1040-5488/17/9407-0000/0 VOL. 94, NO. 7, PP. 00–00
OPTOMETRY AND VISION SCIENCE

ORIGINAL ARTICLE

OPEN

Visually Evoked Potential Markers of Concussion History in Patients with Convergence Insufficiency

Dmitri Poltavski*, Paul Lederer†, and Laurie Kopko Cox‡

ABSTRACT

Purpose. We investigated whether differences in the pattern visual evoked potentials exist between patients with convergence insufficiency and those with convergence insufficiency and a history of concussion using stimuli designed to differentiate between magnocellular (transient) and parvocellular (sustained) neural pathways.

Methods. Sustained stimuli included 2-rev/s, 85% contrast checkerboard patterns of 1- and 2-degree check sizes, whereas transient stimuli comprised 4-rev/s, 10% contrast vertical sinusoidal gratings with column width of 0.25 and 0.50 cycles/degree. We tested two models: an a priori clinical model based on an assumption of at least a minimal (beyond instrumentation's margin of error) 2-millisecond lag of transient response latencies behind sustained response latencies in concussed patients and a statistical model derived from the sample data.

Results. Both models discriminated between concussed and nonconcussed groups significantly above chance (with 76% and 86% accuracy, respectively). In the statistical model, patients with mean vertical sinusoidal grating response latencies greater than 119 milliseconds to 0.25-cycle/degree stimuli (or mean vertical sinusoidal latencies >113 milliseconds to 0.50-cycle/degree stimuli) and mean vertical sinusoidal grating amplitudes of less than 14.75 mV to 0.50-cycle/degree stimuli were classified as having had a history of concussion. The resultant receiver operating characteristic curve for this model had excellent discrimination between the concussed and nonconcussed (area under the curve = 0.857; $P < .01$) groups with sensitivity of 0.92 and specificity of 0.80.

Conclusions. The results suggest a promising electrophysiological approach to identifying individuals with convergence insufficiency and a history of concussion.

(Optom Vis Sci 2017;94:00–00)

Key Words: concussion, convergence insufficiency, magnocellular pathway, VEP

Traumatic brain injury is a serious public health problem in the United States contributing to significant annual mortality and disability. Concussions represent a subset of mild traumatic brain injury on the less severe end of the brain injury spectrum and account for anywhere between 75% and 86% of all traumatic brain injury cases.[1] Until normal brain cellular function is restored, animal and human studies suggest increased postconcussive vulnerability, showing that a repeat brain injury before complete recovery aggravates cellular metabolic changes and results in more significant cognitive deficits.[2,3] Several authors have also reported that the incidence of concussion especially among athletes including children and adolescents may be significantly underestimated, because many athletes failed to report concussions.[4–6]

Individuals with mild traumatic brain injury may present a constellation of visual symptoms that may include oculomotor and accommodative dysfunctions, binocular vision deficits, visual field loss/reduced sensitivity, visual memory deficits, visual attentional problems, vestibular impairment, spatial localization errors, perceptual deficits and visual information processing problems, and visuomotor coordination impairment.[7] A number of studies also suggest that vergence system abnormalities are the most common dysfunction observed in mild traumatic brain injury, with the majority of cases exhibiting convergence insufficiency.[8]

Moreover, unlike the gradual course of recovery seen in certain other types of neuropsychological dysfunction, the oculomotor deficits observed in concussed patients do not appear to resolve on their own.[9,10] On the other hand, administration of oculomotor-based

*PhD
†OD, FAAO
‡MSEE

Department of Psychology, University of North Dakota, Grand Forks, North Dakota (DP); Private Practice, Arlington Heights, Illinois (PL); and Diopsys, Inc., Pine Brook, New Jersey (LKC).

vision therapy has been reported to significantly improve mild traumatic brain injury-related oculomotor deficits.[11]

Nonetheless, a question remains whether there are subtle visual pathway differences between patients with oculomotor deficits and a history of mild traumatic brain injury and those whose similar oculomotor deficits are not associated with previous mild traumatic brain injury history. If such differences between the populations exist, the effectiveness of vision therapy administration may further vary between the two groups of patients. The mild traumatic brain injury group may potentially need special therapeutic adjustments to maximize visual rehabilitation. For example, patients with a history of mild traumatic brain injury often exhibit sensory-gating deficits,[12] increased visual sensitivity to motion, photosensitivity, and photophobia.[13,14] Vision therapy with such patients may include additional use of fusional prism spectacles (for diplopia), tinted spectacles (for photosensitivity), and yoked prism spectacles (for visual-spatial hemispheric inattention with or without a manifest visual field defect).[14]

One promising approach to identification of individuals with a history of mild traumatic brain injury involves examination of P100 wave characteristics of visually evoked potentials. Possible magnocellular deficits have been reported for individuals with a history of mild traumatic brain injury compared with visually normal control subjects based on their P100 visually evoked potential responses to a high-contrast (85%) checkerboard stimulus (1.49-cycle/degree check size) at a very low luminance level (0.3% transmittance; greater P100 latency and smaller amplitude),[15] as well as to low-contrast (20%) checkerboard stimuli of varying sizes (smaller P100 amplitude).[16] Observation of magnocellular deficits in mild traumatic brain injury is also consistent with the results of several non–visually evoked potential studies, which found an elevated coherent motion threshold,[17] increased visual motion sensitivity,[18] and elevated and increased critical flicker frequency threshold values.[19,20]

Single-cell studies in primates showed that the magnocellular pathway is more sensitive to low-contrast stimuli at high temporal and low spatial frequencies than the parvocellular pathway, which is relatively more sensitive to higher-contrast stimuli with low temporal and high spatial frequencies.[21,22] In addition, while parvocellular neurons at the level of the lateral geniculate nucleus of the thalamus preferentially respond to medium to high contrast and do not saturate, magnocellular responses have been reported to either saturate with high contrast[21,23] or show slowing gain with higher contrast.[24] This corresponds well with the suggestion that the magnocellular pathway (transient channel) performs best for motion and localization of objects in space and primarily contributes to the dorsal ''where'' stream that starts in the primary visual cortex and terminates in the parietal lobe and specializes in visual guidance of behavior and motion perception.[25] At the same time, the parvocellular pathway (sustained channel) is optimal for identification of color and fine detail and primarily contributes to the ventral ''what'' visual stream involved with pattern recognition and object identification that begins in the primary visual cortex and terminates in the inferior temporal cortex.[25]

In the present study, we intended to investigate whether differences in the pattern visually evoked potential exist between two study populations: (1) normal patients diagnosed with convergence insufficiency in the course of standard eye examination and (2) patients with a history of concussion diagnosed with convergence insufficiency. We further attempted to differentiate between the magnocellular and parvocellular neural pathways using stimuli that bias the visually evoked potential response in favor of either the transient or the sustained pathway, respectively. Specifically, we manipulated several physical parameters such as the type of visual stimulus (checkerboard vs vertical sinusoidal grating), contrast (85% vs 10%), temporal frequency (2 vs 4 rev/s), and size (0.25 vs 0.50 cycle/degree). This selection was consistent with the types of stimuli and their physical parameters used in previous visually evoked potential reports on patients with mild traumatic brain injury[26] and migraine.[27]

We hypothesized that patients with convergence insufficiency and a history of concussion would primarily show deficits in magnocellular processing on visually evoked potential assessment compared with patients with convergence insufficiency without a history of mild traumatic brain injury, which would be reflected in delayed P100 latencies for vertical sinusoidal gratings.

METHODS

Participants

Patient records for this study were selected from the population of all clinical patients who sought optometric services at a Midwestern clinic between June 2014 and January 2015 and received visually evoked potential evaluation as part of the available diagnostic procedures. All procedures performed in the study were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study after explanation of the nature and possible consequences of the study. Of these 150 patients who were tested, 79 patient profiles were selected based on a diagnosis of convergence insufficiency/binocular dysfunction and included both pediatric (n = 63; mean age, 10.92 years) and adult patients (n = 16; mean age, 35.81 years). Diagnosis of convergence insufficiency and accommodative deficits was established during regular patient visits to the clinic following standard optometric clinical protocols, which included an intake clinical interview about the patient's medical history, biographical information, and present symptoms, as well as an optometric and electrophysiological evaluation using tests of binocular function and visually evoked potential assessment.

Convergence insufficiency is often associated with the presence of asthenopia during convergence and is typically characterized by exophoria that is greater at near than distance, a remote near point of convergence, or decreased positive fusional convergence at near.[28,29] As we showed in our recent study,[30] traditional measures of reduced near point of convergence and decreased positive fusional convergence are not as sensitive to symptoms of convergence insufficiency as associated measures such as the near point of fixation disparity and associated positive fusional convergence. Thus, in the present study, we used the same criteria for diagnosis of convergence insufficiency, which included reduced near point of fixation disparity (≥5-cm break and ≥6-cm recovery) and reduced associated vergence (<16 Δ BO break). Specific symptoms included unusual visual fatigue during near-work tasks

such as reading, slow and inaccurate reading and poor comprehension, loss of focus and concentration, limited visual attention span for critical visual activities at near point, intermittent blurring and double vision, loss of place during sustained near visual tasks, and ocular headaches following sustained near visual tasks, as well as photophobia and motion sickness.

Exclusion criteria included presence of other diagnoses such as strabismus, amblyopia, convergence excess, general neurological delays, or dyslexia. There were 40 male and 39 female patients in the sample. Thirty-five of these patients also reported a history of 1 or more concussions (mean, 1.73; range, 1 to 5 concussions), with the last concussion sustained on average 54.74 months prior to their visually evoked potential evaluation (range, 12 to 360 months). Thirty-one of these patients did not have a history of convergence insufficiency prior to their concussion. The proportion of pediatric patients (<18 years of age) was not significantly different between the two groups (73.5% for the mild traumatic brain injury group and 86.4% for the non–mild traumatic brain injury group, χ^2 = 2.03, P = .25). Similarly, the distribution of men and women between the groups was not statistically significant (45.5% women in the non–mild traumatic brain injury group and 55.9% in the mild traumatic brain injury group, χ^2 = 0.83, P = .36).

Near Point of Convergence

The near point of convergence was measured in accordance with a standard procedure described by Scheiman et al.[31] using a Bernell Accommodative Rule with a single 20/30 target letter. The patient's observed break and recovery values were measured and recorded in centimeters. The procedure was repeated twice for each subject, and average values for break and recovery were then used in the analyses.

Fusional Vergence at Near

Positive fusional vergence and negative fusional vergence at near were measured using a handheld Risley prism in free space with the examiner gradually increasing and decreasing the amount of base-out and base-in prisms, respectively, using the same 20/30 letter target held before the eyes at 40 cm. The break and recovery points were recorded for each prism demand over two successive administrations.

Near Point of Fixation Disparity

The near point of fixation disparity test and its target have been tested and validated in a recent study by Lederer et al.[30] It has been found more sensitive to symptomatic convergence insufficiency than the near point of convergence test.[30] It has also been previously found sensitive to the history of sports-related concussion.[32]

The target used for the testing of the near point of fixation disparity is presented on a silver background, and a 0.70 logMAR reduced Snellen E (20/100 equivalent at 40 cm) lies at the center of the target surrounded by a circle twice the diameter of the Snellen E. At the periphery of the circle are nonius lines: a Polaroid fixation disparity cross. The subject sees the nonius cross dichoptically, with the right eye seeing the top vertical arrow and the right horizontal line and the left eye seeing the bottom vertical arrow and the left horizontal line. The test was administered similarly to the near point of convergence test using the Bernell Accommodative rule. In addition, the subject wore Polaroid vectograph glasses allowing dichoptic viewing of the nonius lines while the Snellen E and the surrounding circle could be binocularly fused. The distance from the nasion, at which nonius lines began to move out of alignment, was recorded as a break point. The target was then moved back to the distance until the nonius lines appeared to be both aligned and clear (recovery point). Each measurement was conducted twice.

Associated Vergence

Associated vergence was measured using the same procedure that was used to measure positive and negative fusional vergence except that the near-point-of-fixation-disparity target was used instead of a single 20/30 letter. The break and recovery measures were recorded twice as the nonius lines began to move out of alignment (break) and back appearing both aligned and clear (recovery), first for divergence and then convergence using BI and BO Risley prisms, respectively.

Visually Evoked Potential

Apparatus and Stimuli

Transient visually evoked potentials were generated using a Diopsys NOVA System (Diopsys, Inc., Pine Brook, New Jersey). The stimuli were presented on an Acer V173 43.18-cm LCD monitor (33.7 × 27 cm) with a refresh rate of 75 Hz.

The stimuli included two checkerboard and two vertical sinusoidal patterns. The checkerboard stimuli were of two sizes: 8 × 8 with 3.38-cm check (2-degree check size) and 16 × 16 with 1.69-cm checks (1-degree check size). Both checkerboard patterns had a Michelson contrast of 85 and mean luminance of 102.22 cd/m^2 and were reversed two times per second (temporal frequency 1 Hz).

The transient pathway stimuli consisted of 0.25- and 0.50-cycle/degree vertical sine wave gratings pattern reversed at a rate of 4 rev/s. Both gratings had a Michelson contrast of 10% and mean luminance of 102 cd/m^2. The 0.25- and 0.50-cycle/degree gratings had a total of four and eight cycles, respectively. Note that the physical width of each half cycle of the 0.25- and 0.50-cycle/degree gratings was equal to the width of the 2- and 1-degree check sizes, respectively.[33]

In all cases, the display was viewed binocularly through natural pupils with optimal refractive correction in place. The viewing distance was set to 1 m, yielding a total display viewing angle of 15.92 degrees. During a recording session, each stimulus pattern was presented three times, with each presentation lasting 20 seconds. The total duration of the stimulus pattern sequence was 240 seconds. The sequence was performed as follows: 2-degree checkerboard 8 (three times); 0.25-cycle/degree vertical sinusoidal grating (three times); 1-degree checkerboard (three times); 0.5-cycle/degree vertical sinusoidal grating (three times).

Analog signals were amplified by a factor of 20,000 (Diopsys Nova Amp; Diopsys, Inc.), bandpass filtered with cutoff frequencies of 0.5 to 100 Hz, and sampled at 1024 Hz for the

checkerboard pattern (512 data points) and 2048 Hz for the vertical sine patterns (1024 data points).

The module automatically measured signal-averaged latency of the exogenous P100 component of the typical N75-P100-N135 complex[34] in response to visual stimulus presentation. This latency represents conduction time between retinal stimulation and excitation of neurons in the primary visual cortex. The module also provided relative amplitude measurements in the form of the difference between the N75 and P100 (delta N75- P100), which is thought to address issues of individual variability attributed to anatomical differences and electrical properties of the testing environment. Visually evoked potential extraction for this system was previously described by Tello et al.[34] and is based on the method developed by Derr et al.[35]

Procedure

During visually evoked potential evaluation, one EEG channel was recorded using Diopsys skin electrodes. The active electrode was placed approximately 4 cm above the inion (Oz location, according to the International 10–20 system), whereas the reference electrode was placed approximately 10 to 11 cm above the nasion (Fz location, according to the International 10–20 system). The left side of the forehead (position Fp1, according to the International 10–20 system) served as ground. In preparation for recording, the skin at each electrode site was scrubbed with Nuprep (D. O. Weaver & Co., Aurora, Colorado) on a cotton-tipped wooden swab. Electrodes were fixed in position with Ten20 conductive paste (D.O. Weaver & Co.) and secured with a small gauze pad with conductive paste applied. Electrode impedance was maintained at less than 10,000 Ω in all cases and was usually less than 5000 Ω.

Each subject was instructed to sit comfortably and steadily approximately 1 m from the test screen and centered along the midline at eye level and blink normally during the procedure. Per the manufacturer's software, a small (0.25-degree radius) red rotating, annular fixation cross target was presented in the center of the test screen to control accuracy of fixation and accommodation, as well as to maintain visual attention. Subjects were instructed to fixate upon the small central target with minimal blinking to reduce any response artifacts. Three 20-second trials were conducted for each stimulus type (checkerboard vs vertical sinusoidal grating) and size (0.25 vs 0.50 cycle/degree).

Statistical Analyses

Our general strategy was to, first, isolate significant predictors of concussion history and then identify specific cutoff values for significant predictors to create a sensitive diagnostic model of concussion. To accomplish the first goal, we ran a series of two-way mixed analyses of variance with group being a between-subject variable and levels of each testing measure constituting a within-subject variable. Those variables, on which the groups significantly differed, were then included into logistic regression analyses using both forward and backward stepwise testing procedures.

For diagnostic modeling, significant variables in the logistic regression analyses were then further evaluated with receiver operating characteristic curves to assess their ability to discriminate between patients with lifetime concussion versus those without any concussion history. To determine the best cutoff values for each significant variable, we first calculated the 25th, 50th, and 75th and 90th percentiles for each measure and then used each of the percentile scores to discriminate between patients with a history of concussion and control patients using area-under-the-curve statistics generated for each receiver operating characteristic curve.[36]

Finally, we directly compared the sensitivity of our statistically derived diagnostic model with the sensitivity of a clinical visually evoked potential model that was based on the general assumption of magnocellular delays in mild traumatic brain injury. If the simple clinical model were at least as accurate as the statistically derived model, preference should be given to a more parsimonious solution. We used the cutoff value of at least a 2-millisecond lag of visually evoked potential responses to transient (VSG) stimuli of both sizes compared with responses to sustained stimuli (checkerboard). The 2-millisecond delay represented a minimal measurable delay of the magnocellular pathway compared with the parvocellular pathway beyond the instrumentation's margin of error (+/−1 millisecond) and was based on the latency of the fastest of the three recorded visually evoked potential responses for each subject, as well as on each subject's average of the three responses (mean).

RESULTS

Mixed Analyses of Variance

Our normality diagnostics revealed significant deviations from normality for most of the oculomotor and visually evoked potential variables, which is fairly common for physiological variables recorded in a clinical sample.[37] Thus, we applied an often recommended Box-Cox transformation[38] to all our skewed data and then ran mixed analyses of variance on these transformed variables.

Mixed analysis of variance did not show significant group × measure interactions for any of the Box-Cox–transformed oculomotor variables of near point of convergence (break and recovery), near point of fixation disparity (break and recovery), fusional vergence at near (break BO, recovery BO, break BI, recovery BI), or associated fusional vergence at near (break BO, recovery BO, break BI, recovery BI). Mean values and SDs for untransformed variables are presented in Table 1.

There was a significant 2 (group) × 4 (stimulus) interaction for Box-Cox–transformed visually evoked potential latencies for the fastest response to checkerboard stimuli and vertical sinusoidal gratings of both sizes ($F_{3,228} = 6.83$, $P < .01$). The fastest response referred to the shortest P100 latency for each subject out of three recorded visually evoked potential responses. The follow-up Dunnett test showed that convergence insufficiency patients with a history of concussion had significantly slower visually evoked potential latencies to both 0.25- and 0.50-cycle/degree vertical sinusoidal gratings compared with the control convergence insufficiency group. There were no significant group differences for checkerboard stimuli of either size (Table 1).

Similarly, there was a significant 2 (group) × 4 (stimulus) interaction for Box-Cox–transformed mean visually evoked potential latencies to checkerboard stimuli and vertical sinusoidal gratings of both sizes ($F_{3,228} = 17.71$, $P < .01$). The mean P100 response latency was calculated for each subject as the average of

TABLE 1.

Raw means, SDs, and Dunnett *t* values for post hoc pairwise comparisons between the control (no history of concussion) and mild traumatic brain injury groups where there was a significant group × measure interaction from a series of two-way analyses of variance conducted on Box-Cox–transformed values for each test

Measures	Lifetime Concussion	No Concussion	Dunnett *t*
Oculomotor			
NPC break, cm	4.17 (2.21)	6.46 (5.83)	N/A
NPC recovery, cm	6.51 (3.02)	9.0 (6.73)	N/A
NPFD break, cm	18.16 (9.55)	19.05 (10.78)	N/A
NPFD recovery, cm	21.68 (8.31)	22.67 (10.12)	N/A
Near regular vergence break BO, Δ	14.32 (8.14)	11.82 (6.82)	N/A
Near regular vergence recovery BO, Δ	11.36 (7.92)	9.26 (6.85)	N/A
Near regular vergence break BI, Δ	13.14 (4.79)	11.97 (5.07)	N/A
Near regular vergence recovery BI, Δ	10.50 (3.88)	9.68 (4.31)	N/A
Near associated vergence break BO, Δ	0.92 (4.14)	2.19 (3.69)	N/A
Near associated vergence recovery BO, Δ	−1.16 (3.36)	−0.26 (3.52	N/A
Near associated vergence break BI, Δ	6.21 (2.38)	7.18 (2.93)	N/A
Near associated vergence recovery BI, Δ	4.25 (2.34)	5.18 (2.82)	N/A
Visually evoked potential latencies, ms			
2-Degree checkerboard fastest	102.54 (7.36)	101.99 (6.93)	−0.67
0.25-Cycle/degree vertical sinusoidal fastest	113.45 (12.43)	104.43 (10.80)	4.48*
1-Degree checkerboard fastest	103.02 (6.75)	102.89 (5.82)	−0.77
0.50-Cycle/degree vertical sinusoidal fastest	107.41 (17.38)	100.74 (10.95)	2.93*
2-Degree checkerboard mean	101.84 (17.18)	105.37 (14.93)	−0.33
0.25-Cycle/degree vertical sinusoidal mean	125.07 (10.94)	110.45 (17.57)	7.80*
1-Degree checkerboard mean	105.90 (6.51)	104.09 (14.05)	−0.33
0.50-Cycle/degree vertical sinusoidal mean	123.17 (20.58)	107.14 (18.24)	5.86*
Amplitudes, μV			
2-Degree checkerboard fastest	21.15 (10.11)	27.65 (12.19)	−4.36*
0.25-Cycle/degree vertical sinusoidal fastest	14.35 (8.38)	17.01 (7.98)	−1.57
1-Degree checkerboard fastest	20.65 (9.89)	27.64 (12.47)	−6.89*
0.50-Cycle/degree vertical sinusoidal fastest	13.93 (9.10)	17.77 (8.93)	−4.39*
2-Degree checkerboard mean	21.28 (10.91)	28.82 (13.70)	−5.56*
0.25-Cycle/degree vertical sinusoidal mean	15.50 (7.41)	18.50 (8.67)	−1.92
1-Degree checkerboard mean	22.15 (8.94)	30.61 (15.76)	−4.57*
0.50-Cycle/degree vertical sinusoidal mean	13.26 (7.52)	19.33 (8.76)	−5.87*

*Significant at $\alpha = 0.01$.

NPC, near point of convergence; NPFD, near point of fixation disparity.

the three sampled responses. The Dunnett test of pairwise comparisons again showed that convergence insufficiency patients with a history of concussion had significantly slower responses to 0.25- and 0.50-cycle/degree vertical sinusoidal gratings compared with the control convergence insufficiency group. None of the pairwise comparisons were significant for the checkerboard stimuli. In general, the variability in P100 latency was greater for the low contrast sine wave gratings compared with high-contrast checkerboard patterns, which is not uncommon (Table 1).[14]

A significant 2 (group) × 4 (stimulus) interaction was observed for Box-Cox–transformed amplitudes of the fastest visually evoked potential response to checkerboard stimuli and vertical sinusoidal gratings of both sizes ($F_{3,228} = 3.18$, $P = .03$). The fastest response amplitude referred to the P100 amplitude of the fastest (out of 3) visually evoked potential response recorded for each subject. The follow-up Dunnett test showed that the concussed group had significantly smaller amplitudes than did the nonconcussed group for both checkerboard stimuli and the 0.50-cycle/degree vertical sinusoidal grating. The untransformed amplitude values, SDs, and corresponding Dunnett *t* values are presented in Table 1.

Similarly, significant 2 (group) × 4 (stimulus) interaction was observed for Box-Cox–transformed mean amplitudes of visually evoked potential responses to checkerboard stimuli and vertical sinusoidal gratings of both sizes ($F_{3,228} = 2.78$, $P = .04$). The mean amplitude referred to the amplitude of the P100 wave averaged over three visually evoked potential responses recorded for each subject. The follow-up Dunnett test again showed that the concussed group had significantly smaller mean amplitudes than did the nonconcussed group for both checkerboard stimuli and 0.50-cycle/degree vertical sinusoidal grating (Table 1).

Logistic Regression

Both forward and backward logistic regression analyses showed that 4 of the 10 visually evoked potential variables (mean latency and amplitude to the 0.50-cycle/degree vertical sinusoidal grating, mean visually evoked potential response latency to the 0.25 vertical sinusoidal grating, and the fastest response amplitude to the 0.50-cycle/degree vertical grating) were retained in the final model and were uniquely significant in predicting concussion history.

TABLE 2.

Forward stepwise (likelihood ratio) logistic regression predicting lifetime history of concussion

Variable	*B*	SE	Odds Ratio	Wald Statistic
Mean 0.25-cycle/degree vertical sinusoidal grating latency, ms	0.05	0.02	1.05	5.22*
Mean 0.50-cycle/degree vertical sinusoidal latency, ms	0.05	0.02	1.05	9.33†
Fastest 0.50-cycle/degree vertical sinusoidal grating amplitude, μV	0.22	0.10	1.24	4.71*
Mean 0.50-cycle/degree vertical sinusoidal amplitude, μV	−0.31	0.11	0.73	8.06†

*Significant at $\alpha = 0.05$.
†Significant at $\alpha = 0.01$.

The model was statistically significant ($\chi^2 = 37.28$, $P < .01$) and had an overall prediction accuracy of 82.1%. Overall, the model accounted for 51% of variability in the dependent measure (Nagelkerke $R^2 = 0.51$). Based on the odds ratios for individual predictors, a convergence insufficiency patient with longer mean response latencies to either 0.25- or 0.50-cycle/degree vertical sinusoidal gratings was approximately 5% more likely to have previously suffered a concussion. On the other hand, a convergence insufficiency patient with a smaller mean P100 amplitude to the 0.50-cycle/degree vertical sinusoidal grating was 26% more likely to have sustained a concussion in the past. These results are summarized in Table 2.

Receiver Operating Characteristic Curves

Next, using receiver operating characteristic curves for the 25th, 50th, 75th, and 90th percentiles, we attempted to identify best cutoff scores for all of the significant variables in order to improve discrimination accuracy of the combined model and make it diagnostically meaningful. None of the percentile scores for the fastest response amplitude to the 0.50-cycle/degree vertical sine wave grating had significant areas under the curve for discriminating between patients with and without a history of concussion. For the 0.25- and 0.50-cycle/degree vertical sinusoidal grating latencies, as well as for the mean 0.50-cycle/degree vertical sinusoidal grating amplitude, 50th percentiles showed the greatest areas under the curve, which were significant at $\alpha = 0.01$. Using these percentiles as cutoff scores, we then created a combined variable, according to which mean latencies to the 0.25-cycle/degree vertical grating greater than 119 milliseconds *or* mean latencies to the 0.50-cycle/degree vertical grating greater than 113 milliseconds *and* mean amplitudes to the 0.50-cycle/degree vertical grating less than 14.75 μV were classified as characteristic of someone with a history of concussion ([MeanVSin_0.25 > 119 *or* MeanVSin_0.50 > 113] *and* MeanVSin_0.50_AMP < 14.75). Conversely, P100 responses with mean latencies equal to or faster than 113 milliseconds and mean amplitudes equal to or greater than 14.75 μV to the 0.50-cycle/degree vertical grating were attributed to someone with no prior history of concussion (MeanVSin_0.50 ≤113 *and* MeanVSin_0.50_AMP ≥ 14.75).

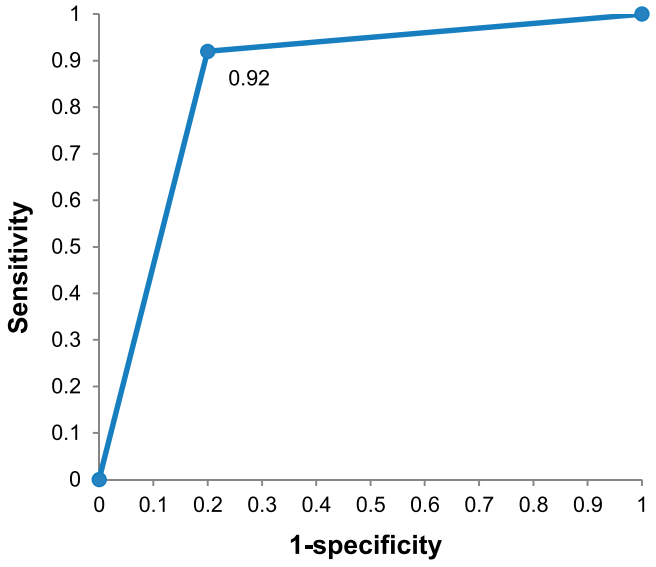

FIGURE 1.

Receiver operating characteristic curve for diagnosis of concussion history based on the mean P100 latency for (0.25-cycle/degree vertical sinusoidal grating >119 milliseconds *or* 0.50-cycle/degree vertical sinusoidal grating >113 milliseconds) and mean 0.50-cycle/degree vertical sinusoidal grating amplitude <14.75 μV. Area under the curve = 0.86 ($P < .01$); sensitivity, 0.92; specificity, 0.80.

The resultant receiver operating characteristic curve for this model had excellent discrimination between the concussed and nonconcussed groups, according to Hosmer and Lemeshow[36] criteria (area under the curve = 0.857; $P < .01$), with sensitivity of 0.92 and specificity of 0.80. The overall discrimination accuracy of the model was 86% (Fig. 1). Twenty-five cases were considered borderline and were not accounted for by the model.[a] Specifically, in situations when a patient's visually evoked potential profile satisfied only one part of the formula for a particular diagnostic category but not the other, the model did not classify these patients, and their data were reported as missing. This occurred in 9 (25.7%) of 35 patients reporting a history of concussion and 16 (36.6%) of 44 control patients.

This new diagnostic model was then compared with our clinical model for concussion diagnosis (see above) that was based on classification of latency differences to both checkerboard stimuli and vertical sinusoidal gratings for fastest and mean responses (fast, mid, and slow). The receiver operating characteristic curve generated for this model was not as good but still had acceptable discrimination between the two groups (area under the curve = 0.77; $P < .01$), with sensitivity of 0.74 and specificity of 0.79. Its overall discrimination accuracy was 76% (Fig. 2). The model failed to classify 27 cases (11 with a history of concussion).

DISCUSSION

The results of the study showed that for patients with convergence insufficiency neither the administration of traditional

[a] Additional inclusion of cases with mean latencies of less than 119 milliseconds to 0.25-cycle/degree vertical gratings to identify those without the previous history of concussion did not result in greater specificity (specificity = 0.77) but excluded more cases (n = 28) from the model.

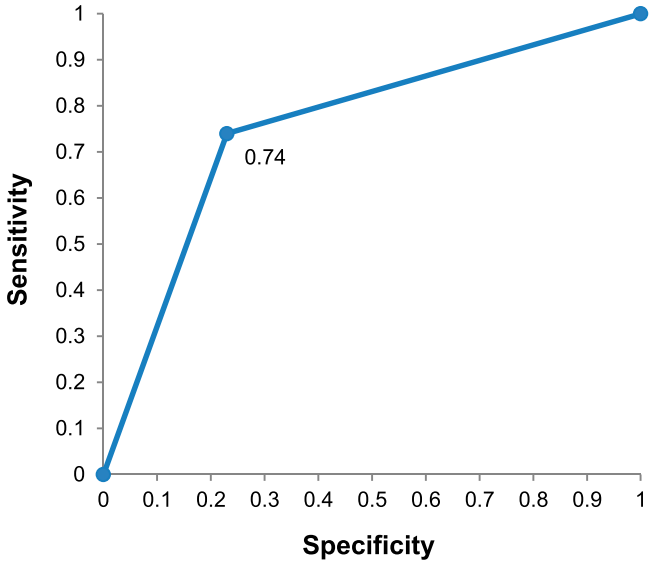

FIGURE 2.

Receiver operating characteristic curve for diagnosis of concussion history based on at least 2-millisecond latency lag for 0.50- and 0.25-cycle/degree vertical sine wave stimuli compared with checkerboard stimuli. Area under the curve = 0.76 ($P < .01$); sensitivity, 0.74; specificity, 0.79.

oculomotor measures of near point of convergence and fusional vergence at near nor the administration of the near point of fixation disparity test and measures of associated vergence were able to further discriminate between patients whose deficits were related to a history of concussion and those whose oculomotor pathology was not related to previous mild traumatic brain injury. Although the near point of fixation disparity measure has shown sensitivity to both concussion history[32] and convergence insufficiency,[30] within the sample of convergence insufficiency patients deficits on this measure were fairly similar between the two groups (Table 1).

Nonetheless, both the statistical and clinical visually evoked potential models discriminated between our concussion and control groups significantly above chance (with 86% and 76% accuracy, respectively). Specifically, in our visually evoked potential protocol, slow (2 rev/s), high-contrast (85%) checkerboard stimuli primarily targeted the parvocellular (sustained) pathway, whereas faster (4 rev/s), low-contrast (10%) vertical sinusoidal gratings targeted the magnocellular (transient) pathway. The convergence insufficiency patients with a previous history of concussion in our sample had significantly slower magnocellular processing ($M_{latency}$ = 123 milliseconds) with significantly lower cortical excitability (smaller amplitude; $M_{amplitude}$ = 12.91 μV) in response to 0.50-cycle/degree vertical sinusoidal gratings compared with the control patient group ($M_{latency}$ = 107 milliseconds; $M_{amplitude}$ = 18.75 μV). Similar response delay was observed in the concussed group for 0.25-cycle/degree vertical sine wave stimuli ($M_{latency}$ = 113 milliseconds) compared with the control group ($M_{latency}$ = 104 milliseconds). As can be seen in Fig. 3, the control group had their mean response amplitudes cluster approximately 100-millisecond latency, showing a pronounced positive skew. The concussion group, on the other hand, had a negatively skewed P100 amplitude distribution showing three peaks between 115 and 145 milliseconds. These results suggest magnocellular deficits in processing of visual stimuli by individuals with convergence insufficiency and a history of concussion.

A prominent difference between the magnocellular and parvocellular pathways is their conduction speeds. Conduction by the axons in the larger magnocellular layers in the lateral geniculate nucleus of the thalamus is faster than that by the smaller cells of its parvocellular layers.[25] A magnocellular advantage has been reported in the primate literature as a latency difference of less than

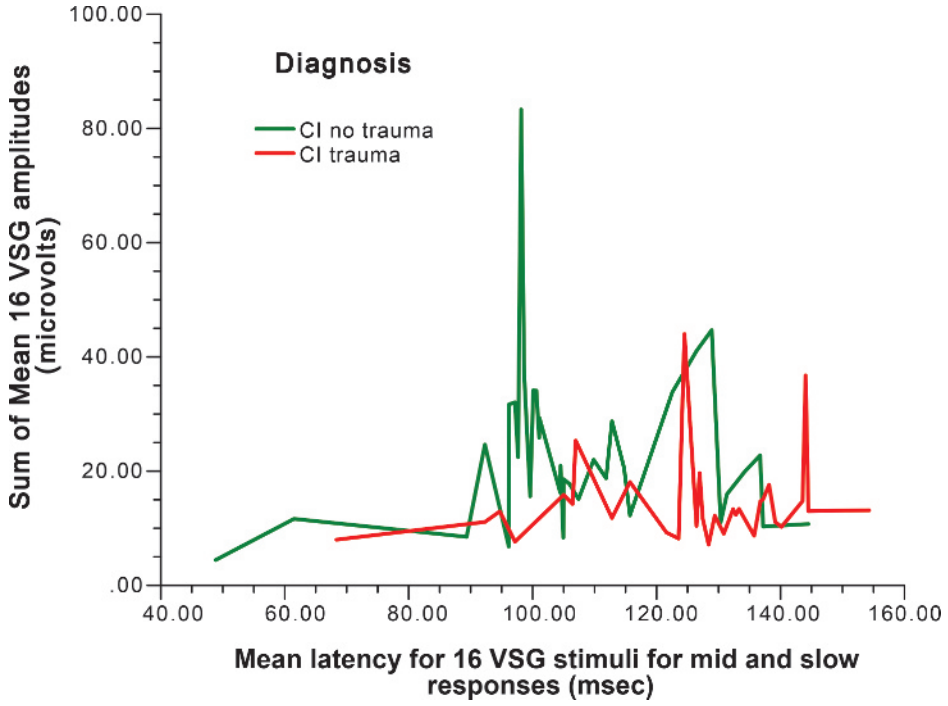

FIGURE 3.

The sum of mean amplitudes for visually evoked potential responses to 0.50-cycle/degree vertical sinusoidal grating as a function of response latency for convergence insufficiency patients with and without concussion history.

10 milliseconds[39] up to a latency of 20 milliseconds[40] and as much as 25 to 30 milliseconds in latency difference in human visually evoked potential studies.[41]

Traumatic axonal injury has been reported to accompany mild traumatic brain injury and to involve axonal stretch associated with ionic imbalances and disturbances in signal conduction.[42] Bain et al.[43] showed that in the absence of an obvious morphological damage a shorter axonal stretch of the guinea pig optic nerve was sufficient to produce significant electrophysiological changes in the form of N35 visually evoked potential latency shift. These findings suggest that it is possible that magnocellular neurons showing faster conduction speeds in an intact human brain may be more vulnerable to morphologically subthreshold axonal injuries than parvocellular neurons, which in turn results in magnocellular signal delays that seem to persist months and years after a head injury.

A possible limitation of the study was the use of the same order of stimulus presentation. In statistical terms, if there was an order effect, the resultant error variance should be similar for the two groups because the same order was applied to both patient groups. From a clinical perspective, however, if there is a reason to believe that the presentation of a checkerboard pattern first would bias the response of the concussion group to a vertical sinusoidal grating to a greater extent than it would in the control group, the order effect would become a confounding variable and should be controlled for in future studies.

Overall, the results of the current study provide support for the development of a diagnostic method that distinguishes magnocellular deficits in individuals with a history of concussion. With further research into this methodology, the criteria for the differential diagnosis of convergence insufficiency and mild traumatic brain injury will become further defined. It is possible that a higher reversal rate of vertical sinusoidal gratings (e.g., 16 rev/s) may bias the P100 response further in favor of the transient pathway and result in a greater percentage of visually evoked potential profile classification. Nonetheless, the fact that both the top-down (clinical) and bottom-up (statistical) models provided good solutions for discrimination between the two groups of patients suggests that the observed magnocellular deficits are real and persistent in individuals with a history of mild traumatic brain injury. Furthermore, since the administration of oculomotor-based therapy to individuals with a history of concussion has produced significant improvements on a number of objective visual measures,[11] it would be of considerable interest to examine the effects of such therapy on rehabilitation of magnocellular processing in these patients. If visually evoked potential–based identification of magnocellular deficits associated with mild traumatic brain injury proves to be robust in larger population studies, this technique can become a valuable diagnostic tool for all modes of medical and rehabilitative treatment of these patients.

ACKNOWLEDGMENTS

LKC is an employee of Diopsys, Inc., which specializes in visually evoked potential software. Under a noncommercial research agreement with coauthor PL, author LKC assisted in development of the visually evoked potential trial module for the study. There is, however, no financial interest involved for any of the authors (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements). None of the authors have any nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this article. The authors received no outside funding for this research.

Received June 3, 2016; accepted May 6, 2017.

REFERENCES

1. National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem (Internet). Atlanta, GA: Centers for Disease Control and Prevention; 2003. Available at: https://stacks.cdc.gov/view/cdc/6544/. Accessed May 27, 2016.
2. Prins M, Hales A, Reger M, et al. Repeat traumatic brain injury in the juvenile rat is associated with increased axonal injury and cognitive impairments. Dev Neurosci 2010;32:510–8.
3. Shrey DW, Griesbach GS, Giza CC. The pathophysiology of concussions in youth. Phys Med Rehabil Clin N Am 2011;22:577–602.
4. McCrea M, Hammeke T, Olsen G, et al. Unreported concussion in high school football players: implications for prevention. Clin J Sport Med 2004;14:13–7.
5. Valovich McLeod TC, Bay RC, Heil J, et al. Identification of sport and recreational activity concussion history through the preparticipation screening and a symptom survey in young athletes. Clin J Sport Med 2008;18:235–40.
6. Williamson IJ, Goodman D. Converging evidence for the underreporting of concussions in youth ice hockey. Br J Sports Med 2006;40:128–32.
7. Ciuffreda K, Kapoor N. Acquired brain injury. In: Taub MB, Bartuccio M, Maino DM, eds. Visual Diagnosis and Care of the Patient with Special Needs, Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.
8. Ciuffreda KJ, Kapoor N, Rutner D, et al. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. Optometry 2007;78:155–61.
9. Covassin T, Elbin RJ. The cognitive effects and decrements following concussion. Open Access J Sports Med 2010;1:55–61.
10. Cohen M, Groswasser Z, Barchadski R, et al. Convergence insufficiency in brain-injured patients. Brain Inj 1989;3:187–91.
11. Thiagarajan P, Ciuffreda K. Accommodative and vergence dysfunctions in mTBI: treatment effects and systems correlations. Optom Visual Perform 2014;2:281–8.
12. Kumar S, Rao SL, Nair RG, et al. Sensory gating impairment in development of post-concussive symptoms in mild head injury. Psychiatry Clin Neurosci 2005;59:466–72.
13. Jackowski MM. Altered visual adaptation in patients with traumatic brain injury: photophobia, abnormal dark adaptation, and reduced peripheral visual field sensitivity. In: Suchoff IB, Ciuffreda KJ, Kapoor N, eds. Visual and Vestibular Consequences of Acquired Brain Injury, Santa Ana, CA: Optometric Extension Program Foundation; 2001;145–73.
14. Kapoor N, Ciuffreda KJ. Vision disturbances following traumatic brain injury. Curr Treat Options Neurol 2002;4:271–80.
15. Fimreite V, Ciuffreda KJ, Yadav NK. Effect of luminance on the visually-evoked potential in visually-normal individuals and in mTBI/concussion. Brain Inj 2015;29:1199–210.
16. Yadav N, Ciuffreda K. Objective assessment of visual attention in mild traumatic brain injury (mTBI) using visual-evoked potentials (VEP). Brain Inj 2015;29:352–65.

17. Patel R, Ciuffreda K, Tannen B, et al. Elevated coherent motion thresholds in mild traumatic brain injury. Optometry 2011;82:284–9.
18. Ciuffreda K, Yadav NK, Ludlam DP. Effect of binasal occlusion (BNO) on the visual-evoked potential (VEP) in mild traumatic brain injury (mTBI). Brain Inj 2013;27:41–7.
19. Chang T, Ciuffreda K, Kapoor N. Critical flicker frequency and related symptoms in mild traumatic brain injury. Brain Inj 2007;21: 1055–62.
20. Schrupp L, Ciuffreda K, Kapoor N. Foveal versus eccentric retinal critical flicker frequency in mild traumatic brain injury. Optometry 2009;80:642–50.
21. Kaplan E, Shapley R. X and Y cells in the lateral geniculate nucleus of macaque monkeys. J Physiol 1982;330:125–43.
22. Schiller P, Logothetis N. The color-opponent and broad-band channels of the primate visual system. Trends Neurosci 1990;13:392–8.
23. Hicks T, Lee B, Vidyasagar T. The responses of cells in macaque lateral geniculate nucleus to sinusoidal gratings. J Physiol 1983;337:183–200.
24. Levitt J, Schumer R, Sherman M, et al. Visual response properties of neurons in the LGN of normally reared and visually deprived macaque monkeys. J Neurophysiol 2001;85:2111–29.
25. Laycock R, Crewther SG, Crewther DP. A role for the ''magnocellular advantage'' in visual impairments in neurodevelopmental and psychiatric disorders. Neurosci Biobehav Rev 2007;31:363–76.
26. Yadav NK, Ciuffreda KJ. Optimization of the pattern visual evoked potential (VEP) in the visually-normal and mild traumatic brain injury (mTBI) populations. Brain Inj 2013;27:1631–42.
27. Huang J, Zong X, Wilkins A, et al. fMRI evidence that precision ophthalmic tints reduce cortical hyperactivation in migraine. Cephalalgia 2011;31:925–36.
28. Cooper J, Jamal N. Convergence insufficiency—a major review. Optometry 2012;83:137–58.
29. Rouse MW, Hyman L, Hussein M, et al. Frequency of convergence insufficiency in optometry clinic settings. Convergence Insufficiency and Reading Study (CIRS) Group. Optom Vis Sci 1998;75:88–96.
30. Lederer P, Poltavski D, Biberdorf D. Confusion inside Panum's area and symptomatic convergence insufficiency. Vis Dev Rehab 2015; 1:46–60.
31. Scheiman M, Gallaway M, Frantz KA, et al. Nearpoint of convergence: test procedure, target selection, and normative data. Optom Vis Sci 2003;80:214–25.
32. Poltavski D, Biberdorf D. Screening for lifetime concussion in athletes: importance of oculomotor measures. Brain Inj 2014;28:475–85.
33. De Valois KK, De Valois RL, Yund EW. Responses of striate cortex cells to grating and checkerboard patterns. J Physiol 1979;291: 483–505.
34. Tello C, De Moraes CG, Prata TS, et al. Repeatability of short-duration transient visual evoked potentials in normal subjects. Doc Ophthalmol 2010;120:219–28.
35. Derr PH, Meyer AU, Haupt EJ, et al. Extraction and modeling of the oscillatory potential: signal conditioning to obtain minimally corrupted oscillatory potentials. Doc Ophthalmol 2002;104:37–55.
36. Bewick V, Cheek L, Ball J. Statistics review 13: receiver operating characteristic curves. Crit Care 2004;8:508–12.
37. Keene ON. The log transformation is special. Stat Med 1995;14: 811–9.
38. Osborne JW. Improving your data transformations: applying the Box-Cox transformation. Prac Asses Res Eval 2010;15:1–9.
39. Maunsell JH, Ghose GM, Assad JA, et al. Visual response latencies of magnocellular and parvocellular LGN neurons in macaque monkeys. Vis Neurosci 1999;16:1–4.
40. Bullier J, Hupé JM, James A, et al. Functional interactions between areas V1 and V2 in the monkey. J Physiol Paris 1996;90:217–20.
41. Klistorner A, Crewther D, Crewther S. Separate magnocellular and parvocellular contributions from temporal analysis of the multifocal VEP. Vision Res 1997;37:2161–9.
42. Gaetz M. The neurophysiology of brain injury. Clin Neurophysiol 2004;115:4–18.
43. Bain A, Raghupathi R, Meaney D. Dynamic stretch correlates to both morphological abnormalities and electrophysiological impairment in a model of traumatic axonal injury. J Neurotrauma 2001;18:499–511.

Dmitri Poltavski
Department of Psychology
University of North Dakota
319 Harvard St, Stop #8380
Grand Forks, ND 58202
e-mail: dmitri.poltavski@und.edu