Non-Invasive Multisensory Rehabilitation of Hemianopia

NCT04963075

IRB00074687

07.15.2021

Protocol version 1.0

Study Title: Non-Invasive Multisensory Rehabilitation of Hemianopia

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Sponsor or funding source: Neuroscience Clinical Trial and Innovation Center (NCTIC) -- Internal

Background, Rationale and Context

Stroke and traumatic injury to visual cortex on one side of the brain frequently produce a profound and permanent blindness in contralesional space (hemianopia), a debilitating condition that causes enormous suffering for patients and their families (Zhang et al., 2006; Goodwin, 2014). The totality of the blindness reflects not just the direct loss of the affected areas, but damage that extends well beyond the anatomical bounds of the lesion, including the superior colliculus (SC) and related visually-dominant structures (McIntosh, 1994; McIntosh et al., 1996; Jiang et al., 2009; Jay and Sparks, 1987a, 1987b; Munoz and Wurtz, 1995a, 1995b; Groh and Sparks, 1996a, 1996b; Harrington and Peck, 1998; Lomber et al., 2001; Burnett et al., 2004, 2007). In a recently-developed animal (cat) model of hemianopia, we have shown that these structures can be re-activated by a noninvasive multisensory training procedure that restores not only visual detection capabilities, but rudimentary pattern discrimination and robustly competitive visual processing (Jiang et al., 2009, 2015; Dakos et al., 2019, 2020; Stein and Rowland, 2020). We have now narrowed the list of mechanisms responsible for this remarkable recovery and identified operational constraints on its success. It is time to make the translational leap to human patients.

The current proposal is to generate "proof of concept" evidence that hemianopia can be successfully rehabilitated in humans when this multisensory rehabilitation paradigm is used, paving the way for clinical trials in which this simple, non-invasive training paradigm can be developed for therapeutic use to treat blindness resulting from cortical damage. Unilaterally blind participants will participate in weekly training sessions in which they are exposed to high-density spatiotemporally congruent and consistent visual-auditory stimulation. They will be tested on a battery of visual tasks probing different levels of function in different environments. These include low-level visual tasks believed to be within the capabilities of subcortical visual circuits in the intact brain and thus have a high probability of recovering (e.g., detection and localization), higher-level visual tasks commonly believed to be the domain of cortex but which may recover (e.g., pattern and shape recognition), and measures of confidence in visually-guided decisions. The "proof of concept" evidence obtained here will provide essential support for NIH investment as well as direct, large-scale clinical trials. The latter would introduce this promising rehabilitation paradigm to a large and diverse patient population that would include a wide enough variety of lesions and individual characteristics to determine how these factors influence the recoverability of specific visual abilities and confidence in visually-guided decision-making.

Objectives

The over-arching objective is to evaluate the functional recovery of vision in hemianopic patients engaged with a multisensory training paradigm. Unilaterally blind participants will participate in weekly training sessions in which they are exposed to high-density spatiotemporally congruent and consistent visual-auditory stimulation. They will be tested on a battery of visual tasks probing different levels of function in different environments in a longitudinal study to track recovery.

Methods and Measures

Design. A group of 6 hemianopic participants will be pre-screened for suitability and baseline (pre-training) performance will be acquired on the battery of visual tasks (see below) and be administered the low-vision visual functioning questionnaire (LV-VFQ-48) to assess quality of life, a dilated ophthalmic exam including Optical Coherence Tomography of the macula/RNFL, a kinetic visual field test with size V, and a 30-2 humphrey visual field with Size V. If the participant has a recent 30-2 exam on file, this may be used instead of collecting a new exam. Participants will receive a second kinetic visual field test and a 30-2 visual field testat the end of the study to measure any changes according to the clinical standard.

They will participate in weekly sessions (1.5-2 hrs) for the next three months. This purposely extends well beyond the window of expected recovery. In initial ("training") sessions, subjects will be exposed (and respond) to spatiotemporally congruent pairs of visual-auditory stimuli presented within their blinded field, with occasional probes of unisensory visual stimuli on both sides of space. Once recovery of visual responsiveness in the contralesional field is observed, sessions will alternate between "training/testing" and "testing only" sessions in which performance on the visual battery will be re-assessed. Because this is a pilot study, the testing battery is extensive. However, the principal hypotheses and predictions are qualitative: subjects will either be able to perform a visual task at some level or not at all.

A high-speed digital video camera mounted behind the participant will record overt movements for later analysis using manual or automated scoring. The subject's face is not included on the video, however, the video obtained contains potentially identifying information and will be secured on an encrypted drive. Multiple data points will be extracted: latency of the initiation of the motor movement, during of execution, and final position. These multiple measures will then be analyzed alongside other data points for the subject after anonymization to determine their changes during the course of experimentation and prognostic value in treatment outcomes.

Apparatus. The perimetry apparatus (similar to that used for animals, scaled for humans) consists of a ~2m diameter semicircular arena with independently-controlled LEDs (space 2.5°) and speakers (spaced 10°) subtending the central 180° of space embedded in the arena wall. Subjects are seated with their chins in a rest while their eyes are tracked by a high-speed camera (ISCAN ETL200). They acquire fixation of a central spot to initiate a trial (but are not forced to maintain fixation during stimulation). They then make saccades to visual or auditory targets as they appear. Latency of movement and final eye position are recorded. All training, and the training/testing of low-level tasks, takes place in this apparatus. A complementary virtual reality (VR) apparatus provides a platform for training and for testing both low-level and high-level vision, and consists of an HTC Vive Eye Pro with eye-tracking capabilities. Custom software developed in C++ and the Unreal Framework presents visual and auditory stimuli within an immersive 3-D environment. Manual HTC controllers are used to control a set of virtual hands to "point" to targets, with latency and final position of eye, gaze, and hand all tracked and recorded. A microphone records subject verbal responses of confidence in both apparatuses. The VR apparatus provides great flexibility in the delivery of training and testing stimuli, and may be used in either setting.

Multisensory training: Multisensory training is accomplished in the perimetry apparatus under dark (.001 lux) and quiet (~30 dB) ambient conditions. Each session begins with 10 mins of briefing and

apparatus calibration. Each trial begins after subjects fixate for 500 ms on a central fixation spot. After a brief (300-600 ms) delay, either a training stimulus (3 f.c. bright light from LED + 75 dB broadband sound from speaker) is activated at 45° of eccentricity in the blind field, or (with lower frequency) a single visual stimulus with same parameters is activated at 45° in the intact or blinded field, or no stimulus is presented at all. Subjects are requested to saccade to any stimuli that appear and otherwise maintain fixation. Stimuli remain active for 3 seconds or for 500 ms after a saccade is made, whichever is shorter. Multisensory training the VR apparatus uses an identical procedure, with the visual and auditory stimuli being an equivalent stimuli produced at the same virtual distance and positions. Trials are presented at a rate of 1/5 sec and continue for 60 mins. Depending on whether it is a purely training or training/testing session, this allows for 500 – 1000 presentations of the visual-auditory training stimulus per session along with 200-400 trials containing single visual or no stimuli. This greatly exceeds the number required in the animal model, and provides the best opportunity for success in sessions of practical duration.

Visual tests: Tests of vision will be conducted on both sides of space and are organized in trials. In each trial the subject acquires fixation for 500 ms before a stimulus is presented after a randomized delay (200-600 ms). Subjects are required to saccade or point to (i.e., "indicate") the stimulus or stimulus-target (<10° error) within 2 seconds or their response is scored as a "No-Go". They are informed of whether their response was "correct" or "incorrect" via an auditory tone after a confidence report (see below). Each test has one or more stimulus levels that are manipulated to create the independent variable(s) of psychometric functions of performance. Detection/Localization: Trials contain either a visual target (LED or 5X5° white square) of manipulated contrast at a randomly-selected location outside of central space (correct response: indicate), or no stimulus anywhere (correct response: No-Go). Competition: Trials contain either no stimuli (correct response: No-Go), or 1 stimulus at a randomly-selected location on either side of space (correct response: indicate), or 2 identical visual stimuli at homotopic locations with randomized eccentricity (correct response: indicate both). Stimulus contrast is manipulated. Multisensory Integration: Trials contain either no stimuli (correct response: No-Go) or brief (100 ms) low-contrast visual or low-volume auditory stimuli presented alone or together at a randomly-selected location (correct response: "indicate"). This evaluates whether the senses can be used synergistically in contralesional space to enhance localization as in intact subjects. Frequency Discrimination: Pairs of oriented gratings with manipulated Δ° and Δf presented on either side of space (correct response: indicate if same, No-Go if different). Shape Discrimination: Unilaterally-presented pairs of simple Efron shapes (see (Whitwell et al., 2014)) with manipulated similarity (correct response: indicate if same, No-Go if different). These shapes consist of stacked rectangles or smoothed splines whose similarity can be quantitatively manipulated and provide a robust, common, and controlled way of assessing shape perception in normal and compromised populations. Subjects will also have the opportunity to report qualitative aspects of any changes in their visual perception during the study.

Testing conditions: Each of the above tests will be evaluated under two different ambient light conditions: normal indoor levels (~300 lux) and darkness (~.001 lux). Lighting conditions are set during the "briefing" period and changed during the "break" (see below), which gives time for dark- or light-accommodation. We will also evaluate conditions in which stimuli are either stationary or moving.

Confidence reports: Subject performance is tracked online and summarized in a numeric "game score" displayed to them after each testing run (see below). On each trial, after making their response (either indicating or No-Go), subjects verbally report a confidence score of 1-3 indicating their confidence in whether they are guessing (1), are unsure (2), or are very confident (3) in their response. The confidence rating translates to the points wagered for that trial. Correct responses increase the game score by double the wagered amount, while incorrect responses decrease the score by the wagered amount.

Testing structure: A 2 hr testing session is divided into two 45-min sets separated by a 10 min "break", with a 10 min "briefing" period at the beginning and 10 min "recapitulation" period at the end. Training/testing sessions contain only a single set. Each trial requires <3-5 seconds. Trials of a single task, stimulus level, and testing condition are conceptually organized into "runs" of 10-12 trials (~ .75-1 min/run with warmup/cooldown). Two runs with the same task and testing condition, but 1-4 stimulus levels, are intermixed within a "block" of 20-96 trials (2-8 min/block). This structure provides ample time to test two blocks of each visual test (e.g., one block stationary, the other moving) within each set. However, testing will be customized for each subject in this pilot to focus on performance limits; e.g., by reducing testing of basic capabilities in later sessions, not extensively testing multiple levels of higher-order capabilities when lower-level ones are not yet intact, and initially testing with wider ranges of stimulus levels before proceeding to narrower ranges.

Subjects selection criteria. To maximize the potential for success, adults aged 18-85 of either sex will be selected based on: (1) diagnosis of a stable homonymous hemianopia (>4 weeks) with absence of hemineglect, (2) a lesion encompassing at least primary visual cortex but sparing parietal cortex, (3) normal auditory and cognitive function, (4) willingness to participate in the three month program, (5) ability to perform the visual discriminations in their intact field. Multiple (n=6) subjects will be recruited for left- and right-sided lesions. Because this is a pilot program, variance across other demographics (e.g., age, gender, race, stroke type) will be noted but are unlikely to be able to be statistically evaluated.

Interventions and Interactions. Subjects will participate in weekly sessions (1.5-2 hrs) for three months, which contains baseline testing, training, repeated testing of visual recovery, and patients will be asked to keep a diary of their experiences with the training, describing what/when they can see. No formal diary will be given to the subject, but asked to write down experiences in a notebook as needed. These pages will be collected at the corresponding study visit and labeled with the subject visit and study identification number by the study coordinator. Training and testing are performed while subjects are comfortably seated and viewing either an array of LEDs and speakers (perimetry apparatus), or VR-integrated screen. Their eye position is tracked. Each trial is participant-initiated by an input device (key press or trigger). After a brief period either no stimulus is presented ("catch trial"), or a selected visual, auditory, or visual-auditory stimulus (or multiple stimuli) will be presented, and the participant makes a response decision, indicating the location of a stimulus in the field, or indicating its identity or identity relative to a co-presented stimulus, and/or indicating confidence in judgment. Responses are indicated either by eye movement, pointing gesture, pointing device, or verbal report (transcribed by experimenter). All stimulus presentations are under the participant's control, and they may freely pause or abort the experiment at any time by verbal statement or failure to fixate. Repeat testing will be attempted if the participant aborts testing after a period of rest.

Outcome Measure(s). A variety of dependent measures are extracted during these experiments, including responses selected, response delay/timing, response accuracy, etc. Responses to visual stimuli will be evaluated over the duration of the experiment to assess recovery of function. The main hypotheses state that subjects will either be able to perform some task at some level or not at all, although there is likely to be quantitative variation in parameters such as response latency, threshold sensitivity, and confidence. In this context, recovery of any visual function is a success. Below we outline two sets of predictions identifying the most credible outcomes and elaborate on the significance of each, although mixed results are also possible.

Modest Rehabilitation: It is possible that hemianopic patients will recover basic reflexive visual functionality, but their capabilities will be limited to those typically associated with "blindsight". In this case, they would be able to detect and localize visual stimuli in the rehabilitated field and use auditory information to enhance this capability. However, they would always choose the intact field in competition tasks, be unable to perform any higher-order discriminations in the contralesional field, and would always

have low confidence in that field even when they can perform visually – a result falling short of that seen in the animal model. Such a result will be less than expected but is not without clinical value: by acquiring the ability to respond to contralesional visual stimuli, rehabilitated subjects can bring them into the sighted field for further analysis.

The Expected Result: However, our expectation is that hemianopic patients will recover visual functionality similar to that observed in the animal model, although the timing of the recovery and the quantitative parameters of the functional endpoints may differ. This means that, after a few weeks of training, they will be able to perform each of the tasks at some level under some conditions. We expect performance to be best under scotopic conditions and for moving stimuli; i.e., testing conditions best suited to driving robust visual responses in SC-mediated visual pathways. There is likely to be an initial separation between performance in visual tasks and confidence, with the former recovering faster than the latter, as the brain adapts and reinterprets activity patterns in remaining circuits as definitive of the visual stimuli generating them.

In either case, future directions will examine the means to improve the rehabilitation method (including calibrating subjects to the sensation of contralesional visual stimuli), examining the impact of the strategy on other domains impacting quality of life (e.g., navigation), an analysis of the underlying circuits using magnetoencephalography, evaluation of the sensitivity of different individual features to the procedure (e.g., age, gender, delay from lesion onset to treatment), a deeper exploration of the limits of functional recovery, and the formalization of a clinical trials protocol.

Analytical Plan. The Humphrey visual field test, kinetic visual field test, and low-vision visual functioning questionnaire (LV-VFQ-48) are standard clinical tests of vision administered before and after training. We expect increases in the number of detected locations and decreases in the thresholds of detection (when detected) at each test location in the hemianopic field, for at least Goldmann size V stimuli and smaller, and significant improvements in quality of life. In addition to these common clinical assays, a more detailed picture of low- and high-level vision will be obtained from the tests described above, which produce psychometric functions (curves relating % correct responses to stimulus level) for each subject and location or side of space. Parameters of these functions describing thresholds and maximum accuracy will, alongside confidence scores and latency, be evaluated for changes over time and across subjects and sides of space in a multilevel multivariate regression model (Gelman and Hill, 2007). Maximum likelihood estimation will be used to estimate parameter distributions to guide future studies.

Human Subjects Protection

Subject Recruitment Methods. Patients will be recruited from the local subject population hospitalized/seen by Neurology at Atrium Health / Wake Forest School of Medicine. To maximize the potential for success, adults (<85) of either sex will be selected based on: (1) diagnosis of a stable homonymous hemianopia (>4 weeks) with absence of hemineglect, (2) a lesion encompassing at least primary visual cortex but sparing parietal cortex, (3) normal auditory and cognitive function, (4) willingness to participate in the three month program, (5) ability to perform the visual discriminations in their intact field. Subjects not meeting these criteria are either poor candidates for rehabilitation given the extent of the deficit relative to the known circuits responsible for recovery in animals (crit. 1-2), will not be suitable for the visual-auditory training paradigm (crit. 3-4), or have visual capabilities that cannot be adequately tested (crit. 5). Multiple (n=6) subjects will be recruited for left- and right-sided lesions. Because this is a pilot program, variance across other demographics (e.g., age, gender, race, stroke type) will be noted but are unlikely to be able to be statistically evaluated.

Informed Consent. Written informed consent will be obtained. The risk of harm or discomfort that may occur as a result of taking part in this research study is not expected to be more than in daily life or from routine physical or psychological examinations or tests. The rights and welfare of study will be protected

through the use of measures to maintain the confidentiality of study information. Study results will be presented or published in lieu of providing individual subjects additional information regarding the study.

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 be used during data collection. Following data collection individual subject files will be destroyed within 5 years and converted to an anonymous generalized 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.

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 organization if appropriate.

References

Burnett LR, Stein BE, Chaponis D, Wallace MT (2004) Superior colliculus lesions preferentially disrupt multisensory orientation. Neuroscience 124:535–547.

Burnett LR, Stein BE, Perrault TJ Jr, Wallace MT (2007) Excitotoxic lesions of the superior colliculus preferentially impact multisensory neurons and multisensory integration. Exp Brain Res 179:325–338.

Dakos AS, Jiang H, Stein BE, Rowland BA (2020) Using the Principles of Multisensory Integration to Reverse Hemianopia. Cereb Cortex 30:2030–2041.

Dakos AS, Walker EM, Jiang H, Stein BE, Rowland BA (2019) Interhemispheric visual competition after multisensory reversal of hemianopia. Eur J Neurosci 50:3702–3712.

Gelman A, Hill J (2007) Data analysis using regression and multilevel/hierarchical models. Cambridge ; New York: Cambridge University Press.

Goodwin D (2014) Homonymous hemianopia: challenges and solutions. Clinical Ophthalmology:1919.

Groh JM, Sparks DL (1996a) Saccades to somatosensory targets. III. eye-position-dependent somatosensory activity in primate superior colliculus. J Neurophysiol 75:439–453.

Groh JM, Sparks DL (1996b) Saccades to somatosensory targets. II. motor convergence in primate superior colliculus. J Neurophysiol 75:428–438.

Harrington LK, Peck CK (1998) Spatial disparity affects visual-auditory interactions in human sensorimotor processing. Exp Brain Res 122:247–252.

Jay MF, Sparks DL (1987a) Sensorimotor integration in the primate superior colliculus. I. Motor convergence. J Neurophysiol 57:22–34.

Jay MF, Sparks DL (1987b) Sensorimotor integration in the primate superior colliculus. II. Coordinates of auditory signals. J Neurophysiol 57:35–55.

Jiang H, Stein BE, McHaffie JG (2009) Cortical lesion-induced visual hemineglect is prevented by NMDA antagonist pretreatment. J Neurosci 29:6917–6925.

Jiang H, Stein BE, McHaffie JG (2015) Multisensory training reverses midbrain lesion-induced changes and ameliorates haemianopia. Nat Commun 6:7263.

Lomber SG, Payne BR, Cornwell P (2001) Role of the superior colliculus in analyses of space: superficial and intermediate layer contributions to visual orienting, auditory orienting, and visuospatial discriminations during unilateral and bilateral deactivations. J Comp Neurol 441:44–57.

McIntosh TK (1994) Neurochemical sequelae of traumatic brain injury: therapeutic implications. Cerebrovasc Brain Metab Rev 6:109–162.

McIntosh TK, Smith DH, Garde E (1996) Therapeutic approaches for the prevention of secondary brain injury. Eur J Anaesthesiol 13:291–309.

Munoz DP, Wurtz RH (1995a) Saccade-related activity in monkey superior colliculus. I. Characteristics of burst and buildup cells. J Neurophysiol 73:2313–2333.

Munoz DP, Wurtz RH (1995b) Saccade-related activity in monkey superior colliculus. II. Spread of activity during saccades. J Neurophysiol 73:2334–2348.

Stein BE, Rowland BA (2020) Using superior colliculus principles of multisensory integration to reverse hemianopia. Neuropsychologia 141:107413.

Whitwell RL, Milner AD, Goodale MA (2014) The Two Visual Systems Hypothesis: New Challenges and Insights from Visual form Agnosic Patient DF. Front Neurol 5:255.

Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V (2006) Natural history of homonymous hemianopia. Neurology 66:901–905.