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Stanga, Paulo, Tsamis, Emmanouil, Siso-Fuertes, Irene et al. (11 more authors) (2021) Electronic Retinal Prosthesis for Severe Loss of Vision in Geographic Atrophy in Age-Related Macular Degeneration: First-in-Human Use. European Journal of Ophthalmology. ISSN 1120-6721

https://doi.org/10.1177/11206721211000680

Electronic Retinal Prosthesis for Severe Loss of Vision in Geographic Atrophy in Age-Related Macular Degeneration: First-in-Human Use

Journal:	*European Journal of Ophthalmology*
Manuscript ID	EJO-20-1957
Manuscript Type:	Clinical trial protocol
Date Submitted by the Author:	28-Nov-2020
Complete List of Authors:	Stanga, Paulo; Central Manchester University Hospitals NHS Foundation Trust Tsamis , Emmanouil; Columbia University, Department of Psychology Siso-Furetes, Irene; Central Manchester University Hospitals NHS Foundation Trust Dorn, Jessy; Second Sight Medical Products, Inc, Sylmar, California, USA Merlini, Francesco; Second Sight Medical Products, Inc, Sylmar, California, USA Fisher, Andy; Focal Point, UK Crawford, Fiona ; Manchester Vision Regeneration (MVR) Lab at Manchester Royal Eye Hospital, NIHR Kasbia, Shakti; Manchester Vision Regeneration (MVR) Lab at Manchester Royal Eye Hospital, NIHR Papayannis, Alessandro; Azienda Sanitaria Universitaria Giuliano Isontina, SC di Oculistica Ospedali di Monfalcone e Gorizia, Monfalcone, Italy Baseler, Heidi; Hull York Medical School; University of York Department of Psychology Morland, Antony; University of York Department of Psychology Hanson, Rachel; University of York Department of Psychology Humayun, Mark; Ophthalmology and Biomedical Engineering, USC Roski Eye Institute, Los Angeles, CA, USA Greenberg, Robert; Second Sight Medical Products, Inc, Sylmar, California, USA
Keywords:	RETINA, Age-Related Macular Degeneration < RETINA, Macular and RPE Dystrophies < RETINA, Inner retinal/Vitreoretinal dystrophies < RETINA, Retinal Pathology / Research < RETINA, Retinitis Pigmentosa < RETINA, Pars Plana Vitrectomy < VITREOUS / ENDOPHTHALMITIS
Abstract:	BACKGROUND: To date there are yet no available approved therapies for Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD). METHODS: Single site, non-randomized safety and efficacy study presenting the preliminary results in a cohort of five late stage AMD (GA) patients successfully implanted with the Argus II Retinal Prosthesis System (Second Sight Medical Products Inc., Sylmar, California, USA). Extensive fundus imaging including retinal photographs from which the GA area was measured. A combination of custom and traditional tests designed for very low vision subjects assessed visual function in study subjects. A Functional Low-Vision Observer Rated Assessment was

	carried out to evaluate the impact of the system on the subject's daily life. In addition, a study to evaluate structural characteristics of the visual cortex of the brain was performed in one subject using magnetic resonance imaging. RESULTS: 7 device-related adverse events were reported, 4 of which were classed as serious adverse events. Retinal detachment was reported in 3 patients and was successfully treated within 12 months of onset. Testing showed an improvement in visual function in 3 of 5 patients with the system turned on. Magnetic resonance imaging assessed in one patient after implantation indicates a selective increase in cortical myelin and thickness in visual brain regions one year post implantation. CONCLUSIONS: Epiretinal prostheses can successfully be implanted in those affected by GA secondary to late-stage AMD and can elicit visual percepts by electrical stimulation of residual neuroretinal elements and improve basic visual function in those affected.

Electronic Retinal Prosthesis for Severe Loss of Vision in Geographic Atrophy in Age-Related Macular Degeneration: First-in-Human Use

Paulo E. Stanga[1,2,3], Emmanouil Tsamis[1,4], Irene Siso-Fuertes1, Jessy D. Dorn[5], Francesco Merlini[5], Andy Fisher[6], Fiona I. J. Crawford[1], Shakti S. Kasbia[1], Alessandro Papayannis[1,10], Heidi A. Baseler[7,8,9], Antony B. Morland[8,9], Rachel L. Hanson[8,9], Mark Humayun[11], Robert J Greenberg[5]

[1] Manchester Vision Regeneration (MVR) Lab at Manchester Royal Eye Hospital, NIHR Manchester Clinical Research Facility and Manchester University NHS Foundation Trust

[2] Division Evolution & Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK

[3]Retina Service, London Vision Clinic, London, UK

[4] Division Pharmacy & Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK

[5] Second Sight Medical Products, Inc, Sylmar, California, USA

[6] Focal Point, UK

[7] Hull York Medical School, UK

[8] Department of Psychology, University of York, UK

[9] York Neuroimaging Centre, University of York, UK

[10], SC di Oculistica Ospedali di Monfalcone e Gorizia, Azienda Sanitaria Universitaria Giuliano Isontina, Monfalcone, Italy

[11] Ophthalmology and Biomedical Engineering, USC Roski Eye Institute, Los Angeles, CA, USA

This article contains additional material: S1 Fig and S1 Table.

Trial registration number on ClinicalTrials.gov: NCT02227498

Short title:

Electronic retinal prosthesis trial in GA-AMD

Financial support:

This research was sponsored by Second Sight Medical Products Inc., Sylmar, California, USA. The sponsor or funding organization participated in the design of the study, data management, data analysis, and review of the manuscript.

Corresponding author:

Prof. Paulo Eduardo Stanga
Consultant Ophthalmologist & Vitreoretinal Surgeon
London Vision Clinic - Retina Lead
138 Harley Street, London W1G 7LA
Email: p.stanga@londonvisionclinic.com

Abstract

BACKGROUND: To date there are yet no available approved therapies for Geographic Atrophy (GA) secondary to age-related macular degeneration (AMD).

METHODS: Single site, non-randomized safety and efficacy study presenting the preliminary results in a cohort of five late stage AMD (GA) patients successfully implanted with the Argus II Retinal Prosthesis System (Second Sight Medical Products Inc., Sylmar, California, USA). Extensive fundus imaging including retinal photographs from which the GA area was measured. A combination of custom and traditional tests designed for very low vision subjects assessed visual function in study subjects. A Functional Low-Vision Observer Rated Assessment was carried out to evaluate the impact of the system on the subject's daily life. In addition, a study to evaluate structural characteristics of the visual cortex of the brain was performed in one subject using magnetic resonance imaging.

RESULTS: 7 device-related adverse events were reported, 4 of which were classed as serious adverse events. Retinal detachment was reported in 3 patients and was successfully treated within 12 months of onset. Testing showed an improvement in visual function in 3 of 5 patients with the system turned on. Magnetic resonance imaging assessed in one patient after implantation indicates a selective increase in cortical myelin and thickness in visual brain regions one year post implantation.

CONCLUSIONS: Epiretinal prostheses can successfully be implanted in those affected by GA secondary to late-stage AMD and can elicit visual percepts by electrical stimulation of residual neuroretinal elements and improve basic visual function in those affected.

Introduction

Almost 1 in 25 people worldwide suffer from severe visual impairment, in the form of low vision or blindness [1]. In a significant proportion, approximately 10 to 20%, visual impairment is irreversible. As a result, vision regeneration has recently become the focus of some exceptional research in an attempt to restore some of the lost vision. Several different approaches have been investigated to restore sight to those suffering from severe visual impairment due to retinal or neurological degenerations, including gene therapy and visual prostheses [2-10]. Age-related Macular Degeneration (AMD) is a disease which describes a broad designation of signs and symptoms which can significantly impact the retina and consequent vision. Early and intermediate AMD are characterised by the presence and size of soft drusen, comprising of lipid deposits at the level of the retinal pigment epithelium (RPE). Late AMD describes the loss of central vision as a result of damage to the macula and can be sub-categorised into two forms: Neovascular AMD and Geographic Atrophy (GA). The latter is characterised by chronic and currently irreversible atrophy affecting the RPE and photoreceptor cells, resulting in a progressive and devastating loss of vision[11]. It is estimated that 30-50 million people are affected by AMD globally and this is likely to increase with the aging population. It is estimated that by 2040 the number affected by late AMD is set to double, and while those with the Neovascular type can receive treatment in the form of Anti- Vascular Endothelial Growth Factor (Anti-VEGF), there is no treatment for those affected by GA currently [12,13].

Humayun et al showed that intraocular direct electronic stimulation of atrophic retina in AMD using a probe during pars plana vitrectomy surgery can elicit visual phosphenes for the duration of the probe-retina contact [14]. The aim of the retinal prosthesis is to elicit neural activity in the remaining retinal neurons by detecting light and converting it into electrical stimuli using artificial devices. As mentioned above, in GA the outer retinal

structures and photoreceptor cells become depleted whereas inner retinal structures are left partially intact and therefore can elicit some visual potential [15]. The Argus® II Retinal Prosthesis System (Second Sight Medical Products Inc., Sylmar, California, USA) is a commercially available device that aims to restore a basic level of vision to patients with profound vision loss from outer retinal dystrophies [16].

Since obtaining a CE mark in 2011 and FDA approval as a humanitarian device in 2013, the device has been predominantly utilised for patients with total loss of vision from rare genetic diseases such as retinitis pigmentosa (RP) and choroideremia [14,16-24]. AMD remains one of the leading causes of registered legal severe visual impairment and irreversible blindness among the elderly in developed parts of the world [25]. Unlike RP or choroideremia, AMD primarily affects the central retina, which is responsible for high resolution vision necessary for reading, driving as well as face and object recognition. Patients do maintain their peripheral vision; however, this does not allow the completion of the aforementioned tasks. Constant use of peripheral vision is also extremely taxing on the patient as they are constantly trying to change their angle of vision by moving their heads and eyes.

Here we describe preliminary safety and efficacy results of five patients with a diagnosis of advanced GA in late-stage AMD implanted with the Argus® II Retinal Prosthesis System.

Methods

The study conformed to World Medical Assembly Declaration of Helsinki 1964 and subsequent revisions. The study was conducted with compliance to the spirit of Good Clinical Practice and appropriate approvals were granted from the Human Research Authority (HRA) and the study was approved by Medicines and Health Products Regulatory Agency (MHRA)

in the UK and the North West Greater Manchester Research Ethics Committee. The study was registered on www.clinicaltrials.gov, trial registration number NCT02227498. Written information was provided to all participants in clear, written form to aid verbal explanations given by the study team. Audio versions of study documents were also prepared and used where applicable. Written informed consent was obtained prior to enrolment of each participant enrolled on to the study.

Trial design

This is a single arm, non-randomised, controlled feasibility study at a single site. Potential candidates were screened to ensure they were eligible for the study until the recruitment target of 5 patients was achieved. The first participant was consented on January 2015 but did not meet the inclusion criteria. The first included participant was consented on April 2015 and the fifth and last included participant was consented on January 2016. To date, the follow-up time ranges from 24 to 36 months approximately. Fig 1 shows the CONSORT flow diagram with further details on screening fails and enrolled participants.

Fig 1. CONSORT Flow Diagram. Progress shown through the phases of the trial (enrolment, intervention allocation, follow-up, and data analysis) up to the first 12 months reported in the present manuscript.

The inclusion criteria were: subjects aged between 25 and 85 years of age who consented to participate in the study; a diagnosis of late-stage AMD (i.e., evidence of drusen and hyperplasia of the RPE in the eye with GA secondary to late-stage AMD as determined by the investigator); severe sight impairment meeting the following additional criteria:

- Visual acuity of logMAR 1.0 (6/60) or worse in both eyes as measured by ETDRS;
- Hand motion or worse central vision in the eye to be implanted, as measured with a pinhole occluder;

- GA (confirmed by Fundus Autofluorescence) of at least 18 mm^2 extent and central scotoma (confirmed by microperimetry) in the central 20° or more.
- In cases of bilateral GA that meet the study criteria, the eye with worse vision (per ETDRS VA and microperimetry results) will be chosen for the study procedure.

Additionally, subjects had to be pseudophakic with an IOL successfully implanted in the study eye at least 2 weeks before baseline testing, or aphakic with a clear capsule; subjects had to be both motivated and competent to learn to use the Argus II System (by the Investigator's assessment), and willing and able to commit to the study requirements (including an understanding of the requirements of the study and acceptance of the time involved in participating). Finally, subjects included in the study must not be suffering from non-ophthalmic serious adverse events (e.g., myocardial infarction, etc.) or from non-curable life-threatening conditions (e.g. cancer) at the time of the Baseline visit.

Criteria for exclusion of the trial were ocular diseases or conditions that could prevent the Argus II implant from working (e.g., optic nerve disease, central retinal artery or vein occlusion, history of retinal detachment, trauma, etc.);; ocular structures or conditions that could prevent the successful implantation of the Argus II Implant or adequate healing from surgery (e.g. extremely thin conjunctiva; axial length <20.5 mm or > 26 mm; corneal ulcers; abnormalities in the typical curvature of the retina like staphyloma and all causes of significant protrusions or depressions at the macular that could compromise the optimal position of the electrode array, active or severe blepharitis, evidence of active sub-macular choroidal neovascularization (CNV) in proposed study eye etc.); ocular diseases or conditions (other than cataracts) that prevent adequate visualization of the inner structures of the eye (e.g., corneal opacity). Also excluded from the trial were those subjects with an Implantable Miniature Telescope in either eye; pre-disposition to eye rubbing or with any disease or

condition that prevents understanding or communication of informed consent, study demands, and testing protocols, including:

- Cognitive decline including diagnosed forms of dementia and/or progressive neurologic disease,
- Psychiatric disease including diagnosed forms of depression;
- Does not speak a principal language associated with the region, and
- Deafness or selective frequency hearing loss that prevents hearing device alarms and alerts.

Additional reasons for exclusion were subjects being pregnant or wishing to become pregnant during the course of the study; participating in another investigational drug or device study that may conflict with the objectives, follow-up or testing of this study; subjects with inability to tolerate general anaesthesia or the recommended antibiotic and steroid regimen associated with the implantation surgery and those subjects with conditions likely to limit life to less than 1 year from the time of inclusion.

[A full list of inclusion/exclusion criteria is also recorded at www.clinicaltrials.gov, trial registration number NCT02227498]

While not a specific exclusion criterion, patients with Stargardt's or other hereditary macular degenerations were not included in this trial. They were excluded on the basis of not meeting the primary inclusion criterion of being diagnosed with late-stage AMD (GA). This determination was made by the investigator after review of the medical history, fundus imaging, and other screening assessments.

Each of the recruited patients, accompanied by at least one family member, had a thorough consultation with our research team to understand the nature of this study and set realistic expectations. All patients gave their written informed consent and the study adhered to the Declaration of Helsinki. The study was approved by Medicines and Health Products

Regulatory Agency (MHRA) in the UK and the North West Greater Manchester Research Ethics Committee. Study procedures carried out to ensure eligibility for the study and to monitor structural and functional changes included the following: optical coherence tomography (OCT), wide-field retinal fundus photography, fundus autofluorescence and fluorescein angiography by means of the OPTOS California (Optomap; Optos PLC., Dunfermline, Scotland, United Kingdom), visual field assessed by the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec Inc., Dublin, CA), testing with modified visual acuity (VA) tests for extremely low vision subjects (described elsewhere [17,19,21]) and completion of the Functional Low-Vision Observer Rated Assessment (FLORA) [26,27].

Surgery

The Argus II System consists of two main components: an extra- and intraocular portion and an external unit worn by the user (Fig 2).

Fig 2. Argus II System. The implant consists of a receiving coil for receiving information and power from the external components of the Argus II System, an electronics package that is secured to the outside of the eyeball using a standard scleral band and that drives stimulation of the electrodes and an electrode array (60 electrodes arranged in a 6 x 10 grid) that is secured to the surface of the retina by a retinal tack (upper row). The implant receives power and data commands wirelessly from an external unit. The externals are composed of the Argus II Glasses and the Argus II Video Processing Unit (VPU) (lower row). A small, light-weight video camera and a transmitting coil are mounted on a pair of glasses. The glasses are connected to the VPU via a cable. The VPU is worn by the subject and it converts the video image captured by the video camera into stimulation commands. The telemetry coils and radio-frequency system are mounted on the ear piece for transmitting data from the VPU to the implant. The implant is provided in both left and right eye configurations. The

device is only implanted in one eye. The study eye was decided according to the requirements set up in the inclusion criteria.

The extraocular portion of the implant was inserted under the extraocular muscles. The implant was fixed to the eye via sutures passed through suture tabs on the implant and secured by a scleral band. In order to insert the intraocular portion implant, core and peripheral vitrectomies were performed, followed by dissection of any epiretinal membrane in the area where the electrode array would be placed. The electrode array was then inserted through an opening in the temporal part of the sclera and secured onto the retina using a retinal tack. Extensive training and support was provided by the study sponsor for the surgical staff involved with the study. Professor Stanga had prior experience with the surgical technique described above from the previous RP study at MREH.

Study assessments

The safety endpoints for this study were the number and nature of adverse events (AEs) in the implanted subjects. AEs and Serious Adverse Events (SAEs) were documented throughout the study and included in the data analysis for safety evaluation.

Visual function was assessed for all implanted subjects between both the implanted and fellow eye, providing data on natural course. Study specific training and certification was provided by Second Sight to ensure that all involved staff were appropriately trained for their role on the study. Visual function testing was carried out by specific research optometrists and assistants named on the study delegation log. ETDRS Visual Acuity (VA), Grating VA, Square Localisation and Direction of Motion tests comprised the visual function tests.

Grating VA, Square Localisation and Direction of Motion tests were custom designed and provided by Second Sight. Monocular visual acuity (VA) was assessed using ETDRS Visual Acuity and Grating VA methods with the system turned On/Off in the study eye.

Traditional methods were used to assess ETDRS VA; central VA measured at 3 meters using the appropriate 3-meter chart. If a score worse than 1.0 logMAR was obtained the test was repeated at 1 meter. Grating VA was necessary in those with a visual acuity between 1.6 and 2.9 logMAR.

Binocular VA was assessed using Square Localisation and Direction of Motion, assessing basic visual function in addition to traditional methods of VA assessment. Square Localisation assessed the subject's ability to determine light localisation by assessing how well the subject could distinguish a white square of varying size against a black background. Direction of Motion assessed motion discrimination by having the subject draw the same direction of a horizontal line presented to them via a touchscreen monitor.

For visual function assessments the subjects served in three ways as their own control: comparisons are performed between the system turned ON and OFF, between implanted eyes and fellow eyes, and between pre-surgery and post-surgery performance When results were compared with the camera ON and OFF and both eyes open, data from a particular subject at a particular time point was analysed with a two-tailed t-test assuming unequal variances. Visual function testing was performed at the baseline visit, 3, 6 and 12 months post-op.

A quality of life questionnaire (QOL) was also performed by each patient with the system turned ON and OFF. The impact of the system on the patients' daily life was rated by expert observers in the Functional Low-Vision Observer Rated Assessment (FLORA) QOL questionnaire. FLORA scores on observed functional vision tasks range from 4 (impossible) to 1 (easy).

Cortical changes

An additional research study was carried out in conjunction with the Argus II feasibility clinical trial to assess the visual cortex of the brain before and after implantation of

the retinal prosthesis. This part of the study was approved by the NHS Health Research Authority (IRAS reference 171426; http://www.isrctn.com/ISRCTN52484108) and the York Neuroimaging Centre Research and Governance Committee. Informed written consent was obtained from all participants, adhering to the Declaration of Helsinki. Magnetic resonance imaging (MRI) was used to assess two structural characteristics in the cerebral cortex (grey matter) of the brain: cortical thickness and cortical myelin levels. Three of the five patients (patients # 133, # 547 and # 628) were scanned 5-19 days before implantation with the epiretinal prosthesis. Post-implantation assessments were carried out 13 months following surgery in patient # 628. Of the remaining two patients scanned pre-implantation, one was deceased and one withdrew for non-study related reasons. Eight sighted, age-matched control participants (4 females, mean age 75.1 years, age range 70-83 years) were also scanned under the same MRI protocol that generated 3D models of the cortical surface [28]. Post-implantation MRI adhered to published safety guidelines on MRI use with the implant device turned OFF [29].

Mean cortical thickness and mean cortical myelin levels were measured in three regions of interest [28] before and after implantation: V1 (primary visual cortex), V2 (secondary visual cortex) and a non-visual control region, OP2, an area in the parietal operculum that has thickness and myelination levels to visual cortex.

Results

We successfully recruited 5 eyes with a diagnosis of late-stage AMD (GA) but no other comorbidity that could affect their vision. Three female and two male patients had the Argus II System successfully implanted in one eye (i.e. 3 right (OD) and 2 left (OS)). The mean age of recruited patients was 75 years (±4.6, range: 70.7–79.9). Due to the (non study-related) death of one participant four months after recruitment, surgical results include data

from 5 participants, but visual function and functional vision results include data from up to four participants. This study presents the initial results following the first 12 months of the study, of which continued for a further 4 years approximately.

Surgical and safety results

During the implantation surgery there were no complications and surgical results are considered reproducible across the 5 implanted eyes. All 5 implants were placed over the centre of the retina (i.e. macula), where structural and functional defects, that is atrophic retinal areas and central scotomas, were identified and correlated. In 3 of the 5 occasions the visible atrophic central area was smaller than the retinal area covered or very nearly covered by the implant electrodes. Adverse Events (AEs) and Serious Adverse Events (SAEs) were documented throughout the study. During the first 12 months of follow up, we recorded 7 study-related AEs of which 4 were classified as SAEs related to the procedure or device. The SAEs were: one localised non-rhegmatogenous retinal detachment (RD) under the cable (Study ID #214), two cases of proliferative vitreoretinopathy (PVR)/retinal detachment (Study IDs #547, #950, and one case of hypotony (Study ID #628).

All SAEs responded to gas injection or pars plana vitrectomy surgery with silicon oil and were all resolved within 1 year of onset. One patient also required retinectomy. In addition, a scleral patch graft was placed in the subject suffering from hypotony to prevent the leakage around the entry site of the cable.

The localized non-rhegmatogenous RD under the cable was observed 1 day after the implantation surgery and may have been induced during a first unsuccessful attempt of array insertion into the vitreous cavity. Prior to array insertion there may have been a non-full thickness choroidal cut at the ends of the 5.2mm incision causing the array to push against the choroid. After this first unsuccessful attempt of array insertion the surgeon ensured a full-

thickness, full-width choroidal cut with a 15° Stab Knife and Hoskins Forceps. The second attempt of array insertion was uneventful. The RD was treated with gas injection.

The two cases of PVR/retinal detachment with a total tractional retinal detachment in the 4 quadrants were observed 1.4 months post-implant and 1.9 months post-implant, respectively. The events were treated with a pars plana vitrectomy, membrane peeling and silicone oil injection. Both patients reported a loss of peripheral vision in the implanted eye that recovered after this treatment. In both cases the artificial perception was not affected by the PVR/retinal detachment.

A non-serious and stable macular oedema (MO) was observed in all patients from approximately 1 month after implantation and during the course of the follow-up (Fig 3). The macular oedemas were not treated because they did not have any impact on the artificial perception elicited by the retinal prosthesis.

Fig 3. Retinal Fundus and Autofluorescence Images at 1 month. Right eye shown with large atrophic macular area (upper left) and Left eye shown with a small atrophic area (lower left). The implant has been placed over the atrophic region. OCT scans from the same eyes show examples of the Macular Oedemas observed in all eyes.

A summary of AEs is given in S1 Table, although further and more specific details on non-serious AEs are beyond the scope of this report.

Electrical Stimulation Results

Pre-implantation baseline tests revealed no signs of visual function over the affected atrophic area of central retina (S1 Fig). Post-implantation, all subjects reported perceiving phosphenes in response to electrical stimulation from electrodes over the atrophic areas, both during direct stimulation by the computer, and during stimulation driven by the real-time video image. Moreover, central visual phosphenes continued to be reported following the resolution of AEs.

Active AEs in one of the participants (inability of the patient to attend the protocol visit and the testing session), and the death of another (unrelated to the implant), resulted in only three patients participating in visual function assessments. Moreover, missed visits and errors in the test administration and capture of data resulted in incomplete functional and structural data collection in the three participants (e.g., missing baseline data in patient #133).

In the object localization task, in which the patient was required to locate a white square on a black touchscreen with both eyes open, one patient (# 133) showed significant improvement in performance with the system ON compared to OFF at two follow-up visits (Fig 4), though the mean error was higher than that seen at 3 months for both ON and OFF conditions.

Fig 4. Square Localization and Direction of Motion Results. Individual results of the performance with system ON (green), system OFF (red) and difference (system OFF- system ON, blue) for square localization and direction of motion tests over time for three of the patients. The excluded participant did not have sufficient data to monitor performance over time due to active AEs. The dotted black line is drawn for reference. Values of the difference (system OFF- system ON) above the reference line indicate improved performance with system ON. Axis labels with an asterisk indicate statistically significant differences ($p < 0.05$) in performance with the System ON versus OFF.

In a visual motion task, in which the patient was asked to draw the direction of motion of a white line moving across a black screen with both eyes open, performance was significantly better with the system ON in two of the patients (# 214 and # 950) at one visit each. The remaining follow up visits and patients, including all assessments of acuity as measured by Grating Visual Acuity, which is performed monocularly, did not show a significant difference in performance with the system ON and OFF.

In contrast to artificial, lab-based visual tasks, usage of the system after one year post-implantation for functional vision in a "real world" environment (Fig 5) was also evaluated. Four subjects participated in the FLORA at baseline and 12 months post-implant. The impact of the system on the patients' daily life was rated by expert observers in the FLORA as positive for one of the participants and as mildly positive for the remaining three. No instances or reports of double vision, visual confusion, or inability to integrate artificial and residual vision were reported on the case narratives or in anecdotal reports from the patients or low vision rehabilitation therapist (data not shown). FLORA scores on observed functional vision tasks range from 4 (impossible) to 1 (easy). All FLORA domains improved with the system ON compared to baseline at one year post-implantation, with the greatest improvement evident in the visual orientation tasks (Fig 5A). However, all visual task domains increased in difficulty relative to pre-implantation with the system OFF (Fig 5B).

Fig 5. Results of the Functional Low-Vision Observer Rated Assessment (FLORA). A) Rating percentages one year after implant activation for the four participants with the system OFF (left column) and ON (right column). B) Average FLORA score differences (N = 4) in two groups (system ON minus OFF at baseline, and System ON minus OFF at 12 months follow-up, respectively) for the different visual task categories. FLORA scores on observed functional vision tasks range from 4 (impossible) to 1 (easy). Difference scores above the OX axis represent better performance with the system ON. Asterisk indicates the only category where system ON performed worse than pre-implantation (interacting with others tasks).

Cortical Changes

Three-dimensional models of the cortical surface were generated using structural MRI data. Fig 6A shows examples of the 3D cortical surface from the patient, providing qualitative visualisation of cortical thickness and myelin levels across the brain. The three

regions of interest (ROI) selected for quantitative measurements are also outlined and labelled – two in visual cortex (V1 and V2) and a third outside of visual cortex (OP2).

Quantitative measurements from each ROI are shown in Fig 6B. Prior to implantation with the retinal prosthesis, mean cortical thickness in V1 and V2 in patient # 628 was below that of age-matched controls, but had increased 13 months post-implantation, while thickness in OP2 (the non-visual region) remained close to that of the control group. Cortical myelination levels in V1 also increased in the patient post-implantation, but remained similar to controls in V2, while levels in OP2 decreased slightly, but remained above that of controls.

Fig 6. Cortical Changes. A) The top two panels are a 3D inflated representation of cerebral cortex of the brain from patient # 628. Left: lateral view; Right: medial view. The top panel represents a cortical myelin map; hot colours (red/yellow/green) indicate highly myelinated areas and colder colours (blue/purple/black) indicate areas with less myelin. The middle panel represents a cortical thickness map (hot colours indicate brain regions with thicker grey matter and colder colours indicate brain regions with thinner grey matter). Three regions of interest representing visual cortex (V1, V2) and a control region (OP2) are outlined in black and indicated with white text/arrows. B) Quantitative structural brain measures from two visual regions (V1, V2) and one nonvisual region (OP2). Left panel: Mean cortical thickness; Right panel: Mean cortical myelin levels. Data shown in red is from patient # 628, pre-surgery, blue bars represent data from the patient post-surgery, and green bars represent averages from a group of age-matched sighted controls (N=8).

Discussion

This study tested for the first time ever the hypothesis that an electronic epiretinal prosthesis may restore functional vision for patients diagnosed with advanced macular geographic atrophy in late-stage AMD, offering artificial vision in the defective central area

of their visual field. This manuscript includes safety and efficacy outcomes and neuro-structural assessments up to the first 12 months after implantation. The reported results show that surgical implantation of an electronic epiretinal prosthesis system is possible in patients with advanced GA, secondary to Late AMD. The results also show that the implant can elicit visual percepts in areas of GA in late AMD patients. Although it is important to take into consideration that our small sample of patients does not allow for a strong statistical interpretation of the structural and functional assessments pre- and post- operatively, study outcomes strengthen our hypothesis that an epiretinal prosthesis approach may be beneficial for this cohort of patients.

In this study we observed 3 retinal detachments (one localised non-rhegmatogenous retinal detachment under the cable and two cases of proliferative vitreoretinopathy/retinal detachment; 3 out of 5 subjects experienced RD) and it represents the major SAE. The percentage of clinical trial subjects with RP implanted with the Argus II Retinal Prosthesis System that experienced RD was 6.7% at 1 year after implantation [16], 6.7% at 3 years [21] and 10.0% at 5 years [30]. The non-rhegmatogenous retinal detachment under the cable observed at post-operative day1 was most probably due to the surgical step of forcing the electrode array through a shorter sclerotomy incision against resistance during the array insertion into the vitreous cavity. To reduce the likelihood of such complication, during the sclerotomy incision, a full-thickness, full-width choroidal cut throughout the entire length of the 5.2mm incision should be made. The root causes of the two cases of proliferative vitreoretinopathy/retinal detachment are unclear. A hypothesis could be that PVR/retinal detachment is due to "chronic chorio-retinal inflammation and/or foreign body reaction" as it has been reported when retinal tacks were initially used for the treatment of retinal detachment [31]. Another hypothesis could be that PVR can originate from the large and traumatic 5.2mm pars-plana incision due to the migration and proliferation of retinal pigment

epithelium (RPE) cells. In fact, PVR-related total retinal detachment was also observed when performing excision with translocation of RPE/Bruch's Membrane from the paramacular area to the subfoveal space during the treatment of AMD [32]. PVR may also develop from vitreous residuals or from hyaloid residuals that go into hyper-proliferation. The Argus II Surgeon Manual recommends performing the vitrectomy after the extraocular placement of the device. This may hinder meticulous removal of minute amounts of vitreous and hyaloid membrane because of the presence of the implant around the eye. Accurate removal of peripheral vitreous with scleral depressed vitrectomy is limited by the presence of the electronics case and the implant coil in the supero-temporal and infero-temporal quadrants.

Vitrectomy may be performed at the beginning of the procedure and before the extraocular placement of the device. Adjuvant combination therapy in the vitrectomy infusion using 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH) for prevention of PVR may also be considered [33].

While serious, the device-related adverse events described above have limited impact on vision in these patients. Baseline visual function was primarily affected by their late-stage AMD and central area of GA prior to implantation, given the level of sight impairment caused.Visual function was mainly assessed through three custom-developed computer-based psychophysical tests with the purpose of specifically assessing a range of low vision as that restored by the retinal implant. These same tests were developed for and have been used in a cohort of patients diagnosed with RP and implanted with the Argus II system [30]. However, visual acuity outcomes are not comparable between studies, due to the persistent and varied visual benefit from this cohort’s peripheral residual vision, an element that RP patients lack. The authors believe that the design and implementation of these visual function tests should be further tailored to the needs of GA-AMD patients so that more robust conclusions can be drawn in the future regarding the integration of both the natural peripheral

vision and the artificial central vision provided by the system. Nevertheless, based on the data obtained so far, it seems possible that a retinal implant could be beneficial to restore some visual function for future late stage AMD (GA) patients.

When FLORA is performed, patients serve as their own control as results are evaluated both with the system ON and OFF. However, it should be pointed out that this is a subjective evaluator-reported assessment and neither the evaluator nor the patient was masked to the operational status of the device when completing the tasks. FLORA outcomes at 12 months after implantation from this study are in good agreement with those found in another published multicentre study (in RP patients) [27]. Our results agree with those of Geruschat et al. in that those tasks related to the use of the system in conditions of maximum light contrast such as the visual orientation tasks, appeared to benefit most from usage of the system [27]. In the present study, performance in tasks involving mobility and interaction with others also improved with the system. Such tasks may enhance patient independence and social interaction. Subjects' improved ability to perform functional vision tasks with the System ON compared to OFF suggests that some integration of artificial central vision and natural peripheral vision may occur; the absence of reported monocular double vision or confusion in the implanted eye is further evidence that stimulation from the implant is not detrimental to these patients.

MRI assessments of the brain pre- and post-implantation evaluated the impact of vision restoration through use of the implant device on the visual cortex. Previous research reports that long-term visual deprivation from AMD results in reduced grey and white matter [34-36]. MRI could therefore identify whether the Argus II device could potentially prevent further cortical reductions or even reverse them by restoring visual input to the brain.

Statistical analysis could not be performed, as only one patient (# 628) completed MRI both pre- and post-implantation. Nevertheless, data for this patient showed an increase

in cortical thickness following 13 months' use of the device from baseline. This increase was observed in both primary visual cortex (V1), the first cortical region in the brain that receives visual inputs, and in secondary visual cortex (V2), and associative visual area. However, no increase in thickness was observed in a control region of the brain not associated with visual processing (OP2). Therefore, the lack of change observed here could indicate that increases in visual cortex are due to use of the Argus II device, but such a conclusion cannot be made without conducting a large-scale study.

Areas with high cortical myelin levels are usually primary sensory or motor in function, reflecting a large proportion of inputs or outputs. In this study, we observed an increase in cortical myelin in the patient in V1 13 months post-implantation, possibly as a result of the restoration of visual input signals from the system. No change was observed in cortical myelin in V2 post-treatment; it is possible such changes might take longer to develop. Whether these reported changes correspond retinotopically to the macula in the implanted eye or to the contralateral eye is yet to be determined. However, the fact that changes were significant enough to affect mean thickness and myelin throughout visual cortex suggests the implant may have a positive effect overall.

In summary, the recruitment of five patients with GA-AMD and their implantation with an electronic epiretinal implant has offered a plethora of information over the first 12 months and potentially opens doors to more research in this area and future clinical indications for artificial vision. Invaluable data is still being collected from four of those patients giving a great opportunity to the research community to assess whether a retinal prosthesis is a feasible approach for the treatment of GA-AMD, one of the most common eye pathologies responsible for severe visual impairment. The system has proven to be safe and favourable in patients with total vision loss from RP and choroideremia. However, the current implant design, which has gained regulatory approval for implantation in patients with severe

outer retinal degeneration and has proven to be beneficial for the above cohort, does not have the same quality of life changing effect on patients with GA secondary to late stage AMD.

Nevertheless, we have here shown for the first time ever that an electronic epiretinal implant can elicit visual percepts by electrical stimulation of residual neuroretinal elements over the atrophic macula that can be incorporated by patients into their residual vision with no visual adverse effects such as monocular confusion or double vision.

It was previously thought that it would be impossible to elicit visual function in atrophic retinal areas with no functional response to focal stimulation by a light stimulus. However, as a result of this study, we strongly believe that further research in this area is now justified and that different approaches in the design of retinal implants themselves (e.g. smaller implant size, larger number of electrodes, redesign of the tack to prevent excessive mechanical forces) and in the image processing software and settings could benefit potential future research candidates.

Post 1-year functional results and AEs will be reported in a separate publication.

This is the First-in-Human use of artificial vision in patients with residual peripheral vision as well as the first implantation of an electronic retinal prosthesis in GA-AMD. We also show, for the first time, Proof of Concept that an electronic retinal prosthesis can elicit visual percepts by electrical stimulation of residual neuroretinal elements in areas of GA in late AMD patients.

Acknowledgments

PE Stanga left the National Health System (NHS), the Manchester Royal Eye Hospital and the University of Manchester in 2019 and continues his Clinical, Surgical and R&D activities at London Vision Clinic, with which he partnered in 2017.

Some of the data reported in this manuscript have been presented in scientific ophthalmological meetings, such as the Association of Research for Vision and Ophthalmology (ARVO), the American Academy of Ophthalmology (AAO) and EURETINA.

The study was sponsored by Second Sight Medical Products Inc., Sylmar, California, USA and was undertaken at the Manchester Vision Regeneration (MVR) Lab at the Wellcome Trust Clinical Research Facility and Manchester Royal Eye Hospital, Manchester Foundation Trust. Principal Study Investigator and Surgeon is Prof Paulo E Stanga, also director of the MVR Lab. Prof. Stanga is no longer part of the above and currently conducts his clinical, surgical and research activities at the London Vision Clinic, where he is Retina Lead, Principal Investigator and Partner.

Apart from the aforementioned authors Emmanouil Tsamis, Irene Siso-Fuertes and Fiona Crawford, the MVR Lab Group also consisted of Research Fellows and Clinical Trial Coordinators who assisted Prof Stanga during this study. These are: Sherif Shaarawy – Clinical Research Fellow, Soon Ch'ng – Clinical Research Fellow, Alessandro Papayannis – Clinical Research Fellow, Katarzyna Chwierjzack – Clinical Research Fellow, Francesco Stringa – Clinical Research Fellow, Salvador Pastor-Idoate – Clinical Research Fellow, Danielle Marrochia – Clinical Trial Coordinator, Niall Doherty – Clinical Trial Coordinator. Prof Stanga would like to thank them for their invaluable assistance during this study course.

The MVR Lab (closed down following the departure of P.E. Stanga) Group would also like to thank the Imaging Department of Manchester Royal Eye Hospital, and Mr Assad Jalil, Consultant, for their help. Also, special thanks should go to Mr Susmito Biswas, Clinical Head of Division, Manchester Royal Eye Hospital, for his support. Further thanks are extended to the York Neuroimaging Centre and its staff for assisting with MRI acquisition.

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Supporting information captions

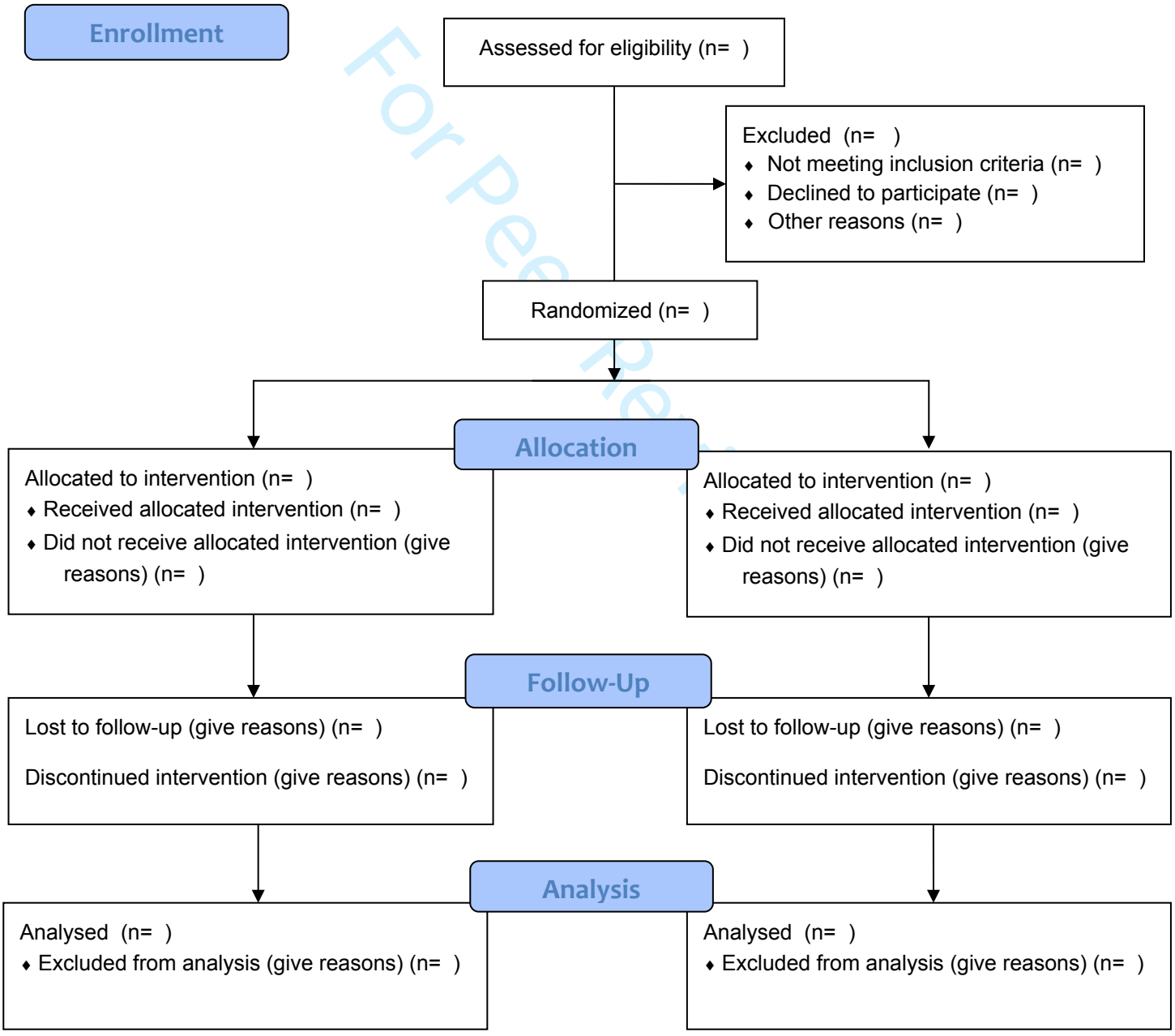
S1 Fig. Fundus Photographs, OCT, and Microperimetry Results.

S1 Table. Summary of Adverse Events (AEs).

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

****Please note this was a single arm, non-randomised, controlled feasibility study****




Electronics Case
Electrode Array
Antenna
Glasses
VPU
Antenna
Camera

Fig 2

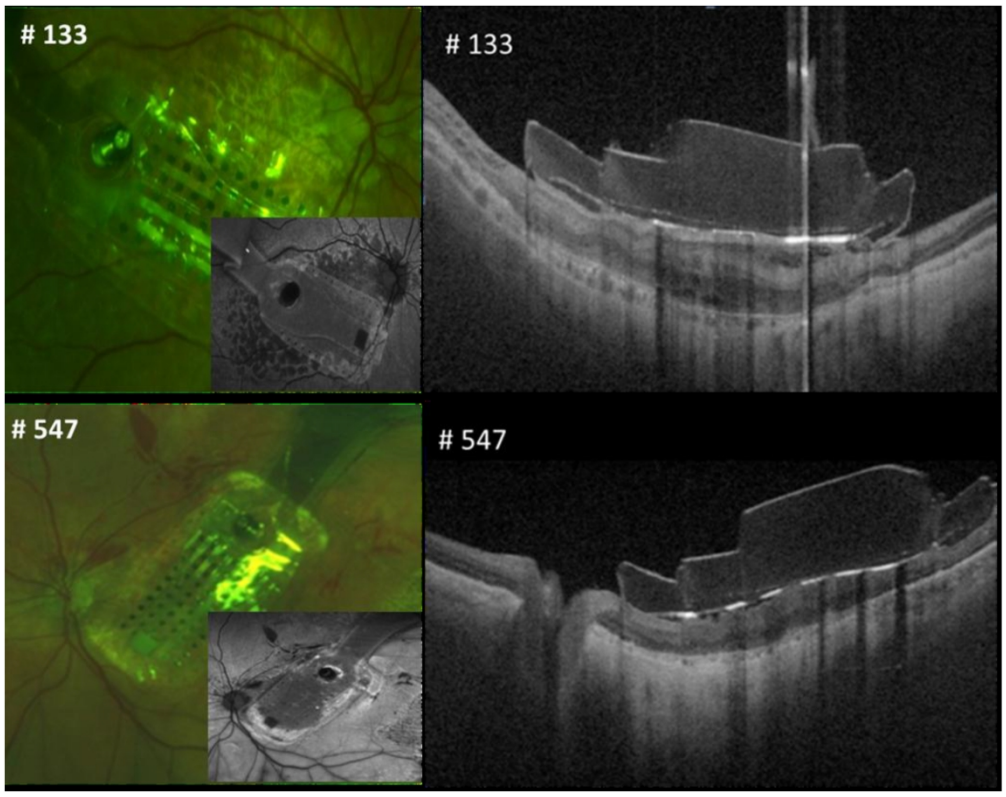


Fig 3

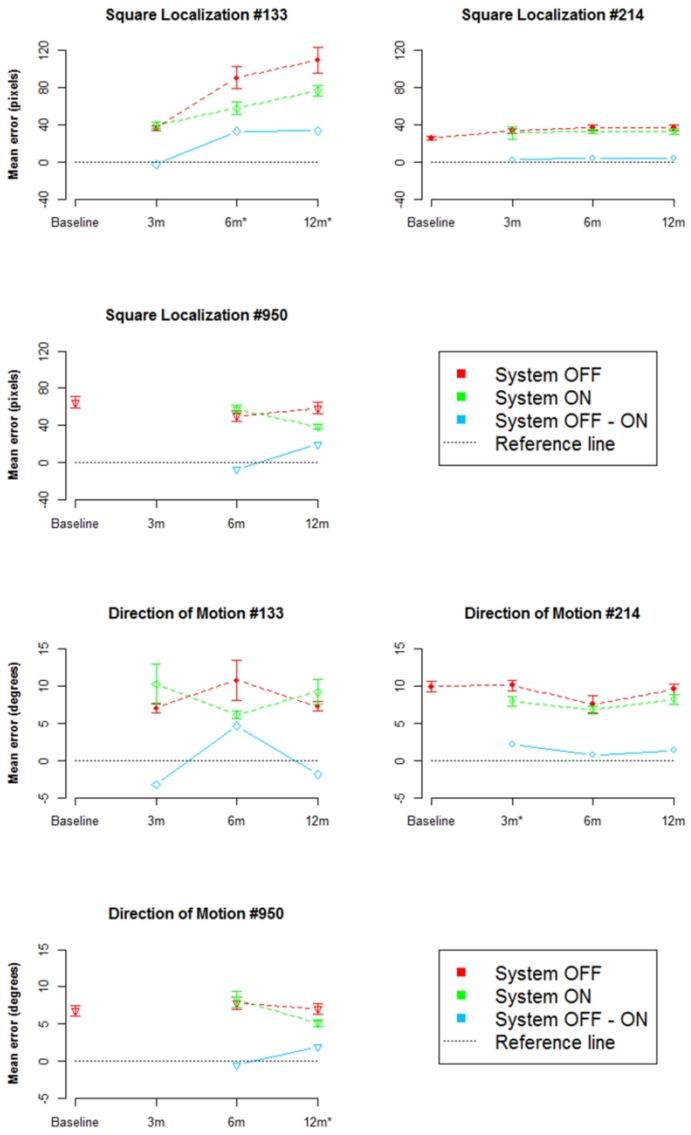

Square Localization #133
Square Localization #214
Square Localization #950
Direction of Motion #133
Direction of Motion #214
Direction of Motion #950
Mean error (pixels)
Mean error (degrees)
Baseline
3m
6m
12m
System OFF
System ON
System OFF - ON
Reference line

Fig 4

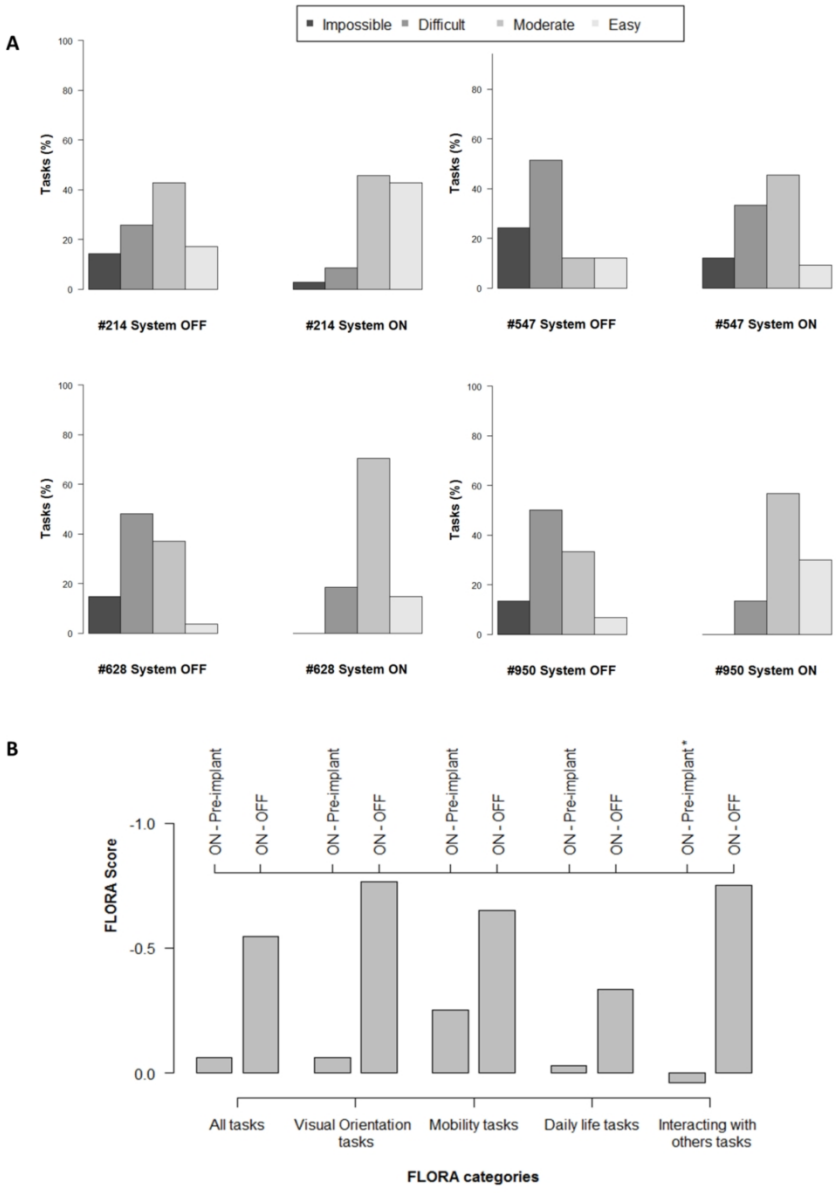

A
Impossible
Difficult
Moderate
Easy
Tasks (%)
#214 System OFF
#214 System ON
#547 System OFF
#547 System ON
#628 System OFF
#628 System ON
#950 System OFF
#950 System ON
B
FLORA Score
-1.0
-0.5
0.0
ON - Pre-implant
ON - OFF
ON - Pre-implant *
All tasks
Visual Orientation tasks
Mobility tasks
Daily life tasks
Interacting with others tasks
FLORA categories

Fig 5

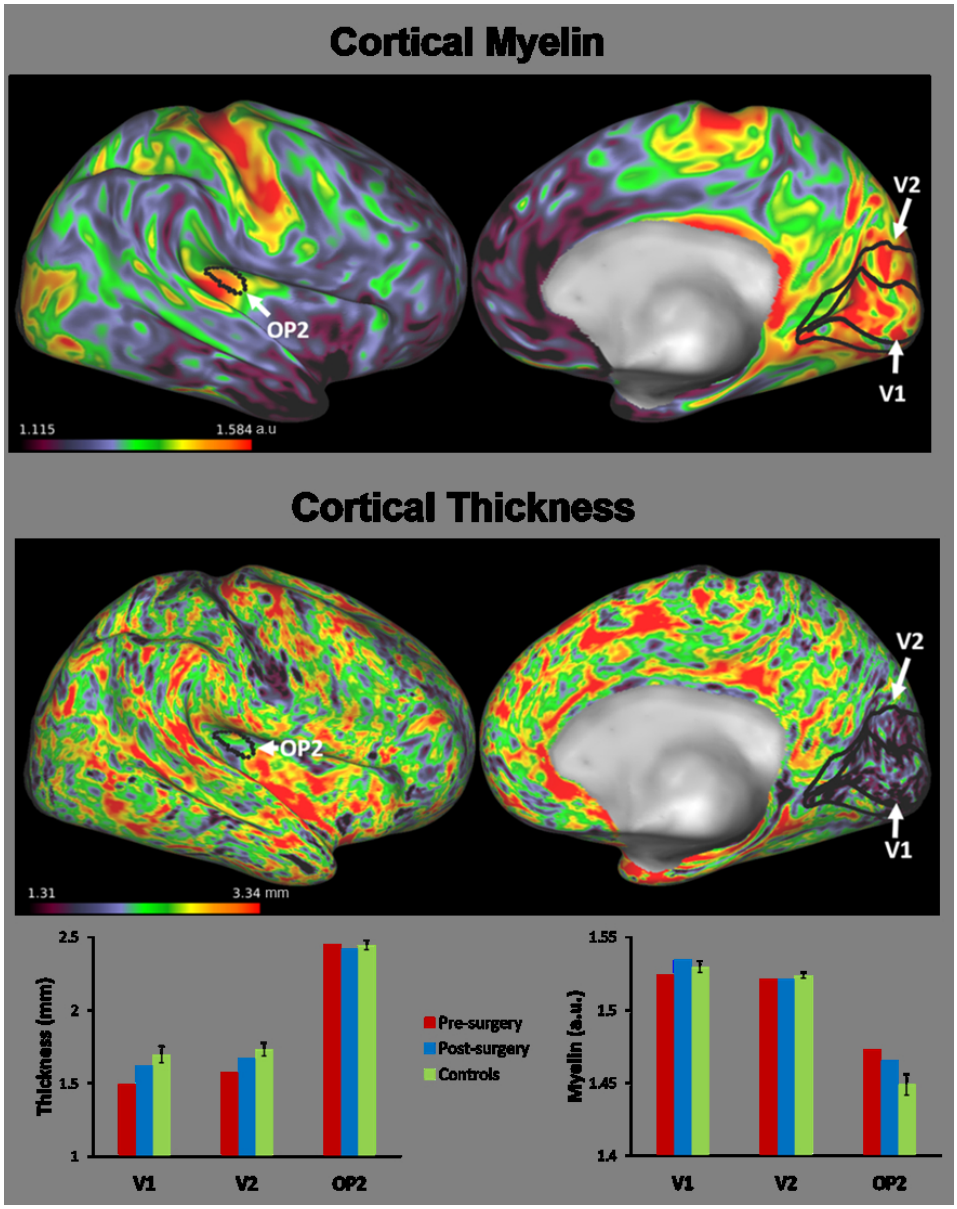
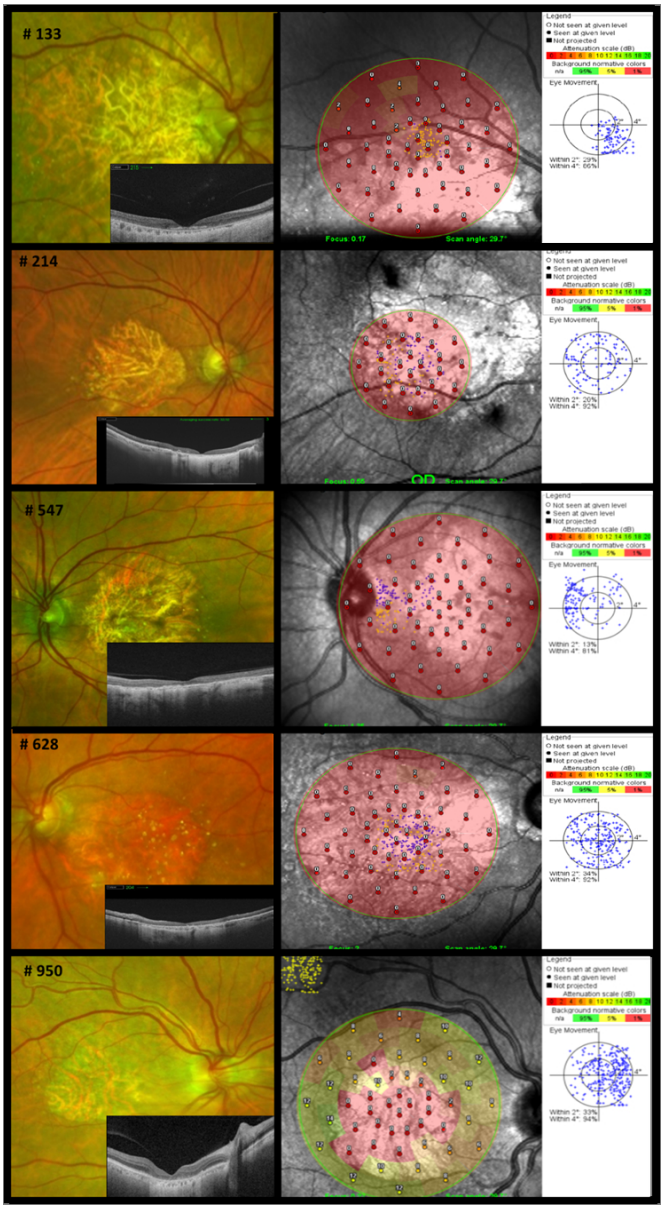

Cortical Myelin
OP2
V2
V1
1.115
1.584 a.u
Cortical Thickness
OP2
V2
V1
1.31
3.34 mm
Thickness (mm)
2.5
2
1.5
1
V1
V2
OP2
Pre-surgery
Post-surgery
Controls
Myelin (a.u.)
1.55
1.5
1.45
1.4
V1
V2
OP2

Fig 6


133
214
547
628
950

Study ID	Total Number of SAEs and AEs, study and non-study related	Total Number of study-related AEs	Total Number of study-related SAEs	Brief description of AEs
# 133	0	0	0	
# 214	2	1	1	Light Sensitivity RD
# 547	2	1	1	Floaters PVR Detachment
# 628	2	1	1	Inflamation - ocular Hypotony
# 950	1	0	1	PVR Detachment