CASE STUDY

nVoke: Assessing microcircuit function in the dorsal striatum

"The nVoke system is exactly what we needed to link changes in activity of interneurons to calcium signaling in striatal output neurons. It enabled us to formulate a new hypothesis about how fast-spiking interneurons function to regulate motor behavior."

– Anatol Kreitzer, Ph.D, UCSF

Overall research goals

Anatol Kreitzer's research is focused on the cellular, synaptic, and circuit-level processes involved in adaptive motor control by the basal ganglia. Mechanisms of basal ganglia circuit function are critical to understanding motivation, action selection, and habit formation, as well as neurological diseases such as Parkinson's disease, Huntington's disease, Tic disorders, obsessive-compulsive disorder, and addiction.

Need

Striatal fast-spiking interneurons (FSIs) have long been proposed to regulate the activity of striatal projection neurons[1,2]. However, the role of this inhibition in striatal network function, and the specific mechanisms underlying this control *in vivo* remain unclear.

Approach

What is the role of striatal fast-spiking interneurons in regulating network function and behavior?

- **Preparation**: Halorhodopsin (inhibitory opsin; red) was injected in dorsal striatum (DLS) to target parvalbumin-positive FSIs in a PV-Cre mouse line. Synapsin-GCaMP6f (indicator; green) was subsequently injected into the same location. (**Figure 1**)
- **Experiment**: nVoke was used to inhibit striatal FSIs in mice and simultaneously image striatal projection neurons (MSN) during motor tasks.

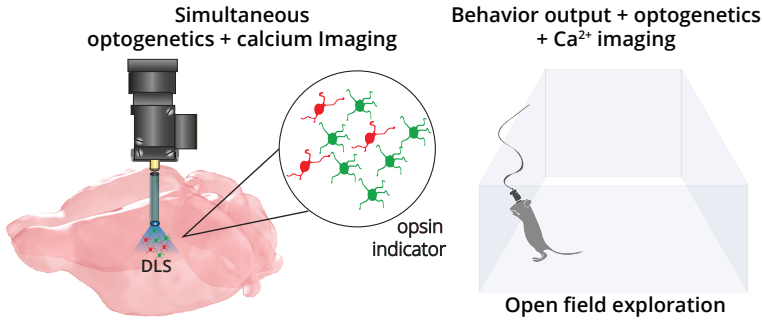

Figure 1. NpHR3.0 (inhibitory; red) opsin in DLS, GCaMP6f (indicator; green) in DLS.

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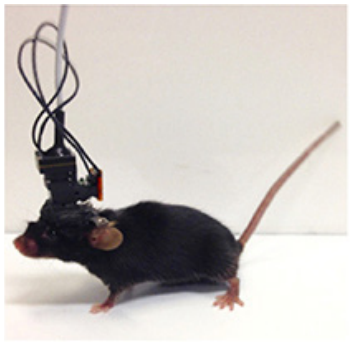
Findings

As shown in *Figure 2*, the mouse is freely exploring an open field. When the light (blue) is turned on to silence (inhibit) the FSI interneurons in dorsal striatum, there is no effect on motor coordination or task performance (in contrast with previous studies).



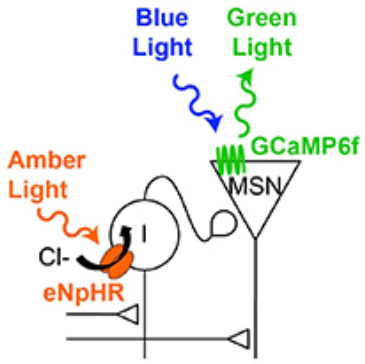


Figure 2. Schematic highlights animal behavior combined with nVoke modulation of cell output.

FSI inhibition increased the calcium (Ca) transients in striatal projection MSNs and impaired motor learning.

Figure 3 shows representative Ca^{2+} traces from an MSN in response to 60x OG-LED light pulse of 5s duration (yellow bar). Note the increased frequency of Ca transients when the light is on.

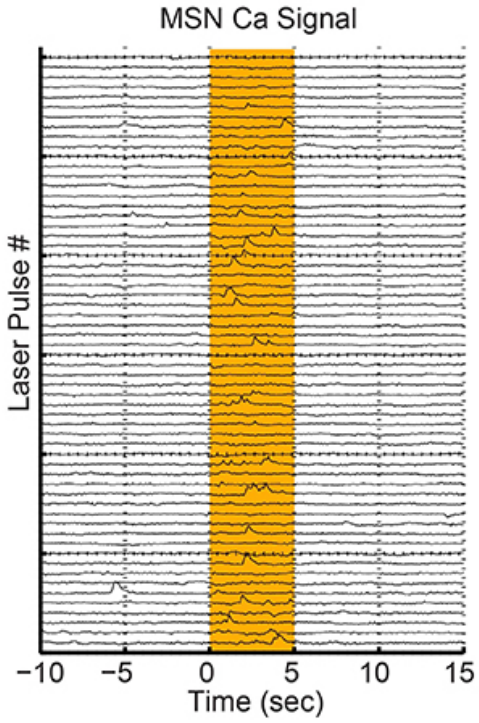


Figure 3. nVoke modulation of Ca^{2+} activity in MSN projection cells.

Functional implications

In order to understand how local interneurons were impacting activity in striatal projection neurons during motor tasks in freely-moving animals, we needed a tool to inhibit interneurons, while simultaneously monitoring activity in principal cells.

The nVoke system is exactly what we needed to link changes in activity of interneurons to calcium signaling in striatal output neurons. It enabled us to formulate a new hypothesis about how fast-spiking interneurons function to regulate motor behavior.

References

1. Gage, G. J., Stoetzner, C. R., Wiltschko, A. B. & Berke, J. D. Selective Activation of Striatal Fast-Spiking Interneurons during Choice Execution. *Neuron* 67, 466–479 (2016). **2.** Koos, T. & Tepper, J. M. Inhibitory control of neostriatal projection neurons by GABAergic interneurons . *Nat Neurosci* 2, 467–472 (1999).

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