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RPPR Final Report
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Task 2: Development and characterization of multi-channel photonic neural probes for optogenetic stimulation employing on-probe wavelength division demultiplexing.

Task 3.1: In vivo demonstration of local optical stimulation using photonic probes and high-speed two-photon imaging

Task 3.2: In vivo demonstration of remote optical stimulation using photonic probes and multi-site electrical recording.

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Eran Segev, Jacob Reimer, Laurent C. Moreaux, Trevor M. Fowler, Derrick Chi, Wesley D. Sacher, Maisie Lo, Karl Deisseroth, Andreas S. Tolias, Andrei Faraon, Michael L. Roukes, Patterned Photostimulation via Visible-Wavelength Photonic Probes for Deep Brain Optogenetics. Neurophotonics 4(1), 011002 (2017), doi: 10.1117/1.NPh.4.1.011002.

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Abstract: Optogenetic methods developed over the past decade enable unprecedented optical activation and silencing of specific neuronal cell types. However, light scattering in neural tissue precludes illuminating areas deep within the brain via free-space optics; this has impeded employing optogenetics universally. Here, we report an approach surmounting this significant limitation. We realize implantable, ultranarrow, silicon-based photonic probes enabling the delivery of complex illumination patterns deep within brain tissue. Our approach combines methods from integrated nanophotonics and microelectromechanical systems, to yield photonic probes that are robust, scalable, and readily producible en masse. Their minute cross sections minimize tissue displacement upon probe implantation. We functionally validate one probe design in vivo with mice expressing channelrhodopsin-2. Highly local optogenetic neural activation is demonstrated by recording the induced response.

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Integrated Photonic Neural Probes for Patterned Brain Stimulation

Caltech



BCM
Baylor College of Medicine

Final Report: 14 August 2017
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Section I. Summary of Proposal and Objectives

A. Innovative claims for the proposed research.

Brain computations, such as perception, learning, and memory, arise from the coordinated activation of large assemblies of neurons distributed across the brain. While major progress has been made in understanding the response properties of individual cells, circuit interactions and their functional implications for brain computations remain poorly understood. A fundamental obstacle to understanding these interactions is the difficulty of observing and manipulating the activity of large distributed populations of neurons in freely behaving animals with single cell and single spike resolution. If the brain were a TV screen with each neuron corresponding to a single pixel, then current methods limit us to viewing or manipulating only a few scattered pixels per experiment.

Methods from integrated photonics provide a promising avenue for overcoming these limitations. Our long-term goal is to create photonic probes that will enable dense and distributed patterned optical stimulation and functional imaging in freely behaving animals and, ultimately, in humans. The development of this transformative technology will require significant investment to create complex multifunctional neural probes that integrate optical stimulation, large-scale spatial multiplexing, and electrical/optical recording. The use of optical signals will enable packing thousands of stimulation and recording sites within ultra-narrow probes ($\sim 50\mu\text{m}$ wide or less) that minimize tissue damage and optimize long-term performance. Leveraging our extensive experience in both nanofabrication and neural stimulation and recording rodents, we aim to develop and demonstrate devices that are both robust and mass producible. This will ultimately enable their large-scale deployment for medical, military, and basic science applications.

B. Objective and tasks of the program.

The main goal of this seedling program is to develop implantable silicon probes that include several photonic waveguides terminated in optical emitters that will be used to locally illuminate small volumes of brain tissue. These photonic probes will be implanted in rodents to enable local optical stimulation of neurons expressing light-activated channels. To reach this objective, the program comprises the three main tasks, namely

Task 1:

Development and characterization of few-channel, direct-coupled photonic neural probes for optogenetic stimulation.

Task 2:

Development and characterization of multi-channel photonic neural probes for optogenetic stimulation employing *on-probe* wavelength division demultiplexing.

Task 3:

In vivo demonstrations of optogenetic stimulation using photonic neural probes.

Section II. Scientific Progress and Accomplishments

Task 1: Development and characterization of few-channel, direct-coupled photonic neural probes for optogenetic stimulation.

We have patterned implantable silicon probes that include several photonic waveguides terminated in optical emitters (e-pixels). These can locally illuminate small volumes of brain tissue. Each waveguide is coupled off-chip to a separate optical fiber that leads to an individual source. The path for achieving this goal required the accomplishment of the following major milestones:

Development of low loss photonic circuitry working in the blue wavelength range

At the starting point of this project, most of the available silicon photonic technology targets the infrared (IR) band. Only very few publications described silicon photonic components working in the visible range. In order to accomplish the project goals, we have developed a complete fabrication process for photonic components based on a thin layer of Silicon Nitride (Si_3N_4). Silicon Nitride is transparent for blue wavelength and is compatible with CMOS fabrication processes. For such short wavelengths the scattering losses in the waveguides are extremely sensitive to the smoothness of the waveguides. Figure (1) shows two SEM images illustrating the improvement in waveguide roughness from one of our fabricated waveguides compared to one of our recent ones. It can be easily noticed that we improved the fabrication process to a stage where we can fabricate very smooth waveguides thus allowing for relatively low loss propagation factor.

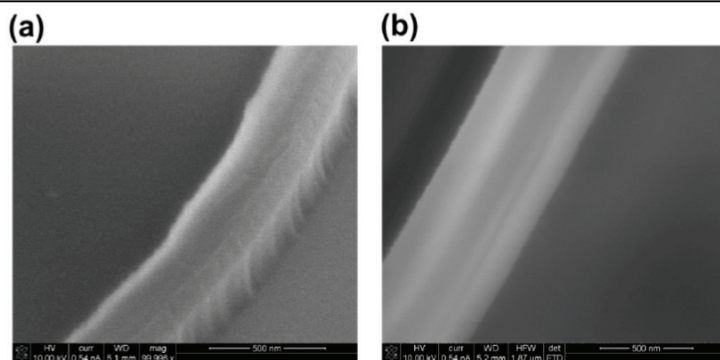


Figure 2: Silicon Nitrate waveguide for blue light. SEM images of (a) non-smooth and (b) smooth waveguides fabricated at the initial and recent stages of the project, respectively.

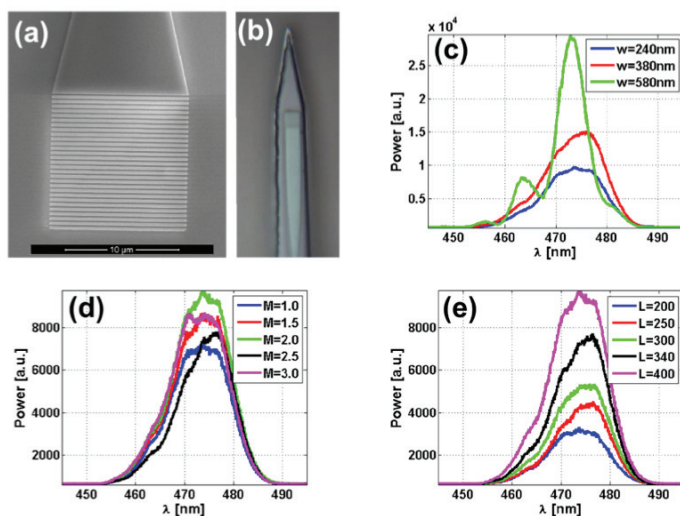
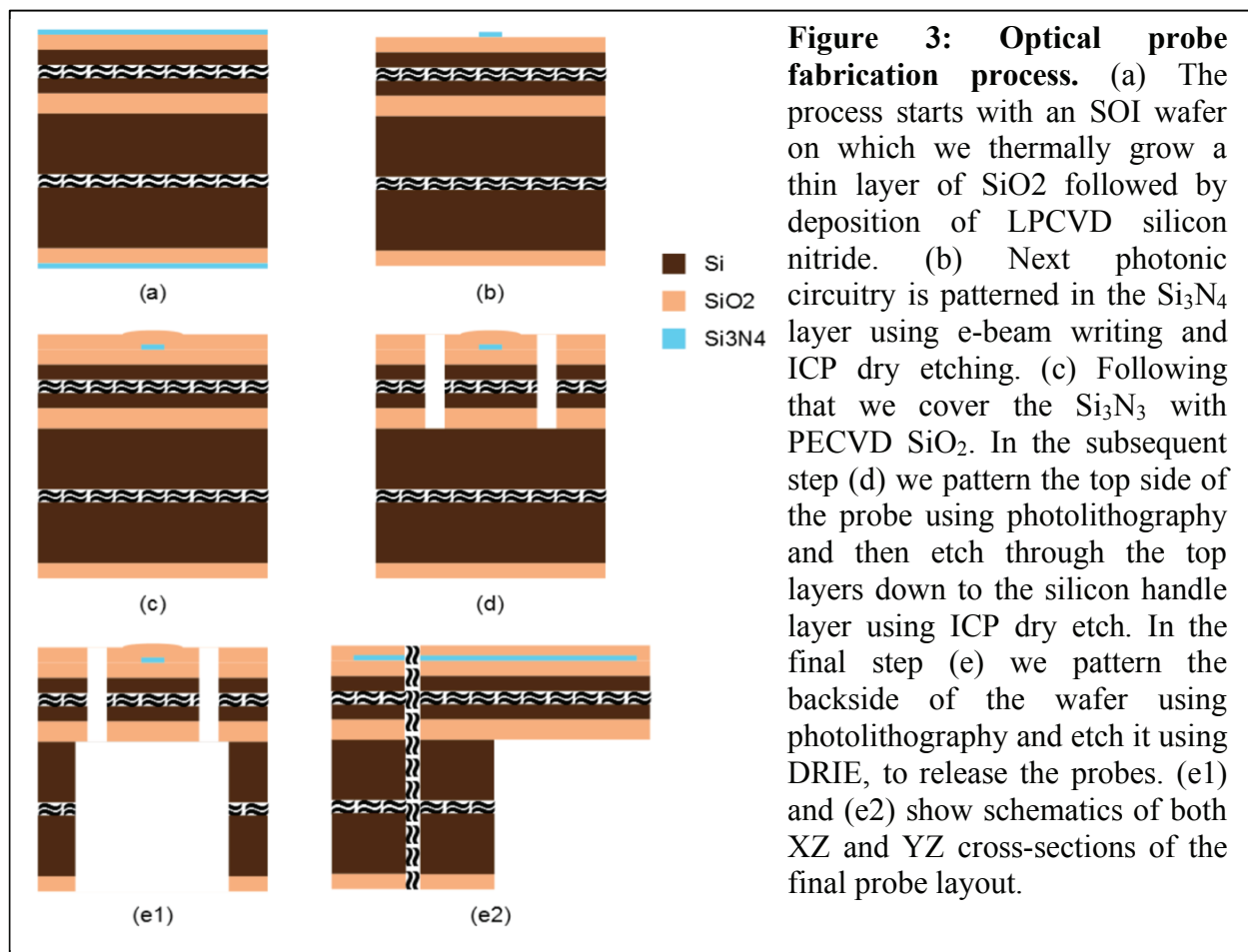


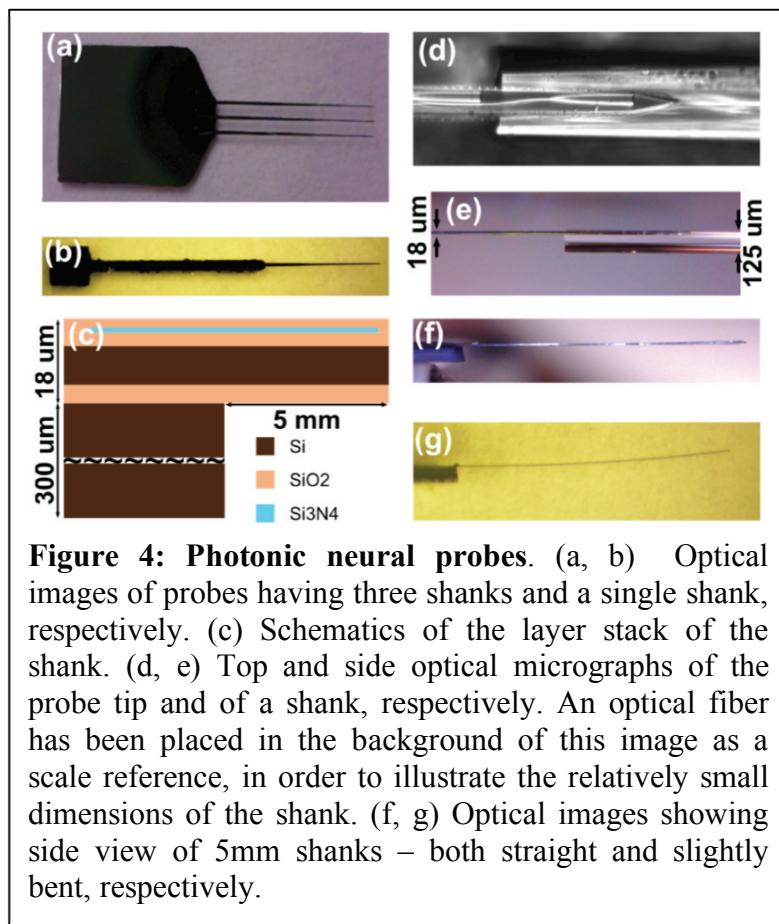
Figure 1: Optical emitter, e-pixel. (a) SEM image of a typical grating coupler. (b) Grating coupler near the tip of a shank. (c)-(e) Measured grating coupler transmittance spectrum as a function of the wavelength, and a function of (a) waveguide width, (b) tapering convexity parameter, and (c) tapering length.



In addition to smooth waveguides we have developed grating couplers for the red and blue wavelength ranges. These grating couplers are used to couple the light into and out of the probe. Figure (2a) shows a SEM image of typical grating coupler, whose size is $10 \times 10 \mu\text{m}^2$. Figure (2b) shows an optical image of a grating coupler fabricated near the tip of a probe. This grating coupler illuminates light perpendicular to the probe surface. As part of the development process we optimized the shape and dimensions of the grating couplers. Figures (2c)-(2e) show the transmittance spectrum of the grating coupler as a function of the wavelength. The various curves in Fig. (2c) correspond to grating coupler that couples light to waveguides having different width. As shown, the wider the output waveguide the higher the efficiency of the grating coupler. The various curves in Fig. (2d) correspond to grating couplers having different convexity, where the higher the M parameter the stronger the convexity. Maximal grating coupler efficiency is achieved for moderate convexity. The various curves in Fig. (2e) correspond to grating couplers having various tapering length. As shown, longer tapering provides better coupling efficiency.

Development of a CMOS-compatible full wafer fabrication process at 100mm (4")

One of the main goals of the project was to develop probes that are fabricated using CMOS compatible fabrication processes, so that at a later stage commercial foundries can fabricate them. The motivation behind this goal was to enable future mass production of these probes and



to make them available to the neuroscience community. Figure (3) shows a summary of our fabrication process, which is explained in more detail in the figure caption.

Another milestone that was achieved as part of the fabrication process development was the ability to precisely control the overall mechanical stresses. These are invariably built in to the layer stack from which the probes are fabricated. This stack is comprised of SiO_2 and Si_3N_4 and can potentially be highly stressed. By careful simulations, engineering, and testing of this layer stack we have managed to produce an almost stress-free multilayer stack. Achieving this is extremely important because it enable us to fabricate probes having almost completely straight shanks. This minimizes the risk of failure and shank breakage

during the process of implantation into brain tissue, when the shanks are subjected to significant mechanical stress.

Figure (4) shows several images and a schematic drawing of our photonic probes. Subplots (4a) and (4b) shows two versions of the probes that have three shanks and a single shank, respectively. The body of the bottom probe is only 250 μm wide, identical to the diameter of the optical fiber that couples to it. Subplot (4c) shows an unscaled schematic drawing of the layer stack from which the probe is fabricated. Subplots (4d) and (4e) show two optical images of the tip region of probes. In order to illustrate the relatively small dimensions of the shank the background includes the image of an optical fiber (125 μm wide). The small dimensions of our probes will significantly reduce the damage that the implantation process causes to the brain tissue. Subplots (4f) and (4g) show optical images of two 5mm long shanks. The bending of the shank shown in subplot (4g) occurs as a result of the internal stresses in the layer stack; these were only moderately compensated in that specific case. Subplot (4f) on the other hand shows the outcome of a well stress compensated design.

Development of compact, efficient and mechanically stable method to couple optical fiber to a photonic probe

There is no single, particularly optimal method to couple light into a silicon photonic circuit. In fact, this continues to be an ongoing research effort in both academia and industry. Solutions have been developed that use a grating coupler, but these require almost a 90° angle between the

optical fiber and the silicon chip. This, in turn, results in a bulky and mechanically unstable assembly. Solutions in which the optical fibers couple horizontally and directly into a photonic waveguide require either highly polished chip facets, which cannot be realized with our probes, or fabrication of “V-groove” assemblies that are hard to realize within the constraints of our complex layer stack. Further, all of the above solutions require precise alignment between the optical fibers and the photonic coupling element. This alignment becomes harder as the wavelengths get shorter – as in the case with the blue light used in this application.

To circumvent these challenges, we have developed a novel coupling technique that utilizes micro-prisms. These have

dimensions of $180 \times 180 \mu\text{m}^2$, and are thus an intermediate size element between the optical fiber and the grating couplers. To employ the micro-prisms we first attach the optical fiber directly to the micro-prism using UV epoxy. Although the light no longer remains confined while propagating in the micro-prism, the prism's small dimensions ensure that the optical beam does not diverge significantly. Subsequent to coupling the fiber and the micro-prism together, the prism is now precisely aligned to a grating coupler and again glued using UV epoxy. Use of the micro-prism permits coupling the optical fiber so that it is almost parallel to the probe surface. Hence this enables a very compact and stable assembly, without degrading the efficiency of the optical coupling.

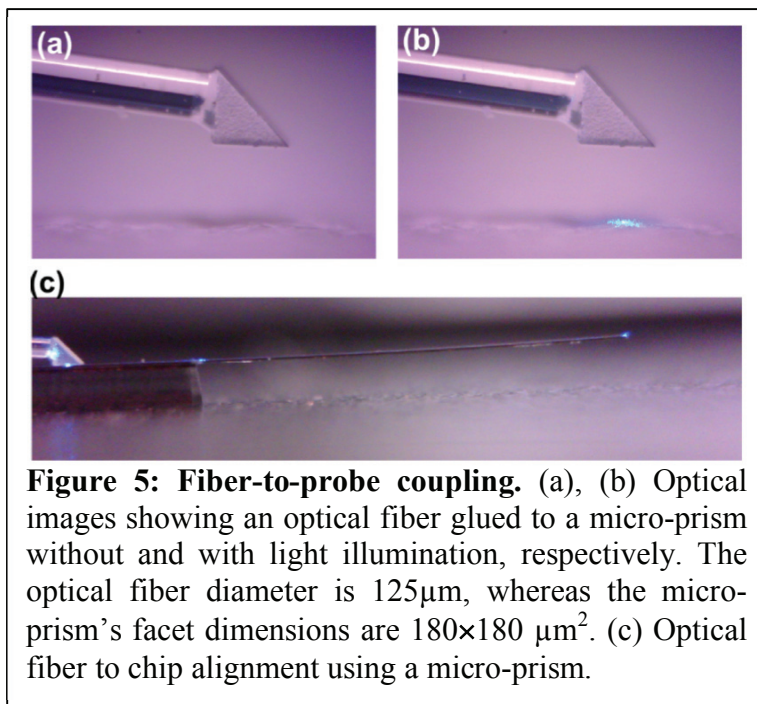


Figure 5: Fiber-to-probe coupling. (a), (b) Optical images showing an optical fiber glued to a micro-prism without and with light illumination, respectively. The optical fiber diameter is $125 \mu\text{m}$, whereas the micro-prism's facet dimensions are $180 \times 180 \mu\text{m}^2$. (c) Optical fiber to chip alignment using a micro-prism.

Figure (5) shows optical images of this coupling process. Images (a) and (b) showing the process of coupling and gluing a micro-prism to the optical fiber. Image (b) shows the blue illumination pattern that is illuminated through the prism. Image (c) shows the one of our optical probes with a micro-prism coupled to one of its inputs. Light is coupled to the chip using this micro-prism and couples out through a grating coupler placed at the tip of the probe.

Characterization of single-channel photonic neural probes in fluorescent solution

After complete assembly of single channel probes, i.e. one emitting pixel (e-pixel), the beam illumination profile was thoroughly characterized as a function of the distance of the light from the probe shank. This characterization was done by imaging the illumination beam: *i*) in fluorescein solution and in fixed mouse brain slices soaked overnight in a fluorescein solution and compared to numerical simulations in Figure (6). Our measurement and simulations results indicate that the light emission is highly directional, low divergence $\sim 30 \text{ mrad}$, at an angle typically ~ 6 degrees normal to the probe surface based on the designed of the output grating

coupler. The high directionality of these beams minimizes overlap between adjacent beams and preserves light intensity levels with increasing propagation distance from the shank.

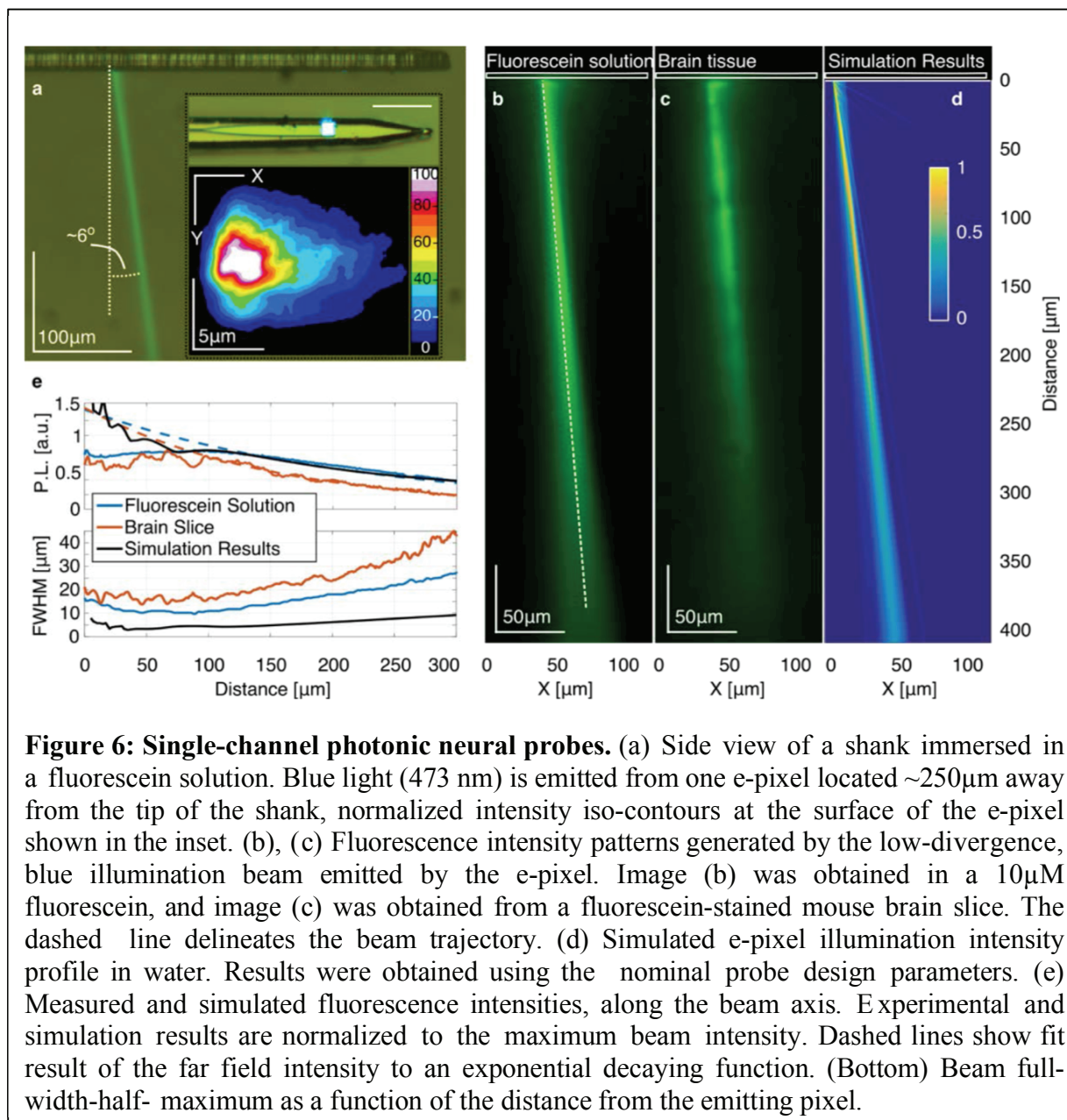


Figure 6: Single-channel photonic neural probes. (a) Side view of a shank immersed in a fluorescein solution. Blue light (473 nm) is emitted from one e-pixel located ~250μm away from the tip of the shank, normalized intensity iso-contours at the surface of the e-pixel shown in the inset. (b), (c) Fluorescence intensity patterns generated by the low-divergence, blue illumination beam emitted by the e-pixel. Image (b) was obtained in a 10μM fluorescein, and image (c) was obtained from a fluorescein-stained mouse brain slice. The dashed line delineates the beam trajectory. (d) Simulated e-pixel illumination intensity profile in water. Results were obtained using the nominal probe design parameters. (e) Measured and simulated fluorescence intensities, along the beam axis. Experimental and simulation results are normalized to the maximum beam intensity. Dashed lines show fit result of the far field intensity to an exponential decaying function. (Bottom) Beam full-width-half- maximum as a function of the distance from the emitting pixel.

Task 2: Development and characterization of multi-channel photonic neural probes for optogenetic stimulation employing *on-probe* wavelength division demultiplexing.

In order to accomplish the task of developing multi-channel photonic probes we transferred AWG technology developed for IR wavelengths to the visible regime (specifically, for blue light). This involved the use of Si₃N₄ photonic layer rather than one comprised of silicon, and also required scaling down all dimensions by at least a factor of three. The resulting AWG is, to our knowledge, the world smallest AWG to date – and the first to work at blue wavelengths. Our

proof-of-concept design supports nine wavelength channels, each of which has a spectral bandwidth of about $\sim 1\text{nm}$. The total footprint of the design varies with design parameters, but is always smaller than $200 \times 200 \mu\text{m}^2$.

Figure (7) shows results from our AWG's prototypes, with SEM images of two of our AWG designs. Over fabrication iterations, we decreased the AWG-footprint area down to $100 \times 150 \mu\text{m}^2$. The graph in Figure (7c) shows the transmittance of the AWG as a function the wavelength of the feed light for each channel.

AWG integration with the optical probes

We have integrated the AWG's within a 3-shanks silicon probes. In this design, each AWG drives a single shank on which we have patterned nine e-pixels. We can individually address each e-pixel by tuning the color of the input light to the AWG. Figure (8) shows two optical images of the integrated optical probes with the AWGs. The silicon probe comprises 3 shanks, each driven by a separate AWG, each shanks, providing nine e-pixels with a $200\mu\text{m}$ pitch. Our use of wavelength division multiplexing makes it possible to independently address on-shank e-pixels by separate temporally modulated multispectral components of the light delivered to the probe. The visible-wavelength AWGs we have developed for this program, have a compact footprint of less than $150\mu\text{m} \times 150\mu\text{m}$; accordingly, they are ideally suited for integration within the heads of our photonic probes.

Characterization of on-probe wavelength division demultiplexing

To address the AWG, as a first demonstration of on-probe wavelength division demultiplexing, we used a mode-locked Ti:Sapphire femtosecond laser to pump in a single pass fashion a thin non-linear crystal of BBO (Beta Barium Borate), to produce a second harmonic signal as shown in Figure (9a). The mode-locked Ti:Sapphire laser is tuned at 946nm wavelength with 70fs pulse-width allowing the generation of blue light at 473nm with $\sim 6\text{nm}$ spectral bandwidth. A dichroic mirror separates the infrared pump light and blue light of interest. The blue light is then coupled to the single-mode optical fiber. We narrowed down the spectral bandwidth of the feed light to the porbe in order to address individual (or two) e-pixel by inserting a band pass (1nm full-half-maximum bandwidth) centered at 473nm , before the fiber launch. By changing the angle of incidence of the blue light onto this filter, the central wavelength can be shifted, thereby enabling tuning of the wavelength feed in regard to the spectral transmission curve (Figure 9b) of the AWG while keeping a 1-nm spectral band. Figure (9c) shows the fluorescence pattern generated by a probe-shank comprising 9 e-pixels routed to

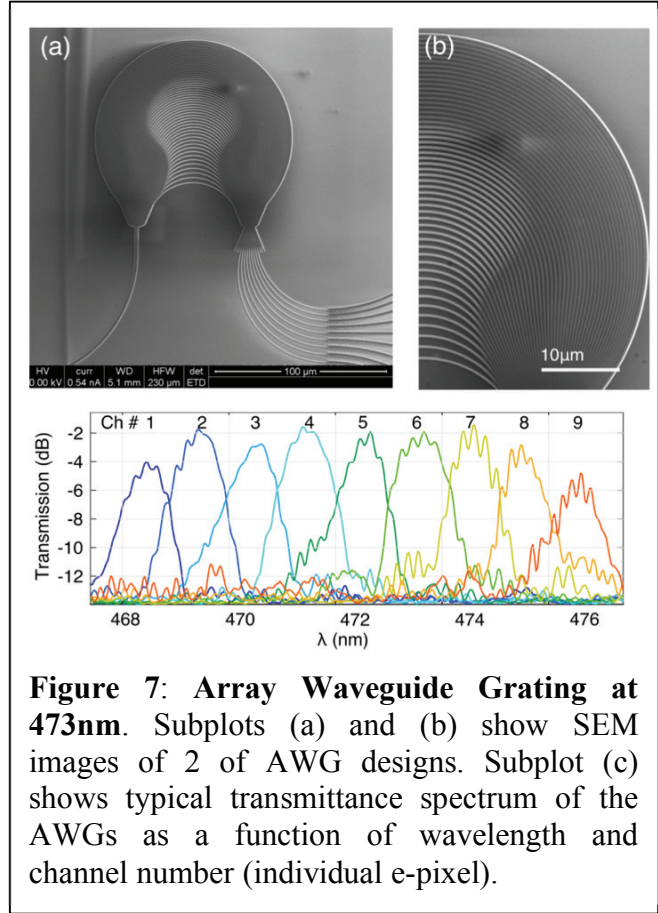
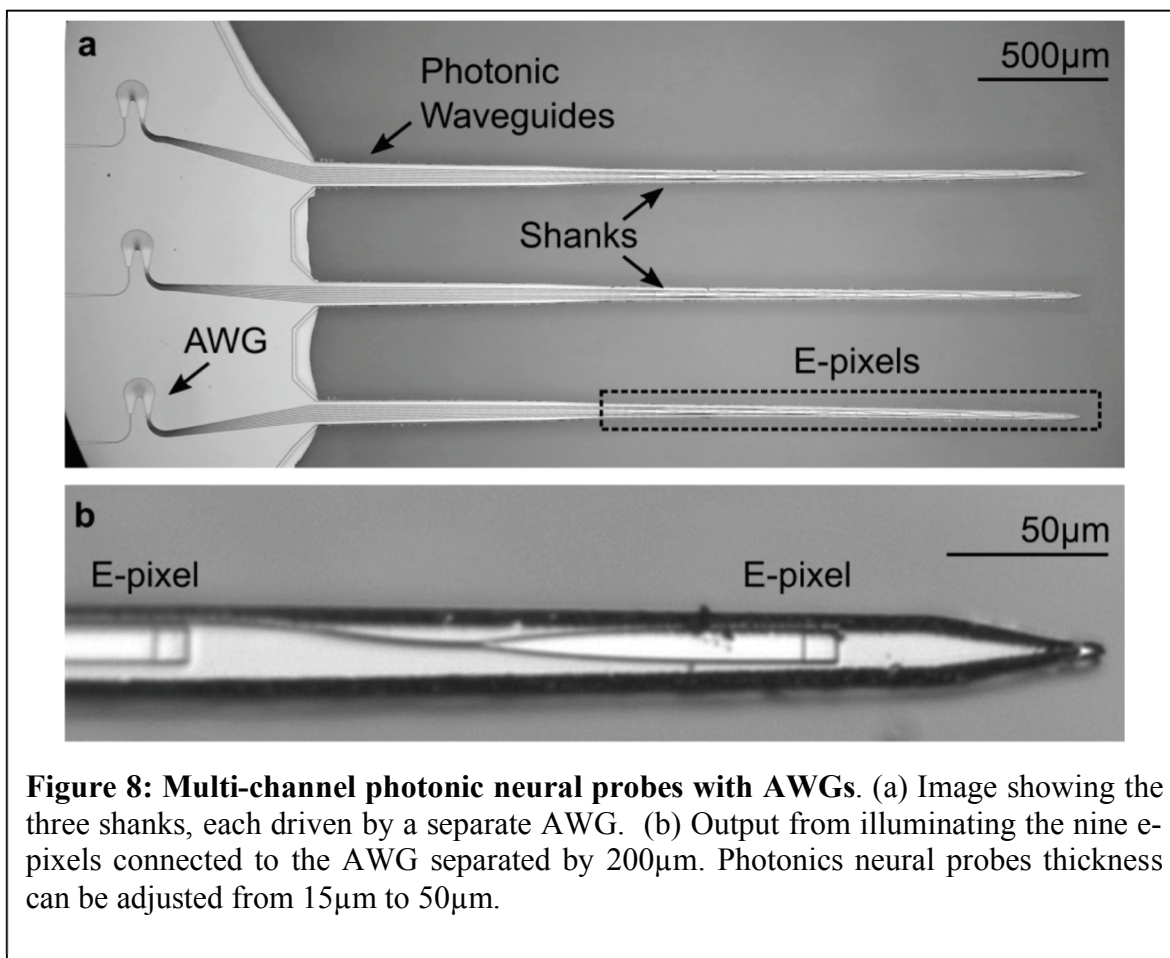


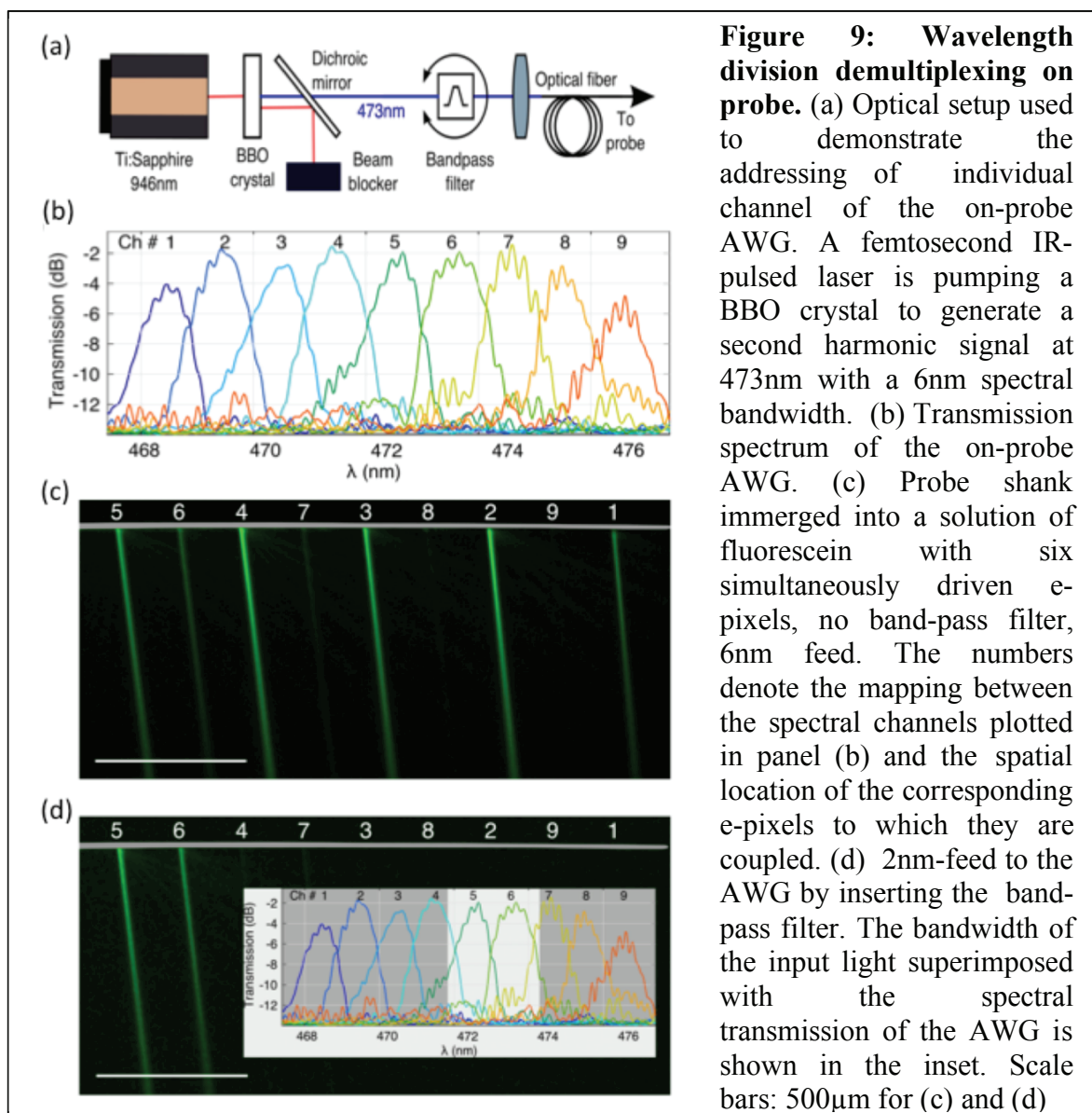
Figure 7: Array Waveguide Grating at 473nm. Subplots (a) and (b) show SEM images of 2 of AWG designs. Subplot (c) shows typical transmittance spectrum of the AWGs as a function of wavelength and channel number (individual e-pixel).



the AWG immersed into a solution of fluorescein feed with ~6nm bandwidth (no band-pass filter). In Figure (9d), the 2nm-band-pass filter is inserted and tuned. The spectral bandwidth of the input light superimposed with spectral response of the AWG is illustrated in the inset. To our knowledge, this is the first successful demonstration of wavelength division demultiplexing in the visible spectrum on probe chip.

Task 3: *In vivo* demonstrations of optogenetic stimulation using photonic neural probes.

The functionality of the probes was validated at Baylor College of Medicine via two-photon functional calcium imaging of cortical neurons co-expressing GCaMP6s and the light-activated channel ChR2, Figure (10). Measurements were performed in an anesthetized, head-fixed adult mouse, placed under a custom two-photon microscope. The photonic probe was implanted at an angle of ~35° relative to the microscope objective optical axis, into the brain cortical layer 2/3. A fiber-coupled 473nm diode laser drives the emitting pixel at the tip of the photonic probe. To prevent saturation of the two-photon microscope photo-detectors during application of optical stimuli, mechanical shutters were used to block light emitted by the probe, see Figure (10a) and (10b) for experimental setup configuration. In these experiments, probe illumination was directed upwards from the surface of the probe into the brain tissue and a population of neurons was imaged approximately 130µm above the probe tip (see dashed white circles in Figures (10c)



and (10g). Blue light pulses of a 200ms duration were delivered by the photonic probe with a repetition rate of 0.2Hz, with an estimated optical output power of $\sim 10\mu$ W at the emitting pixel. The fluorescence response of the GCaMP6s/ChR2-expressing cells was simultaneously recorded by two-photon calcium imaging. We observed reliable activation of neurons by the 473nm-light pulses delivered from the probe. No simultaneous activation of the neighboring neurons – labeled #2, #3, and #4 – was observed in response to the highly-collimated light pulses from the photonic probe. We demonstrated here, the ability to pinpoint excitation to individual neuron within an ensemble of neurons expressing an opsin using our novel neural photonic probes.

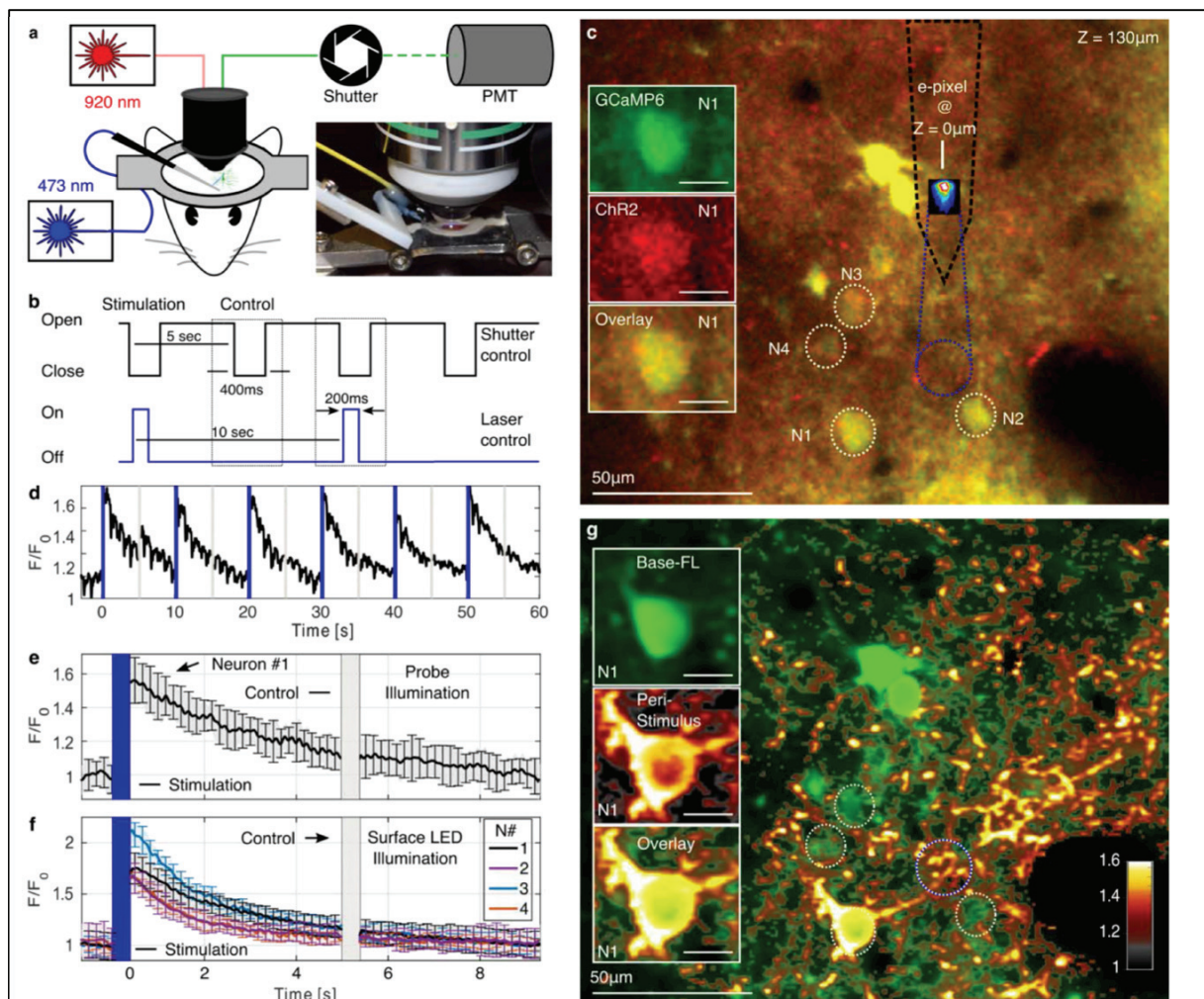


Figure 10: Optogenetic stimulation using photonic neural probes. (a) Schematic of the experimental setup. (b) Illustration of the light excitation sequence. Each sequence includes a single stimulation event and a subsequent control event, during which only the mechanical shutter is activated while no light is emitted by the probe. (c) Visualization of the expression levels of optogenetic actuators and reporters of the imaging site in mouse cortical layer 2/3 (920 nm excitation, Nikon 16x/0.8-NA objective lens; scale bar: 50 μm). Neurons co-expressing GCaMP6s and ChR2-mCherry are identified via two-photon imaging (insets; scale bars 10 μm). The dashed blue circle marks the approximate probe beam, emitted from the probe 130 μm below. Dashed white circles, labeled N1-N4, delineate four co-expressing neurons located in close proximity to the illumination site. (d)-(f) Results from neural excitation. (d) Ca^{2+} transients, measured for N1, showing evoked neural response during sequential excitation and control events. Traces are normalized to base fluorescence level prior to the stimuli event. (e) Peri-stimulus time histogram of N1 for 19 stimulation cycles. (f) PSTH time histogram of N1 to N4 calculated over 15 pulses of wide-field blue (473 nm) illumination delivered through the microscope objective. (g) Peri-stimulus activation calculated at single pixel resolution, across the entire imaging site. Baseline fluorescence in green is calculated over a period of 40 ms prior to the stimuli. The black-red-yellow layer shows the peak peri-stimulus fluorescence, calculated as an average over a 30 ms interval preceding the stimulus event.

Section III. Summary of Results

We have successfully developed and tested ultra-compact multi-pixel implantable silicon-based neural probes for optogenetic stimulation in brain tissue. These probes are minimally invasive, with shanks having a cross-section roughly an order of magnitude smaller than previous state-of-the-art probes. Our fabrication process is fully compatible with semiconductor foundry mass-production methodologies. The compact footprint of these probes is achieved through wavelength division multiplexing. This enables a single optical fiber to carry a multiplicity of separately modulated wavelengths, which are de-multiplexed on the probe chip to permit delivery of temporally patterned light by multiplicity of emitting pixels. We experimentally demonstrate array-waveguide-gratings working in the blue visible spectrum (473nm wavelength). We have experimentally characterized the functionality of these probes in a mammalian brain *in vivo*. Blue light delivered by the probe can be used to excite neurons expressing light-activated channels as validated by simultaneously calcium imaging with two-photon microscopy of neural activity. We demonstrate the ability to pinpoint excitation to one individual neuron within an ensemble of neurons expressing opsins using our novel photonic probes.