From Single Synapses to Clinical Studies: Therapeutic Developments from Optogenetics

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Dopamine

Addiction

Apathy

motivation

Aggressive behaviors

Sexual behaviors

Appetitive behaviors

Reward Deficiency Syndrome

Parkinson's disease

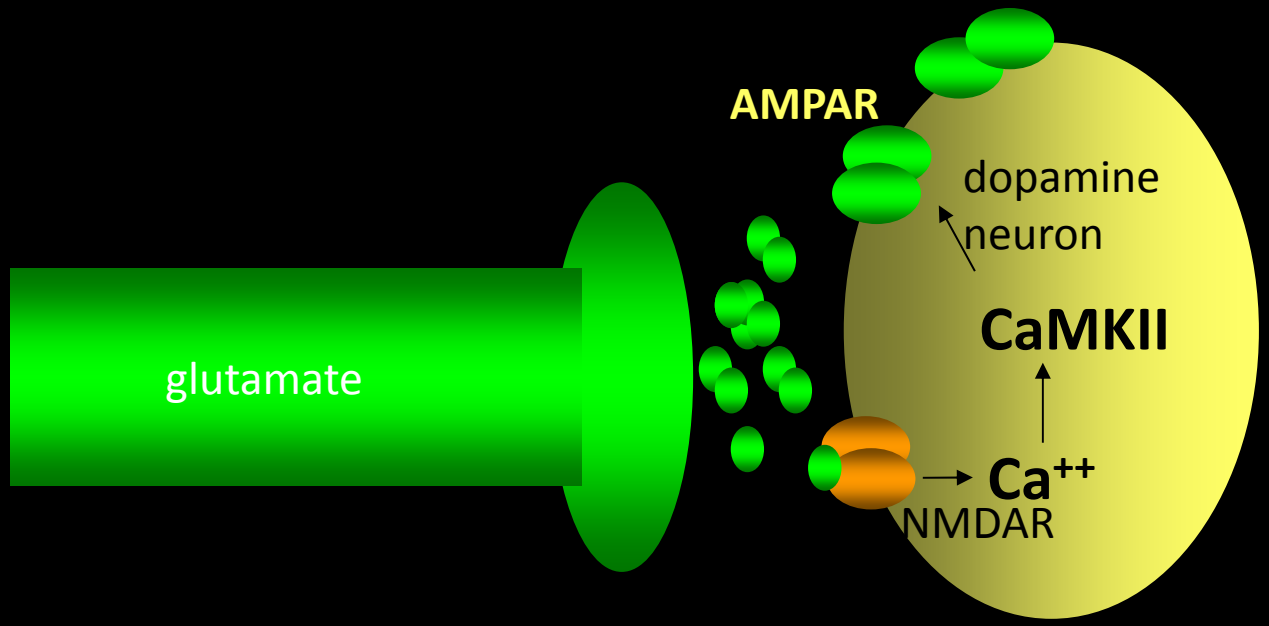
ADHD

Schizophrenia

Sensory neglect

Learning and memory

LTP and dopamine neurons



Bonci and Malenka, 1999; Overton and Clark, 1999

The time course of VTA cocaine-dependent synaptic plasticity

Ungless et al., Nature (2001)

The time course of VTA cocaine-dependent synaptic plasticity

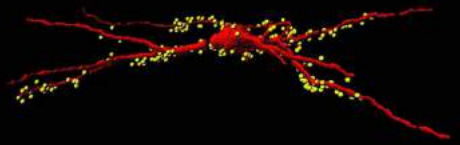
Ungless et al., Nature (2001)

Chen et al., Neuron (2008)

LTP

Cocaine self-administration

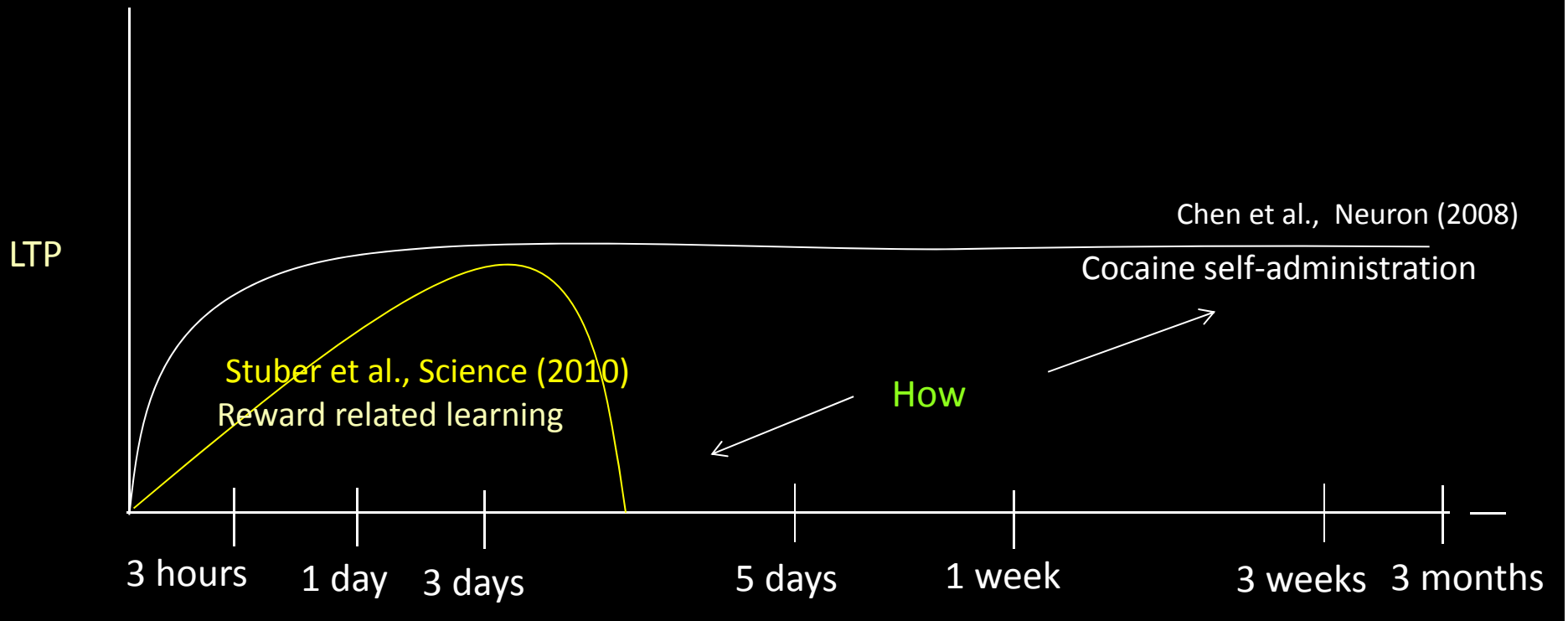
Single cocaine



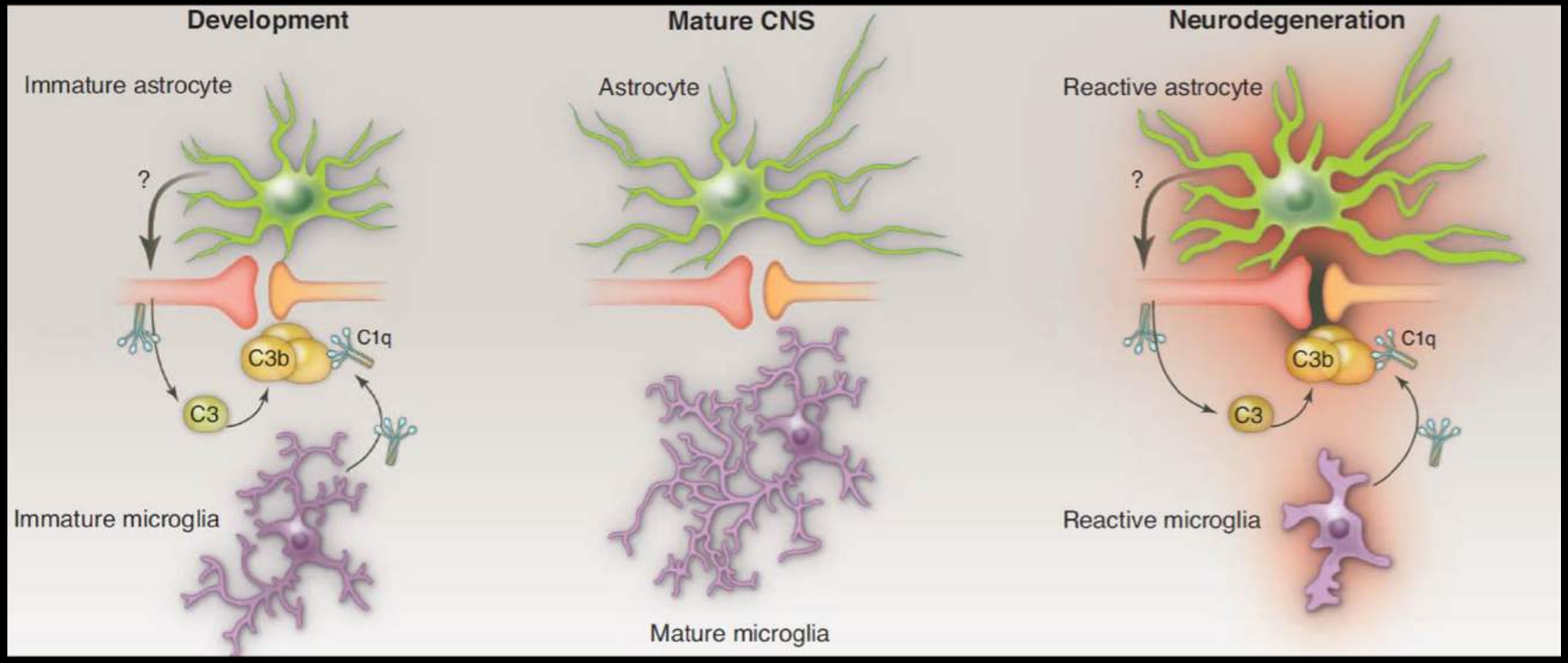
3 hours 1 day 3 days 5 days 1 week 3 weeks 3 months

time

The time course of VTA cocaine-dependent synaptic plasticity

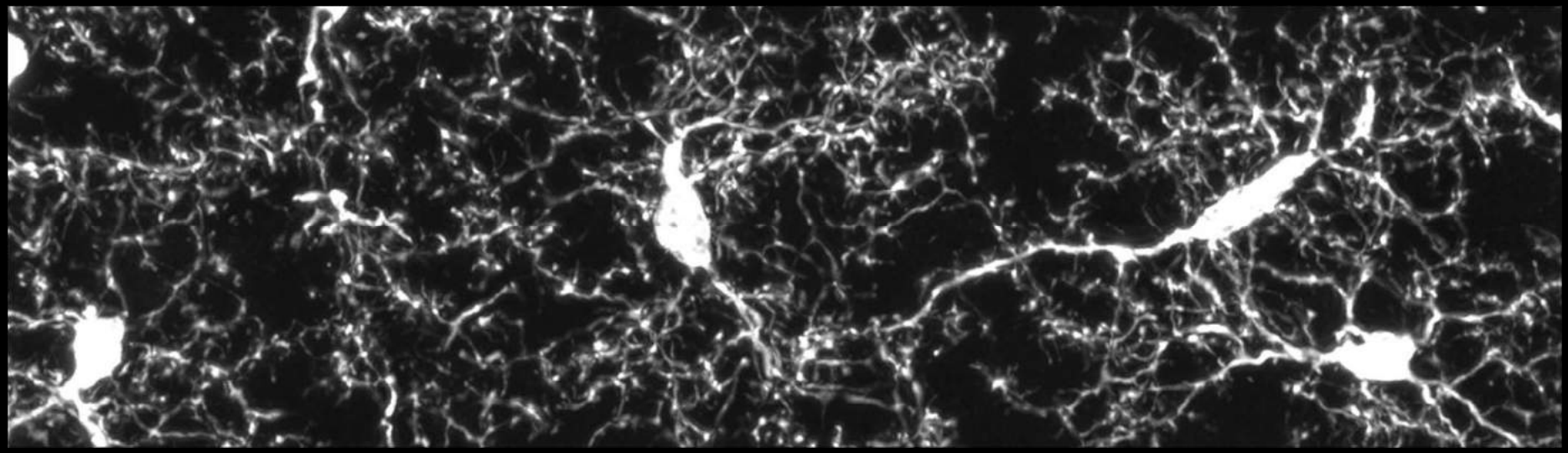


The other players

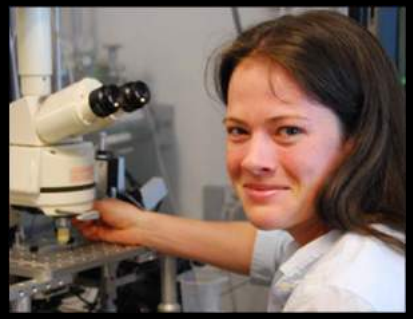


Alterations in microglia have been described in a variety of psychiatric diseases

From Aguzzi, Barres and Bennet, Science (2013)

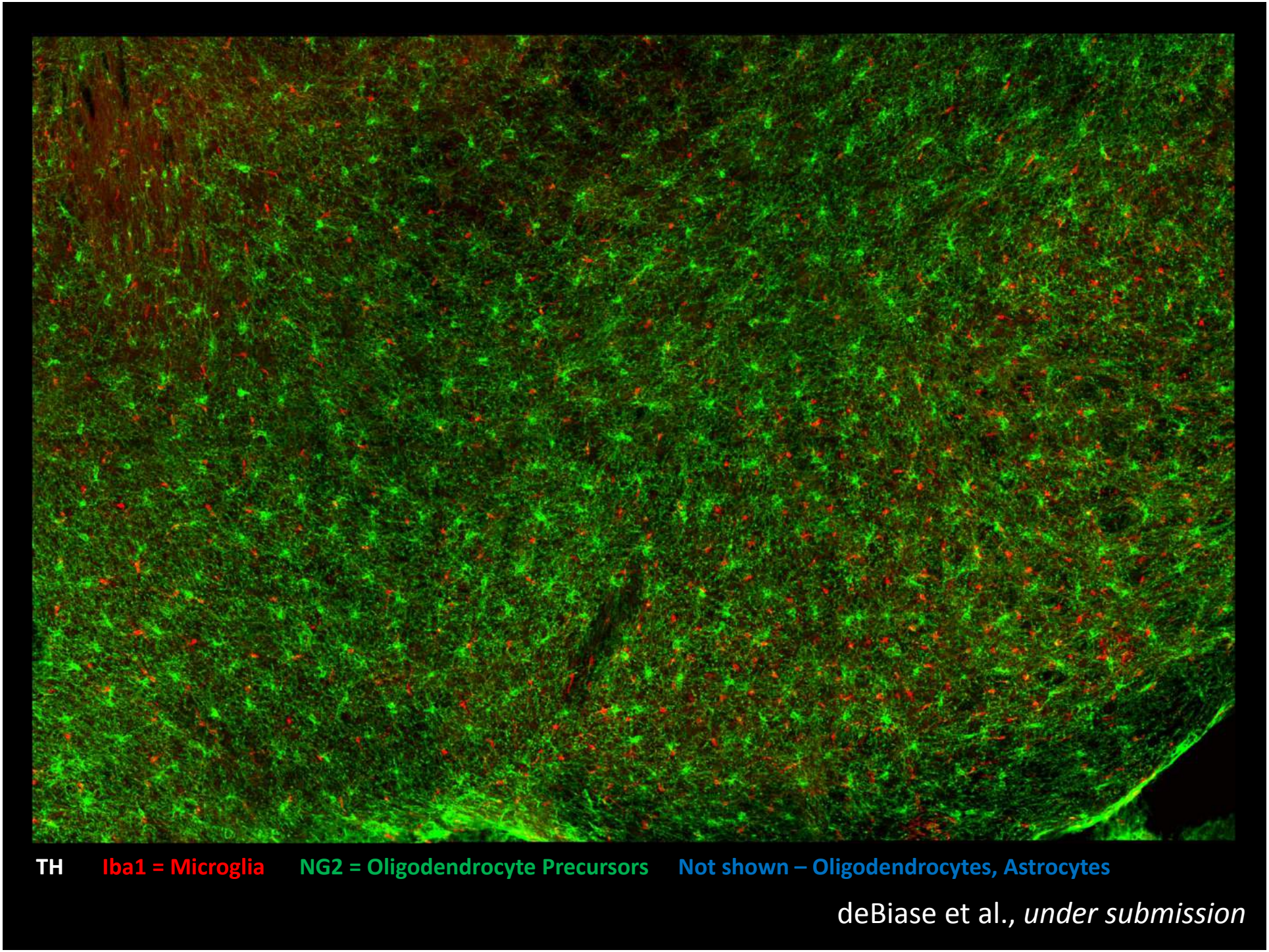


Basic properties of microglial cells in the midbrain and accumbens



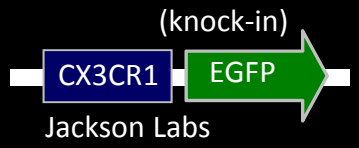
Lindsay de Biase

Mirror project: Wendy Xin (astrocytes)

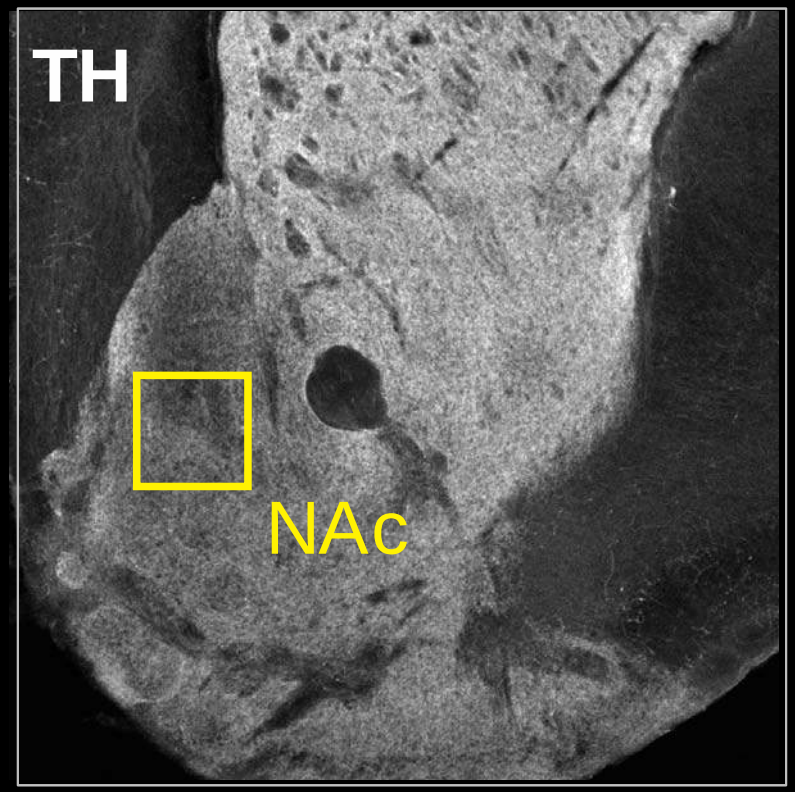


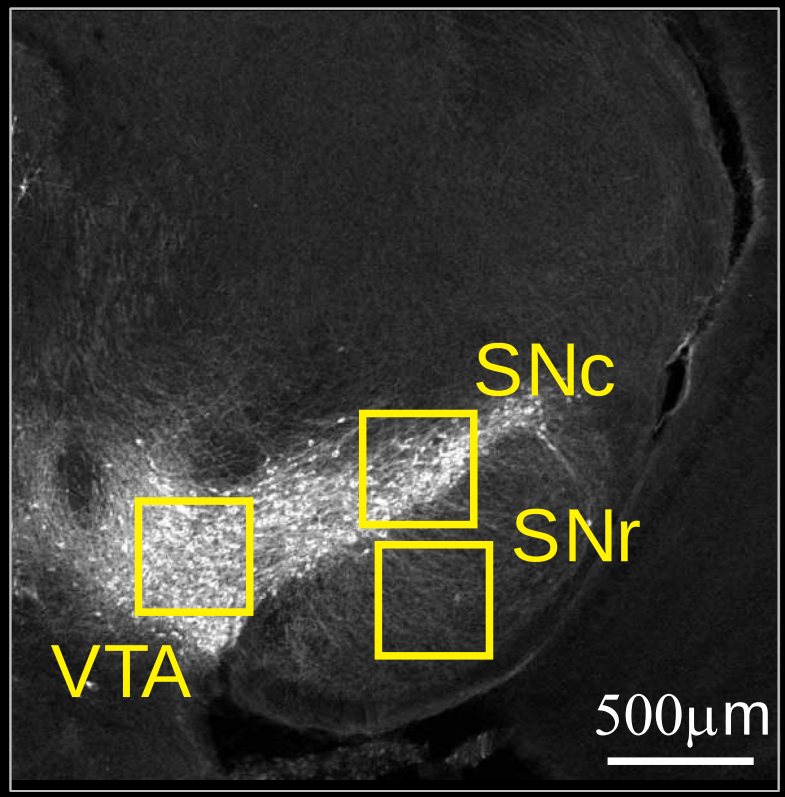
deBiase et al., *under submission*

Regions of interest for study of basal ganglia (BG) microglia



- P58-62
- ♂ and ♀
- perfusion-fixed

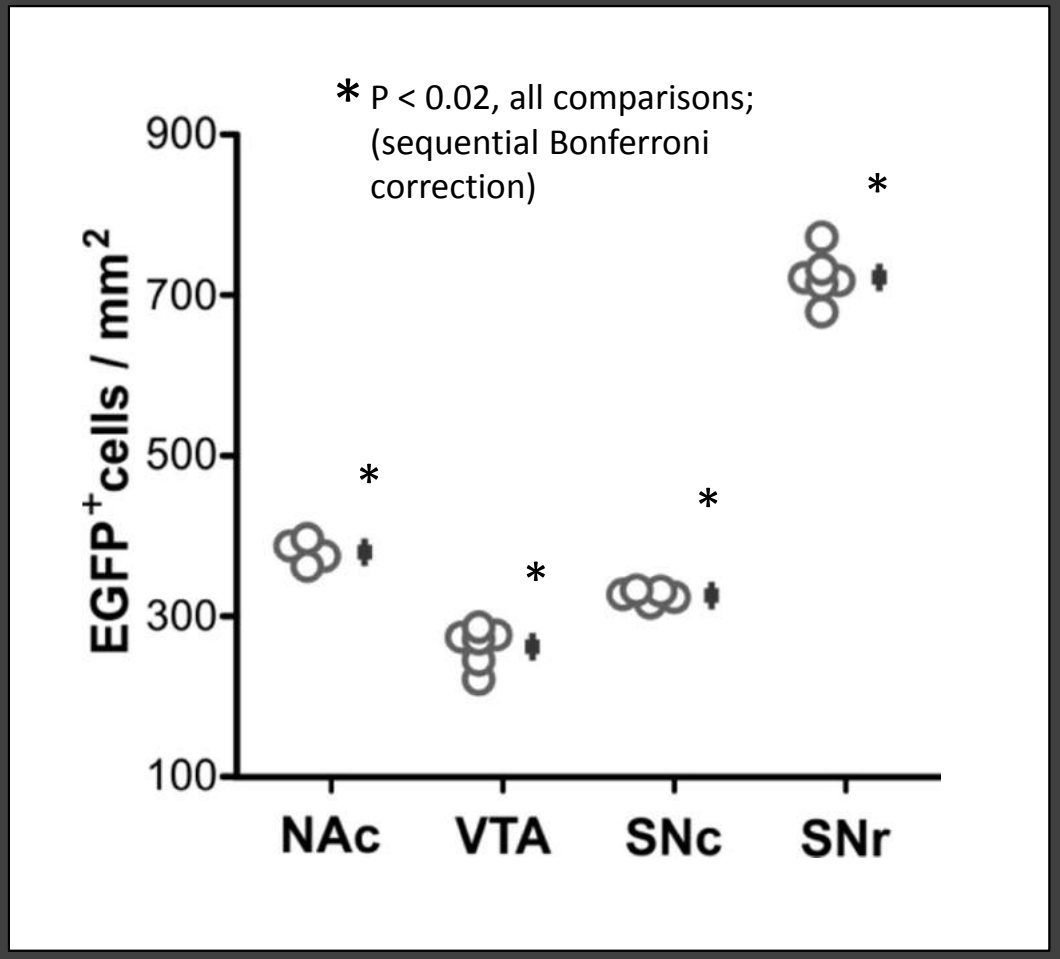




Medial ⟷ Lateral

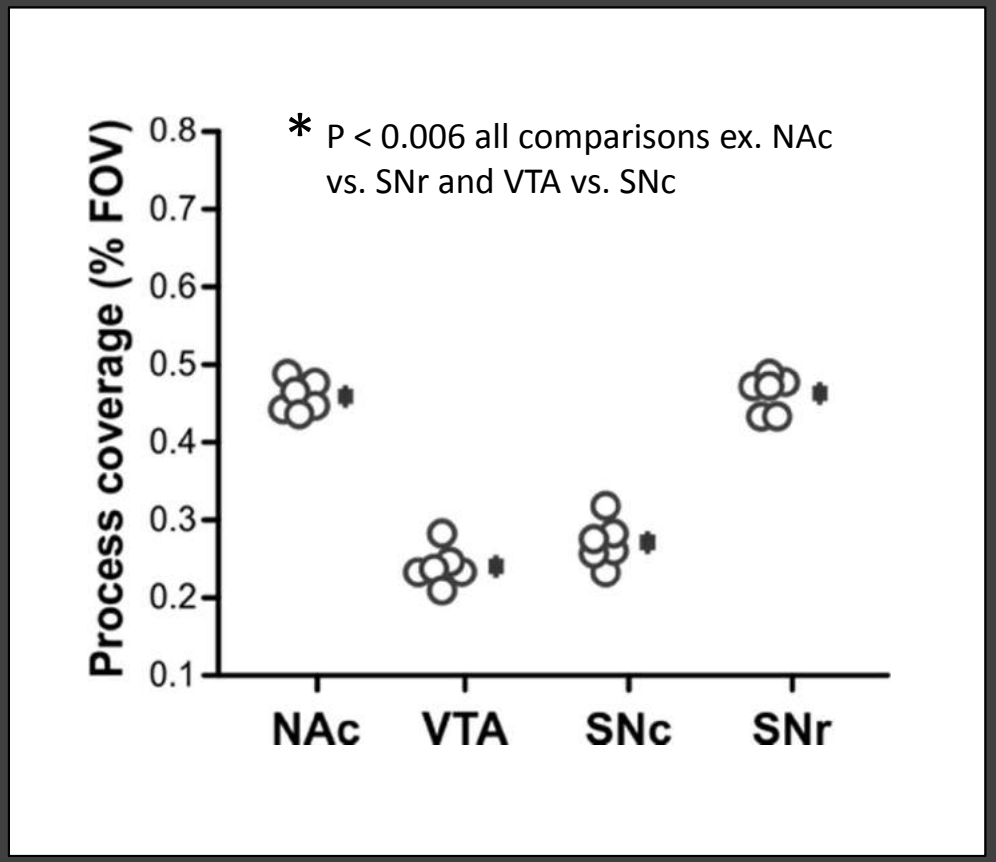
deBiase et al., *under submission*

Density of microglia varies dramatically across BG nuclei



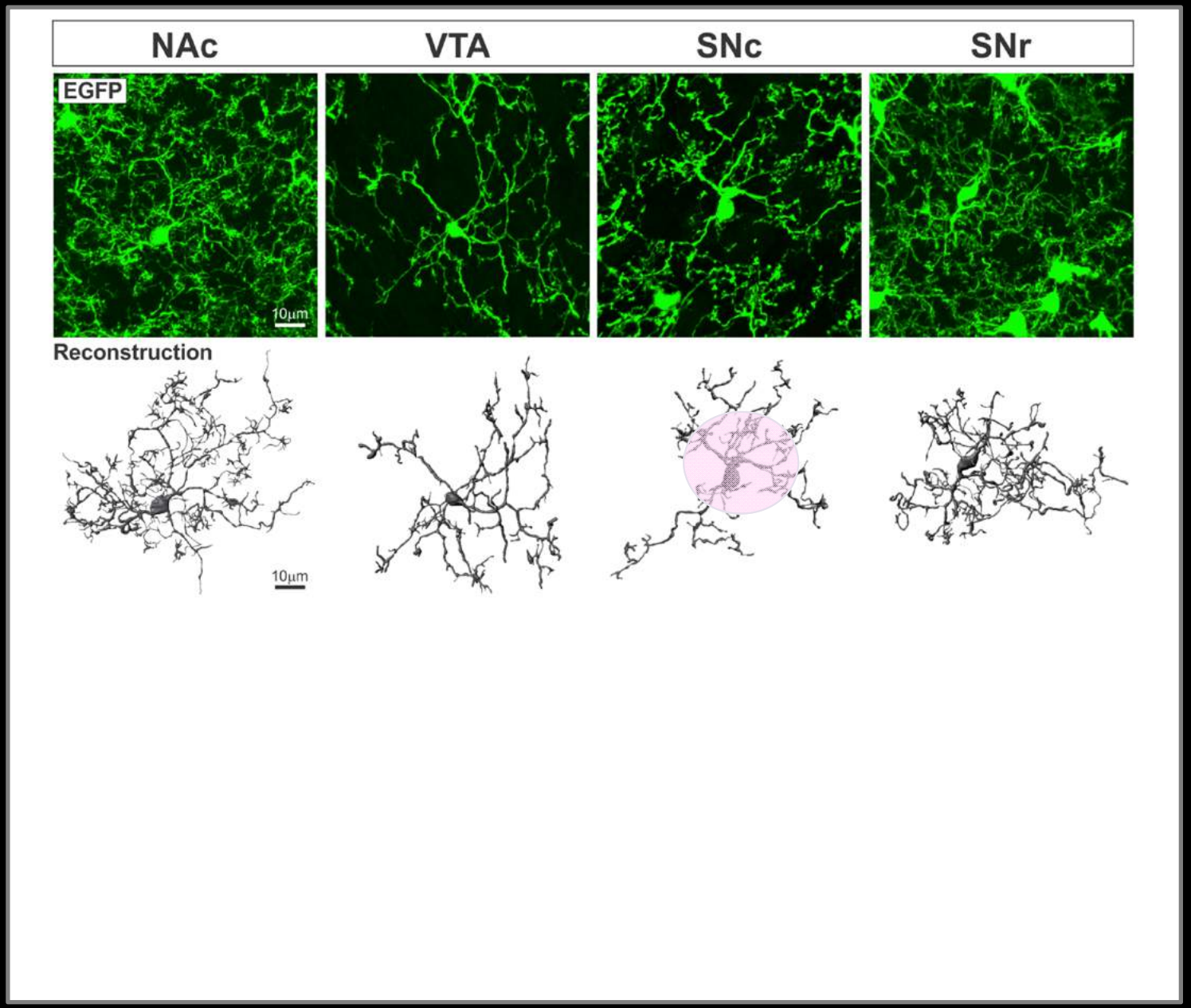
deBiase et al., *under submission*

Morphology of microglia varies dramatically across BG nuclei

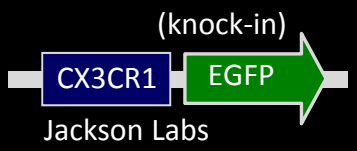


deBiase et al., *under submission*

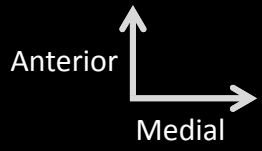
Quantitative analysis of microglial cell morphology



Electrophysiology to probe microglial membrane properties in acute brain slices

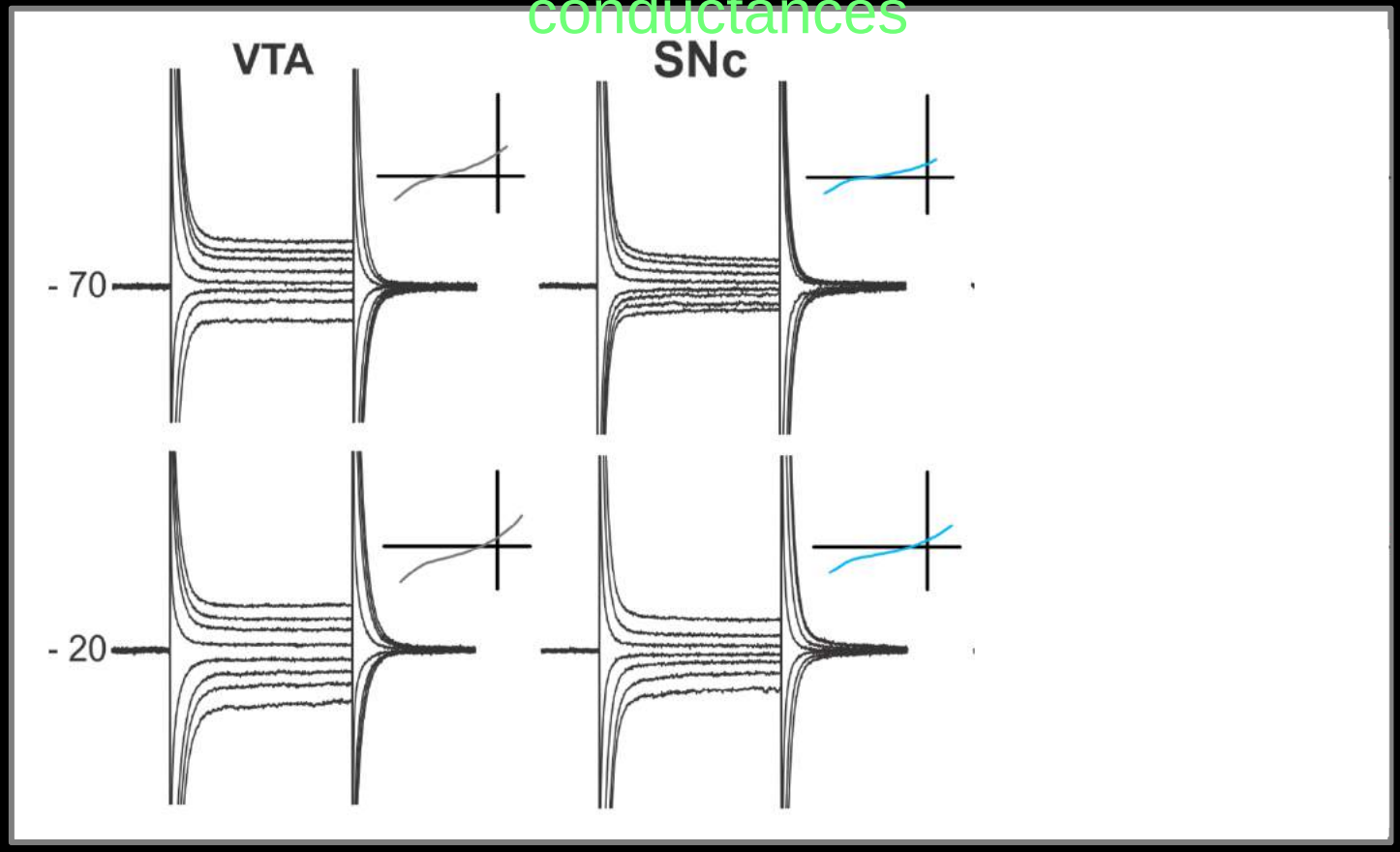


- P35-42
- ♂ and ♀
- Horizontal midbrain section



deBiase et al., *under submission*

SNr microglia express more voltage-activated conductances



10%
(2/21 cells)

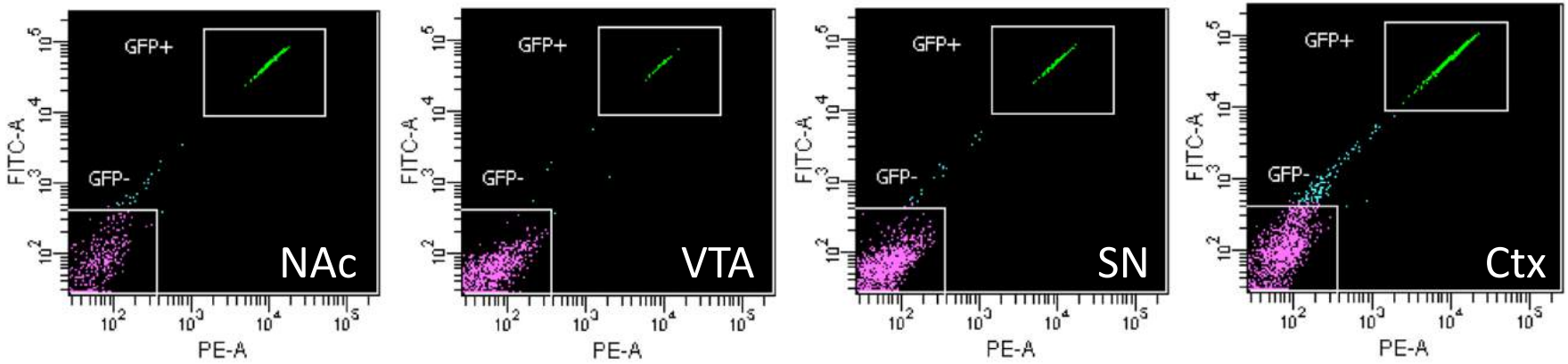
0%
(0/7 cells)

60%
(12/20 cells)

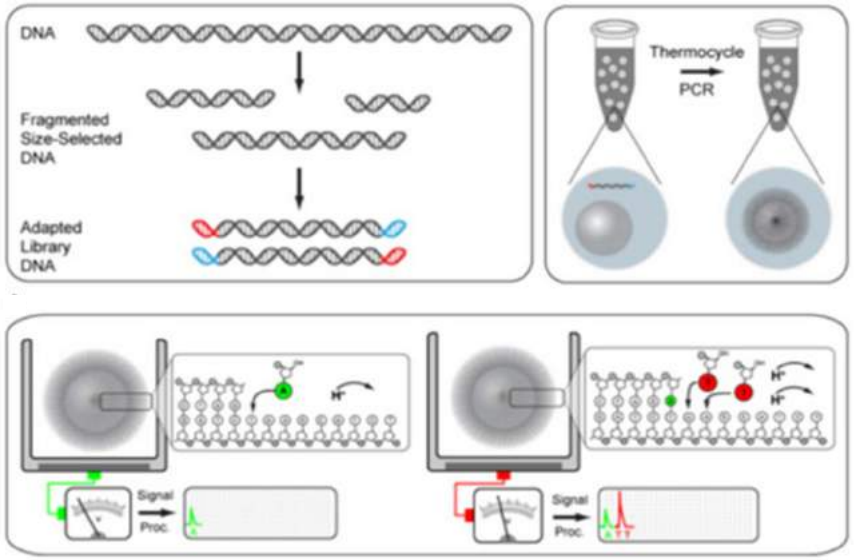
deBiase et al., *under submission*

Analysis of gene expression in microglia

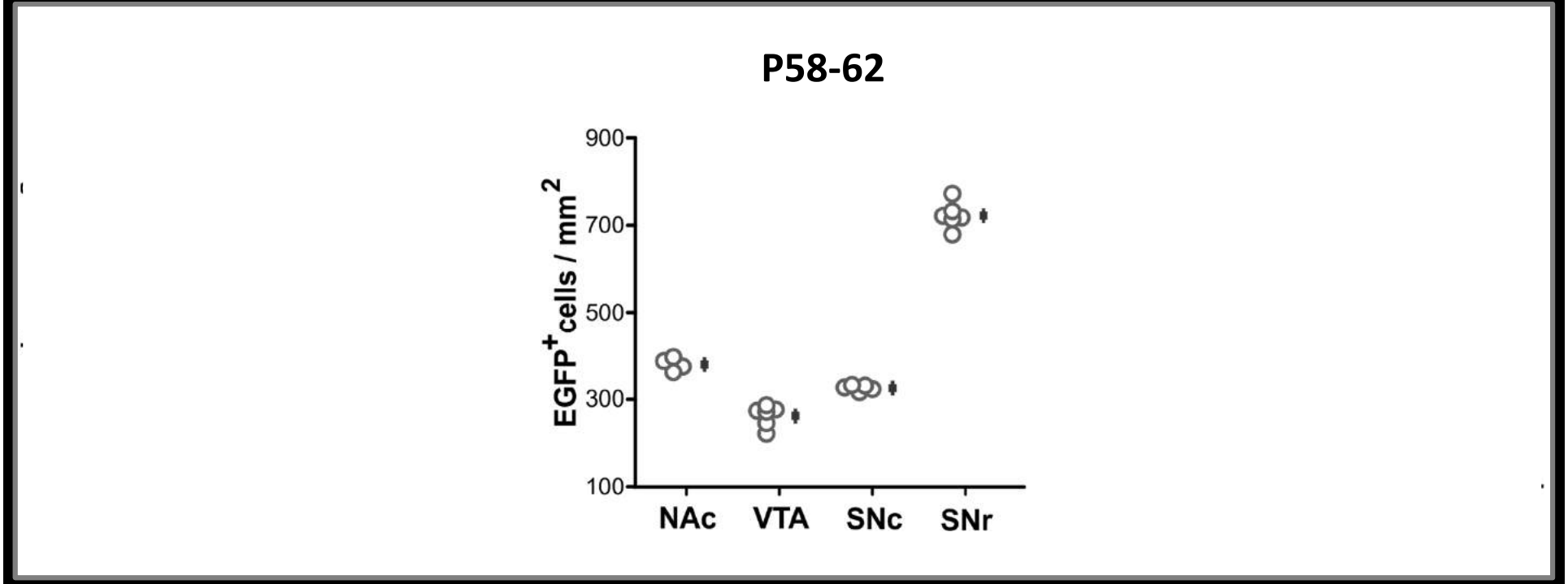
FACS isolation of microglia from specific basal ganglia nuclei



Ion Torrent RNA sequencing
Whole Transcriptome Analysis
(collaboration with NIAAA)

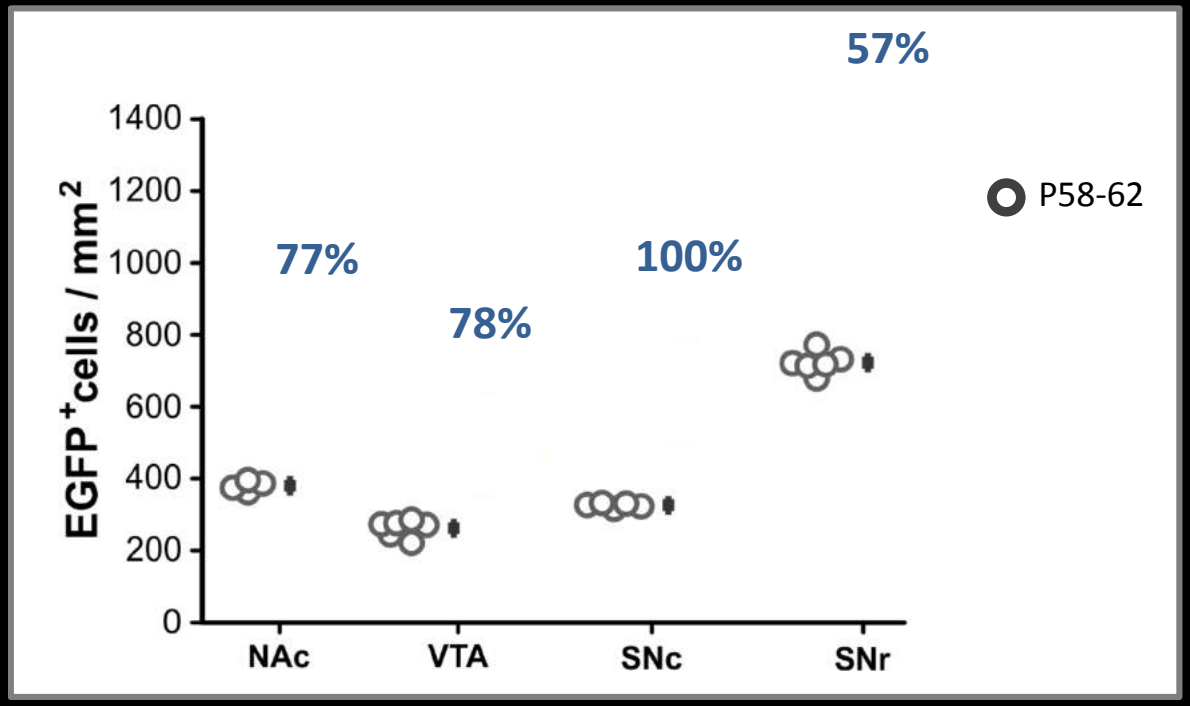


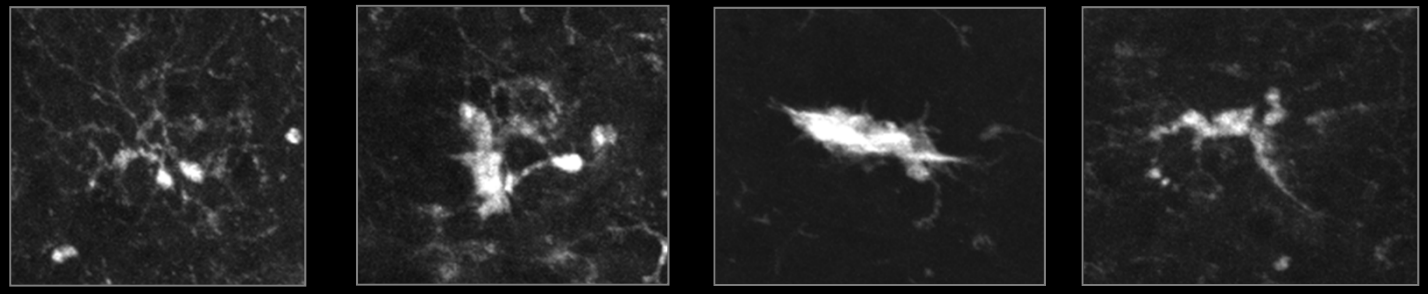
Relative regional differences in microglial cell density are established early in development and persist throughout life



deBiase et al., *under submission*

Microglial responses to aging are not uniform across the BG

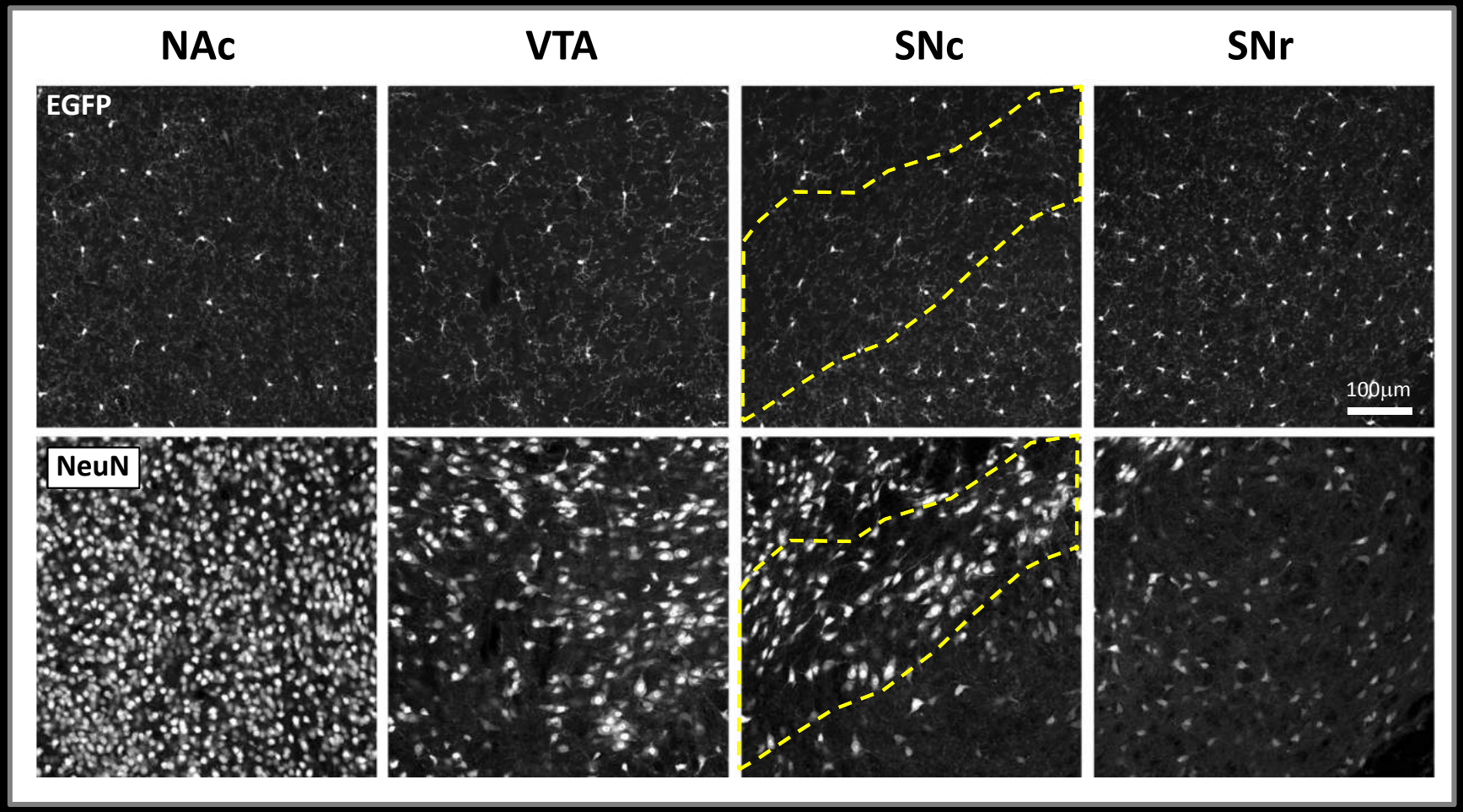




Clustering
Under analysis

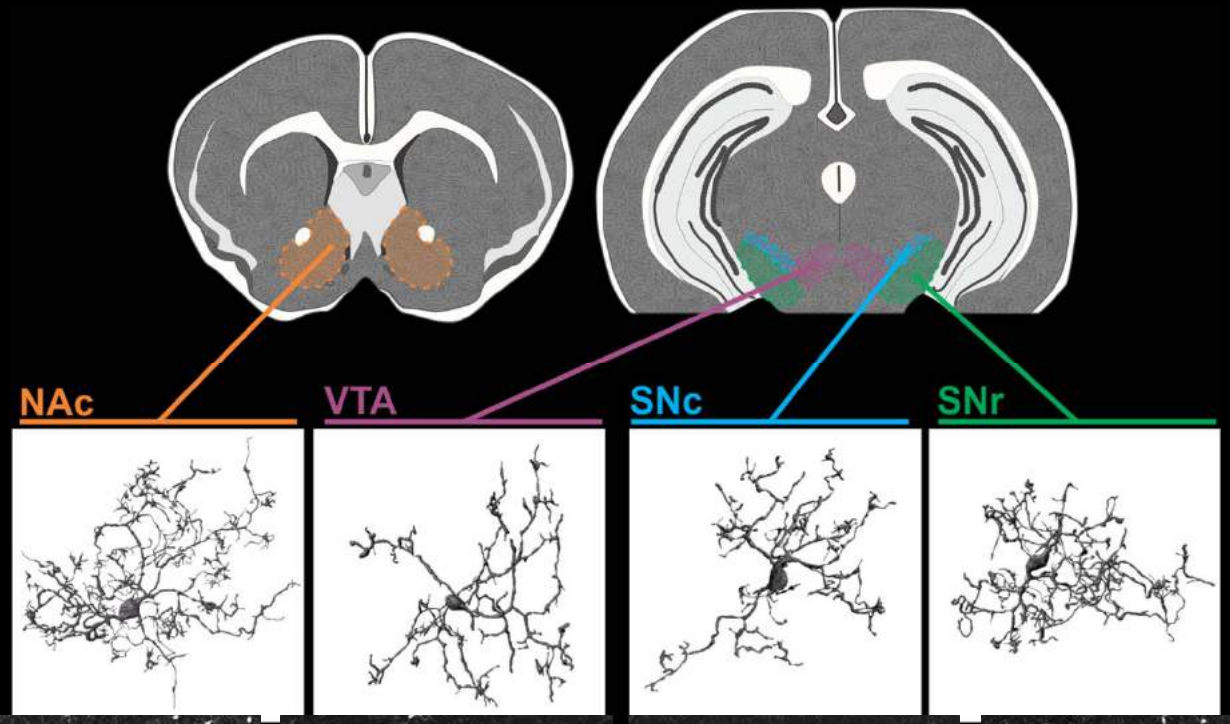
Abnormal morphology (prevalent in midbrain)
A biomarker for aging?

Microglial cell density is not correlated with neuronal density

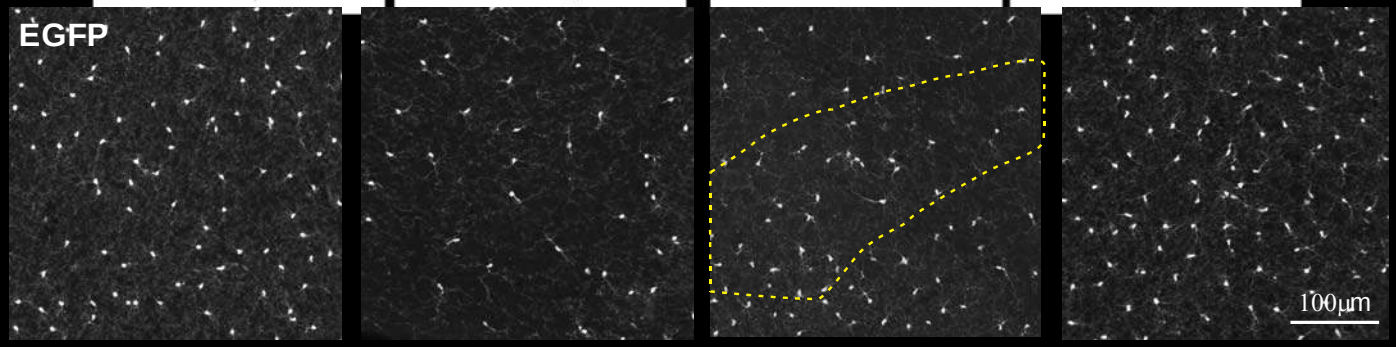


deBiase et al., *under submission*

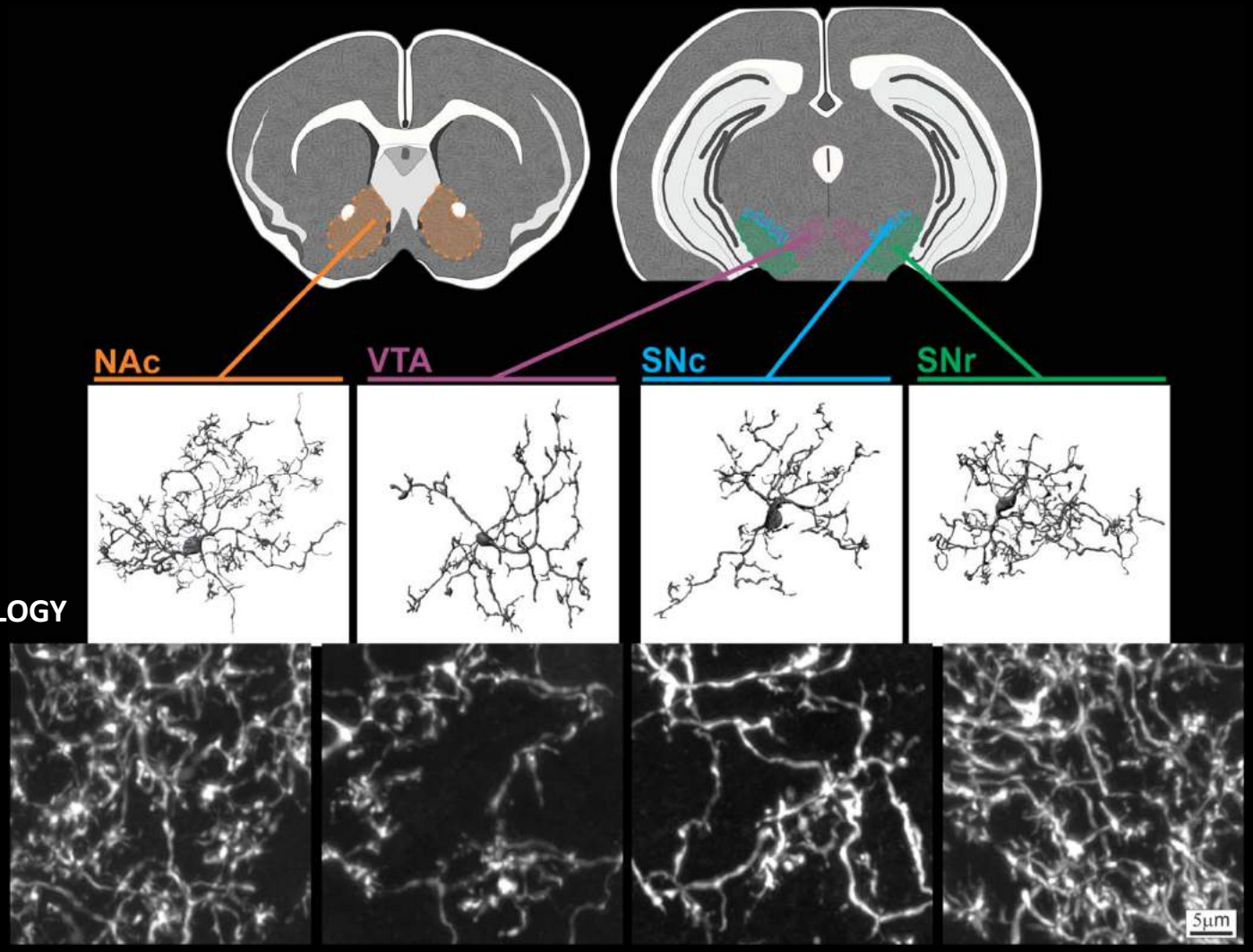
SUMMARY: Distinct microglial phenotypes across the basal ganglia



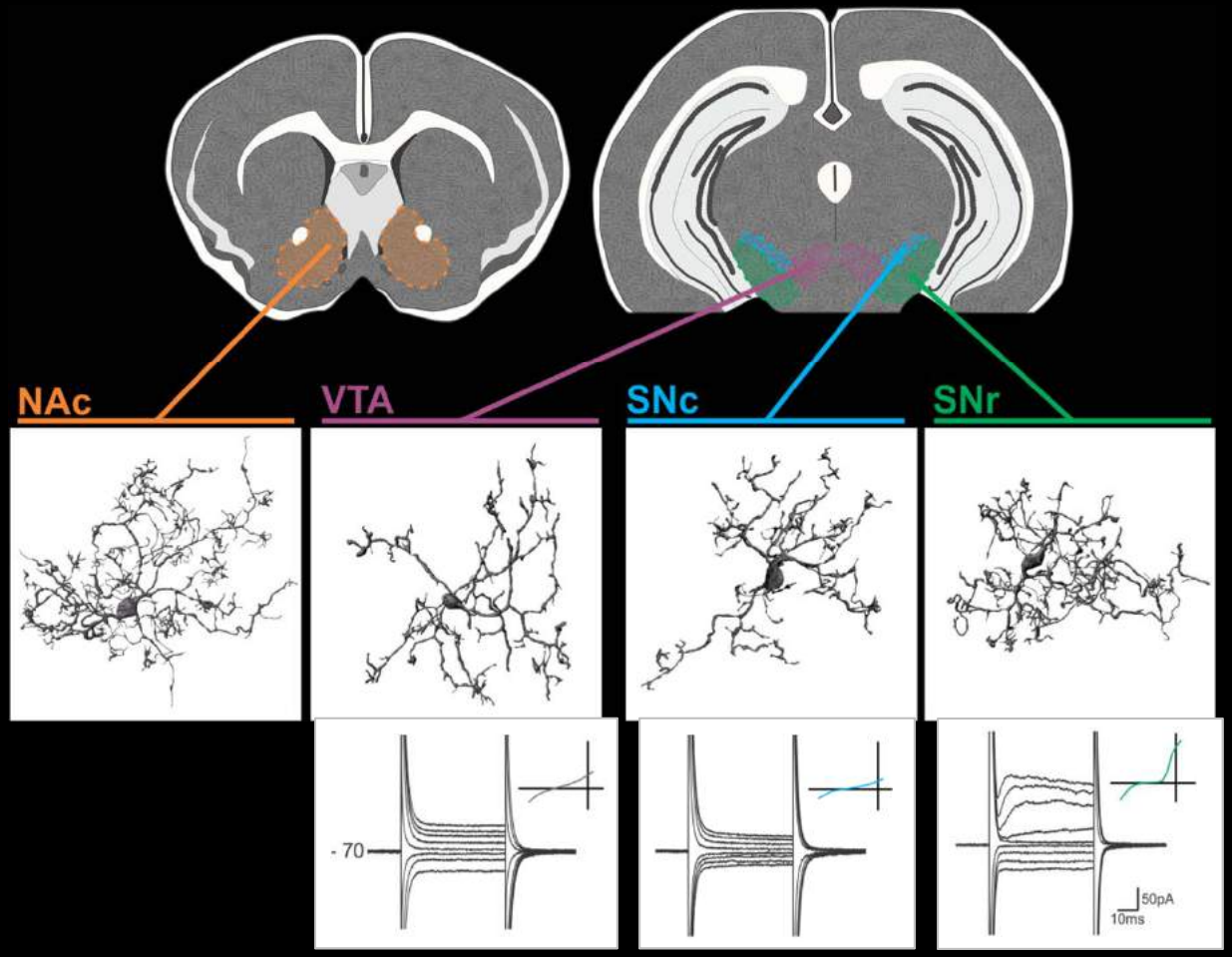
DENSITY



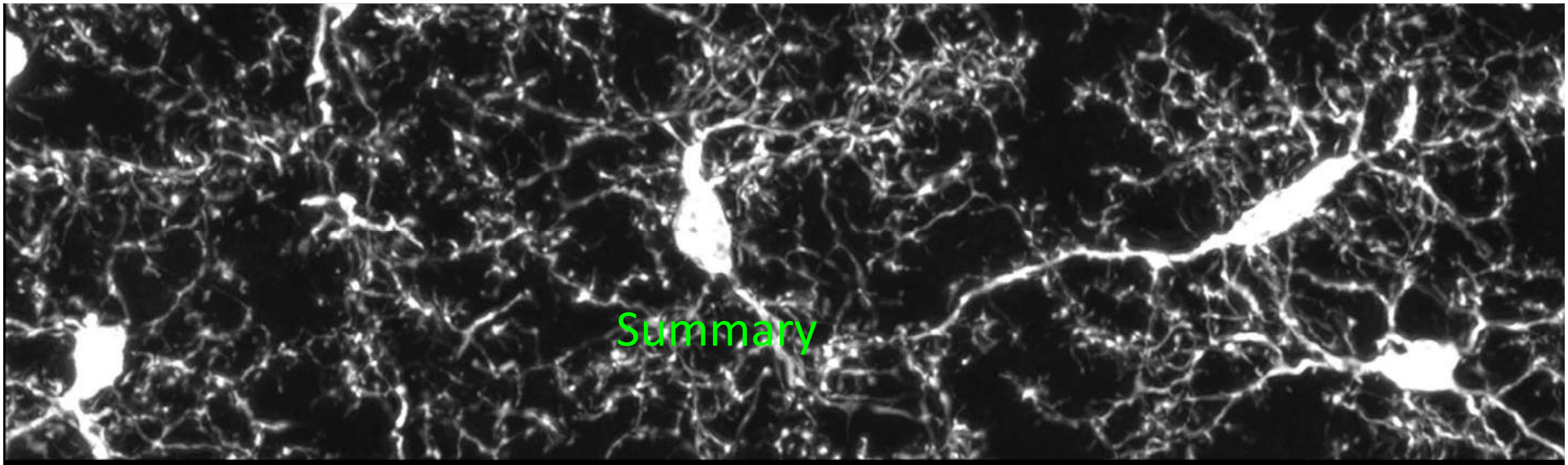
SUMMARY: Distinct microglial phenotypes across the basal ganglia



SUMMARY: Distinct microglial phenotypes across the basal ganglia



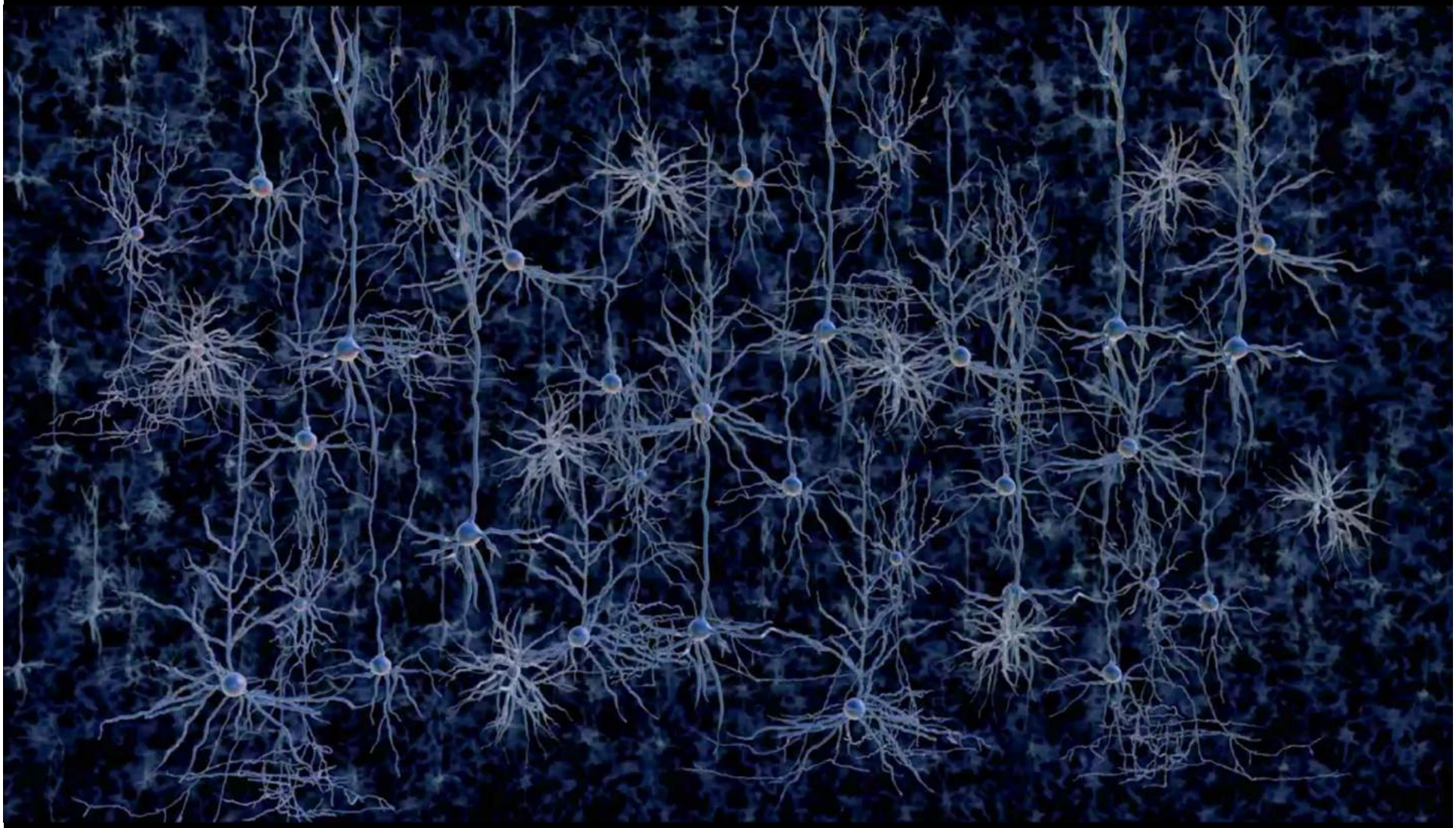
MEMBRANE PROPERTIES



- Microglia within the BG exhibit regionally specific phenotypes and may possess differential capacity to respond to CNS insults

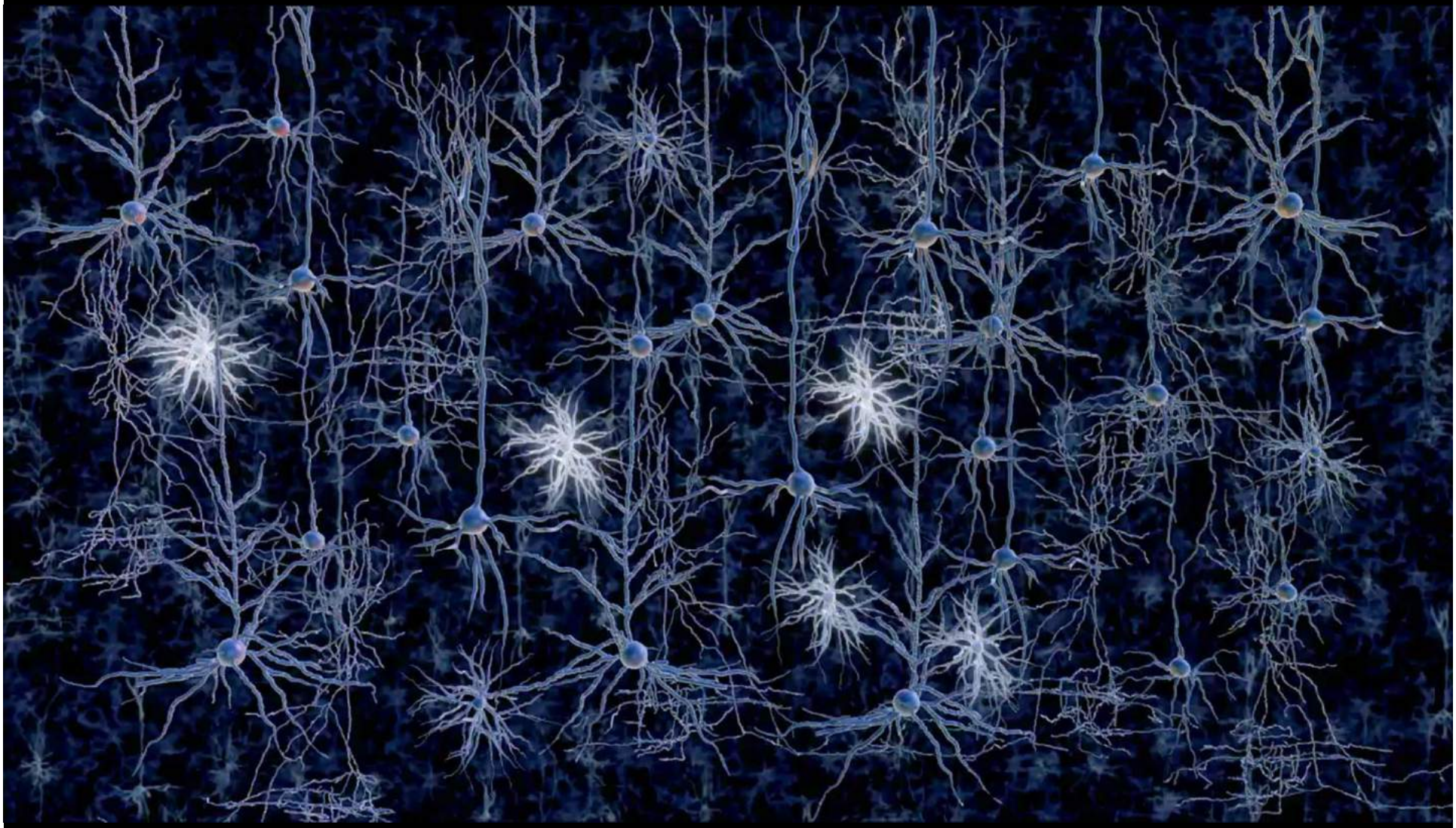
- Foundation for defining how microglia impact synaptic transmission and synaptic plasticity within the BG / reward circuitry in both physiological and pathological contexts (substance abuse, stress-dependent behaviors, psychiatric diseases, neurodegeneration)

Part III: from optogenetic studies to a treatment against cocaine craving



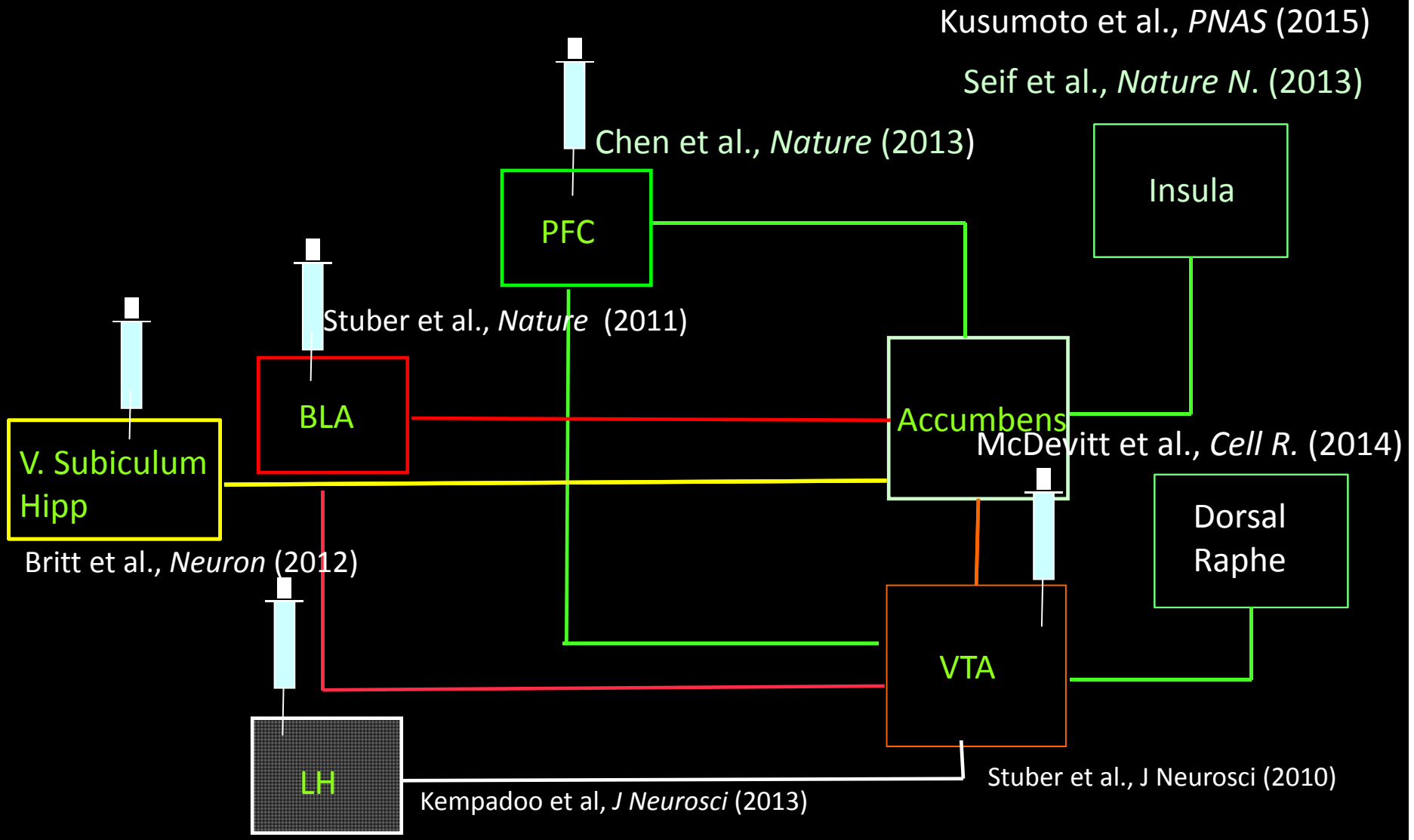
Courtesy of Ed Boyden, MIT

Optogenetics can be also used to silence neurons



Courtesy of Ed Boyden, MIT

Part II: from optogenetic studies to a treatment against cocaine craving



An optogenetic study inspired by human studies based on the broad concept of "hypofrontality" on cocaine abusers

Billy T. Chen

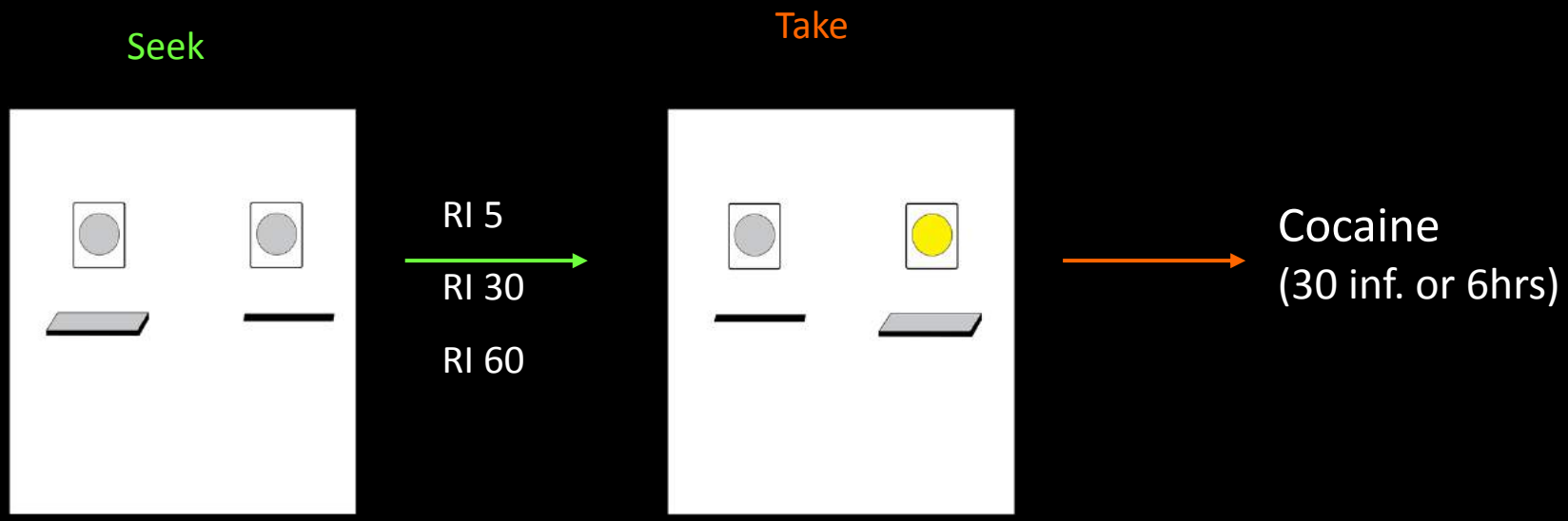
PFC

Decision making processes
Evaluation of expected outcome
Inhibitory control

Self-administration paradigm

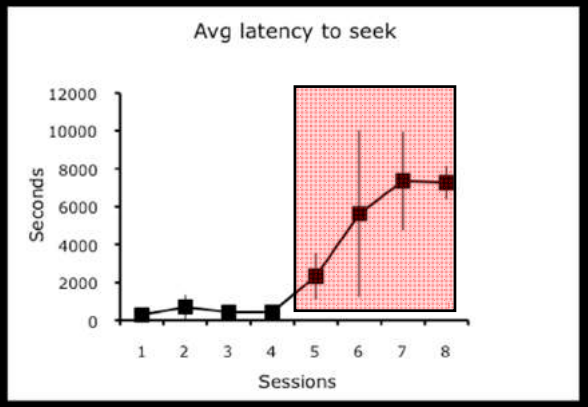
1. Rats are trained to self-administer cocaine on a seek-take chain schedule (about 2 months) *with progressively longer Random Intervals.*

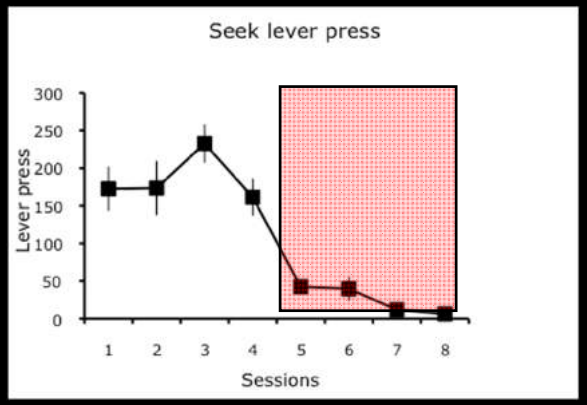
2. At the very end of training, rats receive 4 sessions of non-contingent foot shock in 30% of trials

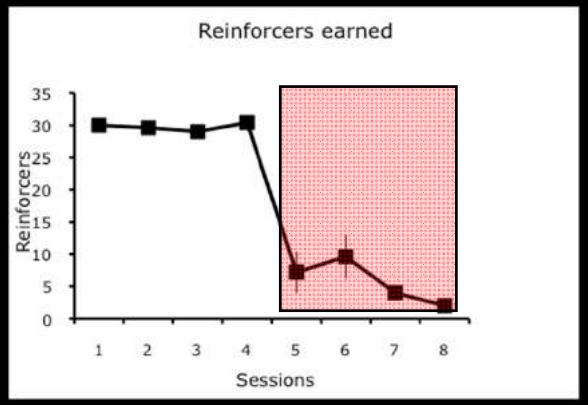


1. Rats are divided into non-compulsive and compulsive groups

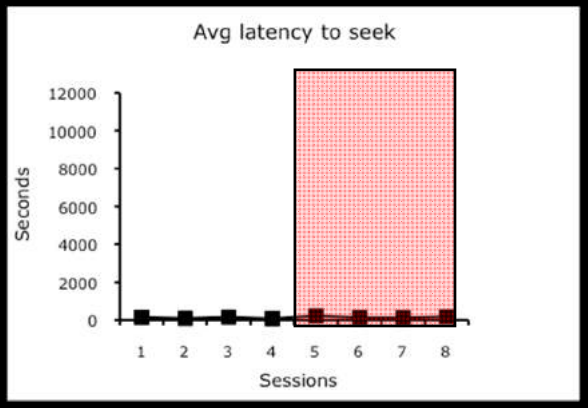
shock sensitive

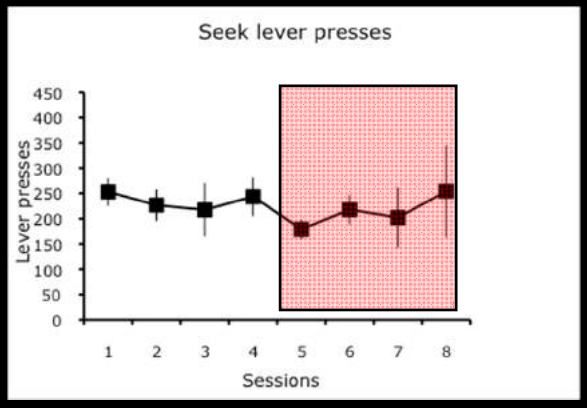


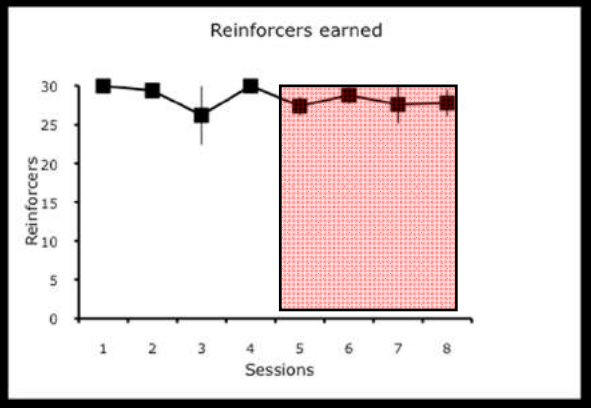




Shock-resistant

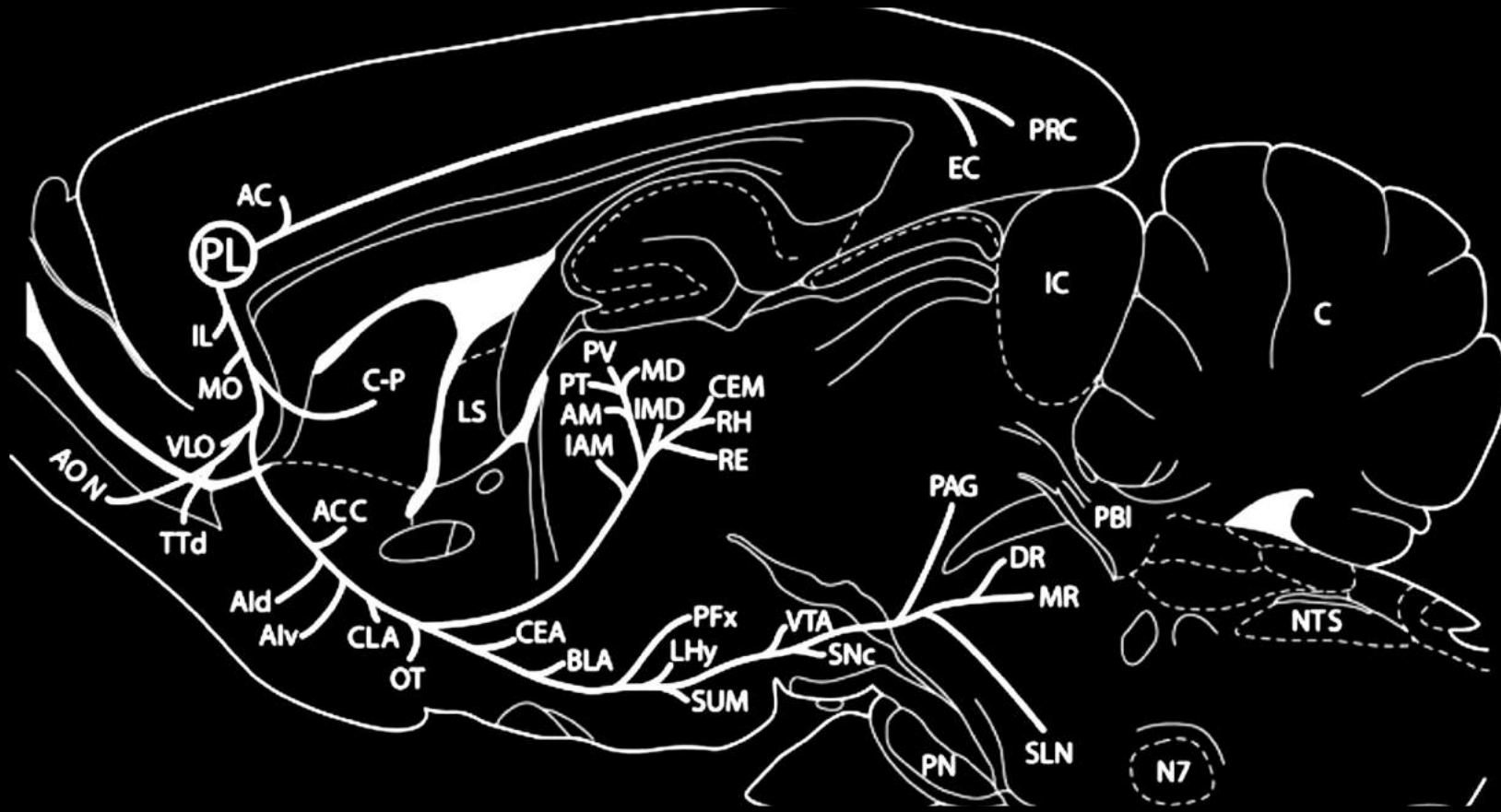






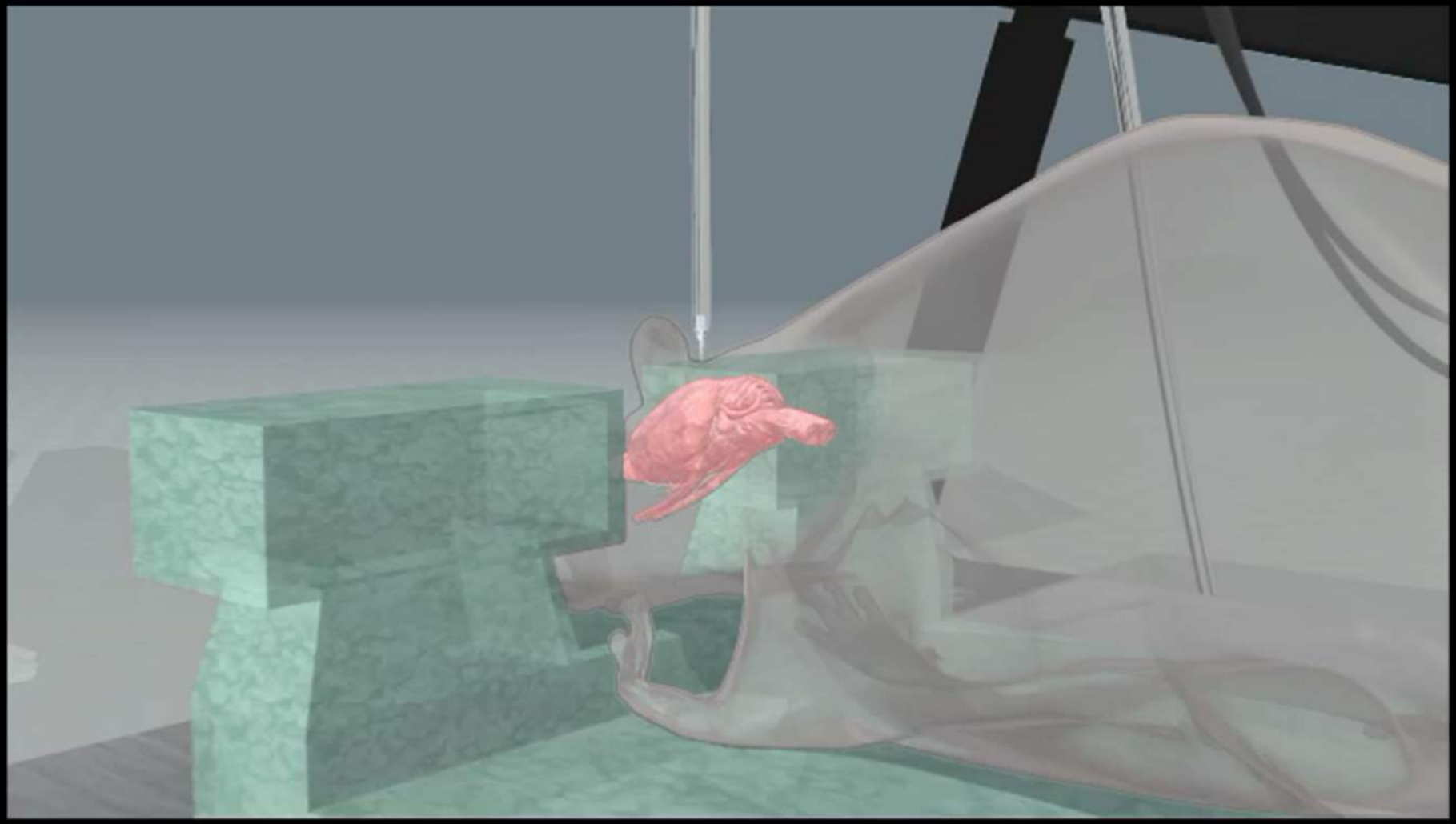
Chen et al., Nature (2013)

The prelimbic cortex is involved in many physiological functions,
including decision making processes



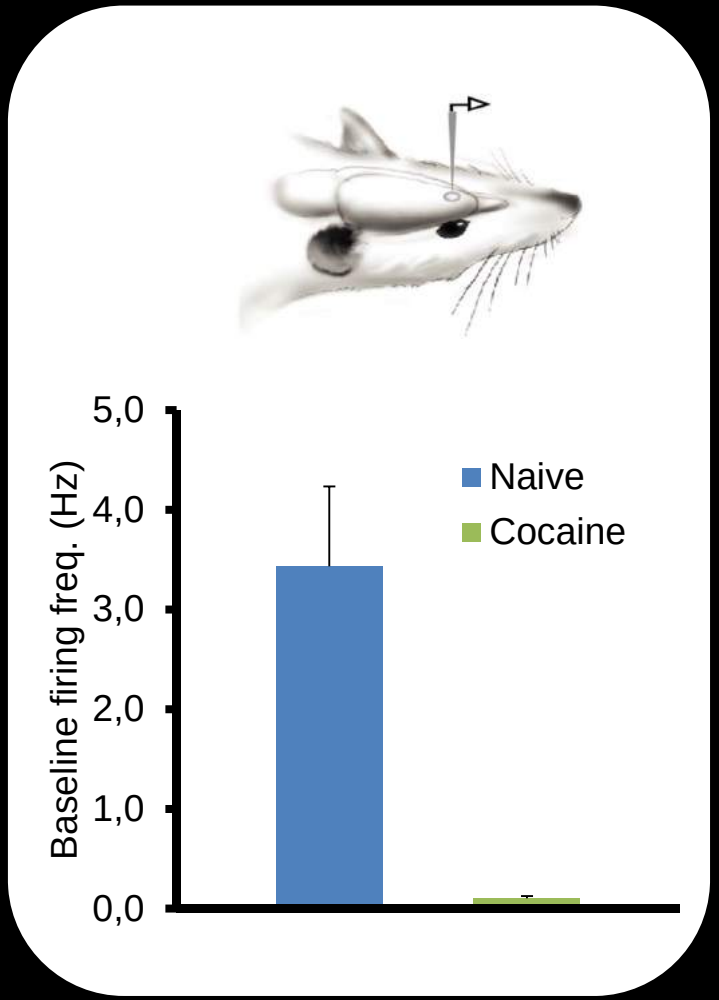
Adapted from Vertes, Neuroscience 2006; 142 1-20)

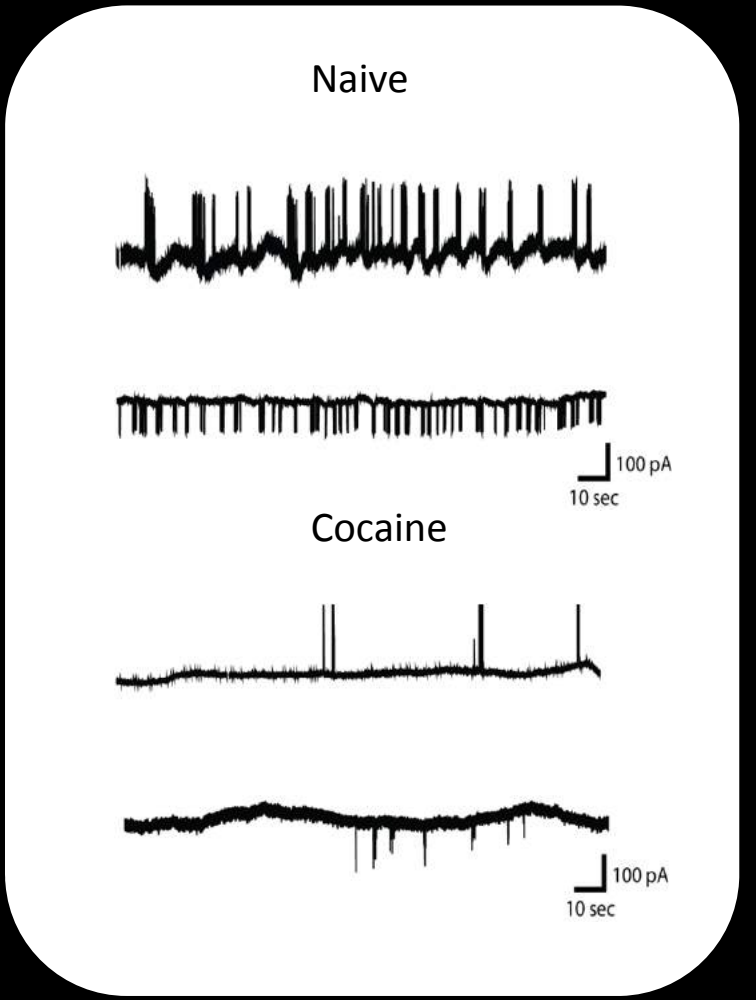
In vivo Patch-Clamp recordings in the prelimbic cortex



Courtesy of Ed Boyden, MIT

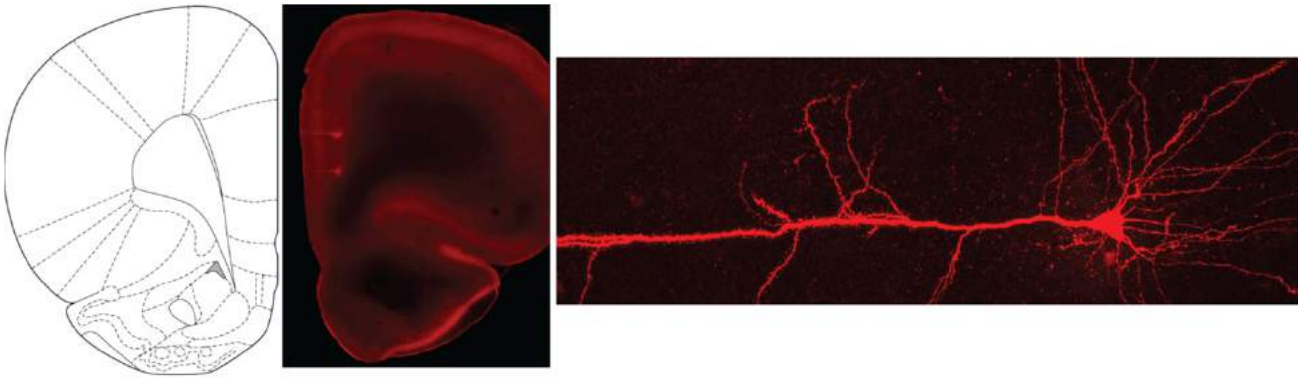
Hypoactivity in prelimbic PFC neurons after long-access cocaine self-administration





Thanks to Rob Froemke, NYU

Long-access to cocaine decreases excitability of deep-layer prelimbic neurons



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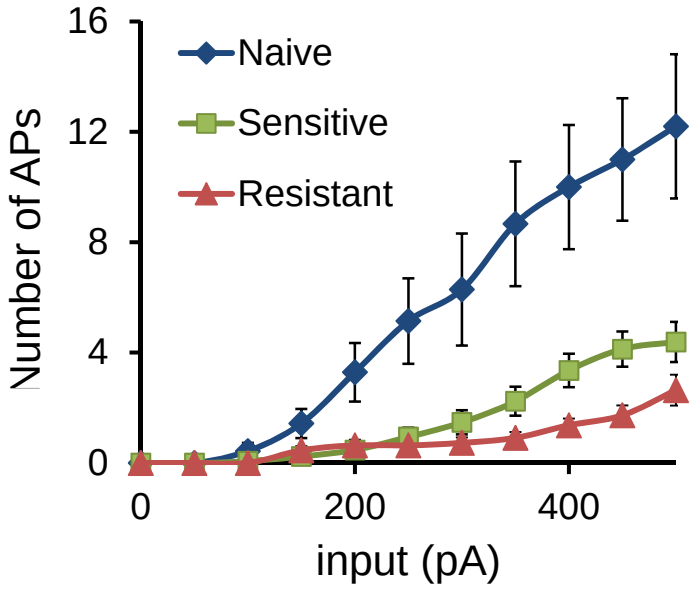


Chen et al., Nature (2013)

Hypothesis:

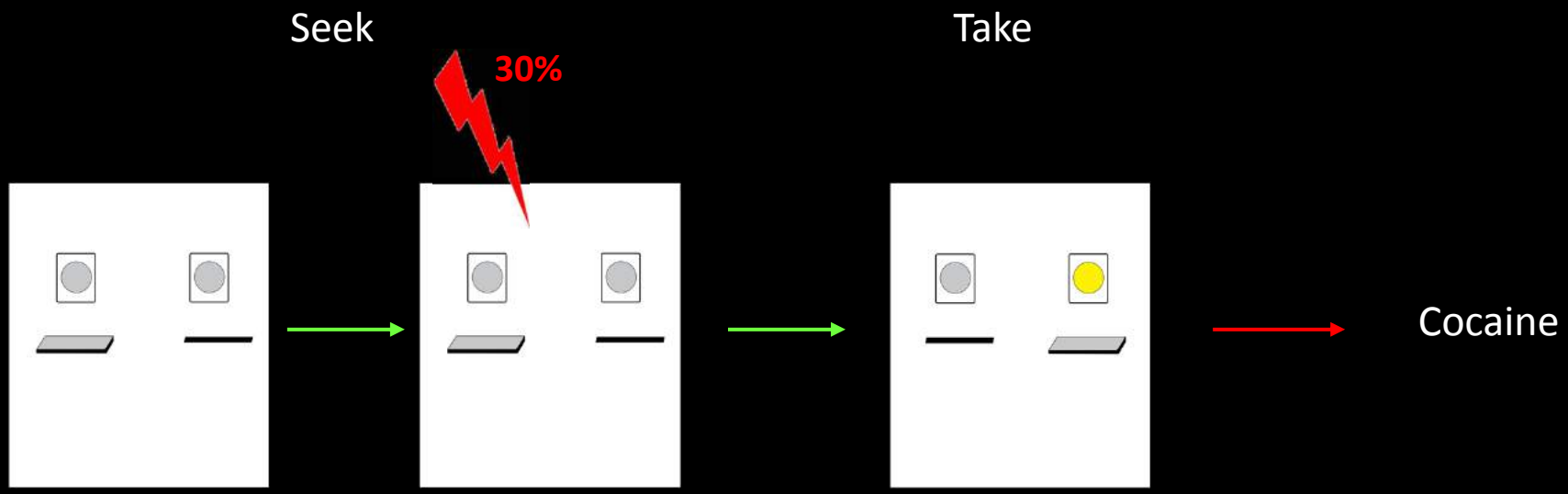
If hypoactivity of the prelimbic cortex is causally linked with cocaine seeking, then

Optogenetic activation of the prelimbic area should reduce cocaine seeking

Laser stimulation procedure

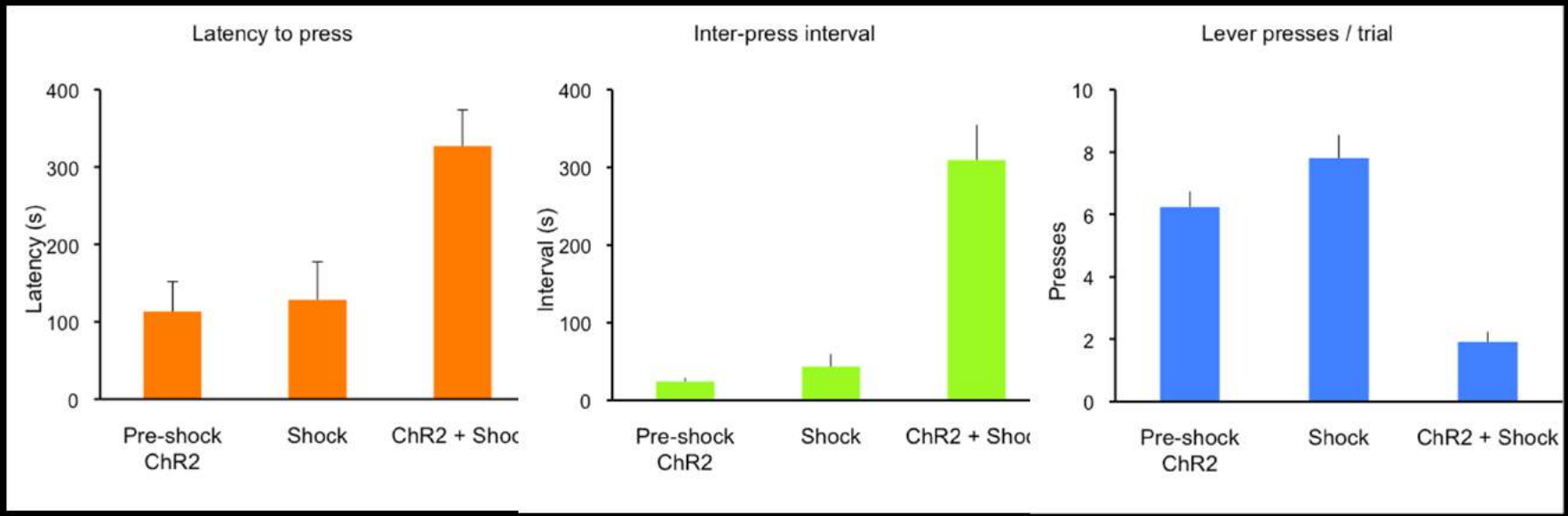
- 4 days of “shock” training

- On day 5, ChR stimulationin the PLCx (@1 Hz) throughout the seek period



Chen et al., Nature (2013)

Prelimbic photostimulation decreases compulsive cocaine seeking only *after* Shock sessions



Chen et al., Nature (2013)

Summary

- ~30% of rats will self-administer cocaine despite negative consequences (SR rats).
- Neurons in the prelimbic region of the PFC are significantly hypoactive active after prolonged cocaine self-administration, with shock resistant rats being the least active.
- Activation of prelimbic neurons via optogenetic decreases cocaine seeking and taking behavior in shock resistant rats
- Inhibition of prelimbic neurons via optogenetics in shock sensitve rats triggers cocaine seeking during shock sessions
- Therapeutic applications testable, immediately