Optogenetic Stimulation of Single Ganglion Cells in the Living Primate Fovea

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Abstract Though the responses of the rich variety of retinal ganglion cells (RGCs) reflect the totality of visual processing in the retina and provide the sole conduit for those processed responses to the brain, we have much to learn about how the brain uses these signals to guide behavior. An impediment to developing a comprehensive understanding of the role of retinal circuits in behavior is the paucity of causal studies in the intact primate visual system. Here we demonstrate the ability to optogenetically activate individual RGCs with flashes of light focused on single RGC somas *in vivo*, without activation of neighboring cells. The ability to selectively activate specific cells is the first step toward causal experiments that directly link retinal circuits to visual experience and behavior.

Introduction

Though only a few classes of light-sensitive cells capture the retinal image in the primate eye, evolution has produced many more classes of retinal ganglion cell (RGC), on the order of 20, each morphologically and physiologically distinct and independently tiling the retina, to convey visual information to the brain. This dramatic expansion of cell classes in the retinal output combined with microelectrode recordings in excised tissue have made it increasingly clear that the diversity of RGCs reflects instead a surprising amount of complex early processing in the mammalian retina, processing that previously been had been thought to reside deeper in the brain (***Gollisch and Meister, 2010***). There is evidence, for example, for specialized circuits that convey directional selectivity(***Barlow et al., 1964***), segregate object from background motion(***Lettvin et al., 1959***), and anticipate moving stimuli(***Berry et al., 1999***). However, we remain uncertain about the direct functional role of these RGC classes because, while ex vivo recordings can characterize the specific stimulus requirements of RGC classes, they are often made in the excised retina that is detached from the downstream visual pathways they serve. Such studies preclude direct manipulations of RGC activity to observe the impact on visual experience or behavior in the awake primate. For example, we cannot say with certainty whether the DS cells recently observed in the non-human primate (NHP) are involved in eye movements, the perceptual experience of motion, or both. Indeed, there is even lingering controversy about the perceptual roles of the most common primate RGCs, the midget and parasol ganglion cells (***Freedland and Rieke, 2022***; ***Patterson et al., 2019***).

To address these controversies, one exciting possibility for the future is the development of studies in which the effect of manipulating RGC responses in the awake behaving animal can be

measured with psychophysical or behavioral measures. There have been formidable challenges to deploying this causal paradigm to study retinal circuits because of their inaccessibility inside the moving eye of the awake behaving primate. Advances in high resolution retinal imaging with adaptive optics now make it possible to observe single RGCs in the living eye (***Gray et al., 2008***). AO has also enabled very accurate eye tracking, making it possible to not only image but also stimulate single photoreceptors repeatedly with focused flashes of light (***Schmidt et al., 2018a***,b; ***Tuten et al., 2017***) in the moving human eye. In addition, viral vectors now allow expression of calcium indicators such as GCaMP6s (***Yin et al., 2013***; ***Godat et al., 2022***) enabling recording from single RGCs *in vivo*. Finally, optogenetic activation of RGCs has been demonstrated in both macaque (***McGregor et al., 2020***) and human (***Sahel et al., 2021***) retina *in vivo*. These recent technical advances taken together now offer the possibility of causal experiments in which single RGCs are optogenetically stimulated in the living primate eye while the behavioral consequences are measured. Here, we demonstrate the first step toward establishing this capability: showing successful stimulation of single RGCs in the living primate eye.

Results and Discussion

The selected cells and their fluorescence traces can be seen in Fig. 1. These recordings were transformed into z-scores using means and standard deviations acquired earlier in the session where no stimulus was present. All targeted cells showed large responses to the optogenetic probe, while the non-targeted cells showed no significant response. Even those non-targeted cells closest to the probe show responses within the normal range. There is no evidence their responses are elevated relative to more distant cells as would be expected if optical cross talk were eliciting responses from nearby cells. Fig. 2 shows all cells' $\Delta F/F$ values plotted against their distance from the targeted cell. These data indicate that only the targeted cell is being activated by the optogenetic stimulus.

Here we show that it is possible to excite individual RGCs expressing an optogenetic actuator in the living monkey eye. When cells are chosen that have especially large separation from their nearest neighbors, this excitation can be achieved without simultaneously stimulating nearby cells. Additional experiments will be required to determine the degree of optical selectivity that can be achieved at slightly larger eccentricities where the RGCs are more densely packed and stacked many cells deep. One approach to reducing the crosstalk problem would be to target a subset of RGC classes with retrograde injections into brain regions that receive a more sparse RGC input from retina. It could also be reduced were it possible to develop viral vectors specific to a particular RGC class. The demonstration of *in vivo* selective activation of individual RGCs lays a possible foundation for future causal studies of RGC function. Such experiments would involve, for example, first, *in vivo* calcium imaging to classify each RGC, followed by psychophysical experiments combined with optogenetic stimulation designed to explore each cell's role in visual behavior. Such experiments would establish a direct link between activation of an individual RGC and visual behavior. Such experiments could help determine whether a given cell class contributes to perceptual experience, subconscious visual behavior, or both. These experiments will face additional challenges such as deploying the technology demonstrated here in the awake behaving animal where eye motion will be larger than in the anesthetized animal. Nonetheless, the single cone tracking and stimulation experiments in the awake human inspire confidence that this will be possible (***Schmidt et al., 2018a***,b; ***Tuten et al., 2017***).

The causal experimental approach has been successful in understanding the roles of neuronal classes in cortex of NHPs for many years, such as the work of Newsome and colleagues who showed that electrical activation of directional selective cells in MT modifies the animal's choices in motion discrimination tasks (***Salzman et al., 1992***; ***Cicmil and Krug, 2015***; ***Parker and Newsome, 1998***). More recently, this paradigm has incorporated optogenetic activation to investigate the function role of localized neural circuitry in cortex. For example, Jazayeri *et al.* directly activated neurons in the primate V1 to demonstrate their relationship to gaze position***Jazayeri et al.*** (***2012***).

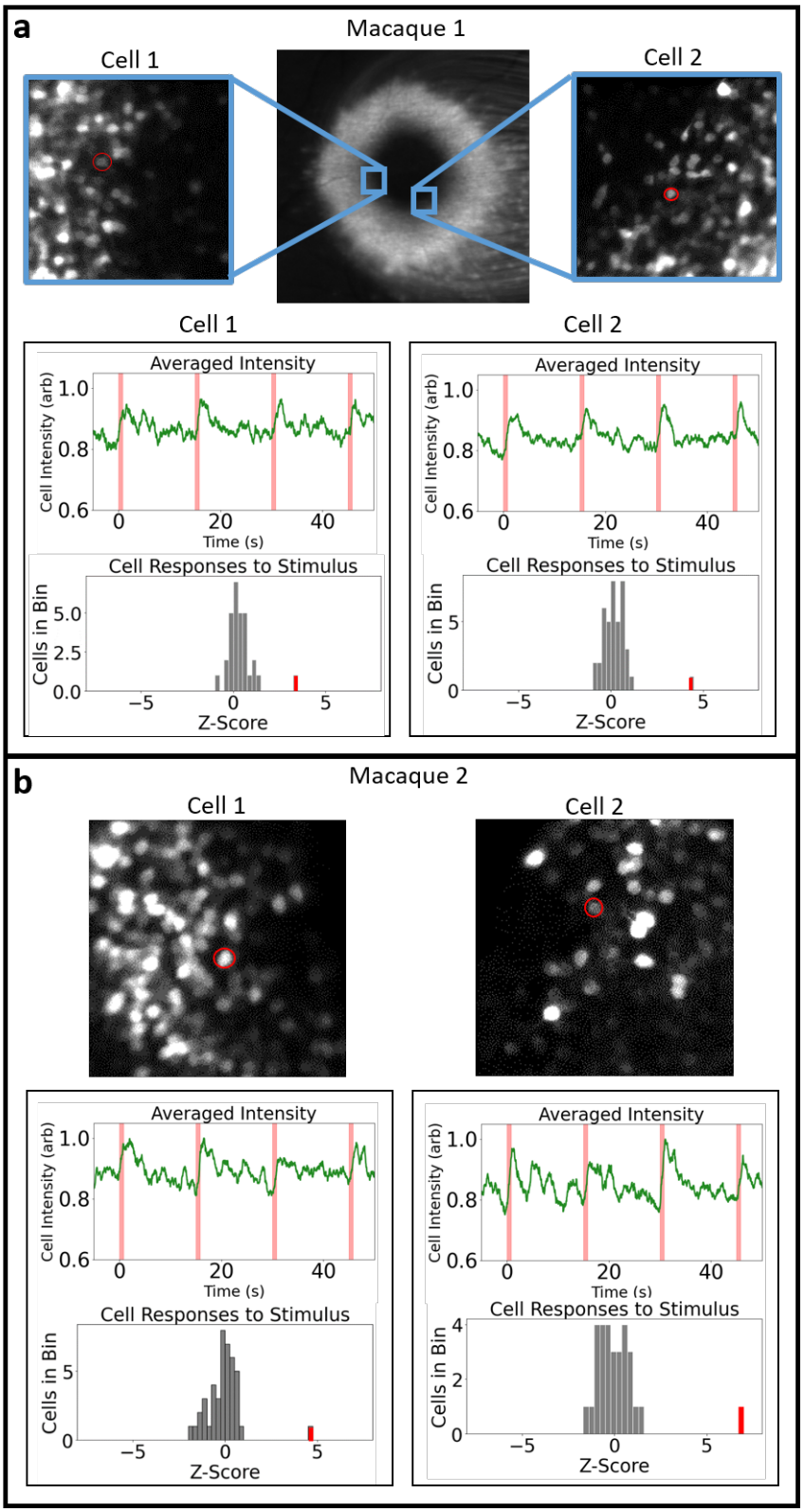

Figure 1. Cells chosen for stimulation. The cell circled in red marks the targeted cell. The averaged fluorescence traces for each cell show the integrated intensity over the cell's soma. The red marks on the time axis represent the onset of the 800 ms optogenetic stimulus. The histograms show each cell's response in terms of z score. (a) Results from male macaque. (b) Results from female macaque. All targeted cells are at similar eccentricities.

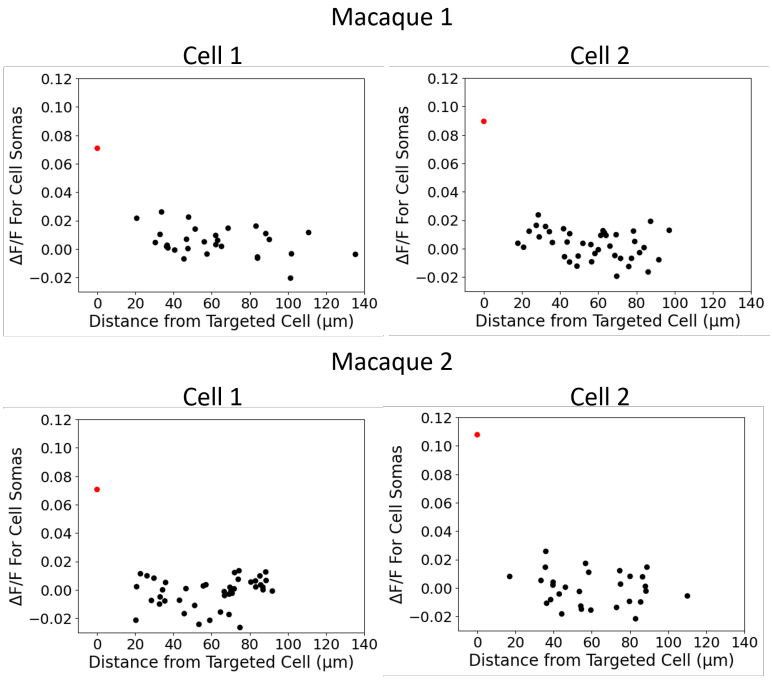

Figure 2. ΔF/F for each cell soma plotted against that cell's distance from the targeted cell. Note that even the nearby cell somas do not show a significantly elevated response (p » 0.05, unpaired t-test) than other cells at more distant locations. The leftmost point on each plot, colored in red, corresponds to the targeted cell itself.

Soma *et al.* applied the technique to motor control, activating posterior parietal and motor cortex neurons to bias limb movements(***Soma et al., 2019***)

In future experiments that will use this approach we will need to demonstrate if the activation of a single RGC can be detected psychophysically in a monkey model. Monkeys are remarkably good at psychophysical experiments, with performance rivalling that of human observers(***Matsuno and Fujita, 2009***). Moreover, analogous experiments in which single cones are targeted with light have shown that visibility can be measured from photon absorption with flashes of light delivered through adaptive optics to single cones from each of the three foveal cone classes(***Williams et al., 1981***; ***Schmidt et al., 2018b***; ***Hofer et al., 2005***). Indeed, the somas of RGCs are substantially easier to selectively target because they are more than five times larger than the cones successfully targeted in these prior experiments.

Nonetheless, the interpretation of causal experiments through optogenetic stimulation of a single RGC is inevitably complicated by the fact that perceptual experience depends on populations cells and the role of any cell in perception will necessary depend on the signals of its neighbors. Neighboring RGCs with overlapping receptive fields to that of the RGC in question will typically not be signalling in the manner is which they normally would. How the brain would interpret such an unusual pattern of excitation is not entirely clear and it may be necessary to control the stimulation of multiple nearby RGCs to develop a clear understanding of their function. Additionally, should it prove possible to realize this paradigm, it could provide valuable data to guide optogenetics-based vision restoration therapies. This could eventually offer the opportunity to instill responses in individual classes of RGCs that lead to a perceptual experience that more closely resembles that generated by the natural environment in the sighted eye.

Methods

Animals and Animal Care

These experiments were performed in two anesthetized *macaca fascicularis*, one male (M1) and one female (M2). Macaques were housed in an AAALAC accredited facility and were provided with care by 4 full time veterinarians, 5 veterinary technicians, and an animal behaviorist from the Department of Comparative Medicine. The animal care staff monitored each animal for signs of discomfort at least twice daily. They were caged in pairs and had free access to lab chow and water. Their diet was additionally supplemented with daily treats including dried fruits, fresh fruits, vegetables, and nuts. All animals have daily access to enrichment items such as puzzle feeders and mirrors, and are provided with movies and/or music. More novel enrichment items such as treat filled bags, snow, or forage boxes were provided weekly. The macaques had access to a large play space with swings and perches on a rotating basis. This study was carried out in strict accordance with the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals and the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. One animal had two lesions of the central fovea, which had removed cone input to many of the labeled RGCs. The RGCs deafferented in this manner are easily distinguishable from those with normal input, and were avoided for study in this experiment.

Injections for Expression of Optogenetic and Calcium Indicator.

Prior to injection, both animals received daily subcutaneous injections of cyclosporine to reduce the possibility of immune reaction to the injection. Blood trough levels were monitored to titrate the dose into the range of 150-200 ng/ml, and these levels were maintained throughout the testing period. The ocular surface was disinfected before injection with 50% diluted Betadine. Coexpression of both an optogenetic actuator (ChrimsonR) and a calcium indicator (GCaMP6s) enabled both stimulation of RGCs and recording of their responses. This was achieved with a single intravitreal injection containing a mixture of two adeno-associated virus (AAV2) based vectors with a ubiquitous CAG promoter, AAV2-CAG-tdTomato-ChrimsonR and AAV2-CAG-GCaMP6s. These vectors were synthesized by the University of Pennsylvania Vector core. The injection was delivered via a 30 gauge needle with a tuberculin syringe into the middle of the vitreous roughly 2 mm behind the limbus. The injection was made in the right eye of M1 and the left eye of M2, and had a total volume of 75 μL. Post-injection, the eyes were monitored with conventional SLO imaging (Heidelberg Spectralis) for adverse events such as inflammation, which was not present in either animal throughout data collection. As previously demonstrated (***Dalkara et al., 2013***), expression was largely confined to an annulus spanning from 0.5° to 2°. The inner edge of this annular region corresponds to the most centrally located RGCs that receive input from the most central fovea, while the outer edge corresponds to the most eccentric location where we presume the inner limiting membrane remained thin enough for penetration of the viral vector. All RGCs that obtained expression are close enough to the foveal center to be displaced from their receptive fields, allowing for direct optogenetic activation of cell somas without stimulation of the cones that drive them.

AO Imaging

Anesthesia and Animal Preparation

Anesthesia and animal preparation were performed by licensed veterinary technicians. Macaques were fasted overnight prior to anesthesia in preparation for ventilation. The morning of an imaging session, macaques were moved to the laboratory and anesthetized with isoflurane. They were placed prone upon a stereotaxic cart, supported by cushions and covered with a warming blanket. The animals were paralyzed for the duration of imaging via an injection of vecuronium bromide. For the duration of paralysis, the animal's heart and respiratory rates, blood oxygenation levels, and electrocardiogram were monitored by a veterinary technician. The animal's pupils were dilated with drops of phenylephrine chloride (2.5%) and Tropicamide (1%), and the eye fitted with a rigid

gas permeable contact lens to maintain corneal hydration. The animal's head was stabilized with ear bars and a chin rest, and the animal's whole body could be rotated via the stereotaxic cart to position the animal for imaging. The macaque was monitored for several hours by a veterinary technician after each session to ensure full and safe recovery from the anesthetic drugs. This procedure was repeated no more than once per week on an individual macaque.

Imaging Procedure

High resolution imaging was performed with an adaptive optics scanning light ophthalmoscope (AOSLO), a complete description of which can be found in (***Godat et al., 2022***). A Shack-Hartmann wavefront sensor in conjunction with an 847 nm laser diode source (QPhotonics) was used for wavefront sensing. The wavefront sensor data controlled a deformable mirror (ALPAO) in a closed-loop configuration operating at 10 Hz to provide correction of ocular aberrations. Reflectance and fluorescence signals were collected with photomultiplier tubes. The RGC layer was imaged using the fluorescent light emitted by the calcium indicator excited with light from a 488 nm laser (Qioptiq), and the optogenetic was excited using the 640 nm line of a multi-line laser (Toptica). The cone mosaic was simultaneously imaged with light from a a 796 nm superluminescent diode (Superlum) to provide a higher SNR helpful for both real-time stimulus stabilization and post-recording image registration. Both uses are based upon cross-correlation of small strips of the image (***Yang et al., 2014***). For stimulus stabilization, only strips located near the stimulus' intended location were used in the cross correlation, allowing the stimulus to be repeatedly presented to the same retinal location. This stabilization is necessary because the heart beat and respiration of the animal cause lateral shifts in the retinal imaging throughout recording of approximately 50 µm. The image registration application is similar in execution and is applied in turn to all sections of the image to obtain a single stabilized video. The motion data from the strip registration of the cone reflectance video was used to stabilize the calcium recording. These methods allowed us to obtain cellular-scale recordings from the primate retina in vivo while correcting for the motion inherent to the living eye.

Cell selection

For this first study, we selected RGCs lying on the innermost edge of the annulus of expression often had large distances between their somas, making them easier to target with optogenetic stimulation without exciting neighboring cells. This crosstalk could potentially enter our measurements both when stimulating and recording. First, scatter from the 640 nm stimulus may illuminate nearby cell somas or underlying fibers of passage. Additionally, these nearby cell somas, their dendritic arbors, and fibers may contaminate the GCaMP recording if they overlap with the cell of interest's soma. We chose cells two cells in each of the two animals that were > 20 µm from their the nearest neighbor to mitigate the possibility of optical crosstalk. Optical crosstalk presents a possible issue because of the overlap between the 488 nm excitation light and our fluorophores' emission spectra, with the absorption spectrum of ChrimsonR. The relevant spectra are shown in Fig. 3. There is significant overlap between the emission wavelengths of our fluorophores and the absorption spectrum of ChrimsonR. The 488 nm imaging light provides a static stimulus to each cell, and does not preclude selectively activating one RGC via the optogenetic probe. We estimate that the emission from GCaMP and tdTomato is at least 4 orders of magnitude lower than this static stimulus, making it unlikely that these caused a significant cell response. Cells within a 1°x1° field of view were imaged at 488 nm (25 µW) for 30 seconds to allow for adaptation to the maintained calcium imaging light. ChrimsonR was then activated by a circular stimulus (640 nm, 750 µW) with a diameter of 12.5 µm, approximately the size of a cell soma. This stimulus was formed by modulating the 640 nm laser source's output to only be on while scanning over the soma of interest at a rate of 25 Hz. The duration of excitation was 800 ms, throughout which the stimulus was stabilized on the cell's soma using the method describe in the imaging procedure section. This stimulus was repeated four times for each trial with a waiting period of 15 seconds between stimuli.

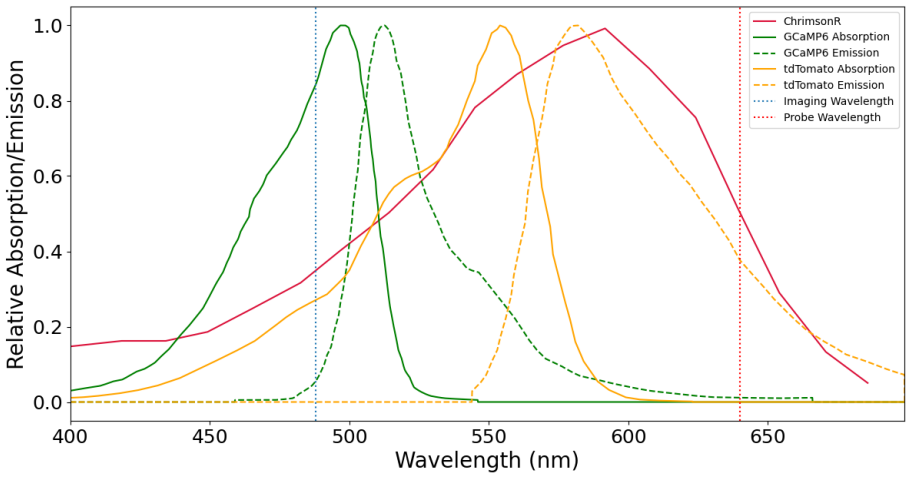

Figure 3. Relevant absorption/emission spectra for our fluorophores and optogenetic actuator. The emission wavelengths of tdTomato and GCaMP6 are well suited to activating ChrimsonR, and the wavelength used to image GCaMP fluorescence stimulates both fluorophores well.

Analysis

Analysis The GCaMP6s recordings were registered using strip registration and the frames averaged to obtain a high SNR image of the RGC mosaic. This registration is necessary because the heart beat and respiration of the animal cause lateral shifts in the retinal imaging throughout recording of approximately 50 µm. The resulting RGC image was manually segmented to create a binary mask that can be applied to each frame of the video. The mask is used to extract the mean brightness of each cell soma for each frame. These brightness values are then used to calculate ΔF/F values for each cell soma in response to each stimulus. This calculation was performed for all cells that remain within the field of view for the entirety of the recording. Cells near the edge of the field of view often move in and out of visibility, obscuring any signals that may be present. The mean and standard deviation of ΔF/F values are calculated for periods during which no stimulus was present using data taken from all labeled RGCs in the subject's retina. These are used to transform the cell responses to stimuli into z-scores.

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Competing Interests

David R. Williams: Patents with the University of Rochester for adaptive optics retinal imaging: US patent 6,199,986 "Rapid, automatic measurement of the eye's wave aberration", US patent 6,264,328 "Wavefront sensor with off-axis illumination" and US patent 6,338,559 "Apparatus and method for improving vision and retinal imaging". Qiang Yang: Patents with the University of Rochester, Canon Inc. and the University of Montana, for image stabilization algorithms: US patent 9,226,656: "Real-time optical and digital image stabilization for adaptive optics scanning ophthalmoscopy", US patent 9,406,133: "System and method for real-time image registration", US patent 9,485,383, "Imaging based correction of distortion from a scanner" and US patent 9,454,084, "Light source modulation for a scanning microscope".

Author Contributions

Peter J. Murphy, Conceptualization, Data curation, Formal analysis, Investigation, Software, Visualization, Methodology, Writing - original draft, Writing - reviewing and editing; Zhengyang Xu, Investigation, Methodology; Juliette E. McGregor, Investigation, Methodology, Writing - reviewing and editing; Qiang Yang, Software, Methodology; William Merigan, Concepualization, Investigation, Methodology, Project administration, Supervision, Resources, Writing - reviewing and editing; David R. Williams, Conceptualization, Project administration, Supervision, Resources, Funding acquisition, Writing - original draft, Writing - reviewing and editing

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Data Availability

All fluorescence recordings, along with example analysis scripts and required supporting files, are available at https://osf.io/zgjsv/

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