The Effect of Vision Therapy on Adult Symptomatic Convergence Insufficiency Subjects: A Functional Magnetic Resonance Imaging Study

THESIS

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Abstract

Introduction: Convergence insufficiency (CI) is a common binocular vision disorder often associated with symptoms when completing near tasks. Vergence/accommodative therapy has been proven to improve symptoms and clinical signs in those with symptomatic CI. Previous literature has not examined the changes that occur in the brain after a course of real versus placebo therapy or using a stimulus with a wide of range vergence demands. The purpose of the current study was to show the changes that occur in the brain with CI therapy by examining the blood oxygenation level dependent (BOLD) signal during a functional magnetic resonance imaging (fMRI) scan before and after real and placebo treatment for convergence insufficiency.

Methods: Adult subjects (n = 7, ages 18-30 years) were recruited and confirmed to have symptomatic CI according to the criteria set forth by the Convergence Insufficiency Treatment Trial (CITT) (symptomatic symptom score, exophoria at least 4Δ greater at near than at distance, receded near point of convergence, insufficient positive fusional vergence). Eligible subjects underwent fMRI scanning while completing a series of vergence tasks. Subjects were then randomized into one of two treatment groups, office-based vergence accommodative therapy (OBVAT, n = 4) or office-based placebo therapy (OBPT, n = 3) in a 2:1 ratio, and completed 12 weeks of vision therapy following the CITT's treatment protocol. After treatment, subjects underwent a second fMRI scan while completing the same vergence tasks. Scans were analyzed with a two-tailed

analysis comparing between pre- versus post-therapy scans in those who completed OBVAT and comparing OBVAT versus OBPT group post-therapy scans (OBVAT n = 3, OBPT n = 2).

Results: The largest areas of activation were found in the occipital lobe. The largest areas of deactivation were generally found in the frontal lobe, but there was significant deactivation found in the occipital lobe pre-therapy and post-OBPT for a step vergence paradigm. A large decrease in spatial size of activation was seen post-OBVAT as compared to pre-therapy. In addition, the z-score value decreased among the areas that were common between the two. The areas of deactivation that were noted pre-therapy were resolved post-OBVAT when completing the easy step vergence paradigm and diminished when completing the hard step vergence paradigm. Post-OBPT showed a decrease in spatial size of activity when compared to the pre-therapy group as well, but not as much as post-OBVAT. The same overall pattern of activation areas was noted post-OBPT and pre-therapy. Regions of interest (ROIs) examined by other eye movement/vergence studies were examined and showed common areas of activation, but showed some difference, mainly in the frontal eye fields (FEF). Post-OBVAT, the active areas of the brain known to be devoted to attention were shown to suggest more of a bottom-up/stimulus driven attentional pathway rather than the top-down pathway noted pre-therapy and post-OBPT.

Conclusion: The current study showed that vision therapy has an effect on the brain in symptomatic CI subjects.

Dedication

This document is dedicated to all those who encouraged me to leave a bad situation and try something new. You are the wind beneath my wings.

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I would like to thank all those who helped me along in this process. My advisor, Dr. Marjean Kulp, helped me along every step of the way and always had great feedback when questions were asked. Dr. Tamara Oechslin clued me in to this project when I first decided to return to The Ohio State University. Without her, I may not be a part of this. Drs. Nicklaus Fogt and Andrew Toole both helped throughout the project and offered great insight. Dr. Nasser Kashou and Chirag Limbachia at Wright State University put in countless hours, completing all fMRI analyses. Without them, there would be no data to examine. Dr. Michael Earley offered great insight concerning all things brain toward the end of the project that were all greatly appreciated.

I would like to thank my committee, Drs. Kulp, Fogt, Toole, and Earley for taking time out of their day to help me make great improvements on my work.

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Chapter 1: Introduction

Convergence Insufficiency

Definition

Convergence insufficiency (CI) is the most common binocular vision disorder encountered in clinical practice.[1] It is characterized by a greater exophoria at near compared to distance, reduced near point of convergence (NPC), and inadequate positive fusional vergence (PFV) abilities. Many of the common symptoms that accompany the condition are as follows: headaches, eyestrain, visual fatigue, diplopia when completing a near task, loss of concentration, problems remembering what has been read, sleepiness while reading, poor comprehension, and movement of print while reading.[2-14] Though much of the attention with CI is based on fusional vergence, there are other components of the vergence system that can play a role in one's ability to accurately converge to a target, and those include the following: accommodative convergence (caused by an increase in accommodation), proximal convergence (due to the nearness of a target), and tonic convergence (a constant in the system).[15,16] The reported prevalence varies with factors such as the age group studied, definition of CI (e.g. number of signs), and population studied; a prevalence range of 2.25 to 8.3% has been reported.[17]

CI generally has an idiopathic origin in the general population.[18] Patients with certain systemic diseases, such as Parkinson's Disease[19], Lyme Disease[20], and those

suffering from migraines[21], have been shown to have a high incidence of CI compared to the general population. Studies have also shown a higher incidence of CI in those that have suffered a traumatic brain injury (TBI).[22-27]

Definition of CI

Definition of CI varies in the literature. More recent studies, including all studies performed by the Convergence Insufficiency Treatment Trial (CITT) study group[11,28-31], have based their definition on a 3-sign criteria: a cover test that shows at least 4Δ more exophoria at near compared to distance, a NPC ≥ 6 cm, and insufficient PFV (base out [BO] to blur or break less than twice the near phoria or <15Δ to break).[32] Some studies have defined CI as meeting one or two of the three signs listed above.

Assessment of Symptoms Associated with CI

Along with clinical signs, a patient's symptoms are important in the diagnosis of CI. If a patient does not perceive that he/she has a problem, it is likely that treatment will not be sought. When a patient is symptomatic, he/she will be more likely to undergo treatment. In order to quantify symptoms, the CITT study group developed the Convergence Insufficiency Symptom Survey (CISS).[3,33,34] While scaled surveys, such as the College of Optometrists in Vision Development Quality of Life (COVD-QOL) questionnaire[35] had also been available, the CISS provided a standardized way to assess a patient's symptoms. The survey consists of 15 questions, read verbatim to each patient by an examiner. The subject is given a response card and only allowed to answer with one of

five different responses (never, infrequently/not very often, sometimes, frequently, or always). Each response is given a score with never receiving 0 points and always receiving 4 points. The responses are totaled and can range from 0 to 60 points. A sample CISS can be found in Appendix A.

In order to determine the best cut-off value to discriminate between those with symptomatic CI and those with normal binocular vision, the survey was tested in a population of 9-18 year olds[3] and a population of 19-30 year olds.[33] In the child population, 47 symptomatic CI subjects and 56 normal binocular vision (NBV) subjects were administered the CISS. For the CI population, a mean score of 30.8 ± 8.4 was obtained, while for the NBV population a mean score of 8.4 ± 6.4 was obtained. A value of ≥ 16 was found to be the best cut point with a sensitivity of 95.7% and a specificity of 87.5%. In the adult population, 46 CI subjects and 46 NBV subjects were given the CISS. The mean score for the CI population was 37.3 ± 9.3, and the mean score for the NBV population was 11.3 ± 8.4.A CISS score of ≥ 21 was found to be the best cut point with 97.8% specificity and 87.0% sensitivity. The study group concluded that a reduction in a patient's score of 10 points or more would be considered a significant reduction in symptoms.[33]

Treatment

The treatment of CI varies among eye care professionals and includes passive approaches with prism and active approaches with home- and office-based therapy. Base-in (BI) prism reading glasses are sometimes recommended in order to reduce the

amount of convergence needed at near by moving the image of the print in regard to a position closer to where the eyes would prefer to be at rest, in an attempt to reduce the vergence demand and subsequently symptoms.[6,29,36,37] To determine the effectiveness of BI reading glasses, the CITT study group performed a trial in which 65 CI subjects, ages 9 to < 18, were randomized to receive BI prism glasses (prescribed according to Sheard's criteria) or glasses with no added prism.[29] Subjects were required to have been wearing the appropriate distance correction (if needed) for 2 weeks. The subjects were told to wear the assigned glasses whenever they would be doing near work for ≥ 5 minutes. The primary outcome measure was the change in CISS mean scores, while the secondary outcome measures were the changes in NPC and PFV mean values. After 6 weeks of wearing glasses, the CISS scores improved in both groups ($p < 0.001$) with 51.6% of those assigned to the BI prism group and 47.1% of those assigned to the placebo group improved to an asymptomatic level on the CISS (< 16). However, there was not a statistically significant difference between groups ($p = 0.71$). There were no statistically significant changes for either group in NPC or PFV. The conclusion made from this study was that BI prism glasses were no more effective in improving signs and symptoms of CI than regular correction or placebo glasses in children.

In a behavioral approach, base-up (BU) yoked prism reading glasses have been used by some practitioners. The BU yoked prisms are said to be "spatially compressive, creating decreased size, decreased distance, downward spatial shift, and downward gaze shift, associated with convergence and inwards body thrust."[38] Studies have not yet investigated the effectiveness of this treatment approach.

The focus of current research has been active vision therapy techniques to improve signs and symptoms of CI. While many studies have shown the efficacy of vision therapy, many lacked true clinical significance due to poor study design.[7,12,39-41] The CITT study group performed a pilot study to compare the effectiveness of office-based vergence/accommodative therapy (OBVAT), home-based pencil push-ups (HBPP), and office-based placebo therapy (OBPT) in a population of children, ages 9-18.[14] At the time of this study, pencil push-ups were the most commonly prescribed vision therapy technique. Pencil push-ups have been used for years and involve bringing a pencil or accommodative target towards the nose until double is noted.[10,11,13,14,30,40,42,43] This type of therapy is considered to be the least expensive as it requires no expensive equipment and little or no follow-up. The CITT pilot study included 38 subjects (15 OBVAT, 11 HBPP, and 12 OBPT) and looked at the CISS score (primary outcome measure) and NPC and PFV (secondary outcome measures) after 12 weeks of treatment. The OBVAT group showed both a statistically ($p < 0.001$) and clinically significant improvement (mean score 9.5 ± 8.2) in CISS score at week 12 compared to baseline. The OBPT group showed a statistically significant improvement ($p = 0.04$) but not a clinically significant improvement (mean score 24.2 ± 11.9). The HBPP group did not show a statistically significant ($p = 0.24$) or clinically significant improvement (mean score 25.9 ± 7.3). There was a statistically significant difference in CISS scores between the OBVAT and the other two groups at the end of the study, but the difference between the OBPT and HBPP groups were not statistically significant. When looking at the secondary outcome measures, the OBVAT group showed statistically and clinically significant improvements

in the NPC and PFV ($p < 0.001$ for both). The OBPT group showed statistically significant improvements in both NPC and PFV ($p = 0.03$ for both), while the HBPP only showed no statistically significant improvement in the NPC ($p = 0.08$) or PFV ($p = 0.22$). There were statistically significant differences in CISS, NPC and PFV between the OBVAT and the other two groups, while there was no difference between the OBPT and HBPP groups ($p = 0.34$). Using the study's guidelines of whether a subject was "cured" (CISS < 16, NPC < 6 cm, and meeting Sheard's criteria for PFV or ≥ 15Δ) or "improved" (CISS < 16 and normalization of either the NPC or PFV), 8 of the 15 subjects met the "cured" standard, while 12 of the 15 subjects met the "improved" standard for the OBVAT group. For the HBPP group, none of the 11 subjects met either the "cured" or "improved" standard. For the OBPT group, 1 of the 12 subjects met the "cured" standard. This study showed that office-based therapy for CI is much more effective in children than the popularly prescribed pencil push-ups, which were no more effective than placebo therapy.

The CITT pilot study also compared the effectiveness of OBVAT, HBPP, and OBPT in 40 young adults, ages 19-30 (12 OBVAT, 15 HBPP, and 13 OBPT).[30] After 12 weeks of treatment, the CISS (primary outcome measure) showed a statistically significant reduction in symptoms across all groups ($p < 0.001$ for all), with the biggest improvement in the OBVAT group. A mean CISS score of < 21 at the outcome visit was only achieved by the OBVAT group. When looking at the secondary outcome measures of NPC and PFV means, a statistically significant improvement in NPC and PFC was noted for all groups. The mean NPC value at the outcome visit only achieved the normal

value of < 6 cm in the OBVAT group. While all groups showed a statistically significant improvement in PFV at outcome, the improvement in the OBVAT group was statistically greater than that in the other groups. No difference was noted between the HBPP and OBPT groups for NPC and PFV. When comparing whether a subject was "cured" or "improved" after therapy based on the study's guidelines, 25% of the OBVAT were "cured" and 25% were improved. In the HBPP group, none were "cured" and 15% were "improved". In the OBPT group, none were "cured", and 13% were "improved". This study showed that in the young adult population, much like the child population, office-based vision therapy is more effective than pencil push-ups, which were similar in efficacy to office-based placebo therapy.

Using this pilot data, the CITT group wanted to examine the effectiveness of the masking in the placebo treatment group.[28] Subjects assigned to office-based therapy were asked whether they believed they were in the active or placebo group. Among those who completed the study, 95% of the OBVAT subjects and 83% of the OBPT subjects felt that they were receiving the active vision therapy. 90% of OBVAT subjects that believed they were receiving the active therapy were "pretty", "somewhat", or "very sure" they were receiving the active therapy, while 89% of the OBPT thought the same. This analysis proved that the placebo therapy was effective at keeping the subjects unaware of what treatment they were receiving.

Upon completion of the pilot study, the CITT Group completed a full-scale, randomized clinical trial to compare the effectiveness of common treatments for CI.[11] Subjects (n = 221) were randomized to OBVAT, OBPT, HBPP, or home-based computer

vergence/accommodative therapy with pencil push-ups (HBCVAT+) group. Home-based computer therapy was included as a treatment group because it had become a popular treatment for CI due to the need for fewer office visits and the ability to potentially monitor the patient's progress remotely. While the office-based groups reported for weekly therapy sessions, the home-based groups received weekly phone calls to monitor their progress and encourage compliance throughout the treatment.[12,36,44] The primary outcome measure was change in the CISS score, and the secondary outcome measures were changes in the NPC and PFV values. All subjects were followed for 12 weeks, with progress checks every 4 weeks.

At the completion of 12 weeks of therapy, the mean CISS score of all four treatment groups were compared. The mean CISS score in the OBVAT group was significantly lower (better) than that in the other groups; symptom scores were on average 6.8 points lower than in the OBPT group ($p < 0.001$), 7.9 points lower than in the HBPP group ($p < 0.001$), and 8.4 points lower than in the HBCVAT+ group ($p < 0.001$). There were no statistically significant differences between the OBPT, HBPP, and HBCVAT+ groups' mean CISS scores ($p \geq 0.38$ for all). The OBVAT group had the highest percentage (72.9%) of subjects that had a CISS < 16 and/or were improved by ≥ 10 points.

When looking at the secondary outcome measure of NPC means, the OBVAT group performed statistically significantly better than the other groups ($p \leq 0.005$ for all). The two home-based groups were statistically significantly better than the OBPT group ($p \leq 0.01$ for both), but there was no statistically significant difference between the two

home-based groups ($p = 0.33$). The percentage of OBVAT subjects that achieved a normal (< 6 cm) or improved (decrease of ≥ 4 cm) NPC break point was higher than in the other three groups (95.0% for the OBVAT group, 77.4% for the HBPP group, 77.0% for the HBCVAT+ group, and 59.3% for the OBPT group).

When looking at PFV, the mean value for the OBVAT group was statistically significantly better than that of the other groups ($p < 0.001$ for all). The mean PFV for the HBCVAT+ group was statistically better than that in the HBPP group ($p = 0.037$) and the OBPT group ($p = 0.008$). There was no statistically significant difference between the HBPP and OBPT groups ($p = 0.57$). The percentage of subjects who reached a normal (>15Δ break and meeting Sheard's) or improved (increase of >10Δ) PFV value was statistically significantly higher in the OBVAT group as compared to the other groups ($p \leq 0.007$ for all, 83.1% for the OBVAT group, 59.6% for the HBCVAT+ group, 56.6% for the HBPP group, and 44.5% for the OBPT group), but there were no statistically significant differences between the other three groups ($p > 0.10$ for all).

Overall, using the CITT definitions of "successful" (CISS <16, normal NPC [<6 cm], and normal PFV [>15Δ break and meeting Sheard's]) or "improved" (CISS <16 or ≥10-point decrease along with normal or improved NPC or PVC), 73% of the subjects in the OBVAT treatment group were considered either "successful" or "improved" at the end of treatment. Comparatively, 43% of the HBPP group, 33% of the HBCVAT+ group, and 35% of the OBPT group were considered "successful" or "improved". Based on these results, it was concluded that office-based vision therapy was significantly more

effective than home-based therapy for the treatment of symptomatic CI in 9- to 17-year-old children.

The subjects who were considered "successful" from each treatment group were also followed 6 and 12 months after completion of therapy.[45] A few subjects from each group were ineligible for analysis due to seeking additional treatment before the 6 and 12-month visits. At the 12-month visit, 84% of the subjects in the OBVAT group (27/32) stayed asymptomatic (based on the CISS scores). Comparatively 66.7% of the HBPP (10/15), 80% of the HBCAVT+ (8/10), and 77% of the OBPT (10/13) groups remained asymptomatic. For the NPC and PFV values at the 12-month visits, the OBVAT group showed no significant decrease in NPC and a significant improvement in PFV. For the HBPP, HBCVAT+, and OBPT groups, there was no significant change in NPC or PFV values. Overall, 87% of the OBVAT group, 67% of the HBPP group, 80% of the HBCVAT+ group, and 69% of the OBPT group were considered "successful" or "improved" at one year. It was concluded that in all treatment groups, subjects who were considered asymptomatic after 12 weeks of CI treatment tended to remain asymptomatic one year post-therapy. However, it should be noted that several of the groups had small numbers of successful subjects to follow.

The efficacy of the placebo masking was also examined with the full-scale CITT data.[46] Among those who completed the study, 93% of the OBVAT subjects and 85% of the OBPT subjects felt that they had received the active vision therapy. Among those who believed they received the active therapy, 91% of OBVAT subjects were "pretty", "somewhat", or "very sure", while 87% of the OBPT thought the same. These results

closely mirrored the results obtained during the pilot study, and proved that the placebo arm used in the trial was effective at masking.

The data from the CITT was further analyzed in order to monitor the time frame of a subject's improvement throughout therapy.[47] From their data analysis, it was shown that signs improve quicker than symptoms during the treatment of CI. It was also concluded that if there is no sign of improvements after four weeks of treatment, the treatment method should be looked at carefully to see if changes need to be made.

While the CITT showed the significantly greater effectiveness of in-office based vision therapy, some still question if other treatments should be ignored. Some questioned whether the modes of therapy could actually be compared due to differences in the amount of weekly time spent doing therapy and homework between the groups.[48] It was calculated that the OBVAT group spent 135 minutes per week on therapy. Comparatively, the HBCVAT+ group and HBPP groups spent 100 minutes and 75 minutes per week respectively on their therapy. It was also pointed out that the compliance in the HBPP group was less than that in the OBVAT group. The CITT group responded to this criticism saying that the treatment options in the CITT were based on the clinically acceptable practices being used.[49] They went on to say that the home-based groups may have been given more attention than they typically would have received in clinical practice because they were called weekly to discuss homework and were seen monthly for their progress evaluations.

While studies have shown that signs and symptoms of CI improve with vision therapy, it is still unclear what physical changes are made during a course of vision therapy.

Saccadic and Vergence Eye Movement Studies in the Brain

Single Cell Recordings during Eye Movements

In order to understand what areas of the brain are responsible for different oculomotor functions, including convergence/divergence, saccades, and pursuits, many single-cell recordings in monkeys have been performed. Through those studies, the discovery of burst neurons, some responsible for convergence/accommodation and some responsible for divergence/accommodation, were located near the nucleus reticularis tegmenti pontis (NRTP)[50] and near the mesencephalic reticular formation, dorsal and lateral to the oculomotor nuclear complex.[51] Although close to areas that are known to be used during saccadic eye movements, the cells identified in these studies did not seem to be active during saccadic movements. Other studies have shown vergence control cells in the area of the frontal eye fields (FEF).[52,53] While the FEF has been known to be responsible for saccadic eye movements, studies have shown that vergence cells have been located in an area just anterior/rostral to this known saccadic center.

Neural Imaging Studies of Eye Movements

Positron emission tomography (PET) scans have been used to study saccadic and vergence eye movement tasks as well.[54] Using a visual task to elicit a near/far response,

the PET scan revealed various regions of the brain that appeared to be responsible for the near response. While this study involved covering the non-dominant eye throughout the stimulus testing during the scan, it did prove that certain areas were responsible for the near response that were not found to be active during simple fixation or the eyes at rest.

Along with PET scans, functional magnetic resonance imaging (fMRI) studies have started to look at areas active in the brain during eye movements.[55] Early studies using the fMRI used monkeys as subjects, but more recent studies have been using this type of imaging for human studies.

Recent fMRI and Convergence Insufficiency Studies

A group out of the New Jersey Institute of Technology's Department of Biomedical Engineering, led by Tara Alvarez, has been using fMRI technology to examine subjects with CI. The group was interested in neurophysiological changes that occurred in CI subjects after a round of vision therapy. They investigated their theory that an increase in blood oxygenation level dependent (BOLD) signal changes would be noticed post-vision therapy.[56-58]

Compared to other brain imaging strategies, using the BOLD signal in an fMRI allows for a small spatial resolution, within a few millimeters, and a relatively short temporal resolution that is dependent upon the rate of blood flow, typically within a few seconds. Neurotransmitters in the brain are released during neuronal activity, thus increasing the amount of blood flow to the area that is being used. Oxygenated hemoglobin (oxyHb) is isomagnetic while deoxygenated hemoglobin (deoxyHb) is

slightly paramagnetic. The magnetic qualities of the deoxyHb cause a small gradient to be found in vessels that are in their at-rest state. When blood is drawn to an area of the brain, the relative amount of deoxyHb in the blood vessels is decreased compared to the amount of oxyHb, causing a disruption in the field gradient. This gradient disruption is seen as a positive activation area during a fMRI.[59]

In a study from 2010, the Alvarez group set out with the goal to "provide data about the changes in the dynamics of the vergence system using objective eye movement recordings and to quantify and correlate neural measurements with these objective outcome measures using functional imaging."[57] Four adult, female CI subjects (ages 20 to 26 years) were recruited and confirmed to have CI. Clinical data points being monitored at the pre-therapy, mid-therapy, post-therapy, and four months to one year post-therapy visits included the following: stereopsis using the Bernell Stereo Randot; NPC, NPC recovery, NFV, and PFV using a pen tip; and near phoria using the Bernell Muscle Imbalance Measure (MIM) card; the CISS was also administered to all subjects post-therapy but only to one subject pre- and throughout therapy.

The visual task for the subject to complete while completing the fMRI involved three light emitting diode (LED) lights secured to the top of three PVC pipes located behind the subject and scanner. The lights were positioned in a way so as to simulate vergence demands of 4^{o} (near), 3^{o} (middle), and 2^{o} (far) targets. The task was broken down into random and predictable portions. During the random portion, one of the three LEDs was illuminated for a time period of 2-5 seconds for a total time of 40 seconds. During the predictable portion, the LEDs were illuminated in order, from 4^{o} to 2^{o}, for 4

seconds at a time for a duration of 40 seconds. The random/predictable cycle was repeated 3.5 times for a total of 280 seconds of the task.

The therapy consisted of in-office and at-home procedures totaling 18 hours, 6 hours at home and 12 hours in office. Home-based therapy included Brock string exercises, involving smooth and step-wise vergence changes, as well as reading text with prism in different orientations that stress convergence and divergence. This was done in two, 10-minute sessions, 3 days a week for 6 weeks. Office-based therapy involved jump vergence movements, using LEDs placed at 2^{o}, 4^{o}, 6^{o}, and 8^{o} along the subject's midline, and ramp vergence movements, using a haploscope that presented a stimulus from 2^{o} to 8^{o} at a rate of 1^{o}/second for 12 seconds and 2^{o}/s for 6 seconds . This was done for 1 hour, 2 days per week for 6 weeks.

The clinical data examined over all CI subjects showed that after therapy, the NPC, RPC, PFV, near phoria, and CISS all improved. Only NFV worsened among all subjects. The regions of interest (ROIs) examined during the fMRI included the following: dorsolateral prefrontal cortex (DLPFC), frontal eye field (FEF), supplemental eye field (SEF), medial frontal gyrus (MFG), precuneus, inferior parietal area, parietal eye field (PEF), Brodmann Areas (BA) 39 and 40, cerebellum, and brain stem. Post-therapy, significant changes in the BOLD signal were found for the DLPFC, FEF, SEF, MFG, cerebellum, and brain stem. For all of these areas, the spatial extent of activation was shown to increase post-therapy. A linear regression analysis was run comparing clinical data changes to BOLD signal changes as a way to determine which areas of the brain were responsible for specific tasks. NPC was noted to be linked to the brain stem.

RPC was linked with the cerebellum. PFV showed links to the frontal regions, parietal regions, and the cerebellum. The near dissociated phoria was linked to the brain stem, FEF, SEF, DLPFC, and cerebellum.[57]

In two papers from 2014, Alvarez and her group used the same stimulus set-up and task design to look at three specific ROIs, the FEF, posterior parietal cortex (PPC), and cerebellar vermis (CV). These three areas were chosen based on the prior knowledge of what the areas are used for during oculomotor, specifically vergence, tasks. BOLD signal percent change was shown to be statistically significant in all three ROIs post-vision therapy, resulting in an increase in BOLD signal across all areas.[56,58]

Reason for Current Study

While prior research has shown significant changes in brain activity post-vision therapy[57,58], the response to a larger range of vergence demands and to placebo versus real therapy has not been shown. In addition, the response to OBVAT has not been previously investigated although it has been shown to be the most effective therapy for CI. Finally, prior studies have investigated only positive changes in BOLD signal activation. It may be beneficial to look at the activation and deactivation areas of the brain during the convergence tasks.

The purpose of the current study was to show the changes (activation and deactivation) that occur in the brain with CI therapy by examining the BOLD signal during an fMRI scan while completing a task which includes a wide range of vergence demands before and after OBVAT and OBPT treatment for convergence insufficiency.

Chapter 2: Methods

Recruitment

Subjects were recruited through the clinics at The Ohio State University College of Optometry and Student Health Center, as well as through referrals from Columbus, Ohio area optometrists, flyers, and an online posting through The Ohio State University. All subjects signed written informed consent documents that were approved by the Institutional Review Board at The Ohio State University in accordance with the Declaration of Helsinki.

Eligibility Examination

Eligibility/Baseline Entrance Testing

All subjects underwent an eligibility exam performed by the same examiner. At the eligibility exam, a battery of clinical testing was performed. Testing was carried out using the CITT protocol with the subject wearing any needed correction.[10,11] Each test will be explained in detail.

Convergence Insufficiency Symptom Survey

The CISS was performed before and after all sensorimotor testing was completed. The subject was given a response card with the five responses for each of the 15

questions. Each question was read as written to the subject, and no examples were given. If the subject gave an unapproved response, the subject was asked to pick from one of the five responses. The two scores were then averaged. This procedure and cut-off value was based on a study by Rouse et al.[33]

Cover Test

A unilateral and alternating cover test was performed for distance and near viewing to determine the distance and near phoria. A 20/30 projected letter was used as the distance target, and a 20/30 letter on a Gulden Fixation Stick (Gulden Ophthalmics, #15302, Elkins Park, PA) was used as the near target. The subject was asked to keep the target clear during testing. Prism was used to neutralize the phoria. Prism was introduced until five reversals were observed on the alternating cover test. The highest amount of prism through which neutrality was observed was documented as the phoria. Any vertical phoria was noted as well.

Positive and Negative Fusional Vergences

Positive and negative fusional vergence ranges at near were measured using the Gulden B-16 horizontal prism bar with values ranging from 1Δ to 45Δ. A Gulden Fixation Stick (Gulden Ophthalmics, #15302) with a vertical column of 20/30 letters was held 40 cm from the subject's eyes. The subject was instructed to fixate the vertical column of letters and attempt to keep the column single and clear through each prism presentation. Base-in (BI) prism was introduced first to obtain the NFV values. Base-out

(BO) was then introduced in three different trails to obtain mean PFV values. Thirty seconds of rest was given between each trial. Horizontal prism was introduced step-wise at a rate of 1 prism presentation every 1-2 seconds. Once the subject reported that he/she could no longer keep the target clear, that prism value was recorded as the blur value. More prism was then introduced until the subject reported that the column was double. That value was recorded as the break value. At the break value, 5Δ more prism was added, and the subject was then instructed to report when the column was single again. At that point, prism was decreased at the same pace until the column was reported as single. That value was recorded as the recovery value. If a subject only reported a break value, an X was documented as the blur value. If a subject did not report a break value but the examiner noticed that an eye deviated, that prism value was noted as the break value. Prism was reduced until the eye was noted to return to its fusion position and that value was noted as the recovery value. If a subject did not report a blur or break value and fusion was maintained at the last prism presented (45Δ), the break value was reported as 50Δ, and fusion was then broken by covering an eye and asking the subject to re-fuse the image. If fusion could not be regained, the amount of prism was reduced until the subject reported recovery of fusion. If fusion was regained immediately after dissociation, the recovery value was recorded as 45Δ.

Near Point of Convergence

NPC was measured using a Near Point Rule (Gulden Ophthalmics #15150) with a printed vertical 20/30 column of letters (Gulden Ophthalmics, #15302). The rule was

placed on the brow above the nose. The fixation target was placed at 40 cm. The subject was asked to keep the target single for as long as possible while the target was moved toward the nose at a rate of 1-2 cm/second. If the subject reported the target as double, he/she was asked if the target stayed two or became one. If the target stayed two (double), the break value was recorded to the nearest 0.5 cm, and the target was brought away from the subject until single was reported, which was recorded as the recovery value. If fusion was regained, the target was brought closer until the target became double. If the subject did not report double but the examiner noticed an eye deviate from fusion, the point where fusion was lost was recorded as the break value; the target was then pulled away from the subject until fusion was observed. If the subject did not report double and an eye did not deviate, fusion was broken for 3-5 seconds, and the subject was asked to report when recovery of fusion occurred. Measurement of NPC was repeated three times, allowing 10 seconds of rest between trials. A cut-off of 6 cm was used based on a study by Hayes et al.[60]

Accommodative Amplitude

Accommodative amplitude was measured in centimeters on the right eye only. The subject was asked to cover his/her left eye. The Near Point Rule with a printed Gulden fixation target (Gulden Ophthalmics), a vertical 20/30 column of letters, was then placed on the brow above the right eye. The subject was asked to keep the vertical column of letters clear for as long as possible while the target was brought closer at a rate of 1-2 cm/second. When the subject reported first sustained blur, the subject was asked if

the target remained blurred or became clear. If the target remained blurred, the amplitude was recorded to the nearest 0.5 cm. If clarity was reported, the target was moved closer until the first sustained blur was reported.

Accommodative Facility

Monocular accommodative facility was performed on the right eye only, with the left eye covered by a cover paddle, using a +/- 2.00 D flipper. A Gulden Fixation Stick (Gulden) with a vertical column of 20/30 letters was held 40 cm from the subject. The subject was asked to make the letters as clear as quickly as possible with each lens. When clarity was achieved, the subject was instructed to say, “Clear.” The number of flips in one minute was recorded. In addition, it was noted whether the subject had more problems with the plus or minus lens or if there was equal difficulty between the two lenses.

Vergence Facility

Vergence facility was performed using a 12-BO/3-BI flipper. A Gulden Fixation Stick (Gulden) with a vertical column of 20/30 letters was held 40 cm from the subject. The subject was asked to report when the column of letters was both single and clear by saying, “Now.” The number of flips in one minute was recorded. In addition, it was noted whether the subject had more problems with BO, BI, or if there was equal difficulty between BO and BI.

Other Vision Testing

Visual acuities were taken monocularly with subject's habitual correction using a projected chart calibrated for optical infinity at distance and a reduced ETDRS chart held at 40cm. Versions were tested using the Broad H testing procedure. Pupil responses were tested using Welch-Allyn transilluminator. Stereoacuity was measured using the Randot Stereoacuity test (Bernell, Mishawaka, IN). Anterior health was examined using a slit lamp. If a cycloplegic refraction had not been completed within the past three months, a cycloplegic refraction was completed, and the posterior health was examined using the slit lamp and binocular indirect ophthalmoscope.

fMRI Stimulus Demonstration

All subjects were given a demonstration of the visual stimulus to be completed while in the scanner. The stimulus was programmed and presented using Visual Basic programming language. A 9-minute, shortened version was presented to the subject while upright and in the supine position.

Inclusion and Exclusion Criteria

Guidelines for classification and inclusion as a CI subject are listed in Table 1. Additional exclusion criteria are listed in Table 2.

CI Inclusion Criteria
18-30 years old
Best-corrected visual acuity of 20/25 or better in each eye at distance and near
Exophoria at near at least ≥ 4Δ greater than distance
Receded NPC of ≥ 6 cm break
PFV blur value of less than 2x the near phoria/failing Sheard's criterion OR less than 15Δ (below minimum normative values)
CISS value ≥ 21
Accommodative amplitude ≥ 5 D
Random dot stereopsis of at least 500"
Eye exam with cycloplegic refraction within the past 3 months
Willingness to purchase and wear glasses or contact lenses to correct refractive error
Willingness to discontinue base-in prism wear
Willingness to discontinue plus add wear
Access to computer with internet to perform the computerized home therapy procedures (HTS)
Willingness to be randomized into either the active or placebo therapy arm of the study
Ability to successfully complete fMRI scanning
No previous treatment with vision therapy
Not personally or living with an eyecare professional, ophthalmology/optometry student/resident, ophthalmic technician, or employed in an eye care setting
No household member enrolled in any vergence therapy study or currently completing vision therapy

Table 1. CI inclusion criteria.

Exclusion Criteria
Any positive ocular history for the following conditions: amblyopia, constant strabismus, vertical phoria > 1Δ, high refractive error, refractive surgery, or manifest or latent nystagmus
Systemic diseases known to affect accommodation, vergence, and ocular motility such as: multiple sclerosis (MS), Graves' thyroid disease, myasthenia gravis, diabetes, and Parkinson's disease
Current use of any ocular or systemic medication known to affect accommodation or vergence such as anti-anxiety agents (e.g. Librium or Valium), anti-arrhythmic agents (e.g. Cifenline or Cibenzoline), anti-cholinergics (e.g. scopolamine), bladder spasmolytic drugs (e.g. Propiverine), hydroxychloroquine, chloroquine, phenothiazines (e.g. Compazine, Mellaril, or Thorazine), tricyclic antidepressants (e.g. Elavil, Nortriptyline, or Tofranil)
History of TBI, neurological disease (e.g. MS or Parkinson's), or any condition that may be in conflict with obtaining normal fMRI scans
Developmental or learning disability that may interfere with treatment
fMRI Exclusion Reasons
Surgical metals or pacemakers
Coronary stent(s), electronic stimulators and pumps, cerebral aneurysm clips, sensitive metallic medical implants, and metallic foreign bodies
MR unsafe surgical implant or device
Metal foreign bodies in or proximal to the eye, brain, heart, or spinal cord
Tattoos on the head or neck, tattoos not obtained by a licensed artist, or any extensive tattoos
Pregnancy or planning pregnancy during study course
Insufficient medical/surgical history on patient
Refusal of patient to remove unsafe person objects, clothing, jewelry, etc. from person prior to entering MRI exam room
Combative, uncooperative patient
Extensive orthodontic work, including wearing braces on teeth or permanent retainers
Left-handed dominance

Table 2. Exclusion criteria.

<u>fMRI Testing Procedure</u>

Set-Up

All fMRI scans were completed at the Center for Cognitive and Behavioral Brain Imaging at The Ohio State University by a trained fMRI technician. The apparatus used

was a Siemens 3 Tesla (T) scanner, with a 12-channel coil. The voxel size was set at 3 x 3 x 3 mm with a repetition time (TR) of 2.5 sec. Figure 1 shows what the scanner set-up looked like. Subjects wore red/blue glasses and watched a rear-mounted computer monitor that contained the stimulus, visible to them through a mirror mounted on the head coil. A 10-second scan known as the localizer was first run locate the brain for all scans. Once the area of interest was adjusted by the technician, a 7-minute anatomical scan was run. The six stimulus paradigms were then completed. Instructions to the subject were to try and keep the red and blue squares fused as best as possible for each presentation in order to see a smaller square floating off the screen. After all paradigms were complete, a last scan, known as the diffusion tensor imaging (DTI) was run. All data from the scans was sent to the Biomedical Imaging Laboratory at Wright State University for analysis.

Figure 1. fMRI set-up.

Paradigm Design

For the purpose of this thesis, only two of the six paradigms will be examined, the easy and hard step vergence sequences. The stimulus involved the subject looking at a random dot stereogram (RDS) target with approximately 500 sec arc disparity such that a small, central square would appear to float in front of the larger target only when fusion was achieved (developed by Andrew Toole). The subject was instructed to look at the

central square during all tasks. When the vergence demand changed, the subject was instructed to do their best to keep the small square visible.

The easy and hard step vergence paradigms each started with 20 seconds of rest (zero vergence demand), followed by 30 seconds of increasing BO demand every 6 seconds, by 2Δ starting with 4Δ and ending with 12Δ for the easy step vergence paradigm and by 5Δ starting with 5Δ and ending with 25Δ for the hard step vergence paradigm. A total of 250 seconds were needed for each of these paradigms.

Vision Therapy

Treatment Groups

After completion of the baseline fMRI scan, each subject was randomized to a treatment group, active (OBVAT) or placebo (OBPT) in a 2:1 ratio, and started therapy within one week. Each therapy visit consisted of at least 55 minutes of procedures (four to five total), questions, and homework instructions.

Active Office-Based Vergence/Accommodative Therapy (OBVAT)

The OBVAT procedures followed those set forth by full-scale CITT study. Therapy was broken down into three phases. Phase one involved techniques aimed to work on gross convergence, positive fusional vergence ranges, and monocular accommodative ability. Phase two involved techniques aimed to work on ramp fusional vergence and monocular accommodative abilities. Phase three involved techniques aimed to work on jump fusional vergence and binocular accommodative facility abilities. Each

phase involved its own set of homework, which was prescribed for 15-20 minutes per day, 5 days per week. A list of procedures and homework for each phase can be found in Table 3. Each procedure had a set of instructions for the therapist to complete with the subject. Once a subject reached the pre-determined endpoint for a certain procedure, it could be discontinued and replaced with a new procedure in the same phase or replaced with a procedure in the next phase higher. At the end of each session, each subject was sent home with a homework log, which listed the specific procedures to be completed until the next therapy session, and instructions on how to perform each procedure, which was reviewed before ending the session. At the beginning of next session, the homework sheet was collected and discussed with the subject, addressing any questions or concerns. In-office OBVAT was completed weekly for 12 weeks.

	VERGENCE IN-OFFICE PROCEDURES	ACCOMMODATIVE IN-OFFICE PROCEDURES	VERGENCE HOMEWORK PROCEDURES	ACCOMMODATIVE HOMEWORK PROCEDURES
PHASE ONE	Brock String Barrel Card Lifesaver Card Vectograms VTS4 Multiple Choice Vergence	Monocular Loose Lens Accommodative Rock Monocular Letter Chart Accommodative Rock	Brock String Barrel Card Lifersaver Card HTS Vergence	Monocular Loose Lens Accommodative Rock Monocular Letter Chart Accommodative Rock HTS Accommodative Rock
PHASE TWO	Vectograms Aperture Rule Eccentric Circles VTS4 Multiple Choice Vergence	Monocular Loose Lens Accommodative Rock Monocular Letter Chart Accommodative Rock	HTS Vergence Eccentric Circles	Monocular Loose Lens Accommodative Rock Monocular Letter Chart Accommodative Rock HTS Accommodative Rock
PHASE THREE	Vectograms Aperture Rule Eccentric Circles Loose Prism Facility VTS4 Jump Ductions	Binocular Accommodative Facility	Eccentric Circles Binocular Accommodative Facility HTS Vergence	Binocular Accommodative Facility HTS Accommodative Rock

Table 3. Office-based vergence/accommodative therapy procedures and homework.

Office-Based Placebo Therapy (OPBT)

Like the OBVAT, the OBPT procedures followed those set forth by the full-scale CITT study. Each week had a list of procedures and times assigned to those procedures. Procedures were designed to not stimulate vergence or accommodation (beyond that occurring in typical near tasks). Every procedure had an endpoint and reason for completing the procedure, aiming to improve equalization of monocular inputs, speed of focus/response, and eye teaming abilities. A set of homework procedures was pre-determined for each week, and the subject was sent home with a homework log and instruction sheet. Each instruction sheet listed a goal for each procedure for the subject to

work toward, much like in the OBVAT group. Homework logs were collected and reviewed each week. In-office OBPT was completed weekly for 12 weeks.

Progress Checks

Before therapy at weeks 4 and 8, a progress check which included the following testing was performed by an examiner masked to the subject's assigned treatment arm: CISS (before and after all testing), cover test (distance and near), NFV, PFV, NPC, amplitude of accommodation, accommodative facility, and vergence facility. After the progress check, a regular therapy session was completed. At week 12, the final outcome exam which included the same testing procedures was performed by the same masked examiner.

Outcome fMRI Scan

The outcome fMRI scan was scheduled within 1 week after the completion of the week-12 progress check. All scanning procedures and paradigms were the same as those completed during the baseline fMRI scan.

Success of Treatment

Using the definitions of successful treatment set forth by the full-scale CITT study[11], subjects were considered either "successful" or "improved" or "non-responder". Anyone not classified as "successful" (regardless of group) was offered additional active

vision therapy. Those classified as “successful” had completed the study and no additional action was taken.

Data Analysis

Progress check data analysis was made using IBM SPSS Statistics (Version 22). fMRI data analysis and examination was made using the FEAT Analysis using the FMRIB Software Library (FSL 5.0.4).

Chapter 3: Results

Enrollment

Seven symptomatic CI subjects (6 females, mean age 26.1 ± 2.5) were randomized into the study. At the time of analysis, seven subjects had undergone eligibility testing with baseline fMRI scan, and six subjects had completed the week 12 exam and outcome fMRI scan. Of the six subjects who had completed the study, only five subjects had their outcome fMRIs available for analysis.

Clinical Data Analysis

Descriptive Statistics

Descriptive statistics were completed for the data from the eligibility exam and can be found in Table 4. One subject did not complete stereoacuity, and one subject did not complete vergence facility. As a group, the mean CISS was 32.6 (± 9.5), mean near cover test was 10Δ exophoria (± 4.3Δ), mean PFV to blur was 13.4Δ (± 1.5Δ), and mean NPC break was 8 cm (± 1.5 cm).

	N	MINIMUM	MAXIMUM	MEAN	STD. DEVIATION
AGE	7	23	30	26.1	2.5
CISS	7	23.5	52	32.6	9.5
GLOBAL STEREO (“)	6	250	250	250	0
LOCAL STEREO (“)	6	20	30	22.5	4.2
DISTANCE CT (Δ, EXOPHORIA)	7	0	8	3.1	3
NEAR CT (Δ, EXOPHORIA)	7	4	16	10	4.3
NFV TO BLUR (Δ)	7	8	14	10.3	2.7
NFV TO BREAK (Δ)	7	10	18	14.3	2.7
NFV TO RECOVERY (Δ)	7	8	14	11.7	2.1
PFV TO BLUR (Δ)	7	12	16.7	13.4	1.5
PFV TO BREAK (Δ)	7	12.7	26.7	19.6	6.4
PFV TO RECOVERY (Δ)	7	7.3	21.7	14.5	6
NPC BREAK (CM)	7	6.2	10.5	8	1.5
NPC RECOVERY (CM)	7	8.5	20.7	11.9	4.1
AMPLITUDE OF ACCOMMODATION (CM)	7	10	15	12	2
ACCOMMODATIVE FACILITY (FLIPS/MIN)	7	0	34	18.5	12
VERGENCE FACILITY (FLIPS/MIN)	6	14	36	25.8	8.5

Table 4. Descriptive statistics at eligibility exam.

Individual Results

Due to the small sample size (total n = 7), statistical comparisons were not possible. For the sake of comparison, individual exam data from the eligibility exam (Table 5) and week 12 progress check (Table 6) will be presented for each subject.

	1	2	3	4	5	6	7
AGE (YEARS)	24	26	29	30	26	23	25
TREATMENT GROUP	OBPT	OBVAT	OBPT	OBVAT	OBVAT	OBVAT	OBPT
CISS	31.5	52	36.5	28.5	23.5	29	27
DISTANCE PHORIA (Δ, EXOPHORIA)	0	2	6	4	8	2	0
NEAR PHORIA (Δ, EXOPHORIA)	6	10	16	14	12	8	4
NFV TO BLUR OR BREAK (Δ)	10	14	14	8	8	10	8
PFV TO BLUR OR BREAK (Δ)	13.3	16.7	12.7	12	13.3	12.7	13.3
NPC BREAK (CM)	8.7	10.5	7.5	8.5	6.2	8.3	6.5
AMPLITUDE OF ACCOMMODATION (CM)	14.5	10.5	12	15	11.5	10.5	10
ACCOMMODATIVE FACILITY (FLIPS/MIN)	23	22	34	18	0	5	27
VERGENCE FACILITY (FLIPS/MIN)	X	24	36	26	14	20	35

Table 5. Eligibility exam data per subject. Subject number across the x-axis.

	1	2	3	4	5	6
TREATMENT GROUP	OBPT	OBVAT	OBPT	OBVAT	OBVAT	OBVAT
CISS	15	19.5	16.5	18	19.5	28.5
DISTANCE PHORIA (Δ, EXOPHORIA)	2	4	4	4	8	2
NEAR PHORIA (Δ, EXOPHORIA)	10	10	12	16	16	6
NFV TO BLUR OR BREAK (Δ)	10	25	10	25	16	20
PFV TO BLUR OR BREAK (Δ)	14	50	22	31.7	43.3	35
NPC BREAK (CM)	4.17	2.83	4.17	3	3.5	4.33
AMPLITUDE OF ACCOMMODATION (CM)	13.5	8	11.5	9	9	8
ACCOMMODATIVE FACILITY (FLIPS/MIN)	33	42	31	44	5	46
VERGENCE FACILITY (FLIPS/MIN)	35	43	30	39	30	34
CISS OUTCOME	Successful	Successful	Successful	Successful	Successful	Non-Responder
PFV OUTCOME	Non-Responder	Successful	Non-Responder	Improved	Successful	Successful
NPC OUTCOME	Successful	Successful	Successful	Successful	Successful	Successful
COMPOSITE OUTCOME	Improved	Successful	Improved	Improved	Successful	Non-Responder

Table 6. Week 12 progress check data per subject. Subject number across the x-axis.

Success of Treatment

Among individuals, CISS improvement was noted in 5 of the 6 subjects (83.3%), with all 5 reaching an asymptomatic level (< 21). PFV values reached normal levels in 3 of the 6 subjects (50%), improved levels in 1 of 6 (16.7%) and non-responder levels in 2 of 6 subjects (33.3%), both of which were in the OBPT group. NPC values reached a normal level in all 6 subjects (100%). When looking at the composite, two subjects were considered successful (33.3%), three were considered improved (50%), and one was considered a non-responder (16.7%)

Among groups, 2 of the 4 subjects (50%) in the OBVAT group were considered successful with treatment, one was improved (25%), and one was a non-responder (25%). Both subjects in the OBPT group were considered improved after 12 weeks of therapy (100%).

fMRI Analysis

Easy Step Vergence Paradigm

Using the FSL software, all scans were overlaid with a MNI152_T1_2mm brain standard and analyzed for the pre-therapy, post-OBVAT, and post-OBPT conditions. For this section, a z-score range of 2.3 to 18.8 for activation and 2.3 to 7.3 for deactivation (with a z-score $\geq$ 2.3 considered significant) was used to locate specific hot spots and clustered areas of activation/deactivation without comparing to any previously documented ROIs. A Talairach Daemon atlas was used to determine which area of the brain was being highlighted. Specific X, Y, and Z coordinates for the MNI152_T1_2mm brain standard were documented and compared across all three groups. Table 7 and 8 list the z-score, coordinates, and location of all the activation and deactivation hot spots respectively for the easy step vergence paradigm. Figures 2 through 6 show the locations of the activation (in red) and deactivation (in blue) hot spots listed in the tables for the pre-therapy, post-OBVAT, and post-OBPT conditions respectively. There was no deactivation noted post-OBVAT.

	Z-SCORE	LOCATION	X	Y	Z
PRE-THERAPY	18.7572	Left occipital lobe, lingual gyrus, white matter	48	18	36
POST-OBVAT	12.1258	Right occipital lobe, lingual gyrus, white matter	41	29	39
POST-OBPT	12.7922	Left occipital lobe, lingual gyrus, gray matter, BA 18	47	20	33

Table 7. Activation hot spots for easy step vergence paradigm.

	Z-SCORE	LOCATION	X	Y	Z
PRE-THERAPY	6.93435	Left frontal lobe, paracentral lobule	45	46	63
POST-OBVAT	No significant areas of deactivation				
POST-OBPT	7.27059	Left frontal lobe, precentral gyrus, gray matter, BA 4	58	53	70

Table 8. Deactivation hot spots for easy step vergence paradigm.

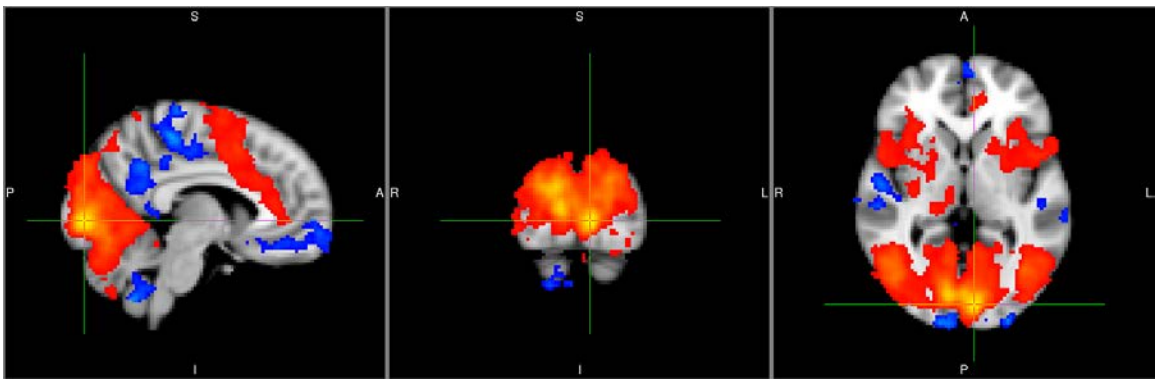

Figure 2. Activation area hot spot for easy step vergence paradigm pre-therapy, 3D FSL image.

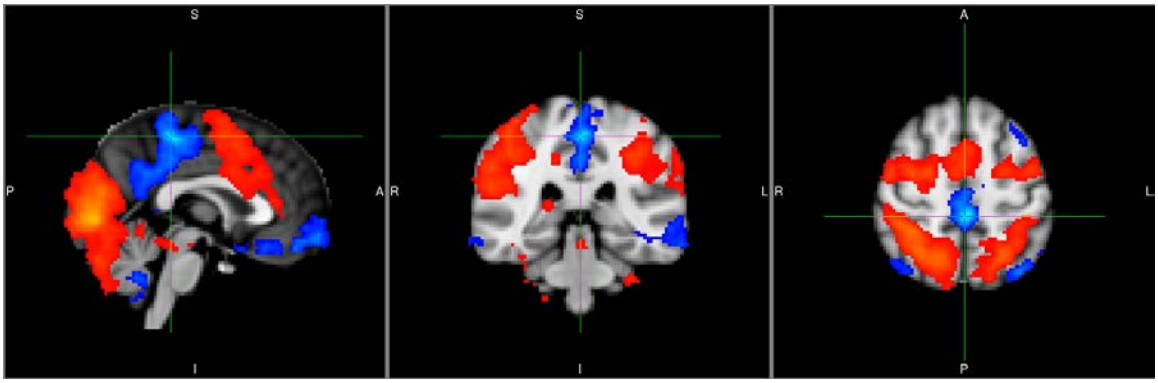

Figure 3. Deactivation area hot spot for easy step vergence paradigm pre-therapy, 3D FSL image.

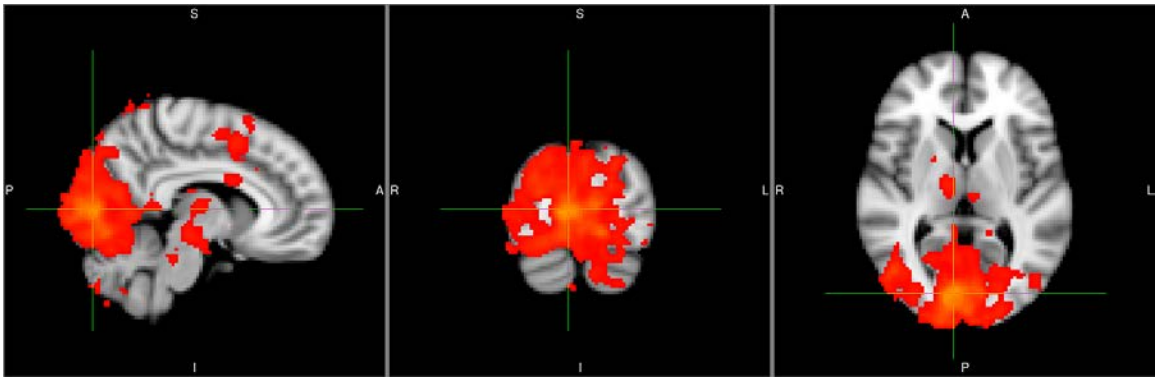

Figure 4. Activation area hot spot for easy step vergence paradigm post-OBVAT, 3D FSL image.

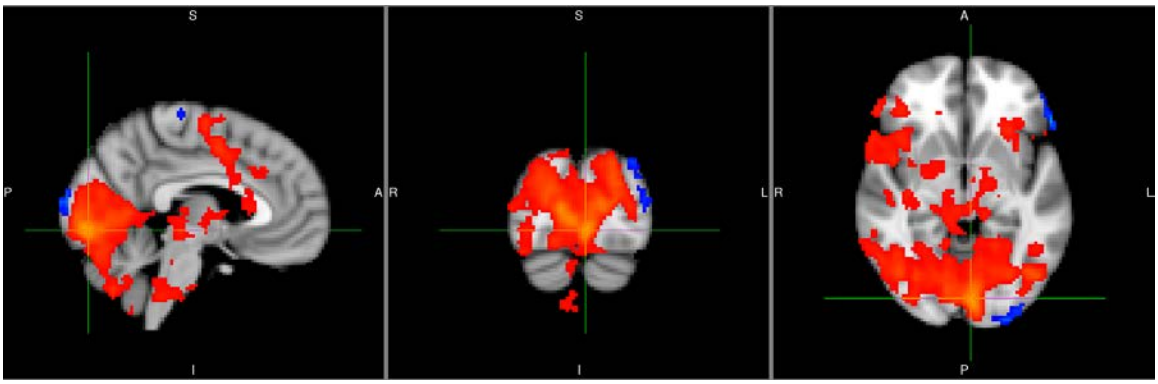

Figure 5. Activation area hot spot for easy step vergence paradigm post-OBPT, 3D FSL image.

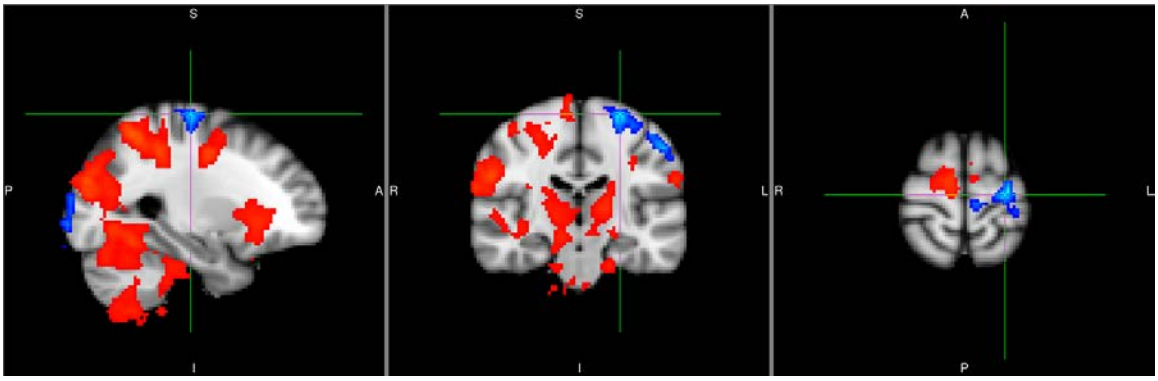

Figure 6. Deactivation area hot spot for easy step vergence paradigm post-OBPT, 3D FSL image.

Brain slice images were generated for activation and deactivation for pre-therapy, post-OBVAT, and post-OBPT. Figures 7 and 8 show the overall activation and deactivation maps, respectively, for the pre-therapy condition. Activation can be seen in clusters mainly in the following areas: the frontal lobe [inferior frontal gyrus, precentral gyrus/BA 6, medial frontal gyrus/BA 6, and the superior frontal gyrus/BA 10], temporal lobe (superior temporal gyrus and middle temporal gyrus/BA 39), parietal lobe (inferior

parietal/BA 40), occipital lobe, and cerebellum (posterior lobe/declive). Deactivation can be seen in clusters in the following areas: the frontal lobe (superior frontal gyrus/BA 8, middle frontal gyrus/BA6, paracentral lobule/BA5, and medial frontal gyrus/BA 10), parietal lobe (superior parietal lobule/BA 7 and precuneus/BA 18), temporal lobe (middle temporal gyrus/BA 21), and occipital lobe (lingual gyrus/BA 17 and inferior occipital gyrus/BA 17).

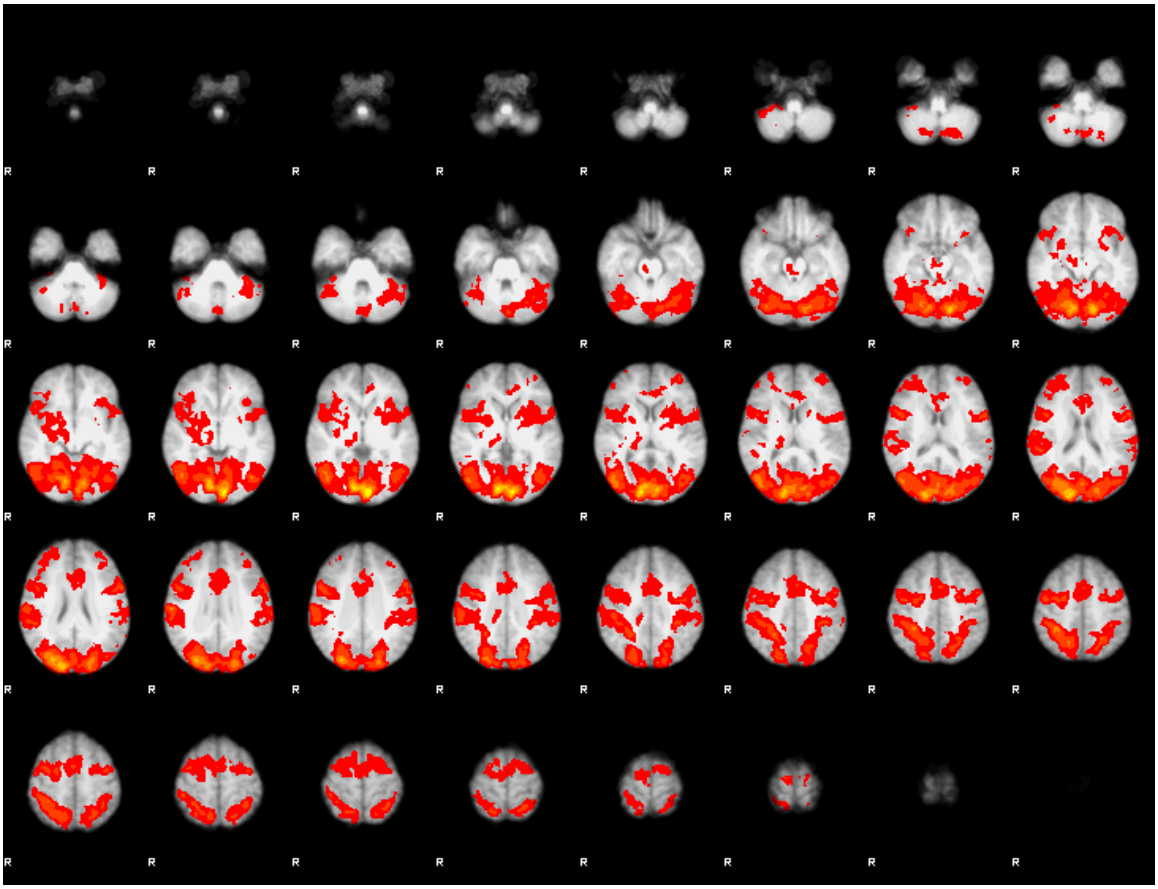

Figure 7. Activation areas for easy step vergence paradigm pre-therapy, sliced image.

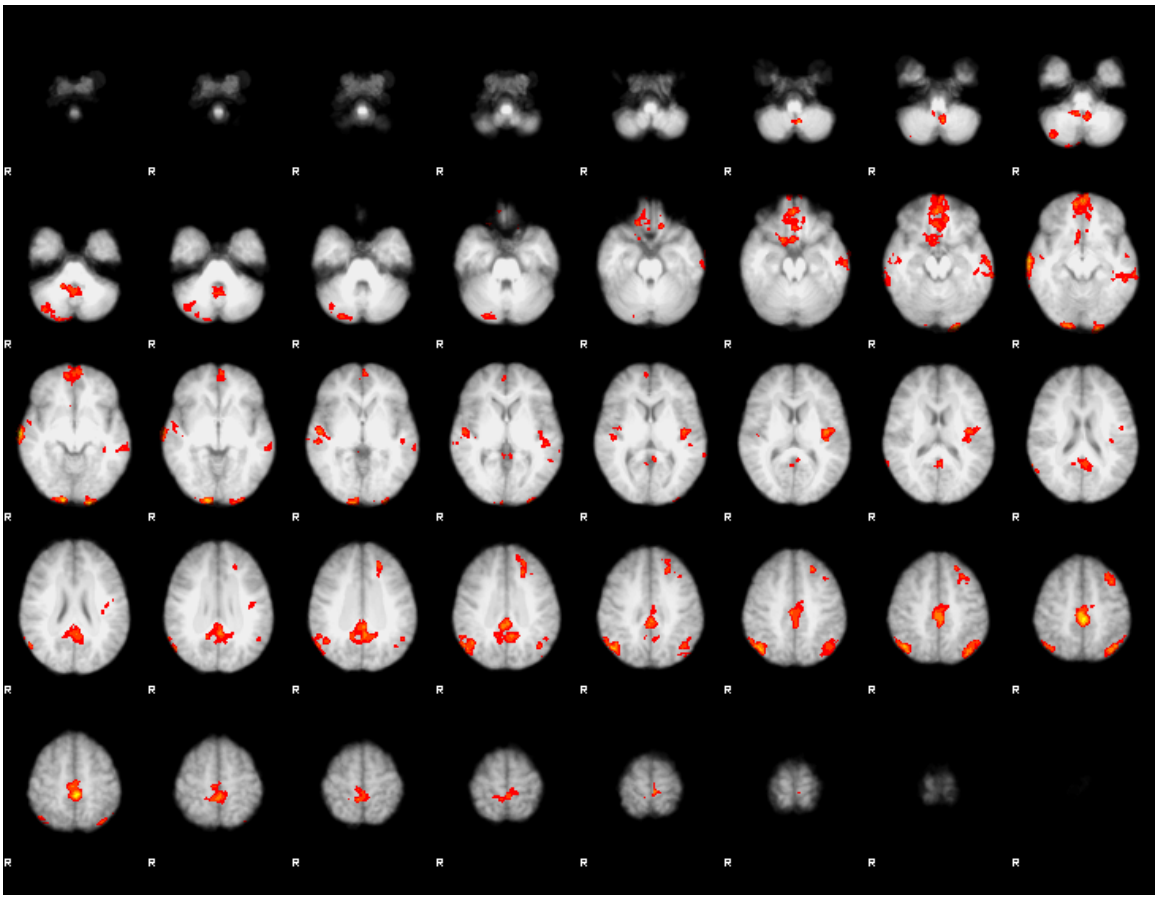

Figure 8. Deactivation areas for easy step vergence paradigm pre-therapy, sliced image.

Figures 9 and 10 show the activation and deactivation slices post-OBVAT. It can be seen that the pre-therapy activation areas seen more anterior/rostral have now decreased in size and area, with the left side areas diminishing in size before the right side areas. Post-OBVAT, there were no areas of deactivation noted.

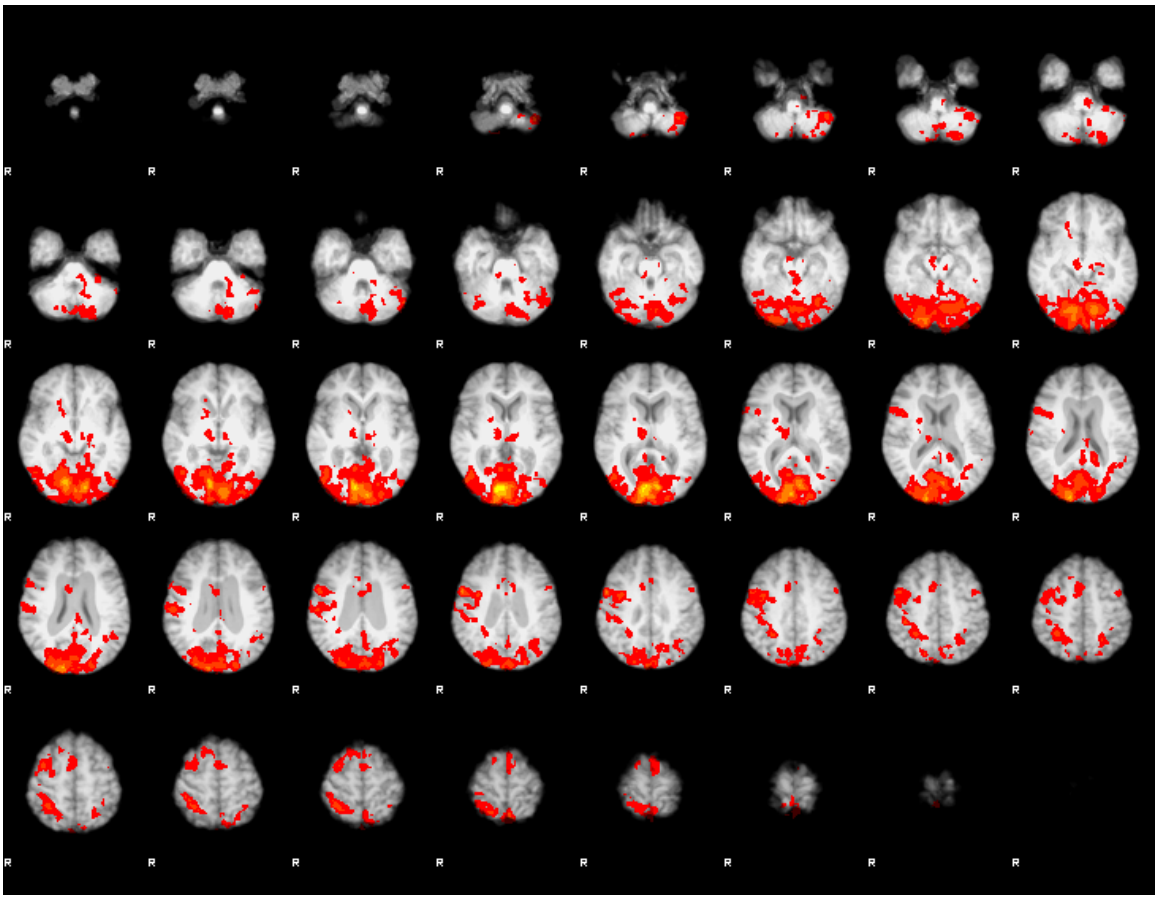

Figure 9. Activation areas for easy step vergence paradigm post-OBVAT, sliced image.

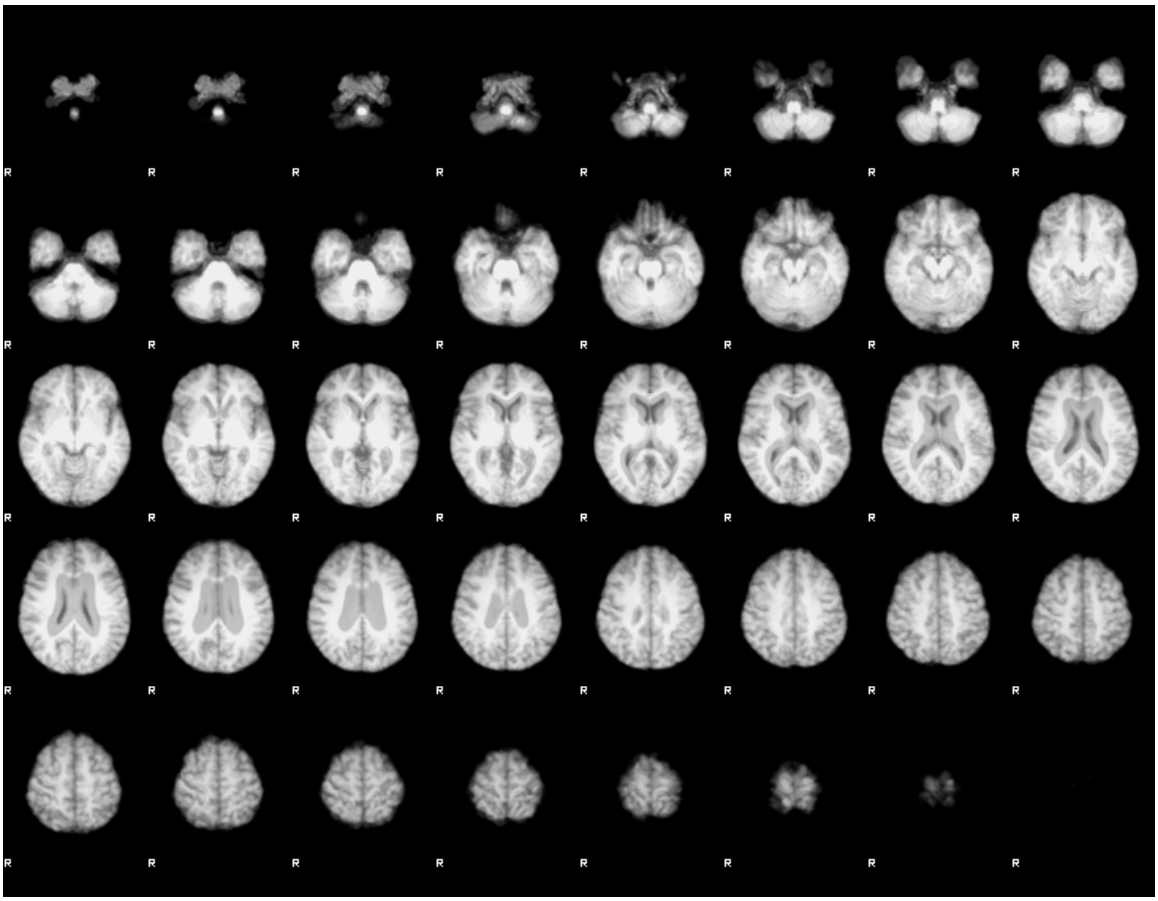

Figure 10. Deactivation areas for easy step vergence paradigm post-OBVAT, sliced image.

When comparing the pre-therapy images to the post-OBVAT images, it can be seen that the areas of activation tend to move posteriorly toward the occipital lobe, meaning there are not as many areas of activation in the more anterior/rostral areas in the brain. Figure 11 shows the overlap of activation areas pre-therapy vs. post-OBVAT.

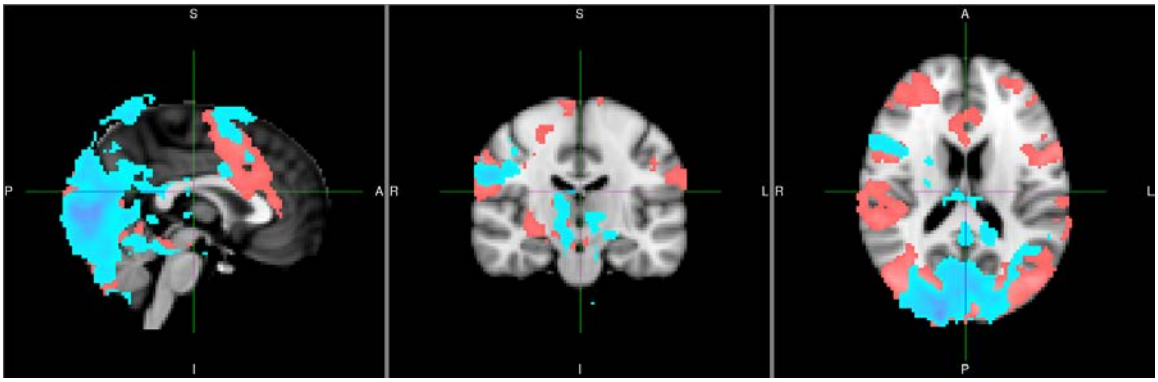

Figure 11. Activation areas for easy step vergence paradigm pre-therapy (pink) and post-OBVAT (light blue).

Figures 12 and 13 show the activation and deactivation slices for post-OBPT. While the overall spatial size and z-scores have decreased post-OBPT, the areas of activation are still similar to the pre-therapy activation areas. For the areas of deactivation, all of the areas of interest in pre-therapy areas showed no activation, except a small area in the occipital lobe. However, new areas of deactivation were seen in the parietal lobe (postcentral gyrus/BA 2) and frontal lobe (precentral gyrus, BA 4; largest area of deactivation seen across all groups). Figures 14 and 15 show the pre-therapy and post-OBPT conditions overlapped for activation and deactivation respectively. While a smaller spatial area is observed post-OBPT, the areas of activation are still in the same general positions seen pre-therapy. Figure 16 shows the activation area comparisons between the post-OBVAT and post-OBPT conditions. As pointed out earlier, more anterior activation areas are decreased post-OBVAT compared to post-OBPT.

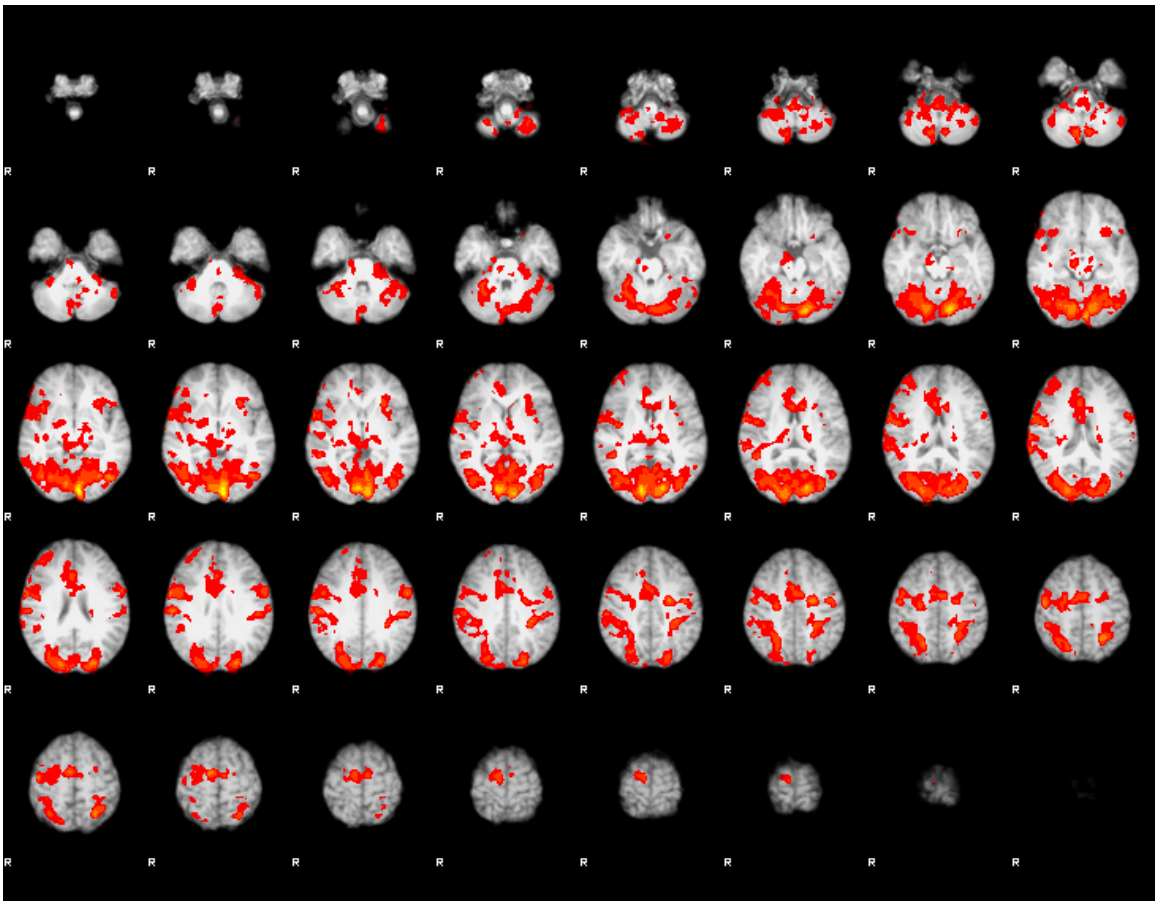

Figure 12. Activation areas for easy step vergence paradigm post-OBPT, sliced image.

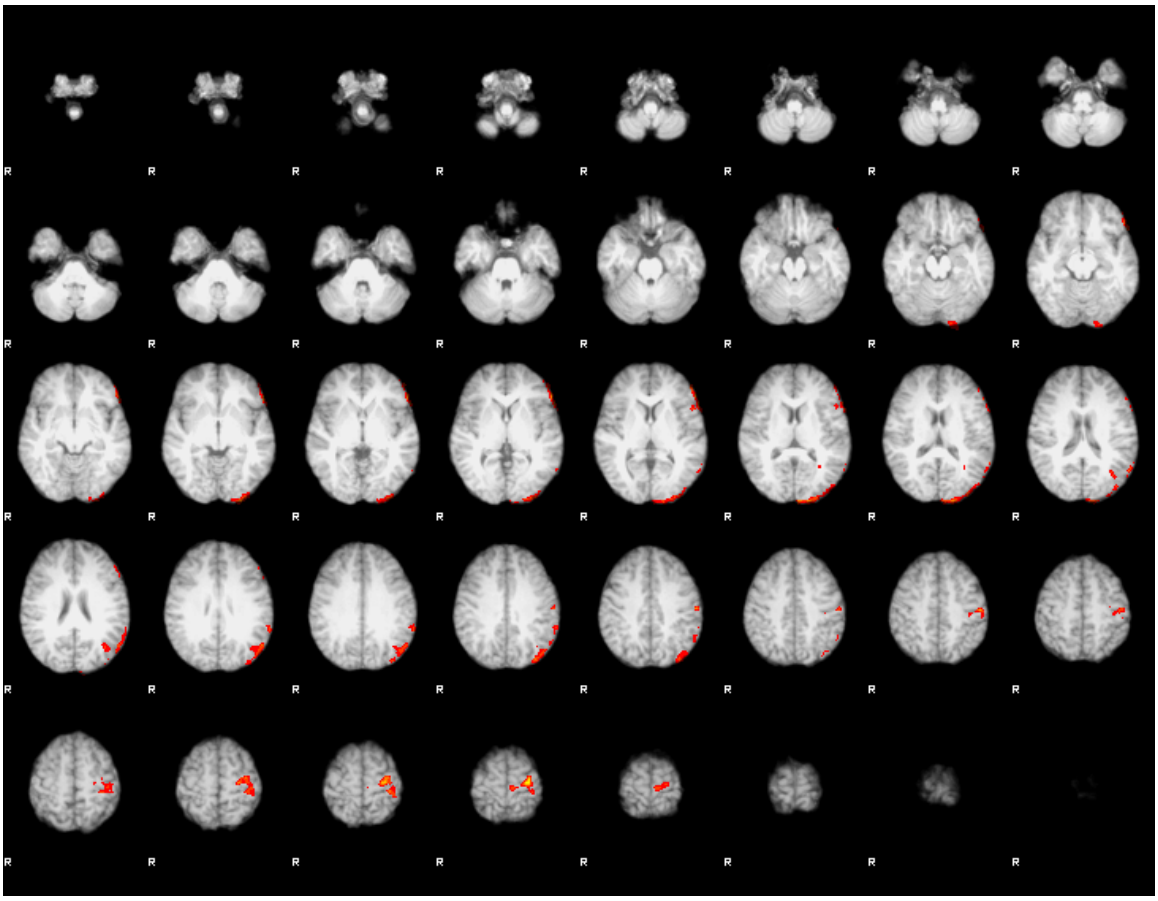

Figure 13. Deactivation areas for easy step vergence paradigm post-OBPT, sliced image.

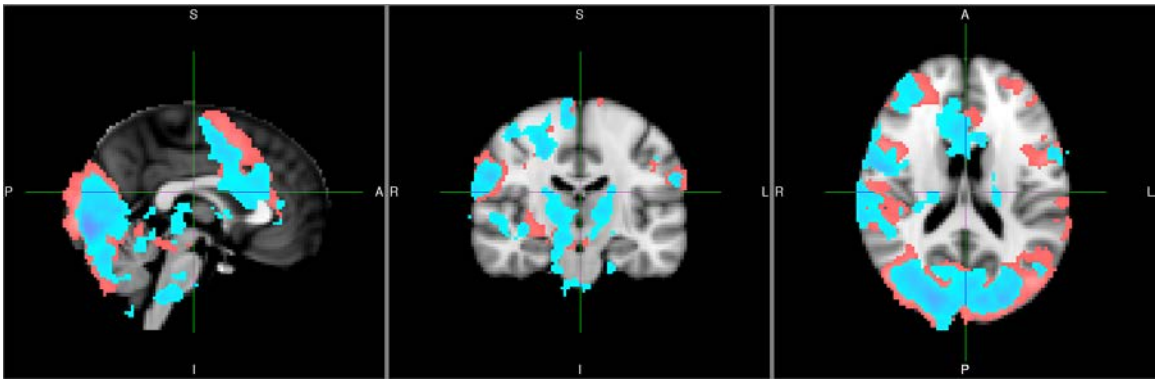

Figure 14. Activation areas for easy step vergence paradigm pre-therapy (pink) and post-OBPT (light blue).

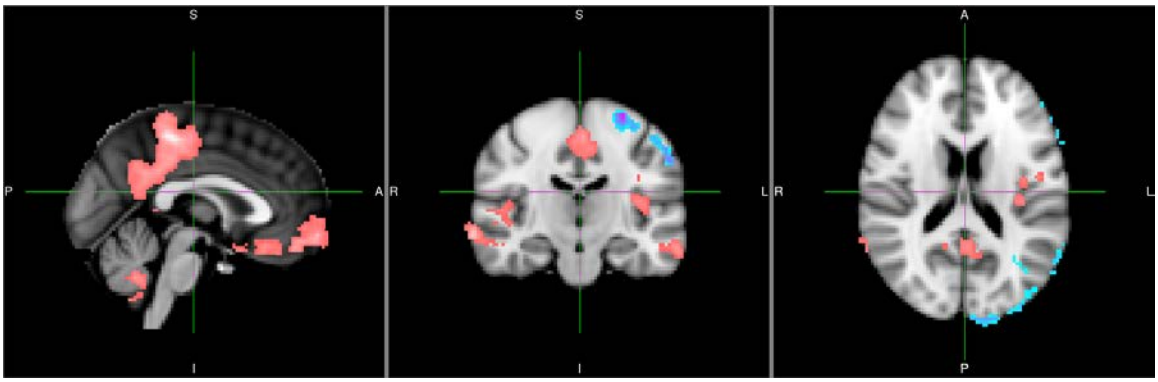

Figure 15. Deactivation areas for easy step vergence paradigm pre-therapy (pink) and post-OBPT (light blue).

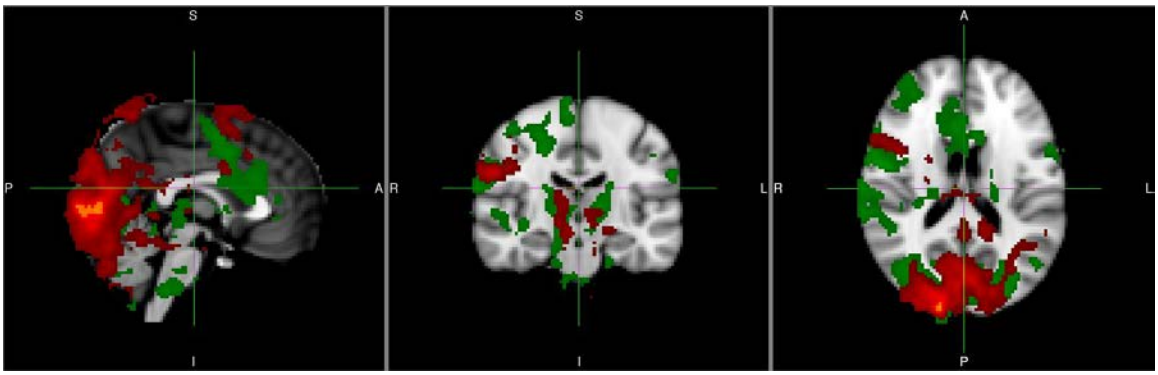

Figure 16. Activation areas for easy step vergence paradigm post-OBVAT (maroon) and post-OBPT (green).

Each 2Δ step of the easy step vergence paradigm was broken down and analyzed individually, starting with step 1 (4Δ) and ending with step 5 (12Δ). Pre-therapy, the largest amount of activation is seen in the first step and is seen mostly posterior. By step 5, the activation areas move mostly anterior (Figures 17 through 21). Pre-therapy, most subjects were able to maintain fusion for the first three steps, but variable results were noted starting at step 4. Post-OBVAT, the largest amounts of activation are seen in steps

1 and 2, also posteriorly. Like in the pre-therapy condition, the posterior activation decreases by step 5, but the more anterior areas of activation are not seen (Figures 22 through 26). Post-OBPT, the general pattern acts like the post-OBVAT condition, however, more activation is seen anteriorly in step 1 post-OBPT than when compared to post-OBVAT (Figures 27 through 30). There was no activation seen in step 4 post-OBPT.

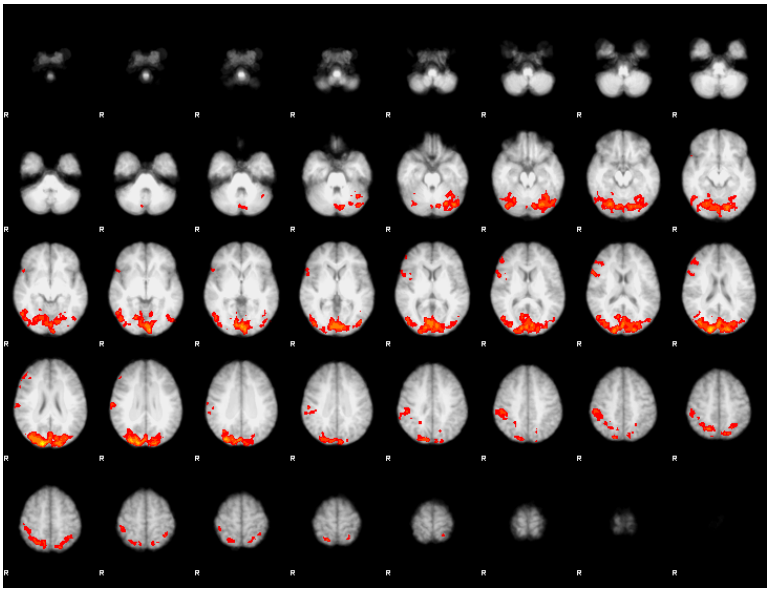

Figure 17. Step 1 for easy step vergence activation pre-therapy.

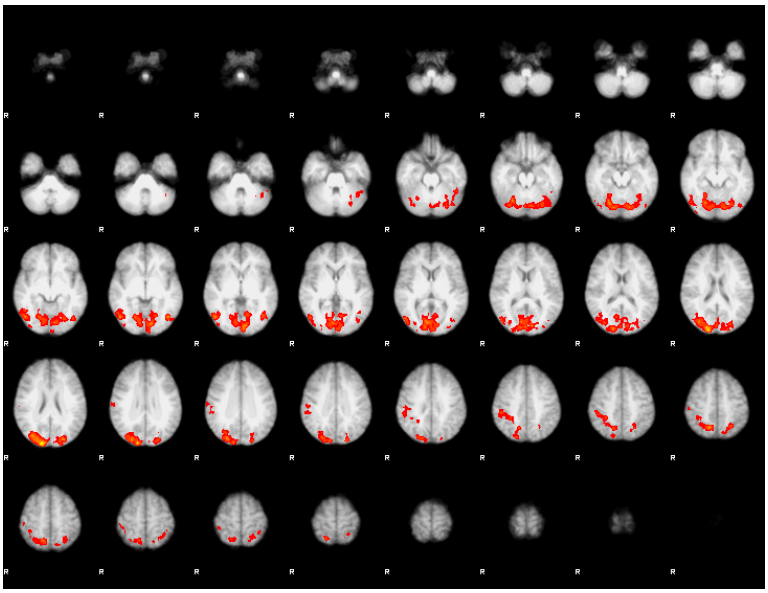

Figure 18. Step 2 for easy step vergence activation pre-therapy.

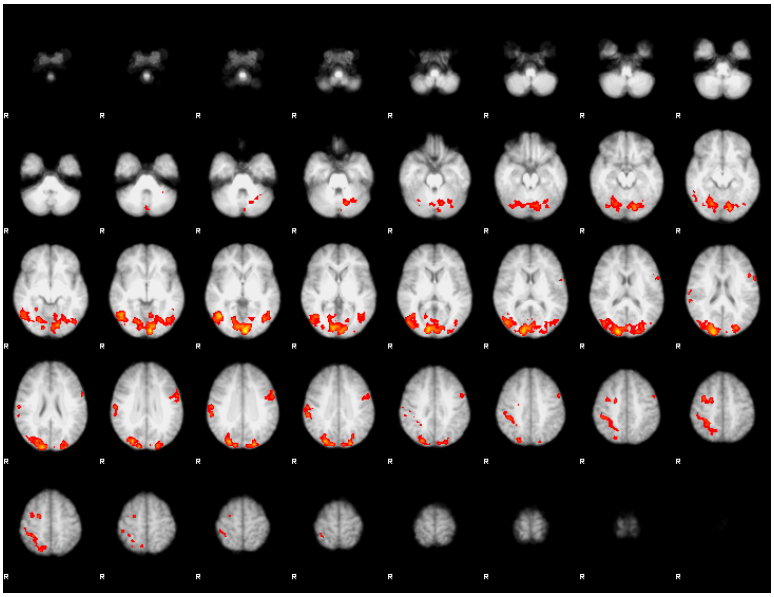

Figure 19. Step 3 for easy step vergence activation pre-therapy.

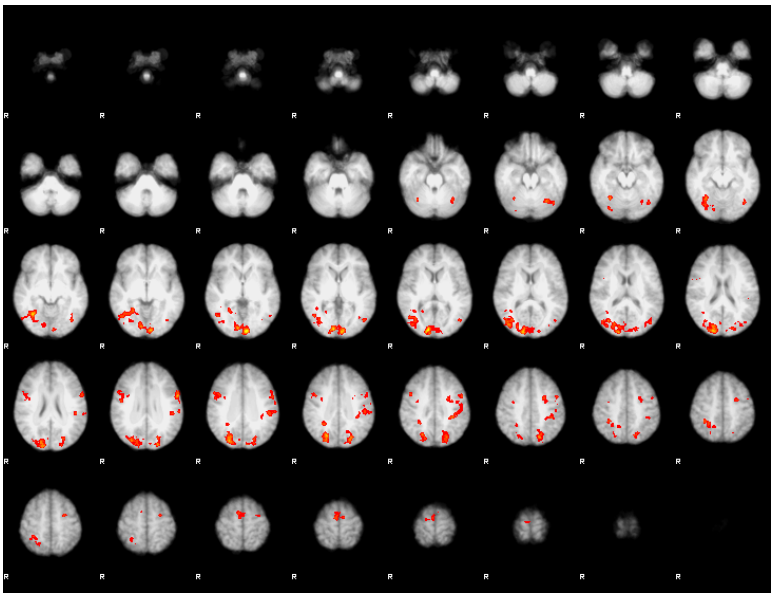

Figure 20. Step 4 for easy step vergence activation pre-therapy.

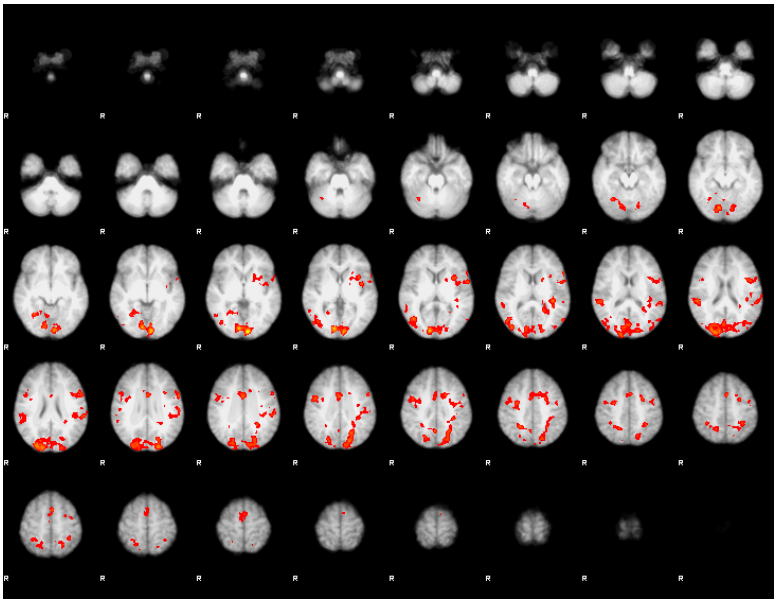

Figure 21. Step 5 for easy step vergence activation pre-therapy.

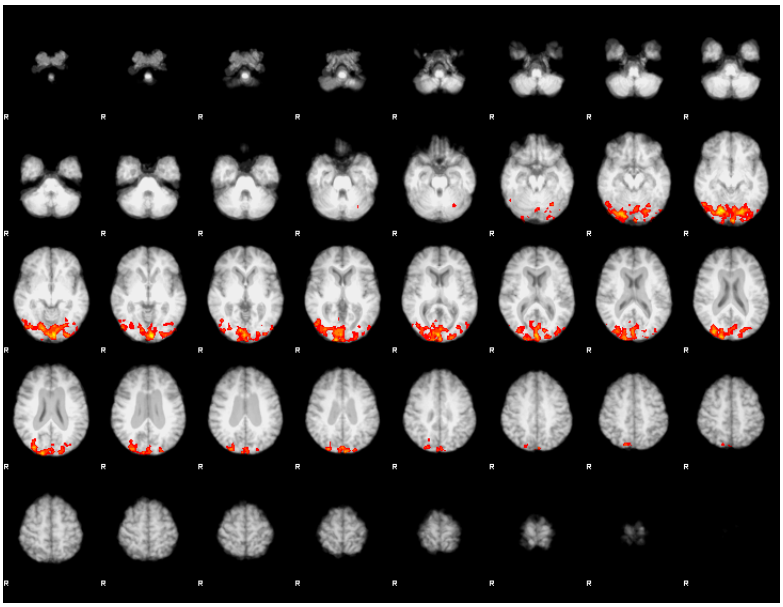

Figure 22. Step 1 for easy step vergence activation post-OBVAT.

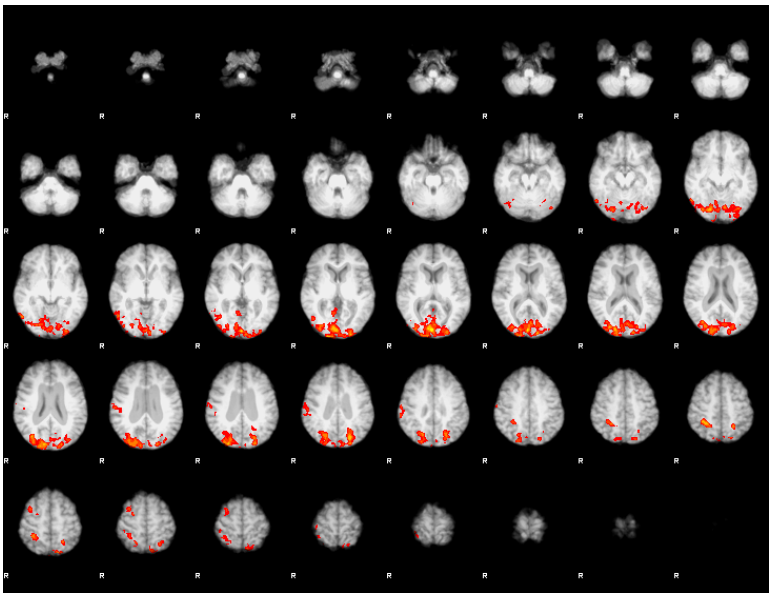

Figure 23. Step 2 for easy step vergence activation post-OBVAT.

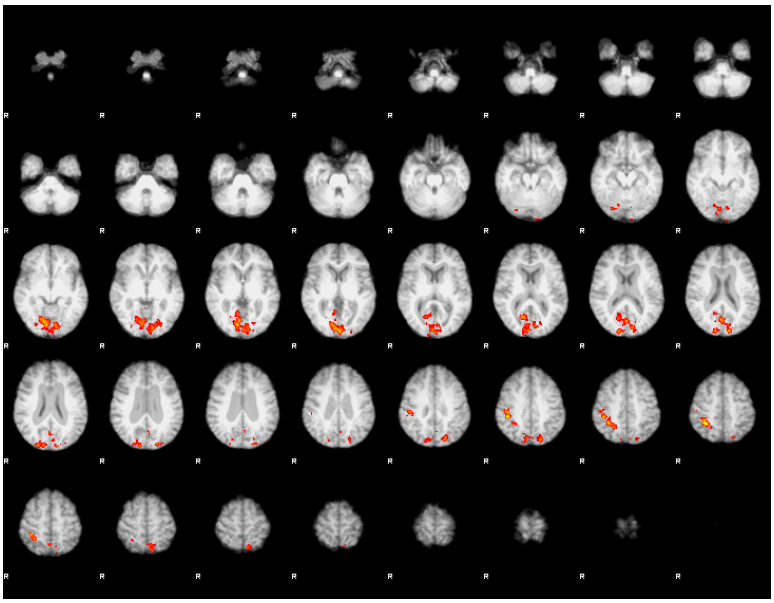

Figure 24. Step 3 for easy step vergence activation post-OBVAT.

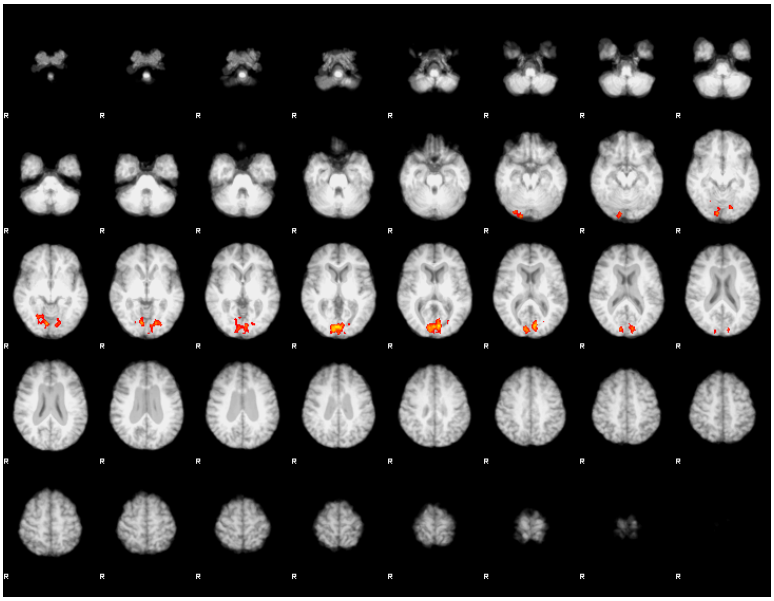

Figure 25. Step 4 for easy step vergence activation post-OBVAT.

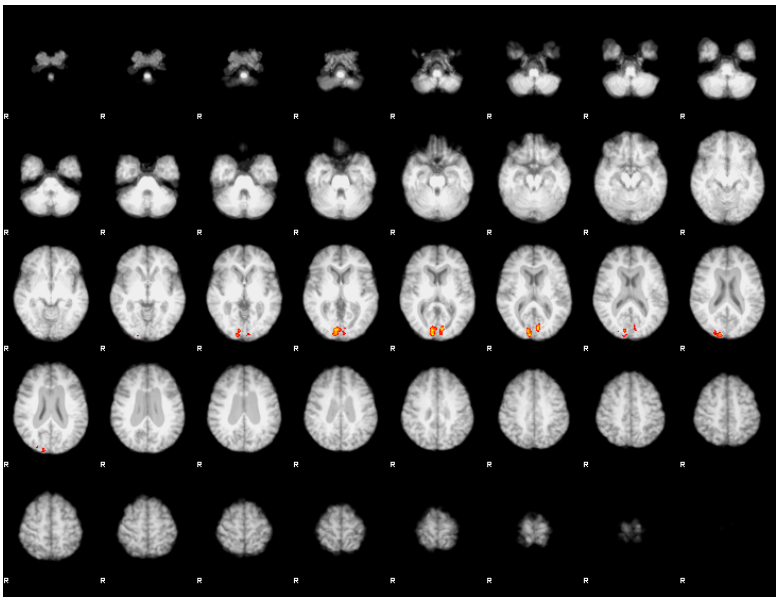

Figure 26. Step 5 for easy step vergence activation post-OBVAT.

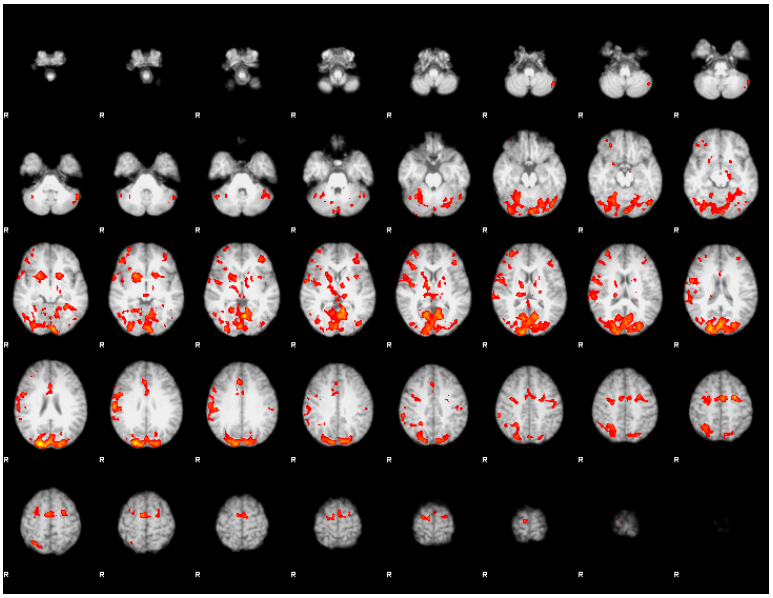

Figure 27. Step 1 for easy step vergence activation post-OBPT.

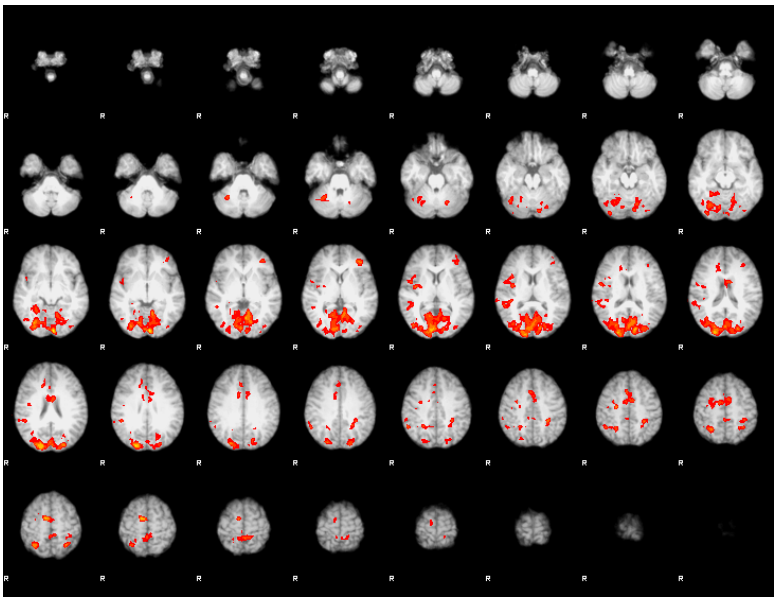

Figure 28. Step 2 for easy step vergence activation post-OBPT.

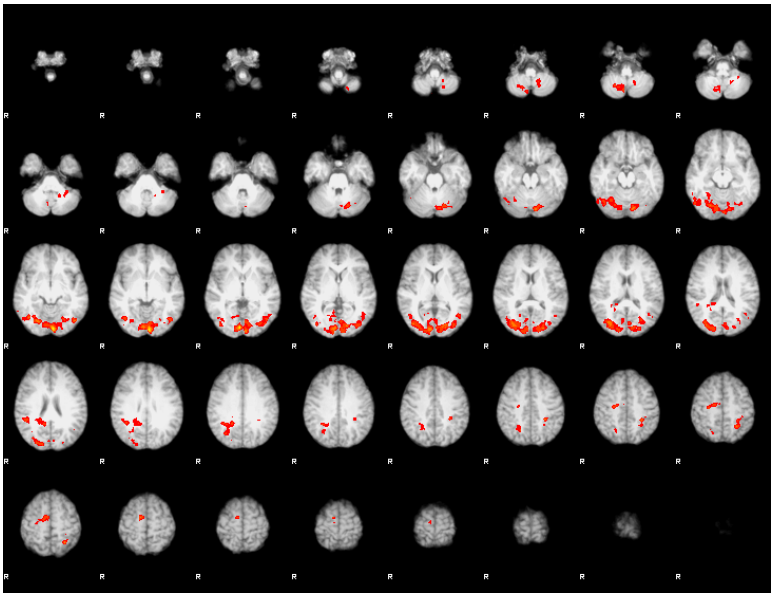

Figure 29. Step 3 for easy step vergence activation post-OBPT.

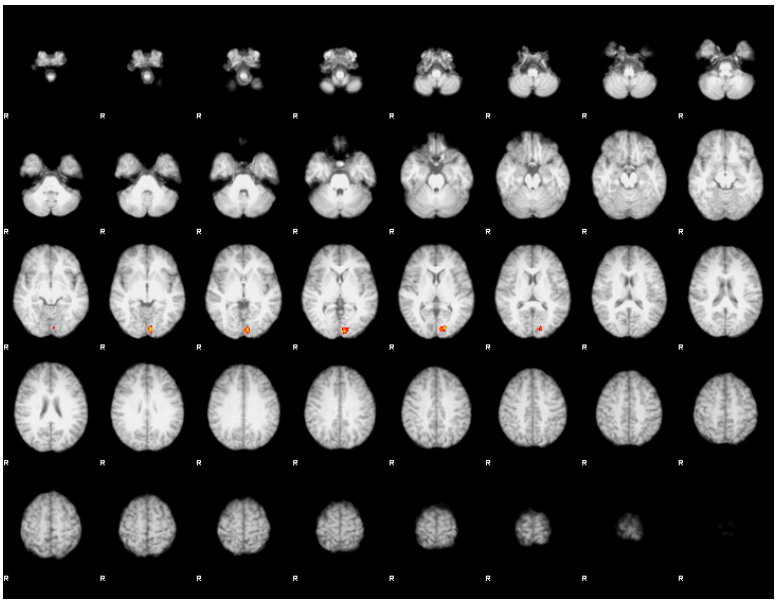

Figure 30. Step 5 for easy step vergence activation post-OBPT.

Based on Alvarez's work, certain ROIs were examined for their role in vergence eye movements. The ROI z-scores from this study and those specific ROIs can be seen in Table 9. A decrease in z-scores is observed across all ROIs post-OBVAT and post-OBPT as compared to the pre-therapy. A lower z-score is seen post-OBVAT as compared to post-OBPT in most areas except the right DLPFC, left medial frontal gyrus, and left precuneus.

	X	Y	Z	PRE-THERAPY Z-SCORE	POST-OBVAT Z-SCORE	POST-OBPT Z-SCORE
DORSOLATERAL PREFRONTAL CORTEX (DLPFC)	Cerebrum, frontal lobe, middle frontal gyrus, BA 9					
RIGHT	18	68	53	6.68146	3.42998	2.90716
LEFT	70	68	53	4.22883	2.49619	3.43448
FRONTAL EYE FIELD (FEF)	Cerebrum, frontal lobe, superior frontal gyrus, BA 8					
RIGHT	33	79	57	NS	NS	NS
LEFT	56	79	57	-4.2803	NS	NS
MEDIAL FRONTAL GYRUS (SEF)	Cerebrum, frontal lobe, BA 6					
RIGHT	42	63	65	3.56118	3.04314	3.39552
LEFT	47	63	65	3.44585	2.39888	NS
PRECUNEUS	Cerebrum, parietal lobe					
RIGHT	33	29	54	6.43975	2.69902	2.72803
LEFT	55	29	54	5.20662	2.74699	NS
INFERIOR PARIETAL	Cerebrum, parietal lobe, BA 40					
RIGHT	26	39	60	6.47598	2.41641	3.18733
LEFT	61	39	60	4.8033	2.33732	3.43829
CEREBELLAR VERMIS	45	25	21	4.83299	3.72466	3.90591

Table 9. ROIs for easy step vergence paradigm. Negative numbers indicate deactivation. NS = Non-significant activation (> -2.3 and < 2.3).

Hard Step Vergence Paradigm

For this section, a z-score range of 2.3 to 19.8 for activation and 2.3 to 7.7 for deactivation (with a z-score ≥ 2.3 considered significant) was used to locate specific hot spots and clustered areas of activation/deactivation without comparing to any previously documented ROIs. Tables 10 and 11 list the z-score, coordinates, and location of all the activation and deactivation hot spots respectively for the hard step vergence paradigm. Figures 31 through 36 show the locations of the activation (in red) and deactivation (in blue) hot spots listed in the tables for the pre-therapy, post-OBVAT, and post-OBPT respectively.

	Z-SCORE	LOCATION	X	Y	Z
PRE-THERAPY	19.7924	Right occipital lobe, lingual gyrus, white matter	40	21	37
POST-OBVAT	13.401	Right occipital lobe, lingual gyrus, white matter	40	22	40
POST-OBPT	10.145	Right occipital lobe, cuneus, white matter	39	21	41

Table 10. Activation hot spots for hard step vergence paradigm.

	Z-SCORE	LOCATION	X	Y	Z
PRE-THERAPY	7.63633	Right occipital lobe, lingual gyrus, white matter	39	13	33
POST-OBVAT	4.24897	Left frontal lobe, precentral gyrus, gray matter, BA 4	61	50	68
POST-OBPT	5.19459	Right occipital lobe, lingual gyrus, gray matter, BA 17	38	13	31

Table 11. Deactivation hot spots for hard step vergence paradigm.

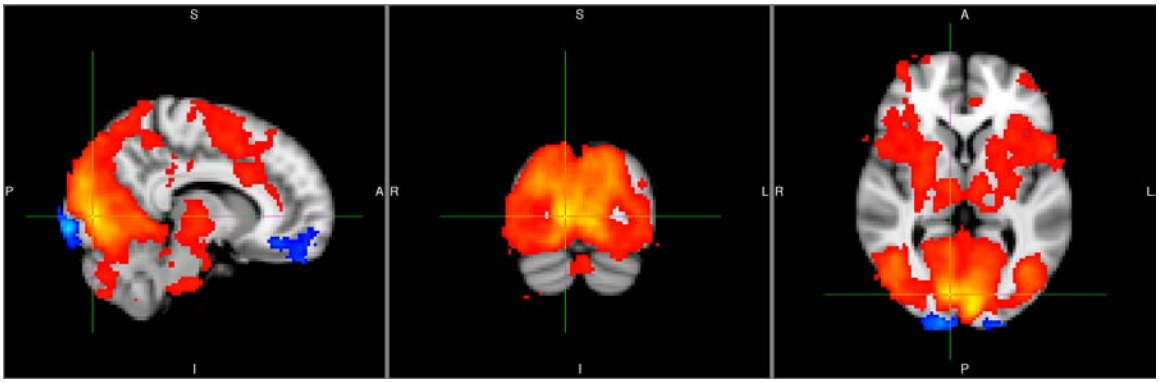

Figure 31. Activation area hot spot for hard step vergence paradigm pre-therapy, 3D FSL image.

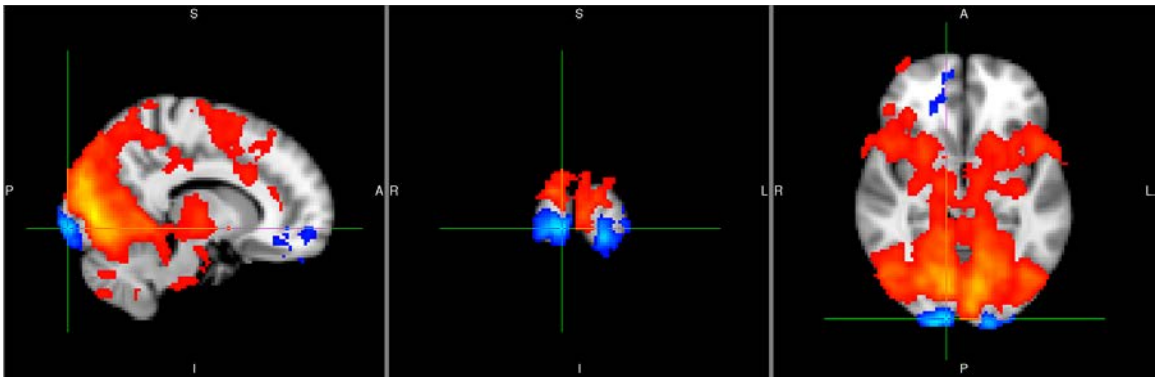

Figure 32. Deactivation area hot spot for hard step vergence paradigm pre-therapy, 3D FSL image.

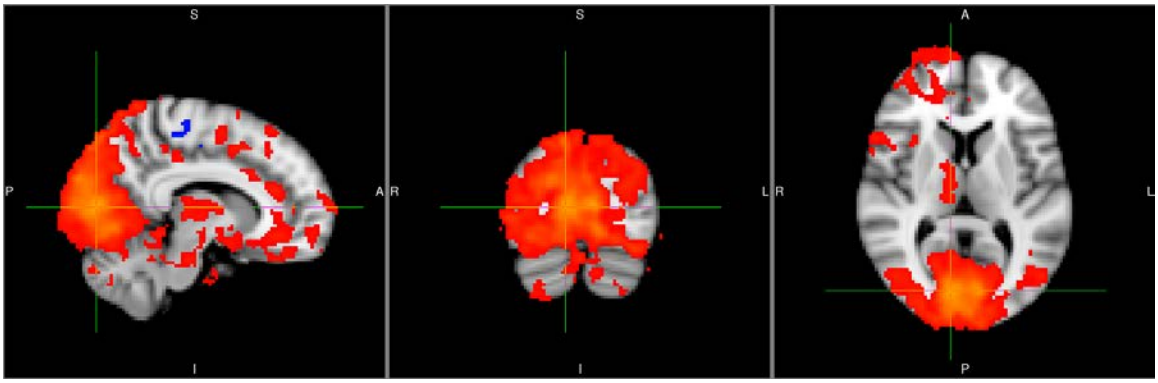

Figure 33. Activation area hot spot for hard step vergence paradigm post-OBVAT, 3D FSL image.

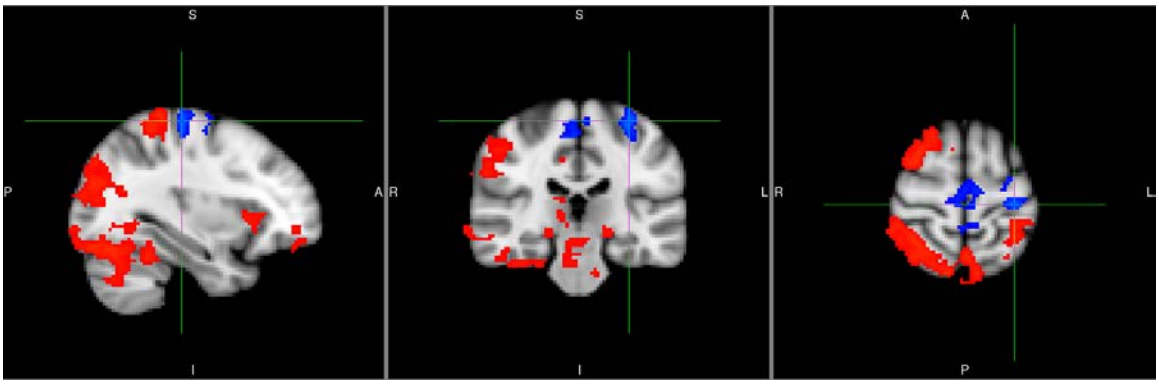

Figure 34. Deactivation area hot spot for hard step vergence paradigm pre-therapy, 3D FSL image.

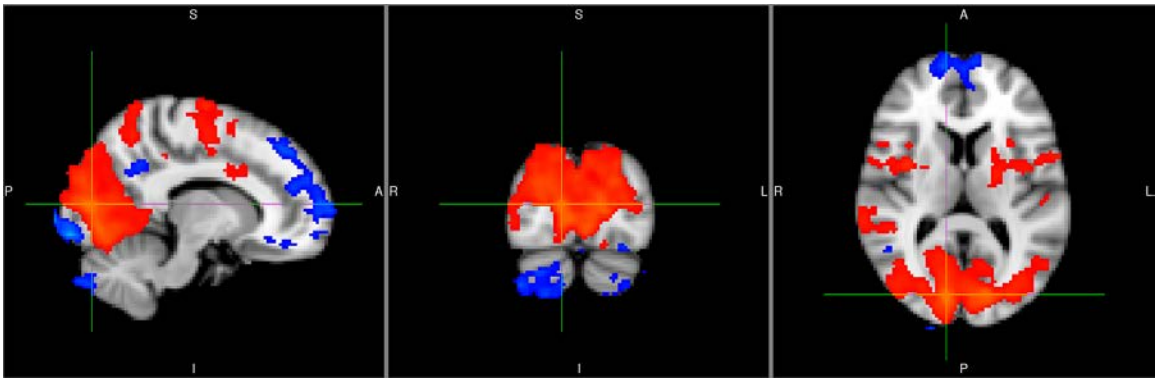

Figure 35. Activation area hot spot for hard step vergence paradigm post-OBPT, 3D FSL image.

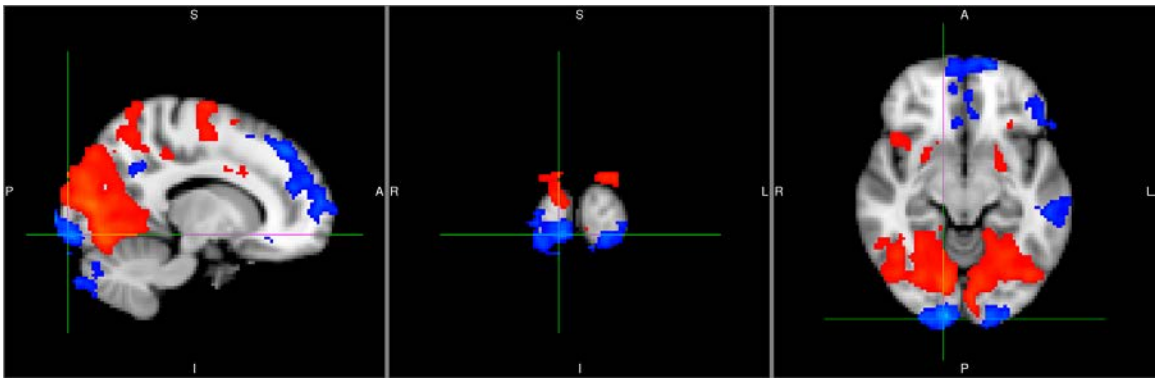

Figure 36. Deactivation area hot spot for hard step vergence paradigm post-OBPT, 3D FSL image.

Brain slice images were generated for activation and deactivation for pre-therapy, post-OBVAT, and post-OBPT. Figures 37 and 38 show the overall activation and deactivation maps, respectively, for the pre-therapy group. Activation can be seen in clusters mainly in the following areas: the frontal lobe (inferior frontal gyrus, medial frontal gyrus/BA 6, and the superior frontal gyrus/BA 9), temporal lobe (fusiform gyrus/BA 37), parietal lobe (inferior parietal lobule/BA 40, postcentral gyrus, and precuneus), occipital lobe (lingual gyrus/BA 17 and cuneus/BA 14), and cerebellum (posterior lobe/declive and anterior lobe/culmen). Deactivation can be seen in clusters in the following areas: the frontal lobe (right medial frontal gyrus/BA 10), parietal lobe (angular gyrus/BA 39), and occipital lobe (lingual gyrus/BA 17).

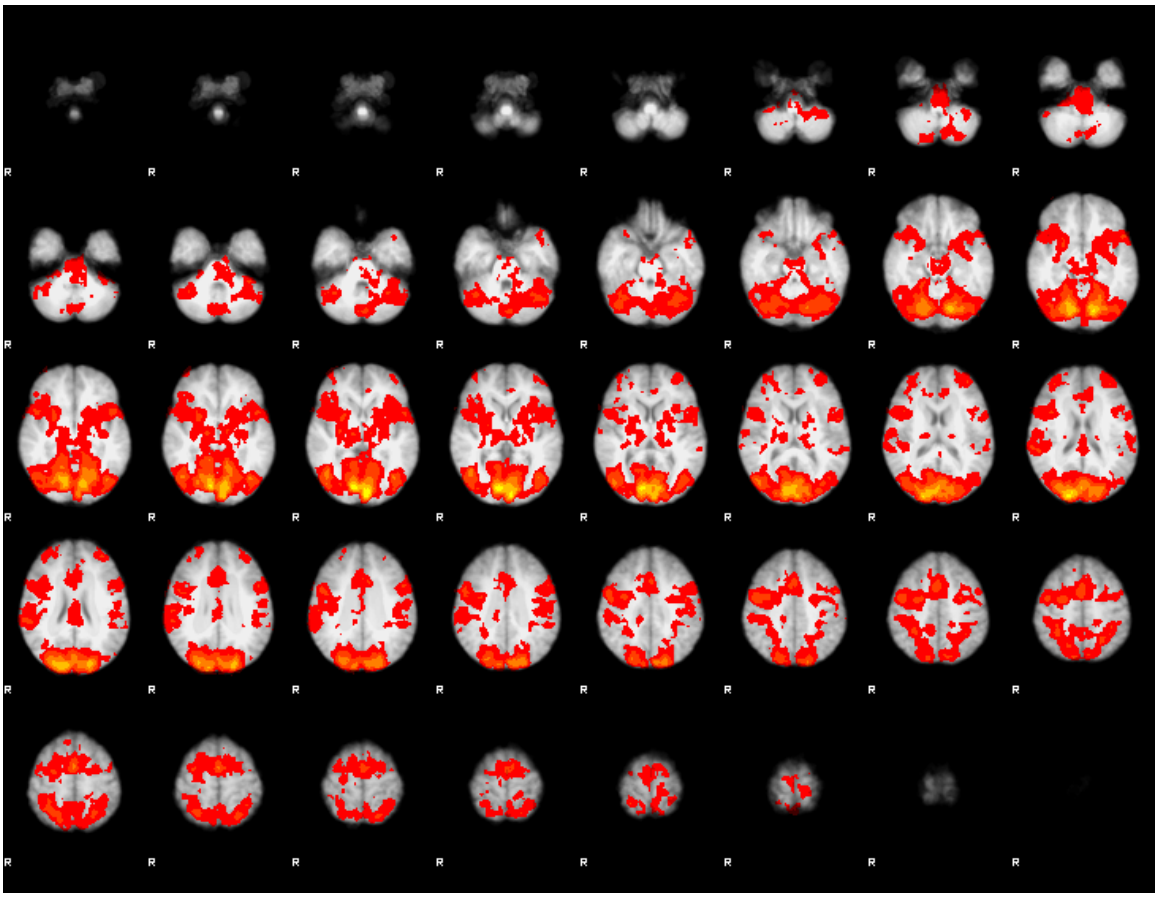

Figure 37. Activation areas for hard step vergence paradigm pre-therapy, sliced images.

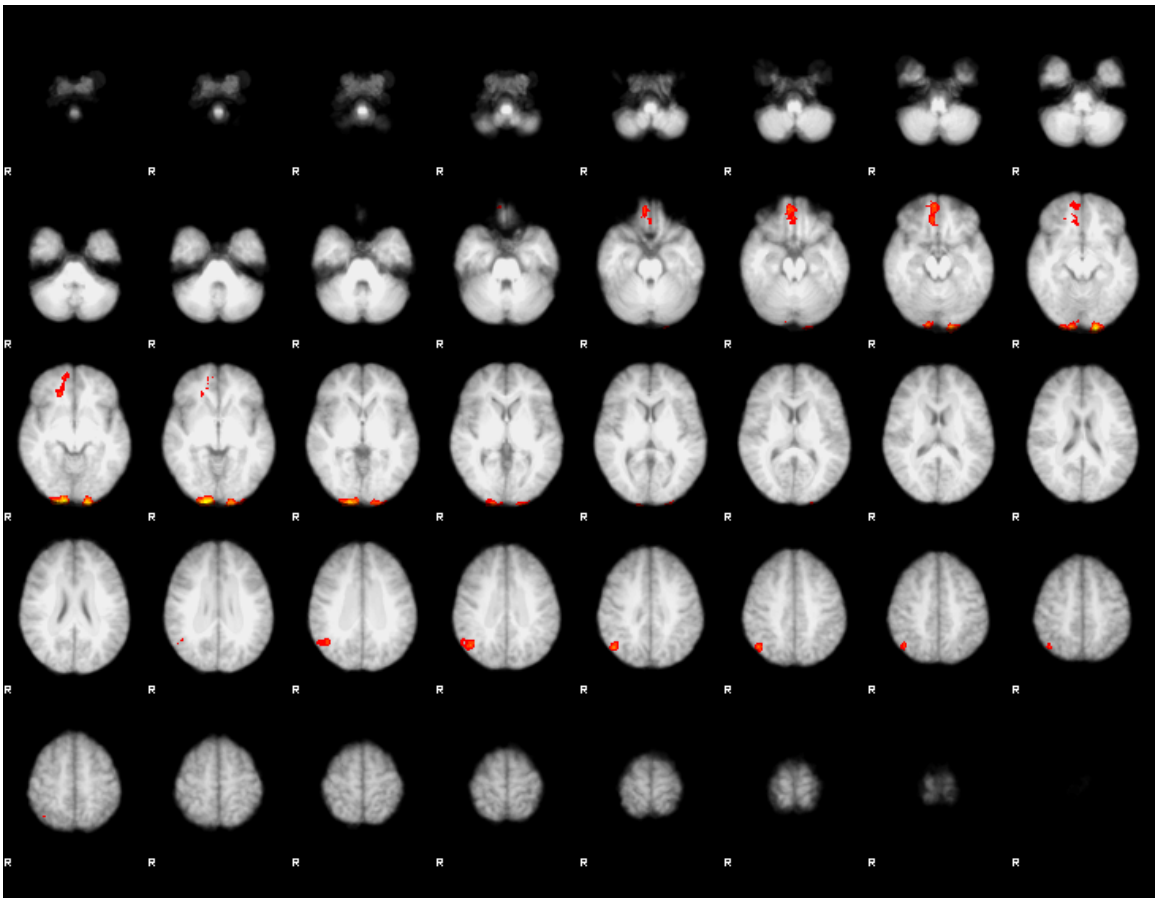

Figure 38. Deactivation areas for hard step vergence paradigm pre-therapy, sliced images.

Figures 39 and 40 show the activation and deactivation slices for post-OBVAT. It can be seen that the pre-therapy activation areas seen more anterior/rostral have now decreased in size and area, with the left side areas diminishing in size before the right side areas, but not as much in comparison to the easy step vergence paradigm changes compared to pre-therapy levels. Post-OBVAT, the deactivation areas seen in the pre-therapy scans reduced a non-significant z-score. Some areas of deactivation in the pre-therapy scans showed up as areas of activation post-OBVAT, including the deactivation hot spot in the occipital lobe. A new areas of deactivation showed up in the frontal lobe

(paracentral lobule/BA 5, medial frontal gyrus/BA 6, and precentral gyrus/BA 4), more on the left side.

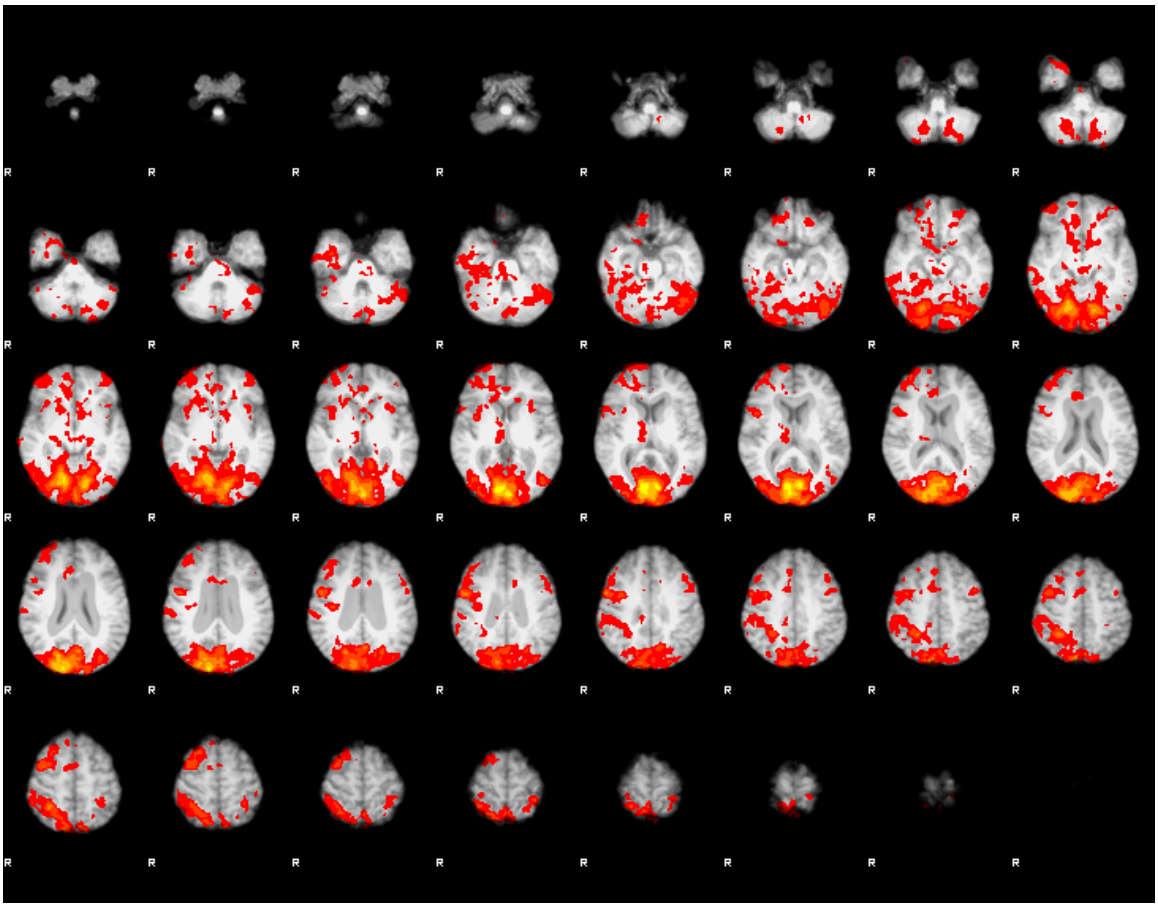

Figure 39. Activation areas for hard step vergence paradigm post-OBVAT, sliced images.

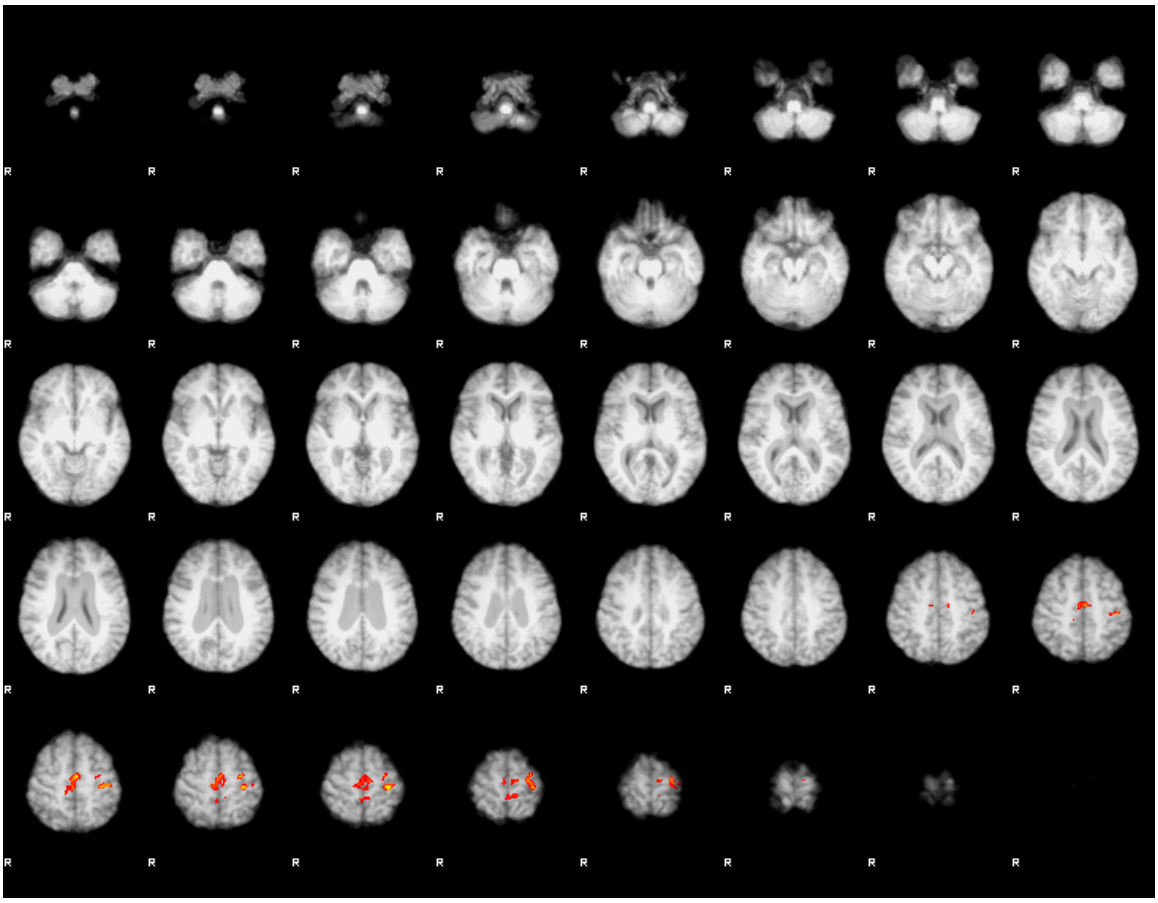

Figure 40. Deactivation areas for hard step vergence paradigm post-OBVAT, sliced images.

When comparing the pre-therapy images to the post-OBVAT images, it can be seen that the areas of activation tend to move posteriorly toward the occipital lobe. More of the anterior areas on the right side remained areas of activation compared to the easy step vergence paradigm pre-therapy and post-OBVAT comparison. Figure 41 shows the overlap of activation areas pre-therapy vs. post-OBVAT. Figure 42 shows the areas of deactivation pre-therapy and post-OBVAT on the same brain.

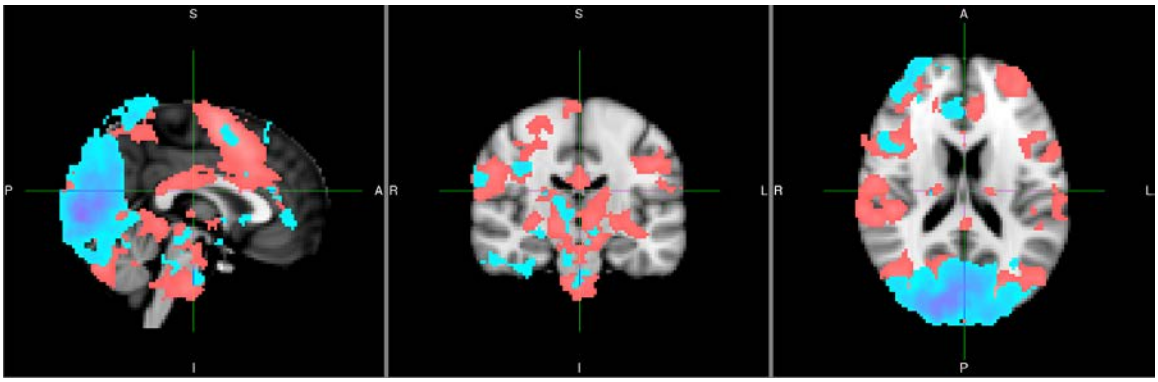

Figure 41. Activation areas for hard step vergence paradigm pre-therapy (pink) and post-OBVAT (light blue).

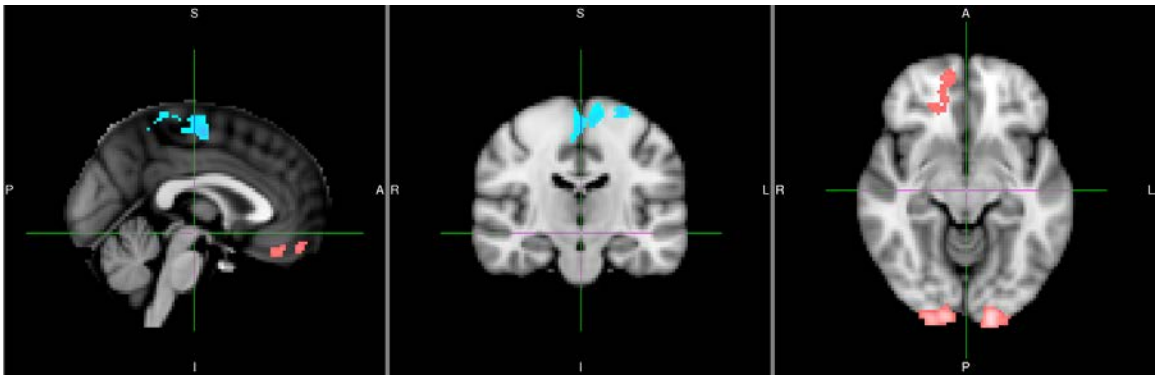

Figure 42. Deactivation areas for hard step vergence paradigm pre-therapy (pink) and post-OBVAT (light blue).

Figures 43 and 44 show the activation and deactivation slices for post-OBPT. While the overall spatial size and z-scores have decreased post-OBPT, the areas of activation are still similar to the pre-therapy activation areas, except for the more anterior areas of the frontal lobe. For the areas of deactivation, all of the areas of interest in pre-therapy showed a decrease in z-scores, but did not reduce to non-significant levels like in the easy step vergence paradigm. New areas of deactivation were seen in the parietal lobe

(precuneus/BA 39), temporal lobe (middle temporal gyrus/BA 39 and superior temporal gyrus/BA 39), frontal lobe (superior frontal gyrus/BA 8/FEF and middle frontal gyrus/BA 8/FEF), and cerebellum (posterior lobe/inferior semi-lunar lobule). Figures 45 and 46 show the pre-therapy and post-OBPT conditions overlapped for activation and deactivation respectively. Again, the spatial area seen post-OBPT is decreased, but the same general activation areas are still present when compared to the pre-therapy. Figure 47 shows the activation area comparisons between the post-OBVAT and post-OBPT. As seen with the easy step vergence paradigm, more anterior activation areas are decreased post-OBVAT compared to post-OBPT, although not as much in comparison to the easy step vergence paradigm.

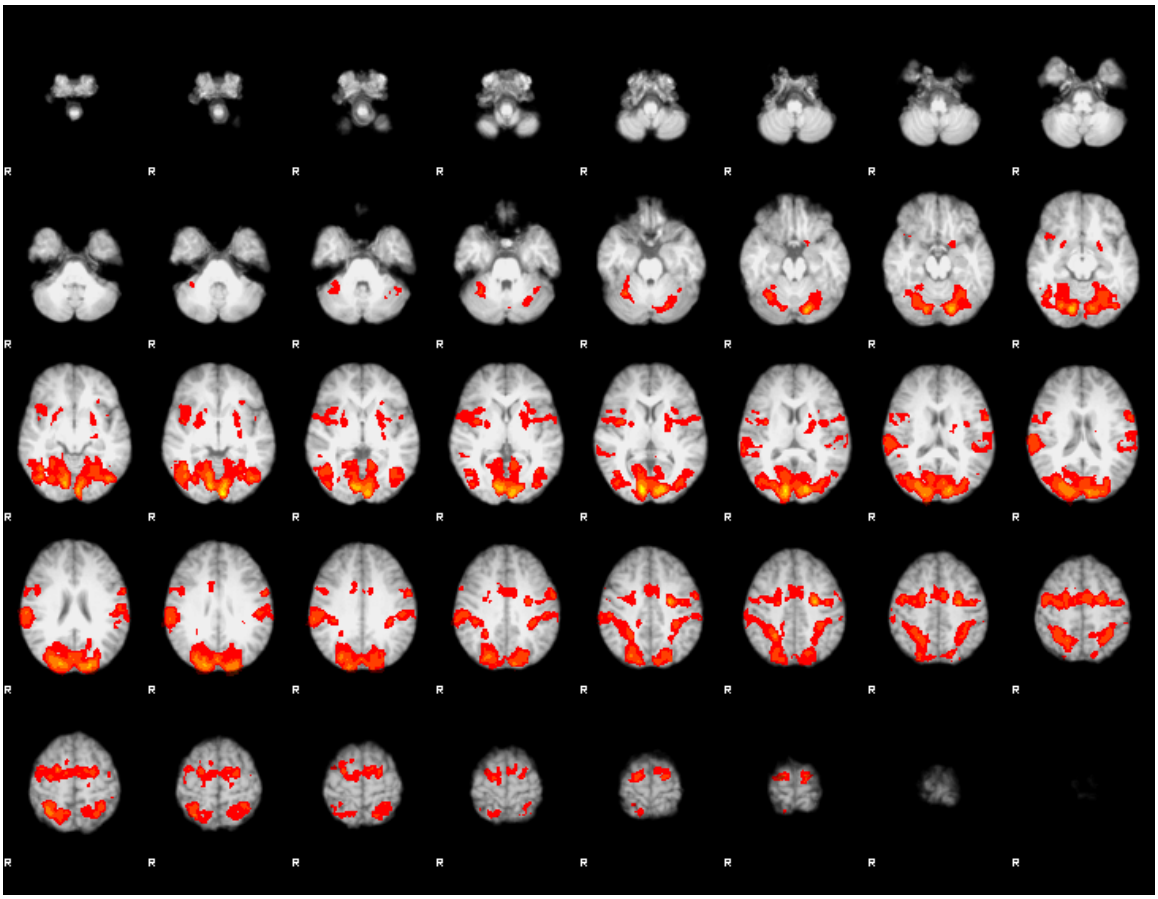

Figure 43. Activation areas for hard step vergence paradigm post-OBPT, sliced images.

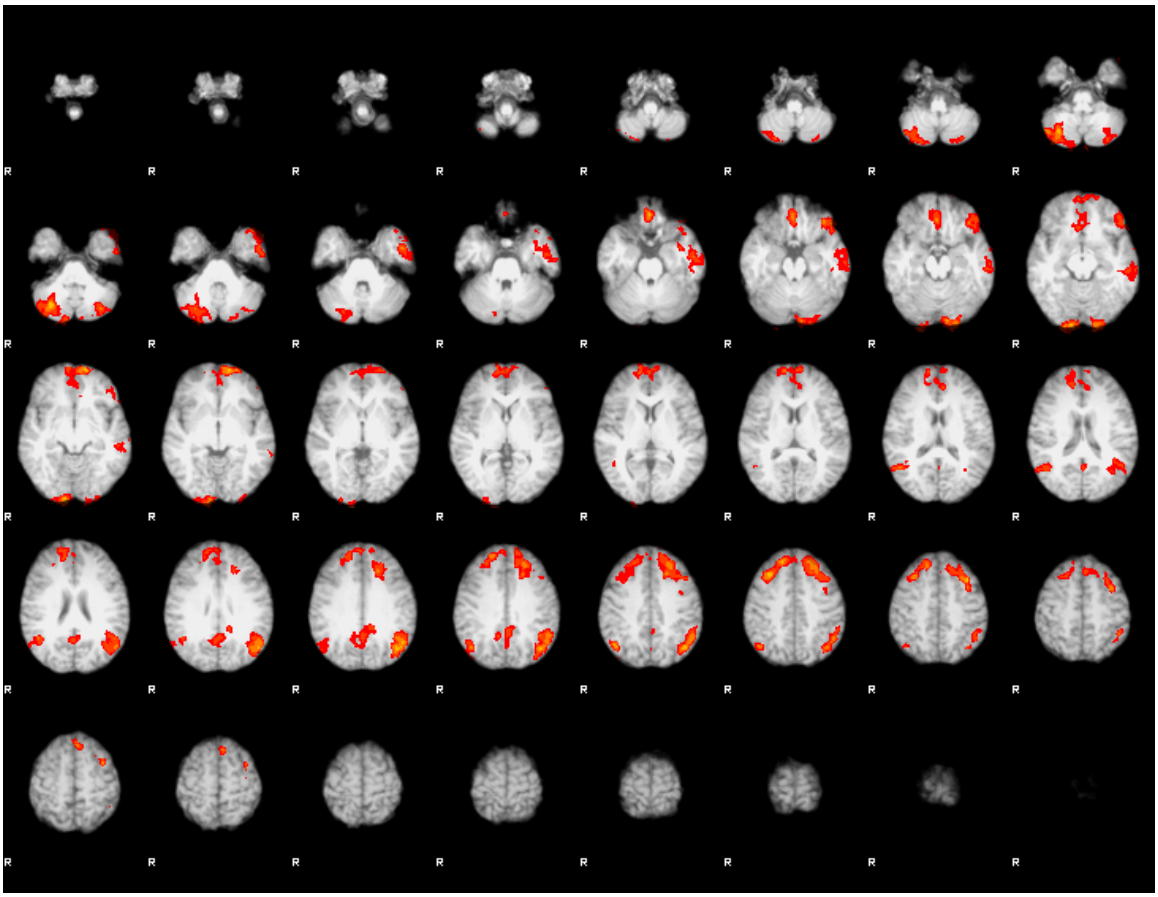

Figure 44. Deactivation areas for hard step vergence paradigm post-OBPT, sliced images.

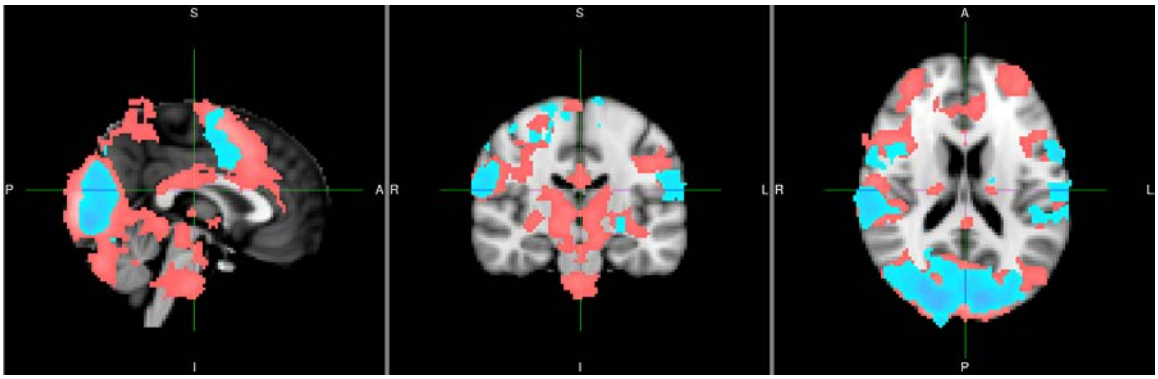

Figure 45. Activation areas for hard step vergence paradigm pre-therapy (pink) and post-OBPT (light blue).

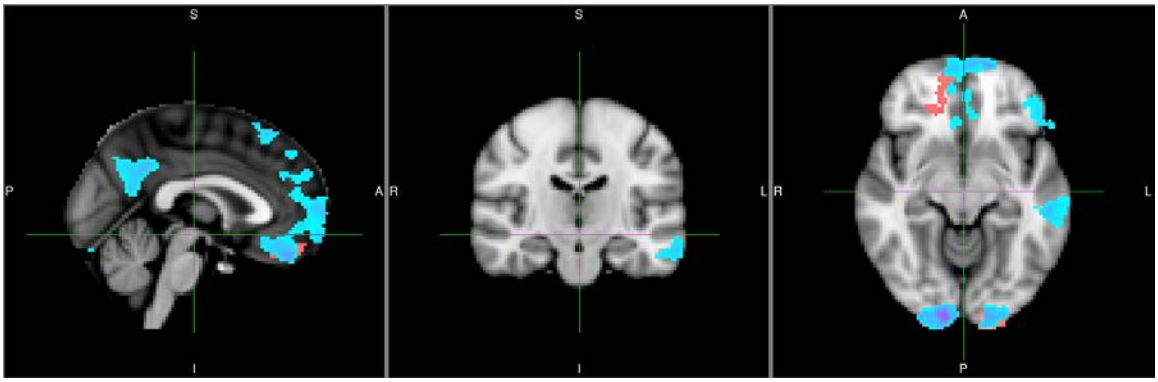

Figure 46. Deactivation areas for hard step vergence paradigm pre-therapy (pink) and post-OBPT (light blue).

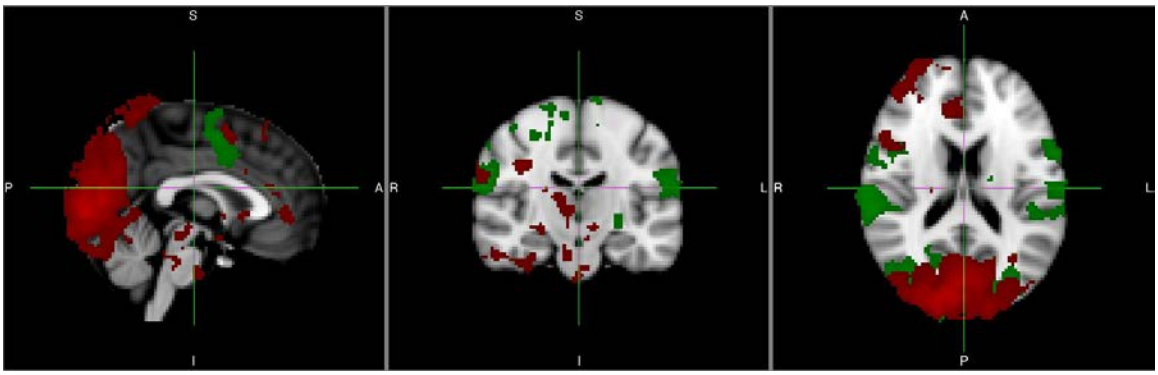

Figure 47. Activation areas for hard step vergence paradigm post-OBVAT (maroon) and post-OBPT (green).

Each 5Δ step of the hard step vergence paradigm was broken down and analyzed individually, starting with step 1 (5Δ) and ending with step 5 (25Δ). Pre-therapy, the least amount of activation is seen in the first step and is seen mostly posterior. At step 3, the activation areas become more scattered and less clustered in the posterior portion of the brain. In step 4, the activation remains posterior, but starts to move laterally away from the posterior pole of the occipital lobe. In step 5, the activation areas remain posteriorly and also move anteriorly (Figures 48 through 52). Pre-therapy, subjects were able to fuse step 1 of the sequence, but variable fusion results were observed between steps 2-5, with most unable to achieve fusion. Post-OBVAT, the least amount of activation is seen in steps 1 and slowly increases in activation until step 5, but does not move laterally or as anteriorly (Figures 53 through 57). Post-OBPT, the highest amounts of activation are seen in steps 1 and 2, and slowly decrease throughout the sequence, much like what was seen for the easy step vergence paradigm (Figures 58 through 62).

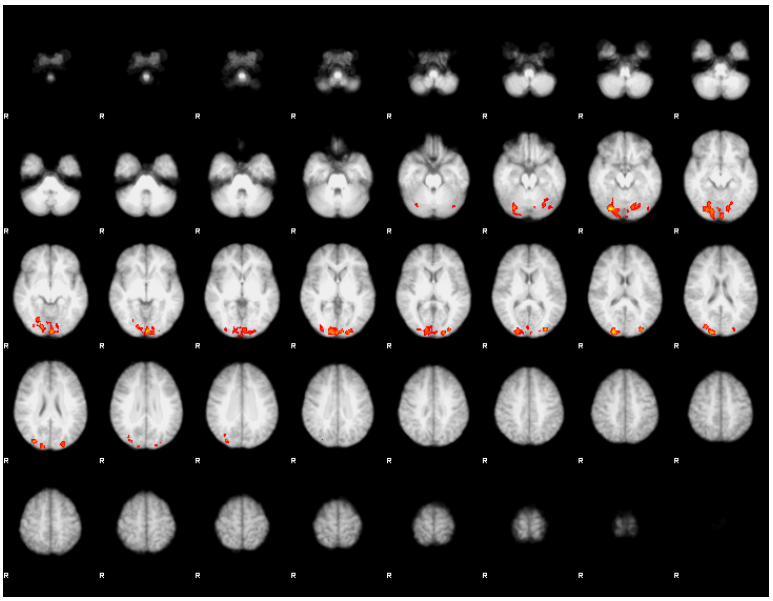

Figure 48. Step 1 for hard step vergence activation pre-therapy.

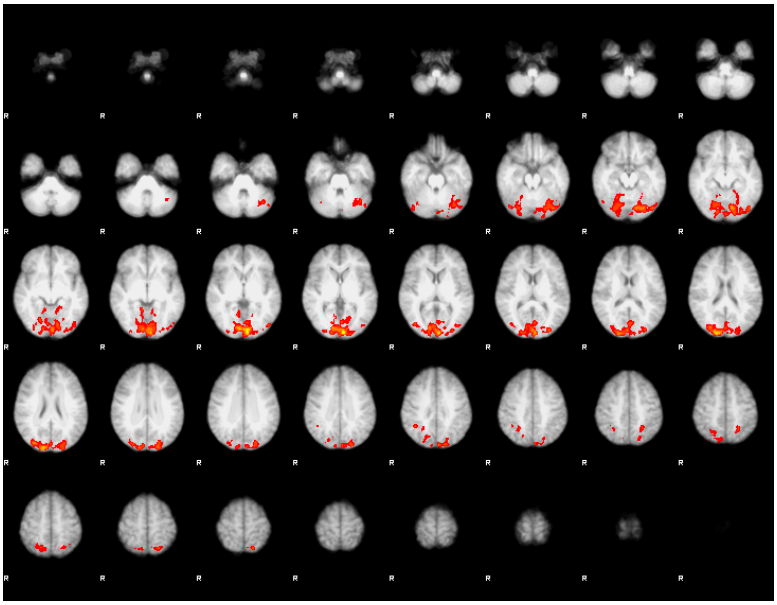

Figure 49. Step 2 for hard step vergence activation pre-therapy.

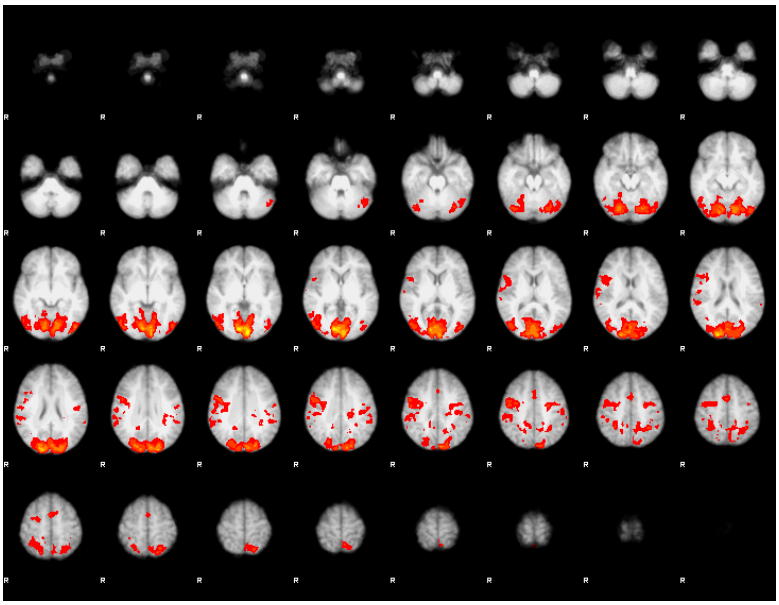

Figure 50. Step 3 for hard step vergence activation pre-therapy.

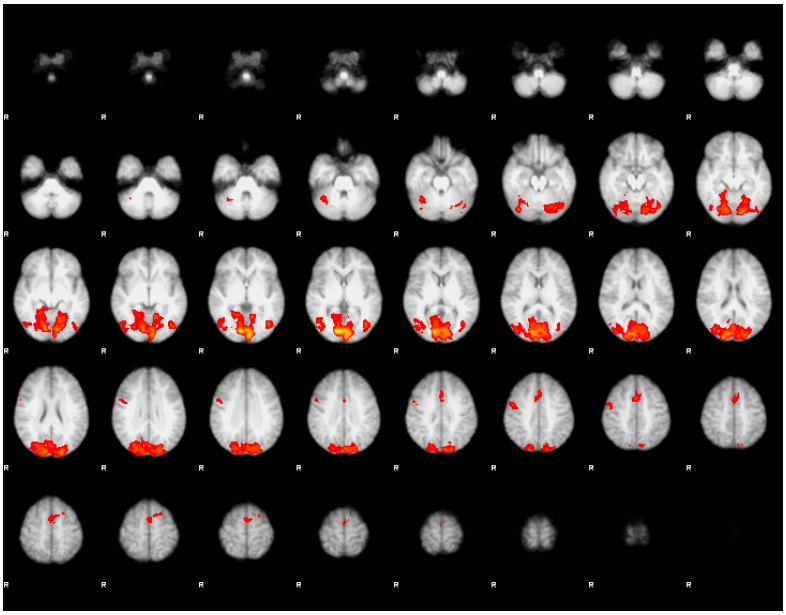

Figure 51. Step 4 for hard step vergence activation pre-therapy.

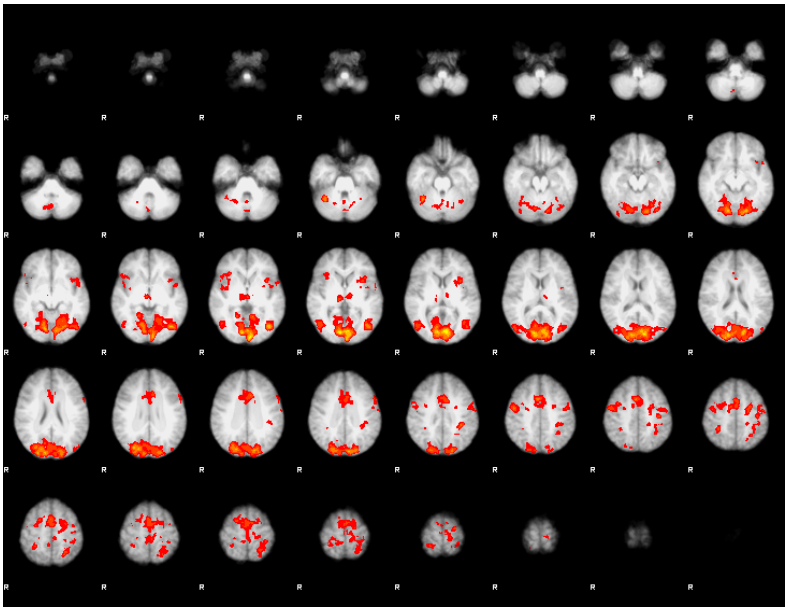

Figure 52. Step 5 for hard step vergence activation pre-therapy.

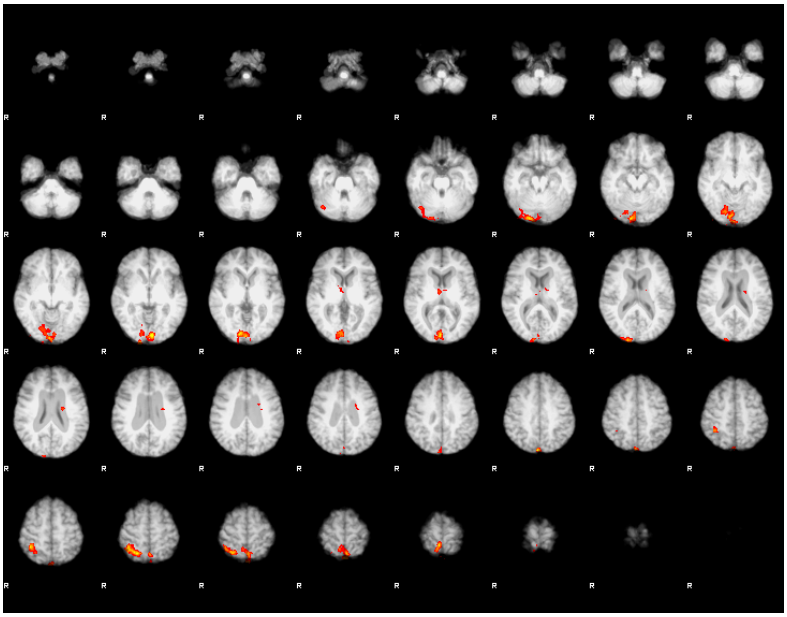

Figure 53. Step 1 for hard step vergence activation post-OBVAT.

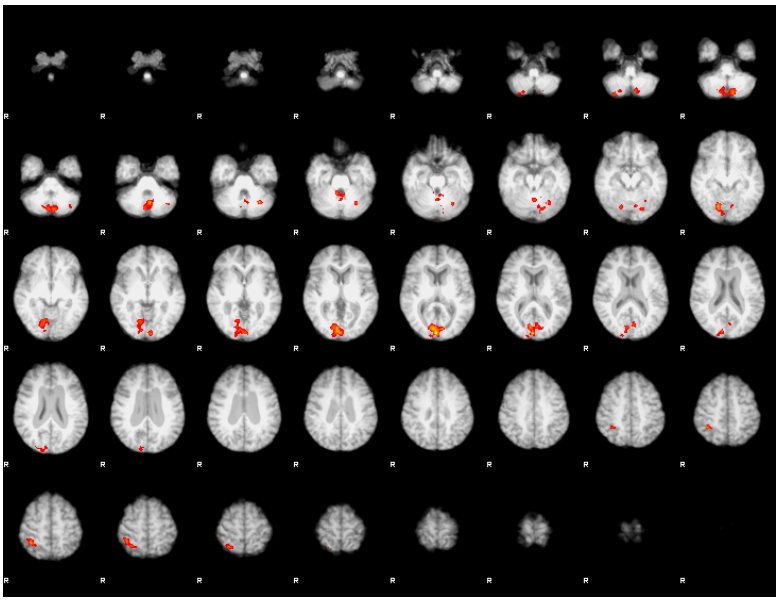

Figure 54. Step 2 for hard step vergence activation post-OBVAT.

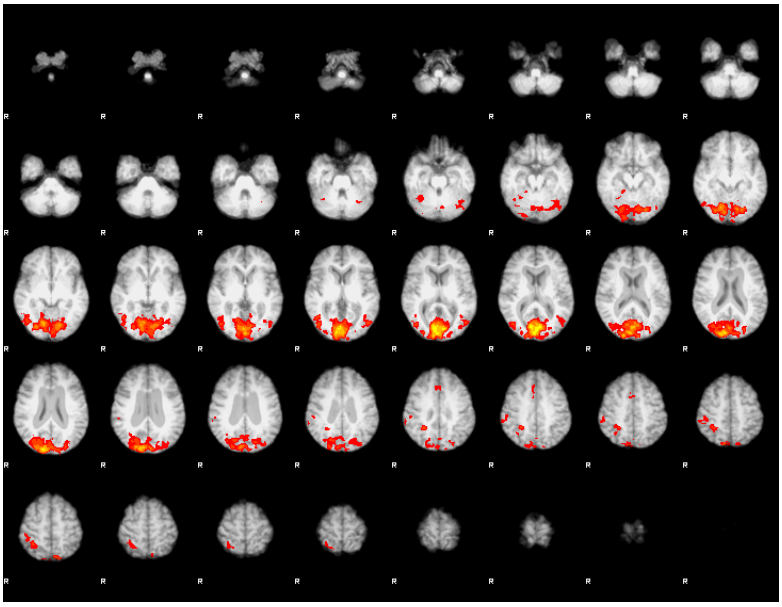

Figure 55. Step 3 for hard step vergence activation post-OBVAT.

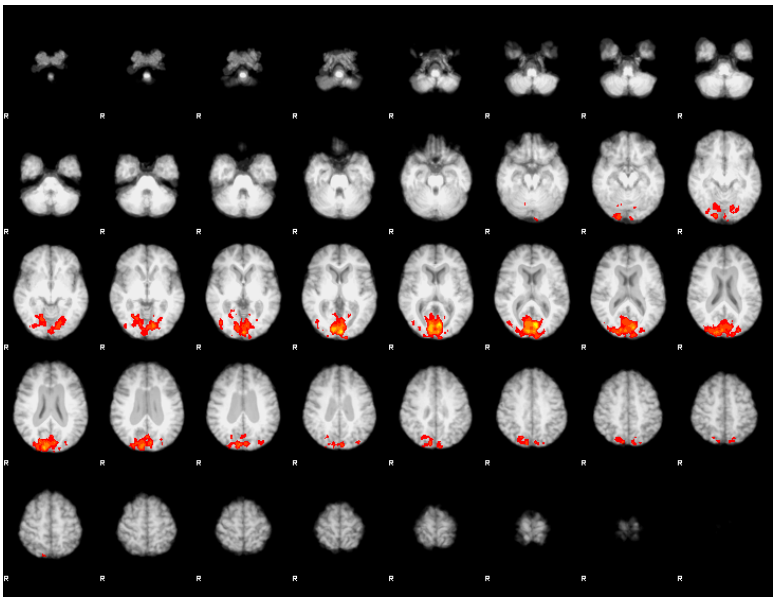

Figure 56. Step 4 for hard step vergence activation post-OBVAT.

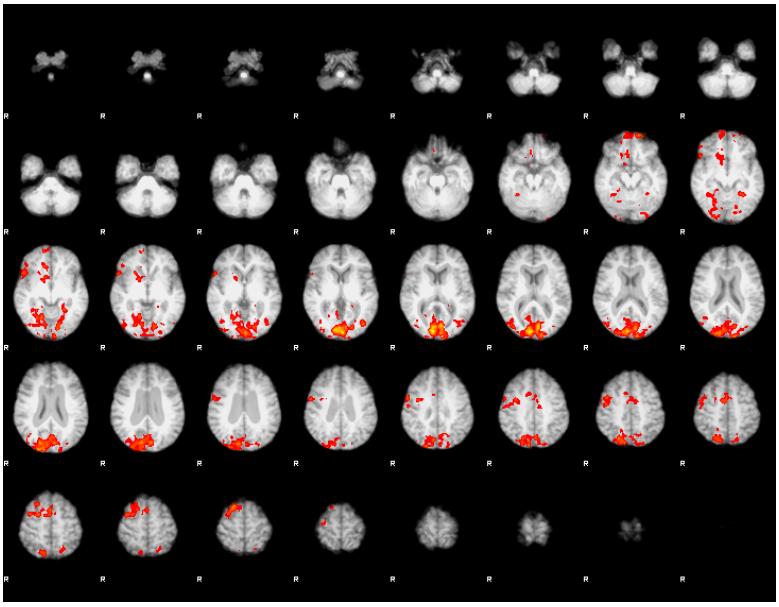

Figure 57. Step 5 for hard step vergence activation post-OBVAT.

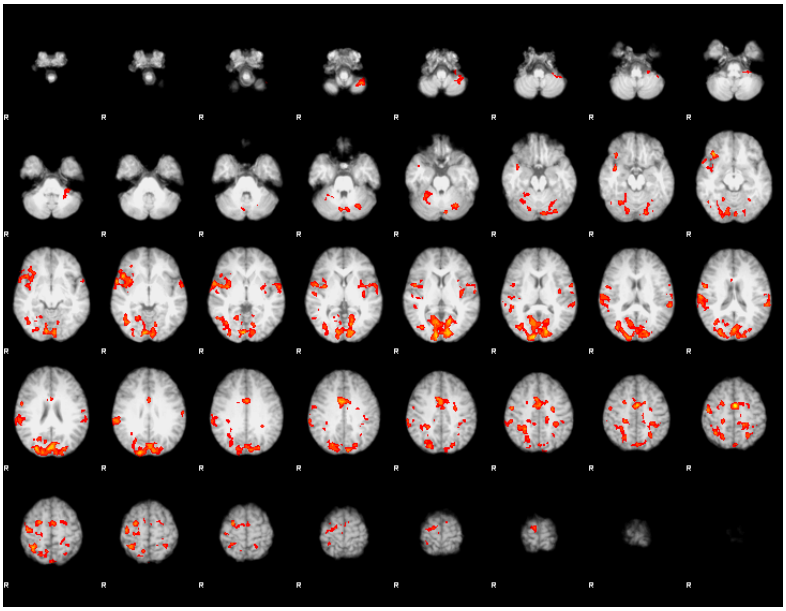

Figure 58. Step 1 for hard step vergence activation post-OBPT.

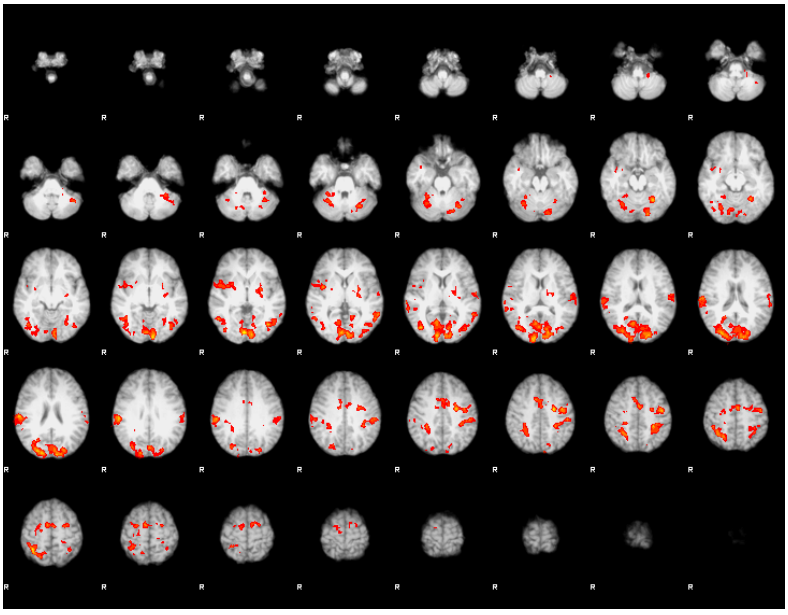

Figure 59. Step 2 for hard step vergence activation post-OBPT.

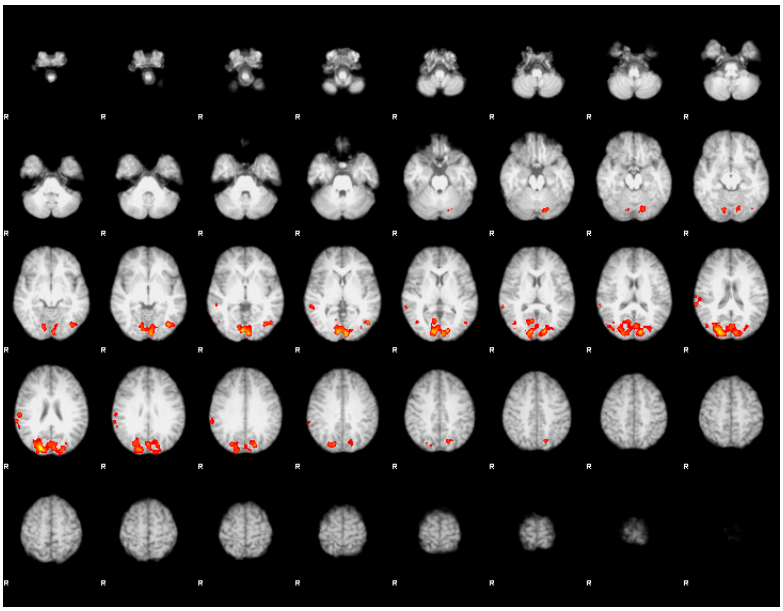

Figure 60. Step 3 for hard step vergence activation post-OBPT.

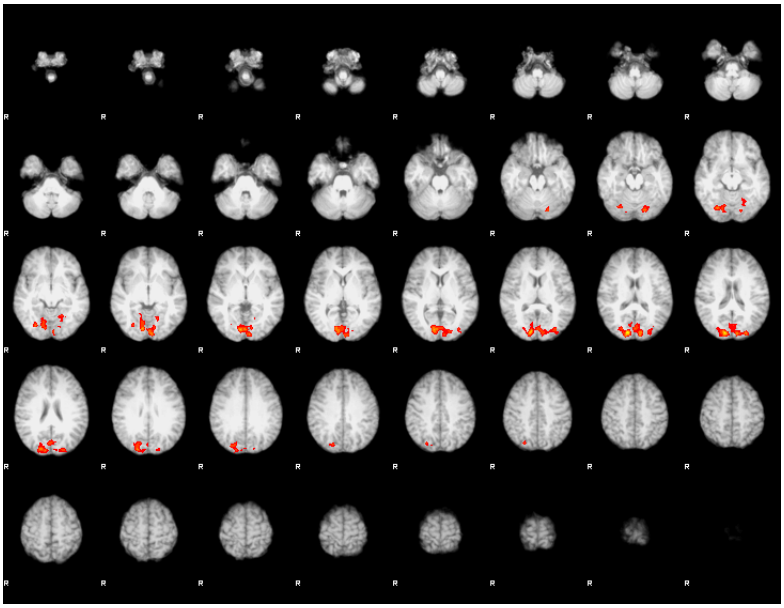

Figure 61. Step 4 for hard step vergence activation post-OBPT.

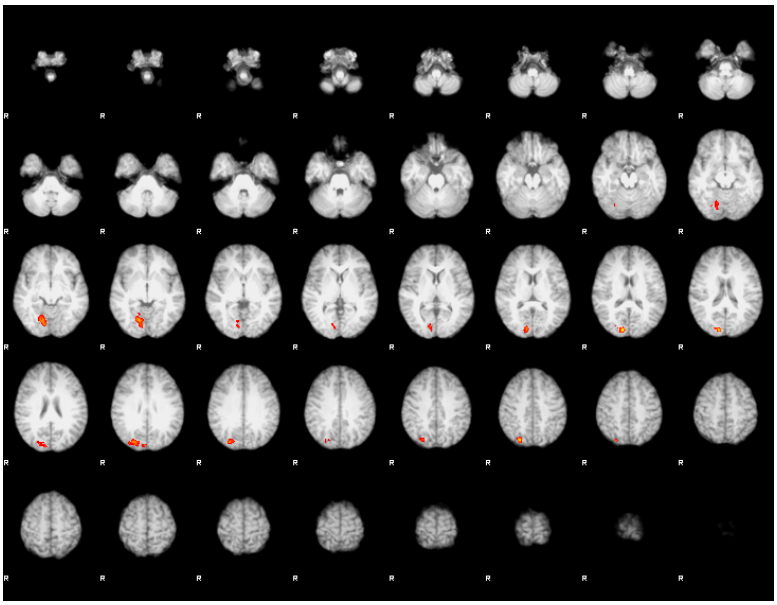

Figure 62. Step 5 for hard step vergence activation post-OBPT.

When comparing the similar vergence demand steps of the easy and hard step vergence paradigms, step 2 (6Δ) of the easy paradigm is comparable to step 1 (5Δ) of the hard paradigm. In addition, step 4 of the easy paradigm is the same vergence demand as step 2 of the hard paradigm (10Δ). Pre-therapy, there are more anterior/frontal lobe areas of activation as well as larger posterior areas seen in step 2 of the easy paradigm compared to step 1 of the hard paradigm. At step 4 of the easy paradigm, the activation moves more anterolateral compared to step 2 of the hard vergence paradigm which showed more of a concentration in the posterior aspect of the brain. The same general pattern can be seen post-OBVAT for the smaller vergence demand steps, but the 10Δ demand steps between the easy and hard vergence paradigms look more similar. Post-OBPT, the smaller vergence demand steps between the two paradigms look similar,

however, there was no activation seen in step 4 of the easy paradigm, and there scattered areas of anterior and posterior activation seen in step 2 of the hard paradigm.

Looking at the same ROIs examined in the easy step vergence paradigm, the same pattern post-OBVAT can be seen when compared pre-therapy, z-score decreases were noticed across all ROIs, except in the right inferior parietal area. When compared to the post-OBPT condition, post-OBVAT had lower z-scores except in the right DLPFC, right precuneus, right inferior parietal, and CV. Post-OBPT, new areas of deactivation were noted in the FEF. Table 12 contains all of the z-scores for the ROIs for the hard step vergence paradigm.

	X	Y	Z	PRE-THERAPY Z-SCORE	POST-OBVAT Z-SCORE	POST-OBPT Z-SCORE
DORSOLATERAL PREFRONTAL CORTEX (DLPFC)	Cerebrum, frontal lobe, precentral gyrus					
RIGHT	17	67	54	5.18769	4.20006	2.59175
LEFT	72	67	54	4.89546	3.21681	3.3211
FRONTAL EYE FIELD (FEF)	Cerebrum, frontal lobe, superior frontal gyrus, BA 8					
RIGHT	33	79	57	NS	NS	-2.85742
LEFT	56	79	57	NS	NS	-3.70853
MEDIAL FRONTAL GYRUS (SEF)	Cerebrum, frontal lobe, BA 6					
RIGHT	43	60	65	6.59677	NS	3.34446
LEFT	47	60	65	4.51648	NS	2.86976
PRECUNEUS	Cerebrum, parietal lobe					
RIGHT	33	29	54	4.57757	3.81847	3.51365
LEFT	52	29	54	3.82623	2.40053	3.30435
INFERIOR PARIETAL	Cerebrum, parietal lobe, BA 40					
RIGHT	26	39	60	3.51931	3.77532	3.24706
LEFT	61	39	60	4.90638	NS	4.0571
CEREBELLAR VERMIS	45	25	21	5.7212	2.43021	NS

Table 12. ROIs for hard step vergence paradigm. Negative numbers indicate deactivation. NS = Non-significant activation (> -2.3 and < 2.3).

Chapter 4: Discussion

This study set out to examine the effects of treatment with vision therapy on adult subjects with symptomatic CI. While there is little work in this specific field, the results offer additional insight into changes in the brain after a course of vision therapy.

Compared to previous literature on fMRI changes with therapy,[56-58] this study used a two-tailed analysis of brain activity, highlighting significant areas of brain activation and deactivation before and after real (OBVAT) and placebo therapy. In addition, a wide range of vergence demands were presented during fMRI. Comparing the two paradigms, the hard step vergence paradigm seemed to show larger areas of activation and deactivation compared to the easy step vergence paradigm across all conditions. Across all conditions and paradigms, the highest levels of activation were seen in the occipital lobe. The areas of highest deactivation varied between the conditions and paradigms. For the easy step vergence paradigm, the highest deactivation areas were noted within areas of the frontal lobe pre-therapy and post-OBPT. There were no areas of deactivation noted post-OBVAT.

During the hard step vergence paradigm, the highest levels of deactivation noted post-OBVAT were in the frontal lobe, much like what was seen pre-therapy and post-OBPT in the easy step vergence paradigm. In contrast, the highest levels of deactivation pre-therapy and post-OBPT were noted in the occipital lobe, near BA 17. One possible

explanation could be the fact that the brain was trying to actively suppress the double image of the stimulus so only one image could be attended to by the brain.

Many brain areas known to be used during attention were noted to be active throughout the different paradigms. These attentional areas are found in multiple locations throughout the dorsal frontal, lateral prefrontal, and parietal cortexes, including the following: medial intraparietal sulcus, precuneus, superior parietal lobule, SEF, FEF, DLPFC, inferior frontal sulcus, temporal parietal junction, inferior parietal lobule, and middle frontal gyrus.[61] It can be pointed out that many of the attentional brain areas have been shown to have a connection with eye movements, as many of these areas were the ROIs proposed by Alvarez in her studies. Many of these areas are connected to each other as the dorsal frontoparietal network (DFPN) and the ventral frontoparietal network (VFPN). According to a review by Corbetta and Shulman, the DFPN is shown to be bilateral and connects the superior parietal lobes, intraparietal sulcus, and frontal lobes. This network is known for attention that is top-down, meaning a person must think about attending to a stimulus before an action is taken. The VFPN is shown to be only in the right hemisphere and connects the temporal parietal junction, inferior parietal lobule, and ventral frontal lobe. This network is known for attention that is bottom-up, meaning that the stimulus itself draws the attention of a person and then causes an action.

When looking at the changes post-OBVAT, it can be seen that most of the frontal and parietal lobe activation areas that were present pre-therapy disappear more on the left side of the brain compared to the right side of the brain. This is an important finding in that pre-therapy, the brain attention areas were activated on both sides of the brain. Post-

OBVAT, only those attention areas on the right side of the brain were activated. It can be inferred that activation of these attentional areas is required for untreated CIs to complete vergence tasks, such as reading, using a computer, etc. These areas are more part of the DFPN and are top-down driven, suggesting the brain has to think about what it wants to do before making the action. This suggests a possible explanation for some of the symptoms reported by symptomatic CIs before therapy such as loss of concentration when doing close work or having trouble remembering what one has read. The extra areas of activation could make it more difficult to perform near tasks due to the amount of planning the brain has to make. Post-OBVAT, it can be seen that only the right side activation areas are seen, part of the VFPN. This shows that the attention is more bottom-up/stimulus driven. Instead of having to plan the near task, a post-therapy CI views any reading task as more reflexive and no extra attention is needed.

While looking at the ROIs brought forth by Alvarez and her group, there seemed to be areas of overlap between this study's findings and those proposed by Alvarez. For the most part, levels of activation decreased post-therapy, typically more in post-OBVAT as compared to post-OBPT. In the hard step vergence paradigm, the reduction varies and does not follow the same pattern as the easy step vergence paradigm, probably due to the difficulty of the stimulus itself. One of the differences seen between this study and those conducted by Alvarez, was in regard to the FEF. For the easy step vergence paradigm, no significant activation was seen across any condition, but there was deactivation noted pre-therapy near BA 8, which is known to be part of the FEF.[62] For the hard step

vergence paradigm, there was no activation in the FEF pre-therapy and post-OBVAT, but there was significant deactivation noted post-OBPT.

When comparing those subjects that went through the active OBVAT to the OBPT, it can be seen that more of a change in brain activity was seen post-OBVAT. When looking at the easy step vergence paradigm, the cluster of activation appeared to move more posterior than when compared to the pre-therapy condition activation maps (see Figure 11). Many of the activation areas noted in the frontal lobe pre-therapy were greatly reduced or gone post-therapy. When comparing pre-therapy and post-OBPT, you can see that although the spatial area of activation is decreased, the overall pattern of activation is still there (see Figure 14). The difference in activation areas seen between post-OBVAT and post-OBPT proves that the changes seen in the brain are not just due to test-retest changes. For the hard step vergence paradigm, the same pattern can be seen pre-therapy versus post-OBVAT and post-OBPT (see Figures 41 and 45), however, more deactivation was noted post-OBPT than any other condition.

One of the conclusions made by Alvarez in her work was that after therapy, the spatial extent and z-scores increase after a course of therapy.[57] The data from the current study suggests the opposite. Compared to our pre-therapy data, the post-OBVAT condition showed a smaller spatial range and decrease in z-sores. The activation areas seemed to be more compact and concentrated in a specific area. This finding supports a prior report of a decreased area of activation post-training in a study that compared golf novices before and after physical training.[63] The study participants completed fMRIs while performing a kinetic motor imagery task of completing a golf swing. The authors

found that the extent of the brain area needed to complete the visual golf swing greatly decreased in the experimental group that received physical training as compared to the control group that did not receive any training. In this study, the OBVAT group that received the real vergence/accommodative training showed a decrease in spatial area and a decrease in activation needed to complete the visual task in the fMRI.

The results from the current study cannot be directly compared to those of prior studies[56-58] due to methodological differences, such as the stimulus design, the range of vergence demand, and the use of different therapy. For example, the stimulus used by Alvarez could be expected to result in changes in the fusional convergence system as well as the accommodative and proximal convergence systems due to the position of the PVC pipes and LED lights in space with the 4^{o} vergence target being closer to the subject's head than the 2^{o} vergence target. On the other hand, the stimulus used in the current study required changes in fusional convergence in order to achieve fusion, while holding proximal and accommodative convergence steady (the stimulus was maintained at the same distance from the subject at all times).

It can be seen that only 50% of those in the OBVAT group were classified as "successful" although 75% were classified as "successful" or "improved". It should be noted that the one subject who was classified a "non-responder" reported a symptom level near asymptomatic levels at the week 8 progress check and was ill the week leading up to the outcome visit. None of the subjects in the placebo group were "successful", but both subjects were classified as "improved". Due to the small sample size, it is not possible to compare these values to those in prior studies.

One limitation of the current study is the limited number of subjects (n = 7), although the sample size is comparable to that of similar fMRI studies.[56-58]

The current results make a significant contribution to the paucity of literature in this area. Future studies should investigate the differences between NBV and CI subjects to look for any major differences between those with CI and those with NBV. In addition, the post-OBVAT condition should then be compared to the NBV group to see if the "successful" subjects mimic what a NBV fMRI analysis looks like.

Appendix A: Sample CISS

		Never	Infrequently (Not Very Often)	Sometimes	Fairly Often	Always
1	Do your eyes ever feel tired when reading or doing close work?					
2	Do your eyes feel uncomfortable when reading or doing close work?					
3	Do you have headaches when reading or doing close work?					
4	Do you feel sleepy when reading or doing close work?					
5	Do you lose concentration when reading or doing close work?					
6	Do you have trouble remembering what you have read?					
7	Do you have double vision when reading or doing close work?					
8	Do you see the words move, jump, swim, or appear to float on the page when reading or doing close work?					
9	Do you feel like you read slowly?					
10	Do your eyes ever hurt when reading or doing close work?					
11	Do your eyes ever feel sore when reading or doing close work?					
12	Do you feel a "pulling" feeling around your eyes when reading or doing close work?					
13	Do you notice the words blurring or coming in and out of focus when reading or doing close work?					
14	Do you lose your place while reading or doing close work?					
15	Do you have to re-read the same line of words when reading?					
	Column Total					
		x 0	x 1	x 2	x 3	x 4
	Total					

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