Virtual Reality for Enhancement of Vision

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1. PURPOSE OF THE STUDY

a. Brief Summary

This project aims to evaluate the use of Virtual Reality (VR) based visual stimulation for the treatment of blindness arising from Glaucoma and other retinal diseases or disorders of the visual system, through regeneration of axons of retinal ganglion cells (RGCs) in humans. In certain cases of blindness, such as in Glaucoma, or in certain injuries, the optic nerves behind the retina of our eyes get damaged, leading to partial blindness, mostly near the periphery of our eye. Recent research in Dr. Huberman's laboratory has identified visual stimulation as a non-invasive model for regeneration of such damaged axons in rodents, back to the vision centers of their brain.

b. Objectives

This project will help us to evaluate the feasibility of using virtual reality-based approaches for retinal regeneration in humans with glaucoma, retinal diseases or other optic injuries. We will use Best corrected visual acuity, Humphrey visual field test, Ocular Coherence Tomography to evaluate functional and structural changes and the National Eye Institute's visual functional questionnaire (VFQ-25).

c. Rationale for Research in Humans

The purpose of the study is to evaluate the effect of VR based stimulation on patients with glaucoma, other retinal diseases or disorders of the visual system and subjects with normal vision.

2. STUDY PROCEDURES

a. Procedures

Screening visit will include eye exam, best corrected visual acuity (BCVA), Humphrey visual field test (HVF), and Ocular Coherence Tomography (OCT), all these tests will be performed as standard of care. Baseline visit will include HVF and VFQ25. VFQ25 could be also applied at screening visit. After subject complete Screening and Baseline visit within 8 weeks, the subject will be trained on how to do VR stimulation. And will be provided a VR headset to take home. The VR or VR stimulation will consist in up to 1 hour per day session that will be done at home Monday through Friday for 12 weeks and the following week BCVA, HVF will be performed. The following week the study subject will start another cycle of 12 weeks of VR stimulation and the following week, will repeat test (BCVA, HVF) and so until the study subject complete up to 8 cycles. At

least 8 weeks after completing the last cycle subject will do HVF, OCT, BCVA and VFQ25. VR 1-hour sessions will consist of an exposure to a non-invasive visual stimulation where the subject will be siting wearing a VR headset. After subjects complete 52 weeks of VR stimulation (4 cycles) they will be able to continue for another 52 weeks (4 cycles), or stop the VR stimulation and we will follow them doing only the testing (Visual acuity, Visual field test, OCT) every 12 weeks for another 12 months. The VR or VR stimulation will be performed as part of research, at no cost, HVF, OCT an eye exam will be considered standard of care and billable to subject insurance.

b. Procedure Risks

The VR stimulation is a designed computational model developed by Stanford University researchers, this model aims to maximize the activity of the neurons in the retina, and it will pose no more than minimal risks involved with using any of the currently commercially available Virtual Reality platforms, such as the Oculus Rift (https://www3.oculus.com/en-us/rift/), or the HTC Vive (https://www.amazon.com/HTC-VIVE-Virtual-Reality-System- Pc/dp/B00VF5NT4I), or the magic leap's system (https://www.magicleap.com/). BCVA, HVF and OCT tests are currently performed at the clinic for regular patient care, and will be used to measure any structural or functional change. The VFQ-25 will also tell us if there is any significant impact in the quality of life/vision of the study subjects.

c. Use of Deception in the Study

No deception will be used.

d. Use of Audio and Video Recordings

No audio or video recording will take place.

e. Alternative Procedures or Courses of Treatment

There are alternative treatments available for glaucoma including drug therapy and surgery that are used to reduce the intraocular pressure. Participants will be able to continue their current glaucoma treatment during their participation in the study and get any of these treatments as needed.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes

g. Study Endpoint(s)

Primary and secondary efficacy endpoints will be measured by:
-Change in visual field by any one of the following three indices:
1. Visual Field Index(VFI)
2.Meand Deviation (MD)
3.Pointwise linear regression (PLR) analysis
-Change in the OCT: retinal nerve fiber layer (RNFL), change in ganglion cell layer, changes in other retina cell layers

-Change in BCVA

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Recently, a groundbreaking paper came out from the Huberman lab (Lim, J. H. A., Stafford, B. K., Nguyen, P. L., Lien, B. V., Wang, C., Zukor, K., ... & Huberman, A. D. 2016. *Neural activity promotes long-distance, target-specific regeneration of adult retinal axons*. Nature Neuroscience) identifying biased visual stimulation as an independent non- invasive modality for retinal regeneration in animal models. They also found that the effects of the visual stimulation were mediated through spiking in the retinal-ganglion cells in the animal models. Also, very recently, Gall et al. (Gall, C., Schmidt, S., Schittkowski, M. P., Antal, A., Ambrus, G. G., Paulus, W., ... & Lux, A. 2016. *Alternating current stimulation for vision restoration after optic nerve damage: a randomized clinical trial*. PloS one, 11(6), e0156134) has reported a mean improvement of 24% in the visual field when they applied repetitive transorbital alternating current stimulation to partially blind patients (optic nerve damage). Earlier, EJ Chichilnsky's research (Pillow, J. W., Shlens, J., Paninski, L., Sher, A., Litke, A. M., Chichilnisky, E. J., & Simoncelli, E. P. 2008. *Spatio-temporal correlations and visual signalling in a complete neuronal population*. Nature, 454(7207), 995-999) has identified a model for generating stimulus leading to correlated spiking activity across a complete population of parasol RGCs in macaques. Matsuura et al. (Matsuura, M., Hirasawa, K., Murata, H., & Asaoka, R. 2015. *The Relationship Between Visual Acuity and the Reproducibility of Visual Field Measurements in Glaucoma Patients*. VA and Visual Field Measurement ReproducibilityIOVS. Investigative ophthalmology & visual science, 56[9], 5630- 5635) recently reported that reproducibility of visual field tests becomes poor with the deterioration of visual acuity, suggesting a relation between the two. A couple key animal studies have led to the formulation of this project, which we mention below.

b. Findings from Past Animal Experiments

Recently, a groundbreaking paper came out from the Huberman lab (Lim, J. H. A., Stafford, B. K., Nguyen, P. L., Lien, B. V., Wang, C., Zukor, K., ... & Huberman, A. D. 2016. *Neural activity promotes long-distance, target-specific regeneration of adult retinal axons*. Nature Neuroscience) that identified biased visual stimulation as an independent non- invasive modality for retinal regeneration in animal models. They also found that the effects of the visual stimulation were mediated through spiking in the retinal-ganglion cells in the animal models. A recent paper in animal models (Baden, T., Berens, P., Franke, K., Rosón, M. R., Bethge, M., & Euler, T. 2016. *The functional diversity of retinal ganglion cells in the mouse*. Nature, 529(7586), 345-350) has used a series of visual stimulation (chirp, moving bars, noise and color), leading to activation (through spiking) of more than 30 functional output channels in the mouse retina. Earlier, EJ Chichilnsky's research has identified a model for generating stimulus leading to correlated spiking activity across a complete population of parasol RGCs in macaques.

We plan to tailor our visual stimulation based on these models.

4. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	Virtual Reality software
Significant Risk? (Y/N)	No

5. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

N/A

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Proparacaine Hydrochloride
Dosage:	0.5%
Source	Byers Eye Institute Clinic
Commercial Product 2	
Name:	Tropicamide
Dosage:	0.5%
Source	Byers Eye Institute Clinic
Commercial Product 3	
Name:	Phenylephrine
Dosage:	2.5%
Source	Byers Eye Institute Clinic

6. PARTICIPANT POPULATION

a. Planned Enrollment

200 subjects with glaucoma or other retinal diseases or disorders of the visual system 100 normal controls (patients with normal vision) General population, above the age of 12, willing to take part in our study, with glaucoma or other retinal diseases or disorders of the visual system or normal controls. All subjects will be recruited at Byers Eye Institute Stanford University

b. Age, Gender, and Ethnic Background

Age >12 both sexes will be recruited. Any ethnic background.

c. Vulnerable Populations

No potentially vulnerable subjects will be actively recruited into this study.

d. Rationale for Exclusion of Certain Populations

Children 12 years old and older will be included in the study. Current VR systems have proven to be safe on children 12 years and older.

e. Healthy Volunteers

100 patients with normal vision (healthy volunteers) will be recruited for the study, as long as they satisfy screening, inclusion and exclusion criteria.

The participants will be exposed to no more than minimal risk, associated with watching media on currently commercially available Virtual Reality platforms, such as the Oculus Rift (https://www3.oculus.com/en-us/rift/), or the HTC Vive (https://www.amazon.com/HTC-VIVE-Virtual-Reality-System-Pc/dp/B00VF5NT4I), or the magic leap's system (https://www.magicleap.com/). Additionally, to protect the welfare of the participants, they will be clearly told in the informed consent, which they will sign before entering the study, that they are free to discontinue at any point if they want.

f. Recruitment Details

Participants will be identified from the Stanford Healthcare clinic population at the Byers Eye Institute at Stanford who meet the inclusion criteria. Participants who are identified during chart review will be notified of their eligibility, after the patient's physician has previously notified the potential research participant and obtained approval to be contacted.

g. Eligibility Criteria

i. Inclusion Criteria

For subjects with glaucoma, other retinal diseases, or disorders of the visual system:
1. Patient age > 12 years
2. Compliance with investigator instructions, tests and visit during subject participation in the study.
3. Sufficient fixation ability
4.Best corrected visual acuity of 20/200 or better in at least one eye, or capable to see the visual stimulus at least in one eye.
For healthy volunteers:
1. Patient age > 12 years
2. Compliance with investigator instructions, tests and visit during subject participation in the study.
3.Best corrected visual acuity of 20/20 in both eyes.
4. Sufficient fixation ability

ii. Exclusion Criteria

1. Electric or electronic implants (such as cardiac pacemaker)
2. Any metal artifacts in the head or truncus area (with the exception of dental implants)
3. Epilepsy and photo-sensibility; acute auto-immune diseases
4. Acute conjunctivitis
5. Pathological nystagmus

h. Screening Procedures

All screening test will be performed at the ophthalmology clinic, pre-screening of potential subjects will be done through Epic system.

i. Participation in Multiple Protocols

As part of the consent process, potential subjects will be asked if they are participating in any other studies. Participating in other studies will not be an exclusion criteria to participate in this study.

j. Payments to Participants

Subjects will not be paid.

k. Costs to Participants

The VR stimulation sessions will not have any cost to the participants, all other procedures (Eye exam, visual field, OCT) will be billable to patient insurance as standard of care, patient will be responsible of any copays.

l. Planned Duration of the Study

The estimated active participation of the study subjects is 24 months.
Screening visit may take about 2-3 hours
The data analysis of all study participants will be approximately 6-8 years.

7. RISKS

a. Potential Risks

Non-invasive visual stimulation procedures frequency - Overall 40 sessions within 8 weeks. Each session around one hour. severity - The visual stimulation procedure will be no more severe than viewing content through any of the currently commercially available Virtual Reality systems, such as the Oculus Rift (https://www3.oculus.com/en-us/rift/), or the HTC Vive (https://www.amazon.com/HTC-VIVE-Virtual-Reality-System-Pc/dp/B00VF5NT4I), or the magic leap's system (https://www.magicleap.com/) There is a risk of experience motion sickness, however the investigators have reduce this at minimum, by ensuring that there is minimal, if any, mismatch of vergence-accommodation and visual proprioceptive cues. reversibility - We do not expect the commercially available VR system we shall use to produce any undesirable effect in any form. Other procedures will be BCVA, HVF, OCT that are usually performed at the clinic as standard of care and possess minimal risk. Risks of Eye Examination and Dilation: A combination of eye drops (phenylephrine, tropicamide and proparacaine hydrochloride) will be used to widen your pupils. These drugs are used routinely in any dilated fundus exam in an ophthalmologist's clinic. It is likely that your eyes may be sensitive to light after they are dilated, but wearing sunglasses helps this, and it will decrease in a matter of hours after you receive the drops. If you find it difficult to drive after receiving dilating eye drops, you should arrange for transportation home after the testing. You may experience temporary glare and blurry vision when eyes are dilated.

Risk of Optical Coherence tomography (OCT) There are no known risks associated with OCT. Risk of Visual field test There are no known risks associated with visual field test.

b. Procedures to Minimize Risk

We plan to use commercially available Virtual Reality hardware, which goes through the standard safety protocols for testing before being available in the mass market. The investigator will keep the participant under active observation at all times during the VR sessions, and will discontinue promptly if the participant feels discomfort at any point. All confidential information will be kept in password-protected Stanford owned computers, accessible only to the investigators registered in this protocol.

c. Study Conclusion

In the event of premature withdrawal from the study, the termination date will be the last date the subject is seen at the clinic or the date of the last telephone contact with the subject.

d. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

Adverse events, protocol deviations, aggregate data analysis reports, progress toward study endpoint(s), participant consent forms.

ii. Person(s) responsible for Data and Safety Monitoring

The Protocol Director.

e. Risks to Special Populations

We will utilize current available VR system that has been already recommended to be used in children 13 years old and older. The Oculus Rift and Samsung's Gear VR headsets are recommended for ages 13+, while Sony's recommendation for its PlayStation VR is ages 12 and up. And Google cardboard headset should be used by kids under adult supervision. The headsets that we will be using will be similar to the current available on the market (Oculus Rift and Samsung's Gear VR headsets), while they use it, they will be sitting and under adult supervision.

8. BENEFITS

The participants may improve their visual acuity and visual field. The knowledge gained from this study can be combined in future with other therapies in patients suffering from lack of vision arising from glaucoma or other retinal diseases, as well as disorders of the visual system.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.