Clinical Trials

Convergence Insufficiency Neuro-Mechanism Adult Population Study: Phoria Adaptation Results

Ayushi Sangoi,[1] Mitchell Scheiman,[2] Chang Yaramothu,[1,3] Elio M. Santos,[1] Suril Gohel,[4] and Tara L. Alvarez[1]

[1]Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey, United States
[2]Pennsylvania College of Optometry, Salus University, Philadelphia, Pennsylvania, United States
[3]School of Applied Engineering and Technology, New Jersey Institute of Technology, Newark, New Jersey, United States
[4]Department of Health Informatics, Rutgers University School of Health Professions, Newark, New Jersey, United States

Correspondence: Tara L. Alvarez, Department of Biomedical Engineering, New Jersey Institute of Technology, 323 Martin Luther King, Boulevard, University Heights, Newark, NJ 07102, USA; tara.l.alvarez@njit.edu.

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Purpose. The purpose of this study was to compare changes in phoria adaptation between young adult binocularly normal controls (BNCs) and participants with symptomatic convergence insufficiency (CI), who were randomized to either office-based vergence accommodative therapy (OBVAT) or office-based placebo therapy (OBPT).

Methods. In the double-masked randomized clinical trial, 50 BNC and 50 CI participants were randomized to the following therapeutic interventions: OBVAT or OBPT with home reinforcement for 12 one-hour office sessions. A 6Δ base-out and 6Δ base-in phoria adaptation experiment at near (40 cm) was conducted using the flashed Maddox rod technique at baseline and at outcome. Measurements included the rate and the magnitude of phoria adaptation.

Results. At baseline, BNC and CI participants had significantly different rates and magnitudes of base-in and base-out phoria adaptation ($P < 0.001$). When comparing the outcome to baseline measurements, significant main effect differences in longitudinal measurements were observed for the magnitude and the rate of phoria adaptation for both base-out and base-in experiments ($P < 0.05$). For the magnitude and rate of phoria adaptation, post hoc analyses using paired *t*-tests revealed that the CI group administered the OBVAT intervention exhibited a significant increase in the magnitude and rate of phoria adaptation compared to baseline for both base-in and base-out phoria adaptation ($P < 0.01$) but not for those administered OBPT.

Conclusions. Phoria adaptation is significantly different at baseline between those with normal binocular vision and symptomatic CI participants. OBVAT significantly improves the rate and magnitude of both base-out and base-in phoria adaptation at near compared to OBPT. Results have clinical implications for new therapeutic interventions.

Keywords: convergence insufficiency (CI), vergence, phoria adaptation, office-based vergence and accommodative therapy (OBVAT), vision therapy

Convergence insufficiency (CI) is the most common binocular vision disorder with reported prevalence rates of 3.4% to 17.6%.[1–9] The associated symptoms, such as blurred vision, double vision, eye strain, headaches, and loss of concentration, may negatively affect quality of life.[10,11] Near visual work, such as reading, using computers, smartphones, tablets, or mixed virtual and augmented reality headsets, are becoming ubiquitous in daily life and these activities may exacerbate visual symptoms for those with symptomatic CI.[10,11]

Although multiple randomized clinical trials (RCTs)[12–21] have demonstrated that office-based vergence and accommodative therapy (OBVAT) is effective for normalizing the near point of convergence (NPC) and positive fusional vergence (PFV), less research has been conducted investigating the underlying mechanisms responsible for CI and how such mechanisms are altered with therapeutic intervention. A basic and widely accepted explanation is that due to a low accommodative convergence/accommodation (AC/A) ratio, there is a greater than normal amount of exophoria at near than at far. In addition, convergence ability (measured through PFV and the NPC) is reduced, leading to an inability to compensate for the exophoria and maintain comfortable, single, and clear vision when engaged in near activities; leading to symptoms.[11,22,23] Others suggest that binocular vision disorders, like CI and convergence excess, may result from underlying adaptive disorders, such as abnormal vergence or phoria adaptation.[23–32]

Phoria adaptation refers to the change in phoria level in response to prolonged fixation or visual demand[26,33,34] and is considered a behavioral measurement that can reduce near visual demand during prolonged viewing, resulting in a reduction in symptoms. Phoria adaptation leads to a change in tonic vergence, which is the resting state of vergence in the absence of disparity, blur, or proximal visual cues.[35] The change in tonic vergence adaptation is believed to

reduce fixation disparity (error in the vergence system) and balance the accommodative and vergence systems.[30,31] Studies have reported changes in phoria induced by sustained visual fixation to physical targets,[36] a stereoscope,[37] and viewing targets through prisms[26–28,38] or lenses.[39] Prior studies report that patients with CI have a reduced ability to adapt their phoria compared to binocularly normal controls (BNCs)[23,28,30,40,41] and their phoria adaptation improves after vision therapy/orthoptics.[29,31,42,43] Sreenivasan and Bobier found that improvements in phoria adaptation may be more closely linked to alleviation of symptoms in patients with CI than clinical measures, such as NPC and PFV.[31] The data from existing studies are promising, and hence support the need for an RCT where participants and examiners are masked and include a placebo control group.

The Convergence Insufficiency Neuro-Mechanism Adult Population Study (CINAPS) was an RCT designed to compare the effectiveness of OBVAT to office-based placebo therapy (OBPT) for symptomatic CI in young adults. A unique design of CINAPS was the inclusion of objective measures of vergence and accommodation, phoria adaptation, and functional magnetic resonance imaging (fMRI) testing in addition to traditional optometric measures of NPC, PFV, and symptoms. These results are reported in separate manuscripts.[21,44,45] Another distinctive purpose of CINAPS was to identify potential underlying visual neural mechanisms that might be related to CI. One of the proposed behavioral measurements studied was phoria adaptation. Herein, we report the changes that occurred between baseline and post-treatment phoria adaptation in a group of young adults with symptomatic CI and another age-matched group with normal binocular vision as well as the potential correlations with positive and negative fusional vergence.

Participants and Methods

This research is part of CINAPS (registered with ClinicalTrials.gov entitled "Neural Mechanism of Vision Therapy for Patients with CI" NCT03593031 in July 2018), a double-masked randomized interventional clinical trial. All participants gave written informed consent. This study followed the tenets of the Declaration of Helsinki, which was reviewed and approved by the New Jersey Institute of Technology Institutional Review Board. Participants were recruited from the Newark, NJ, USA, area, which has a diverse population.

Participant Selection

The study included young adults 18 to 35 years of age primarily from the New Jersey Institute of Technology and Rutgers University-Newark student bodies and included 50 participants with symptomatic CI and 50 with normal binocular vision. The definition of symptomatic CI followed the diagnostic criteria established within multiple previous RCTs.[12,14,17–19] The diagnostic criteria included all of the following: (1) a score of $\geq$21 on the CI Symptom Survey (CISS),[46,47]; (2) a receded near point of convergence ($\geq$6 cm); (3) a near exodeviation at least 4Δ greater than at distance fixation; and (4) an insufficient positive fusional vergence at near defined as failing Sheard's criterion (base-out blur [break if no blur] less than twice the near phoria)[48] or minimal positive fusional vergence at near of $\leq$15Δ base-out break. Exclusion criteria included a history of vision therapy, any history of head injury, including concussion(s), a history of eye disease, or best corrected visual acuity of worse than 20/25. The major eligibility for the normal binocular vision groups included age between 18 and 35 years of age (inclusive), visual acuity 20/25 or better with best correction, and normal binocular vision and accommodation. The complete eligibility criteria for both groups have been published previously.[21,44]

Enrollment/Randomization

An eligibility examination was performed by an optometrist (co-author M.S.) and included best corrected visual acuity at 6 m, non-cycloplegic auto-refraction, CISS, cover testing at distance and near, positive fusional vergence (PFV) and negative fusional vergence (NFV) at near, the near point of convergence, vergence facility at near, and push-up amplitude of accommodation (right eye only). The testing protocol is described in a previous publication.[21] Participants were randomly assigned to receive either OBVAT or OBPT using a randomized vector with a 1:1 allocation ratio (n = 50) generated with a MATLAB program in accordance with the CONSORT 2010 agreement.[49,50] Allocation to therapy type was concealed from investigators and participants.

Treatment Protocols for Both Therapy Groups

Both OBVAT and OBPT are established protocols that have been used in multiple RCTs.[12,18,20,51–53] Both protocols consist of 12 one-hour sessions, administered by a study certified vision therapist. Office-based therapy was administered twice a week unless a participant had a scheduling conflict. Home-based therapy was prescribed to be performed 3 times per week for 10 minutes on days when the participant did not have office-based therapy for a total of 3 hours of home reinforcement. The home therapy utilized the home therapy solution (HTS; visiontherapysolutions.net) computer-based system and was either active or placebo. The placebo software program looked similar to the active therapy but did not change vergence demand. The therapist followed a detailed protocol for either OBVAT or OBPT.[44] OBVAT was designed to improve convergence amplitude, fusional vergence and facility, accommodative amplitude, and facility. The objective of the first phase was to normalize accommodation amplitude, and improve the NPC and PFV using ramp stimuli. The second phase of treatment included step vergence demand to improve positive and negative fusional vergence. The last phase was designed to improve vergence facility and integrate vergence and version eye movements. The therapy techniques utilized the following instrumentation: Aperture Rule, Eccentric Circles, HTS Computer Orthoptics, Vectograms, and monocular accommodative procedures using loose lenses.[22,44] As the therapy progressed, the level of difficulty gradually increased throughout the 12-session sequence. OBPT consisted of procedures designed to have no positive effect on vergence or accommodative abilities beyond normal activities, while simulating the perception of vision therapy. The exact protocol for both groups is described in our prior publication.[44] The goal was to finish therapy within 6 to 8 weeks.

Follow-Up Examination and Test Procedures

A follow-up visit was scheduled after participants completed 12 hours of office-based therapy and 3 hours of home-based therapy following the same procedures as used

in several RCTs.[18,20,21,52,54] An optometrist who was masked to the group assignment repeated all the testing performed at the baseline examination. Another masked, study-certified examiner, then repeated the phoria adaptation experiment.

Initial Phoria and Phoria Adaptation Measurements

Initial Phoria Measurements. The initial phoria was measured using a Muscle Imbalance Measure (MIM) card (Bernell Corp., South Bend, IN, USA) placed along the participant's midline at eye-level at near (40 cm). A Maddox rod was placed in front of the right eye with the lines positioned horizontally. The participant was instructed to maintain focus on the light of a penlight placed at the midpoint of the MIM card, for 15 seconds. After 15 seconds, the right eye was covered and then uncovered (the flashed Maddox rod technique[27,55,56]) and the participant was instructed to report the location of the red vertical line relative to the center of the chart (white light) as soon as the red line was perceived. This measurement process was repeated, and the initial phoria level was determined using the average of these two values. The base-in phoria adaptation experiment was performed first and the participant was given a 15–20-minute break before the base-out adaptation was performed. If the participant's phoria level did not return to the initial measurement after the base-in measurement, then the participant returned on a different day to record the base-out phoria adaptation experiment.

Phoria Adaptation Measurements

The phoria adaptation protocol began after the completion of the initial phoria measurement described above. In addition to the setup described above for the baseline phoria measurement, a handheld 6 base-in Δ wedge prism on a rod was now placed in front of the participant's right eye. The 6 Δ wedge prism was chosen based on previous research showing that this magnitude maximizes the amount of recognizable change in phoria adaptation without creating a level of retinal disparity that a participant with CI would be unable to fuse.[28] This asymmetrical condition (prism only placed before one eye rather than both eyes) was used because previous research demonstrated that an asymmetrical protocol provides a greater change in magnitude and rate of adaptation than a symmetrical condition.[57] To start the procedure, the right eye was occluded for 15 seconds creating an open loop state for the vergence system.[24] As soon as the eye was uncovered, the participant was instructed to report the location of the red vertical line on the MIM card. The participant was then instructed to fixate on a single column of 20/30 letters on a fixation stick (Gulden Fixation Stick # 15302) for 30 seconds and then another phoria measurement was recorded. This measurement was repeated every 30 seconds over a period of 7 minutes, for a total of 15 measurements over the adaptation period.[58] After a break and the participant returning to their baseline phoria measurement, the experiment was repeated with a 6 base-out Δ wedge prism. The co-author (E.M.S.) collected all phoria adaptation data. He was trained and certified by an optometrist, co-author (M.S.) and had prior experience using this exact protocol.[57]

Data Analysis

A custom MATLAB script (version 2019a) was used to analyze the following parameters from the phoria adaptation experiment: the magnitude of phoria adaptation, the time constant, and the rate of phoria adaptation. Each participant's dataset of phoria adaptation values was shifted to that participant's baseline phoria level, by subtracting the baseline level from each of the subsequent 15 phoria points, a process sometimes called normalization. The magnitude was determined by the difference between the first value of the phoria immediately after the prism was placed in front of the eye and the last phoria value taken at the end of the experiment (after 7 minutes of phoria adaptation).

Prior research on phoria adaptation reports that it exhibits an exponential decay.[43] Hence, the exponential decay function was fit to the phoria adaptation data using the MATLAB exponential fit function that minimized the root mean square error to calculate the best fit. The time constant was measured as the point in time when the phoria adaptation reached 63% of the final value, as defined by the standard engineering parameter 1-1/e. The rate of adaptation was calculated using Equation 1 which is the difference between the final and initial phoria measured divided by the time constant (t).

$$\text{Rate of adaptation} = \frac{\text{final phoria measurement} - \text{initial phoria measurement}}{\tau} \quad (1)$$

This measurement procedure has been used in prior studies.[57,59,60] Outliers in the rate of adaptation were defined as rates that were two standard deviations above or below the mean for each group. The group-level results were obtained by averaging all the normalized measurements (shifted to the same starting measurement) and then fit with an exponential curve for each of the following groups: all CI participants during baseline, all BNC participants during baseline, each of the four groups to be administered OBVAT or OBPT during baseline, and then repeated for each group for the outcome measurements. The baseline measures were defined by the change in the magnitude of phoria adaptation in units of prism diopters (Δ) and the rate of phoria adaptation in units of prism diopters per minute. The outcome measures used an identical method as the baseline after 12 one-hour office-based sessions.

Statistics

The study was sufficiently powered as assessed via the following clinical signs and symptoms: NPC, PFV, and CISS,[53] and the data were normally distributed. The following measurements at baseline were compared between the BNC and CI groups using Student's unpaired *t*-tests for the following: NPC, PFV, NFV, near and far phoria, CISS, magnitude of phoria adaptation, and rate of phoria adaptation. Calculations were performed using SPSS Statistics version 20 (IBM, Armonk, NY, USA). Outliers were defined as data points that were more than two standard deviations larger or smaller than the group average and were omitted from statistical analyses. Correlation analyses between PFV and base-out magnitude and rate of phoria adaptation as well as NFV and base-in magnitude and rate of phoria adaptation were assessed using the Pearson's correlation coefficient.

The primary hypothesis tested was that OBVAT would have a significant change in phoria adaptation measures,

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but that OBPT would not. Secondary hypotheses included the following: (1) testing whether significant effects would be observed between the BNC and CI groups in terms of the change in potential improvement and (2) testing the hypothesis that the CI group post-OBVAT would no longer be significantly different than BNC baseline data. A mixed factor repeated measures ANOVA was used to compare the effects of the following: the between factors of therapy type (OBVAT versus OBPT) and participant type (BNC versus CI) with a within factor of time (baseline and outcome). For the repeated measures ANOVA, mean replacement was utilized for one to three participants per group due to outliers where the replacements were evenly distributed between groups to avoid missing data. Paired Student's *t*-tests were used to assess longitudinal differences comparing outcome to baseline measurements for magnitude and rate of phoria adaptation for base-out and base-in experiments when significant main effects were observed. Unpaired *t*-tests assessed whether the CI group post-OBVAT data was significantly different than the BNC baseline data for the phoria magnitude and rate of phoria adaptation.

Results

Clinical Optometric Examination and Longitudinal Results

The study consisted of 50 participants who were diagnosed with symptomatic CI (mean age 20.86 ± 3.57 years, 50% women) and 50 BNC participants with normal binocular vision (21.76 ± 3.32 years, 30% women). Inclusion and exclusion criteria were ensured by an optometrist (co-author M.S.). No significant differences in age, refractive error, or stereopsis between the BNC and CI groups were observed ($P > 0.1$).[44] Full details of the ethnic and racial demographics, refractive errors, and baseline vision parameters of this study were published previously.[44]

The following dependent variables were compared using unpaired *t*-tests of the baseline parameters. For the CI group, the mean and standard deviation for NPC was 10.4 ± 3.5 cm versus the BNC group of 3.8 ± 1.2 cm, which was significantly different (t[98] = 12.5, $P < 0.0001$). For PFV, the CI group mean with standard deviation was 12.5 ± 4.0Δ compared to 27.8 ± 8.4Δ for the BNC group, also significantly different (t[98] = 13.4, $P < 0.0001$). For NFV, the CI group mean was 11.6 ± 3.3Δ, which was significantly different compared to the BNC group mean with standard deviation of 14.0 ± 2.5Δ (t[98] = 4.18, $P < 0.0001$). The near phoria for the CI group was 6.9 ± 3.2Δ and significantly more exophoric than the BNC group of 2.0 ± 2.1Δ (t[98] = 8.91, $P < 0.0001$). The far phoria levels were not significantly different between the CI and BNC groups (t[98] = 1.41, $P = 0.2$). Hence, the AC/A ratio was lower in the CI group compared to the BNC group. The CI participants were more symptomatic with a CISS score of 34.5 ± 7.6 points versus the BNC group CISS score of 8.2 ± 5.3 points (t[98] = 20.0, $P < 0.0001$). These results were reported in our prior manuscript.[44] No significant differences were observed within the baseline parameters for the CI group being randomized to OBVAT compared to the CI group being randomized to OBPT, which was also true for the BNC groups ($P > 0.1$).[44]

Therapy ended when 12 one-hour sessions in the office were completed. Most (92%) participants finished the 12 one-hour sessions within 8 weeks and all participants completed the required sessions within 12 weeks. The improvements in clinical signs and symptoms have already been published.[21] Briefly, the longitudinal study of the therapeutic interventions using paired *t*-tests show that the CI group who was administered OBVAT had a significant improvement in (1) NPC, baseline of 10.5 ± 3.7 cm compared to outcome of 4.5 ± 1.6 cm (t[24] = 7.6, $P < 0.0001$); (2) PFV, baseline of 12.2 ± 3.2Δ compared to outcome of 28.9 ± 10.4Δ (t[24] = 6.4, $P < 0.0001$); and (3) CISS, baseline of 34 ± 9 points compared to outcome of 21.6 ± 8 points (t[24] = 5.6, $P < 0.0001$). Complete analysis of the clinical signs and symptoms are available in a previous publication.[21]

The masking of participants was successful. At the outcome visit, participants were asked whether they were in the active or the placebo therapy and how confident they were in their response using a 5-point Likert scale. For the CI participants prescribed OBVAT, 25 of 25 participants (100%) thought they were in active therapy whereas 21 of 25 (84%) stated they were either very sure or pretty sure of their response. For the CI participants who were assigned to OBPT, 19 of 25 (76%) thought they were in real therapy whereas 40% stated they were either very sure or pretty sure of their response. These results are similar to previous clinical trials using the identical treatment protocols[12,19,52,61] where a detailed comparison is conducted in our prior manuscript.[21]

Baseline Comparison of Phoria Adaptation

All 50 CI and 50 BNC participants completed the base-out and base-in assessments at baseline and outcome phoria adaptation measurements. If after a 15–20-minute break following the base-in phoria experiment, the participant's phoria measurements did not return to their initial measurements within 2Δ, then they were asked to return on a second day. This occurred with six CI and two BNC participants for both the baseline and the outcome assessments. Figure 1 plots the group-level average shifted to the prism values used (also referred to as normalized) with one standard error of the mean for the 6Δ base-out (plot 1A) and 6Δ base-in (plot 1B) to show comparisons between the BNC (green "X" and line) and CI (orange diamonds and line) participants at baseline. Standard error of the mean was used to compare with prior literature. The corresponding exponential fits for each group are shown. The base-out magnitude of phoria adaptation (defined as the change in phoria at the end of the 7-minute test compared to the initial phoria measurement) for the CI group was 3.1 ± 1.0Δ, which was significantly less than the BNC group of 4.2 ± 1.0Δ (t[81] = 4.78, $P < 0.0001$). Data measurements, which were two standard deviations away from the mean, were classified as outliers and removed from statistical analysis. The base-out rate of phoria adaptation for the CI group was 2.2 ± 1.3 Δ/min, which was significantly less than the BNC group rate of 3.2 ± 1.1 Δ/min (t[78] = 3.78, $P < 0.001$). Similar results were observed for base-in phoria adaptation experiment. The base-in magnitude of phoria adaptation for the CI group was 2.3 ± 0.6Δ, which was significantly less than the BNC group of 3.7 ± 1.1Δ (t[84] = 7.25, $P < 0.0001$). The base-in rate of phoria adaptation for the CI group was 1.3 ± 0.8 Δ/min, which was significantly less than the BNC group of 2.3 ± 1.1 Δ/min (t[71] = 4.84, $P < 0.0001$).

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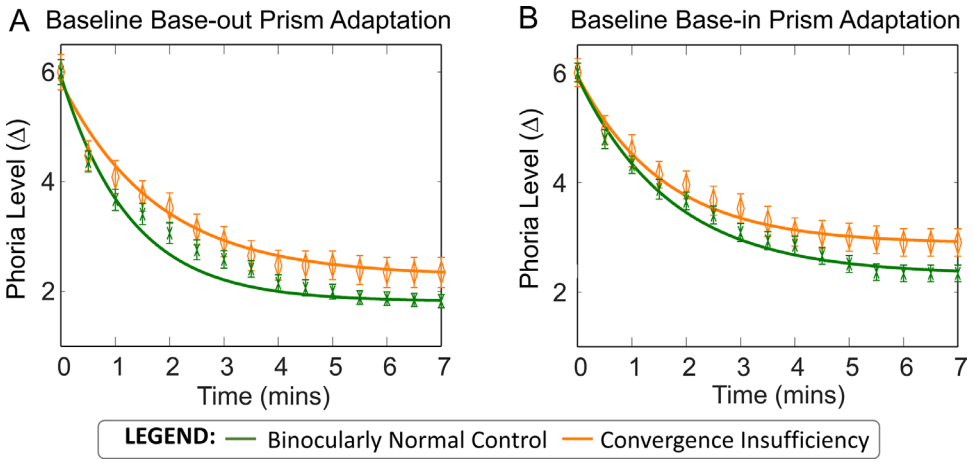

Figure 1. Group-level plot of baseline phoria adaptation data comparing BNCs (green X's) to CI participants (orange diamonds) for base-out (**A**) and base-in (**B**) prism phoria adaptation. Symbols are the average with one standard error of the mean (SEM) to compared with other literature with the exponential curve of best fit.

Longitudinal Study of Phoria Adaptation

The longitudinal results for the BNC (upper plots 2A and 2B) and CI groups (lower plots 2C and 2D) post-treatment (red X's and exponential fit) compared to baseline data (blue squares and exponential fit) were plotted in Figure 2 for the base-out phoria adaptation experiment. Symbols were plotted as the mean shifted to the prism values used with plus and minus one standard error of the mean to compare with other literature. For participants who were administered

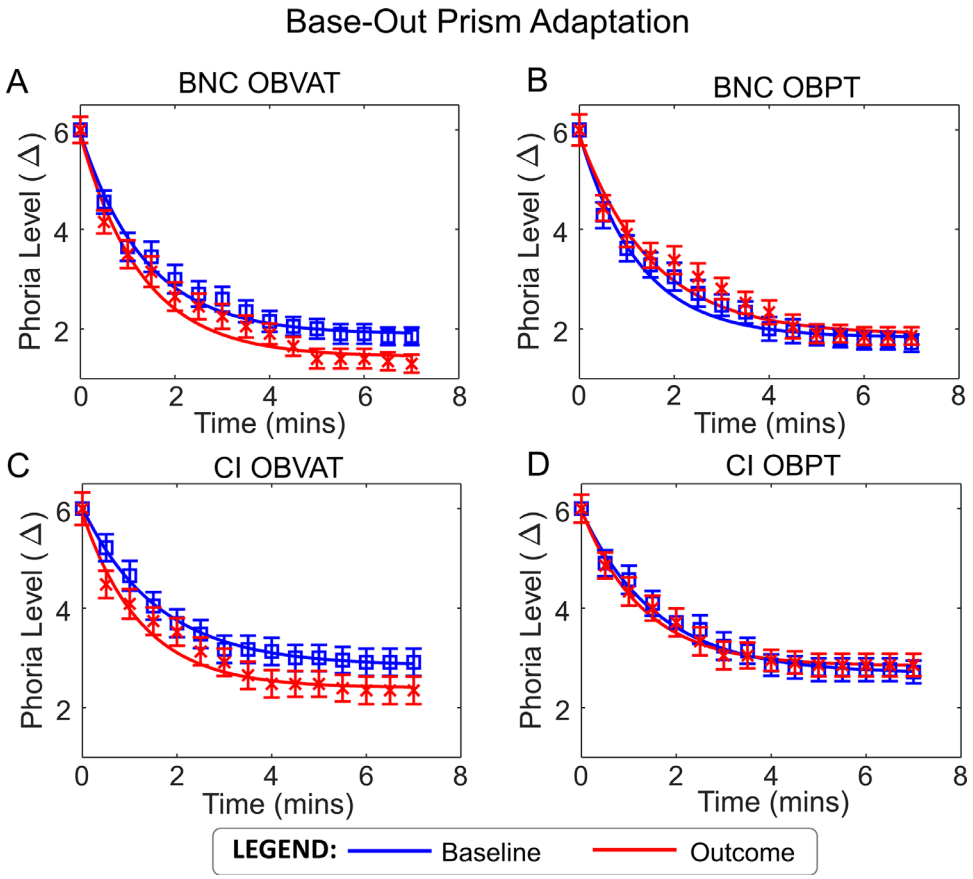

Figure 2. Group-level longitudinal adaptation graphs with base-out prism of baseline compared to outcome post therapy of mean with standard error of the mean (SEM) and exponential fits BNC OBVAT (**A**), BNC OBPT (**B**), CI OBVAT (**C**), and CI OBPT (**D**) groups. Abbreviations: CI, convergence insufficiency; BNC, binocularly normal controls; OBVAT, office-based vergence and accommodative therapy; OBPT, office-based placebo therapy.

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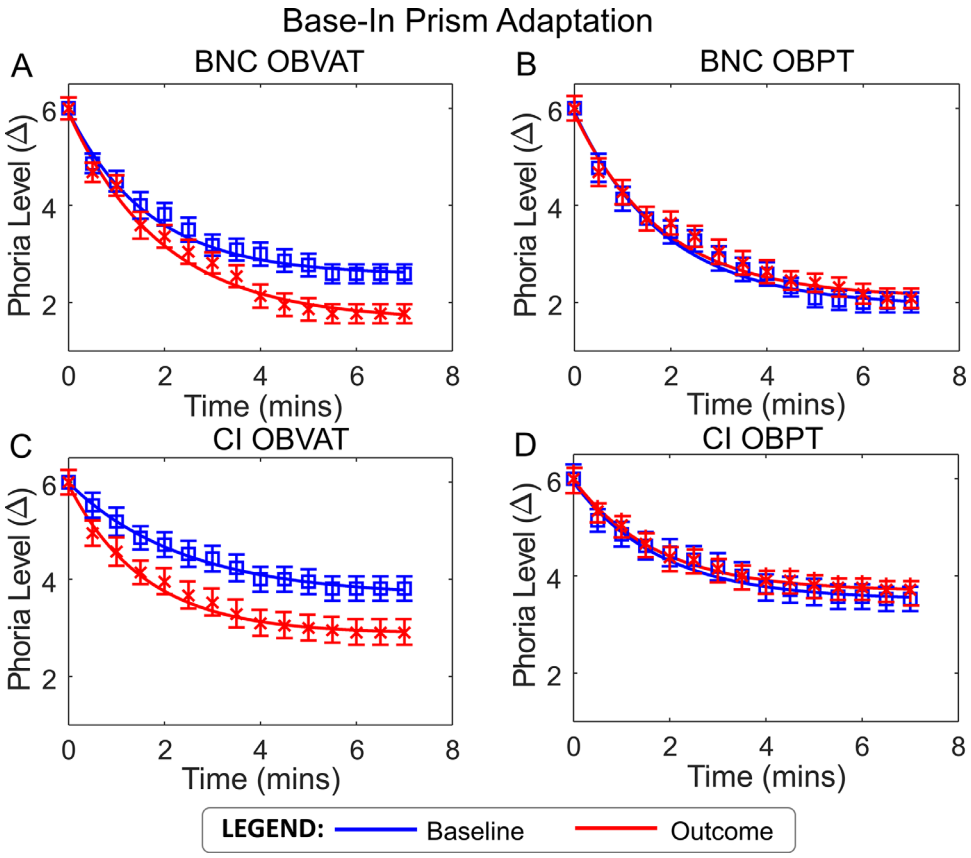

Figure 3. Group-level longitudinal adaptation graphs with base-in prism of baseline compared to outcome post therapy of mean with standard error of the mean (SEM) and exponential fits for the BNC OBVAT (**A**), BNC OBPT (**B**), CI OBVAT (**C**), and CI OBPT (**D**) groups. Abbreviations: CI, convergence insufficiency; BNC, binocularly normal control; OBVAT, office-based vergence and accommodative therapy; OBPT, office-based placebo therapy.

OBVAT, the magnitude and rate of base-out phoria adaptation improved, whereas those who were administered OBPT did not exhibit much change. The nomenclature for Figures 2 and 3 was the same. Like the base-out phoria adaptation experiment, the base-in magnitude and rate of phoria adaptation improved for BNCs and CI participants who were administered OBVAT; yet minimal differences were observed between baseline and outcome magnitude or rate of the base-in phoria adaptation experiment for those who were administered OBPT. The Table listed the descriptive statistics for the longitudinal base-out and base-in phoria adaptation experiments for all groups.

Figure 4 plots the group-level longitudinal results for the rates of the phoria adaptation experiment comparing outcome (grey bars) to baseline (black bars) measurements, which are plotted as the mean with plus and minus one standard deviation. Gender did not have a significant effect. For the base-out rate of adaptation, five BNC and eight CI participants were excluded as outliers defined as more than two standard deviations away from the mean. The mixed factor repeated measures ANOVA was computed. There was one within-subject main factor of time (baseline and outcome) and two between-subject independent factors of therapy type (OBVAT versus OBPT) and participant type (BNC versus CI). The primary hypothesis tested was OBVAT would lead to a more significant change in vision function compared to OBPT. The secondary hypotheses were (1) that a greater change would be observed in the CI group compared to the BNC group, and (2) the CI group post-OBVAT would not be significantly different than the BNC baseline data. The dependent variables included the magnitude and rate of both base-in and base-out phoria adaptation experiments.

For the base-in rate of adaptation, three BNC and nine CI participants were excluded as outliers. The base-in rate of adaptation showed a significant main effect of time ($F[1,96] = 7.2$, $P = 0.009$) in mixed factor repeated measure ANOVA but not for the interactions of time by therapy type or time by participant type ($P > 0.1$). The base-out rate showed a significant main effect of time ($F[1,96] = 5.2$, $P = 0.025$) in the mixed factor repeated measure ANOVA. The base-out rate of phoria adaptation showed a significant interaction for time by therapy type ($F[1,96] = 7.3$, $P = 0.008$) and for time by subject type ($F[1,96] = 6.2$, $P = 0.014$). Post hoc paired *t*-test analyses showed there was a significant change in the rate of phoria adaptation for the CI group who was administered the OBVAT intervention when comparing the outcome measurements to the baseline measurements for the base-in rate of prism adaptation ($t[24] = 3.5$, $P = 0.002$) and the base-out rate of prism adaptation ($t[24] = 3.7$, $P = 0.001$). All other groups (BNC who were administered OBVAT or OBPT and CI who were administered OBPT) did not significantly change ($P > 0.1$) when comparing the outcome measurements to the baseline measurements for the rate of phoria adaptation using paired *t*-tests.

Figure 5 plots the group-level longitudinal results for the magnitude of the phoria adaptation experiment comparing

Table. Descriptive Statistics of the Mean, Standard Deviation, and Change of Outcome Minus Baseline for Base-Out and Base-In Phoria Adaptation Experiments

	OBVAT					
	BNC			CI		
Parameters	**Baseline**	**Outcome**	**Change**	**Baseline**	**Outcome**	**Change**
Base-out magnitude (Δ)	3.4 ± 1.0	4.2 ± 1.3	0.8 ± 1.2	2.9 ± 1.1	3.7 ± 0.9	0.8 ± 1.2
Base-out rate (Δ/min)	4.2 ± 0.8	4.7 ± 0.9	0.5 ± 1.6	2.0 ± 1.3	3.2 ± 1.4	1.2 ± 1.3
Base-in magnitude (Δ)	3.4 ± 1.0	4.2 ± 1.3	0.8 ± 1.6	2.2 ± 0.5	3.1 ± 0.8	0.9 ± 1.0
Base-in rate (Δ/min)	2.1 ± 0.8	2.3 ± 0.8	0.2 ± 1.1	1.2 ± 0.8	2.1 ± 0.8	0.9 ± 1.1
Positive fusional vergence (Δ)	29.0 ± 8.6	32.7 ± 8.5	3.7 ± 8.4	11.0 ± 3.4	28.9 ± 10.4	17.9 ± 10.9
Negative fusional vergence (Δ)	14.2 ± 2.4	17.0 ± 4.1	2.9 ± 3.7	11.6 ± 3.8	15.8 ± 5.3	4.2 ± 4.1
	OBPT					
	BNC			**CI**		
	Baseline	**Outcome**	**Change**	**Baseline**	**Outcome**	**Change**
Base-out magnitude (Δ)	4.2 ± 1.2	4.0 ± 1.1	−0.2 ± 1.2	3.3 ± 0.8	3.1 ± 0.9	−0.2 ± 1.2
Base-out rate (Δ/min)	3.3 ± 1.1	2.7 ± 1.3	−0.6 ± 1.6	2.3 ± 1.3	2.6 ± 1.3	0.3 ± 1.0
Base-in magnitude (Δ)	4.0 ± 1.1	3.9 ± 1.2	−0.1 ± 1.4	2.5 ± 0.7	2.3 ± 0.8	−0.2 ± 0.7
Base-in rate (Δ/min)	2.6 ± 1.3	2.7 ± 1.3	0.1 ± 1.8	1.3 ± 0.4	1.6 ± 0.84	0.3 ± 1.1
Positive fusional vergence (Δ)	26.6 ± 8.3	25.5 ± 9.0	−1.1 ± 9.8	10.5 ± 3.7	17.9 ± 7.5	7.5 ± 8.6
Negative fusional vergence (Δ)	13.8 ± 2.6	16.5 ± 6.6	2.7 ± 5.9	11.4 ± 2.7	13.6 ± 2.8	2.2 ± 3.8

CI, convergence insufficiency; BNC, binocularly normal control; OBVAT, office-based vergence and accommodative therapy; OBPT, office-based placebo therapy.

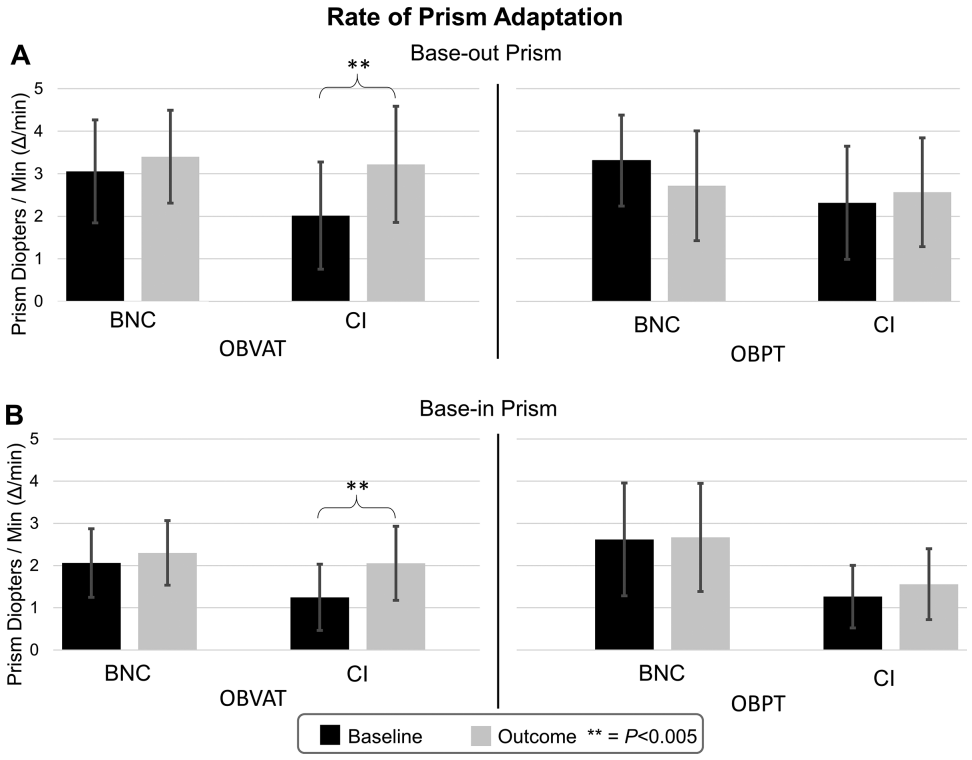

Figure 4. Longitudinal group-level average rates of adaptation for base-out (**A**) and base-in (**B**) prism adaptation plotted with one standard deviation comparing baseline (*black bars*) and outcome (*grey bars*) results.

outcome (grey bars) to baseline (black bars), which are plotted as the mean with plus and minus one standard deviation. For the base-in magnitude of the phoria adaptation, six BNC and seven CI participants were excluded as outliers. The base-in magnitude of the phoria adaptation showed a significant main effect for time ($F[1,96] = 10.1$, $P = 0.002$). An interaction effect was observed for time by therapy type ($F[1,96] = 14.4$, $P < 0.001$) but not for time by participant type ($P > 0.9$). For the base-out magnitude of adaptation, five BNC and eight CI participants were excluded as outliers. The base-out magnitude of phoria adaptation showed a significant main effect for time ($F[1,96] = 5.0$, $P = 0.027$) with a significant

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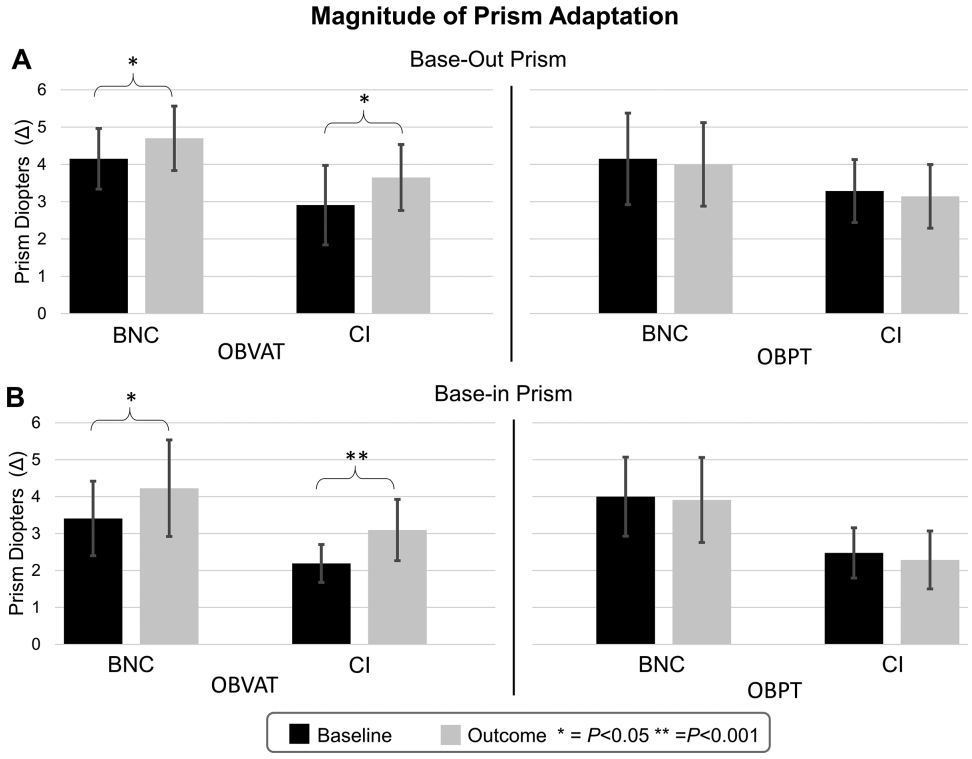

Figure 5. Longitudinal group-level average change in magnitude of adaptation for base-out (**A**) and base-in (**B**) prism adaptation plotted with one standard deviation comparing baseline (*black bars*) and outcome (*grey bars*) results.

interaction between time by therapy type ($F[1,96] = 8.4$, $P = 0.05$). However, no significant interaction was observed between time by participant type ($P = 0.7$). The post hoc paired *t*-tests showed there was a significant change for the CI group who had the OBVAT intervention when comparing the outcome measurements to the baseline measurements for the base-in change in magnitude of phoria adaptation ($t[24] = 4.4$, $P < 0.001$) and the base-out change in magnitude of phoria adaptation ($t[24] = 2.8$, $P = 0.009$). For the BNC group who were administered the OBVAT intervention, significant changes were also observed using a paired *t*-test comparing the outcome to the baseline measures for both the base-in ($t[24] = 2.6$, $P = 0.02$) and base-out adaptation ($t[24] = 2.3$, $P = 0.03$) change in magnitude of phoria. Significant changes were not observed for either the BNC or CI group who received the OBPT intervention for either the base-in or base-out change in magnitude of phoria adaptation ($P > 0.4$).

A correlation analysis was conducted between PFV with the base-out phoria rate and magnitude of phoria adaptation as well as between NFV with the base-in phoria rate and magnitude of phoria adaptation as shown in Figure 6 plots A through D. For the CI dataset, significant correlations were observed between PFV and base-out phoria rate of adaptation assessed via the Pearson's correlation coefficient ($r = 0.35$, $P < 0.0001$), between PFV and base-out magnitude of phoria adaptation ($r = 0.22$, $P = 0.04$), and NFV and base-in rate of phoria adaptation ($r = 0.35$, $P = 0.03$). Significant correlations were not observed for the correlation analysis for CI dataset for NFV and base-in magnitude of phoria adaptation ($r = 0.16$, $P = 0.15$) or the correlations between PFV and NFV and the magnitude and rate of phoria adaptation for the BNC group ($r < 0.16$, $P > 0.14$).

The final statistical analysis addressed the question of whether the CI participants who were administered OBVAT were significantly different than the baseline BNC measurements. Thus, unpaired *t*-tests were conducted on the base-out and base-in rate and magnitude of phoria adaptation measures to determine whether significant differences were observed between the baseline BNC dataset and the CI dataset post-OBVAT. For the base-out and base-in rates of phoria adaptation, the CI group post-OBVAT were not significantly different compared to the baseline BNC group (base-out rate: $t[64] = 0.24$, $P > 0.8$ and base-in rate: $t[63] = 1.02$, $P > 0.3$). Although the base-out and base-in change in phoria magnitudes were still significantly different between the BNC baseline dataset and the CI post-OBVAT dataset (base-out magnitude: $t[64] = 2.16$, $P = 0.035$ and base-in magnitude: $t[63] = 2.26$, $P = 0.027$), the significance level was reduced compared to the baseline data comparison of CI and BNC (base-out magnitude difference at baseline: $t[81] = 4.78$,; $P < 0.0001$ and base-in magnitude difference at baseline: $t[84] = 7.25$; $P < 0.0001$).

Discussion

The results of this study show that symptomatic young adult CI participants had significantly reduced magnitude and rate of base-out and base-in phoria adaptation at near compared to the BNC group. For the CI participants who were administered OBVAT, significant improvements in the magnitude and rate of base-in and base-out phoria adaptation were observed. For the BNC group, significant improvements were observed for the magnitude of the base-out and base-in phoria adaptation for those who were administered OBVAT but not those administered OBPT. For

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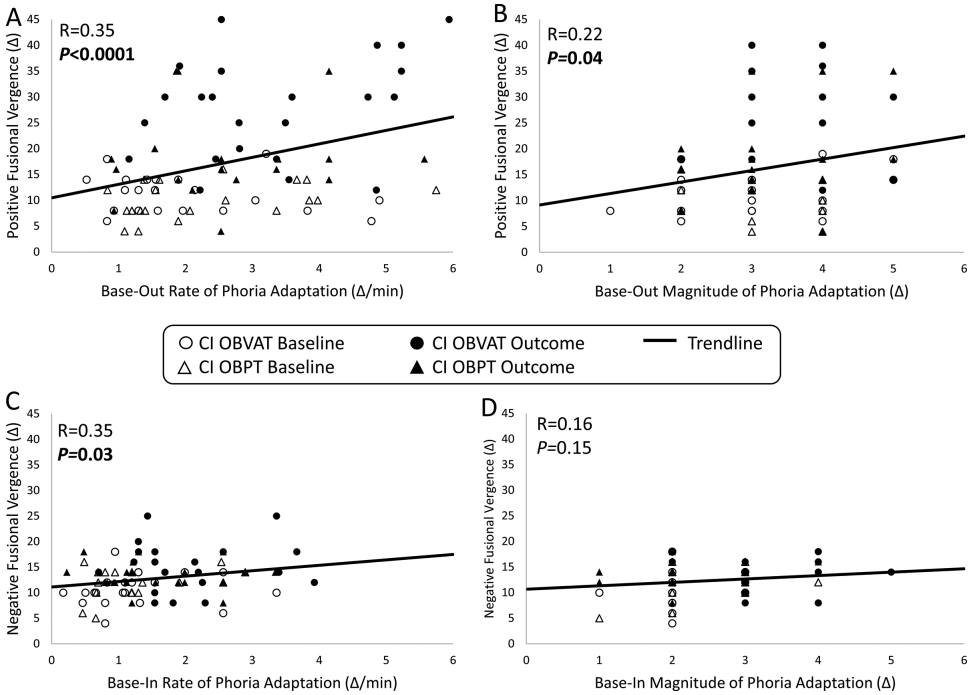

Figure 6. Correlation analysis between positive fusional vergence and base-out rate of phoria adaptation (plot A), positive fusional vergence and base-out magnitude of phoria adaptation (plot B), negative fusional vergence and base-in rate of phoria adaptation (plot C), and negative fusional vergence and base-in magnitude of phoria adaptation (plot D) for CI participants at baseline (open symbols) and outcome (closed symbols) for those participating in OBVAT (*circles*) and OBPT (*triangles*) with the corresponding trend line (*solid black line*). The Pearson's correlation coefficient (R value) and *P* value are shown in the upper left of each plot where significant correlations have a *P* value shown in bold font.

the BNC group, significant changes in the rate of phoria adaptation were not observed for either the base-out or base-in phoria adaptation experiment for either therapeutic intervention.

When comparing the CI rate and magnitude of base-out and base-in phoria adaptation post-OBVAT with the baseline BNC data, no significant differences were observed for the rate of base-out or base-in phoria adaptation between the groups. These results support that OBVAT administered for one hour biweekly for 12 office-based sessions with home enforcement did improve the rate of the phoria adaptation to levels observed within the BNC dataset at baseline. The magnitude of phoria adaptation was still significantly different for both base-out and base-in measures ($P < 0.035$) between the CI post-OBVAT data compared to baseline BNC data. These differences were substantially reduced compared to the CI and BNC baseline data for magnitude of phoria adaptation (baseline data significant differences were $P < 0.001$). Because the magnitude of phoria adaptation improved, one could speculate that perhaps with additional sessions of OBVAT then the differences in phoria adaptation magnitude would be eliminated. Future research with longer therapy durations is needed to determine whether increasing the number of OBVAT sessions further improves vision function.

Disparity Vergence Adaptation

The vergence and accommodation systems are linked through the AC/A and the convergence accommodation/convergence (CA/C) crosslinks.[62,63] Studies have suggested that developmental anomalies to the vergence and accommodation system lead to CI, convergence excess, or high heterophoria.[22,35,64] Adaptation is the ability to modify a system and numerous studies confirm that the fast fusional vergence system[65–67] and the slow fusional vergence system via phoria adaptation[59,68–70] can be modified in BNCs. The ability to adapt the fast fusional is correlated to the ability to adapt the slow fusional vergence system in BNCs, meaning those who can exhibit larger amounts of modification or change to the fast fusional system also exhibit larger amounts of change to the slow fusional vergence system and vice versa.[23,71] The ability to adapt the fast fusional system[72,73] and the slow fusional system[40,41] is reduced in patients with CI and improves post orthoptics/vision therapy.[30,31,43,55,74–77]

Prior studies of phoria adaptation report similar trends as those reported here. Specifically, Sreenivasan and Bobier assessed phoria adaptation using a 12 base-out prism comparing binocularly normal controls to patients with CI before and after orthoptics. They reported significant differences in the magnitude of phoria adaptation between controls and patients with CI at the initial assessment.[31] In their study, the six patients with CI who successfully completed orthoptics achieved significantly improved vision function to levels that were not significantly different than controls. There were a few differences between their study and ours. First, whereas they did assess 12 hours of orthoptics, their dosage was two 30-minute sessions per week compared to the 12 one-hour sessions we used. Second, the prism used for the phoria adaptation experiment was different between the studies. Although their results showed more significant improvement than ours, the trends between the studies were similar. Our results support that the ability

to adapt the slow fusional vergence system assessed using phoria adaptation is reduced in patients with CI compared to BNCs and significantly improves post-OBVAT intervention but not after OBPT.

Phoria Adaptation Correlated to Fusional Vergence

We previously published data showing that positive fusional vergence is significantly reduced in patients with CI and improves post-OBVAT to levels that are within normal ranges[21] as have many other RCTs[12,16,18,61,78] and non-RCTs.[31,43] We extend these findings to show that for patients with CI, the increased positive and negative fusion limits resulting from therapy are correlated with increased rates and magnitudes of phoria adaptation to base out and base in prism, respectively. The improvements of phoria adaptation after vision therapy, reflect an increased tonic vergence and thus increased fusion limits.[75]

Underlying Neural Mechanism

The underlying neural mechanism of phoria adaptation within the cerebellum is controversial. Some studies support that cerebellar activity is responsible in part for phoria adaptation because patients with cerebellar deficit or dysfunction via lesions have a reduced horizontal[79] or vertical[80] phoria adaptation response compared to normal participants. Patients with schizophrenia have also been shown to have reduced cerebellar function and studies find that these patients have reduced phoria adaptation.[81,82] FMRI on patients with CI also supports deficits in the oculomotor vermal areas within the cerebellum compared to BNCs.[45,83–86] Yet, human studies using transcranial stimulation support that the posterior portion of the cerebellum is in part responsible for fast fusional vergence adaptation but not for slow fusional vergence.[87] One neurophysiology study of primates supports that the phoria adaptation neural signal is present within the near response cells within the midbrain.[88] Future longitudinal studies are needed to evaluate which neural substrates are correlated to changes with the ability to adapt the phoria after therapeutic intervention.

Impact to Clinical Care and Future Research

Numerous studies suggest that vision therapy/orthoptics improves phoria adaptation in patients with CI.[43,55,74,75] Future studies may wish to consider therapeutic protocols that dissect vision therapy into components that rehabilitate fast fusional vergence, slow fusional vergence, or accommodation separately to determine how each of these aspects of vision therapy may improve the vergence and accommodation systems. Although some studies have concentrated on improving only disparity vergence,[83,89] most RCTs integrate many techniques that stimulate multiple components of vergence and accommodation systems.[12,14,18,20,21,52,89] The dissection of the components of therapy may lead to a better understanding of how each component of vision therapy alters the underlying neural circuits to improve the vergence and accommodation function. Such knowledge may lead to personalized point of care vergence and accommodation therapeutic interventions.

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