Science

AAAS

Sexually dimorphic (二态) dopaminergic circuits determine sex preference

Published: 10 Jan 2025

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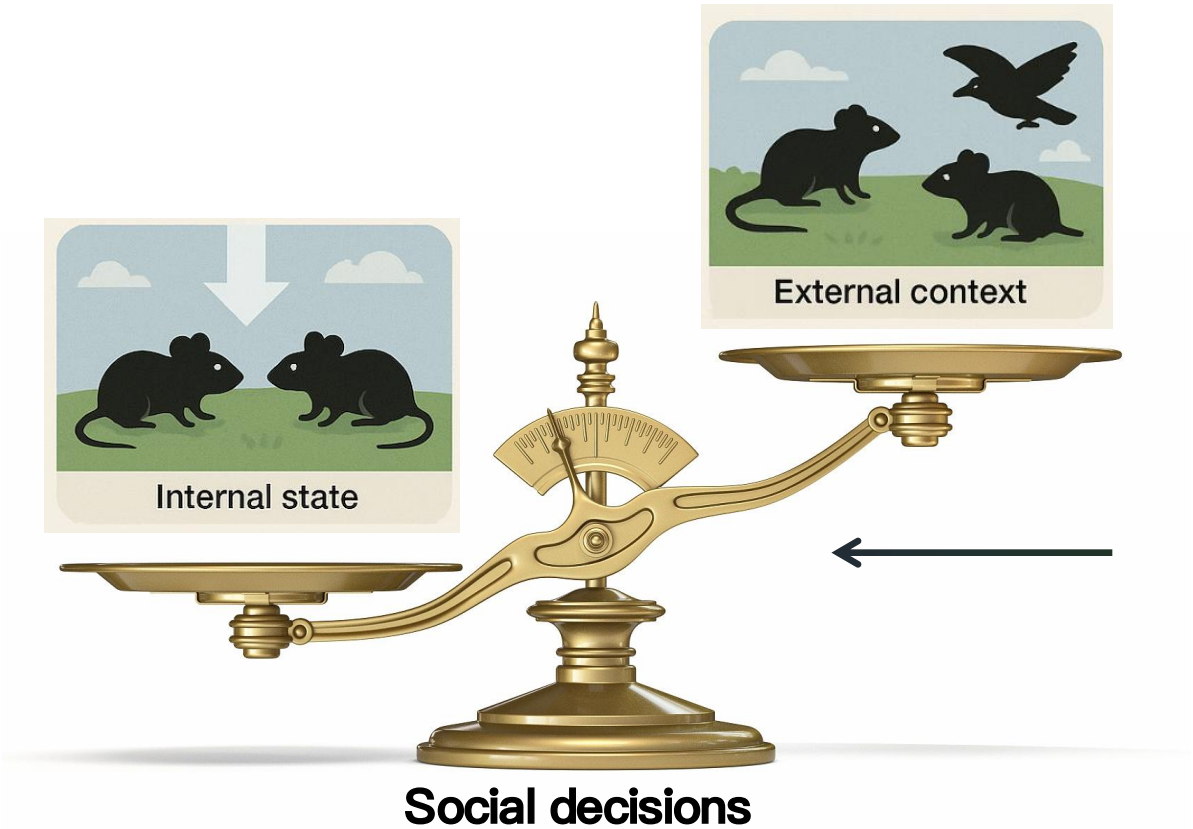
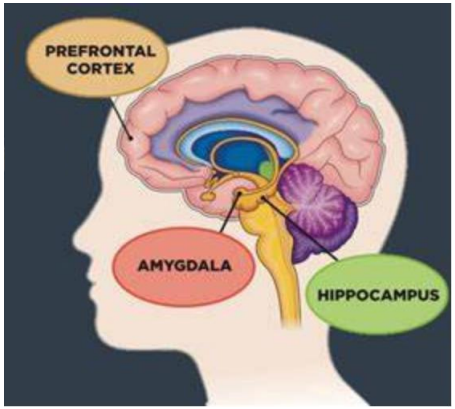
Introduction

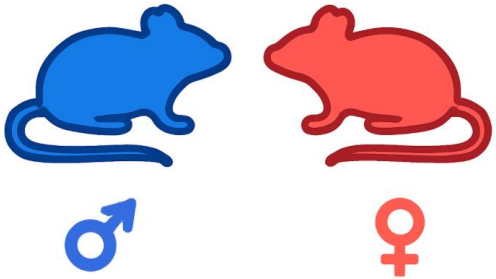
Social decisions



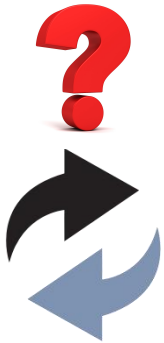


Selection of social partners

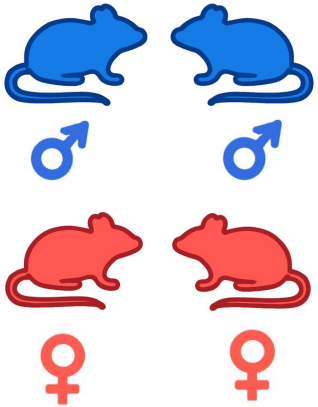
Interact with opposite sex



- Innate requirements of mating and reproduction



Interact with same sex



- Provides social support
- Facilitates collaboration for shared goals

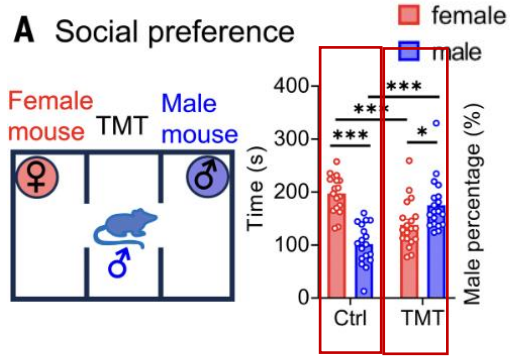
Q1. Under natural conditions, what is the typical sex preference? Does sex preference differ between male and female?

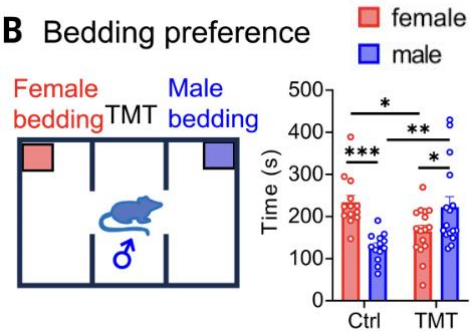
Q2. Does this gender preference shift in response to external disturbances?

Sex preference changes under survival threat

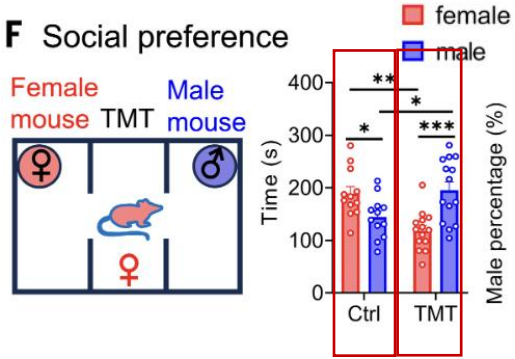
TMT: Gases with the smell of predators (捕食者).

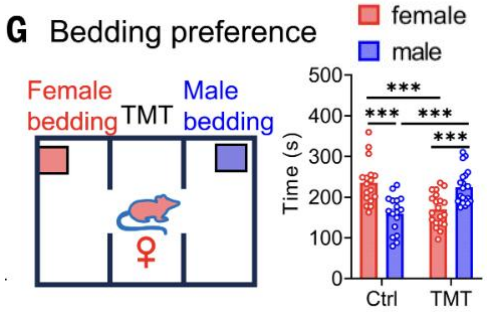
For Male Mice





For Female Mice

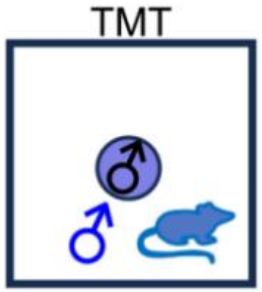


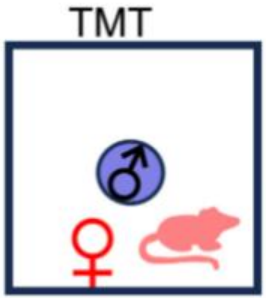


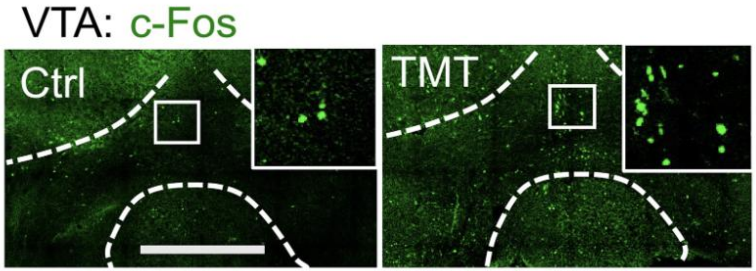
- **Sex preferences of both male and female mice *prefer* :**
  - **female (under natural conditions)**
- **Sex preferences of both male and female mice *changed* :**
  - **from female to male (under survival threat)**

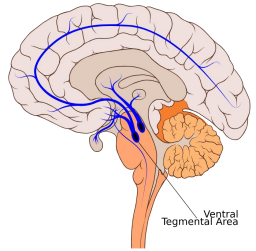
What neural mechanisms drive this change in sex preference?

VTA^{DA} neuron is essential for the switching of sociosexual preference



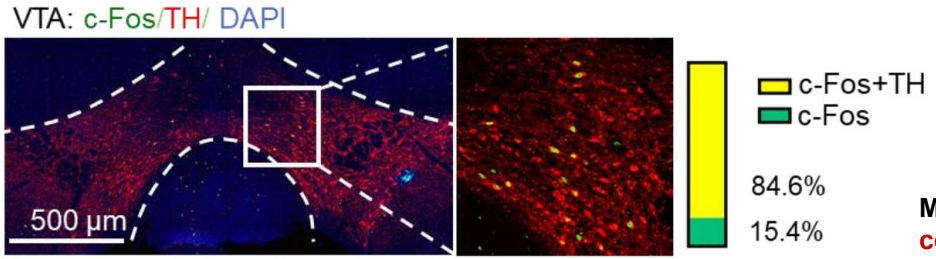






腹侧被盖区
(Ventral tegmental area, VTA)

Increased neural activity in VTA region



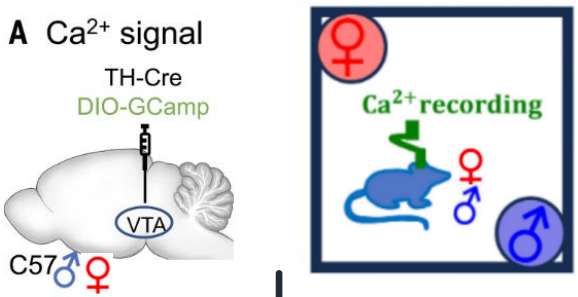
Most c-Fos positive neurons colocalized with TH

TH (tyrosine hydroxylase): specific marker for dopamine (DA, 多巴胺) neurons

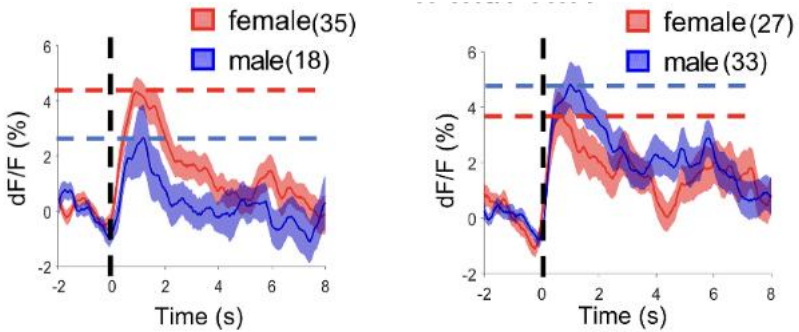
DA neurons in the VTA region (VTA^{DA}) exhibit significant changes in neural activity when TMT treatment is applied

VTA^{DA} neuron is essential for the switching of sociosexual preference

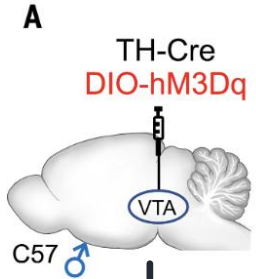
VTA^{DA} neuron activity detection



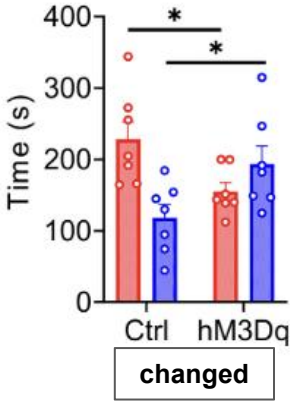
Without TMT → **With TMT**



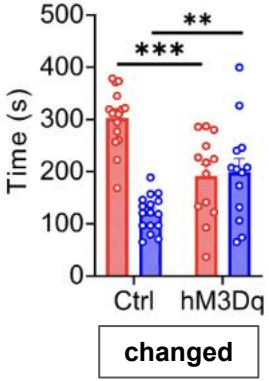
VTA^{DA} neuron activation



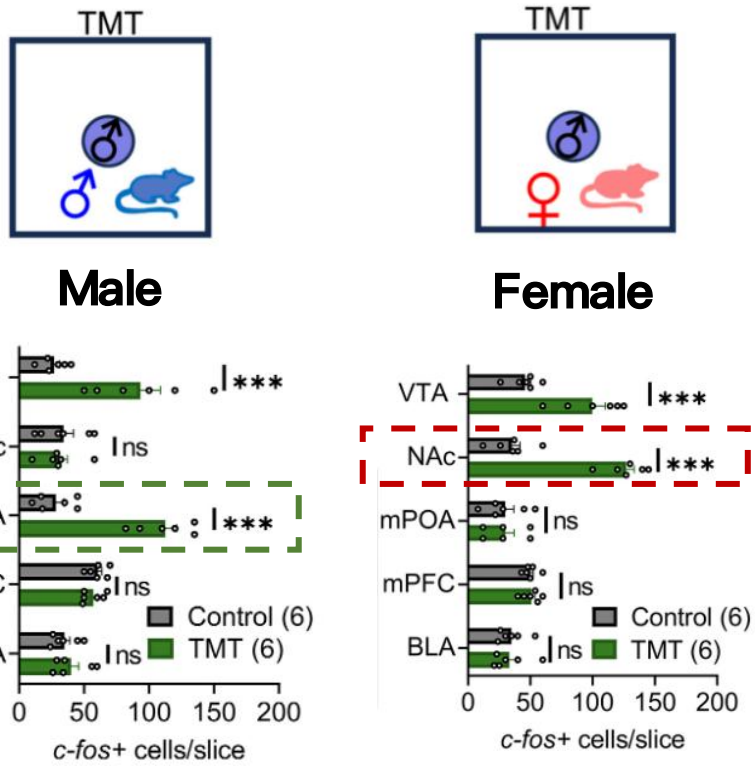
Social preference



Bedding preference



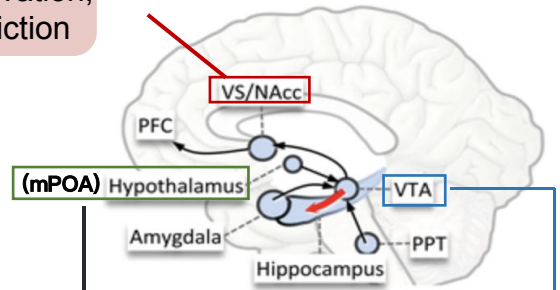
Neuron activity in VTA^{DA} downstream regions



DA pathways may be differentially involved in sociosexual preference modulation.

Reward,
Motivation,
Addiction

VTA^{DA} pathway



Hormonal regulation,
Hunger,
Sex behavior

Origin of the dopamine (DA) reward system

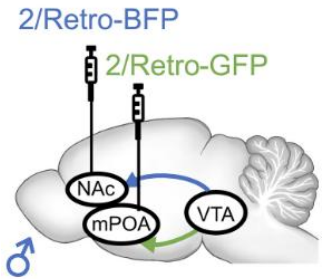
Dopamine (DA) pathway

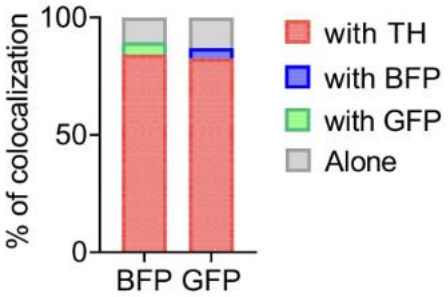
- Reward processing
- Social behaviour regulation

How the VTADA-NAc and VTADA-mPOA pathways are involved in Male Mice social interaction?

Male Mice

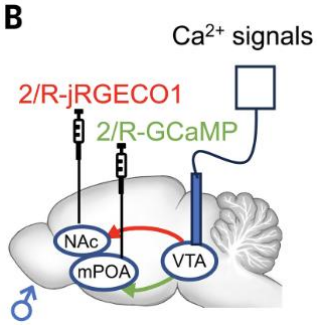
Double retrograde-virus tracing





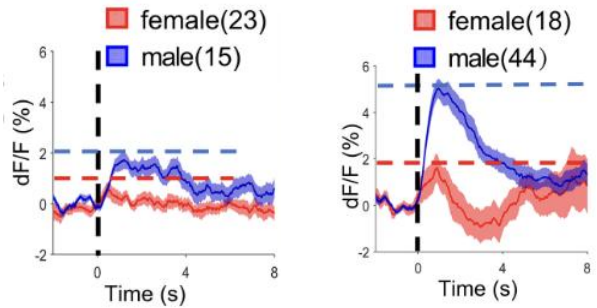
NAc- and mPOA-projecting VTA^{DA} neurons represent distinct populations

Dual-color fiber photometry



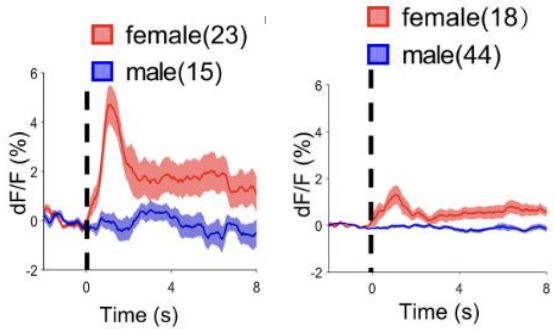
Without TMT **With TMT**

VTA^{DA}→mPOA



Male Preference

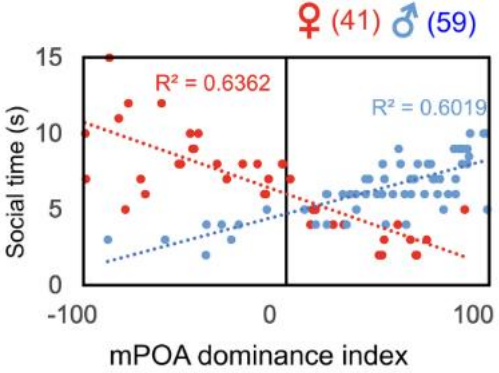
VTA^{DA}→NAc



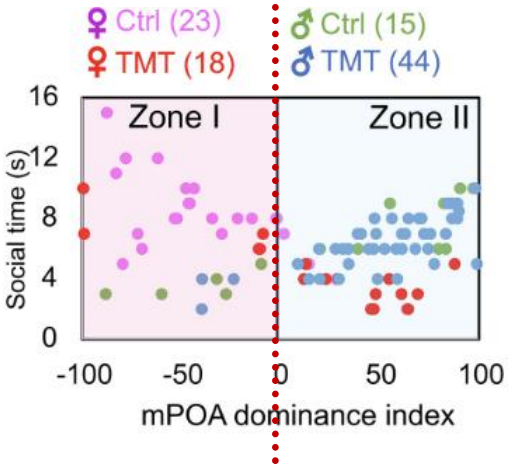
Female Preference

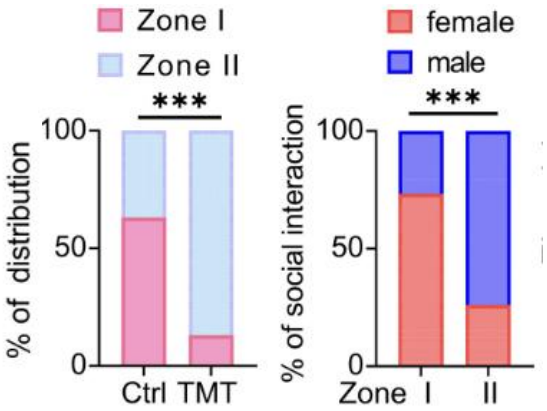
Balance between the VTADA-mPOA and VTADA-NAc projections

Male Mice



$F_{mPOA} = F_{NAc}$





Positively correlated with male interaction

Negatively correlated with female interaction

Zone I: NAc dominant region
Zone II: mPOA dominant region

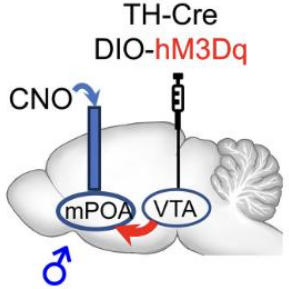
mPOA dominance index

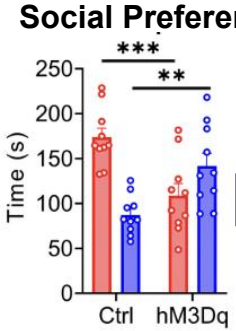
$$D = (F_{\mathrm{mPOA}} - F_{\mathrm{NAc}})/(F_{\mathrm{mPOA}} + F_{\mathrm{NAc}}) \times 100\%$$

Balance between the VTADA-mPOA and VTADA-NAc projections

Male Mice

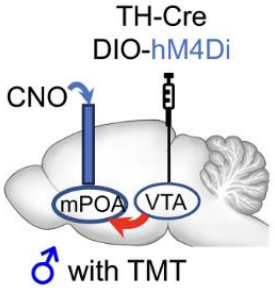
$VTA^{DA} \rightarrow mPOA$

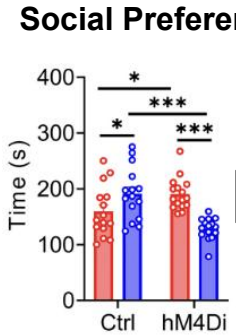




changed

mPOA activation

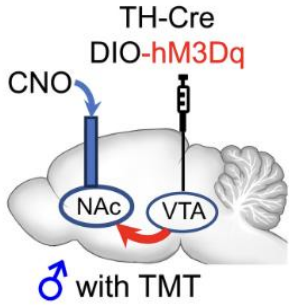


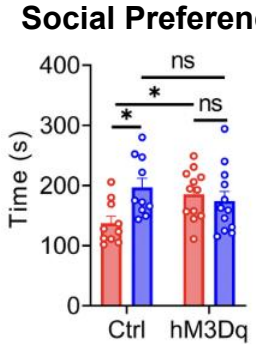


changed

mPOA inhibition

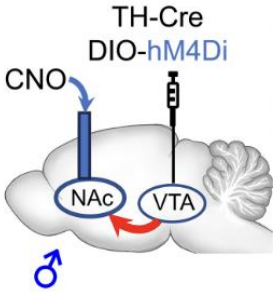
$VTA^{DA} \rightarrow NAc$

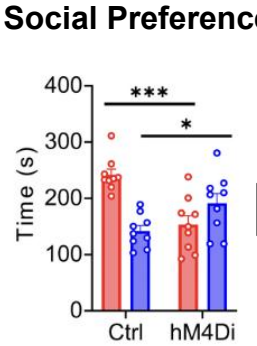




changed

NAc activation





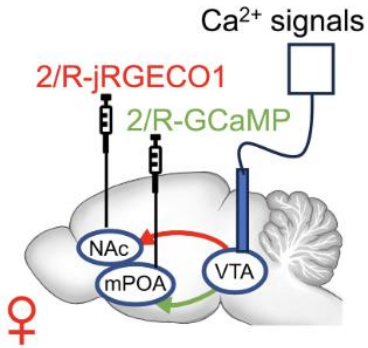
changed

NAc inhibition

VTADA-NAc projection determines female mice social preference.

Female Mice

Double retrograde-virus tracing

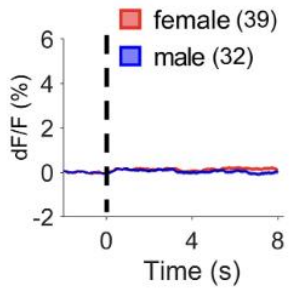


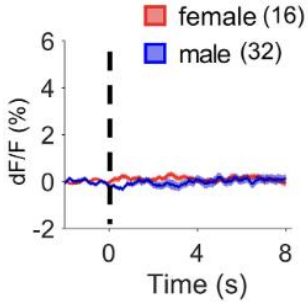
Without TMT

With TMT

VTA DA→mPOA

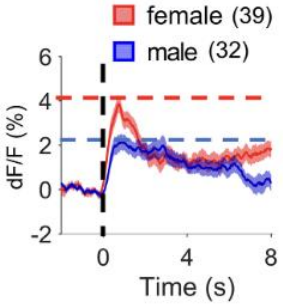
mPOA

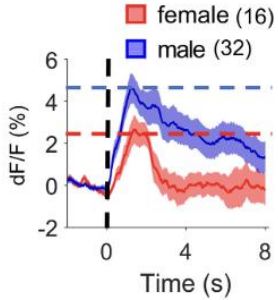




VTA DA→NAc

NAc





Female preference

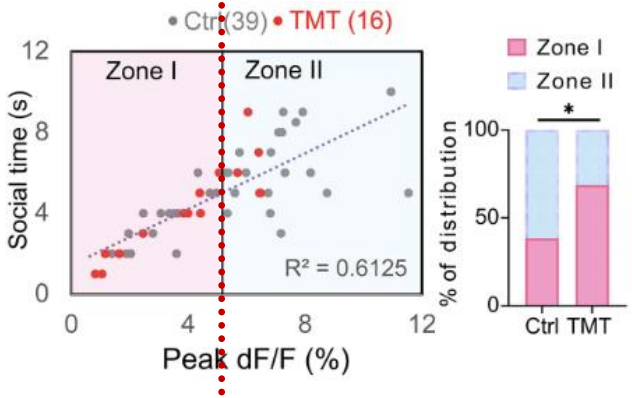
Male preference

VTA^{DA}-NAc projection determines female mice social preference.

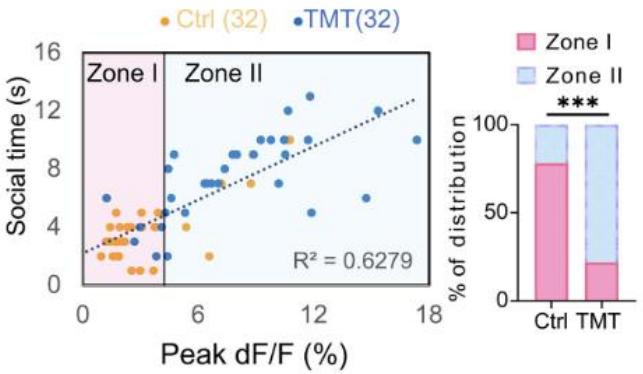
Female Mice

Pearson correlation analysis

Female interaction



Male interaction



Median percentile line of Ca2+ signals

Zone I: Lower excitability of the VTADA–NAc projection
Zone II: Higher excitability of the VTADA–NAc projection

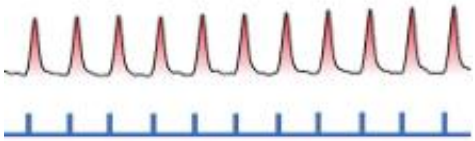
- Why is the **VTADA**-NAc projection positively correlated with both male and female interaction under different conditions?
- Different activity of the VTADA–NAc projection might drive the sex preference change in female mice.

Firing patterns of VTA^{DA}-NAc projection

Firing pattern

Tonic dopamine release

Low-frequency, irregular/spontaneously single-spike firing



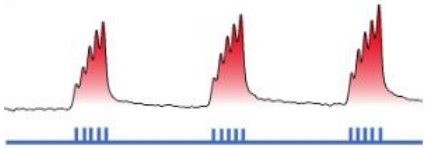
Pattern I: Tonic Firing

Sustained low-frequency (typically ~5-Hz) tonic firing

- **Peak** (half-height width): Larger
- **AUC**: Larger
- **Rise Rate**: Smaller
- **HHD** (half-height duration): Larger

Phasic dopamine release

High-frequency burst firing



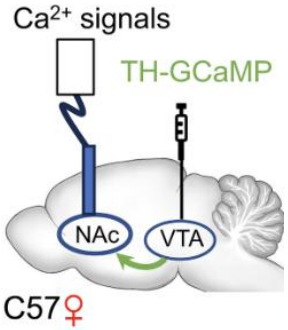
Pattern II: Phasic Firing

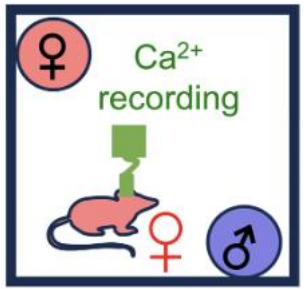
High-frequency (>10-Hz, usually <50-Hz) phasic firing with three to five spikes per burst

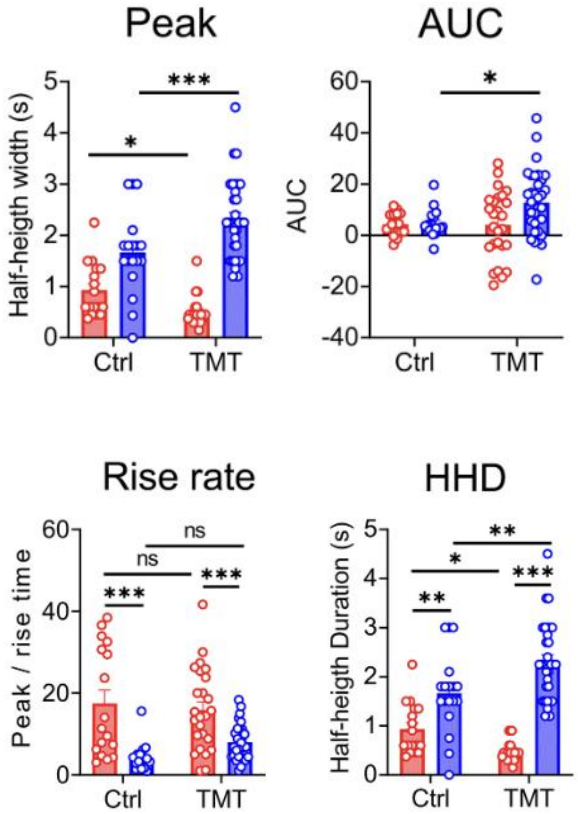
- **Peak** (half-height width): Smaller
- **AUC**: Smaller
- **Rise Rate**: Larger
- **HHD** (half-height duration): Smaller

Firing patterns of VTA^{DA}-NAc projection

Female Mice



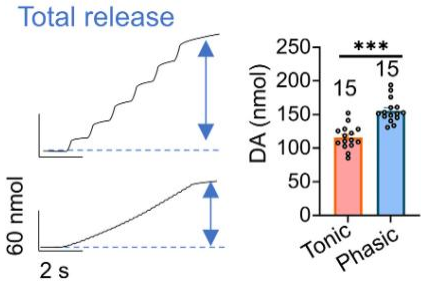




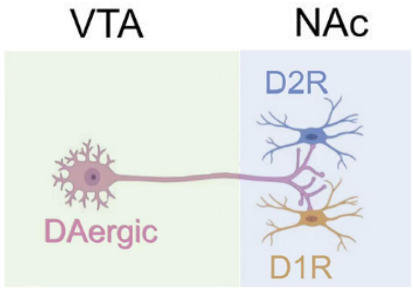
- **Phasic firing** promotes **female** preference.
- **Tonic firing** promotes **male** preference.
- TMT exposure <u>inhibits</u> phasic firing and <u>facillitates</u> tonic firing.

DA transmission in VTA^{DA}-NAc projection

Female Mice



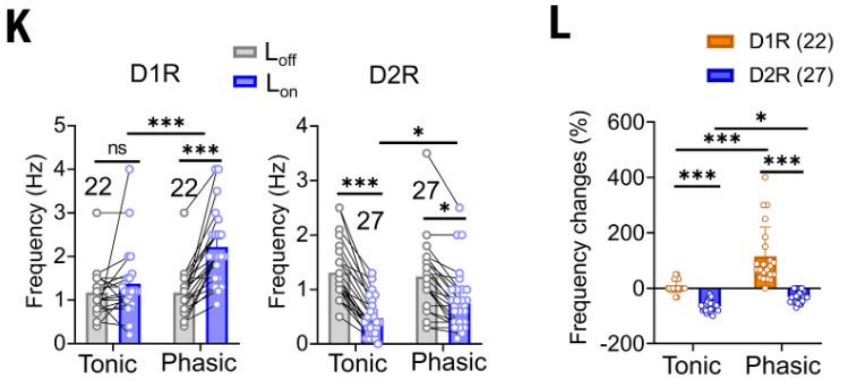
Phasic stimulus: higher DA release
Tonic stimulus: lower DA release



Inhibitory D2R

Excitatory D1R

Whole-cell patch clamp AP recordings

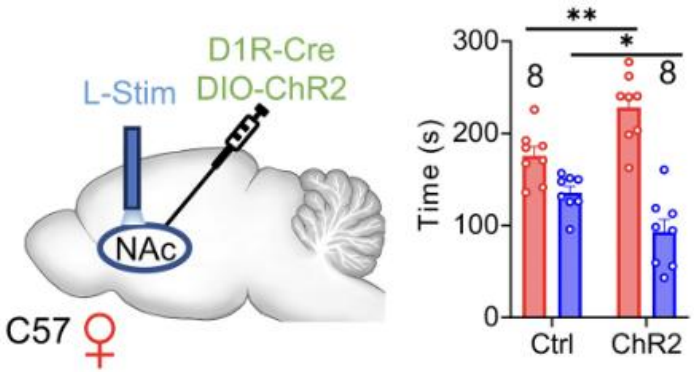


- **D1R are specifically responsive to the phasic firing**
- **D2R are more sensitive to the tonic firing**

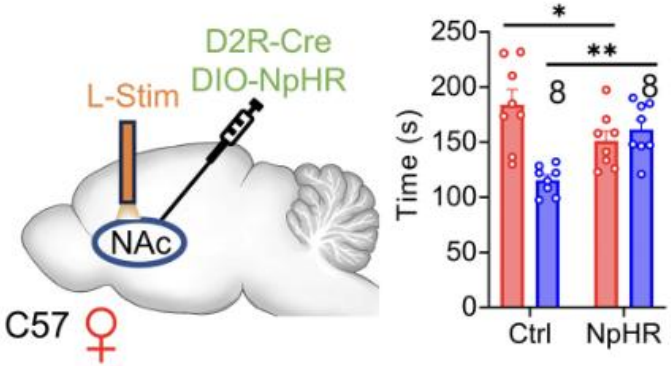
DA transmission in VTA^{DA}-NAc projection

Female Mice

Optogenetic excitation of D1R
Mimic phasic firing



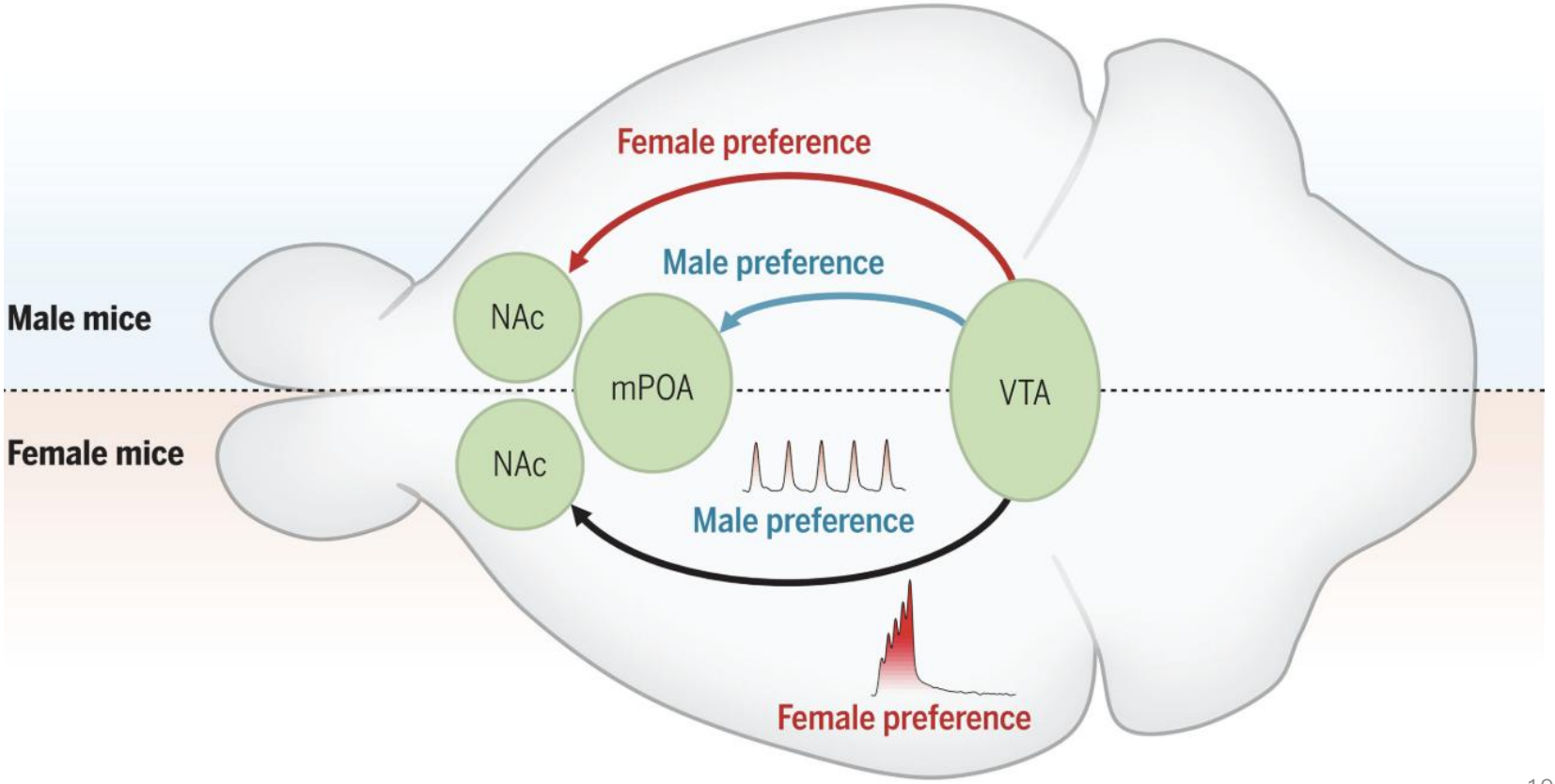
Optogenetic inhibition of D2R
Mimic tonic firing



- **Phasic firing–facilitated DA-D1R transmission and tonic firing–dominated DA-D2R transmission in the NAc determine female mice sex preference.**

Summary

Dimorphic neural circuits that determine sex preference



Thanks for your listening!

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