

## Hardware for Optical Perturbation of 3-D Neural Circuits: Towards High-Throughput Screening of Neural Circuit Targets

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A key feature of neural circuits in the mammalian brain is their 3-dimensionality and geometric complexity. Hardware that enables the optical silencing or driving of neural activity in complexly-shaped brain circuits would enable analysis of the time-resolved contribution of specific neural circuits and activity patterns, to normal and pathological behavior. We here present a suite of hardware technologies capable of multiscale optical neural control, aiming towards abilities such as bilateral inactivation of the entire CA1 field of the mouse hippocampus or lamina-specific addressability of cortical neurons. First, we developed arrays of LED-coupled 200  $\mu\text{m}$  optical fibers, which are end-user customizable, that allow delivery of light to tens of sites in the brain. Very long duration operation is possible via modular fluidic cooling, e.g. 10 LEDs for 30 continuous seconds or 3 LEDs indefinitely. The arrays and cooling systems together weigh <2.5 grams, light enough to be borne on the head of a freely moving mouse. We have also developed electrodes and circuits that allow concurrent neural recording impervious to noise from the LEDs. Second, 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 20  $\mu\text{m}$  wide lightguides running in parallel, and capable of delivering light to many points along the axis of insertion of the probe, akin to existing silicon probes.

We demonstrate implantation of high-count fiber arrays to complex 3-D circuits in the mammalian brain. These technologies will, for example, enable high-throughput screening of neural circuits important for behaviors, thus identifying neural targets from a functional point of view. As a first step towards such a systematic screen, finding neural circuits and activity patterns that can alleviate specific forms of anxiety and post-traumatic stress disorder in a mouse model, we show that we can facilitate the extinction of Pavlovian fear conditioning through manipulation of selective cortical targets in freely moving mice, evidenced by freezing decrease of 73% compared to control mice at the end of the first session of extinction learning ( $p < .02$ ,  $n=5$ ).