

Resting-State Functional Organization of the Brain in Blindness and Sight Recovery

by

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Dedication

This dissertation is dedicated to my beloved family. Thanks for all your support and unconditional love. You have been the light in my heart, through it all.

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Abstract

Reorganization of the human brain after blindness is well-documented, however, subsequent sight restoration can lead to adaptation that is not as well understood. Successful sight restoration therapy must integrate functionally with the visual system for perception to occur. Thus, our study is strongly motivated by the need to understand brain plasticity after regaining vision. In this thesis, I evaluated use of functional magnetic resonance imaging (fMRI) resting-state functional connectivity (rsFC) for vision studies from two angles: 1) from a methodology perspective, I explored the importance of proper data preprocessing on the resulting rsFC outcome, 2) from a neuroscientific perspective, I examined utility of rsFC as a potential metric of blindness and sight restoration.

It has been shown that choice of analysis pipelines can impact the research findings. Therefore, replication studies that aim to reproduce the previously published results are critically necessary. In the first venue of my research, I verified reproducibility of a well-cited published study on ocular blindness using rsFC. By using the original dataset, I utilized another widely used software package to investigate how applying different implementations of the original pipeline or a more rigorous preprocessing stream can alter the outcomes. These alternative workflows changed the distribution of the whole-brain rsFC and functional network densities, reducing the overlap with the original results. Remarkably, the largest rsFC effects appeared to primarily belong to certain connection pairs, irrespective of the pipeline used, likely demonstrating immunity of the larger effects and likely the true results against suboptimal processing. This may highlight the

significance of results verification across different computational streams in search of the true findings.

Functional outcome of using Argus II, as the only retinal prosthesis with FDA approval that has been clinically used, can provide an exceptional opportunity to explore brain's potential for plasticity upon reintroduction of (artificial) vision. Considerable variability in visual performance has been reported across Argus II recipients that remains unexplained. A previous experiment used fMRI to measure tactile-evoked cross-modal responses in visual cortex and reported no significant group-level results between blind and Argus II groups, possibly due to variability in activation baseline across individuals. The rsFC can potentially overcome this issue by providing a more stable metric. Numerous studies have used rsFC to assess cortical reorganization after blindness, nevertheless, it has rarely been utilized to study sight recovery.

In this study, four resting-state runs from 10 sighted, 10 blind, with severe retinitis pigmentosa, and 7 Argus II subjects were included. The whole-brain ROI-ROI rsFC and some graph theory functional network measures were calculated and compared at the group level. Some quantities decreased after blindness but were not reversed by vision restitution, including visual-visual rsFC, visual-frontal rsFC, and some network measures. On the other hand, significant reduction was observed in visual-somatosensory, visual-auditory, visual-motor, and visual-association rsFC after blindness that were all returned to the level of sighted individuals in Argus II recipients. These rsFC measures can potentially serve as biomarkers for blindness and sight restoration, in the absence of or as a complement to the behavioral indices. The proposed metrics can enhance our understanding of variable outcomes among the receivers of sight restorative technologies and enable tracking rehabilitative progress. Future investigation with a larger number

of test subjects for this rare condition can further unveil the profound ability of our brain to reorganize, following vision restoration.

Chapter 1 - Introduction

1.1 Organization of the Visual System

1.1.1 The Eye

In humans, vision is the most sophisticated sense that plays an important role in approximately 80% of our day-to-day activities and cognitive tasks (Ripley & Politzer, 2010). As a result of this prominence, our scientific knowledge of the visual system is more than any other sensory system. Our visual system is composed of the eyes, as the sensory organs, the visual pathways that carry visual information from the eyes to the brain, and the visual cortex, where visual integration and perception ultimately occur. In humans, each eye globe is roughly a sphere with 25 mm diameter that is composed of the anterior and posterior structures with different functions, as shown in Figure 1. On the anterior side, the iris, cornea, lens, ciliary body, and aqueous humor contribute to regulating, refracting, and focusing the light on the light-sensitive posterior part of the eye, the retina, and creating a proper image of the outside world. The posterior structure of the eye is composed of the vitreous body, choroid, and retina. The vitreous body preserves the shape of the eye and is composed of salt, water, and collagen fibers, while the choroid tissue is full of blood vessels and provides oxygen and nutrients to the retina (Armstrong & Cubbidge, 2019).

The retina is the innermost layer of the posterior part of the eye and is sensitive to light. The conversion of the previously formed image to electrical signals and action potentials to be sent to the cortex occur within the retina. As indicated in Figure 1 (Parsons et al., 2021), the retinal pigment epithelium (RPE) layer is the most posterior layer of the retina that surrounds and nourishes the light-sensitive cells, also known as photoreceptors. Rods and cones are two types of photoreceptors that have an inner nuclear region and an outer segment, which contains the photosensitive pigment rhodopsin. The rhodopsin in the photoreceptors converts light into electrical signal through a chemical reaction in response to light exposure. Rods are sensitive to the intensity of light and are active in dim light which makes them crucial for night vision. Cones, on the other hand, are a type of photoreceptors that are sensitive to light wavelength and thus play an important role in red, green, and blue color detection. The central part of the retinal tissue is called the macula, where the image of the central visual field is formed. The macula is pivotal for performing tasks that require seeing fine details such as reading or driving. The fovea is a small depression at the center of the macula with the largest visual acuity. Cones could be found in numerous quantities in the macula compared to the rest of the retina, with the foveal region containing only cones. The larger the density of the cones, the higher the visual acuity, similar to

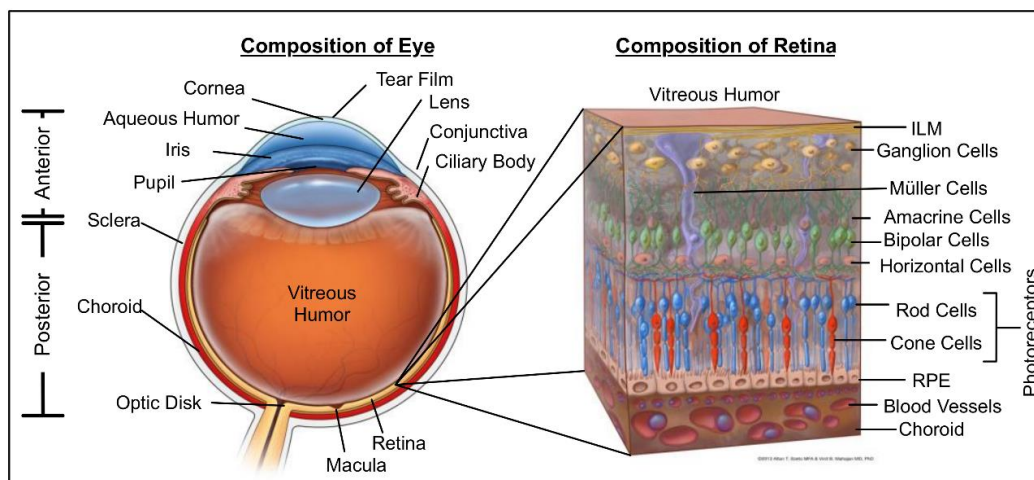


Figure 1 - Structure of the Eye and Retina (Parsons et al., 2021)

the resolution of an image determined by the number of pixels. Fovea also has a pigmented layer, usually appearing yellow upon inspection, that is responsible for protecting the eye by blocking the ultraviolet light.

Upon light exposure of photoreceptors and their resulting hyperpolarization, neural impulses are carried through the subsequent layers of the retina, including horizontal, bipolar, and amacrine interneurons. The cells then temporally and spatially integrate the neural signals and send them to the retinal ganglion cells (RGC), the last retinal layer, where the impulses are then transferred to the cortex via the optic nerve. The nerve fiber layer contains the axons of the RGC. In humans, the optic nerve is made out of about 1 million RGC axons (Cull et al., 2012). The optic nerve leaves the eye at the location of the optic disk, also known as the blind spot, due to the absence of photoreceptors and serving as an entry point for the blood supply. The retina is considered part of the central nervous system, but its location allows non-invasive observation for symptoms of some neurological and vascular diseases such as Alzheimer's disease, multiple sclerosis, and hypertension (Yap et al., 2019). Degenerative diseases such as the ones affecting the photoreceptors can also cause age-related macular degeneration (AMD) and retinitis pigmentosa (RP).

1.1.2 From Retina to Visual Cortex

The electrical signal then travels from the optic nerve through the visual pathway to the cortex. Both left and right optic nerves from each eye pass through a structure at the base of the brain called optic chiasm as indicated in Figure 2 (Hannula et al., 2005). Optic nerve fibers in each eye are said to belong to the nasal half if they are located at a part of the retina closer to the nose, otherwise, they are referred to as the temporal half. The nasal half of the optic nerve travels to the opposite side at the location of the optic chiasm. After the optic chiasm, in the optic tracts, the

nerve fibers on each side are then composed of the temporal half of the ipsilateral retina and contralateral nasal retina, both covering the contralateral half of the visual field. The optic tract on each side then reaches the lateral geniculate nucleus (LGN) on either side of the thalamus. At LGN, some processing on the visual electrical signals occurs before the nerve fibers leave the LGN via the optic radiation towards the primary visual cortex located at the occipital lobe of the cortex. It is important to note that, in addition to LGN, optic nerves also project to superior colliculi and pretectum in the midbrain, involved in imperceptible vision also known as “blindsight” (Kinoshita et al., 2019; Kletenik et al., 2022) Nevertheless, visual perception is predominantly facilitated by LGN.

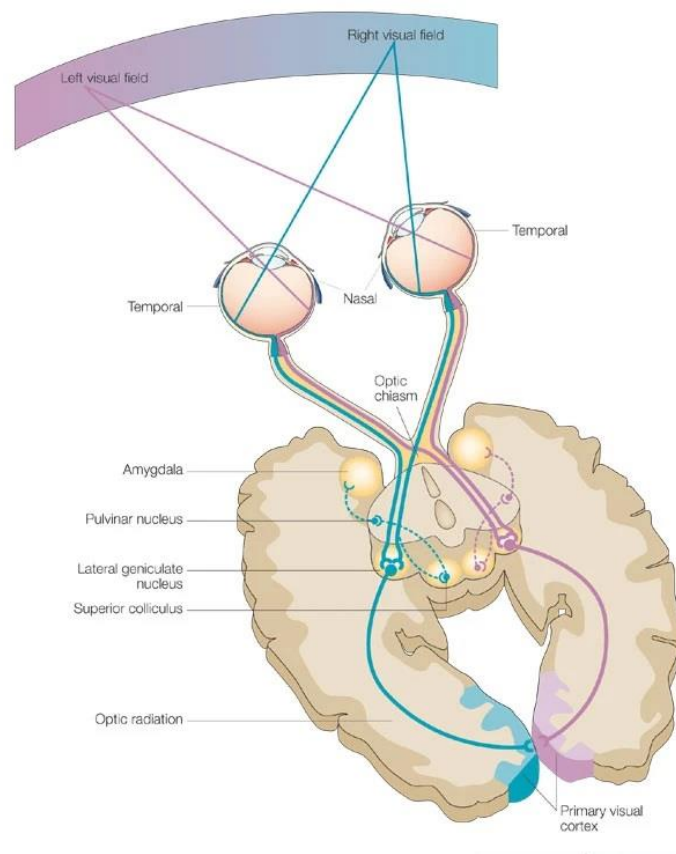


Figure 2 - Primary Visual Pathway. This pathway is composed of the retina, optic nerve, optic chiasm, optic tract, LGN, optic radiation and visual cortex. (Hannula et al., 2005)

The RGC axons that converge on LGN retain a retinotopic organization in the LGN, i.e., nearby areas on the retina project to nearby areas in the LGN. Since the concentration of the ganglion cells is significantly larger in the fovea than in other retinal areas, the LGN and consequently the visual cortex represent the (central) foveal regions relatively more than the peripheral visual field. This phenomenon is known as cortical magnification and signifies that the number of neurons in the primary visual cortex that process a fixed-sized visual stimulation is determined by the location of the visual stimulus in the visual field. If the stimulus is located in the central visual field, a larger number of neurons in the primary visual cortex is dedicated to its processing compared to the same stimuli in the periphery. Additionally, LGN receives feedback from the brain stem and cortex that may help regulate the transfer of visual information from the retinal to the occipital lobe.

1.1.3 The Visual Cortex and Beyond

Primary Visual Cortex

Visual signal traveling from the ipsilateral LGN (contralateral visual field) enters the primary visual cortex, also known as the striate cortex or V1 in the occipital lobe. Figure 3 shows the retinotopic map of V1. The upper panels show the left visual cortex, representing the right visual field. The primary visual cortex is buried inside the calcarine fissure on the medial side of the occipital lobe, with the upper and lower quadrants of the visual field represented in the lower and upper banks of this fissure, respectively. Fovea, mediating the central vision with the best visual acuity, is represented in the occipital pole. The vertical meridians mark the perimeter of the primary visual cortex. The lower left panel shows the unfolded calcarine fissure exposing V1 spanning from the fovea (0° eccentricity) to the periphery (60° eccentricity). The visual field is mapped retinotopically in V1 with polar coordinates. Traveling from the fovea to the periphery on

this map crosses iso-eccentric contours in the visual field that continue to increase in distance (eccentricity) from central vision (from 2.5° to 40°) in the visual cortex. The lower right panel also illustrates the respective map for the right visual field. In the unfolded calcarine fissure in the lower left panel, traveling upward is equivalent to rotating in the counterclockwise direction in the visual field (J. C. . Horton & Hoyt, 1991). In summary, V1 has a topographic map of the visual field, although this representation is largely distorted. This is because of the cortical magnification, described earlier, where about 55% of the V1 surface area is dedicated to the central 10° of the visual field. Despite the stable retinotopic organization in healthy individuals, it is important to note that the size and location of the V1 region vary largely across individuals.

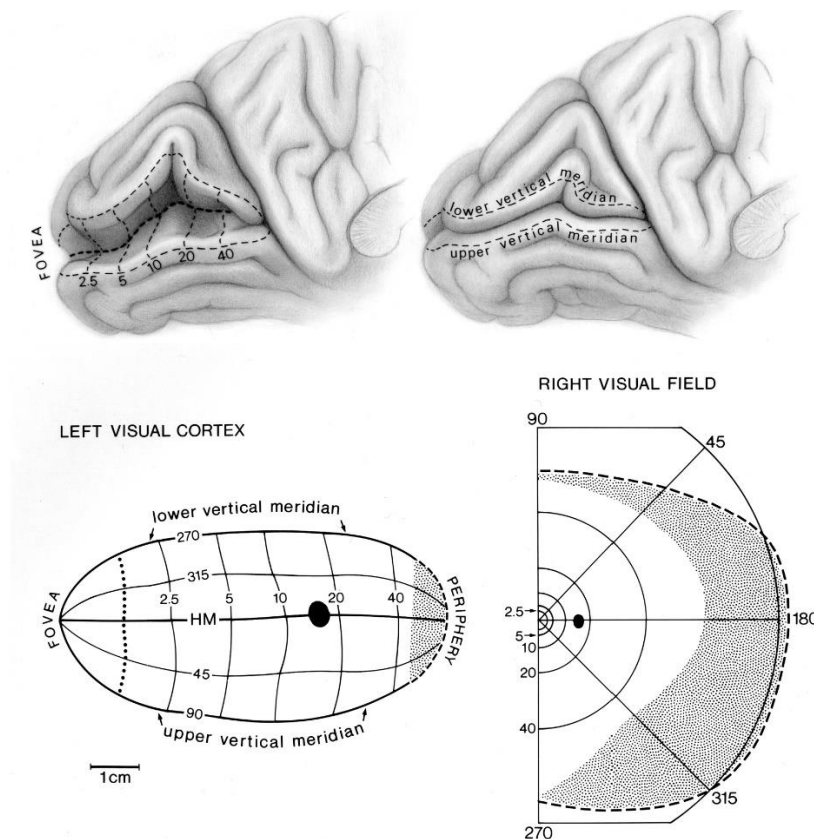


Figure 3 - The Retinotopic Map of Primary Visual Cortex. Every point on the visual field is mapped to a respective location on the primary visual cortex, using polar coordinates. (J. C. Horton & Hoyt, 1991)

Higher Visual Areas in the Cortex

Our visual system is a hierarchical network in which different anatomical regions are connected to each other. This arrangement enables the feedforward of the information from lower to higher levels of visual processing areas as well as feedback of the information in the reverse direction. Higher visual areas generally have larger receptive fields compared to lower visual regions. When the visually evoked signal enters the visual cortex, processing of some basic features of the observed images, such as the orientation, brightness, and color occurs in the primary visual cortex. As the visual information moves up in the visual hierarchy, more abstract and complex features of the visual stimuli are extracted by higher-level visual areas. When the visual response leaves the lower visual areas, it can travel along two structurally and functionally separated visual pathways: the ventral and dorsal streams (Felleman & Van Essen, 1991; Kafaligonul, 2014; Livingstone & Hubel, 1988), as indicated in Figure 4 (Yamasaki & Tobimatsu, 2018).

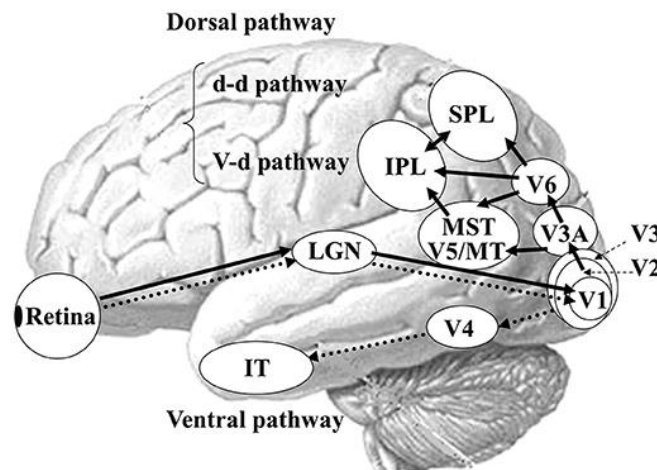


Figure 4 – Two Visual Streams in Humans. Dorsal visual pathway, also known as the “where pathway”, represents spatial and motion properties of the visual scene. Ventral visual pathway, also known as the “what pathway” is responsible for identification of objects, faces, etc. (Yamasaki & Tobimatsu, 2018)

The ventral stream, also known as the “what pathway”, further processes color and is also involved in form perception by sending the extracted information via the lingual gyrus to the temporal areas; more specifically, the information travels to V4 and the inferior temporal cortex. This stream ultimately is involved in object and pattern recognition and segregated regions in this pathway respond to various types of objects. For example, the fusiform face area (FFA) and the lateral occipital complex (LOC) are selective for face and shape identification, respectively, while the parahippocampal place area (PPA) in the parahippocampal gyrus (PhG) is mainly involved with the identification of places and scenes (Coggan et al., 2019; Emberson et al., 2017). The dorsal stream, also known as the “where pathway”, extends dorsally from the primary visual to the parietal cortex and is responsible for visuospatial, motion, and action processing. This pathway has two separated sub-streams, one traveling through V6 (in cuneus gyrus) to the superior parietal lobule (SPL) in the parietal cortex and the other stream reaching the inferior parietal lobule (IPL) in the parietal cortex via V5/MT (middle temporal) and medial superior temporal (MST) area (Tobimatsu & Celesia, 2006). The function of the dorsal stream can be more clear by understanding the role of some of its individual constituent regions; V5/MT is a higher-level visual area in the ventrolateral side of the visual cortex and has been shown to be involved in detecting the existence and direction of motion (Zeki, 2015). MST is on the anterior bank of the superior temporal sulcus, medial to MT, and is known for its involvement in monitoring self-motion and locating objects (Andersen et al., 2000). On the other hand, the SPL and IPL are both parts of the parietal multisensory association cortex. SPL is known to be involved in visuomotor and attention (Corbetta et al., 1995; Lloyd et al., 2006), while the IPL is involved in visuospatial and language processing (Sturm et al., 2016).

As explained, the feedforward hierarchy of the visual cortex enables the flow of visual information from the lower to higher visual areas for the representation of more elaborate and abstract visual features. These high-level representations are ultimately provided to the cognitive areas for attention, decision-making, and memory. On the contrary and in addition to the feedforward connections, the higher-level visual areas provide input that is sent back to the lower-level visual areas, a phenomenon referred to as the reverse hierarchy that facilitates learning and directs selective attention in the lower-level visual neurons (Fine & Park, 2018). There are also feedback projections from the higher-level visual cortex to LGN that modulates the flow of information to the cortex (Kafaligonul, 2014).

1.2 Blindness

In the United States, legal blindness is defined as visual acuity of 20/200 (equal to 1.0 LogMAR) or worse in the better eye or a visual field of 20° eccentricity (angular distance) or less. Visual acuity measures the capacity of identifying Snellen chart characters at 20 feet distance. For example, visual acuity of 20/200 in a blind individual means that they need to stand at a maximum of 20 feet away from test symbols to be able to identify them, however, an individual with ideal vision would be able to read the same symbols from 200 feet away (Caltrider et al., 2022). For measuring the visual field, the automated static perimetry test, such as Humphrey Field Analyzer, calculates the extent of the visual field. The individuals are asked to fixate on a central point, while points in the periphery flash; the extent of the visual field is then determined by identifying the border between regions of perception and no perception of the flashing lights by the individual (Turbert, 2022). In addition to legal blindness, the term near-total visual impairment is referred to individuals who can only count fingers, identify hand motion, and have light perception or a visual field of 5 degrees or less, whereas total visual impairment is when there is no light perception. In

2020, 43.3 million blind individuals were approximated in the entire world, with about 77% above the age of 55 (R. R. A. Bourne et al., 2021). Some major worldwide causes of blindness in individuals with at least 50 years of age have been reported as cataract (15.2 million), uncorrected refractive error (2.3 million), age-related macular degeneration (AMD, 1.8 million), glaucoma (3.6 million), diabetic retinopathy (0.86 million) (R. R. A. Bourne et al., 2021; Iannaccone et al., 2021). As the prevalence of these conditions is higher in older adults and the worldwide aging population is on the rise, the number of affected individuals is expected to increase. Below the age of 60, the leading cause of blindness is retinitis pigmentosa affecting above 1.5 million individuals in the entire world (Cross et al., 2022).

A significant part of my presented research here involves blind individuals suffering from retinitis pigmentosa. RP is a degenerative genetic disorder of the retina that initially causes peripheral vision loss and tunnel vision, but over time can lead to full blindness. A more prevalent type of RP is caused by rod-cone dystrophy where the rod photoreceptors are affected at first leading to night blindness. This results in retinal pigment deposits, photophobia, and mild scotomas in the peripheral vision. As the disease progresses, however, it affects the cone photoreceptors as well, affecting their foveal vision in the daylight. Typically, patients with severe RP have bare light to no light perception. Although the disease can be diagnosed any time from childhood to past midlife, typically it is diagnosed in young adulthood. Pathophysiology of RP is abundant, as it is currently known to be caused by mutation in over 80 genes expressed in photoreceptors and their supporting environment (Retinitis Pigmentosa: For Professionals, 2022). Some leading causes of RP are mutation in genes involved in rod visual pigment and transduction, photoreceptor differentiation, retinal pigment epithelium, cell cytoskeleton, and the required photoreceptors metabolism, leading to photoreceptors destabilization. This hampers the ability of

the photoreceptors to convert light energy to electrical energy. Currently, there is no way to prevent, stop or cure the disease. Disease management generally includes nutrition (vitamin A and E) deficiency therapy and the use of protective sunglasses. Other innovative approaches are under investigation; gene therapy is being explored for specific gene mutations and a single gene therapy approach would not be applicable to mutations in all the genes involved. These treatment studies are in the pre-clinical as well as post-clinical trial phases (Piri et al., 2021). Visual prosthetic devices have also been developed to provide partial vision for RP. These technologies are elaborated on in more detail in the next section.

1.3 Sight Restoration Methods

The majority of the progressive and degenerative diseases do not currently have any cure and instead are managed for symptoms or treated to slow the disease advancement (Menon & Vijayavenkataraman, 2022). Despite progress in sight recovery technologies and their role in providing patients with partial functional gain, the visually impaired are still suffering from sub-optimal vision. Nevertheless, novel technologies are continually developing for restoring vision. Here, some of these approaches are described, which can potentially promise a better future for the visually impaired population.

1.3.1 Cataract Surgery

One of the well-established methods to restore vision is cataract surgery. Cataract is a result of degeneration of the ocular refracting lens leading to lens cloudiness and visual decline. There are various surgical approaches for treating cataract, such as extracapsular cataract extraction (ECCE), femtosecond laser-assisted cataract surgery (FLACS) with intra-ocular lens implantation and phacoemulsification. Presently, the most widely used surgical approach is

phacoemulsification, in which ultrasound is used to emulsify the lens and extract it from the eye. In this method, the tissue damage and operation time are shorter than the older method of ECCE and surgery provides higher visual acuity (Thevi et al., 2014). In 2009, the FLACS was introduced as a novel non-invasive approach (Nagy et al., 2009) that creates a corneal incision by means of a laser and aims to soften the cataract before its extraction. Compared to phacoemulsification, FLACS proved to be a more predictable and less challenging procedure (S. Li & Jie, 2019). Cataract surgeries are mainly performed on older adults since generally cataract initially manifests in the 60s decade of life. Cataract surgeries may also be used for the treatment of congenital cataract, in which the ocular lens is cloudy at the time of birth of an infant. Currently, Project Prakash, a US-based organization provides cataract removal surgeries to reverse congenital blindness in rural Indian children and adolescents (Thomas, 2019).

1.3.2 Gene Therapy

Another novel visual restoration approach is gene therapy in which a healthy copy of a gene sequence is delivered to the cells that provide proteins involved in the retina for vision. In 2007, a gene therapy clinical trial was conducted on Leber Congenital Amaurosis (LCA) sufferers. LCA is a rare inherited vision disorder causing severe congenital blindness. About twenty different genetic mutations can lead to LCA. One of the more common forms of this disease is caused by a mutation in the RPE65 gene that codes for the RPE65 protein in the retina. In the clinical trial conducted on RPE65 patients using the Luxturna drug, the responsible gene was delivered via a virus into the retina. The first phase of the study showed improvement in different functional areas including visual acuity, visual field, microperimetry and pupillary light reflex. Re-administration of the gene into the contralateral eye 3 years later similarly resulted in improvement in the contralateral eye (Bennett et al., 2016). Neuroimaging studies also showed increased activation in

visual cortex in response to visual stimulation (Ashtari et al., 2017). In 2018, Luxturna received FDA approval and a recent study on effect of using Luxturna showed long-term durability of treatment impact up to 7.5 years of sustained full-light sensitivity and up to 5 years of sustainable ambulatory navigation and visual outcomes (Leroy et al., 2022). Another novel approach in this field is referred to as gene editing. In a study using CRISPR-Cas gene editing system, DNA was delivered to the genome to upregulate or downregulate specific genes. The result of this experiment on patients with RP was successful ex vivo (Lino et al., 2018), however, is yet to be tested in vivo.

1.3.3 Optogenetics

Optogenetics is another approach that is fundamentally based on gene therapy. In this technique, however, the target cells are not the photoreceptors and instead are other higher-level retinal neurons that are naturally not light-sensitive. The genes coding light-sensitivity, also known as opsins, are delivered to these target cells and make it possible to turn these neurons on and off. Ideally, these opsins have characteristics close to our natural vision in terms of visible wavelengths, light sensitivity, and temporal resolution. Still, the choice of a proper opsin with an optimum mixture of the above properties is an ongoing challenge. The retinal cell to which opsins are delivered is also a determining factor: the closer the cells are to the photoreceptor layer, the better the quality of the produced images, but the harder the opsin delivery. Recent research has shown that optogenetics has been able to partially restore vision in the blind, where opsins were delivered to the ganglion cells and a goggle worn by the patients produced the appropriate wavelength and intensity to activate the target cells. In a study on 1 RP patient, the subject -was able to identify and locate various objects and the electroencephalographic (EEG) visually evoked responses were observed in the visual cortex area (Sahel et al., 2021). Optogenetics, however, remains an ongoing field of investigation for sight restoration.

1.3.4 Stem Cell Therapy

Another technology that has been utilized for restoring vision is stem cell therapy which is capable of replacing degenerated tissues by means of undifferentiated cells, having the potential to form specialized cells. In severe cases of RP and AMD diseases, with higher levels of degeneration in the photoreceptors, stem cell therapy can deliver new cells with the potential to replace the lost cells. In an experiment in 2015 on age-related macular degeneration and Stargardt's macular dystrophy patients, stem cell therapy resulted in a noticeable improvement in vision, however, the therapy resulted in adverse effects in 2 out of 18 test subjects (Schwartz et al., 2015). For RP, the results of stem cell therapy have not yet been convincing and still ongoing (Brown et al., 2022). Overall, stem cell therapy is still under research for sight recovery, with no FDA-approved treatment.

1.3.5 Visual Prostheses

A visual prosthesis is an electronic device that is implanted somewhere along the visual pathway to restore vision. There are two main types of visual prosthesis, the retinal and cortical prosthesis with the prosthesis location on the retina and visual cortex, respectively. Regardless of the type, the implanted electrode produces a spot of light, also known as phosphene, by applying focal electrical stimulation on the visual pathway.

Retinal Prostheses

Retinal prostheses can be divided into three categories based on the location of the retinal electrode array: epiretinal, subretinal, and suprachoroidal. An epiretinal prosthesis typically has a surface electrode and is placed on the inner retina in the vitreous cavity of the eye and stimulates the RGC layer of the retina. In this way, the implant bypasses the retinal layers and mainly focuses

the stimulation on the RGCs. The advantage of the epiretinal implant is the relatively straightforward surgical implantation and the potential for a large electrode array. One of the epiretinal prostheses is the Argus II manufactured by Second Sight Medical Products which obtained FDA approval for clinical use in 2013. As indicated in Figure 5 (Dagnelie et al., 2017), the system is composed of an internal implant and an externally-worn unit. The internal implant has an intraocular 60-electrode array with 200 μm diameter surface electrodes and 520 μm electrode spacing, providing an effective visual field of $11^\circ \times 19^\circ$. The internal electrode array is supported by an electronic case mounted on the sclera that receives power and data wirelessly. The external system is composed of a pair of goggles with a built-in camera, a video processing unit (VPU), and an accompanying battery. Upon receiving the visual information from the camera, the VPU processes the data and sends it to the internal electronics via external-internal coil communication. Initially, the effect of using Argus II includes light perception which is then followed by phosphene perception. With extensive training, Argus II recipients have been able to perceive motion, identify common objects, reach and grasp objects and read letters of a certain size (Da Cruz et al., 2013; Dorn et al., 2013a; Kotecha et al., 2014). Nevertheless, the best visual acuity obtained with Argus II did not exceed 20/1260 (Humayun et al., 2012). In 2019, the device's manufacturing and surgical implantation, however, has been halted due to a small pool of target patients and low levels of visual acuity obtained.

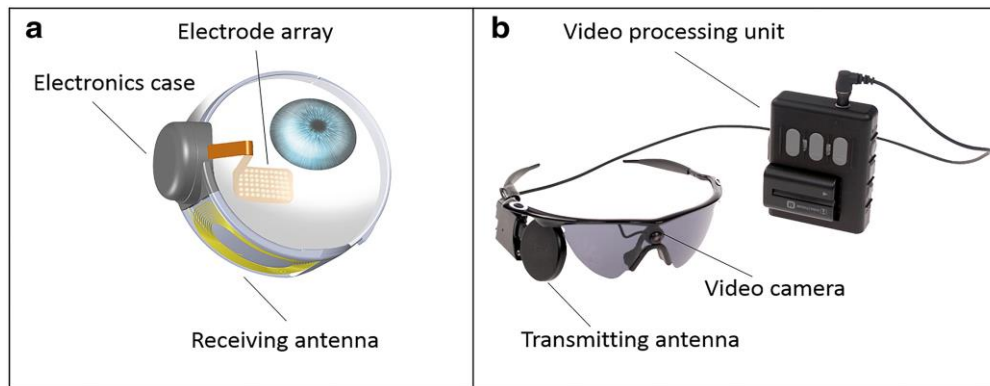


Figure 5 - Argus II Retinal Prosthesis System. (a) The internal implant and (b) external unit work together to stimulate ganglion cells based on the camera reading (Dagnelie et al., 2017).

Another epiretinal prosthesis is Intelligent Retinal Implant System (IRIS) by Pixium Vision. This device obtained CE approval in 2016 and utilizes infrared for wireless communication. In a clinical trial, using IRIS II device resulted in a statistically significant chance of recognizing pictures and detecting - motion (Muqit et al., 2019). There are 2 other epiretinal prostheses, POLYRETINA and OPTO-EPIRET, that are still in the preclinical phase of development.

The second type of retinal prostheses is subretinal. In subretinal prostheses, the stimulating electrode is inserted in the areas between the outer plexiform layer and the RPE layer, e.g., in the bipolar cell layer. Alpha IMS is one of the early subretinal implants developed by the Retinal Implant AG and received CE approval in 2013. In a more advanced version of their device (Alpha AMS), a CMOS chip with a 40x40-pixel grid covering a 3x3 mm² area gated electric current with light energy. In a clinical trial in 2016, the best visual acuity obtained by this implant was 20/546 and a few serious adverse events that occurred were all successfully addressed (Stingl et al., 2013). Nevertheless, Retina Implant AG ceased operation in 2019 which halted any further clinical trials. Another subretinal prosthesis is PRIMA from Pixium Vision which is currently undergoing an FDA feasibility study as of 2018. PRIMA is a direct photovoltaic prosthesis that converts energy

from near-infrared laser to electric energy. Similar to Alpha AMS and IRIS II, PRIMA requires a near-infrared laser input, but no other external current source. The best visual acuity reported by this device was 20/460 (Palanker et al., 2022).

Finally, the third kind of retinal implants is suprachoroidal prostheses that are placed between the choroid and sclera of the eye. In the United States, these devices have not yet obtained FDA approval for clinical use. An advantage of a suprachoroidal prosthesis is that the implantation surgery imposes less risk to the retina. One disadvantage, though, is more non-specific stimulation of the retinal tissue, due to the large distance between the stimulating electrode and the target cells. An exemplary suprachoroidal prosthesis is the implant developed by Bionic Vision Technology (BVT). In a clinical trial in 2018, on 4 participants, performance error was reduced in square localization task and all subjects were able to locate and identify a high-contrast object. Yet, no subject could discern the difference between the background and various presented grating frequencies (Petoe et al., 2021). Clinical studies are still ongoing for BVT.

Cortical Prostheses

The idea of using cortical stimulation to produce phosphenes is not new. In 1968, the first cortical and visual prosthesis was developed by Brindley and Lewin. The implant was composed of 80 electrodes that wirelessly received visual signals and were placed on the visual cortex (Nowik et al., 2020). The device never became clinically available, however, this study served as a feasibility experiment for future works. One advantage of a visual cortical implant is that it bypasses the earlier parts of the visual pathway and consequently could be used for therapy of visual impairment caused by the retina or optic nerve complications. Intracranial cortical prostheses are still under development. One prominent visual cortical prosthesis is Orion that is developed by Second Sight Medical Products. Orion is designed by an adaptation from Argus II

retinal prosthesis and NeuroPace, a neurostimulator originally used for minimizing seizures in epilepsy patients using surface electrodes. Orion is composed of an array of surface electrodes wirelessly connecting to an extracranial telemetry unit. In 2017, feasibility studies for Orion started in 1 subject. In an experiment, the thresholds needed to be reached to stimulate and elicit phosphenes remained stable over 19 months (Niketeghad et al., 2019). Additionally, Orion ran an early feasibility study on 6 subjects. Although a serious adverse event was reported for one patient, for the majority of the participants, performance in square localization task was drastically improved (Business Wire, 2021). Currently, Orion is running a phase 1 study in which the phosphene organization estimates were the most accurate when using relative mapping and bimanual fixation. More improvement to the techniques used is underway for the optimal implementation of Orion (Oswalt et al., 2021).

1.4 Effect of Vision Loss on the Brain

1.4.1 Neuroplasticity

A central property of the nervous system is neuroplasticity. Neuroplasticity is the capability of our nervous system to alter its anatomy or function in response to new stimulation, damage, or development. Blindness offers a great model to explore neuroplasticity, as the change in visual input challenges the brain to adapt itself to understand the environment in the absence of vision. While the neurophysiological changes in the brain following vision loss leads to degradation in visual function, these alterations also give rise to adaptive compensation in which the performance of other senses (tactile/auditory) is enhanced due to heavier reliance on the intact senses, a phenomenon also known as cross-modal plasticity (Silva et al., 2018). Strikingly, the plastic changes in the brain after vision loss not only include sensory but also cognitive performance of the brain, as will be discussed in more detail in section 1.4.4. Additionally, both animal and human

studies contribute to our understanding of blindness, however, translation from animal studies to human subjects should be cautiously done. The visual system in primates is generally more mature than other animals, with more visual sensory regions and reliance on the sense of vision than the majority of non-primates.

Plasticity can be observed at different temporal and spatial scales, i.e., changes can occur over short versus long periods of time, and alterations can arise at the level of neurons versus the entire brain network. Perceptual learning is another concept that is closely related to neuroplasticity. While neuroplasticity represents physiological alterations in the cortex, perceptual learning signifies the resulting change in behavior. In fact, perceptual learning is the behavioral expression of neuroplasticity, where training on a task can facilitate learning due to neuroplasticity (Sagi, 2011).

Losing sight can occur at any developmental stage, giving rise to different categories of blindness. Lack of visual information to the cortex at birth or within the first month after birth is referred to as congenital blindness, in which the affected individual typically continues to have light perception throughout life. Early blindness occurs when vision is lost after birth and before 16 years of age. Any extensive plasticity in the brain is unlikely to happen after this critical period. Finally, if vision loss occurs after the age of 16, it is referred to as late blindness. Late-blind individuals usually have some vision limited to light perception (Fine & Park, 2018).

1.4.2 Manifestation of blindness-induced Neuroplasticity at different scales

The impact of neuroplasticity is observable at various scales. Since the reorganization is more dramatic when vision is lost during the critical period of visual development, here we focus on different scales of neuroplastic changes in early-blind individuals. In early blindness, at the neurotransmitter level, the balance between inhibitory and excitatory neurotransmitters is altered,

leading to a reduction in the inhibitory neurotransmitter GABA and an increase in excitatory neurotransmitter glutamate and choline. Metabolism in the occipital cortex has also been shown to rise (Coullon et al., 2015). This increase in metabolism, astonishingly, weakens the neurovascular coupling (Bengoetxea et al., 2008), ultimately affecting the blood-oxygen-level-dependent (BOLD) visual responses acquired in functional magnetic resonance imaging (fMRI).

Alteration in white matter connections has also been observed following early blindness. In the process of normal development, during the second trimester of pregnancy, cerebral neural pathways start to form prior to having any visual experience. In spite of this, in early-blind individuals, atrophy has been observed in the subcortical visual pathways in the optic tract, optic nerve, and optic radiation (Shu, Li, et al., 2009). Interestingly, the retinotopic organization of the white matter tracts in the primary visual cortex is maintained in spite of blindness (Bock et al., 2013), although with less precision. Resting-state functional connectivity studies also demonstrated the existence of retinotopy in the lower level visual cortex in the congenitally blind (Striem-Amit et al., 2015a) and that the neural circuits involved in the visual system are formed prior to any visual experience. Also, except for some deterioration in occipito-temporal connections observed following early blindness, the tracts between the visual cortex and other regions are predominantly unaffected from blindness (Bock & Fine, 2014). The fact that the early-blind show no reorganization in the cortico-cortical connections between the visual cortex and other brain regions may indicate that these tracts play a functional part in the blind brain.

The anatomical effect of early blindness on the cerebral cortex includes an increase in cortical thickness in the visual areas, simultaneous with a drop in cortical surface area and folding. During the healthy prenatal period, cortical expansion is facilitated by means of neurons migration inside the cortical sheet. This migration is promoted by a special type of progenitor cells. In early

blindness, the density of these progenitor cells is reduced leading to the weakening of the tangential dispersion of migrating neurons and a decrease in the surface area of the cortex (Reillo et al., 2011). In addition, insufficient cortical pruning after birth in the absence of visual experience can contribute to an increase in cortical thickness (Anurova et al., 2015). It is important to note that the time of vision loss seems to affect the severity of plastic changes in the brain, where late blindness has been shown to induce less structural changes in the visual pathway and cortical areas compared with early blindness (Jiang et al., 2009; Park et al., 2009). Although a study on late-blind patients with age-related cataract indicated a decrease in gray matter volume in the anterior cingulate, a cognitive area (Lin et al., 2018). From a functional perspective, a higher-level manifestation of blindness is in cross-modal plasticity. This concept is explained in more detail in section 1.4.4.

1.4.3 Age-Dependent Visual Plasticity and Perceptual Learning

In humans, the critical period for visual system development lasts until the early teenage years, i.e. around the age of 16 (Fine & Park, 2018). Losing sight during (compared with after) this phase impacts the visual cortex differently along the visual hierarchy. Features of the primary visual cortex that are less dependent on visual experience during the critical period will less likely be changeable during adulthood. Although the visual experience has minimal impact on the retinotopic organization of V1 which is driven by molecular cues (Striem-Amit et al., 2015a), it has a significant impact on the orientation and extent of receptive fields, structure of ocular dominance columns, and neuronal tuning properties (Ackman & Crair, 2014; Sherman & Spear, 1982). In contrast, higher levels of the visual cortex remain more plastic during the critical period, in response to congenital and early blindness. In a study on a 24-year-old subject with achiasma, a rare disease in which each side of the visual cortex processes both left and right visual fields due

to the absence of optic chiasm, the retinotopic deformation in V1 did not cause any challenges in visual perception of the received visual signals. This result along with other experiments (Bao et al., 2015; Neitz & Neitz, 2017) show that higher visual areas have a remarkable plastic capacity for adaptation to abnormal primary visual presentations, following vision loss within the sensitive period.

As the age of onset of blindness increases beyond the critical period, the consequence of cortical reorganization becomes less extreme. Whether or not blindness in adulthood results in the generation of new functional synaptic connections is still not yet fully known. One study that evaluated plasticity in the primary visual cortex after the sensitive period found minimal alteration in orientation tuning after prolonged training for the orientation discrimination task in healthy monkeys, however, this finding was not replicated (Ghose et al., 2002; Schoups et al., 2001). Likewise, in another animal study, even more sophisticated tasks such as line bisection did not modify the receptive field properties of the primary visual cortex. Instead, more training affected the top-down impact on the visual cortex. On the other hand, fMRI studies on healthy humans reported some plasticity manifested as an increase in V1 activation in response to trained orientation detection tasks (Furmanski et al., 2004). Nevertheless, since there is an inherent latency in the fMRI BOLD signal, we do not have enough evidence to show that the driving source for this response was due to alteration in top-down influences or the bottom-up properties. Other studies explored how retinal scotoma affected the visual response. FMRI studies on late-blind humans reported visually-evoked responses in the lesion projection zone (LPZ) or shift in retinotopic arrangement (Baker et al., 2008; Ferreira et al., 2017). Yet, these results were not repeated by other researchers (Baseler et al., 2011). One possibility is that the observed LPZ responses could be due to top-down attentional influence since these results were obtained in

experiments that involved a one-back task while they were not observed in experiments involving passive viewing (Baseler et al., 2011; Dilks et al., 2009). Overall, evidence for V1 plasticity in late blindness is weak and inconclusive. Interestingly, neuroplasticity in the primary auditory and tactile cortex appears to be more than in the visual cortex in adulthood. One proposed explanatory idea for this phenomenon is that the auditory and tactile areas incorporate higher subcortical processing of information, compared with the visual cortex. Thus, the primary tactile and auditory cortex are technically higher in their respective sensory pathways, compared with V1 in the visual pathway. This may not be surprising in light of the hypothesis that higher sensory areas are more plastic than lower areas (Baseler et al., 2011).

On the other hand, higher visual cortical areas appear to be differentially affected by blindness later in life. Human subject studies on blind individuals who received sight recovery after the critical period have shown persistent impairment in contrast sensitivity tasks (Fine et al., 2003). However, improvement in performance of this task was seen in cases where sight was recovered before the critical period (Kalia et al., 2014). Thus, learning the contrast sensitivity function seems to be dependent on age. In congenitally- and early-blind individuals, object, shape, and face recognition tasks, generally attributed to the ventral visual stream, remained impaired after sight recovery during late childhood or long after the critical period (Huber et al., 2015a; Sinha et al., 2013). Consequently, learning these tasks may be less dependent on age. Strikingly, motion processing tasks, mediated by the dorsal visual stream, appear to be more immune to the prolonged visual deficit (Saenz et al., 2008). Since processing reading and object recognition (facilitated by the ventral stream) demands higher spatial frequencies, compared with navigational tasks (facilitated by the dorsal stream), vision restoration technologies will be more effective by

providing spatial and navigational information for the dorsal stream, which appears to remain more plastic.

1.4.4 Cross-Modal Plasticity in Blindness

A specific type of adaptive neuroplasticity is referred to as cross-modal plasticity which strikingly leads to the functional integration of different sensory systems in the brain even at the level of the primary sensory cortex (V1). Cross-modal plasticity follows a deprivation in one sensory modality, e.g., vision, that leads to recruitment of the affected cortical sensory area for processing other sensory modalities, e.g., tactile, or auditory. This cortical reorganization will then be manifested in performance enhancement of other sensory systems. These alterations are due to cortical reorganization that is induced by blindness and are mainly driven by the need to interact with and adapt to the altered environment. Numerous studies reported the occurrence of tactile- and auditory-evoked cross-modal responses in the visual cortex after vision loss (Amedi et al., 2007; Burton, 2003; Collignon et al., 2009; Merabet et al., 2009). Interestingly, cross-modal plasticity has been shown to be also experience-dependent. In a study on early and congenitally blind individuals, it was shown that learning Braille reading earlier results in higher tactile-induced visual responses (Liu et al., 2008).

Cross-modal Plasticity in Early versus Late blindness

The time of onset of blindness seems to affect the degree of the induced brain alterations. Compared with early blindness, late blindness has shown to result in less structural changes in the visual pathway and cortical areas as well as weaker cross-modal responses in the visual cortex (J. Jiang et al., 2009; Park et al., 2009; Voss et al., 2008). Nevertheless, both tactile- and auditory-evoked cross-modal responses have been reported in late-blind individuals. The strength and

spread of the tactile-evoked V1 responses have also been shown to be correlated with the degree of vision loss (Burton, 2003; Cunningham et al., 2015).

Cross-modal responses in visual areas were also observed in normally-sighted individuals who were blindfolded for 5 consecutive days. These responses disappeared 24 hours after the removal of the blindfold. Additionally, to investigate the causal influence of the visual cortex on tactile processing, in this study, TMS (Transcranial Magnetic Stimulation) was applied to the visual cortex which impaired Braille reading in the blindfolded group, but not the non-blindfolded group. This effect also disappeared after the removal of blindfolds (Merabet et al., 2008). This important finding indicates that the cross-modal effects in late blindness may similarly be reversible. Importantly, it also indicates that although the underlying mechanism of cross-modal responses is not yet fully known, the cross-modal changes serve a functional role.

It is also important to note that the cross-modal responses in early blindness are not limited to non-visual sensory tasks and also have been observed in response to cognitive tasks, such as during execution of complicated language, memory, and mathematical tasks (Kanjlia et al., 2016; Noppeney et al., 2003). High-level language processing tasks have also been shown to activate primary visual areas in the late-blind (Harold Burton & McLaren, 2006).

Late-blind individuals are usually the main candidate groups for receiving visual prostheses. This is because in late blindness compensatory mechanisms are not developed to the level of early blindness and consequently, the late-blind acquire less enhanced abilities in their intact (auditory and tactile) senses compared with the early-blind where such reorganization hampers their handling of impediments more (Wan et al., 2010). Since vision loss occurs after the natural development of the visual cortex, late-blind patients also have the advantage of having a normally wired visual cortex, leading to more feasible sight recovery.

Theoretical Models for Explaining Cross-modal Plasticity

Researchers have attempted to explain the potentially different underlying cross-modal mechanisms observed in early compared with late blindness. It has been hypothesized that early blindness could weaken the pruning process of intermodal connections between visual and other sensory cortices, naturally occurring during normal development in infancy. Conserving these inter-modal connections can then prevent the reinforcement of natural visual networks. While, in late-blind individuals, because of the stabilizing visual input during the critical period, these inter-modal connections cannot escape the typical pruning process. Consequently, the cross-modal responses in late blindness would not be due to lack of necessary pruning but maybe a result of the strengthening of the cortico-cortical connections between the visual and other sensory cortices that already exist in the normally sighted (O. Collignon et al., 2011). Other studies also seem to be in line with this theory, where applying TMS to the primary somatosensory cortex resulted in activation in V1 for early-blind and not the late-blind group (Wittenberg et al., 2004b).

Over two decades ago, the hypothesis for metamodal plasticity of the brain was raised (Pascual-Leone & Hamilton, 2001). This idea proposes that the brain may be a structure composed of operators that can implement a set function or computation, irrespective of the sensory input provided to each operator. For instance, V5/MT area or the fusiform face area (FFA) are responsible for finding the spatial movement of objects and facial identification, respectively; when vision can offer the most proper information, in the case of normally-sighted individuals, vision supplies the necessary information to these two brain areas. However, in the visually impaired, cortical reorganization in these areas generalizes so they can execute a similar calculation on the received tactile and auditory information. Some research studies seem to agree with the idea of a metamodal brain (Hölig et al., 2014; Jiang et al., 2014), however, concerns have

been raised about the validity of these experiments, due to substantial variation in the location of these regions across the individuals and the anatomical misalignment of the blind and healthy data (Fine & Park, 2018). Another theory claims a supramodal attribute for cortical areas. This idea states that cross-modal responses in the early blind could also be present in sighted humans, but these responses can merely be unmasked following early blindness (Pascual-Leone & Hamilton, 2001; Ricciardi et al., 2014). The metamodal and supramodal theories entail a competitive phenomenon in which different sensory input modalities compete with each other to serve as the most informative input to areas such as V5/MT and FFA.

Even though the discussed hypotheses appear to fit the results of some studies, especially the ones involving sensory cross-modal plasticity, they do not seem to explain other cross-modal responses during cognitive tasks. Performing cognitive tasks, such as language, numerical calculation, and working memory, have been shown by several studies to activate visual areas in the blind (Burton et al., 2003; Kanjlia et al., 2016). One model that attempted to explain these cross-modal responses is the reverse hierarchy. In order to identify the potential role of reverse hierarchy in blindness, we need to first understand this concept in a naturally developed visual cortex. In normally-sighted individuals, retinal stimulation results in responses in LGN and cortex. With the feedforward flow of visual input, responses progressively elaborate to represent more abstract features of the visual scene as it moves higher in the visual cortical hierarchy. These high-level representations then provide the necessary input for cognitive areas that are implicated in attention, action, decision-making, and memory. The reverse hierarchy then provides information feedback from higher- to lower-level visual areas, which facilitates concentrated attention and learning in lower-level neurons in the visual cortex. Following early blindness, it is presumed that higher visual areas involved in spatial motion and object identification send elaborated data back

to lower-level visual areas, similar to feedforward connections from these areas to cognitive regions. These feedback connections then result in more abstraction of the data and cognitive processing in early visual areas (Bedny, 2017). In spite of the theoretical novelty of this theory, it has been subjected to criticism. This is because it is unclear how these assumed feedback connections are then appointed to a feedforward role since such a reorganization requires massive anatomical reconfiguration (Fine & Park, 2018).

1.5 Effect of Vision Restoration on the Brain

1.5.1 Visual Response and Perception following Sight Recovery

One important limitation of sight recovery technologies is the distortion in the reproduced visual images and the ultimate information loss. Current novel restorative technologies, e.g., optogenetics and electronic devices, do not allow for selective stimulation of the target cells in the retina. For example, epiretinal implants can inadvertently stimulate RGC axons and produce comets, instead of the expected phosphenes, or in optogenetics, the delayed response of optogenetic protein can result in diminished temporal resolution (Beyeler et al., 2017). The visual experience produced by these technologies is different from the natural visual stimulation of the retina when a few specialized cells are activated, enabling different necessary pathways with parallel processing (Nassi & Callaway, 2009). Thus, the brain receiving artificial vision needs to learn to perceive the world by learning to interpret the distorted information provided by sight recovery technology.

Studies on visual prosthetic devices have shown that patients' capabilities improve with more training. Nevertheless, there is not enough evidence proving that improved performance is indeed a result of an improved perception of the distorted input. Since the majority of the learning appears to be task-specific, the improved performance could be due to a better interpretation of the

warped information. Nonetheless, sight restoration, especially in late-blind individuals improved visual and behavioral outcomes. Studies on late-blind patients implanted with Argus II retinal prosthesis have shown a reduction in visual field loss (Rizzo et al., 2015) and time since implantation reduced the detection thresholds in the implanted patients (Castaldi et al., 2016). In the primary visual cortex and LGN, functional BOLD responses to visual stimuli also significantly increased in Argus II subjects following the implantation (Castaldi et al., 2016). In contrast, a separate study with two Argus II subjects did not show any visually evoked activation in the visual cortex (Cunningham et al., 2015). In spite of the improvement reported in the experiment by Castaldi et al., performance in basic perceptual functions, such as motion discrimination and contrast sensitivity, did not drastically improve (Castaldi et al., 2016; Dorn et al., 2013a). Generally, perceptual improvement has been observed more significantly for certain tasks, including locating large objects, identifying large letters, independent movement, and navigation (Dorn et al., 2013b; Rizzo et al., 2015). Another sight recovery study on a single wet age-related AMD patient resulted in improved visual acuity and V1 BOLD activations in the posterior visual cortex (Heidi et al., 2011). Finally, in a cortical morphometry study on age-related cataract patients who underwent cataract removal surgery, an increase in gray matter volume in visual and cognitive areas was observed that rendered the gray matter volume at a comparable level to normally-sighted subjects (Lin et al., 2018).

Besides the mentioned behavioral and visual improvements in the late-blind performance, congenitally- and early-blind patients have generally shown a lower degree of reorganization following sight restoration. Sight recovery may never restore some attributes of visual perception that were never experienced by the blind individual during the sensitive period. For instance, in a study on congenital cataract reversal, audio-visual or sound-shape association was never achieved

(Sourav et al., 2019). Early-blind individuals, on the other hand, demonstrated vision restoration, although only partially. In a case study on a subject who lost his vision during the critical period and sight restored in midlife, after extensive training, the subject was able to perform simple tasks, such as perceiving simple forms, motion, and color, but the subject was not able to perform more sophisticated perception tasks, such as identification of complex forms, objects, and faces (Huber et al., 2015b).

1.5.2 Fate of Cross-modal Plasticity following Sight Restoration

In spite of the abundant research on cross-modal plasticity after blindness, it is not yet known whether these alterations will have an adaptive or maladaptive consequence for the potential sight recovery. The idea of the maladaptive effect of cross-modal plasticity is primarily impacted by studies in cochlear implants, where individuals suffering from early and late deafness showed mixed effects from the cross-modal responses in the auditory cortex (Champoux et al., 2009; Land et al., 2016). Contrary to cochlear implant studies, evaluation of cross-modal plasticity after sight restoration has been rare.

In some studies, it has been assumed that cortical reorganizations due to cross-modal plasticity could be maladaptive for sight recovery, especially for sight restoration after the critical period when the brain is generally less plastic (Legge & Chung, 2016). This is because the reorganization may result in other sensory signals to compete with the original sensory input for the recruitment of the affected sensory cortex. In a study on two Argus II patients, tactile stimuli resulted in activation in the primary visual cortex, and time since implantation appeared to favorably affect the cross-modal responses. However, the small number of subjects in this study prevents drawing any concrete conclusion. In another experiment on Argus II recipients, tactile-evoked BOLD responses were observed in V1. Although, large variability in BOLD responses was

reported across the participants. Interestingly, this experiment also found a negative correlation between performance in a shape-matching task and the extent of tactile-evoked V1 BOLD response. (Stiles et al., 2020).

On the other hand, cross-modal plasticity has been considered to have significant adaptive benefits for the blind. Cortical recruitment of remaining neurons in the deprived (visual) cortex by the other (tactile and auditory) senses can serve to sustain these neurons viable, by recruiting them for processing other sensory functions. This is a beneficial impact for any potential sight restoration efforts. Also, such a phenomenon enhances the performance of other senses for better adjustment to everyday life. Sustained (or even enhanced) cross-modal responses after sight restoration are not limited to late blindness as mentioned before and have been also reported in early-blind subjects with adaptive benefits. A few studies have consistently demonstrated the existence of cross-modal plasticity and its adaptive effect on sight restoration in early blindness. A study on two early-blind individuals demonstrated activation in the cortical visual motion area (V5/MT) in response to an auditory motion task, even after partial sight recovery in adulthood. This response was not observed in healthy subjects. Also, both visually- and auditory-evoked responses were present in the visual cortex (Saenz et al., 2008). Similarly, another study found increased auditory motion response in V5/MT region in an early-blind individual who regained partial vision at the age of 46 (F. Jiang et al., 2016). A third study reproduced consistent results, but in congenitally blind individuals who received sight restorative surgery during the critical period. This group showed dramatically elevated auditory motion responses in V5/MT areas compared with healthy controls (Guerreiro et al., 2016). In another case study, a subject with early blindness, sight restored later in life, showed enhanced auditory activations in V1 that overlapped with visual activations. The cross-modal responses, however, decreased in higher visual areas

following vision recovery (Dormal et al., 2015). Recently, a clinical trial study on Leber congenital amaurosis individuals who received sight restorative gene therapy showed enhancement of auditory-evoked responses in the visual cortex after sight recovery that overlapped with visual responses (Mowad et al., 2020). Improvement in different functional areas including visual acuity, visual field, microperimetry, and pupillary light reflex in these patients was reported up to three years after the gene therapy administration. These findings imply that therapeutic sight recovery in early blindness is possible in spite of the sustained cross-modal reorganization in primary visual areas.

1.6 Thesis Overview

1.6.1 Motivation and Impact

Despite extensive scientific efforts, our understanding of cortical plasticity remains insufficient. Argus II retinal prosthesis is the only retinal prosthesis that has ever received FDA approval and had been used clinically before discontinuation. The behavioral and functional impact of using this sight restorative prosthesis provides an invaluable opportunity to not only evaluate the degree of its efficacy in improving the quality of life for the visually deprived but also to explore the brain's potential for reorganization upon reintroduction of (artificial) vision.

Performance results from Argus II recipients revealed improvement in light perception, identification of large letters, locating large objects, and independent movement (Rizzo et al., 2015). For many implant recipients, however, visual performance did not improve as significantly. Some recipients' visual capabilities progressed from the level of light perception to hand motion and for others, it improved further to finger counting. This variability in performance can be due to multiple factors, including the relative difference in retinal degeneration in RP-blind individuals, inherent variability in how the device interacts with the retina, and differential cortical plastic

responses to the reinstated visual input. The research project presented in this thesis has aimed to address this issue from a cortical perspective to determine how vision loss and restoration alter functional cortical reorganization. Understanding these brain alterations can provide insight into why some patients better adapt to artificial vision than others.

Variability was also observed in the visual cortex BOLD responses due to tactile stimulation across Argus II recipients (Stiles et al., 2020). This inconsistency prevented any meaningful difference to be detected between the RP blind and Argus II groups for tactile-evoked BOLD responses in the visual cortex, a measure of cross-modal responses during task execution. Consequently, previous attempts to quantify cortical cross-modal effects in Argus II patients have not been conclusive. Evidently, a reliable index to quantify cross-modal plastic changes following sight restoration is crucial, not only for the effective design of sight restorative technologies but also for more effective provision of clinical rehabilitation.

The reported variability in task-evoked cross-modal responses in the visual cortex could be due to the difference in baseline BOLD activation levels across individuals. The -resting state functional connectivity (rsFC) measure can overcome this issue by providing a better-normalized metric for plasticity. The rsFC refers to the temporal dependence between anatomically separated brain regions, in the absence of any task or stimulation. Numerous experiments studied rsFC before and after blindness and reported alteration in this quantity within the visual cortex and between the occipital regions and other (sensory/non-sensory) cortical areas (Murphy et al., 2016; Nuzzi et al., 2018; Wen et al., 2018; Y. Yu et al., 2020). This index, however, has rarely been used to quantify functional changes in the brain due to sight recovery. One study investigated rsFC between the visual and auditory cortex in blind patients who received sight restorative gene therapy (Mowad et al., 2020). Although this was a qualitative assessment, the study proved the feasibility

of using this measure for tracking plastic changes after vision restoration. Therefore, we aimed to evaluate the effect of visual deprivation and restitution on rsFC, not only between visual and other sensory regions but also between different regions of the entire brain and to extract properties of the brain functional network.

Overall, we hypothesize that rsFC can serve as a complementary metric of cross-modal plasticity of the brain following visual deprivation and restoration. This can potentially shed light on the unexplained variability observed in behavioral and neuroimaging studies in Argus II recipients. To test this hypothesis, a larger number of subjects are needed to provide for more reliable group-level analyses. Since Argus II patients are rare, we combined our Argus II neuroimaging data collected at the University of Michigan (UM) with similar data collected at the University of Southern California (USC). Both centers are now part of the Human Connectome Low Vision (HCLV) project, under the larger Human Connectome Project (HCP). Implementation of the HCLV neuroimaging project at UM and data collection harmonization with the USC center provided us with a total of 8 Argus II subjects, a much larger subject pool than previously used for similar Argus II experiments.

Reliable quantification of functional cross-modal plasticity of the brain will provide the initial step towards understanding device performance and cortical response variability and predicting the outcome of therapy in the prosthesis candidates. This knowledge can empower therapy optimization and promote enhanced restorative outcomes for patients with RP disease (and potentially other types of blindness such as AMD). The contributions from this study will inform visual prostheses engineers to devise improved designs and can highlight new targets for future technologies in artificial vision. It will also offer dramatic scientific insight into cortical plastic capacity in the vision-deprived and vision-restored brain, serving the scientific community from

basic neuroscience to translational neural engineering. On the other hand, healthcare professionals will be able to deliver better rehabilitation care, being equipped with more reliable plasticity metrics to potentially gauge the level of recovery based on an individual's need. The result is improved quality of life for patients by reducing the burden of low vision, including the inability to work effectively, dependency on caretakers, and impediments to attaining a more active and productive life.

A different focus of our work in this thesis has been on the replication of neuroimaging studies in blindness. Neuroimaging fMRI studies are prone to false findings. This could be a result of a smaller number of subjects for neuroimaging studies due to cost, but false results could be a result of various sources of noise and artifact, especially for rsFC analyses. This highlights the significance of preprocessing methods in providing the groundwork before any connectivity analysis and statistical inference. Numerous studies have shown that the choice of analysis pipelines can impact the research findings (Carp, 2013; Lindquist et al., 2019; Poldrack et al., 2017). As a result, replication studies that aim to reproduce the previously published results with a different set of methodologies are critically necessary. To that end, we aimed to replicate the rsFC results of a frequently cited scientific paper on ocular blindness. By using the identical data as the original study, we focused on the effect of methodology on results. Additionally, using HCLV RP and Argus II neuroimaging data, we aimed to reproduce the blindness-induced functional changes in the brain that have been reported by some studies in the past (Murphy et al., 2016; Nuzzi et al., 2018; Wen et al., 2018; Y. Yu et al., 2020). This enabled us to verify the replicability of these research studies by using a different dataset.

1.6.2 Dissertation Aims and Organization

This dissertation encompasses two broad venues of study; the first venue, included in Chapter 2, verifies the reproducibility of a well-cited rsFC study on early blindness from a methodology standpoint. The second venue, included in Chapters 3 and 4, seeks to shed light on the functional reorganization of the brain following vision loss and recovery, from a neuroscientific perspective. The series of aims investigated in this dissertation are organized as follows:

Chapter 2 Examines the replicability of an ocular blindness rsFC study. Two alternative computational streams were tested against the original pipeline. We hypothesize that different and more rigorous preprocessing pipelines can alter the rsFC results.

Chapter 3 investigates somatosensory-visual rsFC following blindness and sight restoration. Could visual-somatosensory resting-state functional connectivity provide a reliable biomarker of functional plasticity? We hypothesize that similar to the visual-auditory rsFC result of a previous sight recovery study, visual-somatosensory rsFC is enhanced with sight restoration with Argus II.

Chapter 4 Explores alteration in the whole-brain rsFC and properties of the brain functional network in response to blindness and Argus II implantation. We sought to verify whether, in addition to the findings in Chapter 3, there are other connectivity pairs that are affected by vision loss and recovery at the level of the brain network. We hypothesize that not only the connectivity between visual and other sensory, motor and association areas are altered by deprivation, in line with several previous studies on blindness, but also that some of these altered connectivity measures are reversed after the vision reestablishment.

Chapter 5 summarizes the findings and contributions of this thesis as well as suggestions for future work.

Chapter 2 - Replication of an Ocular Blindness Neuroimaging Study

2.1 Introduction

Emergence of high-dimensional neuroimaging data has given birth to new challenges, with concerns being raised in recent years regarding reproducibility and control for biological and nonbiological sources of noise in MR-derived signals (Klapwijk et al., 2021; Kriegeskorte et al., 2009; Lindquist et al., 2019). While neuroimaging is a useful tool for answering scientific questions, decisions are made at each stage of analysis to mitigate sources of potential noise, including data collection, choice of spatial and temporal image processing techniques, statistical assessment, and order of their application, which can each impact the study outcomes. Within the past decade, numerous algorithms have been developed to minimize the effect of contamination of this data from noise and artifact and best practices have been proposed to optimize data collection and analysis (Maumet et al., 2016; Nichols et al., 2017; Poldrack et al., 2008, 2017), although there has yet to be consensus in the field.

Functional magnetic resonance imaging studies in particular, are vulnerable to spurious signals and challenges in replicating results. One investigation exposed a large number of studies with inflated correlation results between the fMRI blood-oxygen-level-dependent (BOLD) response and behavioral measures (Vul et al., 2009). The questionably large correlations in these studies were attributed to the biased methods adopted for correlation analysis. Statisticians also probed into some of the widely used fMRI analysis packages and discovered that some of these methods in effect inflate the rate of false positives (Eklund et al., 2016). FMRI studies are also often underpowered (Marek et al., 2022), potentially leading to larger type I error and lower

positive predictive values (Button et al., 2013). These are a few examples of how spurious results in fMRI studies can be partially attributed to inappropriate statistical methodologies and/or inherently low statistical power.

Additional factors rendering fMRI studies prone to poor reproducibility are the flexibility in selection and combination of analysis techniques and insufficient reporting of detailed procedures in design, acquisition, and computation (Poldrack et al., 2008). Earlier modeling studies indicated that greater flexibility in design and computational approaches is associated with a greater probability of false positive errors (Ioannidis, 2005). This is true of fMRI in which nearly each study may have a unique analysis pipeline (Carp, 2012a), resulting in significant variability in estimates of the strength, location, and statistical significance of activations (Carp, 2012b). With the emergence of open-source neuroimaging analysis tools, additional sources of analytical variability have recently been acknowledged, as analysis pipelines for the same overarching procedure are implemented differently in nearly each software package (Poldrack et al., 2017). Consequently, replicating fMRI studies becomes challenging, as algorithm implementation and the ordering of preprocessing steps have been shown to influence study results (Carp, 2013; Lindquist et al., 2019). As a result, replication studies using a different dataset, computational approach, or pipeline are critically important in fMRI studies to validate the previously published findings or to reveal sources of variability.

In the present replication study, we attempted to reproduce the resting-state functional connectivity findings of an original study by Bauer and colleagues in 2017 (Bauer et al., 2017). The original work explored the alterations in rsFC in a group of subjects with early ocular blindness compared with sighted controls. The study reported increased temporal correlations in BOLD signal derived from rsFC between inferior frontal and temporal areas, as well as a more

predominant decrease in correlations between occipital and frontal, occipital and somatosensory/motor, temporal and parietal, temporal, and frontal cortices and within the temporal in early-blind as compared to the sighted control subjects. Importantly, some of the works prior to this primary study reported a decrease in visual-somatosensory and visual-auditory rsFC (Bedny et al., 2011; Harold Burton et al., 2014; Striem-Amit et al., 2015b) and increased rsFC in visual-frontal and visual-parietal areas following blindness (Harold Burton et al., 2014; Heine et al., 2015; Watkins et al., 2012). In the present replication study, by using the dataset utilized for the original work, we aimed to repeat the analysis with a different, but widely used software package for the analysis of rsFC and to include more rigorous handling of the effects of known noise and artifacts. In our first replication approach, we cleaned the data by using the minimal preprocessing procedure similar to the original paper. In the second attempt, some of the main preprocessing and denoising protocols are incorporated that are typically suggested to reliably prepare the resting-state fMRI (rsfMRI) data for rsFC analysis.

2.2 Methods

2.2.1 The Target of Replication

In this replication study, we utilized the same neuroimaging data acquired as a part of the original research article (Bauer et al., 2017). Briefly, 9 sighted control (SC) and 11 early ocular blind (EB) subjects were included in the analysis of rsFC. Anatomical T1-weighted (T1W) scans (TE = 3.1 ms, TR = 6.8 ms, flip angle = 9°, voxel size 0.98 x 0.98 x 1.20 mm, turbo spin echo) and one 7 min rsfMRI run (TE = 30 ms, TR = 3000 ms, flip angle = 80°, voxel size 2.75 x 2.75 x 3.00 mm, single-shot EPI) were obtained on a 3T Philips Intera Achieva scanner. Subjects were blindfolded and were not guided to perform any directed task within the scanner. For each subject, a static fieldmap acquisition was also completed (TE1 = 2.3 ms, TE2 = 4.6 ms, TR = 20 ms, flip

angle = 10°, voxel size 1.02 x 1.02 x 3.00 mm, fast field echo). The experiment was approved by the Institutional Review Board at the Massachusetts Eye and Ear Infirmary, Boston, MA, USA and a written consent form was obtained from each participant.

By keeping the data identical, we focused on replicating the resting-state functional connectivity results, presented in the original paper, using a different set of methodologies. Therefore, this work sought to reveal whether the same results are obtained by altering the analysis protocol. This replication work also helped us identify a coding error in implementing the correction for multiple comparisons in the original study. Specifically, I identified an unintentional computational error in the false discovery rate (FDR) calculation used in the multiple comparison corrected contrast results presented in Figure 3B and Table 4 in the original paper. After applying an updated FDR correction to both the replication results and the preprocessed data from the original paper, it was found that none of the originally reported connections from the contrasts of interest survived the multiple comparison correction. Undeniably, discovery of null scientific results and reporting them remains crucial and valuable to the advancement of science and thus is just as important as reporting the significant results. In addition, it is helpful to communicate the uncorrected results, especially to reveal any underlying trends in the data (Poldrack et al., 2008; Poline et al., 2006). Consequently, we aimed to focus on reproducing the initial uncorrected results presented by the primary research article and took a closer look at the influence of each pipeline on the effect sizes of interest.

2.2.2 Differences and Similarities between the Pipelines under Study

The original paper reports that analysis was mainly implemented by the publicly available software package FSL FEAT v. 6.00 (Jenkinson et al., 2012) and FreeSurfer v. 5.3.0 (Fischl, 2012) to perform skull-stripping using BET, static fieldmap correction, realignment and temporal

regression of motion parameters and their derivatives. The rsfMRI data was coregistered to T1W structural scans using boundary-based registration (BBR) (Greve & Fischl, 2009) and 68 parcellations from the Desikan-Killiany atlas (Desikan et al., 2006) were reverse transformed into subject-specific space to serve as regions of interest (ROIs) using FreeSurfer. A custom MATLAB (MathWorks, Natick, MA, USA) script was used to bandpass-filter the functional data between 0.01 Hz and 0.1 Hz, detrend the BOLD signal, calculate Fisher transformed Pearson correlation coefficients (z) between each region of interest (ROI) pair and create a 68x68 functional connectivity matrix for each subject. Group-level results were created by averaging the z values for each connection within each group. Between-group contrast maps were computed by applying a two-sample t -test to z values of both groups.

We devised two different preprocessing pipelines using the CONN toolbox 20.b (Whitfield-Gabrieli & Nieto-Castanon, 2012b) to replicate the original results, which were generated using FSL v. 6.00 (Jenkinson et al., 2012). In the first pipeline, we attempted to perform steps as similar as possible to the primary paper. We call this the replication minimum (RMin) model. In the second pipeline, we incorporated a more comprehensive set of processing steps, strongly recommended for rsfMRI data (Andersson et al., 2001; Molloy et al., 2014; Muschelli et al., 2014), for the removal of unwanted contamination with noise and artifacts prior to the subsequent statistical analysis. We refer to this scheme as the replication full (RFull) model. The original work and the replication models performed the preprocessing and ROI extraction in subject-specific space to minimize the effect of between-subject variability (Bijsterbosch et al., 2020).

Similar to the original article, the RMin model implemented a subject-specific volumetric analysis, used Desikan-Killiany atlas to parcellate the brain, and incorporated static fieldmap

correction, realignment, temporal linear regression of motion parameters, band-pass filtering, and detrending. However, as Table 1 shows, although the pipeline steps are similar, there are inherent differences stemming from different algorithms used in FSL and CONN to implement each step. Specifically, the B0 unwarping used in the original study is based on a method that applies both realignment and susceptibility distortion correction at the same time to reduce the effect of interpolation on blurring (Jenkinson et al., 2002; Jenkinson & Smith, 2001). In the RMin model, the CONN toolbox uses SPM analysis package that in turn relies on the algorithm implemented in the Fieldmap toolbox to correct the geometric distortion of the EPI images (Jenkinson, 2003; Jezzard & Balaban, 1995). Additionally, the head motion is corrected by applying a rigid body transformation, but while the original study used MCFLIRT (Jenkinson et al., 2002), the RMin model used a procedure described in (Friston et al., 1995). Coregistration of low-resolution functional images to high-resolution structural images in the original work uses the BBR method in FreeSurfer, however, the RMin model uses a modified version of a prior work by Collignon and colleagues (A. Collignon et al., 1995) with a change in the interpolation technique for a smoother cost function and faster convergence.

In the RFull model, preprocessing was performed in subject-specific surface space using the same atlas, range, and method for bandpass filtering and detrending as the original paper. However, in this model, we supplemented the preprocessing steps originally included in the primary study with additional protocols to remove the residual spatial and temporal distortions still present in the data. Importantly, the RFull model additionally corrected for the susceptibility distortion-by-motion interaction.

Table 1 - Side-by-side Comparison of the 3 Pipelines under Study. Both (Min and Full) Replication Models used CONN toolbox vs FSL toolbox in the original paper. In the RMin model, the goal was to maintain the same preprocessing steps as the original paper, although the implementation of these steps was different between the 2 toolboxes. The RFull model attempted to correct for the influence of additional noise and artifact sources known to be crucial in reducing the false positive rate in rsFC analysis. Differences between each replication model and original paper are highlighted in gray. Abbreviations: aCompCor = anatomical component-based noise correction, DCT = discrete cosine transform.

	Original Paper	RMin Model	RFull Model
Analysis Tool	FSL FEAT 6.00 and FreeSurfer 5.3.0	CONN 20.b/SPM12 and FreeSurfer 7.1.1	CONN 20.b/SPM12 and FreeSurfer 7.1.1
Preprocessing Space	Subject-specific Volumetric	Subject-specific Volumetric	Subject-specific Surface-based
Atlas	Desikan-Killiany	Desikan-Killiany	Desikan-Killiany
Static Fieldmap Correction	Yes (Jenkinson 2001 & 2002)	Yes (Jezzard 1995 & Jenkinson 2003)	Yes (Andersson 2001)
Fieldmap-by-motion Interaction Correction	No	No	
Realignment	Yes (Jenkinson 2002)	Yes (Friston 1995)	
Slice-timing Correction	No	No	Yes
Coregistration to Subject-specific Volumetric Space	Boundary-based Registration (Greve 2009)	Rigid Body Transformation (Collignon 1995)	Rigid Body Transformation (Collignon 1995)
Resampling to Subject-specific Surface Space	N/A	N/A	Yes
Motion Parameters Regression	Yes	Yes	Yes
aCompCor	No	No	Yes
Scrubbing	No	No	Yes
Effect of (Rest) Session	No	No	Yes
Band-pass Filtering	Yes (0.01-0.1 Hz) DCT (performed by CONN)	Yes (0.01-0.1 Hz) DCT	Yes (0.01-0.1 Hz) DCT
Temporal Filtering Done After Regression	Yes	Yes	Yes
Detrending	Yes	Yes	Yes

RFull model combined the static fieldmap correction with realignment and susceptibility distortion-by-motion interaction correction into a single step in CONN, which uses SPM12 Realign & Unwarp procedure (Andersson et al., 2001). The susceptibility distortion-by-motion interaction is the degree to which motion interacts with the deformation field and is approximated by the derivative of the deformation field in relation to the motion. Neither the original paper nor the RMin model incorporated correction for this interaction term.

Additionally, the RFull model corrected for the temporal offset in slice acquisition times (Henson et al., 1999). Scrubbing was also performed in CONN to identify potential outlier scans and temporally regress them out. A scan was considered an outlier whenever the global BOLD signal changed more than 5 standard deviations or when a composite motion measure exceeded 0.9 mm. To calculate this motion measure, CONN assumes a 140x180x115 mm bounding box around the brain and the composite motion measure is computed as the largest displacement among six points each being placed at the center of 6 faces of the bounding box. The rsfMRI data was then resampled at the location of surface projections estimated for each subject using FreeSurfer. Also, since no physiological data was recorded during the acquisition, in the RFull model, we decided to utilize the anatomical component-based noise correction (aCompCor) procedure (Behzadi et al., 2007). In this method, noise is modeled from the white matter and cerebrospinal fluid areas, as the average BOLD signal as well as the Principal Component Analysis first 4 components of the BOLD signal in these areas. These noise components were temporally removed using a general linear model, along with the previously extracted motion parameters and scrubbing confounds. Finally, the resting session block was convolved with the hemodynamic response function and modeled as another source of noise to account for the initial magnetization transients.

2.2.3 Replicated and Novel Analyses Performed

Similar to the original paper, for the replication streams, Pearson correlation coefficients between ROI pairs were calculated and Fisher z-transformed to ensure a normal distribution. Each subject's Fisher z values were then used to create between-group rsFC contrast matrices by applying two-sample t-tests to z values across the 2 groups for each connection pair. The resulting p -values of the contrasts were thresholded for $p < 0.05$ to yield uncorrected results for the rsFC matrices. Since less than half of the connection pairs ($68 \times 67 / 2 = 2278$) were redundant in each rsFC matrix, we merged the positive ($EB > SC$) and negative ($EB < SC$) matrices together in a single rsFC map that contained both contrasts. This combined rsFC matrix was created for the results of both replication models and is a reproduction of Figure 3A in the original paper. In addition, to facilitate the comparison between the replication and the original work, we calculated the density of each of the resulting connectivity matrices by finding the percentage of connections that survived the thresholding ($p < 0.05$) for each pipeline and contrast. The number of connections in the replication work that survived this threshold and were common with the results from the original work was also calculated as the overlap with the original (OWO) results for each replication pipeline and contrast. Similarly, the percentage of such overlap (OWO%) was also computed as the percentage of thresholded results in the original work that are commonly discovered in the corresponding replication results. The calculations of network density and overlap were not a part of the original article.

In addition to replicating the mentioned figures in the original paper, we inspected the distribution of each group's effect size (z values) that further illustrated the effect of each of the 3 pipelines. Another quantity we examined that was not in the original article, was the network density that was calculated for each group and each pipeline. The density was computed in two

ways by finding the percentage of connections that either passed the uncorrected thresholding ($p < 0.05$) or the multiple comparison FDR correction, out of all the possible connections in the network. Finally, for each group and each analysis stream, the top 1% of all the z values for each pipeline and subject group were extracted and displayed in the corresponding circular connectograms. Overlap of the top 1% of the z values in the replication works with the original result was also computed and reported.

2.3 Results

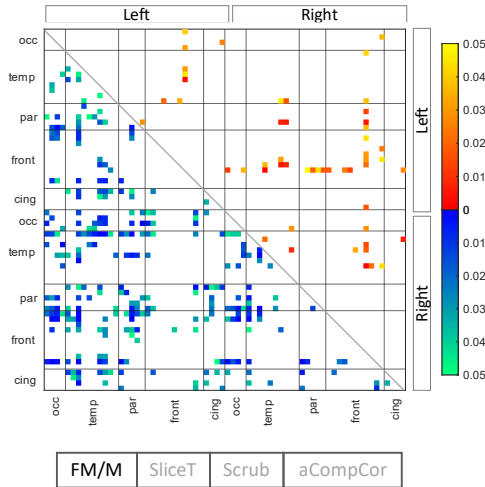
2.3.1 Replication of Between-group Contrast Results

We initially aimed to recreate the connectivity matrices for the positive ($EB > SC$) and negative ($EB < SC$) contrasts as had been presented in Figure 3A of the original work. The rsFC matrices containing uncorrected p -values ($p < 0.05$) from the original and replication pipelines are indicated in Figure 6A-C, where the warmer and colder colors represent $EB > SC$ and $EB < SC$ contrasts, respectively. The main preprocessing steps incorporated in each pipeline are also recorded below each matrix. Both the RMin and RFull models present different results compared with the original paper. Although, the RMin model produced connection pairs that were shared with the results of the original work, mainly involving the frontal (for $EB > SC$) and temporal areas (for $EB < SC$). The density of each network and the (percentage of) overlap with the results from the original work were also computed for each contrast. The density of the positive contrast results was relatively unchanged in the RMin model compared to the original results (2.41% vs 2.28%) with uncorrected results appearing mainly in the frontal lobe in both cases.

D = 12.03%
M = 274

A Original Paper

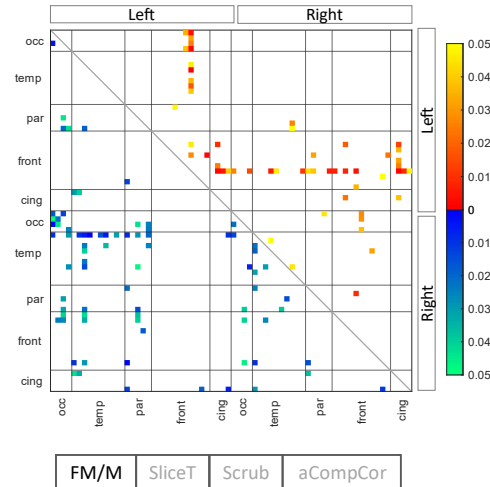
D = 2.28%
M = 52



D = 3.42%
OWO = 57
OWO% = 20.80%

B Replication (Min)

D = 2.41%
OWO = 15
OWO% = 28.85%



D = 5.93%
OWO = 30
OWO% = 10.95%

C Replication (Full)

D = 6.89%
OWO = 5
OWO% = 9.61%

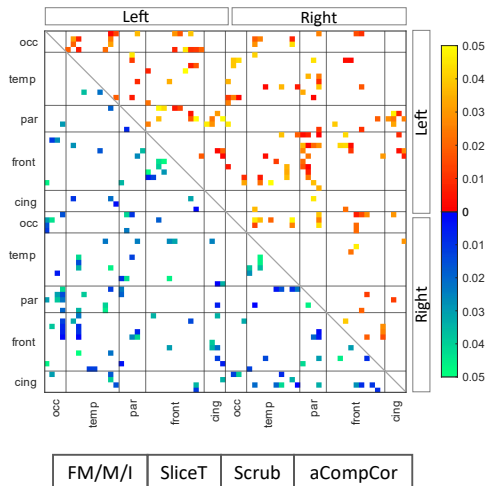


Figure 6 - Between-group Contrast Results for the 3 Preprocessing Pipelines. Between-group EB>SC (warmer colors) and EB<SC (colder colors) FC contrast results are shown for the original paper (A), the replication min model (B) and replication full model (C). The EB>SC network density remained relatively unchanged for the replication min model while increased in the replication full model compared with the original work. The EB<SC network density decreased in both replication models. Overall, the uncorrected FC network in the replication full model showed less overlap with the results from the original work compared with the replication min model. Abbreviations: FM=fieldmap correction, M=motion correction, I=fieldmap-motion interaction, SliceT=slice-timing correction, Scrub=scrubbing, aCompCor=anatomical component-based correction, D=density, M=number of uncorrected pairs in the original work, OWO=overlap with the original, %OWO = percentage of overlap with the original.

On the other hand, the density of the negative contrast results declined in the RMin model vs the original results (3.42% vs 12.03%). The results of the RFull model in Figure 6C showed an increase in the network density for positive contrast (6.89% vs 2.28%) and a decrease for the negative contrast (5.93% vs 12.03%). Overall, the RMin model presented a higher overlap of both positive and negative contrasts with the original results (28.35% and 20.80% respectively) compared with the RFull model (9.61% and 10.95% respectively). As explained in section 2.2.1, the FDR correction presented in Figure 3B of the original work was determined to be invalid and as a result, was not considered for replication in this study.

Figure 7 shows the uncorrected ($p < 0.05$) results, for the 2 contrasts in the form of circular connectograms for each of the 3 pipelines under study. Each connectogram incorporates 68 ROIs extracted from Desikan-Killiany atlas, comprising frontal, cingulate, temporal, parietal, and occipital lobes. The left and right hemispheres of the graph represent ROIs in the left and right hemispheres of the brain. The connections between ROIs are color-coded depending on the magnitude of p -values for a more granular representation of the uncorrected results. This representation was created to provide a direct comparison with Figures 5C and D in the original paper. The description of the ROI acronyms can be found in Table 3 in Appendix A. For a close-up presentation of a connectogram ring illustrating ROI elements, please see Appendix H.

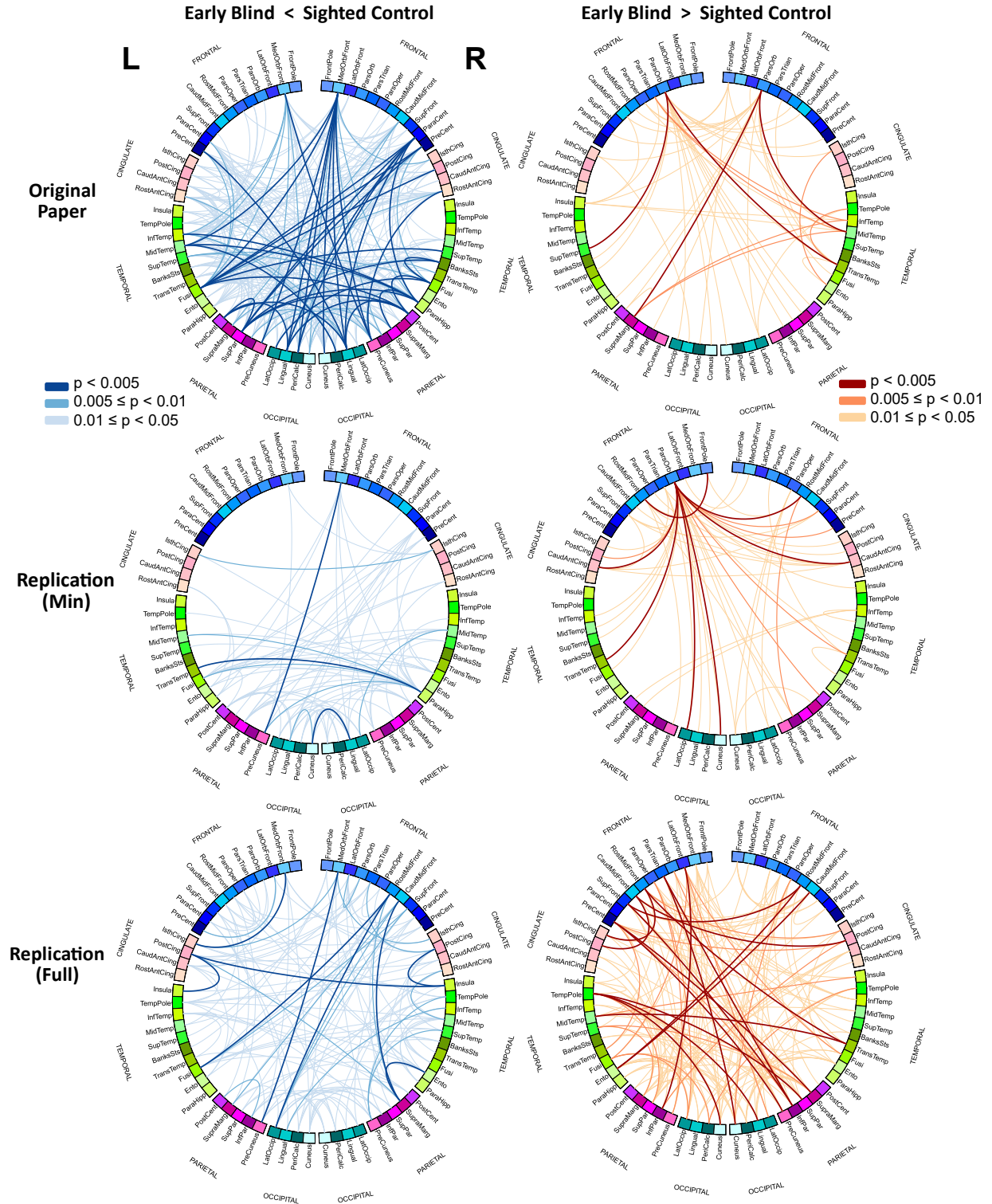


Figure 7 - Circular Connectograms of Uncorrected Connections. Circular connectograms of the uncorrected connections ($p < 0.05$) further illustrates the difference between the pipelines' outcomes. Each connectogram is composed of 68 ROIs extracted from Desikan-Killiany atlas with ROIs from left and right brain hemispheres represented on left and right separately. See Appendix A for ROI names abbreviations. For a close-up presentation of a connectogram ring illustrating ROI elements, please see Appendix H.

2.3.2 Effect of Pipelines on Individual Groups

To further analyze the effect of the three different analysis streams, we inspected how each of the approaches influenced the distribution of the effects (z values) as shown in Figure 8A and B for the early-blind and control study groups. For both groups, the z values resulted from the original work (shown in red) and the RMin model (shown in violet) are centered around more positive z values (0.37 and 0.68 for SC and 0.32 and 0.68 for EB, for the original paper and RMin model respectively), compared to RFull model where z values are centered closer to zero for both groups (0.02 for SC and 0.01 for EB).

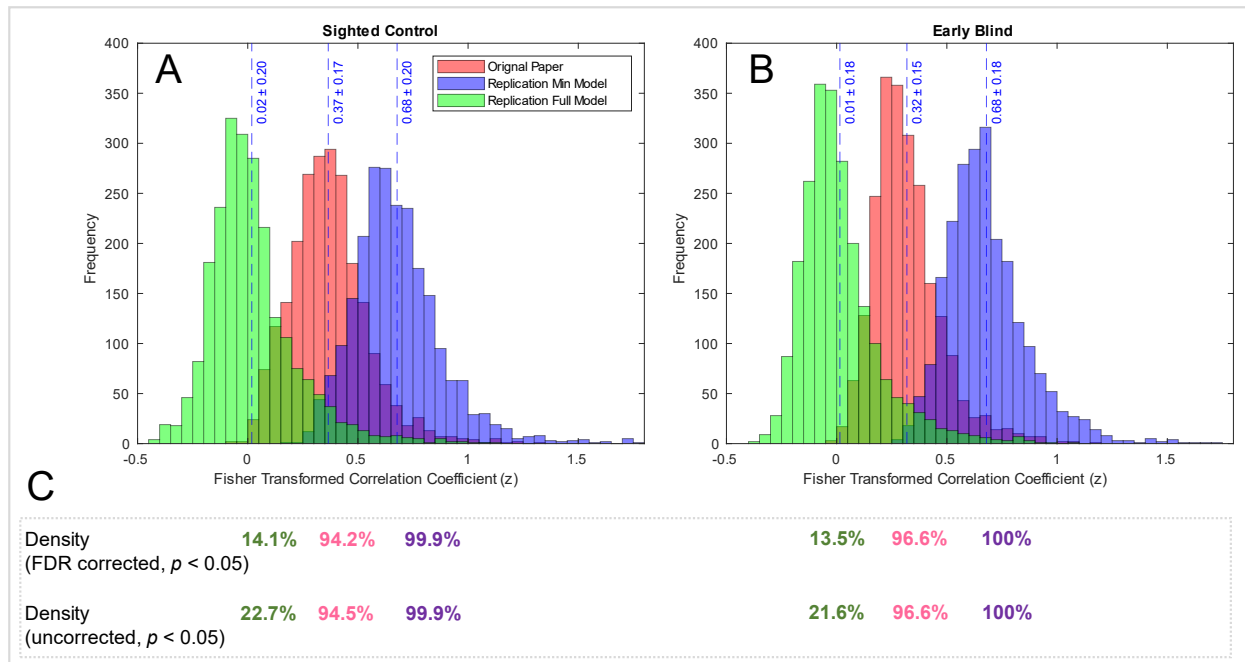


Figure 8 - Distribution of FC Effects for individual Groups. The distribution of FC effects (z values) is shown for SC (A) and EB (B) groups. While the results of the original study and the replication min model are centered around more positive z values, the replication full model shifted the distribution more towards zero. The density of the (corrected and uncorrected) network shown in (C) was affected by the selected preprocessing pipeline, with the original work and replication min model presenting density closer to 100% and the replication full model presenting a drastically reduced density.

As opposed to the between-group contrast results for rsFC analysis, the individual group results yielded connections that passed the multiple comparison correction. The density of the functional

connectivity (FC) networks after thresholding (uncorrected, $p < 0.05$) and after correction for multiple comparisons (FDR, $p < 0.05$) is summarized for each pipeline and group in Figure 8C. The density of the FC network followed the same trend as the z-distributions, with the RFull model presenting a drastically reduced network density for both corrected and uncorrected results (14.1% and 22.7 in SC, 13.5% and 21.6% in EB), compared with the network density of corrected and uncorrected results from the original work (94.2% and 94.5% for SC, 96.6% and 96.6% for EB) and the RMin model (99.9% for SC and 100% for EB in both corrected and uncorrected results).

2.3.3 Connection Pairs with the Largest Effects

Finally, to uncover the specific connection pairs that more strongly survive each of the three preprocessing pipelines, we identified connections that constitute the top 1% of z values for each group and each pipeline. The results are summarized in the form of circular connectograms in Figure 9. To measure the degree to which the result of each replication stream overlaps with the original pipeline, we calculated the overlap with the original as the number of common connections in the top 1% z values between the original and each replication model.

Out of the 23 connections (top 1% of all the z values) in the original work, 19 (83%) and 16 (70%) connection pairs overlapped with the top 1% z values in the RMin model for SC and EB groups respectively. There were 15 (65%) overlapping connections between the original and RFull models for either SC or EB group. Table 2 indicates the connection pairs that comprised the top 1% of effects and were shared among all the 3 pipelines for the SC and EB groups. This included both intra- and inter-hemispheric links.

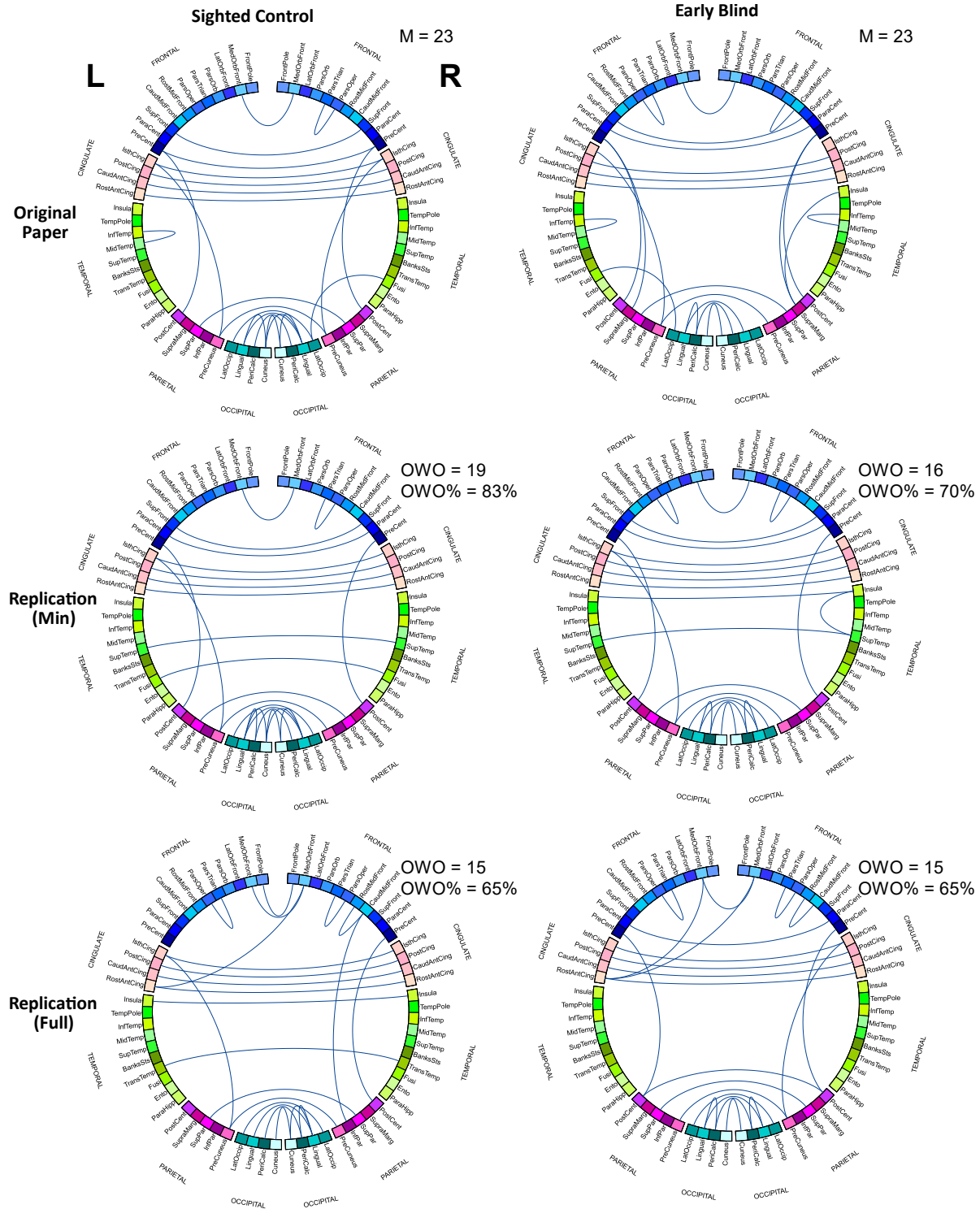


Figure 9 – Connections Pairs with the Largest Effects for Each Pipeline. Connections pairs that constitute the top 1% of z values in the z-distribution (99% percentile and higher) were identified for each pipeline and each group. These pairs are shown as links in the circular connectograms. Both RMin and RFull models present results with notable overlap with the results from the original analysis. Abbreviations: M=number of pairs identified in the original study comprising the top 1% of z values, OWO=overlap with the original (number of links in the replication models that overlap with the original results). See Appendix A for ROI names abbreviations. For a close-up presentation of a connectogram ring illustrating ROI elements, please see Appendix H.

Table 2 – Connections with the Largest Effects Independent of the Choice of Pipeline. The table contains the connection pairs that comprised the top 1% of FC effects and were common between all the 3 pipelines for sighted control and early-blind groups separately. These links connected the left and right hemispheres (inter-hemispheric) or different ROIs within each left/right hemisphere (intra-hemispheric). Abbreviations: CaudAntCing = Caudal Anterior Cingulate, IsthCing = Isthmus Cingulate, LatOccip = Lateral Occipital, MedOrbFront = Medial Orbitofrontal, PostCing = Posterior Cingulate, PreCuneus = Precuneus, PeriCalc = Pericalcarine, PreCent = precentral, PostCent = Postcentral, ParsTrain = Pars Triangularis, ParsOperc = Pars Opercularis, ParaCent = Paracentral, RostAntCing = Rostral Anterior Cingulate, SupPar = Superior Parietal.

Sighted Control				
Inter-hemispheric	frontal	cingulate	parietal	occipital
	MedOrbFront	IsthCing PostCing CaudAntCing RostAntCing	SupPar PreCuneus	LatOccip Cuneus PeriCalc Lingual
Left Intra-hemispheric	cingulate-parietal			
	IsthCing-PreCuneus			
Right Intra-hemispheric	frontal-parietal	frontal-frontal	occipital-occipital	
	PreCent-PostCent	ParsTrain- ParsOperc	Lingual-Cuneus	
Early Blind				
Inter-hemispheric	frontal	cingulate	parietal	occipital
	MedOrbFront and ParaCent	PostCing CaudAntCing RostAntCing	SupPar PreCuneus	Cuneus PeriCalc Lingual
Left Intra-hemispheric	frontal-parietal	frontal-frontal	occipital-occipital	
	PreCent-PostCent	ParsTrian- ParsOper	Lingual-PeriCalc	
Right Intra-hemispheric	frontal-parietal			
	PreCent-PostCent			

2.4 Discussion

The present replication study was not able to reproduce the results of the original paper, using either of the two pipelines used for the replication. Although the between-group contrast FC maps for the RMin model presented connection pairs implicating frontal (for EB>SC) and

temporal (EB<SC) regions similar to the findings in the original work. Overall, the overlap with the original results was less in the RFull model for both contrasts compared with the RMin model.

A closer examination of the distribution of FC effects after using each pipeline revealed that z values for both the original and RMin models were centered around more positive values whereas the RFull model shifted the effect values towards zero. This, in effect, resulted in the uncorrected and multiple comparison corrected networks that were noticeably less dense in the RFull model compared to the other pipelines under study. In other words, the RFull model reduced the number of positive (and likely false positive) findings. This is due to the expected influence of all the additional processes incorporated in the RFull model; for instance, aCompCor estimates and removes the residual effect of non-neural noise sources like cardiac signal, respiration, and head motion (Behzadi et al., 2007; Muschelli et al., 2014) and has been shown to likely increase the sensitivity and specificity of brain network's positive rsFC correlations (Chai et al., 2012). Slice timing correction, another step that is excluded from the original study, has been shown to improve the extraction of functional networks and increase the accuracy of the BOLD time series associated with each voxel by removing temporal offsets (Parker & Razlighi, 2019). Additionally, since the structural artifacts, such as motion, can interact with the magnetic field (Bijsterbosch et al., 2020), in the RFull model we incorporated the removal of susceptibility distortion-by-motion interaction. This step provides a better estimate of the fieldmap and its derivative with respect to motion and thus further reduces the residual motion-related variance (Andersson et al., 2001).

In our RMin model, when we attempted to implement the same preprocessing steps as the original work, both the between-group contrasts and the group-level results still showed discrepancies from the original study. Further investigation into the potential sources of this incongruity revealed that similar steps are in effect implemented based on different algorithms in

the two software packages used. FSL, used in the original work, implements the static field map correction and realignment based on the methods proposed by Jenkinson 2001 & 2002 (Jenkinson et al., 2002; Jenkinson & Smith, 2001) and (boundary-based) registration based on (Greve & Fischl, 2009). In contrast, CONN/SPM 12, used in the RMin model, implements each of these steps with other distinct algorithms (A. Collignon et al., 1995; Friston et al., 1995; Jenkinson, 2003; Jezzard & Balaban, 1995). Therefore, the incongruity observed between the original study and RMin model may be due to dissimilar implementations of the same steps in the two software packages, a source of irreproducibility previously highlighted in other studies (Carp, 2012b).

Besides the contribution of diverse computational schemes, another factor that can lie at the heart of the irreproducibility of the results from the original study is the low statistical power. It is reasonable that finding study participants with the specific visual deficit under study in the original paper can be complicated, nevertheless, the small sample size will result in low power. Collecting rsfMRI data for longer periods from each subject could have minimized this effect (Poldrack et al., 2017).

Interestingly, the highest FC effects (z values) appeared to predominantly belong to specific connection pairs regardless of the analysis pipeline. This demonstrates that large FC effect sizes are more likely to remain immune to the adverse effects of suboptimal preprocessing pipelines. On the other hand, these large z values likely represent the true results, as it has been previously demonstrated that the true positive findings are inclined to replicate more across studies, while this does not hold true for the false positive results (Moonesinghe et al., 2007). The observed overlap in connections among different preprocessing streams in this study may underscore the importance of results verification across different pipelines in search of the true results; an ultimate goal particularly critical for studying clinical populations.

It is important to emphasize that the findings of this replication study are limited by the specific computational toolboxes used, CONN and SPM, and their release versions. In addition, the small number of participants and the inherently low statistical power of the study may hinder any reproducibility effort, regardless of the analytical pipeline used. Lastly, although the three processing streams under study were conceptually and qualitatively compared throughout the study, the main goal of this article has been to investigate whether the original results can be achieved by utilizing a different set of computational streams on the same data.

2.5 Conclusion

The aim of our study was to conceptually replicate the rsFC findings of an original study of early ocular blindness (Bauer et al., 2017). We were not able to fully replicate the results in the original study with our two proposed preprocessing pipelines, partly due to the addition of more rigorous steps for the removal of the noise and artifacts, and also likely due to different implementations of the same steps. Importantly, we highlighted some specific functional connection pairs in the study group that tend to arise regardless of the computational stream.

Chapter 3 - Sight Restoration Reverses Blindness-induced Cross-modal Functional Connectivity Changes between the Visual and Somatosensory Cortex at Rest

A version of this work was published in the journal Frontiers in Neuroscience in Perception

Science section

Negin Nadvar, Noelle Stiles, Jeiran Choupan, Vivek Patel, Hossein Ameri, Yonggang Shi, Zhongming Liu, John Jonides and James Weiland

3.1 Introduction

Visual impairment has a limiting effect on the quality of life for the affected individuals by restricting their day-to-day activities including interaction with the environment and social opportunities. Vision rehabilitation teaches skills that help individuals play a more active and satisfying role in society (R. Bourne et al., 2012; Khorrami-nejad et al., 2016; National Academies of Sciences Engineering and Medicine et al., 2016), but rehabilitation does not improve vision itself. Sight restoration approaches have reached clinical trials and, in some cases, regulatory approval. Gene therapy (Apte, 2018; Ashtari et al., 2017; Bennett et al., 2016; Lee et al., 2019; Wang et al., 2020), optogenetic (McClements et al., 2020; Simon et al., 2020), and retinal prostheses (BLOch et al., 2019; Cheng et al., 2017; Fernandes et al., 2012; Stingl et al., 2013; Zrenner, 2013; Zrenner et al., 2011) have all been tested in patients with retinal disease. The degree of vision restoration provides patients with improved mobility and object detection. However, in most cases, recipients of these new therapies still have a significant visual impairment in spite of

the regained function. While behavioral experiments that assess functional vision in real-world scenarios are the most important endpoints, measures of the cortical response to vision restoration can provide complementary information that explains clinical outcomes and guides future development of improvements in these therapies.

Finding biomarkers that help gauge patients' improvement during post-sight restoration rehabilitation is a consequential need. The fMRI BOLD activation response has been utilized for assessing brain plasticity following sight restoration. One study showed that prolonged use of the Argus II implant increased the fMRI BOLD response to visual stimuli in the primary visual cortex (Castaldi et al., 2016). Another neuroimaging experiment performed on retinal gene therapy patients demonstrated significantly enhanced fMRI activation in the visual cortex in response to visual checkerboard stimulation (Ashtari et al., 2017), compared to the same measurement made in the same individuals prior to therapy.

Resting-state functional connectivity has been used to gauge the plastic changes in the brain following sensory deprivation. This approach has been extensively studied with different analysis methods (Barkhof et al., 2014; Biswal et al., 1995; Bullmore & Sporns, 2009; Iraj et al., 2016; K. Li et al., 2009; Lv et al., 2018; Peltier & Shah, 2011; Seitzman et al., 2019; van den Heuvel & Hulshoff Pol, 2010; Van Dijk et al., 2010). The rsFC analysis reveals the relationship between spontaneous brain activity in different parts of the brain in the absence of any cognitive or sensory stimulation. Numerous rsFC studies have inspected alterations in functional connectivity between the visual cortex and other sensory or cognitive areas of the brain following vision loss. This literature robustly shows that following visual sensory deprivation in congenital, early, and late blindness, rsFC decreases both within the visual cortical areas (Dai et al., 2013; Heine et al., 2015; Hou et al., 2017; Huang, Zhou, et al., 2019; Liu et al., 2008; Murphy et al., 2016; Qin et al., 2014;

Y. Yu et al., 2020) and between the visual cortex and other sensory (somatosensory or auditory) cortices (Bauer et al., 2017; Dai et al., 2013; Huang, Zhou, et al., 2019; Liu et al., 2008; Murphy et al., 2016; Striem-Amit et al., 2015b; Wen et al., 2018; Wittenberg et al., 2004a; C. Yu et al., 2008a). In contrast, the rsFC between the visual cortex and cognitive regions of the brain has been shown to be enhanced following vision loss (Bauer et al., 2017; Heine et al., 2015; Murphy et al., 2016; Sabbah et al., 2016, 2017; Striem-Amit et al., 2015b; Wen et al., 2018; Y. Yu et al., 2020); a phenomenon that has been attributed to increased top-down influence in visual cortex due to visual deprivation.

In contrast to the abundant literature supporting the functional plastic changes in the brain following blindness, there are few studies that have examined alterations in functional connectivity after sight restoration. A single analysis study on the effect of sight recovery 3 years after gene therapy application showed that rsFC between the visual and auditory areas was enhanced after sight restoration, partially reversing the effect of blindness (Mowad et al., 2020) and supporting the feasibility of using rsFC as a biomarker of vision restoration. To further investigate the relationship between rsFC and vision restoration, we studied functional connectivity in a cohort of retinitis pigmentosa patients who were implanted with the Argus II retinal prosthesis, to determine if this treatment which partially restores vision also reverses, in full or part, the plastic changes induced by loss.

3.2 Methods

3.2.1 Human Subjects

Twenty-seven subjects were included in the analysis and separated into 3 groups: 10 healthy controls (HC - 5 females, age 54.50 ± 13.84), 10 RP blind (RP - 3 females, age 51.10 ± 12.92), and 7 Argus II subjects (3 females, age 64 ± 9.71). The difference in age among the groups

was insignificant ($F(2,24) = 2.40, p = 0.11$). Details of the subjects' demographic and clinical information are included in Table 4 and Table 5 in Appendix B and C. The RP subjects were all blind with visual acuity of worse than 20/200 and visual field of less than 20°, except for subject 13 that had a visual acuity of 20/80-2 and 20/50+2 and a visual field of 2° or less in both eyes. The Argus II subjects were legally blind from RP. Their baseline vision was bare light or no light perception, per the FDA-approved indication for Argus II. Twenty out of 27 subjects were recruited and consented at 2 Human Connectome for Low Vision (HCLV) data collection centers per the approved Institutional Review Board at each center: the University of Michigan (UM) and the University of Southern California (USC); this includes 3 HC, 10 RP, and 5 Argus II subjects at USC and 2 Argus II subjects at UM. The remaining 7 HC subjects' data was sourced from the Human Connectome Project for Aging (HCP-A) public database (Bookheimer et al., 2019). One additional Argus II subject's neuroimaging data was collected at USC; however, the subject was determined to be a significant outlier and was removed from the analysis. For more details, please see the Subject Outlier Identification section in Appendix E. Resting-state functional runs showing subject motion more than 1 mm in any of the x, y, and z directions were excluded from the analysis. Also, the resting-state runs were included in the analysis only if they were acquired at the beginning of the sessions before any other task performance. These criteria resulted in the exclusion of 22 out of 112 runs from the analysis among all the subjects in all the sessions.

3.2.2 Argus II Retinal Prosthesis

The Argus II retinal prosthesis is an epiretinal implant, which was the first retinal prosthesis with FDA approval obtained in 2013 and CE approval in 2011. The system is composed of an internal implant unit and an externally worn unit. The internal system contains an intraocular array with an area of 3.5 by 6 mm, covering an area of 11x19 degrees of the visual field. The array is a

6x10 grid of platinum surface electrodes of 200 μm diameter, spaced 575 μm apart. The supporting electronic case is sutured to the sclera and inductively receives power/data from the external system. The external unit contains a video camera mounted on a pair of glasses worn by the patient, a video processing unit (VPU), and a battery. The camera transmits the visual data to VPU where data is processed, sent to the external coil, and relayed to the internal circuitry. RP patients using Argus II were able to perceive motion (Dorn et al., 2013a) and showed the best visual acuity of 20/1260 (Humayun et al., 2012).

3.2.3 Experimental Paradigm

The neuroimaging experiment from the UM, USC, and HCP-A data followed the same paradigm. Each scan visit was composed of two scanning sessions separated by a break. The MRI scans were composed of structural and rsfMRI scans. During the rsfMRI runs, subjects were asked not to engage in any task while lying in the scanner. Upon the completion of the T1W scan, the technicians reviewed the quality of structural images during the first scan session and a re-scan was performed during the second scanning session if the scan quality was deemed low from the first session. The participants completed a total of four runs of rsfMRI with eyes being open under a dark foam mask at UM and USC. This was done due to the inability of blind subjects to fixate. For HCP-A rsfMRI runs, healthy controls were asked to fixate while lying in the scanner.

3.2.4 Data Acquisition

For each subject, 1 anatomical and 4 resting-state functional runs (2 runs per scan session) were acquired. Structural MRI scans at USC were acquired using a 3T Siemens Prisma scanner. The T1W structural scans used MPRAGE (Magnetization Prepared Rapid Gradient Echo) 3D acquisition, voxel dimension $0.8 \times 0.8 \times 0.8 \text{ mm}^3$, TI (inversion time)/ TE (echo time)/ FA (flip

angle) = 1000 ms/ 2.22 ms/ 8°. The resting-state functional runs were obtained with 2D gradient-echo (GRE) echo-planar imaging (EPI) acquisition with multiband (MB) acceleration factor = 8, voxel size 2 x 2 x 2 mm³ with TR (repetition time)/ TE/ FA = 800 ms/ 37 ms/ 52° with a total of 420 volumes for each run. At UM, T1W images were obtained with a 3T GE MR750 scanner with 3D Spoiled Gradient Echo (SPGR) with inversion recovery magnetization preparation, voxel size 0.5 x 0.5 x 0.8 mm³, TI/ TE/ FA = 1060 ms/ Min Full/ 8° ('Min Full' refers to the minimum TE to obtain full echo acquisition). Functional runs were acquired with interleaved GRE-EPI, MB = 6, voxel size 2.4 x 2.4 x 2.4 mm³, and TR /TE/ FA = 800ms/ 30ms/ 52°. Field maps were acquired and used to correct the geometric distortion in EPI due to magnetic field inhomogeneities. Scan parameters for HCP-A structural and functional data were identical to USC parameters (Harms et al., 2018). Harmonization of the data between the HCLV collection centers at USC and UM was investigated using the data from a traveling subject and a Function Biomedical Informatics Research Network (fBIRN) phantom as a part of a previous study (Nadvar et al., 2019). Refer to Appendix D for a summary of the results of this analysis.

3.2.5 Data Preprocessing

Field inhomogeneity inside the scanner (fieldmap) was calculated with the FSL Topup function and an in-house Linux bash and MATLAB script. Using the Realign and Unwarp function in combination with the Fieldmap toolbox in SPM, the susceptibility distortion, motion artifact, and susceptibility-by-movement interaction were corrected. The first 12 volumes were removed to ensure reaching steady state (and additionally the last 46 volumes were removed for HCP-A data due to a different length) yielding 420 volumes for each functional run. The reference volume for motion and field map correction was the 10th volume for UM data and the single-band reference volume (SBRef) for USC and HCP-A data. Motion correction parameters were created

and used as regression covariates. The origin of the structural and functional images was manually set at the anterior commissure to enhance the outcome of the co-registration and normalization to the standard template. Potential outlier volumes were flagged using MATLAB CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012a) with the global BOLD signal above 5 standard deviation or frame-wise displacement of more than 0.9 mm, creating the scrubbing regression covariate. Using indirect segmentation and normalization in CONN, the functional and anatomical images were first co-registered using affine transformation. The structural image was then normalized to standard MNI space and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). This process continued iteratively until convergence, yielding non-linear spatial transformation parameters that were then applied to both anatomical and functional images; these images were resampled to isotropic 1 mm and 2 mm voxels, respectively. Functional images were spatially smoothed with a Gaussian kernel with 4 mm full-width-at-half-maximum (FWHM). The anatomical component-based noise correction (aCompCor) was also implemented using CONN to further minimize physiological noise; the first 5 principal components of the BOLD in WM and CSF were extracted to be used as confounding effects. All the confounding factors, including the 6 translation/rotation motion parameters and their derivatives, scrubbing covariate and WM/CSF covariates were linearly regressed out of the BOLD signal. Finally, the time series were bandpass filtered between [0.008 0.09] Hz and linearly detrended.

3.2.6 Statistical Analysis

Seed-based connectivity (SBC) maps were calculated using CONN; bivariate Pearson correlation coefficients between the average BOLD signal in primary visual cortex (V1) ROI and the BOLD time series in the rest of the brain were first computed and Fisher z-transformed. Group-level SBC maps were created by applying a one-sample t-test to the Fisher's z values associated

with each voxel across subjects. A two-sample t-test was used for contrast analysis between the groups. The second-level analysis results were corrected for multiple comparisons using cluster-level inference to control for false positives. Parametric statistics were applied using Gaussian Random Field theory (Worsley, 1996) with an uncorrected voxel threshold of $p < 0.001$ and a cluster-level threshold of $p < 0.05$ for cluster size FDR correction. ROI-ROI functional connectivity between V1 and post-central gyrus (PostCG) was also calculated as Fisher-transformed correlation coefficients between these 2 ROIs BOLD time series, representing the effect size. Additionally, we looked at the spread of significant FC in a target ROI. This was defined as the cortical volume (in mm^3) with a statistically significant connection to the seed in group-level FC maps corrected at the cluster level. Considerations of data normality, effect size, and power are further investigated as a part of Appendix F.

3.2.7 ROI Selection

The 2020 Julich-Brain atlas (V2.9), an intricate volumetric atlas based on the cytoarchitecture of the brain (Amunts et al., 2020), was used for the definition of ROIs. Given our a-priori hypothesis regarding the primary visual and somatosensory cortex, we extracted these 2 ROIs from the atlas: the V1 was formed by combining the respective left and right ROIs from the atlas. PostCG which is the location of the primary somatosensory cortex was defined by merging the area 1, 2, 3a, and 3b on the left and right sides as defined by the atlas.

3.3 Results

3.3.1 How Does RP Blindness Affect Functional Connectivity to V1 at Rest?

In order to evaluate the impact of blindness on functional connectivity with the primary visual cortex, we obtained the SBC maps for HC and RP groups as well as the between-group contrast as indicated in Figure 10 (A), (B) and (C), each corrected for multiple comparisons using Gaussian Random Field Theory with uncorrected voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ FDR corrected for cluster size. In both the HC and RP groups, V1 showed strong functional connectivity to different parts of the occipital cortex, primary and secondary somatosensory cortex as well as inferior temporal areas. Blue color-coded regions in Figure 10 (C) highlight areas in the RP group with significantly lower functional connectivity to V1 compared with HC. In the indicated seed-to-voxel functional connectivity map in Figure 10 (C), these areas overlap with parts of higher-level visual areas such as the cuneus and lateral

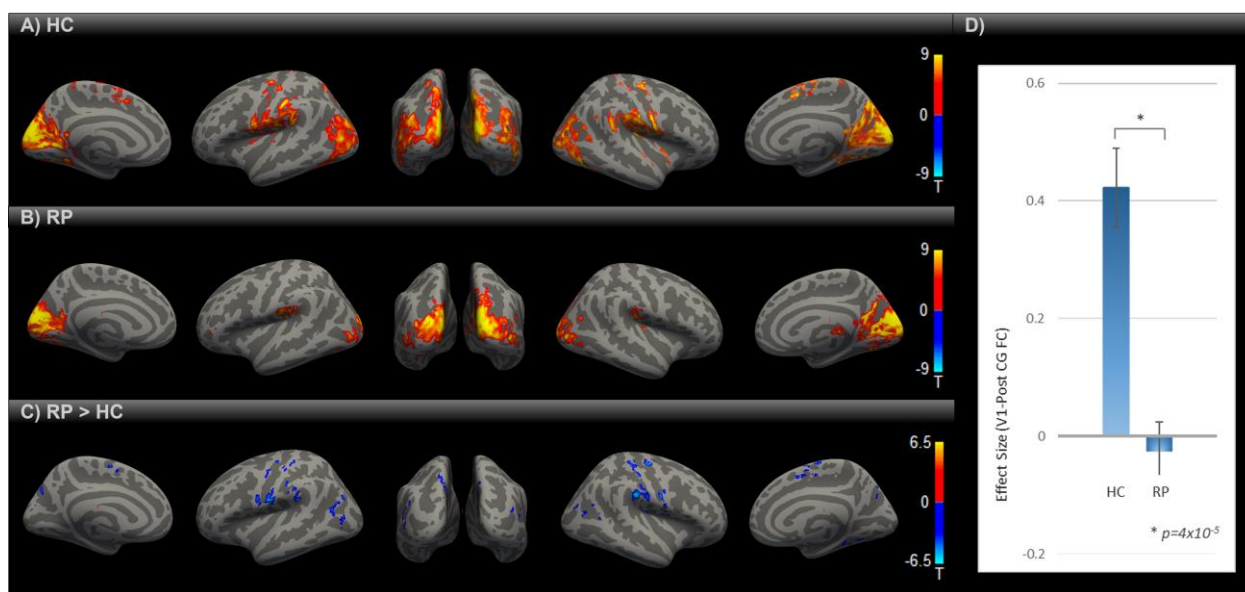


Figure 10 - Comparing rsFC between RP and HC. Group-level rsFC maps using V1 as the seed for HC (A), RP (B) and RP>HC contrast (C) were corrected for multiple comparisons using Gaussian Random Field Theory with uncorrected voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ FDR corrected for cluster size. Areas with lower rsFC to V1 covered regions of higher-level visual, primary/secondary somatosensory, motor, and parietal association cortex (blue blobs in (C)). V1-to-PostCG ROI analysis (D) showed significantly lower rsFC effect size in RP vs HC, using two-sample T-test ($t(18) = -5.39$, $p = 4 \times 10^{-5}$).

occipital cortex as well as regions in primary and secondary somatosensory areas, motor cortex, and some parietal association areas. In the ROI-to-ROI analysis (Figure 10 (D)) between V1 and PostCG, the effect size (Fisher z-transformed correlation coefficient value) was significantly lower in RP compared with HC ($t(18) = -5.39, p = 4 \times 10^{-5}$).

3.3.2 How Does Partial Sight Restoration with Argus II Alter Functional Connectivity to V1 at Rest?

We evaluated how partial sight restoration with Argus II can alter intrinsic brain connectivity in RP blindness. SBC maps for RP and Argus II (Figure 11 (A) and (B)) groups were calculated and corrected for multiple comparisons with uncorrected voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ FDR corrected for cluster size. Both groups demonstrated functional connectivity between V1 and other visual areas as well as inferior

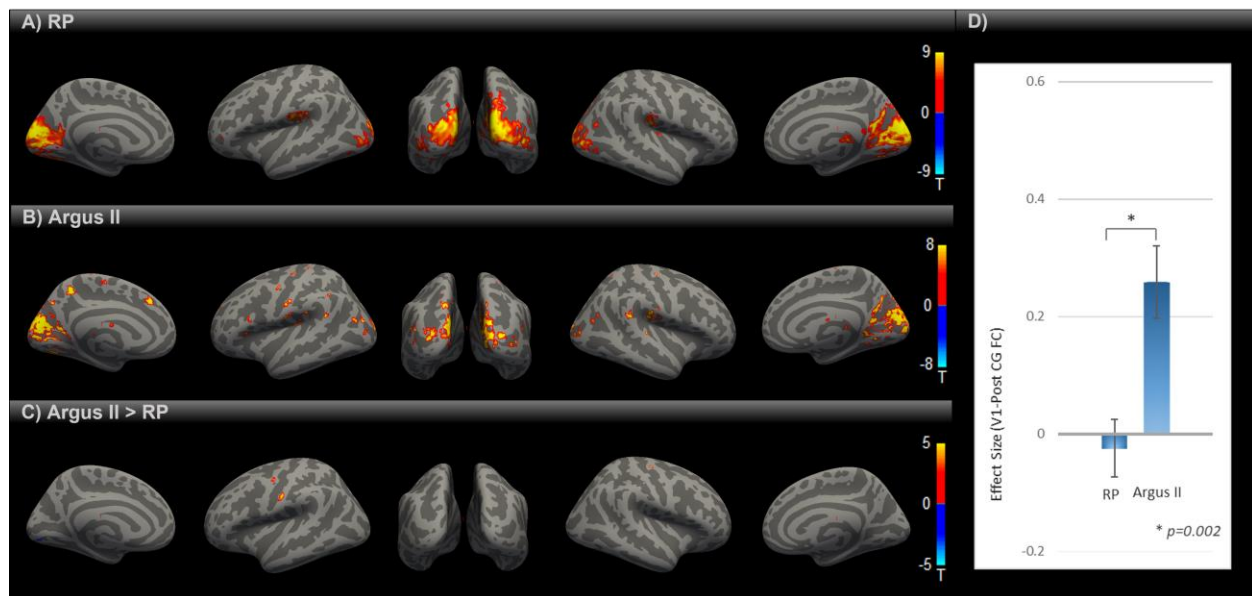


Figure 11 - Comparing rsFC between Argus and RP. Whole-brain rsFC map using V1 as the seed is calculated at the group level for RP (A) Argus II (B) and contrast Argus II > RP (C). rsFC maps were corrected for multiple comparisons using Gaussian Random Field Theory with uncorrected voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ FDR corrected for cluster size. Areas having higher rsFC in Argus II than RP involved regions in pre- and post-central gyrus. The ROI-to-ROI rsFC analysis between V1 and PostCG (D) additionally showed significant ($t(15) = 3.62, p = 0.002$) enhancement of this connectivity in Argus II compared with RP.

temporal areas. The contrast map between the two groups, corrected for multiple comparisons, similarly, is shown in Figure 11 (C). Intriguingly, the seed-to-voxel functional connectivity map in Figure 11 (C) revealed parts of primary motor and somatosensory (pre- and post-central gyrus) with enhanced rsFC to V1 in the Argus II compared with the RP group. The ROI-to-ROI analysis between our two areas of interest (V1 and PostCG) in Figure 11 (D) showed that the functional connectivity significantly increased after partial sight restoration with Argus II ($t(15) = 3.62, p = 0.002$).

3.3.3 How Close Are the Results in the Sight-Restored to the Normally Sighted?

Having observed enhanced rsFC after sight restoration as demonstrated in Figure 11, an intriguing question is whether this was a partial or full reversal when compared with normally-sighted individuals. To that end, we compared the functional connectivity maps for HC and Argus II groups (Figure 12 (A), (B) and (C)), after correcting for multiple comparisons using Gaussian Random Field Theory with uncorrected voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ FDR corrected for cluster size. The seed-to-voxel functional connectivity map in Figure 12 (C) shows that sight restoration with Argus II was not able to fully reverse the blindness-induced decrease in rsFC within the visual cortex, especially between V1 and higher visual areas, as indicated by small blue color-coded regions in medial and lateral sides of the higher-level occipital cortex. Interestingly, partial sight restoration was able to reverse alterations in V1 functional connections with pre-and post-central gyrus. As indicated in Figure 12 (D), ROI-to-ROI functional connectivity between V1 and PostCG showed no significant difference between the HC and Argus II groups in a two-sample t-test with $t(15) = -1.72, p = 0.10$.

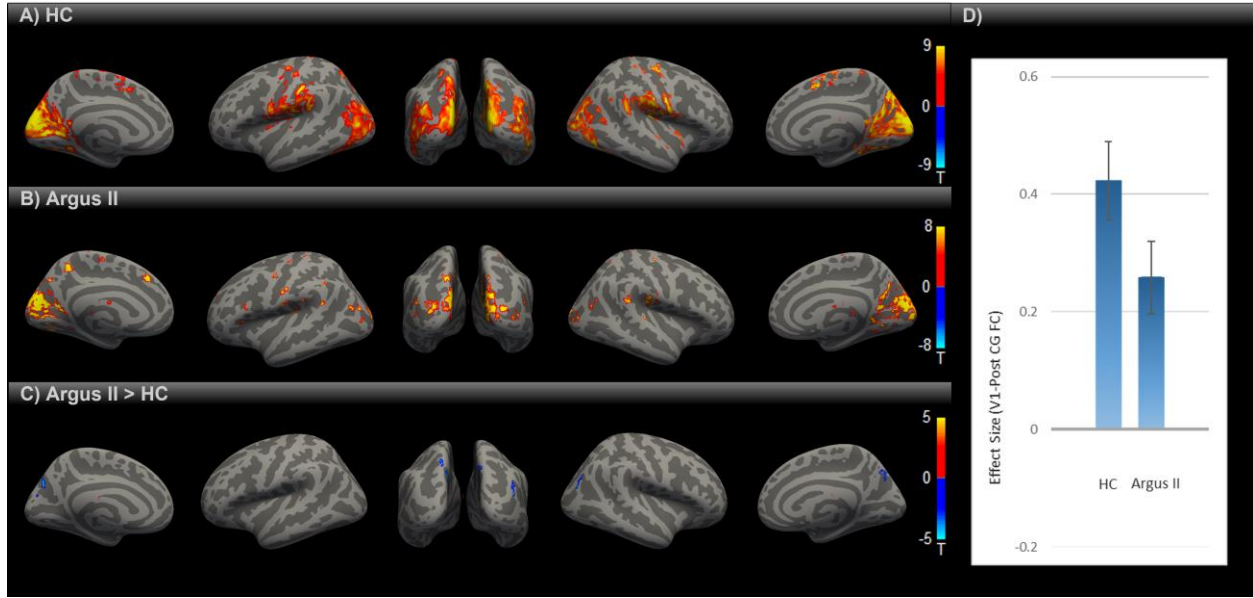


Figure 12 - Comparing rsFC between Argus II and HC. Using the V1 seed, the group-level rsFC maps for Argus II (A), HC (B) and Argus II > HC contrast (C) were corrected for multiple comparisons using Gaussian Random Field Theory with uncorrected voxel-level threshold of $p < 0.001$ and cluster-level threshold of $p < 0.05$ FDR corrected for cluster size. As shown in the contrast map, the areas depicting lower rsFC to V1 were found in some higher-level visual areas (shown in blue). The ROI-to-ROI rsFC analysis (D) revealed no significant difference in the V1-PostCG rsFC effect size between Argus II and HC groups, $t(15) = -1.72$, $p = 0.1$.

3.3.4 Effect of Blindness and Sight Restoration on the Spread of Significant Functional

Connectivity to V1

In order to evaluate how blindness and sight restoration affect functional connectivity, one approach is to look at the strength of this connection as described in Figures 1 through 3. Another way of evaluating such alterations is to consider how broadly the connectivity patterns spread over a target ROI. To examine this, we defined another metric that measures the extent of significant functional connectivity as the volumetric area in the target ROI that has a significant functional connection to the source ROI. Using V1 as the source ROI and PostCG as the target ROI, we computed the extent of significant connections for HC, RP, and Argus II groups, as indicated in Figure 13 (B). Figure 13 (A) shows that the calculated volumetric spread of functional connectivity

to V1 in PostCG was 5961 mm³ in HC group. This metric decreased to 0 mm³ for RP and again increased to 842 mm³ for the Argus II group.

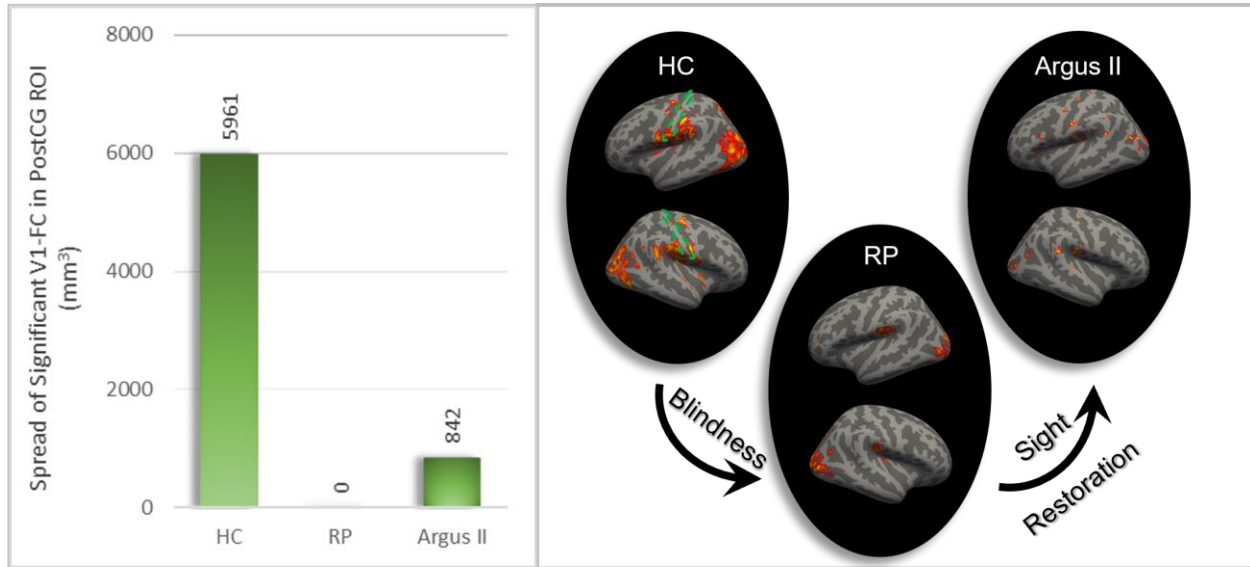


Figure 13 - Extent of rsFC to V1. The volumetric extent in PostCG that shows significant rsFC to V1 as the seed was calculated in mm³ (A). This spread of connectivity drastically reduced after blindness and partially increased following sight restoration in Argus II. Areas in the whole brain with significant rsFC to V1 for each of the 3 study groups are shown on the right (B). The dotted green area represents PostCG/primary somatosensory cortex boundary.

3.4 Discussion

In this study, we investigated how the loss and the subsequent re-introduction of visual input can affect visual-somatosensory functional connectivity at rest. At the group level, the healthy controls demonstrated areas of the somatosensory cortex with significant rsFC to V1. In the blind RP group, these regions were significantly reduced in rsFC with V1. Additionally, we evaluated the effect of partial sight restoration with the Argus II retinal prosthesis at the group level. The results clearly indicated a change in the opposite direction as a significant increase in visual-PostCG rsFC in Argus II compared with the blind RP group. Importantly, this level of

increase rendered the somatosensory-visual rsFC in the Argus II group at a level close to the healthy controls, as no significant difference in rsFC was observed between the two regions in the contrast analyses, with either connectivity maps or ROI analyses. Additionally, the extent of regions in the somatosensory cortex with significant rsFC to V1 followed the same change in direction as the strength: reduction in the RP blind compared with HC and enhancement in Argus II versus the fully blind RP group. Visual-somatosensory rsFC values for individual subjects are included in Appendix I, Table 9.

We focused on visual-somatosensory rsFC. This choice allowed us to take advantage of the many prior studies of the effects of blindness on visual-somatosensory cross-modal plasticity, against which we could compare our findings. We observed that RP blindness reduces visual-somatosensory rsFC; this finding is consistent with many prior experiments that evaluated rsFC in late-blind individuals (Dai et al., 2013; Huang, Zhou, et al., 2019; Murphy et al., 2016; Wen et al., 2018; Wittenberg et al., 2004a). There is also similar evidence for this reduction in rsFC in the congenitally (Murphy et al., 2016; Striem-Amit et al., 2015a) and early-blind (Bauer et al., 2017; Liu et al., 2008; Wittenberg et al., 2004c) individuals. Strikingly, some other studies on the blind observed the involvement of the visual cortex in processing of language and mathematics as well – examples of higher-level cognitive tasks (Bedny et al., 2011; Kanjlia et al., 2016). rsFC has been shown to increase between visual and cognitive areas following blindness (Bauer et al., 2017; Heine et al., 2015; Murphy et al., 2016; Sabbah et al., 2016, 2017; Striem-Amit et al., 2015a; Wen et al., 2018). Such an effect on functional connectivity following vision loss has been attributed to an increase in top-down impact on the visual cortex. One model that has been proposed to explain these unexpected alterations is the reverse hierarchy. In normally-sighted individuals, as the information is fed forward through the visual hierarchy, more and more complex and abstract

visual features will be processed, which will then serve as an input to cognitive regions such as attention and decision. The feedback connection from higher to lower regions in the visual hierarchy serves to enforce selective attention and learning. It has been proposed that in early-blind individuals, this reverse connection serves to further elaborate information from higher-level visual areas and provide an input containing abstract information into the lower-level visual areas, giving rise to cognitive processing in these regions. Reverse hierarchy, however, has its own limitations in explaining the observed cognitive processing in the visual cortex (Bareket et al., 2017; Fine & Park, 2018).

Previous studies attempted to evaluate brain alteration following visual restoration by using fMRI BOLD activation as the metric. A study looked at the tactile-evoked cross-modal BOLD responses in occipital regions in 2 Argus II prosthesis patients (S. Cunningham et al., 2015), one 5 weeks and the other 15 weeks following implantation. The qualitative assessment of their results indicated that the strength and extent of activation in these subjects seemed to be affected by the time since implantation for these 2 cases, with the subject with a longer time post-surgery demonstrating tactile-evoked visual activation levels closer to the group with normal vision. However, given that only two subjects were evaluated, no firm conclusions can be drawn from this study. In another study, auditory-evoked cross-modal BOLD responses were evaluated in patients sight restored using RPE65 gene therapy technology (Mowad et al., 2020). In their qualitative comparison of the study groups, they found that the baseline blind RPE65 subjects had enhanced activations within the bilateral visual cortices due to auditory stimulus, whereas 3 years later these activation patterns were significantly elevated. Furthermore, in their study, the visual-auditory rsFC was qualitatively shown to be reduced in the baseline blind RPE65 subjects compared to healthy controls, whereas it slightly increased 3 years following gene therapy compared to baseline

RPE65 subjects. Although the results were based on a qualitative comparison of activation maps between groups and not based on group-level contrast maps, their findings have important scientific implications.

Similar to the observations using gene therapy, our study revealed enhanced rsFC between V1 and PostCG following partial sight recovery with Argus II retinal prosthesis. This represents a reversal of the cross-modal plasticity that was initially induced by blindness, as manifested at rest by using functional connectivity as the metric. The noted alteration in rsFC is remarkable in that it was observed despite the fact that retinal prosthesis patients regain merely basic vision and only occasionally use their prosthetic implant. It is important to note that functional connectivity during rest was used as the metric in our study to investigate plastic changes in the brain following vision loss and restoration. How functional plastic changes manifest during task execution has been shown to be different from rest in blindness. In a study on early-blind individuals, Pelland and colleagues (Pelland et al., 2017) looked at the apparent disagreement between task-dependent activation or connectivity and resting-state functional connectivity in the blind, i.e. increase in cross-modal responses in the visual cortex during a non-visual sensory task and the decrease in rsFC between non-visual sensory and visual cortex. They hypothesized that such a decrease in rsFC in early-blind individuals may be due to the involvement of the visual cortex in a larger number of processing modes during rest, when the brain is more available to explore various modes, resulting in an increase in functional connectivity variability at rest. On the other hand, increased functional connectivity during task execution might be due to brain involvement in limited modes, resulting in lower functional connectivity variability during task. Therefore, it is important to note that the rsFC for groups presented in our study does not smoothly generalize to the brain state during the execution of sensory tasks, such as tactile tasks. However, our finding

shows that rsFC could be potentially used as a measure of functional plastic changes detectable during resting state in response to visual sensory loss and restoration.

Our findings are limited by the relatively small number of participants. As such, we were unable to conduct a deeper analysis that might have revealed links between patient characteristics and rsFC. Recruitment is a challenge for any study and Argus II patients are rare. Yet, a larger study that allows stratification and correlation analysis (using patient characteristics) has the potential to provide valuable information that can benefit the on-going development of visual prostheses and other sight restoration therapies. Factors such as device usage, duration of blindness, age, and time since implantation could all conceivably play a role in the functional organization of the brain after the therapeutic intervention. Our findings can serve as a starting point for such a study or be included in a meta-analysis of other, similar studies that can increase the robustness of the results through pooling of data.

3.5 Conclusion

We showed that decreases in resting-state functional connectivity, due to blindness, were partially reversed by vision restoration. Despite advancements in vision restoration technologies, the vision provided remains well below healthy vision and patient outcomes vary greatly. To better understand this variability, metrics associated with vision improvement are essential. The rsFC is a tool that has been broadly used to track functional changes in the brain following blindness. Studies of rsFC to investigate sight recovery are relatively rare. The goal of our study was to evaluate the effect of blindness on visual-somatosensory rsFC, but also to further track changes in this quantity after partial sight restoration with Argus II retinal prosthesis. Our investigation showed that visual-somatosensory rsFC has the potential to serve as a biomarker for functional plastic changes in the brain following vision recovery.

Chapter 4 - Functional Brain Network Alterations in Response to Blindness and Sight Restoration

4.1 Introduction

Out of the five senses in humans, vision is the most crucial and complicated sense. By some estimates, vision facilitates about 80% of our daily activities, cognition, learning and perception (Ripley & Politzer, 2010). In the United States, visual impairment has affected over 7 million people, with approximately 1 million individuals in this pool declared blind (Flaxman et al., 2021). With progressive vision loss and the aging population on the rise, these figures are expected to grow. Loss of this important sense leads to an array of physical and psychological challenges in the affected individuals (Khorrami-nejad et al., 2016), by increasing the risk of falls, poor quality of life, loneliness, isolation, anxiety, and depression. Visual impairment decreases independence and autonomy and increases the cost of health care and provisions for daily activities. It has been the goal of the vision restoration community to enhance the quality of life, work opportunities and well-being of the visually impaired by devising therapeutic technologies.

Some of the most recent vision restoration technologies including gene therapy, retinal prostheses and stem cell (Cideciyan et al., 2018; Lee et al., 2019; Surendran et al., 2021) have attempted to tackle the issue from different angles. However, there is still significant variability among the individuals who receive these therapies, and such variability remains primarily unexplained. One of the factors that can potentially hinder recovery has been attributed to the organizational changes in the blind brain. Such alterations in the brain have been observed even in late-blind individuals who lose sight after a critical developmental period (Dan et al., 2019; Huang,

Dan, et al., 2019; Y. Yu et al., 2020). Functional changes, in particular, have been reported in the late-blind where the visual cortex is recruited for processing other tasks that help individuals use functioning sensory modalities for basic shape perception and localization (i.e., tasks typically guided by vision). Thus, restoration of input to the visual cortex may conflict with this adaptation, negatively impacting the quality of the restored vision, the adaptation that enhances other senses, or both. Studying brain changes following blindness and finding ways to quantify this plasticity can be crucial for the effective design of sight recovery technologies and the provision of clinical rehabilitation.

Changes in resting-state functional connectivity following vision loss have been studied extensively as a potential quantifiable measure that is affected in response to congenital, early, and late blindness (Murphy et al., 2016; Nuzzi et al., 2018; Wen et al., 2018; Y. Yu et al., 2020). The rsFC within the visual cortex as well as between the visual cortex and other sensory, motor, and association regions has been frequently reported to weaken in response to vision loss (Dai et al., 2013; Dan et al., 2019; Liu et al., 2008; Nuzzi et al., 2018; Sabbah et al., 2016; Wen et al., 2018; C. Yu et al., 2008b; Y. Yu et al., 2020). However, this measure has been rarely evaluated after sight restoration. In a recent study from our group, blind subjects showed a significantly diminished rsFC between primary visual (V1) and primary somatosensory cortex which was reversed with partial sight restoration using Argus II retinal prosthesis (Nadvar et al., 2022). Similarly, in a former study (Mowad et al., 2020) on blind subjects with RPE65 gene mutation, a qualitative assessment revealed lower rsFC between V1 and primary auditory cortex after blindness and higher rsFC three years after sight restorative gene therapy. These two studies found altered rsFC between visual cortex and another sensory cortex ROI, but only examined interactions between a limited number of ROIs. No other study, to our knowledge, has investigated whole-

brain functional reorganization in the brain after restoring vision. Therefore, one of our key aims in this study is to investigate network-wide changes in functional connectivity in the blind and sight-restored brain.

Starting about three decades ago, a multi-disciplinary effort to understand complex systems led to the utilization of graph theory and network science in diverse areas, such as sociology, transportation, molecular biology, and neuroscience (Barabási, 2013). In neuroscience, the application of graph theory for understanding the behavior and topology of brain structural and functional networks, also known as network neuroscience, goes back to the introduction of the term “Human Connectome” in 2005 (Sporns et al., 2005). This relatively new approach defines the brain as parcellations (nodes) connected by links (edges) and uses an adjacency matrix composed of nodal interconnections. For functional networks, such an adjacency matrix contains the temporal correlations between the nodes.

Network measures adopted from graph theory have been recently utilized for connectivity analysis of the human brain in a handful of studies. Studies of structural connectivity on blind subjects reported a decrease in global density and efficiency of the whole brain and the visual system, along with a decrease in nodal degree within the visual system (Shu, Liu, et al., 2009; Zhou et al., 2022). A few studies also used graph theory for analysis of functional connectivity networks in the brain; whole-brain and visual-network density as well as nodal degree in sensory and language-related association areas have been reported to be significantly lower after blindness (Ding et al., 2022; Huang, Dan, et al., 2019; Pedersini Id et al., 2020). In spite of the few studies on blindness, to our knowledge, currently, there is no examination of network metrics following sight restoration. In order to explore functional organization from a network neuroscience

perspective, in this work, we evaluated alterations in network density and efficiency, as global metrics, and weighted nodal degree, as a local metric, in response to vision loss and restoration.

4.2 Methods

For the whole-brain ROI-ROI functional connectivity and graph theory analysis completed in this chapter, the same experimental elements as described in Chapter 3 were utilized. These include subject groups, i.e., 10 healthy control (HC), 10 RP blind (RP), and 7 sight-restored subjects with Argus II retinal prosthesis (Argus II), experimental paradigm, imaging acquisition technique, and preprocessing steps. In summary, for 10 HC, 10 RP blind, and 7 Argus II subjects, four runs of resting-state functional magnetic resonance imaging per subject were included in our study, along with the structural T1W images of each subject's brain. For a more detailed explanation of the human subjects, the experimental condition, data acquisition, and preprocessing, please refer to section 3.2 in Chapter 3.

4.2.1 The ROI-ROI Functional Connectivity across the Whole Brain

ROI-ROI functional connectivity matrices were constructed by finding the Pearson correlation coefficient between the average BOLD times series -between two ROIs. For ROI selection, please refer to section 4.2.3. The correlation values were calculated between all possible pairs of 39 ROIs, yielding $39 \times 38 / 2 = 741$ unique connection pairs. This resulted in a 39×39 z adjacency matrix for each subject that is symmetrical around the main axis. The Pearson correlation coefficient (r) was converted to z with Fisher's z transformation (R A Fisher, 1915; Ronald Aylmer Fisher, 1921). The group functional connectivity matrix was then computed by finding the average z values for each connection pair, across all the subjects in a group. For comparing ROI-ROI rsFC between groups, two-sample t-tests were applied to each connection

pair value across the two subject groups under study. The t-values associated with each of these tests were used to create the raw uncorrected between-group contrast connectivity matrix.

Since the entire between-group contrast matrix incorporated multiple tests, a parametric cluster-based inference, based on functional network connectivity (Jafri et al., 2008), was used to correct for multiple comparisons. As indicated in Figure 14, this method first attempts to find groups of functionally related ROIs by a clustering approach such as hierarchical clustering (Sorensen, 1948). For each of these identified clusters, it then applies a general linear model (a multivariate parametric analysis) across all the connections in each cluster. This results in an F -statistics and an uncorrected p -value for each cluster. The cluster results are then corrected for multiple comparisons using cluster-level FDR approach (FDR-corrected $p < 0.05$) (Benjamini & Hochberg, 1995). This is followed by a post-hoc inference in which each individual connection in the entire matrix is thresholded by the uncorrected $p < 0.05$ height (connection level).

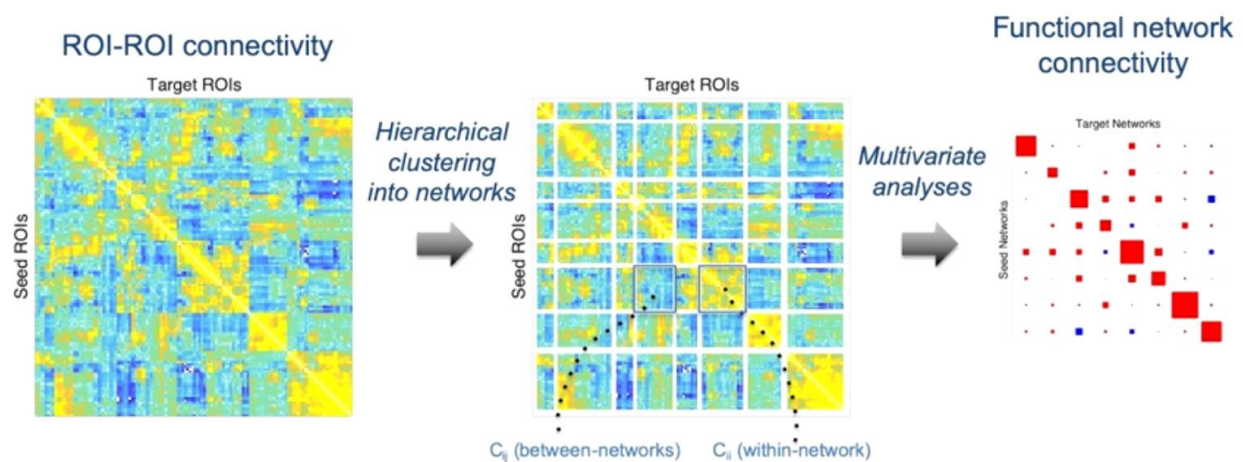


Figure 14- Functional Network Connectivity Approach (Jafri et al., 2008) – Clusters of functionally related ROIs are first identified. An F -statics (and a p -value) is assigned to each cluster, after applying a multivariate parametric analysis across all the ROIs in a cluster. An FDR correction is then applied at the cluster-level correcting for multiple comparisons across clusters. The image is adopted from (Nieto-Castanon, 2020).

4.2.2 Graph Theory Measures

Thresholding

The first step in preparing a functional connectivity matrix for the functional graph or network analysis involves thresholding. This step involves the selection of certain stronger edges to be included in the graph for analysis. Thresholding by an absolute value can result in bias in the analysis. This is due to the inherent individual differences in rsFC values that can result in different numbers of edges surviving thresholding for different subjects. Consequently, proportional thresholding is instead suggested, where the density of the networks under study remains the same. In our study, we used an array (0.9 to 0.1 with decrements of 0.1) of proportional threshold values to evaluate graph metrics. For example, a proportional threshold of 0.9, preserves the top 90% rsFC values and discards the bottom 10%. As investigated by previous studies (Garrison et al., 2015), using proportional thresholding ensures higher stability for the network metrics and reduces the threshold-related bias. For tracking the global density metric, however, an absolute array of thresholds (0.1 to 0.9 with increments of 0.1) were utilized to reveal how absolute thresholding alters the density itself.

Definitions

Three fundamental metrics adopted from graph theory were utilized to further illustrate differences between subject groups from a graph-based perspective (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). The first metric used was the global (connection/edge) density which is a measure of the wiring cost of a network. The global density is defined as the ratio of the actual number of edges in the network to the total number of possible edges as indicated in *Equation 1*, where N is the number of nodes and E is the total number of existing edges in the network.

$$Global\ Density = \frac{E}{N(N-1)/2} \quad \text{Equation 1}$$

The second global graph measure used was global efficiency which reflects the efficiency of information transfer in a network. The concept of global efficiency is closely related to the shortest path length. For a weighted network, the path length is equal to the total sum of edge lengths. In functional connectivity networks, since weights represent association and proximity, the edge length is inversely related to edge weight. Consequently, the path length between two nodes is defined as the summation of inverse edge weights comprising that path. As Equation 2 shows, the global efficiency metric is then computed as the average inverse shortest path length, where N is the total number of nodes and $L_{i,j}$ represents the path length between node i and j .

$$Global\ Efficiency = \frac{1}{N(N-1)/2} \sum_{i \neq j} \frac{1}{\min \{L_{i,j}\}} \quad \text{Equation 2}$$

For each subject and each threshold level, the global density and efficiency were calculated for the entire brain network, the visual, somatosensory, and auditory systems. The ROI constituents of the sensory systems are described in more detail in the section 4.2.3. For each between-group contrast, a non-parametric Kolmogorov-Smirnov (K-S) test (Massey, 1951) was applied to the global density (and efficiency) values across each group pair under study at each threshold value.

Finally, the last metric used was nodal strength (weighted degree), a local graph measure that measures the brain-wide influence of a node. The weighted degree of a node is defined as the sum of the weights of all the edges incident in a node, as indicated in Equation 3, where w_{ij} represents normalized weights such that $0 \leq w_{ij} \leq 1$ for all i and j nodes.

$$\text{Weighted Degree of node } i = \sum_{j \neq i} w_{ij} \quad \text{Equation 3}$$

The weighted degree was calculated for each of the 39 nodes for each subject. For each between-group contrast, a K-S test was applied to compare the values of the weighted degree for each node, across the two subject groups under study. The uncorrected p -value associated with each test is then corrected for multiple comparisons across the 39 ROIs, using the FDR approach and reported as q -value.

4.2.3 ROI Selection

In this study, we used Julich-Brain v2.9 (Amunts et al., 2020), a cytoarchitectonic atlas that is originally comprised of 282 small regions. For our whole-brain ROI-ROI functional connectivity analysis and evaluation of graph theory metrics, a total of 39 larger ROIs were derived from the Julich-Brain v2.9 atlas, as detailed in Appendix G. For the global density and efficiency analysis of the sensory systems, a subset of finer ROIs was utilized where 32 ROIs cover the primary and higher visual areas in ventral and dorsal visual pathways (V1, V2, CunG, LingG and LOC, FusG, PhG), 16 ROIs incorporate the primary and secondary somatosensory cortex (PostCG and -pOperc), and 18 ROIs cover the primary and secondary auditory cortex (Heschl and STG).

4.3 Results

4.3.1 Whole-brain ROI-ROI Functional Connectivity Analysis

The ROI-ROI functional connectivity matrices were computed for each subject in each of the HC, RP, and Argus II groups in terms of Fisher's Z-transformed correlation coefficient. The average connectivity matrices for HC, RP, and Argus II groups are shown in panels A and B in Figure 15, Figure 16, and Figure 17.

In order to calculate the group contrast matrices, for each connection pair, a two-sample t-test was applied to the raw z values across the subjects for each pair of compared groups. The RP > HC, Argus II > RP, and Argus II > HC between-group contrast matrices are shown in panel C of Figure 15, -Figure 16, and Figure 17 in terms of t-statistics. Each of these raw connectivity matrices are then corrected for multiple comparisons using the parametric cluster-based Functional Network Connectivity approach with connection threshold $p < 0.05$ (uncorrected) and cluster threshold $p < 0.05$ (FDR-corrected) as indicated in panel D of Figure 15, Figure 16, and Figure 17. For better presentation of the significant results, in all the matrices presented in Figure 15, Figure 16, and Figure 17, the rows and columns are re-ordered to place the ROIs from the same brain lobes next to each other, according to the Julich anatomical atlas.

4.3.2 Effect of RP Blindness on Whole-brain Functional Connectivity at Rest

The uncorrected between-group contrast matrix (Figure 15 panel C) indicates connection pairs with both increased (mainly involving the frontal lobe) and decreased (between visual cortex and sensory, association and motor areas) rsFC after blindness. A closer observation of the visual ROIs results shows the visual cortex increased connectivity with the frontal lobe, and decreased connectivity with sensory, motor, and association cortices, in addition to relatively unchanged connectivity with the limbic system. However, the connections that survived the multiple comparison correction (Figure 15 panel D) were limited to pairs with decreased connectivity between the lower visual areas (V1 and V2) and the primary/secondary somatosensory (postCG and pOperc), primary/secondary auditory (Heschl and STG), motor (SMA and preCG) and the association areas (SPL, IPS, and POS). Importantly, within the visual system, the connectivity was also significantly lower in RP compared with HC. This was mainly observed between the lower visual areas and parts of the dorsal visual pathway (including CunG) as well as between the lower

visual areas and the ventral visual pathway (including LOC, FusG, and PhG). For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.

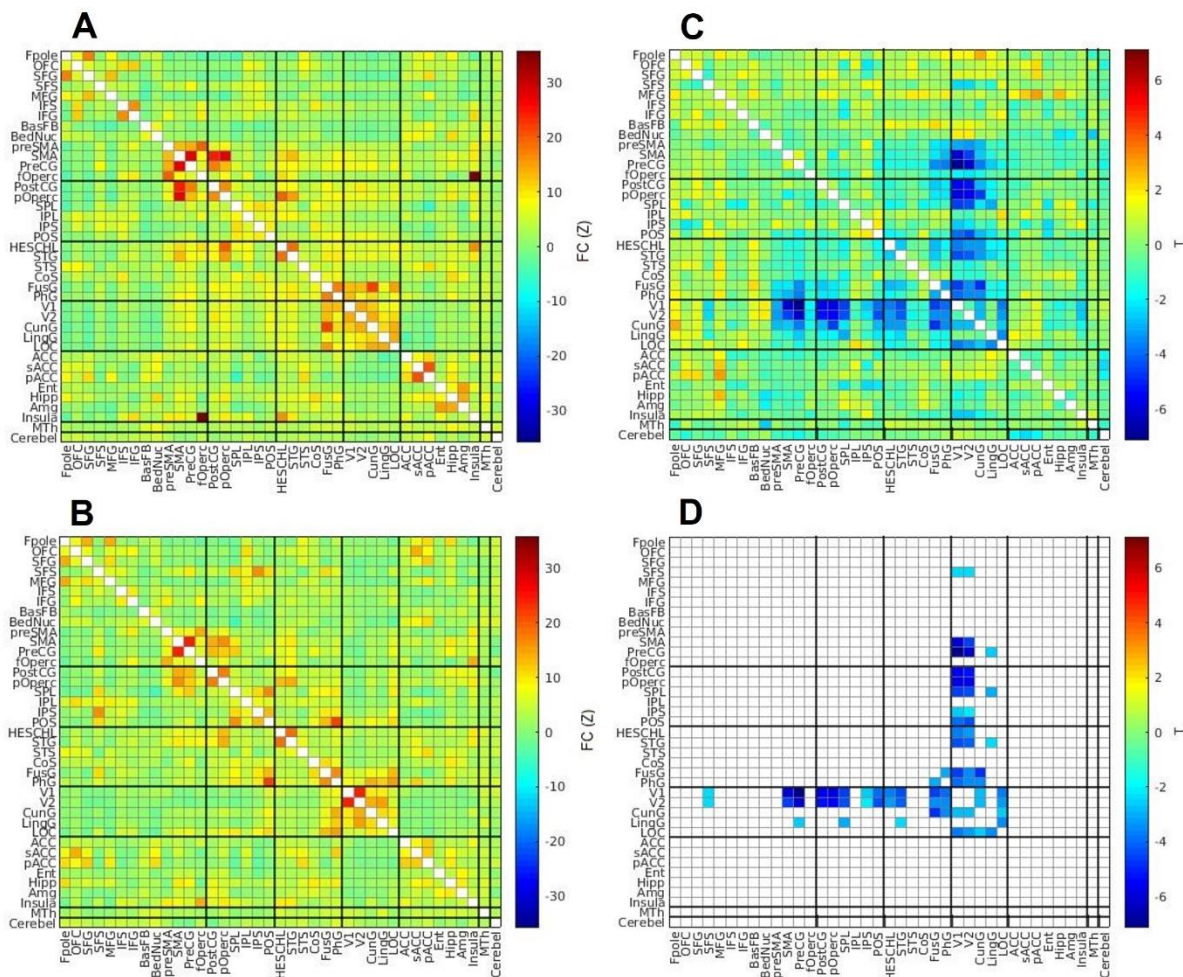


Figure 15 - RP > HC Between-Group Contrast ROI-ROI rsFC Map. Raw uncorrected group ROI-ROI connectivity maps are calculated in term of Fisher's Z transformed correlation coefficient for each of the (A) HC and (B) RP groups. (C) The uncorrected between-group contrast map for RP > HC is calculated using two-sample t-tests and (D) corrected for multiple comparisons using cluster-based Functional Network Connectivity approach with connection threshold $p < 0.05$ (uncorrected) and cluster-threshold $p < 0.05$ (FDR-corrected). For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.

4.3.3 Effect of Sight Restoration with Argus II on Whole-brain Resting-state Functional Connectivity

The raw Argus II > RP group contrast ROI-ROI results are indicated in Figure 16 panel C in terms of t-statistics. The contrast map shows connection pairs with increased rsFC in response to Argus II sight restoration compared with RP blindness; this includes connections between the visual cortex and auditory, somatosensory, and motor areas, and to a lesser degree, between some higher-level cognitive areas and the visual and association regions. Within-visual cortex

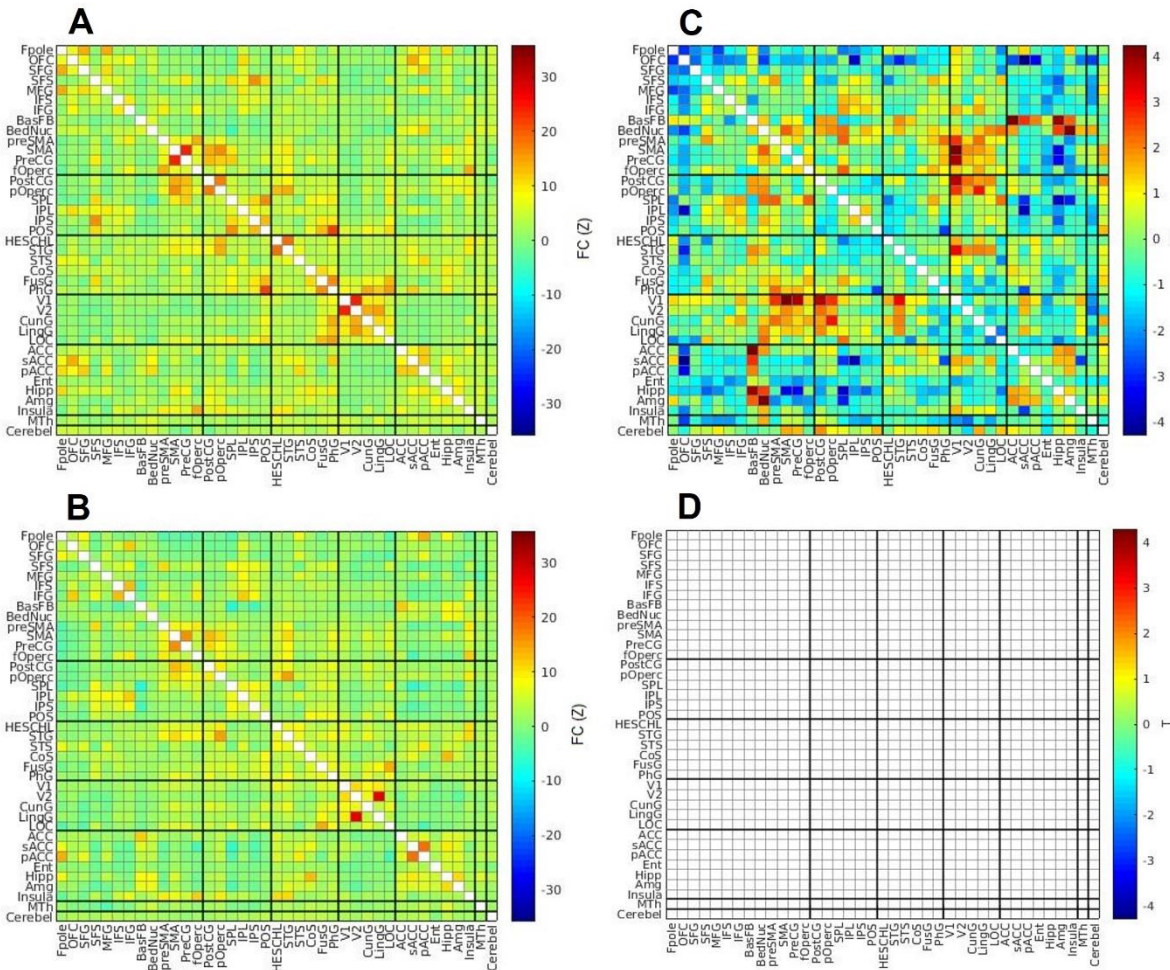


Figure 16 - Argus II > RP Between-group Contrast ROI-ROI rsFC Map. Raw uncorrected group ROI-ROI connectivity maps are calculated in term of Fisher's Z transformed correlation coefficient for each of the (A) RP and (B) Argus II groups. (C) The uncorrected between-group contrast map for Argus II > RP is calculated using two-sample t-tests and (D) corrected for multiple comparisons using cluster-based Functional Network Connectivity approach with connection threshold $p < 0.05$ (uncorrected) and cluster-threshold $p < 0.05$ (FDR-corrected). For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.

connectivity did not tend to alter after sight restoration. On the other hand, some connection pairs presented lower connectivity in Argus II compared with RP; this included connections involving some higher-level cognitive areas and the limbic system. Despite the relative changes observed in ROI-ROI rsFC after sight restoration, none of these alterations survived the multiple comparison correction, as shown in Figure 16, panel D, and thus none have any statistical significance at the network level.

4.3.4 Difference in Whole-brain Functional Connectivity between the Argus II Sight Restored and Healthy Controls at Rest

Figure 17 panel C shows the connectivity matrix for group contrast Argus II > HC. Overall, the uncorrected matrix includes connection pairs with lower, moderately higher, and unchanged rsFC in Argus II subjects compared with the HC. More specifically, compared with healthy controls, the visual cortex in Argus II subjects appears to be more strongly connected to the cognitive frontal areas and some parts of the limbic system; and more weakly connected to the motor, association, and sensory cortices, including the visual cortex. Nevertheless, after correcting for multiple comparisons, only regions involved in the visual system (including visual cortex, FusG, and PhG) survived the correction, with lower rsFC in Argus II compared with HC. This decrease in within-visual system connectivity mainly incorporated the rsFC between the ventral visual pathway (LOC, FusG, and PhG) and the entire visual system.

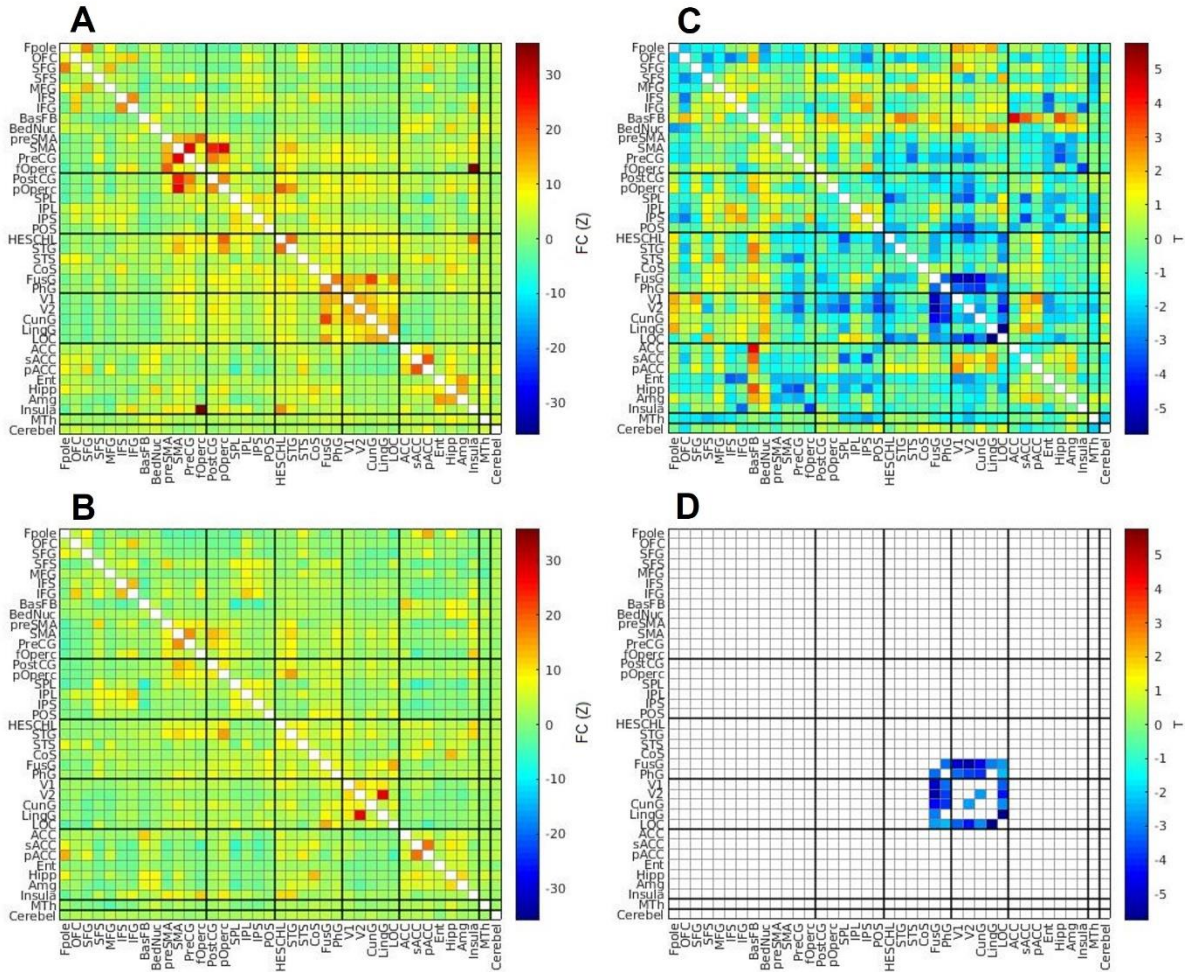


Figure 17 - Argus II > HC Between-group Contrast ROI-ROI rsFC Map. Raw uncorrected group ROI-ROI connectivity maps are calculated in term of Fisher's Z transformed correlation coefficient for each of the (A) Argus II and (B) RP groups. (C) The uncorrected between-group contrast map for Argus II > HC is calculated using two-sample t-tests and (D) corrected for multiple comparisons using cluster-based Functional Network Connectivity approach with connection threshold $p < 0.05$ (uncorrected) and cluster-threshold $p < 0.05$ (FDR-corrected). For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.

Figure 18 (A) illustrates the pairs with significant reduction in rsFC in the blind group compared with the sighted controls. Figure 18 (B) illustrates connection pairs in the Argus II group that remained significantly lower than the sighted group. Only the right hemisphere is used to illustrate connections for clarity. The red spheres represent the ROIs and the blue links connecting them represent the t-values associated with the between-group contrast. Thicker links show larger t-values.

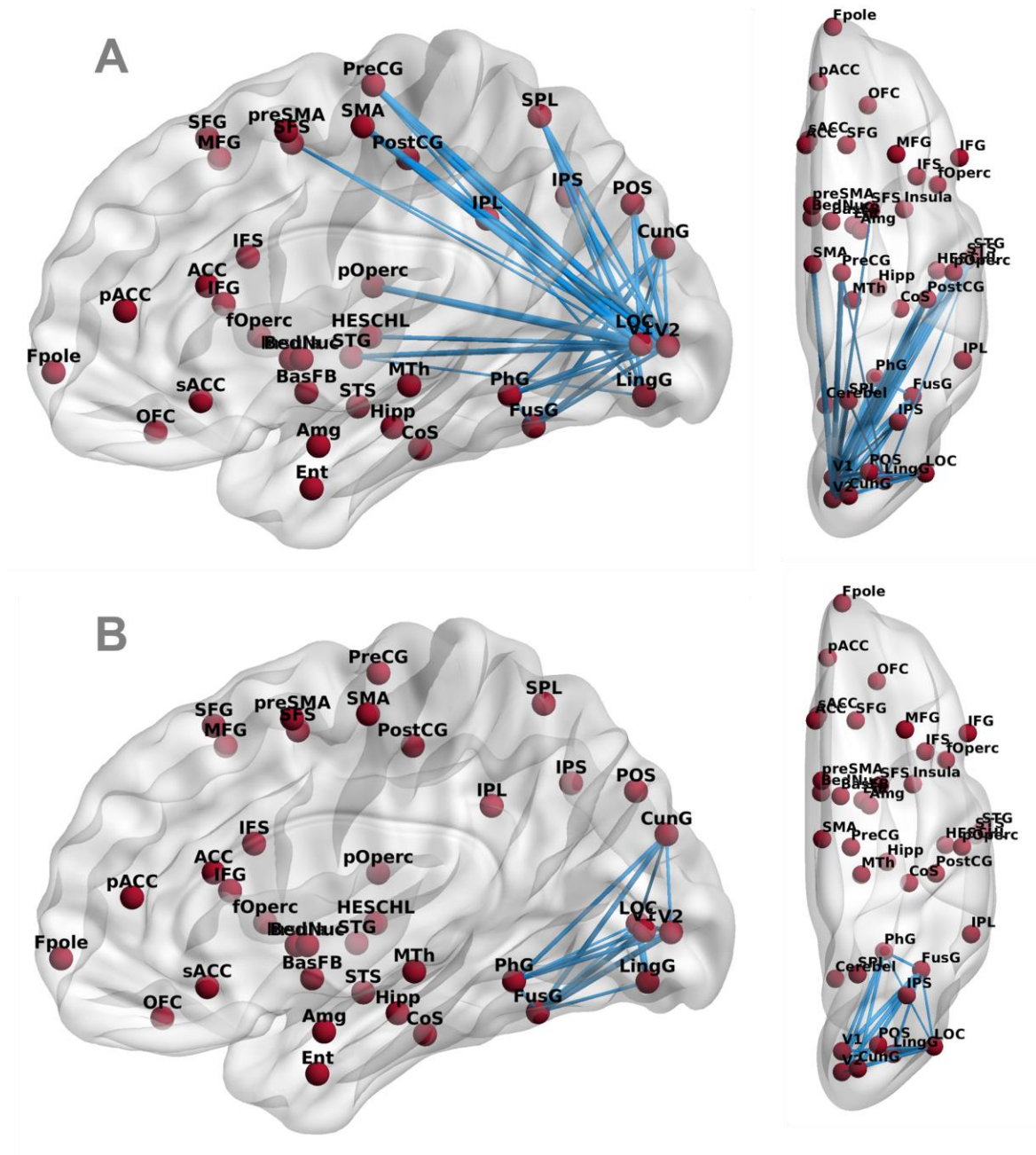


Figure 18 – Illustration of RP > HC and Argus II > HC ROI-ROI rsFC Between-group Contrast Results. (A) shows the pairs with significant reduction in rsFC in blind group compared with the sighted controls. (B) illustrates connection pairs in the Argus II group that remained significantly lower than the sighted group. The sagittal (left) and axial (right) views of the transparent cortical surface in the right hemisphere are illustrated. The red spheres represent the ROIs and the blue links connecting them represent the t-values associated with the between-group contrast. Thicker links show larger t-values. See appendix G for the description of ROI acronyms. The images were produced by BrainNet Viewer software package (Xia et al., 2013).

4.3.5 Graph Theory Network Measures Examination

In addition to the ROI-ROI rsFC, one local (weighted nodal degree or strength) and two global (global density and global efficiency) metrics were investigated for the groups under study to provide a different and complementary view of the alterations in the brain networks in response to blindness and sight restoration.

Global Metrics for the Whole Brain

Using the 39 defined ROIs extracted from the Julich-Brain atlas, the whole-brain global density of the brain network was quantified as indicated in Figure 19. Panel A shows the density values (in terms of percentage), color-coded for different absolute threshold values on the y-axis from 0.1 through 0.9 with 0.1 increments and on the x-axis for different subjects comprising the three groups (HC, RP, and Argus II). Panel B groups density values for each threshold separately. As is expected, for all the subjects (regardless of the group), density decreases as more rigorous thresholding is applied. Panel C illustrates the density for different threshold values for each subject in HC (red), RP (green), and Argus II (yellow) groups. Panel D shows the group average density per threshold for each of the 3 groups. For each threshold value, the density is compared between each pair of groups by applying a one-sided K-S test for all the possible contrasts (HC > RP, RP > Argus II, HC > Argus II, HC < RP, RP < Argus II and HC < Argus II). The resulting p -values are shown in the table in panel E. The significant ($p < 0.05$) tests are highlighted in blue. As mentioned in the methods section, between-group contrast results that are consistent across thresholds, particularly for the non-extreme threshold values, could potentially reflect consequential results. Overall, no significant changes in density could be observed between the groups at the thresholds under study.

Similarly, the global efficiency of the whole brain is quantified in Figure 20. The proportional thresholding is used for evaluating efficiency to keep the network density the same while comparing groups at each threshold. As was expected and pointed out by other previous studies (Garrison et al., 2015), using the proportional (and not absolute) thresholding leads to more stable results across a wide array of thresholds. Despite the apparent decrease in global efficiency following blindness (green vs red curves in panels C and D), neither blindness, nor sight restoration resulted in significant changes in the global efficiency of the brain as indicated in panel E table.

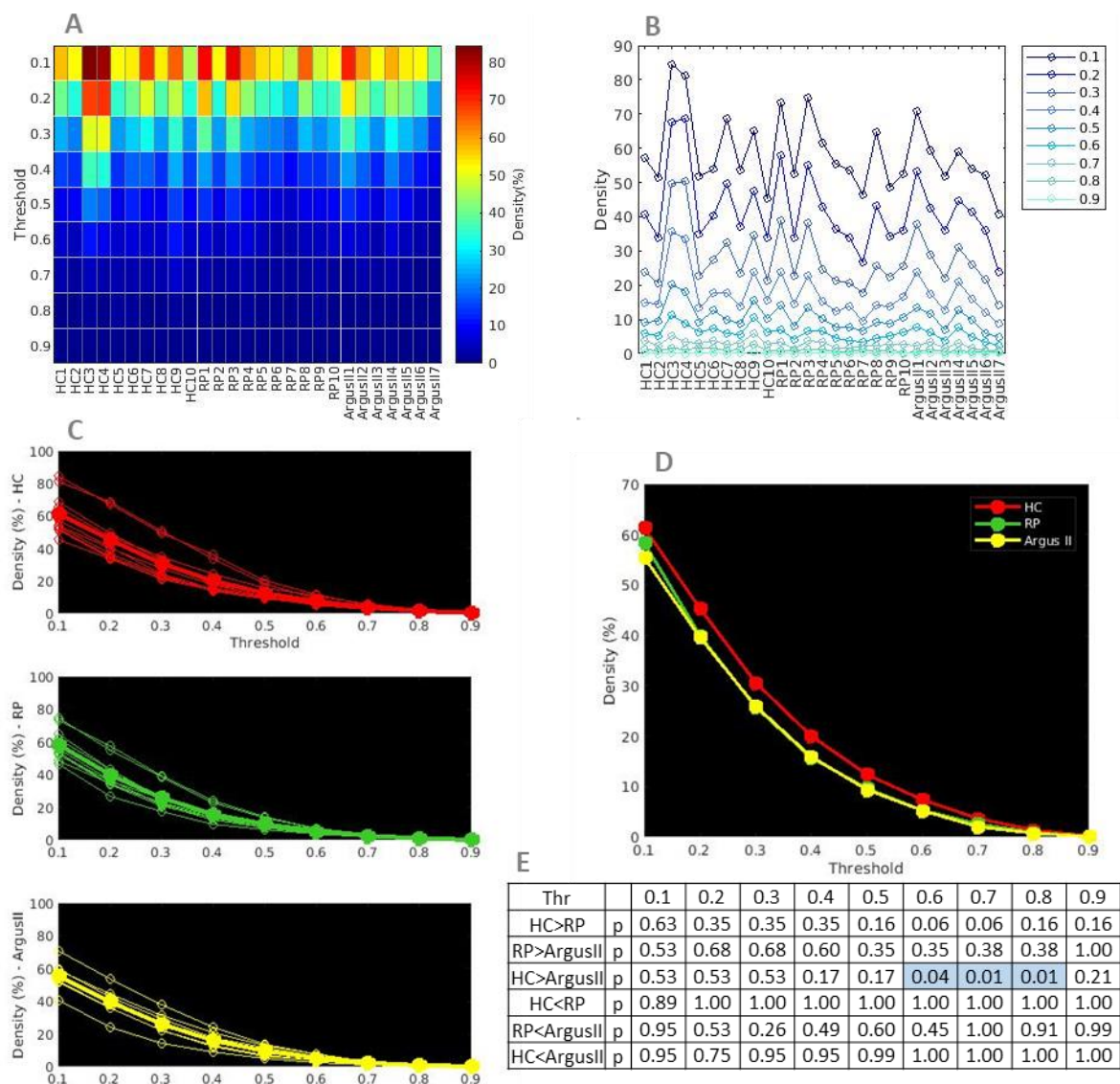


Figure 19 – Whole-brain Global Density. Density values for each subject at each absolute threshold value are illustrated (**A** and **B**). Effect of different levels of absolute thresholding on the whole-brain global density is shown for each subject in each group (HC, RP and Argus II) (**C**) and for each group average (**D**). Between-group non-parametric K-S test comparison was done at each threshold for each between-group contrast (**E**). Tests resulting in $p < 0.05$ are highlighted in blue.

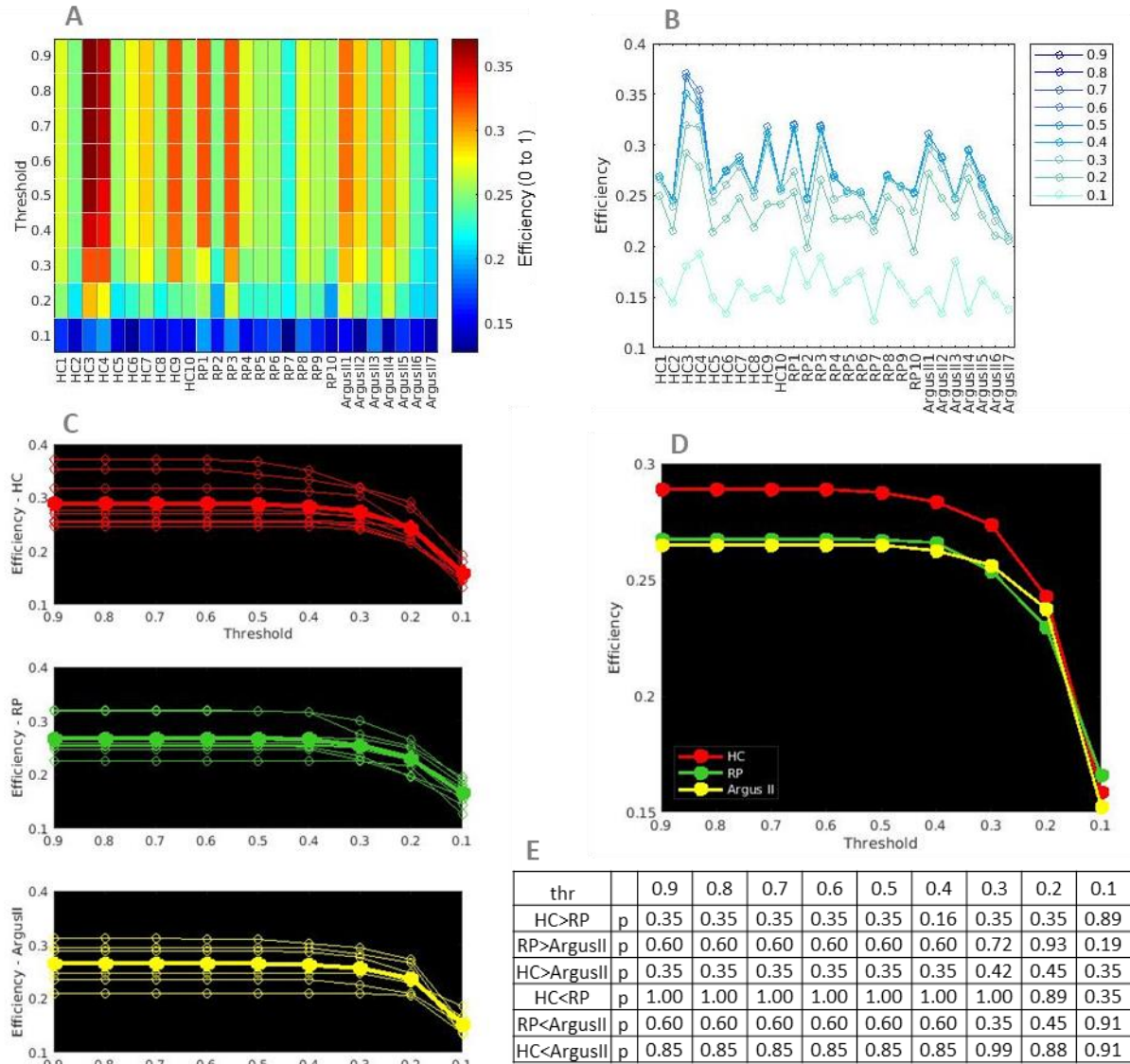


Figure 20 - Whole-brain Global Efficiency. Efficiency values for each subject at each proportional threshold value are illustrated (A and B). Effect different levels of proportional thresholding on whole-brain global efficiency is shown for each subject in each group (HC, RP and Argus II) (C) and for each group averages (D). Between-group non-parametric K-S test comparison was done at each threshold for each between-group contrast (E). No test results were significant.

Global Metrics for the Sensory Systems

Global density was also calculated for the visual sensory system as a network. Figure 21, panels A through D show how the global density of the network of the visual system changes for each group at each absolute threshold. As the panel E table illustrates, the majority of the threshold values resulted in a significant decrease in density in RP vs HC subjects (K-S test, $p < 0.05$). Sight restoration with Argus II also resulted in further significant reduction in the density compared with the RP group (K-S test, $p < 0.05$), in such a way that the visual-system density in the Argus II group remained significantly lower than the HC group (K-S test, $p < 0.05$).

As Figure 22 shows, for the majority of threshold values, the efficiency of the visual system, consisting of primary and higher-level visual areas, also decreased significantly with blindness (RP < HC) and sight recovery (Argus II < RP). In addition, it remained significantly lower in Argus II compared with the HC group (Argus II < HC).

For the somatosensory system, consisting of primary and secondary somatosensory areas, both the global density (Figure 23) and efficiency (Figure 24) did not alter in response to blindness or sight restoration

For the auditory system, consisting of the primary and secondary auditory areas, the density (Figure 25) and efficiency (Figure 26), appeared moderately (although not significantly) lower in RP vs HC group across the majority of the threshold values. This alternation remains relatively unchanged in Argus II vs RP subjects, resulting in statically significantly lower auditory-system density and efficiency in Argus II compared with HC subjects

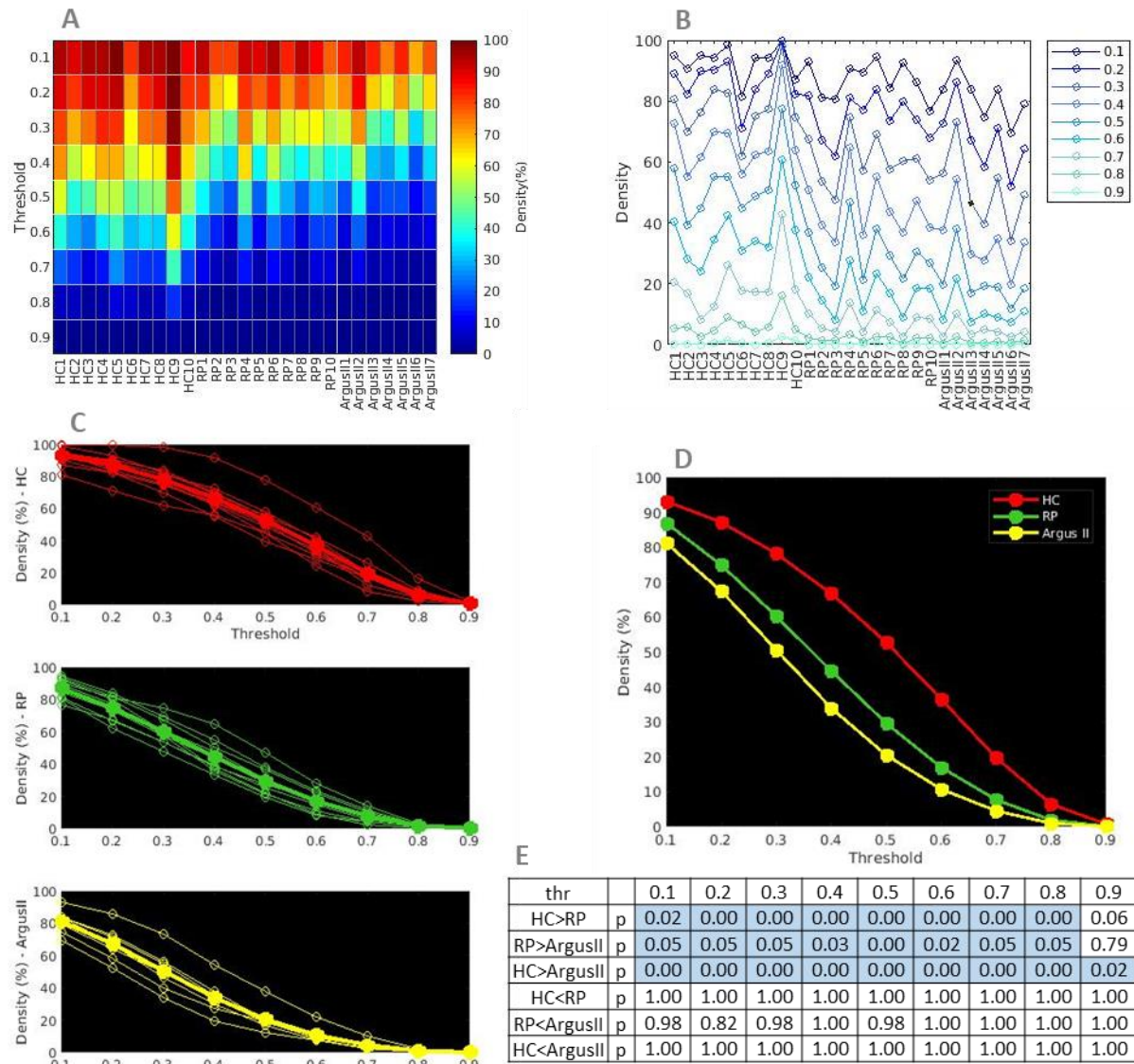


Figure 21 – The Visual-system Global Density. Density values for each subject at each absolute threshold value are illustrated (A and B). Effect of levels of absolute thresholding on visual-system global density is shown for each subject in each group (HC, RP and Argus II) (C) and for each group average (D). Between-group non-parametric K-S. test comparison was done at each threshold for each between-group contrast (E). Tests resulting in $p < 0.05$ are highlighted in blue. The visual system includes ROIs covering V1, V2, CunG, LingG, LOC, FusG and PhG.

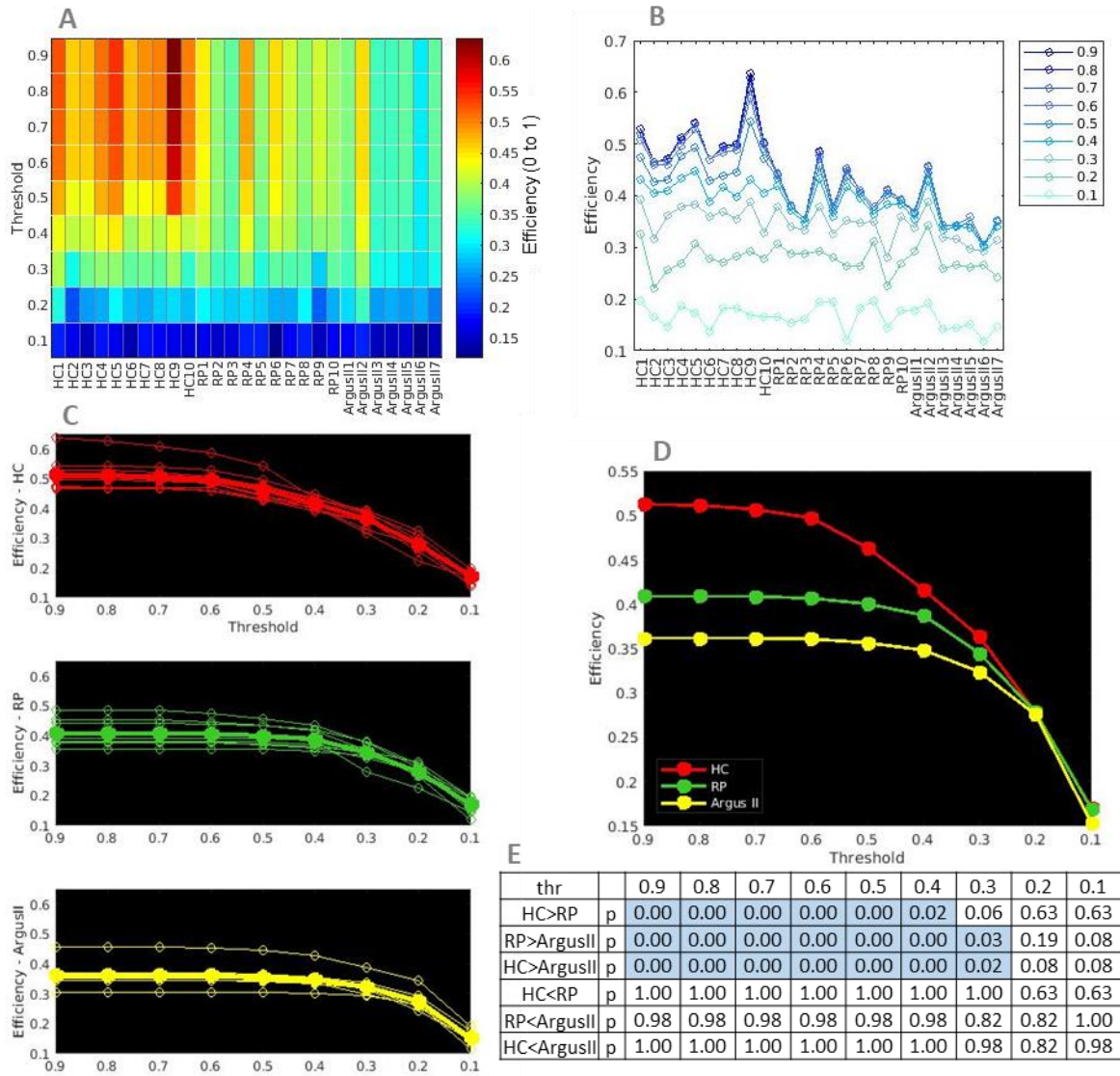


Figure 22- Visual-system Global Efficiency. Efficiency values for each subject at each proportional threshold value are illustrated (A and B). Effect of levels of proportional thresholding on visual-system global efficiency is shown for each subject in each group (HC, RP and Argus II) (C) and for each group average (D). Between-group non-parametric K-S test comparison was done at each threshold for each between-group contrast (E). Tests resulting in $p < 0.05$ are highlighted in blue. The visual system includes ROIs covering V1, V2, CunG, LingG, LOC, FusG and PhG.

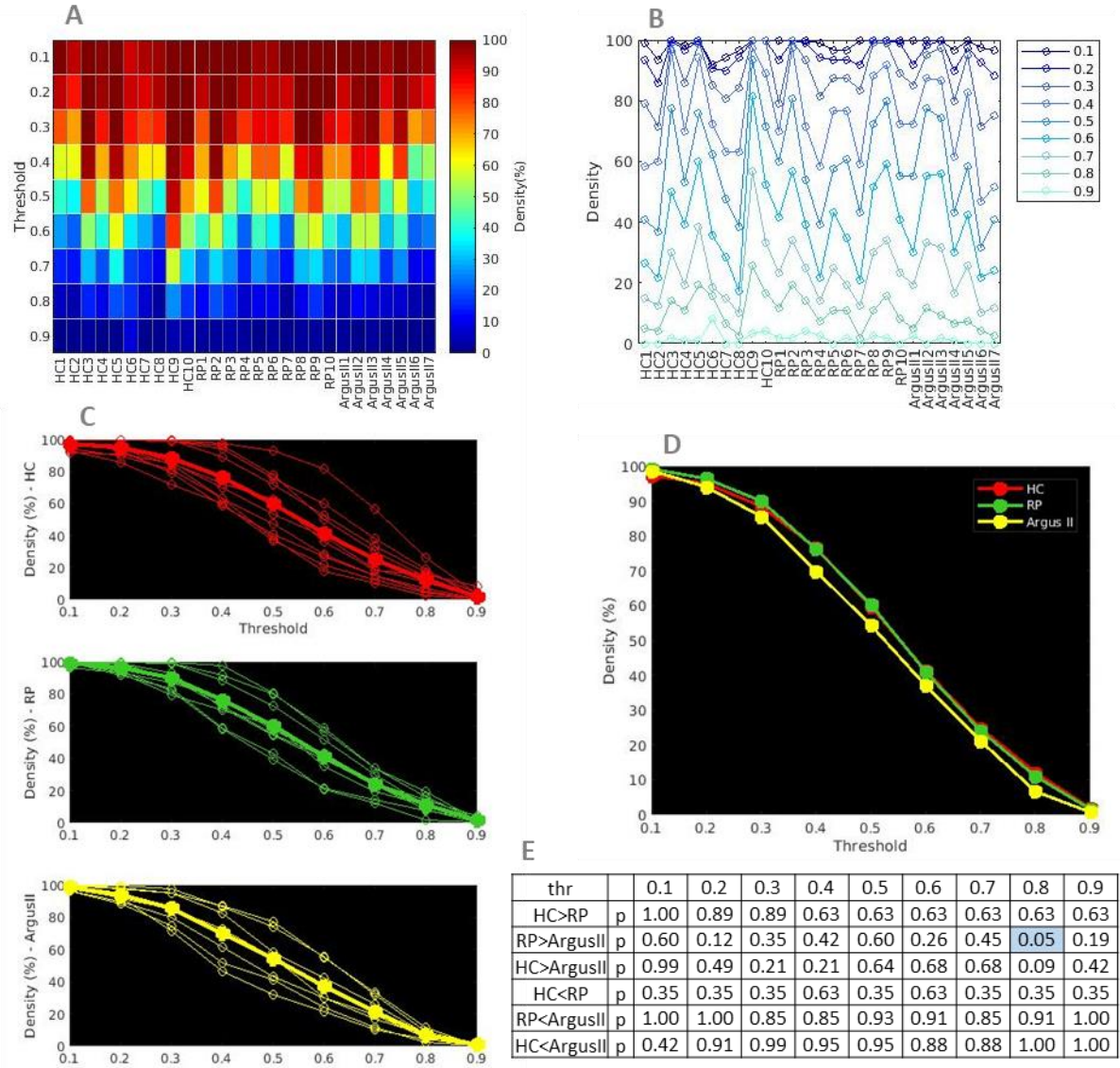


Figure 23 - The Somatosensory-system Global Density. Density values for each subject at each absolute threshold value are illustrated (**A** and **B**). Effect of levels of absolute thresholding on somatosensory-system global density is shown for each subject in each group (HC, RP and Argus II) (**C**) and for each group average (**D**). Between-group non-parametric K-S test comparison was done at each threshold for each between-group contrast (**E**). Tests resulting in $p < 0.05$ are highlighted in blue. The somatosensory system includes ROIs covering PostCG and pOperc.

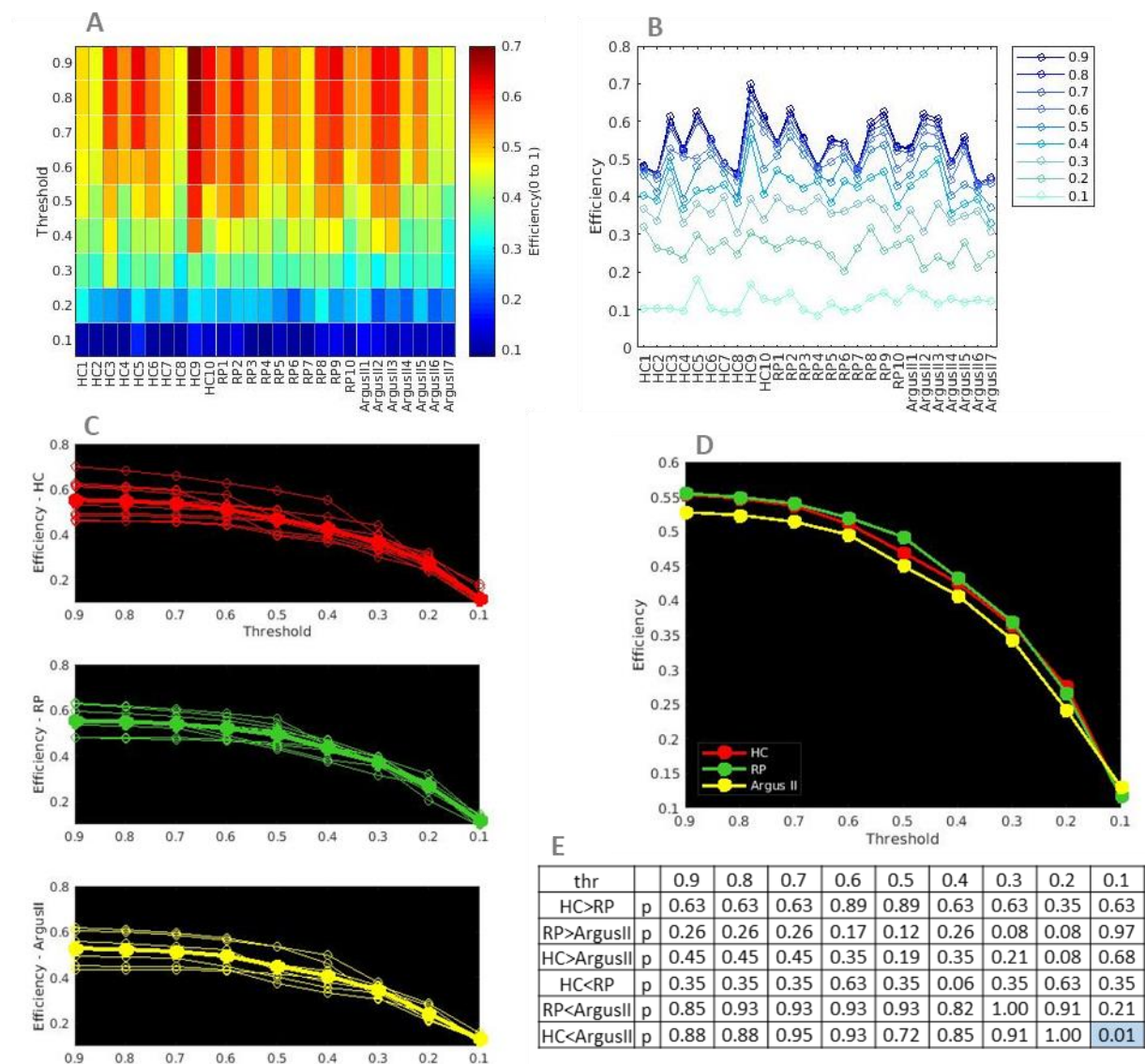


Figure 24 - The Somatosensory-system Global Efficiency. Efficiency values for each subject at each proportional threshold value are illustrated (A and B). Effect of levels of proportional thresholding on somatosensory-system global efficiency is shown for each subject in each group (HC, RP and Argus II) (C) and for each group average (D). Between-group non-parametric K-S test comparison was done at each threshold for each between-group contrast (E). Tests resulting in $p < 0.05$ are highlighted in blue. The somatosensory system includes ROIs covering PostCG and pOperc.

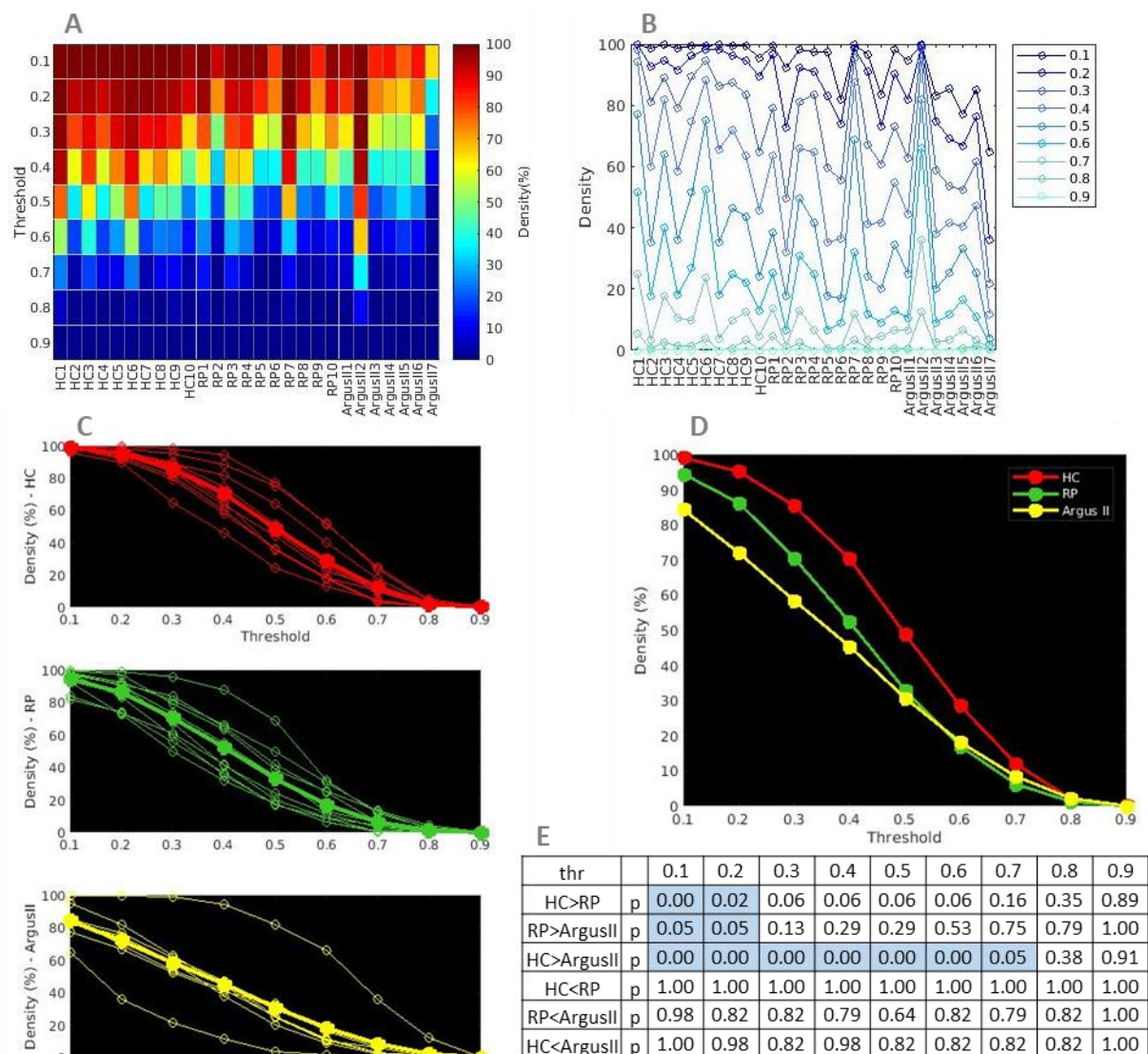


Figure 25 - The Auditory-system Global Density. Density values for each subject at each absolute threshold value are illustrated (A and B). Effect of levels of absolute thresholding on auditory-system global density is shown for each subject in each group (HC, RP and Argus II) (C) and for each group average (D). Between-group non-parametric K-S test comparison was done at each threshold for each between-group contrast (E). Tests resulting in $p < 0.05$ are highlighted in blue. The auditory system includes ROIs covering Heschl and STG.

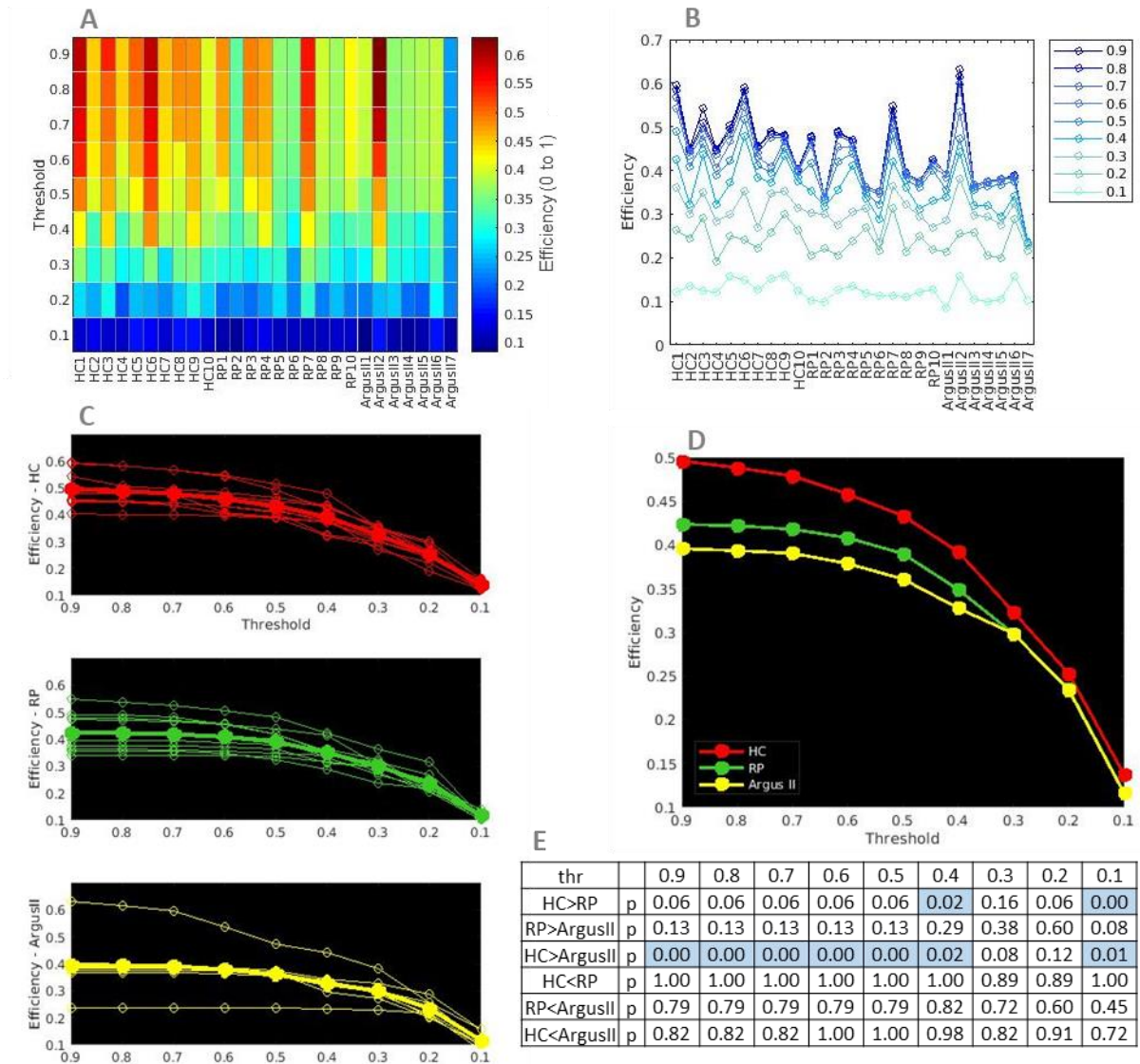


Figure 26 – The Auditory System Global Efficiency. Efficiency values for each subject at each proportional threshold value are illustrated (A and B). Effect of rigor of proportional thresholding on auditory system global efficiency is shown for each subject in each group (HC, RP and Argus II) (C) and for each group averages (D). Between-group non-parametric K-S test comparison was done at each threshold for each between-group contrast (E). Tests resulting in $p < 0.05$ are highlighted in blue. The auditory system includes ROIs covering Heschl and STG.

Local Metrics: Weighted Degree (Strength)

Another quantified measure adopted from graph theory was nodal weighted degree (or strength). This quantity was calculated for each node and for each subject. Figure 27 shows the weighted degree for four different thresholding limits: no threshold, proportional threshold of 0.7,

0.4, and 0.1 in panels A, B, C, and D respectively. Each panel shows the color-coded value of strength, for each subject on the x-axis and each of the ROIs under study on the y-axis. A qualitative examination of the heatmaps indicates trends in alteration of this quantity for sensory cortices. The visual cortex (V1, V2, CunG, LingG, and LOC), somatosensory (PostCG, pOperc), auditory (Heschl, STG) and motor (SMA, PreCG) areas all generally showed diminished strength in RP compared with HC. After sight restoration, the strength was sustained at a low level for the visual cortex but partially enhanced for non-visual sensory and motor cortices in Argus II compared with RP. This trend was evident under all the threshold levels under study.

Figure 28, Figure 29, Figure 30, and Figure 31 illustrate the quantitative comparison of the group results for each ROI at no threshold, proportional threshold of 0.7, 0.4, and 0.1, respectively. The upper panel in each of these figures shows the average weighted degree for each ROI for HC (red), RP (green), and Argus II (yellow) groups. The lower panels in these figures demonstrate the results of a one-sided K-S test for each of the 6 contrasts under study in terms of uncorrected (p) and FDR-corrected across 39 ROIs (q) values. The highlighted cells in blue represent the uncorrected significant results ($p < 0.05$) and in orange represent the FDR-corrected significant tests ($q < 0.05$).

For the thresholds under study, although the areas involved in dorsal and ventral visual pathways (V1, V2, CunG, LingG, LOC, POS, SPL, FusG, and PhG) as well as the motor (SMA and PreCG), somatosensory (PostCG and pOperc) and auditory (Heschl and STG) cortices tend to decrease in weighted degree, in response to blindness, this alteration was deemed significant only for V1, V2, and CunG after multiple comparison corrections. Generally, the nodal strength for these 3 ROIs tends to stay low after sight restoration, with some intermediate threshold values resulting in significantly lower strength in these ROIs in Argus II vs HC group.

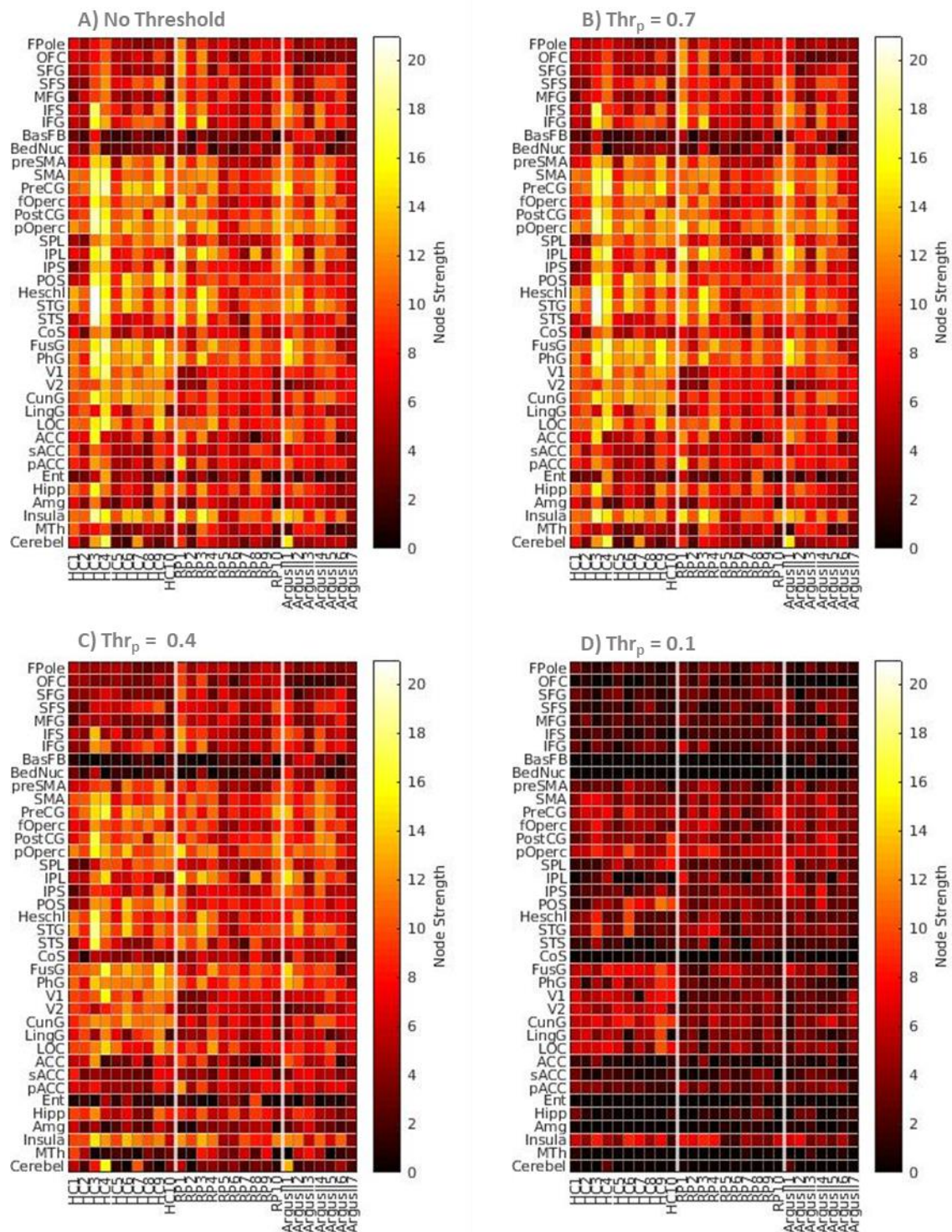
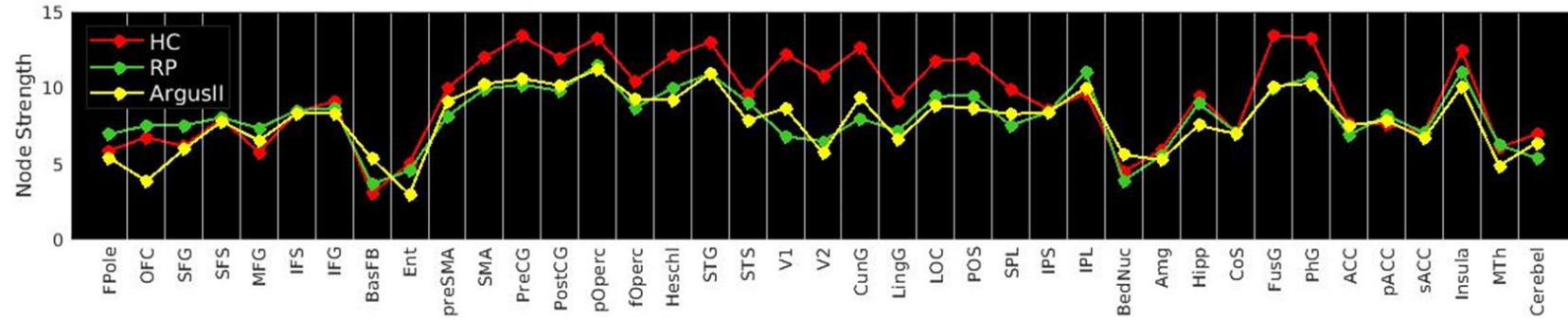
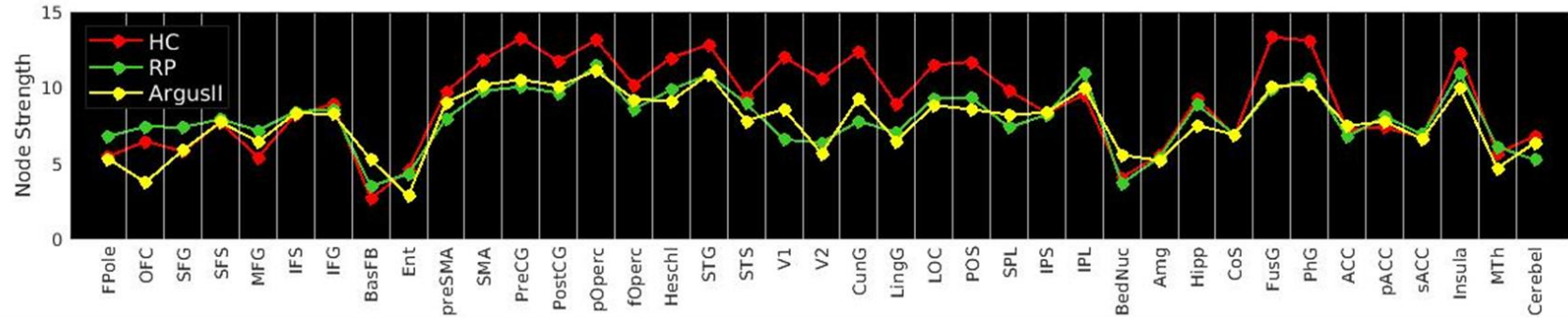


Figure 27 – Weighted Nodal Degree (Strength). Weighted degree is color-coded for each ROI (y-axis) and each subject (x-axis) without thresholding (A) and after applying sparsity-based proportional thresholding (Thr_p) at 0.7 (B), 0.4 (C) and 0.1 (D) to the functional connectivity matrix. For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.



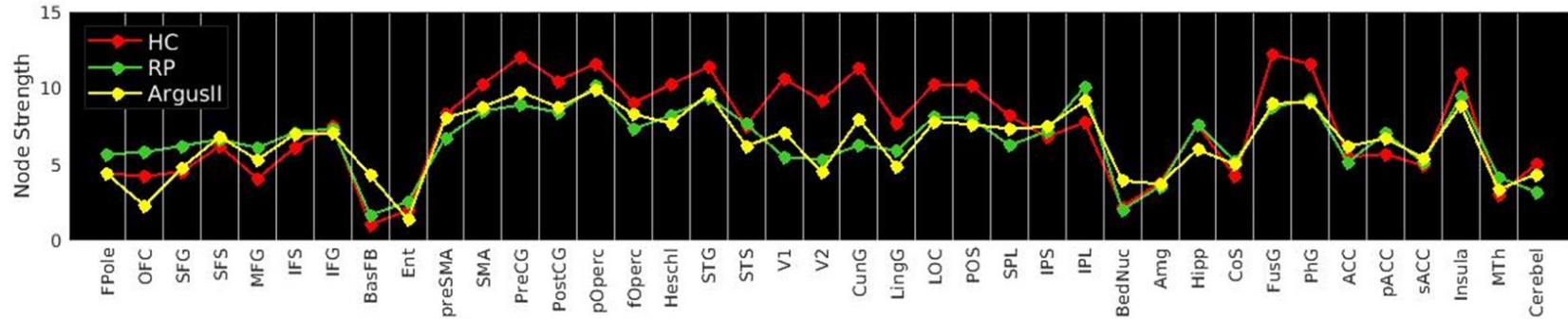
ROIs		Fpole	OFC	SFG	SFS	MFG	IFS	IFG	BasFB	Ent	preSMA	SMA	PreCG	PostCG	pOperc	fOperc	HESCHL	STG	STS	V1	V2	CunG	LingG	LOC	POS	SPL	IPS	IPL	BedNuc	Amg	Hipp	CoS	FusG	PHG	ACC	pACC	sACC	Insula	MTh	Cerebel
HC > RP	p	1.00	0.89	0.89	0.63	0.89	0.89	0.63	0.63	0.35	0.35	0.16	0.06	0.16	0.06	0.16	0.16	0.16	0.63	0.00	0.00	0.00	0.16	0.35	0.02	0.02	0.35	0.63	0.35	0.63	0.35	0.63	0.02	0.06	0.63	0.63	0.63	0.35	0.89	0.35
	q	1.00	0.99	0.96	0.82	0.94	1.02	0.79	0.88	0.86	0.81	0.61	0.31	0.56	0.27	0.51	0.41	0.47	0.77	0.00	0.01	0.01	0.44	0.76	0.15	0.12	0.72	0.85	0.63	1.02	0.60	0.74	0.10	0.24	0.98	0.94	0.91	0.69	0.91	0.66
RP > ArgusII	p	0.03	0.00	0.38	0.35	0.49	0.45	0.68	1.00	0.09	0.88	0.91	0.60	0.72	0.21	0.68	0.35	0.68	0.42	1.00	0.42	0.93	0.38	0.42	0.19	0.82	0.45	0.49	0.98	0.53	0.35	0.72	0.72	0.45	0.72	0.68	0.42	0.60	0.26	0.75
	q	0.50	0.15	1.49	1.95	1.00	1.10	1.10	1.03	1.15	1.01	1.01	1.07	1.00	1.65	1.06	1.71	1.02	1.36	1.00	1.25	1.01	1.36	1.16	1.84	0.97	1.04	0.95	1.04	0.98	1.52	0.96	0.93	0.98	0.90	0.98	1.09	1.02	1.70	0.92
HC > ArgusII	p	0.75	0.00	0.68	0.42	0.91	0.45	0.64	0.82	0.12	0.42	0.26	0.17	0.35	0.09	0.60	0.17	0.42	0.42	0.02	0.00	0.04	0.08	0.12	0.01	0.05	0.42	0.45	0.82	0.42	0.21	0.68	0.12	0.08	0.72	0.53	0.21	0.29	0.12	0.53
	q	0.81	0.07	0.80	0.78	0.91	0.65	0.78	0.86	0.45	0.74	0.57	0.47	0.68	0.38	0.76	0.44	0.71	0.68	0.15	0.01	0.33	0.43	0.41	0.11	0.32	0.65	0.63	0.84	0.63	0.52	0.78	0.38	0.37	0.80	0.71	0.49	0.59	0.35	0.68
HC < RP	p	0.06	0.63	0.06	0.35	0.06	0.35	0.89	0.16	0.89	0.89	1.00	1.00	1.00	0.89	1.00	0.63	1.00	0.63	1.00	1.00	1.00	0.89	1.00	0.63	0.63	0.35	0.16	0.89	0.63	0.63	0.63	1.00	0.89	0.89	0.35	0.16	0.89	0.63	0.63
	q	2.16	2.23	1.08	1.53	0.72	1.97	1.65	1.53	1.51	1.45	1.30	1.26	1.22	1.58	1.18	2.05	1.15	1.36	1.11	1.08	1.05	1.39	1.03	1.89	1.75	1.38	1.02	1.34	1.29	1.64	1.53	1.00	1.29	1.24	1.72	1.22	1.20	1.44	1.23
RP < ArgusII	p	0.91	1.00	1.00	0.75	0.85	0.75	0.49	0.19	0.91	0.21	0.64	0.60	0.35	0.29	0.49	0.85	0.49	0.85	0.09	0.53	0.08	0.68	0.91	0.93	0.60	0.82	0.91	0.08	0.68	0.95	0.75	0.60	0.64	0.38	0.53	0.53	0.75	0.85	0.53
	q	1.11	1.03	1.00	1.27	1.19	1.22	2.12	1.84	1.07	1.65	1.31	1.47	1.95	1.88	1.91	1.15	1.73	1.11	1.15	1.71	2.99	1.26	1.04	1.01	1.38	1.18	1.01	1.50	1.20	1.00	1.17	1.30	1.25	1.87	1.58	1.47	1.13	1.07	1.37
HC < ArgusII	p	0.91	1.00	0.60	0.42	0.53	0.64	0.88	0.02	1.00	0.68	0.99	1.00	0.99	1.00	0.91	1.00	0.97	0.85	1.00	1.00	1.00	0.68	1.00	0.91	0.68	0.64	0.19	0.19	0.68	1.00	0.64	0.98	1.00	0.35	0.38	0.21	0.95	0.85	0.13
	q	1.69	1.30	2.35	2.03	2.28	2.27	1.72	0.59	1.26	1.89	1.43	1.22	1.38	1.34	1.61	1.18	1.51	1.85	1.15	1.11	1.08	1.76	1.05	1.54	1.65	2.08	2.46	1.84	1.56	1.03	1.92	1.47	1.00	2.28	2.14	1.65	1.55	1.75	2.56

Figure 28 – Weighted Nodal Degree in the Absence of Thresholding. Weighted degree (strength) was calculated for each of the 39 ROIs. The average weighted degree for each of the 39 ROIs is shown for HC (red), RP (green) and Argus II (yellow) groups (**upper panel**). Between-group comparison was quantified by applying K-S test for each between-group contrast at each ROI (**lower panel**). The p-values were then corrected for multiple comparisons with FDR correction, yielding an associated q-value. Test results with uncorrected $p < 0.05$ are highlighted in blue, and for FDR-corrected $p < 0.05$ are highlighted in orange. For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.



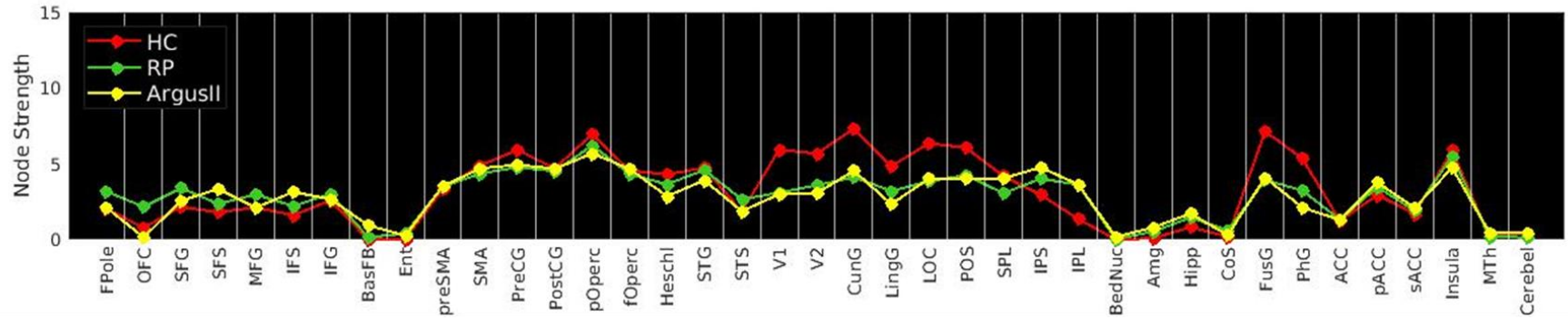
ROIs		Fpole	OFC	SFG	SFS	MFG	IFS	IFG	BasFB	Ent	preSMA	SMA	PreCG	PostCG	pOperc	fOperc	Heschl	STG	STS	V1	V2	CunG	LingG	LOC	POS	SPL	IPS	IPL	BedNuc	Amg	Hipp	CoS	FusG	PhG	ACC	pACC	sACC	Insula	MTh	Cerebel
HC > RP	P	1.00	0.89	0.89	0.63	1.00	0.89	0.63	0.63	0.35	0.35	0.16	0.06	0.16	0.06	0.16	0.16	0.16	0.89	0.00	0.00	0.00	0.06	0.16	0.02	0.00	0.35	0.63	0.35	0.63	0.35	0.89	0.02	0.06	0.63	0.63	0.63	0.35	0.89	0.35
	q	1.03	1.05	1.02	1.02	1.00	0.99	0.82	0.88	0.81	0.76	0.56	0.31	0.51	0.27	0.47	0.44	0.41	0.96	0.00	0.04	0.01	0.24	0.38	0.12	0.03	0.72	0.85	0.69	0.98	0.60	1.09	0.10	0.22	0.94	0.91	0.79	0.66	0.94	0.63
RP > ArgusII	P	0.03	0.00	0.42	0.35	0.49	0.45	0.68	1.00	0.29	0.88	0.88	0.60	0.72	0.21	0.91	0.35	0.68	0.42	1.00	0.42	1.00	0.38	0.49	0.38	0.82	0.45	0.49	0.98	0.38	0.35	0.72	0.72	0.45	0.72	0.68	0.42	0.60	0.17	0.75
	q	0.50	0.08	1.36	2.28	1.00	1.10	1.10	1.05	2.26	1.04	1.01	1.07	1.03	2.06	1.01	1.95	1.06	1.25	1.03	1.16	1.00	1.66	0.95	1.49	1.00	1.04	0.91	1.06	1.36	1.71	1.00	0.96	0.98	0.93	1.02	1.09	1.02	2.18	0.95
HC > ArgusII	P	0.75	0.00	0.72	0.42	0.91	0.45	0.64	0.98	0.12	0.42	0.26	0.17	0.42	0.09	0.60	0.17	0.42	0.42	0.02	0.00	0.04	0.09	0.12	0.01	0.05	0.42	0.45	0.98	0.42	0.29	0.79	0.12	0.08	0.72	0.53	0.42	0.29	0.12	0.53
	q	0.84	0.04	0.85	0.86	0.96	0.65	0.78	1.01	0.45	0.81	0.64	0.47	0.78	0.43	0.76	0.44	0.74	0.71	0.15	0.01	0.33	0.38	0.41	0.11	0.32	0.68	0.63	0.98	0.65	0.66	0.85	0.38	0.43	0.82	0.71	0.63	0.63	0.35	0.68
HC < RP	P	0.06	0.35	0.16	0.35	0.06	0.35	0.89	0.16	0.63	0.89	1.00	1.00	1.00	0.89	1.00	0.63	1.00	0.63	1.00	1.00	1.00	0.89	1.00	0.63	0.63	0.35	0.16	0.89	0.63	0.63	0.63	1.00	0.89	0.89	0.35	0.35	0.89	0.63	0.63
	q	2.16	2.29	2.04	1.38	1.08	1.97	1.58	1.53	2.05	1.45	1.30	1.26	1.22	1.51	1.18	1.89	1.15	1.23	1.11	1.08	1.05	1.39	1.03	1.75	1.64	1.25	1.22	1.34	1.17	1.53	1.44	1.00	1.29	1.24	1.72	1.53	1.20	1.36	1.29
RP < ArgusII	P	0.91	1.00	1.00	0.75	0.72	0.75	0.49	0.19	0.91	0.21	0.64	0.60	0.35	0.29	0.42	0.85	0.49	0.85	0.08	0.53	0.17	0.42	0.60	0.98	0.60	0.60	0.91	0.08	0.68	0.95	0.49	0.60	0.64	0.38	0.53	0.88	0.75	0.85	0.53
	q	1.07	1.03	1.00	1.13	1.12	1.09	1.73	1.84	1.04	1.65	1.14	1.38	1.95	1.88	1.81	1.15	1.59	1.11	2.99	1.47	2.18	1.63	1.30	1.04	1.24	1.17	1.01	1.50	1.10	1.03	1.47	1.12	1.09	1.87	1.37	1.07	1.05	1.07	1.28
HC < ArgusII	P	0.68	1.00	0.60	0.42	0.35	0.60	0.88	0.00	1.00	0.68	0.99	1.00	0.99	1.00	0.91	1.00	0.97	0.85	1.00	1.00	1.00	0.68	1.00	0.91	0.68	0.91	0.19	0.19	0.42	1.00	0.64	0.98	1.00	0.35	0.38	0.21	0.95	0.60	0.13
	q	1.76	1.30	2.13	1.81	2.28	1.96	1.72	0.15	1.26	1.65	1.43	1.22	1.38	1.34	1.69	1.18	1.51	1.75	1.15	1.11	1.08	1.56	1.05	1.61	1.47	1.54	2.46	1.84	1.63	1.03	1.78	1.47	1.00	1.95	1.87	1.65	1.55	1.81	2.56

Figure 29 - Weighted Nodal Degree after Proportional Thresholding ($Thr_p = 0.7$). Weighted degree (strength) was calculated for each of the 39 ROIs. The average weighted degree for each of the 39 ROIs is shown for HC (red), RP (green) and Argus II (yellow) groups (**upper panel**). Between-group comparison was quantified by applying K-S test for each between-group contrast at each ROI (**lower panel**). The p -values were then corrected for multiple comparisons with FDR correction, yielding an associated q -value. Test results with uncorrected $p < 0.05$ are highlighted in blue, and for FDR-corrected $p < 0.05$ are highlighted in orange. For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.



ROIs		Fpole	OFC	SFG	SFS	MFG	IFS	IFG	BasFB	Ent	preSMA	SMA	PreCG	PostCG	pOperc	fOperc	Heschl	STG	STS	V1	V2	CunG	LingG	LOC	POS	SPL	IPS	IPL	BedNuc	Amg	Hipp	CoS	FusG	PhG	ACC	pACC	sACC	Insula	MTh	Cerebel
HC > RP	p	1.00	0.63	0.89	0.89	1.00	0.89	0.63	1.00	0.35	0.16	0.06	0.02	0.06	0.16	0.06	0.06	0.16	0.89	0.00	0.00	0.00	0.16	0.16	0.02	0.02	0.35	0.89	0.63	0.63	0.63	1.00	0.00	0.06	0.63	1.00	0.63	0.16	0.89	0.16
	q	1.11	1.07	1.16	1.20	1.08	1.12	0.94	1.05	0.69	0.47	0.27	0.12	0.24	0.44	0.22	0.20	0.41	1.09	0.00	0.01	0.00	0.38	0.36	0.10	0.09	0.66	1.05	1.02	0.98	0.91	1.03	0.03	0.18	0.88	1.00	1.12	0.34	1.02	0.32
RP > ArgusII	p	0.08	0.00	0.26	0.60	0.38	0.72	0.68	1.00	0.42	1.00	0.72	0.85	0.85	0.68	1.00	0.53	0.91	0.21	1.00	0.64	1.00	0.35	0.68	0.29	0.49	0.35	0.49	0.97	0.49	0.01	0.64	0.72	0.82	0.93	0.68	0.79	0.60	0.45	0.19
	q	1.00	0.08	1.70	1.38	1.49	1.12	1.26	1.11	1.48	1.08	1.07	1.11	1.07	1.20	1.05	1.28	1.11	1.65	1.03	1.31	1.00	1.71	1.15	1.61	1.47	1.52	1.36	1.11	1.27	0.14	1.25	1.03	1.10	1.10	1.10	1.10	1.30	1.47	1.84
HC > ArgusII	p	0.75	0.00	0.72	0.85	0.99	0.72	0.53	1.00	0.17	0.75	0.13	0.17	0.19	0.09	0.72	0.05	0.29	0.42	0.00	0.00	0.02	0.05	0.09	0.01	0.13	0.75	0.45	1.00	0.53	0.19	0.98	0.02	0.03	0.82	0.91	0.68	0.35	0.45	0.53
	q	0.98	0.00	1.03	0.98	1.05	1.00	0.89	1.03	0.47	0.95	0.43	0.44	0.46	0.34	0.96	0.24	0.63	0.81	0.01	0.01	0.12	0.21	0.31	0.08	0.39	0.92	0.84	1.00	0.86	0.43	1.06	0.10	0.14	0.97	1.01	1.02	0.72	0.80	0.82
HC < RP	p	0.06	0.02	0.06	0.35	0.02	0.16	0.89	0.35	0.35	1.00	1.00	1.00	1.00	0.89	1.00	1.00	1.00	0.35	1.00	1.00	1.00	0.89	1.00	0.63	0.63	0.35	0.06	0.89	0.63	0.35	0.35	1.00	0.89	0.63	0.16	0.16	1.00	0.35	0.35
	q	0.72	0.61	0.54	0.92	0.30	1.02	1.58	1.53	1.38	1.44	1.39	1.34	1.30	1.51	1.26	1.22	1.18	1.25	1.15	1.11	1.08	1.45	1.05	1.36	1.29	1.15	0.43	1.39	1.23	0.86	1.06	1.03	1.34	1.17	0.87	0.77	1.00	0.98	0.81
RP < ArgusII	p	1.00	1.00	0.98	0.49	0.72	0.72	0.64	0.00	0.91	0.17	0.75	0.35	0.49	0.64	0.26	0.97	0.72	0.79	0.03	0.93	0.12	0.95	0.79	0.64	0.17	0.60	0.91	0.08	0.42	1.00	0.79	0.26	0.53	0.38	0.64	0.38	0.49	0.98	0.68
	q	1.05	1.03	1.09	1.47	1.21	1.16	1.39	0.15	1.18	1.31	1.13	1.52	1.36	1.31	1.46	1.11	1.12	1.14	0.59	1.13	1.13	1.12	1.10	1.25	1.09	1.38	1.14	1.00	1.36	1.00	1.06	1.28	1.28	1.49	1.19	1.36	1.27	1.06	1.20
HC < ArgusII	p	0.68	1.00	0.60	0.42	0.17	0.49	0.53	0.00	0.93	0.68	1.00	1.00	0.91	1.00	0.85	1.00	0.97	0.53	1.00	1.00	1.00	0.91	0.91	0.91	0.68	0.35	0.08	0.03	0.68	0.91	0.45	0.98	0.93	0.35	0.09	0.19	0.95	0.60	0.29
	q	1.56	1.22	1.57	1.63	1.31	1.59	1.58	0.03	1.34	1.47	1.18	1.15	1.61	1.11	1.58	1.08	1.26	1.47	1.05	1.03	1.00	1.54	1.47	1.42	1.39	1.71	1.00	0.50	1.32	1.36	1.60	1.24	1.30	1.52	0.86	1.23	1.28	1.47	1.61

Figure 30 - Weighted Nodal Degree after Proportional Thresholding ($Thr_p = 0.4$). Weighted degree (strength) was calculated for each of the 39 ROIs. The average weighted degree for each of the 39 ROIs is shown for HC (red), RP (green) and Argus II (yellow) groups (**upper panel**). Between-group comparison was quantified by applying K-S test for each between-group contrast at each ROI (**lower panel**). The p-values were then corrected for multiple comparisons with FDR correction, yielding an associated q-value. Test results with uncorrected $p < 0.05$ are highlighted in blue, and for FDR-corrected $p < 0.05$ are highlighted in orange. For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.



ROIs		Fpale	OFC	SFG	SFS	MFG	IFS	IFG	BasFB	Ent	preSMA	SMA	PreCG	PostCG	pOperc	fOperc	Heschl	STG	STS	V1	V2	CunG	LingG	LOC	POS	SPL	IPS	IPL	BedNuc	Amg	Hipp	CoS	FusG	PhG	ACC	pACC	sACC	Insula	MTh	Cerebel
HC > RP	P	1.00	1.00	1.00	1.00	1.00	0.63	0.63	1.00	1.00	0.63	0.35	0.16	0.63	0.63	0.35	0.63	0.63	0.89	0.00	0.00	0.00	0.00	0.00	0.06	0.16	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.02	0.35	0.89	0.63	0.63	0.89	0.63
	q	1.44	1.39	1.34	1.30	1.26	1.75	1.12	1.22	1.18	1.53	1.25	0.68	1.44	1.36	1.15	1.29	1.07	1.45	0.02	0.04	0.03	0.03	0.02	0.27	0.61	1.15	1.11	1.08	1.05	1.03	1.00	0.07	0.09	1.06	1.39	1.23	1.17	1.34	1.64
RP > ArgusII	P	0.08	0.00	0.13	0.93	0.02	0.93	0.68	1.00	0.91	0.38	0.97	0.64	0.60	0.49	0.68	0.21	0.29	0.09	0.53	0.26	0.82	0.09	0.91	0.53	1.00	0.17	0.75	1.00	1.00	0.85	0.53	0.82	0.03	0.79	0.91	0.68	0.53	1.00	0.97
	q	0.75	0.00	0.73	1.17	0.29	1.13	1.32	1.11	1.26	1.25	1.14	1.31	1.30	1.47	1.26	0.92	1.03	0.69	1.47	1.02	1.28	0.57	1.22	1.37	1.08	0.82	1.27	1.05	1.03	1.23	1.28	1.23	0.33	1.28	1.18	1.20	1.21	1.00	1.11
HC > ArgusII	P	0.75	0.03	0.82	1.00	0.45	1.00	0.53	1.00	1.00	0.75	0.68	0.08	0.49	0.26	0.82	0.12	0.68	0.91	0.00	0.00	0.04	0.01	0.01	0.13	0.64	1.00	1.00	1.00	1.00	0.91	0.97	0.02	0.01	0.91	1.00	0.98	0.35	1.00	0.79
	q	1.47	0.17	1.39	1.30	1.26	1.26	1.28	1.22	1.18	1.40	1.47	0.33	1.27	0.85	1.33	0.45	1.39	1.42	0.15	0.07	0.20	0.11	0.08	0.47	1.47	1.15	1.11	1.08	1.05	1.36	1.35	0.10	0.07	1.31	1.03	1.32	1.05	1.00	1.39
HC < RP	P	0.06	0.06	0.02	0.35	0.02	0.16	0.63	0.89	0.35	0.35	0.63	1.00	0.63	0.89	0.35	0.35	0.35	0.16	0.89	1.00	1.00	0.89	1.00	0.63	0.35	0.02	0.02	1.00	0.06	0.16	0.35	1.00	0.89	0.63	0.35	0.63	0.89	0.89	1.00
	q	0.43	0.36	0.61	0.86	0.30	0.77	1.07	1.24	1.25	0.72	0.98	1.18	1.23	1.29	1.15	0.81	1.06	0.68	1.20	1.15	1.11	1.16	1.08	1.02	0.76	0.15	0.20	1.05	0.31	0.61	0.98	1.03	1.12	1.17	0.92	1.12	1.34	1.09	1.00
RP < ArgusII	P	1.00	1.00	1.00	0.19	0.82	0.12	0.38	0.12	0.60	0.42	0.49	0.21	0.60	0.91	0.42	0.91	0.91	0.68	0.82	0.82	0.49	1.00	0.19	0.82	0.19	0.17	0.72	0.82	0.49	0.42	1.00	0.60	1.00	0.49	0.29	0.42	0.91	0.45	0.82
	q	1.15	1.11	1.08	1.84	1.33	4.51	1.66	2.25	1.24	1.63	1.27	1.18	1.17	1.18	1.48	1.14	1.11	1.20	1.28	1.23	1.19	1.05	1.47	1.18	1.23	2.18	1.21	1.14	1.12	1.36	1.03	1.12	1.00	1.06	1.41	1.25	1.07	1.26	1.10
HC < ArgusII	P	0.79	1.00	0.35	0.08	0.38	0.17	0.42	0.04	0.17	0.79	0.75	1.00	0.60	1.00	0.38	0.99	0.38	0.49	0.91	1.00	1.00	0.91	1.00	0.68	0.42	0.12	0.02	0.82	0.03	0.09	0.82	1.00	1.00	0.49	0.19	0.38	0.91	0.72	0.98
	q	1.33	1.22	1.37	0.75	1.36	0.94	1.09	0.55	0.82	1.28	1.33	1.18	1.24	1.15	1.25	1.25	1.15	1.12	1.31	1.11	1.08	1.26	1.05	1.32	1.02	0.75	0.59	1.28	0.50	0.69	1.23	1.03	1.00	1.06	0.82	1.07	1.22	1.33	1.28

Figure 31 - Weighted Nodal Degree after Proportional Thresholding ($Thr_p = 0.1$). Weighted degree (strength) was calculated for each of the 39 ROIs. The average weighted degree for each of the 39 ROIs is shown for HC (red), RP (green) and Argus II (yellow) groups (**upper panel**). Between-group comparison was quantified by a K-S test for each between-group contrast at each ROI (**lower panel**). The p-values were then corrected for multiple comparisons with FDR correction, yielding an associated q-value. Test results with uncorrected $p < 0.05$ are highlighted in blue, and for FDR-corrected $p < 0.05$ are highlighted in orange. For explanation of the ROI acronyms, please refer to Table 8 in Appendix G.

4.4 Discussion

4.4.1 *The ROI-ROI rsFC Outcomes and Their Relevance to the Previous Studies*

Our whole-brain ROI-ROI rsFC analysis revealed a statistically significant decrease in rsFC following blindness between the lower visual areas (mainly V1 and V2) and visual regions involved in dorsal and ventral visual streams (LOC, FusG, PhG, and CunG), the motor (PreCG and SMA), primary and secondary somatosensory (PostCG and pOperc), primary and secondary auditory (Heschl and STG) and parietal association (SPL, IPS, and POS) cortices. This result is consistent with the major results of numerous studies on the effect of early and late blindness on rsFC across the brain (Dai et al., 2013; Dan et al., 2019; Liu et al., 2008; Mowad et al., 2020; Nuzzi et al., 2018; Sabbah et al., 2016; Wen et al., 2018; C. Yu et al., 2008a; Y. Yu et al., 2020). Additionally, previous studies reported a significant increase in rsFC between the occipital and frontal lobe (IFG, MFG, and SFG) after blindness (Dai et al., 2013; Liu et al., 2008; Sabbah et al., 2016; Y. Yu et al., 2020). Similarly, our uncorrected results showed a moderate increase in rsFC between visual areas and some higher cognitive areas in the frontal lobe (Fpole, OFC, SFG) although this pattern did not survive the multiple comparison correction.

In our analysis of sight restoration, compared with the RP group, Argus II subjects did not demonstrate a significant change in rsFC after correcting for multiple comparisons, however, the uncorrected results uncovered a modest increase in the rsFC between visual areas and motor, somatosensory and auditory (and not visual) cortices. Our result was consistent with a previous study where a qualitative assessment of an a-priori connection (visual-auditory) indicated an enhancement in this pair's rsFC following sight restoration with gene therapy (Mowad et al., 2020).

Finally, after correcting for multiple comparisons, the only connection pairs whose rsFC in the Argus II group did not reach the level of healthy controls were between higher levels of the ventral visual stream (LOC, FusG, and PhG) and nearly all the ROIs in the visual system. In the Argus II group, the connection pairs involving the visual cortex with the motor and non-visual sensory cortices were partially reinstated after sight recovery, as these connectivity pairs were not found to be significantly different from the healthy controls. This observation is not beyond expectations, as the uncorrected ROI-ROI results showed a moderate increase in rsFC for these connection pairs in Argus II compared with the RP group. Similarly, in a study by our group (Nadvar et al., 2022) on an a-priori (visual-somatosensory) connection pair, this connection showed diminished rsFC after RP blindness that was, partially but significantly, reversed after sight restoration.

It is also important to note that, in line with some previous studies (Dai et al., 2013; Liu et al., 2008; Sabbah et al., 2016; Y. Yu et al., 2020), we observed a moderate increase in rsFC between visual cortex and some higher cognitive areas in the frontal lobe after blindness. After partial sight restoration, these connections' rsFC remained either unchanged or fairly increased, especially for connections involving the primary visual cortex. This resulted in the connectivity between visual and some frontal lobe regions in Argus II subjects to modestly exceed the level of HC. In other words, sight restoration did not tend to change the visual-frontal alterations, initially provoked by blindness, in the opposite direction. The frontal-visual rsFC alterations mainly involved Fpole, OFC, and SFG that are responsible for higher-level cognitive tasks such as monitoring action outcome, decision making, reasoning, and working memory (Boisgueheneuc et al., 2006; Koechlin, 2011; Stalnaker et al., 2015). Consequently, the enhanced visual-frontal rsFC could reflect a heightened top-down influence on visual areas that could potentially be explained

by reverse hierarchy theory (Fine & Park, 2018). Our study showed that such functional reorganization is likely triggered by blindness and sustained even after the reintroduction of vision.

4.4.2 Alterations in Graph Theory Measures in Light of Earlier Findings

In the second part of our study, analysis of the global network metrics (global density and efficiency) of the entire functional brain network remained unaffected by both blindness and sight restoration. When these two measures were quantified for the visual system network, nevertheless, a significant decrease was observed in response to both vision loss and restoration. In addition, using Argus II for sight recovery did not reverse the blindness-induced changes in global density and efficiency for both visual and auditory systems. These findings regarding the visual network are in agreement with another study (Pedersini Id et al., 2020) that reported a reduction in the visual system's global density after blindness but disagrees with this study for the whole brain analysis, which reported a reduction in global density for entire brain network following vision loss.

While global (edge) density reflects the wiring cost of the network, global efficiency represents integrative information processing across remote brain regions (van Wijk et al., 2010). Generally, global efficiency and characteristic path length (another global metric) are closely but inversely related. Characteristic path length refers to the mean shortest path length in the network. Since, in contrast to the characteristic path length, the global efficiency can be meaningfully measured for networks with disconnections (Rubinov & Sporns, 2010), we selected this network measure for our analysis.

Global density and efficiency of the functional auditory system were also moderately reduced after blindness and remained low even after vision recovery. This might be attributed to alterations in the secondary auditory cortex (STG) and its involvement in face perception. It has

been hypothesized that perception of face identity, mediated by the visual cortex and FusG, and perception of eye gaze, mediated by superior temporal areas, are both required for face perception (Hoffman & Haxby, 2000; Puce et al., 1998; Stigler & McDougle, 2013). Therefore, we hypothesize that reduction in the density and efficiency of the auditory system, and the sustained low values after vision restoration could be credited to the impairment of gaze identification in superior temporal areas.

Interestingly, for all the graph analyses implicating the global density and efficiency, the results of the two quantities changed in agreement with each other, i.e., the global density of the networks changed in the same direction as the global efficiency for the group contrasts under study. This could be because the higher density entails more connections and routing paths that can potentially lead to information propagation with higher efficiency.

Our analysis of the weighted (node) degree highlighted a significant reduction in node degree for lower visual areas following blindness for the majority of the threshold values used, while these blindness-induced alterations remained predominantly unrecovered after sight restoration. Similar to our results, other functional network studies on both late and early blindness showed a decrease in (binary) nodal degree, particularly in the visual regions (Ding et al., 2022; Huang, Dan, et al., 2019). Due to the lack of sufficient network neuroscience studies on sight restoration, we are not currently able to compare our existing vision recovery results against any prior studies.

It is important to note that the reported alterations in the network metrics were comprised of changes that were consistent across the majority of the threshold values included in the study. Thresholding the adjacency matrix, which is performed before extracting the graph measures, ensures that the non-significant and spurious connections do not obscure the topology of

significant connections. Although some studies evaluate network metrics merely at a fixed threshold, we evaluated networks over a wide range of reasonable threshold values to avoid thresholding bias (Bullmore & Sporns, 2009). Also, when feasible, we made use of proportional thresholding, as studies have shown higher stability of network measures across sparsity-based compared with correlation-based thresholding (Garrison et al., 2015).

4.4.3 Relationship between the Graph Metrics and the ROI-ROI rsFC Results

The reduction in density of the visual and auditory regions in response to blindness and sight restoration is anticipated from observing the visual and auditory within-network connectivity values in the rsFC matrices, where these sub-networks appear sparser in RP compared with HC as well as in the Argus II in comparison with RP group.

Moreover, the results obtained from the weighted degree measure are not surprising, given the definition of the weighted degree as the summation of weights of all the connections leading to the node under study. A close examination of $RP > HC$ between-group contrast ROI-ROI rsFC matrix for each row/column associated with lower visual areas indicates a larger number of connection pairs with a reduction in rsFC and fewer pairs with an increase in rsFC which leads to an overall lower weighted degree for the lower visual regions. Similarly, in the $Argus\ II > HC$ between-group contrast rsFC matrix, the rows/columns representing lower visual areas present a relative balance between the number of connections with increase and decrease in rsFC with a slight inclination towards a decrease in connectivity. This results in modestly (but not significantly) lower strength for lower visual areas in the sight restored compared with the HC.

Overall, the ROI-ROI rsFC values between the lower visual and other non-visual sensory, motor and association areas were diminished by blindness and mainly reversed after sight restoration. As for the graph theory metrics, although we observed alterations in response to

blindness, partial vision reestablishment did not reverse any of the network measures under study. Consequently, we hypothesize that the ROI-ROI rsFC between visual and non-visual sensory, motor, and association areas can potentially serve as a more suitable biomarker, signifying loss of vision and its reintroduction. Admittedly, in the future, testing this hypothesis requires a larger number of subjects and correlation studies with subjects' behavioral measures.

4.5 Conclusion

Studying the rsFC across the entire brain identified connectivity pairs that were significantly diminished in the RP blind group compared with healthy individuals. These pairs were comprised of visual-somatosensory, visual-auditory, visual-motor, and visual-somatosensory functional connections. In the Argus II sight-restored group, the rsFC of these pairs returned to the level of healthy individuals. I hypothesize that the noted rsFC pairs can potentially serve as biomarkers of blindness and sight restoration and, along with behavioral measures, can further inform researchers and clinicians in the field of visual restoration.

Chapter 5 – Conclusion and Future Work

5.1 Summary of the Main Contributions

This thesis contributed to our understanding of resting-state functional connectivity in blindness and sight restoration. The main contributions are listed below.

1. One primary contribution of the presented replication work of a well-cited ocular blindness neuroimaging study (Bauer et al., 2017) was the discovery of -an error in significant findings of the original paper. During the process of replication, a coding mistake in the calculation of the multiple comparison correction was identified. The unintentional computational error resulted in erroneous FDR calculation. As a result, all the between-group contrast results, originally reported as significant, were rendered invalid after applying an updated FDR correction. This was an important discovery, since some of the originally reported blindness-induced alterations in rsFC, e.g., reduction in visual-frontal rsFC, were in contrast with the findings of other studies (Yu et al., 2020). Identification of this miscalculation removes the source of bewilderment for researchers who may base their hypothesis on the original flawed findings. More generally, this demonstrates the importance of replication in neuroimaging studies.

2. The neuroimaging fMRI studies may benefit from the knowledge that the highest effect sizes, regardless of the computational pipeline used, would likely reflect the true results. In the presented replication study, the largest rsFC z values primarily belonged to specific connection pairs for the three preprocessing streams under study. It was previously shown that the true positive (and not the false positive) results tend to replicate more across studies. The overlap in connection pairs

observed in the presented study may highlight the significance of results verification across various pipelines, in quest of the true results, particularly for clinical studies.

3. In replication works, utilizing similar preprocessing steps that are implemented with different algorithms can differentially impact the resulting fMRI data and rsFC outcome. This is consistent with previous studies that proposed varying implementations of the same procedure could be a source of irreproducibility (Carp, 2012b).

4. One main contribution of my neuroimaging study of Argus II subjects is that the rsFC measures between the early visual cortex and tactile, auditory, motor and parietal association cortices can potentially serve as biomarkers of neuroplastic changes in response to both blindness and sight restoration. Admittedly, establishing such metrics as biomarkers require future longitudinal studies with larger number of subjects, correlating these quantities with patients attributes as well as tracking them before and after sight restoration for each individual Argus II recipient. Previously, Mowad et al. demonstrated the feasibility of using visual-auditory rsFC for studying brain reorganization in early-blind individuals who received RPE65 gene therapy (Mowad et al., 2020). My work not only replicated their findings in Argus II subjects but additionally revealed other novel rsFC pairs that are reduced with vision loss and subsequently reversed to the level of sighted individuals in reaction to regaining vision.

5. The proposed rsFC metrics appear to be more stable and consequently more suitable for quantification of blindness and sight restoration-induced plasticity in Argus II recipients compared with previous attempts that used task-induced cross-modal BOLD activations. In the latest attempt, inconclusive group-level tactile-evoked BOLD responses in the visual cortex were reported in Argus II subjects (Stiles et al., 2020), possibly due to variability in baseline BOLD activation levels across individuals.

6. Sight recovery with Argus II is not able to fully reverse the blindness-induced rsFC alterations within the visual cortex, especially between the higher levels of the ventral visual stream and the visual cortex. This finding further confirms the former proposition by (Beyeler et al., 2017) that impairment of ventral visual stream tasks, such as face and object recognition, persists even over a decade of vision recovery, reflecting a lack of plastic capacity in the visual “what pathway” later in life.

7. Restoring vision does not reverse the possible blindness-induced top-down influences manifested as rsFC alterations between visual and cognitive areas. In the RP subject pool under study, late blindness moderately enhanced the rsFC between visual and higher cognitive areas, consistent with previous studies (Dai et al., 2013; Liu et al., 2008; Sabbah et al., 2016; Y. Yu et al., 2020), and partial sight restoration with Argus II further, but mildly, strengthened this functional connection, a novel effect never previously explored in reaction to return of vision.

8. In the brain functional network analysis, the (edge) density and efficiency of the visual system as well as the nodal weighted degree of some visual areas can be potentially used to signify blindness, as they all demonstrated a clear reduction in response to blindness. Importantly, these effects were robustly consistent across an array of tested thresholds. The level of partial sight recovery with Argus II, however, did not reverse these metrics alterations.

Overall, scientific research is still ongoing for understanding cortical reorganization triggered by loss or return of vision. In human neuroimaging studies, BOLD task activation and rsFC have been the two important measures utilized to quantify plasticity after blindness. As the visual prostheses technologies advance, understanding the efficacy of the existing and future sight restoration approaches necessitates reliable quantification of the resulting brain reorganization. This thesis recommends the use of visual-somatosensory, visual-auditory, visual-motor, and

visual-association rsFC as potential indices of brain functional plasticity, both for blindness and vision recovery. The visual-visual and visual-frontal rsFC as well as the functional network metrics investigated in this work are not advised to be used in sight recovery studies, as my research indicated their alteration primarily in response to blindness and not vision re-establishment. The proposed rsFC metrics, in the absence of or as a complement to the behavioral metrics, can enhance our understanding of variable outcomes among the receivers of sight restorative technologies and enable tracking rehabilitative progress.

5.2 Recommendations

Due to the large number of analysis steps involved in resting-state neuroimaging analysis and the potential diversity in their implementations, my recommendation to any study involving rsFC analysis is to include details of methods in the publication. This should include specifics of data collection, data processing, and statistical inference. The original study we attempted to replicate here did not explicitly state whether certain preprocessing steps were executed, or the precise execution order of some steps was not clear, e.g., temporal filtering done before or after the application of regression. Although we were able to obtain this information by correspondence with the original authors, leaving such small but vital details can harm the transparency and reproducibility of the results. Additionally, neuroimaging studies, and in particular rsFC experiments, should ideally be replicated either with a different dataset, analytical pipeline, or implementation method, to verify the validity of the results.

For future sight restoration approaches, it is important to note that the development of such technologies can benefit from the proposed metrics in this thesis. I would recommend engineers and clinicians in the field to record rsFC between the (primary) visual areas and somatosensory, auditory, association, and motor cortices in the sight restoration candidates, prior to and after

receiving the therapeutic interventions. By recording these measures before and after sight recovery, engineers should be able to determine the functional level of plasticity induced by the restorative method and adjust the therapy parameters or design of the approach accordingly. This is applicable to the design of any sight recovery means, including electronic devices, gene therapy, optogenetics, and stem cell therapy. Moreover, clinicians should utilize and track the suggested rsFC quantities at different stages of rehabilitation after sight restoration and potentially adjust the training according to each individual's level of reorganization revealed by rsFC. Demonstrating the utility of the proposed measures as a rehabilitation aid requires longitudinal clinical studies on vision restoration recipients of various technologies. Certainly, the rsFC indices should be used as complementary trackers of neuroplasticity along with behavioral measures. However, in case of a lack of improvement in visual function after vision recovery, the proposed metrics would provide a means to quantify functional changes likely not yet manifested in the behavior.

Future studies with a larger number of subjects should investigate the correlation between rsFC and the visual performance of individuals. Performance variability among the sight restored can be more thoroughly understood by utilizing the rsFC metrics. Inter-subject differences in behavioral outcomes could be explained by different levels of alteration in functional correlation between the visual cortex and other sensory, motor, and association areas.

The effect of patient characteristics on the rsFC measures should also be examined by the researchers who continue this work. A larger number of subjects are required to enable such stratification and correlation studies. Individual attributes, such as the age of onset of blindness, duration of blindness, age at the time of prosthesis implantation, time since implantation, age at the time of the study, duration, and frequency of device usage, can possibly influence functional

plasticity and alter rsFC measurements. The findings of this thesis can provide the first step toward such larger studies.

For visual prosthetic technologies that can be switched on and off by the implant recipients, one important feature that I would recommend to be built into the prosthesis is to record the device usage times. The lack of this capability in the Argus II device prevented us from running a controlled study in which plastic cortical changes would be monitored after planned device usage durations that would progressively increase. Currently for Argus II, running such an experiment requires reliance on patients' accounts of their device usage, which is prone to error.

Whole-brain functional connectivity during tactile, auditory, and motor tasks should also be evaluated for Argus II subjects. The current thesis proposes the use of functional connectivity during rest to quantify plastic changes in the brain. Manifestation of functional plasticity during task execution has been shown to be different from rest; in blind subjects, a non-visual sensory task led to enhancement in cross-modal BOLD responses in the visual cortex and an increase in functional connectivity between the non-visual sensory and visual cortices (Pelland et al., 2017) during task performance. Consequently, I strongly recommend the exploration of these functional connectivity metrics for the brain state during task execution. I hypothesize alteration in the same functional connectivity pairs to occur while performing a sensory or motor task, but in the opposite direction (compared to rest) for blindness and sight restoration.

Alterations in rsFC attributes should also be replicated across different sight restoration technologies, and for different types of blindness. For late blindness, regardless of the pathology, we hypothesize that, like RP subjects, similar whole-brain rsFC alterations are induced by different sight recovery approaches. In congenital and early blindness, however, the rsFC metrics proposed in this study may not be reversible with sight restoration and can be differently affected. Since

cortical plasticity has been shown to be severely diminished later in life for congenital and early-blind individuals, particularly with limited prior visual experience.

Network neuroscientists are encouraged to explore network metrics other than the ones used in this thesis. The global (edge) density and efficiency as well as the local weighted degree for early visual areas were clearly weakened after vision loss in this study. Unlike rsFC, however, these measures remained mainly unchanged following the return of sight. The network metrics under study, which are measures of influence and information integration in the network, do not appear to measure cross-modal sensory changes and therefore may not be sensitive to partial sight recovery. Other network attributes that measure network segregation, such as modularity are appropriate candidates to be investigated instead that quantify the level to which a network can be divided into inter-connected clusters. Segregation metrics quantify aspects of the brain functional network, different from the ones measured in this study and may more accurately uncover cross-modal changes.

Appendices

Appendix A – Desikan-Killiany Atlas ROIs (Chapter 2)

Table 3 – Description of ROI Name Abbreviations for Desikan-Killiany Atlas

ROI Name Abbreviation	ROI Full Name	ROI Name Abbreviation	ROI Full Name
FrontPole	Frontal Pole	InfTemp	Inferior Temporal
MedOrbFront	Medial Orbitofrontal	MidTemp	Middle Temporal
LatOrbFront	Lateral Orbitofrontal	SupTemp	Superior Temporal
ParsOrb	Pars Orbitalis	BanksSts	Banks of Superior Temporal Sulcus
ParsTrian	Pars Triangularis	TransTemp	Transverse Temporal
ParsOper	Pars Opercularis	Fusi	Fusiform
RostMidFront	Rostral Middle Frontal	Ento	Entorhinal
CaudMidFront	Caudal Middle Frontal	ParaHipp	Parahippocampal
SupFront	Superior Frontal	PostCent	Postcentral
ParaCent	Paracentral	SupraMarg	Supramarginal
PreCent	Precentral	SupPar	Superior Parietal
IsthCing	Isthmus Cingulate	InfPar	Inferior Parietal
PostCing	Posterior Cingulate	PreCuneus	Precuneus
CaudAntCing	Caudal Anterior Cingulate	LatOccip	Lateral Occipital
RostAntCing	Rostral Anterior Cingulate	Lingual	Lingual
Insula	Insula	PeriCalc	Pericalcarine
TempPole	Temporal Pole	Cuneus	Cuneus

Appendix B - Demographic Information (Chapter 3 and 4)

The age and gender information for the participants along with their respective groups of study are presented below.

Table 4 - Test Subjects Demographic Information. Abbreviations: HC = healthy control, RP = retinitis pigmentosa, USC = University of Southern California, UM = University of Michigan and HCP-A = Human Connectome Project, Aging.

Subject	Group	Data Source	Age	Gender
1	HC	USC	36	F
2	HC	USC	44	M
3	HC	USC	64	F
4	HC	HCP-A	64	M
5	HC	HCP-A	38	M
6	HC	HCP-A	45	F
7	HC	HCP-A	53	M
8	HC	HCP-A	54	F
9	HC	HCP-A	75	F
10	HC	HCP-A	72	M
11	RP	USC	57	M
12	RP	USC	52	M
13	RP	USC	55	M
14	RP	USC	44	F
15	RP	USC	24	M
16	RP	USC	48	M
17	RP	USC	40	M
18	RP	USC	70	F
19	RP	USC	60	F
20	RP	USC	61	M
21	Argus II	USC	62	F
22	Argus II	USC	46	M
23	Argus II	USC	61	F
24	Argus II	USC	65	M
25	Argus II	USC	76	M
26	Argus II	UM	70	M
27	Argus II	UM	71	F

Note: The data was acquired from 1 subject before and after the retinal prosthesis implantation surgery. This is included as subject 19 (before) and 23 (after) in Table 1.

Appendix C - Clinical Information (Chapter 3 and 4)

Table 5 - RP and Argus II Test Subjects Clinical Information. Abbreviations: LP = light perception, NLP = no light perception, R = right, L = left, N/A = not available.

Subject	Group	Duration of Blindness (years)
11	RP	24
12	RP	24
13	RP	51
14	RP	37
15	RP	17
16	RP	N/A
17	RP	35
18	RP	52
19	RP	N/A
20	RP	30

Subject	Group	Duration of Blindness (years)	Duration of Prosthetic Use (months)	Frequency of Device Usage (days/week)	Total Rehabilitation Training (hours)	Did Subject attend Univ or Second Sight for additional testing?	Vision Left	Vision Right	Eye with Implant
21	Argus II	17	55	7	12	Yes, visited Second Sight several times for 1-week visits	LP	NLP	R
22	Argus II	20	19.5	3.5	24	Yes, visited Second Sight once	LP	LP	R
23	Argus II	N/A	6.5	N/A	N/A	Yes, visited USC	LP or less	LP or less	L
24	Argus II	26	23	1	30	Yes, visited Second Sight five times for 1-week visits	LP	NLP	R
25	Argus II	38	19	7	13	Yes, visited University of Minnesota four times for 1-2 days each	NLP	NLP	R
26	Argus II	38	48	7	5.75	Yes, visited second sight at least once for a 1-week visit	LP	LP	L
27	Argus II	19	69	2	2.67	N/A	NLP	NLP	L

Appendix D - Summary of the Results of the MRI Acquisition Harmonization between UM and USC Centers (Chapter 3 and 4)

One challenge in merging multicenter neuroimaging data is to derive standardized data features that best signify each center's performance in spite of the inevitable variation in acquisition due to scanners or adopted procedures. In the current work, we aimed to harmonize the acquisition of the magnetic resonance imaging (MRI) data involved in Human Connectome Low Vision (HCLV) project at two imaging centers: University of Southern California (USC) and University of Michigan (UM). To achieve this goal, we executed a case study in which we recruited a traveling subject, a normally-sighted male adult, at both locations. One T1-weighted (T1W) structural and six block-design task functional MRI runs were acquired with identical paradigms at each center. At USC, a 3T Siemens Prisma scanner was used with voxel size 2x2x2 mm (functional) and 0.8x0.8x0.8 mm (structural) and a multiband (MB) factor of 8 for functional runs. At UM, a 3T MR750 GE scanner was used with MB factor of 6, voxel size 2.4x2.4x2.4 mm (functional) and 0.5x0.5x0.8 mm (structural). Preprocessing consisted of homogeneity, physiological noise, field map, motion and slice-timing corrections as well as smoothing, high-pass filtering, registration to T1 MNI152 template. One T1W and one fMRI run were also obtained from a spherical water-based fBIRN phantom filled with agar gel at each center. In order to quantify the performance of the different scanners, we calculated spatial SNR (Signal-to-Noise-Ratio), spatial CNR (Contrast-to-Noise-Ratio; for gray matter (GM) vs white matter (WM) vs CSF) and temporal SNR. In order to make an equitable assessment between the two centers, same repetition time ($TR = 0.8$ s) and number of volumes were used for each pair of functional runs;

also, the spatial and temporal SNR/CNR values were normalized per unit volume to account for differences in voxel sizes at two centers (nSNR/nCNR). Mean spatial nSNR was 42.9/317.1 (human/phantom) at UM and 25.8/54.6 (human/phantom) at USC. Mean spatial nCNR values for GM-WM, GM-CSF, WM-CSF contrasts were respectively 23.6, 15.6 and 39.3 at UM and 9.7, 11.7 and 21.4 at USC. Mean temporal nSNR across voxels of the subject at both locations yielded comparable results (mean of 3.5 vs 3.7 (UM vs USC) across all tasks), whereas this quantity for phantom data was 8.3 vs 16.8 (UM vs USC).

Appendix E - Subject Outlier Identification (Chapter 3 and 4)

Inspection of the ROI-ROI rsFC value between V1 ROI and the rest of the brain for Argus II subjects appeared to reveal a visually noticeable difference in connectivity values for one of Argus II subjects (subject A1 in Figure 32) compared to the rest of the Argus II subjects. In order

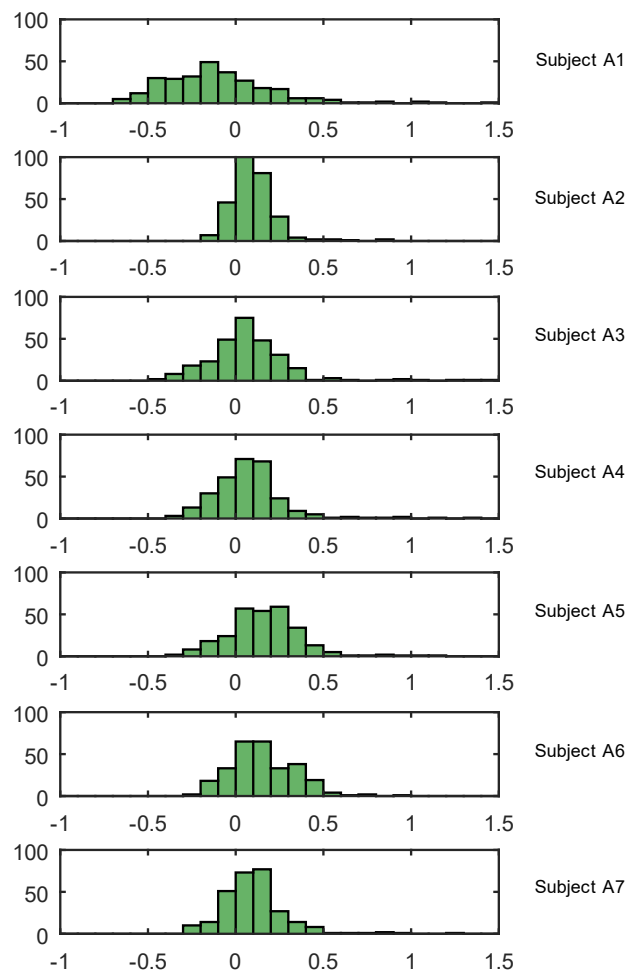


Figure 32 - Distribution of FC Values between V1R and the Rest of the ROIs. Each panel shows the histogram representing the distribution of ROI-ROI FC values (Z) between V1R ROI and the rest of the ROIs (a total of 282 ROIs as defined by 2020 Julich-Brain atlas (V2.9)) for each of Argus II subject.

to further quantify this apparent difference and investigate the possibility of an outlier subject, we conducted the following analysis.

The two sample Kolmogorov-Smirnov (Massey, 1951) (K-S) test was applied to the FC values for each pair of the 8 Argus II subjects. The result of the test along with the corresponding significance values are presented in Table 6. Although the K-S test resulted in significant differences for many subject pairs, the p-values involving subject 1 (the first 7 rows in Table 6) appears to be much smaller than the p-values of other pairs. In order to further look into this difference, we computed the Kernel Density Estimate (KDE) of the 28 p-values shown in Table 6 to non-parametrically estimate the probability density function of these p-values. The resulting KDE is presented in Figure 33.

Table 6 - K-S Tests Applied to FC values between Subject Pairs (seed: V1R). Each row shows the result of applying a 2-sample K-S test to each pair of subjects' FC values, chosen from 8 Argus II subjects. A significant result shows a significant difference between the FC values of the two tested subjects.

Subject X	Subject Y	Result of K-S test (1=significant, 0=not significant)	p-value
1	2	1	6.97089309993593e-38
1	3	1	6.93239843710648e-20
1	4	1	1.35924974213780e-20
1	5	1	3.54802990051738e-33
1	6	1	5.07240627626964e-35
1	7	1	2.20911730868039e-31
1	8	1	3.58561896807544e-18
2	3	1	0.000225142319645637
2	4	1	0.000459224709912611
2	5	1	4.79676489906896e-11
2	6	1	1.07714885509768e-06
2	7	0	0.171026625615983
2	8	1	4.24562726253443e-07
3	4	0	0.807870160297195
3	5	1	6.04460383474617e-08
3	6	1	2.65444757082276e-06
3	7	1	0.0232395981009300
3	8	0	0.342271446958233
4	5	1	1.55841627759349e-10
4	6	1	1.07714885509767e-06

4	7	1	0.0298681593025658
4	8	0	0.245735550358943
5	6	0	0.291177067509870
5	7	1	4.24562726253445e-07
5	8	1	2.21988668722729e-12
6	7	1	0.000909825128536422
6	8	1	1.50746508283792e-09
7	8	1	0.000322716091874584

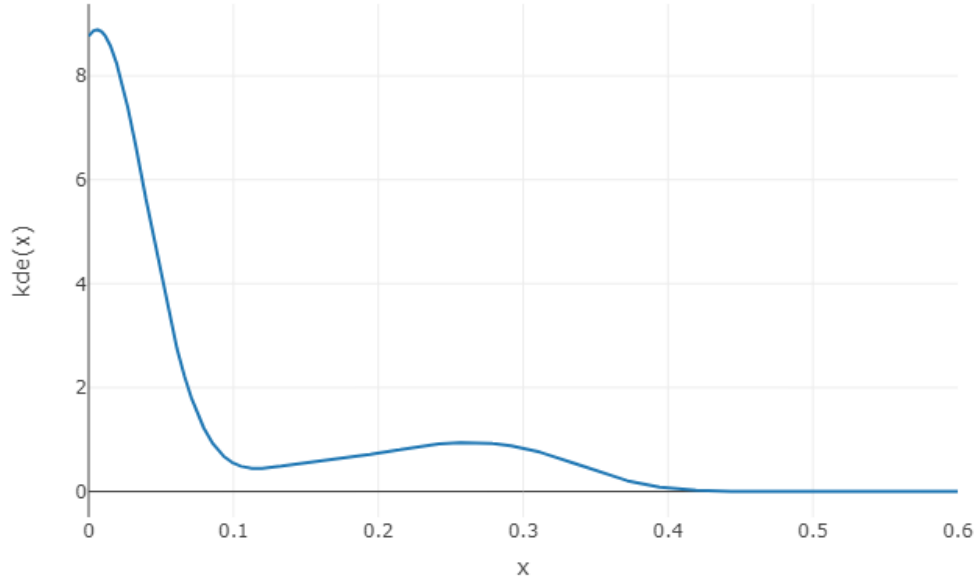


Figure 33 - Kernel Density Estimate of the p -values (seed: V1R). The KDE was computed for all the p -values presented in Table 6. X -axis represents the p -values.

As indicated in Equation 4, we integrated the KDE function presented in Figure 33, for the p -values involving subject 1. The result was an incredibly small probability value of 3.14×10^{-17} , indicating that **subject 1** is very far from all other participants in this study. This is strong evidence that subject 1 may be an outlier.

$$P_{1:8}(x < p[7]) = CDF_{1:8}(3.58 \times 10^{-18}) = \int_0^{3.58 \times 10^{-18}} kde(x)dx = 3.14 \times 10^{-17} \quad \text{Equation 4}$$

We repeated the same analysis for V1L (V1 left) ROI as the seed as indicated in Figure 34, Table 7 and Figure 35. The investigation resulted in similar outcome as indicated in Equation 5. Consequently, Argus II subject 1 was removed from the rest of the analysis for rsFC.

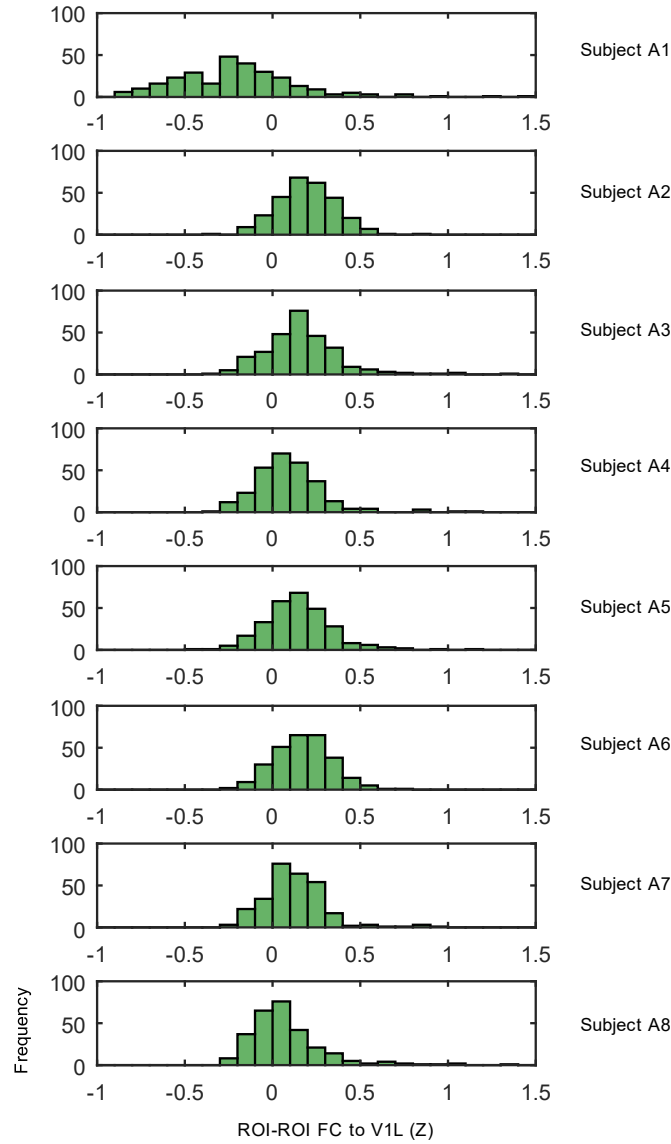


Figure 34 - Distribution of FC Values between V1L and the Rest of the ROIs. Each panel shows the histogram representing the distribution of ROI-ROI FC values (Z) between V1L ROI and the rest of the ROIs (a total of 282 ROIs as defined by 2020 Julich-Brain atlas (V2.9)) for each of Argus II subject.

Table 7 - K-S Tests Applied to FC values between Subject Pairs (seed: V1L). Each row shows the result of applying a 2-sample K-S test to each pair of subjects' FC values, chosen from 8 Argus II subjects. A significant result shows a significant difference between the FC values of the two tested subjects.

Subject A	Subject B	Result of K-S test (1=significant, 0=not significant)	p-value
1	2	1	2.94356628930396e-59
1	3	1	3.03552098721553e-48
1	4	1	6.97089309993593e-38
1	5	1	1.07224777262513e-47
1	6	1	1.92148901841483e-57
1	7	1	1.30900831014120e-46
1	8	1	5.07240627626964e-35
2	3	1	0.0381090965854382
2	4	1	7.75629702972784e-12
2	5	1	0.00175087512674723
2	6	0	0.171026625615983
2	7	1	4.24562726253445e-07
2	8	1	3.43425341613383e-19
3	4	1	4.12178256834523e-06
3	5	0	0.460999028158125
3	6	0	0.205784138661939
3	7	1	0.0104793476841627
3	8	1	2.21988668722730e-12
4	5	1	7.31835598435305e-05
4	6	1	1.29798392677044e-08
4	7	1	0.00175087512674723
4	8	0	0.115524418832263
5	6	0	0.0606996862648646
5	7	0	0.0939042216839960
5	8	1	7.66041130793069e-09
6	7	1	1.47728642708130e-05
6	8	1	1.11347885308774e-14
7	8	1	1.69708801772414e-06

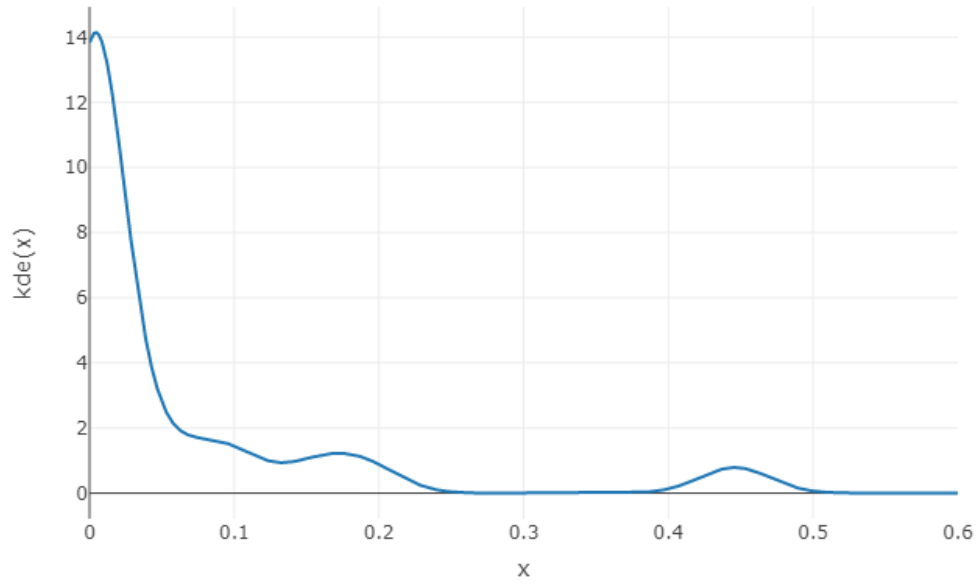


Figure 35 - Kernel Density Estimate of the p -values (seed: V1L). The KDE was computed for all the p -values presented in Table 7. X-axis represents the p -values.

$$P_{1:8}(x < p[7]) = CDF_{1:8}(5.07 \times 10^{-35}) = \int_0^{5.07 \times 10^{-35}} kde(x)dx = 7.012714 \times 10^{-34}$$

Equation 5

Appendix F - Normality Test, Effect Size and Power (Chapter 3 and 4)

1) Normality Test

For each of the 3 subject groups (or a combination of the groups), for each voxel, a two-sample Kolmogorov-Smirnov (K-S) test (Massey, 1951) was applied for comparison with a normal distribution with the same mean and standard deviation, as follows.

K-S test for each voxel (between HC + RP + Argus II and a normal distribution with the same mean and standard deviation):

Number of voxels with significant results / percentage (uncorrected): 198 / 8.3961e-04%

Number of voxels with significant results / percentage (corrected): 0 / 0

K-S test for each voxel (between HC and a normal distribution with the same mean and standard deviation):

Number of voxels with significant results / percentage (uncorrected): 14 / 5.9366e-05%

Number of voxels with significant results / percentage (corrected): 0 / 0

K-S test for each voxel (between RP and a normal distribution with the same mean and standard deviation):

Number of voxels with significant results / percentage (uncorrected): 32 / 1.3569e-04%

Number of voxels with significant results / percentage (corrected): 0 / 0

K-S test for each voxel (between Argus II and a normal distribution with the same mean and standard deviation):

Number of voxels with significant results / percentage (uncorrected): 1 / 4.2404e-06%

Number of voxels with significant results / percentage (corrected): 0 / 0

2) Effect Size

The ROI-to-ROI analysis for RP > HC contrast resulted in a statistically significant result with an effect size of -0.45. Another previous study that looked at the effect of blindness in late-blind vs healthy control subjects showed an approximate effect size of -0.15 between left/right V1 and Pre/Post central gyrus (Wen et al., 2018). The ROI-to-ROI analysis for Argus II > RP contrast resulted in a statistically significant result with an effect size of 0.28. To our knowledge, no sight restoration study has quantified such effect size prior to this work. The ROI-to-ROI analysis for Argus II > HC did not result in any significant result.

3) Power Analysis:

For power analysis for RP>HC contrast, we used an approximate effect size of -0.15, obtained from an older study on the effect of late blindness (Wen et al., 2018). We also used the sample size of our study (10 (HC) + 10 (RP) – 2) and the desired type I error rate (0.05). Therefore, assuming an effect size of -0.15, a statistical power of 0.95 was yielded. For Argus II > RP contrast, to our knowledge, no sight restoration study has quantified such effect size prior to this work.

Appendix G – Julich Brain 2020 Atlas ROIs (Chapter 3 and 4)

Table 8 - Julich-Brain 2020 Atlas ROIs. The Julich-Brain v 2.9 atlas includes 282 small ROIs or 39 larger ROIs and detailed below

Small ROI Number	Small ROI Acronym	Large ROI Acronym	Large ROI Full Name	Large ROI Number
1	Area Fp1 (Fpole) r	Fpole	Frontal Pole	1
2	Area Fp1 (Fpole) l			
3	Area Fp2 (Fpole) r			
4	Area Fp2 (Fpole) l			
5	Area Fo1 (OFC) r	OFC	OrbitoFrontal Cortex	2
6	Area Fo1 (OFC) l			
7	Area Fo2 (OFC) r			
8	Area Fo2 (OFC) l			
9	Area Fo3 (OFC) r			
10	Area Fo3 (OFC) l			
11	Area Fo4 (OFC) r			
12	Area Fo4 (OFC) l			
13	Area Fo5 (OFC) r			
14	Area Fo5 (OFC) l			
15	Area Fo6 (OFC) r			
16	Area Fo6 (OFC) l			
17	Area Fo7 (OFC) r			
18	Area Fo7 (OFC) l			
19	Area 8d1 (SFG) r	SFG	Superior Frontal Gyrus	3
20	Area 8d1 (SFG) l			
21	Area 8d2 (SFG) r			
22	Area 8d2 (SFG) l			
23	Area 6d3 (SFS) r	SFS	Superior Frontal Sulcus	4
24	Area 6d3 (SFS) l			
25	Area 8v1 (MFG) r	MFG	Middle Frontal Gyrus	5
26	Area 8v1 (MFG) l			
27	Area 8v2 (MFG) r			
28	Area 8v2 (MFG) l			
29	Area IFS1 (IFS) r	IFS	Inferior Frontal Sulcus	6
30	Area IFS1 (IFS) l			
31	Area IFS2 (IFS) r			
32	Area IFS2 (IFS) l			
33	Area IFS3 (IFS) r			

34	Area IFS3 (IFS) l			
35	Area IFS4 (IFS) r			
36	Area IFS4 (IFS) l			
37	Area IFJ1 (IFS, PreCS) r			
38	Area IFJ1 (IFS, PreCS) l			
39	Area IFJ2 (IFS, PreCS) r			
40	Area IFJ2 (IFS, PreCS) l			
41	Area 44 (IFG) r	IFG	Inferior Frontal Gyrus	7
42	Area 44 (IFG) l			
43	Area 45 (IFG) r			
44	Area 45 (IFG) l			
45	Ch 4 (Basal Forebrain) r	BasFB	Basal Forebrain	8
46	Ch 4 (Basal Forebrain) l			
47	Ch 123 (Basal Forebrain) r			
48	Ch 123 (Basal Forebrain) l			
49	Entorhinal Cortex r	Ent	Entorhinal Cortex	9
50	Entorhinal Cortex l			
51	Area 6ma (preSMA, mesial SFG) r	preSMA	Pre-supplementary Motor Area	10
52	Area 6ma (preSMA, mesial SFG) l			
53	Area 6mp (SMA, mesial SFG) r	SMA	Supplementary Motor Area	11
54	Area 6mp (SMA, mesial SFG) l			
55	Area 4a (PreCG) r	PreCG	Pre-central Gyrus	12
56	Area 4a (PreCG) l			
57	Area 4p (PreCG) r			
58	Area 4p (PreCG) l			
59	Area 6d1 (PreCG) r			
60	Area 6d1 (PreCG) l			
61	Area 6d2 (PreCG) r			
62	Area 6d2 (PreCG) l			
63	Area 3b (PostCG) r	PostCG	Post-central Gyrus	13
64	Area 3b (PostCG) l			
65	Area 1 (PostCG) r			
66	Area 1 (PostCG) l			
67	Area 2 (PostCS) r			
68	Area 2 (PostCS) l			
69	Area 3a (PostCG) r			
70	Area 3a (PostCG) l			
71	Area OP1 (pOperc) r	pOperc	Parietal Operculum	14
72	Area OP1 (pOperc) l			
73	Area OP2 (pOperc) r			
74	Area OP2 (pOperc) l			
75	Area OP3 (pOperc) r			
76	Area OP3 (pOperc) l			
77	Area OP4 (pOperc) r			
78	Area OP4 (pOperc) l			
79	Area Op5 (Frontal Operculum) r	fOperc		15

80	Area Op5 (Frontal Operculum) l		Frontal Operculum	
81	Area Op6 (Frontal Operculum) r			
82	Area Op6 (Frontal Operculum) l			
83	Area Op7 (Frontal Operculum) r			
84	Area Op7 (Frontal Operculum) l			
85	Area Op8 (Frontal Operculum) r			
86	Area Op8 (Frontal Operculum) l			
87	Area Op9 (Frontal Operculum) r			
88	Area Op9 (Frontal Operculum) l			
89	Area TE 1.0 (Heschl) r	Heschl	Heschl's Gyrus	16
90	Area TE 1.0 (Heschl) l			
91	Area TE 1.1 (Heschl) r			
92	Area TE 1.1 (Heschl) l			
93	Area TE 1.2 (Heschl) r			
94	Area TE 1.2 (Heschl) l			
95	Area TE 2.1 (STG) r	STG	Superior Temporal Gyrus	17
96	Area TE 2.1 (STG) l			
97	Area TE 2.2 (STG) r			
98	Area TE 2.2 (STG) l			
99	Area TE 3 (STG) r			
100	Area TE 3 (STG) l			
101	Area TI (STG) r			
102	Area TI (STG) l			
103	Area TeI (STG) r			
104	Area TeI (STG) l			
105	Area TPJ (STG/SMG) r			
106	Area TPJ (STG/SMG) l			
107	Area STS1 (STS) r	STS	Superior Temporal Sulcus	18
108	Area STS1 (STS) l			
109	Area STS2 (STS) r			
110	Area STS2 (STS) l			
111	Area hOc1 (V1, 17, CalcS) r	V1	V1	19
112	Area hOc1 (V1, 17, CalcS) l			
113	Area hOc2 (V2, 18) r	V2	V2	20
114	Area hOc2 (V2, 18) l			
115	Area hOc3d (Cuneus) r	CunG	Cuneus Gyrus	21
116	Area hOc3d (Cuneus) l			
117	Area hOc4d (Cuneus) r			
118	Area hOc4d (Cuneus) l			
119	Area hOc3v (LingG) r	LingG	Lingual Gyrus	22
120	Area hOc3v (LingG) l			
121	Area hOc4v (LingG) r			
122	Area hOc4v (LingG) l			
123	Area hOc4la (LOC) r	LOC	Lateral Occipital Complex	23
124	Area hOc4la (LOC) l			
125	Area hOc4lp (LOC) r			

126	Area hOc4lp (LOC) l	POS	Parieto-Occipital Sulcus	24
127	Area hOc5 (LOC) r			
128	Area hOc5 (LOC) l			
129	Area hOc6 (POS) r			
130	Area hOc6 (POS) l			
131	Area hPO1 (POS) r			
132	Area hPO1 (POS) l			
133	Area 5Ci (SPL) r	SPL	Superior Parietal Lobule	25
134	Area 5Ci (SPL) l			
135	Area 5L (SPL) r			
136	Area 5L (SPL) l			
137	Area 5M (SPL) r			
138	Area 5M (SPL) l			
139	Area 7A (SPL) r			
140	Area 7A (SPL) l			
141	Area 7M (SPL) r			
142	Area 7M (SPL) l			
143	Area 7P (SPL) r			
144	Area 7P (SPL) l			
145	Area 7PC (SPL) r			
146	Area 7PC (SPL) l			
147	Area hIP1 (IPS) r	IPS	Intra Parietal Sulcus	26
148	Area hIP1 (IPS) l			
149	Area hIP2 (IPS) r			
150	Area hIP2 (IPS) l			
151	Area hIP3 (IPS) r			
152	Area hIP3 (IPS) l			
153	Area hIP4 (IPS) r			
154	Area hIP4 (IPS) l			
155	Area hIP5 (IPS) r			
156	Area hIP5 (IPS) l			
157	Area hIP6 (IPS) r			
158	Area hIP6 (IPS) l			
159	Area hIP7 (IPS) r			
160	Area hIP7 (IPS) l			
161	Area hIP8 (IPS) r			
162	Area hIP8 (IPS) l			
163	Area PF (IPL) r	IPL	Inferior Parietal Lobule	27
164	Area PF (IPL) l			
165	Area PFcm (IPL) r			
166	Area PFcm (IPL) l			
167	Area PFm (IPL) r			
168	Area PFm (IPL) l			
169	Area PFop (IPL) r			
170	Area PFop (IPL) l			
171	Area PFt (IPL) r			

172	Area PFt (IPL) l			
173	Area PGa (IPL) r			
174	Area PGa (IPL) l			
175	Area PGp (IPL) r			
176	Area PGp (IPL) l			
177	BST (Bed Nucleus) r	BedNuc	Bed Nucleus	28
178	BST (Bed Nucleus) l			
179	CM (Amygdala) r	Amg	Amygdala	29
180	CM (Amygdala) l			
181	MF (Amygdala) r			
182	MF (Amygdala) l			
183	LB (Amygdala) r			
184	LB (Amygdala) l			
185	SF (Amygdala) r			
186	SF (Amygdala) l			
187	VTM (Amygdala) r			
188	VTM (Amygdala) l			
189	CA1 (Hippocampus) r	Hipp	Hippocampus	30
190	CA1 (Hippocampus) l			
191	CA2 (Hippocampus) r			
192	CA2 (Hippocampus) l			
193	CA3 (Hippocampus) r			
194	CA3 (Hippocampus) l			
195	HC-Parasubiculum (Hippocampus) r			
196	HC-Parasubiculum (Hippocampus) l			
197	HC-Presubiculum (Hippocampus) r			
198	HC-Presubiculum (Hippocampus) l			
199	HC-Prosubiculum (Hippocampus) r			
200	HC-Prosubiculum (Hippocampus) l			
201	HC-Subiculum (Hippocampus) r			
202	HC-Subiculum (Hippocampus) l			
203	HC-Transsubiculum (Hippocampus) r			
204	HC-Transsubiculum (Hippocampus) l			
205	HATA (Hippocampus) r			
206	HATA (Hippocampus) l			
207	DG (Hippocampus) r			
208	DG (Hippocampus) l			
209	Area CoS1 (CoS) r	CoS	Collateral Sulcus area 1	31
210	Area CoS1 (CoS) l			
211	Area FG1 (FusG) r	FusG	Fusiform Gyrus	32
212	Area FG1 (FusG) l			
213	Area FG2 (FusG) r			
214	Area FG2 (FusG) l			
215	Area FG3 (FusG) r			
216	Area FG3 (FusG) l			
217	Area FG4 (FusG) r			

218	Area FG4 (FusG) l			
219	Area Ph1 (PhG) r	PhG	Parahippocampal Gyrus	33
220	Area Ph1 (PhG) l			
221	Area Ph2 (PhG) r			
222	Area Ph2 (PhG) l			
223	Area Ph3 (PhG) r			
224	Area Ph3 (PhG) l			
225	Area 33 (ACC) r	ACC	Anterior Cingulate Cortex	34
226	Area 33 (ACC) l			
227	Area p24ab (pACC) r	pACC	Pregenua Anterior Cingulate Cortex	35
228	Area p24c (pACC) l			
229	Area p24c (pACC) r			
230	Area p24ab (pACC) l			
231	Area p32 (pACC) r			
232	Area p32 (pACC) l			
233	Area 25 (sACC) r	sACC	Subgenual Anterior Cingulate Cortex	36
234	Area 25 (sACC) l			
235	Area s24 (sACC) r			
236	Area s24 (sACC) l			
237	Area s32 (sACC) r			
238	Area s32 (sACC) l			
239	Area Ia1 (Insula) r	Insula	Insula	37
240	Area Ia1 (Insula) l			
241	Area Ia2 (Insula) r			
242	Area Ia2 (Insula) l			
243	Area Ia3 (Insula) r			
244	Area Ia3 (Insula) l			
245	Area Id1 (Insula) r			
246	Area Id1 (Insula) l			
247	Area Id2 (Insula) r			
248	Area Id2 (Insula) l			
249	Area Id3 (Insula) r			
250	Area Id3 (Insula) l			
251	Area Id4 (Insula) r			
252	Area Id4 (Insula) l			
253	Area Id5 (Insula) r			
254	Area Id5 (Insula) l			
255	Area Id6 (Insula) r			
256	Area Id6 (Insula) l			
257	Area Id7 (Insula) r			
258	Area Id7 (Insula) l			
259	Area Id8 (Insula) r			
260	Area Id8 (Insula) l			
261	Area Id9 (Insula) r			
262	Area Id9 (Insula) l			
263	Area Id10 (Insula) r			

264	Area Id10 (Insula) l			
265	Area Ig1 (Insula) r			
266	Area Ig1 (Insula) l			
267	Area Ig2 (Insula) r			
268	Area Ig2 (Insula) l			
269	Area Ig3 (Insula) r			
270	Area Ig3 (Insula) l			
271	CGL (Metathalamus) r	MTh	Metathalamus	38
272	CGL (Metathalamus) l			
273	CGM (Metathalamus) r			
274	CGM (Metathalamus) l			
275	Dorsal Dentate Nucleus (Cerebellum) r	Cerebel.	Cerebellum	39
276	Dorsal Dentate Nucleus (Cerebellum) l			
277	Ventral Dentate Nucleus (Cerebellum) r			
278	Ventral Dentate Nucleus (Cerebellum) l			
279	Fastigial Nucleus (Cerebellum) r			
280	Fastigial Nucleus (Cerebellum) l			
281	Interposed Nucleus (Cerebellum) r			
282	Interposed Nucleus (Cerebellum) l			

Appendix H – A Sample Circular Connectogram (Chapter 2)

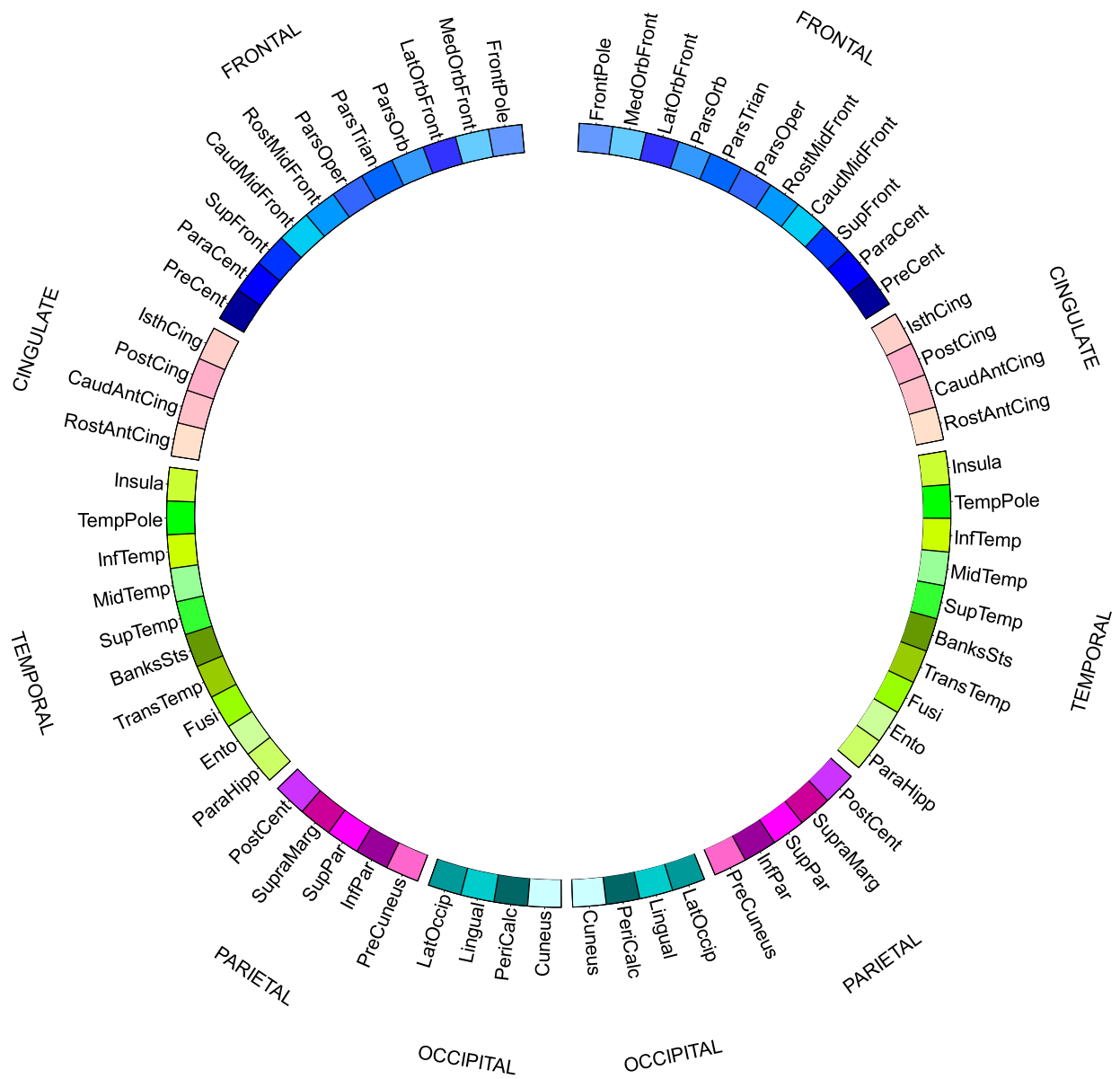


Figure 36 – Elements of Replicated Connectograms in Chapter 2

Appendix I – Individuals' V1-S1 rsFC Values (Chapter 3)

Table 9 - V1-S1 rsFC Values for Individual Subjects

Subject	Group	V1-S1 rsFC (Z)	Subject	Group	V1-S1 rsFC (Z)	Subject	Group	V1-S1 rsFC (Z)
1	HC	0.48	11	RP	-0.03	21	Argus II	0.36
2	HC	0.38	12	RP	-0.04	22	Argus II	0.09
3	HC	0.60	13	RP	0.00	23	Argus II	0.09
4	HC	0.53	14	RP	0.05	24	Argus II	0.48
5	HC	0.08	15	RP	-0.14	25	Argus II	0.42
6	HC	0.40	16	RP	0.21	26	Argus II	0.25
7	HC	0.25	17	RP	0.15	27	Argus II	0.12
8	HC	0.21	18	RP	0.05			
9	HC	0.46	19	RP	-0.19			
10	HC	0.82	20	RP	-0.30			

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