ENVIRONMENTAL LOCALIZATION MAPPING AND GUIDANCE FOR VISUAL PROSTHESIS USERS

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SINGLE IRB PROTOCOL

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A Introduction

A1 Study Abstract

About 1.3 million Americans aged 40 and older are legally blind, a majority because of diseases with onset later in life, such as glaucoma and age-related macular degeneration [1]. Second Sight has developed the world's first FDA approved retinal implant, Argus II, intended to restore some functional vision for people suffering from retinitis pigmentosa (RP).

The Argus II Retinal Prosthesis System developed by Second Sight is a medical device regulated by the FDA's Humanitarian Device Exemption H110002. The Argus II system comprises three sub-system components: the internal Implant, the external Video Processing Unit (VPU) and Glasses, and the supporting Clinical Fitting System.

In this era of smart devices, generic navigation technology, such as GPS mapping apps for smartphones, can provide directions to help guide a blind user from point A to point B. However, these navigational aids do little to enable blind users to form an egocentric understanding of their surroundings, they are not suited to navigation indoors, and do nothing to assist in avoiding obstacles to mobility. The Argus II, on the other hand, provides blind users with a form of artificial vision that provides limited visual representation of their surroundings that improves a user's ability to orient themselves and traverse obstacles, yet the user's vision remains significantly limited by the low resolution and dynamic range of the system which

is thus limited in its ability to provide high-level navigation and semantic interpretation of the surroundings. The proposed study aims to address these limitations of the Argus II through a synergy of artificial vision and state-of-the-art simultaneous localization and mapping (SLAM) and object recognition technologies.

Users of the Argus II device will participate in the study while using their Argus II device according to its intended use. Other non-medical devices that will be used as part of this study include the following (see Section D3):

- Headphones for receiving auditory information about the environment;
- Vibrotactile stimulator to perceive, through vibrations on a participant's skin, information about the environment;
- Virtual reality headset (used only by normal-sighted participants in order to simulate the visual experience of a prosthetic vision user)
- Portable central processing unit to integrate all environmental information and relay the information in informative ways back to the user using the various forms of sensory feedback, including the Argus II system or a head mounted display (HMD), the headphones, and a vibrotactile stimulator.

This study is driven by the hypothesis that orientation and navigation performance for users of retinal prosthetics can be greatly improved by incorporating SLAM, stereo/depth based and object recognition technologies conveying spatial environmental information via a combination of artificial vision and auditory and/or haptic feedback. SLAM enables the visual prosthesis system to construct a map of the user's environment and locate the user within that map. Ultimately, we expect that this technology will allow users to create an effective spatial image of the environment, that is, a continuously updated representation of locations in 3D space that supports volitional action for independent navigation with minimal cognitive load.

A2 Purpose of the Study Protocol

This is a prospective observational case series study. We will develop and test a navigational aid system which 1) constructs a map of unfamiliar environments and localizes the user in that environment using SLAM technology 2) automatically identifies navigationally-relevant objects and landmarks in that environment using object recognition and 3) provides sensory feedback via multiple modalities for navigation, obstacle avoidance, and object/landmark identification.

We will test the system's potential with both Argus II users and with normally sighted participants (by simulating a retinal prosthesis via a head-mounted display that emulates the capabilities of the Argus II device).

The human subject tests fall into three groups: in Group 1, target identification and localization tasks test the basic capabilities of the system for conveying characteristics (e.g. shapes, sizes, movement direction) and location information

about objects that would be targets for navigation or action. In this group, participants will be stationary and only be asked to rotate/pan their head to acquire camera-generated targets. In Group 2, egocentric localization and spatial image updating tasks test how well the system provides spatial parameters, particularly distance, from optical flow and non-visual sources, leading to the formation of the spatial image. Finally, Group 3 tasks test the system in its function of guiding navigation and assess learning effects.

In all three groups, various instantiations of the system are contrasted as follows. The **Basic system** is the standard Argus II device. The **Augmented system** enhances the imagery for visual feedback compared to the standard Argus II system by decluttering the scene and adding discriminative features to convey object identities. The features to be utilized will be determined after tests in Group 1, but the general goal is to add spatial and/or temporal uniqueness without cluttering the display. The third system, the **Augmented + Modal system**, adds non-visual cues. Initially, we are targeting two non-visual augmentation modalities including (i) verbal and non-verbal auditory feedback along with spatial sound for purposes such as to convey the identity, distance, and direction of objects relative the user and (ii) haptic feedback for purposes such as to direct users how to adjust their head azimuth and elevation in order to acquire a landmark or waypoint within their field of view.

The enhanced imagery information for visual feedback used in the Augmented and Augmented + Modal modes of the system will be computed by the navigation system developed in this study and communicated to the Argus II using a built-in video input on the Argus II that enables visual information provided from an external source to be displayed by the user's implant. No alterations, including software or hardware changes, will be made to a participant's Argus II system during this study.

B Background

B1 Prior Literature and Studies

The Argus II system is a fully portable medical device approved by the FDA for commercial sale in the United States under the Humanitarian Device Exemption (HDE) program. It consists of implanted and external components (see Figure 1).

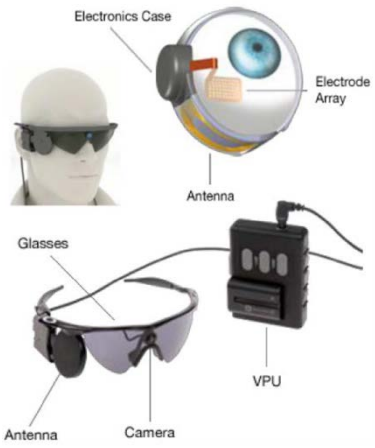

Figure 1 - Argus II Retinal Prosthesis System

The implant is an epiretinal prosthesis that includes a receiver, electronics, and an electrode array that are surgically implanted in and around the eye. The array has 60 electrodes arranged in a 10x6 rectangular grid [2], [3]. It is attached to the retina over the macula with a retinal tack. The external equipment includes glasses, a video processing unit (VPU) and a cable. The glasses include a miniature video camera, which captures video images, and a coil that transmits data and stimulation commands to the implant. The VPU converts the video images into stimulation commands and is body-worn. The cable connects the glasses to the VPU. The Argus II system operates by converting video images into electrical energy that activates retinal cells, delivering the signal through the optic nerve to the brain where it is perceived as light.

Retinal implant technologies are just emerging, and the Argus II currently serves as a complementary device to the long cane and guide dog for complex tasks, such as O&M. Due to the low resolution and highly limited field of view of the retinal implant, visual prosthesis users must use continuous head scanning, both horizontal and vertical, to observe the visual field of normal human vision. This skill has been trained and demonstrated in previous studies [4], [5] which were based on “radar vision” [6], a scheme using head scanning to locate a high-contrast object in an uncluttered background.

Our proposed efforts focus on technology that will help develop the Argus II, and other prosthetic vision devices, into stand-alone aids capable of enabling people with profound vision loss to regain their independence, just as cochlear implants developed from lip-reading aids into fully functional devices capable of restoring speech understanding in as little as two decades [7].

B2 Rationale for this Study

To enhance the Argus II capabilities, we will be adding recognition-enabled navigational technologies for these visual prosthesis users. This will consist in delivering enhanced visual cues optimized for user recognition and to provide auditory / verbal cues as well as haptic information through vibrotactile stimulators.

We will recruit approximately 25 to 35 normally sighted adults, and approximately 5 to 15 retinal prosthesis users. We will test sighted participants in order to establish baseline levels for processing the information delivered when the optic nerve is healthy and intact. We do not claim that Argus II users will be comparable in performance; in fact, testing will be directed at the implanted users to characterize a range of performance compared to baseline.

Our Johns Hopkins University Applied Physics Laboratory (JHU/APL), Johns Hopkins Medicine Wilmer Eye Institute (JHM/Wilmer), and Second Sight teams have been collaborating for the past several years to advance the capabilities of the Argus II system and improve performance of Argus II recipients, including developing capabilities for object recognition and stereo vision, and have extensive experience in designing and developing SLAM software and algorithms in the field of robotics. In addition to the investigators at Wilmer Eye Institute and Second Sight who have extensive experience in working with retinal prosthesis users, our team includes Dr. Roberta Klatzky, who has a long history of research working with visually impaired individuals and studying the impact of human neurophysiology and psychology on the design of instruments and devices that can be used as navigational aids for the blind.

C Study Objectives

C1 Primary Aim

The primary aim of this study is to ascertain whether our system allows Argus II recipients to form a "spatial image" of their environment, that is, a continuously updated representation of locations in three dimensional space that supports volitional action for independent navigation.

C2 Rationale for the Selection of Outcome Measures

The outcome measures derive directly from the goals of this study, namely the ability to identify and localize targets, with and without movements, and navigate through a field comprised of these targets.

D Study Design

D1 Overview or Design Summary

Testing will be conducted at JHU/APL, JHM/Wilmer and at JHU Homewood campus.

This study will be conducted with three different sets of participants.

- One set of eligible participants will consist of Argus II users, with a total of approximately 5 to 15 such participants expected to be recruited for this study. These tests may take place across all test sites.
- A separate set of eligible participants will consist of normally sighted individuals from JHU/APL's staff of over 7,000. To simulate the visual perception of the Argus II users, these participants will be equipped with a head-mounted display, such as an Oculus Rift, that simulates the field of

view and pixelated array of the retinal prosthesis. A total of approximately 25 to 35 such participants are expected to be recruited for this study. These tests will take place at JHU/APL.

- Another set of eligible participants will consist of normally sighted individuals from interested students and staff from JHU Homewood campus. Similar to the JHU/APL study group, these participants will be equipped with a head-mounted display that simulates the field of view and pixelated array of the retinal prosthesis. A total of approximately 10 such participants are expected to be recruited for this study. These tests are expected to take place at JHU Homewood campus, but could utilize JHU/APL campus if needed.

For information regarding recruitment and informed consent for these participant groups, refer to Section D2.b.

The study itself will consist of two phases which are expected to be conducted over the course of 1-5 testing days (longer for Argus II users, due to setup time requirements, shorter for normally sighted subjects). In the first phase (Group 1 and Group 2 tasks, see Section A2 and below), subjects will be trained to identify and localize objects within an unfamiliar environment by providing them information either via the Argus II device or the head mounted display that simulates the perception of a visual prosthesis. These tests will be conducted to assess the capabilities of the system for conveying identity and location information about objects that could be targets for navigation or action. Compared with the **Basic** system, we will then assess how well the augmented systems (**Augmented** and **Augmented + Modal** systems, refer to Section A2) function in providing spatial parameters, particularly distance, using visual but also non-visual sources of information including haptic/vibrotactile and auditory feedback.

The identification and localization tests (Group 1) use common psychophysical judgments such as the following: discriminating between two alternatives by saying which is present in the field of view, touching a tablet computer to indicate the apparent location of a target in the frontal plane, and looking for targets by rotating the head and pointing when one is found. In the egocentric localization and spatial updating tasks (Group 2), the participants will make similar psychophysical judgments, but now in the context of movement, for example requiring the participants to walk several meters towards a visible target. For example, in some trials participants may be asked to move backwards to the origin (with aid of a guide), then verbally estimate the distance to the target or point with a joystick toward it. Similarly, in other trials, after walking toward the target with vision present, they may be asked to move forward a short distance without vision and make the same types of judgments.

The second phase of testing (Group 3 tasks), will involve using the information gleaned from the first phase to assess participants' ability to navigate through an unfamiliar environment. This phase will again compare user performance using the

Basic system with user performance using the **Augmented** and **Augmented + Modal** systems where contextual information associated with the task is conveyed to users via enhanced visual, auditory, and haptic modalities.

Our algorithms for mapping the environment and localizing the user will provide the core autonomous navigational capability of the system. As the user traverses their environment, object recognition will be used in concert with the spatial localization and mapping technology to automatically detect key navigational features (e.g., doors, signs, etc.) and store these locations in the map. Once stored in the map, these semantic attributes may then be verbally queried by the user for navigation, e.g., “lead me to the nearest restroom”.

The enhanced imagery generated by the **Augmented** and **Augmented + Modal** systems will be achieved without modifying the Argus II device. The imagery content for these modes will be computed by algorithms of the navigation system and then transmitted via video link to the Argus II for display to the Argus II user.

Figure 2 represents an example scenario where an Argus II user has requested guidance to the nearest door. The door has already been identified by object recognition during algorithm testing and stored in the system’s map of the environment. The path to the door is impeded by a couch, which is also stored in the map as an obstacle labeled by object recognition. Upon receiving the user request, the system computes a path around the couch to the door and initiates navigational cues to guide the user along the planned path. As the user progresses along this path, the door is enhanced (brightened) in artificial vision as being the target destination. Nearby obstacles (such as the couch) are also shown through the prosthesis (or the simulated prosthesis for normally sighted participants), while the system’s stereo-vision-based obstacle detection feature continually monitors the scene for both mapped and previously undetected obstacles along the way.

In addition to the navigation itself, participants will provide numerical ratings on scales to indicate the mental (cognitive) load of the task, perceived effort, and ease of travel. Participants will also provide qualitative answers to questions pertaining to their experience using the system, such as what elements of the system were more or less helpful and how they believe the system could be improved.

During the consent process, participants will be given the opportunity to consent to audio-video recordings being taken of them while performing the tasks of this study. Consenting to audio-video recording is not mandatory for subjects to participate in the study. For those participants who consent to audio-video recording, the recordings may be used to help analyze the participant’s performance in the study and may be used in presentations of the methods and outcomes of the study before a general audience. Audio-video recordings will not be used for advertising or non-study related purposes.

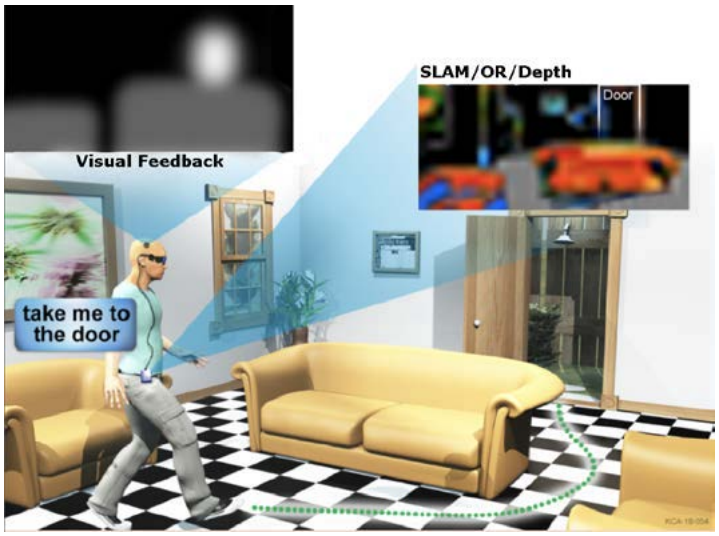

Figure 2 - Example navigation scenario for a blind user; although not shown in the figure, information communicated by the system to the user also enables the user to mentally form an egocentric spatial image of their surroundings.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Criteria for inclusion of normally sighted individuals:

- Subject speaks English;
- Subject is an adult (at least 18 years of age);
- Subject has the cognitive and communication ability to participate in the study (i.e., follow spoken directions, perform tests, and give feedback);
- Subject is willing to conduct psychophysics testing up to 4-6 hours per day of testing on 3-5 consecutive days;
- Subject has visual acuity of 20/40 or better (corrected);
- Subject is capable of understanding participant information materials and giving written informed consent.
- Subject is able to walk unassisted

Criteria for inclusion of Argus II users:
The inclusion criteria for the study are the following:

- Subject is at least 25 years of age;
- Subject has been implanted with the Argus II system;
- Subject's eye has healed from surgery and the surgeon has cleared the subject for programming;
- Subject has the cognitive and communication ability to participate in the study (i.e., follow spoken directions, perform tests, and give feedback);
- Subject is willing to conduct psychophysics testing up to 4-6 hours per day of testing on 3-5 consecutive days;

- Subject is capable of understanding patient information materials and giving written informed consent;
- Subject is able to walk unassisted (for participation in mobility tasks).

The aim for the normally sighted group is to avoid any visual acuity issues that could impact the participant's performance in the study. Therefore, we require a visual acuity of 20/40 or better with correction, which is sufficient to perceive the low-resolution visual feedback that will be displayed to sighted users using the VR headset. We also require sighted participants to be adults, as experiments with this group simulate a medical device that is used by only adults. For the Argus II group, the minimum FDA-approved age for use of the Argus II device is 25. We do not require a maximum age limit for this study group, but do require that participants are able to walk unassisted for participation in mobility tasks. Participants in the Argus II group who are not able to walk unassisted may still participate in non-mobility tasks, such as stationary tasks that evaluate the participant's ability to perceive and understand various forms of visual feedback provided to their retinal implant.

2.a Exclusion Criteria

Exclusion criteria for all subjects is the following:

- Subject is unwilling or unable to travel to testing facility for at least 3 days of testing within a one-week timeframe;
- Subject does not speak English;
- Subject has language or hearing impairment.

The requirement that subjects speak English and do not have a language or hearing impairment is due to the fact that this study involves use of a voice-enabled navigational aid that subjects will interact with via a speech interface both to control the system and to receive specific forms of information feedback from the system regarding the subjects' surroundings. The voice-enabled device leverages autonomous speech recognition and speech synthesis capabilities with support for only the English language. Therefore, it is required for subjects to both speak and hear English in order to fully utilize the capabilities of the navigational aid being developed for this pilot study; however, future accommodations may be made for non-English speakers or hearing impairments.

2.b Subject Recruitment Plans and Consent Process

As described in Section D1, this study will be conducted with three different sets of participants.

- The Argus II user group of participants will be recruited from Argus II users who have given their consent to be reached for human subject tests in previous non-significant risk studies. Subjects will learn about the study via phone call from a member of our study team.

- A normally sighted group of participants will be recruited from JHU/APL's staff of over 7,000. Interested candidates will be informed of the study through IRB-approved lab-wide human subject testing email distributions. Interested candidates will contact the PI and, if they meet inclusion/exclusion criteria, they will coordinate a time with the study team that would allow for experiments to take place.
- Another normally sighted group of participants will be recruited from JHU Homewood's students and staff. For this group of JHU Homewood participants, all direct recruitment will be conducted only by Nicolas Norena Acosta, a member of the study team who is both a full-time staff member of APL and a graduate student within the Whiting School of Engineering and who is not involved in the academic supervision of students at JHU Homewood. This recruitment by Nicolas Norena Acosta will be conducted by word-of-mouth and/or through IRB-approved human subject testing email distributions. Interested candidates will contact Nicolas Norena Acosta and, if they meet the inclusion/exclusion criteria, they will coordinate a time with the study team that would allow for experiments to take place.

Prior to beginning the study, the PI or study team members qualified to consent, will walk each interested candidate through the consent form, providing additional details about the study, and if a candidate is still interested, consents and has time, they will be able to begin the first testing day immediately after providing informed consent. Study participants are also free to leave the study at any time.

2.c Risks and Benefits

This is a non-significant risk study in which no medical procedures will be performed. It is not a treatment, and it has no impact on healthcare or health itself. There will be no exchange of information with physicians.

Elements of minimal risk are described herein. We divide the risks into three groups: common to all participants, Argus II users only, and normally sighted users only.

As described in Section D1, the tasks associated with this study require a participant to walk slowly or stand in place while making simple judgments such as pointing to a target in space, judging distance, and discriminating identities or direction of motion of target objects.

Risks for All Participants:
Navigating through an unfamiliar environment with limited visibility (delivered through the HMD for normally sighted participants) involves a *risk of tripping or stumbling over obstacles* deliberately placed in the environment. Our team has worked in this kind of testing and to-date this risk has never materialized. This is due to a combination of ensuring the participants understand the requirement to

walk slowly toward their intended targets, as well as team attentiveness and experience surrounding the execution of these tasks while standing in close proximity to assist as necessary.

The non-medical devices used in this study, including headphones and vibrotactile stimulators, have insignificant risk similar to use of headphones and vibration-enabled devices such as a smart watch, a now very common device in everyday life.

Additionally, subjects may *become tired or fatigued* during the testing. Experiments require focused concentration of the participants which may lead to fatigue. For similar reasons, minor discomforts such as headaches or backaches may occur. Participants may take as many breaks as they need and may discontinue testing at any time.

Participants may also become *frustrated or disappointed* if they feel they are not performing well. We will remind participants that this technology is novel and has potential benefits for other Argus II users and others with very limited visual acuity. As mentioned above, we will ask participants whether they want to interrupt testing to discuss this in more detail or if they wish to withdraw altogether.

The research information obtained from human subjects will consist of eligibility data, user-specific configuration settings for the Argus II device, sensor data required to create maps of the testing environment, and behavioral data (includes video). As a result, there is a risk of *breach of confidentiality*. This is mitigated by ensuring that all PII is stored on password protected computers at all sites.

Risks for Argus II Users:
For Argus II users there are no risks associated with using the Argus II device that are greater than the risks that participants face using their Argus II device in their everyday lives. In accordance with the device's Safety and Probable benefit document (https://www.accessdata.fda.gov/cdrh_docs/pdf11/H110002B.pdf), the following precautions will be followed:

- In the event of any undesirable sensation when using the device, all operations will be halted, and Argus II glasses will be removed or the Argus II Visual Processing Unit (VPU) will be turned off.
- Argus II users will only use a VPU that has been specifically programmed for them by their clinician or Second Sight personnel.
- Argus II users will continue to use their other mobility aides, such as a cane, at all times.

Risks for JHU/APL Participants:
Normally sighted study participants at JHU/APL will be asked to don a head mounted display for extensive periods of time. In addition to the common risks mentioned above, there is a *risk of dizziness and fatigue* caused by extensive use of the HMD. As above, this risk is mitigated by taking as many breaks as

participants request as well as interrupting testing and potentially resuming on a different day if requested by a participant. Here too, participants are free to withdraw from the study at any time.

Benefits:

Potential benefits that individual participants may experience from taking part in this research stems from the new sensory information afforded to prosthetic vision users by providing them with object recognition and navigational capabilities, as well as the addition of haptic and auditory sensory feedback to supplement prosthetic vision. This may help current and future prosthetic vision users to independently form mental maps of their surroundings using their prosthetic vision device and allow users to gain confidence in using the device for navigating new environments.

2.d Early Withdrawal of Subjects

In all cases, expected time commitments will be clearly communicated to participants ahead of time. It will also be clearly communicated to participants that they may choose to withdraw from the research at any time for any reason.

2.e When and How to Withdraw Subjects

Subjects will be withdrawn early from the study anytime upon subject request. It is also possible that other factors may contribute to the need for early withdrawal. For example, a malfunction of the system may cause us to have to stop testing. No special procedures are associated with withdrawing a subject early from this study other than to discontinue testing. Participants will be compensated for their time spent participating in the study prior to early withdrawal as described in Section I3.

2.f Data Collection and Follow-up for Withdrawn Subjects

In case of early withdrawal, no further data gathering nor follow-up will be conducted with the subjects. As for all subjects, if a subject consents to be contacted for future research, they may be contacted later for future studies.

D3 Study Device

3.a Description

The following devices are used in this study. No device will be used with any study participant prior to being reviewed and approved by Johns Hopkins' clinical engineering services (CES).

- Argus II Retinal Prosthesis System: used in this study by Argus II users who have a pre-existing implanted retinal prosthesis. This is an FDA approved device and will be used according to its intended use.

- Head Mounted Display: used in this study by normally sighted users to simulate the field of view and visual acuity provided by the Argus II device. For this device we will use a virtual reality headset, such as the Oculus Quest or HTC Vive or equivalent. Use of this device in the study will require review and approval by Johns Hopkins Clinical Engineering Services (CES) prior to being used in the study.
- Embedded Processing Platform and Sensors: an embedded processing platform will be used to process information acquired by the various environmental sensors and to run the algorithms for image processing and navigation. Imagery displayed to users will be computed by this platform. For Argus II users, the computed images will be transmitted to the Argus II system for display via the retinal prosthesis, whereas, for sighted users, the computed images will be transmitted to the HMD device. The embedded processing platform and associated sensors will be battery powered. The system will be carried by the user via a beltpack or other suitable means of mobility, along with head gear for carrying the head-mounted sensors. This system will incorporate various sensors such as an RGB camera, depth sensor, and inertial measurement unit (IMU) for sensing objects and tracking the environment. Example environmental sensors that may be used include the Intel RealSense Depth Camera D435i and Intel RealSense LiDAR Camera L515 or similar. Use of the embedded platform and sensors will require review and approval by Johns Hopkins Clinical Engineering Services (CES) prior to being used in the study.
- Wearable Haptic Device: used in this study to augment sensory feedback delivered back to the user, such as to guide the user in a direction to turn their head in order to visually locate an object of interest. This device will be battery-powered and designed to be worn and used by a human with insignificant risk. Specifically, we will embed haptic actuators (such as the Zorb vibrotactile actuators from Somatic Labs) within a body-worn device that when donned provides localized haptic feedback to signify directionality. For example, a neckband device may provide localized vibration points behind the neck, over each shoulder, and in front of the chest, with each vibration point signifying one of the four cardinal look directions (up, down, left, and right). This device will also require review and approval by Johns Hopkins Clinical Engineering Services (CES) prior to being used in the study.
- Wearable Audio Device: used in the study to augment sensory feedback delivered back to the user by using voice and/or audible tones to communicate, such as communicating the identity or locations of objects in the scene or communicating which direction to turn in order to advance towards a destination. For this device we will use either conventional or bone-conduction headphones such as the Aeropex from Aftershokz or equivalent or other form of wearable speakers such as the neck-worn Soundwear Companion from Bose or equivalent. This device

will also require review and approval by Johns Hopkins Clinical Engineering Services (CES) prior to being used in the study.

3.b Treatment Regimen

The Argus II device will be used in accordance with its intended use. All other devices will require IRB CES approval for use in human testing.

E Study Procedures

E1 Screening for Eligibility

As described in Section D2.b, subjects will be recruited from normally sighted populations at the Johns Hopkins University Applied Physics Laboratory and JHU Homewood campus as well as from lists of users of the Argus II device who have participated in prior studies associated with their device and who have granted consent to be contacted for future studies. As long as interested candidates meet the inclusion criteria and are not rejected by the exclusion criteria they will be eligible to participate in this study.

E2 Schedule of Measurements

Testing is expected to be conducted over a 1-5 day period for each participant. We anticipate that testing will require less time for the normally sighted participants than for the Argus II users.

E3 Visit 1

Apart from the consent process that occurs at the beginning of the first visit, the testing performed during the study visits will be similar to each other. For the consent process, the PI or authorized study team member will guide interested subjects through the informed consent form. Following consent, participants will be asked to perform three groups of tasks, as described in Section D1. Participants will be informed during consent that while breaks will be provided during the course of testing, they are also free to interrupt testing at any time to take breaks.

E4 Following Visits

See Section E3.

E5 Safety and Adverse Events

Study team members will complete all IRB training required to conduct the experiments described in this application prior to being involved in any human subject testing.

Communication between sites is primarily facilitated via working conference meetings held at least once per month between key team members from each site. Planning for significant protocol events regarding the study, such as amendments to study protocols, annual approvals, etc., will be discussed among all sites in these meetings, as well as communicated between sites via email where appropriate. A Box share folder has also been set up to host and distribute information among all sites and will serve as a single point of reference for obtaining the most up-to-date information regarding the study, such as the most current version of the study protocol.

Both the PI (Dr. Billings) and the site-PI's at each study location will be responsible for monitoring participant safety, evaluating the progress of the study, reviewing procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses, in accordance with guidance provided by the IRB of record. In case of protocol events or deviations at participating sites, any team member aware of the issue will promptly notify the PI (Dr. Billings) and site-PI, and a report will be promptly submitted to the IRB (and sponsoring agency if appropriate) per the JHM IRB's prompt reporting requirements, as described further below.

The research data will be reviewed every day that data are collected, and the accrued data reviewed again at the end of the study to ensure its validity and integrity. The PI will conduct study team meetings on at least a monthly basis to discuss study progress, data quality and any unanticipated problems or findings will be reported upon occurrence. Reports concerning the progress of the study and subject status will be provided in the study closure report or when requested by the IRB.

If any protocol changes are needed, they will not be implemented prior to IRB approval, with possible exception of minor or administrative deviations which do not affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects. If a protocol deviation occurs which meets this definition for a minor deviation, the deviation will be reported to the JHM IRB at the time the continuing review application is submitted in eIRB using the Protocol Deviation Summary Sheet (R.F. 4).

In the event of an emergency protocol deviation taken without prior IRB approval to protect the life or physical well-being of a participant, it will be reported to the sponsor and the IRB of record as soon as possible, but not later than 5 days after the emergency situation occurred.

The research teams at all site locations will monitor subjects for adverse events throughout the study. Adverse events that fit the following criteria will be reported to JHM IRB within 10 working days from the time when the principal investigators become aware of them per JHM IRB policy:

- Event is UNEXPECTED (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- RELATED or POSSIBLY RELATED to participation in the study (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the study); and

- Suggests that the study PLACES SUBJECTS OR OTHERS AT A GREATER RISK OF HARM (including physical, psychological, economic, or social harm) than was previously known or recognized.

The following unanticipated problems that are not adverse events will also be reported to the IRB within 10 days of becoming aware of them:

- Unanticipated problems that do not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the study, or significantly impact the integrity of study data. An example of this might be a report of accidental destruction of a study record;
- Unplanned protocol deviations/violations that have already occurred, that may adversely affect the rights, safety or welfare of subjects or the integrity of the study data, AND for which IRB approval was not obtained.

In reporting any deviations or adverse events to the IRB, the PI will submit a report to the IRB of record in eIRB via a Further Study Action for Protocol Event Report.

In addition to reports issued to the IRB, any unanticipated problem involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR 46 or IRB requirements must be reported to the sponsoring agency (NIH) and to the Office for Human Research Protections (OHRP), HHS, per NIH policy.

5.a Medical Monitoring

i Investigator only

N/A. This is a non-significant risk study and interested candidates will not be undergoing medical procedures as part of this study.

5.b Definitions of Adverse Events

An adverse event is any undesirable experience associated with the use of a medical product in a patient. Adverse events may occur during the course of this study. The medical device that will be used in these studies is the FDA HDE approved Argus II Retinal Prosthesis System.

5.c Classification of Events

See Section E5.

5.d Data Collection Procedures for Adverse Events

See Section E5.

5.e Reporting Procedures

See Section E5.

5.f Adverse Event Reporting Period

See Section E5.

5.g Post-study Adverse Event

This is a non-significant risk study, no post-study adverse events are anticipated.

E6 Study Outcome Measurements and Ascertainment

Our study will determine whether the following hypotheses are correct:

1. The augmented systems expand users' ability to identify targets in the field of view and to usefully interpret the egocentric information obtained from the retinal prosthesis by augmenting the basic Argus II device with the capability of decluttering the scene and by providing discriminative information to convey object identities and locations.
2. Aided by the augmented system, the retinal prosthesis is capable of enabling the formation of an externalized spatial image that aids navigation.

These hypotheses will be tested statistically with sighted subjects (see Section F) by measuring proportion correct assessments as well as through bias and precision measurements. Argus II subjects will be assessed individually to determine whether augmentation leads to lower error, and their error will be quantified through comparisons with the sighted subjects.

F Statistical Plan

F1 Sample Size Determination and Power

No significance testing will be possible with Argus II participants due to the small number of people expected to be recruited for each Argus II participant group in this study (approximately 5).

Importantly, however, we will use the sighted subjects, who simulate the performance of Argus II users through the head mounted display conveying information similar to what is perceived by Argus II users, as a baseline. As described in G3, we characterize performance by Argus II users on any given task relative to this baseline.

In particular, for tests with sighted subjects, we use within-subject factorial designs and test with conventional ANOVA statistics; inter-subject correlations between abilities tests can also be computed. We use sample sizes based on prospective power analysis. A sample size of 20-30 subjects was calculated with [9] to achieve

a power greater than 0.80 at the 0.05 level of significance, using effect sizes from previous studies reporting perceived spatial layout in within-subject designs [10]. As a more general point, the experiments use a within-subject design, in which every subject provides a replicate of the entire study. In psychophysical research (i.e., where a physical variable is parametrically explored), these designs are typically done with populations on the order of 10-20 participants. The proposed sample is also consistent with similar studies of navigation by spatial updating (e.g., [11]).

F2 Analysis Plan

For each measure, the Argus II participants will be characterized by the z-score distance of their performance from the sighted participants (as computed with their mean and variance). We will use two other approaches to assess the Argus II participants' performance: (i) Use standards from the literature for basic psychophysical effects, including setting .2 as an effective d' score for 2- choice discrimination, based on Cohen's d effect-size statistics; setting 25% as the expectation for a size difference threshold, and setting a standard of 15° for absolute pointing error based on screening cutoffs in previous work. (ii) Set standards by considering the device capabilities; in particular, use distance expressed in device pixels between target and pointing locations in order to measure localization error. Finally, we intend to test the effects of learning by assessing performance over time. For this, we will fit trends to the measures over repeated trials and assess the linear component for a positive slope.

F3 Statistical Methods

See previous sections for additional information about the methods employed for this study.

G Data Handling and Record Keeping

G1 Confidentiality and Security

Every effort will be made to keep Personally Identifiable Information (PII) associated with the study confidential: (1) subjects will be assigned a code number and only the code number will be used to identify the limited clinical information that will be analyzed; (2) the computers on which the data will be stored are password protected and all of them are located in offices with key locks; (3) written documents concerning the study will be kept in locked cabinets; (4) all personnel involved in human subject testing will have completed the appropriate HIPAA training and be fully aware of the need for confidentiality regarding PII. No health information will be acquired for this study.

G2 Training

All study team members are required to take IRB compliance training. At a minimum, this consists in Basic Human Subjects Research (CITI) training, Health Privacy Issues for Researchers training, and Conflict of Interest and Commitment training per JHM IRB policy, in addition to Good Clinical Practice training as required by NIH. PIs are also required to take Research Ethics Workshops About Responsibilities and Duties of Scientists training.

G3 Records Retention

In accordance with IRB policy, records will be retained for five years after the date of the last publication associated with the study.

G4 Performance Monitoring

Data will be analyzed following each testing session to evaluate system performance.

H Study Monitoring, Auditing, and Inspecting

H1 Study Monitoring Plan

This is a non-significant risk study. The PIs at each site are responsible for the monitoring and execution of the testing. The JHM IRB, as the single IRB of record, will be responsible for reviewing the study protocols, consent forms, and case report forms.

H2 Auditing and Inspecting

This is a non-significant risk study. The JHM IRB regularly conducts audits to ensure that studies are in compliance.

I Study Administration

I1 Organization and Participating Centers

The following centers are involved in the study described in this protocol:

- Johns Hopkins University Applied Physics Laboratory, Laurel, MD
- Johns Hopkins Medicine, Wilmer Eye Institute, Baltimore, MD
- Johns Hopkins University Homewood Campus, Baltimore, MD
- Carnegie Mellon University, Pittsburgh, PA

I2 Funding Source and Conflicts of Interest

This research is supported by National Institutes of Health (NIH) National Eye Institute (NEI) grant number 1R01EY029741-01.

I3 Subject Stipends or Payments

Subjects recruited from the Applied Physics Lab will be paid for their time in accordance with APL policies. Subjects recruited from the JHU Homewood campus will be uncompensated. Argus II users will be reimbursed for their costs associated with the study, such as travel to the testing facility and lodging, and will be provided with meals throughout their participation in the study.

I4 Study Timetable

Testing will commence upon IRB approval of the study and continue through the duration of the grant, expected to end in July 2024. Requests for changes in research and extensions to the protocol will be made as necessary during this time.

J Publication Plan

Deidentified data and results from this study may be submitted for submission to peer-reviewed conferences and journals, as well as abstracts and presentations at sector specific conferences (e.g. NIH Brain Initiative meeting).

K Attachments

K1 Informed consent documents

Informed consent documents are attached.

L References

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M Safety Protocols for COVID-19

Per JHU IRB guidance, we will not enroll any participants in this study until the COVID-19 emergency for Tier 3 research studies has been lifted by the IRB.