An Optogenetic Brain System (OBServ) to Restore Visual Perception in the Blind

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ABSTRACT

Ultra-large mesoscopic imaging advances in the cortex open new pathways to develop neuroprosthetics to restore foveal vision in blind patients. Using targeted optogenetic activation, an optical prosthetic can focally stimulate spatially localized lateral geniculate nucleus (LGN) synaptic boutons within the primary visual cortex (V1). If we localize a cluster within a specific hypercolumn's input layer, we will find that activation of a subset of these boutons is perceptually fungible with the activation of a different subset of boutons from the same hypercolumn input module. By transducing these LGN neurons with light-sensitive proteins, they are now sensitive to light and we can optogenetically stimulate them in a pattern mimicking naturalistic visual input. Optogenetic targeting of these purely glutamatergic inputs is free from unwanted co-activation of inhibitory neurons (a common problem in electrode-based prosthetic devices, which result in diminished contrast perception). We must prosthetically account for rapidly changing cortical activity and gain control, so our system integrates a real-time cortical read-out mechanism to continually assess and provide feedback to modify stimulation levels, just as the natural visual system does. We accomplish this by reading-out a multi-colored array of genetically-encoded and transduced bioluminescent calcium responses in V1 neurons. This hyperspectral array of colors can achieve single-cell resolution. By tracking eye movements in the blind patients, we will account for oculomotor effects by adjusting the contemporaneous stimulation of the LGN boutons to mimic the effects of natural vision, including those from eye movements. This system, called the Optogenetic Brain System (OBServ), is designed to function by optimally activating visual responses in V1 from a fully-implantable coplanar emitter array coupled with a video camera and a bioluminescent read-out system. It follows that if we stimulate the LGN input modules in the same pattern as natural vision, the recipient should perceive naturalistic prosthetic vision. As such, the system holds the promise of restoring vision in the blind at the highest attainable acuity, with maximal contrast sensitivity, using an integrated nanophotonic implantable device that receives eye-tracked video input from a head-mounted video camera, using relatively non-invasive prosthetic technology that does not cross the pia mater of the brain.

PATIENTS AND THE NEED FOR FOVEAL RESTORATION

- No current therapy restores high-acuity foveal vision due to catastrophic damage
  - to the eye
  - to the optic nerve
  - to retinal ganglion cells (RGCs)
- More than 200 Million people suffer from foveal vision loss:
  - macular degeneration
  - traumatic ocular injury
  - glaucoma

THREE PREMISES FOR FOVEAL RESTORATION

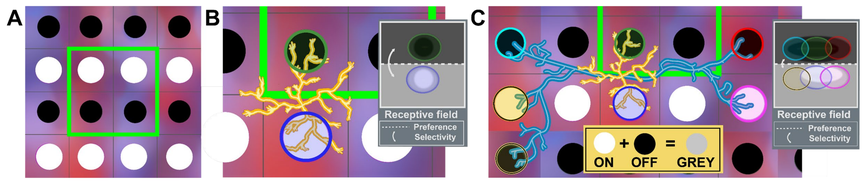
1. Restoring fovea vision is the primary goal
   - Patients with foveal islands of sparing do well
   - Failing to fix the fovea = blindness (< 20/200 vision)
2. Successful prosthetic stimulation of the smallest visible object could serve as the building block for any visual stimulus
   - As in natural vision
3. We must stimulate with naturalistic synaptic spatiotemporal precision
   - Synaptic precision of avoids unwanted targets
   - Leverages existing circuits
   - Optimizes resolution
   - Optimizes Signal/Noise

CURRENT ELECTRODES CANNOT ACHIEVE THESE GOALS

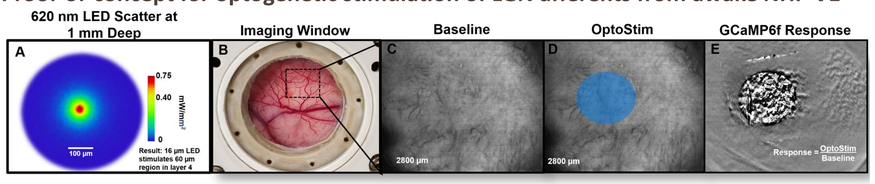
- Electric fields (**E**s) Cannot Precisely Select Targets (smallest r ≥ 100 µM)
  - > 4 million times larger than synaptic boutons

APPROACH

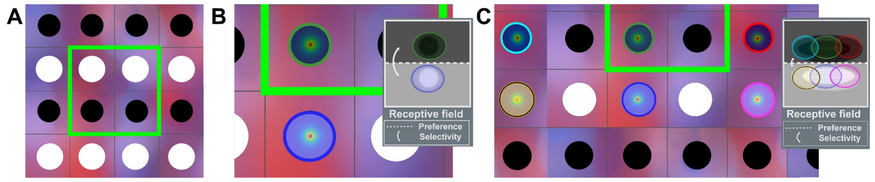
LGN afferent maps determine V1 maps. A) OD and OO columns. B,C) RF model



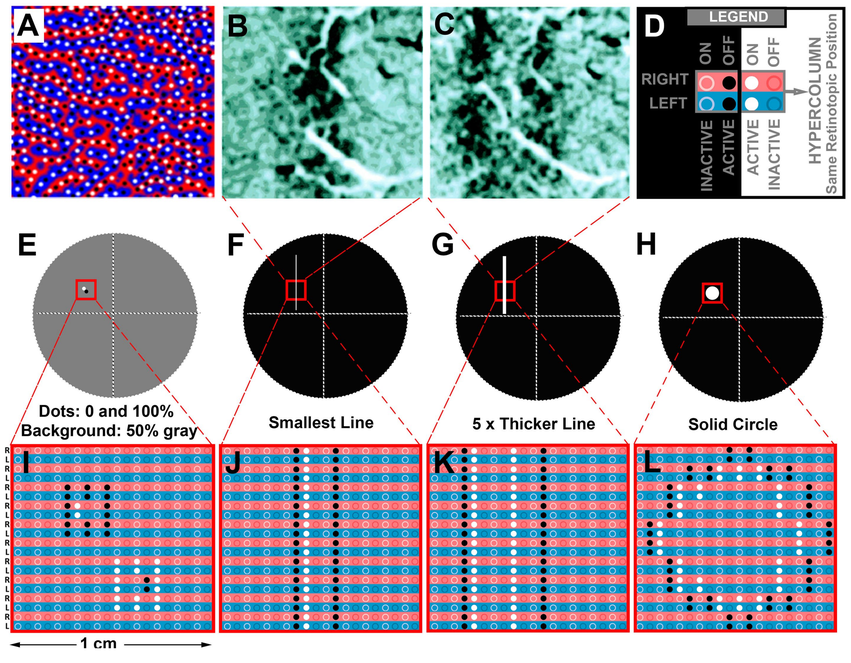
Proof-of-concept for optogenetic stimulation of LGN afferents from awake NHP V1



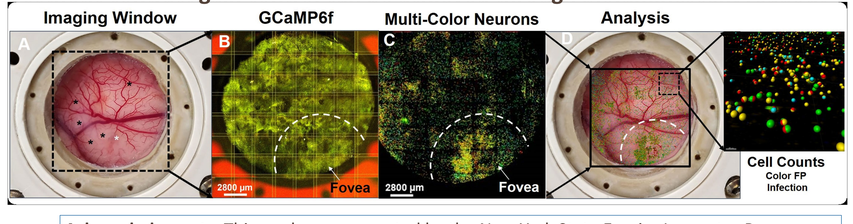
Targeted optostimulation of LGN afferents can replace natural inputs.



Patterned inputs to targeted OO and OD afferents will drive shape perception



Prosthetic contract gain control can be achieved through bioluminescent readout



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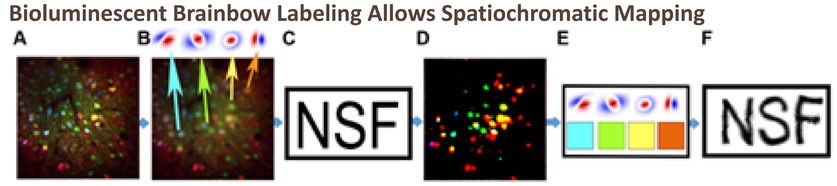
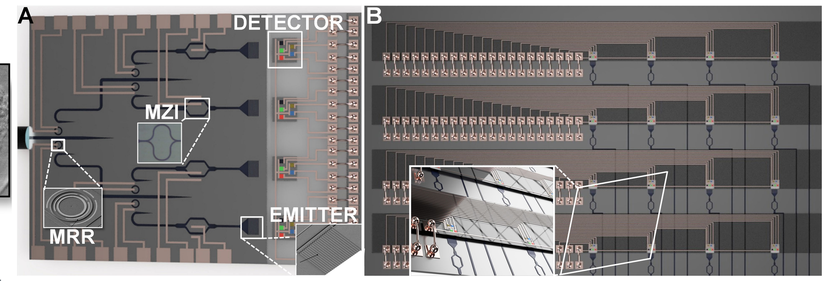
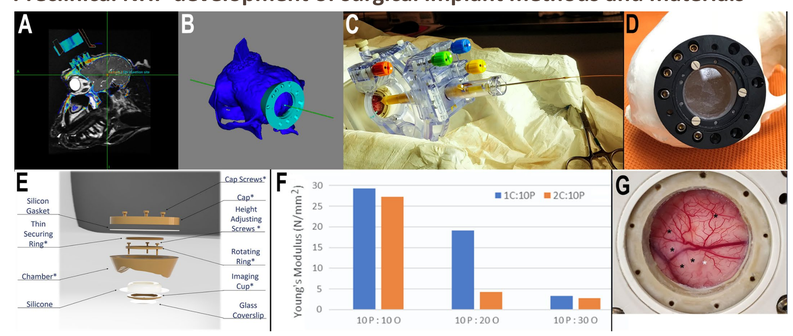
Bioluminescent Brainbow Labeling Allows Spatiochromatic Mapping



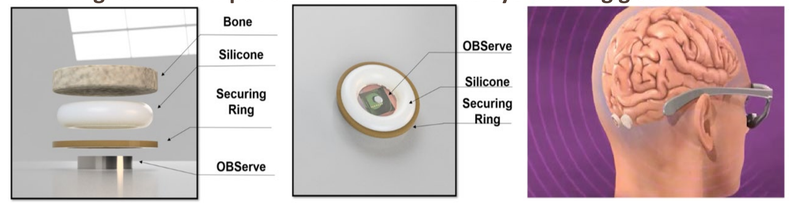
Solution: Coplanar emitter/detector dyad nanophotonic chip with 128 µm pitch



Preclinical NHP development of surgical implant methods and materials



Human implant hardware derives from the NHP hardware and materials we developed, to position the photonics chip against the foveal V1 cortex, while receiving real-time input and control from the eye-tracking glasses.



CONCLUSIONS

Our proposed solution to restoring vision arises from the premises that true restoration will require synaptic prosthetic stimulation at the highest attainable resolution of the natural visual system. If achieved, by optogenetically stimulating the isolated afferent inputs to V1 for each individual input dimension, the downstream visual system will respond as if the inputs were natural, with naturalistic perception as the outcome. The system requires a breakthrough nanophotonic coplanar emitter/detector chip that individually targets the specific isolated of OO and OD LGN input columns within the V1 hypercolumns map in the foveal region to be restored (the island of sparing). Prosthetic contrast gain control is provided through feedback to the emitter using spatiochromatic bioluminescent recording of cortical responses. Advanced surgical methods and materials have been developed to work in conjunction with live eye-tracking of the visual scene, to modify the visual inputs to the brain in real-time.