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A MULTI-SITE INTERVENTIONAL PILOT STUDY USING TRANSORBITAL ALTERNATING CURRENT STIMULATION FOR PEOPLE WITH GLAUCOMA

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Study Intervention: Repetitive transorbital alternating current stimulation to treat visual impairment in people with glaucoma

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List of Abbreviations

ACS = alternating current stimulation
BOLD = blood-oxygen-level dependent
CS = contrast sensitivity
D-KEFS = Delis-Kaplan Executive Function System
EEG = electroencephalography
EST = electrical stimulation therapy
ETDRS = Early Treatment Diabetic Retinopathy Study
FDA = Food and Drug Administration
fMRI = functional magnetic resonance imaging
GAS = Geriatric Anxiety Scale
HIPAA = Health Insurance Portability and Accountability Act
HRQoL = health-related quality of life
IOP = intraocular pressure
IRB = Institutional Review Board
LIFE-H = Assessment of Life Habits
logMAR = logarithm minimal angle of resolution
M = magnocellular
MD = mean deviation
MNRead = Minnesota Low Vision Reading Test
MRI = magnetic resonance imaging
NYULMC = NYU Langone Medical Center
OCT = optical coherence tomography
OCT-A = OCT angiography
ON = optic nerve
PERG = pattern electroretinography
PI = principal investigator
PSQI = Pittsburgh Sleep Quality Index
QoL = quality of life
RGC = retinal ganglion cell
RNFL = retinal nerve fiber layer
rtACS = repetitive transorbital alternating current stimulation
SF-36 = 36-Item Short Form Survey
TICS-m = Telephone Interview for Cognitive Status-modified
VA = visual acuity
VEP = visual evoked potential
VF = visual field
VFQ-39 = 39-item Visual Functioning Questionnaire
VRQoL = vision-related quality of life
WAIS-IV = Wechsler Adult Intelligence Scale-Fourth Edition

Study Summary

Title	**A Multi-site Interventional Pilot Study Using Transorbital Alternating Current Stimulation for People with Glaucoma**
Short Title	rtACS for people with glaucoma
IRB Number	s16-02005
Methodology	Prospective, randomized controlled (active versus sham repetitive alternating current stimulation [rtACS]) double-masked pilot study. Participants and interventionist masked to group.
Study Duration	February 2017 to December 2021
Study Center(s)	NYU Langone Eye Center New York Eye and Ear Infirmary of Mount Sinai
Objectives	(1) Determine an effect of rtACS on ophthalmic structure and function (from eye to visual brain) (2) Assess the methodology of procedures for assessment of people's functional ability and quality of life to determine an effect of rtACS (3) Assess the feasibility and implementation of the pilot study protocol for a larger multi-site, randomized controlled trial
Number of Subjects	n = 16
Diagnosis and Main Inclusion Criteria	Adults with moderate to severe stage glaucoma, absent ocular and certain systemic comorbidities
Study Intervention	rtACS to treat visual impairment in people with glaucoma
Reference therapy	Sham stimulation
Statistical Methodology	Descriptive statistics, multivariate analyses, and estimates of effect and variance for between and within groups (active versus sham rtACS) analyses

1 Introduction

This document is a clinical research protocol for a human clinical research study. This study will be conducted in compliance with the written protocol and in accordance with U.S. federal research regulations, Good Clinical Practices standards, and NYU Langone Medical Center (NYULMC) institutional research policies and procedures.

The proposed pilot study will test the preliminary efficacy and feasibility of an intervention protocol for repetitive transorbital alternating current stimulation (rtACS) for the treatment of visual impairment in people with glaucoma. We will evaluate a study protocol to use in future clinical trials to test the effectiveness of rtACS to ameliorate the progressive effects of vision loss both structurally and functionally in the eye, the visual pathway, and in regard to people's independence (i.e., functional ability).

1.1 Background

Vision is the dominant sense[1] humans use to interact with and understand the many facets of everyday life. Vision is integral within other sensory systems as well (e.g., vestibular system). The health of people's visual system influences how they learn, communicate, work, engage in leisure, and interact with the environment that surrounds them. Vision changes as a normal part of aging. Aging Americans are living longer; the generation of Americans living into older age (i.e., Baby Boomers) is a larger population cohort than previous generations. The number of Americans aged 65 years and older, ages when people are more vulnerable to vision loss due to age-related eye diseases, is projected to increase from approximately 47.8 million (2015) to 98.2 million (2060).[2] Visual impairment is one of the 10 most common causes of disability in the U.S.[3] In a 2014 population survey, 11.3% of adults aged 45 to 64 years and 13.5% of adults aged 65 years and older reported some form of vision-related difficulty.[2,4]

The number of Americans with major chronic eye diseases is increasing[5] and visual health is increasingly a major public health concern.[6] Adults with degenerative eye diseases, who are at greater risk for progressive vision loss, live with an uncertainty that their vision may deteriorate over time and that currently there is no cure or means to reverse the progression. Vision loss is associated with a higher prevalence of chronic conditions,[7] death,[8] falls and injuries,[9] depression and social isolation.[10,11] People with visual impairment have higher odds of receiving informal care and lower odds of reporting a favorable health status than people without visual impairment.[12] Glaucoma is one of the most prevalent causes of progressive visual impairment and is a leading cause of irreversible blindness.[13]

1.1.1 Glaucoma

Glaucoma affects people's capabilities to perform daily living tasks (i.e., functional ability)[14-19] and their quality of life (QoL),[20-22] even when people were unaware of their diagnosis.[21] The prevalence of glaucoma is increasing. In the U.S. the estimated number of Americans with glaucoma will more than double from 2.7 million (2010) to 7.3 million in 2050.[23] As many as 50% of affected people with glaucoma are unaware of their diagnosis.[24] The estimated U.S. direct medical costs for glaucoma-related health care are approximately $2.9 billion annually,[25] an estimated $748 million for Medicare beneficiaries.[26] However, these financial estimates do not account for indirect costs of financial burden on individuals, caregivers, and non-governmental healthcare payers.

The silent burden of glaucoma is its insidious nature. The pathophysiology of glaucoma is not well understood; factors contributing to its progression include mechanical, vascular, and biochemical mechanisms.[27] The structures in the eye affected by glaucoma are neural (e.g., retinal ganglion cells), vascular (e.g., central artery and vein), and connective (e.g., trabecular meshwork) tissues. Glaucoma is typically characterized by increased intraocular pressure (IOP), retinal nerve fiber layer (RNFL) and optic nerve (ON) damage, and progressive loss of visual fields (VFs). Glaucoma is a chronic optic neuropathy that manifests through damage (degeneration) to the ON and death of retinal ganglion cells (RGCs). RGCs are neurons in the eye that transmit visual information from the retina to the brain via the ON.

In glaucoma, secondary damage to and death of RGCs result in visual function deficits, such as VF defects and diminished contrast sensitivity (CS).[28,29] These secondary damages are attributed to primary damage at the ON head and lamina cribrosa, a vulnerable area where the ON connects with the axons of

RGCs (Figure 1). In the visual system, information about the visual world is acquired, processed, and conveyed from the retina to visual centers in the brain by distinct, parallel information pathways (e.g., parvocellular and magnocellular pathways). These pathways represent different types of RGCs, thus play different roles in visual function. Glaucoma appears to selectively affect the magnocellular (M) pathway; this fact is important in understanding how degenerative changes in glaucoma that affect M cells result in selective loss of particular visual functions. While RGCs are selectively affected by glaucoma, glaucomatous damage extends beyond the retina to upstream cortical networks[30-34] employed in vision.

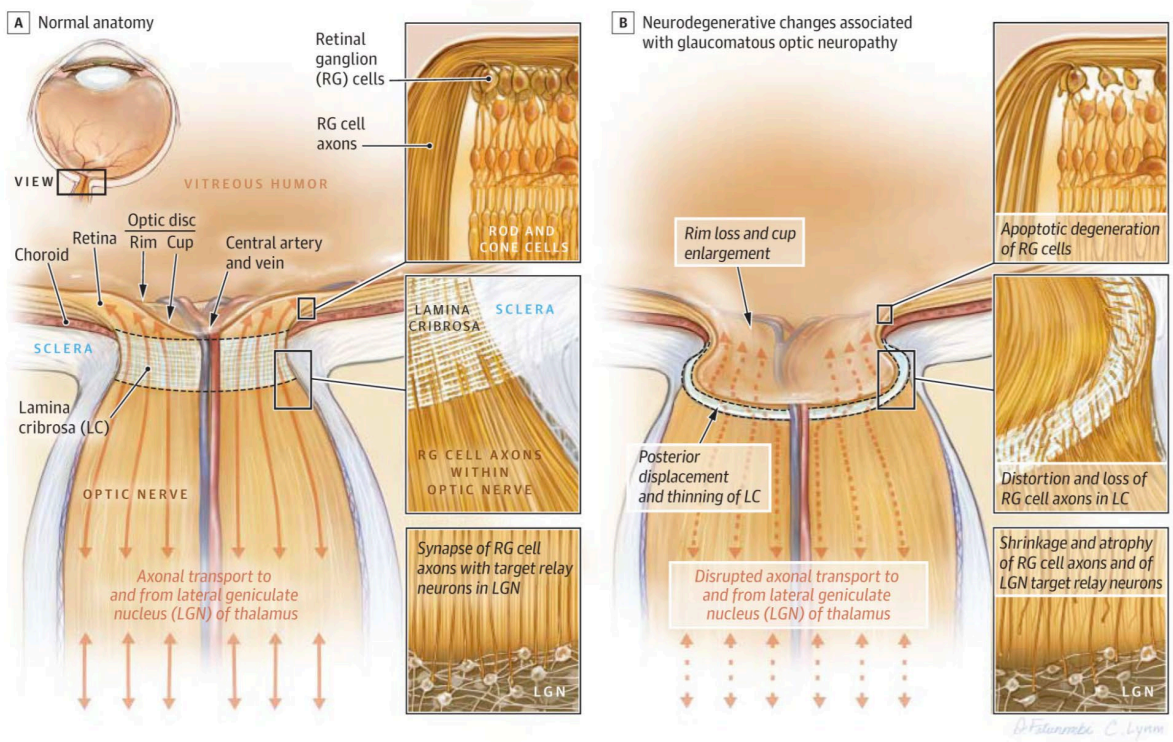

Figure 1. A. The optic disc is composed of neural, vascular, and connective tissues. The convergence of the axons of retinal ganglion cells (RGCs) at the optic disc creates the neuroretinal rim; the rim surrounds the cup, a central shallow depression in the optic disc. RGC axons exit the eye through the lamina cribrosa (LC) forming the optic nerve, and travel to the left and right lateral geniculate nucleus, the thalamic relay nuclei for vision. **B.** Glaucomatous optic neuropathy involves damage and remodeling of the optic disc tissues and LC that lead to vision loss. With elevated intraocular pressure, the LC is posteriorly displaced and thinned, leading to deepening of the cup and narrowing of the rim. Distortions within the LC may initiate or contribute to the blockade of axonal transport of neurotrophic factors within the RGC axons followed by apoptotic degeneration of the RGCs. Strain placed on this region also causes molecular and functional changes to the resident cell population in the optic nerve (e.g., astrocytes, microglia), remodeling of the extracellular matrix, alterations of the microcirculation and to shrinkage and atrophy of target relay neurons in the lateral geniculate nucleus.[35]

1.1.1.1 Glaucoma Treatment

By the time glaucoma is diagnosed there is irreversible impairment to eye structures; there are no interventions to restore function or reverse damage. The mainstay of treatment is management of IOP (Figure 2), pharmaceutically and/or surgically, because IOP is the only modifiable risk factor to date, though it is only one of the multiple contributors to glaucoma (e.g., loss of neurotrophic factors, localized ischemia, excitotoxicity). Beyond IOP, there is no clinical treatment for neuronal tissue loss associated with glaucoma progression. And herein lies a large focus in research: how do we intervene at the neural level to prevent further disease progression and treat the damage that neural tissue has already sustained? Two approaches are neuroprotection and neuroplasticity.

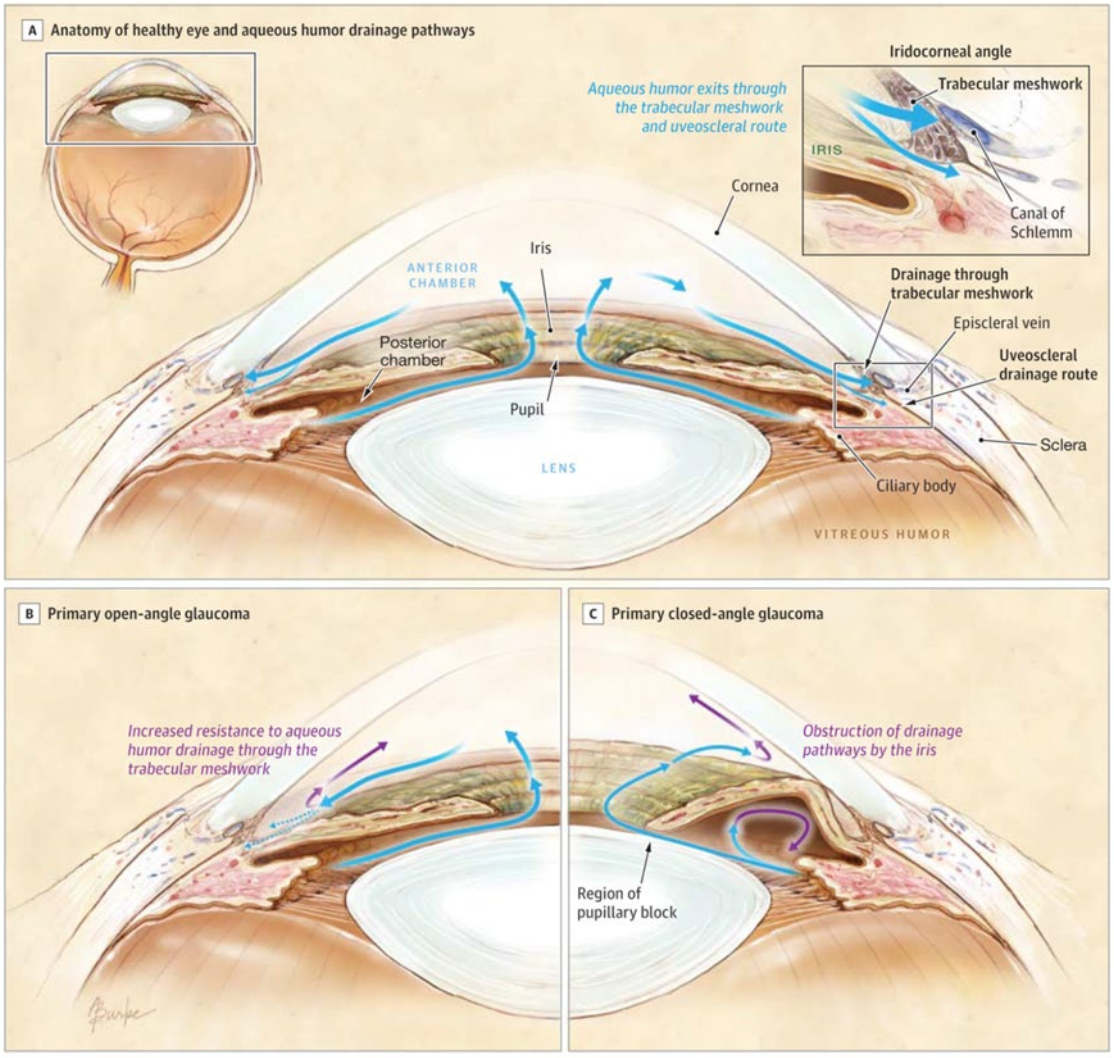

Figure 2. Aqueous humor drainage pathways of healthy (A) and glaucomatous (B, C) eyes as it relates to elevated intraocular pressure.[35]

1.1.1.1.1 Neuroprotection

Neuroprotection refers to the relative preservation of neuronal integrity (i.e., neuronal structure and/or function) to slow or prevent disease progression. Measuring the neuronal morphology of key structures affected by glaucoma (e.g., RNFL), even with current imaging technology, remains limited; no imaging tools are able to distinguish between complete versus partial defects versus healthy RGCs. Some RGCs survive even within damaged retinal regions.[36] Thus, one focal point of neuroscience is to develop therapeutic methods called neuroprotective therapies. Neuroprotection involves recovery, regeneration, or inhibiting specific biochemical pathways that influence neuronal health. Specific to glaucoma, neuroprotection involves targeted treatment of neurons of the visual pathway, but primarily RGC axons.[37] There is limited evidence that neuroprotective therapies are clinically effective in glaucoma.[27,37-39] Neuroprotective effects in the central nervous system are transient[40] and only delayed the progression of neuronal degeneration in animal studies.[41,42]

1.1.1.1.2 Neuroplasticity

Another promising area of neuroscience gaining attention in vision research is neuroplasticity. Neuroplasticity is the brain's ability to reorganize itself during normal aging, disease, or following injury; it

is the ability of the brain to change its functional architecture by modulating synaptic efficacy so that the neurons in the brain compensate and adapt their functions in response to change. With innovative imaging technologies, it will be possible to advance human studies research of the neuroplasticity of the visual pathway.

One conceptualization of neuroplasticity, the residual vision activation theory,[43] suggests that there are areas of residual visual capabilities in the retina within the areas that are damaged by disease or injury. Essentially, areas of residual vision may exist either on the border of the damaged areas of the retina (i.e., border of the scotoma) or within the impaired VF. A portion of cells may survive within a damaged structure; thus, some degree of function exists. Given the parallel processing and retinotopic nature of the visual system network, disease or injury that occurs at the site of early visual processing affects upstream neuronal networks.[30-34,44,45] The integrity of the surviving neurons determines how much information reaches higher cortical regions. The idea that there is residual potential within damaged structures means that there may be a potential to alter the surviving neural tissue at the site of the defect and thus influence brain network connectivity (i.e., neuroplasticity).

The residual vision activation theory also suggests that there is therapeutic value in regions of the VF where respondents demonstrate reduced stimulus detection thresholds or in areas where they respond less reliably or slowly to the stimulus presentations. The partially damaged areas may be more susceptible to sensitivity changes, attention, and fatigue, all factors generally thought to be negative, that influence the inherent nature of subjective measurement of visual function. However, while these areas may be viewed as variable outcomes or less severely affected, they may be a critical target for intervention because these regions may represent only partially damaged function. Studies reported a non-linear relationship between structural damage in the eye and visual function;[43] the visual system involves many brain mechanisms and networks that include feedback loops with higher-order, top-down processes of cognition that influence visual function. For example, typically people with glaucoma consciously notice VF defects later than clinicians identify structural impairment of the retina (see Attachment 1).

The goal of intervention based on the principles of neuroplasticity is to activate neuronal residual capabilities in the areas of residual vision. Activating surviving cells leads to increased synaptic activity and repeated activation elevates cell activity, which strengthens synaptic efficacy. One therapeutic method of influencing neuroplasticity is electrical stimulation therapy (EST). And, repetitive sessions of EST are necessary to produce cumulative effects as shown in neurophysiology studies and clinical trials in rehabilitation. In this study we will evaluate the effect of one method of electric current stimulation, rtACS, as an intervention to treat visual impairment in people with glaucoma.

1.1.2 Brain Electrical Connectivity

The brain is comprised of billions of neurons connected to each other via synapses. Neural processing involves communication within local ensembles of neurons and between long-range networks of neurons via the synapses. Ensembles of neurons in the brain connect to form functionally specialized networks and communicate with each other via the generation and transmission of electrical impulses carried along their axons. Neuronal network activity occurs through rhythmic firing patterns of synaptic interactions, in which the rhythmic changes in electric potential result in synchronized input to other brain regions, thus evoking oscillatory brain activity (i.e., rhythmic activity pattern).[46] When groups of neurons spike in synchrony (i.e., nearby neurons firing very close to or at the same time), they give rise to oscillations that reflect neuronal activity which can be measured (i.e., changes in the electric field). As a result, synchronized activity generates a more pronounced electric field (Figure 3). This electrical signal activity of neuronal networks is measured by electrophysiological methods, such as electroencephalography (EEG), which provide information about the temporal relationships between synchronous responses.

While there are open questions about the functional role of cortical oscillators, there is a growing consensus that oscillations are an organizing factor by which neurons and neuronal networks communicate and thereby enable cognition and behavior.[47,48] The point in time within a waveform cycle (i.e., phase) influences neuronal firing rates over a wide range of frequency bands: delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (>30 Hz). Studies found frequency-specific coherence between cortical areas as a function of behavioral demands (e.g., sleep, wake, solving a mathematical calculation);[49] which gives evidence for the possible role of oscillations and functional connectivity in a specific frequency band.[50] The functional role of brain oscillations in a variety of cognitive functions is important to understanding brain processing.[47] Cognitive processes rely on synchronous activity of large ensembles of functionally linked neurons that occur at distinct frequency bands according to the extension of the network configuration.[51-54] Evidence supports that brain oscillations play a key role in motor, perceptual, and cognitive processes.[47,49,55-58] In the healthy brain, neuronal networks operate in synchrony. In neurological disease, alterations of neuronal networks and loss of cells and their connections result in disturbances in synchronous neuronal firing.

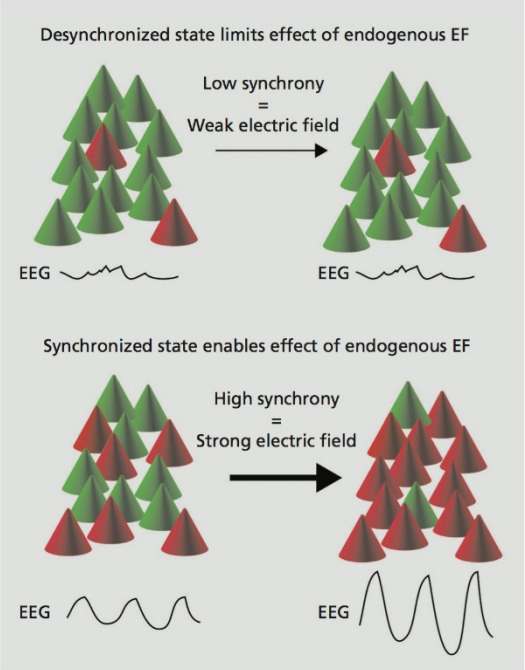

Figure 3. Illustration of how synchronized activity generates a more pronounced electric field (EF).[46]

1.1.3 Alternating Current Stimulation

EST to the brain uses an electric current to exert an external modifying influence (i.e., modulation) to activate or to inhibit brain processes. Initial studies have found EST to be effective in a range of clinical conditions to treat functional deficits (i.e., behavioral performance) related to dyslexia,[59] stroke,[60-62] spinal cord injury,[63] cognition,[64] and depression.[65] Recent studies evaluated the use of EST for the treatment of ophthalmic disease;[66,67] evidence supported the use of EST to prolong retinal survival, preserve visual function, and modulate cortical excitability.[66,68] This study will use one method of non-invasive EST called alternating current stimulation (ACS).[69]

The application of ACS is a relatively recent therapeutic development. ACS influences brain physiology on a network level through synchronization of neuronal network firing using a low-intensity sinusoidal waveform electric current (Figure 4) to induce neuroplastic changes.[69] The current intensities produced are lower in magnitude than other stimulation techniques, such as transcranial magnetic stimulation or electroconvulsive therapy, that are approved by the Food and Drug Administration (FDA) for certain conditions. Francis and colleagues (2003) demonstrated that neurons are sensitive to low-intensity electrical fields and that neuronal networks are more sensitive to field modulation than the average single neuron.[70] The theory behind ACS is that neuronal network activity can be entrained over time (i.e., endogenous oscillating element starts to cycle with the same period as the exogenous stimulus) in a frequency band-specific manner when the exogenous stimulus is similar to that of the endogenous electrical field of that network.[71-77] Neurons acting in synchrony with the stimulation frequency can potentially induce restoration of function following disease or injury. Consequently, the brain activity in the range of the electrical stimulation frequency is then enhanced.[72,78-80]

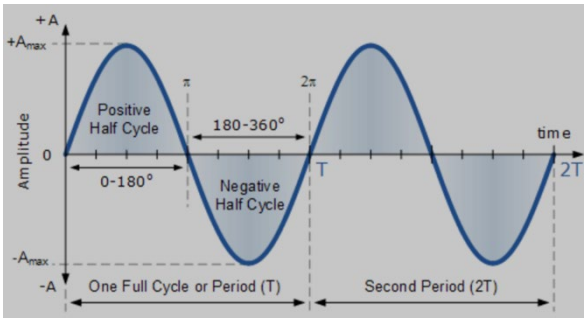

Figure 4. Sinusoidal waveform.

Entrainment using ACS seems to alter aspects of perception dependent on the frequency of the stimulation. Only physiologically meaningful brain rhythms can be entrained.[71,81] In this study, ACS is used to modulate brain oscillations at the alpha frequency. The alpha rhythm is modulated by visual stimuli, likely relies on interaction dynamics between the thalamus and cortex (including occipito-parietal areas of the brain), and is thought to reflect the spontaneous rhythms of visual areas.[82,83] Studies reported decreased alpha band activity in people who were congenitally blind[84,85] or had ON impairment.[80,86-88] Occipital alpha oscillation is synchronized to cyclic activity in visual thalamic relay neurons in the lateral geniculate nucleus; therefore, likely involved in signal transmission involved in visual perception[89] particularly in the early (retinotopic) stages of visual information processing.[90] Therapeutically, brain oscillations are used to modulate function (i.e., behavioral performance). Studies demonstrated that transcranial ACS induced frequency-specific effects on brain dynamics as measured by EEG.[72,77,91,92] This specific stimulation paradigm has been applied to modulate vision, motor function, somatosensation, and cognitive and mood disorders.[77,81,93,94]

The intervention delivered in this proposed study is rtACS. Transorbital refers to the site of electrode placement and stimulation delivery; electrodes are placed on the skin near the eye. While transcranial ACS likely modulates neural oscillation focally in several brain regions (based on electrode montage[95]), rtACS may be effective in more directly modulating the neural oscillation of visual networks because the plasticity induced by ACS is more effective when it starts in the early stages of visual processing (e.g., retina).[96,97] By placing the electrode montage transorbitally, the current flow targets a physiological trajectory toward the retina and ON. rtACS is a non-invasive application of electric current to stimulate the retina to induce synaptic efficacy, in particular those cells that have some measure of dysfunction but are not dead, and oscillations of nearby neuronal ensembles. While there is emerging study on the mechanisms of ACS, what is established is that sustained ACS (minutes) can produce changes in brain oscillations and that these changes are plastic and cumulative with repeated sessions (Figure 5). rtACS requires further study to fully leverage this treatment modality for maximal clinical benefit in people with glaucoma.

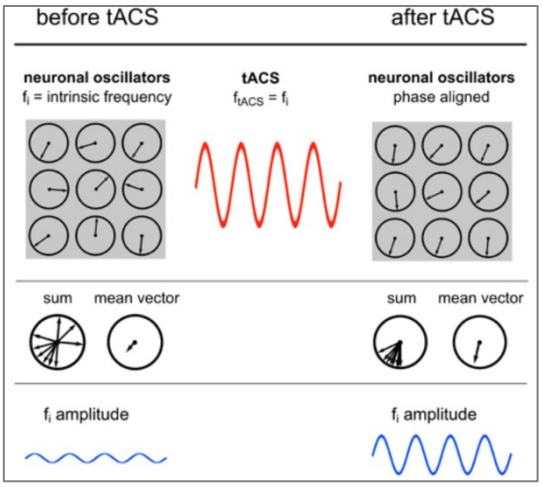

Figure 5. Illustration of the proposed underlying neuronal mechanism of the power increase by synchronization. Upper row: Single neuronal oscillators, depicted as vectors on a unit circle, with a specific intrinsic frequency synchronized to an external sinusoidal force with the same frequency. Middle row: The mean resultant vector of the single oscillating elements represents the amplitude of the oscillation. Due to phase alignment of each single oscillator to the external oscillation, the length of this mean vector increases and likewise the amplitude. Lower row: Schematic illustration of the amplitude recorded via EEG.[73]

With innovative imaging technologies, human studies research of the neuroplasticity of visual pathway structures has advanced. The theory of neuroplasticity is that after damage, structures with residual visual capabilities can be reactivated through repetitive stimulation leading to improved visual function and brain network connectivity.[43] rtACS is a non-invasive application of weak electric current used to exert an external modifying influence on brain processes through synchronization of neuronal network firing. The mechanism of rtACS is to stimulate the retina to influence RGCs, in particular those cells that have some measure of dysfunction but are not dead, and oscillations of nearby neuronal ensembles. rtACS has successfully been used in the rehabilitation of visual impairments in people with optic neuropathies;[80,86-88,98] however, we do not know the clinical value of rtACS specifically for people with glaucoma, including the effect of rtACS on people's functional ability and QoL.

1.1.4 Clinical Data to Date: Repetitive, Transorbital Alternating Current Stimulation

The following clinical data is summarized from the published literature for rtACS in people with ophthalmic diseases. All of the studies reviewed involved administration of rtACS in people with ON impairment. Attachment 2 summarizes the studies' published rtACS protocols.

In a retrospective data analysis of 446 people, Fedorov and colleagues (2011) reported that following rtACS participants' VFs significantly increased ($p < .001$) by 7.1% and 9.3% in the right and left eyes, respectively, as measured by kinetic perimetry.[98] Significant improvements ($p < .01$) in distance visual acuity (VA) were also reported for each eye. A sample of 62 people received an additional course of rtACS 6 to 9 months following the first treatment. During the stimulation-free interim following the first course of treatment, VFs decreased by 4.6% ($p = .11$) and 5.6% ($p = .08$) in the right and left eyes, respectively. After the second course of rtACS, participants' VFs remained significantly improved ($p < .05$) in each eye compared to their baseline status (VFs increased 3.9% and 4.9% from the first course of treatment to following the second course of treatment in the right and left eyes, respectively).

In a masked, randomized controlled trial,[86] participants who received rtACS (n = 12, 19/24 eyes) demonstrated significant improvement post-intervention in their detection accuracy (high resolution perimetry) in the defective VF areas ($p = .03$) and VA ($p < .05$), both near and far, compared to a sham stimulation group (n = 10, 14/20 eyes). Effect sizes, comparing rtACS to sham, were moderate (.51 to .67) for changes in detection accuracy measured in both the defective and the entire VF and reaction time (high resolution perimetry). Alpha frequency significantly increased ($p < .001$) in EEG recordings following rtACS. At 2-month follow-up, all participants who received rtACS (including those in the sham group who were offered rtACS once allocation was revealed, n = 29/40 eyes) demonstrated a significant improvement in their detection accuracy measured in both the defective and entire VF and reaction time ($p \leq .05$), mean threshold (static perimetry, $p < .01$), and near VA ($p < .01$).

In a multi-center, masked, randomized controlled trial,[88] participants who received rtACS (n = 45) demonstrated significant improvement post-intervention in detection accuracy (high resolution perimetry) in both the defective and entire VF ($p < .001$), decreased reaction time (high resolution perimetry, $p = .02$), improved mean threshold (static perimetry, $p < .01$), and mean eccentricity (kinetic perimetry, $p = .04$) compared to the sham stimulation group (n = 37). Detection accuracy in the entire VF was significantly different between groups in favor of rtACS ($p = .01$). Additionally, alpha frequency significantly increased ($p = .01$) following rtACS. At 2-month follow-up, the rtACS group continued to demonstrate significantly better detection accuracy in the entire VF ($p = .03$) and mean threshold ($p = .01$) compared to the sham stimulation group.

Gall and colleagues (2011) reported QoL outcomes, using pooled data from two separate but similarly designed studies, for a combined number of 42 participants.[99] The effect of rtACS on both vision-related and health-related QoL was compared between participants who received rtACS (n = 24) versus a sham stimulation (n = 18). Significant differences between groups were reported in regard to vision-related quality of life (VRQoL) for general vision ($p = .04$), distance activities ($p = .02$), and social functioning ($p = .03$) and for health-related quality of life (HRQoL) in the mental health component score ($p = .01$) and emotion-related role limitations ($p = .03$).

Schmidt and colleagues (2013) conducted an open-label, prospective study and reported significant effects of rtACS on alpha frequency ($p = .01$) in participants who received rtACS (n = 18) compared to a sham stimulation (n = 6).[80] The study demonstrated that, with repeated sessions, rtACS induced enhancement of alpha oscillations following a progressive amplification over the 10-day course of the intervention. Concerning visual perceptual performance (high resolution perimetry), detection accuracy improved following rtACS by 17.8% ($p < .001$).

Bola and colleagues (2014) conducted a case-control, randomized controlled trial for rtACS (n = 7) versus sham stimulation (n = 8) with 13 age-matched healthy controls.[87] At baseline participants with ON impairment exhibited a breakdown in alpha frequency compared to the healthy controls ($p < .05$), which was associated with worse visual perceptual performance measured by high resolution perimetry (VF

size, r = .53, p = .04; reaction time, r = -.58, p = .03). Following rtACS the alpha frequency was strengthened (p = .03) compared to the sham stimulation group and was associated with better visual perceptual performance (detection accuracy, r = .57, p = .04; reaction time, r = -.56, p =.05). The authors suggested that alpha frequency in the resting state could be a marker for both loss and restoration of visual perceptual capabilities in people with ON impairment; vision loss may not just relate to tissue damage but also to breakdown of synchronization in the neuronal network.

1.2 Investigational Device

We will use the DC-Stimulator MC (neuroConn GmbH, Ilmenau, Germany) to deliver the rtACS intervention per protocol. The device is considered a medical device using the definition by the FDA. Non-invasive or cutaneously administered electrical stimulation devices are deemed a Category B, Class II medical device, for which the DC-Stimulator MC qualifies.[100] rtACS is a non-invasive procedure because it does not involve penetrating the skin or a body cavity. The DC-Stimulator MC is a non-significant risk device based on: (i) it is not an implantable device, (ii) it is not used for supporting or sustaining human life, (iii) it is not used for substantial importance to diagnose, cure, mitigate, or treat disease, and (iv) it does not present a potential for serious risk to the health, safety, or welfare of a participant. The device labeling (in accordance with FDA regulations at 21 CFR §812.5) includes name and place of manufacturer, contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.[101] Additionally, the device displays the label: *Caution for United States Owners and Operators: Investigational Device. Federal (or U.S.) law limits this device to investigational use*.

The DC-Stimulator MC was chosen for this study based on its capacity to deliver the established rtACS intervention protocol documented in previous efficacy, safety, and interventional studies.[80,86-88,98] The DC-Stimulator MC is an investigational, multi-channel electrotherapy device consisting of a programmable waveform generator that connects to electrodes to deliver a non-invasive weak electric current. Technical and safety information related to weak current stimulation protocols have been published.[102] Weak electric current devices are used in the U.S. for basic and clinical research with Institutional Review Board (IRB) approval.[100] The DC-Stimulator MC allows for frequency band stimulation in the range of 0-1,000 Hz and currents up to 3,000 μA (peak-to-peak) with adjustable phase for ACS. Unique to this device, it can be used simultaneously with functional magnetic resonance imaging (fMRI) with minimal artifacts related to the electrical interference (though we are not using the MRI function for this study). Additionally, it has a computer-controlled sham stimulation function for masking interventionist to study group. The device will be used to deliver a weak electric current stimulation protocol to participants via electrodes placed transorbitally, with one reference electrode positioned elsewhere.

1.3 Research Risks & Benefits

1.3.1 Risk of Investigational Device

Safety and tolerability of EST in both animal and human studies are published[102-107] and to our knowledge there have been hundreds of EST studies in the U.S. designated non-significant risk by IRB review. Evidence suggests that there is a general lack of observations concerning adverse events or adverse effects, only documentation of mild side effects. In experimental protocols following evidence-based dose and delivery parameters, the mild side effects of ACS included: local skin reddening, skin tingling, skin itching, skin warming sensation, nausea, diffuse or migraine-like headache, blurred vision, forgetfulness, difficulty concentrating, dizziness, general fatigue, sleeping difficulties (temporary), spontaneous phosphenes (independent of stimulation), blood pressure fluctuation, and difficulty breathing.[103,106,108] The safety of ACS has been tested[80,81,86-88,98] and researchers conclude that ACS, as applied in a dose-specific manner, is safe and tolerable.

We will assess and document per protocol adverse events (safety) and adverse effects (tolerability, see sections 6 and 8). To minimize the risk for adverse events and adverse effects, there are no deviations to the established rtACS protocol used in previous studies in this study design. Standard parameters for the application of weak current stimulation in general are[100]: (1) current is less than 2.5 mA, (2) the current is applied through electrodes that are known to minimize skin burns at the specific current level administered to a participant, (3) the current application duration is less than 20 to 60 minutes per

session, and (4) sessions are not more frequent than two times per day. Tolerability of EST is specific to (1) dose (session duration, amplitude, electrode size and position, number of sessions) and (2) participant exclusion and treatment protocol.[46,103,109,110] Additionally, the device will be checked prior to and following the delivery of rtACS for each session.

1.3.2 Other Risks of Study Participation

The targeted physiological effect of rtACS is to induce neuroplastic changes in the visual system to minimize visual impairment. The established rtACS protocol we will use in this study has been safe and effective within its stimulation parameters. The current is weak, such that it can hardly be felt. However, if parameters are not followed, or changed in any manner that affect the dose, this might lead to maladaptive plasticity rather than adaptive or positive effects on neural plasticity. To minimize the risk of any deviation from the rtACS protocol, at each contact with a participant, research personnel will examine and document that: the rtACS device is functioning properly, the experimental setup is performed per protocol, and specific questioning and examination (as appropriate) is performed to the participant.

Infrequent risks that may occur include fatigue, breach of confidentiality of participants' identifiable information (medical record information and questionnaire data), or participants may experience frustration in regard to the administration of particular tests (e.g., attention/information processing) and/or the time to complete study procedures. To minimize the occurrence of fatigue, participants will be informed that they may stop as frequently as needed to rest at time points appropriate to the standardization of the test being administered. Research personnel will provide assistance in the administration of assessments per standardized protocol as needed. To reduce the likelihood of a breach of confidentiality, access to participants' personal information will be limited to research personnel on a need-to-know basis. Additionally, we will secure personal identifiers and clinical information in a separate location and limit access to this information by using linking codes assigned to study data and password protected electronic files to maximize confidentiality. Screening forms will be placed in a locked file cabinet and stored separately from participants' identification files. We also will provide assurance to the participant that the recorded information will not be reused or disclosed to any other person or entity (other than members of the research team) except as required by law or for authorized oversight of the study. Participants will be advised to inform research personnel if they feel any frustration or discomfort about answering questions on the questionnaires. To minimize frustration or discomfort with these questions, participants will be educated on their purpose in this study and assisted as per standardized protocol in the completion of assessments. Any comments from participants and/or assistance provided by research personnel will be documented for tracking purposes.

1.3.3 Potential Benefits

rtACS has been associated with improved visual function and QoL in people with visual impairment resulting from optic neuropathy.[99] In addition to the potential benefits of improved visual function and QoL, we will explore the potential benefits of rtACS in regard to participants' functional ability. We anticipate no direct benefit from sham rtACS in regard to visual function, QoL, and functional ability.

2 Study Objectives

In this proposed pilot study, we will assess the feasibility of procedures that are key to the conduct of a multi-site randomized controlled trial to explore the influence of rtACS versus sham stimulation on neuronal morphology and physiology to improve people's visual function, functional ability, and QoL. The expected outcomes (hypotheses) for this project are that (1) rtACS activates viable but poorly or non-functional RGCs to improve their structural and functional capabilities, (2) measures of retinal, ON, and visual brain structures and function will correspond with improvement in visual function, and (3) changes in visual function following rtACS will be associated with improvements in participants' functional ability and QoL.

2.1 Primary Objectives

2.1.1 **Objective: Assessment of Ophthalmic Structure and Function**

Evaluate procedures to identify changes in vision following rtACS compared to sham stimulation at baseline, post-intervention and 4 weeks (follow-up) to inform the design of a multi-site collaborative clinical trial for participants with glaucoma

2.1.1.1 **Aim 1:** Evaluate the data collection and data management methods to measure the targeted outcomes (structural and functional capabilities) of neuronal physiology and reorganization of the visual pathway (from eye to visual brain)

2.1.1.1.1 Image structures of the visual pathway with advanced technologies to determine the effect of rtACS on structure and function

2.1.1.1.2 Assess areas of visual function to determine the effect of rtACS

2.1.2 **Objective: Assessment of Functional Ability and QoL**

Evaluate procedures to assess participants' functional ability and QoL following rtACS compared to sham stimulation at baseline, post-intervention and 4 weeks (follow-up) to inform the design of a multi-site collaborative clinical trial for participants with glaucoma

2.1.2.1 **Aim 2:** Evaluate the data collection and data management methods to measure objective ability/disability and subjective well-being

2.1.2.1.1 Assess the feasibility of procedures for assessment of functional ability (objective ability/disability) to determine the effect of rtACS

2.1.2.1.2 Assess the feasibility of procedures for assessment of vision-related and health-related QoL to determine the effect of rtACS

2.2 Secondary Objective

2.2.1 Objective: Assessment of Feasibility and Implementation of Procedures

Evaluate the feasibility and implementation of procedures for a clinical trial protocol (rtACS versus sham stimulation) at baseline, post-intervention, and 4 weeks (follow-up) to inform the design of a multi-site collaborative clinical trial for participants with glaucoma

2.2.1.1 **Aim 3:** Evaluate the data collection, data management methods, and study procedures for targeted outcomes other than the primary objectives

2.2.1.1.1 Evaluate recruitment, enrollment procedures and retention, and participants' adherence to procedures between multiple sites

2.2.1.1.2 Assess data entry and data management procedures between multiple sites

2.2.1.1.3 Assess the feasibility of procedures for assessment methods other than primary objectives

3 Study Design

3.1 General Design

The goal of this prospective, randomized controlled double-masked pilot study is to establish a structured protocol for the delivery of rtACS sessions (participants randomized to either active or sham rtACS groups) with repeated assessments at baseline, post-intervention, and 4 weeks (follow-up) to inform the

design of future clinical trials for people with glaucoma (Table 1). The participants and interventionists will be masked to study group. Ten daily sessions will be administered across 2 weeks. The electrode montage is per protocol; electrodes will be placed transorbitally (eyes closed) with a reference electrode placed elsewhere. Dose will be administered per protocol for session duration (< 60 minutes continuous stimulation), amplitude (peak-to-peak), electrode size, electrode position (transorbital), and number of sessions (10).

Table 1. Anticipated study timeline

	2017		2018-2020	2021
Major tasks	Feb-Oct	Nov	Dec	Jan-Dec
Recruit and train research personnel				
Screening and assessment protocols finalized				
Develop protocol manual, codebook, and data entry procedures				
Recruitment				
Data collection				
Data processing				
Data analysis				
Summative data analysis and dissemination of findings				
Presentation / publication of initial and ongoing findings				

Recruitment goal: 16 participants

Anticipated date of starting recruitment: April 2017

Anticipated date of completing recruitment: December 2020

Anticipated date of completing statistical analysis: December 2021

Participants will be randomized in 1:1 ratio to the rtACS and sham stimulation groups using block randomization stratified by centers. Random varying block sizes will be used to balance group allocation and minimize the risk of unmasking group assignment, and a randomization table will be computer generated accordingly. A research staff member not directly involved in the conduct of the study will conduct allocation concealment. Participants will complete screening, baseline, pre- and post-session, post-intervention, and follow-up assessments (Figure 6). The Pre-/Post-session Questionnaire includes brief measures to monitor any stimulation- and research-related effects.

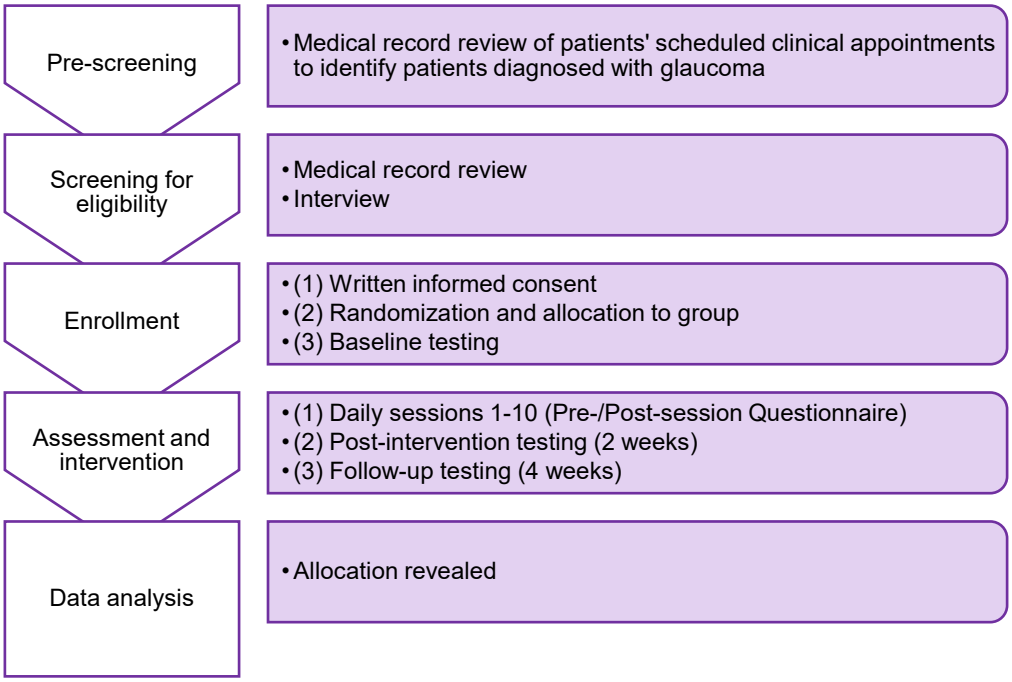

Figure 6. Study Flow Chart

The timeline for assessment procedures involves 1-2 visits for baseline testing, 10 daily visits for rtACS or sham stimulation sessions (across 2 weeks), 1-2 visits for post-intervention testing, and 1-2 visits for follow-up testing (4 weeks following intervention); a total of 13-16 visits. The variability in the number of sessions is based on the circumstance that an imaging assessment may need to be scheduled on a separate day due to device availability. Participants may be contacted, following data collection of the study assessments, to request information pertinent to this research study.

3.2 Primary Study Endpoints

3.2.1 Assessment of Ophthalmic Structure and Function

3.2.1.1 **Assess neuronal structure and function (see section 2.1.1.1.1)**

Optical coherence tomography (OCT): Spectral domain OCT is a commonly used imaging technology to evaluate glaucomatous structural damage and to detect glaucomatous progression.[111,112] It is a non-invasive technique that allows for in vivo cross-sectional imaging of the ON head and RNFL. The clinical utility of OCT is that it enables a comprehensive assessment of the thickness of the RGC and ganglion cell nerve fiber (i.e., RNFL) layers as they approach the ON head.[113] Studies demonstrated that OCT is a reliable and reproducible method to measure RNFL and macular thickness and demonstrated sensitivity and specificity in discriminating glaucomatous eyes from healthy eyes.[114-119]

We will measure (1) peripapillary RNFL thickness (μm), (2) macular ganglion cell-inner plexiform layer thickness (μm), and (3) ON head cup-to-disc ratio (%); all three measures are determined from the device software automatically. Testing will be performed using an FDA approved device for its approved indication and will require 10 minutes to perform. Testing results will be printed and included with participants' source documents.

OCT angiography (OCT-A): There is a growing body of evidence suggesting that glaucoma pathogenesis is related to vascular dysfunction.[120-122] OCT-A is a new, non-invasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information to generate a three-dimensional map of the retinal and choroidal vasculature. In people with glaucoma, OCT-A may be

a useful tool for evaluating vasculature using density mapping and flow index (0-1), which measures the area of large vessels and both the area (vessel density) and velocity of capillaries.[123,124] Testing will be performed using an FDA approved device for its approved indication and will require 10 minutes to perform. Testing results will be printed and included with participants' source documents.

Multi-modal magnetic resonance imaging (MRI):
Functional magnetic resonance imaging (fMRI) is a neuroimaging procedure that measures brain activity by detecting changes in hemodynamics. fMRI typically uses the blood-oxygen-level dependent (BOLD) contrast to map activity in the brain and has been studied to assess how glaucoma affects brain function.[125,126] We will use an established protocol for assessment of visual function,[125,126] using MRI-compatible visual occlusion spectacles, to measure functional activity and connectivity in different brain regions with and without visual stimulation to each eye.

Diffusion MRI is a neuroimaging procedure that uses the diffusion of water molecules to generate contrast in magnetic resonance images to map white matter integrity in the brain. Studies reported compromised structural integrity of the optic radiations and frontal lobe in people with glaucoma.[126] We will use diffusion MRI to measure structural connectivity (e.g., tract-based spatial statistics of fractional anisotropy maps) of vision-related structures.

MRI scans have long been held to be a safe way to non-invasively visualize tissue in adults. This study will be performed in an FDA approved scanner. Testing will be administered per standardized protocol and will require up to 90 minutes to perform. MRI testing may be scheduled on a separate day than other testing due to timing, location of MRI facility, and patient scheduling. Testing results will be included with participants' source documents.

Electrophysiology:
Visual evoked potential (VEP) non-invasively assesses the function of visual pathway structures (from retina to visual cortex) by measuring the electrical activity of the occipital cortex (amplitude [μA], latency [ms]). VEP is used clinically to detect glaucomatous changes and discriminates glaucomatous eyes from health eyes.[127,128]

Pattern electroretinography (PERG) non-invasively assesses the function of RGCs by measuring electrical activity of the cells (magnitude [μV]). PERG is used clinically to diagnose and manage glaucoma.[129-131]

Testing will be performed using an FDA approved device for its approved indication and will require 15 minutes to perform. Testing results will be printed and included with participants' source documents.

3.2.1.2 **Assess areas of visual function (see section 2.1.1.1.2)**

Visual field: A VF test is a method to measure the full extent of the areas visible to an eye (i.e., objects seen centrally and in the periphery) when the eye is fixated straight ahead. VF loss is one of the leading visual function deficits resulting from glaucoma. Hence, VF testing is a benchmark assessment in ophthalmic standard of practice to quantify severity of glaucoma. We will use the Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA), using the Swedish Interactive Thresholding Algorithm, to measure VF. Specifically, we will use the mean deviation (dB), a measure of VF sensitivity through threshold testing. The mean deviation is the deviation from the expected threshold value for a person of the same age and ethnicity. The Humphrey Visual Field Analyzer is a reliable and valid testing method for VF integrity and is considered a gold standard for the diagnosis and measurement of glaucoma.[132,133] Testing will be administered per standardized protocol and will require 20 minutes to perform. Testing results will be printed and included with participants' source documents.

Visual acuity: A VA test is a method to measure people's ability to distinguish detail clearly. We will use the Early Treatment Diabetic Retinopathy Study (ETDRS) VA tests, as they are the worldwide standard for VA testing in ophthalmic disease, to measure both near and far acuity (logMAR). Testing will be

administered per standardized protocol and will require 5 minutes to perform. Testing results will be documented and included with participants' source documents.

Contrast sensitivity: CS is the ability to detect detail having subtle gradations in color or luminance between a target and its background. It is measured over a range of spatial frequencies and contrast levels. In people with glaucoma, CS had a strong correlation with and was a significant predictor of people's performance of daily tasks.[134] We will use the Pelli-Robson Contrast Sensitivity Chart, considered the gold standard, to measure CS (log units). Testing will be administered per standardized protocol and will require 5 minutes to perform. Testing results will be documented and included with participants' source documents.

3.2.2 Assessment of Functional Ability and QoL

Per standardized assessment guidelines and in order to accommodate and minimize the amount of time subjects may be willing and/or able to participate in research procedures at the Eye Center, assessments of functional ability and QoL may be coordinated with subjects for virtual administration (e.g., via phone, Webex, etc.).

3.2.2.1 **Assess the feasibility of procedures for assessment of functional ability (see section 2.1.2.1.1)**

Assessment of Life Habits (LIFE-H), short form 3.1: The LIFE-H is a 77-item questionnaire developed to measure: (1) how a respondent accomplishes regular activities and social roles and (2) respondent's satisfaction with how regular activities and social roles are accomplished.[135-138] Regular activities and social roles are daily tasks that are valued by people and ensure their survival and well-being in society throughout their lifespan. Regular activities include nutrition, fitness, personal care, communication, housing, and mobility and social roles include responsibilities, interpersonal relationships, community life, education, employment, and recreation. Testing will be interviewer-administered per standardized protocol and will require 30 minutes to complete. The questionnaire will be included with participants' source documents.

Minnesota Low Vision Reading Test (MNRead): The MNRead is a standardized assessment designed to measure reading performance in three ways: (1) reading acuity (the smallest print that can just be read), (2) maximum reading speed (reading speed when performance is not limited by print size), and (3) critical print size (the smallest print read that supports maximum reading speed).[139] Evidence suggests that reading speed is slower among people with glaucoma compared to normal-sighted controls[140] and reading performance had a significant influence on people's reading engagement (e.g., reading avoidance or restriction of tasks that required sustained reading).[141] Testing will be administered per standardized protocol and will require 10 minutes to perform. The MNRead score sheet will be included with participants' source documents.

3.2.2.2 **Assess the feasibility of procedures for assessment of vision-related and health-related QoL (see section 2.1.2.1.2)**

National Eye Institute Visual Functioning Questionnaire (VFQ-39): The 39-item VFQ is designed to measure VRQoL. It is a frequently used measure of VRQoL in vision science research. The VFQ-39 is divided into 12 subscales: general health, general vision, ocular pain, near vision, distant vision, vision-specific social functioning, vision-specific role difficulties, vision-specific mental health, vision-specific dependency, driving, peripheral vision, and color vision. Responses are rated on either Likert or dichotomous (yes/no) scales. Testing will be self-administered per standardized protocol and will require 25 minutes to complete. The questionnaire will be included with participants' source documents.

36-Item Short Form Survey (SF-36): The SF-36 is a 36-item questionnaire developed to measure HRQoL. It is divided into eight subscales: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health. The SF-36 also includes a single item that probes a respondent's perceived change in health. Testing will be self-administered per standardized protocol and

will require 25 minutes to complete. The questionnaire will be included with participants' source documents.

3.3 Secondary Study Endpoints

3.3.1.1 **Evaluate recruitment, enrollment, and adherence procedures (see section 2.2.1.1.1)**

The following feasibility information, at minimum but not limited to, that pertains to recruitment and enrollment will be tracked: number of scheduled clinical appointments reviewed, number of patients considered potentially eligible as determined during review of the clinical appointment schedule, number of patients who are potentially eligible but express no interest in participating in the study, number of patients who are determined ineligible following screening procedures, and etc. Additionally, data will be collected in regard to participants' adherence to the study protocol regimen. All information obtained during pre-screening activities of those patients who do not enroll in the study will be de-identified and destroyed after feasibility information is documented.

3.3.1.2 **Assess data entry and data management procedures (see section 2.2.1.1.2)**

Data will be entered and managed using an NYU and Health Insurance Portability and Accountability Act (HIPAA) compliant data collection system. Feasibility of this system between sites and timing of data entry/management will be assessed.

3.3.1.3 **Assess evaluation methods: Other (see section 2.2.1.1.3)**

Demographic Questionnaire: Data will include gender, ethnicity, race, education, living situation, marital status, caregiver assistance, socioeconomic status, date of glaucoma diagnosis, medical and eye histories, glaucoma treatment regimen, glaucoma symptoms measured with the Glaucoma Symptom Scale,[142] and depression risk measured with the Patient Health Questionnaire-9.[143,144] The demographic questionnaire will be self-administered and require 15 minutes to complete; research personnel will be present to answer questions or assist as needed. The questionnaire will be included with participants' source documents.

Delis-Kaplan Executive Function System (D-KEFS): The D-KEFS is a neuropsychological test used to measure executive function, normed for ages 8-89 years.[145] The test consists of nine sub-tests designed to stand alone. To address the potential that improved performance following intervention is an artifact of attention versus effect of the intervention, we will administer the Verbal Fluency Test that is comprised of three testing conditions: Letter Fluency, Category Fluency, and Category Switching. The test has an alternate form that can be used at post-intervention and/or follow-up. We chose this sub-test to eliminate any visual component and the test was shown to be sensitive to the effect of EST. The Verbal Fluency Test will require 5 minutes to perform. The Verbal Fluency Test score sheet will be included with participants' source documents.

Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV): The WAIS-IV is designed to measure intelligence and cognition, normed for ages 16-90 years.[146] The test consists of 10 sub-tests and 5 supplemental sub-tests designed to stand alone. To address the potential that improved performance following intervention is an artifact of attention versus effect of the intervention, we will administer the Digit Span sub-test, for which respondents must recall a series of numbers as presented in order. We chose this sub-test to eliminate any visual component and the test was shown to be sensitive to the effects of EST.[146] The Digit Span test will require 5 minutes to perform. The Digit Span score sheet will be included with participants' source documents.

Pre-/Post-session Questionnaire: A data collection form and questionnaire designed specifically for this study will track basic health-related and intervention-related information including the following data: heart rate, blood pressure, visual skin observation at electrode sites, any changes in participant's typical glaucoma therapy regimen prescribed by their physician, and symptoms. It will be completed at baseline, each study intervention visit (1-10), and post-intervention. The form will require 5 minutes to complete. The questionnaire will be included with participants' source documents.

Post-intervention Interview: A subjective, open-ended visual function interview, used clinically by collaborators of this study for patients who received rtACS, will be conducted for participants to report their subjective functional and related experiences in association with the rtACS intervention.

4 Subject Selection and Withdrawal

We will enroll 16 participants with confirmed glaucoma (moderate stage or worse but not total blindness). Participation will be open to those with all types of glaucoma who meet the eligibility criteria (described below). Patients will be recruited until the estimated sample size is achieved, the metric for which is when the total number of enrolled participants projected to be randomized to the intervention group complete the rtACS protocol through the follow-up time point.

4.1 Inclusion Criteria

Participants must meet the following inclusion criteria in order to participate in the pilot study.

1. Aged 50-70 years
2. Live in a community, residential setting (i.e., non-institutionalized, not homeless)
3. Diagnosis of glaucoma (not type-specific, excluding traumatic glaucoma)
   a. Glaucoma severity (Hodapp-Parrish-Anderson[147]): Moderate defect or worse in both eyes but not total blindness (must be able to perform VF testing, Table 2)
   b. Because of the inherent variability in subject's performance of the visual field test (the test being a subjective, behavioral test influenced by factors such as alertness and wakefulness), one eye must test at MD ≤ -6.0 dB and the other eye may test at MD ≤ -3.0 dB. This criterion will allow for qualification of subjects for whom their disease is considered moderate but their visual field testing demonstrates variability.
4. VF defects present for at least 6 months
5. Clear optical apparatus
6. Best-corrected VA of 20/200 (1.0 logMAR) or better in at least one eye
7. Commitment to comply with study procedures (2 week period of intervention sessions) with baseline, post-intervention, and follow-up visits
   a. Scheduling
   b. Testing

Table 2. Hodapp-Parrish-Anderson Classification

Classification of defect:
• MD ≤ -6.0 dB • ≥ 25% of the points (18) are depressed below the 5% level and ≥ 10 points are depressed below the 1% level on the pattern standard deviation plot • ≤ 1 point in the central 5° can have a sensitivity of 0 dB • Only one hemifield may have a point with sensitivity of < 15 dB within 5° of fixation OR points within the central 5° with sensitivity < 15 dB in both hemifields

MD=mean deviation.

Modification 05.24.2017
Original inclusion criteria number 1 is changed from aged 50-70 years to aged 50-80 years.

4.2 Exclusion Criteria

Participants that meet any of the following criteria will be excluded from the pilot study.

1. Diagnosed optic neuropathy/pathology other than glaucoma
2. End-stage organ disease or medical condition with subsequent vision loss (e.g., diabetes, stroke)
3. Other diseases of the retina or cataracts responsible for worse than 20/70 best-corrected VA
4. Pathological nystagmus
5. Acute conjunctivitis
6. Photosensitivity to flickering lights
7. IOP > 27 mmHg at baseline
8. Non-ocular/ocular surgery within the previous 2 months to enrollment date
9. Medically diagnosed memory disorder or Telephone Interview for Cognitive Status-modified (TICS-m) score ≤ 27

10. Electric or electronic implants (e.g., cardiac pacemaker)
11. Metallic artifacts/implants in head and/or torso (titanium screw and dental implants are allowed)
12. Diagnosed epilepsy
13. Epileptic seizure within the past 3 years of enrollment date
14. Auto-immune disease, acute stage (e.g., rheumatoid arthritis)
15. Metastatic disease
16. Certain mental diseases/psychiatric conditions (e.g., schizophrenia) that would preclude reliable testing and participation
17. Certain unstable medical conditions (e.g., diabetes, diabetes causing diabetic retinopathy)
18. Addiction (e.g., drug/alcohol dependence)
19. Systemic hypertension (> 160/100 mmHg)
20. Pregnant or breast-feeding women
21. Any severe skin condition (e.g., blisters, open wounds, cuts or irritation) or other skin defect which compromise the integrity of the skin at or near stimulation locations
22. 10-item Geriatric Anxiety Scale (GAS-10) score ≥ 12
23. Claustrophobia (to limit functional neuroimaging)
24. Obesity (MRI weight limit: <300 pounds)
25. Received rtACS in the past

4.3 Subject Recruitment and Screening

4.3.1 Recruitment [NYU Langone Eye Center and New York Eye and Ear Infirmary of Mount Sinai]

Recruitment procedures include pre-screening activities and an introduction of the research study to potentially eligible patients by ophthalmologists (including the clinical staff under their supervision) and/or members of the research team. Patients will be recruited in New York, New York, from the following centers: NYU Langone Eye Center and New York Eye and Ear Infirmary of Mount Sinai (referred to as Centers from this point forward).

- Recruitment from the Centers will occur simultaneously.
- Patients will be recruited in accordance with the pace the research personnel are able to schedule recruitment and screening activities.
- Patients will be recruited until the estimated sample size is achieved, the metric for which is when the total number of enrolled participants projected to be randomized to the intervention group complete the rtACS intervention through the follow-up time point.

NYU Langone Health will enroll NYU employees, including those working within the Department of Ophthalmology. Employees, who are listed on the delegation log as study team member, will not be enrolled into the research study.

IRB approved advertisements are distributed and displayed at approved NYU Langone Health locations. Interested employees will approach the study team members to discuss the study. The eligibility determination procedures will follow the standard methods listed above. The study team members will emphasize that participation is voluntary. The person obtaining consent will also emphasize that the candidate's decision will not affect their employment within NYU Langone Health and/or NYU School of Medicine.

Procedure

- *Pre-screening activities:* Patients' clinical appointments scheduled with ophthalmologists involved in this study will be reviewed to identify potential participants with a known medical diagnosis of glaucoma. Additionally, patients' relevant medical histories will be reviewed preparatory for research only to identify exclusionary medical and/or ophthalmic criteria. Trained research personnel in partnership with a clinical research coordinator and/or clinical staff will complete these procedures during the week prior to the scheduled appointment. This step will be implemented: 1) to minimize the time burden for patients and physicians in regard to research activities associated with determining study eligibility and 2) to allow patients time to consider participation in this study to maximize the efficiency of the screening process.

- Patients' medical records will be reviewed only to identify whether they generally meet the research study eligibility criteria (see Attachment 3, Pre-screening Form).
- For those patients identified as potentially eligible for the study, a research notification alert will be provided to the clinical team the day of the patient's clinical appointment (see Attachment 3, Physician Form).
- In addition to the eligibility criteria identified during the medical record review and only when all criteria are met, the patient's age and phone number(s) listed as the means of contact will be documented in order to verify the correct response on the TICS-m.
- Following pre-screening activities, de-identified information will be entered into a password protected electronic research file for tracking purposes (see Attachment 3, Tracking Form: Clinical Appointments Review). Recruitment forms for non-enrolled patients will be disposed of, following PHI procedures, once the data is entered into the research file.

- An ophthalmologist, using conventional techniques, will examine patients during their clinical appointment (routine standard of care). Physicians will complete the appropriate Physician Form (see Attachment 3) to indicate there was no change in patient's medical history (as it relates in general to the eligibility criteria for this study) identified during the pre-screening review of patient's medical record. For those patients who generally meet the eligibility criteria, the physicians will introduce the research study. If a patient expresses interest in learning more about the study, research personnel will discuss the study with the patient (no research activities conducted other than exchange of general information about the study and answering any questions; see Attachment 4, Recruitment Script [recruitment section only]).

    - Research personnel will be present as often possible at the Centers on those days when the physicians involved in this study are scheduled with clinical appointments.
    - When research personnel are not physically available to discuss the study, the patient will provide his/her contact (phone) information for the research team and the process will be documented on the Physician Form. The patient will be informed that a trained research team member will contact him/her to discuss the research study. The research personnel's contact information will be provided to the patient so he/she is aware of whom to expect will be contacting him/her. Once the patient has been contacted by research personnel, his/her contact information will be immediately destroyed. If the patient decides to engage in screening activities, procedures as outlined for screening will be followed.

4.3.2 Recruitment [Other]

In the case when NYU Langone Eye Center/a member of the research team is contacted by an entity other than an NYU Langone Health patient in regard to rtACS research, general information in regard to the purpose of the protocol and the eligibility requirements to participate will be provided. In said case, said entity may send a copy of both the (1) ophthalmic health record and (2) medical health record of the potential candidate to Dr. Joseph Panarelli at NYU Langone Eye Center, attention toDr. Maria De Los Angeles Ramos Cadena, for review in regard to eligibility. It is the responsibility of the interested entity to request from their eye care and primary medical providers the release of their ophthalmic and medical health records, respectively, to be sent to NYU Langone Eye Center. Said records sent to NYU Langone Eye Center will be scanned to EPIC by ophthalmology clinical staff; the records are reviewed by research personnel and a glaucoma specialist involved in this study as part of the pre-screening research procedures. In the case when clarification of ophthalmic and/or medical health histories is required, the record's provider will be contacted to clarify details that pertain to eligibility for this protocol.

After review of the ophthalmic and medical health records, screening procedures for the screening interview (the same as those already established, see section 4.3.3) will be conducted (see Attachment 4, Recruitment Script, Verbal Consent, and Screening Interview) which further queries/verifies potential participants' ophthalmic and medical health histories. If eligible to participate in the protocol, said entity

will follow the same protocol and procedures as established for subjects recruited from New York Eye and Ear Infirmary of Mount Sinai.

4.3.3 Recruitment: Flyer

An IRB approved recruitment flyer will be displayed at NYU Langone Eye Center and may be used in conjunction with discussions with interested persons in regard to rtACS. When a potential subject contacts a study team member, information regarding the next steps for eligibility determination will be conducted.

4.3.4 Screening

Screening procedures will be performed to identify patients' eligibility to participate in this study. All participants will be screened to determine that they meet all eligibility criteria. Screening procedures to determine eligibility will be performed by trained research personnel. The screening procedures were designed such that the screening tools that require patient interaction can be administered either face-to-face or via the telephone. This screen is minimal risk to the patient and collected information will be maintained in secured, locked files. De-identified information (assigned a study screening code [screen pass or screen fail]) will be entered into a secure, NYU and HIPAA compliant database. When a patient is not eligible, they will be considered a screen fail. No additional information will be collected. Only study personnel will have access to said records. Clinic recruitment tracking data will be collected (see Attachment 4, Tracking Form: Clinic Recruitment). For any patient who is determined not to be eligible or declines to participate, any identifiable health information that was collected will be disposed of, following PHI procedures, once the de-identified tracking data is entered into the research file.

There are two components to the screening process (see Attachment 4): 1) interview and 2) medical record review. Screening procedures will require less than 30 minutes of patient's time.

4.3.4.1 **Screening Interview**

The screening interview (see Attachment 4, Recruitment Script) involves educating patients about the study and obtaining their verbal permission to conduct screening activities (under waiver of documentation of consent). Interview questions pertain to eligibility criteria, anxiety and cognitive screens.

Anxiety: The GAS-10 is a 10-item instrument that measures anxiety symptoms in adults/older adults; items were derived from the range of anxiety disorder symptoms in the DSM-IV-TR.[148,149] The GAS-10 will be administered to patients to minimize variance for the purposes of a pilot study. Per the expert recommendation of collaborators who administer the rtACS intervention, the basis for including this test as part of the screening process is that said collaborators have found that people with greater anxiety have a poorer response to rtACS. The GAS-10 will be administered per protocol. Patients who score ≥12 are excluded from the study based on receiver operating characteristic analyses. Eligibility for enrollment in the study based on the GAS-10 score will be indicated on the Recruitment Script form.

Cognition: The TICS-m is a 13-item instrument that will be administered as part of the screening process to identify potential patients with a cognitive impairment who are likely unable to accurately complete self-report questionnaires.[150,151] The TICS-m can be administered either face-to-face or via the telephone, which is why it is the tool chosen for the screening process. The TICS-m will be administered per protocol. Patients who score ≤ 27 are excluded from the study; based on score interpretation that these people have greater than mild cognitive impairment.[152] Eligibility for enrollment in the study based on the TICS-m score will be indicated on the Recruitment Script form.

- *Setup:* The GAS-10 and TICS-m will be administered in a distraction free room. When administered via the telephone, patients will be prompted that they should be in a distraction free area and should not be interrupted during the interview.

4.3.4.2 **Medical Record Review**

A review of patients' ophthalmic medical records will be conducted as part of the screening process to ensure there were no significant changes identified during their ophthalmic examination to determine patients' eligibility for this pilot study (see Attachment 4, Screening Form). Eligibility for enrollment in the study based on the medical record review will be indicated on the Screening Form. Patient identifiable information will only be recorded from the medical record after patients enroll in the study.

Procedure: Screening

- When trained research personnel are present at the Centers, screening procedures will be conducted the same day as the clinical appointment per patient's availability.
    - Research personnel will be present as often possible at the Centers on those days when the physicians involved in this study are scheduled with clinical appointments.
    - Screening procedures will be conducted in a private room, distraction free, to safeguard privacy.
- When trained research personnel are not available to conduct screening activities, the patient's verbal permission that his/her information can be shared with the research team will be obtained and documented and the patient will be informed that a trained research team member will contact him/her to discuss the research study and screening procedures. The research personnel's contact information will be provided to the patient so he/she is aware of whom to expect will be contacting him/her.
    - Patients will be contacted via phone unless otherwise specified by the patient at the time when verbal permission was obtained and documented.
    - Research personnel will contact patients within two business days of being informed of the patient's permission that his/her information can be shared with the research team. Three attempts will be made within 7 days. After three attempts, research personnel will initiate no further phone contact.
- When patients are not able or available to participate in screening activities the same day as their clinical visit, screening procedures will follow those described for when trained research personnel are not available.
- Once all screening procedures are completed and the information analyzed, patients will be informed of their eligibility to participate in this study.
    - Patients will be informed of their eligibility to participate in the study as soon as possible, no more than two business days following completion of screening procedures. This timeframe is established to account for potential variability in the timing of the screening procedures, patients' availability, and documentation of medical record review.
- For those patients who meet the eligibility criteria and agree to participate in the study, trained research personnel will schedule a date and time to meet with the patient to review and obtain written informed consent prior to initiating administration of study assessments (see Attachment 4, Participant Visit Schedule).

In the case when NYU Langone Eye Center/a member of the research team is contacted by an entity other than an NYU Langone Health patient in regard to rtACS research, the screening interview will be conducted via phone. A health records review will be conducted again to confirm no conflicting reports between information gathered during the screening interview with what is documented in the entity's health records. All other screening procedures are the same as conducted for the Centers.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Research personnel will monitor participants throughout the course of the study. Participants may be withdrawn from the study as decided by trained research personnel prior to the expected completion of that participant's role in the study. Reasons for withdrawal may include, but not be limited to:

- Adverse event
- Change in status relevant for inclusion or exclusion eligibility
- Change in medical diagnosis or treatment
- Non-compliance with study protocol
- Atypical skin condition*
- Atypical headache**
- Atypical discomfort***

*Erythema (skin reddening) is not a criterion for withdrawal. It is an anticipated effect (monitored) that may occur following the intervention as a result of increased blood flow at the site of the electrodes due to vasodilation as a secondary effect of current application across the skin and tissue barriers.
**Headaches naturally occur in the normal population. Atypical headache is an unusual headache either in occurrence or in intensity.
***Atypical discomfort entails an event when a participant expresses a desire to terminate a session, i.e., electrical stimulation would be aborted. In this case, when a participant requests to terminate a session, they will be withdrawn from the study.

Because the risk profile of ACS is very low, no research-related injury is anticipated. The delivered current is weak, such that it can hardly be felt. In the unlikely event that a participant reports clinically-relevant harm from the study, this information will be conveyed to the study physician who will evaluate the participant. The physician will ensure that the participant has appropriate medical follow-up when indicated. If the event is serious and unexpected, the event will be reported to the IRB, per their reporting guidelines.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

In the case when a participant is withdrawn from the study, prior to the expected completion of that participant's role in the study as decided by trained research personnel, we will obtain written permission to collect relevant follow-up data that directly pertains to the safety of that participant in regard to the intervention (e.g., adverse event/adverse effect related to intervention). Participants may withdrawal their consent to participate in the study at any time. Any identifiable research or medical information recorded for or resulting from the participant's participation in the study prior to the date that the participant formally withdrew consent (written notification of withdrawal) may be used and disclosed by the investigators for the purposes of the study described above.

5 Study Device

5.1 Description

The DC-Stimulator MC (neuroConn, GmbH, Ilmenau, Germany) will be used to deliver the rtACS protocol. It can be classified a Category B, Class II non-significant risk medical device. It has the capacity to deliver the established rtACS protocol documented in previous efficacy, safety, and interventional studies. It is a multi-channel electrotherapy device consisting of a programmable waveform generator that connects to electrodes to deliver a non-invasive, weak electric current (see section 1.2).

5.2 Treatment Regimen

After obtaining written informed consent, participants will be allocated (1:1 ratio) to either rtACS or sham stimulation intervention group. The intervention protocol for each group involves 10 daily sessions delivered over 2 weeks, 1 session per day, < 60 minutes of continuous/sham stimulation (0-100 Hz) per day following the established dose parameters. The rtACS group will receive the stimulation dose per protocol. During a sham stimulation session, the DC-Stimulator MC will be programmed accordingly which may include brief periods of stimulation at the beginning and/or end of the session, serving to

mimic the effects of a true stimulation session. Researchers report this is necessary to designing the masking component of this study.

5.3 Method for Assigning Subjects to Treatment Groups

For the randomization scheme, participants will be randomized (1:1 ratio) to the rtACS and sham stimulation groups using blocked randomization stratified by Centers (to determine any differences between the Centers). Random varying block sizes will be used to balance group allocation and minimize the risk of unmasking group assignment, and a randomization table will be computer generated accordingly. A statistician will generate a randomization table and a research staff member indirectly involved in the conduct of this study will conduct the process of allocation. Participants will be assigned in the order that they are enrolled. The randomization and allocation concealment will be uploaded to a secure database.

5.4 Subject Compliance Monitoring

Research personnel will monitor and document participants' compliance with attendance at scheduled baseline assessments, daily intervention sessions, and follow-up assessments. As part of the recruitment process, patients will be interviewed in regard to their availability to attend 10 daily sessions over a 2-week period. Participants' baseline assessments will be scheduled to accommodate their schedule within reason and the timeframe for the conduct of this study. In the event when an enrolled participant is unable to adhere to the study protocol, consideration for withdrawal will be discussed and documented by the research team.

5.5 Prior and Concomitant Therapy

During the study, participants will continue their normal glaucoma treatment regimen prescribed by their physician. Any change in said regimen or clinical procedures will be evaluated based on the eligibility criteria for this study.

5.6 Packaging

N/A. The DC-Stimulator MC device will be owned by NYULMC Department of Ophthalmology and will be used for this study for all participants at NYU Langone Eye Center. The device is treated like any patient-care instrument used within the department. Therefore, there are no individual packaging or kits for each participant. Each participant will have their own set of electrodes that will be managed per protocol (i.e., setup and cleaning), kept in individually labeled and sealed storage vessels, and will be stored in a research-designated space. In the event of device malfunction, a back-up device and extra electrodes will be stored onsite to avoid disruption of the study procedures.

5.7 Masking of Study

Interventionist will be masked to rtACS versus sham stimulation intervention group. He/she will not be involved in the allocation process. The DC-Stimulator MC has a programmable sham feature to maintain masking. A trained personnel who is not involved in data collection or analysis will be involved in the setup of the DC-Stimulator MC according to group allocation and rtACS protocol for each participant, following setup parameters and current standards for masking. Participants will be blind to group allocation. Following completion of the 10 daily sessions, interventionist and participants will be asked to guess the assigned condition during follow-up assessments.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Study Device

The DC-Stimulator MC will be purchased and shipped from neuroCare Group GmbH, Rindermarkt 7, 80331 München, Germany to NYU Langone Eye Center, 240 East 38th Street, 13th floor, New York, NY 10016. Upon receipt of the device (including backup device), an inventory will be performed and designated staff will verify that the shipment contains all the items noted in the shipment inventory. Any

damaged piece in a given shipment will be reported to research personnel and documented. The DC-Stimulator MC will be used for this study for all participants at NYU Langone Eye Center.

5.8.2 Storage

The devices and supplies will be located in a treatment room designated for research purposes at NYU Langone Eye Center. The backup device will be appropriately placed for storage in a locked room.

6 Study Procedures

Screening procedures will be conducted in a research-designated room at the Centers appropriate for the setup and confidentiality for the interview procedures. Baseline assessments, intervention sessions, post-intervention and follow-up assessments for all participants will be conducted in a research-designated room at NYU Langone Eye Center.

Per standardized assessment guidelines and in order to accommodate and minimize the amount of time subjects may be willing and/or able to participate in research procedures at the Eye Center, assessments of functional ability and QoL may be coordinated with subjects for virtual administration (e.g., via phone, Webex, etc.).

The IRB-approved recruitment script used during the screening procedures for this study will be used for contacting new patients, in conjunction with the COVID-19 Updates Research Participant Recruitment script provided by the OSR/IRB. In addition, the applicable COVID information sheet for potential and enrolled subjects will be provided in the appropriate situation and while they are applicable to subjects.

Trained personnel who are not involved in data collection or analysis will be involved in the programming of the DC-Stimulator MC according to group allocation for each participant and the masking procedures that distinguish the delivery of rtACS versus sham stimulation. All intervention procedures will be conducted the same for both groups (rtACS and sham). Adverse events/adverse effects will be assessed in either condition.

Refer to Attachment 5 for the study schedule of events and Attachment 6 for documentation forms described below.

6.1 Visit: Baseline

Within five business days prior to the start of intervention sessions, the informed consent procedures and baseline assessments will be administered.

6.1.1 Process of Consent

Trained research personnel will review the consent form with the patient and explain the purpose of the study, the procedures, as well as risks and benefits.

- Review study requirements
- Allow patient to read consent
- Answer questions
- Patient will sign consent

A copy of the consent form will be given to the patient. All questions will be addressed before acquiring a patient's signed consent. The signed consent form will be placed in the Regulatory Binder, kept separate from participant data. The consent process will be documented on the Case Report Form. Each participant will be asked whether they wish to receive documentation linking them to the study.

6.1.2 Assessments

Ophthalmic examination: Procedures follow standard practice including examination by an ophthalmologist and testing includes: recording medical and family history, VA testing, axial length, IOP and central corneal thickness measurements, slit lamp examination, indirect ophthalmoscopy, and

stereophotography of the optic nerve head, macula, and nerve fiber layer. The total time requirement for the ophthalmic examination is approximately 45 minutes.

The following assessments (approximate minutes to complete) will be administered at baseline: Pre-/Post-session Questionnaire (5), VF (20), VA (5), CS (5), OCT (10), OCT-A (10), VEP and PERG (15), Demographic Questionnaire (15), Verbal Fluency Test (5), Digit Span (5), LIFE-H (30), MNRead (10), VFQ-39 (25), SF-36 (25), and PSQI (10).

The total time requirement for participants for baseline testing is approximately 3 hours in addition to the ophthalmic examination.

MRI testing will be performed at baseline and will require up to 2 hours. Baseline assessments may be scheduled on separate days due to timing, location of MRI facility, and patient scheduling.

The Brief COPE questionnaire (Attachment 10) will be included in the battery of questionnaires. The Brief COPE is a 28-item questionnaire designed to measure effective/ineffective coping in response to a stressful life event. The time requirement for the questionnaire is less than 5 minutes. The questionnaire is included in order to capture effective/ineffective ways subjects cope with the COVID-19 situation and in order to determine whether their response to their lived experience with the COVID-19 situation may influence other study outcomes. The Brief COPE has been validated.[155,156]

Pittsburgh Sleep Quality Index (PSQI) will be included in the battery of questionnaires. The PSQI is a validated 10-item questionnaire designed to measure sleep quality. Evidence suggests RGCs are involved in circadian photoreception to regulate homeostasis; modulating a non-visual response to light associated with sleep. Testing will be administered per standardized protocol and will require < 10 minutes to perform. For subjects who have completed research procedures through follow-up, we will contact them to conduct the questionnaire.

6.2 Visit: Daily intervention sessions 1-10

Beginning on a Monday, 10 daily intervention sessions will be scheduled to span 2 weeks (excluding the weekend). Prior to each daily session on the same date, trained personnel will check the DC-Stimulator MC and other necessary equipment that will be used during the session for quality and integrity of function (see Research Activity Checklist). The Pre-/Post-session Questionnaire will be completed (5 minutes). The stimulation protocol (rtACS or sham) will be delivered, requiring approximately 90 minutes including all associated procedures including setup.

The total time requirement for participants for daily sessions is approximately 1 hour.

6.3 Visit: Post-intervention

Post-intervention assessments will be scheduled for administration within five business days of participants' last intervention sessions.

Ophthalmic examination: Procedures follow standard practice including examination by an ophthalmologist and testing includes: recording medical and family history, VA testing, axial length, IOP and central corneal thickness measurements, slit lamp examination, indirect ophthalmoscopy, and stereophotography of the optic nerve head, macula, and nerve fiber layer. The total time requirement for the ophthalmic examination is approximately 45 minutes.

The following assessments (approximate minutes to complete) will be administered: Pre-/Post-session Questionnaire (5), VF (20), VA (5), CS (5), OCT (10), OCT-A (10), VEP and PERG (15), Verbal Fluency Test (5), Digit Span (5), LIFE-H (30), MNRead (10), VFQ-39 (25), SF-36 (25), and Post-intervention Interview (60).

The total time requirement for participants for post-intervention testing is 3 hours in addition to the ophthalmic evaluation.

MRI testing will be performed at post-intervention and will require up to 2 hours. Post-intervention assessments may be scheduled on separate days due to timing, location of MRI facility, and patient scheduling.

The Brief COPE questionnaire (Attachment 10) will be included in the battery of questionnaires. The Brief COPE is a 28-item questionnaire designed to measure effective/ineffective coping in response to a stressful life event. The time requirement for the questionnaire is less than 5 minutes.

6.4 Visit: Follow-up

Follow-up assessments will be scheduled for administration 4 weeks following the participants' last intervention sessions.

Ophthalmic examination: Procedures follow standard practice including examination by an ophthalmologist and testing includes: recording medical and family history, VA testing, axial length, IOP and central corneal thickness measurements, slit lamp examination, indirect ophthalmoscopy, and stereophotography of the optic nerve head, macula, and nerve fiber layer. The total time requirement for the ophthalmic examination is approximately 45 minutes.

The following assessments (approximate minutes to complete) will be administered: Pre-/Post-session Questionnaire (5), VF (20), VA (5), CS (5), OCT (10), OCT-A (10), VEP and PERG (15), Verbal Fluency Test (5), Digit Span (5), LIFE-H (30), MNRead (10), VFQ-39 (25), and SF-36 (25).

The total time requirement for participants for follow-up testing is approximately 3 hours in addition to the ophthalmic examination.

MRI testing will be performed at follow-up and will require up to 2 hours. Follow-up assessments may be scheduled on separate days due to timing, location of MRI facility, and patient scheduling.

The Brief COPE questionnaire (Attachment 10) will be included in the battery of questionnaires. The Brief COPE is a 28-item questionnaire designed to measure effective/ineffective coping in response to a stressful life event. The time requirement for the questionnaire is less than 5 minutes.

7 Statistical Plan

7.1 Sample Size Determination

Given the objectives of this pilot study (see section 2) and limited data about the effect of rtACS for people with glaucoma, we estimate to enroll 16 participants to complete the study protocol. Our rationale for this number includes the following considerations: feasibility, quantifying an estimate of effect and estimate of variance, and validating methodologies.[153] We are using a block randomization scheme with a 1:1 allocation ratio for rtACS versus sham stimulation groups to collect data to inform the characterization of each group. We anticipate finding little to no effects in the sham stimulation group for a control but we establish equal allocation to groups to assess potential placebo effect.

7.2 Statistical Methods

All study participants will be included in efficacy analyses as randomized (intent to treat population). Treatment effects on all outcomes will be estimated with 95% confidence interval. Supportive analyses will include estimating effects in study participants who received at least five sessions of their randomized assigned treatment as supportive analyses and hypothesis testing with two-sided tests at significance level of 0.05.

The primary outcome variables that will be evaluated in this study are structure and function of the retina and visual pathway (using imaging and electrophysiological technology), visual function, functional ability,

and QoL. Secondary outcome variables include feasibility of procedures and methodologies for recruitment, enrollment, data collection and data management.

Subjective demographic and clinical characteristics will be analyzed using descriptive statistics. Continuous variables will be described by means and standard deviations (or by median and interquartile range for skew distribution) and categorical variables will be described by frequencies (count) and percentages. Overall, to analyze our aims and test our hypotheses we will use between and within group comparison analyses (e.g., *t*-tests) to evaluate change scores from baseline to post-intervention and follow-up between rtACS and sham stimulation groups. We will use effect size calculations to evaluate the magnitude of differences between and within groups. Additionally, we will quantify an estimate of variance using 95% confidence interval. Analyses will be conducted using R statistical computing software.

Aim 1 (2.1.1.1): Measure structural and functional capabilities of neuronal physiology and reorganization of the visual pathway (from eye to visual brain)

We will calculate change scores between baseline and study end scores on primary outcome variables. These difference scores will then be described and compared between and within groups for: 1) structure and function of the retina and visual pathway measures and 2) visual function. We will perform a multivariate analysis to examine the correlation between measures of retinal and visual pathway structure/function and measures of visual function. We will quantify estimates of effect and estimates of variance.

Aim 2 (2.1.2.1): Measure objective ability/disability and subjective well-being (i.e., QoL)

We will perform a multivariate analysis to examine the correlation among measures of visual function, functional ability, and QoL.

Aim 3 (2.2.1.1): Evaluate the data collection, data management methods, and study procedures for targeted outcomes other than the primary objectives

We will use descriptive statistics to analyze secondary outcomes to measure feasibility of procedures and methodologies for recruitment, enrollment, data collection and data management, etc.

7.3 Subject Population(s) for Analysis

Our primary analysis will be an intention to treat analysis. The data for all participants randomized into the study, regardless of study group, will be subjected to the study analyses, both for the primary and any applicable secondary analyses.

8 Safety and Adverse Events

Both the IRB and participants will be notified immediately of any new information in regard to this pilot study that affects participants' participation in the study. Unexpected and serious adverse events that occur will be reported to the IRB according to the IRB protocol. The primary investigator (PI) and research investigator(s) involved will monitor a review of the outcome, anticipated effects, and adverse event data in determining whether the study should continue, change, or terminate. If there is a major unresolved dispute between a research investigator and a research participant or between research investigators, a letter will be submitted to the IRB describing the dispute and identifying the parties involved.

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria.

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, etc.)

- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm)

Unanticipated Adverse Device Effect
An unanticipated device effect is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Serious injury
Any injury or illness that is any one of the following:

- life-threatening
- results in permanent impairment of a body function or permanent damage to body structure
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered adverse events if the abnormality:

- results in study withdrawal,
- is associated with a serious adverse device effect,
- is associated with clinical signs or symptoms,
- leads to additional treatment or to further diagnostic tests, or
- is considered by the investigator to be of clinical significance.

Based on International and U.S. guidelines on serious adverse events from medical devices (including the Office of Human Research and Protection of the U.S. Department of Health and Human Services; FDA regulations at 21 CFR §312.32[a]; 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice; ISO/DIS 14155-Clinical investigations of medical devices in humans, Good Clinical Practices, 2008), we classify a severe adverse event related to rtACS as a documented event that:

1) Based on scientific judgment is determined to be caused or aggravated by the application of current to the head, such that serious adverse events not linked to stimulation are excluded, even if they are subject to reporting requirements, AND
2) Results in irreversible damage of brain tissue, OR
3) Results in persistent disability or incapacity that produces an unwanted and substantial disruption of a person's ability to conduct normal life functions (i.e., the adverse effect resulted in an unwanted significant, persistent or permanent change, impairment, damage or disruption in the participant's body function/structure, physical activities and/or QoL), OR
4) Results in unexpected inpatient hospitalization or prolongation of existing hospitalization, where emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event), OR
5) Results in death or is life-threatening where the patient was at substantial risk of dying as a result of the adverse event, or use of the device was discontinued based on evidence rtACS might have resulted in death, OR

6) Medical or surgical interventions were necessary to preclude permanent imminent impairment of a body function due to rtACS, or prevent permanent damage to a body structure, due to rtACS.

8.2 Recording of Adverse Device Effects

Prior to and at each contact with the participant, the investigator will evaluate adverse device effects by examination and, as appropriate, by specific questioning. Information on all adverse device effects will be recorded immediately in the source document and in the appropriate adverse effect module of the Research Activities Checklist (see Attachment 7) and Case Report Form. All clearly related signs, symptoms, and abnormal diagnostic procedure results will be recorded in the source document, grouped under one diagnosis.

All adverse device effects occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse device effects that are still ongoing at the end of the study period will be followed up to determine the final outcome (see section 8.3).

The minimum initial information to be captured in the participant's source document concerning the adverse device effect includes:

- Study identifier
- Study Center
- Subject number
- Device model and serial number
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment
- Current status
- Whether study treatment was discontinued
- Whether the event is serious and reason for classification as serious

8.3 Reporting of Adverse Device Effects and Unanticipated Problems

8.3.1 Investigator Reporting: Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to participants or others. The following describes the NYULMC IRB reporting requirements, though investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report promptly, but no later than 5 working days:
Researchers will submit reports of the following problems promptly but no later than 10 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the PI, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to participants or others, or placed them at increased risk*

- ***Unanticipated adverse device effect***: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).

Other Reportable events:
The following events will be promptly reported to the IRB, though no later than 10 working days:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency (e.g., analysis indicates lower-than-expected response rate or a more severe or frequent side effect, other research finds arm of study has no therapeutic value, FDA labeling change or withdrawal from market).

Reporting Process
The reportable events noted above will be reported to the IRB using the Reportable Events Log (see Attachment 7) or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory Binder.

8.4 Recording and Reporting of Anticipated Effects

At each contact with the participant, the investigator will seek information on the occurrence of any known (anticipated) effects of the intervention by specific questioning and, as appropriate, by examination (see Attachment 7, Adverse Event Reporting). Information on all anticipated effects will be recorded immediately in the source document. All clearly related signs, symptoms, and abnormal diagnostic procedure results will be recorded in the source document, grouped under one diagnosis.

All anticipated effects occurring during the study period will be reported to the appropriate research personnel involved in the participants' intervention programs. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Any effects that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any effects that occur after the study period will be recorded and reported promptly. The minimum initial information to be captured in the subject's source document concerning the anticipated effects are listed in section 8.2.

Documented cases of mild side effects related to delivery of ACS which occasionally occurred include: erythema (skin reddening), skin tingling, skin itching, skin burning sensation, sensation of warmth at site of electrode placement, nausea, diffuse or migraine-like headache, facial muscle twitching, blurred vision, short-lived localized head pain or pressure, weak headache, forgetfulness, difficulty concentrating, change in mood, dizziness, general fatigue, sleeping difficulties (temporary), spontaneous phosphenes (independent of stimulation), blood pressure fluctuation, and difficulty breathing (103, 106).

Participants may experience double vision and difficulty in near vision tasks (e.g., reading), which is common, as an effect of dilating eye drops used during the clinical vision evaluation. Additionally, dilating eye drops may cause: redness of the eye, tearing or stinging of the eye, feeling faint or dizzy, and/or sensitivity to light. As it is standard of care, it is recommended that participants arrange for someone to

assist them in their transportation after the study visit. It is also recommended participants wear sunglasses when they go outside or into a brightly lit room. The effects of these dilating drops will disappear within 3-4 hours after they are instilled in the eye. Pupillary dilation may cause an increase in eye pressure or the possibility of an angle-closure event, which happens in a rare configuration of the eyes. There is a low risk that the instrument used to check participants' eye pressures (standard of care) might cause a scratch on the cornea. All participants will be examined clinically before dilating drops are instilled to identify eyes at risk, in which no dilation drops will be used. If either of these risks should occur, the participant will be treated immediately at no cost.

There is minimal risk of eye infection to participants from the ophthalmic testing procedures. To reduce the risk of eye infection, all exposed surfaces near the eye, as well as chin rest and forehead rest of the instruments, will be cleaned with alcohol before participants are examined per standard practice.

Some research subjects have reported mild discomfort with MRI scans. MRI uses a strong magnetic field to create images of the body. Because of the strong magnetic field, there are risks. One possible risk is burns to the skin. There is an increased risk of burns from devices that conduct electrical energy. These devices can include metallic objects or skin tattoos. These devices can be either in or on the patient in order for a skin burn to occur. The FDA has found that 70% of all who reported injuries from MRIs were burns to the skin. To reduce this risk, all participants who are scanned in this study must complete thorough screening to ensure that no conductive materials are present in or on the participant's body. Additionally, the power limits of the magnet will be adjusted as necessary. Another possible risk is that a metal object could be pulled into the scanner and hit the participant. To reduce this risk, everyone near the magnet will remove all metal from his/her clothing or pockets when in the scanning environment. Participants will be carefully screened to ensure no metal objects enter the magnetic field and they will be asked to place all metallic and magnetic objects in their possession (e.g., keys, jewelry, credit cards) in a secure location outside the magnet room.

The magnetic fields, at the strengths used, are felt to be without harm and the MRI scanning procedures fall within the FDA guidelines for radiofrequency electromagnetic field exposure. It is felt these are safe levels and less hazardous than a comparable x-ray computed tomography examination. Exceptions include if a person has electrically, magnetically, or mechanically activated implants (such as cardiac pacemaker), or clips on blood vessels in their brain, or other metallic objects in their body such as shrapnel, bullets, buckshot, or metal fragments. Therefore, participants will be carefully screened for previous exposure to metallic fragments or to implanted devices.

If participants are prone to claustrophobia, they will be asked to notify the researcher in charge of the scan, who will discontinue the scan upon the participant's request. The MRI scanner makes loud knocking or beeping sounds during imaging; earplugs will be provided to help reduce this noise. Due to the rapid rate of change of the magnetic gradients during imaging, peripheral nerve stimulation is possible. If this happens, participants may feel creeping or tingling sensations, typically along their arms or lower back. Dizziness and nausea may occur if the participants move their head in the bore of the magnet. Finally, rarely there may be some heating from the radio frequency coils, the cables to the coils, response and physiological monitoring devices. If at any time participants feel discomfort, they will be instructed to contact the operator immediately. They will also be instructed in how to use an emergency handheld device to inform the operator if they wish to immediately stop scanning and be removed from the magnet.

8.5 Unmasking Procedures

Allocation to group (unmasking) will be revealed once all participants complete the study procedures. In the event when the safety of the participant is in question, per protocol participants will be assessed by the physicians involved in this study and care directed and/or referred accordingly. Given the consistent reports for safety and tolerability of rtACS across several clinical trials, we don't anticipate the occurrence of any adverse events or adverse effects that are the direct consequence of rtACS; therefore, there is likely not a justifiable need for unmasking to occur prior to the study's end.

At the study's end, the staff personnel who managed the allocation concealment and randomization processes will reveal the allocation (database) to the study research team involved in any subsequent communication with participants. Participants will be informed of their group randomization at the conclusion of their participation in the study via face-to-face or phone conversation with research personnel, documented in the participant's source document.

In the unlikely event when unmasking is deemed to occur related to managing an adverse event, the unmasking will be reported with the adverse event. In the unlikely event when unmasking is not associated with an adverse event, unmasking will be reported to the research team in an immediate and timely manner.

8.6 Medical Monitoring

It is the responsibility of the PI to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9). Medical monitoring will include a regular assessment of the number and type of adverse events. The PI and lead research investigators and personnel will be ultimately responsible for the data safety monitoring of the overall study and will meet bimonthly to monitor data, recruitment, retention, confidentiality, and adherence to the study protocol.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of HIPAA (1996). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

All medical information collected from participants and documentation related to their participation in the study will be kept in a locked cabinet designated for research conducted at NYU Langone Eye Center during the conduct of the study. Unique patient identifiers will be used to label all data; a password-protected linking file will be accessible to/managed by the study PI and Co-PI. Strict standards of confidentiality will be upheld at all times.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. Source data will be kept in participant files that will be physically located in a locked filing cabinet in a locked office at NYU Langone Eye Center during the conduct of the study. Research data will be entered online through the NYU and HIPAA compliant database, designed specifically for this study. An anonymous database number will be assigned to each participant and will be used for both the data entry sheets and the patient follow-up sheets. Data collected using the Linking File Form (see Attachment 6), which includes the participant's name and study ID number, will be stored separately from participants' data files in a password protected electronic file. Access to this data will be restricted to study personnel only. The assigned ID will code participant data and identifying information will not be presented or published to maintain participant privacy and confidentiality.

9.3 Case Report Forms

The study Case Report Form (see Attachment 6) is the primary data collection instrument for the study. All data requested on the Case Report Form will be recorded. All missing data will be explained. If a space on the Case Report Form is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialed and dated. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

A list of all persons authorized to perform study procedures will be maintained in the Regulatory Binder. All study related essential documentation will also be kept in the Regulatory Binder. The assigned study staff will maintain participants’ study files and source documentation. Study files will be kept locked in the research offices. Following completion or termination of the study, all study documents will be kept for a minimum of 2 years as required by the IRB.

9.5 Electronic Medical Record and Release of Study-Related Information

In compliance with the 21st Century Cures Act, some research-related information in subjects’ Electronic Medical Records will not be immediately available in order to protect the randomization integrity of the research. The suppressed information will be accessible to subjects once the study is concluded. The information to be suppressed includes: visual field results, OCT imaging, and ophthalmic report.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Data and Safety Monitoring Plan

We will utilize operating procedures for reviewing patient safety data and source data generated from this study. This will include routine monitoring according to the Data and Safety Monitoring Plan (see Attachment 8), allowing for adequate time and space for such monitoring activities and that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities. The following aspects will be specifically monitored: enrollment and retention, data collection, confidentiality, multi-centers, breaches from the study protocol, and any adverse event.

Data and safety monitoring will include monthly meetings between the PI, research investigators, study coordinators, and pertinent study research personnel as necessary. The Data and Safety Monitoring Plan encompasses the research-related activities as they apply to recruitment and screening procedures conducted at New York Eye and Ear Infirmary of Mount Sinai. At these meetings, the research team will review the clinical ratings, assessments, clinical course, and study processes for each active participant as they apply to each Center. Specific attention will be given to data quality and timeliness, HIPAA compliance, safe storage of data, and data backup of electronic source data. Attention will also be given to participant recruitment, accrual and retention, participant risk versus benefit, adverse events, and other factors that can affect study outcome, including scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

There are no predetermined stopping rules for this pilot study. As needed, a yearly report will be submitted to the IRB during the renewal as to the frequency of monitoring and a summary report addressing any recommendations to adjust the risk/benefit ratio, participant privacy, or confidentiality procedures.

All data will be shared with previous PI Joel Schuman for study analysis.

10.2 Auditing and Inspecting

The research investigators will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The investigators will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to U.S. and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable NYULMC and federal regulatory requirements.

This protocol and any amendments will be submitted to a properly constituted IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

No deviation from the protocol will be implemented without prior review and approval of the IRB, except where it may be necessary to eliminate an immediate risk to a participant. In such case, the deviation will be reported to the IRB according to its policies and procedures.

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. See Attachment 9 for a copy of the Participant Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a participant, using the IRB-approved consent form, will be obtained before that participant undergoes any study procedure. The participant and the investigator-designated research professional obtaining the consent will sign the consent form.

Research investigators who will obtain consent will be trained in the consent process. The process of informed consent will follow the outline as described in section 6. Trained research personnel involved in the administration of assessments will review and obtain written informed consent of participants who enroll in the study.

12 Study Finances

12.1 Funding Source

This pilot study is funded through the NYULMC Department of Ophthalmology. Charges will be billed only for procedures performed as part of participants' routine clinical care. No study-related procedures will be billed to the participant but to the research program within the Department of Ophthalmology.

12.2 Subject Stipends or Payments

In an effort to maximize the rate of enrollment in this study, participants will receive a payment of $20.00 (gift card) after the completion of each study visit. The payment process will follow departmental and NYU guidelines. Participants, nor their insurance provider, will be charged for any of the procedures or tests performed solely for the purpose of this research study.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the research investigators. One co-investigator, Heather Livengood, will be the primary research personnel responsible for coordinating publication of the results of this pilot study.

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