Imaging of Convergence Insufficiency Treatment Effects (ICITE) Pilot Study: Design and Methods

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Keywords: convergence insufficiency, functional magnetic resonance imaging, eye movements

ABSTRACT

Background: The blood-oxygen-level-dependent (BOLD) signal from functional magnetic resonance imaging (fMRI) identifies brain activation during specific tasks. This paper describes the design and methodology of the Imaging of Convergence Insufficiency Treatment Effects (ICITE) Study, a two-phase study comparing BOLD activations during vergence eye movements in symptomatic convergence insufficiency (CI) subjects (1) to those with normal binocular vision (NBV) and (2) after office-based vergence/accommodative therapy (OBVAT) versus office-based placebo therapy (OBPT).

Methods: Young adults, 18 to 30 years, with NBV or symptomatic CI (near exophoria at least 4Δ [prism diopters] greater than at distance, receded near point of convergence [NPC], and insufficient positive fusional vergence [PFV]) were enrolled. During fMRI scanning, subjects were instructed to fuse a random-dot stereogram stimulus with vergence demands ranging from -3Δ to +25Δ. CI subjects were then randomized to 12 weeks of OBVAT or OBPT. Vision and fMRI examination at outcome were performed by a masked examiner. BOLD signal at baseline was compared between NBV and CI patients. Later, the BOLD response at baseline was compared to that following vision therapy for those with CI.

Conclusion: The imaging results are expected to advance understanding of neurological mechanisms of CI and the effects of therapy on the vergence system, which in turn may guide development of future research that could lead to new treatment strategies.

INTRODUCTION

Convergence insufficiency (CI) is characterized by clinical signs of a near phoria that is greater than that found at distance, a receded near point of convergence (NPC) and reduced...
positive fusional vergence (PFV) ranges. Further, those with CI often report symptoms that include blurred vision, headaches, double vision, loss of concentration, frequent loss of place, and trouble remembering what was read. Office-based vergence/accommodative therapy (OBVAT) with home reinforcement has proved to be successful in reducing patient symptoms and in improving clinical signs.

Given the increase in near work demands as tablets and smartphones have increasingly become more popular in classrooms and offices, visual fatigue is also a commonly reported symptom of binocular vision disorders, such as CI. This is thought to be caused by a centrally-based, neurological mismatch between the accommodative and vergence response to visual stimuli, not simply muscle fatigue in the extraocular muscles. This suggests that differences in brain activity may be observable in imaging studies of individuals with CI.

A variety of imaging techniques have been used to investigate brain activity related to vision. Early studies involving electrical stimulation of targeted structures within the brains of monkeys were able to differentiate between cells to initiate convergence and divergence eye movements. More recent studies have used advanced imaging techniques to map brain activity of accommodation and vergence eye movements.

Functional magnetic resonance imaging (fMRI) is a non-invasive method that has become a major research tool in studying brain function with use of the blood-oxygen-level-dependent (BOLD) signal to indicate magnitude and spatial extent of regional neural activity. Alvarez, Jaswal, Gohel and Biswal, 2014, used fMRI analysis to compare convergence activation of CI subjects both before and after vision therapy (VT) treatment as well as with normal binocular vision (NBV) controls. In all scans (NBV, CI before VT, and CI after VT) they found significant activation in regions of interest of the human brain (frontal eye fields, posterior parietal cortex, and cerebellar vermis) during small-angle convergence demands (2 and 4 degrees; or, approximately 3.5 and 7 prism diopters, Δ). While this study supports the theory that observable differences are present in CIs during brain imaging, prior research has not investigated changes in activation to typical near vergence demands (15 PD, or 6.9 degrees) or changes in response to a random dot stereogram (RDS) target presented at a fixed distance and accommodative demand. In addition, prior research of brain activation during convergence has not included treatment with office-based vergence/accommodative therapy (OBVAT), which has been shown to be the most successful treatment in reducing patient symptoms and in improving clinical signs in both children and adults or a placebo therapy control group (OBPT).

The purpose of the Imaging of Convergence Insufficiency Treatment Effects (ICITE) study is to compare the spatial extent and magnitude of fMRI BOLD signals related to vergence eye movements with an RDS stimulus 1) between subjects with CI versus NBV and 2) before and after therapy in subjects with CI.

METHODS

The ICITE study adhered to the tenets of the Declaration of Helsinki and received approval of The Ohio State University Biomedical Institutional Review Board. All subjects provided written informed consent prior to completing study-related procedures and completed comprehensive screening for safety within an MRI scanner.

Baseline Procedures

All subjects completed an eligibility exam to evaluate their binocularity. Normal binocular vision was determined by standard normative values. The presence of CI was defined according to the criteria used in the Convergence Insufficiency Treatment
Table 1. Inclusion and exclusion criteria at baseline

**Inclusion Criteria for all subjects:**
- Informed consent and willingness to participate in the study
- Age 18-30 years
- Best corrected visual acuity of 20/25 or better in each eye at distance and near
- Cycloplegic refraction within the past 3 months.
- Willing to wear correction for any significant refractive error
- No prior orthoptic or vision therapy treatment
- No amblyopia, strabismus, vertical phoria >1Δ, history of refractive surgery, or manifest or latent nystagmus
- No systemic diseases known to affect accommodation, vergence, or ocular motility
- No current use of any ocular or systemic medication known to affect accommodation, vergence or ocular motility
- No history of brain injury or neurological disease
- Able to successfully complete baseline fMRI imaging

**Inclusion Criteria for NBV patients:**
- Heterophoria at distance and near between 2Δ esophoria and 6Δ exophoria with no more than 6Δ between distance and near measures
- Adequate near point of convergence of <6-cm break
- Negative fusional vergence at near >7Δ break/5Δ recovery
- Positive fusional vergence at near >10Δ break/7Δ recovery
- Normal accommodative amplitude OD (greater than 15–0.25x age as measured by push-up testing)
- Random dot stereoacuity of 500” or better
- No previous near addition lens use or prism use

**Inclusion Criteria for CI patients:**
- Willingness to participate in randomization to active versus control therapy
- Presence of symptomatic convergence insufficiency (CI):
  1) Exophoria at near at least 4Δ greater than at far,
  2) Receded near point of convergence of ≥6-cm break,
  3) Insufficient positive fusional convergence (i.e., failing Sheard's criterion or <15Δ base-out blur (or break if no blur)),
  4) Convergence Insufficiency Symptom Survey score of ≥21
- Accommodative amplitude ≥5 D
- Willingness to discontinue wearing base-in prism or add, if applicable
- Subject or household member of subject is not an eye care professional, ophthalmology/optometry student/resident, ophthalmic technician, or employed in an eye care setting
- No household members enrolled in I-CITE or currently undergoing vergence therapy
- Developmental or learning disability that may interfere with treatment (investigator discretion)

**Exclusion Criteria for all subjects for fMRI**
- High refractive error not corrected by contact lenses that is beyond the range of the fMRI-safe trial lens set
- Any MRI unsafe surgical implants or devices
- Metal foreign bodies in or proximal to the eye, brain, heart or spinal cord, or of uncertain location
- Tattoos on the head or neck, tattoos obtained by a non-licensed artist or outside of the United States, or extensive/large tattoos anywhere on one's body
- Pregnancy
- Insufficient medical/surgical history on patient
- Refusal to remove unsafe personal objects, clothing, jewelry, etc. from person prior to entering MRI exam room or uncooperative patient
- Extensive orthodontic work, including wearing braces
- Left-handed dominance
Trial (CITT) studies. Complete criteria for each group are shown in Table 1. Baseline eligibility testing included sensorimotor evaluation with assessment of symptoms, cover testing at distance and near, NPC, and PFV. Testing followed the CITT protocol manual of procedures. The CISS was administered to all subjects both before and after testing and then averaged with a symptomatic score being ≥21 in adults. Distance and near phorias were measured by unilateral and alternating cover testing with prism neutralization. Near point of convergence was determined (break and recovery) using a 20/30, vertical column of letters (Near Point Rule, Gulden Ophthalmics, Elkins Park, PA; mean of 3 measures to nearest half centimeter). Blur, break and recovery were measured to determine positive fusional vergence ranges with a prism bar while the subjects viewed a 20/30, vertical column of letters at 40 cm (Fixation Sticks, Gulden Ophthalmics, Elkins Park, Pennsylvania; mean of 3 measures).

Measures of accommodative amplitude (push-up method; right eye only), accommodative facility (cycles per minute [cpm] with ±2.00 D flippers with 20/30, vertical column of letters at 40 cm; right eye only) and vergence facility (cpm using 12Δ BO/3Δ BI prism flippers with 20/30, vertical column of letters at 40 cm) were also obtained. Eye tracking (ISCAN, Woburn, MA) was performed for each subject during a brief vergence eye movement task to demonstrate the stimulus and to determine whether the subject would be able to understand similar tasks during the fMRI scan. An ocular health examination and cycloplegic refraction were performed if not done within the past 3 months. If the cycloplegic refraction indicated a significant change from the current prescription (more than 0.50 D of myopia, 1.50 D of hyperopia, or 0.75 D of astigmatism or anisometropia), eligibility testing was repeated with the new refractive error correction, after the subject had worn the new correction for at least two weeks. Eligible subjects (NBV and CI) were scheduled for an fMRI scan to be performed within the two weeks following the eligibility exam. Subjects completed a comprehensive fMRI safety screening prior to scanning. All fMRI scans were performed while viewing the stimuli within a Siemens 3.0-Tesla imager (Siemens Medical Systems, MR software version 12 with a 12-channel array head coil, Brainwave software) at the Center for Cognitive and Behavioral Brain Imaging (CCBBI), Psychology Building, The Ohio State University, Columbus, Ohio. Magnetization-prepared rapid gradient-echo (MPRAGE) sequences were collected for anatomical images using the following parameters: repetition time (TR) of 1950 ms, echo time (TE) of 4.44 ms, matrix size of 224 x 256, flip angle (FA) of 12 degrees, and a voxel resolution of 1.0 mm³, isotropic. Functional images were collected using the following imaging parameters: TR of 2500 ms, TE of 28 ms, matrix size of 72 x 72, FA of 76 degrees, and voxel resolution of 3 mm³, isotropic.

Subjects were positioned supine and head-first in the scanner within a dimly-lit room. The stimuli were projected from the control room onto a computer monitor placed behind the bore of the scanner. It was visible to the supine subject through a tilted mirror placed 11 cm above the subject’s face and on the 12-channel helmet coil. Once the subject and scanner bed were moved into the scanner, the screen was 59 cm from the mirror giving a 70-cm, reflected, viewing image of the stereogram stimulus. Subject head motion was restricted with the use of cushions packed around the head and headphones within the helmet coil. Instructions to the subject were to try and keep the target single as best as possible for each presentation in order to see a smaller, 3-D target floating in front of the screen.

Subjects performed eye movement tasks during the fMRI scan (Figure 1). The stimulus was an anaglyphic random-dot stereogram written in Visual Basic (Microsoft, Kirkland, WA) by one of the study investigators (AJT).
The testing stimulus was modeled after the stimulus used in the Home Therapy Solutions (HTS) therapy program (Home Therapy Solutions, Gold Canyon, Arizona).²⁰ The overall stimulus was 7.3 degrees vertically by 6.7 degrees horizontally and was comprised of square elements of 2.0 minutes of arc. The stereogram contained a central square (3.3 degrees) with 480" of crossed disparity such that when viewed binocularly the central square was perceived to be raised in front of the larger background rectangle. To properly view the stimulus, subjects wore paper, red-blue, 3-D anaglyph glasses (American Paper Optics, Bartlett, Tennessee).

Our RDS target was expected to stimulate blur accommodation as well as proximal vergence. However, as the stimulus was presented at a fixed distance, accommodative and proximal vergence demands are expected to be constant throughout the procedure.⁴ Thus, any activation differences noted between converged states and resting states are presumed to be due to changes in fusional vergence. The flexibility of the stimulus design allowed presentation of vergence demands comparable to common close work demands. The usable range of vergence demands (0Δ to ±25Δ (limited by the width of the computer display monitor) relative to the standard vergence demand for the 70-cm viewing distance) provided lower convergence demands that could be fused by pre-therapy CIs as well as higher convergence demands expected to be within the range of those with NBV.⁴,¹⁹

The order of fMRI scanning procedures was the same for all subjects. Functional MRI testing began with an anatomical localizer and an MPRAGE anatomical scan to later use to apply each subject’s functional data. Common fMRI designs (block and event-related) were utilized, with an easy and hard version of each

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**Figure 1:** Diagrams of stimulus presentations during fMRI scans: (a) blocks of convergence step ramps (easy: 2-Δ steps from 2 to 12Δ, hard: 5-Δ steps from 5 to 25Δ) and (b) jump vergences (event-related presentations of convergence [easy: 8Δ, hard: 16Δ] or divergence [3Δ] alternating with randomized rest periods [0Δ] of 4-7 seconds).
(see Figure 1 and Table 2). Block designs of step convergence compared the BOLD response during alternating blocks of “on-task” activity (increasing convergence demands) and “off-task” rest (0-Δ vergence demand). The on-task and off-task durations were 30 seconds and 20 seconds, respectively (repeated 5 times; Figure 1a). The easy step paradigm began with a 4-Δ demand and increased by 2Δ every 6 seconds to a maximum of 12Δ. The hard step began with a 5-Δ demand and increased by 5Δ every 6 seconds to a maximum of 25Δ. Event-related designs of jump vergence presented brief periods of alternating vergence (6 seconds, convergence or divergence) and rest (randomized 4 to 7 seconds; 4 minutes total duration; Figure 1b). The easy jump paradigm included stereogram targets with 8-Δ convergence and 3-Δ divergence demands, while the hard jump design included stereogram targets with 16-Δ convergence and 3-Δ divergence demands. The block designs provide high statistical power to detect differences while the event-related designs avoid the potential confounding of the predictability of repeated blocks of consistent duration.\textsuperscript{2} The total scan time was less than an hour. While binocular eye tracking was not available within this scanner set-up, an Eyelink 1000 eye-tracking system allowed for monitoring of a video feed of both of the subjects’ eyes on a computer screen. The video feed of the eye movements was also recorded with a Sony Handycam HDR-CX240 video camera (Sony Corporation, Konan Minato, Tokyo, Japan) for potential post-fMRI analyses. The baseline scan completed participation for NBV subjects.

### Therapy

After baseline testing and fMRI scan, the CI subjects were randomized (2:1) to 12 weeks of either OBVAT or OBPT therapy performed during weekly, hour-long, in-office sessions. Therapy was performed as outlined by the CITT protocol. During these therapy visits, subjects performed 3 to 5 therapy procedures as directed by a study-trained therapist. Each hour-long visit also included time to review homework procedures and answer questions.

<table>
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<tr>
<th>Paradigm</th>
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<td>Easy step convergence</td>
<td>Block</td>
<td>• Thirty-second “on” blocks of convergence step ramps</td>
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<td>Hard step convergence</td>
<td>Block</td>
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<td>• Alternated with 20-second periods of rest (zero demand; off condition)</td>
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<td>Easy jump vergence</td>
<td>Event-related</td>
<td>• 6-second periods of vergence (on condition)</td>
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<td>° The same randomized sequence of convergence (8Δ BO) and divergence (3Δ BI) demands was presented to all subjects.</td>
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<td>° The same randomized sequence of rest was presented to all subjects.</td>
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<td>Hard jump vergence</td>
<td>Event-related</td>
<td>• 6-second periods of vergence (on condition)</td>
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<td>° The same randomized sequence of convergence (16Δ BO) and divergence (3Δ BI) demands was presented to all subjects.</td>
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<td>° The same randomized sequence of rest was presented to all subjects.</td>
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Subjects were assigned reinforcement home therapy activities 15-20 minutes per day, 5 days per week. The OBVAT protocol followed three phases of techniques designed to each work on accommodation (monocular, binocular), vergence (gross, ramp fusional, jump fusional), and their integration. Within each phase, subject progress was indicated by meeting pre-determined endpoints for each activity. OBPT activities were not designed to treat either accommodation or vergence beyond that required by typical near tasks.

Progress visits were performed by a masked examiner every four weeks. After 12 weeks of therapy, vision testing and fMRI scanning were repeated by an examiner masked to the subject’s assigned treatment. Subjects who showed normal symptoms (a CISS score of less than 21) and signs of CI (NPC break less than 6.0 cm and PFV >15 PD BO and meeting Sheard’s criterion) were defined as “successful;” those showing normal or improved CISS score (≥10-point decrease) and either normal or improved NPC (improved by ≥4 cm) or normal or improved PFV (>10Δ BO increase) were considered “improved;” and, those who did not demonstrate any significant improvement in signs or symptoms were designated a “non-responder.” After the outcome fMRI scan, subjects were unmasked to their treatment. Subjects who had been randomized to OBPT and were not successful were offered OBVAT at no cost and an optional, third fMRI scan after an additional 12 weeks of treatment.

fMRI Analysis

All data from the scans were processed at the Image Analysis Lab at Wright State University using FMRI Expert Analysis Tool (FEAT) in FMRIB Software Library (FSL 5.0.4). The initial pre-processing of individual fMRI dataset was carried out within FEAT. Pre-processing involved motion correction, high pass temporal filtering and Gaussian spatial smoothening. To assess significant activations during the processing step, a general linear model was designed to describe each experimental paradigm. Each model was compared with the time-series of every voxel of the individual fMRI dataset. Based on the fitting of the model with the time-series data, z-score values were assigned to every voxel of the dataset. The activation threshold was set for z-scores ≥ 2.3, and a cluster significance was set to p < 0.05. This produced z-statistic maps for individual fMRI datasets. The z-statistic maps of individual subjects were registered to their respective anatomical images and then to a standard brain template (MNI152_T1_2mm).

For higher-level processing (group comparisons), the statistical outcomes from the individual-level processing were grouped as NBV and CI. Within the FEAT analysis, Gaussian random field theory was used to correct for multiple comparisons. Then, an unpaired t-test comparison was carried out between the two groups by modeling fixed-effect variance. The procedure to compare the pre- versus post-OBVAT and pre- versus post-OBPT groups was similar. However, instead of an unpaired t-test, a paired t-test was used for making these comparisons. The group comparison analyses yielded z-statistic maps that showed highlighted clusters in the brain regions where the activation significantly differed between the two groups (z-score ≥ 2.3, p < 0.05). It also produced z-statistic maps with highlighted clusters in the regions where the group, on average, exhibited significant activation (z-score ≥ 2.3, p < 0.05). To obtain a quantitative measure of the mean activation in each group, the total voxels in all significantly active clusters were counted. This provided a quantitative measure of the spatial extent of activation. The peak magnitude within an active cluster was reflected by the voxel(s) that had highest z-score value. The images were then created using the FSLView component of the software.

Previously identified ROIs specific to vision- and attention-related functions were investigated
and compared. Additional ROIs were identified by scanning all paradigm data files using FSLView within the FSL software package to identify any regions of significant BOLD response. Descriptive statistics (mean, median, standard deviation, and proportions) of each of the clinical variables were estimated. In all of the proposed data analyses, assumptions are being evaluated and appropriate nonparametric methods used, as needed, with common statistical software. Unless specifically stated otherwise, p-values less than 0.05 are considered significant.

EXPECTED OUTCOMES

The main outcome of this study is the BOLD response during the vergence tasks. The BOLD signals are used to identify anatomical regions for vergence eye movements in NBV subjects as well as to compare signal activation between ROIs for vergence eye movements in NBV and CI subjects, both in magnitude and spatial extent. The stimuli were presented at a fixed distance while the vergence demand was altered. Subjects are expected to employ fusional vergence in response to these changes in vergence demand. However, since it was not possible to monitor accommodation during the fMRI, a potential limitation of the study is that changes in accommodation cannot be ruled out. As part of the first phase of the study, the BOLD signals are being compared between the NBV and symptomatic CI subject groups. In the second phase, the BOLD signal response from the step convergence designs is being compared before and after OBVAT or OBPT therapy.

CONCLUSIONS

The imaging results of this study are expected to lead to further understanding of potential cortical differences between individuals who possess CI versus those with NBV; any potential differences may provide evidence of underlying, neural mechanisms for CI. Further, comparisons between pre- and post-therapy fMRI scans of CIs (real versus placebo) will show any changes in BOLD response due to convergence therapy on the cortical vergence system. Once any neural mechanisms and changes have been identified, future research and therapy protocols for CI may potentially be able to be designed to target these regions and lead to new treatment strategies.

Disclosures

The authors of this paper have no conflicts of interest to disclose regarding any products used in this research study.

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