NCT04230486
IRB Approved Date: 7/20/20
Study Title: Visual-Auditory Stimulus Training to Restore Visual Functions in Homonymous Hemianopia Patients

Principal Investigator, Co-investigator(s): Huai Jiang, PhD

Sponsor or funding source: Wake Forest University of Health Sciences

Background, Rationale and Context

Hemianopia (also known as hemianopsia or haemianopia) is characterized by blindness in one hemifield and is a common consequence of stroke or trauma-induced injury to visual cortex. Hemianopia has profound effects on activities of daily living, robbing those affected of their independence [1, 2, 3, 4]. Current commercial rehabilitation techniques used to treat hemianopia patients are based on learning oculomotor compensation strategies and only focus on helping patients manage the condition, rather than recovering the lost visual field [5, 6, 7]. There is little disagreement that more effective rehabilitative strategies are needed [3. 6-14].

More recently, the topic of cross-modal induced plasticity has attracted growing attention with respect to treating hemianopia [15-20,]. Studies of hemianopia animal models at Wake Forest School of Medicine by Dr. Huai Jiang and his colleagues have provided insight into an important mechanism of visual field recovery [21, 22]. In these studies, hemianopia cats were induced by large unilateral visual cortex ablation and then rehabilitated using auditory and visual stimuli to activate the subcortical visual pathway to restore the lost visual functions. While fixated on a central point, the cats were tasked with making repeated, food-rewarded orienting movements to a salient, concurrent auditory and visual cue delivered at a single peripheral location (45°) within the anopic hemifield [21, 22]. After 1 month of rehabilitation, all rehabilitated animals were capable of responding to visual cues at azimuths of up to 105° left to right. This powerful technique was also successful in rehabilitating anesthetized hemianopic animals [23, 24].

These studies have found: 1) Concurrent auditory-visual stimulation is essential for successful rehabilitation. 2) Using a single peripheral location (45°) within the anopic hemifield can be more effective in reinstating the entire hemifield than using multiple locations. 3) Two weeks is the minimum time needed for the rehabilitation to yield effects. 4) A rehabilitative strategy, using an asymmetric trials ratio of 9:1 (hemianopia:intact stimulus location) can shift patient attention to the "blind" side and facilitate the rehabilitation [10].

Such training reinstates the visual hemifield and basic visuomotor competencies within several weeks by facilitating the re-emergence of visual activity in the deep layers of the superior colliculus via training-induced alterations to inputs that these neurons receive from lesion-spared regions of an association cortex [21]. In hemianopia animals, rehabilitative training with auditory-visual cues induced intrinsic plasticity via the involvement of the subcortical visual pathway [21].

Currently there are several different approaches to the rehabilitation of hemianopia, however most focus on helping patients adapt to their condition, and none of these strategies are capable of restoring significant areas of the patient's visual field. There is little disagreement that more effective rehabilitative strategies are urgently needed.

This non-invasive training technique has the potential of being the first treatment capable of significantly restoring the visual field in hemianopia patients. This protocol details the initial steps needed to translate the technique from animal models to humans.

Objectives

Recent findings in animal hemianopia models have led to developments of a novel rehabilitation strategy that uses spatiotemporally coincident cross-modal (auditory-visual) cues, focused 45° in the

hemianopic field, to initiate responses to events in the 'blind' hemifield. Training the hemianopic animals with this non-invasive rehabilitation strategy dramatically reversed experimentally-induced hemianopia. Improvements in the visual field could be observed just 2 weeks after the start of daily rehabilitation training, and full recovery (animals could detect stimuli over 75° in the hemianopic field) took place after 1 month. The visual field expansion from rehabilitation persisted without further training sessions when cats were tested 12 to 21 months following the rehabilitation.

We hypothesize this rehabilitation strategy will also be successful in human subjects. The proposed project aims to translate animal hemianopia research to a noninvasive rehabilitation system for use by human visual hemianopia patients. The specific objectives of the program can be enumerated as follows:

Specific Aim 1: Determine the efficacy of an intervention using cross-modal stimulation training to restore visual function in homonymous hemianopia patients.

Specific Aim 2: Assess the long-term effects of rehabilitation through follow-up visits after the completion of rehabilitation.

Methods and Measures

Design

This study will test a rehabilitation technique for treating visual hemianopia and compare results against measures from patients pre-intervention. We will recruit all interested patients with visual hemianopia and will assess visual field, visual capabilities, quality of life, and brain images as part of our research measures.

Setting

Rehabilitation training sessions and progress tests will be performed on the Wake Forest Baptist Medical Center Campus and in subjects' homes. Since administering the Humphrey visual field test requires specific equipment, subjects will visit an optometrist's office for these tests. Subjects will perform the remaining visual tests on the Wake Forest Baptist Medical Center Campus.

Subjects selection criteria

- **Inclusion Criteria**
    - Adult volunteers diagnosed with homonymous visual hemianopia / hemianopsia (ages 18-99)
    - MRI or CT scan demonstrating lesion in the occipital lobe of the brain and/or affecting white matter tracts that provide visual input to the occipital lobe of the brain
    - Brain injury due to ischemic or hemorrhagic causes that occurs after age 18 and at least 6 months prior to screening visit
    - Demonstration of good fixation on visual training task

- **Exclusion Criteria**
    - Volunteers who are unable to complete the study tasks or understand instructions
    - Subjects that are not able to provide written consent or verbal assent
    - Subjects who are not available to complete all rehabilitation sessions
    - Physical, neurological or mental disability that would interfere with study intervention
    - Concurrent participation in "vision therapy" other than standard occupational or physical therapy

- **Sample Size**

The goal of this project is to obtain proof the rehabilitation technique has the potential to be successfully translated to humans. To achieve this goal, we will recruit a sample size of 10 hemianopia subjects in this study in hopes of having at least 5 participants complete all study sessions. This study is exploratory; the findings from this study will be used to design future studies. The observed treatment response pattern will be reported, and those data used for informed estimates of incidence for future research. Prior animal model studies demonstrated a high success rate in the rehabilitation strategy, with 100% of 11 hemianopic cats regaining visual field. Assuming that 80% of subjects will have a successful result, using n=5 subjects will allow for estimation of a 95% confidence interval with width 0.35 units either side of the estimate [22].

Interventions and Interactions

Interventions

Cross-Modal Visual Auditory Rehabilitation - Cross-modal visual auditory rehabilitation is based on the rehabilitation paradigm derived from previous animal model studies. The rehabilitation will be carried out using a virtual reality rehabilitation (VR) system. The rehabilitation system uses a customized commercial wireless VR headset, the Samsung Gear VR, to run custom-made rehabilitation software.

The cross-modal rehabilitation software provides a gray colored, neutral environment for patients, with minimal distractions from rehabilitation. Subjects will be asked to fixate on a colored fixation spot in the center of the visual field for 1 second before being randomly presented with either a visual stimulus in the normal intact visual field or a spatiotemporally coincident audio-visual stimulus in the hemianopic side. Auditory-visual stimulus and visual stimulus will be presented at a ratio of 9:1 respectively. The design of the fixed, predictable timing and 9:1 ratio will help subjects shift their attention to the blind field.

Auditory stimulus consists of a brief burst of white noise, lasting approximately 100 ms. Visual stimulus is a white colored orb positioned against the dark, neutral background and will be displayed for 1-2 seconds. The longer duration of the visual stimulus will serve to provide stimulus location feedback for patients. Patients will be instructed to orient their eyes and head toward stimuli in the hemianopic field and to push a button on a controller upon detecting stimuli. This part of the task will serve to boost motivation and maintain attention during training. The software will also record these responses and reaction times, based on the button presses, and store this data for later review. The next trial will begin 3-4 seconds after the visual or auditory-visual stimulus disappears and when the patient re-fixates on the fixation point.

Cross-modal visual auditory rehabilitation consists of a total of 200 trials / day (about 30 min) over 1 month. Given the results from animal model studies, we expect progress to be observable after 2-3 weeks of cross-modal rehabilitation, and completion of rehabilitation 1 month after the start of cross-modal training.

While we expect most patients will perform rehabilitation using the virtual reality rehabilitation system, patients may also complete rehabilitation with a free-field frame device if they are not comfortable with using a VR headset. The free-field frame device uses a semi-circular frame to hold LED lights (visual stimulus) and speakers (auditory stimulus) in front of the patient. These lights and speakers can be used to deliver the same cross-modal visual auditory rehabilitation paradigm. The device is also used to perform peripheral visual field tests, and is described in more detail below in *peripheral visual field test*.

Tests

Humphrey Visual Field (HVF) Test - The HVF test is a common test given to map the visual field. During the HVF test, light is projected into a white bowl with a standardized background light intensity to form a circular stimulus, around 30 cm away from the patient's eye. The overall field mapping technique used is a form of static perimetry, where a stimulus appears in various areas of the field of vision. The patient indicates when they can see the stimulus and the perimetrist then records the point where the stimulus was seen. These datapoints are used to determine the patient's visual field.

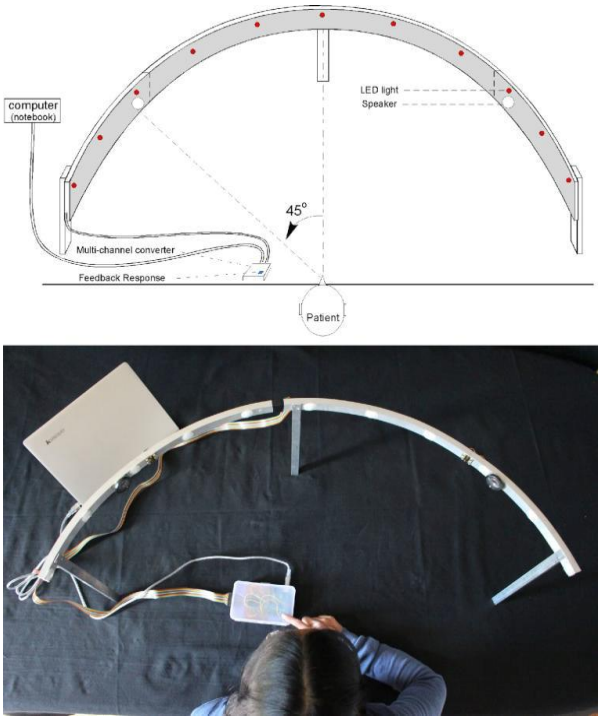

Figure 1: Free-field frame device

Peripheral Visual Field Test - Since the Humphrey visual field test only measures up to 30° in the periphery, an additional peripheral visual field test will be administered using a semi-circular frame device (fig. 1) set 50 cm in front of the subject with LED lights acting as visual stimulus, located at azimuths of 15°, 30°, 45°, 60°, and 75°, as well as a center fixation light. Lights will be presented at a random time with a fixation period between each trial and locations selected randomly. Subjects will be asked to fixate on the center fixation light while lights are presented at random locations at random times (0-1.5 seconds). Upon detecting a light, subjects will press a button. Subject responses will be used to determine how far in the periphery, up to 75°, a subject can see. The test will present a total of 5 trials at each location in both the intact and hemianopic side, as well as 5 trials with no stimuli.

Sound Localization and Visual Fixation Test - This test uses the free-field frame device to position visual and auditory stimuli, in the form of LED lights and speakers, at different angles of the patient. The patient is asked to maintain visual fixation on a lit LED light straight ahead during the test. Speakers will play a brief burst of white noise from a random location 15° or 45° on either the left or right side. The subject will be asked to identify where the sound is originating from either verbally or using a button response pad. During this test, subjects' eyes may be videotaped or photographed. These recordings or photos will be reviewed by a member of the study team to confirm the subject is able to properly maintain visual fixation.

Virtual Reality (Visual Field) Progress Test - At the end of each rehabilitation session, subjects will perform a brief 5-minute test using the VR system to track rehabilitation progress. The test consists of 30 trials with visual stimulus presented either 15°, 30°, 45° in either the hemianopia field or the intact field at random time intervals.

Grating Acuity Test - Visual acuity will be tested using a standard grating test. Subjects will be presented with a 10°x10° square window filled with either a horizontal or vertical grating, located 5° from the fixation point on a computer screen in their hemianopic or intact side. Gratings will start from 0.2 cycles per degree and progress to larger sizes of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, then 5.0 cycles per degree. The test will comprise of 5 trials for each grating. Subjects will be asked to identify whether the grating is horizontal or vertical by either pushing buttons on a response pad or verbally. Responses will be recorded for each question.

Color Vision Test - The color vision test will be administered on a computer. While focused on a central fixation point, subjects will be presented with a colored 10° x 10° block located 5° in the anopic hemifield and be asked to verbally identify the color. A member of the research team will record these responses. The color in each trial will be randomly picked among the color choices of white, black, red, orange, yellow, green, blue, and violet. Each color will be displayed at least 3 times.

Shape Recognition Test - Subjects will be presented with basic shapes in their hemianopic side on a computer monitor. Shapes will be colored black and be displayed on a white background in a 10° x 10° square window located 5° in the previously hemianopic side. Subjects will be asked to fixate on a central point and verbally identify each object or express uncertainty. Verbal responses will be recorded for later analysis. During this test, subject responses may be audiotaped in order to capture their responses. This test will consist of 20 trials.

Questionnaires

The NEI VFQ-25 and VA LV VFQ-48 questionnaires are designed to assess the taker's quality of life regarding limitations due to low vision.

National Eye Institute Visual Function (NEI VFQ-25) Questionnaire - The NEI VFQ-25 is a reliable 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). It is especially useful in settings such as clinical trials, where interview length is a critical consideration to measure the influence of visual impairment on quality of life. NEI-VFQ questions patients regarding the quality of general vision, social functioning, visual dependency, near vision and color vision.

Veterans Affairs Low Vision Visual Function (VA LV VFQ-48) Questionnaire- The VA LV VFQ-48 is a self-report instrument designed to measure difficulty visually impaired persons have performing daily activities. The VA LV VFQ-48 has been used to measure low vision outcomes for individual patients and programs, and to compare treatment protocols across diverse settings.

Interactions

Interactions with subjects are outlined in the included timeline (Fig 2).

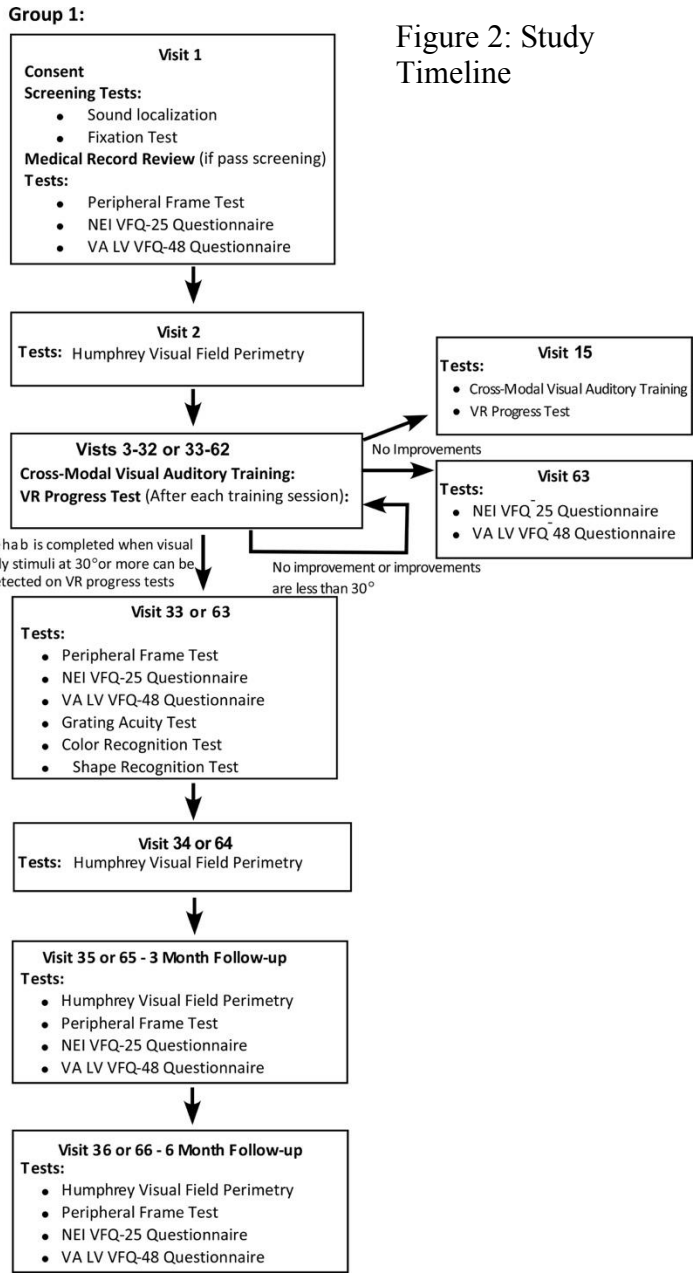

Figure 2: Study Timeline

Study Session 1: Consent, Screening, and Pre-Intervention Tests (2 hours)

Consent documents will be provided ahead of the first visit through email or mail for subjects to review ahead of time to help them make an informed decision about participating in the study. Prior to this visit, subjects will be contacted by phone or email by a study member to answer any questions they may have. Upon arrival in this initial consent and screening visit, subjects will be given time to read through the consent form so they may make an informed decision on their study participation. A study team member will then review the consent form verbally with the patient and make sure the patient understands the study. Subjects will be informed of the requirements of the study, and of the time commitment needed to perform rehabilitation before signing.

Once patients have agreed to participate in the study and have signed the consent form, patients will be asked to perform a sound localization and visual fixation test.

Sound Localization and Visual Fixation Testing: Possessing the ability to localize sound is essential in properly implementing the rehabilitation strategy, which relies on subjects to respond to auditory and visual training stimuli. As part of the screening process, subjects' ability to detect the approximate location of sound will be assessed. Subjects will be asked to fixate on a light straight ahead and be presented with sound from 15° or 45° on either the left or right side. The location of the sound will be randomly picked by a computer program. Subjects will be asked to identify the side the sound originated from and the approximate location. Study staff will log these responses on a computer. Subjects with responses accurate 90% or higher will be considered to have passed the test and be eligible for the study.

This test will be conducted using the free-field frame device (fig 1), which uses a semicircular frame to hold LED lights and 4 speakers fixed to 15° and 45° positions. Eye tracking or a camera recording of the subject's eyes may be used to ensure the subject is properly fixating on the light. The eye tracking camera may take photographs and video for the study team to later review. If a subject cannot maintain visual fixation or identify the origin of sound, the visit and study will end and they will be compensated $40 for their travel.

To verify their hemianopia condition, subjects will be asked to provide relevant medical records, which will be used to confirm diagnosis. Subjects will be instructed to bring their medical records, with proof of hemianopia diagnosis, to the screening visit. After they have passed the sound localization and visual fixation test, a study member will review these records to make sure the subject is eligible to continue the study. Since the effects of hemianopia can vary between patients due to the extent and location of brain damage, copies of relevant records may be kept to aid data analysis. These copies will be kept in a locked and secure storage location. Patients will be assigned a subject id and any identifying personal information will be redacted from these copies. If the patient is deemed ineligible during the study, any copies made of these records will be promptly destroyed.

During this visit, baseline measurements for subjects will be obtained. Subjects will undergo a peripheral visual field test and be asked to complete 2 quality of life questionnaires: the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) and the Veterans Affairs Low Vision Visual Function Questionnaire (VA LV VFQ-48). Subjects are expected to spend up to 2 hours for this visit.

(Optional) Study Session 2: Pre-Intervention Test - Humphrey Visual Field Test (1 hour)

Subjects will report to an optometrist, who will administer the Humphrey Visual Field Test, using a size V stimulus. This visit will be separate from the other pre-intervention tests due to the special equipment needed for the Humphrey Visual Field Perimetry. This visit is expected to take up to 1 hour. This visit may be omitted if subjects have a recent Humphrey Visual Field Perimetry test result and gives the study team permission to view and keep a copy of the result.

Study Sessions 3 – 32: Cross-Modal Rehabilitation Training (30 minutes each day)

Each cross-modal rehabilitation training session will take place either on the Wake Forest Baptist Medical Center Campus or in subjects' homes, if subjects find traveling to the Wake Forest campus to be too difficult to do daily. For patients who are performing rehabilitation at home, the study team will regularly call and check-in with the subject in order to make sure the patient is not experiencing any problems. The VR rehabilitation system will send data such as duration of rehabilitation and progress test results through a cellular network, in order to monitor compliance and track rehabilitation progress. The data will only be linked to a study identifier to maintain privacy. Initial rehabilitation sessions will be done at the Wake Forest Baptist Medical Center campus to ensure subjects understand how to use the rehabilitation device and are capable of performing rehabilitation at home.

In each rehabilitation session, subjects will sit down, put on a virtual reality headset with a pair of headphones, and use a button on a handheld controller to interact with the rehabilitation system. In order to make sure subjects are correctly performing rehabilitation, the headset may be outfitted an eye tracking system consisting of a camera and low intensity infrared lights to collect data on patient's eye movements.

The virtual reality headset and headphones will provide visual and auditory stimulation used in the rehabilitation training. Each rehabilitation session will consist of 200 trials. At the end of each rehabilitation session, subjects will perform a brief 2-minute VR visual field progress test with the VR system to track rehabilitation progress. The rehabilitation will be considered complete once patients can reliably detect stimuli 45° in the hemianopic field.

If patients cannot detect stimuli at 15° by the end of 30 days of rehabilitation, they will repeat the rehabilitation for one more month, in order to determine if the slow progress or lack of progress is caused by simply not spending enough time performing rehabilitation.

Study Session 63: Post Rehabilitation Tests - Subject visual field did not increase (1 hour)

If no visual field improvement (measured by virtual reality visual field progress tests) has occurred at the end of the 2nd round of rehabilitation, subjects will complete one last visit, where they will be given the

NEI VFQ-25 and VA LV VFQ-48 questionnaires to complete. This visit will occur on the Wake Forest Baptist Medical Center campus.

Study Session 33: Post Rehabilitation Tests - Subject visual field increase (1.5 hours)
If a subject shows visual field expansion in the virtual reality visual field progress test, subjects will be given a **Peripheral Visual Field Test, NEI VFQ-25** and **VA LV VFQ-48 Questionnaires** in order to measure visual field expansion and improvements in quality of life**.**

In previous animal studies, rehabilitated hemianopic animals could only detect spatial frequencies of 2 cycles/degree compared to over 5 cycles/degree in the (normal) intact animals. We hypothesize the subcortical visual pathway mediating the restored visual functions may not have the same capabilities as the visual cortex it is replacing. Therefore, recovered vision may have lower visual acuity. The different pathways involved in cross-modal rehabilitation may also affect abilities for shape recognition in the newly recovered visual field. We will explore whether this is the case with a simple **shape recognition test**, **visual acuity test**, and **color vision test** during this visit. Subjects will complete this visit on the Wake Forest Baptist Medical Center campus.

Study Session 34: Humphrey Visual Field Post-Intervention Test (1 hour)
Subjects will report to an optometrist for a **Humphrey Visual Field** perimetry test.

Study Session 35: 3 Month Post-Intervention Follow-up Tests (1 hour)
Subjects will complete a follow-up visit 3 months after the end of rehabilitation on the Wake Forest Baptist Medical Center campus. The follow-up visit will consist of a peripheral visual field test, and NEI VFQ-25 and VA LV VFQ-48 questionnaires.

Study Session 36: 6 Month Post-Intervention Follow-up Tests (1 hour)
Subjects will complete a final follow-up visit 6 months after the end of rehabilitation on the Wake Forest Baptist Medical Center campus. The follow-up visit will consist of a peripheral visual field test, and NEI VFQ-25 and VA LV VFQ-48 questionnaires.

Outcome Measure(s)

The primary outcomes for all participants will be the visual field measurements from Humphrey Visual Field and peripheral frame test, with comparisons made before (visits 1 and 2) and after treatment (visits 34 and 35 or visits 63 and 64).

Secondary outcome measures will include differences in quality of life questionnaire results from before (visit 1) and after treatment (visit 33 or 63) and changes in VR progress test results during the course of rehabilitation (visits 3-32 and 33-62 if a subject repeats rehabilitation).

Exploratory outcome measures will be collected in subjects with restored visual fields. The qualities of recovered visual field will be examined with visual acuity, color recognition, and shape recognition tests after rehabilitation (visit 33 or 63).

Analytical Plan
Results will be analyzed initially using descriptive statistics. The improvement of visual detections will be assessed by using a two-way ANOVA on the percentages of visual detections to stimuli presented in the hemianopic hemifield in the peripheral visual field tests before and after rehabilitation. Comparisons for subjects will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Other inferential statistical analysis will be conducted as appropriate.

Human Subjects Protection

Subject Recruitment Methods

Subjects with homonymous hemianopia on either the left and right side of the visual field will be recruited using resources from Wake Forest University Health Sciences' Clinical and Translational Science Institute (CTSI). Members of the PI's research team will perform recruitment. Coordination of potential participants' visit will be done by phone or in person conversation or by email.

Subjects may be recruited for the study via internet advertisements. Advertisements will include listings on researchmatch.org, and Wake Forest School of Medicine's online study recruitment website (www.wakehealth.edu/beinvolved). Potential participants may also be identified through several means including, but not limited to, physician/health professional referral and utilization of Wake Forest CTSI Data Extraction services. The study team will contact homonymous hemianopia patients who may be interested in participating in the study using Wake Forest's i2b2 database, from which the study team will pull contact information and relevant medical information of past patients. Contact information, age, gender, and the date of hemianopia diagnosis may be obtained in order to find patients who fit the inclusion criteria. All contact information will be stored on password-protected computers that are kept behind locked doors for which only the PI's research team will have access keys and passwords.

Monetary Compensation

Subjects will receive $200 compensation for their travel costs upon completing rehabilitation and test visits. To increase study schedule adherence, each subject will be compensated at a fair market value for their research follow up visits to reduce attrition rates and to ensure that there is no coercion. Subjects will be paid $50 for each completed follow-up visit.

Study-related barriers

A possible concern with the use of virtual reality headsets is motion sickness [25]. Motion sickness may occur due to conflicting sensory inputs from the visual system and vestibular system. This may occur in virtual reality games where the user is rapidly moving their head and the virtual reality hardware fails to keep up with displaying matching visuals. We have made efforts to minimize the risk of patient discomfort by keeping rehabilitation sessions short and eliminating any movements in the program that patients are not initiating. The rehabilitation consists of 20-30 minutes sessions and the device has been previously tried by a hemianopia patient, who gave positive feedback regarding it's comfort and ease of use. We have also made sure the virtual reality system we are using contains more than enough processing power to run the rehabilitation software. However, in case subjects are unable to perform rehabilitation in the virtual reality environment provided by the VR headset, subjects can also complete rehabilitation using the free-field frame device mentioned earlier, used to administer the peripheral frame test. While less portable, the device is capable of delivering the same rehabilitation treatment using led lights and speakers.

Participants may be discouraged by the large time commitment required for the study. However, when compared to current available clinical treatments, the time commitment required for the cross-modal rehabilitation study is less time intensive. Current treatments, such as visual restoration therapy, require time commitments of around 30 minutes of twice daily therapy for 6 or more months and may not offer much improvement in visual field expansion [13, 15, 16]. The study is designed with the assumption that subjects will be motivated to continue rehabilitation by the potential benefits, though subjects will also be compensated for their travel.

Participants may find daily travel to Wake Forest campus difficult. To reduce barriers from travel, subjects may perform rehabilitation in their homes to minimize the strain and time commitment required

from travel. Patients who perform any rehabilitation session at home will be provided with a phone number on which a member of the research team could be contacted during working hours if they need any advice or if the equipment fails. If needed, a study team member will also be available to visit patients' homes to help set-up the rehabilitation system and troubleshoot any issues.

To encourage continued participation, subjects will also be allowed to miss up to 3 consecutive rehabilitation sessions without affecting the course of rehabilitation in the first 2 weeks. If subjects do miss over 3 consecutive sessions, the 30 days of rehabilitation will be restarted. The days since the start of rehabilitation will be reset to 0 once rehabilitation restarts, and the event will be noted. This will be explained to subjects before the start of rehabilitation. Subjects will be allowed the chance to restart the rehabilitation twice before being excluded for noncompliance. If subjects cannot do rehabilitation treatments for more than 5 consecutive days and cannot be contacted, they will be withdrawn from the study and considered lost to follow-up.

Informed Consent

Signed informed consent will be obtained from each subject prior to the start of any interventions. The consent form will be written in plain language so that individuals will be able to understand the information in the consent form. In addition to providing individuals with a consent form, members of the research team will verbally outline each aspect of the consent form with subjects to make sure each subject understands the study requirements, purpose, and potential risks and benefits. If the subject has any questions, they will be referred to the investigator for answers. Consent will be obtained within the Wake Forest Baptist Medical Center by members of the study team.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study. Paper documents will be shredded, electronic documents will be securely deleted using software that will delete and overwrite sensitive disk space), consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

References

1. Chen CS, Lee AW, Clarke G, Hayes A, George S, Vincent R, Thompson A, Centrella L, Johnson K, Daly A, Crotty M (2009) Vision-related quality of life in patients with complete homonymous hemianopia post stroke. *Top Stroke Rehabil* 16:445-453.
2. Clarke G (2005) Incidence of neurological vision impairment in patients who suffer from an acquired brain injury. *Int Congress Series* 1282:365-369.
3. Goodwin D (2014) Homonymous hemianopia: challenges and solutions. ClinOphthalmol. 8: 1919–1927.
4. PambakianAL, Kennard C (1997) Can visual function be restored in patients with homonymous hemianopia? Br J Ophthanlmol 81:324-8.
5. Zihl J Rehabilitation of visual disorders after brain injury. U.K. Psychological Press 2000.
6. Schofield TM, Leff AP (2009) Rehabilitation of hemianopia. *Curr Opin Neurol* 22:36-40.
7. Peli E. Field expansion for homonymous hemianopia by optically induced peripheral exotropia. Optom Vis Sci 2000; 77:453–464.
8. http://www.hemianopia.org/index_files/Estimatedcosts.htm
9. Roth T, Sokolov AN, Messias A, Roth P, Weller M, Trauzettel-Klosinski S (2009) Comparing explorative saccade and flicker training in hemianopia. Neurology vol. 72 (4): 324-331.
10. Mueller I, Mast H, Sabel BA. Recovery of visual field defects: a large clinical observational study using vision restoration therapy. Restor Neurol Neurosci 2007; 25:563–572.
11. Horton JC (2005) Disappointing results from Nova Vision's visual restoration therapy. Br J Ophthalmol. 89(1): 1–2.
12. Reinhard J, Schreiber A, Schiefer U, Kasten E, Sabel BA, Kenkel S, et al. (2005). Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. Br. J. Ophthalmol. 89, 30–35.
13. Glisson, C. C. (2006). Capturing the benefit of vision restoration therapy. Curr. Opin. Ophthalmol. 17, 504–508.
14. Kasten E, Bunzenthal U, and Sabel BA (2006). Visual field recovery after vision restoration therapy (VRT) is independent of eye movements: an eye tracker study. Behav. Brain Res. 175, 18–26.
15. Bolognini N, Rasi F, Coccia M, Ladavas E (2005) Visual search improvement in hemianopic patients after audio-visual stimulation. *Brain* 128:2830-2842.
16. Passamonti C, Frissen I, Làdavas E (2009) Visual recalibration of auditory spatial perception: two separate neural circuits for perceptual learning. Eur J Neurosci 30(6):1141-50.
17. Bolognini N, Leo F, Passamonti C, Stein BE, Ladavas E (2007) Multisensory-mediated auditory localization. *Perception* 36:1477-1485
18. Leo F, Bolognini N, Passamonti C, Stein BE, Ladavas E (2008) Cross-modal localization in hemianopia: new insights on multisensory integration. *Brain* 131:855-865.
19. Bertini C, Grasso PA, Làdavas E. The role of the retino-colliculo-extrastriate pathway in visual awareness and visual field recovery. Neuropsychologia. 2016 Sep;90:72-9.
20. Grasso PA, Làdavas E, Bertini C (2016) Compensatory recovery after multisensory stimulation in hemianopic patients: Behavioral and neurophysiological components. Front. Syst. N.eurosci., 24 May 2016.
21. Jiang H, Stein BE, McHaffie JG (2015) Multisensory training reverses midbrain lesion-induced changes and ameliorates haemianopia. Nature Communications 6: 7263
22. Dakos, AS, Wakler, EM, Jiang, H, Stein, BE, and Rowland, BA. Interhemispheric visual competition after multisensory reversal of hemianopia. European J neurosci 20 August 2019. PMID:31430406.
23. Jiang H, Rowland BA, Stein BE (2017) Crossmodal exposure during anesthesia reverses lesion induced hemianopia. Soc. Neurosci. Abst. 43:775.13, 2017.
24. Jiang H, Rowland BA, Stein, BE (2018) Ameliorating hemianopia by cross-modal training. Soc. Neurosci. Abst. 44: 2018.

25. Brooks JO, Goodenough RR, Crisler MC, Klein ND, Alley RL, Koon BL, Logan WCJr.c, Ogleb JH, Tyrrella RA, Wills RF (2010). "Simulator sickness during driving simulation studies". Accident Analysis & Prevention 42: 788–769.

Appendix

1. Copy of the National Eye Institute Visual Function (NEI VFQ-25) Questionnaire
2. Copy of the Veterans Affairs Low Vision Visual Function (VA LV VFQ-48) Questionnaire
3. Consent form
4. Advertisement text