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The Convergence Insufficiency Neuro-mechanism in Adult Population Study (CINAPS) Randomized Clinical Trial: Design, Methods, and Clinical Data

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Abstract

Purpose—To describe the design and methodology of the Convergence Insufficiency Neuro-mechanism in Adult Population Study (CINAPS), the first randomized clinical trial (RCT) studying young adults with symptomatic convergence insufficiency (CI) using a combination of traditional clinical tests, objective eye movement recordings, and functional brain activities as outcome measures.

Methods—In this double-masked RCT, binocularly normal controls (BNC) (N=50) and CI patients (N=50) are randomized into office-based vergence/accommodative therapy (OBVAT) or office-based placebo therapy (OBPT). Outcome measures included clinical signs and symptoms, phoria adaptation, forced fixation disparity curves, binocular rivalry, vergence and saccadic objective eye movements, and task-induced functional brain activities. This study is registered on [ClinicalTrials.gov](https://clinicaltrials.gov).

Results—No significant baseline differences are observed between the BNC ($p>0.4$) or CI ($p>0.3$) participants assigned to OBVAT or OBPT for age, near point of convergence (NPC), positive fusional vergence (PFV), phoria at distance and near, amplitude of accommodation, or the Convergence Insufficiency Symptom Survey (CISS). Significant differences are observed between the CI and BNC cohorts at baseline measurements for NPC, PFV, difference in phoria from far to near, amplitude of accommodation, and CISS ($p<0.001$). For the CI patients, 26% had a comorbidity of accommodation insufficiency, and 16% self-reported ADHD.

Conclusion—Features of the study design include the following: standardized diagnostic and office-based therapeutic intervention, placebo treatment arm, masked clinical outcome examinations, objective eye movement recordings, functional imaging, phoria adaptation, fixation disparity curves and binocular rivalry measurements.

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Declaration of interest statement

No potential conflict of interest is reported by the authors.

Keywords

convergence insufficiency; randomized clinical trial; vergence; eye movement; functional MRI

Introduction

Convergence insufficiency is a prevalent condition affecting 4.2% to 17.6% of the general population.^{1–6} Clinical signs of CI include an exodeviation that is greater at near than at distance, a receded near point of convergence, and reduced positive fusional vergence at near.⁷ Over the past 25 years, this condition has been studied extensively, through the validation of diagnostic tests^{8–10} and symptom surveys,^{11–14} the establishment of diagnostic criteria,^{15–18} and multiple randomized clinical trials demonstrating the effectiveness of office-based vergence/accommodative therapy compared to base-in reading glasses,¹⁶ home-based pencil push-ups,^{18–20} and home-based computer therapy.^{18,20} These studies, along with a systematic review²¹ and meta-analysis²¹ have shown significant changes in traditional clinical measures, such as positive fusional vergence at near, the near point of convergence, and accommodative amplitude and facility, that persist for at least one year after completion of therapy.^{22,23} Improvement in symptoms, as measured by symptom surveys like the Convergence Insufficiency Symptom Survey (CISS), has also been demonstrated.^{17,24} What is not as clear, however, are the underlying neural changes and mechanisms responsible for these robust changes.

Studies investigating neural changes and mechanisms of vision therapy for CI patients have established an investigative pathway using objective eye movement recording,^{25–32} functional magnetic resonance imaging (fMRI),^{25,33,34} phoria adaptation,^{29,35,36} and fixation disparity.^{29,37–39} These studies have found significant changes in convergence peak velocity to symmetrical 4° disparity vergence step stimuli, significant changes to peak functional activation in the frontal eye fields, parietal eye fields, cerebellum and primary visual cortex, improvement in the magnitude and rate of phoria adaptation and a reduction in fixation disparity post therapeutic interventions compared to baseline measurements. However, the sample size in all previous studies is considered small and would not be considered statistically powered studies.

The purpose of the Convergence Insufficiency Neuro-mechanism in Adult Population Study (CINAPS) is to identify the underlying neural mechanism(s) that significantly change after office-based vergence/accommodative therapy (OBVAT). This report describes the standardized protocol established for this randomized clinical trial (RCT), including the diagnosis of CI, and a description of clinical testing and therapy procedures. Further, the methods for the acquisition and analysis of objective eye movement recordings, imaging assessments, phoria adaptation and fixation disparity measurements to be collected are also described. The objective eye movement assessments includes an investigation of disparity vergence eye movements with an emphasis on exploring the Dual Mode Theory,^{40–45} investigation of which of the Maddox vergence components (disparity, blur and proximal visual cues)^{46,47} are modified post therapy, and assessment of changes in phoria adaptation, forced fixation disparity curves, and binocular rivalry. Eye movement outcome

measurements assess the Maddox components specifically disparity, blur and proximal inputs to the vergence. Data analysis for all objective eye movement responses include the following: latency, peak velocity, final amplitude and the variability between eye movements which are needed to assess the vergence and saccadic systems. Functional imaging will allow an objective measurement of functional activity by assessing the magnitude and spatial extent of the blood oxygen level dependent (BOLD) signal. With a more complete and sophisticated appreciation of the neural mechanisms underlying the success of vision therapy, researchers and clinicians should be able to modify current treatment strategies and increase treatment effectiveness for this prevalent condition.

Materials and Methods

The tenets of the Declaration of Helsinki are followed throughout the study. The institutional review boards of the New Jersey Institute of Technology and Rutgers University approved the protocol and informed consent forms. All participants provided written informed consent. The study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) as Neural Mechanism of Vision Therapy for Patients with Convergence Insufficiency: .

Study Design and Aims

The study is a double-masked, placebo-controlled, RCT. Participants between the ages of 18 to 35 years with either symptomatic convergence insufficiency (CI) or normal binocular vision are recruited and randomized to one of two interventions: 1) office-based vergence/accommodative therapy (OBVAT), or 2) office-based placebo therapy (OBPT). The participant is assigned to either OBVAT or OBPT therapy using a randomized vector with a 1:1 allocation ratio (n=50) created by a random number generator within a custom MATLAB program using the procedures described in the CONSORT 2010.^{48,49} The allocation sequence is concealed from investigators and participants. During the consent process, participants are told that they would be randomly assigned to either active or placebo therapy and would not be told which therapy group they are assigned to until all outcome measures are successfully collected. For the CI patients who participated in OBPT, participants are told that they could then participate in active therapy at the end of the study at no additional cost to them. Participants in each treatment group receive 12 hours of office-based treatment (1 to 2 sessions per week, each session lasting about one-hour in duration) and 3 hours of home reinforcement (3 sessions per week, each session lasting for about a ten-minute duration). Figure 1 provides an overview of the study design.

The specific aims of the study are: 1) to compare the effectiveness of OBVAT to OBPT for improving clinical measures and symptoms in young adults with symptomatic CI; 2) to investigate the changes in the underlying neural mechanisms of the oculomotor system after vergence/accommodative therapy including the Dual Mode components of the disparity vergence eye movement system, the Maddox components of vergence (disparity, blur, and proximal stimuli), phoria adaptation, forced fixation disparity curves, and binocular rivalry; and 3) to study the following vergence system cortical and subcortical regions of interest (ROI): bilateral frontal eye fields, supplementary eye field, bilateral parietal eye fields,

oculomotor vermis with surrounding cerebellar regions, and primary visual cortex using stimulus-induced functional MRI tasks.

Patient Selection

Symptomatic convergence insufficiency—Major eligibility criteria included age between 18 to 35 years of age (inclusive) and meeting the study definition of symptomatic CI. This definition of CI is: 1) a score of ≥ 21 on the CISS; 2) exophoria at near at least 4 prism diopters () greater than at distance; 3) a receded near point of convergence of ≥ 6 cm break, and 4) insufficient positive fusional vergence (i.e., failing Sheard's criterion⁷ or positive fusional vergence < 15 base-out) at near (measured at 40 cm along participant's midline). Sheard's criterion states that for an individual to be comfortable, the positive fusional vergence blur measurement must be at least twice the magnitude of the near phoria.⁵⁰ This study is of young adults and a blur measurement is not always reported. When a blur measurement is not available, the break measurement is used for Sheard's criterion. Complete inclusion and exclusion criteria are listed in Table 1.

Normal binocular vision—Major eligibility criteria included age between 18 to 35 years of age (inclusive), visual acuity 20/25 or better with best correction, normal binocular vision and accommodation. Table 1 lists complete inclusion and exclusion criteria.

Accommodation Insufficiency—Amplitude of accommodation is the primary measure used for the diagnosis of accommodation insufficiency (AI). AI is diagnosed when the amplitude of accommodation is at least 2 diopters (D) below the minimum age-appropriate amplitude according to Hofstetter's formula of 15 minus one quarter of the participant's age.⁵¹

Eligibility Examination/Protocol

Clinical testing is performed by an optometrist at the eligibility examination and included best-corrected visual acuity at distance (6 m) and near (40 cm), non-cycloplegic auto-refraction, CISS, stereopsis, cover/uncover (unilateral cover) test at distance and near, alternate cover test with prism neutralization at distance and near, negative fusional vergence (blur, break, and recovery) at near, positive fusional vergence (blur, break, and recovery) at near, near point of convergence break and recovery, vergence facility at near, and push-up accommodative amplitude. This battery of tests has been used in previous RCTs.^{52,53}

Protocol for Clinical Baseline and Outcome Measures

The near point of convergence and amplitude of accommodation is measured with the Astron International Accommodative Rule (Bernell Corporation, Mishawaka, IN, USA). The device consists of a rod with a movable, single column of letters (20/30 equivalent at 40 cm). Positive fusional vergence (convergence amplitudes) at near is measured with a horizontal prism bar (Gulden B-16 horizontal prism bar levels from 1 to 45 , Gulden Ophthalmics, Elkins Park, PA, USA) while the patient fixates on a hand-held fixation target (Gulden Fixation Stick # 15302) with a single column of letters of 20/30 equivalent. Refraction is measured with a Grand Seiko Binocular Autorefractor (WR-5100K, Bensenville, IL, USA).

Stereopsis is measured with the Stereo Randot Test (Bernell Corporation, Mishawaka, IN, USA).

The CISS is administered before any other test. Each response is scored as 0 to 4 points, with 4 representing the highest frequency of symptom occurrence (i.e., always). The 15 question scores are summed to obtain the total CISS score. The lowest possible score (least symptomatic) is 0 and the highest is 60 (most symptomatic). A symptom score ≥ 21 has been found to differentiate young adults with symptomatic CI from those with normal binocular vision with a sensitivity of 97.8%, specificity of 87%, and an interclass correlation coefficient of 0.885.^{11,12}

Patient compliance

The home therapy is computer-based and data about the number of sessions performed, time spent, and performance achieved are all accessible to the research team through the internet. Participants for both OBVAT and OBPT are encouraged to perform their home-based activities during each office-based session. Home-based therapy patient compliance is calculated by dividing the number of sessions completed at home by the maximum number of at-home sessions prescribed, which is 18 home sessions for this study.

Clinical Outcome Measures for Successful and Improved Remediation

The primary outcome measure for the RCT is a composite of two clinical measures used to assess the treatment outcome. A successful outcome is defined as a near point of convergence <6 cm, and for positive fusional vergence passing Sheard's criterion⁷ or having a base-out break finding >15 . An "improved" outcome is defined as a decrease (improvement) in the NPC of >4 cm, and an increase in positive fusional vergence of ≥ 10 .

A secondary outcome measure is the CISS score. We designed the study with the CISS as a secondary outcome because it is a subjective measure, and chose the less subjective, composite measure of clinical findings as the primary outcome measure. In a previous study, the CISS score of <21 is considered "successful" and a decrease of ≥ 10 points is improved.¹¹⁻¹⁴

Objective Eye Movement Measures

Overview—Three objective eye movement protocols are conducted: 1) Dual Mode Components of vergence experiment, 2) Maddox Components of vergence experiment, and 3) a saccadic experiment. All experiments used novel instrumentation shown in Figure 2A. Two graphics cards (NVIDIA GeForce GTX 760, Santa Clara, CA, USA) are used to allow a single computer to communicate with one control monitor and a total of four stimulus monitors, enabling virtually instantaneous stimulus presentation on any monitor so that the transient and steady-state portions of the eye movement responses could be studied. Stimulus monitors 1 and 2 (SM1 and SM2) form a traditional haploscope which keeps the focal distance from the retinal to the visual stimulus virtually constant and allowed the amount of retinal disparity to be changed while keeping the blur stimulus constant. The addition of visual displays SM3 and SM4 allow for a change in focal length and hence a blur stimulus. This addition also enables the presentation of monocular stimuli, as a stimulus is

presented from SM3 to SM1 in a darkened room, where no stimuli are present on SM4 and SM1, creates a monocular stimulation to the left eye. SM3 and SM4 are placed 1m away from the participant's eye (1D accommodative demand) and SM1 and SM2 are placed 40 cm away from the participant's eye (2.5D accommodative demand). Hence, looking at a target on SM4 to SM2 stimulates a 1.5D accommodative, blur step-change.

An ISCAN RK-826PCI infrared ($\lambda = 940$ nm) binocular tracking video-based eye movement tracking system (Burlington, MA, USA) is placed 38 cm away from the participant's midline per the manufacturer's recommendation. This system has a frame rate of 240 frame per second. Left and right eye movements are collected independently. Participants are centered in front of two partially reflective mirrors (50%), see Figure 2A. Each mirror displayed the respective image from a stimulus monitor. The system called the NJIT VisualEyes 2020 System is a custom software package written in LabVIEW™ 2013 SP1 Virtual Instrument (National Instrument, Austin, TX, USA) that digitizes the horizontal and vertical position of the left and right eye movements with the horizontal diameter of each pupil using 16-bits.⁵⁴ A PlusOptix PowerRef 3 (Atlanta, GA, USA) is also integrated into the design to record the accommodation response from the human eye lens at 50 Hz.

Eye movement responses are calibrated with 6 monocular targets at 1°, 3°, 5°, for vergence stimuli farther from the participant and at 4°, 5° and 6° for vergence stimuli closer to the participant. These monocular demands are presented to the left and to the right eye independently. Monocular calibration is important to reduce the influence of fixation disparity.⁵⁵ CI participants tend to have more fixation disparity compared to BNC.³⁷

Dual Mode Components of Vergence Eye Movement Experiment—The Dual Mode theory specifies that the fast fusional vergence system is composed of a preprogrammed system called the fusion initiating component (FIC) and a feedback system called the fusion sustaining component (FSC).^{42,56,57}

The CINAPS Dual Mode components of vergence eye movement experiment systematically studies the fast-fusional disparity vergence system using vergence step (also called jump vergence or jump duction) stimuli that studies the FIC. A disappearing symmetrical vergence step instantaneously changes from one angular vergence demand to another for a presentation time of only 100 msec.^{41,58} Since the presentation time is 100 msec and vergence latency is typically 180 to 220 msec, the error signal needed for a feedback loop system is not available when the eyes begin to move.⁵⁹ This is important because the absence of a target (no error signal) prevents the feedback system or the FSC component from being stimulated. Hence, the disappearing step stimulates predominantly the FIC. The initial vergence angular demands are between 2° to 12° in increments of 2° for the convergence and divergence step stimuli. The timing of these vergence step stimuli are randomized between 0.5 to 2.0 seconds as are the starting and ending vergence angular demand. Stimuli are pseudo-randomized to reduce the influence of prediction which is known to decrease latency and increase vergence peak velocity.^{60,61}

The FSC is assessed with ramp stimuli that are presented after an initial vergence 2° step stimulus. Slow and fast ramps of 1°/s and 4°/s, respectively, are used to assess the stability,

gain, and error of the FSC. These two speeds are chosen to study the FSC and FIC in different combinations. Vergence ramps of less than 1.4 °/s generally produce a smooth vergence response (mostly FSC) while speeds of more than 2.7 °/s elicit more step-like vergence (combination of FSC and FIC).^{62,63} Hence, the Dual Mode experiment systematically studies the fast-fusional disparity vergence system by using stimuli that isolate the FIC or FSC or studied both components when stimulated together. This experiment requires about 35 minutes to complete.

Maddox Components of Vergence Eye Movement Experiment—Maddox described the following three primary cues to stimulate the vergence system: disparity, blur and proximal cues.⁴⁷ In BNCs, studies concur that disparity and blur are the two major inputs to the vergence and accommodative systems, respectively.⁶⁴ While many studies assume that proximal input is minimal, Schor showed that looming stimuli, which gives a participant a sense of objects being close or far, is an important factor.^{65,66} Horwood dissected the visual environment to study disparity, blur, and proximal cues to the vergence and accommodation systems in esotropic or exotropic patients and found that the patients' responses to cues differed significantly from BNCs.⁶⁷ The contribution of disparity, blur, and proximal cues to generate vergence and accommodative responses from CIs before and after OBVAT is unknown.

The CINAPS Maddox components of vergence eye movement experiment studied the vergence eye movement position (using the ISCAN) and the accommodation response (using the PlusOptix PowerRef 3) stimulated by the following cues: disparity (d), blur (b), and proximal (p), in blocks of all cues [dbp], one cue deprived [db(-p); dp(-b); bp(-d)], and one cue only [d; b; p]. Proximal vergence is stimulated via looming a stimulus^{66,68} (visual stimulus that changes size as a function of distance from participant's midline) and is diminished (open-looped) when it is scaled to subtend the same visual degrees within the retina at different distances. Accommodative vergence is stimulated via blur by placing objects at difference distances away from participant and is diminished (open-looped) when using a Difference of Gaussian (DoG) stimulus that has low spatial frequency.⁶⁹ Disparity vergence is stimulated binocularly when each eye views its own image offset (disparate) from the other eye and is diminished (open-looped) when one eye is occluded (monocular viewing).

Disparity, Blur, Proximal (dbp) Stimulus Setup: Natural viewing conditions stimulate all three vergence components (dbp combined cues) via binocularly (d cue) viewing a target of high acuity (b cue) that subtends a larger field at near than far i.e. looming target (p cue). For the blur used within the accommodation only stimulus setup (b cue), the participant views a high acuity target (Maltese cross) target monocularly and this target is designed not to change the vergence disparity or proximal demand (scaled). For the disparity only stimulus setup (d cue), a traditional haploscope is used to keep targets at the same focal distance using a scaled DoG stimulus, reducing both blur and proximal cues. For the proximal only stimulus setup (p cue), monocular viewing of a looming DoG target is used. Visual Stimuli are shown in Figure 2B.

Studying the Maddox components of vergence required the use of all four stimulus monitors shown in Figure 2A. The visual stimuli to be studied are shown in Figure 2B, including the Maltese cross to stimulate accommodation, the Gabor patch that uses a DoG stimulus to study foveal disparity, and the DoG ring for peripheral stimulation. Stimuli are summarized in Table 2. All three cues for natural viewing conditions (dbp) is conducted at the beginning and at the end of the experimental session to assess whether visual fatigue is impacting the vergence and accommodation systems.^{70,71} This experiment requires about 50 minutes to complete.

Saccadic Eye Movement Experiment—The Saccadic eye Movement experiment is included as a control to verify that the instrumentation for eye movement data acquisition is working properly for each participant. It is unknown whether saccades are dysfunctional in CI patients. Saccades are typically easier to measure compared to vergence because they are an order of magnitude faster.^{72–74} Other studies report that the saccadic system improves post vision therapy for those with vergence dysfunctions supporting an interaction between the systems.⁷⁵ In addition, patients with CI may utilize saccades to facilitate binocular coordination.^{30,76} We hypothesize that if a CI participant is unable to initiate or maintain fusion for the vergence stimuli but is able to accurately initiate and maintain saccadic movements, it suggests that the dysfunction is mostly within the vergence system and the saccadic system is not the dominant dysfunction. In addition, the ability to initiate saccades rule out an instrumentation problem for eye movement data acquisition. The saccadic eye movement experiment uses simple saccadic stimuli. Leftward and rightward 5° and 10° saccades are presented at a 40 cm working distance from the midline of the participant. Saccades are presented on the haploscope using stimulus monitors SM1 and SM2. This experiment requires about 2 minutes to complete.

Objective Eye Movement Recording Data Analysis—After raw eye movement data are calibrated, the vergence position is calculated by taking the difference of the right and left eye positional data (in degrees). For analysis purposes, convergence is plotted as positive and divergence is plotted as negative. Vergence data are filtered with a second-order low pass Butterworth filter with a cut off frequency of 40 Hz, while saccade data are filtered with a cut off frequency of 120 Hz. The latency, time to peak velocity, maximum velocity, and positional steady state amplitude are measured for all eye movements from the following three eye movement experiments: Dual Mode, Maddox, and Saccades, see Figure 3. The response latency is automatically measured as the time when the vergence eye position increases from the initial vergence angle by an increment of 10% of the total stimulus movement, (for example, 0.4° or 0.6° for the 4° and 6° vergence steps, respectively) see Figure 3A. A two-point central difference algorithm is used to compute the vergence velocity response.⁷⁷ The time to the peak velocity, maximum value of the velocity and final response amplitude are measured. The fusion initiating component (FIC) of vergence is measured within the phase plane (Figure 3B) which is a plot of velocity (in degrees / sec) as a function of position (in degrees). The raw eye movement data (blue line Figure 3B) is fit with a second order polynomial (green line Figure 3B). The non-zero root of the polynomial is the FIC as shown by the 'X' in Figure 3B.^{42,60} Peak velocity will be a primary outcome of

this study because the vergence response correlates to the velocity-encoding burst cell described within the midbrain.⁷⁸

Forced Fixation Disparity Curves (FDC)

Fixation disparity is defined as the small vergence misalignment when viewing binocularly.⁷⁹ A FDC is a graphical representation of the fixation disparity as a function of vergence demand (changed using a prism) and can be used to predict the influence of phoria on vergence accuracy and phoria adaptation.⁸⁰ Several independent laboratories have shown that FDCs with steep slopes and larger fixation disparities are found more frequently in visually symptomatic participants compared to BNCs and improve post vision therapy.^{29,39,79,81,82} Fixation disparity is related to the peak velocities of the fast fusional vergence system.^{83–85} The FDC serves as a measurement to assess the ability to adapt the visual system to near and far space. We hypothesize that the slope of the FDC will differ between BNC and CIs before OBVAT, and that the slope will become less steep for CIs who report a reduction in visual symptoms (via CISS) after OBVAT. A Sheedy Disparometer is used.⁸¹ The experiment began with the participant wearing habitual correction. The prismatic demand is alternated between a base in (BI) and base out (BO) prism between the range of 2 to 20 in increments of 2 and then from 25 to 45 in increments of 5 until the participant reports diplopia. The following parameters are assessed: 1) slope, 2) shape, 3) center of symmetry, 4) associated phoria, and 5) fixation disparity.

Phoria Adaptation

Phoria adaptation is mediated using predominantly the slow fusional vergence system.⁸⁶ A Bernell Muscle Imbalance Measure (MIM) card (Bernell Corp., South Bend, IN) is positioned at eye level along the participant's midline 40 cm away from the participant. Two baseline phoria measurements are recorded using the flashed Maddox rod technique.⁸⁷ The occluded eye is covered for 15 seconds and the participant is instructed to report the location of the vertical red streak on the MIM card. The participant then holds a 6 BI prism and sustains fixation on an 20/30 letter chart placed on the top of the MIM card for 30s and the phoria measurement is repeated through the prism. A total of 15 recordings are measured each separated by 30 seconds for a total of 7.5 minutes of phoria adaptation. Participants are given a 5 to 10-minute break so that their phoria returns to its baseline measurement. If the phoria does not return to the baseline value within 10 minutes, then the participant will return on another day. The protocol is repeated with a 6 BO. A total of 15 measurements are recorded, each separated by 30 seconds of sustained fixation. The change in the magnitude, the time constant and the rate of phoria adaptation are assessed. The hypothesis tested is that the CI participants would have a reduced magnitude, time constant, and rate of phoria adaptation compared to BNCs and these measures would improve post OBVAT.^{29,35,36,88}

Binocular Rivalry

Some clinicians view CI as a motor disorder with relatively normal sensory function because stereopsis is typically normal.⁷ However, one paper suggests that CI patients have an unstable monocular eye preference.³⁰ Hence, it is unclear whether differences may exist between BNC and CI participants for sensory perception. A binocular rivalry experiment is

conducted using a horizontal and vertical Gabor patch presented on SM1 and SM2 of the instrumentation shown in Figure 2A similar to methodology described by Ooi.⁸⁹ A custom computer script is used so that a participant would press the arrow up or arrow down on a computer keyboard to quantify the number of horizontal versus vertical percepts to assess sensory dominance.

Functional MRI (fMRI) Experiments

Data Acquisition—Participants are positioned supine onto the gantry of a 3T Siemens TRIO (Siemens Medical Solutions USA), see Figure 4A. Participants are centered with the 12-channel head coil so that they are symmetrically positioned into the MRI. This facilitates consistency in the data and allowed better acquisition of eye movement data. Video-oculography is performed with an EyeLink 1000 camera (Ottawa, Ontario, Canada) recording the right eye at 250 frames per second. Participants are verbally instructed to limit head motion. Foam wedges are placed around the head to minimize involuntary head motion. Data are acquired with an axial configuration. High resolution anatomical volumes are acquired using a magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence. The MP-RAGE imaging protocol has the following parameters: time of repetition (TR) = 1900 ms, time of echo (TE) = 2.52 ms, T1 = 900 ms, flip angle = 9°, field of view (FOV) = 256 mm, and a total of 176 acquired slices. The voxel resolution is 1.0×1.0×1.0 mm³. The fMRI protocol for all task-induced and resting state scans use an echo planar imaging (EPI) pulse scan sequence that have the following parameters: TR = 2000ms, TE = 13ms, Field of View = 192mm, flip angle = 90°, 53 axial slices acquired at a resolution of 3.0×3.0×3.0 mm³. The total amount of time in the fMRI scanner is 90 minutes to complete all experiments.

Stimuli during FMRI Experiment—The following tasks are conducted during the fMRI experiment: vergence symmetrical step eye movement, sensory stimulation from vergence eye movement stimuli, saccade eye movement stimuli, phoria adaptation, finger tapping, and breath hold. A five-minute rest scan is also acquired.

Vergence Symmetrical Step Eye Movement Task: Vergence stimuli alternated between the following three blocks shown in Figure 3B: 1) 21 sec of sustained fixation, 2) frequency of low occurrence (FLO) task block lasting 18 sec evoking 4 vergence movements (about 4.5 sec allotted per stimulus), and 3) frequency of high occurrence (FHO) block lasting 19 sec evoking 8 vergence movements (about 2.4 sec allotted per stimulus). The exact timing per vergence stimulus varied up to 1 sec to reduce the influence of prediction.⁹⁰ There are five cycles presented ending with a rest block. The total acquisition time is 416 sec with a total of 208 volumes. The FLO block visual sequence of binocular symmetrical vergence demand stimuli are presented in the following order: 4° Convergence (Con), 4° Con, 6° Divergence (Div), 4° Con. The FHO block visual sequence of binocular symmetrical vergence demand stimuli are presented in the following order: 4° Con, 4° Con, 6° Div, 4° Con, 4° Con, 6° Div, 4° Con, 4° Div. The block design of rest intermixed between FLO and FHO blocks is engineered to reduce the possibility of artifacts from blood flow changes that may oscillate at the same frequency as our experiment and is modeled after a prior fMRI experiment studying saccades.⁹¹ This visual sequence will evoke both the afferent sensory pathway and

the efferent motor pathway. This visual sequence is preformed twice within the same visit. Participants are first shown the visual stimuli shown in Figure 3C in the laboratory and allowed to practice fusing the images. With these stimuli, when the images are properly fused using convergence, the middle and inner square appears to be closer to the observer compared to the outer square (Figure 3D, Converging). Conversely, when the eyes are fused using the divergence system, the middle and inner square appears further away from the participant compared to the outer square (Figure 3D, Diverging).

Sensory Stimulation to Vergence Eye Movement Task: This scan is identical to the vergence symmetrical step eye movement task except the participant is instructed to fixate on the middle of the screen and not move their eyes. This experiment is conducted to image the regions of interest that are involved in the sensory pathway of the vergence network. We know whether the participants are doing the experiment properly when the eye movement responses from the scanner are inspected and sustained fixation is observed. This experiment evokes predominantly the sensory afferent pathway. By taking the difference between the motor and sensory data sets, it is hypothesized to yield predominantly the efferent motor portion of the vergence network.

Saccade Eye Movement Task: The protocol structure is similar to the vergence eye movement task of rest blocks in between the FLO and FHO blocks, Figure 4B. For saccade fMRI experiment, the rest block is 16 seconds in duration and the FLO and FHO blocks are each 24 seconds in duration. During the rest block, participants sustain fixation. During the FLO block, 12 saccades are presented; in the FHO block, 24 saccadic stimuli are presented. The saccades are between 2° and 6° in magnitude into the right or left visual field. Similar eye rotations magnitudes for the saccade and vergence experiments are chosen so that the eye movement monitor did not need to be adjusted between the vergence and the saccadic experiments. The sequence is repeated 5 cycles ending with a rest block of sustained fixation. The total time of this scan is 416 seconds acquiring 208 volumes.

Finger Tapping Task: The finger tapping task is a control task. The hypothesis is that we are not training the finger motor system and hence the results of the finger tapping task should be very similar within a longitudinal study comparing baseline measurements to the measures after therapeutic intervention. This task sequence is simplistic and is rest (16 seconds) followed by the participant tapping their fingers slowly (20 seconds) followed by the participant tapping their finger quickly (20 seconds), both self-paced. The sequence is repeated 3 times ending with a rest block. The total time is 184 seconds acquiring 92 volumes.

Phoria Adaptation Task: This sequence involves sustained fixation for 90 sec durations for 6 blocks. The participants alternate between viewing a target with a 2° convergence demand and then an asymmetrical vergence target with a 14° convergence demand. The difference between these two angular demands is 12° which is about 6 .The 6 base out or base in stimuli are chosen based upon the phoria adaptation experiments conducted on CI and BNC showing statistically significant differences in phoria adaptation rates and magnitudes.^{35,92} Sustained fixation is shown to adapt the phoria.⁹³⁻⁹⁶ Our group has shown that an

asymmetrical 6 phoria adaptation task has a faster time constant compared to a symmetrical 6 phoria adaptation task.⁹⁷ This task is 540 seconds or 270 volumes. This task is designed to study the slow fusional vergence system which is stimulated via phoria adaptation.

Breath Hold Task: The breath hold task alternates between rest which is breathing normally (30 seconds) and the participant holding their breath (20 seconds). This sequence is repeated for 4.5 cycles ending with normal breathing. The total time is 230 seconds or 115 volumes. Established literature reports that the breath hold experiment is a study of the hemodynamic response of each participant's brain.⁹⁸

Rest Scan: The rest scan is 300 seconds in duration and is conducted to study the resting state networks of the brain. A total of 150 volumes are acquired.

Data Analysis for fMRI

Individual-Level fMRI Imaging Data Analyses

fMRI data preprocessing: After image acquisition, the data are preprocessed using the SPM12 toolbox in MATLAB. All the functional volumes are realigned to the first functional volume in the sequence in order to reduce the influence from minor head motion. Then, the functional volumes are co-registered to same participant's anatomical MP-RAGE images. The anatomical images are segmented into three different tissue types and tissue probability maps pertaining to cerebral spinal fluid (CSF), white matter (WM) and grey matter (GM). After segmentation, a normalization step is performed where deformation fields (a transfer function) are derived to map anatomical and functional images into Montreal Neurological Institute (MNI) standard space⁹⁹ for group-level analyses. Principal component analysis is conducted on the BOLD fMRI time series of the CSF and WM voxels and the first 5 principal components of each are extracted. A total of 34 nuisance variables are regressed from the dataset. These include six head motion parameters, six auto-regressors of head motion parameters, six quadratics of head motion parameters, six quadratics of auto-regressors,^{100,101} and ten principal components (five for CSF and five for WM).^{102,103} This regression facilitates the reduction of the effect of physiological noises on the BOLD fMRI signal. The resulting functional volume is filtered with a high pass filter (cutoff frequency of 0.01 Hz). The data are spatially smoothed using a Gaussian kernel with 6 mm full width half maximum (FWHM).

Voxel-based whole brain activation map generation: A general linear model with a canonical waveform (double gamma function, the SPM default) shown below is used to calculate the voxel-wise single participant beta weights stimulated by each of the following tasks: 1) vergence eye movement, 2) sensory stimulation to vergence system, 3) phoria adaptation, 4) saccade, 5) finger tapping and 6) breath hold.

$$HRF = G(6,0.125) - \frac{G(16,0.125)}{32} \quad \text{Eq. (1)}$$

Region-of-Interest (ROI)-based activation analyses: Prior pilot research studying BNC and CI participants who participate in vision therapy observe changes within the following regions of interest (ROI): the bilateral Frontal Eye Fields (FEF), Supplementary Eye Field (SEF), and bilateral Parietal Eye Fields (PEF).^{104–106} The cerebellar vermis, also termed the oculomotor vermis, is active during a saccadic motor learning task.¹⁰⁷ Hence, task-induced activation in the following ROIs are studied: bilateral FEF, SEF, bilateral PEF, and the oculomotor vermis. The primary visual cortex is studied as part of the visual sensory neural substrate. Broca's region is also studied since it is not activated during an eye movement or finger tapping task and serves as an ROI to study the variability from a non-task-induced region. Each ROI is defined using 5mm radius spheres centered on the peak activation voxel in the BNC dataset at baseline.

Group-Level Statistics for fMRI: The beta weight maps from the individual participants are converted to T-statistics values, or T-maps. Group level activation maps are obtained from T-maps with a significance level of $p < 0.05$ corrected for multiple comparisons by using false discovery rate (FDR) with the FMRIB (Functional Magnetic Resonance Imaging of the Brain) Software Library (FSL) randomize function. There are two group-level statistical analyses. First, the T-maps reflect voxel level activity in response to each task, which is used to compare population group data sets. Specifically, the T-maps from BNC cohort data set are compared with the CI cohort data set using a two-sample t -test. Paired t -tests are performed between pre- and post-therapy sessions to assess longitudinal effects of therapy for both the BNC dataset and the CI dataset. Second, an ROI-based group-level analysis is performed. The peak and mean T-statistics per ROI are reported within each identified 5mm sphere. A repeated measure ANOVA is used to determine statistical differences between the 4 cohorts (CI and BNC participants post-OBVAT and CI and BNC participants post-OBPT).

Power Analysis

The sample size calculation is performed using paired t -tests with equal variance for CI participants from both OBVAT and OBPT. The CITT defined the clinically relevant true mean difference for CISS, NPC, and PFV to be 10, 4cm, and 10 with a standard deviation of 12, 4.5cm, and 11.3, respectively.⁵³ This gives a standard deviation of the difference (OBVAT minus OBPT) to be 19, 2cm, and 19, respectively. Assuming 80% power, Alpha = 0.05, and adjusting for a 90% retention rate, results in the number of participants needed to be 28, 4, and 28, respectively. Using the maximum sample size for all three conditions to be satisfied yields a cohort size for recruitment goal of 28 per arm (56 controls and 56 CIs). This recruitment goal is needed to attain the needed 25 samples per cohort after 10% retention loss for a sufficient statistically powered study.

Randomization

Each participant is assigned to either OBVAT or OBPT using a randomized vector with a 1:1 allocation ratio created by a random number generator within a custom MATLAB script which follows the randomization procedures describe in CONSORT 2010.^{48,49} The randomization algorithm assigns patients to the two treatment groups with equal probability. Access to the randomized vector is only accessible to the research coordinator and is not

available to the clinical examiner or the primary investigator of the study. The clinical examiner and the study primary investigator are masked from the randomization process.

Therapeutic Intervention

The treatment prescribed is either office-based vergence/accommodative therapy (OBVAT) or office-based placebo therapy (OBPT). Participants are scheduled for 1 or 2, one-hour therapy sessions per week during which office-based procedures are performed, home therapy procedures are demonstrated, and the therapist verbally motivated the patient to maximize adherence. Home-based computerized therapy is performed 3 days per week for 10 minutes per session on the days when office-based therapy is not performed.

Office-Based Vergence/Accommodative Therapy (OBVAT)—Vergence/accommodative therapy is administered by a study-certified therapist and is performed on an individual basis. The treatment program consists of 3 phases. Within each phase, therapy procedures are arranged sequentially from the easiest to the most difficult. Participants participated in one to two weekly visits lasting approximately 60 minutes per visit and are prescribed 10 minutes of home therapy procedures to be completed 3 days per week. The vergence therapy is primarily designed to improve fusional vergence by maintaining accommodation at the plane of the target while changing the vergence demand. In such a situation, the participant must use fusional vergence, rather than accommodative/vergence to maintain single binocular vision. A variety of therapy techniques (Vectograms, Aperture Rule, Eccentric Circles, Computer Orthoptics) are used to achieve these goals. The therapy is carefully sequenced to gradually increase the level of difficulty of the tasks. The therapy program is summarized in Table 3.

Office-Based Placebo Therapy (OBPT)—Placebo therapy is administered by a study-certified therapist and is performed on an individual basis. Therapy procedures in this treatment arm are designed to simulate actual vision therapy without having a known effect on vergence, accommodation, or saccadic function.¹⁰⁸ Therapists are asked to maintain the same level of enthusiasm as they did for the vergence/accommodative therapy procedures which has been shown to be an effective placebo therapy.¹⁰⁸ The placebo therapy program includes 16 in-office therapy procedures and home reinforcement therapy procedures that are designed to look like real vergence/accommodative therapy procedures but did not stimulate vergence, accommodation, or fine saccadic eye movements beyond normal daily visual activities. Multiple procedures are performed during each office therapy visit and computerized home-training procedures are assigned for home reinforcement therapy each week. Placebo procedures include traditional vergence/accommodative therapy procedures modified to be monocular rather than binocular (e.g., Brock string), binocular procedures modified so that there is no alteration of disparity vergence demand (e.g., computer orthopter, stereoscope), procedures using lenses with no dioptric power (plano or yoked prism lenses), and computer visual perceptual therapy with filter glasses. Placebo therapy procedures also include testing procedures that did not require significant demand on the vergence, accommodative, or fine saccadic eye movement systems (e.g., ductions, Bailey-Lovie acuity testing, after image testing, Hess Lancaster screen testing, modified Thorington phoria testing, and double Maddox rod cyclophoria testing). To further simulate real therapy,

we design some procedures to have increasing levels of difficulty. As in real therapy, patients frequently wear filter glasses and are told that the glasses ensured that both eyes are being used together. In addition, goals (such as improving how the eyes work together as a team) are established for each placebo procedure, and the therapist tells the participant the goal of each procedure before beginning the technique to motivate the participant and simulate real therapy.¹⁰⁸ CI patients who are enrolled in OBPT are given the opportunity to enroll in OBVAT once all post-OBPT measurements are attained.

Outcome Examination

The outcome examination is scheduled after the participant completes 12 sessions of office-based therapy and is performed by a masked examiner. The clinical testing, objective eye movement recordings, and fMRI are all repeated with the same techniques described for the baseline assessments.

Participant and Investigator Masking

All participants are masked regarding their group assignment (i.e., real / OBVAT or placebo / OBPT). While it is not feasible to mask the therapists responsible for treating the participants, the clinician responsible for obtaining the outcome measures is masked to participant treatment assignment. Participants are assigned an alphanumeric identifier where BNC and CI participants are randomly intermixed, as is their assignment to OBVAT or OBPT interventions.

Group-Level Statistical Analyses

A family-wise error rate α -level of 0.05 is used to assess statistical significance. The basic linear model representing our design is: $Y_{ijk} = \mu + \pi_j + \tau_{d[i,j]} + s_{ik} + \beta_{\text{baseline}} X_{ik} + e_{ijk}$ where Y_{ijk} = the CISS observation on the k^{th} participant (1 to 25), in the j^{th} time period, for the i^{th} arm/sequence (1 to 4); μ = a constant effect; π_j = the time effect at period j (2 time measurements at before and after); $\tau_{d[i,j]}$ = a direct treatment effect (OBVAT or OVPT) at arm i and time period j , i.e., direct treatment effect due to interaction between arm i and time j ; s_{ik} = the effect associated with the participant k corresponding to arm i , i.e., participant k and arm i interaction effect; baseline reading X_{ik} corresponding to the 100 participants are added in the model; and e_{ijk} = the random error term corresponding to each observation. Our first strategy is to begin with an analysis of covariance (ANCOVA) model. Gender is assessed as a covariate. If a potential problem arises with these assumptions for an ANCOVA model to hold true, then transformation methods, weighted least squares methods, and generalized linear model methods will be evaluated and compared to determine the correct model for our dataset. The results are generalized by including the participant as random in the random effects model. A paired t -test is used to compare the baseline and post-treatment measurements from the assessments. The direct treatment effects due to interactions between groups and time periods (before and after therapy) are analyzed post-hoc using several tests such as Tukey's method. Adjustments for multiple comparisons are completed to ensure an overall error rate α -level of 0.05.

Results

Enrollment began in August 2015 and ended on April 2018. Participants are recruited from the northern NJ metropolitan area. Eligibility examinations are performed on 295 participants ages 18–35 years (inclusive); 105 (35.6%) are eligible, and 100 (95.2% of those eligible) agreed to participate. Reasons for non-participation included unwillingness of the participant to be randomized, feelings that the study required too much time, transportation issues, and unwillingness of some participants to complete the at-home therapy procedures.

The summary of the participant parameters including age, gender, race, ethnicity, self-report of attention deficit attention disorder (ADHD), and type of refraction by each participant cohort is tabulated in Table 4. Gender, race and ethnicity are collected per the guidelines of the National Institutes of Health. While there are differences between the two groups for gender, race and ethnicity, published data or clinical rationale do not suggest that therapy results would differ based on gender, race or ethnicity. Participants are asked which category they identified with or if they preferred not to answer. A spherical equivalent refraction of < -0.25 is classified as myopia, $-0.25D$ to $+0.50D$ as emmetropia, and $>+0.50D$ as hyperopia. Participants are categorized as antimetropia when the spherical equivalent refraction of one eye is myopic and the other is hyperopic. There are several meaningful differences at baseline in the refractive error distribution among the 4 groups. While the presence of uncorrected refractive error could affect treatment,¹⁰⁹ for this study, all participants wore spectacle or contact lens correction for all clinical measurements and therapy procedures. Thus, there is negligible concern that the differences in refractive error observed at baseline could have affected treatment outcomes.⁷

Twenty-five BNC and 25 CI participants are randomly assigned to each of OBVAT and OBPT treatment groups, totaling 50 participants (25 BNC and 25 CI) per group being assigned to each therapeutic intervention. Table 5 displays the eligibility data by treatment group for CI and BNC populations. Figure 5 displays the clinical signs and symptoms used to diagnosis a patient with CI. None of the differences between the CI patients in OBVAT and OBPT groups for near point of convergence, positive fusional vergence at near, the difference between near and far phoria, or CISS are clinically meaningful.

Table 6 compares the 50 BNC and the 50 CI clinical parameters. Significant differences are observed for all horizontal vergence and accommodative parameters. No significant difference is observed for age, global stereopsis, vertical phoria, or refraction.

All 100 participants successfully completed 12 office-based vision therapy sessions, reaching 100% compliance for the office-based therapy sessions. There were 18 sessions of home-based therapy prescribed for each therapy. For participants assigned to the OBVAT cohort, the average number of sessions that were completed was 4.3 sessions with a standard deviation of 4.4 sessions. Thus, 24% patient compliance for OBVAT was observed. For the OBPT cohort, the average number of sessions performed at home was 5.4 sessions with a standard deviation of 4.7 sessions, which was a compliance of 30%.

Discussion

CINAPS is the culmination of interdisciplinary clinical and engineering research. Its foundations are built on strengths from previous RCTs such as CITT with novel eye movement instrumentation custom designed and built by biomedical engineers to assess both the Dual Mode and Maddox components of vergence. It is the first RCT using a combination of traditional clinical measures, objective eye movement recording, and functional imaging. Not only will the trial yield new information about the effectiveness of OBVAT for the treatment of symptomatic CI in young adults, it will also provide valuable information about the underlying mechanisms responsible for changes in clinical signs and symptoms.

The major eligibility data selected for the CI participants are identical to those used in previous RCTs that have studied adult participants with symptomatic CI. In addition, we use the identical OBVAT procedures used in previous CITT studies. These similarities will allow us to compare outcomes with previous studies.

Regarding the baseline data, we did not find any meaningful demographic differences between the BNC or CI participants randomized to OBVAT versus OBPT interventions. However, as expected, there are clinically meaningful differences at baseline between the CI and BNC participants for NPC, PFV and eye alignment assessed as the difference between near and far phoria. There has been one other RCT with young adult participants.¹⁷ The baseline data for the main indicators of CI are quite similar between the two studies. In this study, the mean age was slightly lower (21.1 years in CINAPS vs. 24.3 in CITT), while the NPC (12.4 cm in CINAPS vs. 13.5 cm CITT), PFV at near (10.6 in CINAPS vs. 11.8 in CITT) and CISS score (33.9 in CINAPS vs. 37.3 in CITT) are similar.¹⁷

The innovative aspects of the CINAPS study are the assessments used to quantitatively study the slow and fast fusional vergence systems through the Dual Mode eye movement experiment and the phoria adaptation experiment, respectively, and the modification of these experiments to be conducted within a functional MRI (fMRI) experiment to assess the metabolic activity of the cortical and subcortical regions. The fMRI assessment coupled with eye movement behaviors is important because it addresses the following questions: What is the functional difference in the brain and hence eye movements between BNC and CI participants? What modifications does OBVAT evoke in the brain and thus eye movements to lead to a long-term remediation of symptoms in most CI patients? If CINAPS is successful in providing information about the neural underlying factors that contribute to success, clinicians may be able to use this information to modify therapy protocols and personalize vision therapy procedures to each patient's vergence system. Such a targeted approach has the potential to increase treatment effectiveness and lower the cost.

One study limitation is that eye movement recording with the MRI center is monocular. However, the goal of the eye tracking response within the MRI center is to determine whether vergence eye movements are being initiated and we are able to determine that vergence eye movements are initiated during the imaging sessions.

Convergence Insufficiency Comorbidity with Accommodative Insufficiency

Accommodation insufficiency (AI) is reported as a comorbidity for patients with CI at incidences of 15.6% (N=1201),³ 18.5% (N=299),¹¹⁰ and 39% (N=392)¹¹¹. CINAPS studied the young adult population and 26% of our CI participants also had AI, which is consistent with the previous studies.

While other studies do not specifically categorize participants as having a diagnosis of AI, they do report amplitude of accommodation and age which are part of the diagnostic criteria for AI. The CITT results studying children report that 29% of the participants studied had decreased amplitude of accommodation compared to normal values,²³ similar to the CINAPS prevalence of 26% of the young adult participants with CI. In the CITT study of young adults, the authors reported an amplitude of accommodation between 8.0 +/- 2.5 D to 8.4 +/-3.3 D for an average age of 24 years,¹⁷ which is similar to our results (8.36 ± 2.18 D). These collective independent studies suggest that AI is commonly associated with CI in both children and young adults.

Convergence Insufficiency Comorbidity with Attention Deficit Hyperactivity Disorder (ADHD)

The oculomotor neural substrates used to mediate a vergence response have some overlap with the visual attention network.¹¹² Since there are shared neural substrates particularly within the fronto-parietal areas then it may be possible that patients with CI are more likely to also have a diagnosis of ADHD. The information about ADHD is acquired through participant self-reporting. Some studies report that patients with CI are more likely to have ADHD^{113,114} while another does not.¹¹⁵

Conclusion

CINAPS has a unique design in that it builds on the strengths of CITT and integrates objective eye movement experiments, phoria adaptation, forced fixation disparity curves, binocular rivalry and functional imaging. No clinically meaningful differences are observed per participant type for the OBVAT or OBPT intervention arms. The baseline data reports that 26% of the CI patients also are diagnosed to have AI and 16% of CI self-reported a diagnosis of ADHD.

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References

1. Cooper J, Jamal N. Convergence insufficiency-a major review. *Optometry*. 2012;83(4):137–158. <http://www.ncbi.nlm.nih.gov/pubmed/23231437>. Accessed August 27, 2016. [PubMed: 23231437]
2. Hussaindeen JR, Rakshit A, Singh NK, et al. Prevalence of non-strabismic anomalies of binocular vision in Tamil Nadu: report 2 of BAND study. *Clin Exp Optom*. 2017;100(6):642–648. doi: 10.1111/cxo.12496 [PubMed: 27859646]
3. Wajuihian SO, Hansraj R. Vergence anomalies in a sample of high school students in South Africa. *J Optom*. 2016;9(4):246–257. doi:10.1016/j.optom.2015.10.006 [PubMed: 26750804]

4. Rouse MW, Borsting EJ, Hyman L, et al. Frequency of convergence insufficiency among fifth and sixth graders. The Convergence Insufficiency and Reading Study (CIRS) group. *Optom Vis Sci.* 1999;76(9):643–649. [PubMed: 10498006]
5. Davis AL, Harvey EM, Twelker JD, Miller JM, Leonard-Green T, Campus I. Convergence Insufficiency, Accommodative Insufficiency, Visual Symptoms, and Astigmatism in Tohono O'odham Students. *J Ophthalmol.* 2016;2016:1–7. doi:10.1155/2016/6963976
6. Nunes AF, Monteiro PML, Ferreira FBP, Nunes AS. Convergence insufficiency and accommodative insufficiency in children. *BMC Ophthalmol.* 2019;19(1):58. doi:10.1186/s12886-019-1061-x [PubMed: 30791877]
7. Scheiman M, Wick B. *Clinical Management of Binocular Vision, Heterophoric, Accommodative, and Eye Movement Disorders.* 4th ed. (Shaw R, ed.). Philadelphia: J.B. Lippincott; 2014.
8. Scheiman M, Gallaway M, Frantz KA, et al. Nearpoint of convergence: test procedure, target selection, and normative data. *Optom Vis Sci.* 2003;80(3):214–225. <http://www.ncbi.nlm.nih.gov/pubmed/12637833>. Accessed April 11, 2019. [PubMed: 12637833]
9. Hayes GJ, Cohen BE, Rouse MW, De Land PN. Normative values for the nearpoint of convergence of elementary schoolchildren. *Optom Vis Sci.* 1998;75(7):506–512. <http://www.ncbi.nlm.nih.gov/pubmed/9703039>. Accessed April 11, 2019. [PubMed: 9703039]
10. Rouse MW, Borsting E, Deland PN, Convergence Insufficiency and Reading Study (CIRS) Group. Reliability of binocular vision measurements used in the classification of convergence insufficiency. *Optom Vis Sci.* 2002;79(4):254–264. <http://www.ncbi.nlm.nih.gov/pubmed/11999151>. Accessed March 31, 2019. [PubMed: 11999151]
11. Rouse MW, Borsting EJ, Mitchell GL, et al. Validity of the Convergence Insufficiency Symptom Survey: A Confirmatory Study. *Optom Vis Sci.* 2009;86(4):357–363. doi:10.1097/OPX.0b013e3181989252 [PubMed: 19289977]
12. Rouse MW, Borsting EJ, Lynn Mitchell G, et al. Validity and reliability of the revised convergence insufficiency symptom survey in adults. *Ophthalmic Physiol Opt.* 2004;24(5):384–390. doi:10.1111/j.1475-1313.2004.00202.x [PubMed: 15315652]
13. Borsting EJ, Rouse MW, Mitchell GL, et al. Validity and reliability of the revised convergence insufficiency symptom survey in children aged 9 to 18 years. *Optom Vis Sci.* 2003;80(12):832–838. <http://www.ncbi.nlm.nih.gov/pubmed/14688547>. Accessed April 11, 2019. [PubMed: 14688547]
14. Borsting E, Rouse MW, De Land PN. Prospective comparison of convergence insufficiency and normal binocular children on CIRS symptom surveys. *Convergence Insufficiency and Reading Study (CIRS) group.* *Optom Vis Sci.* 1999;76(4):221–228. <http://www.ncbi.nlm.nih.gov/pubmed/10333184>. Accessed April 11, 2019. [PubMed: 10333184]
15. Scheiman M, Rouse MW, Kulp MT, Cotter SA, Hertle R, Mitchell GL. Treatment of Convergence Insufficiency in Childhood: A Current Perspective. *Optom Vis Sci.* 2009;86(5):420–428. doi:10.1097/OPX.0b013e31819fa712 [PubMed: 19319008]
16. Scheiman M, Cotter S, Rouse M, et al. Randomised clinical trial of the effectiveness of base-in prism reading glasses versus placebo reading glasses for symptomatic convergence insufficiency in children. *Br J Ophthalmol.* 2005;89(10):1318–1323. doi:10.1136/bjo.2005.068197 [PubMed: 16170124]
17. Scheiman Mitchell Mitchell GL, Cotter S, Kulp MT, et al. A Randomized Clinical Trial of Vision Therapy/Orthoptics versus Pencil Pushups for the Treatment of Convergence Insufficiency in Young Adults. *Optom Vis Sci.* 2005;82(7):E583–E595. doi:10.1097/01.opx.0000171331.36871.2f
18. Pediatric Eye Disease Investigator Group. Home-Based Therapy for Symptomatic Convergence Insufficiency in Children. *Optom Vis Sci.* 2016;93(12):1457–1465. doi:10.1097/opx.0000000000000975 [PubMed: 27575992]
19. Scheiman M, Mitchell GL, Cotter S, et al. A Randomized Clinical Trial of Vision Therapy/Orthoptics versus Pencil Pushups for the Treatment of Convergence Insufficiency in Young Adults. *Optom Vis Sci.* 2005;82(7):E583–E595. doi:10.1097/01.opx.0000171331.36871.2f
20. Scheiman M, Cotter S, Mitchell GL, et al. Randomized clinical trial of treatments for symptomatic convergence insufficiency in children. *Arch Ophthalmol.* 2008;126(10):1336–1349. doi:10.1001/archophth.126.10.1336 [PubMed: 18852411]

21. Scheiman M, Gwiazda J, Li T. Non-Surgical Interventions for Convergence Insufficiency. (Scheiman M, ed.). UK: John Wiley & Sons, Ltd; 2011:CD006768. doi: 10.1002/14651858.CD006768.pub2
22. Convergence Insufficiency Treatment Trial (CITT) Study Group. Long-Term Effectiveness of Treatments for Symptomatic Convergence Insufficiency in Children. *Optom Vis Sci.* 2009;86(9): 1096–1103. doi:10.1097/OPX.0b013e3181b6210f [PubMed: 19668097]
23. Scheiman M, Cotter SA, Kulp MT, et al. Treatment of accommodative dysfunction in children: results from a randomized clinical trial. *Optom Vis Sci.* 2011;88(11):1343–1352. doi:10.1097/OPX.0b013e31822f4d7c [PubMed: 21873922]
24. Scheiman M, Mitchell GL, Cotter S, et al. A Randomized Clinical Trial of Treatments for Convergence Insufficiency in Children. *Arch Ophthalmol.* 2005;123(1):14. doi:10.1001/archophth.123.1.14 [PubMed: 15642806]
25. Alvarez TL, Vicci VR, Alkan Y, et al. Vision therapy in adults with convergence insufficiency: Clinical and functional magnetic resonance imaging measures. *Optom Vis Sci.* 2010;87(12). doi: 10.1097/OPX.0b013e3181fef1aa
26. Scheiman MM, Talasan H, Lynn Mitchell G, Alvarez TL. Objective Assessment of Vergence after Treatment of Concussion-Related CI: A Pilot Study. *Optom Vis Sci.* 2017;94(1):74–88. doi: 10.1097/OPX.0000000000000936 [PubMed: 27464574]
27. Scheiman M, Talasan H, Alvarez TL. Objective Assessment of Disparity Vergence after Treatment of Symptomatic Convergence Insufficiency in Children. *Optom Vis Sci.* 2019;96(1):3–16. doi: 10.1097/OPX.0000000000001320 [PubMed: 30570596]
28. Talasan H, Scheiman M, Li X, Alvarez TL. Disparity vergence responses before versus after repetitive vergence therapy in binocularly normal controls. *J Vis.* 2016;16(1):7. doi: 10.1167/16.1.7.
29. Sreenivasan V, Bobier WR. Increased onset of vergence adaptation reduces excessive accommodation during the orthoptic treatment of convergence insufficiency. *Vision Res.* 2015;111(Pt A):105–113. doi:10.1016/j.visres.2015.04.001 [PubMed: 25891521]
30. van Leeuwen AF, Westen MJ, van der Steen J, de Faber JT, Collewijn H. Gaze-shift dynamics in subjects with and without symptoms of convergence insufficiency: influence of monocular preference and the effect of training. *Vision Res.* 1999;39(18):3095–3107. <http://www.ncbi.nlm.nih.gov/pubmed/10664807>. Accessed August 27, 2016. [PubMed: 10664807]
31. Thiagarajan P, Ciuffreda KJ. Short-term persistence of oculomotor rehabilitative changes in mild traumatic brain injury (mTBI): A pilot study of clinical effects. *Brain Inj.* 2015;29(12):1475–1479. doi:10.3109/02699052.2015.1070905 [PubMed: 26308101]
32. Miniussi C, Sprenger A, Stein JF, et al. Benefits from Vergence Rehabilitation: Evidence for Improvement of Reading Saccades and Fixations. *Front Integr Neurosci* | www.frontiersin.org. 2016;10:33. doi:10.3389/fnint.2016.00033 [PubMed: 27812325]
33. Alvarez TL, Jaswal R, Gohel S, Biswal BB. Functional activity within the frontal eye fields, posterior parietal cortex, and cerebellar vermis significantly correlates to symmetrical vergence peak velocity: An ROI-based, fMRI study of vergence training. *Front Integr Neurosci.* 2014;8(JUNE). doi:10.3389/fnint.2014.00050
34. Widmer DE, Oechslin TS, Limbachia C, et al. Post-therapy Functional Magnetic Resonance Imaging in Adults with Symptomatic Convergence Insufficiency. *Optom Vis Sci.* 2018;95(6):505–514. doi:10.1097/OPX.0000000000001221 [PubMed: 29787484]
35. Brautaset RL, Jennings AJM. Effects of orthoptic treatment on the CA/C and AC/A ratios in convergence insufficiency. *Invest Ophthalmol Vis Sci.* 2006;47(7):2876–2880. doi:10.1167/iovs.04-1372 [PubMed: 16799027]
36. Sreenivasan V, Bobier WR. Reduced vergence adaptation is associated with a prolonged output of convergence accommodation in convergence insufficiency. *Vision Res.* 2014;100:99–104. doi: 10.1016/j.visres.2014.04.003 [PubMed: 24759573]
37. Saladin JJ. Convergence insufficiency, fixation disparity, and control systems analysis. *Am J Optom Physiol Opt.* 1986;63(8):645–653. [PubMed: 3766694]

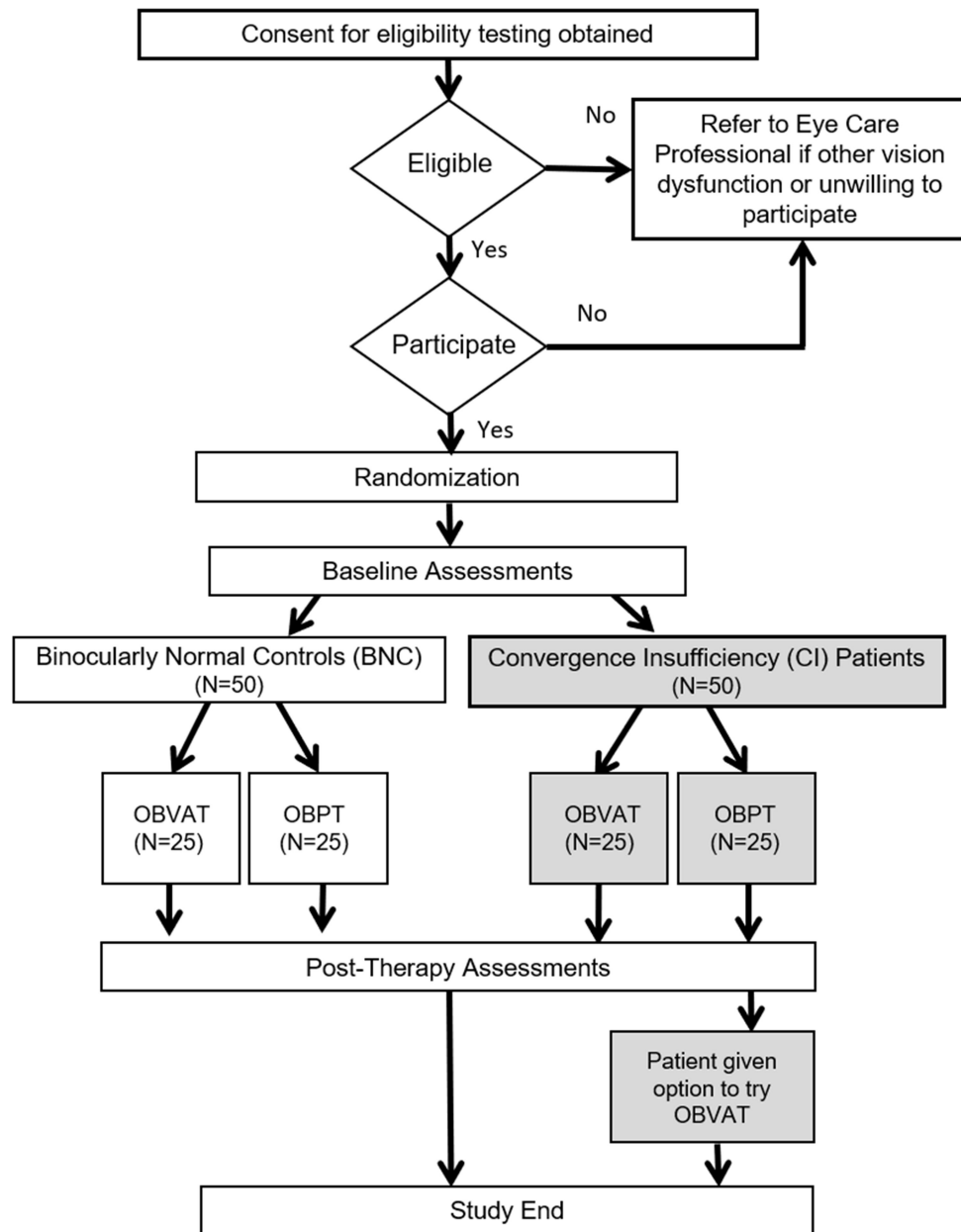
38. Cooper J, Selenow A, Ciuffreda KJ, et al. Reduction of asthenopia in patients with convergence insufficiency after fusional vergence training. *Am J Optom Physiol Opt.* 1983;60(12):982–989. <http://www.ncbi.nlm.nih.gov/pubmed/6660282>. Accessed July 12, 2019. [PubMed: 6660282]
39. Dalziel CC. Effect of vision training on patients who fail Sheard's criterion. *Am J Optom Physiol Opt.* 1981;58(1):21–23. <http://www.ncbi.nlm.nih.gov/pubmed/7212013>. Accessed July 12, 2019. [PubMed: 7212013]
40. Semmlow J, Yuan W, Alvarez T. Short-term adaptive control processes in vergence eye movement. *Curr Psychol Cogn.* 2002;21(45):343–375. https://academic.oup.com/milmed/article-abstract/183/suppl_1/9/4959946%0Ahttps://academic.oup.com/milmed/article/183/suppl_1/9/4959946.
41. Alvarez TL, Semmlow JL, Yuan W, Munoz P. Disparity vergence double responses processed by internal error. *Vision Res.* 2000;40(3):341–347. doi:10.1016/S0042-6989(99)00175-3 [PubMed: 10793906]
42. Alvarez TL, Semmlow JL, Yuan W. Closely Spaced, Fast Dynamic Movements in Disparity Vergence. *J Neurophysiol.* 1998;79(1):37–44. doi:10.1152/jn.1998.79.1.37 [PubMed: 9425174]
43. Alvarez TL, Semmlow JL, Yuan W, Munoz P. Dynamic details of disparity convergence eye movements. *Ann Biomed Eng.* 1999;27(3):380–390. doi:10.1114/1.162 [PubMed: 10374730]
44. Alvarez TL. A pilot study of disparity vergence and near dissociated phoria in convergence insufficiency patients before vs. after vergence therapy. *Front Hum Neurosci.* 2015;9(JULY):419. doi:10.3389/fnhum.2015.00419 [PubMed: 26283944]
45. Chen Yung-Fu, Lee You-Yun, Chen Tainsong, John L, Semmlow TLA, Chen YF, Lee YY, Chen T, Semmlow JL, Alvarez TL. Review: Behaviors, Models, and Clinical Applications of Vergence Eye Movements. *J Med Biol Eng.* 2010;30(1):1–15.
46. Morgan M The Maddox Classification of Vergence Eye Movements.: *Optometry & Vision Science.* *Optom Vis Sci.* 1980;57(9):57–60. http://journals.lww.com/optvissci/Abstract/1980/09000/The_Maddox_Classification_of_Vergence_Eye.3.aspx.
47. Maddox EE. Investigations in the Relation between Convergence and Accommodation of the Eyes. *J Anat Physiol.* 1886;20(Pt 3):475–508. <http://www.ncbi.nlm.nih.gov/pubmed/17231636>. Accessed April 11, 2019.
48. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. *PLoS Med.* 2010;7(3):1000251. doi:10.1371/journal.pmed.1000251
49. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010;63(8):e1–e37. doi:10.1016/J.JCLINEPI.2010.03.004 [PubMed: 20346624]
50. Sheard C Zones of Ocular Comfort. *Am J Optom.* 1930;7:9–25.
51. Hofstetter HW. A Comparison of Duane's and Donders' Tables of the Amplitude of Accommodation. *Optom Vis Sci.* 1944;21(9):345–363. https://journals.lww.com/optvissci/Citation/1944/09000/A_COMPARISON_OF_DUANE_S_AND_DONDERS__TABLES_OF_THE.1.aspx. Accessed April 20, 2019.
52. CITT-ART Investigator Group, Scheiman M, Mitchell GL, et al. Convergence Insufficiency Treatment Trial - Attention and Reading Trial (CITT-ART): Design and Methods. *Vis Dev Rehabil.* 2015;1(3):214–228. <http://www.ncbi.nlm.nih.gov/pubmed/26942226>. Accessed September 5, 2016. [PubMed: 26942226]
53. Convergence Insufficiency Treatment Trial (CITT) Study Group. The Convergence Insufficiency Treatment Trial: Design, Methods, and Baseline Data. *Ophthalmic Epidemiol.* 2008;15(1):24–36. doi:10.1080/09286580701772037 [PubMed: 18300086]
54. Guo Y, Kim EH, Alvarez TL. VisualEyes: a modular software system for oculomotor experimentation. *J Vis Exp.* 2011;(49):1–6. doi:10.3791/2530
55. Jaschinski W Individual Objective and Subjective Fixation Disparity in Near Vision. Martinez-Conde S, ed. *PLoS One.* 2017;12(1):e0170190. doi:10.1371/journal.pone.0170190 [PubMed: 28135308]

56. Semmlow JL, Hung GK, Horng JL, Ciuffreda K. Initial control component in disparity vergence eye movements. *Ophthalmic Physiol Opt.* 1993;13(1):48–55. <http://www.ncbi.nlm.nih.gov/pubmed/8510948>. Accessed August 27, 2016. [PubMed: 8510948]
57. Semmlow JL, Yuan W, Alvarez T. Short-term adaptive control processes in vergence eye movement. *Curr Psychol Cogn.* 2002;21(45):343–375. https://academic.oup.com/milmed/article-abstract/183/suppl_1/9/4959946%0Ahttps://academic.oup.com/milmed/article/183/suppl_1/9/4959946.
58. Alvarez TL, Semmlow JL, Yuan W. Closely spaced, fast dynamic movements in disparity vergence. *J Neurophysiol.* 1998;79(1):37–44. <http://www.ncbi.nlm.nih.gov/pubmed/9425174>. Accessed August 27, 2016. [PubMed: 9425174]
59. Alvarez TL, Semmlow JL, Pedrono C. Divergence eye movements are dependent on initial stimulus position. *Vision Res.* 2005;45(14):1847–1855. doi:10.1016/j.visres.2005.01.017 [PubMed: 15797774]
60. Alvarez TL, Bhavsar M, Semmlow JL, Bergen MT, Pedrono C. Short-term predictive changes in the dynamics of disparity vergence eye movements. *J Vis.* 2005;5(7). doi:10.1167/5.7.4
61. Alvarez TL, Semmlow JL, Yuan W, Munoz P. Comparison of disparity vergence system responses to predictable and non-predictable stimulations. *Cah Psychol Cogn.* 2002;21(2–3).
62. Semmlow JL, Hung GK, Ciuffreda KJ. Quantitative Assessment of Disparity Vergence Components. Vol 59 [Association for Research in Vision and Ophthalmology, etc.]; 1986 <https://iovs.arvojournals.org/article.aspx?articleid=2159946>. Accessed March 26, 2019.
63. Alvarez TL, Semmlow JL, Pedrono C. Dynamic assessment of disparity vergence ramps. *Comput Biol Med.* 2007;37(7):903–909. doi:10.1016/j.combiomed.2006.03.009 [PubMed: 16737692]
64. Stark L, Kenyon RV, Krishnan VV, Ciuffreda KJ. Disparity vergence: a proposed name for a dominant component of binocular vergence eye movements. *Am J Optom Physiol Opt.* 1980;57(9):606–609. <http://www.ncbi.nlm.nih.gov/pubmed/7425083>. Accessed August 27, 2016. [PubMed: 7425083]
65. Schor CM. A dynamic model of cross-coupling between accommodation and convergence: simulations of step and frequency responses. *Optom Vis Sci.* 1992;69(4):258–269. <http://www.ncbi.nlm.nih.gov/pubmed/1565425>. Accessed August 27, 2016. [PubMed: 1565425]
66. McLin LN, Schor CM, Kruger PB. Changing size (looming) as a stimulus to accommodation and vergence. *Vision Res.* 1988;28(8):883–898. doi:10.1016/0042-6989(88)90098-3 [PubMed: 3250084]
67. Horwood AM, Riddell PM. A novel experimental method for measuring vergence and accommodation responses to the main near visual cues in typical and atypical groups. *Strabismus.* 17(1):9–15. doi:10.1080/09273970802678602
68. McLin LN, Schor CM. Voluntary effort as a stimulus to accommodation and vergence. *Invest Ophthalmol Vis Sci.* 1988;29(11):1739–1746. <http://www.ncbi.nlm.nih.gov/pubmed/3182206>. Accessed August 27, 2016. [PubMed: 3182206]
69. Kotulak JC, Schor CM. The effects of optical vergence, contrast, and luminance on the accommodative response to spatially bandpass filtered targets. *Vision Res.* 1987;27(10):1797–1806. <http://www.ncbi.nlm.nih.gov/pubmed/3445469>. Accessed August 27, 2016. [PubMed: 3445469]
70. Yaramothu C, Santos EM, Alvarez TL. Effects of visual distractors on vergence eye movements. *J Vis.* 2018;18(6):2. doi:10.1167/18.6.2
71. Yaramothu C, Greenspan LD, Scheiman M, Alvarez TL. Vergence Endurance Test: A Pilot Study for a Concussion Biomarker. *J Neurotrauma.* 3 2019:neu.2018.6075. doi:10.1089/neu.2018.6075
72. Leigh RJ, Zee DS. *The Neurology of Eye Movements.*; 2016 <https://books.google.com/books?hl=en&lr=&id=v2s0BwAAQBAJ&oi=fnd&pg=PP1&dq=zee+and+leigh&ots=4pwi0gySwN&sig=TWfChdSm-5ch3SL67rpJl2kZq6E#v=onepage&q=zeeandleigh&f=false>.
73. Semmlow JL, Chen Yu-F, Granger-Donnetti B, Alvarez TL. Correction of Saccade-Induced Midline Errors in Responses to Pure Disparity Vergence Stimuli. *J Eye Mov Res.* 2008;2(5):1–13.
74. Semmlow JL, Chen YF, Alvarez TL, Pedrono C. Saccadic Behavior during the Response to Pure Vergence Stimuli I: General Properties. *J Eye Mov Res.* 2007;1(2):1–11.

75. Morize A, Brémond-Gignac D, Daniel F, Kapoula Z. Effects of Pure Vergence Training on Initiation and Binocular Coordination of Saccades. *Investig Ophthalmology Vis Sci.* 2017;58(1):329. doi:10.1167/iovs.16-19837
76. Alvarez TL, Kim EH. Analysis of saccades and peak velocity to symmetrical convergence stimuli: Binocularly normal controls compared to convergence insufficiency patients. *Investig Ophthalmol Vis Sci.* 2013;54(6). doi:10.1167/iovs.13-11797
77. Bahill AT, Kallman JS, Lieberman JE. Frequency limitations of the two-point central difference differentiation algorithm. *Biol Cybern.* 1982;45(1):1–4. <http://www.ncbi.nlm.nih.gov/pubmed/7126687>. Accessed September 5, 2016. [PubMed: 7126687]
78. Mays LE, Porter JD, Gamlin PD, Tello CA. Neural control of vergence eye movements: neurons encoding vergence velocity. *J Neurophysiol.* 1986;56(4):1007–1021. doi:10.1152/jn.1986.56.4.1007 [PubMed: 3783225]
79. Sheedy JE. Actual measurement of fixation disparity and its use in diagnosis and treatment. *J Am Optom Assoc.* 1980;51(12):1079–1084. <http://www.ncbi.nlm.nih.gov/pubmed/7204818>. Accessed March 26, 2019. [PubMed: 7204818]
80. Cooper J Clinical implications of vergence adaptation. *Optom Vis Sci.* 1992;69(4):300–307. <http://www.ncbi.nlm.nih.gov/pubmed/1565431>. Accessed September 5, 2016. [PubMed: 1565431]
81. Sheedy JE, Saladin JJ. Phoria, vergence, and fixation disparity in oculomotor problems. *Am J Optom Physiol Opt.* 1977;54(7):474–478. [PubMed: 931014]
82. Saladin JJ, Sheedy JE. Population study of fixation disparity, heterophoria, and vergence. *Am J Optom Physiol Opt.* 1978;55(11):744–750. [PubMed: 752265]
83. Jaschinski W, Švede A, Jainta S. Relation between fixation disparity and the asymmetry between convergent and divergent disparity step responses. *Vision Res.* 2008;48(2):253–263. doi:10.1016/j.visres.2007.11.004 [PubMed: 18164741]
84. Schor CM. The relationship between fusional vergence eye movements and fixation disparity. *Vision Res.* 1979;19(12):1359–1367. <http://www.ncbi.nlm.nih.gov/pubmed/532102>. Accessed August 27, 2016. [PubMed: 532102]
85. Patel SS, Ömen H, White JM, Jiang BC. Neural network model of short-term horizontal disparity vergence dynamics. *Vision Res.* 1997;37(10):1383–1399. doi:10.1016/S0042-6989(96)00279-9 [PubMed: 9205729]
86. Schor CM. Analysis of tonic and accommodative vergence disorders of binocular vision. *Am J Optom Physiol Opt.* 1983;60(1):1–14. [PubMed: 6829693]
87. Han SJ, Guo Y, Granger-Donetti B, Vicci VR, Alvarez TL. Quantification of heterophoria and phoria adaptation using an automated objective system compared to clinical methods. *Ophthalmic Physiol Opt.* 2010;30(1). doi:10.1111/j.1475-1313.2009.00681.x
88. Brautaset RL, Jennings JAM. Horizontal and vertical prism adaptation are different mechanisms. *Ophthalmic Physiol Opt.* 2005;25(3):215–218. doi:10.1111/j.1475-1313.2005.00276.x [PubMed: 15854067]
89. Ooi TL, He ZJ. Sensory eye dominance. *Optometry.* 2001;72(3):168–178. <http://www.ncbi.nlm.nih.gov/pubmed/11294588>. Accessed March 27, 2018. [PubMed: 11294588]
90. Alvarez TL, Semmlow JL, Yuan W, Munoz P. Comparison of disparity vergence system responses to predictable and non-predictable stimulations. *Curr Psychol Cogn.* 2002;21(3):243–261.
91. Kimmig H, Greenlee M, Gondan M, Schira M, Kassubek J, Mergner T. Relationship between saccadic eye movements and cortical activity as measured by fMRI: quantitative and qualitative aspects. *Exp Brain Res.* 2001;141(2):184–194. doi:10.1007/s002210100844 [PubMed: 11713630]
92. Brautaset RL, Jennings JAM. Distance vergence adaptation is abnormal in subjects with convergence insufficiency. *Ophthalmic Physiol Opt.* 2005;25(3):211–214. doi:10.1111/j.1475-1313.2005.00274.x [PubMed: 15854066]
93. Kim EH, Vicci VR, Han SJ, Alvarez TL. Sustained fixation induced changes in phoria and convergence peak velocity. *PLoS One.* 2011;6(6):e20883. doi:10.1371/journal.pone.0020883 [PubMed: 21698110]
94. Kim EH, Granger-Donetti B, Vicci VR, Alvarez TL. The relationship between phoria and the ratio of convergence peak velocity to divergence peak velocity. *Investig Ophthalmol Vis Sci.* 2010;51(8):4017–4027. doi:10.1167/iovs.09-4560 [PubMed: 20335602]

95. Kim EHEH, Vicci VRVR, Han SJSJ, Alvarez TLTL. No Title. 2011;6(6):e20883. doi:10.1371/journal.pone.0020883
96. Kim EH, Vicci VR, Granger-Donetti B, Alvarez TL. Short-term adaptations of the dynamic disparity vergence and phoria systems. *Exp Brain Res*. 2011;212(2):267–278. doi:10.1007/s00221-011-2727-7 [PubMed: 21594645]
97. Santos EM, Yaramothu C, Alvarez TL. Comparison of symmetrical prism adaptation to asymmetrical prism adaptation in those with normal binocular vision. *Vision Res*. 2018;149:59–65. doi:10.1016/j.visres.2018.06.004 [PubMed: 29940191]
98. Birn RM, Diamond JB, Smith MA, Bandettini PA. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage*. 2006;31(4):1536–1548. doi:10.1016/J.NEUROIMAGE.2006.02.048 [PubMed: 16632379]
99. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003;19(3):1233–1239. doi:10.1016/S1053-8119(03)00169-1 [PubMed: 12880848]
100. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. *Magn Reson Med*. 1996;35(3):346–355. <http://www.ncbi.nlm.nih.gov/pubmed/8699946>. Accessed April 21, 2019. [PubMed: 8699946]
101. Yan C-G, Cheung B, Kelly C, et al. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage*. 2013;76:183–201. doi:10.1016/j.neuroimage.2013.03.004 [PubMed: 23499792]
102. Behzadi Y, Restom K, Liao J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage*. 2007;37(1):90–101. doi:10.1016/j.neuroimage.2007.04.042 [PubMed: 17560126]
103. Servatius RJ, Spiegler KM, Handy JD, Pang KCH, Tsao JW, Mazzola CA. Neurocognitive and Fine Motor Deficits in Asymptomatic Adolescents during the Subacute Period after Concussion. *J Neurotrauma*. 2018;35(8):1008–1014. doi:10.1089/neu.2017.5314 [PubMed: 29278998]
104. Jaswal R, Gohel S, Biswal BB, Alvarez TL. Task-modulated coactivation of vergence neural substrates. *Brain Connect*. 2014;4(8):595–607. doi:10.1089/brain.2013.0216 [PubMed: 24773099]
105. Alvarez TL, Jaswal R, Gohel S, Biswal BB. Functional activity within the frontal eye fields, posterior parietal cortex, and cerebellar vermis significantly correlates to symmetrical vergence peak velocity: an ROI-based, fMRI study of vergence training. *Front Integr Neurosci*. 2014;8:50. doi:10.3389/fnint.2014.00050 [PubMed: 24987340]
106. Alkan Y, Biswal BB, Taylor PA, Alvarez TL. Segregation of frontoparietal and cerebellar components within saccade and vergence networks using hierarchical independent component analysis of fMRI. *Vis Neurosci*. 2011;28(3):247–261. doi:10.1017/S0952523811000125 [PubMed: 21554775]
107. Desmurget M, Pélisson D, Urquizar C, Prablanc C, Alexander GE, Grafton ST. Functional anatomy of saccadic adaptation in humans. *Nat Neurosci*. 1998;1(6):524–528. doi:10.1038/2241 [PubMed: 10196552]
108. Kulp M, Mitchell GL, Borsting E, et al. Effectiveness of Placebo Therapy for Maintaining Masking in a Clinical Trial of Vergence/Accommodative Therapy. *Investig Ophthalmology Vis Sci*. 2009;50(6):2560. doi:10.1167/iovs.08-2693
109. Dwyer P, Wick B. The influence of refractive correction upon disorders of vergence and accommodation. *Optom Vis Sci*. 1995;72(4):224–232. <http://www.ncbi.nlm.nih.gov/pubmed/7609947>. Accessed January 15, 2019. [PubMed: 7609947]
110. Borsting E, Rouse MW, Deland PN, et al. Association of symptoms and convergence and accommodative insufficiency in school-age children. *Optometry*. 2003;74(1):25–34. <http://www.ncbi.nlm.nih.gov/pubmed/12539890>. Accessed March 26, 2019. [PubMed: 12539890]
111. MARRAN LF, DE LAND PN, NGUYEN AL. Accommodative Insufficiency Is the Primary Source of Symptoms in Children Diagnosed With Convergence Insufficiency. *Optom Vis Sci*. 2006;83(5):281–289. doi:10.1097/01.opx.0000216097.78951.7b [PubMed: 16699440]

112. Corbetta M Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems? *Proc Natl Acad Sci U S A.* 1998;95(3): 831–838. doi:10.1073/PNAS.95.3.831 [PubMed: 9448248]
113. Borsting E, Rouse M, Chu R. Measuring ADHD behaviors in children with symptomatic accommodative dysfunction or convergence insufficiency: a preliminary study. *Optom - J Am Optom Assoc.* 2005;76(10):588–592. doi:10.1016/j.optm.2005.07.007
114. Granet DB, Gomi CF, Ventura R, Miller-Scholte A. The Relationship between Convergence Insufficiency and ADHD. *Strabismus.* 2005;13(4):163–168. doi:10.1080/09273970500455436 [PubMed: 16361187]
115. Mezer E, Wygnanski-Jaffe T. Do Children and Adolescents with Attention Deficit Hyperactivity Disorder have Ocular Abnormalities? *Eur J Ophthalmol.* 2012;22(6):931–935. doi:10.5301/ejo.5000145 [PubMed: 22505050]



OBVAT: Office-based Vergence Accommodative Therapy
 OBPT: Office-based Placebo Therapy

Figure 1:
 Study Design

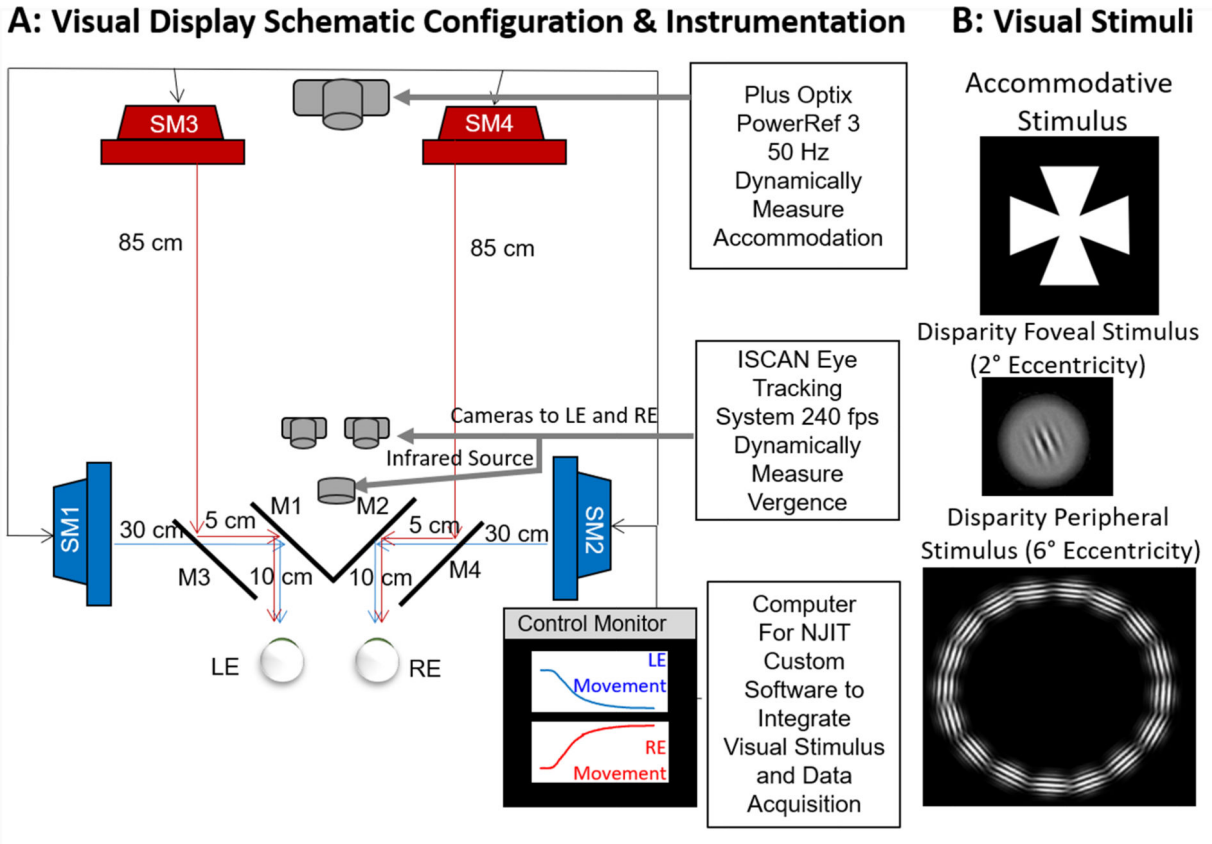


Figure 2.
A: Instrumentation and **2B:** Visual Stimuli for the Objective Eye Movement Experiments.
 SM = Stimulus Monitor; M = Mirror; LE =Left Eye; RE = Right

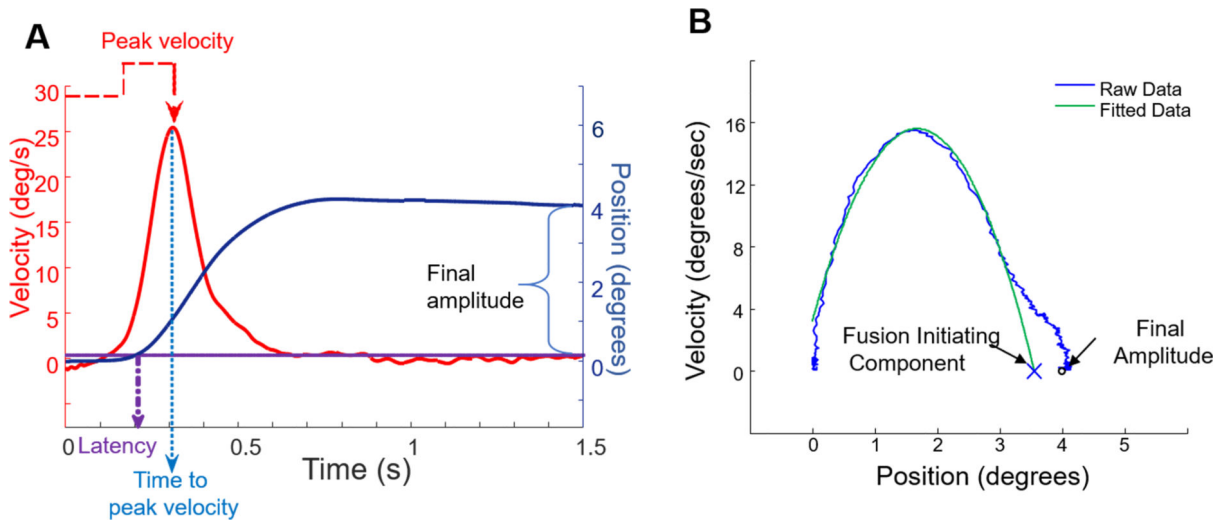


Figure 3.

A: Eye movement data analysis showing latency, time to peak velocity, peak velocity and final amplitude of eye movements for position trace as a function of time (blue line) and velocity as a function of time (red line). **B:** Phase plane analysis showing raw eye movement trace (blue line) and 2nd order polynomial fit (green line). The nonzero root is the fusion initiating component of disparity vergence.

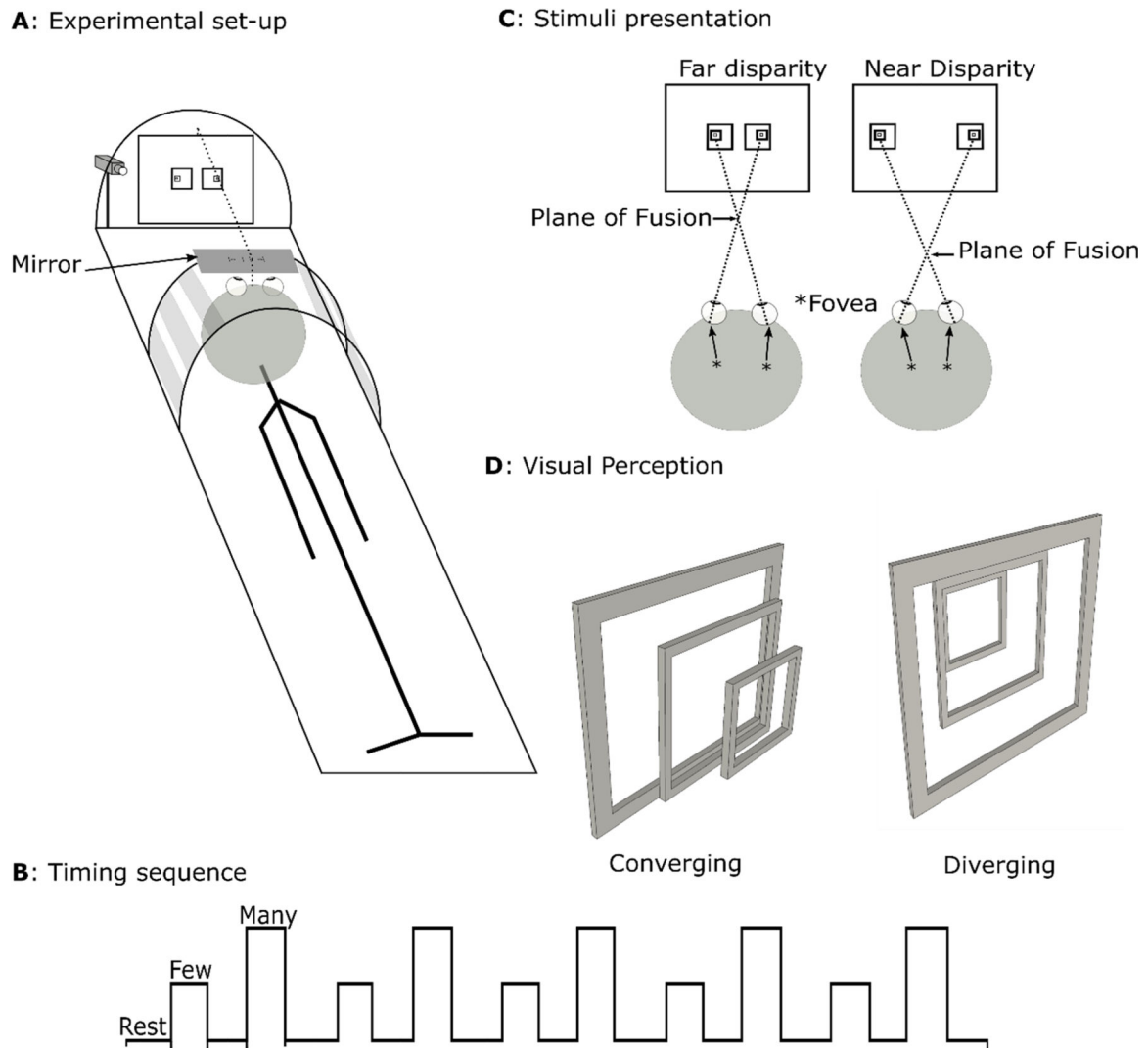


Figure 4. **A:** Functional MRI experimental set-up. **4B:** Timing Sequence diagram of rest, FLO (few) stimuli, and FHO (many) stimuli blocks. **4C:** Visual stimuli showing the difference of far and near disparity, **4D:** 3D representation of visual perception of visual stimulus converging and diverging.

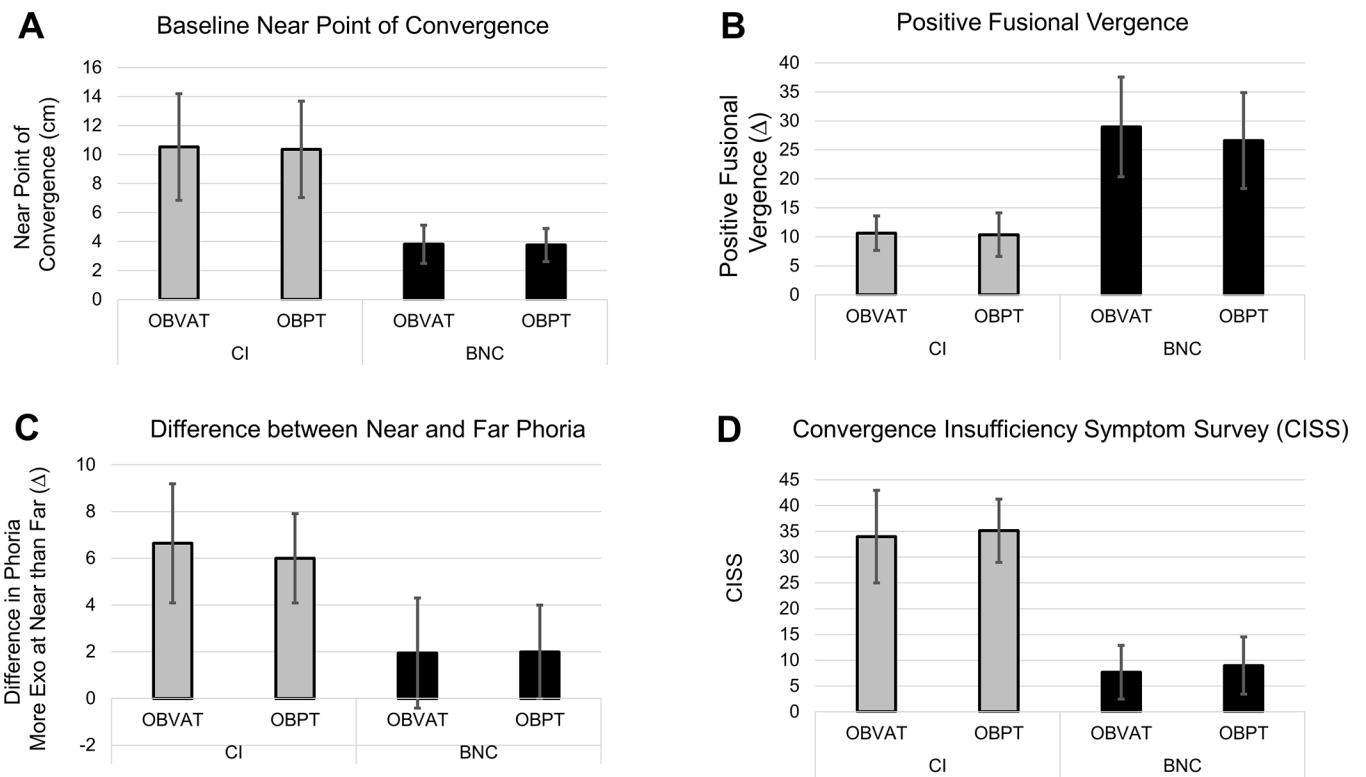


Figure 5: Baseline clinical signs and symptoms used to diagnosis patients with CI (gray bars) compared to baseline data for BNC (black bars). **5A:** Near point of convergence. **5B:** Positive Fusional Vergence. **5C:** Difference in near and far phoria where on average participants are more exophoric at near compared to far. **5D:** Visual symptoms documented by CISS.

Table 1 –
Eligibility and Exclusion Criteria for Convergence Insufficiency

Eligibility Criteria for Convergence Insufficiency (CI) Participants
Age 18 to 35 years
Best-corrected visual acuity of 20/25 or better in both eyes at distance
Convergence Insufficiency Symptom Survey score ≥ 21
Exodeviation at near at least 4° greater than at far
Receded near point of convergence of ≥ 6 cm at break
Insufficient positive fusional convergence [i.e., insufficient positive fusional vergence (i.e., convergence amplitudes) at near defined as failing Sheard's criterion [base-out blur (break if no blur observed) less than twice the near phoria]
Random dot stereopsis appreciation of 500 seconds of arc or better
Wearing appropriate refractive correction (spectacles or contact lenses) for at least 2 weeks
Informed consent and willingness to participate in the study and be randomized
Exclusion Criteria for CI Participants
Constant strabismus at distance
Vertical heterophoria ≥ 2 at distance or near
≥ 2 lines interocular difference in best-corrected visual acuity
Accommodative amplitude <5 D in either eye as measured by Donder's push-up method
Manifest or latent nystagmus
History of strabismus surgery or refractive surgery
History of head trauma or known disease of the brain
Diseases known to affect accommodation, vergence, or ocular motility
Inability to comprehend and/or perform any study-related test
Eligibility Criteria for Normal Binocular Control (BNC) Participants
Age 18 to 35 years
Best-corrected visual acuity of 20/25 or better in both eyes at distance
Convergence Insufficiency Symptom Survey score <21
Difference between near and far phoria <6
Normal near point of convergence (NPC) of <6 cm break
Normal positive fusional vergence (PFV) at near (i.e., passing Sheard's criterion or PFV ≥ 15 base-out break)
Normal amplitude of accommodation (minimum of $15-1/4$ age)
Best-corrected distance visual acuity of 20/25 or better in each eye
Random dot stereopsis appreciation of 500 seconds of arc or better
Wearing appropriate refractive correction (spectacles or contact lenses) for at least 2 weeks
Exclusion Criteria for BNC Participants
Constant strabismus at distance
Vertical heterophoria ≥ 2 at distance or near
≥ 2 lines interocular difference in best-corrected visual acuity
Manifest or latent nystagmus
History of strabismus surgery or refractive surgery
History of head trauma or known disease of the brain
Diseases known to affect accommodation, vergence, or ocular motility

Inability to comprehend and/or perform any study-related test

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Table 2 –

Visual Stimuli for Maddox experiment for d (disparity), b (blur), and p (proximal)

Type of Cue(s)	Response	Visual Stimulus
All Cues	d b p	Binocular, Maltese Cross, looming
Two Cues (one cue missing)	d b (no p)	Binocular, Maltese Cross, scaled
	d p (no b)	Binocular, DoG, looming
	b p (no d)	Monocular, Maltese Cross, looming
One cue only (two cues missing)	only d	Binocular on Haploscope, DoG (central stimulus), scaled
	only d	Binocular on Haploscope, DoG ring (peripheral stimulus), scaled
	only b	Monocular, Maltese Cross, scaled
	only p	Monocular, DoG, looming
All Cues	d, b, p	Binocular, Maltese Cross, looming

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Table 3 –
Office-Based Vergence/Accommodative Therapy Procedures

CINAPS Vergence/Accommodative Therapy Protocol						
	Phase 1		Phase 2		Phase 3	
	O	H	O	H	O	H
Gross Convergence						
Brock String						
Barrel Card						
Voluntary Convergence						
Fusional Vergence*						
Clown & Quoits Vectograms	C		R		J	
Computer Orthoptics (RDS)	C	C	R	R	J	J
Life Saver Cards			C			
Aperture Rule			R		J	
Eccentric Circles			C		J	
Accommodative						
Monocular Loose Lens Facility						
Monocular Letter Chart Facility						
Bulls Eye Rock						
Lens Sorting						
Stereoscope Bi-Ocular Facility						
Prism Dissociation Bi-Ocular Facility						
Computer Orthoptics Accommodative Rock						
Binocular ± 2.00 D Flipper Facility						

RDS = random dot stereograms; O = office therapy; H = home therapy; C = techniques emphasize convergence amplitudes (positive fusional vergence) only; R = ramp/smooth positive & negative fusional vergence procedures; J = jump vergence procedures, some with added prism, mainly change from convergence to divergence demand, some from no vergence demand to a moderate convergence or divergence demand

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Table 4 –

Age, Gender, Race, Ethnicity, Self-Report of Attention Deficit Hyperactivity Disorder, and Refractive Error for each of four Cohorts and of entire study

Participant Type	Convergence Insufficiency CI (N=50)		Binocular Normal Controls BNC (N=50)		Total Study (N=100)
	OBVAT (N=25)	OBPT (N=25)	OBVAT (N=25)	OBPT (N=25)	
Age (years)	21.08 ± 3.60	20.64 ± 3.06	21.88 ± 4.06	21.64 ± 2.46	21.3 ± 3.46
GENDER					
Male	56%	44%	76%	64%	60%
Female	44%	56%	24%	36%	40%
RACE					
American Indian / Alaskan Native	4%	0%	0%	0%	1%
Asian	32%	36%	28%	72%	42%
Black or African American	0%	8%	12%	0%	5%
White	52%	32%	44%	24%	38%
Prefer not to answer	12%	24%	16%	4%	14%
ETHNICITY					
Hispanic or Latino	12%	32%	12%	4%	15%
Not Hispanic or Latino	88%	68%	88%	96%	85%
Prefer not to Answer	0%	0%	0%	0%	0%
Self-Report of Attention Deficit Hyperactivity Disorder (ADHD)					
yes	16%	16%	0%	0%	8%
no	84%	84%	100%	100%	92%
Refraction					
Myopia	56%	36%	44%	56%	48%
Emmetropia	36%	44%	44%	36%	40%
Hyperopia	4%	16%	12%	0%	8%
Antimetropia	4%	0%	0%	8%	3%
Accommodative Insufficiency	24%	28%	0%	0%	13%

Table 5 –

Comparison within CI and BNC populations of the optometric exam parameters between cohorts entering OBVAT and OBPT. Statistically significant differences are reported in bold font.

Participant Type	Convergence Insufficiency CI(N=50) Mean ± Standard Deviation		Statistical Comparison Between CI Cohorts	Binocular Normal Controls BNC (N=50) Mean ± Standard Deviation		Statistical Comparison Between BNC Cohorts
	OBVAT (N=25)	OBPT (N=25)		OBVAT (N=25)	OBPT (N=25)	
Age (years)	21.08 ± 3.60	20.64 ± 3.06	t(48) = 0.47; <i>p</i> >0.5	21.88 ± 4.06	21.64 ± 2.46	t(48)=0.25; <i>p</i> >0.5
CISS Score	33.96 ± 8.97	35.12 ± 6.13	t(48) = 0.50; <i>p</i> >0.5	7.68 ± 5.21	8.96 ± 5.56	t(48)=0.84; <i>p</i> =0.4
Near Point Convergence Break (cm)	10.52 ± 3.67	10.36 ± 3.32	t(48) = 0.16; <i>p</i> >0.5	3.82 ± 1.31	3.76 ± 1.15	t(48) = 0.17; <i>p</i> >0.5
Near Point Convergence Recovery (cm)	12.42 ± 4.21	12.62 ± 3.94	t(48) = 0.17; <i>p</i> >0.5	4.94 ± 1.43	5.24 ± 1.39	t(48) = 0.75; <i>p</i> =0.5
Positive Fusional Range Base-Out Blur/Break ()	10.64 ± 2.98	10.56 ± 3.76	t(48) = 0.08; <i>p</i> >0.5	28.96 ± 8.61	26.60 ± 8.27	t(48)=1.0; <i>p</i> =0.3
Positive Fusional Range Base-Out Recovery ()	8.80 ± 3.56	9.36 ± 4.46	t(48) = 0.49; <i>p</i> >0.5	25.12 ± 7.46	24.32 ± 8.01	t(48) = 0.37; <i>p</i> >0.5
Negative Fusional Range Base-In Blur/Break ()	11.60 ± 3.83	11.56 ± 2.62	t(48) = 0.04; <i>p</i> >0.5	14.16 ± 2.37	13.84 ± 2.64	t(48) = 0.45; <i>p</i> >0.5
Negative Fusional Range Base-In Recovery ()	11.44 ± 3.24	10.96 ± 2.46	t(48) = 0.59; <i>p</i> >0.5	12.16 ± 2.58	12.88 ± 3.22	t(48) = 0.87; <i>p</i> =0.4
Vergence Facility Near	18.44 ± 14.96	15.88 ± 13.95	t(48) = 0.63; <i>p</i> >0.5	35.46 ± 8.35	30.68 ± 11.74	t(48) = 1.66; <i>p</i> >0.1
Monocular Accommodative Amplitude OD (D)	8.33 ± 2.54	8.62 ± 1.88	t(48) = 0.46; <i>p</i> >0.5	11.63 ± 1.8	10.58 ± 1.35	t(48) = 2.33; <i>p</i>=0.02
Monocular Accommodative Amplitude OS (D)	8.36 ± 2.39	8.36 ± 2.00	t(48) = 0; <i>p</i> >0.5	11.29 ± 1.73	10.52 ± 1.43	t(48) = 1.71; <i>p</i> =0.09
Near Horizontal Phoria ()	7.20 ± 3.35 (exo)	6.52 ± 3.00 (exo)	t(48) = .80; <i>p</i> =0.5	2.04 ± 2.35 (exo)	2.04 ± 1.97 (exo)	t(48) = 0.00; <i>p</i> >0.5
Near Vertical Phoria ()	0.0 ± 0 ortho	0.0 ± 0 ortho	No Difference	0.13 ± 0.45 (hyper)	0.02 ± 0.10 (hypo)	t(48) = 1.63; <i>p</i> >0.1
Distance Horizontal Phoria ()	0.56 ± 1.78 (exo)	0.52 ± 2.4 (exo)	t(48) = 0.07; <i>p</i> >0.5	0.10 ± 0.38 (exo)	0.12 ± 0.67 (exo)	t(48) = 0.13; <i>p</i> >0.5
Distance Vertical Phoria ()	0.0 ± 0 ortho	0.0 ± 0 ortho	No Difference	0.06 ± 0.22 (hyper)	0.0 ± 0 (ortho)	t(48) = 1.36; <i>p</i> =0.2
Difference Horizontal Phoria (more exo at near than far) ()	6.64 ± 2.55	6.00 ± 1.83	t(48) = 1.02; <i>p</i> =0.3	1.94 ± 2.36	1.92 ± 2.00	t(48) = 0.03; <i>p</i> >0.5
OS Spherical Equivalent (D)	-0.92 ± 1.86	-0.94 ± 1.83	t(48) = 0.04; <i>p</i> >0.5	-1.32 ± 1.89	-0.86 ± 1.66	t(48) = 0.92; <i>p</i> >0.3
OD Spherical Equivalent (D)	-0.92 ± 2.09	-0.77 ± 1.53	t(48) = 0.29; <i>p</i> >0.5	-1.42 ± 2.05	-0.95 ± 1.74	t(48) = 0.87; <i>p</i> >0.3
Local Stereopsis (arc sec)	35.80 ± 12.56	36.20 ± 14.45	t(48) = 0.10; <i>p</i> >0.5	31.20 ± 13.79	27.80 ± 9.90	t(48) = 1.00; <i>p</i> >0.3
Global Stereopsis (arc sec)	250 ± 0.00	250 ± 0.00	No Difference	250 ± 0.00	250 ± 0.00	No Difference

Table 6 –

Statistical Comparison of Convergence Insufficiency patients to Binocularly normal controls. Statistically significant differences are reported in bold font.

Participant Type	Convergence Insufficiency CI (N=50) Mean ± Standard Deviation	Binocular Normal Controls BNC (N=50) Mean ± Standard Deviation	Statistical Comparison Between BNC and CI Cohorts
Age (years)	20.86 ± 3.57	21.76 ± 3.32	t(98) = 1.31; <i>p</i> =0.2
CISS Score	34.54 ± 7.63	8.18 ± 5.34	t(98) = 20.01; <i>p</i> < 0.0001
Near Point Convergence Break (cm)	10.44 ± 3.46	3.79 ± 1.22	t(98) = 12.82; <i>p</i> < 0.0001
Near Point Convergence Recovery (cm)	12.52 ± 4.04	5.09 ± 1.22	t(98) = 12.45; <i>p</i> < 0.0001
Positive Fusional Range Base-Out Blur/Break ()	10.60 ± 3.36	27.78 ± 8.44	t(98) = 13.37; <i>p</i> < 0.0001
Positive Fusional Range Base-Out Recovery ()	9.08 ± 4.00	24.72 ± 7.67	t(98) = 12.78; <i>p</i> < 0.0001
Negative Fusional Range Base-In Blur/Break ()	11.58 ± 3.25	14.00 ± 2.49	t(98) = 4.18; <i>p</i> < 0.0001
Negative Fusional Range Base-In Recovery ()	11.20 ± 2.86	12.52 ± 2.91	t(98) = 2.29; <i>p</i> < 0.03
Vergence Facility Near	17.16 ± 14.38	33.02 ± 10.40	t(98) = 6.32; <i>p</i> < 0.0001
Monocular Accommodative Amplitude OD (D)	8.48 ± 2.22	11.09 ± 1.66	t(98) = 6.66; <i>p</i> < 0.0001
Monocular Accommodative Amplitude OS (D)	8.36 ± 2.18	10.90 ± 1.61	t(98) = 6.63; <i>p</i> < 0.0001
Near Horizontal Phoria ()	6.86 ± 3.17 (exo)	2.04 ± 2.14 (exo)	t(98) = 8.91; <i>p</i> < 0.0001
Near Vertical Phoria ()	0.0 ± 0 (ortho)	0.05 ± 0.33 (hyper)	t(98) = 1.07; <i>p</i> =0.3
Distance Horizontal Phoria ()	0.54 ± 2.09 (exo)	0.11 ± 0.54 (exo)	t(98) = 1.41; <i>p</i> =0.2
Distance Vertical Phoria ()	0.0 ± 0 (ortho)	0.03 ± 0.16 (hyper)	t(98) = 1.33; <i>p</i> =0.2
Difference Horizontal Phoria (more exo at near than far) ()	6.30 ± 2.39	1.93 ± 2.16	t(98) = 9.59; <i>p</i> < 0.0001
OS Spherical Equivalent (D)	-0.52 ± 1.62	-0.84 ± 1.78	t(98) = 0.94; <i>p</i> =0.3
OD Spherical Equivalent (D)	-0.47 ± 1.69	-1.08 ± 1.96	t(98) = 1.67; <i>p</i> =0.1
Local Stereopsis (arc sec)	36 ± 13.40	29.50 ± 12.01	t(98) = 2.55; <i>p</i> < 0.01
Global Stereopsis (arc sec)	250 ± 0.0	250 ± 0.0	No Difference