnaire was developed by the World

Health Organization (WHO) to screen adults for attention-deficit/hyperactivity disorder.[42] Sensitivity and specificity are 56 and 98, respectively, and test-retest reliability is 0.87. Part A (9 questions) of this questionnaire dealing with attention was used in Experiment #2 to detect and differentiate mTBI with versus without an attentional deficit. Each question is scored based on "how they have felt and conducted themselves" over the past 6 months. The rating scale ranged from 0-4, with 0 signifying "never felt and conducted" to 4 signifying "very often felt and conducted". Scores can fall into three pre-specified categories: 0-16, 17-23, and 24 or greater, signifying that the subject was unlikely, likely, and highly likely to manifest an attentional deficit, respectively. The ASRS was performed only in Experiment #2.

Alpha Attenuation Ratio (AR)

Two alpha attenuation ratios (ARs) related to the attentional state were calculated.[24,26] The first was the measured alpha power (μV2) during the "eyes-closed (EC)" condition divided by the measured alpha power during the "eyes-open (EO)" condition. An EC ÷ EO AR value of ≥2.00 suggested the presence of normal attention.[26,27] The second AR was calculated as the measured alpha power during the "eyes-closed number counting (ECNC)" condition divided by the measured alpha power during the "eyes-closed (EC)" condition. Fuller[24] found that an ECNC ÷ EC AR of <1.00 suggested the presence of normal attention.

Oculomotor Vision Rehabilitation (OVR) and the VEP

Oculomotor vision rehabilitation (OVR), i.e., vision therapy, was provided to the seven individuals with mTBI in Experiment #3 using a crossover, interventional experimental design clinical trial. The OVR consisted of training each of the three oculomotor systems, i.e., version, vergence, and accommodation, with such training indirectly including an attentional component.[34,35] OVR was performed twice a week for six weeks for a total of 9 hours, 3 hours for each oculomotor system. There was also a similar placebo arm to the protocol (see Thiagarajan[43-48] for details).

DATA ANALYSIS

GraphPad Prism 5.04 software was used to perform the graphical and data analyses. One-way and two-way ANOVAs were performed, as well as t-tests, to analyze the data. The coefficient of variation (CV = standard deviation ÷ mean) of the alpha wave responses was calculated to assess repeatability.[26,27] The CV value can range from 0.00 to 1.00.49 This value represents the *intra*-subject variability: the smaller the value, the less the variability, and the better the repeatability.

RESULTS

Experiment #1: Objective assessment of the human visual attentional state.[26]

VEP responses

The group mean VEP amplitude (18.27 μV, SEM = 1.80) and latency (104.10 ms, SEM = 0.68) values were found to be within normal limits for our laboratory.

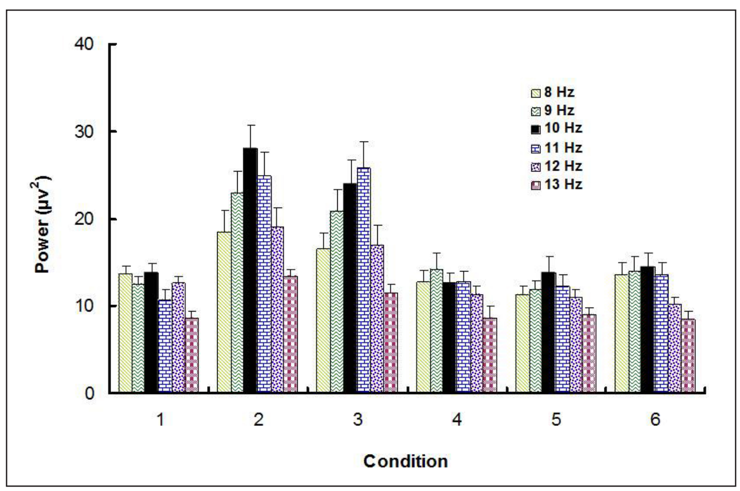

Figure 4: Average alpha-power values across the six test conditions at each frequency (mean, +1 SEM). (Reprinted with permission from Willeford et al.[26], Documenta Ophthalmologica)

Power spectrum

The group mean power spectrum value at each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for the 6 attentional test conditions are presented in Figure 4. The eyes-closed (EC) and eyes-closed number counting (ECNC) values averaged across the 6 alpha frequencies were found to be significantly higher than for the other 4 eyes-open (EO) conditions ($p < 0.05$). In addition, the mean EC ÷ EO AR was higher than 2.00, mainly at 10 Hz (2.17, range = 0.88 to 4.04) and 11 Hz (2.93, range = 1.02 to 14.94). The mean ECNC ÷ EC AR was found to be lower than 1.00 at all alpha frequencies, except 11 Hz. Both group AR values were normal.[24]

The mean coefficient of variation (CV) was used to assess repeatability. CV values ranged from 0.48 to 0.64 for the alpha response averaged across all frequencies and subjects, which suggested reasonably good repeatability.

Visual Search and Attention Test (VSAT)

The VSAT percentile scores ranged from the 11th to the 95th percentile (mean = 52.61, SEM = 29.32). Each subject's score was above the abnormal 2nd percentile. Three scored in the borderline range (i.e., 11th, 12th, and 16th percentile). However, the ARs between these three borderline subjects and the top three performing subjects were not significantly different ($p > 0.05$).

Correlations

Linear regression analysis was used to assess the correlation between the alpha EC ÷ EO ARs and VSAT percentile scores at each alpha frequency. There were significant correlations at 8, 9, and 10 Hz ($r = +0.55$ to $+0.69$, all $p < 0.05$). The correlation was found to be highest at 10 Hz ($r = +0.69$), as shown in Figure 5.

Experiment #2: Objective assessment of attention in mild traumatic brain injury (mTBI) using the visual-evoked potential (VEP).[35]

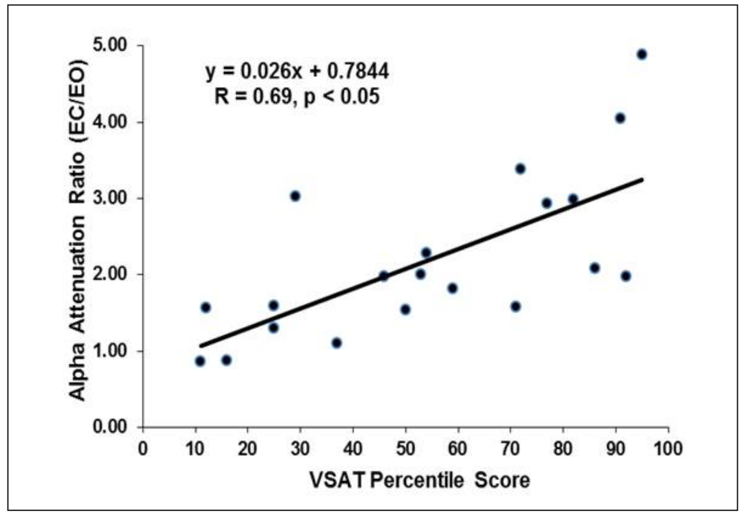

Figure 5: Correlation between the attenuation ratio (AR) (EC ÷ EO) at 10 Hz and the VSAT percentile score. (Reprinted with permission from Willeford et al.[26], Documenta Ophthalmologica)

VEP responses

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.

Power Spectrum

The group mean power spectrum values at each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for the 3 attentional test conditions for individuals with mTBI *and* an attentional deficit are presented in Figure 6A. The ECNC power values averaged across the 6 alpha frequencies were found to be significantly higher than for the EO and EC conditions ($p < 0.05$), thus demonstrating the presence of abnormal dampening with the eyes closed.

The group mean power spectrum value at each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for the 3 attentional test conditions for individuals with mTBI but *without* an attentional deficit are presented in Figure 6B. The EC and ECNC conditions power values averaged across the alpha frequencies were found to be significantly higher as compared to the average EO condition ($p < 0.05$), thus demonstrating the presence of normal attentional abilities,

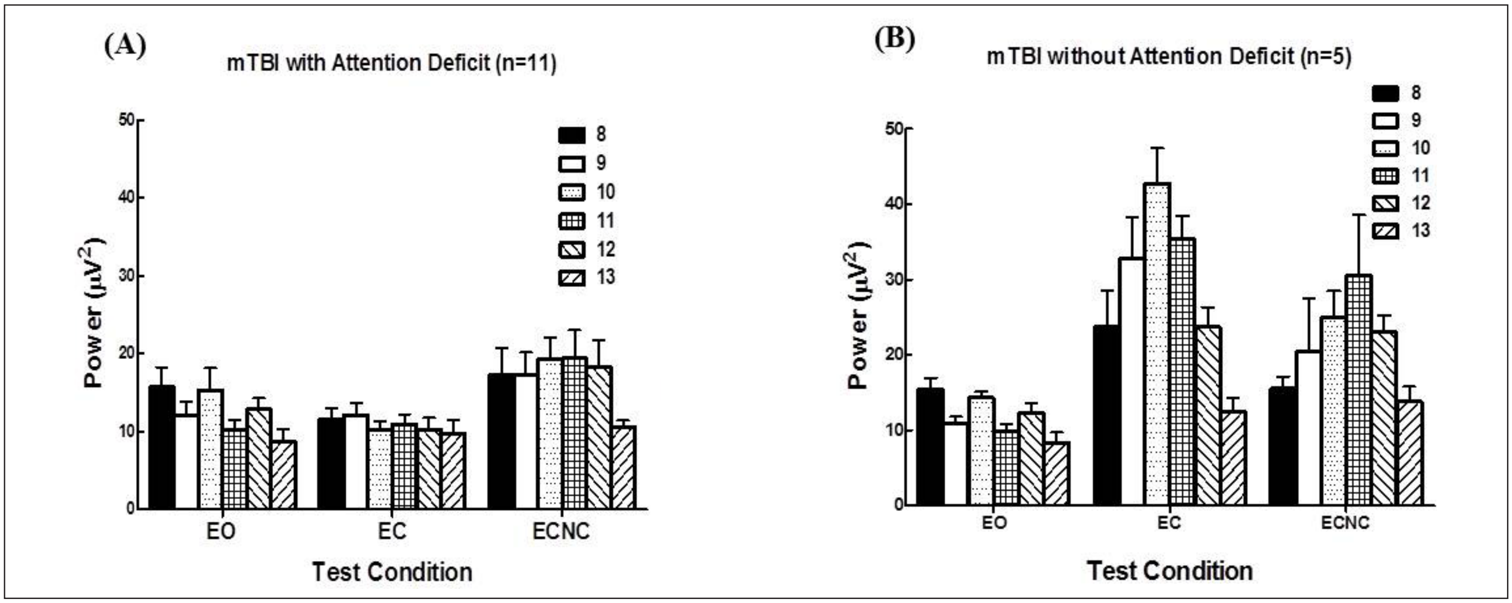

Figure 6: The group mean power spectrum value (μV^2) at each alpha band frequency (8-13 Hz) for the 3 test conditions. Plotted is the mean +1 SEM. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit. Symbols: EO = eyes-open, EC = eyes-closed, and ECNC = eyes-closed number counting, conditions.

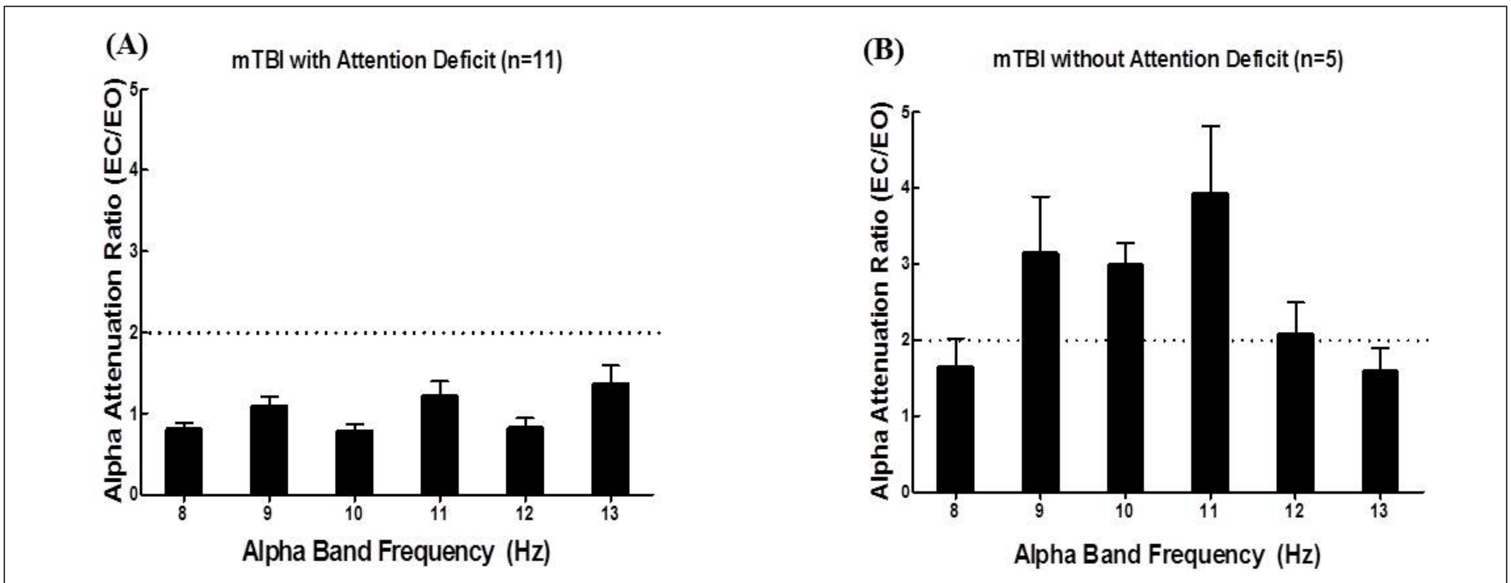

Figure 7: The group mean alpha attenuation ratio (AR) (EC ÷ EO) for each alpha frequency. Plotted is the mean +1SEM. Dashed line = lowest normative AR level. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit.

similar to that found in Experiment #1 in the visually-normal population for these same three conditions (Figure 4).[26]

Comparisons were also performed between those having mTBI with versus without an attentional deficit for the EO, EC, and ECNC test conditions, with the power values averaged across the 6 alpha frequencies. The EC and ECNC power values in mTBI *without* an attentional deficit were significantly higher, as compared to the EO and EC power values in mTBI *with* an attentional deficit ($p < 0.05$), thus suggesting normal attention in the former group.

The coefficient of variation (CV) analysis was used to assess repeatability. CV values for all parameters were typically found to be extremely small (median = 0.09, range = 0.003 to 0.58) in the two mTBI subgroups, thus suggesting excellent repeatability.

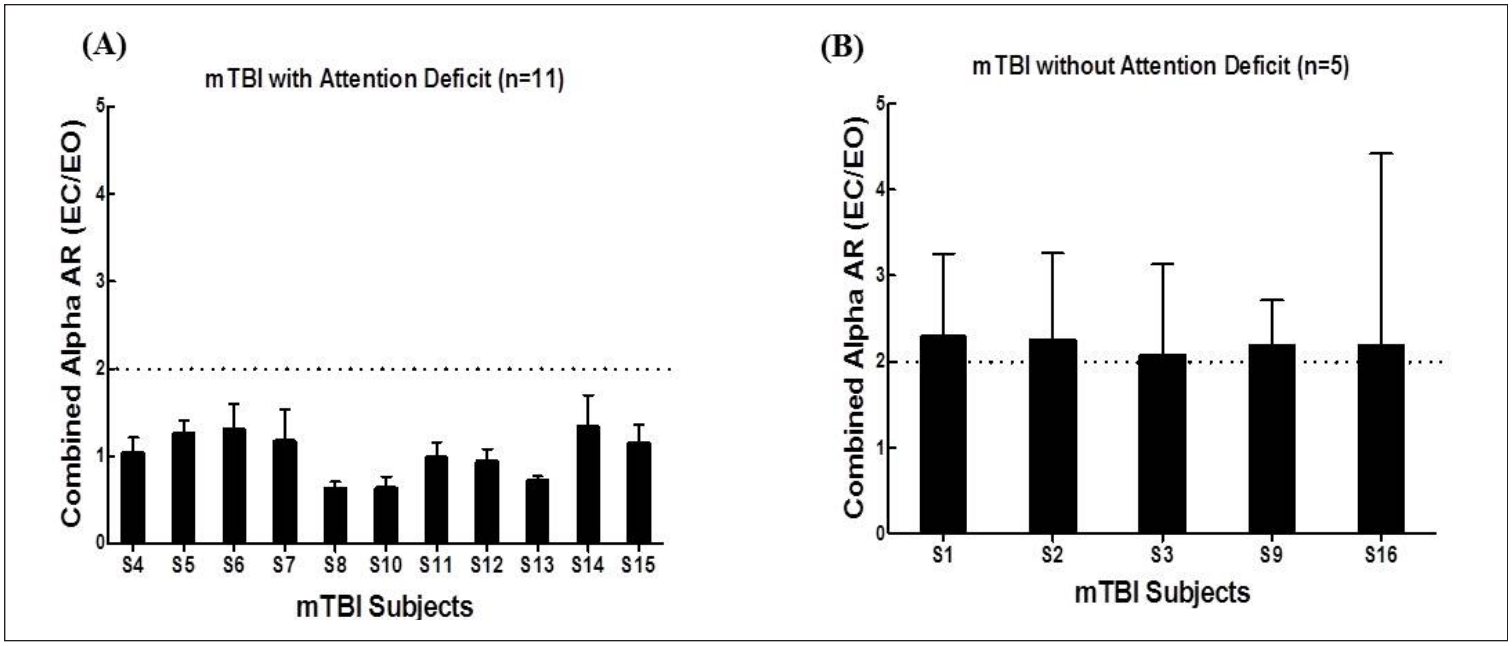

Figure 8: The combined attenuation ratio (AR) (EC ÷ EO) across the alpha frequency band (8-13 Hz) for each subject. Plotted is the mean +1SD. Dashed line = lowest normative AR level. (A) Individuals with mTBI and an attention deficit, (B) Individuals with mTBI without an attention deficit.

Alpha Attenuation Ratio (AR): Individual Alpha Frequencies

The group mean EC ÷ EO AR for *each* alpha frequency for individuals with mTBI *and* an attentional deficit is presented in Figure 7A. The mean EC ÷ EO AR at each alpha frequency was significantly lower (i.e., abnormal, all $p < 0.05$) than the normative AR value of ≥2.00 (range = 0.81 to 1.36). In addition, the mean ECNC ÷ EC AR at each alpha frequency was significantly higher (i.e., abnormal, all $p < 0.05$) than the normative AR value of <1.00 (range = 1.27 to 2.24).

The group mean EC ÷ EO AR for *each* alpha frequency for individuals with mTBI but *without* an attention deficit is presented in Figure 7B. The mean EC ÷ EO AR at 9, 10, 11, and 12 Hz was ≥2.00 (range = 1.59 to 3.92), which was normal.26 In addition, the mean ECNC ÷ EC AR at 8, 9, 10, 11, and 12 Hz was <1.00 (range = 0.59 to 1.10), which was also normal.[24,26]

Alpha Attenuation Ratio (AR): Combined Across the Alpha Frequency Band (8-13 Hz)

The EC ÷ EO AR combined and averaged across the alpha frequency band (i.e., from 8-13 Hz) for each individual with mTBI *and* an attentional deficit is presented in Figure 8A. The EC ÷ EO AR for each subject was lower than the mean normative AR value of ≥2.00. The group mean EC ÷ EO AR combined and averaged across the alpha frequency band was 1.01 (SEM = 0.07), with a range from 0.62 to 1.33. In addition, the ECNC ÷ EC AR combined and averaged across the alpha frequency band for most individuals (except subjects #12 and 13) was higher than the normative AR value of <1.00, which was abnormal. The group mean ECNC ÷ EC AR combined across the alpha frequency band was 1.79 (SEM = 0.96), with a range from 0.86 to 4.33.

The EC ÷ EO AR combined and averaged 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 8B. The EC ÷ EO AR was ≥2.00, which was normal.[26] The group mean EC ÷ EO AR combined across the alpha frequency band was 2.19 (SEM = 0.03), with a range from 2.07 to 2.18. In addition, the ECNC ÷ EC AR combined and averaged across the alpha frequency band for each individual was <1.00, which was *normal.*[24,26] The group mean ECNC ÷ EC AR combined across the alpha frequency band was 0.806 (SEM = 0.02), with a range from 0.71 to 0.86.

There was a significant difference between those having mTBI with versus without an attentional deficit for the EC ÷ EO AR combined across subjects and averaged across the alpha frequency band. It was significantly higher in the mTBI subgroup without an attentional deficit ($p < 0.05$), thus suggesting normalcy in this subgroup.

There was a significant difference between those having mTBI with versus without an attentional deficit for the ECNC ÷ EC AR combined across subjects and averaged across the alpha frequency band. It was significantly smaller in mTBI without an attentional deficit ($p > 0.05$), thus suggesting normalcy in this subgroup.

Visual Search and Attention Test (VSAT)

The VSAT percentile scores for each subject are presented in Table 1. 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, in mTBI *without* a self-reported attentional deficit *(n=5)*, the mean VSAT percentile score was 68.80 (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. Comparison between the two groups for the VSAT scores revealed no significant difference ($p > 0.05$).

Adult ADHD Self-Report Scale (ASRS)

The Part A questionnaire scores for the ASRS test for each subject are presented in Table 1. In mTBI *with* a self-reported attentional deficit *(n=11)*, the mean score was abnormal, i.e., 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 normal, i.e., 12.40 (SEM = 1.36), with a range from 8 to 16. None of the scores for those with mTBI *and* an attentional deficit fell within the normal range. Comparison between the two groups for the ASRS scores revealed that it was significantly higher in those having mTBI *and* an attentional deficit ($p < 0.05$), thus suggesting presence of an attentional deficit.

Correlation

Linear regression analysis was performed to assess the correlation between the AR, ASRS, and VSAT for all individuals with mTBI (n=16). The following correlations were found be significant. First, the correlations between EC ÷ EO AR and the ASRS score at most alpha frequencies were significant: 8, 9, 10, 11, and 12 Hz ($r = -0.62$ to -0.83, all $p \ll 0.05$). The correlation was highest at 10 Hz ($r = -0.83$) (Figure 9). Second, the correlations were also significant between the EC ÷ EO AR combined and averaged across the alpha frequency band and the ASRS scores ($r = -0.76$, $p < 0.05$). Lastly, the correlation between the ECNC ÷ EO AR and the ASRS was significant only at 8 Hz ($r = -0.53$, $p < 0.05$). In contrast, there were no significant correlations with the VSAT percentile scores. Thus, the objective ARs were correlated with the subjective ASRS, but not with the subjective VSAT, attentional scores.

Experiment #3: Effect of oculomotor vision rehabilitation (OVR) on the visual-evoked potential and visual attention in mild traumatic brain injury.[28]

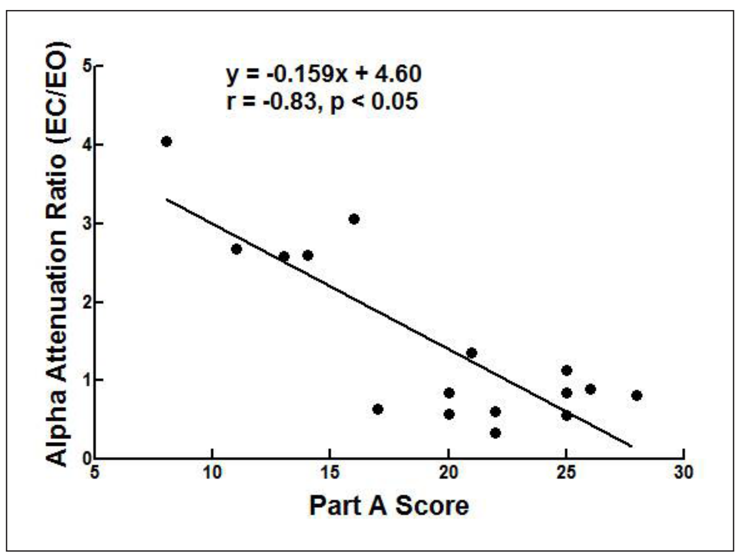

Figure 9: Correlation between the attenuation ratio (AR) (EC ÷ EO) at 10 Hz and the Adult ADHD Self-Report Scale (ASRS) Part A questionnaire scores.

VEP Responses

The group mean VEP amplitude was significantly increased (i.e., from 17.40 to 19.15 μV), and its variability was significantly decreased (i.e., from 1.89 to 1.03 μV), following the OVR. There was no change in mean latency (i.e., before = 105.53 ms and after = 105.63 ms) and its variability (i.e., before = 1.35 ms and after = 1.64 ms) following the OVR. Latency values were the same and within the normal limits before (105 ms) and after OVR (105 ms).

Power Spectrum

The group mean power spectrum values at each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for the EO and EC attentional test conditions for individuals with mTBI (n = 7) *before* oculomotor vision rehabilitation (OVR) are presented in Figure 10A. The EC power values combined and averaged across the 6 alpha frequencies were significantly higher than for the EO condition ($p < 0.05$). However, the AR values were only normal at two of the six individual alpha frequencies (i.e., 9 and 10 Hz).

The group mean power spectrum values at each alpha band frequency (i.e., 8, 9, 10, 11, 12, and 13 Hz) for the EO and EC attentional test conditions for individuals with mTBI *after* oculomotor vision rehabilitation (OVR) are presented in Figure 10B. The EC power values combined and averaged across the 6 alpha frequencies were significantly higher than for the EO condition ($p < 0.05$). However, AR values were now normal at four of the six individual alpha frequencies (9, 10, 11, and 13 Hz).

Most importantly, comparison of the EC condition before and after OVR showed a significant increase ($p < 0.05$) in the power values averaged and combined across all 6 alpha frequencies (compare Figure 10A and 10B). In contrast, there was no difference in the EO power values before and after the OVR. The former result suggests increase in attentional ability following OVR. The latter result is consistent with this notion.

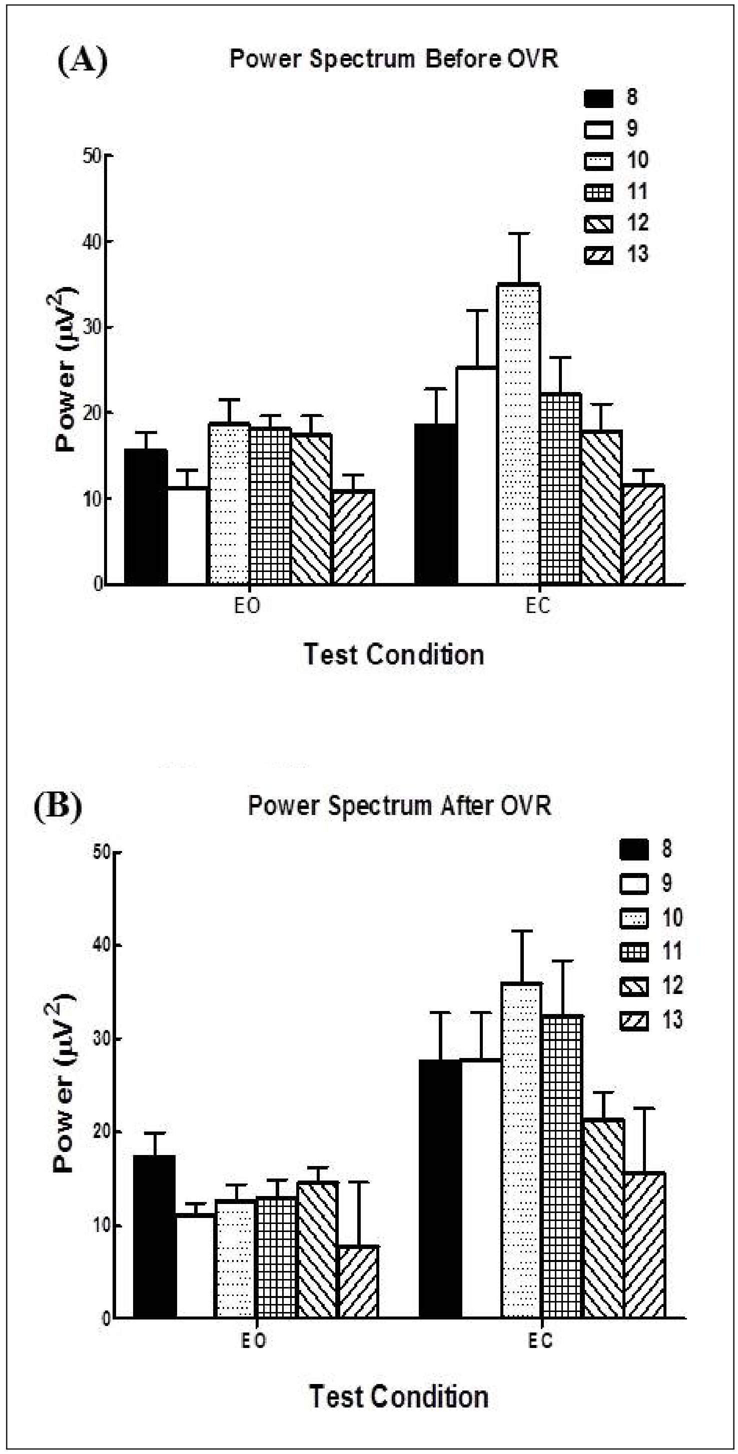

Figure 10: The group mean power spectrum value (μV^2) at each alpha band frequency (8-13 Hz) for the 2 test conditions. Plotted is the mean +1 SEM. (A) Before OVR, (B) After OVR. Symbols: EO = eyes-open, and EC = eyes-closed, conditions.

Alpha Attenuation Ratio (AR): Individual Alpha Frequencies

The group mean AR for *each* alpha frequency before and after the OVR is presented in Figure 11A. The EC ÷ EO AR increased numerically at each frequency and attained the normal value

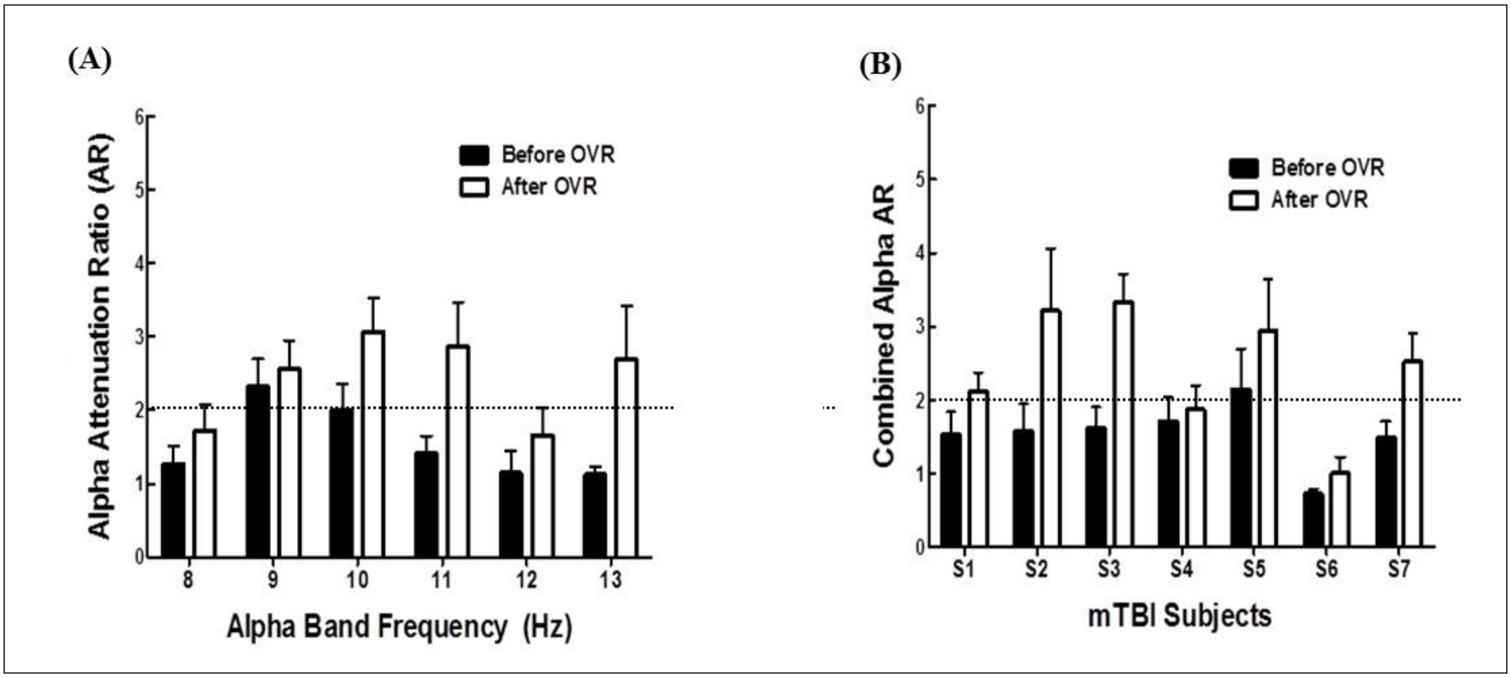

Figure 11: Correlation between the attenuation ratio (AR) (EC ÷ EO) at 10 Hz and the VSAT percentile score. (Reprinted with permission from Willeford et al.[26], Documenta Ophthalmologica)

of 2 (with +1 SEM added to the mean) after the OVR. The EC ÷ EO AR significantly increased following the OVR at 3 of the 6 alpha frequency sub-bands (i.e., 10, 11, and 13 Hz) (all $p < 0.05$), thus suggestive of increased attention following the OVR.

Alpha Attenuation Ratio (AR): Combined Across the Alpha Frequency Band (8-13 Hz)

The EC ÷ EO AR combined and averaged across the alpha frequency band (i.e., from 8-13 Hz) before and after the OVR is presented in Figure 11B for each subject. The EC ÷ EO AR increased numerically in each subject and normalized in all but one subject (S6). There was also a significant increase in the combined alpha EC ÷ EO AR following the OVR ($p < 0.05$), thus suggestive of increased attention following the OVR.

VSAT Pre/Post Scores

There was a significant increase ($p < 0.05$) in the mean VSAT score following the OVR. Pre-OVR, it was 40.25 +12.31 (SEM), whereas post-OVR, it was 59.50 +9.28 (SEM).[28]

DISCUSSION

The findings of the three reviewed studies[26,28,35] clearly demonstrate that the VEP technique can be used to detect and assess attention in both the visually-normal and mTBI populations in a rapid, repeatable, quantitative, and objective manner. Furthermore and very importantly, the VEP approach was able to differentiate *between* the visually-normal and mTBI groups, *as well as* between individuals having mTBI with versus without an attentional deficit. Of particular note, an increase in attentional state was found in those with mTBI following successful OVR. The attenuation ratio (AR) metric was found to be useful to assess and detect an individual's attentional state in both the visually-normal and mTBI populations. Of interest, and a critical finding, the objective ARs were correlated with the subjective attentional tests. Lastly, these findings demonstrate that human attention could be assessed as early as the primary visual cortex (V1) in both the VN and mTBI populations.

Alpha Attenuation Ratio (AR)

These findings confirmed that the AR could be used as a clinical metric to assess one's attentional state objectively. Willeford et al.[26] found that an EC ÷ EO AR of ≥2 and an ECNC ÷ EC AR of <1 was suggestive, and even predictive, of having normal attention. The ARs in our studies were consistently found to be abnormal in those with mTBI and an attentional deficit, and normal in individuals with mTBI but without an attentional deficit. Furthermore, the significant increase in the EC ÷ EO AR found following OVR suggests a positive impact on the mTBI attentional state, as well as demonstrating residual visual neuroplasticity, *even* in an adult, compromised brain.

Subjective Attention Test (VSAT and ASRS)

Two subjective attentional tests were performed: VSAT and ASRS. The VSAT percentile scores were correlated with the AR values in the visually-normal group, but not in the mTBI population; rather here the ASRS scores were correlated with the AR values in the mTBI group. This discrepancy might be attributed to one or more of the following reasons. Due to larger spread of AR values in the visually-normal as compared to the mTBI group, there would be more likelihood of a significant correlation. However, we believe that other factors are more likely to be involved. Both the AR values and the VSAT percentile scores were found to be within normal limits in the visually-normal group. In contrast, the AR values were in the abnormal range, whereas the VSAT scores were in the normal range, in those with mTBI having an attentional deficit. The ASRS questionnaire was able to differentiate between mTBI with versus without an attentional deficit *100%* of the time, but this was only true *18%* of the time with the VSAT. In addition, the EC ÷ EO AR values were correlated with the ASRS score at nearly all frequencies (except at 13 Hz), whereas the ECNC ÷ EC AR values were correlated only at the 8 Hz alpha frequency. Overall, these findings suggest that the ASRS questionnaire and the EC ÷ EO AR are better to detect and assess individuals with mTBI for presence of a general/visual attentional deficit.

Oculomotor Vision Rehabilitation (OVR): VEP and Alpha Responses

Yadav et al.[28] demonstrated objectively the positive effect of OVR at the visuo-cortical level in those with mTBI. There was enhancement in both the VEP and alpha responses following the OVR. The VEP amplitude increased, and its variability decreased, with correlated improvement in alpha-based attentional state. As mentioned earlier, all OVR has an embedded attentional training component by its very nature:[33,34] patients were instructed to remain vigilant during the specified vision therapy tasks involving both detection and discrimination of the visual stimulus attributes (e.g., blur). Therefore, an increase in alpha power during the EC condition following the OVR was not surprising, and in fact, expected. Furthermore, the subjective VSAT percentile scores also increased significantly following the OVR. Improvement in the objectively-based attentional parameters at the V1 cortical level was consistent with the clinically-based subjective attentional test results, thus lending credibility to each approach.

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[30] (1999), and others,[50,51] 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, asynchronous activity occurs during the EC ("relaxed") attentional state, and thus these individuals cannot "block" information processing from occurring. The asynchronous neuronal activity would cause attenuation, or suppression/damping, of the alpha band power via signal cancellation.[52]

The opposite is believed to occur in the EO condition. In individuals with normal attention, asynchronous 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.[52] In individuals with mTBI and an attentional deficit, asynchronous activity occurs during all three conditions, and thus presence of relative attenuation. The findings of the present studies are consistent with the proposed mechanism of Klimesch,[30] and others.[50,51]

Neurophysiological Substrates

There are several neural substrates that are likely to contribute to the VEP/alpha response. For the EO condition, the contributors include V1-V4 and the thalamus.[53] For the EC condition, the contributors include the thalamo-cortical pathway.[30] Other neural regions may participate, but this remains speculative.

Clinical Implications

The findings of these three studies were instrumental in formulating a clinical attentional test protocol in those with mTBI, as described below:

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

2. Subjective test – The Adult ADHD Self-Report Scale (ASRS) Part A attention questionnaire should be administered to assess the attentional state.

3. Objective attentional test – The following two test condition should be performed to measure the VEP and alpha band power responses to calculate the AR value:

A. Eyes open (EO)
B. Eyes-closed (EC)

Number of trails – 5 trials, each of 20 seconds, per test condition should be performed and averaged.

The EC ÷ EO AR should be quantified at each alpha band, as well as combined and averaged across the alpha frequency bands. These objective findings should be consistent with the individual's case history and the ASRS Part A questionnaire scores, and furthermore assistive in making the final diagnosis with a high degree of certainty. Our proposed objective protocol would be beneficial to clinicians in assessing and detecting one's attentional state rapidly, quantitatively, reliably, and objectively. Due to its objective nature, the proposed attentional test protocol may also be helpful in the cognitively-impaired and non-verbal populations, as well as in the pediatric population, in which attentional deficit (e.g., ADHD) is suspected. The software for the alpha-band assessment of attention is available from the Diopsys company (www.diopsys.com).

Study Limitations

There were two possible study limitations. First, there were a relatively few number of subjects with mTBI in the OVR experiment. Second, these studies included only those with mTBI, and not individuals with moderate or severe TBI.

CONCLUSIONS

The present findings clearly demonstrate that the VEP, an objective approach, can be used clinically to rapidly and quantitatively detect and assess attention in the mTBI population. This was achieved by measuring the alpha power under different attentional states and calculating the respective alpha AR values, which were correlated with the subjective attentional tests scores. The AR values were found to be beneficial in differentiating between the visually-normal and mTBI populations, as well as between those having mTBI with versus without an attentional deficit. The increase in the mean VEP amplitude following the OVR suggested enhanced and more synchronized neural activity within V1. Similarly, the increase in the mean VSAT score following the OVR suggested enhancement in attentional ability, which is consistent with the notion that OVR has an embedded attentional component. The VEP technique has the potential to become an additional tool in the clinician's diagnostic armamentarium for objectively-based attentional assessment in the optometric practice.

ACKNOWLEDGMENTS

We would like to thank the College of Optometrists in Vision Development (COVD) for funding to K.J.C and N.K.Y, the Army/DoD for Awards (W81XWH-10-1-1041 and W81XWH-12-1-0240) to K.J.C, and the SUNY, Graduate Program for funding this project. We would also like to thank the American Optometric Foundation (AOF) for awarding the Ezell Fellowship to N.K.Y and P.T. Lastly, we are grateful to DIOPSYS Inc., Pine Brook, New Jersey for providing the VEP system for these studies.

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