Revealing brain circuits underlying sensory processing, plasticity, and neuropsychiatric disease

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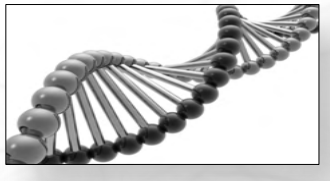
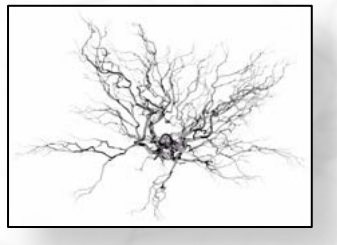
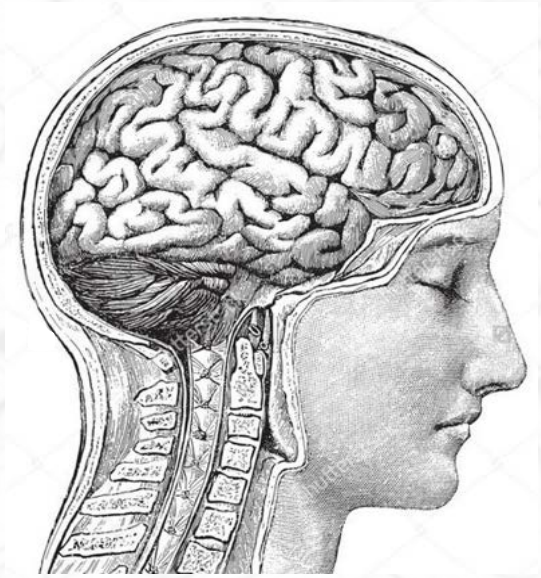
The main objective: to reveal mechanisms of how brain circuits are formed and function

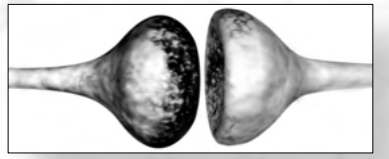


genes



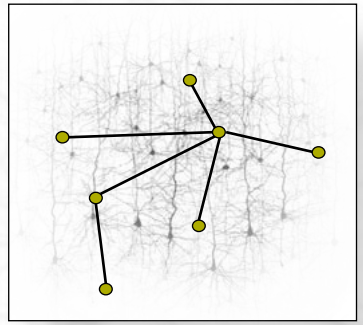
differentiation / specification





synaptogenesis

Biological function
-physiology
-behavior



connectivity

Dysfunctional brain circuits underlie neurological disorders

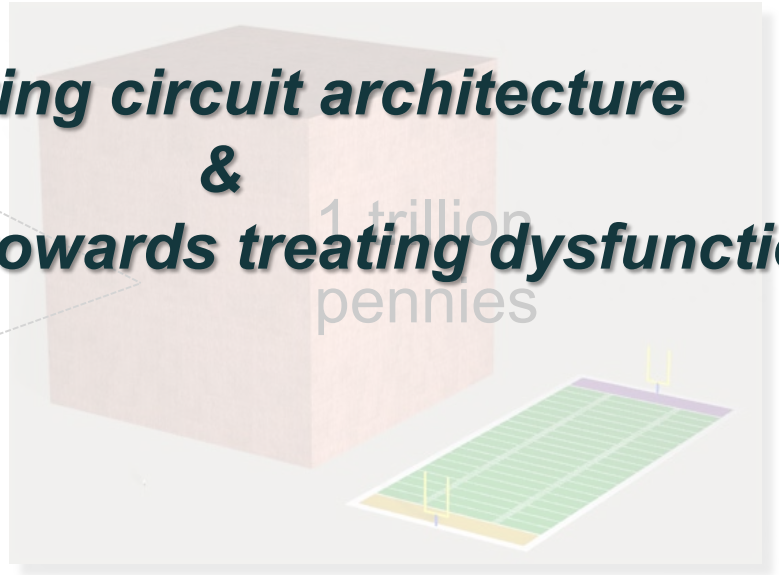
- Neurodevelopmental / cognitive disorders
- Neurodegenerative diseases
- Neuropsychiatric disorders
- Addictive / behavioral disorders

Brain architecture, circuitry, and function is complex

- 1 billion neurons
- 1 trillion connections

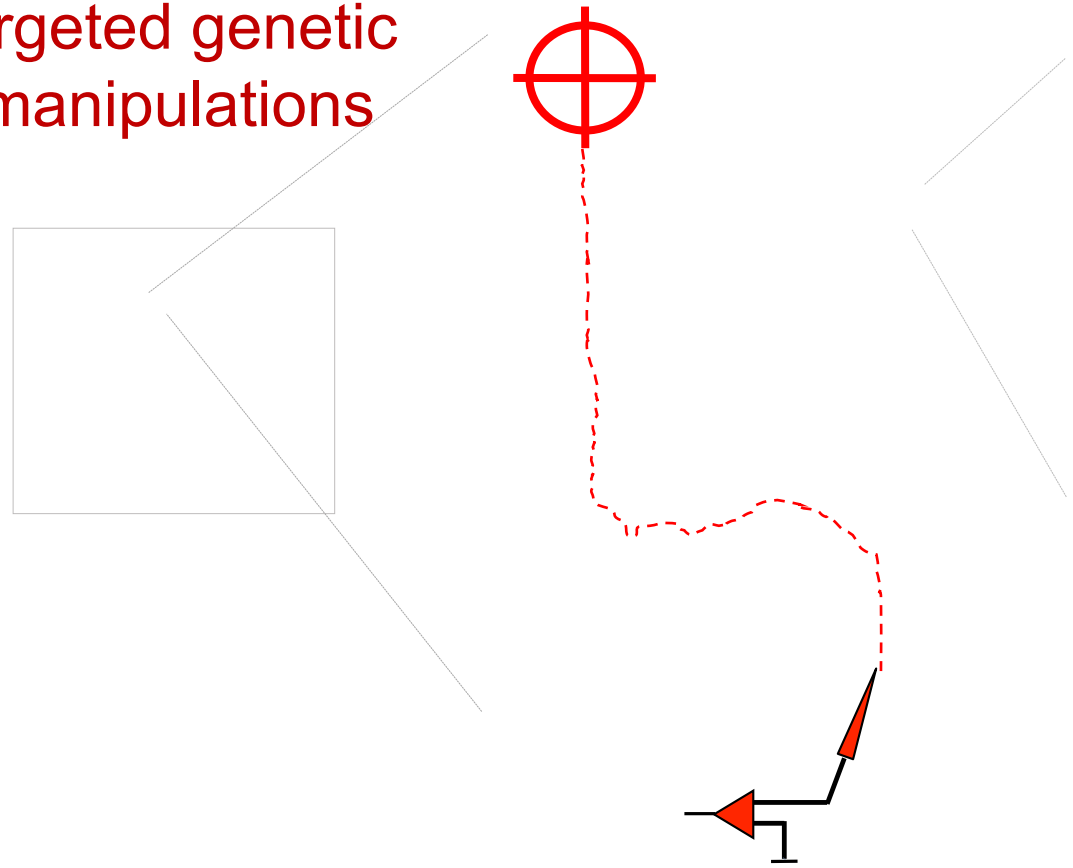
The Path Forward

elucidating circuit architecture
&
exploiting complexity towards treating dysfunction / disease



Genetic methods to mark, monitor, & manipulate neurons in mice allows brain circuit investigation

targeted genetic manipulations



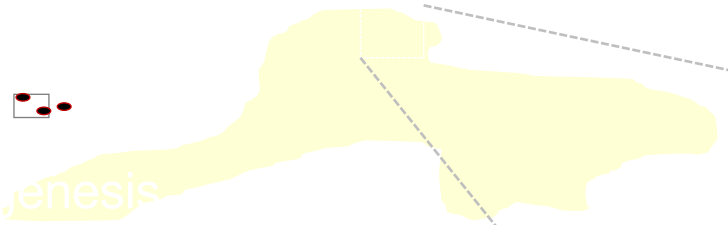
- in vivo imaging
- electrophysiology
- optogenetics
- single cell sequencing
- anatomical tracing
- circuit mapping

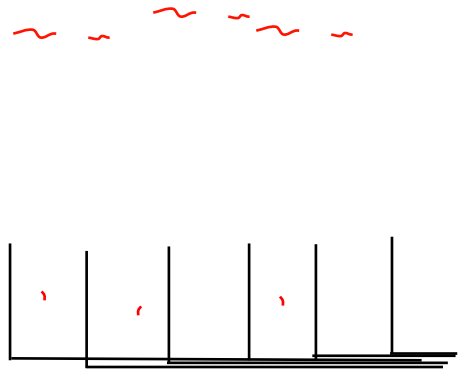
The mouse olfactory system is a useful experimental model to study circuit formation & function

Behavior

Tractability

Anatomy





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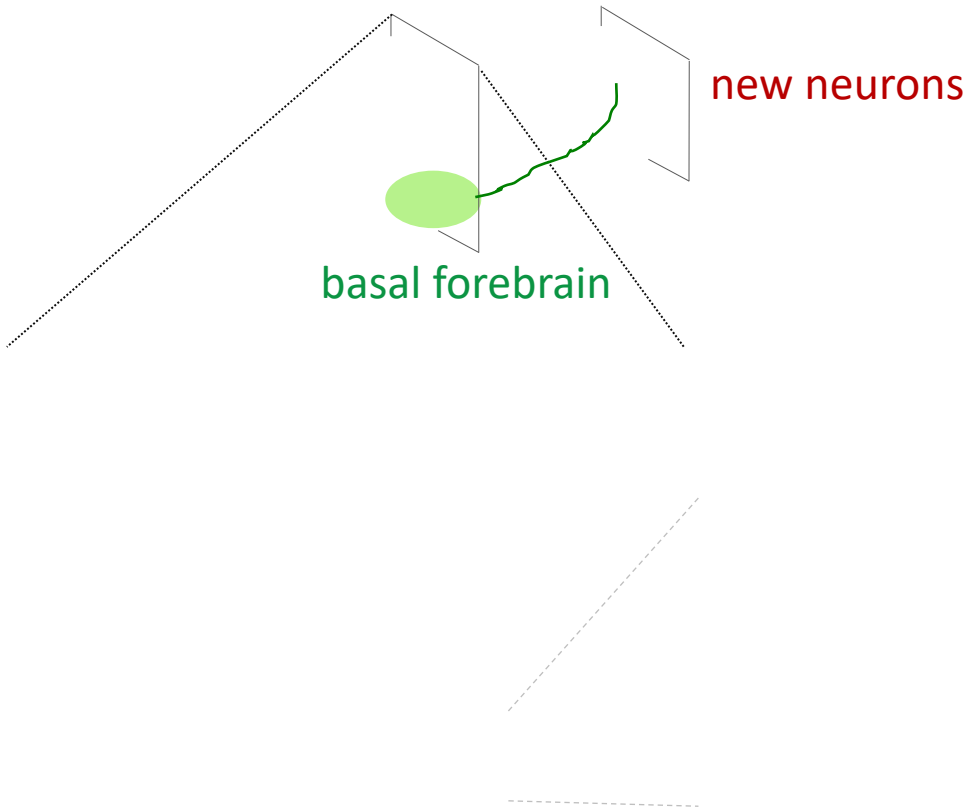
The cholinergic basal forebrain provides inputs onto adult-born neurons

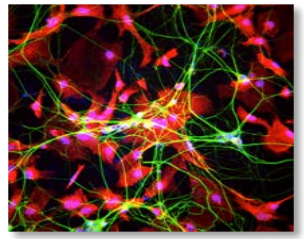


Rabies-EGFP	Rabies-EGFP	anti-ChAT	merge

ChAT = Choline acetyltransferase = acetylcholine synthesis

Cholinergic signaling is a candidate to influence circuit integration of adult-born neurons

- Cholinergic signaling influences olfaction

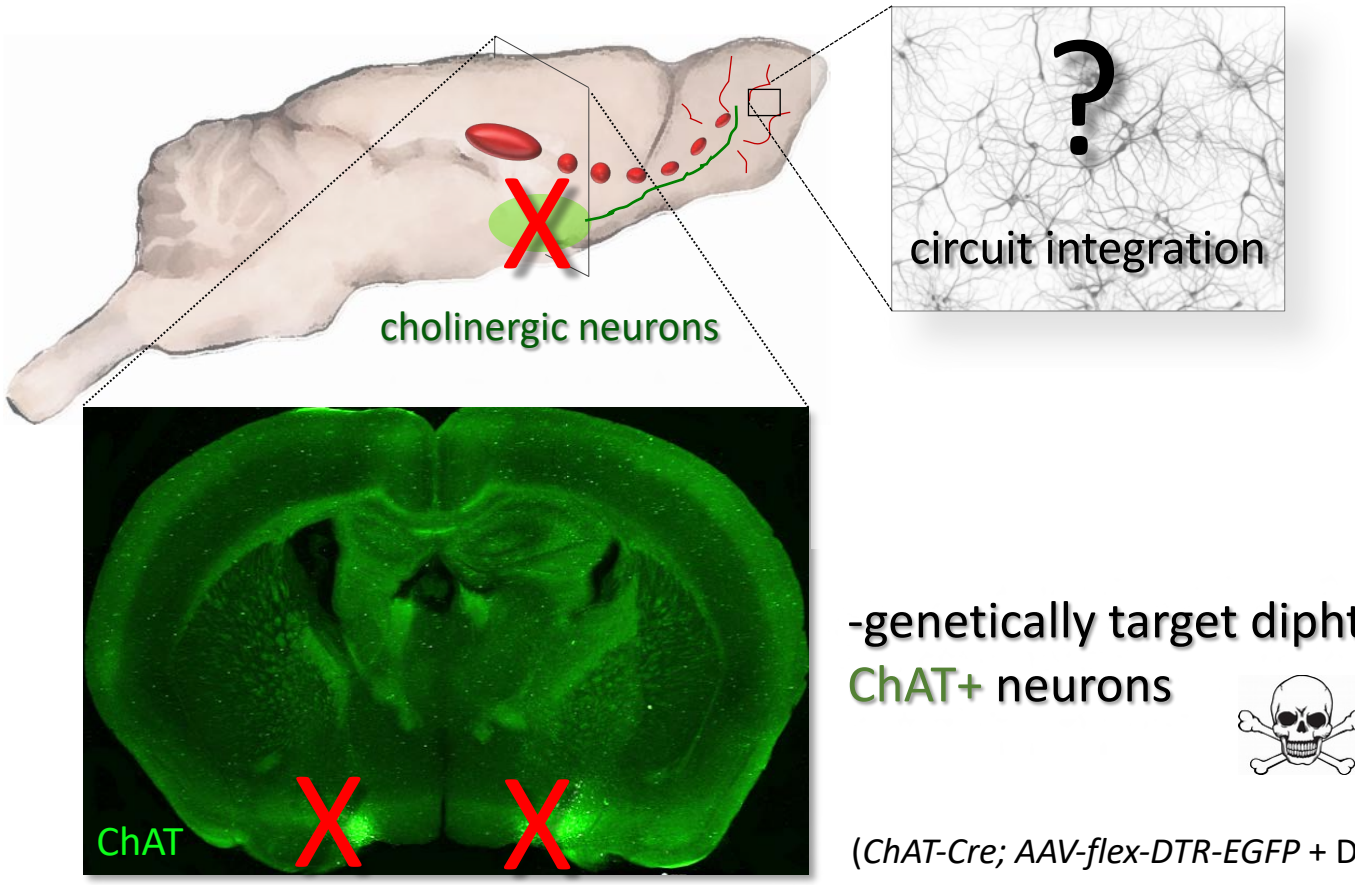


- Acetylcholine is synaptogenic

- Cholinergic signaling is linked to reward/arousal/plasticity

- Alzheimer's models treated with acetylcholinesterase blockers show increased adult-born neuron integration

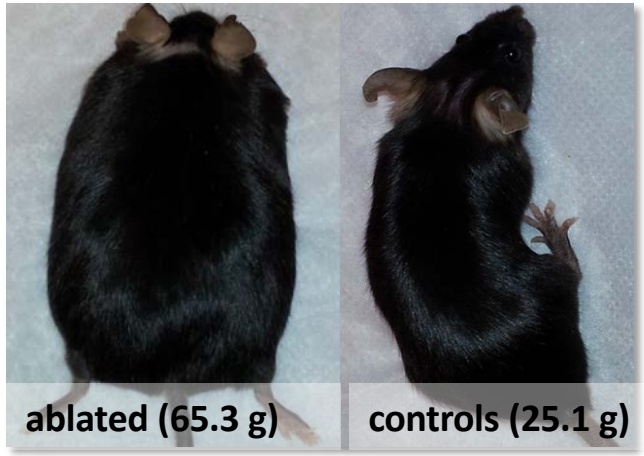
What happens to the adult-born neurons if we genetically manipulate cholinergic basal forebrain inputs?



-genetically target diphtheria toxin receptor to ChAT+ neurons (+DT)

(*ChAT-Cre; AAV-flex-DTR-EGFP* + DT injections)

Genetically targeted ablation of basal forebrain cholinergic neurons results in severe and rapid-onset obesity



Herman et al., *2016*

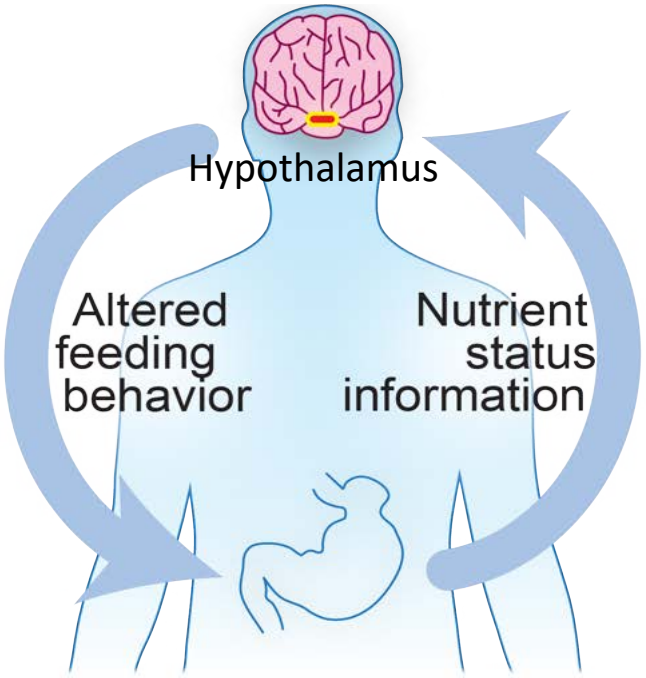
Loss of cholinergic basal forebrain signaling increases drive to eat, unchecked food consumption, and hyperphagia

Neural Stem Cells / Synapses / Plasticity →

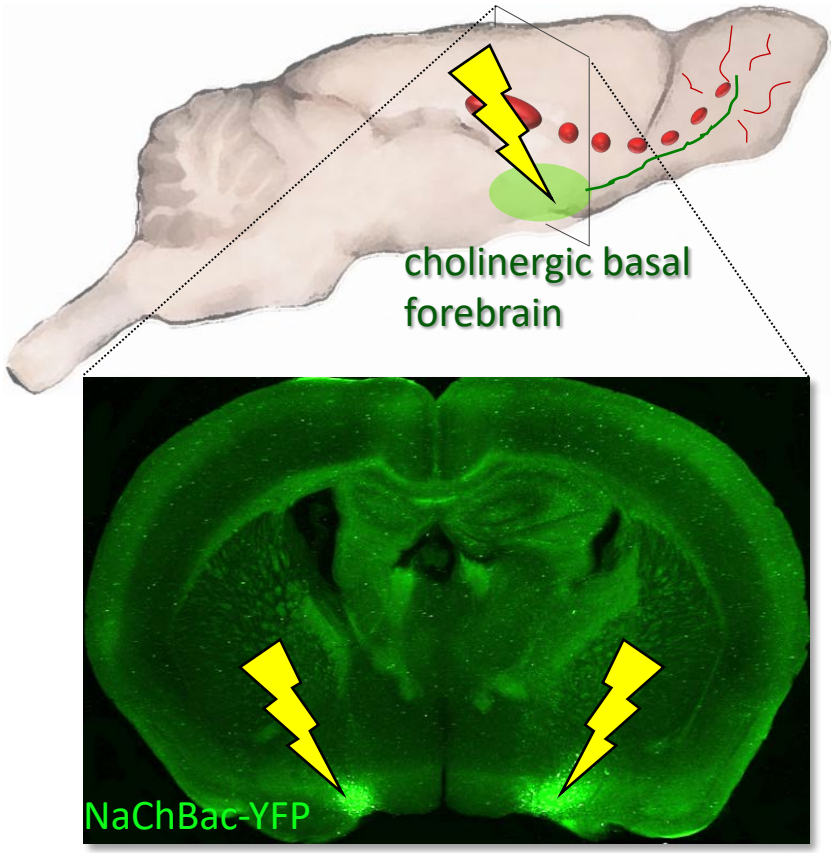
-Basal Forebrain-
feeding / addiction / aversion circuits

The central nervous system controls food intake

Homeostatic mechanisms



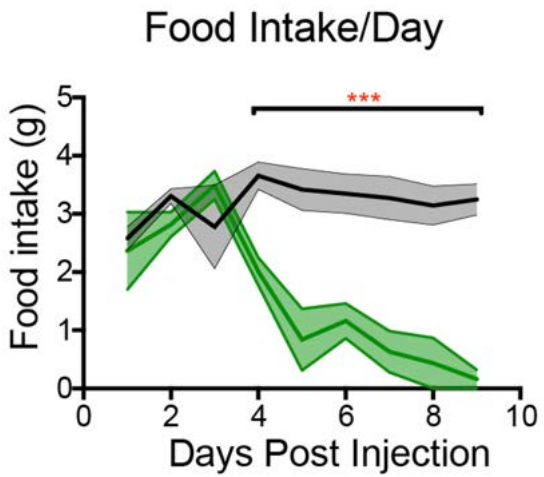
What happens if we genetically increase the activity of cholinergic basal forebrain inputs?

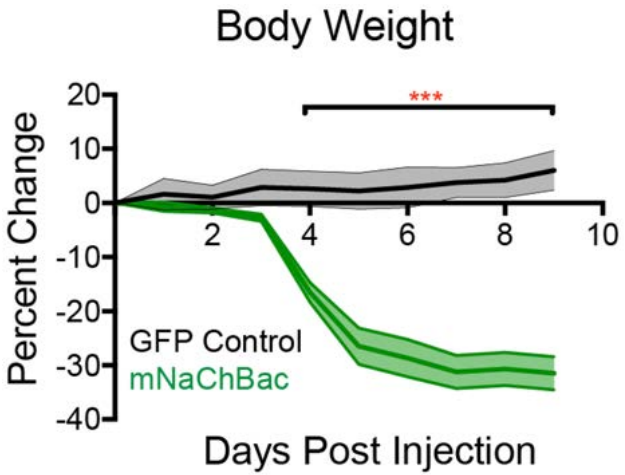


-genetically target NaChBac to basal forebrain neurons
(NaChBac = “leaky” sodium channel)

(*Vlut2-Cre; AAV-flex-NaChBac-YFP)*

Chronic activation of basal forebrain neurons causes decreased feeding & dramatic weight loss





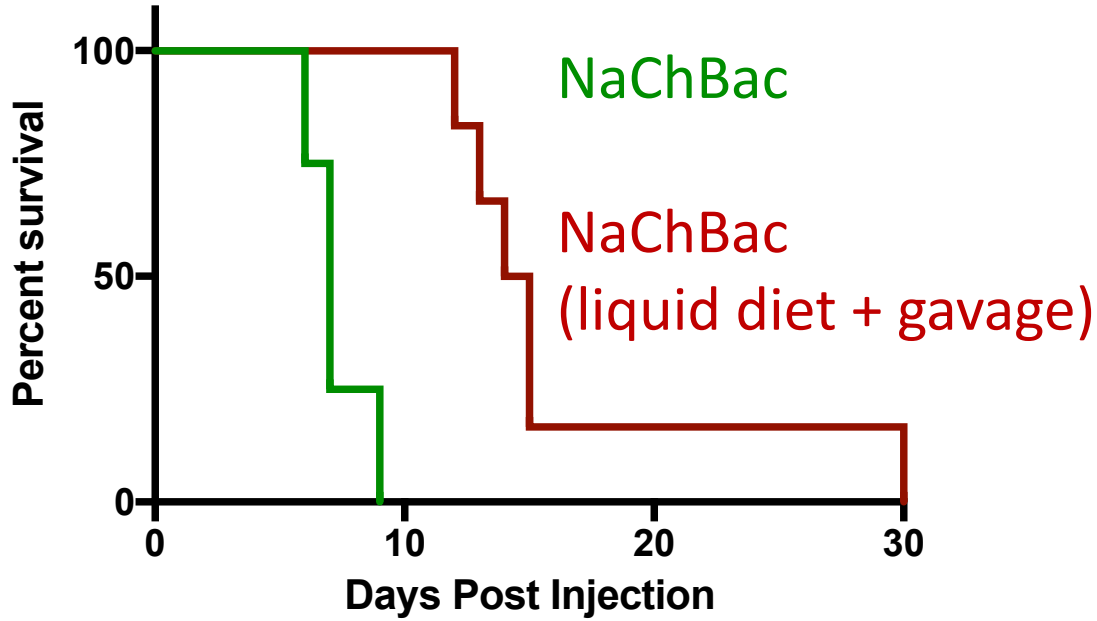
Patel et al., *2019*

Chronic activation of basal forebrain neurons induces voluntary hypophagia without initial metabolic dysfunction

No Changes in serum hormones (prior to malnutrition)

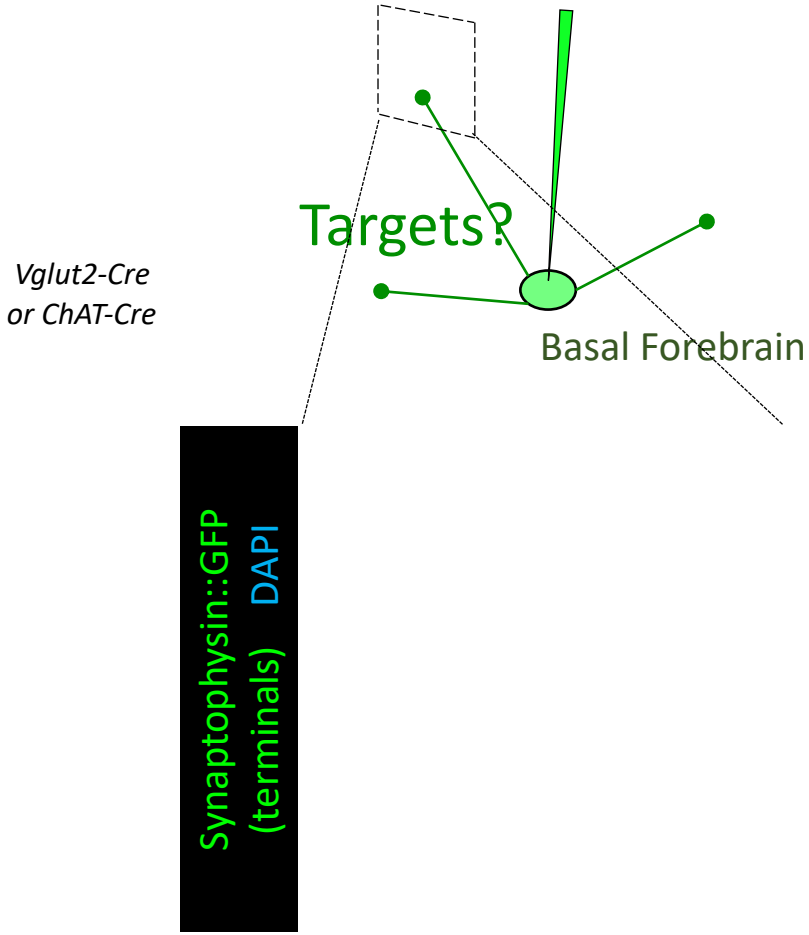
- **Pituitary**
  - *ACTH, FSH, GH, Prolactin, & TSH*
- **Thyroid**
  - *Free T4 & T3*
- **Glucose Metabolism**
  - *Glucose & Insulin*
- **Appetite Hormones**
  - *Leptin & Ghrelin*

Starvation can be rescued



Labeling basal forebrain neuron terminals reveals downstream brain targets

AAV-Flex-Synaptophysin::GFP



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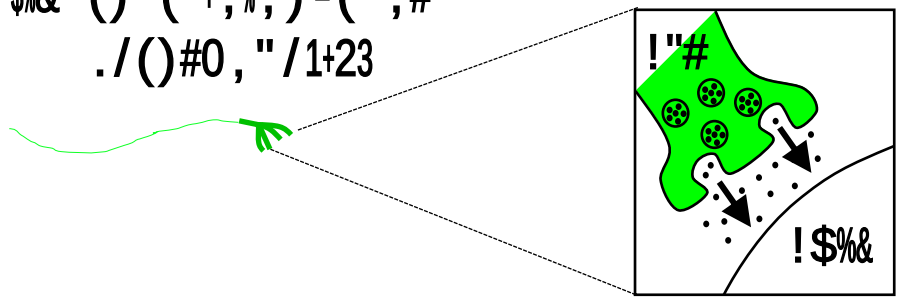
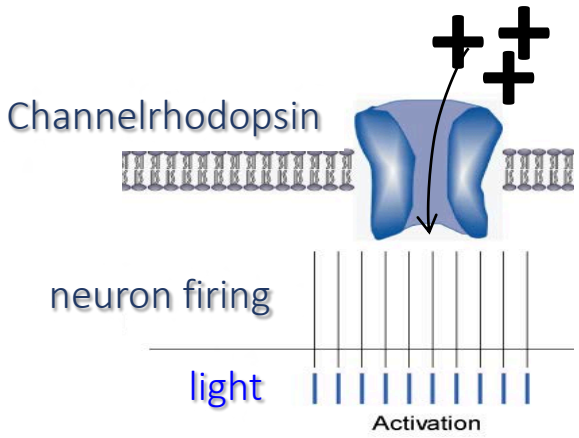
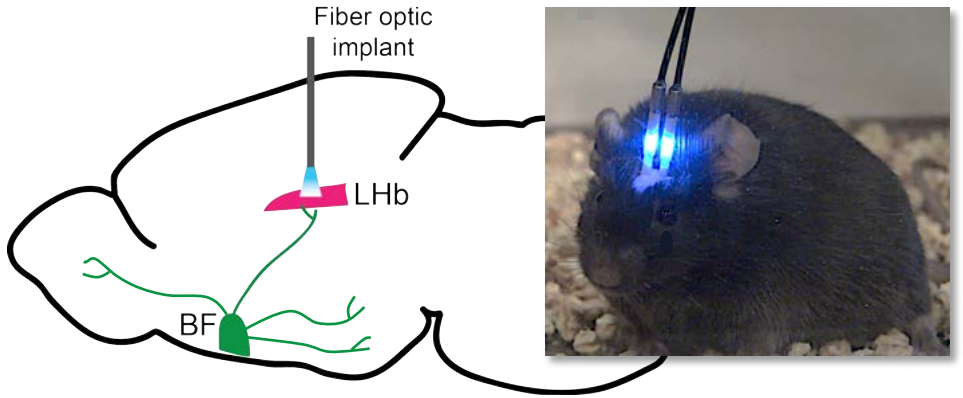


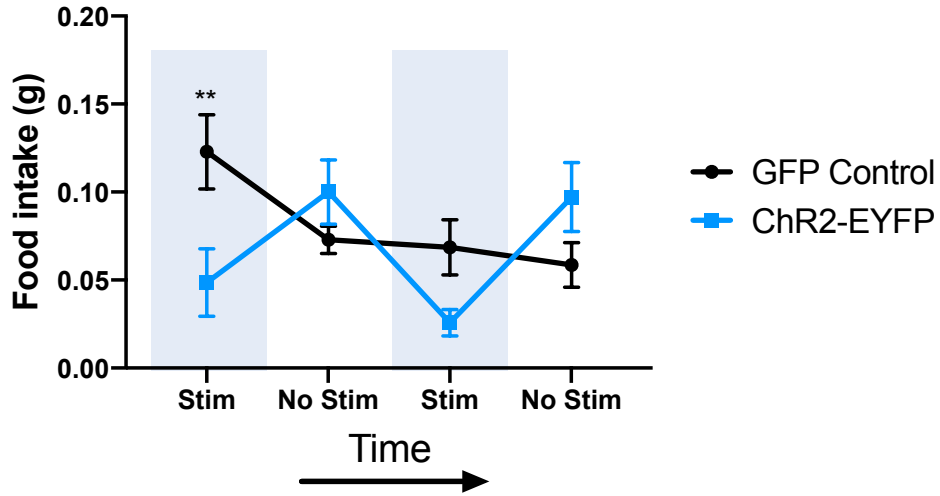
(target identification)

Activation of basal forebrain LHb inputs decreases feeding

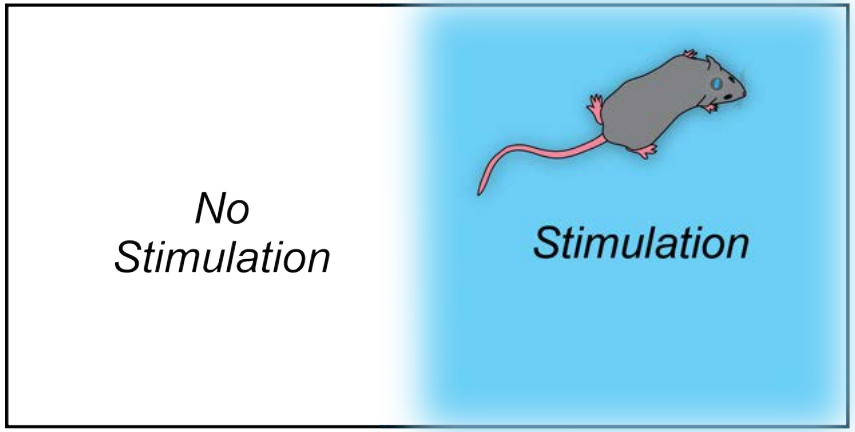


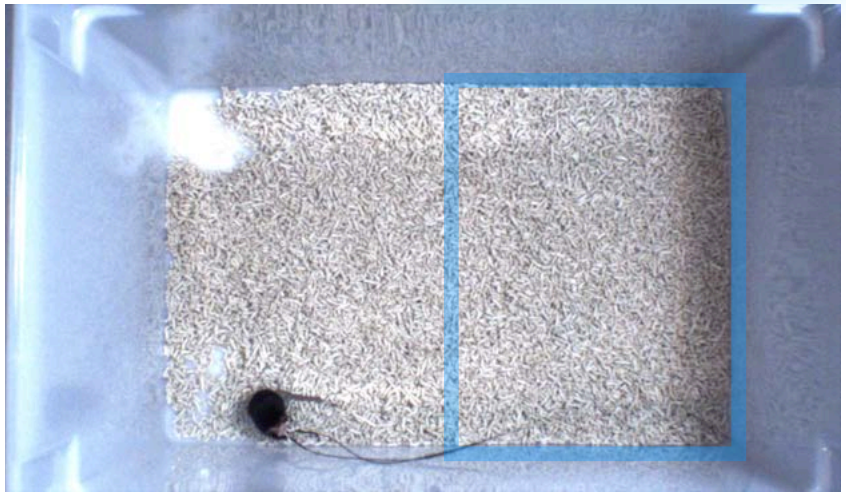


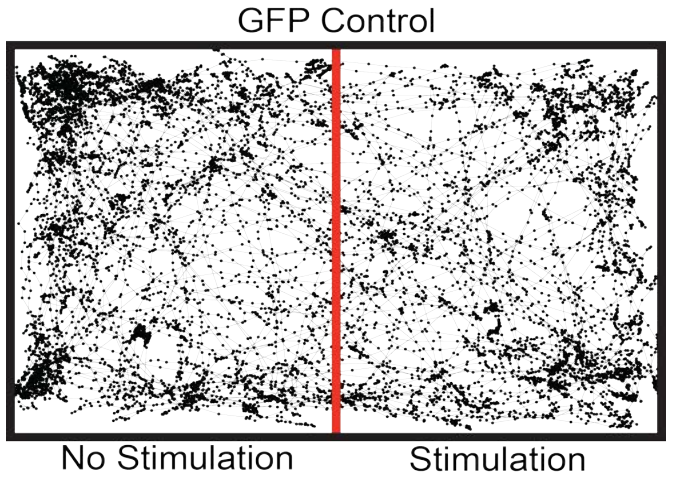
(*Vglut2-Cre; AAV-flex-ChR2-EYFP*)

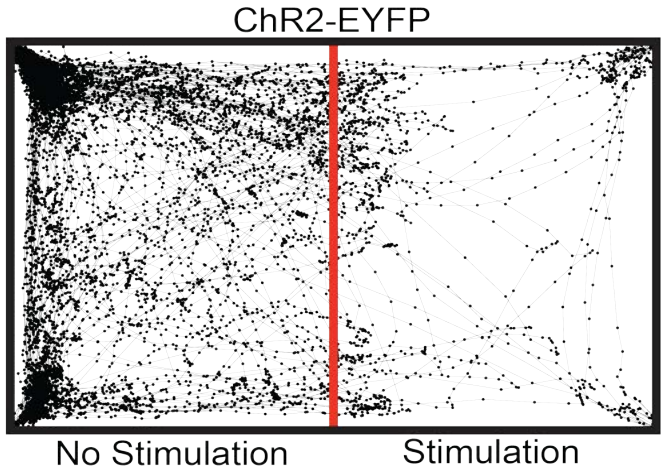


Optogenetic activation of basal forebrain-to-LHb inputs elicits aversion/avoidance

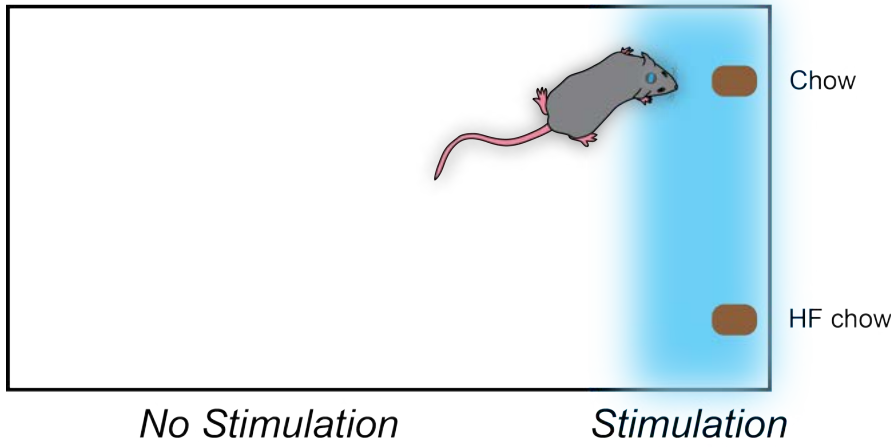


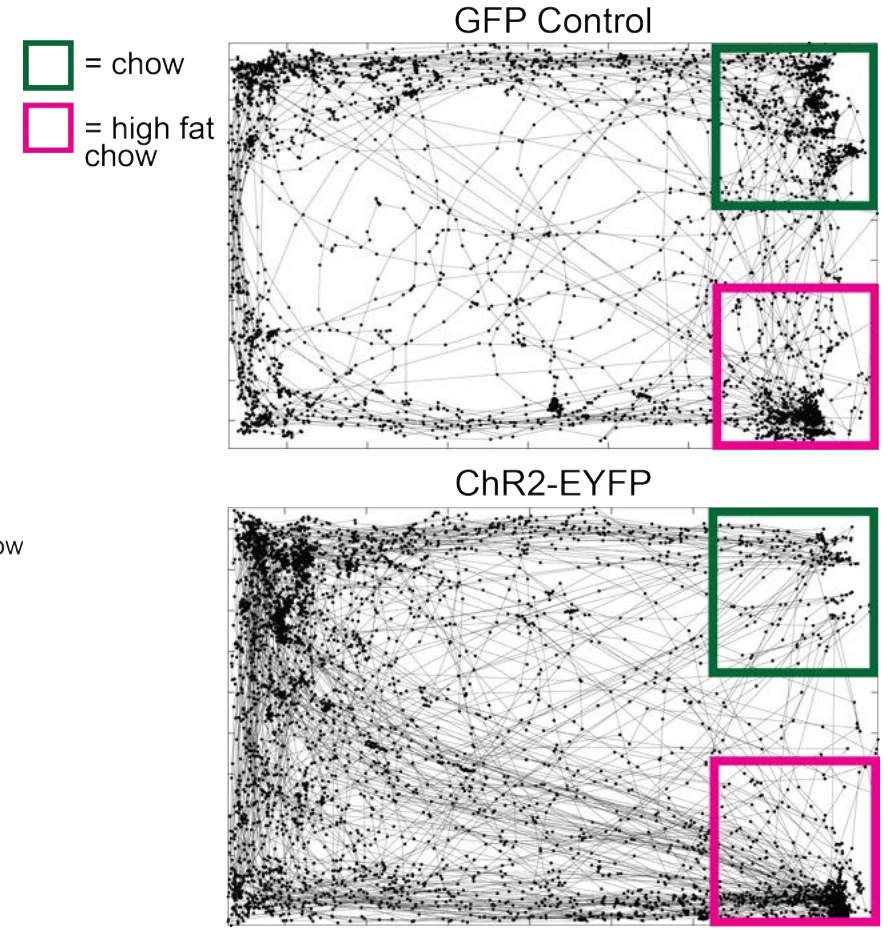




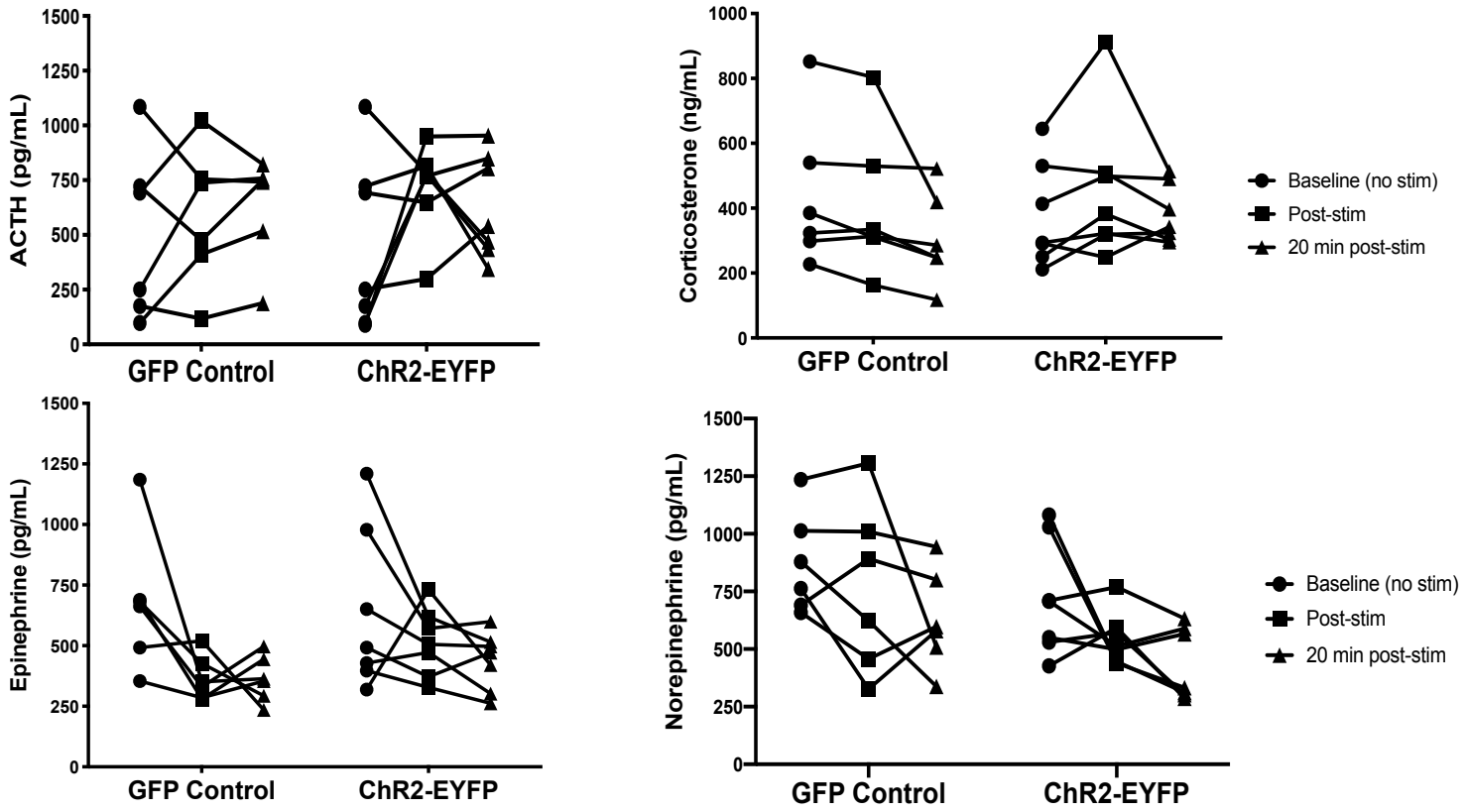


Optogenetic activation of basal forebrain-to-LHb inputs elicits avoidance in the presence of food



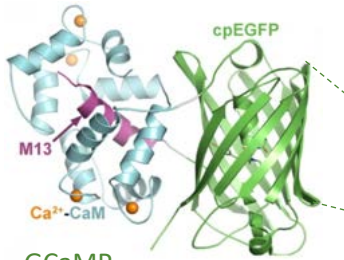


Stress response hormones are not affected with activation of basal forebrain-to-LHb circuit activation



Basal forebrain drive to LHb is "reflexive", and can bypass higher order processing

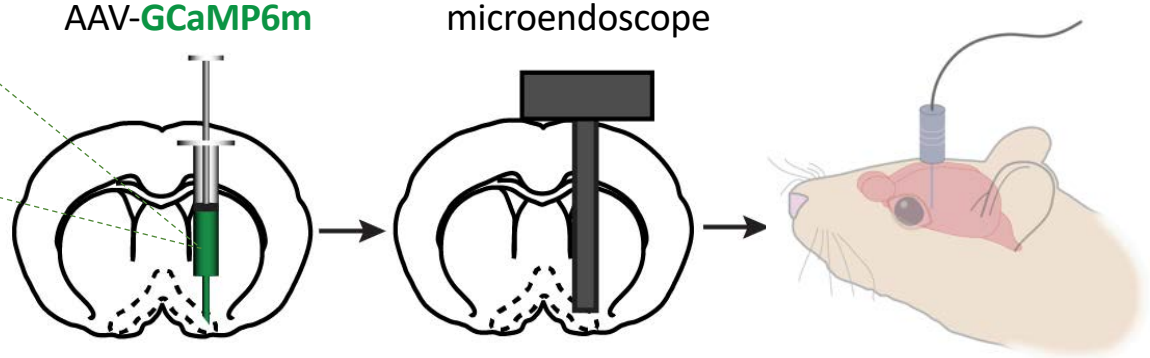
In vivo imaging reveals food responses in basal forebrain



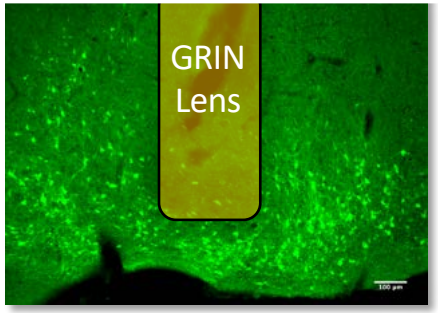
GCaMP
(Ca+2 responsive GFP)

AAV-**GCaMP6m**

microendoscope

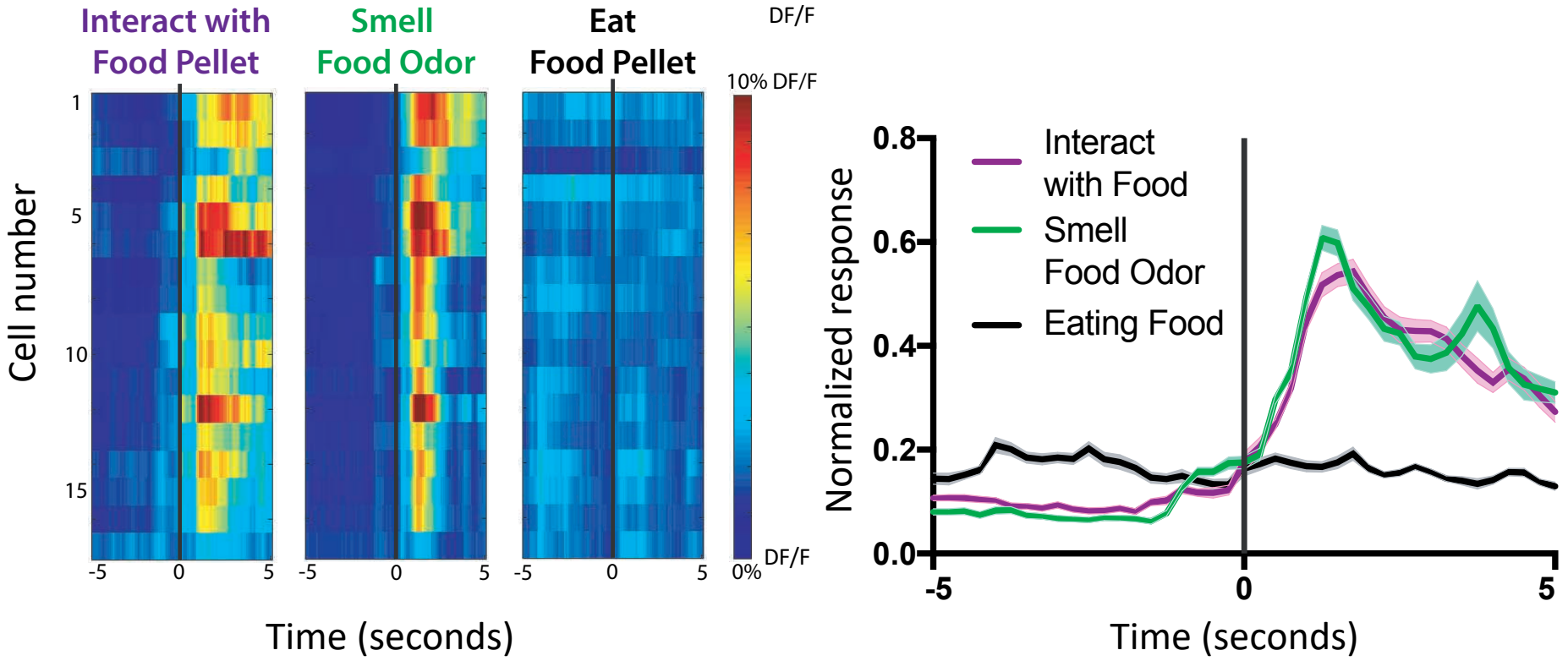


(*Vglut2-Cre or ChAT-Cre; AAV-flex-GCaMP6m*)

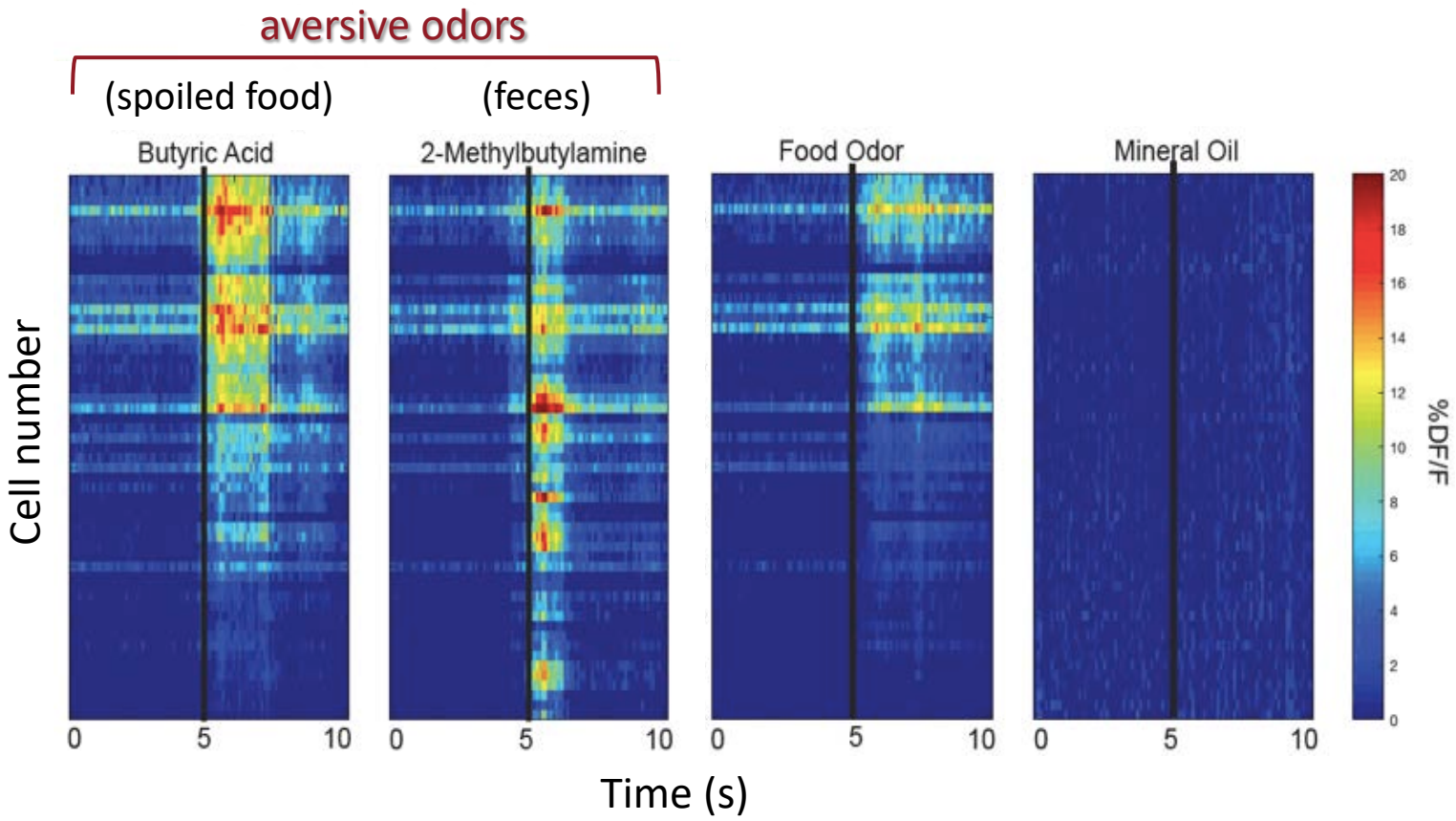


GCaMP6m

Basal forebrain neurons are activated by food-related stimuli



Naturally aversive odors more strongly activate basal forebrain neurons than food



Basal forebrain-to-LHb circuits override homeostatic feeding mechanisms

The cholinergic basal forebrain is a potent integration center that modulates behavioral and physiological output

Sensory cues

Memory, experience, & cognition

AChRs (nicotine)

Cholinergic basal forebrain

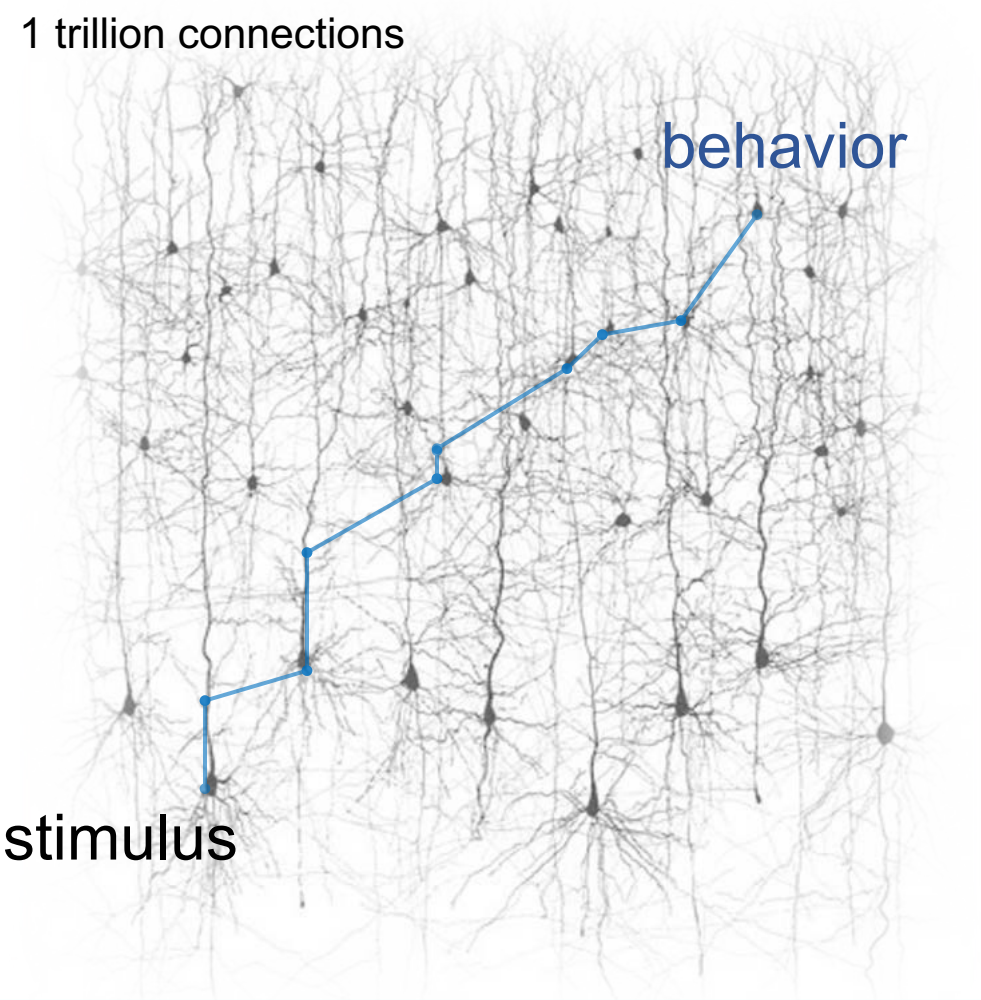
Hypothalamus

Amygdala

Lateral Habenula

Exploiting circuit complexity may be an approach to treating dysfunction / disease

- 1 billion neurons
- 1 trillion connections



Exploiting circuit complexity may be an approach to treating dysfunction / disease

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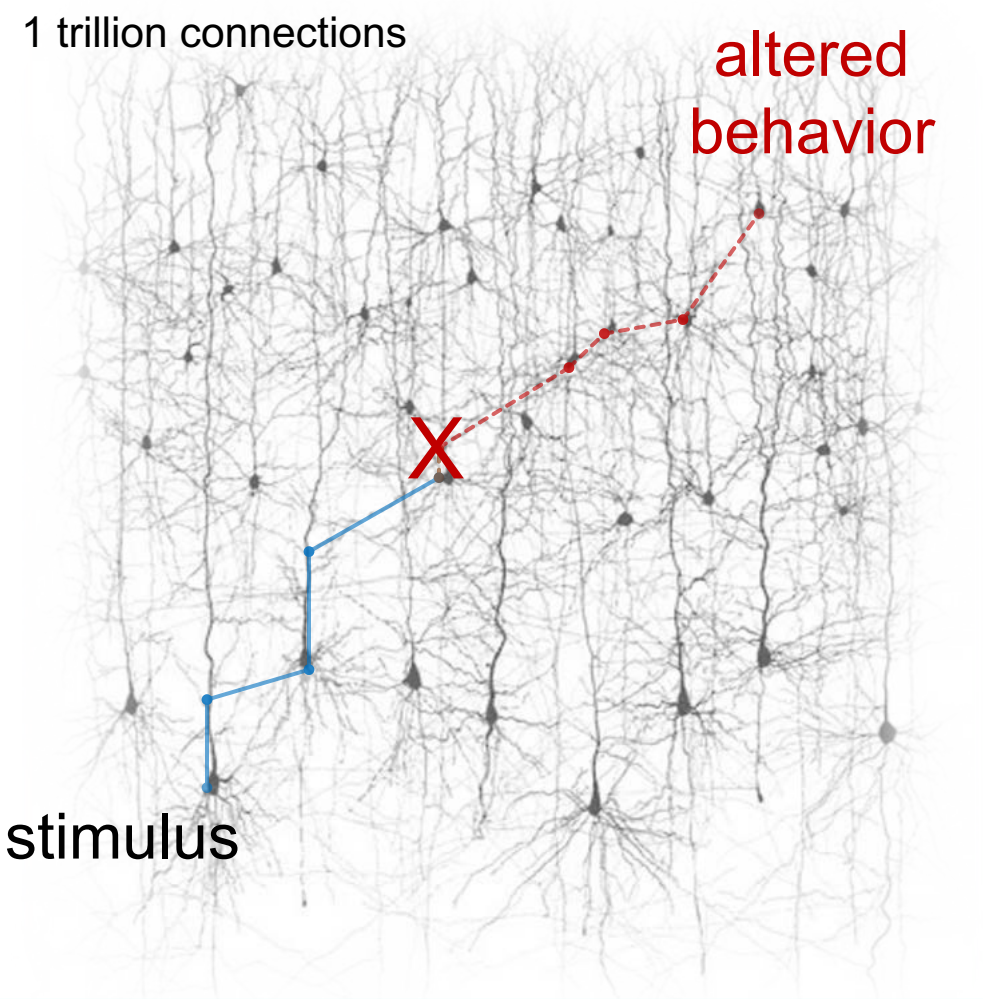

Exploiting circuit complexity may be an approach to treating dysfunction / disease

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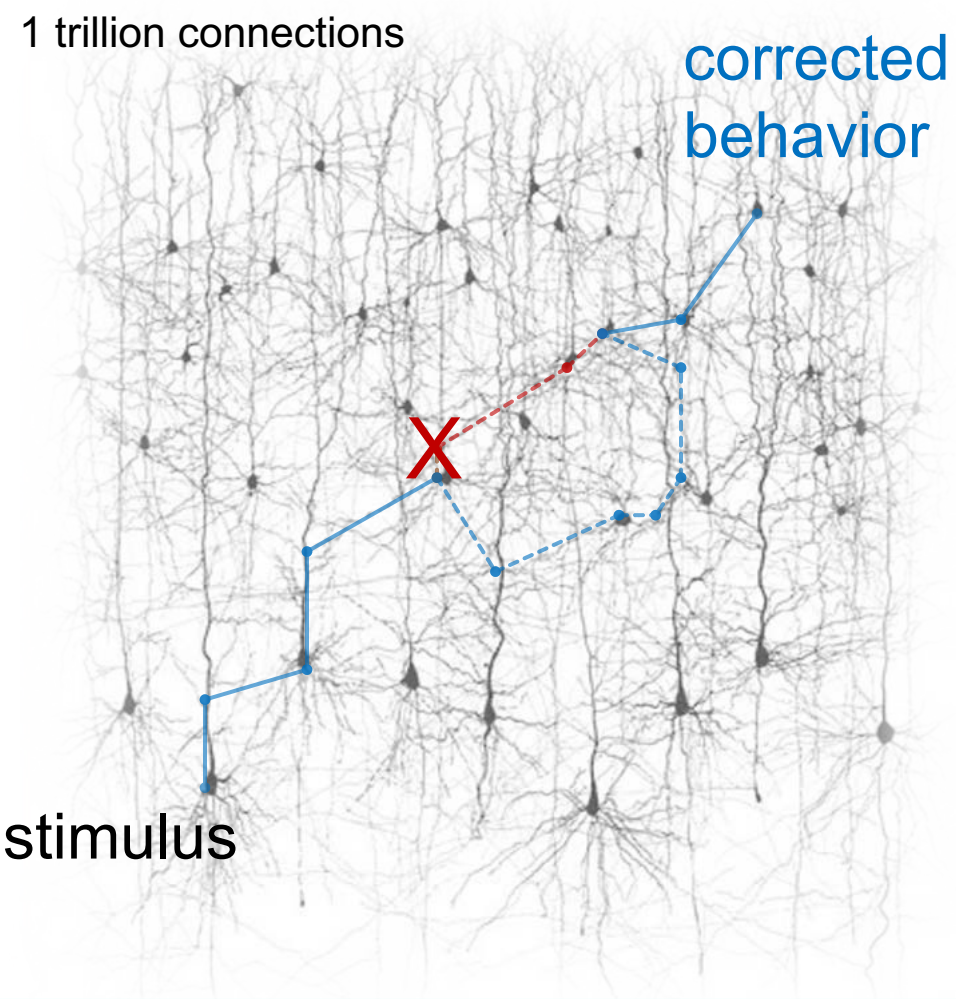
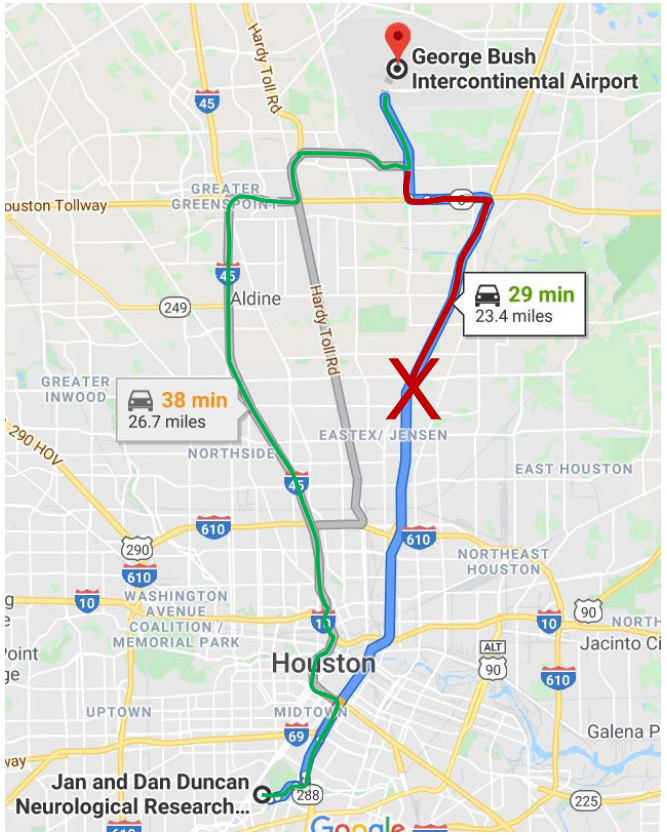
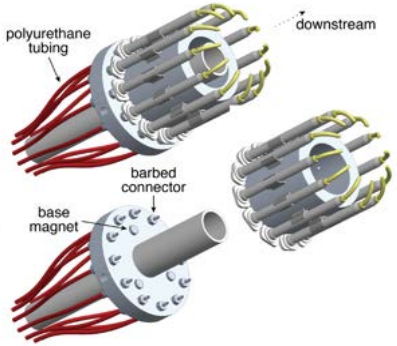
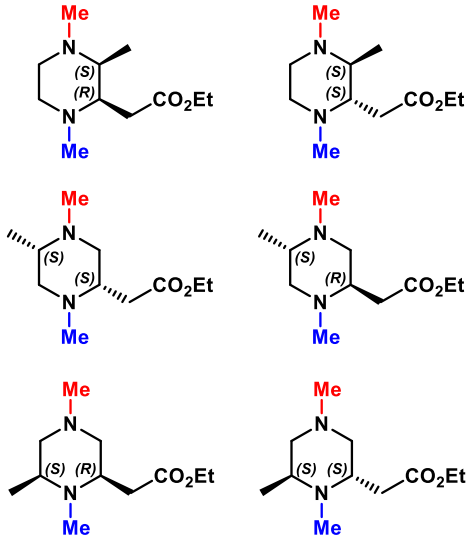


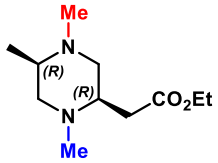


In vivo imaging can be used to screen for compounds that gate aversion / reward / feeding circuitry

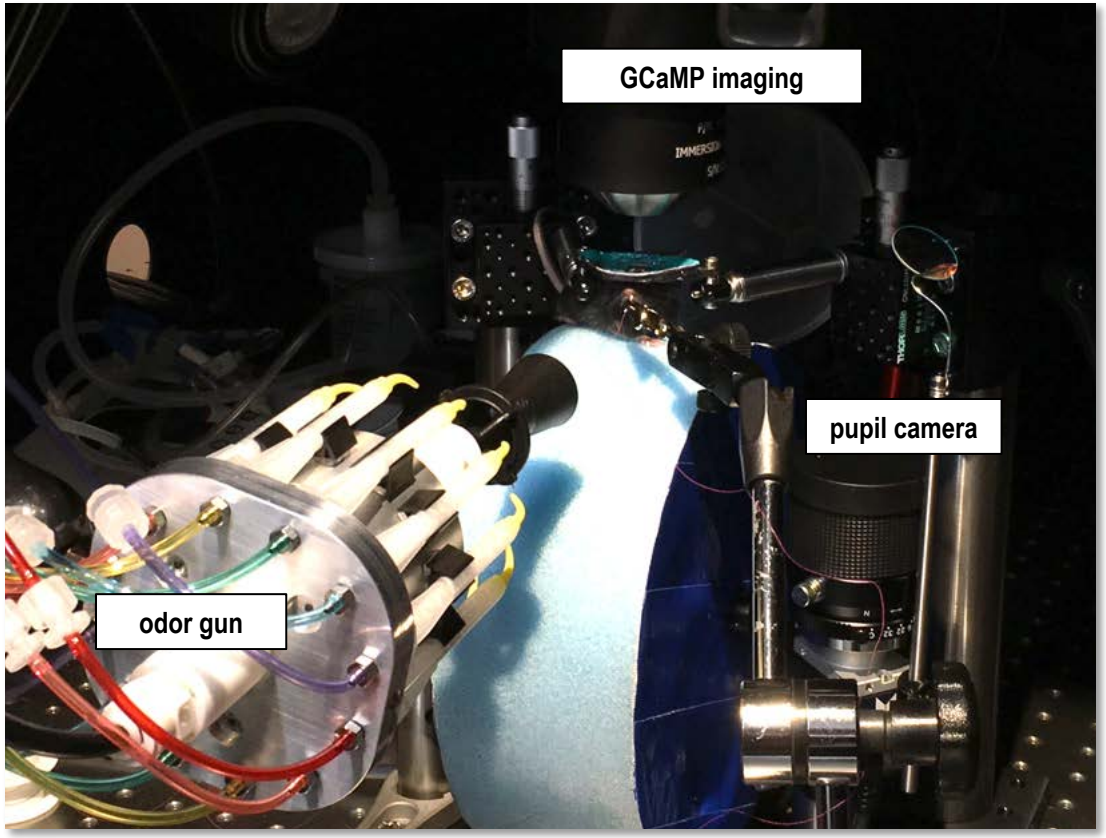




Dr. Damian Young
Pharmacology & Chemical Biology
BCM / NRI



piperazine or nicotine backbones



Acknowledgements

TAMEST
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Brain & Behavior Foundation
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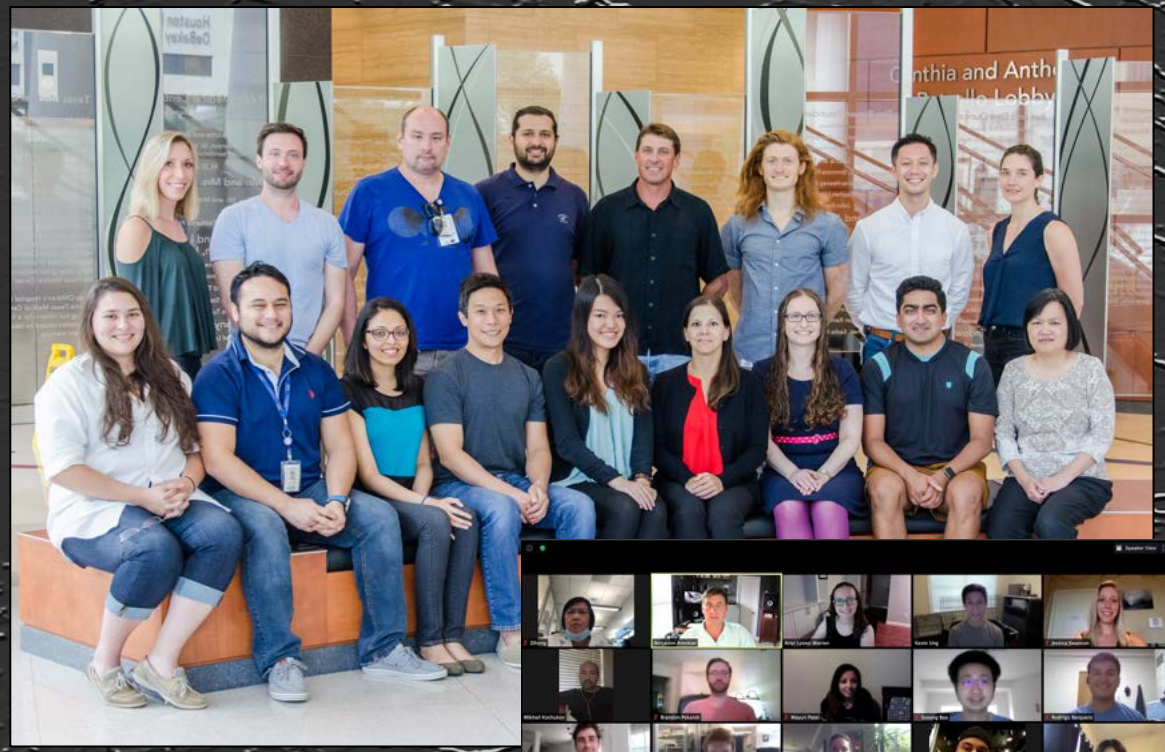
NARSAD
NHARP
DOD

McNair Foundation



Collaborator on this work
Qingchun Tong (UTH)

Alumni associated with this work
Isabella Herman, Alex Herman

"It's not what you gather but what you scatter that tells what kind of life you have lived."