Official Title: A Randomized, Double-Blind, Placebo-Controlled Pilot Study to Evaluate Non-invasive Brain Stimulation Effects on Orientation and Mobility Performance in Adults with Visual Impairments.

Date: 17th December, 2025

Protocol outline

Note: Items in BLUE are meant to indicate when the clinician is acting.

Population of interest and eligibility criteria

Individuals with constricted visual fields (those who use a white cane for traveling daily and those who do not use a white cane).

Individuals with constricted visual fields will be considered **eligible** to participate in the study if they:

- Are healthy, capacitated adults with binocular constricted visual field loss (due to either retinitis pigmentosa (RP), rod-cone dystrophy, or advanced glaucoma) resulting in functional vision losses. These individuals with visual impairments can be those who have been previously trained by an Orientation and Mobility (O&M) specialist to independently travel with the long white cane daily (since the length of the white cane and tip at the base are based on personal preference, they should be willing to use their own white cane for the study), and those who do not necessarily use a cane for travelling.
- Have binocular visual acuity or best corrected binocular visual acuity no better than 6/12 or 20/40 or +0.30 logMAR (inclusive) with no eccentric viewing, and visual fields no better than 70 degrees in total in each eye.
- Are over the age of 18 (inclusive) and has full legal capacity to provide informed consent.
- Have read and fully comprehends the information in the consent letter.
- Are willing and capable of adhering to instructions and maintaining the outlined appointment schedule.

Individuals with constricted visual fields will be considered **ineligible and therefore excluded** from the study if they:

- Are involved in other recent eye-related studies, either clinical or research-related. To be eligible they would have to wait at least one week for studies not involving brain stimulation, and four weeks for studies in which they receive brain stimulation before they could participate in this study.
- Have been diagnosed with dementia or self-reported dementia with no formal diagnosis.
- Have been diagnosed with a cognitive impairment or self-reported cognitive impairment with no formal diagnosis.
- Have been diagnosed with physical or motor impairments resulting in walking and/or balancing issues or self-reported physical or motor impairments resulting in walking and/or balancing issues with no formal diagnosis.

- Have been diagnosed with vestibular disorders or dysfunctions which affects one's balance and/or mobility or self-reported vestibular disorders or dysfunctions which affects one's balance and/or mobility with no formal diagnosis.
- Are unable to follow the researcher's instructions.
- Are anticipating treatment (including ocular surgery) for any eye disease within the duration of the study.
- Have any ocular pathology in addition to retinitis pigmentosa (RP), rod-cone dystrophy, or advanced glaucoma, which can diminish their visual acuity and/or their visual field, however wearing glasses or contact lenses, as well as mild cataract of grade 2 or below is acceptable.
- Have severe hearing impairment.
- Are pregnant or trying to get pregnant.
- Fit any of the typical contraindicators for brain stimulation. See contraindicator section below.

For all participants the contraindications for brain stimulation are:

- Diagnosed with epilepsy or have previously experienced an epileptic seizure.
- Implanted medication pump or implanted electronic device, including defibrillator or pacemaker.
- Any metal implants in the head (excluding tooth fillings).
- Active electric implants anywhere in the body (especially the head region).
- On psychoactive medication for any psychiatric or neurological conditions including but not limited to depression and schizophrenia.
- Areas of sensitive skin located on the face or head, or a skin condition on the face, or regularly use medication to alleviate skin irritation on the face.
- Recurring headaches.
- Previous head injury or skull fracture or head/brain surgery.
- Heart disease, neurological condition, or a history of cardiac or neurological surgery.
- Current or historical cancerous or noncancerous brain tumor, or other abnormalities in brain structure.

The goal is to recruit **20 participants.**

Initial phone screening

1. Complete the Preliminary Screening Form by kindly requesting a response for each item.
2. If potential participants come from the practices of local optometrists and ophthalmologist within the Region of Waterloo as well as nearby regions of Ontario, they will be asked to complete the "Consent to Disclose Personal Information, Pursuant to the Personal Health Information Protection Act, 2004 (PHIPA)" letter in order to obtain a report consisting of ocular diagnoses including their duration, as well as any treatment they may be receiving. The purpose of obtaining this report is to document their diagnoses (including duration and treatment).
3. Confirm ocular health by reviewing health records in VisualEyes if the participant is a patient at the University of Waterloo Optometry Clinic or by reviewing report if participant is not a patient at the University of Waterloo Optometry Clinic.

Visit/Session 1: Screening

1. Present and discuss contents of the Consent form and obtain participant's signature. Ensure that the participant indicates: (i) whether or not they wish to be informed of incidental findings; (ii) whether or not they allow the researchers to videorecord them as they complete the O&M course during visits 2 and 3.

2. Perform clinical tests:
    - Measure corrected distance and near visual acuity (VA) binocularly.
    - Measure contrast sensitivity (CS) binocularly.
    - Perform Hirschberg test. *
    - Perform extraocular motilities test. *
    - Measure peripheral visual fields with Humphrey Field Analyzer (HFA).

    *Tests to be performed by clinicians.

    Prior to performing the aforementioned clinical tests, the clinician will remind the participant that the tests are not meant to substitute an eye examination, and it is crucial that they see their primary eye care provider for a comprehensive assessment as often as their optometrist advises.

4. Re-screen contraindications for brain stimulation. For individuals with constricted visual fields ask questions regarding whether or not they use a long white cane for travel, and any orientation and mobility (O&M) training they may have received.

Note:

- *If their VisualEyes record or external report reveals additional eye issues that can have an impact on their visual acuity and/or visual field, they will not be invited to participate in the study.*
- *The purpose of the Hirschberg and motility tests is solely for documentation purposes, so that the researchers know the variables, which may be impacting vision. However, the results of the visual acuity and visual field tests will be used to confirm eligibility of both groups.*
- *If the brain stimulation questionnaire indicates that it is not safe to perform brain stimulation, then they will be reimbursed for their time and removed from the study.*
- *If an incidental/atypical finding is found on the Humphrey Field Analyzer visual field test, and the participant indicated that they wish to be notified of such findings, the research team will report the finding to the ethics board by submitting form 108. Upon the board's recommendation, the research team will inform the participant in-person during the participant's subsequent visit and explain that "as the visual field test was purely for research purposes, the research team are not able to provide diagnoses, but the visual field test results came back with a potentially atypical finding. Sometimes, these findings are harmless and represent normal human variation, but sometimes they may be indicative of some pathology." We will then provide them a copy of the visual field results, which contains the incidental finding and will encourage the participant to discuss the finding with their optometrist or*

ophthalmologist so that they can explore whether additional care is warranted. In some cases, we can also directly send the results to their clinician if we have this information.

- *If they indicate on the consent form that they do not want to be told of atypical/incidental findings, then no letter will be issued, and they will not be notified.*

IF PATIENT QUALIFIES FOR STUDY:

- Randomly select stimulation codes to determine active and placebo/sham schedule for next two visits. The order of active and placebo presentation will be randomised so that neither the participant nor the researcher will know what the subject will receive on each day. The researcher will only unmask the type of stimulation after the entire study is completed.

<u>Visits/Sessions 2-3: Brain stimulation and completion of O&M tasks (recall that one day is active stimulation and the other is sham/placebo (order randomized)).</u>

Note:

- *Visits/sessions 2 and 3 must be separated by at least 48 hours (no more than a week).*
- *The same mobility course will be tested 6 times (3 measuring time points (pre, post1, post 2) x 2 treatment days (active and placebo)). The location of the obstacles in each trial (pre, post 1, and post 2) will not be varied, but rather the location of the obstacles on each treatment day for courses 2 to 4 will be randomized. Moreover, given that courses 3 and 4 only have one obstacle each, it would also help to change what the actual object is for both courses on both treatment days. Whilst course section #1 must be done first, the order of completing the other three courses will also be randomized. In addition, for each course section, the start and end points/direction will also be varied. For example, the participant will start at the usual staring point in "pre" but in "post 1" they will start the course from the end point, that is, in the opposite direction. These should all help to minimize practice effects.*

1. Verify that their general health has not changed since their last visit.

2. Verify that their vision/eyesight has not changed since their last visit.

3. Verify that they got close to full night of sleep, that is more than 5 hours; and they have refrained from consuming more than 2 alcoholic beverages within the past 24 hours.

4. Complete orientation and mobility (O&M) course→ these results will serve as an "**O&M pretest**" set of results.
   - O&M parameters to measure include:
     - Time taken to complete a specific section of the course,
     - Number of errors,
     - Percentage preferred walking speed (PPWS),

- Visual detection distance (VDD),
- Visual identification distance (VID).

5. Stimulation (either active or sham/placebo; using the two different codes generated at the first visit) for 20 minutes whilst the patient is quietly seated. Since we cannot have more than one orientation and mobility (O&M) course, and we are concerned about the learning effect from repeatedly doing the course, we will stimulate the participant for 20 minutes, and then have them wait for 2 minutes before moving on to step 5 below.

6. Complete orientation and mobility (O&M) course 2 mins after stimulation→ these results will serve as an "**O&M post-test 1/immediately after stimulation**" set of results.
   - O&M parameters to measure include:
     - Time taken to complete a specific section of the course,
     - Number of errors,
     - Percentage preferred walking speed (PPWS),
     - Visual detection distance (VDD),
     - Visual identification distance (VID).

7. Complete orientation and mobility (O&M) course 30 mins after stimulation→ these results will serve as an "**O&M post-test 2/30 minutes after stimulation**" set of results.
   - O&M parameters to measure include:
     - Time taken to complete a specific section of the course,
     - Number of errors,
     - Percentage preferred walking speed (PPWS),
     - Visual detection distance (VDD),
     - Visual identification distance (VID).

8. Participant fills out brain stimulation adverse effects form. The form consists of a 3-point questionnaire whereby participants record their subjective sensation during stimulation with 1 indicating no sensation at all, and 3 indicating an extremely strong sensation. Sensations include, itching, headache, trouble concentrating, and pain to name a few. Clinician consulted if participant fills out any of the categories with a rating of 3, which indicates severity. These will be reported to the Office of Research Ethics (ORE) as an adverse event, and the ORE will be consulted for guidance to ensure safety of all study participants.

9. Complete renumeration.

10. Thank the participant for their participation in the study.

11. To determine the effectiveness of sham/placebo, ask the participant at the end of visit/session 3 which of the two visits they thought they received active stimulation.

<u>Brain stimulation details</u>

- High frequency tRNS (hf-tRNS) stimulation of V1 within the occipital pole (2 mA peak to peak, current intensity bounded between -1mA and +1mA with 0 mean, 20 minutes, 30 seconds

ramp up and down; Placebo: 30 second ramp-up and down periods, with no current applied otherwise) (Pavan et al., 2019) using a neuroConn DC Stimulator Plus or neuroConn DC Stimulator MC (neurocaregroup.com) and two 5 cm x 5 cm rubber electrodes either placed inside 0.9% saline homogeneously soaked sponges or covered in a 1-2 mm thick layer of Ten20 conductive paste. Both electrodes will be positioned on either side of Oz, more specifically over O1 and O2, as given by the International 10-20 EEG electrode placement system, in a lengthwise manner and separated by 2-3 finger widths (van der Groen et al., 2022). The location of each electrode, namely the anode or cathode will be randomized in terms of which is positioned over O1 and O2. This randomization will be done for each participant, however, once the order is selected, it will be kept constant on both treatment days for the participant. Care will be taken to ensure a dry section of scalp between electrodes. Maximum impedance ≤ 15 kilo- ohms. Electrodes will be secured using rubber straps.

O&M measures of performance

The following mobility performance parameters will be measured:

- **Time taken to complete a specific section of the course-** this will be measured for each course section using a stopwatch.

- **Number of errors-**
    - Mobility errors are essentially any unintentional contact of any part of the body and/or collisions with static (fixed/steady/stable obstacles) objects, obstacles, or boundaries (stumbles, bumping into objects, brushing into branches, and high stepping (anticipating a step that is not present)).
    - Orientation errors include incorrect turns, taking a wrong direction, deviation errors (such as veering or zig-zagging), corrections, not navigating the course correctly after making contact with an obstacle.
    - Other errors related to travel include abrupt changes in walking speed, changes in gait or abnormal foot placement, loss of balance, hesitating/stopping, interventions of instructors or bystanders.
    - The use of one's hand to search or trail along a wall, as well as cane-contact with an obstacle, inner or outer shoreline will not be regarded as errors as they are strategies used to maintain one's orientation and mobility (O&M) in the environment using tactile senses. However, to avoid any ambiguity, both participants with constricted visual field who use a white cane, as well as those with constricted visual fields who do not need a white cane for travelling, will be asked to verbalize any orientation and mobility (O&M) strategies, such as trailing, for example, that they apply on the orientation and mobility (O&M) course (Chang et al., 2020; Leat & Lovie-Kitchin, 2006; Roentgen & Gelderblom, 2012).
    - Throughout the entire orientation and mobility (O&M) course (sections 1-4), the subject will be instructed to walk the respective pathways without touching any obstacles at a pace that is comfortable to them. The researcher will carefully observe them and will note the number of each kind of error mentioned above.

- **Percentage preferred walking speed (PPWS)-** The walking speed of the individual who is visually impaired in an environment with obstacles expressed as a percentage of their preferred walking speed in an unobstructed path.
    - Walking speed- total distance travelled divided by the total time to completion. Travel distance can be measured using a portable digital laser range finder, and time using a stopwatch.
    - Subjects will be instructed to walk along a straight, flat, obstacle-free path **(Course section #1)** at a pace, which is comfortable to them. They will be informed that there are no obstacles or steps on the path. The time to complete the path and the distance of the path will be measured in order to calculate their preferred walking speed (PWS). The participants will be asked to walk the course four times, twice in either direction, and the average speed of the four trials will be recorded as their preferred walking speed (Chang et al., 2020; Leat & Lovie-Kitchin, 2006).
    - Subjects will then be instructed to walk along a pathway in which there may be obstacles **(Course section #2)**, and safely negotiate them without touching any of the obstacles. They will also be asked to verbally inform the researcher of any orientation and mobility (O&M) strategies, such as trailing, they apply on the orientation and mobility (O&M) course (Chang et al., 2020; Leat & Lovie-Kitchin, 2006). The time to complete the path and the distance of the path will be measured in order to calculate their preferred walking speed (PWS) in an obstructed path, and together with the preferred walking speed (PWS) in an unobstructed path (obtained from course section #1) their percentage preferred walking speed (PPWS) can be calculated.

- **Visual detection distance (VDD) and Visual identification distance (VID)-**
    - **VDD-**The distance (in meters) at which an individual detects an obstacle in their travel path, even if they cannot identify it.
    - **VID-** The distance (in meters) at which an individual can correctly identify an obstacle in their travel path.
    - For **both course sections # 3 and 4**, the participant will be instructed to walk along a pathway in which there will be a single obstacle. They will be told to avoid touching the obstacle when navigating the course. Course section #3 is meant to be training, whilst course section #4 is meant to collect visual detection distance (VDD) and visual identification distance (VID) data. Both sections will be marked in meters so that distances can be easily measured. Alternatively, a portable digital laser range finder can be used for measuring the two distances. As they start the course a stopwatch will be started so the time it takes to detect the obstacle can be measured. The participant will be asked to stop the moment they detect the obstacle on the course. At that point, the experimenter will pause the stopwatch, and record the distance as the visual detection distance (VDD). The participant will then be asked to continue along the path, and the stopwatch will be resumed. They will be told to stop the moment they can correctly identify the obstacle. The researcher will then stop the stopwatch and record the distance as the visual identification distance (VID). To ensure that the

participant does not look at their feet and wait until there are within a few meters of the obstacle before stopping, they will be instructed to look ahead at all times when navigating the course. It is important to note that visual detection distance (VDD) and visual identification distance (VID) can be the same if the participant can identify the obstacle at the same point, they detect it.

- As previously mentioned, course section #3 is a form of training, whereas in course section # 4 data is collected. To facilitate sufficient practice, whilst also allowing the data to be collected within the planned time points, the participants will complete course section #3 twice (once in either direction).
- Two researchers will be needed for sections# 1-4. One will be with the participant to provide instructions and record data; whilst the other will be ahead of the participant to make sure that the path is clear, record the times, and confirm that the obstacle is still in place (if that section has obstacles), as well as videorecord the session once consent was obtained from the participant at the first visit thereby allowing us to do so. By videorecording the participant as they complete the course task we will be able to obtain more accurate measures of time, and the number of errors (Leat & Lovie-Kitchin, 2006).

O&M Course details

Course design

- Orientation and mobility (O&M) course will be composed of an array of static natural and artificial (man-made) obstacles. Static natural obstacles refer to fixed/steady/stable obstacles that are either readily found in the environment (e.g., potted plants) or form part of the architecture of the building (e.g., a pole or a sealed doorway). Artificial obstacles are made of light materials such as polystyrene, rubber foam, soft cardboard, or paper. The course will be divided into 4 sections, each section geared towards evaluating a different measure of orientation and mobility (O&M) performance.

Course details

- **Course section #1, no obstacles-** A straight, flat, obstacle and pedestrian-free path such as a corridor. It will be used primarily to measure preferred walking speed. Using a corridor will allow a natural yet bounded travel path with a defined shoreline (Roentgen & Gelderblom, 2012).
  - **Measurements-** Time taken to complete the course, Number of errors, Preferred walking speed which will be used to calculate PPWS (Percentage preferred walking speed) after completing course section #2.
- **Course section #2, obstacles**- An indoor space leading to the outdoors or a more opened space still within the building. It will consist of potted plants, overhanging palm frond, chairs, door frames, and doors to negotiate. There will be no physical steps, but it is possible that there may be changes in the contrast of the floor or a wooden meter rule will be placed on the floor in order to stimulate

contrast changes or create a false step (Leat & Lovie-Kitchin, 2006; Roentgen & Gelderblom, 2012). Since is not feasible to have two O&M courses (one for each of the two treatment days), we will position all moveable obstacles at different distances/locations during visits 2 and 3, as well as record the different distances/location of each item. In addition, the start and end points/direction will also be varied. For example, the participant will start at the usual staring point in "pre" but in "post 1" they will start the course from the end point, that is, in the opposite direction. This will aid to reduce practice effects whilst maintaining the complexity of the course.

    - **Measurements-** Time taken to complete the course, Number of errors, Preferred walking speed in an obstructed path which will be used to calculate PPWS (Percentage preferred walking speed) after completing course section #2.

- **Course section #3, training for VDD and VID-** A straight indoor corridor consisting of one obstacle. Given that courses 3 and 4 only have one obstacle each, the actual object use for both courses on both treatment days may be changed. In addition, the start and end points/direction will also be varied. For example, the participant will start at the usual staring point in "pre" but in "post 1" they will start the course from the end point, that is, in the opposite direction. These should all help to minimize practice effects. To measure distances, the course will be marked in meters, so the object detection and object recognition distances can be easily measured and recorded. Alternatively, a portable digital laser range finder can be used for measuring the two distances (Leat & Lovie-Kitchin, 2006; Roentgen & Gelderblom, 2012).

    - **Measurements-** Time taken to complete the course, Number of errors, Visual detection distance (VDD), and Visual identification distance (VID).

- **Course section #4, measuring VDD and VID-** Another straight indoor corridor different from that used in section 3. Given that courses 3 and 4 only have one obstacle each, the actual object use for both courses on both treatment days may be changed. In addition, the start and end points/direction will also be varied. For example, the participant will start at the usual staring point in "pre" but in "post 1" they will start the course from the end point, that is, in the opposite direction. These should all help to minimize practice effects. To measure distances, the course will be marked in meters, so the object detection and object recognition distances can be easily measured and recorded. Alternatively, a portable digital laser range finder can be used for measuring the two distances (Leat & Lovie-Kitchin, 2006; Roentgen & Gelderblom, 2012).

    - **Measurements-** Time taken to complete the course, Number of errors, Visual detection distance (VDD), and Visual identification distance (VID).

References

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