Modular Cortex-M0 MCU Platform for Wireless, Controlled Deep Brain LED-Fiber Coupled Optical stimulation in Optogenetics

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CONTROLLED deep brain optical stimulation in a wireless platform for the study of neural systems is a critical advancement for the optogenetic and electroceutical toolboxes[1-4]. This technology enables less restrictive and more clinically relevant experiments. Primary challenges involve systems level integration of efficient LED-optical fiber coupling, ultra-low power algorithms, and reliable wireless powering all in a sub-cubic centimeter footprint for rodent compatibility.

LEDs are an attractive light source; however, they suffer from relatively inefficient coupling to optical fibers in mechanically insecure systems. As the device étendue is limited by the optical fiber (NA = 0.37, diameter = 200 μm), optical throughput is maximized by placing the light guide directly at the source. Using a modified ferrule-based system, irradiances of ~30 mW/mm^2 (wavelength = 470 nm) are produced with ~64 mW input power. As ChR2 is activated by a minimum of 1 mW/mm^2 [5], there is sufficient optical throughput to drive behavior in optogenetic mice. The microcontroller (MCU) is the central processing unit. It digitally programs a constant current driver to control the current (1.8-20 mA) through the LED. The embedded algorithm is interrupt driven and manages power consumption with low duty cycle operations. The MCU can be wirelessly or internally triggered to stimulate. During deep sleep modes, the power consumption is less than 30 μW. Two 50 μA-Hr solid-state batteries in parallel with a capacitor bank are used to supply instantaneous high current demands. For continued optimization and expansion of the subsystems, the optical, MCU, and power modules are on separate boards and communicate through low insertion force connectors.

Validation of the optical module was performed *in vivo* by demonstrating tethered behavioral rotations in line 18, Thy1-ChR2 mice. The optical fiber was implanted in the right motor cortex (area M2) and 30-second stimulation (20 Hz, 3 ms pulse width) periods resulted in obvious and significant left rotations. To validate the wireless device, a three-chamber conditioned place preference (CPP) behavioral paradigm was performed. We generated B6.SJL-(CAG-COP4*H134R/TdTomato);Slc6a3-cre mice (*Slc6a3-Cre*) by crossing B6.(ROSA)26Sor<tm27.1(CAG-COP4*H134R/tdTomato)> and B6.SJL-*Slc6a3*$^{tm1.1(cre)Bkmn}$/J mice. These mice express the channelrhodopsin / *TdTomato* cassette selectively in dopaminergic neurons. Optical fibers were targeted at the right ventral tegmental area (VTA) of both *Slc6a3-Cre*+ and *Slc6a3-Cre*- mice (negative control). A 15-minute pre-test (day 1), six 30-minute conditioning sessions (days 2-4) and a 15-minute post-test (day 5) were performed. Conditioning sessions alternated between stimulation and no stimulation. Stimulation (20 pulses at 20 Hz, 1 minute period, 10 mA LED current) was triggered with an internal timer after the MCU, power, and optical modules were connected. When compared to controls, conditioned *Slc6a3-Cre*+ mice significantly increased their preference for the conditioned chamber (post-test versus pre-test).

Controlled deep brain optical stimulation was demonstrated *in vivo*. This technology is readily available for the scientific community to perform freely behaving optogenetic experiments.

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