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Presentation Abstract

Program#/Poster#: 388.1/GG96

Title: Integrated microstructure lightguides for ultradense optical neural control of 3-dimensional neural circuits

Location: South Hall A

Presentation Time: Monday, Oct 19, 2009, 8:00 AM - 9:00 AM

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Abstract: A key feature of neural circuits in the mammalian brain is their 3-dimensionality and geometric complexity. The ability to optically drive or silence neural activity in complexly-shaped brain circuits (such as the entire CA1 region of the hippocampus, the reticular nucleus of the thalamus, or a specific layer of frontal cortex), for milliseconds to seconds at a time, would enable analysis of the time-resolved contribution of specific neural circuits, and specific neural activity patterns, to normal and pathological behaviors. In recent years we have developed optogenetic molecular reagents for neuroscience, starting with channelrhodopsin-2 (ChR2) and *N. pharaonis* halorhodopsin (Halo/NpHR), as well as other novel and useful reagents to be described at this conference (Arch, spHalo, and Mac), that enable neural circuits to be activated and silenced with different colors of light. However, the ability to manipulate neural circuits in their geometric complexity still requires significant innovation, to confront the dense and difficult matter of the brain. Ideally, it would be possible to construct miniature linear probes containing many lightguides terminating at different depths, thereby enabling one to illuminate many (>20) targets along the length of the probe. Each guide should be independently controllable, while insuring sufficient power (>200 mW/mm²) out of each port to effectively activate and silence neural targets, as desired. Here we present the design and implementation of mass-fabricatable multi-lightguide microstructures, produced using standard microfabrication techniques. Each microstructure is a 200-micron wide insertable probe comprising many miniature lightguides running in parallel, and capable of delivering light to many points along the axis of insertion of the probe. Such a design maximizes the

flexibility and power of optical neural control while minimizing tissue damage. By assembling 2-D arrays of such linear probes, we can deliver multiple colors of light in 3-dimensional patterns throughout the brain, at the resolution of tens to hundreds of microns, thus furthering the causal analysis of how complex neural circuits generate behavior. Such devices will allow the substrates that causally contribute to neurological and psychiatric disorders to be systematically analyzed via novel neural control tools. Given our recent efforts on testing such reagents and devices in nonhuman primates, these innovations may also enable a new generation of optical neural control prosthetics, contributing directly to the treatment of intractable brain disorders.

Disclosures: **A.N. Zorzos**, None; **J.G. Bernstein**, None; **E. Boyden**, None; **C.G. Fonstad**, None.

Keyword(s): optical fiber
neural circuits
optogenetic

Support: A.Z. was supported by an NSF Graduate Fellowship.

E.S.B. acknowledges support from the: NIH Director's New Innovator Award (DP2 OD002002-01), NSF (0835878 and 0848804), McGovern Institute Neurotechnology Award, Department of Defense, NARSAD, Alfred P. Sloan Foundation, Jerry Burnett Foundation,

SFN Research Award for Innovation in Neuroscience, MIT Media Lab, Benesse Foundation, and Wallace H. Coulter Foundation.

[Authors]. [Abstract Title]. Program No. XXX.XX. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2009. Online.

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