

Optogenetic investigation of neural circuits underlying brain disease in dopaminergic system

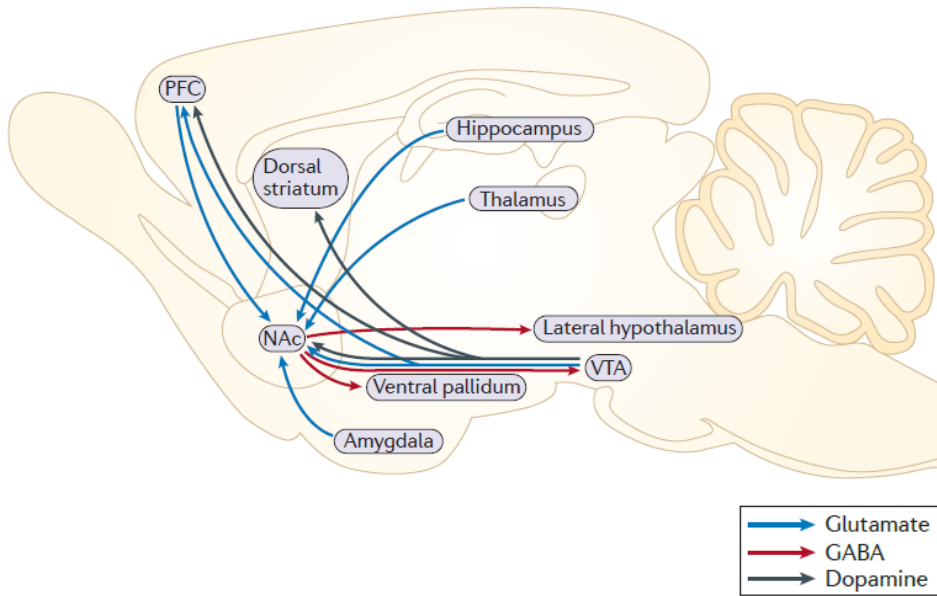


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Dopaminergic system



1. Mesolimbic pathway

: Ventral tegmental area (VTA) ► Nucleus accumbens (NAc)

2. Mesocortical pathway

: Ventral tegmental area (VTA) ► Pre frontal Cortex (PFC)

3. Nigrostriatal pathway

: Substantia nigra (SN) ► Striatum

4. Tuberoinfundibular pathway

: Hypothalamus ► Pituitary gland

■ The roles of dopamine in the brain

● Nigrostriatal

- Motor control
- Parkinson's Disease (PD)



● Mesolimbic/Mesocortical

- Memory
- Motivation & Emotion
- Reward & Desire
- Addiction
- Schizophrenia



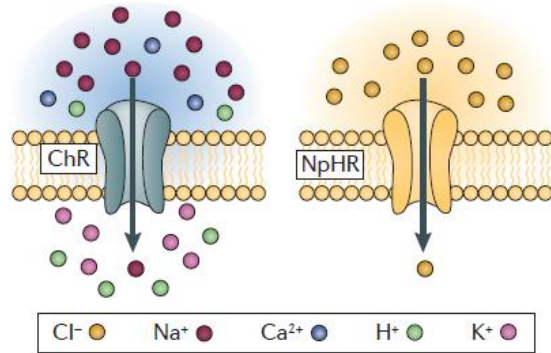
● Tuberoinfundibular

- Hormonal regulation
- Maternal behavior
- Pregnancy
- Sensor processes

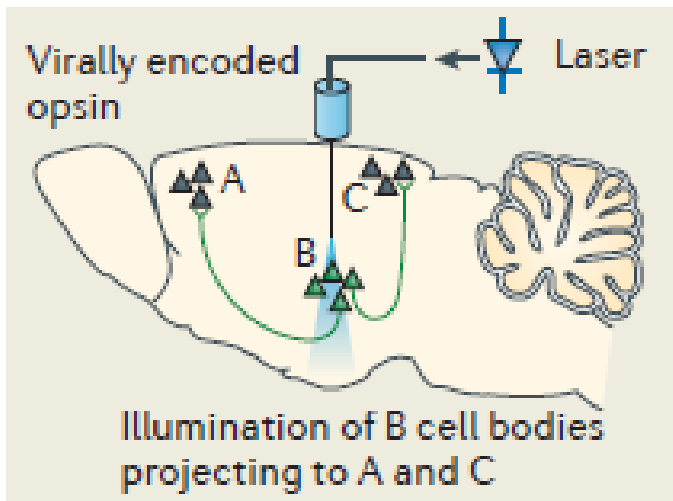


Optogenetics

Major class of single-component optogenetic tools



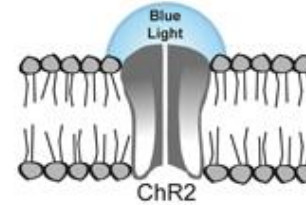
- ◆ Cation-permeable channels for membrane depolarization : channelrhodopsin (ChRs)
- ◆ Chloride pump: halorhodopsin (NpHR)



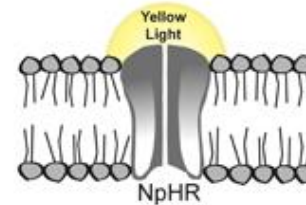
Steps to optogenetics

Step 1.

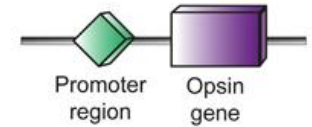
Neuronal activation



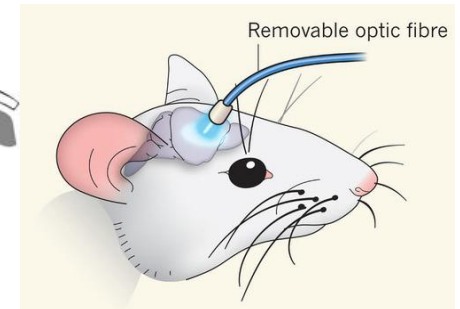
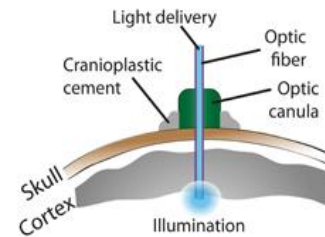
Neuronal inhibition



Step 2.



Step 3.



Today's topic



Decoding Neural Circuits that Control Compulsive Sucrose Seeking

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Picower institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts institute of technology

• Interests

Behavior, Learning and Memory, Anxiety, Autism, Obesity, Synapses, Amygdala, Dopamine, Limbic System, Cellular Physiology, Valence, Motivation, Neurochemistry, Optogenetics, Imaging



Dopamine neurons modulate neural encoding and expression of depression-related behaviour

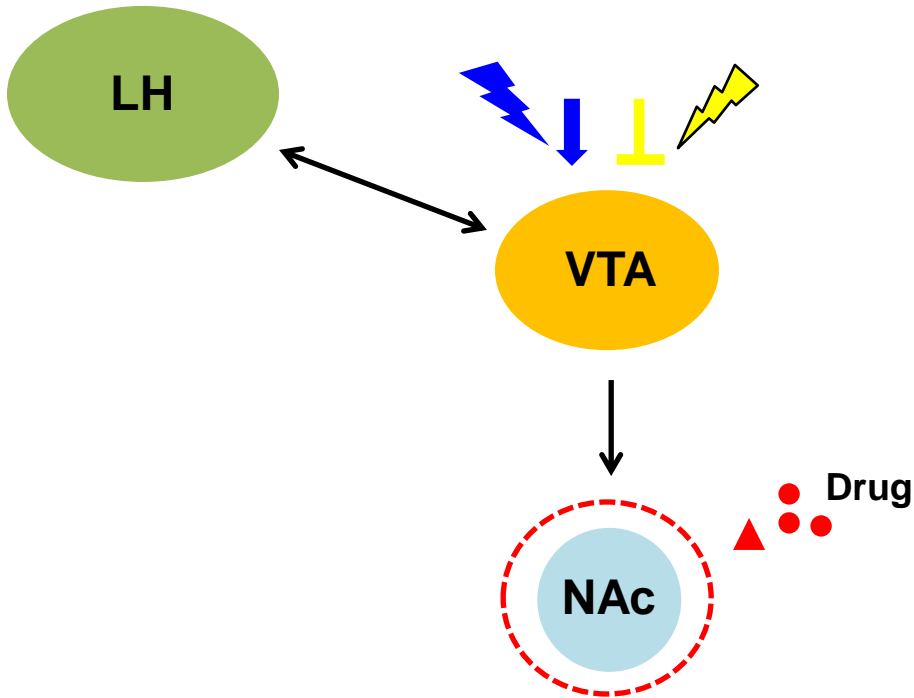
Kay M. Tye^{1,2*}, Julie J. Mirzabekov^{2*}, Melissa R. Warden^{2*}, Emily A. Ferenczi^{2,3}, Hsing-Chen Tsai^{2,3}, Joel Finkelstein², Sung-Yon Kim^{2,3}, Avishek Adhikari², Kimberly R. Thompson², Aaron S. Andalman², Lisa A. Gunaydin², Ilana B. Witten² & Karl Deisseroth^{2,3,4,5,6}

Karl Deisseroth, M.D., Ph.D.

D.H. Chen Professor of Bioengineering and Psychiatry and Behavioral Sciences, Stanford University

• Interests : Optogenetics, Neural circuit, Clarity

Model

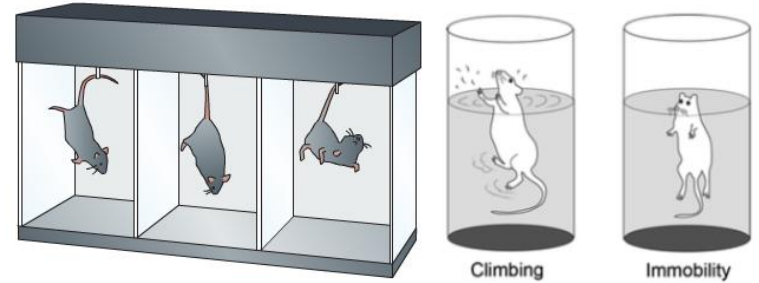


Behavioral changes

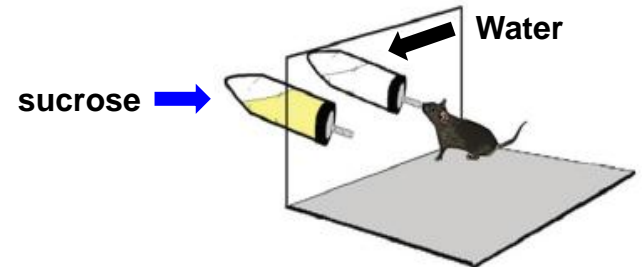
Parameters

1. Depression-like behavior

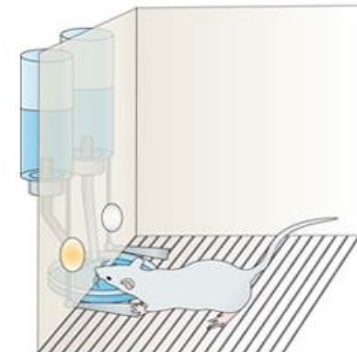
- Tail-suspension test, Forced-swim test



2. Sucrose preference test

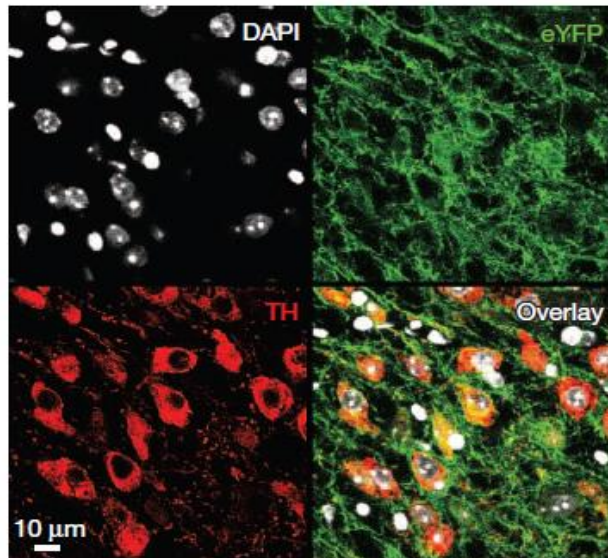
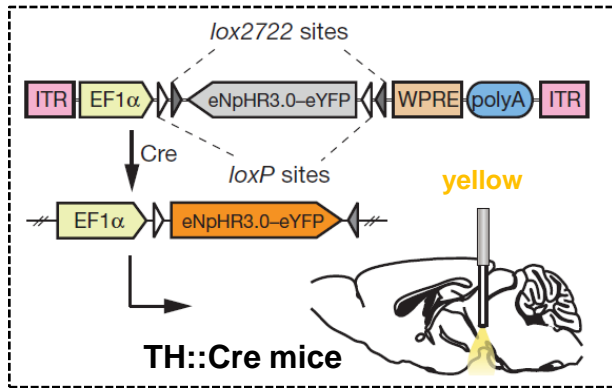


3. Self-administration system



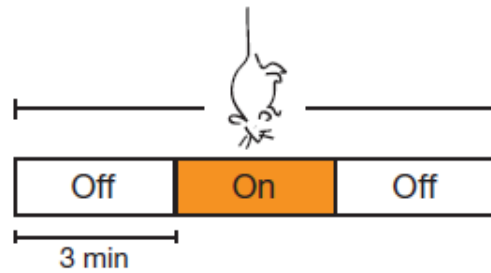
Selective inhibition of VTA dopamine neurons induces a depression-like behavior

Cre-dependent AAV

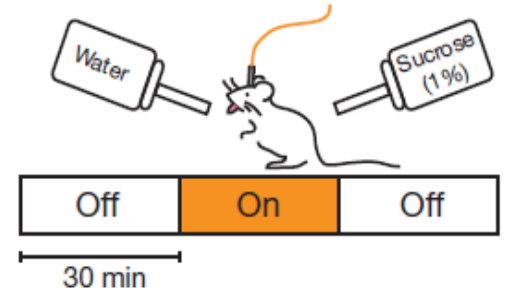


Experimental scheme

Exp 1. Tail-suspension test

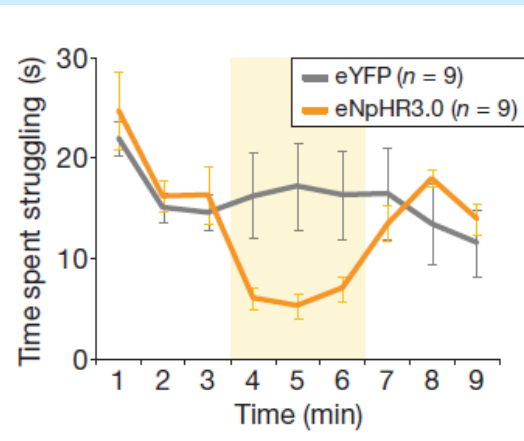


Exp 2. Sucrose preference test

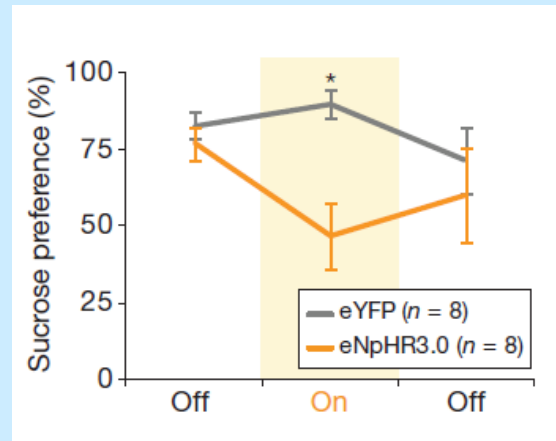


Results

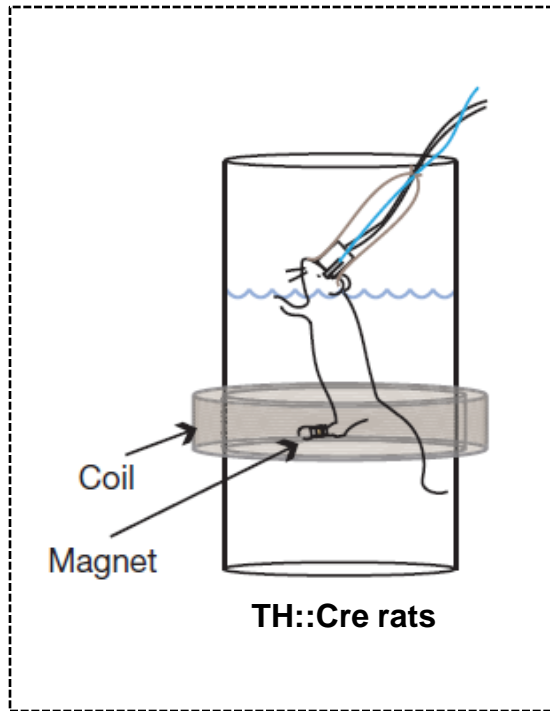
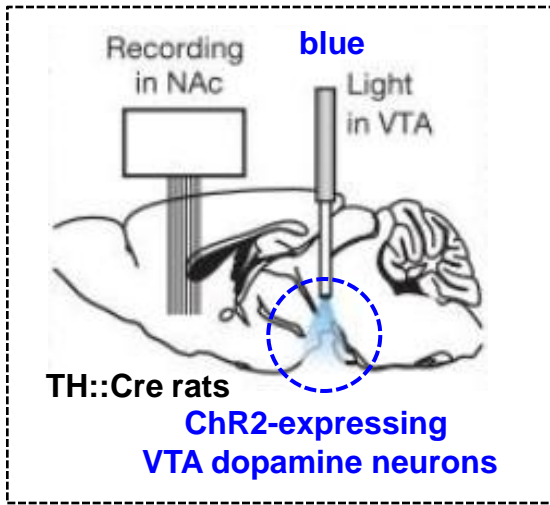
• Exp 1.



• Exp 2.

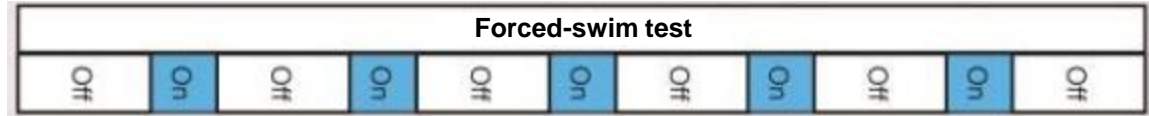


Activation of VTA dopamine neurons modulates escape-related behavior

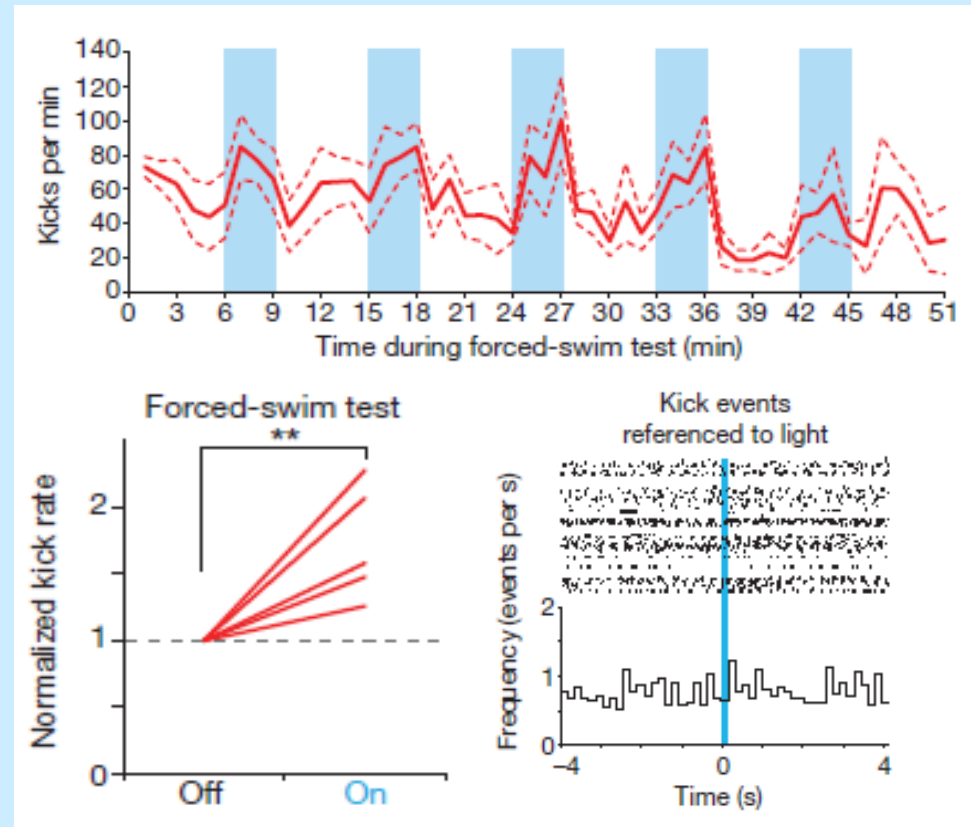


Experimental scheme

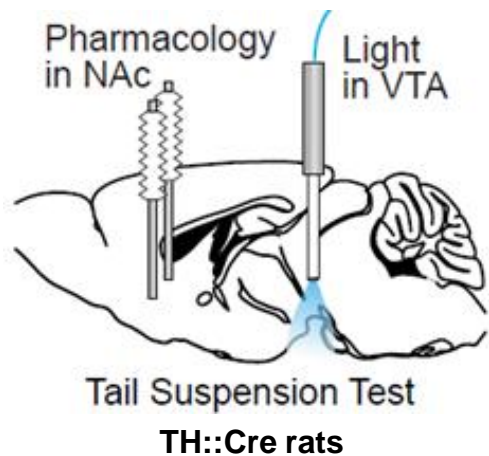
Continuous *in vivo* electrophysiological recording session



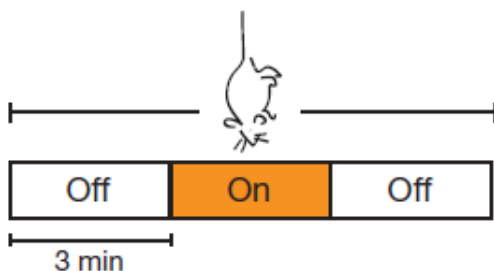
Results



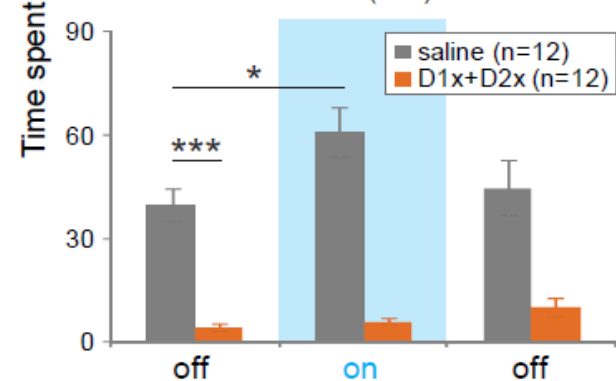
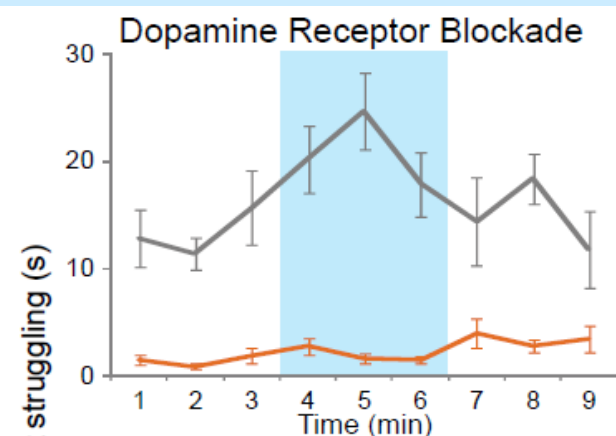
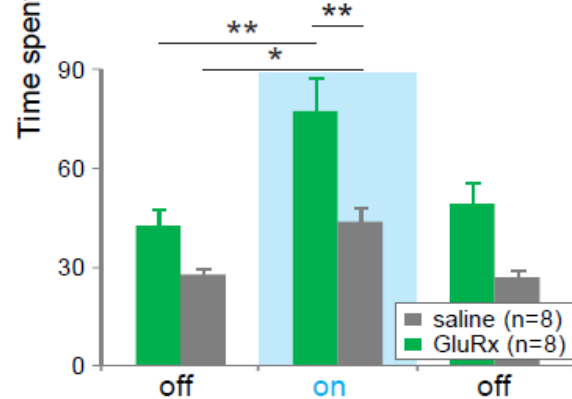
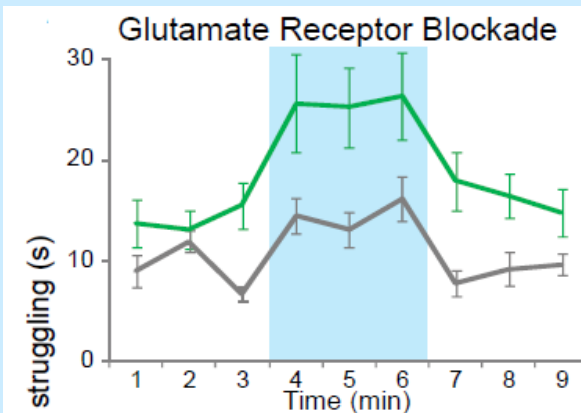
Dopamine receptor signaling is required for mediating escape-related behavior



Experimental scheme

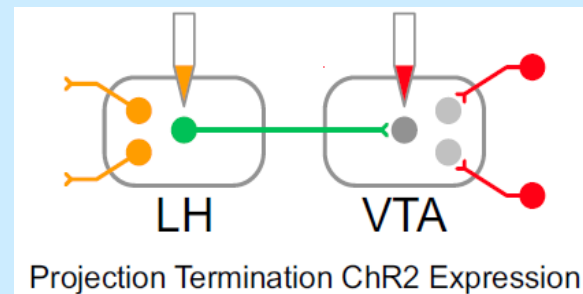
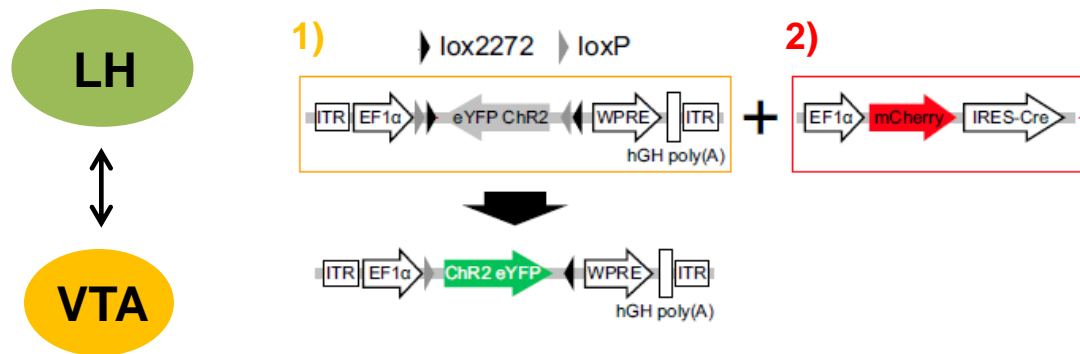


Results

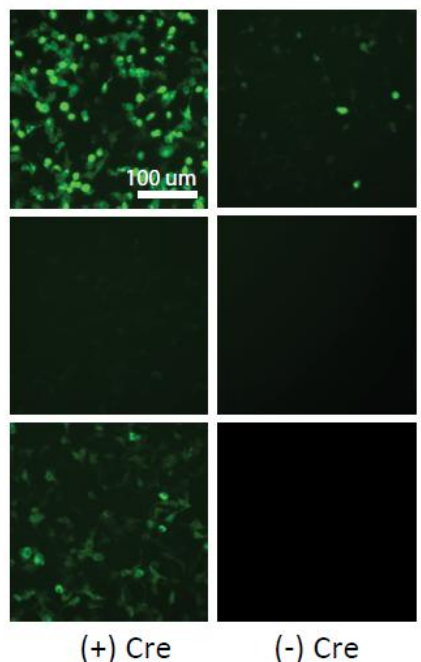
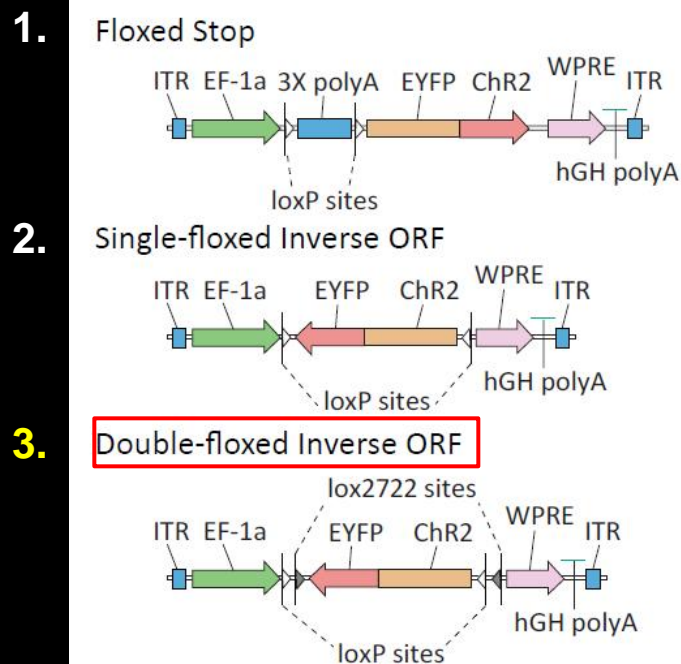


Dopamine-receptor blockage in the NAc reduced baseline struggling and blocked the light-induced reversal of reduced struggling.

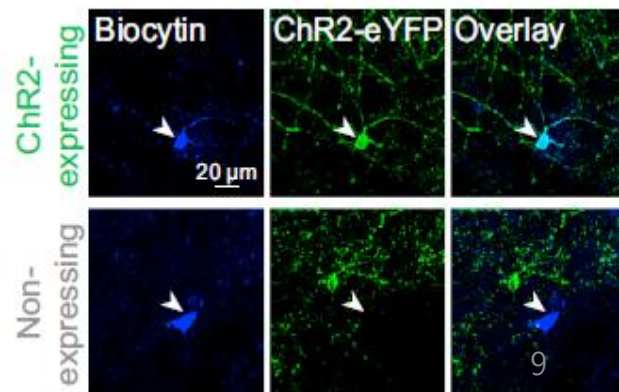
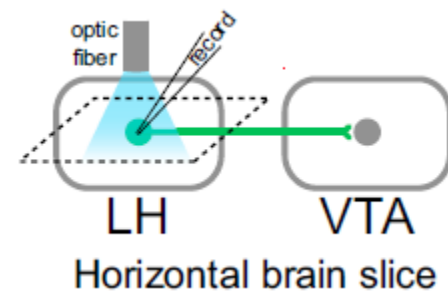
Phototagging LH-VTA projection



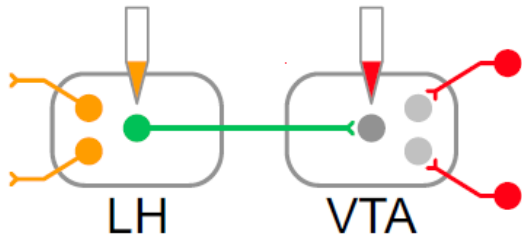
Double-floxed inverse open reading frame (DIO)



Whole-cell patch-clamp



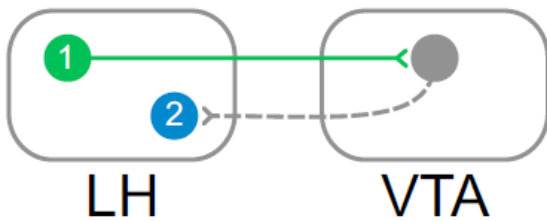
Two populations of neurons with different response latencies to photostimulation



Projection Termination ChR2 Expression

■ Hypothesis

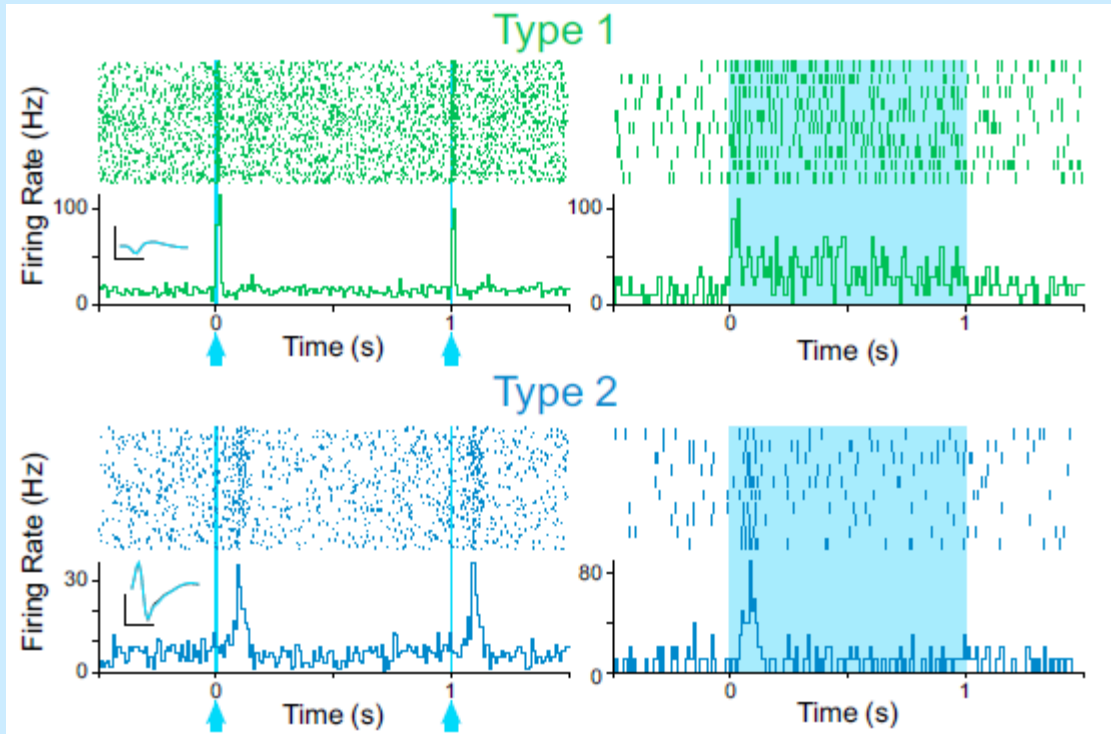
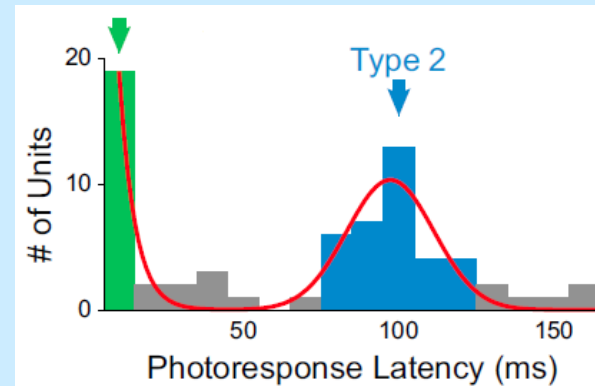
Model 1.



Model 2.

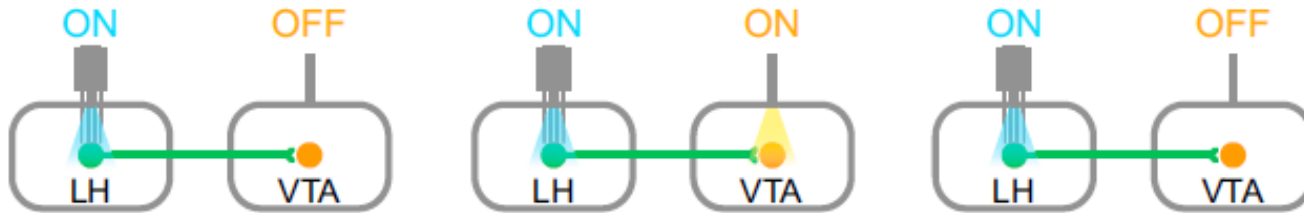


◆ Results



Type 2 LH neurons receive input from the VTA rather than via local axon collaterals

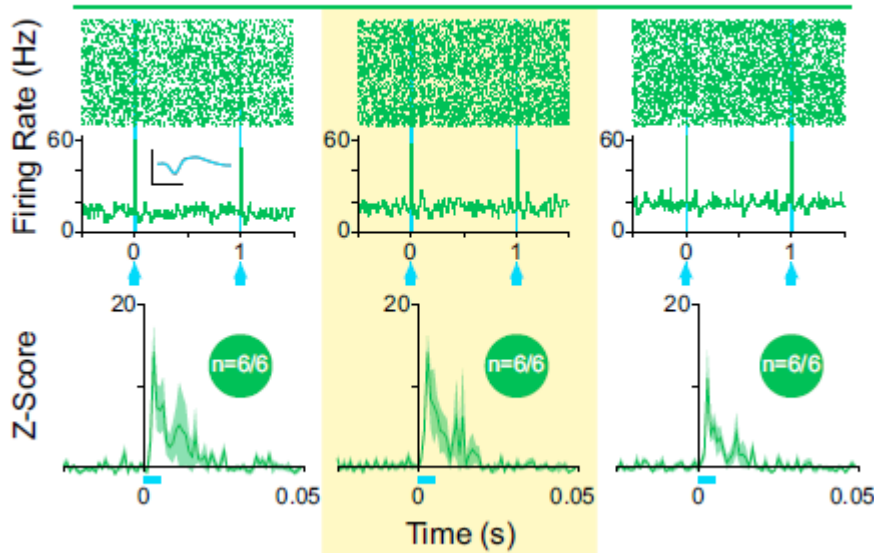
Experimental scheme



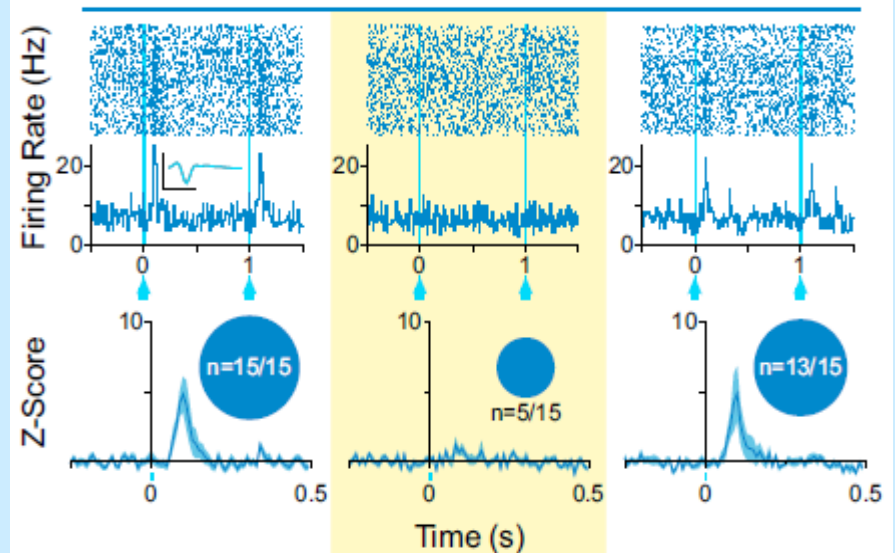
Results

● Enhanced halorhodopsin 3.0 (NpHR)

Type 1



Type 2

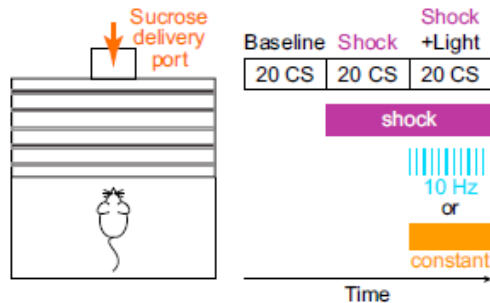


Inhibition of the VTA selectively attenuates the photoresponse of Type 2, but not Type 1, units.

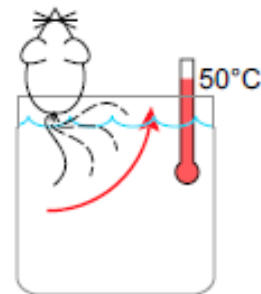
Natural occurring neural activity during a sucrose self-administration task

Experimental scheme

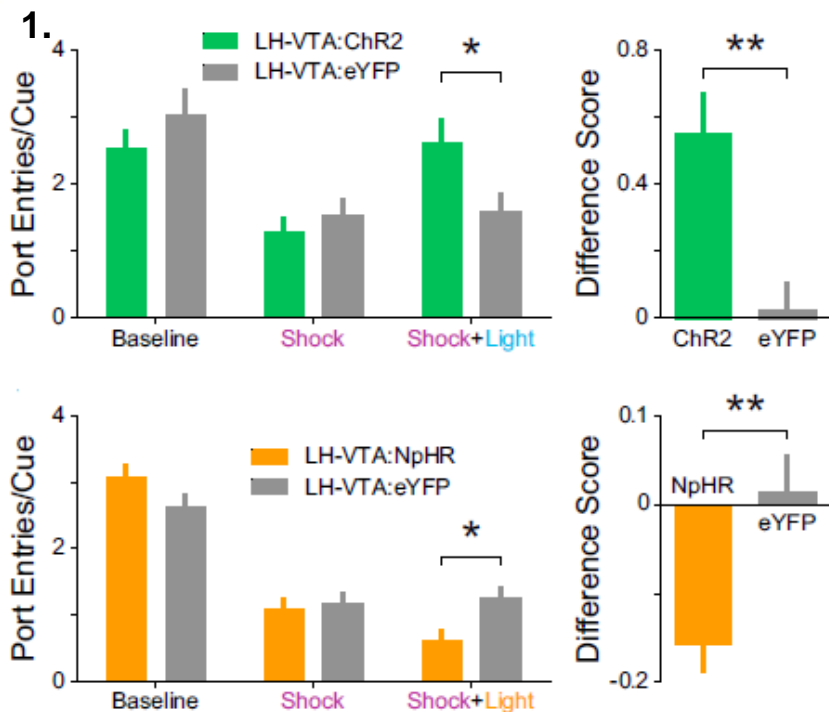
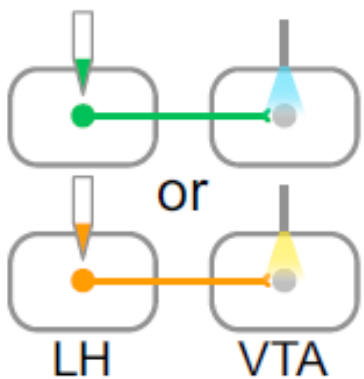
Exp 1.



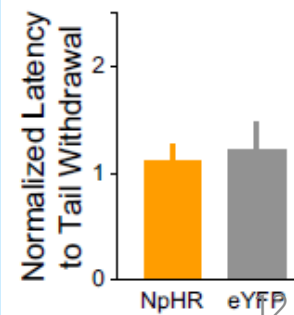
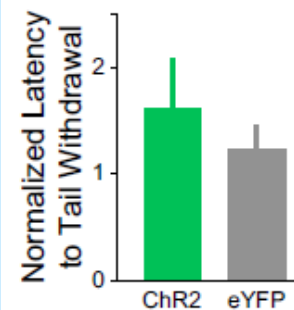
Exp 2.



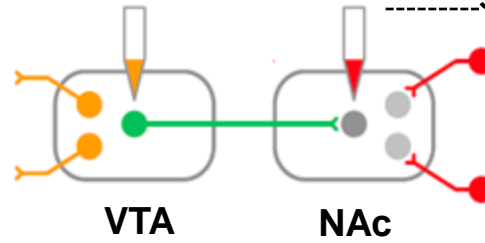
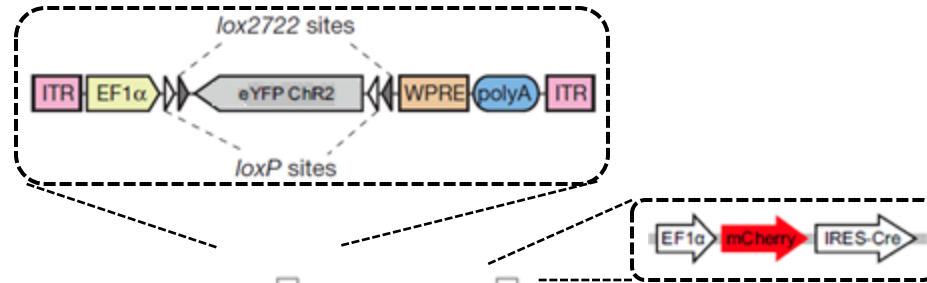
Results



2.

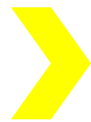


Model 1



WT mice

(Stereotaxic surgery: VTA and NAc)

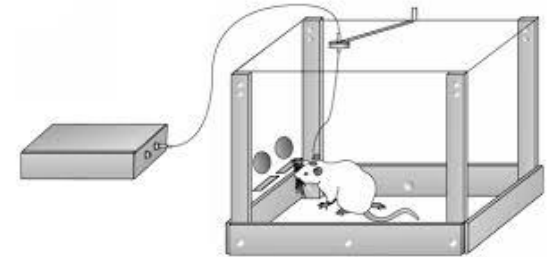
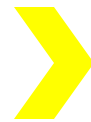


Sucrose-addiction



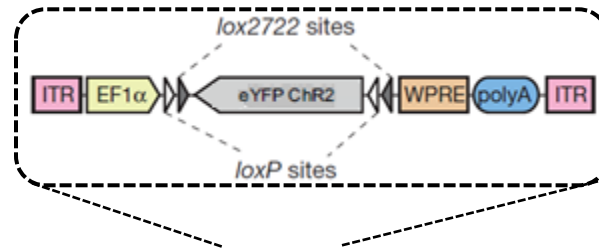
WT mice

(Stereotaxic surgery: VTA or NAc)



↑
shock

Model 2



Injection

Blue light



Rev-erba::Cre mice

(Stereotaxic surgery: VTA or NAc)



Sucrose-addiction



Rev-erba::Cre mice

(Stereotaxic surgery: VTA or NAc)



?

↑
shock

References

Nieh EH, Matthews GA, Allsop SA, Presbrey KN, Leppla CA, Wichmann R, Neve R, Wildes CP, Tye KM. (2015) Decoding neural circuits that control compulsive sucrose seeking. *Cell*. 160:528-41.

Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai HC, Finkelstein J, Kim SY, Adhikari A, Thompson KR, Andalman AS, Gunaydin LA, Witten IB, Deisseroth K. (2013) Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*. 493:537-41.

Tye KM and Deisseroth K. (2012) Optogenetic investigation of neural circuits underlying brain disease in animal models. *Nat Rev Neurosci*. 13:251-66.

Saunders A, Johnson CA, Sabatini BL. (2012) Novel recombinant adeno-associated viruses for Cre activated and inactivated transgene expression in neurons. *Front Neural Circuits*. 6:47.