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Remote-controlled mice

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What if expression of a light-sensitive protein could be triggered wirelessly, on demand? What if optogenetics and neuropharmacology could be implemented in an untethered, freely moving animal model? Such technology would allow for a plethora of neurobiological experiments that are currently confounded by repeated animal handling, tissue-damaging cannulas, and tangled optical cables. In the July 30 issue of *Cell*, Jeong and colleagues introduce such a technology. The ultrathin and flexible devices, termed wireless optofluidic probes, enable remote control of drug infusion and optical manipulation in the deep brain regions of freely moving mice engaged in behavioral tasks [Jeong et al., 2015] (see Figure 1).

Jeong et al. leveraged the latest advances in microcontact printing techniques and flexible electronics to produce wireless optofluidic probes comprised of multiple functional components. A transparent flexible polydimethylsiloxane (PDMS) ribbon with four drug delivery channels was integrated with a polyethylene terephthalate (PET) filament carrying microscale inorganic light-emitting diodes (μ LEDs) previously developed by the same group [Kim et al., 2013]. The resulting probe had an overall thickness of $\sim 80 \mu\text{m}$, and a low bending stiffness of 13–18 N/m, minimizing the neural tissue damage. The four microfluidic channels were connected to individual reservoirs, allowing each drug to be pumped independently and released on-demand. The optofluidic probe was designed to interface with a battery-powered infrared wireless module that allowed for independent control μ LEDs.

The individually controlled wireless fluid infusion presents a powerful tool for numerous applications in systems neuroscience and circuit mapping. For example, expression of multiple genes can now be altered wirelessly at different time points using separate viral injection steps. Multiple injections have previously required separate surgeries that compromised animal health, extended recovery time, and produced severe neural tissue damage. The optofluidic probe also allows for multiple behavioral assays to be conducted with a single subject. As a simple proof of principle, authors have demonstrated infusions of a peptide [D-Ala², N-MePhe⁴, Gly-ol]-enkephalin (DAMGO), μ -opioid receptor (MOPR) agonist, or a control fluid into the ventral tegmental area (VTA). From a meter away, it was

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possible to trigger stereotyped rotations in mice, characteristic of unilateral DAMGO delivery into the VTA, while the delivery of control fluid did not induce any notable effect.

The combinatorial optical and microfluidic operation of the probes was also demonstrated in a reward-related preference task probing the dopaminergic projection from the ventral tegmental area to the nucleus accumbens shell (NAcSh). The authors implanted their optofluidic probes in the NAcSh of transgenic mice. In these mice, specific expression of Channelrhodopsin 2 (ChR2) in dopaminergic neurons and their processes was established by a separate viral injection into the VTA. By switching the μ LEDs on from a distance, the authors were able to remotely activate VTA-to-NAcSh dopaminergic projection and drive real-time place preference. The latter was then abolished by simultaneous wirelessly-triggered infusion of SCH23390, a dopamine receptor D1 antagonist.

The probes developed by Jeong and colleagues present a technological leap forward. Future extensions of their technology may include integrated micro-electromechanical systems (MEMS) components such as microfluidic pumps, which should enable multiple injections over the course of long-term *in vivo* studies. The overall weight and electronic complexity, however, will have to be carefully considered to accommodate experiments in small subjects. Another direction for future improvement could be the incorporation of electrical recording capabilities. Electrophysiology, when combined with behavioral experiments and pharmacological and optogenetic manipulation, would provide a more systematic understanding of both neural circuitry and the brain. Furthermore, incorporation of neural recording is an essential step on the way towards closed-loop systems for effective treatment of neurological and psychiatric disorders [Rosin et al., 2011].

Future directions of wireless integrated neural interface devices will likely take off through multidisciplinary efforts bridging electrical engineering, materials science, mechanical engineering, and bioengineering. Advanced circuit design and microfabrication will enable more complex feedback and control systems. New materials and mechanical platforms are anticipated to yield a versatility of modalities for recording and modulation of neural networks with ever increasing spatial and temporal resolution. Finally, close collaborations between basic neuroscientists and engineers such as the one that led to the development of the optofluidic probes, will be essential to the conception of biologically-relevant technologies for brain mapping as well as future therapies for the diseases of the nervous system.

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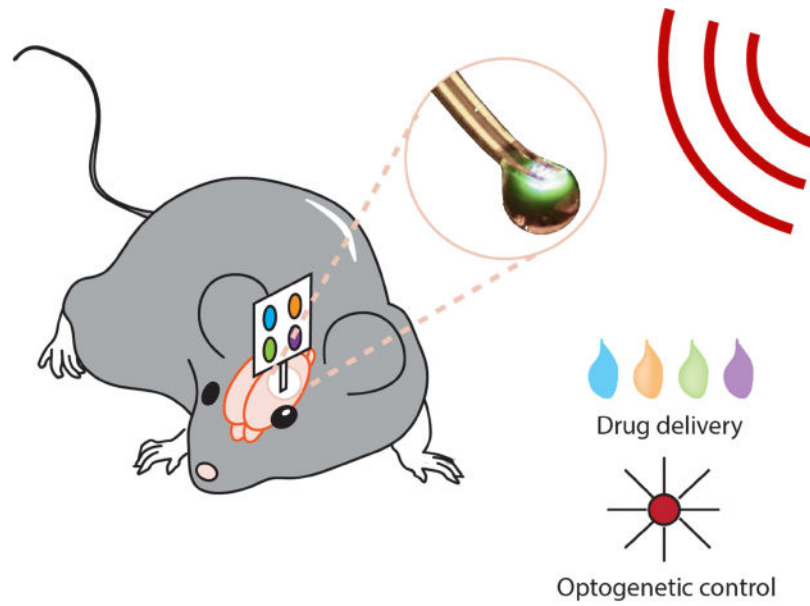


Figure 1. Wireless optofluidic control of mouse behavior. An ultrathin, flexible optofluidic probe can be implanted in a mouse brain. This allows for discrete infusion of multiple drugs and photostimulation with high spatiotemporal resolution. The fluid and light delivery are controlled wirelessly using infrared sensors, which enables manipulation of mouse behavior in a completely untethered manner. (Credit: X. Jia, MIT, and Y. Wang, University of Hong Kong.)