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Effect of luminance on the visually-evoked potential in visually-normal individuals and in mTBI/concussion

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Abstract

Purpose—To assess quantitatively the effect of luminance on VEP amplitude and latency in visually-normals (VN) and patients with mild traumatic brain injury (mTBI).

Methods—VN individuals ($n = 20$) and those with mTBI ($n = 19$) participated. Those with mTBI were assessed 1–10 years post-injury (mean = 4.97 years), with the exception of one subject. Pattern VEP testing was employed using the DIOPSYSTTM NOVA–TR system, with a 74 cd m^{-2} baseline luminance. Luminance levels were reduced with five different neutral density (ND) filters (0.5, 1.0, 1.5, 2.0 and 2.5) and compared to the baseline response. All testing was performed under binocular-viewing conditions with full refractive correction in place.

Results—In both groups, mean VEP amplitude reduced with decrease in luminance ($p < 0.05$). At each luminance level, the mean VEP amplitude was significantly lower in mTBI than in the VN population ($p < 0.05$). In both groups, the mean VEP latency increased progressively with reduction in luminance ($p < 0.05$), with it being significantly higher in mTBI than in the VN population ($p < 0.05$).

Conclusions—High luminance levels produced an optimal VEP response in both populations. VEP amplitude was robust, whereas latency progressively increased in both groups as luminance decreased. The latency increase with decreased luminance was significantly larger in those with mTBI, thus suggesting that latency can be used to differentiate reliably between VN individuals and those with mTBI.

Keywords

Amplitude; latency; luminance; magnocellular pathway; mild traumatic brain injury (mTBI); objective biomarker; visually-evoked potential; VEP

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Introduction

Overview of mild traumatic brain injury (mTBI)

Mild traumatic brain injury is a major public health and medical problem in the US, where there are ~1.7 million new cases each year [1]. The majority occur from motor vehicle accidents and assaults in the younger population (15–24 years old) and from falls in the older population (>65 years old) [2]. In a report published by the Centers for Disease Control and Prevention, ~75% of all TBIs are attributed to concussions or other forms of mild TBI [1]. Unlike moderate or severe traumatic brain injuries that produce evidence of head trauma on MRI and CT scans, mTBI does not. This makes it impossible to diagnose with typical brain imaging. However, advances in diffusion tensor imaging (DTI) show promise [3].

Since 2000, ~250 000 cases of TBI that occur each year in the US have involved military service members [4–7]. In fact, traumatic brain injury (TBI) has been termed the ‘invisible wound’ by the Department of Defense (DoD) [4, 8]. Most of the returning veterans have been categorized as having ‘mild’ brain injury (i.e. mTBI), on the basis of conventional clinical criteria and lack of intracranial irregularities imaged either with computed tomography (CT) or conventional magnetic resonance imaging (MRI) [9].

Recent attention has also been directed toward sport-related concussions, both in professional and recreational sports [10]. Previously considered as a ‘normal part of the game’, the long-standing and detrimental effects of sports-related concussions are now actively being investigated, with athletes who have received concussions reporting and displaying more symptoms and memory impairment when compared to their non-concussed cohorts [11, 12]. Sport-related brain injuries, such as concussions, are the second most common cause of traumatic brain injury in athletes of 15–24 years of age [13].

Traumatic brain injury can result in a constellation of neurological dysfunctions, including the sensory, motor, cognitive, attentional, languages, behavioural and perceptual domains [14–16]. More specifically, an array of visual disturbances are common side-effects that often follow a traumatic brain injury [17, 18]. These include photosensitivity, visual attentional deficits, ocular motor problems, visual motion sensitivity and visual field defects, to name a few [15, 19–21].

Deficits in the magnocellular system, which can be selectively isolated by specific visual-evoked potential (VEP) stimuli, may be responsible for some of the aforementioned visual dysfunctions. Isolation of the magnocellular pathway is possible by modulating luminance of the VEP test stimulus [22]. This approach has proven useful in diagnosing mTBI [22]. Studies have demonstrated that diffuse axonal injury [23] within the visual pathway resulting from concussion and head trauma may cause impaired and slowed visual processing [24] and, furthermore, produce dissimilar and more variable VEP findings in the mTBI population when compared to the VN population [19, 25]. Increased VEP variability is one of the hallmark signs of mTBI [19, 26], frequently concomitant with an increase in the P100 latency and a decrease in the VEP amplitude.

Visually-evoked potential (VEP) overview

The visual-evoked potential (VEP) refers to the electro-physiological signal obtained from correlated neural activity in the visual cortex in response to a time-locked visual stimulus [27]. The recorded activity is primarily activated by cone photoreceptors in the central 15° of the visual field [27–29], which corresponds to ~50% of the primary visual cortex (i.e. cortical magnification factor) [29, 30]. The recording of VEPs has been an established method to obtain reproducible, objective and quantitative data related to the integrity of the early visual pathways in the clinical and laboratory setting for decades [21, 31–33]. Specifically, pattern VEPs with checkerboard stimuli have been used to detect visual dysfunction clinically and to investigate the pathophysiology of an array of neurological diseases (e.g. multiple sclerosis, optic neuritis), as well as to assess visual acuity objectively [34, 35].

The VEP waveform has two principal components: an initial negative peak at 70–80 milliseconds (N75) and a larger positive peak at 90–110 milliseconds (P100). The voltage difference between these two parameters constitutes the VEP amplitude. The time of the P100 component is the latency. The overall VEP response reflects the functional integrity of central vision at several levels along the early afferent visual pathway, beginning in the retina, through the optic nerve and optic radiations, and ultimately ending in the occipital cortex [36].

Optimal VEP parameters (e.g. check size, test duration and contrast level) have been established not only to ensure rapid and repeatable findings in the laboratory, but to make this approach more clinically valuable and easy to use. Studies in normals have found that the optimal check size stimulus for the pattern VEP is 20min arc, and that the optimal test duration is 20 seconds, both at 20% and 80% contrast levels [19, 37]. However, current studies have not addressed optimization of the *luminance parameter*.

At high luminance levels and low temporal frequencies, the *parvocellular pathway* dominates the processing of visual information, while at low luminance levels and high temporal frequencies, the *magnocellular pathway* dominates [22]. It has been found in a previous study that patients with a history of mTBI exhibited elevated coherent motion thresholds (CMT) [38], which suggests damage to the magnocellular pathway in this population. Their critical flicker fusion frequency was also slightly altered [39, 40], which is consistent with the above idea. Therefore, determining the optimal luminance level that can objectively isolate the magnocellular from the parvocellular pathway, while still producing high quality VEP responses, is both clinically useful and necessary for a differential probe. This is especially true when rapid and accurate assessments are needed in symptomatic patients who appear to be ‘normal’ based on current MRI and CT scans after receiving a head trauma.

VEP studies in the visually-normal (VN) population

Many stimulus conditions can affect the VEP response, such as stimulus size, contrast and test duration, as mentioned previously [19, 41]. Over the last several decades, researchers have investigated the effect of these stimulus conditions on VEP responsivity in the VN

population, thus resulting in well-established protocols that have been standardized to maximize and optimize VEP responsivity [19, 27]. Unfortunately, few studies have been conducted to assess the effect of *luminance* on both the amplitude and latency of the pattern VEP in VNs. Furthermore, the past results are equivocal, as described below.

Froehlich and Kaufman [42] assessed the effect of luminance on monocular VEPs in the VN adult population ($n=16$), aged 18–45 years, and in patients with optic neuritis ($n=3$), aged 20–48 years. They used an alternating checkerboard pattern 30min arc at 85cm, with a temporal frequency of 1.8 reversals/second (0.9Hz). Contrast was 94%. Baseline luminance was 116.49cdm^{-2} , which was then decreased using the following neutral density (ND) filter values: 0.0, 0.6, 1.0, 1.3, 1.6 (100%, 30%, 10%, 6% and 2.5% transmittance, respectively). This ranged from $116.49\text{--}3.31\text{cdm}^{-2}$, respectively. With regard to latency, there was a non-linear relationship, with it progressively increasing from 100 milliseconds (0.0 ND filter) to 130 milliseconds (1.6 ND filter). However, changes in luminance had no significant effect on the pattern VEP amplitude, even at a 1.6 ND filter level, where consistent responses could still be obtained (2.5% transmittance, 3.31cdm^{-2}).

Most recently, Markó et al. [43] studied the effect of luminance on dynamic random-dot, correlogram-evoked visual potentials ($n=10$). Using red and green stimulus channels with red–green goggles for dichoptic presentation, VN subjects viewed the stimulus for 70 seconds at 1 metre. Contrast was 70%. Luminance was 9.47cdm^{-2} for the brightest pixel. Luminance was reduced with ND filters by factors ranging from 0.5–0.003 and, thus, luminance levels ranged from $5.5\text{--}0.03\text{cdm}^{-2}$. However, amplitude values were only recorded down to 0.06cdm^{-2} , since below this luminance level, a discernable response was only evident in one subject. They found an increase in latency of 57% with decreased luminance, with no change in amplitude. The lack of effect on VEP amplitude was attributed to an inability of the dynamic random-dot correlograms and motion-onset stimulation to activate luminance-encoding neuronal populations in the visual cortex.

Although the previously cited studies found no significant affect of luminance on VEP amplitude, one did find a decrease in mean amplitude when assessed under low luminance conditions. Brannan et al. [44] tested normal readers ($n=32$, 17 males and 15 females; mean age=10 years) and ‘disabled readers’ ($n=29$, 19 males and 10 females; mean age=11 years) using monocular and binocular VEPs with sinusoidally-modulated checkerboard patterns. While contrast was held constant at 60%, the stimulus temporal frequency was modulated at 1.88, 7.5 and 15 reversals per second. Two luminance levels were used: 55cd m^{-2} and 0.76cd m^{-2} . Under the higher luminance condition, both normal and disabled readers had similar amplitudes ($\sim 10\text{ }\mu\text{v}$ and $9\text{ }\mu\text{v}$, respectively, estimated per their figure 4). In contrast, under the lower luminance condition, normal readers had a mean amplitude of $\sim 7\text{ }\mu\text{v}$, while disabled readers had a mean amplitude of $\sim 5.5\text{ }\mu\text{v}$ (estimated per their figure 4). There was approximately a 30% reduction in VEP amplitude at low luminance levels in the visually-normal readers and a 60% reduction in VEP amplitude at low luminance levels in the disabled readers when compared to their respective mean VEP amplitude at high luminance levels, thus suggesting the presence of a magnocellular deficit in the disabled readers.

No studies have assessed the effect of luminance on the pattern VEP in those with a history of concussion/mTBI. Thus, the purpose of the current study was to assess quantitatively the effect of luminance on the VEP amplitude and latency, with a goal toward optimization of luminance level for the VEP, both in the concussion/mTBI and visually-normal populations. Furthermore, it may be possible to use the luminance VEP parameter as an objective biomarker that may aid in the diagnosis of mTBI, which was one of the goals of the study. Thus, the final goal was to use luminance VEP parameters as a biomarker to diagnose mTBI. Since it is well established that the mTBI population has deficits in the magnocellular pathway [39, 40, 44], which is responsible for processing low luminance visual information, and they exhibit diffuse axonal injury, which results in increased neural processing time [24], it is hypothesized that, when compared to VN controls, those with mTBI will exhibit both a delay (i.e. increase) in latency and a decrease in amplitude in the VEP at low luminance levels.

Materials and methods

Subjects

Twenty visually-normal subjects (14 females and six males) with a mean age (SD) of 24.5 years (± 1.5) and a range of 22–28 years, were recruited from the students and faculty at SUNY College of Optometry. Each had a corrected visual acuity of 20/20 or better both binocularly and monocularly at distance and near, with normal contrast sensitivity [45]. Mean refractive error was -3.25 D, with a range from $+2.50$ D to -7.50 D. Mean astigmatism was -1.63 D. Subjects with a history of concussion, mild traumatic brain injury (mTBI) or seizures, as well as having strabismus, amblyopia, ocular or systemic disease and/or neurological disease were excluded from this group.

Nineteen subjects (13 females and six males) with concussion/mTBI recruited from the NYC Soccer Association, as well as from the students and faculty at SUNY College of Optometry, were tested. They had a mean (SD) age of 26.7 years (± 5.3), with a range from 22–44 years. There was no statistically significant difference between ages of the two groups [$t(38)=1.78$; $p=0.08$]. Their concussion/ mTBI was caused by either a sports-related injury ($n=13$), motor vehicle accident ($n=2$), war trauma ($n=1$) or other traumatic events ($n=3$). The head trauma occurred within a time period of 1–10 years (mean= 4.97 years) prior to VEP testing, with one exception (i.e. 3 days post-trauma) and, thus, they were past the natural recovery period of 6–9 months post-injury [46]. 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) posttraumatic amnesia (PTA) lasting less than 24 hours and (3) Glasgow Coma Scale score of 13–15. This was determined per their medical records and/or self-reported history. All subjects had corrected visual acuity of 20/20 or better both binocularly and monocularly at distance and near, with normal contrast sensitivity [45]. Mean refractive error was -2.50 D, with a range from plano to -5.50 D. Mean astigmatism was -1.50 D. Subjects with a history of seizures, cognitive dysfunction, strabismus, amblyopia, ocular or systemic disease and/or any degenerative neurological disease were excluded (see Table I).

The study was approved by the IRB at the SUNY College of Optometry. Written informed consent was obtained from each subject prior to commencement of the experiment.

Apparatus

VEP system—The DIOPSYSTTM NOVA–TR VEP system (Diopsys, Inc., Pine Brook, NJ) was used to present a black-and-white, alternating, checkerboard pattern stimulus. This system also recorded and analysed the VEP signals obtained from the three Grass gold cup scalp electrodes (Grass Technologies, Astro-Med, Inc., West Warwick, RI), which were 1cm in diameter and consisted of a ground, a reference and an active electrode. This system has been used in the brain injury laboratory for over 3 years for several experiments [21].

Neutral density (ND) filters and viewing spectacles—Five different neutral density (ND) filters were used: 0.5, 1.0, 1.5, 2.0 and 2.5 (see Table II). Their diameter was 25.4mm. Each glass ND filter was coated with an Inconel[®] metallic coating, which provided spectrally-uniform attenuation over the wavelength range from 400–2000nm (Newport Corporations, Irvine, CA). To fabricate the ND test spectacles (Figure 1), each ND filter was placed into a black spectacle frame and glued to the front of the plano power carrier lens. The remaining plano power lens carrier portion surrounding the neutral density filter was painted black to prevent peripheral stray light from the surrounding area from entering the eye. Separate test spectacles were fabricated for each ND value.

Stimulus

The standard central-field ($17^{\circ} \text{H} \times 15^{\circ} \text{V}$), black-and-white, checkerboard pattern (64×64 , equivalent to 20 min arc) alternated at a temporal frequency of 1Hz (two reversals per second). The Michelson contrast was 85%. The stimulus was viewed binocularly with both the full refractive correction and the ND test spectacles in place at a viewing distance of 1 metre. All testing was performed binocularly, as the VEP increased by up to 27% in visually-normal individuals, as compared to monocularly, due to binocular summation effects [19, 20]. This enhanced amplitude would allow for better discrimination of more subtle effects between the two diagnostic groups. In addition, all testing was performed with full refractive correction in place to optimize the quality of the retinal image and, hence, the VEP amplitude [19, 20]. The baseline stimulus luminance was 74cdm^{-2} . Test duration was 20 seconds per trial [37].

Procedures

Electrode placement—The active electrode was placed at the Oz position, 2.5cm above the inion. The reference electrode was placed at the Fz position, ~10% of the distance from the nasion to the inion. Finally, the ground electrode was placed at the Fp2 position on the right side of the forehead. These electrode placements were slightly modified from international standards [27] to reduce preparation time in the clinical population, per the manufacturer's instructions. Procedures for electrode preparation have been previously explained in Yadav and Ciuffreda [19].

Instructions—Each subject was instructed to sit comfortably and steadily with their head placed in an adjustable floor-mounted, headrest/chinrest assembly positioned 1 metre from

the test screen and centred along the midline at eye level. Prior to commencing the experiment, each subject was instructed to fixate and focus on a small (0.5° diameter), red, rotating circle that was in the centre of the test screen to control accuracy of fixation and accommodation, as well as maintain visual attention, which is part of the manufacturer's software. Subjects were instructed to blink approximately every 5 seconds to prevent the occurrence of dry eye and uncontrolled blinking, as well as to reduce the number of artifacts registered by the system. Any trial with greater than five artifacts was discarded [19]. Throughout each trial, subjects were reminded to fixate and focus on the centre of the red circle. Furthermore, they were informed when the trial was half completed and when there was 5 seconds left, to maintain their attention and alertness [48].

Trials—Five trials were conducted for each test condition. Based on the findings of Froehlich and Kaufan [42], there was no need to repeat the baseline measurement at the end of the entire test period, since a decremental response did not occur as a result of the length of the test or the test conditions. The first condition for each subject was their baseline, in which no ND filter was in place. These baseline trials were assessed for normalcy of response prior to any further testing; all subjects produced responses which were within normal limits for the laboratory [19, 37]. Then, the ND filters were introduced in a counterbalanced manner to prevent any order effect (e.g. progressive light adaptation effect) over the range of the specified transmittance levels (Table II).

Data analysis

The VEP amplitude and P100 latency were recorded for each of the six test conditions (0.0–2.5 ND, in 0.5 steps) for each subject. For each condition, the trial value that either exceeded 1 SD from the mean of the five trials or was the most deviant one was deleted for that subject to control for outlier effects [19, 49]. Both the mean and standard deviation of the four remaining trials within each test condition for each subject were stored. The mean amplitude and latency values were calculated for each subject and then the group average was determined. The group mean values ± 1 SEM were analysed and graphically displayed for each parameter as a function of ND filter value. Each response profile was initially fitted with both a linear and an exponential function and the fit having the highest r^2 value was used to describe the data, i.e. the linear regression in all cases. A p -value of 0.05 was considered to be statistically significant.

A one-way, ANOVA statistical analysis was performed using GraphPad Prism, version 5 software for each group's data for the factor of luminance. This was done to determine the optimal luminance level that resulted in the least amount of variability, but with normal latency, to optimize the VEP response.

In addition, a two-way, repeated-measures ANOVA was performed using STATISTICA, version 7 software, between the two groups for the factors of luminance and diagnostic group. This was done to determine at which luminance level a significant *difference* in amplitude and/or latency might be present between the two groups.

Lastly, repeatability was assessed in three subjects within each group. The same test conditions were repeated for each trial 4–59 weeks after the initial test session. The

coefficient of variation (CV=standard deviation/mean) was calculated to determine repeatability of the VEP response [21]. The CV can range from 0.00–1.00 [50]. This value represents the intra-subject variability, with a smaller value indicating better repeatability.

Results

Amplitude

VN—The group mean amplitude for the VN subjects is presented in Figure 2(a). A one-way ANOVA was performed on the group mean for the factor of luminance. There was a significant effect of luminance on the VEP amplitude [$F(1,5)=8.32$; $p=0.0001$], with it decreasing as luminance decreased. A post-hoc Fisher LSD test was performed, and the results revealed several relevant and significant comparisons (Appendix Table A1). In addition, linear regression analysis was performed between the ND filter values and the related mean VEP amplitude values ($Y=-5.69X+28.84$). There was a significant, negative correlation ($p=0.0130$; $r=-0.905$).

The group mean amplitude variability for the VN subjects is presented in Figure 2(b). A one-way ANOVA was performed on the group mean for the factor of luminance. There was no significant effect of luminance on VEP amplitude variability [$F(1,5)=0.59$; $p=0.71$].

mTBI—The group mean amplitude for those with mTBI is presented in Figure 2(a). A one-way ANOVA was performed on the group mean for the factor of luminance. There was a significant effect of luminance on the VEP amplitude [$F(1,5)=12.27$; $p=0.0001$], with it decreasing as luminance decreased. A post-hoc Fisher LSD test was performed and the results revealed several relevant and significant comparisons (Appendix Table A2). In addition, linear regression analysis was performed between the ND filter values and the related mean VEP amplitude values ($Y=-4.64X+22.91$). There was a significant, negative correlation ($p=0.0134$; $r=-0.910$). All mean values were below (i.e. lower) than for the VN cohort (binominal test, $p<0.05$).

The group mean amplitude variability for individuals with mTBI is presented in Figure 2(b). A one-way ANOVA was performed on the group mean for the factor of luminance. There was a significant effect of luminance on VEP amplitude variability [$F(1,5)=2.33$; $p=0.047$], with it first increasing and then decreasing as luminance decreased. The post-hoc Fisher LSD test results showed several significant comparisons (Appendix Table A3).

VN vs. mTBI—A two-way, repeated-measures ANOVA was performed on the group means for the factors of diagnostic group and luminance level. There was a significant effect of both diagnostic group [$F(1,1)=15.49$; $p<0.0001$] and luminance level [$F(1,5)=18.33$, $p<0.0001$] on the VEP amplitude, with it increasing as luminance decreased and, furthermore, with it decreasing to a greater extent in those with mTBI than in VN. The post-hoc Fisher LSD test results showed several significant comparisons (Appendix Table A4).

A two-way, repeated-measures ANOVA was also performed on the group mean amplitude variability for the factors of luminance and diagnostic group. There was no significant effect of luminance on VEP amplitude variability [$F(1,5)=1.62$; $p=0.16$]. However, there was a

significant effect of diagnostic group on VEP amplitude variability [$F(1,1)=5.43$; $p=0.021$], with it decreasing as luminance decreases and with it initially increasing and then decreasing to a greater extent in those with mTBI than in the VN individuals. The post-hoc Fisher LSD test results showed several significant comparisons (Appendix Table A5).

Latency

VN—The group mean P100 latency values for the VN subjects are presented in Figure 3(a). A one-way ANOVA was performed on the group mean for the factor of luminance. There was a significant effect of luminance on VEP latency [$F(1,5)=187.7$; $p=0.0001$], with it progressively increasing as luminance decreased. A post-hoc Fisher LSD test revealed significant comparisons between all conditions (table not included). In addition, linear regression analysis was performed between the ND filter values and the related mean VEP latency values ($Y=23.49X+90.20$). There was a significant, positive correlation ($p=0.0007$; $r=+0.98$).

The latency variability for the VN subjects is presented in Figure 3(b). A one-way ANOVA was performed on the group mean for the factor of luminance. There was a significant effect of luminance on VEP latency variability [$F(1,5)=8.83$; $p=0.0001$]. A post-hoc Fisher LSD test was performed and the results revealed a significant comparison at the 2.5 ND filter level only (table not included).

mTBI—The group mean P100 latency values for those with mTBI are represented in Figure 3(a). A one-way ANOVA was performed on the group mean for the factor of luminance. There was a significant effect of luminance on VEP latency [$F(1,5)=76.59$; $p=0.0001$], with it progressively increasing as luminance decreased. A post-hoc Fisher LSD test revealed significant comparisons between *all* conditions (table not included). In addition, linear regression analysis was performed between the ND filter values and the related mean VEP latency values ($Y=25.44X+90.57$). There was a significant, positive correlation ($p=0.0006$; $r=+0.98$).

The latency variability for those with mTBI is presented in Figure 3(b). A one-way ANOVA was performed on the group mean for the factor of luminance. There was a significant effect of luminance on VEP latency variability [$F(1,5)=2.67$; $p=0.026$]. A post-hoc Fisher LSD test was performed and the results revealed a significant comparison at the 2.5 ND filter level only (table not included).

VN vs. mTBI—A two-way, repeated-measures ANOVA was performed on the group means for the factors of luminance and diagnostic group. There was a significant effect of diagnostic group [$F(1,1)=7.58$; $p<0.01$] and luminance level [$F(1, 5)=213.68$; $p<0.0001$] on VEP latency. The post-hoc Fisher LSD test results showed significant comparisons at *all* levels (table not included).

A two-way, repeated-measures ANOVA was performed on the group means for the factors of luminance and diagnostic group on latency variability. There was a significant effect of diagnostic group [$F(1,1)=14.77$; $p<0.001$] and luminance level [$F(1,5)=6.61$; $p<0.0001$] on VEP amplitude variability, with it increasing as luminance decreased and, furthermore, with

it increasing to a greater extent in those with mTBI than in the VN individuals. The post-hoc Fisher LSD test results showed several significant comparisons (Appendix Table A6).

Repeatability

Three visually-normal and three individuals with mTBI were re-tested under the same test conditions to assess repeatability, an average 40.6 weeks (range=4–59 weeks) after their initial testing. The coefficient of variation (CV) was calculated for each subject (Table III). The low values (ranging from 0–0.305) suggest excellent repeatability.

Discussion

The purpose of the present investigation was to assess the effect of luminance on VEP amplitude and latency, with a goal toward optimization of this critical stimulus parameter to develop and propose a comprehensive VEP protocol, specifically for use in *both* the concussion/mTBI and VN populations. VN subjects were first tested to obtain normative data that could then be used for comparative purposes in those with mTBI. While VEP studies on luminance have been conducted in the VN population [42–44], the results have been equivocal and, furthermore, none have been conducted in the mTBI population.

The data obtained from the VN group showed an average latency increase of ~63 milliseconds between the baseline luminance and that found with the 2.5 ND filter, a 38% increase. This finding is consistent with previous studies, for example, which showed that, by decreasing luminance by a factor of 10 (equal to ND=1.0), mean latency of the P100 increased by 10–15 milliseconds [51–54]. Even at the lowest luminance level, VEP response modulation was still present and, thus, there was no evidence of either saturation or a ‘noise’ limiting phenomenon.

With regard to the effect of luminance on VEP amplitude in the VN group, the previous results were equivocal, as mentioned earlier. While some researchers, such as Markó et al. [43], found that the VEP amplitude was independent of luminance, others found that it was not. For example, a 15% decrease in amplitude with a 10-fold decrease in luminance (ND filter=1.0) was found by Halliday et al. [52]. The results of the present investigation are consistent with Halliday et al.’s [52] general findings. An average decrease of ~15 μV in VEP amplitude from the baseline (ND=0.0) condition (22.01 μV) to the ND filter=2.5 condition (7.8 μV), a 65% decrease, was found in the VN population, which is considerable.

Similarly, a decrease in VEP amplitude was found with reduction of luminance in the mTBI group. It went from 18.45 μV to 6.03 μV , a 67% decrease, with the 2.5 ND filter as compared with baseline.

Lastly, in the mTBI group, an increase in latency was found with decreased luminance. It increased by 67 milliseconds, a 61% increase, with the 2.5 ND filter as compared with baseline. This is consistent with previous studies in VN individuals, as described earlier.

Latency mechanism

Latency in both groups exhibited a consistent and progressive increase as luminance decreased, as mentioned above. An increase in latency has been shown to be associated with an increase of overall neuronal processing time [41, 55–57]. This can be attributed to the fact that ND filters decrease stimulus intensity (i.e. luminance) and, therefore, global retino-cortical stimulation and its responsivity are reduced [57, 58]. Changes in luminance affect the neuronal discharge latency [59, 60] and, therefore, the increase in VEP latency found in the present study may be attributed to a delay in general/overall neurosensory processing [41].

The specific neural site for this delay has been debated by many. Di Russo et al. [61] concluded that the P100 latency was generated at the level of the striate (V1) and extrastriate cortical (V2, V3 and V4) neural generators and, therefore, it was the location of the neural delay. Yet others, such as Saint-Amour et al. [62], speculated that the P100 latency was generated in a top-down processing mode from the frontal and parietal lobes to the cerebral cortex and extra-striate cortical areas, including V1, thus suggesting a more complex and multi-level phenomenon. Further research is needed in this important area to delineate the potential neural sites and pathways.

Amplitude mechanism

Amplitude of the VEP signal reflects the magnitude of the global neuronal response [63, 64]. The VEP amplitude and its variability exhibited differential effects with change in luminance in the VN group. It reduced with decrease in luminance, whereas the VEP amplitude variability exhibited relatively little change. With respect to the small changes in response variability, this may be related to the fact that spike generation *in vivo* contributes to response variability, where neuronal membrane potential and conductance are continuously changing. This disequilibrium is a natural feature of neurons, since each neuron displays a unique threshold and membrane potential, which could explain the ever present and continuously changing variability [65].

Likewise, the VEP amplitude and its variability showed differential effects with change in luminance in the mTBI group. The VEP amplitude exhibited little change with addition of the initial ND filter. In fact, it was not until addition of the 2.5 ND filter that a statistically significant decrease in amplitude was evident ($p<0.001$). In contrast, the amplitude variability was not significantly different between any of the trials, but, when compared to the visually-normal group, it was significantly larger ($p<0.05$).

The following mechanism may explain the amplitude findings in both groups. A commonly established feature of sensory cells that transmit to the visual cortex is that of a 'generator potential'. If the threshold for an individual neuron is exceeded, a neuronal discharge, i.e. action potential, occurs [66]. Action potential threshold is correlated with the rate of change of the membrane potential preceding a spike [65] and a primary function of neurons is the processing and transformation of these incoming action potentials into specific patterns of synaptic output [67]. There are two main factors that contribute to such synaptic processing: temporal summation and spatial summation [67]. Branco and Häusser [67] showed that

neuronal discharge recorded from individual pyramidal cells in the cortex increased in magnitude and duration as a result of an increase in number of action potentials received by the cell. This increase in response magnitude was accounted for by the temporal and spatial summation of the synaptic input exhibited by the cell [68]. Conversely, by decreasing the neuronal discharge, for example by decreasing stimulus luminance, there would be a decrease in both the temporal and spatial summation of the corresponding action potentials in the cortical neurons. These findings may provide the mechanism for a decrease in VEP amplitude with decreased luminance.

Optimization

VN—Previously, the laboratory optimized the VEP parameters of contrast, check size and test duration in both the VN and mTBI populations [21, 37]. With the current data, a fourth critical stimulus parameter, namely luminance, has now been optimized, with it producing the *largest* VEP amplitude in conjunction with a *normal* latency. To optimize the VEP protocol for the VN population, the magnitude of the VEP amplitude, latency and their related variabilities were assessed. In the VN subjects, baseline measurements (i.e. 0.0 ND filter) resulted in both the largest VEP amplitude response with corresponding normal latency values (~100 milliseconds) [69], along with the least variability. Therefore, the baseline luminance condition with ND=0 (i.e. 74cdm^{-2}) is optimal in the VN population, as used in conjunction with the other three optimized parameters [21, 36, 37].

mTBI—To optimize the VEP response in those with mTBI, the 0.5 ND filter (i.e. 32cd/m^{-2}) produced both the largest VEP amplitude and reduced variability. However, with regard to VEP latency, the 1.0 ND (7.4cdm^{-2}) resulted in the least amount of variability, but it also produced mean latency values exceeding normal limits (i.e. 120 milliseconds), which produces a dilemma to test the mTBI population optimally using a *single* ND filter.

While the individual parameters stated above may be used to optimize VEP responsivity for each VEP parameter individually, for simplicity and ease of application in a clinical setting, the 0.5 ND can be used to determine the optimal VEP response for both latency and amplitude in both the VN population and in those with mTBI, given that differences in baseline VEP values for ND=0.0 and ND=0.5 were not statistically significant for any parameters. Thus, if a 0.5 ND filter is not available, measurement with an ND=0 filter (i.e. no filter) can provide an adequate response that would also function to approximate response optimization with respect to both amplitude and latency in both diagnostic groups.

Differentiating VN from mTBI

To discriminate *between* the two groups, in conjunction with the other optimized VEP stimulus parameters, the 2.5 ND filter findings showed large and significant differences in both mean latency and its variability between the two groups in several individuals. Furthermore, with the 2.5 ND, a similar effect was found between *each* group's amplitude and corresponding amplitude variability. The importance of this point will be considered later.

While there was a consistent effect between relative amplitude and luminance level, this VEP parameter of amplitude was *not* clinically ideal for differentiating VN from mTBI. Mean amplitude variability was high between subjects in the present study in the VN group, as might be expected in any population-based investigation, with normal baseline amplitude values ranging from 10–60 microvolts. This large variation has been attributed to the fact that neurons have different voltage and time dependent properties as a result of unique sodium channel activation and inactivation thresholds found within individual neurons [70]. Action potential thresholds and transduction rates vary according to the rate of change of the membrane potential preceding the spike and size of the axon; therefore, both spike generation and conduction speed contribute to the response variability found in each trial. Furthermore, there is an effect of gender. Females have larger VEP amplitudes than males, on average, due to females having a thinner cranium [71]. This allows more of the small microvoltage changes to reach the outer cranium and VEP electrode. General amplitude variation has been observed in a number of population-based studies [72, 73], thus making differentiation based on this parameter between the VN from those with mTBI problematic.

However, the findings in the present study showed that, at a given luminance level, mean *latency* had a relatively narrow distribution across subjects within their respective groups, i.e. VN or mTBI, at a given luminance level and, furthermore, it exhibited similar values to those found by others [60, 64]. This consistency was attributed to the fact that the visually-evoked neuronal firing rates and spike latencies were found to be only weakly correlated with visually-evoked fluctuations in membrane potential. Therefore, differences in latency found with the 2.5 ND between the VN and mTBI groups can be attributed to the neurological differences, specifically at the cerebral cortex and extra-striate cortical levels, as explained earlier.

Lastly, and related to the above, the effect of luminance may be an indicator, or potential *objective biomarker*, for concussion/mTBI. Using an optimal luminance level while performing a VEP, along with the aforementioned optimal parameters (i.e. check size, contrast and test duration) could assist in the more accurate and/or early diagnosis of those with either suspected or likely concussion/mild traumatic brain injury. Such testing would allow for earlier treatment, as well as direct objective monitoring of visual rehabilitation effects, using the VEP [21, 74], in conjunction with other conventional clinical testing (e.g. near point of convergence) [75, 76]. Furthermore, due to the excellent repeatability of the VEP as demonstrated here and elsewhere [27], an optimal luminance level may be used to establish baseline measurements *prior* to deployment or sport seasons, so that subsequent tests can then be compared to when a concussion is suspected.

Related to the above, previous studies, such as those conducted by Lachapelle et al. [77] and Gaetz and Weinberg [76], found that 13% of those with mTBI exhibited a delayed latency with respect to the upper limit found in the VN population and, furthermore, that 30% of those with mTBI exhibited a latency increase greater than 2.5 SD when compared to the visually-normal cohort, respectively. This is consistent with the 30% predictability found in the present study with use of the 2.5 ND filter.

Additional clinical implications

From the latency data described earlier, it is possible to use VEP as an adjunct test to objectively and differentially diagnose mTBI from the visually-normal population with the use of a single ND filter (i.e. 2.5 ND filter), with 30% predictability on the basis of latency alone. With this ND filter, there is a large, consistent and significant difference in latency for this target parameter between the two populations.

Proposed protocol

Based on the results from the present study, in combination with the findings by this laboratory in previous studies [21, 36], it is proposed that the following protocol be used clinically to *optimize*, VEP responsivity, in *both* the visuallynormal and mTBI populations, as well as to *differentiate* between the two populations in some patients:

- *Check size*: 20min arc.
- *Contrast*: high contrast (85%).
- *Luminance*: For optimization: 74cdm^{-2} (ND=0); For possible differentiation: 0.222cdm^{-2} (ND=2.5).
- *Trial duration*: 20 seconds.
- *Number of trials*: five trials, with the outlier being removed, and then the mean of the remaining four trials used and considered to be representative of the individual's overall VEP response.

The proposed protocol should help clinicians by reducing VEP test time, yet provide optimal and reliable VEP results. The above protocol will also help prevent patient fatigue and reduce response variability, while yielding maximum VEP amplitude and latency, thus improving VEP repeatability, in an individual subject/patient and in the differential diagnosis, as well as in monitoring of clinical conditions such as mTBI.

Study limitations

There were two limitations to the present study. First, subjects with either moderate or severe head injury were not tested. Such testing would provide additional insight into the mTBI neurophysiological process and related traumatic brain dysfunction. These individuals will likely exhibit a greater difference in terms of latency, when compared to both the VN and mTBI populations. This information may also be helpful in terms of their prognosis. Second, the age range of the population tested was relatively narrow (22–44 years). This should be expanded considerably to assess generality of the present findings with both higher and lower age ranges.

Conclusions

From the present study, it was found that decreasing luminance of a stimulus influences the pattern VEP response in a consistent way by increasing latency and eventually decreasing amplitude, in both the visually-normal adult population and in those adults with mTBI, with the effects being greater in the mTBI group. The increase in latency and decrease in

amplitude in both groups under the lower luminance levels reflected the underlying physiological neuronal firing rate, with less firing frequency, at the lower intensities. The increase in latency with reduced luminance was found to a greater extent in those with mTBI. This latency increase, in addition to the increase in response variability, may reflect neuro-cortical deficits [78, 79], with the resultant increase in neural noise due to structural disconnectivity [80], that are more prevalent in this population, likely in the magnocellular pathway. Furthermore, latency could be an indicator or *objective biomarker* for concussion/mTBI. That is, based on the present study's findings, it may even be possible to differentiate reliably between VN individuals and those with mTBI using specific test conditions/parameters.

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Appendix

Table A1.

Post-hoc comparisons in the VN group for amplitude.

	0.0	0.5	1.0	1.5	2.0	2.5
0.0					X	X
0.5					X	X
1.0						X
1.5						X
2.0	X	X				X
2.5	X	X	X	X	X	

X's signify ND filter comparisons that were significantly different ($p < 0.05$).

Table A2.

Post-hoc comparisons in the mTBI group for amplitude.

	0.0	0.5	1.0	1.5	2.0	2.5
0.0					X	X
0.5				X	X	X
1.0					X	X
1.5		X				X
2.0	X	X	X			X
2.5	X	X	X	X	X	

X's signify ND filter comparisons that were significantly different ($p < 0.05$).

Table A3.

Post-hoc comparisons in the mTBI group for amplitude variability.

	0.0	0.5	1.0	1.5	2.0	2.5
0.0						
0.5						
1.0						
1.5					X	
2.0					X	
2.5			X	X		

X's signify ND filter comparisons that were significantly different ($p < 0.05$).

Table A4.

Post-hoc comparisons between the VN group and the mTBI group for amplitude.

VN	mTBI					
	0 ND	0.5 ND	1.0 ND	1.5 ND	2.0 ND	2.5 ND
0 ND	X	X	X	X	X	X
0.5 ND	X	X	X	X	X	X
1.0 ND					X	X
1.5 ND					X	X
2.0 ND						X
2.5 ND	X	X	X	X	X	

X's signify ND filter comparisons that were significantly different ($p < 0.05$).

Table A5.

Post-hoc comparisons between the VN group and the mTBI group for amplitude variability.

VN	mTBI					
	0 ND	0.5 ND	1.0 ND	1.5 ND	2.0 ND	2.5 ND
0 ND						
0.5 ND			X			
1.0 ND			X	X		
1.5 ND			X			
2.0 ND			X			
2.5 ND			X	X		

X's signify ND filter comparisons that were significantly different ($p < 0.05$).

Table A6.

Post-hoc comparisons between the VN group and the mTBI group for latency variability.

VN	mTBI					
	0ND	0.5 ND	1.0 ND	1.5 ND	2.0 ND	2.5 ND

VN	mTBI					
	0ND	0.5 ND	1.0 ND	1.5 ND	2.0 ND	2.5 ND
0 ND				X	X	X
0.5 ND					X	X
1.0 ND				X	X	X
1.5 ND					X	X
2.0 ND					X	X
2.5 ND		X	X			

X's signify ND filter comparisons that were significantly different ($p < 0.05$).

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Figure 1.
Test spectacles with neutral density filters attached and the surrounding plano carrier lens area blackened out.

Figure 2.

(a) Visually-normal group vs. mTBI group mean amplitude with change in ND/luminance. Plotted is the mean $\pm$ 1 SEM. (b) Visually-normal and mTBI mean amplitude variability with change in ND/luminance.

Figure 3.

(a) Visually-normal group vs. mTBI group mean latency with change in ND/luminance. Plotted is the mean ± 1 SEM. (b) Visually-normal and mTBI mean latency variability with change in ND/luminance. Error bars are smaller than symbol size.

Table I.

Demographics of individuals having mTBI.

Subject number/Age (years)/Gender	Years since first injury	Type of injury: MVA/ Sports/Fall	General/Visual symptoms
TBI 1/36/F	20	Sports	<ul style="list-style-type: none"> – nauseous for 30 minutes – headache for 24 hours – saw 'stars' at injury – felt like she was moving at time of injury – LOC for 5 minutes – motion sensitive – reading comprehension problems – photosensitivity
TBI 2/28/M	1	Sports	<ul style="list-style-type: none"> – photosensitivity – slow visual processing – slow written/verbal responses
TBI 3/23/F	6	Sports/snowboarding	<ul style="list-style-type: none"> – LOC 10 minutes – ASOC 1 hour – HA for 1 day
TBI 4/24/F	2	Sports/snowboarding	<ul style="list-style-type: none"> – nauseous for 2 hours – boat and plane sickness
TBI 5/44/M	8	Explosions	<ul style="list-style-type: none"> – ASOC for 1 minute – motion sickness – unstable walking through stores
TBI 6/23/F	7	Sports	<ul style="list-style-type: none"> – HA for a day – ASOC for 2 hours – reading comprehension difficulties
TBI 7/26/F	3	Snowboarding	<ul style="list-style-type: none"> – motion sickness in car
TBI 8/25/F	2	MVA	<ul style="list-style-type: none"> – HA for 3 months – photosensitivity – reading difficulties
TBI 9/25/F	7	Sports	<ul style="list-style-type: none"> – ASOC for 24 hours – feels uncomfortable in crowds – vertigo for a few months – feels uncomfortable laying down (supine) and leaning backwards – difficulty focusing while reading
TBI 10/29/F	12	Sports	<ul style="list-style-type: none"> – ASOC for 30 minutes – nauseous for 8–10 hours after initial injury
TBI 11/23/F	2	Sports	<ul style="list-style-type: none"> – ASOC for 30 minutes – HA for 1 week
TBI 12/22/M	2	Sports	<ul style="list-style-type: none"> – dizzy for 1 week – nausea for 24 hours – blurry VA for 1 week
TBI 14/23/F	0.5	'Hit head at a bar'	<ul style="list-style-type: none"> – ASOC for 45 minutes – nausea for 4–6 hours – HA
TBI 15/28/F	3	Fainted due to a gall bladder attack	<ul style="list-style-type: none"> – ASOC for 10 minutes – external bleeding of cranium – transient visual motion sensitivity immediately after episode
TBI 16/26/M	3	Assaulted	<ul style="list-style-type: none"> – LOC; woke up in hospital – HA 1 week – memory impaired 1 week following injury
TBI 17/24/F	5	Fell off bunk bed	<ul style="list-style-type: none"> – LOC for a few seconds – transient decreased VA immediately thereafter – HA, light flashes for 24 hours
TBI 18/25/M	6	Sports	<ul style="list-style-type: none"> – photosensitivity – visual motion sensitivity – LOC for a few seconds – ASOC for 1 week

Subject number/Age (years)/Gender	Years since first injury	Type of injury: MVA/ Sports/Fall	General/Visual symptoms
TBI 19/23/F	3 days	Hit the back of head on a bar table and then the ground	<ul style="list-style-type: none">– HA for 2 weeks– HA since injury– photosensitivity– visual motion sensitivity– ASOC 4–6 hours– nausea

LOC, Loss of consciousness; ASOC, Altered state of consciousness; HA, Headache; MVA, Motor vehicle accident; VA, Visual acuity.

Table II.

Each neutral density (ND) filter and its corresponding transmittance, effective stimulus luminance and contrast.

ND filter	Transmittance	Effective luminance	Contrast
Baseline 0.0	100%	74 cdm ⁻²	85%
0.5	50%	37 cdm ⁻²	85%
1.0	10%	7.4 cdm ⁻²	85%
1.5	3%	2.22 cdm ⁻²	85%
2.0	0.8%	0.592 cdm ⁻²	85%
2.5	0.3%	0.222 cdm ⁻²	85%

Table III.

Coefficient of variation (CV).

	Subject #	AMP	P100
mTBI	#3	0.305	0.026
	#11	0.305	0.026
	#19	0.057	0.009
VN	#3	0.0015	0
	#6	0.14	0.014
	#15	0.116	0.0009