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P1: Developing a task to study neural correlates of causal inference for perception of object motion and depth in macaques

Amir-Mohammad Alizadeh, Ranran L. French, Gregory C. DeAngelis

Because movements of both the observer and objects in the world contribute to retinal image motion, the brain needs to infer the combination of observer and object movement that generates image motion, which is a causal inference problem. Our goal is to understand the neural basis of these computations by studying the perceptual and neural interactions between three ecologically-related variables: self-motion, object motion, and depth. In a previous study, human subjects judged the depth of an object, as well as its motion in the world, while lateral self-motion was simulated by optic flow. When asked to simultaneously report both depth and object motion, subjects showed depth biases that depend on their causal inference regarding object motion in the world.

We are developing a comparable task for macaque monkeys, in which they view a scene that consists of a textured ground plane, stationary objects on the ground plane, and a target object that may be stationary or moving relative to the scene. Many different combinations of depth, object velocity in the world, and self-motion velocity are presented, such that retinal velocity is not a reliable indicator of object motion in the world. Monkeys are being trained to report whether the target object is moving vs. stationary in the scene. Once animals are trained, we will simultaneously record neural activity from parietal area 7a and visual areas MT/MSTd using laminar electrode arrays. We will test the hypothesis that representations of depth and self-motion velocity update based on the animal's inference regarding object motion in the world.

P2: Causal inference modulates optic flow parsing in the macaque

Grace F. DiRisio, Yelin Dong, Zhe-Xin Xu, and Gregory C. DeAngelis

Retinal image motion arises from two sources: the observer's self-motion and movement of objects in the environment. To guide behavior, the observer needs to determine whether retinal motion vectors arise from one source (self-motion) or two (self-motion and object movement). This is a problem of causal inference. Previous work has suggested a mechanism called "flow parsing", in which optic flow associated with self-motion is subtracted to compute object motion in the world. Behavioral biases consistent with flow parsing have been observed in both humans and macaques, and we have observed neural correlates of flow parsing in area MT.

However, flow parsing should only be performed if an object is moving relative to the world. If the observer believes that an object is stationary in the world, then its motion should instead be integrated with that of nearby background elements. Thus, we hypothesize that causal inference modulates flow parsing. We trained a macaque to report whether a random dot stimulus moves clockwise or counter-clockwise relative to a reference direction, while optic flow simulates self-motion. By manipulating the flow field, we measure perceptual biases under conditions that favor motion integration vs. flow parsing. Consistent with causal inference, preliminary results demonstrate a transition from flow parsing to motion integration as the object's velocity becomes more similar to background flow. Our next steps will involve investigating how this transition is manifest in neural activity in macaque MT.

P3: Online estimation and tracking of perceptual biases for studying causal inference

Yelin Dong, Gabor Lengyel, Sabyasachi Shivkumar, Grace F. DiRisio, Ralf Haefner, Gregory C. DeAngelis

A fundamental task for the brain is to make inferences about objects and events in the world that give rise to sensory input (causal inference). To study neural mechanisms of causal inference, it is valuable to measure perceptual biases resulting from the inference process. In humans, perceptual biases are often measured in psychophysical tasks without providing decision feedback, such that feedback does not alter intrinsic biases. In experimental animals, measurement of perceptual biases is complicated by the fact that rewards need to be provided to motivate task performance. If animals are rewarded veridically, then their intrinsic biases may diminish through reinforcement-based learning. Thus, there is a critical need for methods to estimate perceptual biases in real-time and to reward animals for performance around their intrinsic biases.

We developed a Bayesian framework for estimating and tracking perceptual biases online, and we apply this method to behavioral data from a direction discrimination task in which background optic flow induces perceptual biases. The framework decomposes overall biases into a combination of perceptual and decision biases, the latter of which may vary over time. Prior distributions for the biases can be specified, and the algorithm automatically updates its posterior estimates of perceptual biases after each trial is completed. This approach allows us to measure intrinsic perceptual biases that reflect causal inference without them being shaped by rewards, and should be broadly applicable to many types of experiments.

P4: Coordinate Transforms Mediating Tactile Motion Representations with the Hand

Himanshu Ahuja, Catalina Feistritzer, Sabyasachi K. Shivkumar, Ralf M. Haefner, Gregory C. DeAngelis, and Manuel Gomez-Ramirez

Our ability to perceive motion information on the skin is key to manipulating dynamic objects in the environment. Previous studies show that the brain derives tactile motion representations by integrating cues of the object that impinge on the skin (e.g., speed, force, direction), a mechanism known as the Full Vector Average model. This model was derived from studies that placed the hand in the same posture. Yet, object perception with the hand is a highly dynamic function. Thus, it is key to study whether motion inputs on the skin are transformed by hand position, and whether these transformations depend on the reference frame of the motion discrimination judgement. Here, we asked human participants to discriminate motion stimuli on the index finger in a hand-centric or sternum-centric reference frame, while the stimulated hand was placed in different postures. Human participants were instructed to judge whether a stimulus was moving to the left- or right-side (relative to their sternum) or towards vs. away from their thumb (i.e., hand-centric task). The data revealed that humans flexibly represent tactile motion information according to the instructed reference frame, with motion judgements relative to the sternum perceived with higher sensitivity. Furthermore, we found a response bias that is not only posture dependent, as has previously been reported but also dependent on the reference frame in which the judgment is made. We also developed a Bayesian generative model that accounts for the motion percepts in different reference frames and postural configurations. These data show that perceptual representations of tactile motion are generated by neural circuits that integrate cutaneous and proprioceptive inputs from the hand, and are under control of goal-directed cortical signals.

P5: The role of proinflammatory cytokines in retinal ganglion cell death

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Glaucoma is a neurodegenerative disease that leads to the death of retinal ganglion cells (RGCs), the main output neurons of the retina, and is the second leading cause of blindness in the world. Therefore, identifying the molecular mechanisms underlying how glaucomatous injury leads to RGC death is crucial. Recent studies have supported a novel role for inflammatory extrinsic signaling as an early driver of glaucomatous neurodegeneration. Specifically, two cytokines have been implicated as potential early drivers of RGC death: interleukin 1 alpha (IL1A) and tumor necrosis factor (TNF). Intravitreal injection of TNF is sufficient to drive RGC death at a delayed rate, ~8-12 weeks post-injection. However, the potential contribution of IL1A in driving RGC death has not been assessed. To assess whether these cytokines alone or in combination are sufficient to drive RGC loss, eyes of 2-5-month-old C57BL/6J male and female mice were intravitreally injected with 2 µL of IL1A alone (1 mg/mL), TNF (100 µg/mL), IL1A+TNF, or PBS. Combined injection of TNF and IL1A resulted in 20% RBPMS+ RGC loss 14 days post-injection. Injection of TNF or IL1A alone did not result in RGC loss at this early timepoint. Thus, IL1+TNF, but not IL1A or TNF alone, was sufficient to drive RGC loss 14 days post injection. In addition, 12 weeks following IL1+TNF application there was no exacerbated loss of RGCs. Assessment at 1,3,5,7 and 10 days following IL1+TNF injection revealed that RGCs are dying via apoptosis starting at 3 days as shown by cleaved-caspase 3 activation To determine the downstream signaling required for IL1+TNF-induced degeneration, mice with homozygous Jun^{fl} alleles that were conditionally recombined in retinal neurons and macroglia with Six3-cre, mice deficient in Sarm1, and mice deficient in the sole interleukin 1 receptor Il1r1 were injected with IL1+TNF. While JUN was activated 3 days following IL1+TNF injection, Six3-cre^{+} $Jun^{fl/fl}$ RGCs were not protected 14 days following IL1+TNF insult. However, mice with deletion of Sarm1 or Il1r1 showed no significant loss of RGCs post-IL1+TNF. In summary, combined intravitreal injection TNF and IL1A was sufficient to drive RGC loss 14 days after injury. Studies have shown that TNF is sufficient to kill 15-20% RGCs 8-12 weeks post-injection, but our findings show that combined application of TNF and IL1A acted in a rapid and synergistic manner to drive RGC death. Furthermore, we show that this death was SARM1 dependent and JUN independent, which contrasts with their roles in RGC death after axonal injury.

P6: High resolution alterations to the RPE – Photoreceptor complex secondary to pentosan polysulfate maculopathy

Kristen Bowles Johnson

Pentosan polysulfate (PPS) toxicity was first described in 2018. Progressive parafoveal outer retinal and RPE atrophy can occur even years after the cessation of PPS. Although PPS toxicity has extensive outer retinal damage in severe cases, the fovea typically remains intact. PPS toxicity could be a good model to investigate the cellular scale changes that occur in outer retinal atrophy using adaptive optics ophthalmoscopy. This case series reveals the variety of cellular scale alterations in the RPE and photoreceptor structure secondary to PPS maculopathy and provides a baseline for future studies of disease progression.

P7: Comparison of visual tuning and pre-saccadic attention modulation between area MT and MTC of the marmoset monkey

Amy Bucklaew[1], Shanna Coop[2], Jude Mitchell[2]; [1]Neuroscience Graduate Program, University of Rochester, [2]Brain and Cognitive Sciences, University of Rochester

While the middle temporal (MT) area has been extensively studied at the neural level to understand mechanisms of motion processing and selective attention, much less is known about the adjacent strip of parafoveal cortex, area MTC. In the macaque, area MT lies at the bottom of the superior temporal sulcus requiring deep electrode penetrations that traverse white and gray matter before reaching it. MT neurons are typically identified based on their receptive field (RF) size and direction selective responses. However, adjacent area MTC (also called V4t) has been reported to contain neurons with similar sized RFs, a significant portion of which have motion selective responses (Rosa & Elston, 1998). Here we examined the visual response properties and the modulation by pre-saccadic attention of area MTC, comparing it directly against MT in the same animal. We made recordings from linear arrays as a marmoset monkey performed a saccade foraging task selecting between peripheral random dot motion stimuli. Both area MT and MTC lie exposed at the cortical surface in the marmoset, making it possible to distinguish their border based on their retinotopy across successive recordings. We found that MTC had fewer neurons with direction selective responses consistent with previous reports (Rosa and Eltson 1998) and had more neurons selective for the orientation and spatial frequency of flashed gratings. We also measured how pre-saccadic attention modulates neural tuning curves for motion direction, comparing responses where a saccade was made towards the RF (i.e., attended) versus away from it. Neurons in both areas showed increases in baseline firing and in the gain of their tuning curves, but the increases in gain where larger in MTC while the increases in baseline were smaller. Despite a weaker net motion tuning in MTC, those neurons showed larger percentage increases in neural sensitivity for motion direction.

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P8: Image scanning microscopy for in vivo ganglion cells classification

Yongyi (Christie) Cai, David R. Williams, James R. Fienup, Sara Patterson, Juliette E. McGregor, William H. Merigan

Among the ~20 types of ganglion cells (RGCs) that have been anatomically identified in the primate retina, only the most common have been characterized physiologically, mainly in the peripheral retina. The reason for the highly specified RGCs remains unclear. To study the essential yet understudied RGC types physiologically, in vivo classification is required, mainly by visualizing the fine structure of dendritic arbors at a subcellular scale. We will develop a versatile image scanning microscope (ISM) based on an existing adaptive optics scanning laser ophthalmoscope (AOSLO), enabling superresolution and high contrast for a full characterization of RCG types. We demonstrate the predicted advantages from ISM on resolution and signal intensity by simulating the imaging process using histological RGCs images. The results show ISM raises the peak intensity of the tiny identifying features in the dendritic arbor above the background noise much more effectively than AOSLO with an estimated 5.6-fold increase in SNR and a 24% resolution improvement.

P9: Unilateral V1 damage leads to micro-offsets of monocular fixation towards the cortically-blinded field

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Worldwide, between 20-57% of strokes result in vision loss or partial cortically-induced blindness. The consequences of this condition are not only perceptual but also visuomotor; it is known that saccades in these patients are biased towards their blind field. Since this condition normally impairs extrafoveal vision, it's often assumed that fixation is unaffected and that fixational eye movements are normal.

To test these assumptions, we measured fixational eye movements in 11 patients (age=56±4yrs, 2F/9M) and 10 aged-matched control observers (age=45±4yrs, 6F/2M) using a high-precision digital Dual-Purkinje Image eyetracker. Under monocular viewing, in alternative trials, participants either performed an active foveal 4AFC high-acuity discrimination task, or a passive fixation task in which they maintained the gaze on a central 16'x16' target for 5s. Stimuli in the acuity task consisted of isolated digits presented for 500 ms, and their size was adjusted using an adaptive procedure.

Our results show that fixation precision was comparable between patients (Bivariate-Contour Ellipse Area [BCEA] =3.2±0.20deg^2) and controls (BCEA = 2.9±0.17deg^2). However, while controls' gaze was centered on the fixation target during the passive task, patients exhibited significant offsets in gaze position. Offsets were present throughout the fixation duration and were systematically biased toward the blind field, with an average shift of 4.2'±1.1' (unpaired t-test, $p = 0.024$), but they disappeared when patients performed the high-acuity foveal task. Patients and controls also had similar visual-acuity thresholds, indicating that gaze offsets recorded in the passive fixation task were not due to reduced foveal vision. These findings show that cortical blindness affecting extrafoveal vision introduces micro-offsets in gaze position during passive fixation. We posit that this abnormal behavior may reflect an attentional bias toward the blind field when patients are not engaged in a foveal task.

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P10: Consequences of Eye's Optics and Geometry for Retinal Image Motion

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A substantial body of evidence supports the long-standing hypothesis that the visual system uses luminance modulations from eye movements to encode spatial information in the temporal domain. For simplicity, eye movements are commonly assumed to translate the image across the retina consistently, yielding luminance modulations with uniform statistics across the visual field. However, in reality, the optics and kinematics of the eye interact to yield a more complex pattern of image motion. Here we show that these considerations may have functional consequences for neural encoding and emmetropization. Using a detailed optical model of the rotating eye with a non-spherical retina, we examined two conceptually separate but geometrically related factors that contribute to retinal image motion: (1) Optical distortion, the mapping of visual space onto the retina, which is influenced by the eye's refracting properties; and (2) motion transfer, the amount of motion at each point of the retinal image, which depends on the eye's center of rotation. In an emmetropic eye accommodated to infinity, we find that retinal image motion increases nonlinearly across retinal eccentricity, with ~30% greater retinal image speed in the periphery compared to the fovea. This effect implies that the characteristics of luminance modulations induced by eye movements also vary with eccentricity. Specifically, during fixation, luminance modulations will deliver increasingly more power at low spatial frequencies as eccentricity increases. This transformation is altered in non-emmetropic eyes due to differences in eye shape, with each diopter of spectacle refraction resulting in a ~3% change in peripheral retinal image motion. Since there is greater motion in hyperopic eyes and less motion in myopic eyes relative to emmetropic eyes, the statistics of image motion provide a cue to the sign of blur, which can be accessed from the temporal content of neural signals.

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P11: Longitudinal tracking of immune cells to inner and outer retinal inflammation in the living eye

Derek Power*, Kosha Y Dholakia*, Jesse Schallek

DP and KYD have contributed equally

Inflammation associates with a number of disease processes and in the retina, is thought to cause or exacerbate common blinding conditions including uveitis and age-related macular degeneration (AMD). We have recently demonstrated new capabilities of tracking single immune cells in the living eyes of mice using Adaptive Optics Scanning Laser Ophthalmoscopy (AOSLO). Here we track the behaviors, morphology and topography of immune cells in response to two models of inflammation in the eye: 1) A vitreal lipopolysaccharide (LPS) injection that mounts an immune response similar in some aspects to uveitis and 2) a deep retinal laser lesion approach to model AMD. For both models, we imaged immune cell position and anatomy for two cohorts of C57BL/6J and Cx3CR1 mice using non-invasive AOSLO with near infrared (confocal and offset-aperture) and fluorescent modalities (confocal). Cell position and retinal phenotype were characterized by anatomy using AOSLO and Optical Coherence Tomography (OCT). In the LPS model, systemic immune cells were seen to participate in the inflammatory cascade in the inner retina six hours after the vitreal LPS injection. No change in microglia morphology or location was observed in the outer retina. In the laser lesion model, we observed a primary outer retinal phenotype with the outer nuclear layer showing dense hyperreflectance with OCT. The origin of such changes has not yet been characterized with histology, however, we observed an aggregation of amoeboid CX3CR1-positive cells at the lesion site within 18-hours post-lesion, indicating a targeted axial lesion which regionally recruits an immune cell response. These studies show the first signs of an early and specific immune response that is geographically, axially, and temporally specific in response to the damage cues presented to the retina.

P12: Measurement of Collagen Fiber Structure in Photo-Crosslinked Ocular Tissue

James A Germann, Eduardo Martinez-Enriquez, Susana Marcos

The structure and organization of collagen fibers affect the mechanical strength of the ocular tissue. For example, the interweaving of the anterior stroma provides resistance to deformation, while the lamellar organization in the posterior stroma leads to a lower mechanical strength in the posterior stroma than the anterior. Thus, the mechanical strength of a tissue and the collagen fiber organization are correlated. Photo-crosslinking (CXL) is a photo-therapy that increases the number of covalent bonds between collagen fibrils and other fibrils/proteins in the extra cellular matrix. To test the effects of CXL on ocular tissue, samples of rabbit cornea and sclera were treated with two different CXL procedures; riboflavin installation & ultraviolet irradiation (UVX) and rose bengal installation & green (532 nm) irradiation (RGX). Untreated tissue was also kept as a control. After treatment, the tissue was removed from the ocular globe and placed in a custom built second harmonic generation (SHG) microscope. Infrared light (Coherent MaiTai, 800 nm, 80 fs or Fyla SCHx, 950-1150nm, 18fs) was focused with a high NA objective into the sample. The focus of the objective was rastered on the focal plane with a pair of galvonometer mirrors and the depth of the focus in the sample was controlled with a pen motor. Signal was collected in the forward (through the sample) direction. Image stacks of collagen fibers were taken through the depth of the ocular tissue and order coefficient (OC) analysis was performed on each image. For OC analysis, each image was Fourier transformed and the points with the greatest Fourier Coefficients (N_{points} = lateral resolution of the image) were used as analysis points. The number of analysis points falling in 180 overlapping 7.5° windows were counted and the standard deviation of the number of points per window was computed. This quantitative value (the OC) has a value of 1 when the fibers are perfectly straight and oriented in the same direction, and has a value of 0 when the fibers have a random orientation. In corneas, which were treated in vivo and tested one or two months after treatment, the OC value of collagen fibers increased by 27% and 20% (RGX/UVX, $p<0.01$) after the first month and 38% and 33% (RGX/UVX, $p<0.01$) after two months, with notable increases in the anterior portion of the stroma. In CXL sclera, the OC value change by +5.1%/+3.9% (RGX/UVX, $p<0.05$) in the posterior-nasal sclera and by -1.5%/+2.2% (RGX/UVX, $p<0.05$) in the posterior-temporal sclera. For most tissue types, the fiber orientation became more uniform in direction and straighter post-CXL. The effects of CXL were greater in the cornea than in the sclera, which is unsurprisingly given the opacity of the sclera. However, the increase in OC value in sclera might make CXL a viable option for the retardation of pathologic myopia.

P13: Name: In vivo calcium imaging reveals L/M opponent ganglion cells consistent with single cone receptive fields at the macaque foveal center

Tyler Godat, Optics Ph.D.

The fovea is specialized for high spatial resolution and color vision, but there is a paucity of recordings that elucidate how retinal ganglion cells (RGCs) at the very center of the fovea facilitate this specialization. Here, we optically record responses using adaptive optics scanning light ophthalmoscopy in three macaques to spatial and chromatic stimuli using calcium indicators in the living eye to characterize the receptive field (RF) properties of RGCs serving the foveal center.

P14: Investigating the lysosomal degradation and autophagy dysfunction in CLN3 disease RPE

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CLN3 disease (Batten disease, juvenile neuronal ceroid lipofuscinosis) is a rare neurodegenerative disease with vision loss as its first clinical symptom. The atrophy of photoreceptors and the underlying retinal pigment epithelium (RPE) is a prominent phenotype in CLN3 disease patients' retina. Furthermore, phagocytosis of daily shed photoreceptor outer segments (POS) by RPE cells, a cellular process essential for photoreceptor cell survival, is shown to be compromised in mouse ($Cln3^{\Delta ex1-6}$) and induced pluripotent stem cell (iPSC)-derived models of CLN3 disease carrying the common 966bp deletion mutation in CLN3; the molecular mechanism causing impaired POS phagocytosis in CLN3 disease is unknown. CLN3 has been postulated to play a role in the lysosomal-autophagy pathway and studies have shown decreased protein degradation due to lysosomal-autophagy dysfunction. Our goal was to examine whether lysosomal-autophagy dysfunction contributes to the POS phagocytosis defect by affecting the RPE's digestion of ingested POS. We used patient-derived iPSC-RPE and isogenic embryonic stem cell (ESC; H9)-derived RPE harboring the common 966bp CLN3 mutation paired with control iPSC-RPE derived from unaffected family members and ESC-RPE derived from parental H9, respectively. Mature pluripotent stem cell (PSC: ESC/iPSC)-derived RPE were challenged with physiologic POS level (20 POS/RPE cell) for 2h. Quantitative Western blot and immunocytochemical analyses were utilized to compare the rate of degradation of ingested POS in control versus CLN3 PSC-RPE at the 24h timepoint post-POS feeding. This timepoint of 20-24h post-POS feeding has been previous established as sufficient duration to degrade POS in control PSC-RPE. Additionally, expression and localization of key proteins/enzymes in the lysosomal-autophagy pathway were evaluated by Western blotting and immunocytochemistry. Notably, patient-derived PSC-RPE showed i) decreased rate of POS degradation, ii) altered expression of lysosomal proteins (LAMP1 and CTSB), and iii) decreased ratio of LC3II/LC3I (an indicator of autophagy function) compared to control PSC-RPE. Thus, our results indicate lysosomal-autophagy dysfunction contributes to impaired POS processing in CLN3 disease. Ultimately, comprehending the molecular basis of POS processing defect in CLN3 disease will have significant therapeutic implications.

P15: Binocular rivalry under naturalistic viewing conditions

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In binocular rivalry (BR), visual perception alternates every few seconds between incompatible left- and right- eye images, appearing at times as a mixture of both. Widely used in psychology and cognitive neuroscience studies, the visual experience of BR is largely absent in the natural environment. This raise concerns that BR might be a laboratory artefact and it is not suitable for studying natural vision. To investigate, we first quantified the incidence of interocular conflict with a 3D simulation, iterating through different spatial configurations of fixation distances, depth separations and lateral displacements between two planar objects. Having ascertained that conflict stimuli were not unique to the laboratory and could originate from depth separated objects, we examined the effect of depth separation on rivalry dynamics. Rivalling stimuli (drifting or stationary gratings) were presented in a cue-rich, 3D hallway model rendered in virtual reality, arranged either in a non-ecological or ecological spatial layout. Subjects (n=22) reported periods of exclusive visual percepts (i.e., seeing only one motion direction) during extended BR viewing. The results showed that, regardless of ecological validity or stimulus type, depth separation does not eliminate BR. In contrast, depth separation may increase BR coherence for motion stimuli in non-ecological layouts, with fewer periods of mixed dominance for drifting gratings at different depths (15.3% versus 21% in same depth conditions). Thus, our results suggest that BR can occur under more naturalistic conditions and is not a mere laboratory artefact. We also propose that the discrepancy between naturalistic and laboratory experiences regarding interocular conflict could be explained by BR findings obtained with conventional means.

P16: Laminar organization and diversity of area MT receptive fields in the marmoset

Halle E. Hangen
Shanna H. Coop
Jude F. Mitchell

The marmoset is a useful model for visual neuroscience due to its high acuity fovea, smooth cortex, and similar organization of visual processing areas with humans One visual area of interest is cortical area MT, which contains highly motion-selective cells. Here we examined spatial receptive fields across depth and extracellular cell types, cataloging them by features including receptive field size, radial elongation, and motion selectivity. We mapped receptive fields in an awake monkey viewing a set of visual motion stimuli while recording across laminar depth – using Neuronexus silicone linear arrays. The receptive field mapping stimulus consisted of between 4 to 32 dots, each plotted at a random position on the screen and moving in a random direction for a limited lifetime of 50ms with asynchronous updating. We estimated the mean firing rate as a function of dot position and direction. The raw neuronal waveform data was preprocessed, and spikes sorted using Kilosort2. Only well isolated single units were included for subsequent analyses. To perform current source density (CSD) analyses to estimate laminar depth, we also measured local field potentials in response to a full-field contrast change. We find that the CSD – a method typically used in primary visual cortex – can provide an estimate of the MT input layer based on an early latency current sink. We also find that the distribution of extracellular waveform shapes is bi-modal based on peal-to-trough duration with separation of narrow and broad-spiking types. Receptive field properties and motion selectivity varied both as a function of laminar location and extracellular cell type. These results suggest a diversity of function across cortical layers and cell types within area MT.

P17: Visual and motor contributions to saccadic suppression in the fovea

Janis Intoy, Margaret Carpenter, Michele Rucci

Visual sensitivity is transiently attenuated around the time of saccades, a phenomenon known as saccadic suppression. This phenomenon and its origins have been traditionally studied with large saccades and peripheral stimuli, but it is now known that suppression also occurs during small saccades (microsaccades) when stimuli are presented in the fovea. Due to their small amplitude and lower speeds, microsaccades yield little visual masking and retinal smear, the commonly assumed retinal contributors to saccadic suppression, suggesting an important role from possible efference copies associated with microsaccades. Here, we investigate the visual and motor contributions of microsaccades to perceptual suppression within the fovea. We measured contrast sensitivity in a high-acuity task designed after primate social grooming, a task that naturally elicits frequent microsaccades. Observers searched for fleas (targets) amongst dust particles (distractors) embedded in either a naturalistic noise field or uniform background. Targets and distractors were 5 arcmin squares, and targets distinguished themselves by a 10 ms contrast pulse. Subjects either actively searched the targets or passively observed a reconstruction of the visual stimulation recorded during an earlier active trial. A high-resolution system for gaze-contingent display coupled to a digital DPI eye-tracker enabled precise measurement of oculomotor activity in the active condition and its subsequent replay under retinal stabilization in the passive viewing condition. First, we show that a strong suppression occurs at the time of microsaccades regardless of the stimulus background, though a textured background enhances the effect. Second, the dynamics of perceptual suppression are significantly different when the microsaccades are performed or simulated: suppression was delayed and longer-lasting in the passive condition. Therefore, extraretinal modulations first suppress and then enhance sensitivity immediately before and after a saccade. These results show that both the visual consequences and the motor commands associated with microsaccades impact visual sensitivity within the fovea.

P18: Visual anisotropies within the foveola

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It's well established that vision in the periphery and parafovea is characterized by asymmetries; humans are better at discriminating items along the horizontal meridian compared to the vertical meridian. Similarly, sensitivity in the lower visual field is better than in the upper visual field. Current evidence shows that the extent of these asymmetries decrease with eccentricity, suggesting that they may be absent in the central 1deg fovea. However, due to technical limitations this has never been examined. Thanks to high-precision eyetracking and a gaze contingent display control allowing for more accurate localization of gaze, we probed fine visual discrimination at different isoeccentric locations across the foveola and compared it with corresponding locations in the periphery.

Participants (n=10) performed a two-alternative forced-choice discrimination task while maintaining fixation on a central marker. Performance was tested at 8 locations, approximately 20 arcmin from the preferred locus of fixation. The same task was replicated at 4.5 degrees eccentricity (n=7) and the stimuli size was adjusted to account for cortical magnification.

Our results show that, similarly to what happens in the visual periphery, humans are more sensitive to stimuli presented along the horizontal than the vertical foveal meridian. While the magnitude of this asymmetry across the meridians is smaller in the fovea than extrafoveally, the magnitude of asymmetry along the vertical meridian is equal. Furthermore, foveal asymmetry on this meridian is flipped compared to what is found extrafoveally: objects in the upper foveal meridian are discerned more easily than those in the lower meridian.

These findings show that even foveal vision is characterized by perceptual anisotropies and that their characterization is in part different from what is found in the rest of the visual field. Furthermore, while some asymmetries are larger extrafoveally, others are present to the same extent at both scales.

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P19: Temporal modulations of extrafoveal sensitivity to changes during fixation

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Being able to correctly identify sudden changes in the environment is crucial for survival. Here we examine how sensitivity to brief changes is modulated over time during the course of fixation and whether it is impacted by the salience of surrounding stimuli.

Subjects (n=6) maintained fixation on a central marker, either at rest or right after a saccade. An 8 cpd gabor patch, 1 deg in size, was presented 8 degrees away from the center of gaze. The orientation of the gabor changed briefly (50 ms) at a variable time (0-450 ms) either from saccade landing or from stimulus onset. Subjects were instructed to determine the direction of the orientation change. The gabor could be flanked either by salient or non-salient circular blobs of the same size (1.4 degrees center-to-center distance). To prevent visual fading stimuli were presented at high contrast and were jittered throughout the presentation time.

Our results show that subjects' ability to discriminate the direction of sudden orientation changes was best right after the stimulus onset and upon saccade landing (0-150 ms) and it decreased over time during the course of fixation. On average, performance dropped by 30% around 350 ms. Importantly, the perceptual salience of the surrounding did not influence performance, suggesting that in this task the visual system is capable of actively suppressing salient distractors at no cost. These findings show that the ability to discriminate sudden changes in the visual surrounding varies drastically during the short periods of fixation in between saccades.

Acknowledgements: Facebook inc.

P20: In vivo and ex vivo characterization of macaque ganglion cells projecting to the superior colliculus

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Purpose: The macaque retina conveys visual information to the brain via ~20 anatomically distinct retinal ganglion cell (RGC) types. Yet only the most common LGN-projecting types have been characterized physiologically. Many of the remaining RGCs project to the superior colliculus (SC), an evolutionarily ancient region implicated in eye movements and, most recently, perceptual decision making. Here we catalog SC-projecting RGC types in the macaque retina and develop an approach to anatomically identify and physiologically characterize them in the living eye.

Methods: Injections of the retrograde tracer rhodamine dextran were aimed at the foveal SC in two macaques. Two stereotaxic-coordinate based injections were made in one macaque, and one MRI-guided injection was made in the second. Rhodamine expression was mapped with a fundus camera, then imaged in detail with adaptive optics scanning light ophthalmoscopy (AOSLO). The second macaque also expressed the genetically-encoded, calcium indicator GCaMP6s in the ganglion cell layer (Fig. 1). In the first macaque, postmortem ex vivo imaging with a confocal microscope supplemented the in vivo imaging of rhodamine expression.

Results: Each injection labeled a sparse population of SC-projecting RGCs, consistent with earlier reports. We imaged the rhodamine-labeled RGCs in vivo with AOSLO, and some could be coaligned with GCaMP6sexpressing RGCs. The calcium responses of RGCs in rhodamine-labeled regions did not differ from areas without rhodamine expression. We traced the dendritic fields of 64 rhodamine-labeled RGCs that were imaged ex vivo with a confocal microscope, identifying parasol, smooth monostratified, large sparse, broad thorny and narrow thorny RGCs.

Conclusions: A complete account of the retinal input to the SC has been elusive since the rarity of many SC-projecting RGC types makes them difficult to target for physiological investigation. The anatomical approach developed here could address this gap in knowledge, laying the foundation for subsequent in vivo measurements of the response properties of these rare and understudied RGC types.

P21: Retinal Ganglion Cell Segmentation with the Machine Learning Based Program ‘ilastik’

Edith Koo

Purpose: To improve signal to noise ratios of AOSLO images in vision restoration and retinal physiology studies, segmentation masks are required. Current methods of manual segmentation are labor intensive and highly variable especially when different individuals segment cells. Thus, a machine-learning based approach was investigated: ilastik. Ilastik is user friendly, requires no machine learning expertise, and uses relatively few annotated data sets.

Methods: Images of foveal RGCs in the living primate were captured by imaging the fluorescence calcium indicator GCaMP6s with an adaptive optics scanning light ophthalmoscope. The dataset was divided into 3 subsets: training, validation, and testing. To evaluate the performance of ilastik and manual segmentation, the precision, recall, and F1 scores were computed for the testing dataset.

Results: In the comparison between ilastik and manual segmentations of various individuals, ilastik exhibited an average F1 score of 0.80 which was comparable to the performance of the student that originally trained the classifier (F1= 0.81). Student 2’s average F1 score for the same data set was 0.59.

Conclusions: Ilastik performed more similarly to Student 1 who trained the classifier. Consequently, this suggests that the approach of using a common classifier can save time and generate consistent results. This may be preferable to manual segmentations by different individuals which results in high variability. Ilastik may be useful to other CVS members for similar applications.

P22: Visual perception in schizophrenia: assessing predictive processing in the earliest stages of the visual cortical hierarchy

Edmund Lalor & Brian Keane

Schizophrenia is a serious psychiatric disorder characterized by hallucinations, delusions, and disordered thinking and behavior that impairs daily functioning. As per the NIH's Research Domain Criteria framework, we might gain a deeper understanding of this disorder by focusing on basic dimensions of functioning and how they relate to behavior and neural systems. With this in mind, research in recent years has sought to link psychosis with dysfunction in "predictive perception". According to this framework, perception is an intrinsically predictive process that involves inferring the causes of our sensory inputs by combining those inputs with prior beliefs about the states of the world. And it has been proposed that psychosis is the result of maladaptive inferences based on inappropriately weighting prior beliefs relative to sensory input. However, testing this idea is complicated by the challenge involved in interpreting neurophysiological measures of perception in terms of feedforward sensory activity vs top-down predictions, and by the heterogeneity seen across individuals with schizophrenia. Here we introduce two innovative stimulus/analysis frameworks aimed at deriving EEG responses from the earliest stages of human visual cortex that are not overly complex in terms of their hierarchical generative architecture. The first experiment aims to derive so-called "perceptual echoes" from human visual cortex. These "echoes" are novel measures of recurrent activity in early visual cortex that have been modeled as outputs from a predictive coding architecture, albeit based upon some unproven assumptions. The second aims to leverage a powerful visual illusion to dissociate weak bottom-up stimulus changes from strong top-down predictions. We present preliminary data that suggests differences in processing between groups based on two healthy controls and two patients with schizophrenia. We aim to develop this project further by collecting more data, including from patients with bipolar disorder as a clinical control, and by using a combination of spatiotemporal analyses and effective connectivity modeling, to further interpret the causal architecture of our EEG responses. Ultimately, we hope this work will produce robust and interpretable indices of predictive perception, and new insights on the role played by predictive perception in the symptomatology of psychotic disorders.

P23: The role of microglial β2 adrenergic signaling in Alzheimer's disease pathology

Linh Le

Alzheimer's disease (AD) is the most common age-related dementia, accounting for the progressive cognitive impairment and compromised life quality of millions of people worldwide. In AD pathophysiology, plaque and tangle accumulation trigger an inflammatory response that mounts positive feed-back loops between inflammation and protein aggregation, aggravating neurite damage and neuronal death. One of the earliest brain regions to undergo neurodegeneration is the locus coeruleus (LC), the predominant site of norepinephrine (NE) production in the central nervous system (CNS). In animal models of AD, dampening the impact of noradrenergic signaling pathways, either through administration of beta blockers or pharmacological ablation of the LC, has been shown to heighten neuroinflammation through increased levels of pro-inflammatory mediators. Since microglia are the resident innate immune cells of the CNS, it is reasonable to postulate that they are responsible for translating the loss of NE tone into exacerbated disease pathology. Recent findings from our lab demonstrated that noradrenergic signaling inhibits microglia dynamics via the β2 adrenergic receptor (β2AR), suggesting a potential anti-inflammatory role for microglial β2AR signaling. Thus, I hypothesize that microglial β2 adrenergic signaling is progressively impaired during AD progression, which leads to the chronic immune vigilant state of microglia that worsens disease pathology. To test this hypothesis, I will characterize changes in microglial β2AR signaling as a function of amyloid pathology and determine whether these changes are caused by endogenous NE loss, altered microglial β2AR expression, or a combination of both during disease progression. In fact, my preliminary results show that LC neurons and their projections degenerate early and progressively in the 5xFAD mouse model of AD. Furthermore, plaque-associated microglia appear to lose their sensitivity to β2AR stimulation early in amyloid pathology but gain back some of the sensitivity as disease progresses, suggesting that although endogenous NE system is progressively lost, microglial sensitivity to NE may show compensatory change.

P24: Saccade-amplitude dependent enhancement of visual sensitivity

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Eye movements transform a spatial scene into luminance modulations on the retina. Recent work has shown that this transformation is highly structured: within the temporal range of human sensitivity, saccades deliver power that increases in proportion to spatial frequency up to a critical frequency and remains constant beyond that. Importantly, the critical frequency depends on the saccade, increasing with decreasing amplitude. Therefore, a larger saccade delivers a more effective input than a smaller one below the critical frequency. Here we tested the perceptual consequences of this input reformatting by examining how large and small saccades (6° and 1° amplitude) affect contrast sensitivity. To control for individual variability in the contrast sensitivity function, we measured relative sensitivity between two spatial frequencies: a reference, selected at the critical frequency for the smaller saccade (0.5 cycle/deg); and the probe, which, in separate experiments, either had a lower or higher frequency (0.1 or 2.5 cycles/deg). We predicted that, compared to the smaller saccade, the larger saccade will enhance probe visibility when the probe is at a lower spatial frequency than the reference, but not when the probe is at a higher spatial frequency. Subjects (N = 7) made an instructed saccade while presented with a plaid composed of overlapping orthogonal gratings (±45° orientation) at the two frequencies and reported which was more visible. We systematically varied the contrast of the probe to measure the point of subjective equality with the reference. Special care was taken to ensure that perceptual responses were primarily driven by saccade transients. Our results closely follow theoretical predictions. Specifically, psychometric functions following small and large saccades only differed when the probe was a lower frequency than the reference, in which case the larger saccade significantly enhanced the probe contrast. These results show that post-saccadic visibility critically depends on saccade amplitude.

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P25: Visual acuity under temporal modulation

Ruitao Lin, Janis Intoy, Michele Rucci

Temporal modulation of stimulus contrast is shown to enhance sensitivity for a low spatial frequency target. Such a pattern is evident at all retinal locations, and sensitivity is shown to be uniform across the retina with proper scaling of stimulus size. While temporal contrast modulation is shown to improve acuity at the periphery, no study has investigated whether visual acuity within the foveola can benefit in a similar manner. Human observers (N=7) were presented with a Snellen E optotype temporally modulated with either a sinusoidal or square-wave contrast-reversal function (0, 3, 6 and 9 Hz) at 2 eccentricities (0 and 7.5 degrees). Square-wave modulation benefits peripheral acuity but not foveal acuity at 3 Hz, while sinusoidal modulation of stimulus contrast does not improve acuity at either location. Based on such discrepancies, ongoing work is conducted to characterize temporal sensitivity functions within the foveola

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P26: Moving toward a unifying framework for perceptual decision making that combines threshold and reaction time approaches

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Perceptual decision making has been long studied using two largely independent approaches. Threshold measurement is the predominant approach in psychophysics that excels at quantifying stimulus strength required for accurate perceptual decisions. In parallel, reaction time (RT) paradigms along with associated accumulation-to-bound models have been used to estimate components of perceptual decision making (e.g., decision time, non-decision time, and drift rate). It is unknown, however, whether both approaches yield the same conclusion about the sensitivity of the sensory system. To answer this question, we conducted two experiments (total n=23) where we estimated both RTs and duration thresholds for a motion and a static discrimination task. Duration threshold (DT) is defined as the shortest stimulus presentation duration sufficient to make accurate perceptual decisions. RTs and choices were fitted by a drift diffusion model (DDM, Wiecki et al., 2013). If the DDM is correct, there should be a close relationship between DTs and drift rates, allowing us to accurately predict DTs from RT data.

In the motion task (Newsome & Pare, 1988), we found a close correspondence between the empirical DTs and the DTs predicted by the DDM across 6 levels of motion coherence (10%-100%; r=0.81, p <0.0001). Surprisingly, in the static orientation discrimination task (8 contrast levels, 2%-100%), there was very little correlation between DTs and drift rates. While DTs, as expected, improved monotonically with increasing contrast, RT drift rates saturated at 6% stimulus contrast.

In summary, we show a close correspondence between duration thresholds and RT drift rate for the well-established motion coherence task. This result supports the common conceptualization of drift rate as a proxy for perceptual sensitivity. However, we do not find the same correspondence in the static orientation discrimination task, indicating a surprising limitation of the DDM and experimental approaches based on it.

P27: Investigating task-dependence of choice probability and noise correlations during task learning and task switching in V4

Shizhao Liu

To better understand neural computations happening in the sensory cortex, we study how the brain combines incoming sensory information (bottom-up) and prior beliefs/knowledge (top-down). Two important quantities for understanding neural representation underlying perceptions are (1) choice probability (CP): how well variation of a single neuron's response to the same stimulus predicts the subject's choice and (2) noise correlation: how responses of pairs of neurons covary around their mean response to a given stimulus. Multiple prior studies have found above chance CPs in the visual cortex, and non-zero noise correlations, which has raised the question of whether they are the result of feedforward or feedback mechanisms. One of the main approaches to study this question is to investigate the relationships between CP and noise correlations and neuronal sensitivity to the task-relevant stimulus (d-prime). A positive CP - d-prime relationship was first revealed in MT with multiple replications of this result; for other areas of the visual cortex (V1, V4) results are still inconclusive. Such a relationship is compatible with both feedforward and feedback mechanisms. Previous studies also showed that both learning and selective attention decreased noise correlations between neurons. On the other hand, models of hierarchical probabilistic inference predict an increase of noise correlations aligned with d-prime*d-prime (alignment of sensitivity) of neuron pairs over the course of learning due to feedback mechanisms. We will test these predictions using trials that are interleaved such that trial-by-trial task-switching occurs within a session, so that task-related changes CPs and noise correlations can be directly studied.

To do so, we used Utah array to record populations of V4 neurons from one macaque monkey while he was (1) learning one coarse orientation-discrimination task and (2) switching between two coarse orientation-discrimination tasks within a session. We found a significant positive correlation between choice probability and task sensitivity (d-prime) of neurons and that this correlation was absent before the monkey learned the task, and increased as the monkey's performance improved. We further found that during task-switching sessions, CP for one task is positively correlated with d-prime of the same task, but not with d-prime with the other task. For a given neuron its CP changed between two tasks in accordance with the change of its sensitivity.

P28: Investigating the effects of surgical intraocular pressure on corneal endothelial cell viability using intact porcine eyes

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Purpose: Although it is widely accepted that corneal endothelial cell (CEC) damage occurs during phacoemulsification surgery, it remains unclear if the elevated intraocular pressure (IOP) used during phacoemulsification contributes significantly to this damage. Using a novel experimental method enabling quantification of CEC damage in intact porcine eyes, we tested the hypothesis that elevated IOP under conditions relevant to phacoemulsification surgery leads to increased CEC damage.

Methods: Corneal endothelia of fresh, intact explanted porcine eyes were stained with two nucleic acid viability dyes and imaged through a fluorescence microscope without removing the cornea from the globe. The anterior chambers of the eyes were perfused with BSS to a pressure of 73.6mmHg (bottle height=100cm) for 10min (n=4) prior to restaining and reimaging. Baseline images were analyzed using custom algorithms to determine initial total cell counts (TC_1) and damaged/dead cell counts (DC_1). Images acquired after pressurization were analyzed to obtain final cell counts (TC_2, DC_2). CEC damage was quantified as the change in percent of cell damage/death, PCD ($PCD=100*DC_2/TC_2–100*DC_1/TC_1$). As a negative control, additional eyes were pressurized to a physiological IOP of 18.4mmHg for 10min (n=4). The experimental and negative control groups were compared using a two-tailed Student's t-test. As a positive control, one eye was perfused with deionized water at a pressure of 18.4mmHg for 10min.

Results: There was no significant difference in mean PCD values between the experimental (0.22%) and negative control (0.30%) groups ($p=0.78$). The positive control sample yielded a PCD of 84.5%, indicating that the method is able to detect CEC damage.

Conclusions: Our results suggest that the elevated IOP used over the duration of phacoemulsification surgery does not lead to a significant increase in CEC damage. However, further studies are needed to expand the sample size and ensure statistical power. Notably, the mean PCD measured in the experimental group was less than the yearly decrease in the central CEC density of healthy individuals (0.59%), strongly suggesting that surgical IOP alone does not result in clinically-significant CEC damage.

P29: Alignment and validation of an AOSLO for imaging the human cone mosaic in the central fovea

Benjamin Moon, Soh Hang Liu, Glory Linebach, Ashley M. Clark, Sanjana Kapisthalam, Samantha K. Jenks, Michele Rucci, Martina Poletti, and Jannick P. Rolland

Imaging the human foveal cone mosaic in vivo with cellular resolution provides rich opportunities for studying foveal anatomy and its impact on visual perception and eye movements. Achieving cellular resolution at the center of the fovea—where cones are smallest and most densely packed—requires an optimized and well-aligned adaptive optics scanning laser ophthalmoscope (AOSLO). An active alignment strategy was implemented using a portable Shack-Hartmann wavefront sensor to measure the wavefront aberrations after each relay telescope in the AOSLO. This alignment process enabled a diffraction-limited scanning and light delivery system to be realized. Additional system testing was conducted to calibrate the scanning field of view, correct for the distortions introduced by the sinusoidal motion of the resonant scanner, and measure the system resolution with a three-bar resolution target for each of the three spectral imaging channels in the system. In vivo human retinal images were collected with the system, demonstrating that the smallest cones at the center of the fovea are resolved. These high-resolution images will be used in subsequent analyses to investigate the relationship between foveal cone density, visual acuity, and fixational eye movements in humans with normal vision.

P30: Optogenetic Stimulation and Calcium Imaging of Single Ganglion Cells in the Living Macaque Fovea

Peter Murphy

The perceptual roles of most retinal ganglion cell (RGC) classes are controversial in part because we lack a paradigm for measuring the perceptual consequences of activating cells of only one class in the living primate eye. Recent success in classifying single RGCs with *in vivo* calcium imaging (McGregor 2018, PLoS One, 13), *in vivo* optogenetic activation of RGCs en masse (McGregor 2020, Nat. Commun. 11, 1703; Sahel 2021, Nat. Med. 27., 1223), and *in vivo* targeted excitation of single cones (Harmening 2014, J. Neurosci. 34, 5667) now bring such a paradigm within reach. As a first step, we demonstrate the optogenetic stimulation of single foveal RGCs in the living macaque.

P31: A linguistic representation in the visual system underlies successful lipreading

Aaron R Nidiffer, Cody Zhewei Cao, Aisling O'Sullivan, Edmund C Lalor

There is considerable debate over how visual speech is processed in the absence of sound and whether neural activity supporting lipreading occurs in visual brain areas. Much of the ambiguity stems from a lack of behavioral grounding and neurophysiological analyses that cannot disentangle linguist and energetic contributions from visual speech. To address this, we recorded EEG from human observers as they watched silent videos, half of which were novel and half of which were previously rehearsed with the accompanying audio. We modeled how the EEG responses to novel and rehearsed silent speech reflected the processing of low-level visual features (motion, lip movements) and a categorical representation of linguistic units, known as visemes. The ability of these visemes to account for the EEG – beyond the motion and lip movements – was significantly enhanced for rehearsed videos in a way that correlated with participants' trial-by-trial ability to lipread that speech. Source localization of viseme processing showed clear contributions from visual cortex, with no strong evidence for the involvement of auditory areas. We interpret this as support for the idea that the visual system produces its own specialized representation of speech that is 1) well-described by categorical linguistic features, 2) dissociable from lip movements, and 3) predictive of lipreading ability. We also suggest a reinterpretation of previous findings of auditory cortical activation during silent speech that is consistent with hierarchical accounts of visual and audiovisual speech perception.

P32: Divisive normalization as a mechanism for hierarchical causal inference in motion perception

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We live in a highly dynamic environment in which the visual system constantly infers the hierarchical motion structure embedded in the scenes to estimate the motions of particular objects. Previously (Shivkumar et al., 2020), Bayesian causal inference has been proposed as a framework to model hierarchical motion perception. Nevertheless, the neural correlates underlying the causal inference model remain still elusive. In this work, we used a normalization model to fit the neural predictions of our causal inference model to a motion integration/segregation task. A normalization model incorporating neurons from a heterogenous population with natural neural tuning properties and interaction terms between the center and surrounding neurons in the normalization pool can capture the causal inference neural predictions. Our results suggest that divisive normalization can serve as a mechanism to implement causal inference at the neural circuit level in the brain.

P33: Developmental Perfluorohexanoic Acid (PFHxA) Exposure Affects Brain Development

Elizabeth Plunk

Since the phase out of legacy per- and polyfluorakyl substances (PFAS) due to the long-term health effects such as hypothyroidism[1], attention deficit/hyperactivity disorder, and autism spectrum disorder (ASD) following gestational exposures, industries have effectively replaced them with next generation, short-chain PFAS. Perfluorohexanoic acid (PFHxA) is one of the replacements. PFHxA is a large chemical component in aqueous film forming foam (AFFF) which migrates into water and soil systems contaminating drinking water and food. Epidemiology studies have reported that PFHxA has an efficient blood to breast milk translation showing that infants are exposed via breastmilk. PFHxA has also been reported in serum of pregnant women and passes through the placenta. This suggests that exposure to PFHxA could affect brain development, although this has not yet been studied in depth.

With this knowledge, we hypothesize that gestational and lactation exposure to perfluorohexanoic acid (PFHxA) in a mouse model alters maternal thyroxine (T4) levels thereby indirectly causing perturbations in neuronal and glial development in offspring. Using Cx3Cr1 G/- mice, which fluorescently label all microglia in the brain, and immunohistochemistry to stain mature neurons, we analyzed microglia density across the cerebellum, hippocampus, and corpus callosum, as well as cortical thickness on postnatal day (P)21 in offspring., in order to determine how maternal PFHxA exposure affected the developing brain. We used propylthiouracil (PTU) , which is known to disrupt thyroid signaling as a positive control. Our results show complex effects of PFHxA exposure on microglial development, suggesting that these immune cells may be vulnerable to developmental actions of PFHxA.

Understanding PFHxA exposure during brain development will aid policy makers in protecting the consumer by regulating PFHxA industrial use.

P34: The majority of mouse retinal microvessels are a-sma+

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The distal extent of alpha smooth muscle actin on microvessels varies between different studies. In both in vivo and ex vivo imaging a-sma was expressed on branch orders as high as five and on vessels less than 7 um in diameter. This vessel diameter necessitates single file red blood cell flow, the scale at which metabolic oxygen exchange is maximized. Thus, very precise control of blood flow is possible.

P35: Do Marmosets Reach Predictively for Moving Targets?

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Visual information plays a critical role in the planning and on-line correction of coordinated movements. Primates especially utilize vision in reaching behavior. Studies of reaching in macaques indicate that the dorsal premotor and the medial intraparietal cortices are involved in on-line corrections that guide the hand towards dynamic targets. However, the specific behavioral contributions of circuit connections between these two areas have not been determined, due to technical challenges associated with circuit targeting and behavioral training in macaques. Marmosets provide an accessible experimental model for this research due to their lissencephalic brains that facilitate intraparietal targeting and innate insect hunting behavior that facilitate dynamic reach testing. We set out to generate high fidelity descriptions of marmoset hands as they reach for live crickets and ask whether unrestrained marmosets reach predictively for moving crickets. We developed a novel machine learning approach to achieve marker-less tracking of the hand and the cricket, and determined their spatiotemporal interplay during reaching. We utilized kinematic data and a multivariate linear modeling approach to demonstrate the influence of cricket motion on the future hand motion of reaching marmosets. Our findings suggest that marmosets incorporate cricket motion into their reaches in a predictive fashion. Furthermore, there is a specific time window when cricket motion strongly influences marmoset hand motion. These behavioral characterization and modeling results will provide a foundation for future research using optogenetic tools in marmosets to determine the circuit mechanisms underlying predictive reaching and online corrections.

P36: Causal inference can explain hierarchical motion perception and is reflected in neural responses in MT

Sabyasachi Shivkumar, Zhexin Xu, Gábor Lengyel, Gregory DeAngelis, Ralf Haefner

Causal inference (CI) has recently been proposed as a universal computational motif in the brain (Shams & Beierholm 2020). However, how CI is implemented by neural circuits, and its signatures in terms of single neuron responses, are still unclear. We have investigated this question in the context of complex motion processing. Motion perception deviates from retinal motion (Johansson 1973) a computation that can be understood in terms of hierarchical CI over which moving elements to integrate into coherent 'groups' vs segment into different ones (Gershman et al. 2016, Shivkumar et al. 2020). Yet, most of our understanding of the neural basis of motion processing is in terms of retinal motion, delegating potential CI computations to downstream cortical areas (Rohe et al. 2015, 2019).

Our work makes two contributions: first, we present new psychophysical evidence for the hierarchical nature of this process using a display of hierarchically nested groups of moving dots. Second, we use the hierarchical CI model fit to psychophysical data to derive quantitative neural predictions for neurons representing the variables in our model. At each level, our model contains two types of variables: one that represents the retinal motion predicted by the larger surround, and one that represents the difference between the actual local motion and that predicted from the surround. The predicted neural responses show remarkable similarity to two classes of neurons found in area MT: neurons with suppressing and with reinforcing surrounds (Born & Bradley 2005). Finally, we present new neurophysiological data from area MT in a macaque monkey where the velocity-dependent pattern of surround suppression of neural responses agreed with that predicted for the relative variable in our CI model. Our results show that signatures of CI are already present at the early stages of sensory processing, and suggest that they may be implemented by local computations.

P37: Title: Temporal dynamics of peri-microsaccadic perceptual modulations in the foveola

Zoe Stearns and Martina Poletti

It is known that vision at the saccade goal is briefly enhanced before the eyes start to move. This enhancement is followed by a plummet in sensitivity as the eyes relocate the center of gaze. Recent work has shown that a similar modulation unfolds at the foveal scale for microsaccades. Here we examine these selective modulations of foveal vision at a finer temporal grain before, during and after the onset of microsaccades.

Fixational eye movements were recorded with a high-resolution digital Dual Purkinjie Image eye-tracker while subjects performed a 2AFC discrimination task. Subjects (N=7) were required to shift their gaze to one of two possible locations surrounding a central fixation marker based on the direction indicated by a cue. Stimuli were flashed at those locations at variable times around the onset of the gaze shift. Stimuli appeared 0.3 deg from the initial fixation. A response cue appeared after landing and subjects reported the orientation of the stimuli previously presented at the location indicated by this cue.

Our findings show that stimuli presented at the microsaccade goal were perceptually enhanced. The extent of this enhancement was such that discrimination performance at this location equated performance when stimuli were presented at the preferred locus of fixation (82%±0.1% vs 85%±0.1%, $p=0.75$). On the other hand, sensitivity at isoeccentric locations opposite to the microsaccade goal, was impaired compared to baseline (61%±0.1% vs 78%±0.1%, $p<0.01$). This modulation started ~160ms prior to the microsaccade onset. High acuity vision was severely impaired if stimuli were presented when the eyes were in flight. However, within 50 ms from microsaccade landing perception rapidly recovered back to baseline. These findings show that foveal vision drastically changes around the time of microsaccades, and that pre-microsaccadic modulation of foveal vision equates fine spatial vision at the microsaccade goal to that at the preferred locus of fixation, where acuity is highest.

P38: in vivo imaging of the microglia following cranial irradiation

Alexandra Strohm

Brain irradiation is widely used in the treatment of cancer patients. Unfortunately, patients receiving this treatment often experience symptoms of cognitive decline including memory loss, motor dysfunction and social issues that decrease the quality of their remaining lifespan. Animal studies suggest that cognitive dysfunction may stem from the loss of dendritic spines, the structures that serve as postsynaptic sites of excitatory synapses. Recent studies also implicate microglia, the highly reactive and motile immune cells of the brain, in mediating cognitive deficits following irradiation. Microglia make physical contacts with dendritic spines and engage in synaptic pruning. Thus, dysregulation of this microglial function could contribute to synaptic loss following radiation. Despite a growing body of evidence suggesting that radiation perturbs homeostatic microglia function and facilitates cognitive decline through a loss of synaptic structure, **it is unknown how brain radiation impacts the dynamic functions of microglia over time.** Current studies only assess a single timepoint using a cohort design, missing possible alterations in critical processes like ongoing microglia dynamics occurring within individuals before and after cranial irradiation. Understanding the impact of radiation on functions of highly dynamic cells, such as microglia, in a temporally complex process requires a dynamic *in vivo* approach. We paired *in vivo* two-photon microscopy with transgenic models that label cortical microglia to follow these cells and determine how they change over time in cranial irradiated mice and their control littermates. *We hypothesize that brain irradiation disrupts microglia dynamics corresponding with morphological changes.* Our preliminary results in male mice show brain irradiation reduces microglia cell number by Week 2 and persists through week 4. However, microglia do not appear to change their clustering patterns when taking overall cell number into account following irradiation. Microglia motility appears to be increased the day of irradiation and again at Week 4 following irradiation, while microglia surveillance is decreased at intermediate timepoints following irradiation. We assessed microglia morphological changes overtime in complexity, cell body area, cell body shape, soma area and soma shape. We found that microglia complexity is decreased by Week 4 following irradiation. Overall cell body area appears to decrease at all timepoints following irradiation compared to controls. There is an increase in cell body circularity and roundness at early timepoints. Cell soma area and shape do not seem to be impacted by irradiation. Together these results suggest little change in somatosensory cortex in the microglia dynamics and morphology assessed following irradiation. Future studies will assess how microglia interact with neuronal compartments and dendritic spines following irradiation *in vivo*. Upon injury, microglia rapidly respond by releasing cytokines, undergoing morphological changes, and migrating towards sites of damage. To assess potential pathways by which microglia may respond and be recruited to sites of radiation injury, we explored fractalkine signaling and purinergic P2Y12 signaling. We exposed adult male CX3CR1$^{GFP/+}$, CX3CR1$^{GFP/}$, and CX3CR1$^{GFP/+}$ P2Y12$^{-/-}$ mice to partial cranial irradiation. 10 Gy was delivered to the left hemisphere only using the SARRP. Cortical sections were imaged using confocal microscopy. Co-staining

with DAPI allowed for manual delineation of cortical subregions. At 6 hours following irradiation S1 microglia in male CX3CR1$^{GFP/+}$ mice showed no differences in density or morphology between irradiated (IR) and non-irradiated control hemispheres, in contrast to what has been described in the hippocampus. However, in mice without P2Y12 and fractalkine, microglial arborization was reduced in the IR hemisphere. This data supports the idea that the timescale of microglial changes may be different in the cortex versus the hippocampus and that P2Y12 as well as fractalkine signaling modulates microglial responses to radiation.

P39: Adaptive optics fluorescence lifetime imaging ophthalmoscopy of the human RPE

Janet Tang

In the retinal pigment epithelium (RPE), the fluorescence lifetime (FL) of lipofuscin granules, related to their composition, may be a useful biomarker of retinal health. Clinical fluorescence lifetime imaging ophthalmoscopy (FLIO) has been used to investigate retinal changes with age, eccentricity, and disease, such as AMD. With an adaptive optics scanning light ophthalmoscope (AOSLO) at 532 nm excitation, we have previously imaged the RPE cell mosaic. Adaptive optics FLIO (AOFLIO) of the RPE mosaic can improve: confocality - mitigating the effects of lens and inner-retinal fluorescence, sampling density and resolution, and foveal imaging by using a longer excitation wavelength to avoid macular pigment absorption. We show the first implementation of AOFLIO in healthy people.

To specifically target lipofuscin, a custom-built adaptive optics scanning light ophthalmoscope was used for reflectance and FL imaging in 4 subjects (up to 14 locations across the macula; 24-39 YO). RPE autofluorescence was excited with 532Δ10 nm (50 ps pulse width, 80 MHz repetition rate, 15 μW average power) and collected 575-725 nm (1.4-1.7^{o} square field of view, 25 Hz frame rate, ≤60 s exposure). FL data was analyzed using custom and commercial software (Becker & Hickl GmbH). A two-component exponential function $a_1 e^{-t/\tau_1} + a_2 e^{-t/\tau_2}$ was fit to the decay curve at each binned pixel. Mean FL was calculated by $\tau_m = a_1\tau_1 + a_2\tau_2$ where τ_n is the FL and a_n is the relative contribution. The phasor coordinates (g and s) were also calculated at each pixel by taking the real and imaginary discrete Fourier transform of each histogram and evaluation at the repetition frequency. τ_n, a_n, g, and s were averaged across each AOFLIO image.

The measured τ_m is within the range expected for lipofuscin (247.3±27.8 ps, ranging from ~200–270 ps) (widefield FLIO long spectral channel attributed to lipofuscin: Dysli et al., 2017; *ex vivo*: Docchio et al., 1991; Schweitzer et al., 2007; Feldman et al., 2018). An ANOVA conducted on mean data from 40 locations across 4 subjects revealed no significant differences in τ_1 (160.12±27.67, p=0.36), τ_2 (1040.45±84.85, p=0.74), or g and s (0.67±0.12, p=0.46 and 0.17±0.03, p=0.44). The average τm across two visits for 5 locations in 2 subjects was not significantly different (paired t-test, p=0.32). Similarly, a Hotelling's T2 test on the average s and g components for each image yielded no significant difference (p=0.20). A safety analysis of AOFLIO raised no safety concerns.

These are the first measurements using AOFLIO to image the human RPE mosaic. Our results suggest AOFLIO will be repeatable within and between young healthy subjects. We expect larger variations with age and disease related to composition and function of the RPE mosaic. AOFLIO has potential to provide normative and longitudinal information about RPE health with age and in diseased retina.

P40: Inhibition of retinoic acid synthesis rescues vision in mice with cone-sparing retinitis pigmentosa

Dr. Michael Telias, Assistant Professor, Flaum Eye Institute

In retinitis pigmentosa (RP), the loss of photoreceptors in the outer retina triggers pathophysiological spontaneous hyperactivity in the downstream inner retinal neurons. Hyperactivity reduces the signal-to-noise ratio, obscuring light responses from surviving cones. Retinoic acid (RA)-signaling is necessary and sufficient to cause hyperactivity, and inhibiting its receptor (RAR) reduces hyperactivity and improves ex-vivo light responses and in-vivo light perception. In this study we used the FDA-approved drug disulfiram, a non-selective aldehyde dehydrogenase blocker, to inhibit RA-synthesis. Our results show that oral administration of disulfiram to rd10 mice with cone-sparing RP reduces RA-dependent gene transcription and spontaneous hyperactivity in the retina. Treatment with disulfiram preserved contrast-sensitivity in-vivo and sharpened neuronal responses in the primary visual cortex (V1) to orientation-selective visual stimuli and naturalistic images. Our results demonstrate that functional blindness is the combined consequence of photoreceptor loss and inner retinal remodeling. Reduction of hyperactivity in the inner retina was able to unmask light responses from surviving cones without affecting the degeneration process in the outer retina. We propose that disulfiram might be able to boost residual vision in RP patients and improve artificial light responses generated by vision restoration technologies.

P41: The Design and Construction of a Dual Adaptive Optics Ophthalmoscope for Advanced Stimulation and Imaging of Retinal Ganglion Cells

Doran Teverovsky

The adaptive optics ophthalmoscope has transformed retinal research since its inception by providing cellular scale resolution while imaging the retina *in vivo*. This project seeks to extend the capabilities of adaptive optics ophthalmoscopes by removing certain limitation to the field of view. This represents an improvement in the ability to study retinal ganglion cells, and single cell psychophysics.

P42: Digital high-resolution eye-tracking using Purkinje Images

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Precisely measuring eye movements and accurately localizing gaze are vital to understanding how humans acquire and process visual information. Here we present recent advances using the Dual Purkinje Image (DPI) approach, an eye-tracking method originally developed by Cornsweet and Crane in 1973. This method enhances resolution by measuring relative, rather than absolute, motion of reflections generated by surfaces at different distances from the eye rotation axis, specifically the cornea and the back of the lens (first and fourth Purkinje images, P1 and P4, respectively). These images move similarly under translation but differentially under rotations, facilitating rejection of translation artifacts. DPI methods have traditionally been implemented in cumbersome and fragile analog devices, which have remained restricted to specialized laboratories. However, recent advances in imaging technology and computational power now allow the DPI approach to be enriched with the flexibility and intelligence of digital systems and implemented in more compact and practical devices. We describe oculomotor measurements obtained with a digital DPI, which directly images the P1 and P4 reflections of an infrared beam by means of a high-speed camera. A real-time algorithm running on a dedicated GPU extracts the Purkinje images and uses them as a metric for eye rotation. Experimental results with both artificial and real eyes demonstrate that this system can resolve sub-arcminute eye rotations at 1Khz sampling rate. We show that the main DPI artifact, the post-saccadic movement of the lens, is highly predictable. The lens rebound lasts less than 20 ms for saccades of all sizes and has magnitude equal to ~14% of the saccade amplitude for saccades larger than 2o. We further show that the DPI approach can lead to arcminute-accuracy localization of the line of sight and can be implemented in a head-mounted device with minimal loss of resolution.

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P43: Calcium responses to optogenetic stimulation decay more rapidly in primate retinal ganglion cells after photoreceptor ablation

Zhengyang Xu

A number of vision restoration therapies aim to restore light sensitivity to retinal ganglion cells (RGCs) following extended periods of blindness. In rodent models of retinal degeneration, physiological changes in RGCs after photoreceptor (PR) loss have been reported but this has not been investigated in primate. By expressing both a calcium indicator (GCaMP6s) and an optogenetic actuator (ChrimsonR) in foveal RGCs of a macaque, we use in vivo imaging to assess changes in RGCs in the weeks and years following PR loss.

AAV2-CAG-GCaMP6s and AAV2-CAG-ChrimsonR-tdTomato were co-injected into the vitreous. Cones were ablated with a Mai-Tai pulsed laser (0.8 x 0.7o, 106 ms, 120-150mW, 730 nm) delivered through an adaptive optics scanning light ophthalmoscope (AOSLO). GCaMP fluorescence from 218 RGCs in two eccentricity matched regions of the fovea was collected using AOSLO and tracked over 10 weeks. In the first location (long-term deafferented) PR input was removed 2 years prior to recording, while in the second location (short-term deafferented) PR input was removed 1 week prior to recording. A 0.5 s optogenetic stimulus (1 mW, 640 nm) was delivered to the RGCs and the GCaMP fluorescence recorded for 90 s. The signal decay was fitted with an exponential model.

Optogenetic responses in RGCs persisted for over 2 years following PR ablation. The mean time to peak calcium response did not differ significantly between the long-term (1.43±0.17s SD) and the short-term (1.45±0.30s SD) deafferented RGCs (unpaired t-test, $p=0.05$, $n=654$). The mean decay constant of the calcium response decreased 2.1 fold (2.5±0.5 s to 1.2±0.2 s SD) in the 8 weeks post PR ablation ($p<0.001$, paired t-test, $n=109$), with 87% of this decrease occurring within the first 5 weeks. The decay constant did not decrease further from week 8 to 10.

By expressing both an optogenetic actuator and a calcium indicator in foveal RGCs, we tracked the development of altered RGC physiology in vivo in the weeks and years following PR loss. The presence of optogenetic responses 2 years after PR loss and the stability of the rise time are promising for vision restoration therapies targeting RGCs. However, the two fold reduction in the decay constant of the calcium response suggests that restored activity may be impacted by changes in the inner retina weeks after PR loss.

P44: Spatial resolution of pre-microsaccadic perceptual enhancements across the foveola

Yue Zhang, Natalya Shelchkova, Ashley Clark and Martina Poletti
Brain and Cognitive Sciences, University of Rochester

We previously showed that before the onset of a microsaccade, fine spatial vision is enhanced at the microsaccade goal. In this study, we investigated the spatial resolution of this phenomenon and examined to which extent this enhancement spreads to foveal locations surrounding the microsaccade target. In addition, we examined how microsaccade preparation impacts sensitivity at the preferred locus of fixation where fine spatial vision is highest.

Observers (n = 7) fixated on a marker surrounded by eight location placeholders presented foveally and arranged in a circle (20' radius). Observers were then instructed to shift their gaze at the location indicated by a central saccade cue. Subjects naturally used microsaccades to relocate their gaze. Nine probes (7'x2' tilted bars) were briefly presented, one at each location and one at the center of gaze, before the onset of the microsaccade. After microsaccade landing, a response cue appeared. Observers reported the orientation of the probe previously presented at the location indicated by the response cue.

Our findings show that pre-microsaccadic enhancements of sensitivity are limited to the microsaccade goal: decrease in performance was observed at the locations surrounding (7' edge-to-edge distance) the microsaccade goal (1.9 vs. 0.4 and 0.3 d', $p < 0.002$). Furthermore, we observed an interaction between microsaccade landing precision and the degree of pre-microsaccadic enhancement, i.e. the performance decreased as microsaccades landed further away from the goal location (2.3 to 1.3 d'). Lastly, a modulation of pre-microsaccadic attention on the preferred locus of fixation was found before microsaccade onset: observers' sensitivity at the center of gaze decreased by more than half compared to baseline.

These findings provide us a better understanding of how pre-microsaccadic attention modulates our foveal vision. They show that every time we make a microsaccade, our foveal vision is reshaped at not only the microsaccade goal but also other non-attended locations, even those that are adjacent to the goal and the center of gaze.

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P45: Task-dependent head-eye coordination during natural fixation

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Humans acquire visual information by continually moving their eyes and head. Pioneering studies reported that, during natural fixation, head-eye coordination is tuned according to the task to yield a suitable amount of retinal image motion (Steinman, 1986). But what type of motion is suited for a given task? Recent experiments indicate that structuring the temporal luminance flow impinging onto the retina is an important function of eye movements. In high-acuity tasks, observers tune their fixational eye drifts so that the luminance modulations delivered within the range of temporal sensitivity enhance high spatial frequencies (Intoy & Rucci, 2020). To resolve minute eye movements, in these previous experiments, the head of the observer was strictly immobilized. Here we use a new custom device to examine how retinal image motion varies across tasks during natural head-free fixation. We recorded head and eye movements by means of scleral coils and passive markers, using an apparatus that integrated a motion capture system (OptiTrack) with a specially designed coil system with three highly uniform, oscillating, magnetic fields. Human observers (N=8) conducted a set of natural tasks, which included visual search, sorting objects by color, an acuity test, and sustained fixation on markers. Our results confirm that head-eye fixational coordination changes systematically across tasks. Critically, we show that changes in motor activity alter the information content of visual input signals by modulating the distribution of spatial frequency power delivered within the bandwidth of human temporal sensitivity. That is, humans jointly coordinate fixational head and eye movements according to the tasks' demands in ways that emphasize the relevant spatial frequency range in the temporal luminance flow. These results indicate that that task-dependent tuning of head-eye coordination effectively acts as a selection mechanism in spatial frequency.

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P46: Accelerating photoreceptor replacement therapy with *in vivo* cellular imaging in primates

Hector Baez, Zhengyang Xu, Karteek Kunala, Sara Patterson, Vamsi Gullapalli, David DiLoretto, Juliette McGregor

Retinal degenerative diseases cause irreversible blindness through malfunction and death of photoreceptors in the retina. Stem cell regenerative therapies have the potential to restore vision, but technical challenges make the quantitative evaluation and tracking of vision restoration difficult. We leverage fluorescence adaptive optics scanning light ophthalmoscopy (FAOSLO), a novel photoreceptor ablation model in non-human primates, and a two-step micro-aggregate surgical transplantation procedure to optimize the most promising cell-based therapies in primates. Utilizing *in vivo* retinal ganglion cell calcium imaging, we classify cells based on response to a flickering LED stimulus, pairing this with photoreceptor ablation opens up the possibility of tracking changes in particular RGC classes after long term deafferentation. Lastly, we report that transplanted photoreceptor precursor aggregates survive *in vivo* for at least 4 weeks post transplantation.