

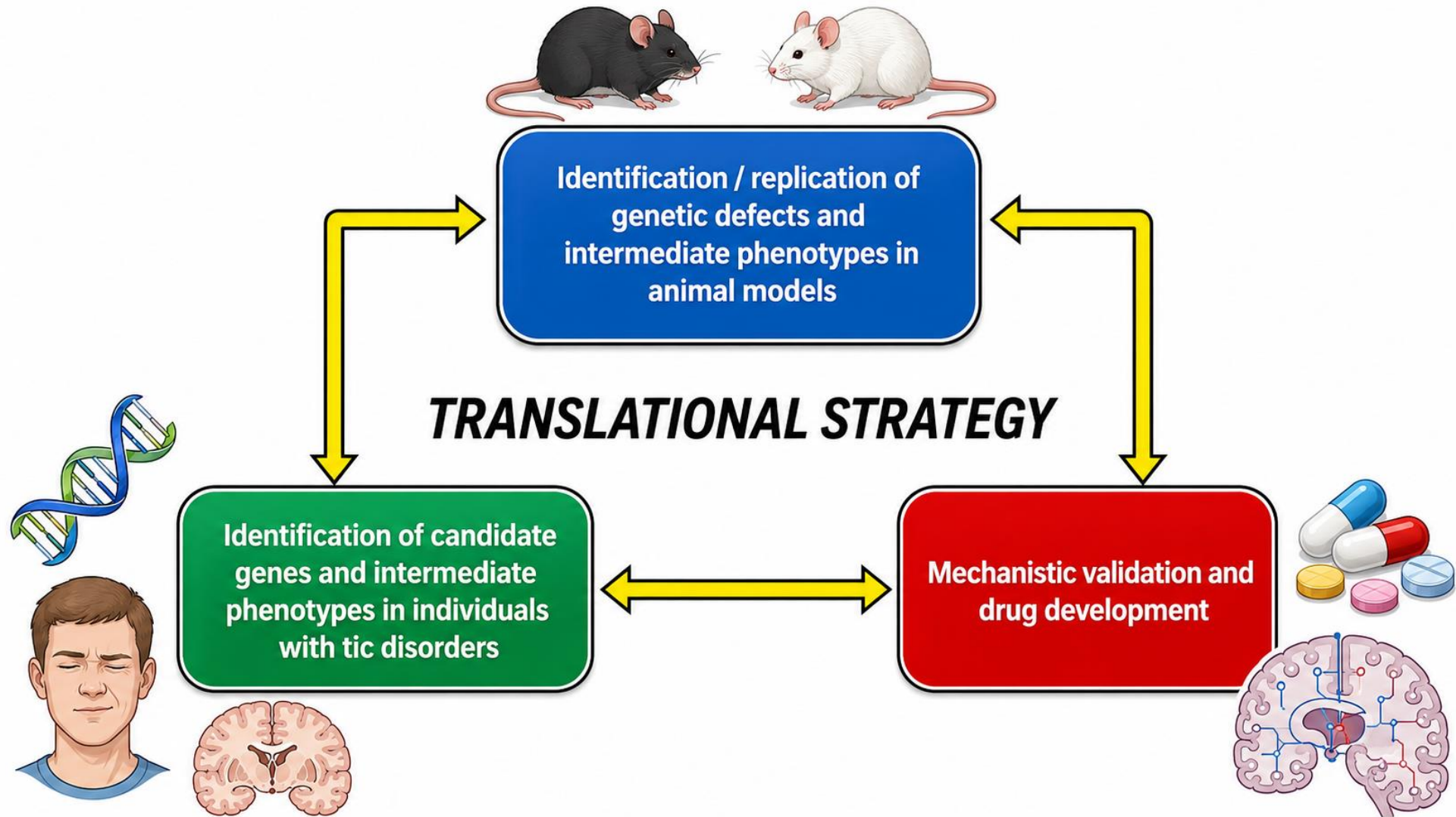


# Animal models of tic disorders

Marco Bortolato, MD PhD

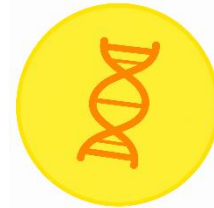
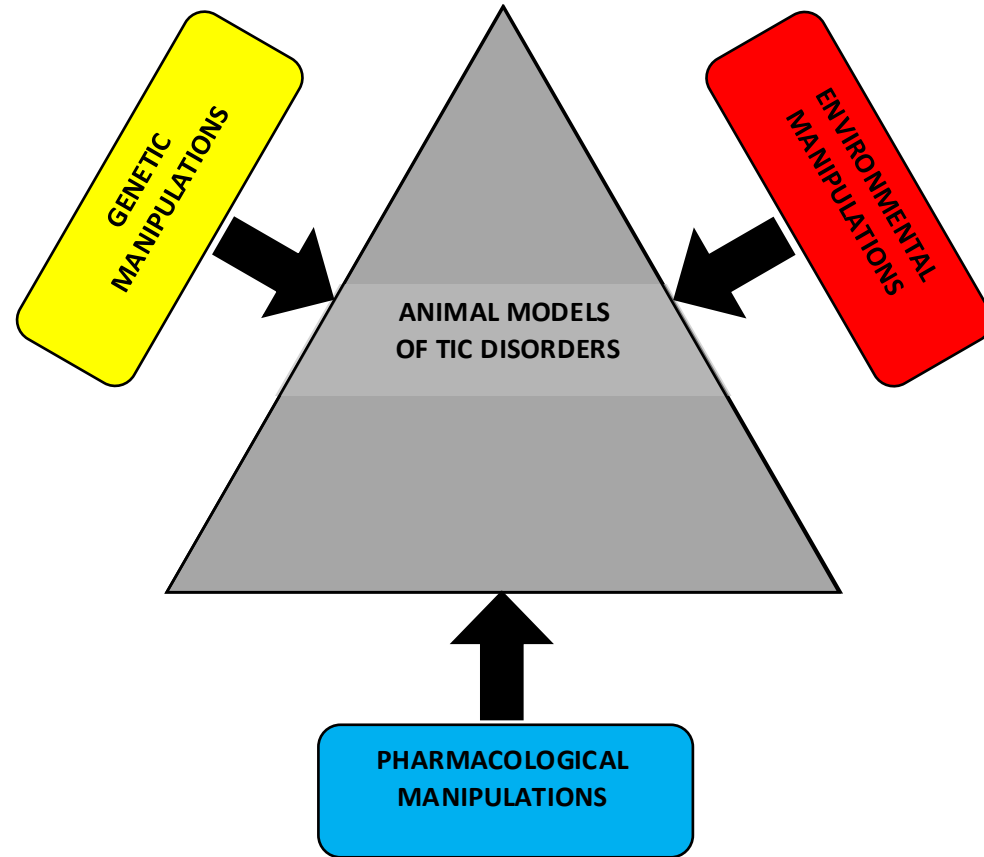
Department of Cellular and Systems Pharmacology, College of Pharmacy, University of Florida, Gainesville, FL, USA

**ESSTS 2026 • Ljubljana, Slovenia • June 17–19, 2026**



Animal models cannot reproduce the syndrome, but isolate **specific components**, and test them in a loop between clinic and bench.

# How can we generate animal models of TD?



**Genetic manipulations:** based on alterations of the key genes associated with TD

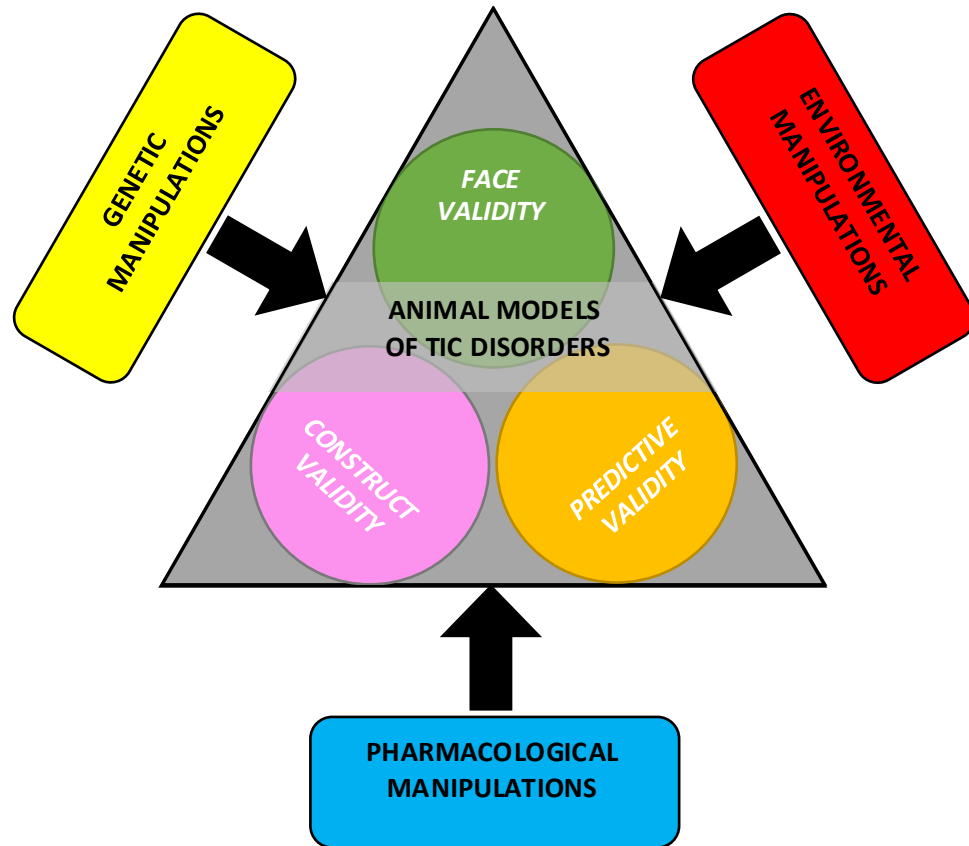


**Environmental manipulations:** based on exposure to factors associated with higher risk for TD



**Pharmacological/lesional manipulations:** based on reproducing the key neurotransmission and neurobiological abnormalities in TS

# How can we **validate** animal models of TD?



**Face validity:** analogy between the behavioral performance of the animal models and the signs/symptoms in TS



**Construct validity:** congruence between the pathophysiology of TS and the neurobiology of behaviors in animal models

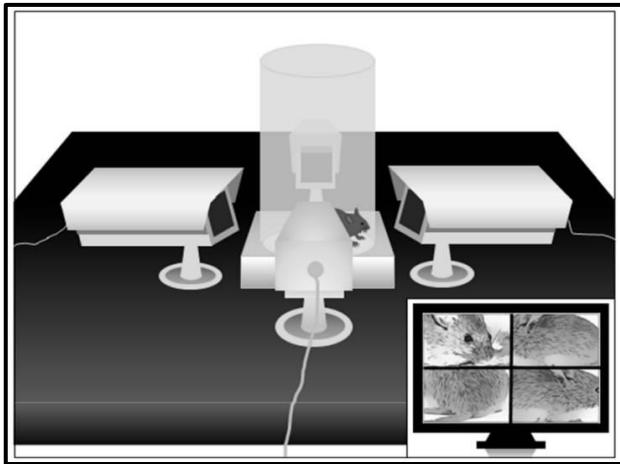


**Predictive validity:** sensitivity of animal model to validated treatments (antipsychotics, clonidine etc.) or risk factors (stress, sleep deprivation, etc.)

## Face validity: tic-like behaviors

Tic-like manifestations in animals can vary from **rapid jerks /bursts** (mimicking simple tics) to **repetitive stereotypies** (complex tics)

Our lab has developed novel methods to capture these fine movements for both manual and AI-assisted automated evaluation



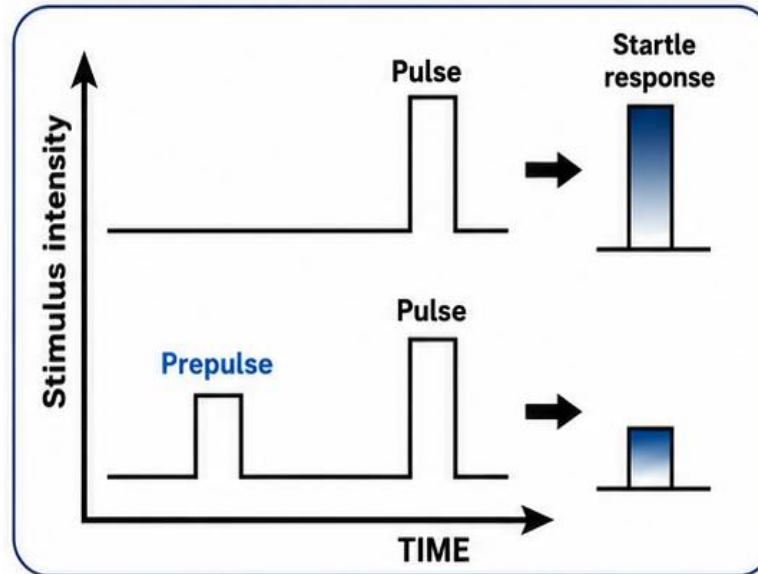
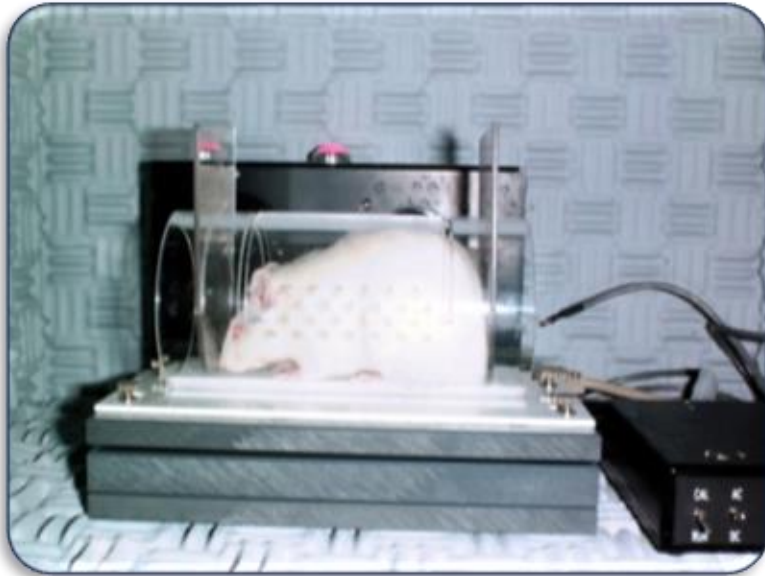
Tic-like jerks



Grooming stereotypies

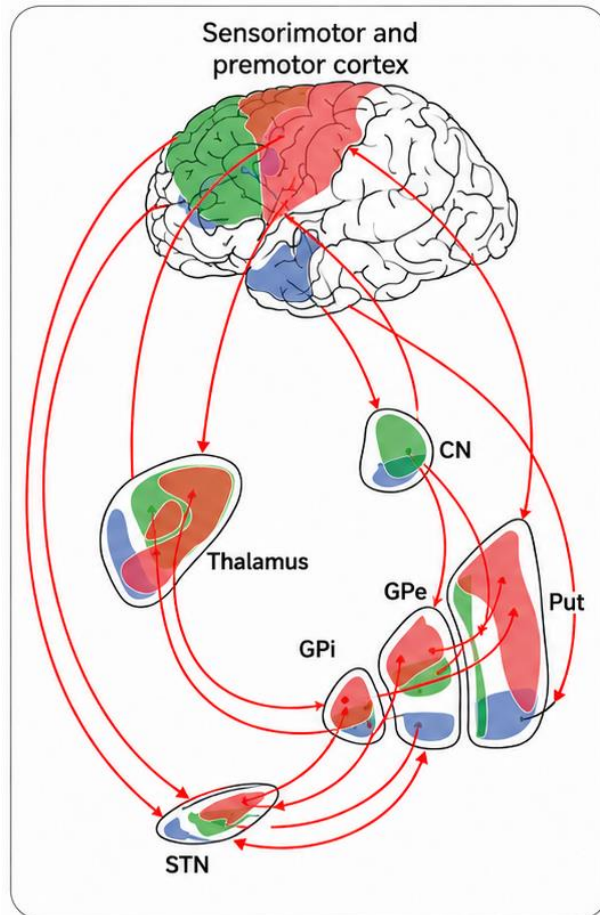
## Face validity: prepulse inhibition (PPI) of the startle

Inhibition of the startle response to an intense, sudden acoustic stimulus, mediated by the exposure to a low intensity prestimulus.

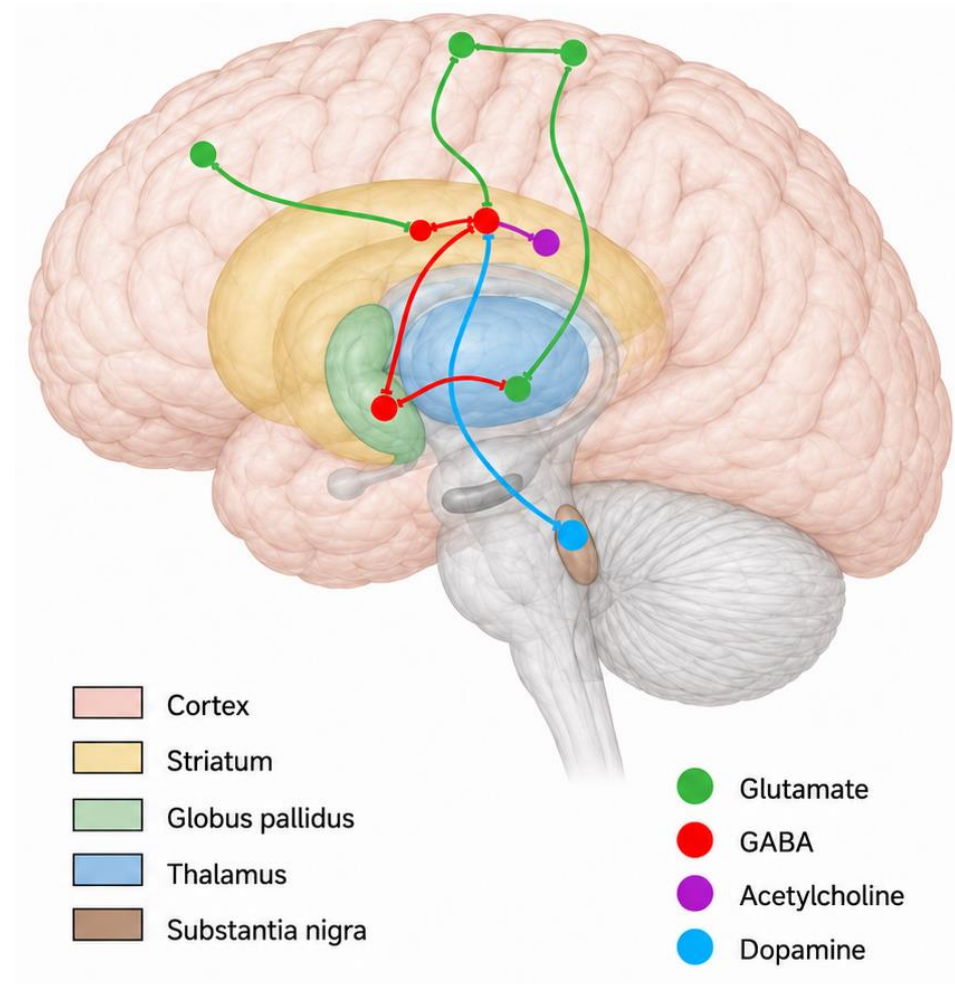


PPI is the best-validated **cross-species** operational index for sensorimotor gating; its spontaneous deficits are observed in many disorders, including **tic disorders**.

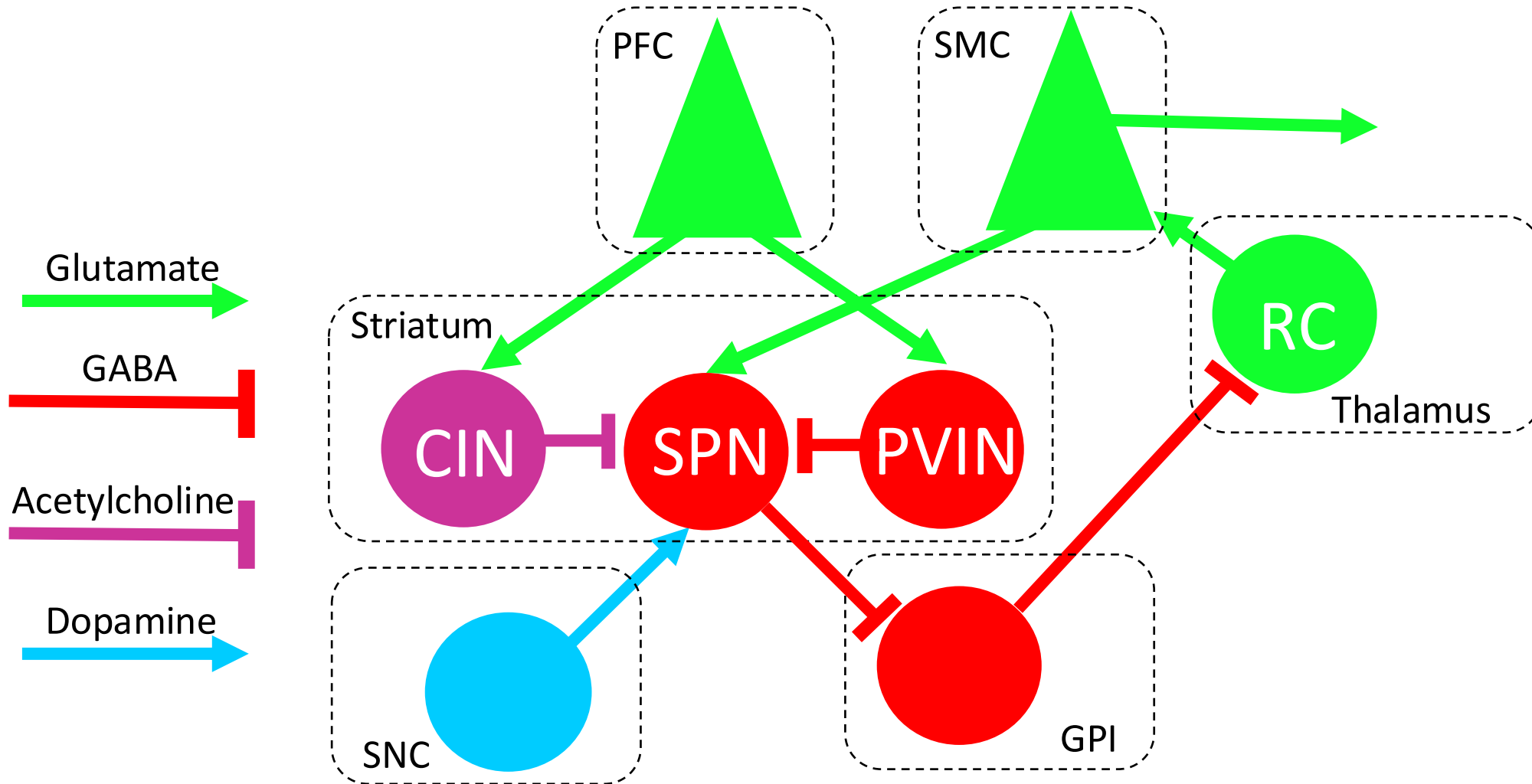
# Neurobiological circuitry in tic generation



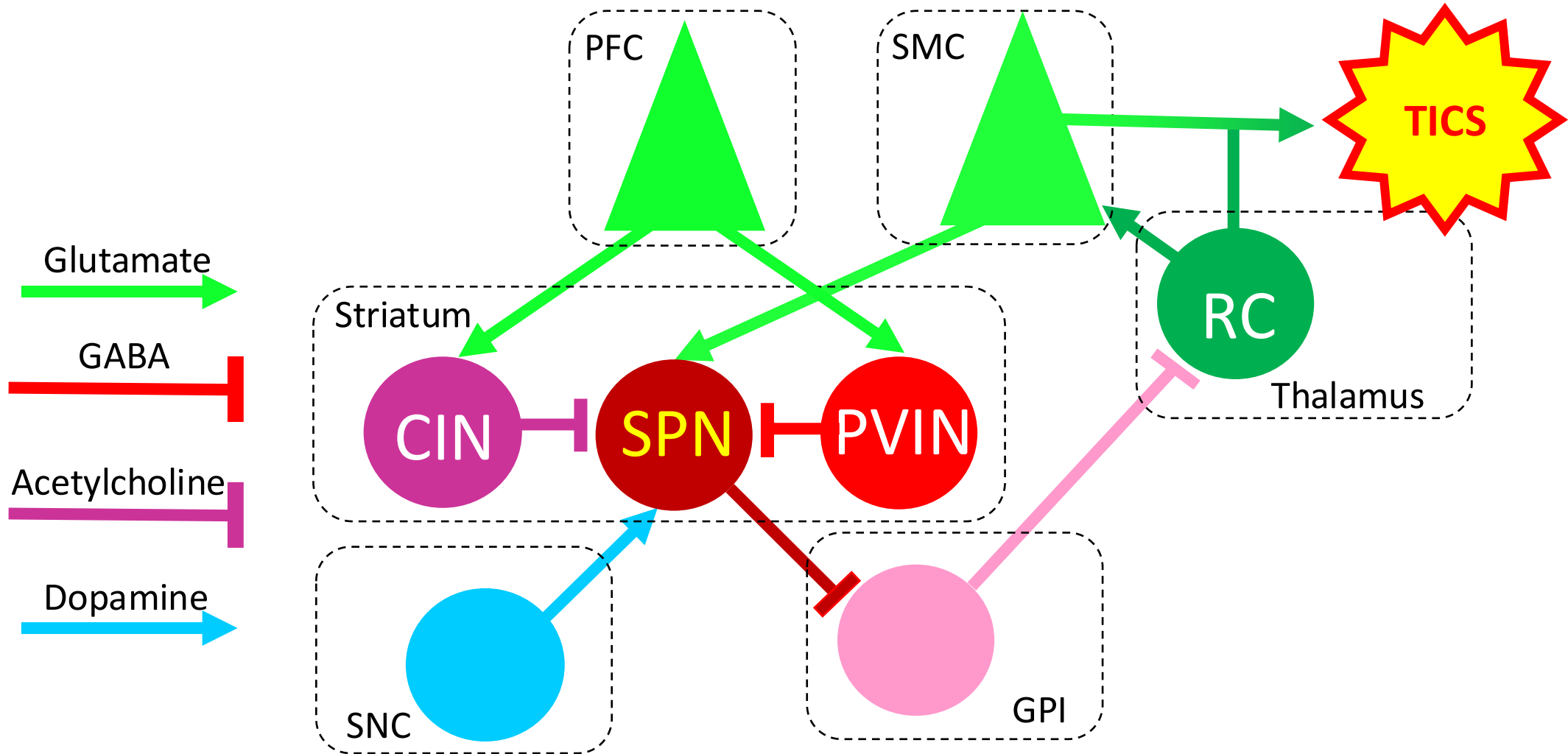
Adapted from Lapidus et al., 2014



# Simplified schema of the CSTC circuitry



# Activation of striatal projection neurons within aberrant foci leads to tics



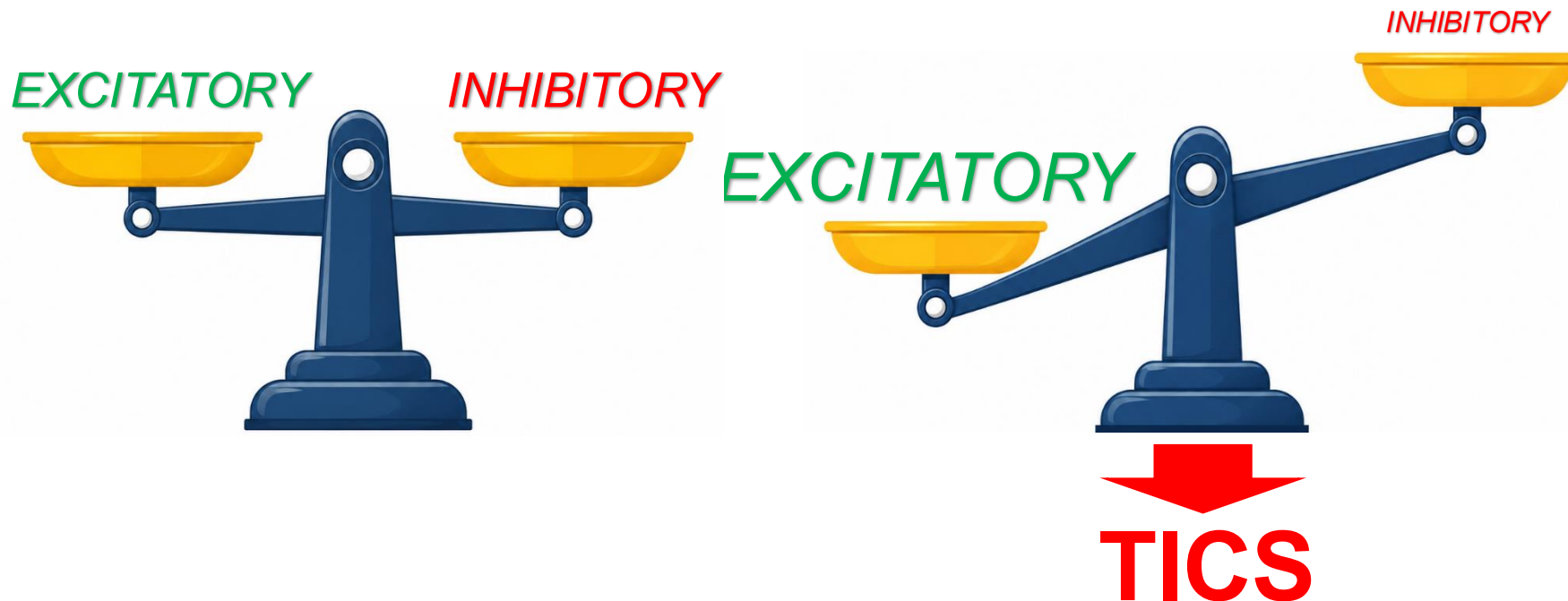
# Tics results from signal imbalances in striatal projection neurons

## Excitatory signals:

- Glutamate from cortex
- Glutamate from thalamus
- Dopamine from substantia nigra

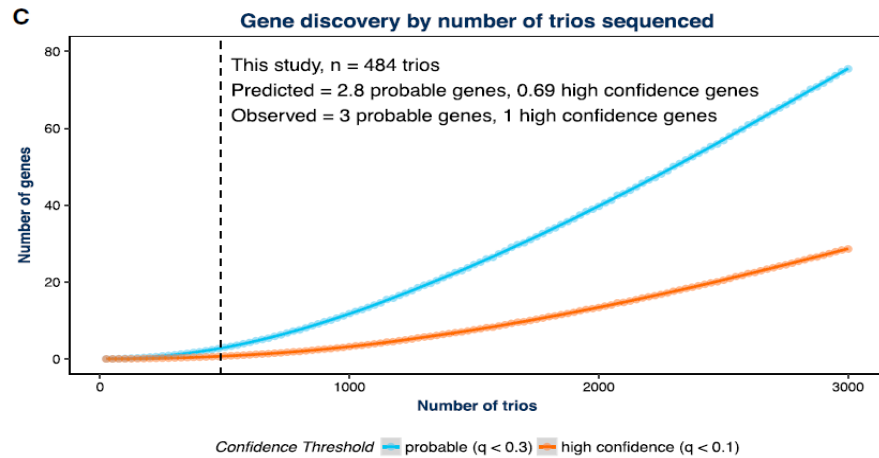
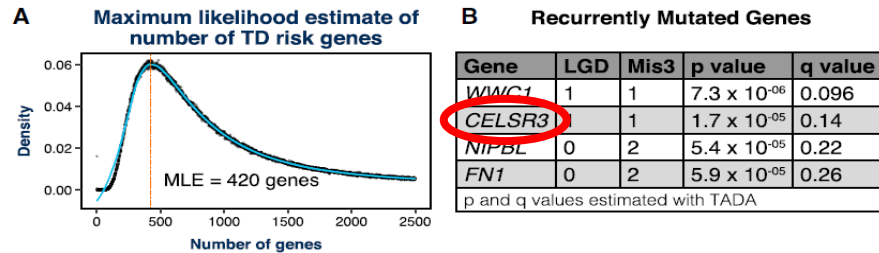
## Inhibitory/regulatory signals:

- Acetylcholine from str. interneurons
- GABA from str. interneurons
- Prefrontal control on interneurons



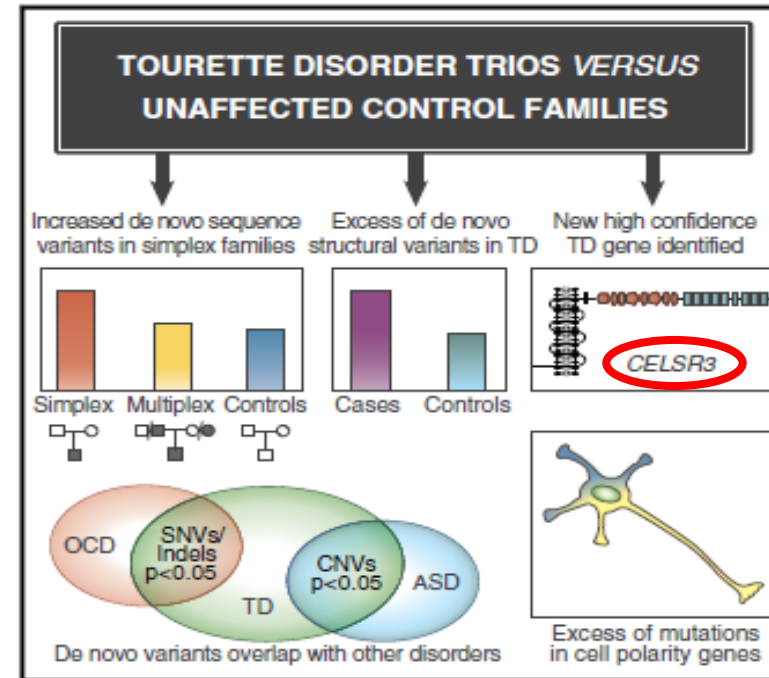
# CELSR3: the first high-risk gene in Tourette syndrome

## De Novo Coding Variants Are Strongly Associated with Tourette Syndrome



Wilsey *et al.*, 2017

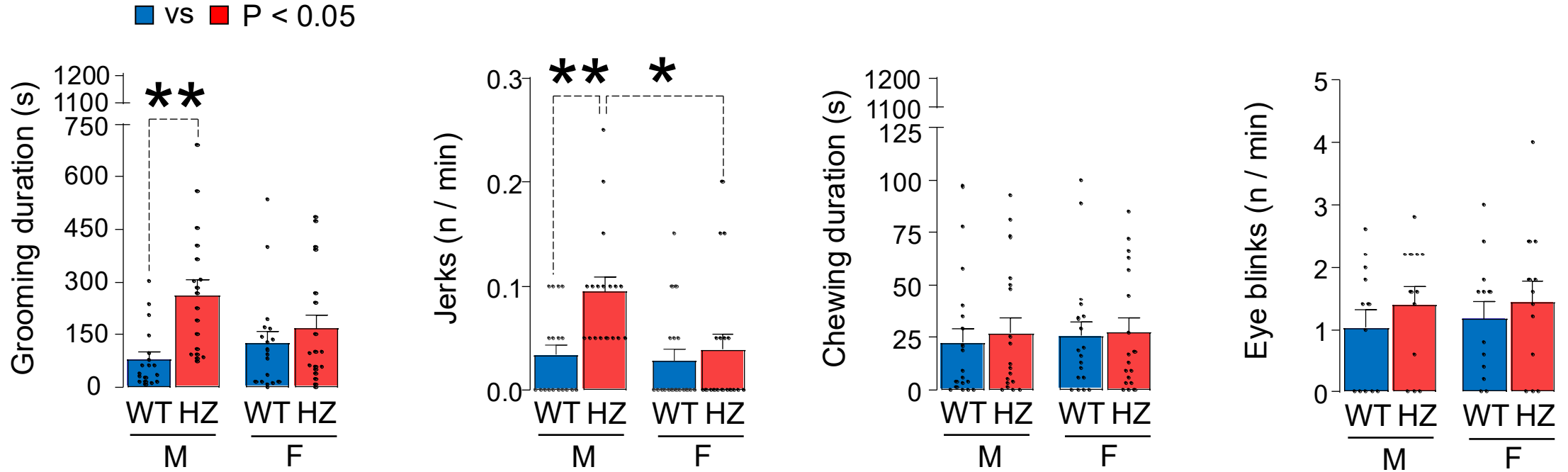
## De Novo Sequence and Copy number Variants Are Strongly Associated with Tourette Syndrome and Implicate Cell Polarity in Pathogenesis



Wang *et al.*, 2018

CELSR3 is an atypical cadherin included that coordinates cellular orientation. It plays a key role in **axon guidance, tract formation, and the development of dopaminergic circuitry.**

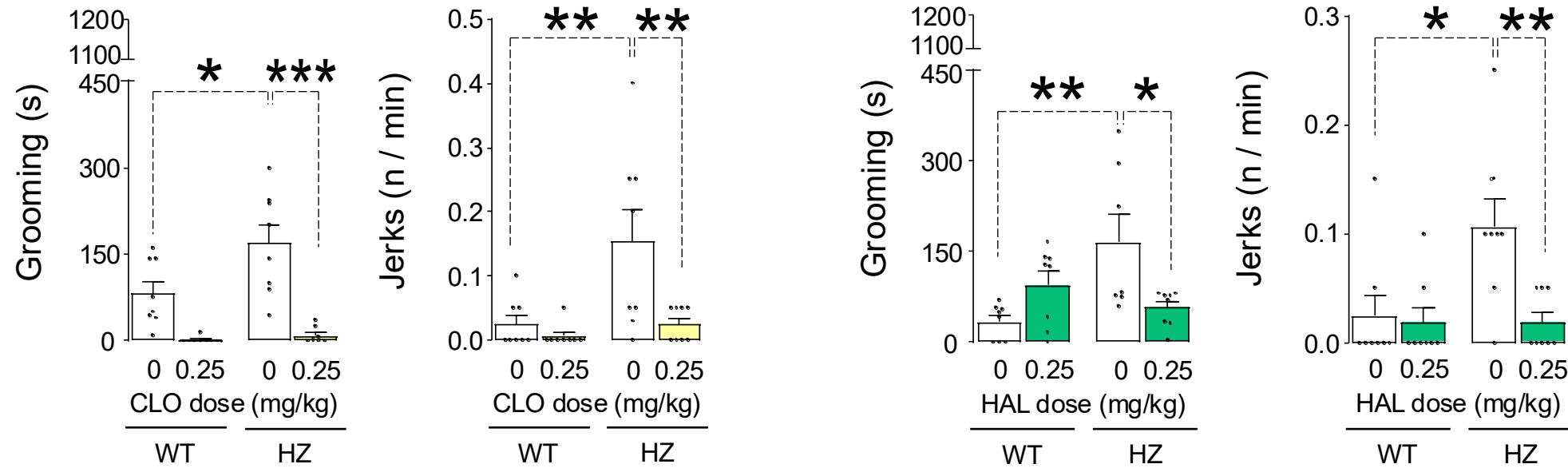
# Face-validity: CELSR3 HZ juvenile adult mice exhibit increased tic-like responses



Cadeddu *et al*, Mol Psych, 2025

CELSR3 HZ mice also showed PPI deficits

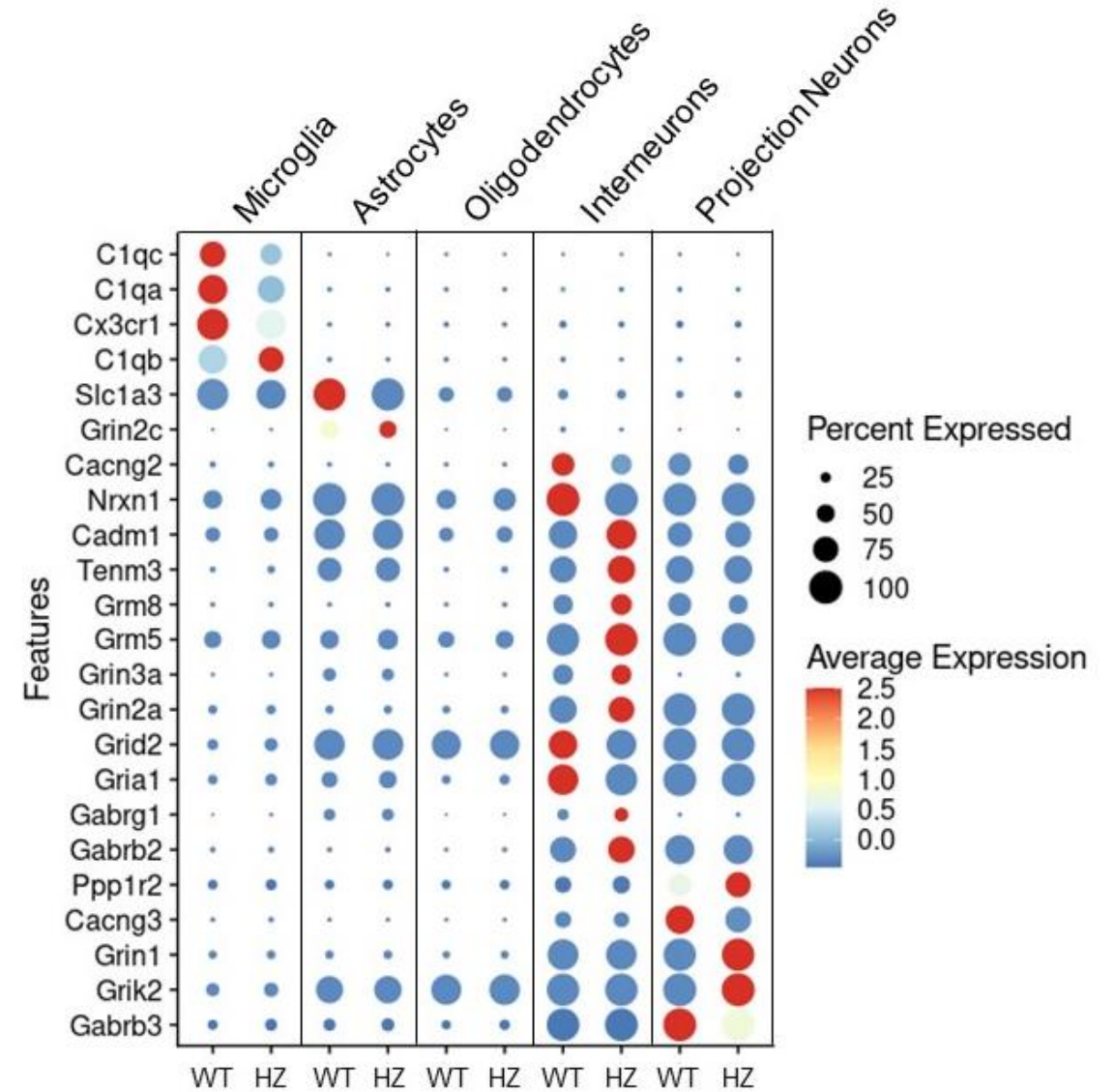
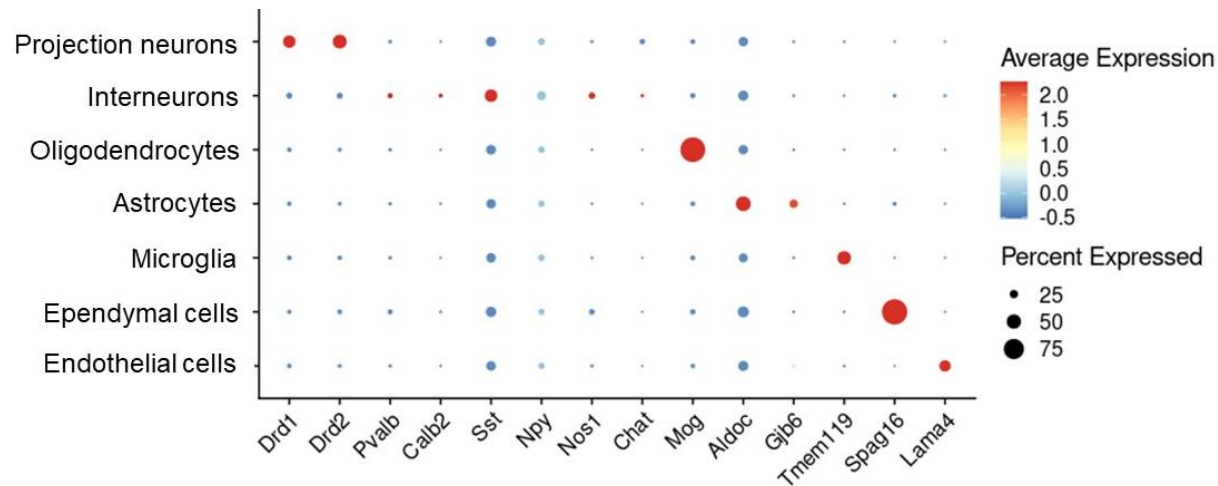
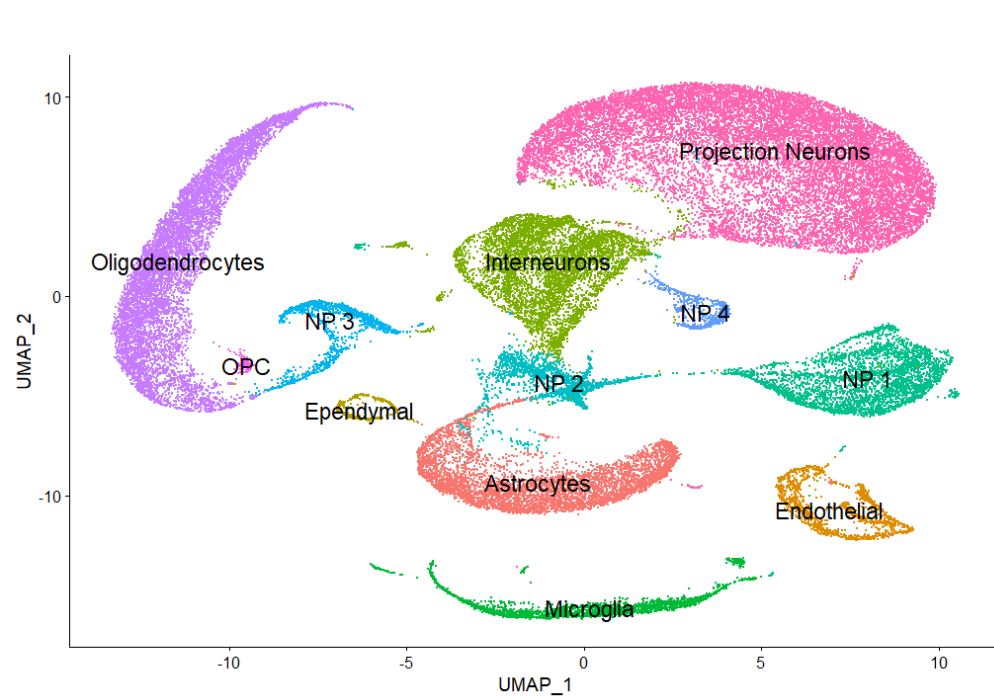
# Predictive validity: Tic-like behaviors in CELSR3 HZ mice are opposed by benchmark TS therapies



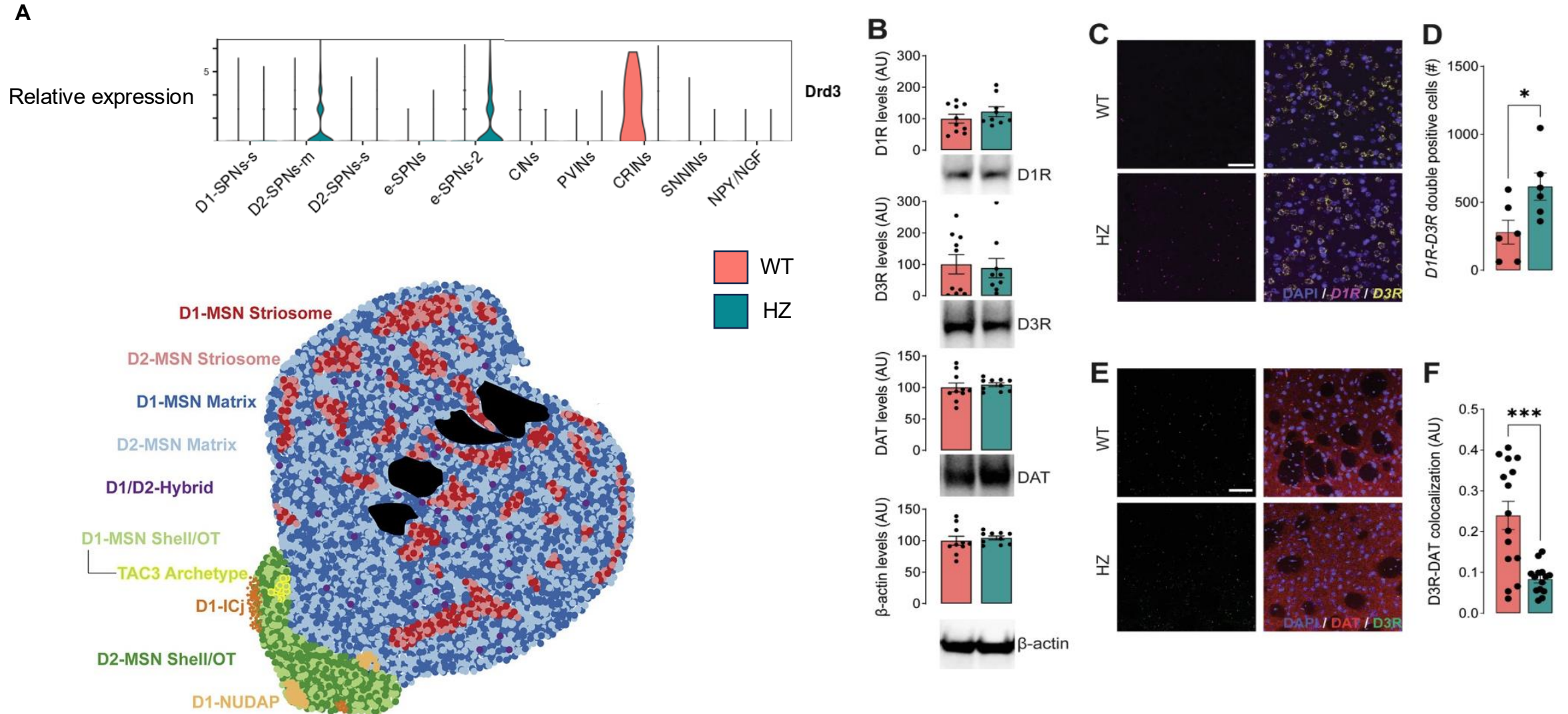
**HALOPERIDOL**

**CLONIDINE**

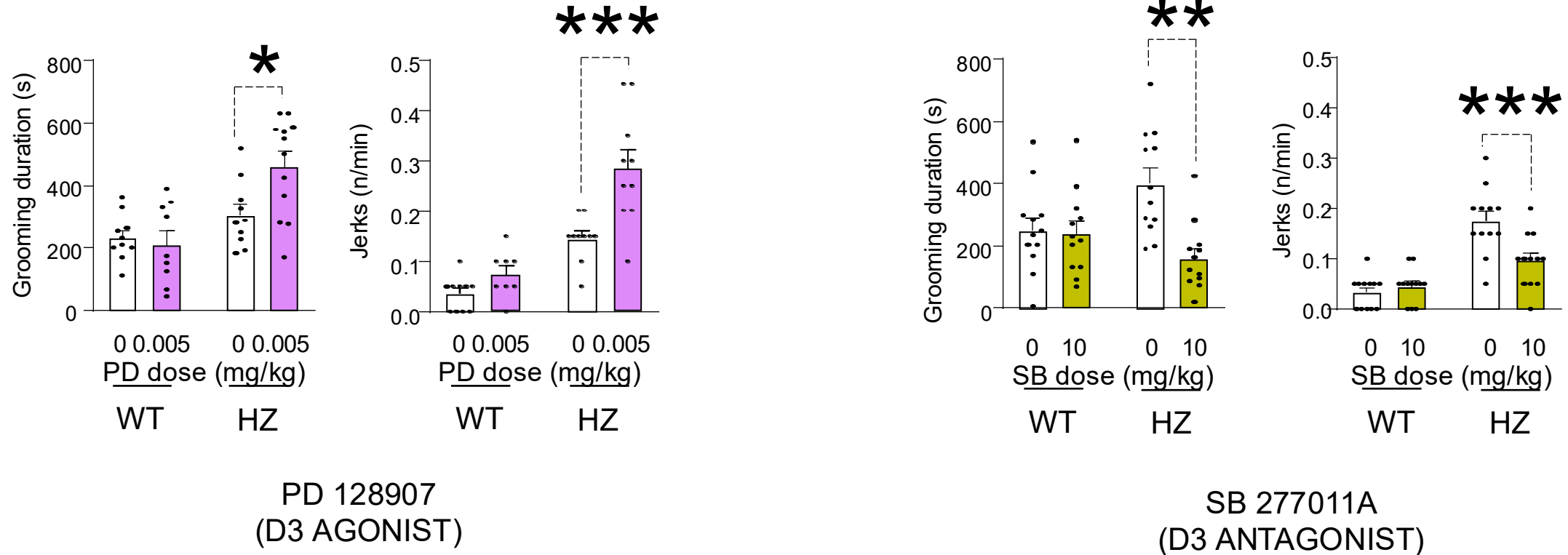
# Celsr3 HZ mice exhibit subtle alterations in striatal neurons and microglia



# The striatum of CELSR3 deficient mice has a higher number of D3-positive D1-SPNs



# Tic-like behaviors in CELSR3 HZ mice are mediated by D3 dopamine receptors



PD 128907  
(D3 AGONIST)

SB 277011A  
(D3 ANTAGONIST)



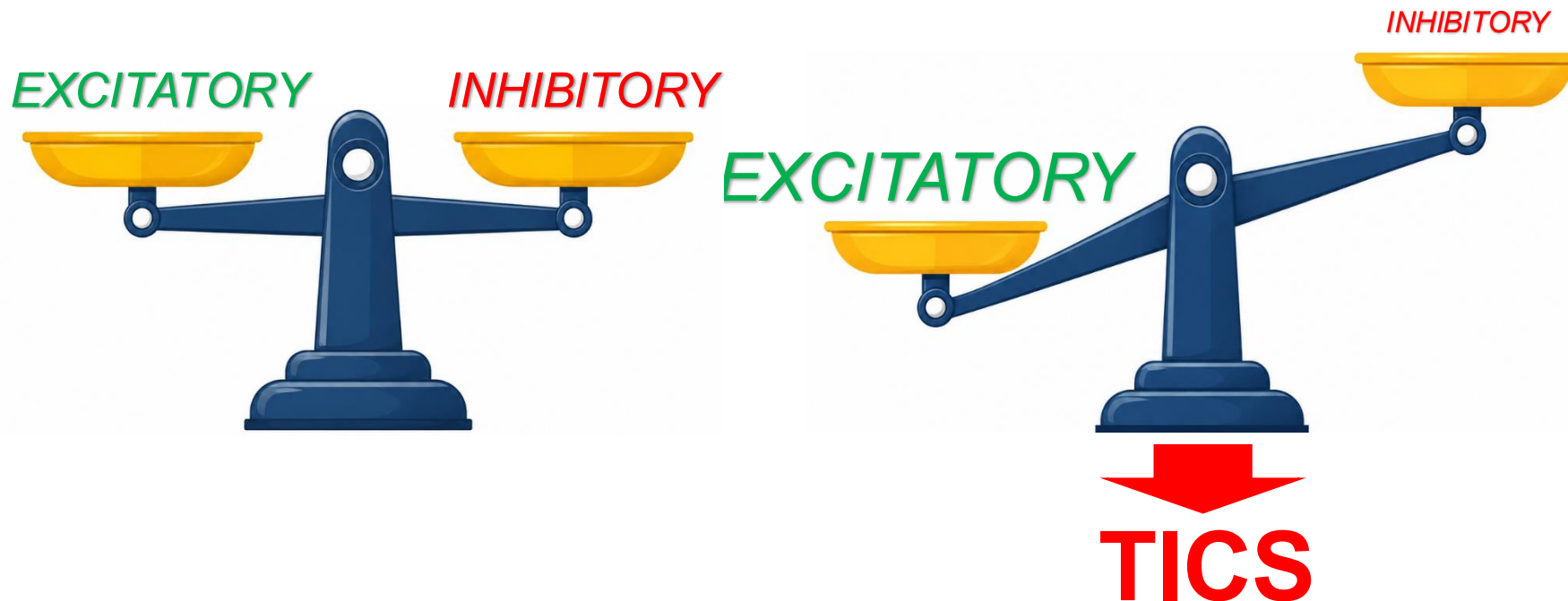
# Tics results from signal imbalances in striatal projection neurons

## Excitatory signals:

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- Dopamine from substantia nigra

## Inhibitory/regulatory signals:

- Acetylcholine from str. interneurons
- GABA from str. interneurons
- Prefrontal control on interneurons



# Local disinhibition in the striatum leads to tic-like movements

Motor tics evoked by striatal disinhibition in the rat

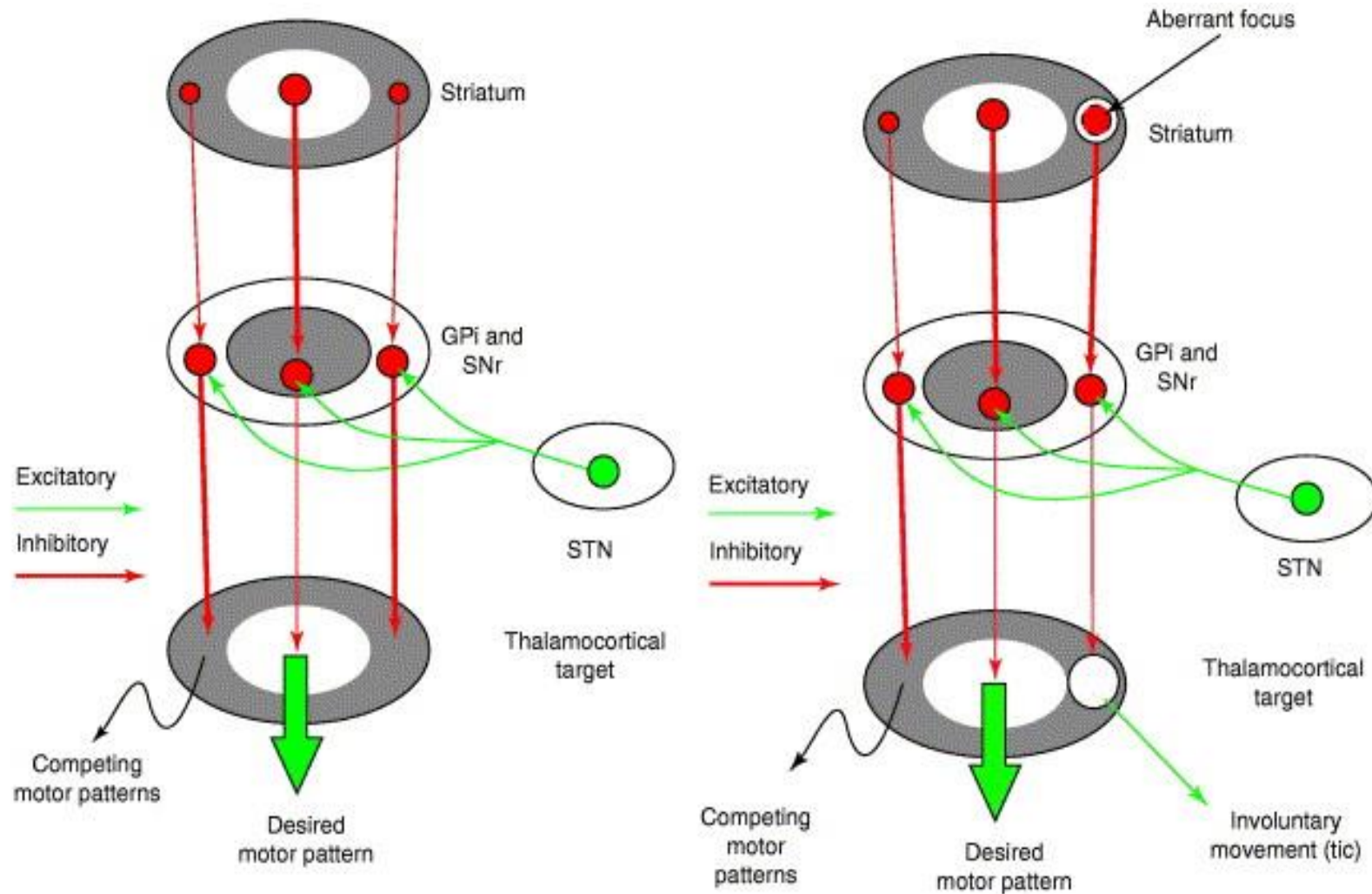
Maya Bronfeld, Dorin Yael, Katya Belelovsky, Izhar Bar-Gad  
The Leslie & Susan Goldschmied (Gonda) Multidisciplinary Brain Research Center,  
Bar-Ilan University, Ramat-Gan, Israel

Supplementary video

From Bronfeld et al., 2013

Unilateral intrastriatal injection of **GABA-A receptor** produce contralateral tic-like behaviors in primates and rodents

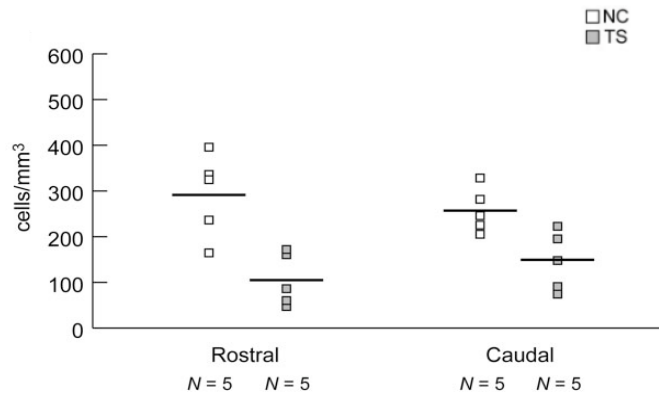
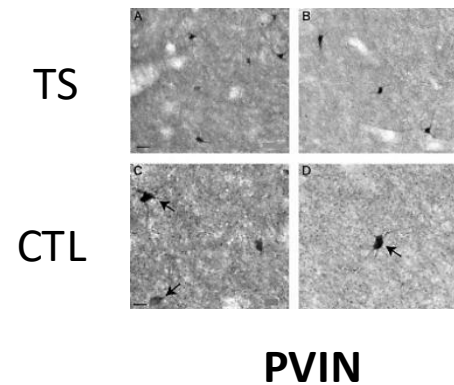
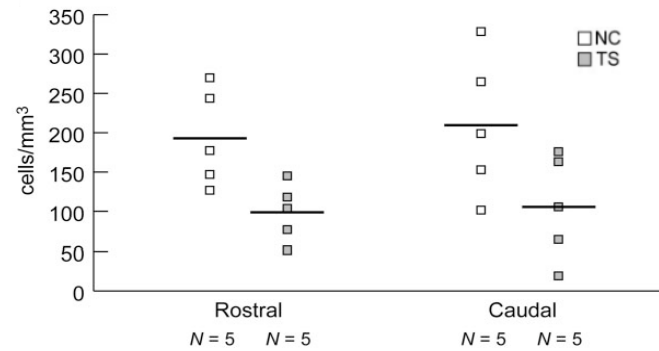
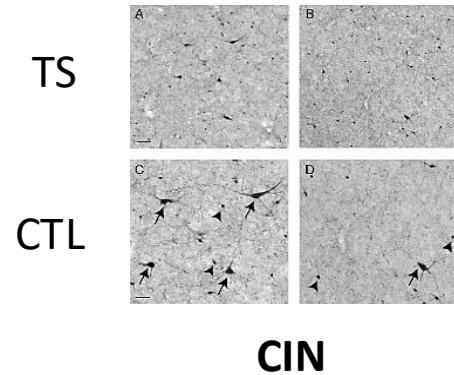
# Aberrant foci



Adapted from Albin and Mink 2006

Tics are related to areas of **hyperactivity in the striatum** (aberrant disinhibition foci), which override “**center-on surround-off**” contrast for the proper activation of desired motor pattern and silencing of competing movements

# Striatal interneuronal deficits facilitate tics

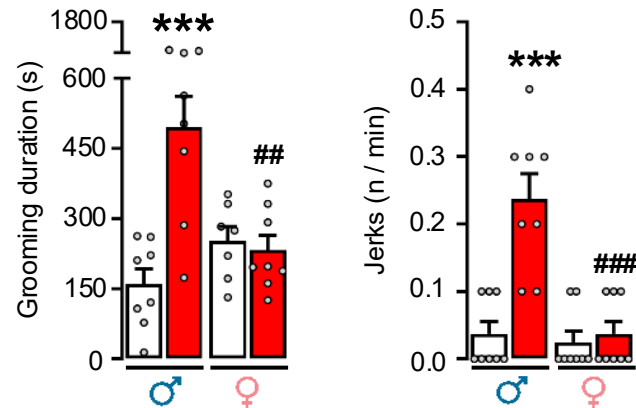
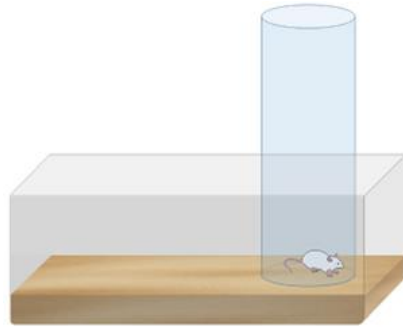
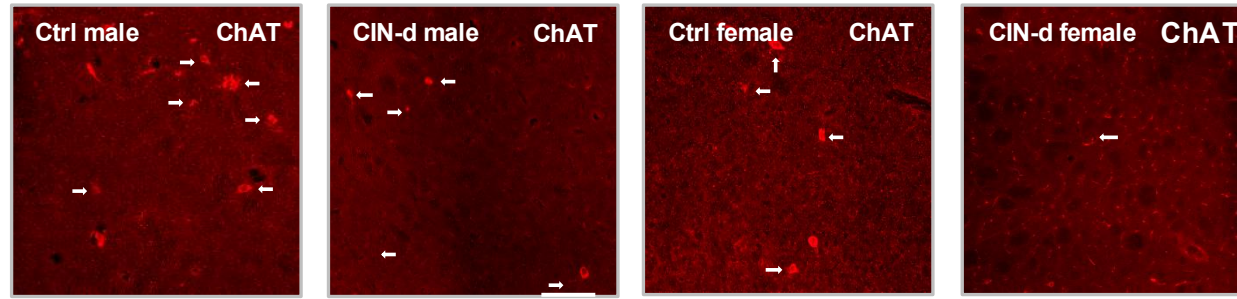


	CAUDATE	HEAD	BODY
<b>CIN</b>		- 53.5%	- 44.9%
<b>PVIN</b>		- 60.1%	- 54.6%

	PUTAMEN	ROSTRAL	CAUDAL
<b>CIN</b>		- 48.7%	- 49.5%
<b>PVIN</b>		- 63.9%	- 43.2%

The striatum in TS features significant deficits in **cholinergic (CIN)** and parvalbumin-GABAergic (PVIN) interneurons (Kalanithi et al., 2005; Kataoka et al., 2011; Lenington et al., 2016)

## CIN-d mice: face and construct validity

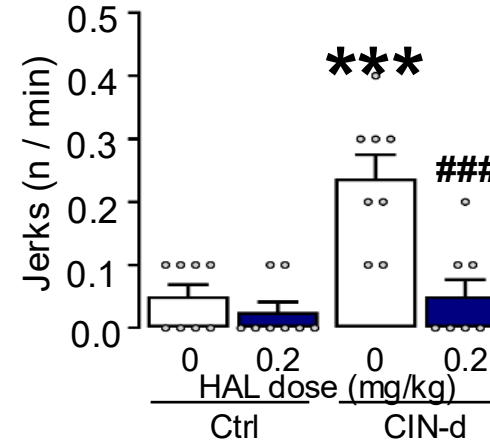
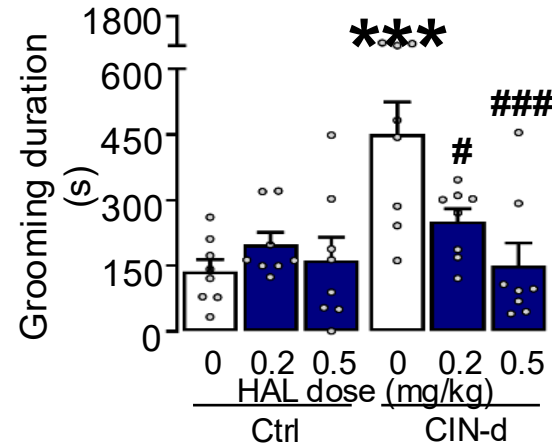


Cadeddu *et al*, Neuropsychopharmacology, 2023

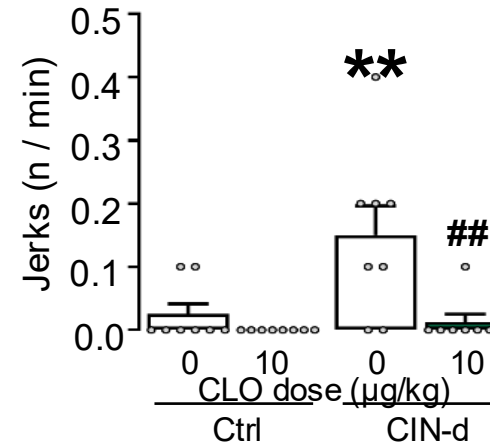
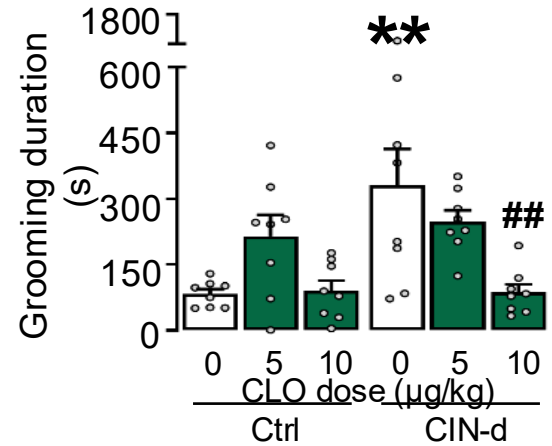
CIN-d mice do not exhibit any spontaneous TS-relevant behavior. However, male, but not female CIN-d mice exhibit **tic-like responses and PPI deficits when exposed to acute stress**, such as in the case of spatial confinement

# CIN-d mice: predictive validity

## Haloperidol (HAL)



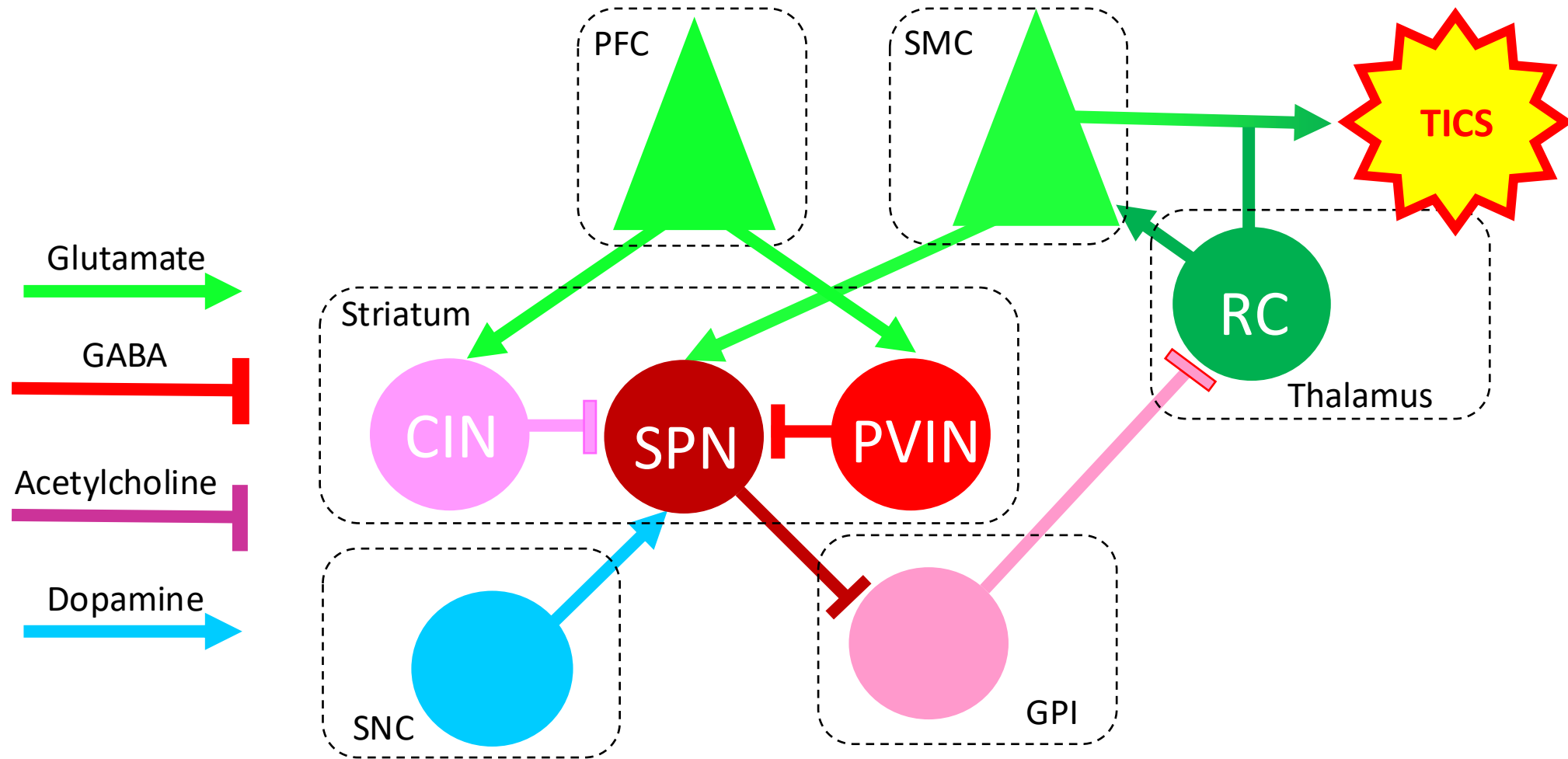
## Clonidine (CLO)



Cadeddu *et al*, Neuropsychopharmacology, 2023

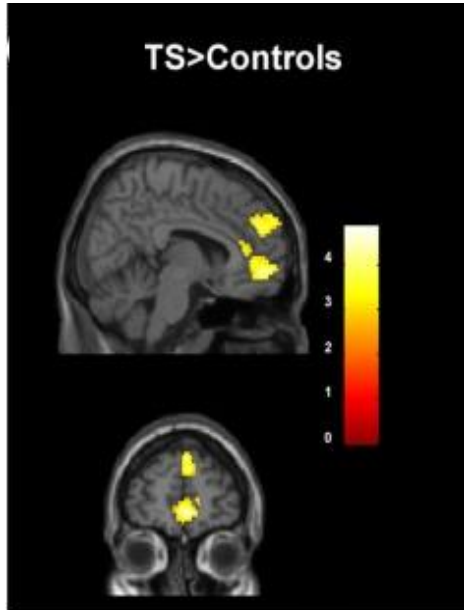
Tic-like behaviors and PPI deficits in CIN-d mice are sensitive to **all benchmark therapies for tic disorders**.

# Striatal interneuronal deficits promote tics

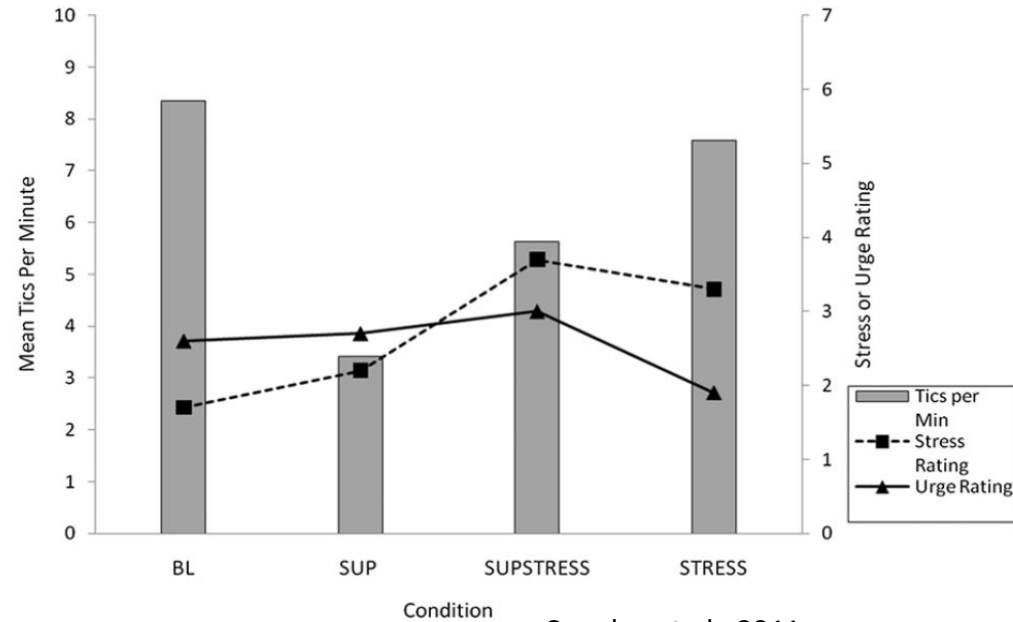


However, interneuron deficits leads to tics  
**only in males and in the presence of stress.**

# Prefrontal cortex activation enables tic suppression



Van der Salm et al., 2018



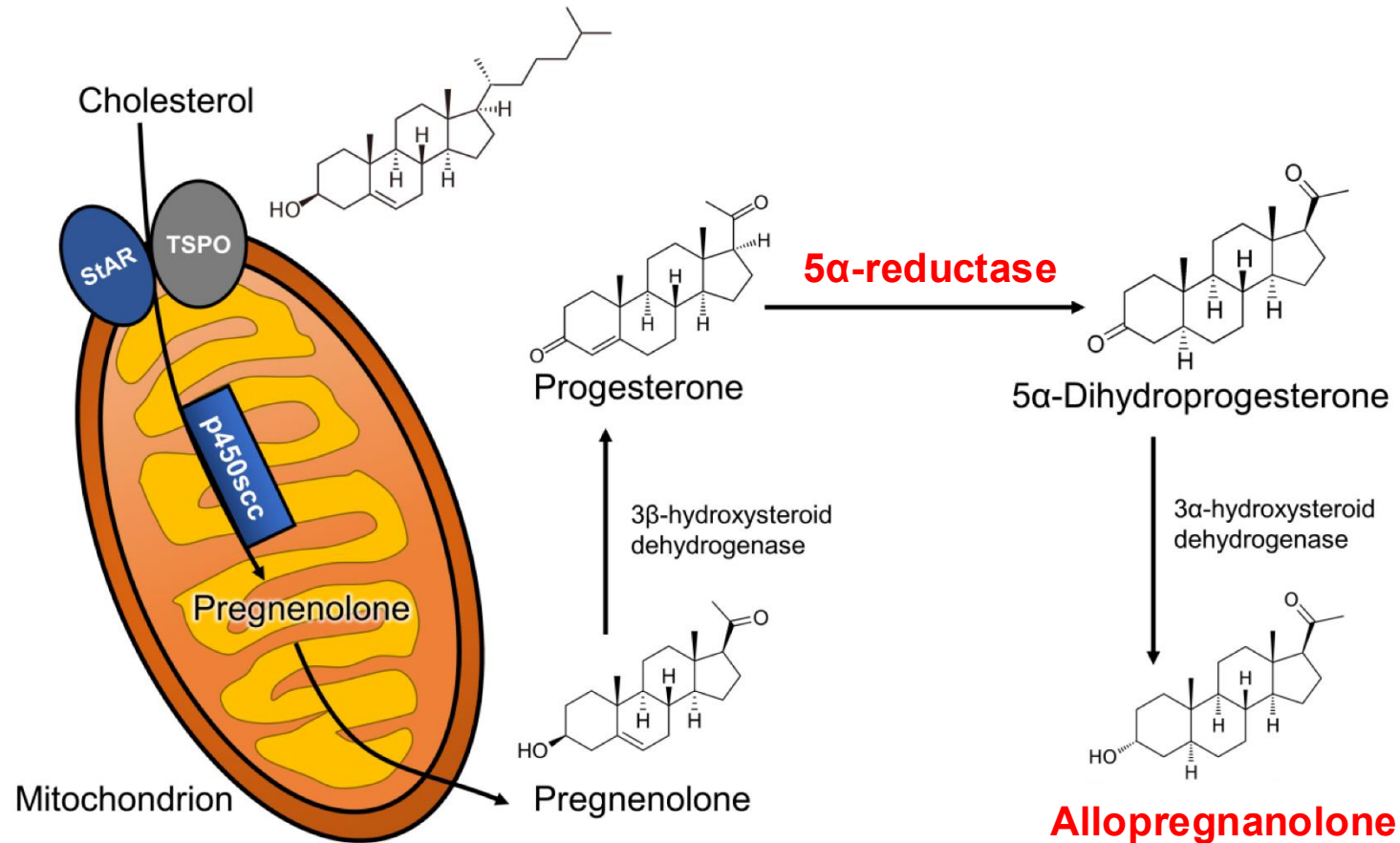
Conelea et al., 2011

**Tic suppression increases PFC activity in TS**

**Some types of stress may reduce the ability to suppress tics → inhibitory effect on PFC**

These effects are particularly pronounced in the **dorsolateral PFC**

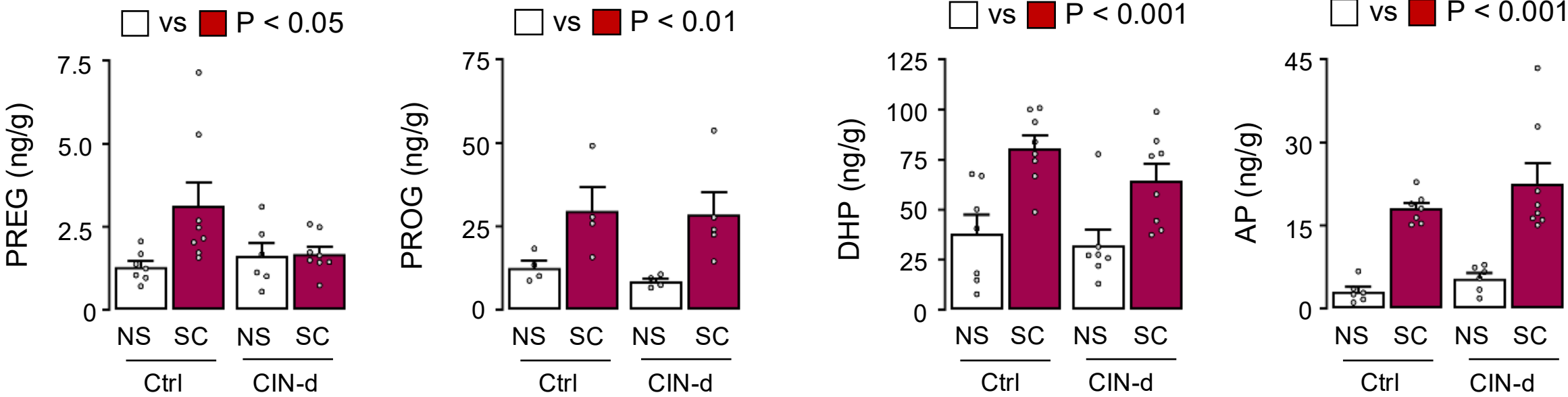
# Neurosteroids



**Allopregnanolone** (AP) is a key orchestrator of acute stress response and resilience

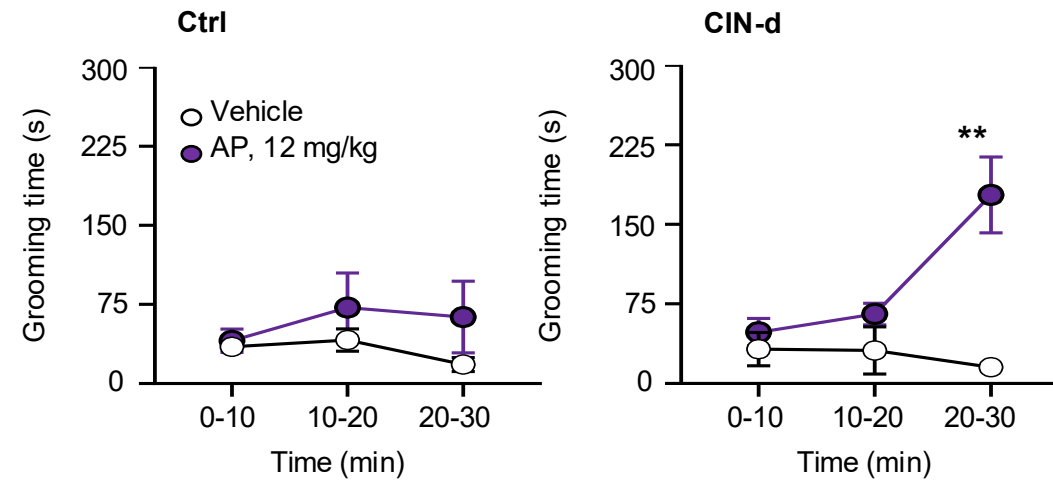
**The enzyme 5 $\alpha$ -reductase catalyzes the rate-limiting step of AP**

# Spatial confinement increases neurosteroid levels in the PFC of CIN-d male mice

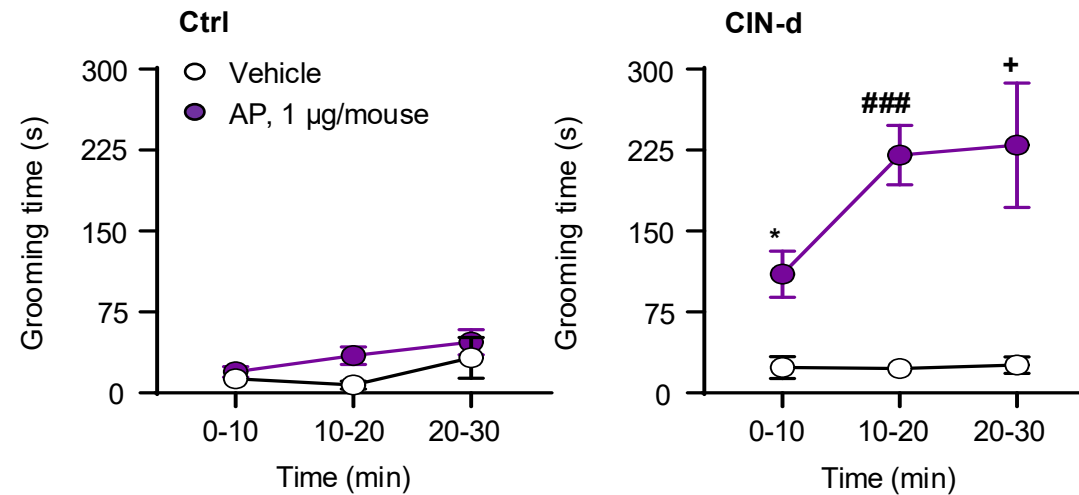


# Systemic and intra-PFC AP increases tic-related behaviors in CIN-d male mice

## Systemic AP



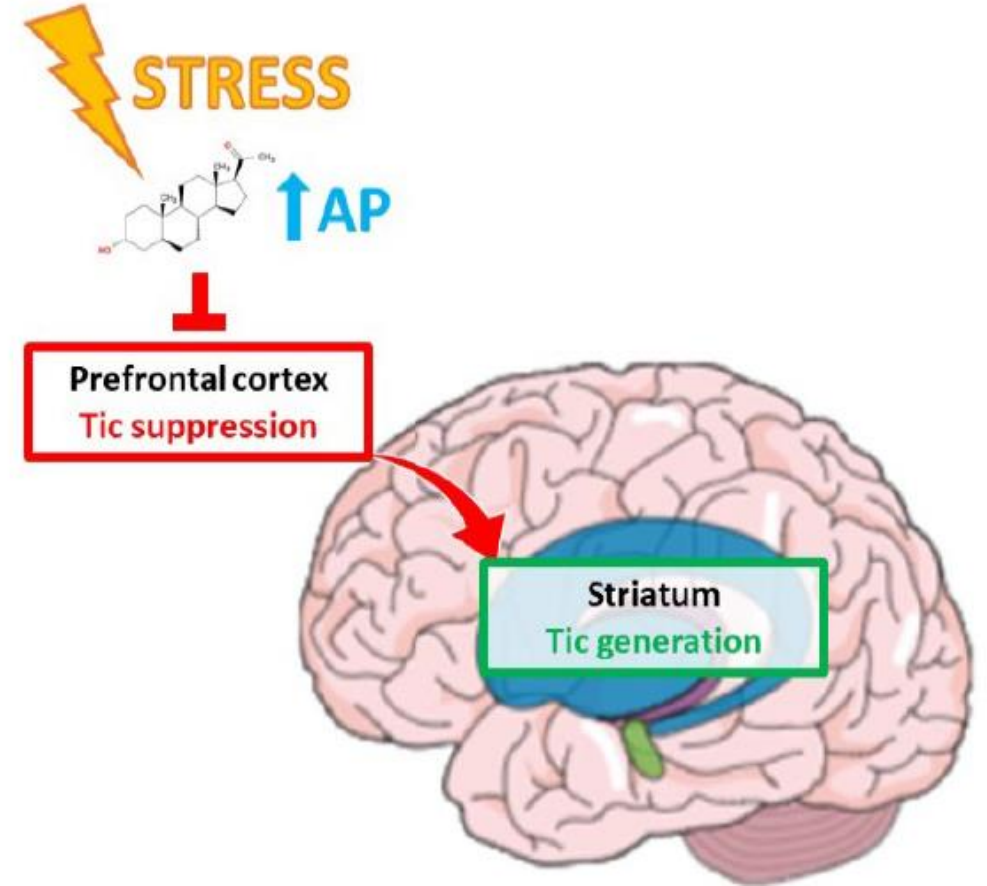
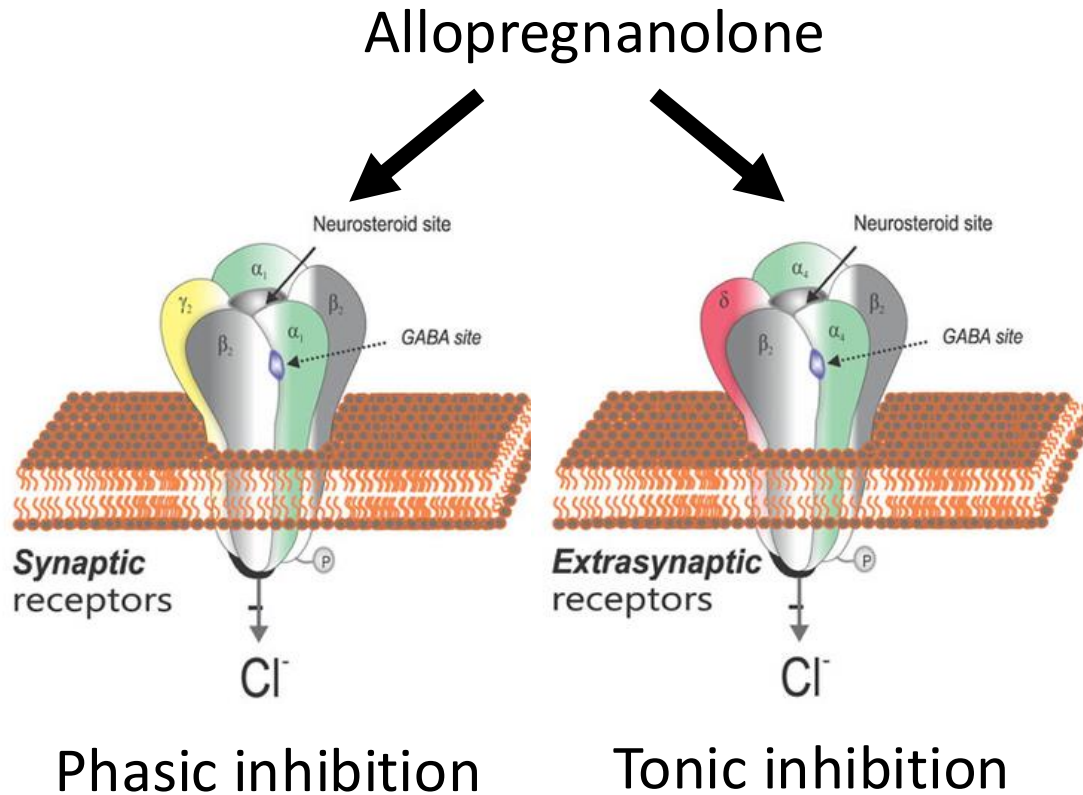
## Intra-PFC AP



Cadeddu *et al.*, Neuropsychopharmacology, 2023

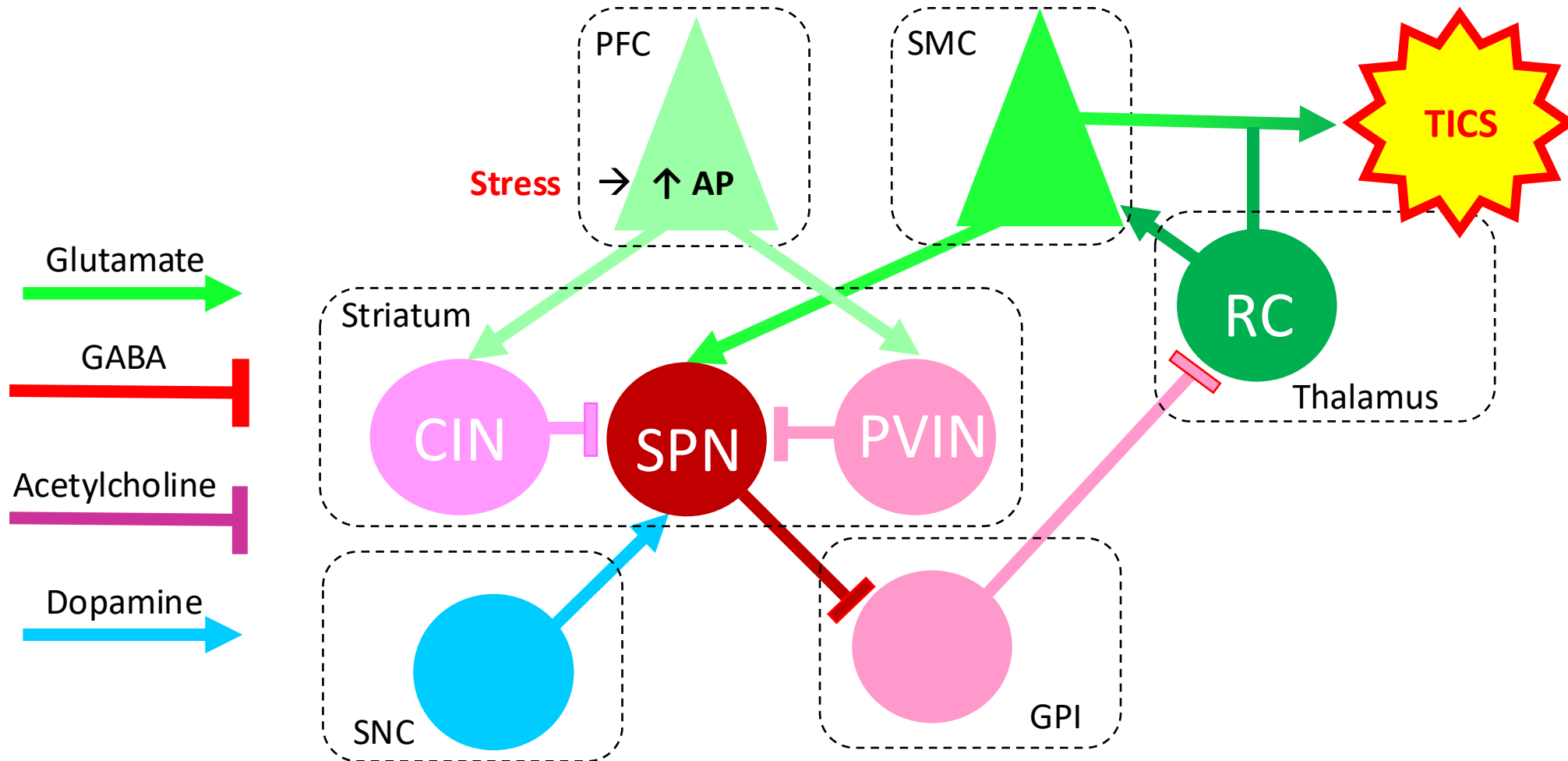
AP also mediates the exacerbation of tic-like behaviors in other mouse models

# Allopregnanolone activates GABA-A receptors

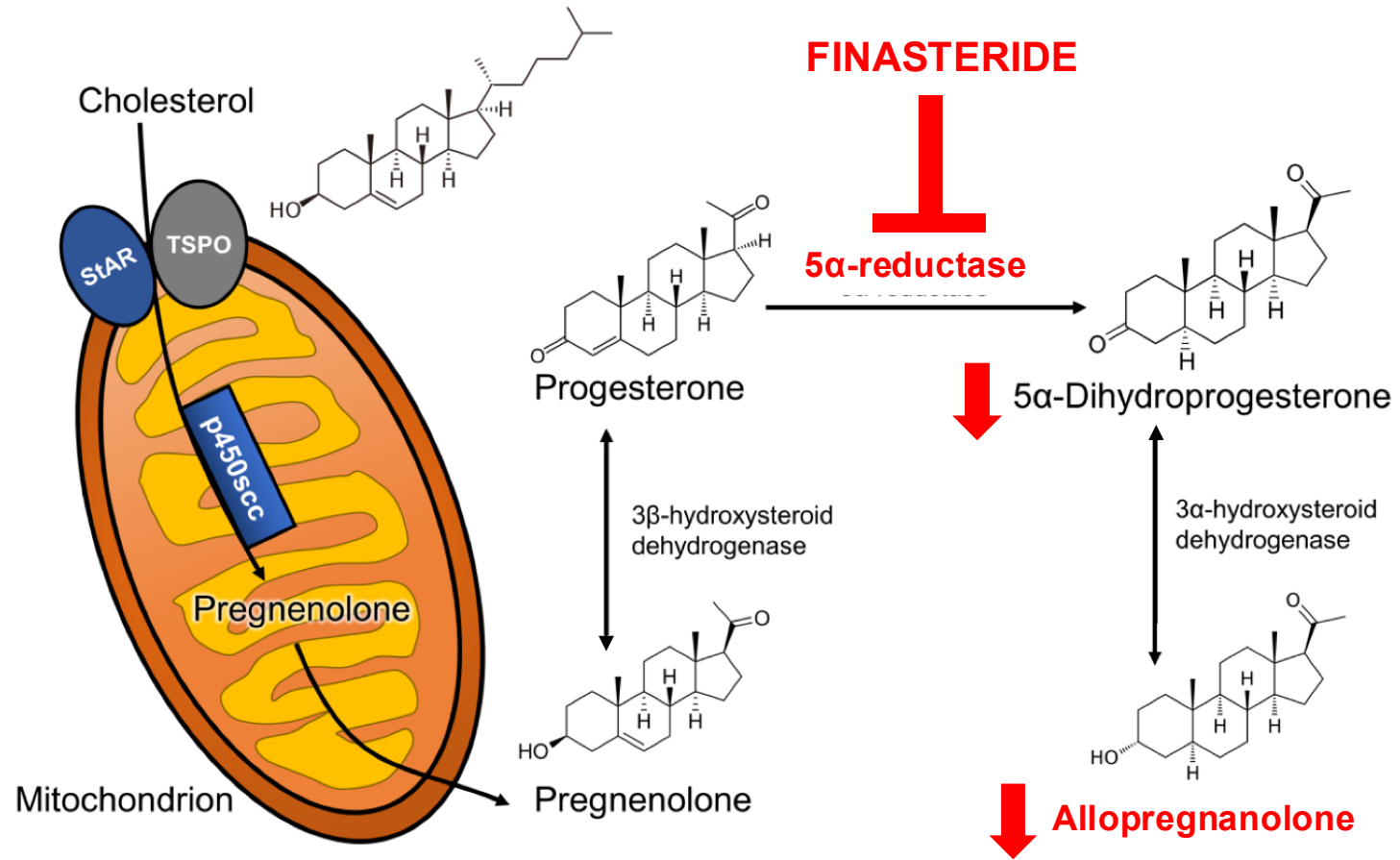


AP inhibits PFC functions by activating GABA-A receptors → **lower ability to suppress tics**

# Stress exacerbates tics by promoting AP synthesis in the PFC

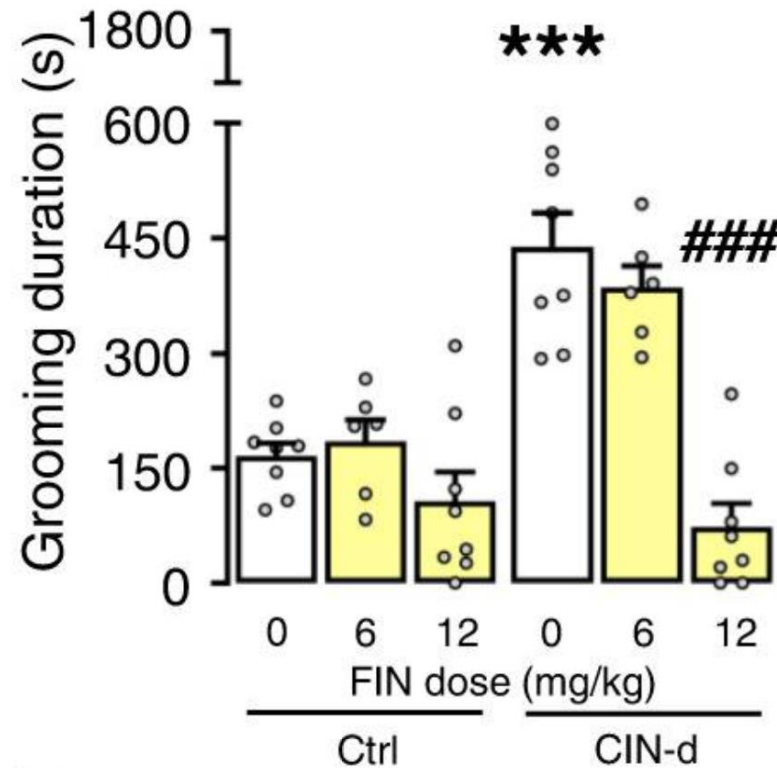


# FINASTERIDE



- Approved by FDA for treatment of benign prostatic hyperplasia and alopecia in humans
- By blocking 5α-reductase, finasteride reduces the synthesis of several neuroactive steroids
- **Finasteride also dramatically reduces AP synthesis in the PFC**

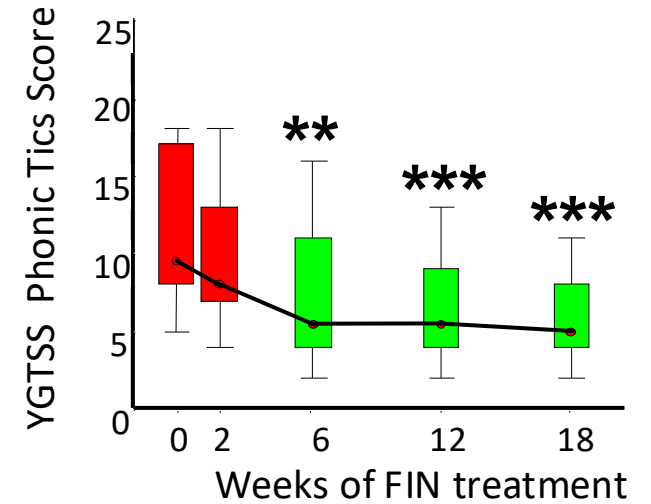
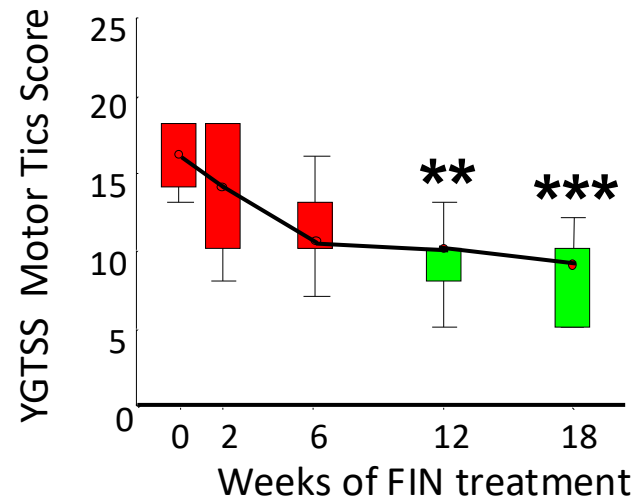
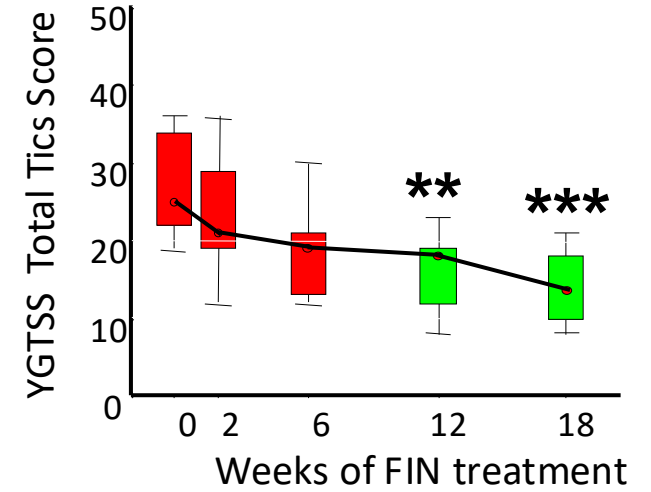
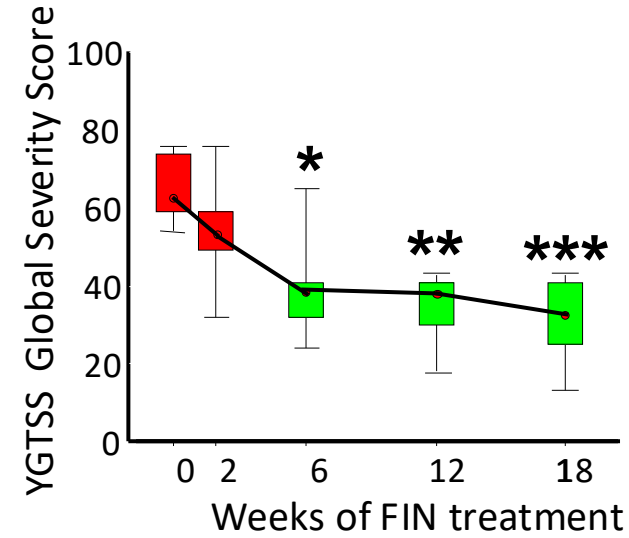
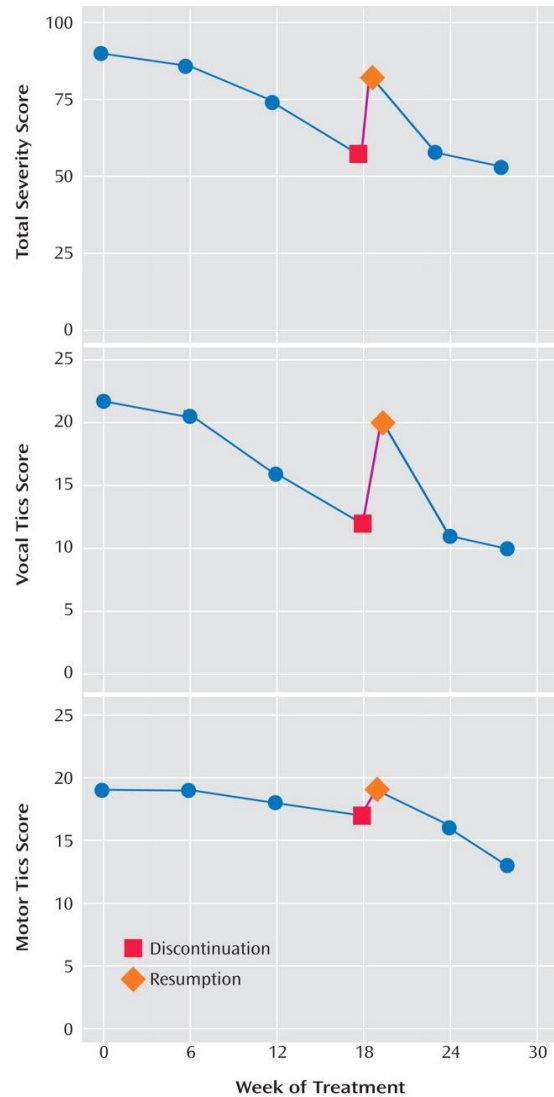
## Finasteride counters the enhancement in grooming stereotypies induced by stress in CIN-d mice



Cadeddu et al, *Neuropsychopharmacology*, 2024

Finasteride and other 5 $\alpha$ R inhibitors also **ameliorate tic-like behaviors in CELSR3 mutant mice.**

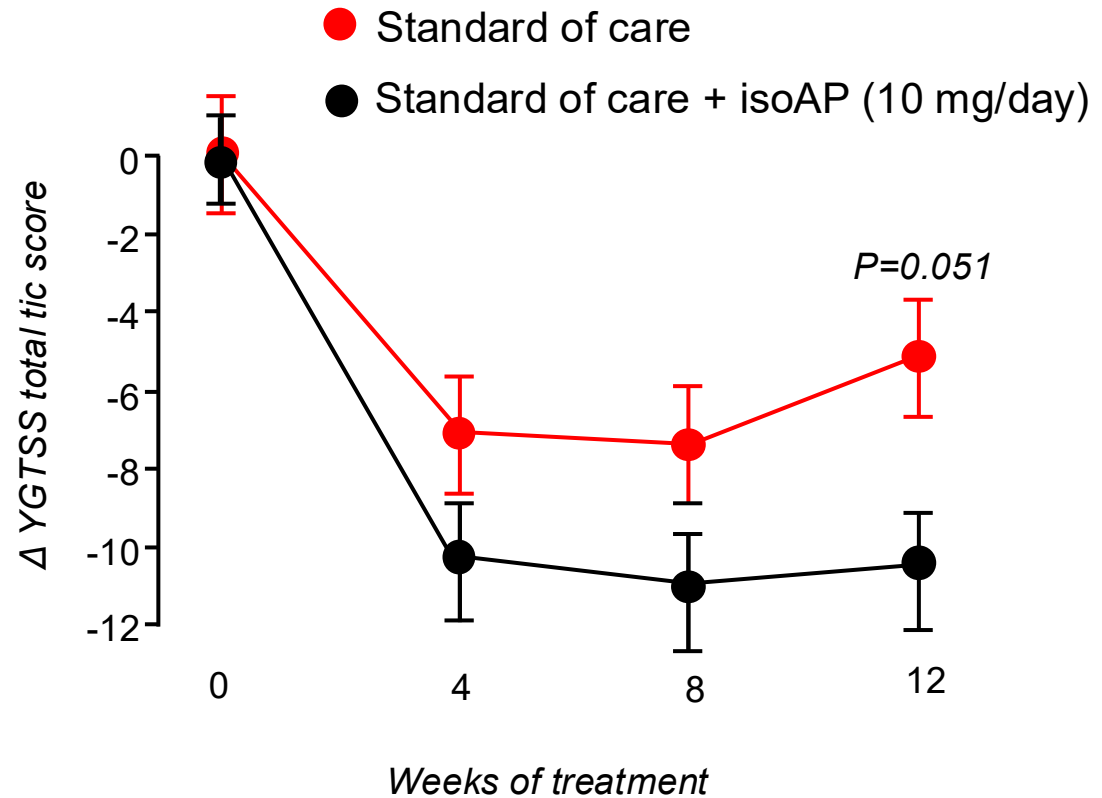
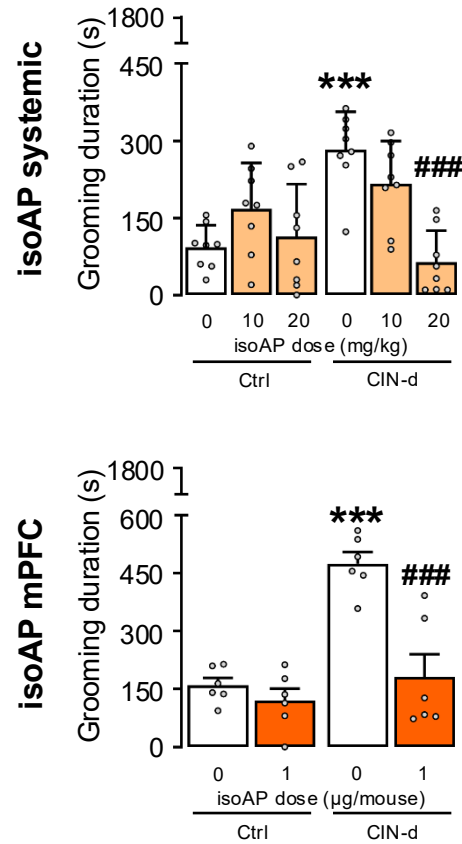
# Finasteride reduces tics in treatment-refractory Tourette syndrome patients



Bortolato et al , *Am J Psych*, 2007

Muroni et al, *Mov Disord*, 2011

# The AP antagonist isoAP has positive effects in mouse models of tic disorders and Tourette syndrome patients



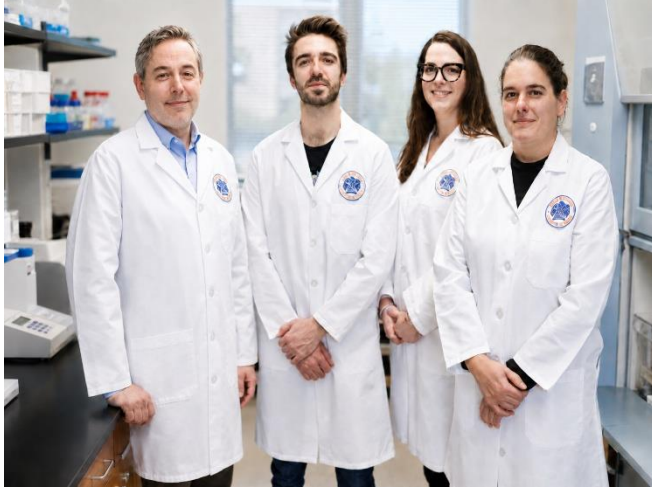
Cadeddu *et al.*, 2023, Neuropsychopharmacology

Phase II-a study with 26 patients  
H. Biernat & N. M. Mol Debes

# Conclusions and take-home messages

- **Animal models of TS are instrumental to study TS pathophysiology**
- Using complementary models of TS may be a key strategy to identify new therapeutic targets and putative treatments
- We documented that **CELSR3-deficient mice exhibit tic-like behaviors** due to shifts in **D<sub>3</sub> dopamine receptors** in the dorsal striatum
- Our data indicate that stress may exacerbate symptoms via increased synthesis of the neurosteroid **allopregnanolone** in the dorsolateral PFC
- Therapies that reduce allopregnanolone signaling (such as finasteride and **isoallopregnanolone**) may have promising potential for TS

# Acknowledgments



## Lab members:

**Caterina Branca, PhD**

**Giulia Braccagni, PhD**

**Madeleine Mueller, PhD**

**Easton VanLuik, BS**

**Roberto Cadeddu, PhD**

**Gabriele Floris, PhD**

**Sean C Godar, PhD**

**Laura J Mosher, PhD**

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Simona Scheggi (U Siena)

Graziano Pinna (UIC)

Philip Moos (U Utah)

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