Clinical and Functional Imaging Changes Induced from Vision Therapy in Patients with Convergence Insufficiency

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***Abstract*— Office-Based Vergence/Accommodative Therapy (OBVAT) is an effective treatment for convergence insufficiency (CI) and remediates symptoms in about 75% of patients. Hence, the study of CI patients can serve as a systems-level model to understand the neural mechanisms evoked from rehabilitation. Symptomatic young adult CI patients (N=25) participated in 12 hours of OBVAT and were compared to 25 binocularly normal controls (BNC) using unpaired *t*-tests. CI patients have significantly lower near point of convergence and positive fusional vergence and were more symptomatic compared to BNC ($p<0.0001$). Using paired *t*-tests, significant differences ($p<0.0001$) were observed between CI patients' baseline and post-OBVAT measurements where the near point of convergence decreased, positive fusional vergence increased, and the results from the Convergence Insufficiency Symptom Survey (CISS) decreased. Using paired *t*-tests, the mean beta weights of the functional activity significantly increased for the frontal eye fields ($p<0.01$) and the oculomotor vermis ($p<0.05$) for CI patients post-OBVAT compared to baseline measurements. These data demonstrate that OBVAT increases functional activity within the brain and improves clinical function and visual symptoms in CI patients.**

I. Introduction

Convergence insufficiency (CI) is a common binocular vision disorder with a prevalence between 4.2% to 17.6% of the general population [1]–[5] and up to 50% of patients with post concussive syndrome [6]–[9]. CI often results in symptoms that include headaches, eyestrain, blurred vision, diplopia, and loss of place while reading [10]. Convergence (divergence) is the inward (outward) rotation of the eyes. The vergence system binocularly coordinates disjunctive eye rotation to perceive the world as single. A Cochrane Review concluded that office-based vision therapy is an effective therapeutic intervention for CI [11]. Randomized clinical trials (RCT) studying vision therapy in children report an effectiveness of about 75% for office-based vision therapy that is sustained at least one-year post treatment [12], [13]. Since the remediation of visual symptoms lasts at least one year, it is presumed that changes occur within the brain. Yet, the underlying neural mechanism by which vision therapy leads to a remediation of vision symptoms and improvement in clinical vision function is not well understood.

The first aim of this study was to identify the underlying neural circuit of the vergence system in binocularly normal controls (BNC), and to compare that to the neural circuit of the vergence system of patients with CI during a vergence eye movement task. The second aim was to study CI patients longitudinally through 12 hours of Office-Based Vergence and Accommodative Therapy with home reinforcement (OBVAT), which was the vision therapy protocol used in previous RCTs [14]–[17]. Part of the second aim was to quantify how clinical signs, symptoms, and functional activity of the vergence neural circuit change between pre- and post-OBVAT measurements and to identify which parameters were significantly changing. This study tested the hypothesis that significant improvements would be observed in clinical vision function with a significant increase in peak activation for functional activity within the vergence neural circuit.

II. Methodology

A. Subjects

Symptomatic CI patients (N = 25, 20.3 ± 3.2 years, 10 males) and asymptomatic BNC (N = 25, 21.3 ± 3.1 years, 14 males) participated in this study. All subjects signed informed consent in accordance with the Declaration of Helsinki approved by the New Jersey Institute of Technology Institutional Review Board.

Subjects were diagnosed as CI or BNC by one of the co-authors who is an optometrist (MS). Exclusion criteria included head injury, visual dysfunction other than CI and systemic diseases that affect accommodation, vergence, or ocular motility (i.e. multiple sclerosis, Graves' thyroid disease, myasthenia gravis, diabetes, or Parkinson's disease). Symptomatic CI was defined using near point of convergence, positive fusional vergence, the difference between near and far phoria and the presence of visual symptoms. Near point of convergence (NPC) is the point alone midline when a target becomes diplopic. One parameter to be diagnosed with CI was

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an NPC of ≥ 6 cm. Phoria is the resting level of the eye when one eye is occluded and is measured at near (40 cm) and at far (6 m). The second parameter needed for the diagnosis of CI is a near exodeviation of phoria that is as at least 4Δ greater than at distance fixation. Positive fusional vergence (PFV) is the addition of prismatic demand until the point where binocular fusion is no longer attained. The third parameter of a CI diagnosis is has having a PFV failing Sheard's criterion [18] which is a PFV less than twice the near phoria [19] or the minimum positive fusional vergence at near of ≤15Δ base-out. Last, the CI diagnosis includes that patient symptoms. Symptomatic is defined as a response score of ≥21 on the Convergence Insufficiency Symptom Survey (CISS) for young adults. These definitions are based upon the standards established within the Convergence Insufficiency Treatment Trial (CITT) RCT [20].

B. Clinical Signs and Symptoms

All testing was performed with the subjects wearing the appropriate refractive correction. The clinical exam included the following parameters: NPC, PFV, dissociated phoria at near and far, and the CISS. NPC was defined as the distance along the midsagittal plane from the nasion where a subject reported diplopia using a 20/30 vertical visual target measured in cm with a near point rule (Bernell model: GR5). PFV was measured with a Gulden horizontal prism bar (model: B12 EZ View) which has a range of 1Δ, 2Δ to 20Δ (increments of 2Δ), and 25Δ to 45Δ (increments of 5Δ). The prism bar was held over the right eye with the base out. A clinician held a 20/30 vertical column of letters along the midsagittal plane 40 cm away and increased the prism strength slowly until the subject reported diplopia. This was recorded as the positive (base out) fusional vergence at break.

Subject symptoms were tabulated using the CISS, which contains 15 questions and uses a 5-point Likert scale. The higher the score, the more symptomatic the subject. It assesses common vision symptoms such as blurry and double vision. A score of 21 or greater is classified as being symptomatic for young adults. CITT designed and validated the CISS and reports that it has a sensitivity of 98% and specificity of 87% in young adults [21], [22].

C. Therapeutic Intervention

Therapy was performed with the subjects wearing the appropriate refractive correction. OBVAT has been studied as the therapeutic intervention in several double-masked, RCTs [14]–[17]. It has a reported 73% effectiveness rate in the pediatric population without head injury [6]. It is a three phase therapeutic intervention described in a prior publications. [14]–[17]. The first phase trains gross convergence using instruments such as the Brock string (Bernell model: BC109), a Barrel Card and voluntary convergence. Fusion vergence exercises include the following: Clown and Quoits Vectograms, Computer orthoptics, Aperature Rule, Life Saver Cards, loose prisms, and eccentric circles. The accommodative interventions include, 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 and binocular ± 2.0 D Flipper Facility.

The instruments used included the following: Vectograms (Bernell model: SOV2), loose prisms (Bernell Model: APS30), the Aperture Rule (Bernell model: BC1050BK), Eccentric Circles (Bernell Model: KEY411), and computer-based therapy using Computer Orthoptics VTS4 from Home Therapy Solutions (HTS) described in detail in a prior publication [20]. Vision therapists were certified using the same criteria established in the CITT studies by one of the co-authors (MS). CI patients participated in one or two sessions per week, for 50-60 minutes per session, over a 6 to 8 week duration, for a total of 12 hours of OBVAT. Patients also used the HTS computer-based vision therapy program for home-based vision therapy, which was logged and monitored by the vision therapist. Subjects were asked to perform home exercises three times per week for about 10 minutes per day on the days that they did not participate in office-based therapy. This equated to about 3 hours of home-based vision therapy.

D. Imaging Acquisition and Visual Stimulus

Subjects were first brought to the laboratory to learn how to fuse the visual stimuli shown in Fig. 1. When the eyes were converging, the middle and inner square would give the perception of being closer to the person compared to the outer square. Conversely, when the eyes were diverging, the middle and inner square would give the perception of being further away from the subject compared to the outer square. After learning how to fuse the targets, subjects were aligned within the center of the MRI magnet so that vergence stimuli were symmetrical along the midsagittal plane. Subjects were visually adapted to look at far to relax the vergence system. The resting state of the eye (phoria) influences the vergence system [23]–[25]. This functional imaging methodology is similar to other published papers [26]–[29].

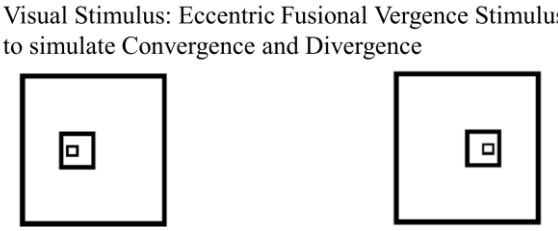

Figure 1: Visual stimulus used during fMRI experiment for left eye (left) and right eye (right).

Data were collected on a 3T Siemens TRIO using a 12-channel head coil to acquire data within an axial configuration. High resolution anatomical volumes acquired using a magnetization-prepared rapid acquisition with gradient echo (MPRAGE). The MPRAGE imaging protocol consisted of the following parameters: TR = 1900 ms, TE = 2.52 ms, T1 = 900 ms, with a total of 176 acquired slices. The voxel resolution was 1.0x1.0x1.0 mm3. Subjects were verbally instructed to limit head motion and foam wedges were placed around head.

Vergence stimuli alternated 5 times between the following three blocks: 1) 15 sec of sustained fixation, 2) 19 sec evoking 4 vergence movements (4.75 sec allotted per stimulus), and 3) 18 sec evoking 8 vergence movements (2.5 sec allotted per stimulus). The fMRI protocol used an echo planar imaging (EPI) pulse scan sequence that had the following parameters: TR = 2sec, TE = 13ms, Field of View = 192mm, flip angle = 90°, 53 axial slices acquired at a resolution of 3.0x3.0x3.0 mm^3. The total acquisition time was 416 sec (about 7 min).

E. Imaging Processing

After image acquisition, the data were realigned and co-registered to reduce the influence from minor head motion using SPM12. Data were mapped into Montreal Neurological Institute (MNI) standardized space for group-level analyses. The anatomical images were segmented into cerebral spinal fluid and white matter images and BOLD fMRI time series were derived from these tissue types. Regression was performed using the 6 head motion parameters within and between imaging volumes and the first 5 principal components from a principle component analysis performed on the BOLD fMRI time series of the cerebral spinal fluid and white matter segments. This was done to reduce false positive activation due to physiological noise and participant movement aritfacts. A high pass filter with a cutoff frequency of 0.01 Hz was applied. Data were smoothed using a Gaussian kernel [(6 mm full width half maximum (FWHM)]. A general linear model with a canonical waveform for the hemodynamic response was used to calculate voxel-vise subject level activation maps in response to vergence stimuli. These beta weight maps were used to compare the baseline and post-OBVAT CI datasets.

Masks were applied to the data to identify the following regions of interest (ROI): Frontal Eye Fields (FEF), Supplementary Eye Field (SEF), and Parietal Eye Field (PEF) [30], [31]. The cerebellar vermis and declives are reported in saccadic motor learning also termed the oculomotor vermis [32]. These masks were applied because prior pilot research showed change within these ROIs for CI patients [31]. ROIs are 5- or 7-mm spheres centered on the peak activation in BNC dataset at baseline depending on the size of the anatomic area. The beta weight per ROI is reported as the mean of the ROI within this sphere with the MNI coordinates of the centroid of the sphere. Activation maps were obtained from t-maps with $p<0.5$ corrected for multiple comparison by using false discovery rate (FDR).

F. Statistics

Group-level statistics were performed using the software package SPSS. Paired *t*-tests were used to determine whether significant changes were observed in the CI patients' baseline and post-OBVAT datasets. The following parameters were analyzed: NPC, PFV, CISS score, and beta weights of the ROIs described above. Unpaired *t*-tests were used to compare the BNC data to the CI patient data post-OBVAT to determine whether there was a significant difference between patients post-OBVAT and controls.

III. Results

A. Clinical Vision Parameters and Vision Symptoms

All subjects had normal stereopsis with a global stereopsis of 250 arc sec and local stereopsis of <70 arc sec or better. Using a paired *t*-test, NPC significantly decreased from 10.5 ± 3.7 cm at baseline to 4.5 ± 1.6 cm post-OBVAT in CI patients [$t(24)=7.6$; $p<0.001$], see Fig. 2. NPC is considered normal when it is < 6 cm [33]. Data from 25 BNC (green bar Fig. 2) are plotted for comparison to 25 CI patients at baseline (red bar Fig. 2) and 25 CI patients post-OBVAT (blue bar Fig. 2). The NPC for baseline BNC data compared to the CI post-OBVAT data were not significantly different using an unpaired *t*-test [$t(48)=1.9$; $p>0.05$]. The dash dotted line with an arrow denotes abnormality is shown in Fig. 2 for reference.

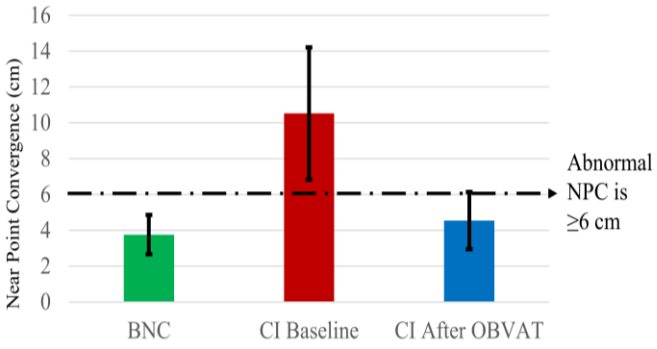

Figure 2: Near Point of Convergence (NPC) (cm). Average ± one standard deviation. Dash dotted line delineates normal from abnormal values.

PFV at fusional break increased from 12.2 ± 3.2 prism diopter (Δ) at baseline for CI patients to 34.44 ± 11.7Δ post-OBVAT, which is a statistically significant change using a paired *t*-test [$t(24)=8.6$; $p<0.001$]. PFV at the break is considered abnormal when it is 15Δ or less and a change of 10Δ or more is considered clinically significant [33]. BNCs had a PFV of 31.8 ± 8.7Δ for comparison. No significant difference was observed between the baseline data of BNC and the data of CI patients post-OBVAT [$t(48)<1.0$; $p>0.32$] using an unpaired *t*-test. The dash dotted line with an arrow where PFV is considered is abnormal is plotted in Fig. 3 for reference.

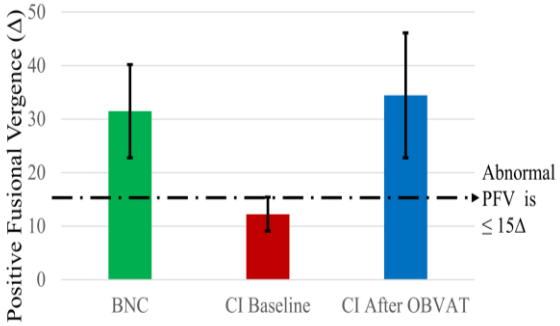

Figure 3: Positive Fusional Vergence (PFV) prism diopters (Δ). Average ± one standard deviation. Dash dotted line delineates normal from abnormal values.

The mean CISS score decreased from 34.0 ± 9.0 to 21.6 ± 8.0 post-OBVAT for the symptomatic CI patients. The change was significant [t(24)=5.6; $p<0.001$]. BNC were asymptomatic as observed by their CISS scores of 9.0 ± 5.6 and were plotted for comparison. While the BNC CISS score was still significantly less compared to the CISS score from the CI patients post-OBVAT, by clinical definitions most of these patients were diagnosed as asymptomatic since the threshold set by CITT is 21 for young adults [t(48) = 6.1; $p<0.001$]. The criteria for symptomatic as defined by CISS was shown as a dash dotted line with arrow in Fig. 4. While the CI patients post OBVAT where still more symptomatic than BNCs, the CISS is a subjective measurement and it is more important to observe the within subject symptom response compared to between group differences.

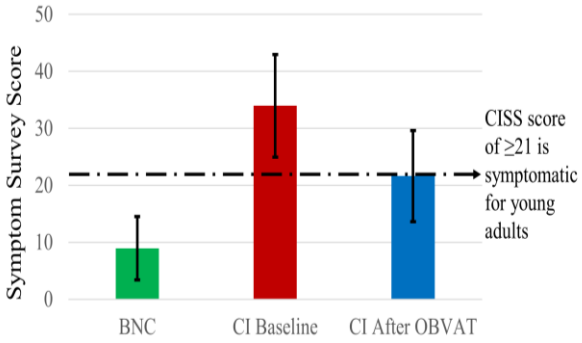

Figure 4: Convergence Insufficiency Symptom Survey. Average ± one standard deviation. Dash dotted line delineates symptomatic from asymptomatic.

B. Functional Imaging Data

Spatial activation maps were plotted using Analysis of Functional NeuroImages (AFNI) [34] where images were the average of 25 subjects each in MNI space. Only functional activity that was significantly ($p<0.05$) correlated to the hemodynamic response are shown. The hemodynamic response is a canonical waveform of the experimental block design of rest compared to the block with 8 vergence eye movements. All data are corrected for multiple comparisons using FDR. Two axial slices were shown to compare BNC (Fig. 5A), CI patients at baseline (Fig. 5B), and the same CI patients post-OBVAT (Fig. 5C). Axial slice 50 Superior was used to observe functional activity within the FEF, SEF, and PEF (arrows in Fig. 5 left) and axial slice 18 Inferior was used to observe function activity within the oculomotor vermis (arrow in Fig. 5 right).

Functional activity was observed for the vergence neural network within the FEF, SEF, PEF, and oculomotor vermis. The spatial extent and peak functional activity were greater in BNC compared to CI patients at baseline (Fig. 5 A compared to B). After OBVAT, the CI patients showed an increase in spatial extent and peak activity compared to baseline measurements (Fig. 5B compared to C).

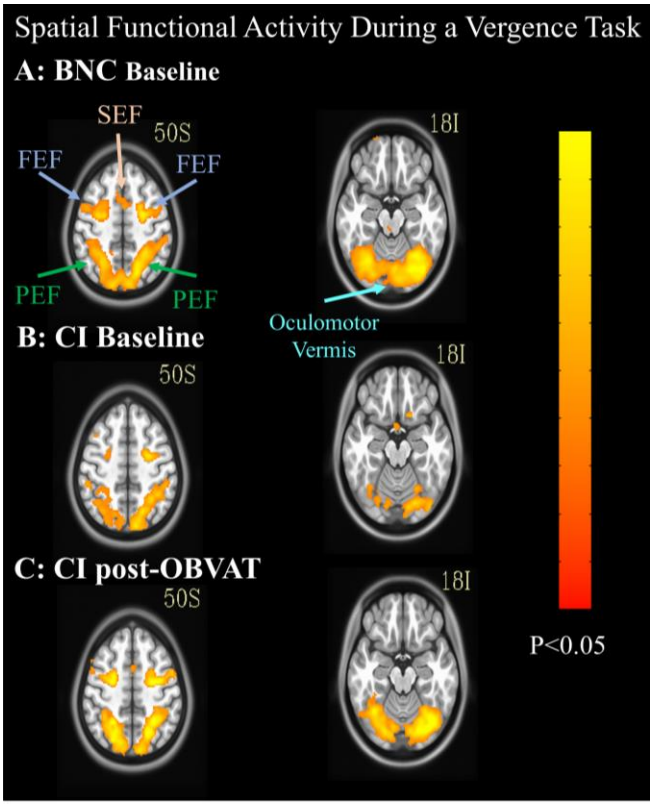

Figure 5: Group-level spatial activation of frontal eye fields (FEF), supplementary eye field (SEF), parietal eye fields (PEF) from axial slice 50S and oculomotor vermis from axial slice 18I using one sample *t*-test of BOLD signal and canonical waveform of experimental design. Data from 25 BNC (plots 5A), 25 CI patients at baseline (plots 5B) and same 25 CI patients post-OBVAT (plots 5C).

A group-level analysis was performed on the mean activation beta values of the right FEF for a 7 mm sphere centered at MNI: 26R, 8A, and 52S and the left declive also called the oculomotor vermis for a 5 mm sphere centered at MNI: 26L, 69P, and 17I. MNI coordinates are in mm. This location was compared before and after OBVAT (Fig. 6). The peak of the beta weights within a 7 radius ROI centered at this MNI location had a mean ± the standard error of the mean (SEM) for the BNC dataset of 0.063 ± 0.013 within the FEF and 0.183 ± 0.041 within the oculomotor vermis. For FEF of the same spatial location as BNC dataset, the CI patients for their baseline dataset had a mean ± SEM of 0.026 ± 0.013, which significantly increased to 0.074 ± 0.011 post-OBVAT [t(24)=2.9; $p<0.01$]. For the oculomotor vermis of the same spatial location as the BNC dataset, the CI patients for their baseline dataset had a mean ± SEM of 0.087 ± 0.033, which significantly increased to 0.175 ± 0.032 [t(24)=2; $p=0.05$] post-OBVAT [t(24)=2; $p=0.05$]. When comparing the BNC baseline data to the CI post-OBVAT, no significant difference was observed for the FEF [t(45.9)=1; $p>0.4$] or the oculomotor vermis [t(45.4)=0.02; $p>0.9$].

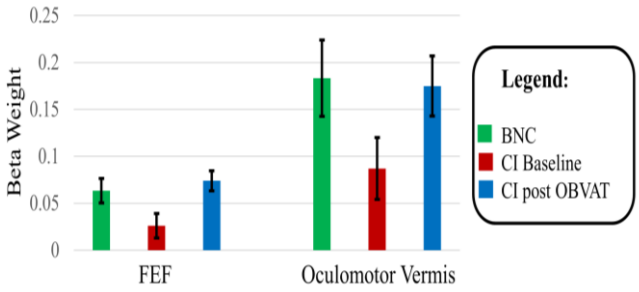

Figure 6: Functional activity mean beta weight ± standard error of mean (SEM) from a 7 mm sphere within Right FEF [MNI (in mm): 26R 8A 52S] and Functional activity mean beta weight ± SEM from a 5 mm sphere within Left Cerebellar Declive called Oculomotor Vermis [MNI: 26L 69P 17I].

IV. Discussion

A. Neural Mechanisms of Vision Therapy for CI

Two studies, one from our team and one from an independent research team, both conducted pilot studies (N=4) to study CI patients before and after vision therapy using functional MRI. Our study observed changes within the FEF, SEF, PEF, and cerebellum post vision therapy compared to baseline measurements [35]. While the other study reported changes within the occipital lobe post-OBVAT compared to baseline [36]. Both results support an increase in functional strength quantified as an increase in the magnitude of the BOLD signal. Yet, with such small sample sizes, it is difficult to determine whether the result would generalize to a larger population. This current study extends prior results and concludes that significant changes in peak activation were observed within the vergence neural circuit specifically the FEF and the oculomotor vermis. One explanation of these results is that the neuronal action potentials mediating the vergence response are more in phase or synchronized post-vision therapy compared to baseline and may explain in part how OBVAT leads to a sustained reduction in vision symptoms.

B. Comparison to Functional Imaging Studies Using Other Vision Rehabilitation Protocols

Saccades are the side to side eye movements and critical in order to read because these movements bring the world that we are foveating on into the brain. A rehabilitation study reported increased functional activity post therapy in those with mild traumatic brain injury using a saccadic training protocol [37]. Studies on dyslexic patients report increased activation in the left parietotemporal and occipitotemporal regions in dyslexic patients who improved their ability to read in adulthood compared to dyslexic patients who did not [38]. A vision restoration training study on patients with cerebral blindness reports an increase in visual receptive fields correlated to an increase in the amplitude of the BOLD signal [39]. Similar to other vision training tasks for other patient populations, our study supports that fMRI is a tool that can quantify the underlying neural mechanisms evoked by therapeutic interventions.

C. Future Direction and Study Limitations

Future studies should include a study arm of CI patients who participate within a sham therapy to determine how much of the change is potentially due to procedural learning of the assessments. It would also be beneficial to understand how BNC may change through OBVAT as well.

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