# Putative novel pharmacological treatments for tic disorders: insights from animal models

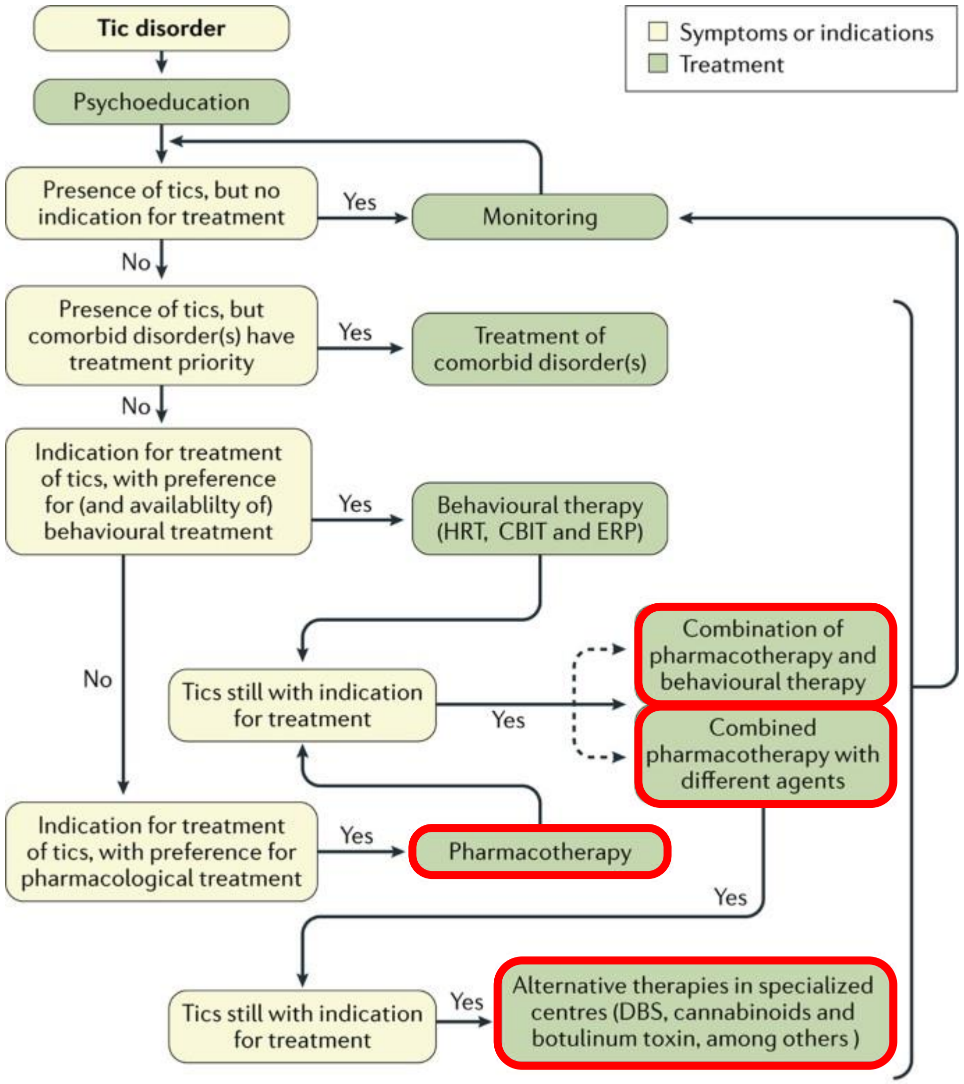
**Presented By**:

Marco Bortolato, MD PhD

# Disclosures

- MB is a member of the advisory board for Asarina Pharmaceuticals and has received research funding from Asarina, Lundbeck, and Alceptor Pharmaceuticals

# Treatment algorithm of tic disorders




Nature Reviews | Disease Primers

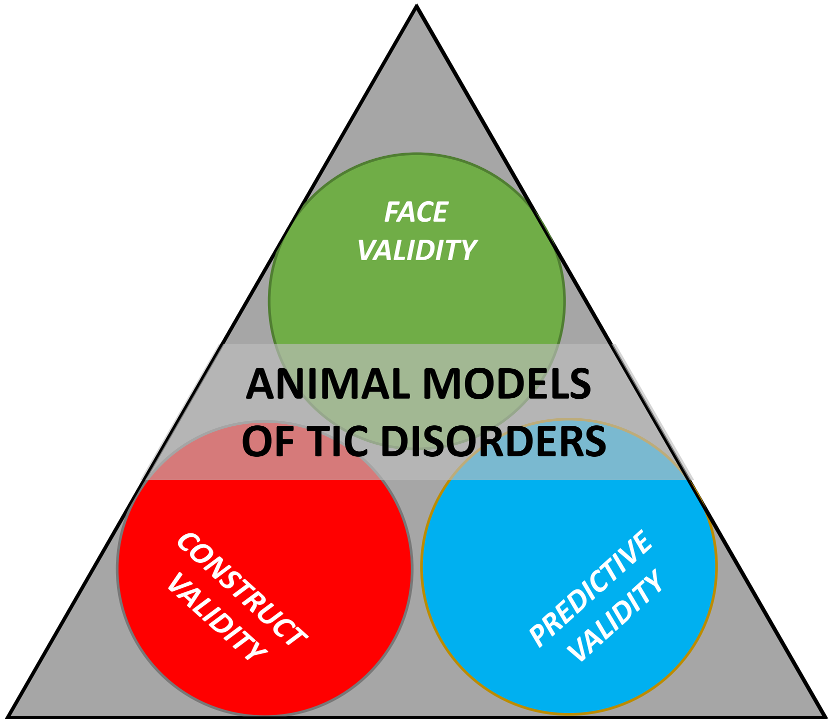
# Pharmacotherapy of tic disorders

| | Medications | Recommendation | Evidence quality |
|---|---|---|---|
| Antipsychotics | Haloperidol | Weak | High |
| | Pimozide | Weak | High |
| | Fluphenazine | Weak | Low |
| | Metoclopramide | Weak | Low |
| | Risperidone | Weak | High |
| | Aripiprazole | Weak | Moderate |
| | Olanzapine | Weak | Low |
| | Quetiapine | Weak | Very low |
| | Ziprasidone | Weak | Very low |
| Alpha 2 agonists | Clonidine | Strong | Moderate |
| | Guanfacine | Strong | Moderate |
| Other drugs | Topiramate | Weak | Low |
| | Baclofen | Weak | Very low |
| | Botulinum toxin | Weak | Low |
| | Tetrabenazine | Weak | Very low |
| | Cannabinoids | Weak | Low |

The development of new drug treatments for tic disorders with high efficacy, tolerability, and safety is an urgent and unmet need

To date, most therapeutic developments for tic disorders have been based on the repurposing of already-approved drugs

# Animal models of Tourette syndrome




***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

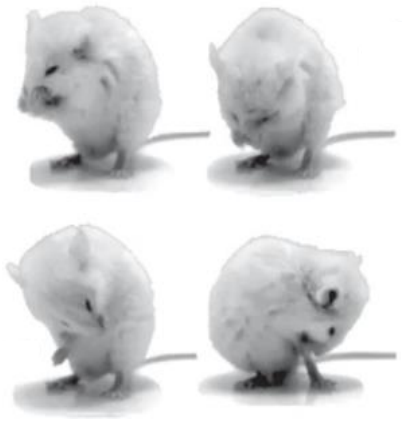
***Predictive validity***: sensitivity of animal model to validated treatments (antipsychotics, clonidine etc.) or risk factors (stress, sleep deprivation, etc.)

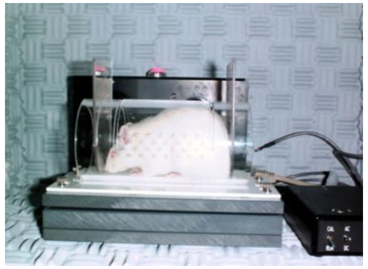
# Testing paradigms for face validity

## Tic-like responses

-Tic-like manifestations in animals can vary from **rapid bursts** to **repetitive stereotypies**

-Differences may be related to the specific mechanisms driving the semivoluntary mechanism (i.e., focal inhibition in the striatum vs dopamine hyperactivity etc.)

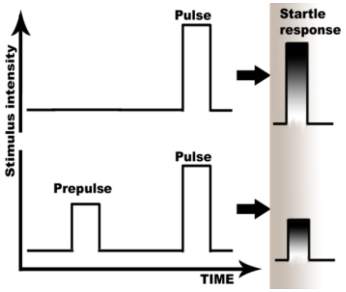




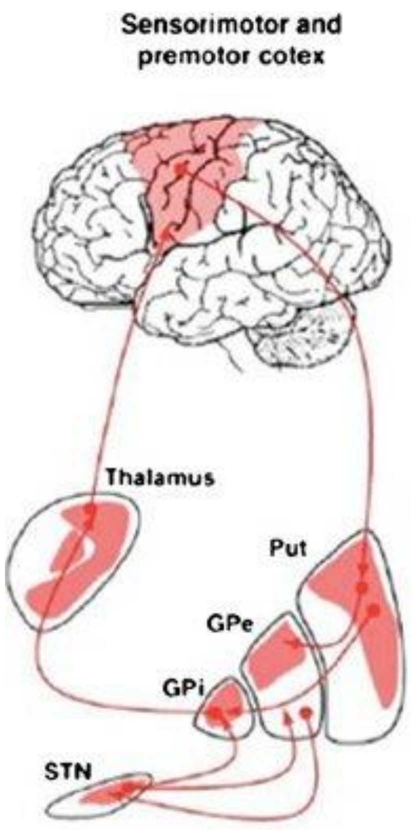
## Prepulse inhibition (PPI) of the startle

-PPI is the best-validated cross-species operational index for **sensorimotor gating**;

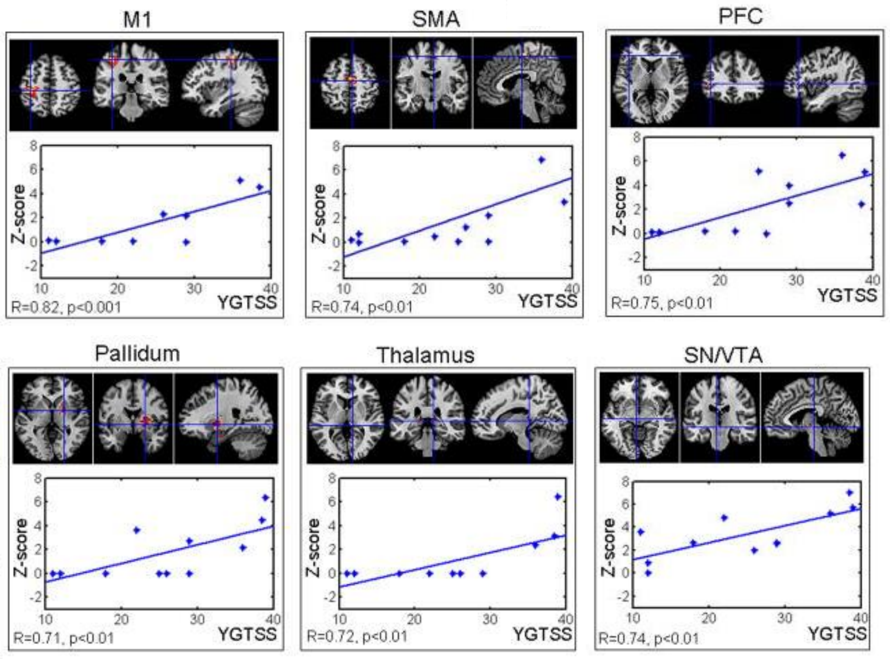
-TS individuals exhibit PPI deficits



# Pathophysiology of Tourette Syndrome




Adapted from Lapidus et al, 2014



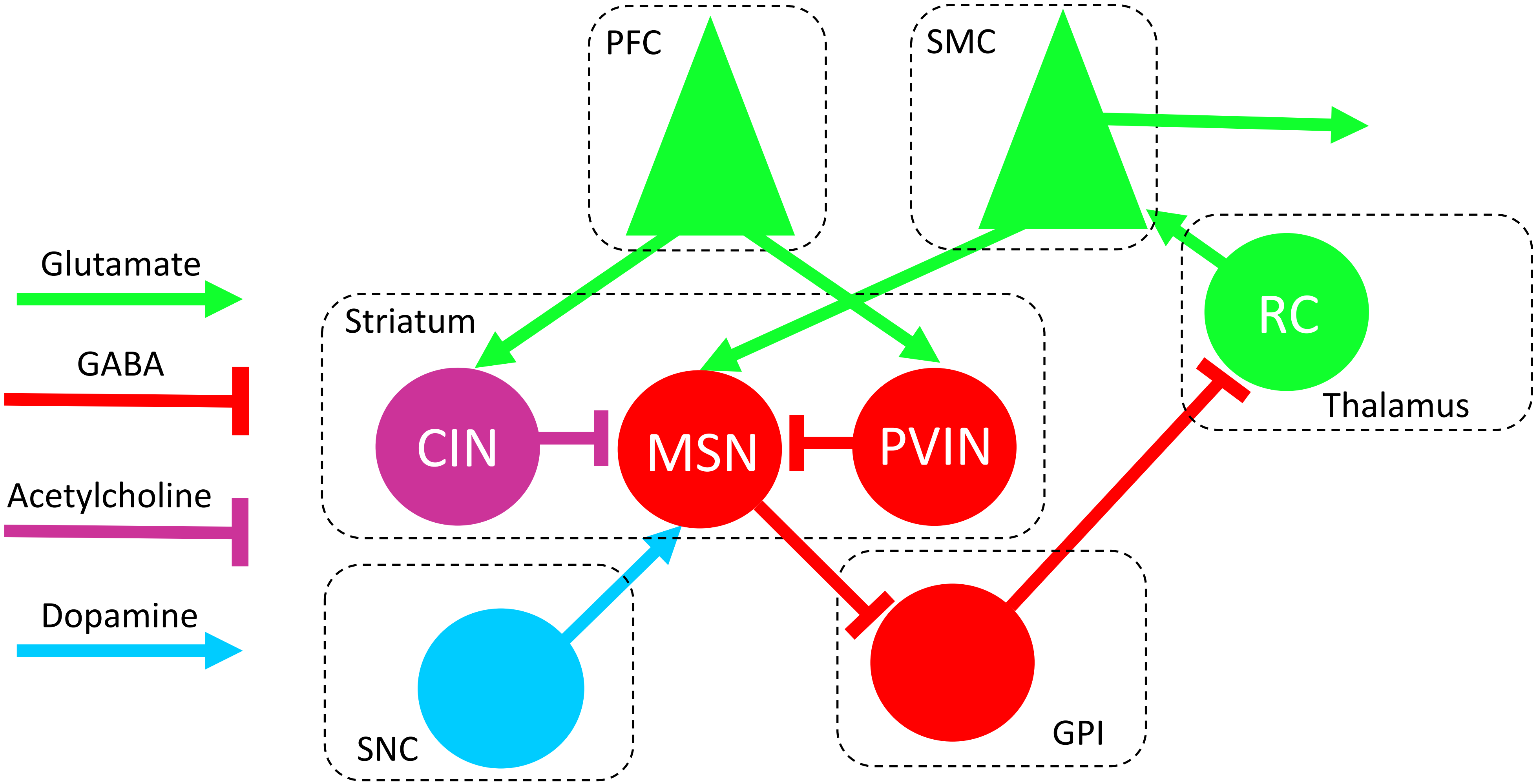

Wang et al., 2011

TS patients exhibit **stronger neural activity** in **sensorimotor cortex, putamen, pallidum,** and **substantia nigra**

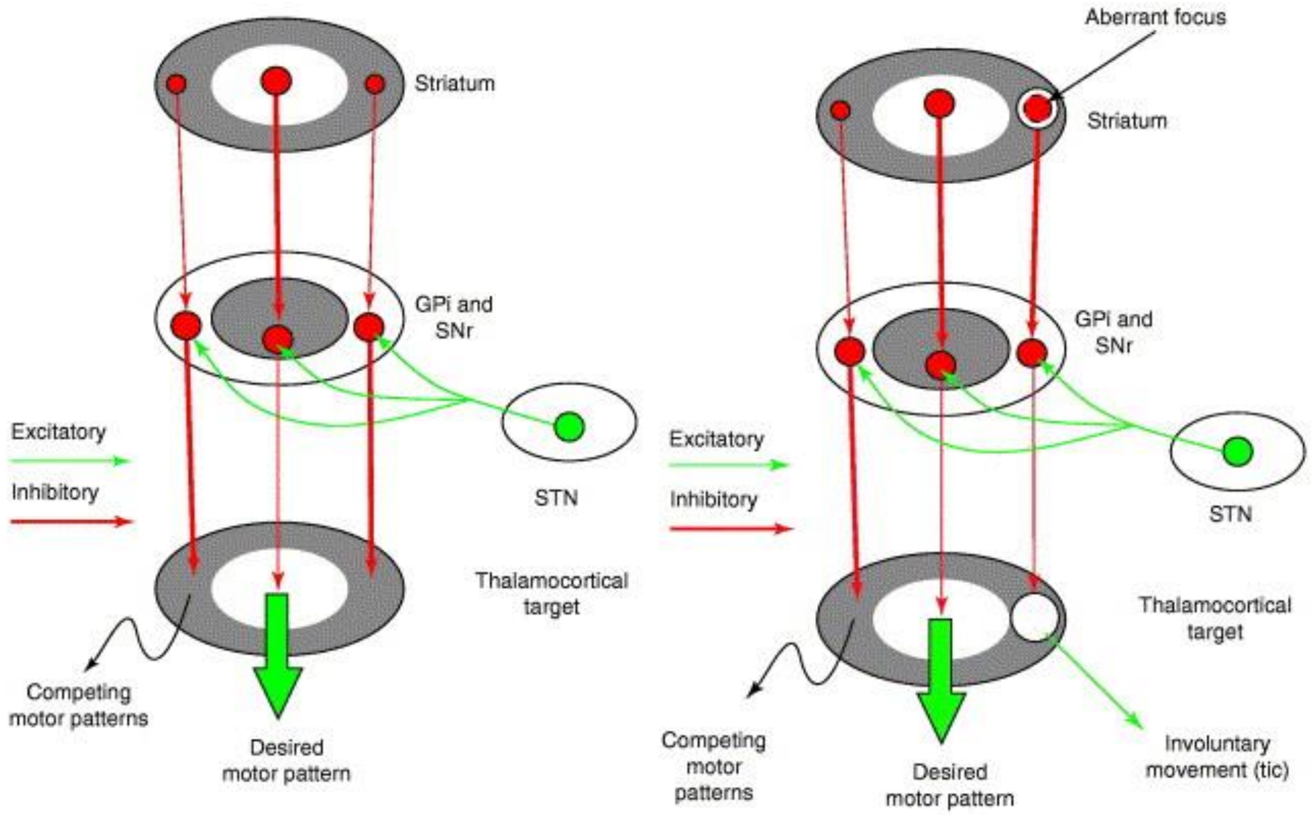
Activity in these areas correlate positively with tic severity

TIC CON

# Simplified schematization of CSTC circuitry



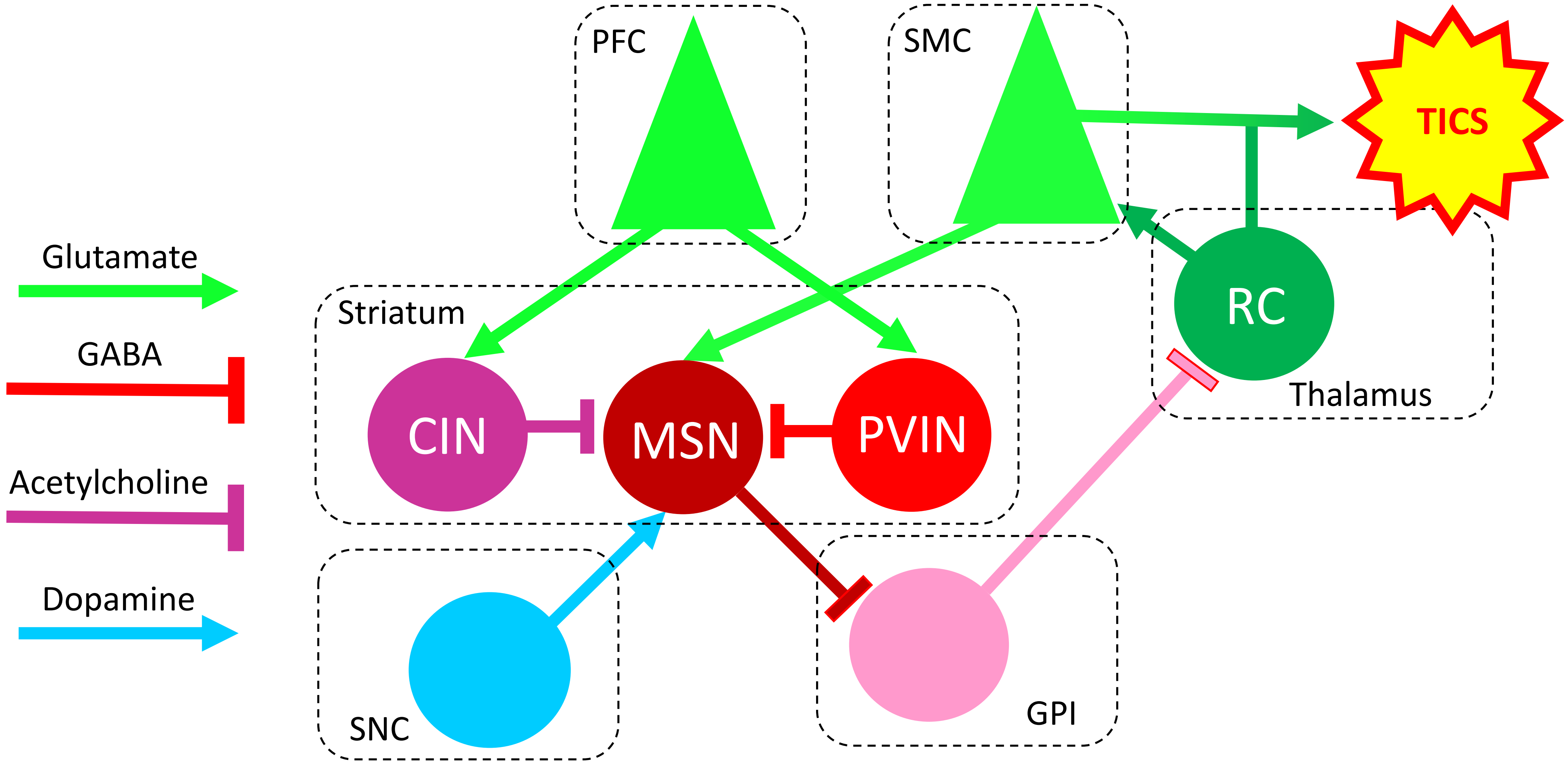
# Aberrant foci




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

# Hyperactivation of medium spiny neurons leads to tics



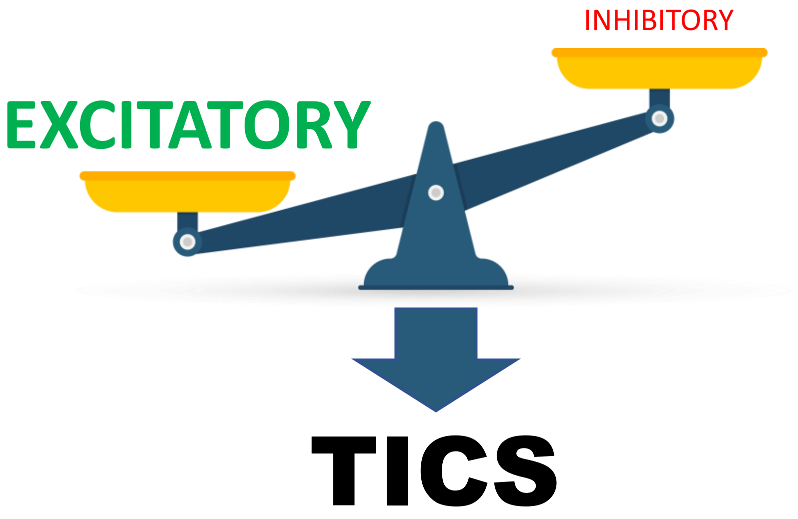
# Tics are the result of signal imbalances in medium spiny neurons

**Excitatory signals:**

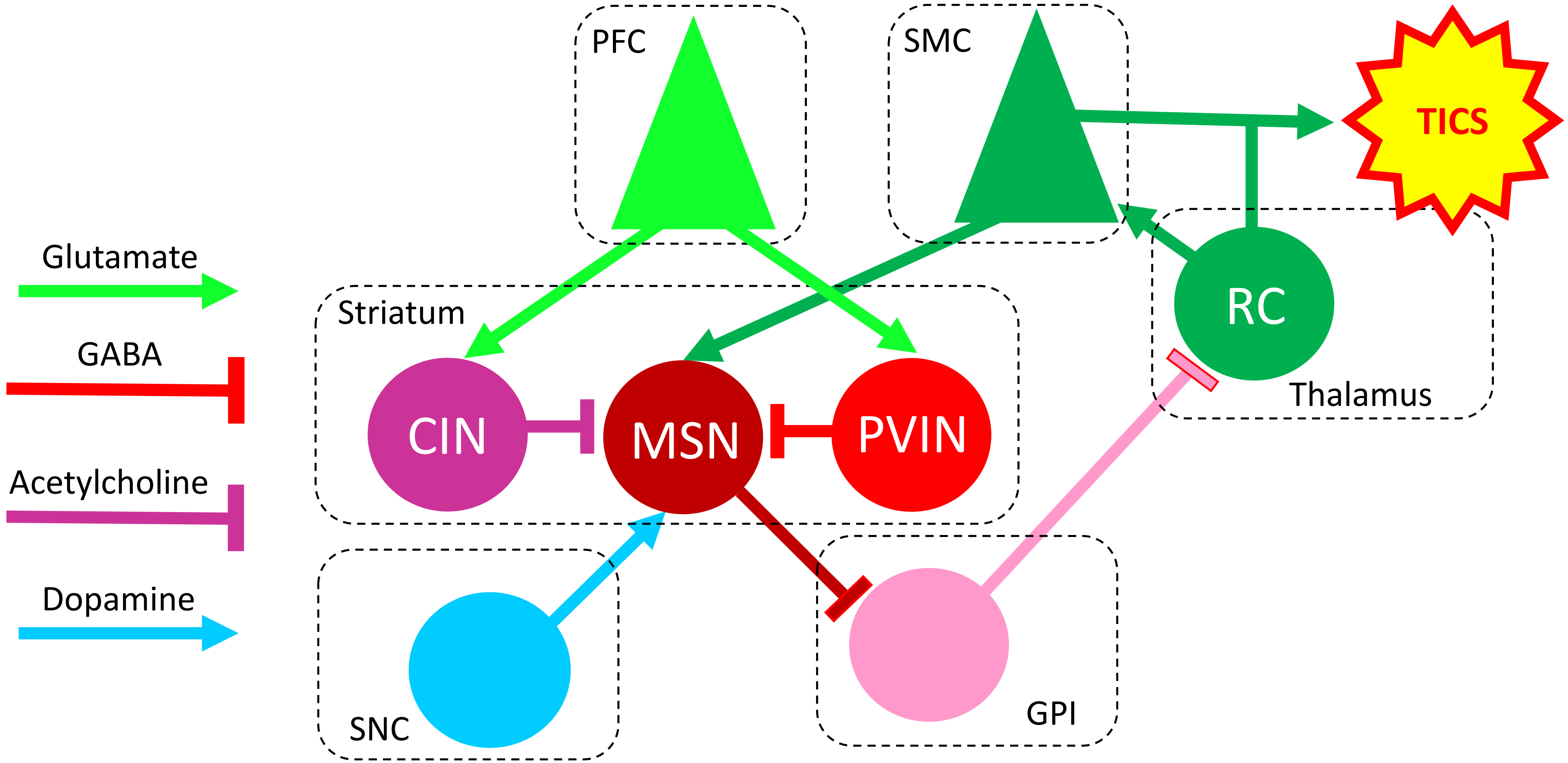
- Glutamate from cortex
- Glutamate from thalamus
- Dopamine from substantia nigra

**Inhibitory signals:**

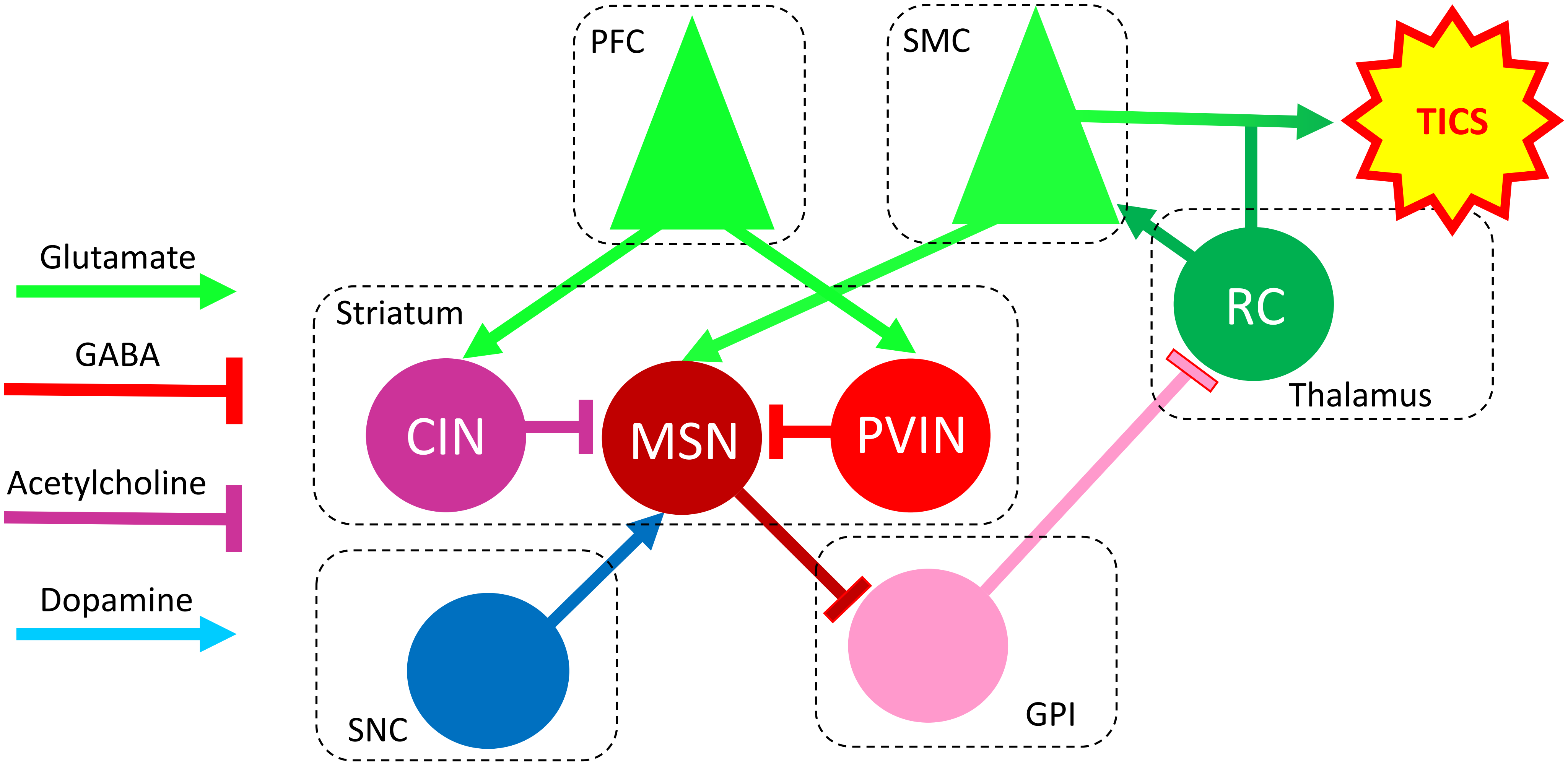
- Acetylcholine from str. interneurons
- GABA from str. interneurons
- Prefrontal control on interneurons

# Activation of sensorimotor cortex



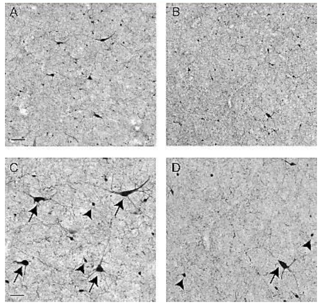
# Activation of dopaminergic pathways

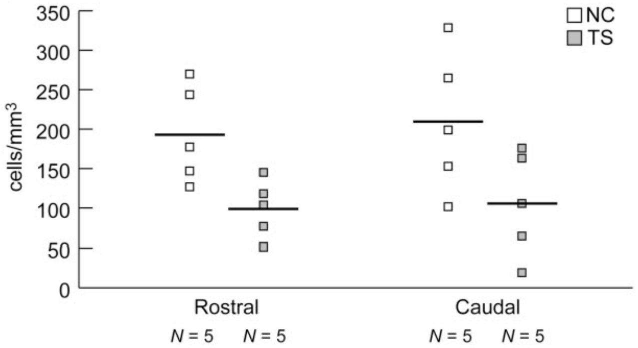


# Striatal interneuronal deficits in TS

TS

CTL



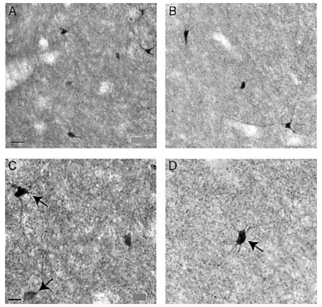


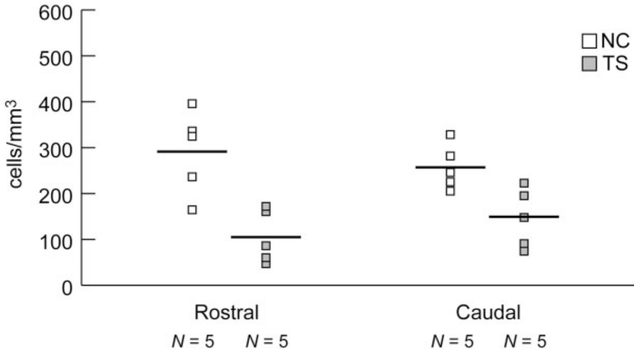

CIN

| CAUDATE | HEAD | BODY |
|---|---|---|
| CIN | - 53.5% | - 44.9% |
| PVIN | - 60.1% | - 54.6% |
| CRIN | - 60.5% | - 51.9% |

TS

CTL



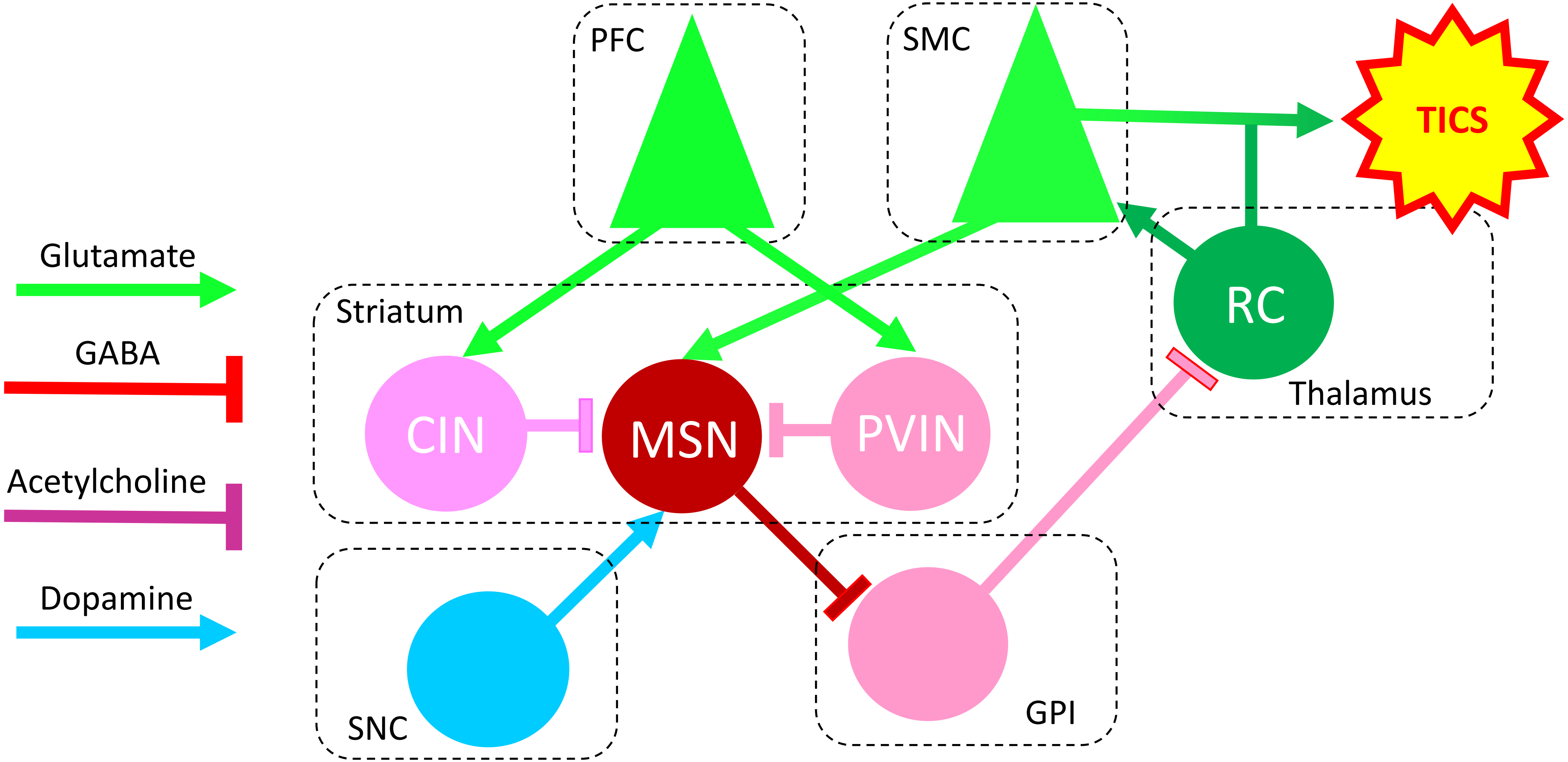



PVIN

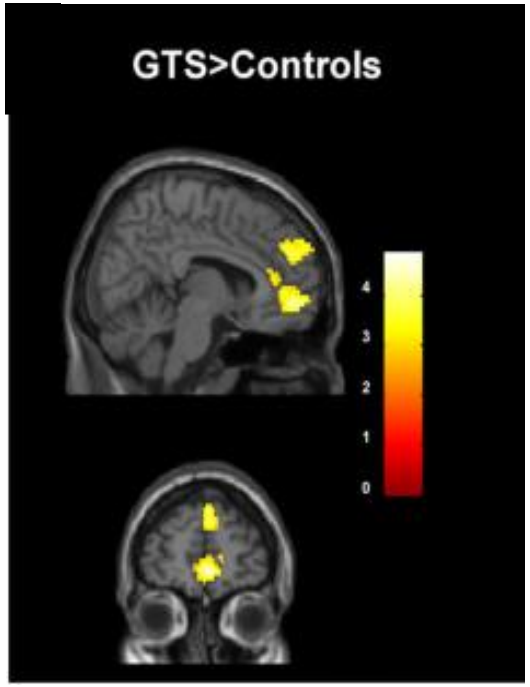
| PUTAMEN | ROSTRAL | CAUDAL |
|---|---|---|
| CIN | - 48.7% | - 49.5% |
| PVIN | - 63.9% | - 43.2% |
| CRIN | - 61.1% | - 38.3% |

The striatum in TS features significant deficits in **cholinergic (CIN),** parvalbumin-GABAergic (PVIN) and Nitric Oxide Synthase1/Neuropeptide Y/Somatostatin-GABAergic interneurons (Kalanithi et al., 2005; Kataoka et al., 2011; Lennington et al., 2016)

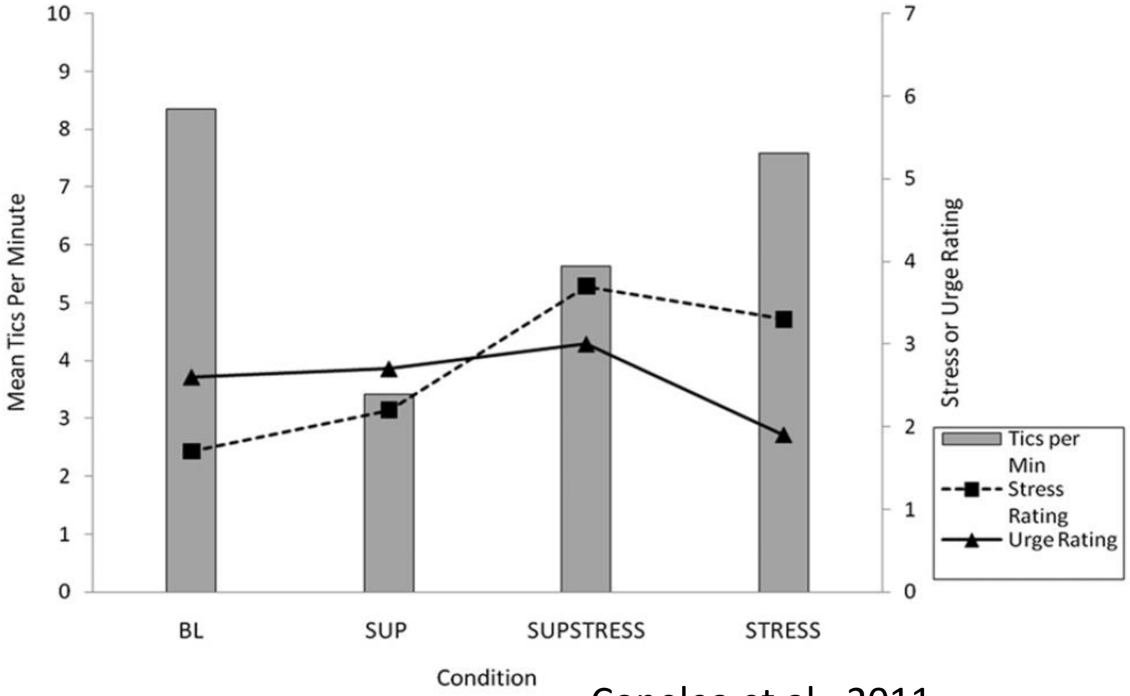
# Loss of interneurons



# Prefrontal cortex activation enables tic suppression




Van der Salm et al., 2018

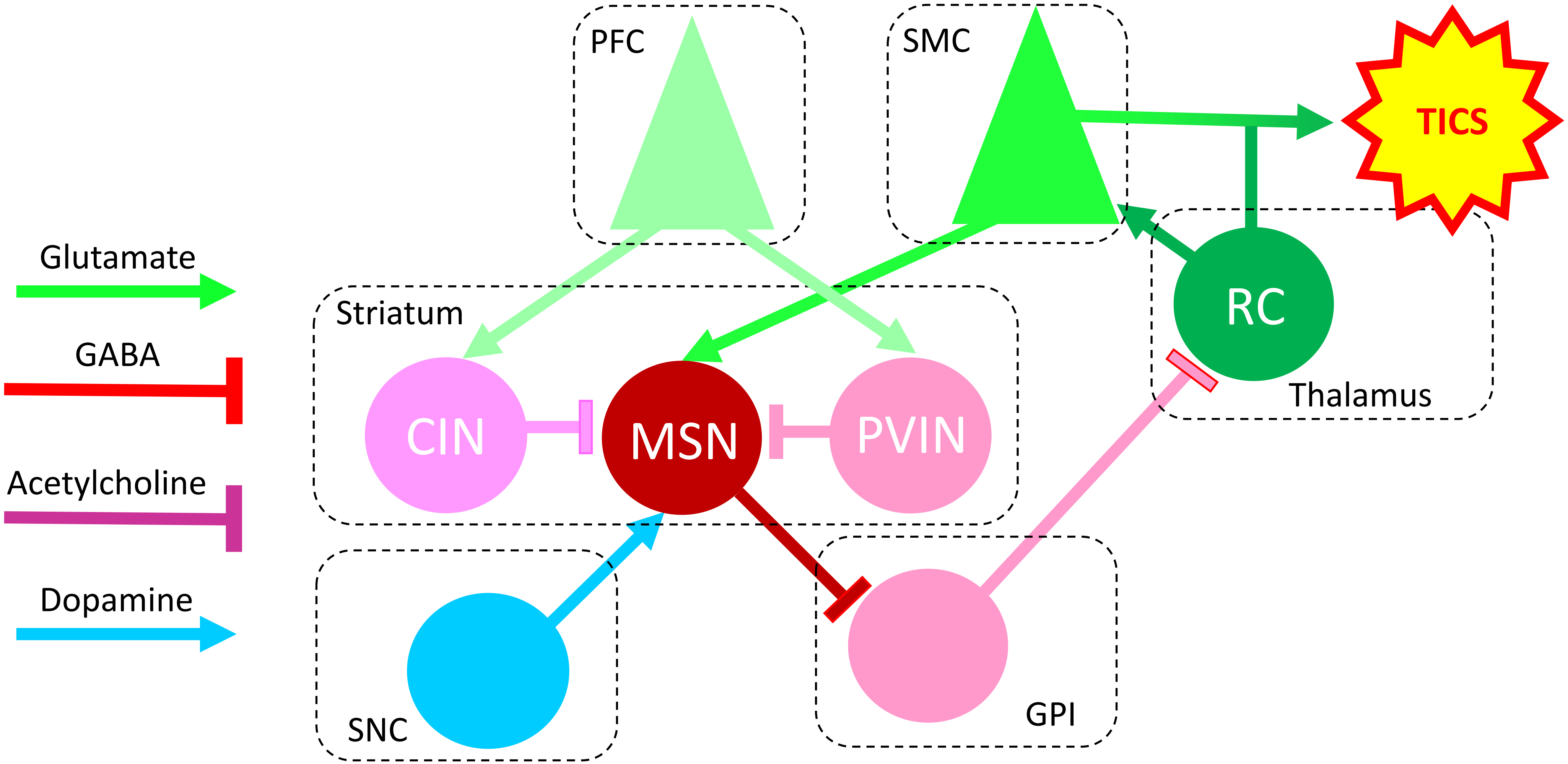



Conelea et al., 2011

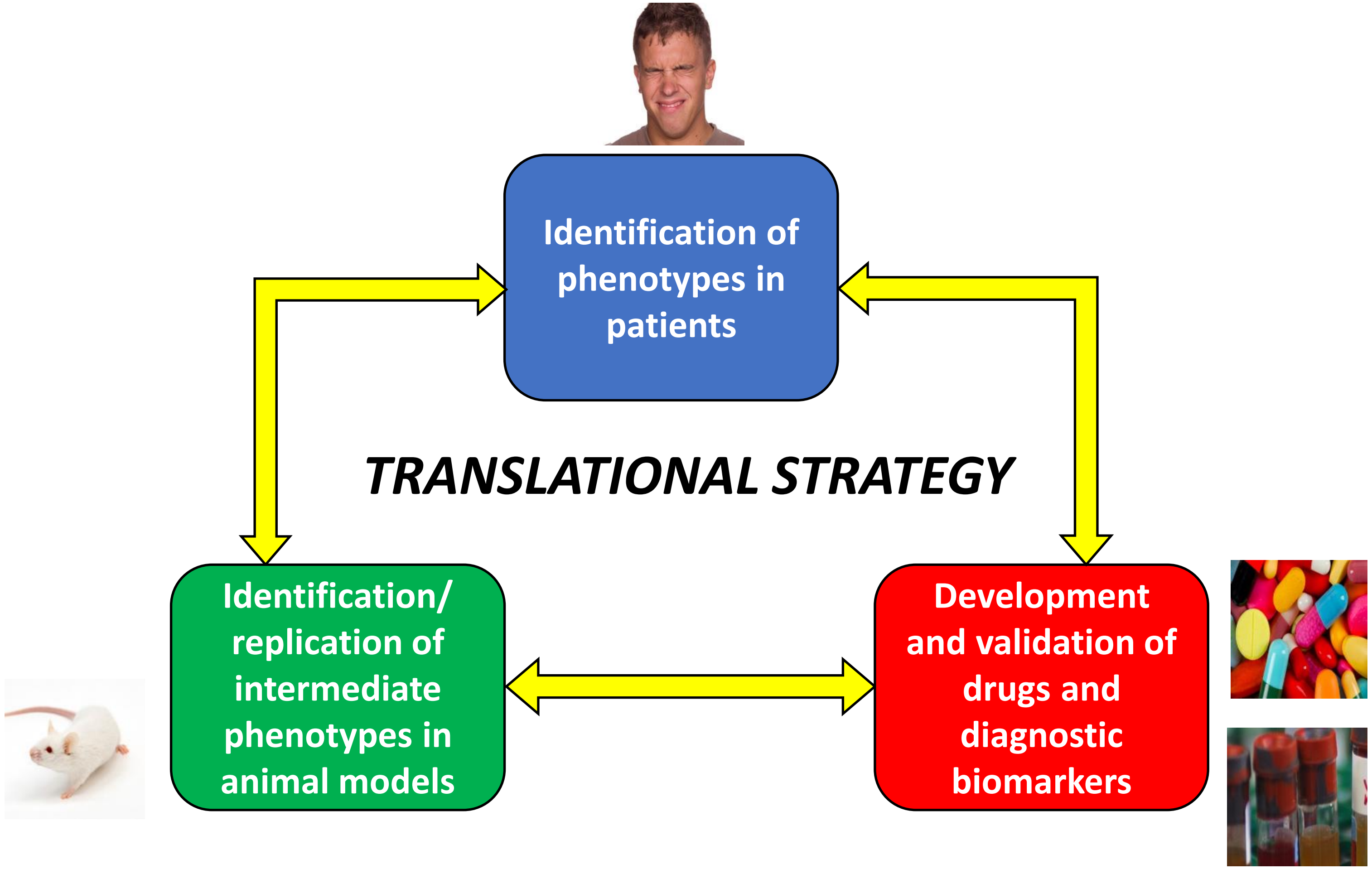
Recent evidence shows that **tic suppression increases PFC activity in TS**

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

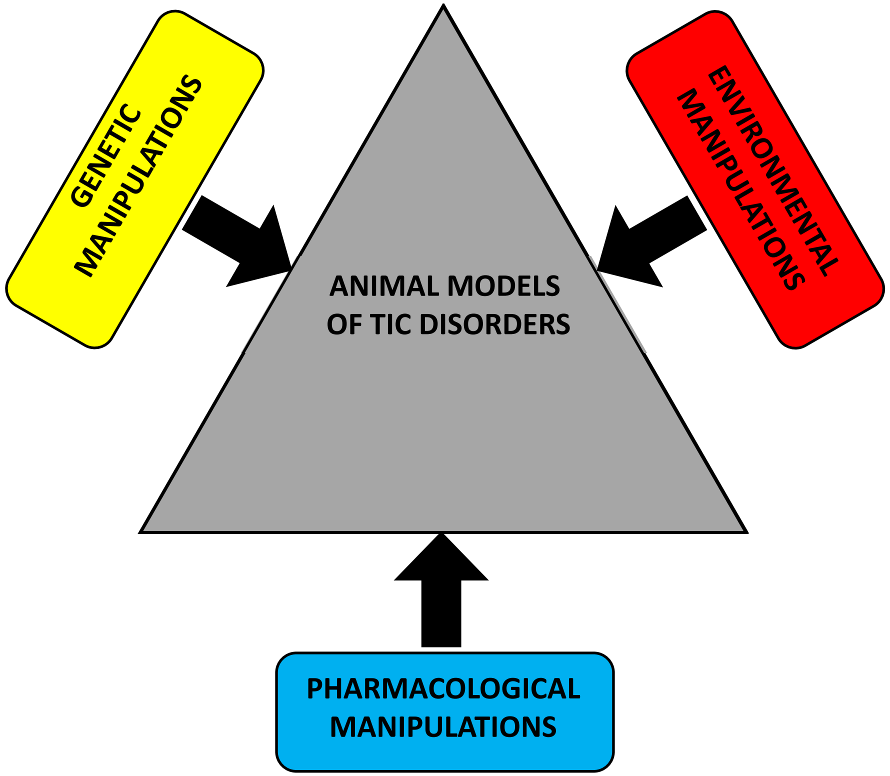
# Insufficient prefrontal control



# Developing animal models of TS



# How do we generate animal models of TS?




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

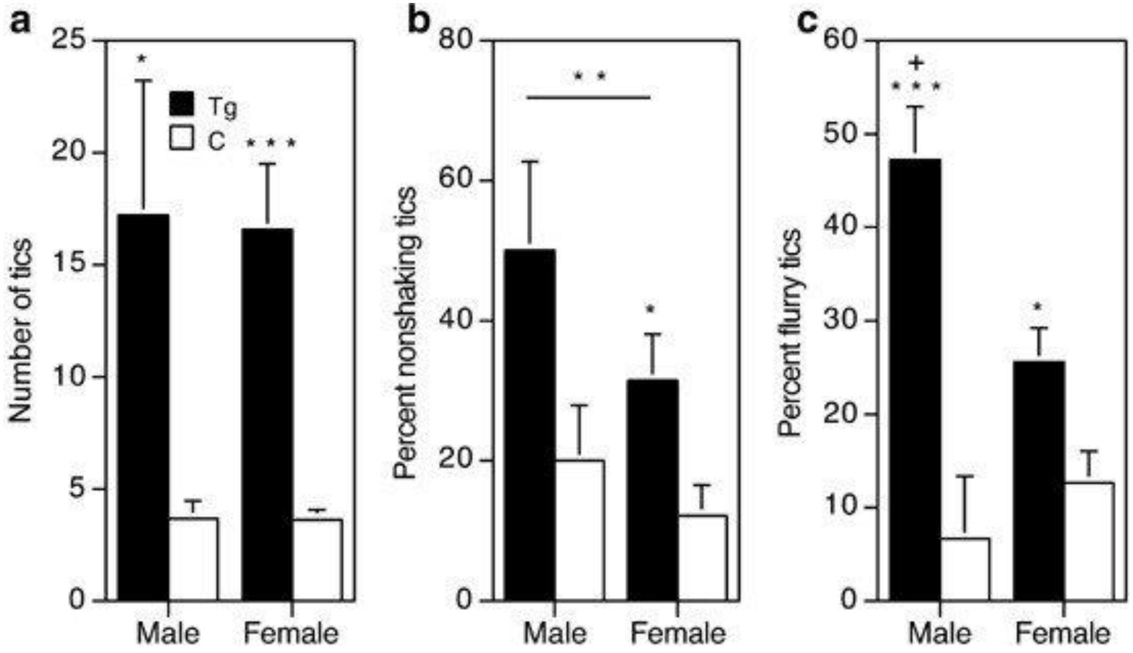
***Environmental manipulations*:**
based on exposure to factors associated with higher risk for TS

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

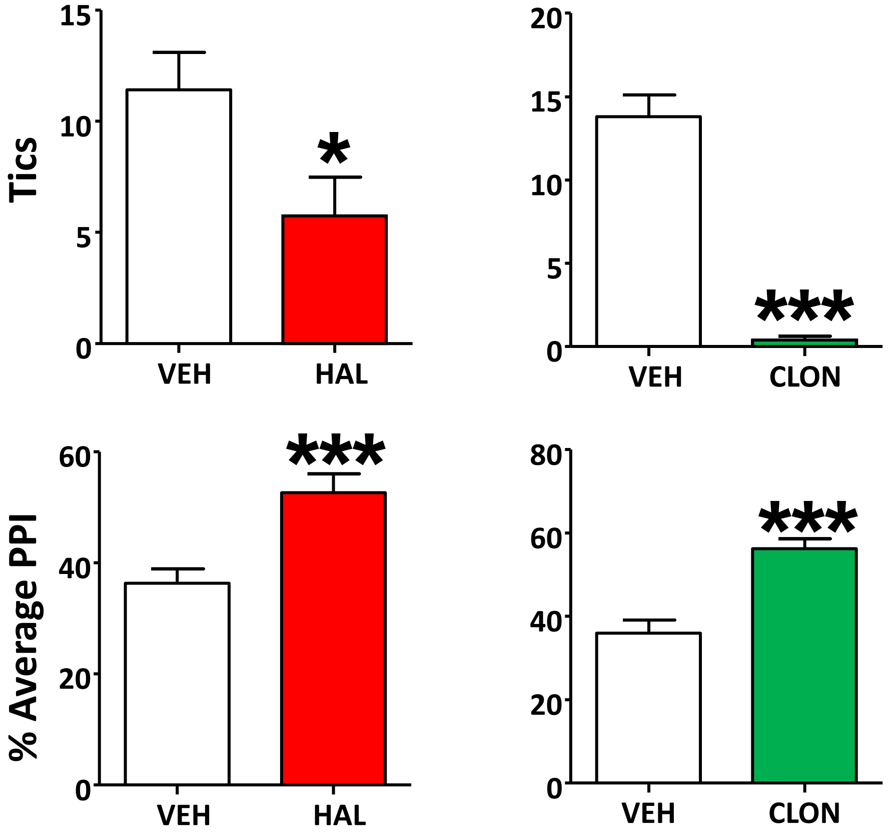
# Animal models of Tourette syndrome

| | | |
|---|---|---|
| **GENETIC MANIPULATION** | DAT1 | PPI deficits, perseverative behaviors |
| | MAOA | Perseverative and stereotyped behaviors |
| | SLITRK1 | Anxiety-like behaviors |
| | NLGN4 | Repetitive behaviors |
| | CNTNAP2 | Perseverative and stereotyped behaviors |
| | HDC | Perseverative and stereotyped behaviors |
| | DLGAP3 | Excessive grooming |
| **ENVIRONMENTAL MANIPULATIONS** | Early-life stress | Impulsivity, perseverative and stereotyped behaviors |
| | Early-life inflammation | Increasing grooming and rearing |
| **PHARMACOLOGICAL/ LESIONAL MANIPULATIONS** | Dopaminergic activation | PPI deficits, perseverative behaviors |
| | Striatal GABAergic antagonism | Tics |
| | **Cortical neuropotentiation** | **Tics, Repetitive behaviors, PPI deficits** |
| | **Interneuron depletion** | **Repetitive behaviors, PPI deficits** |

# D1CT-7 mice: a model of cortical neuropotentiation



# D1CT-7 mice are sensitive to hallmark TS therapies

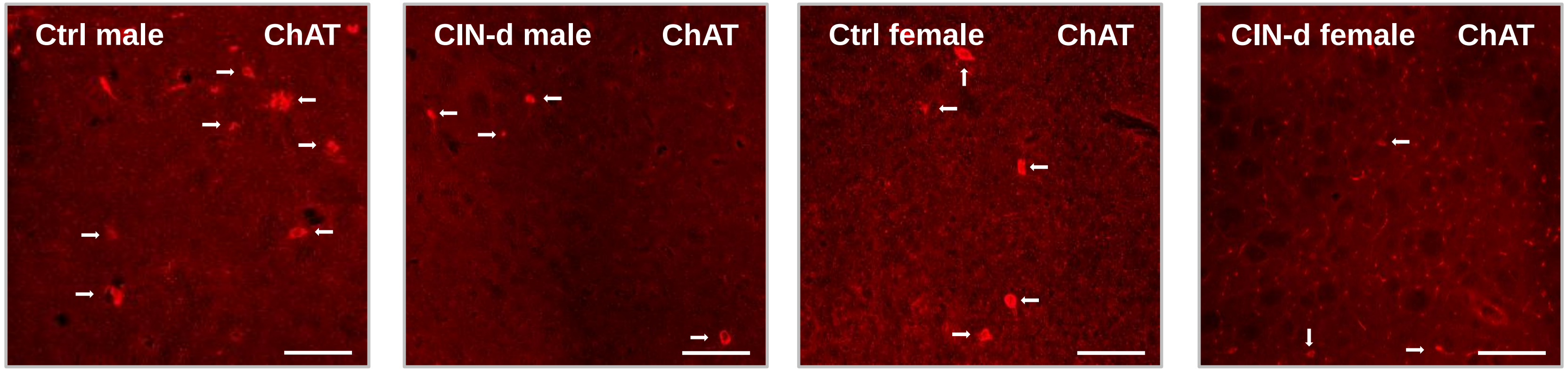


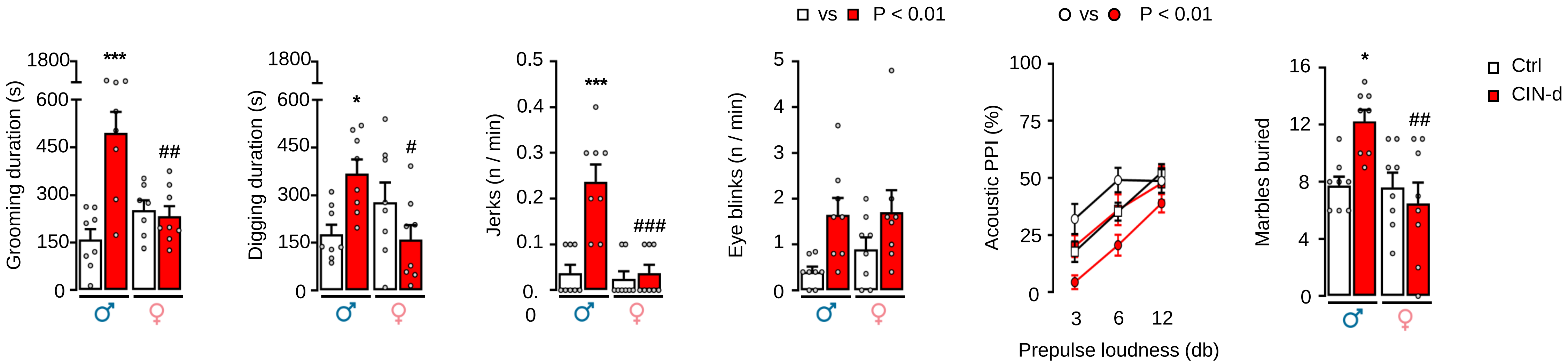

Haloperidol (0.3 mg/kg, i.p.)

Clonidine (0.2 mg/kg, i.p.)

**Godar *et al*, Br. J. Pharmacol, 2015**

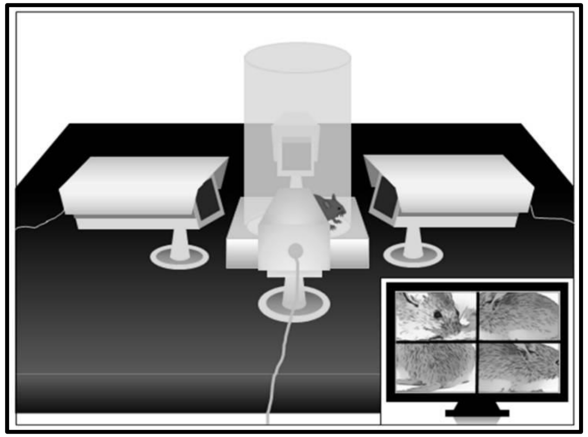
# CIN-d mice: a model of striatal disinhibition




**Cadeddu *et al*, Neuropsychopharmacology, 2023**

# CIN-d mice: a model of striatal disinhibition

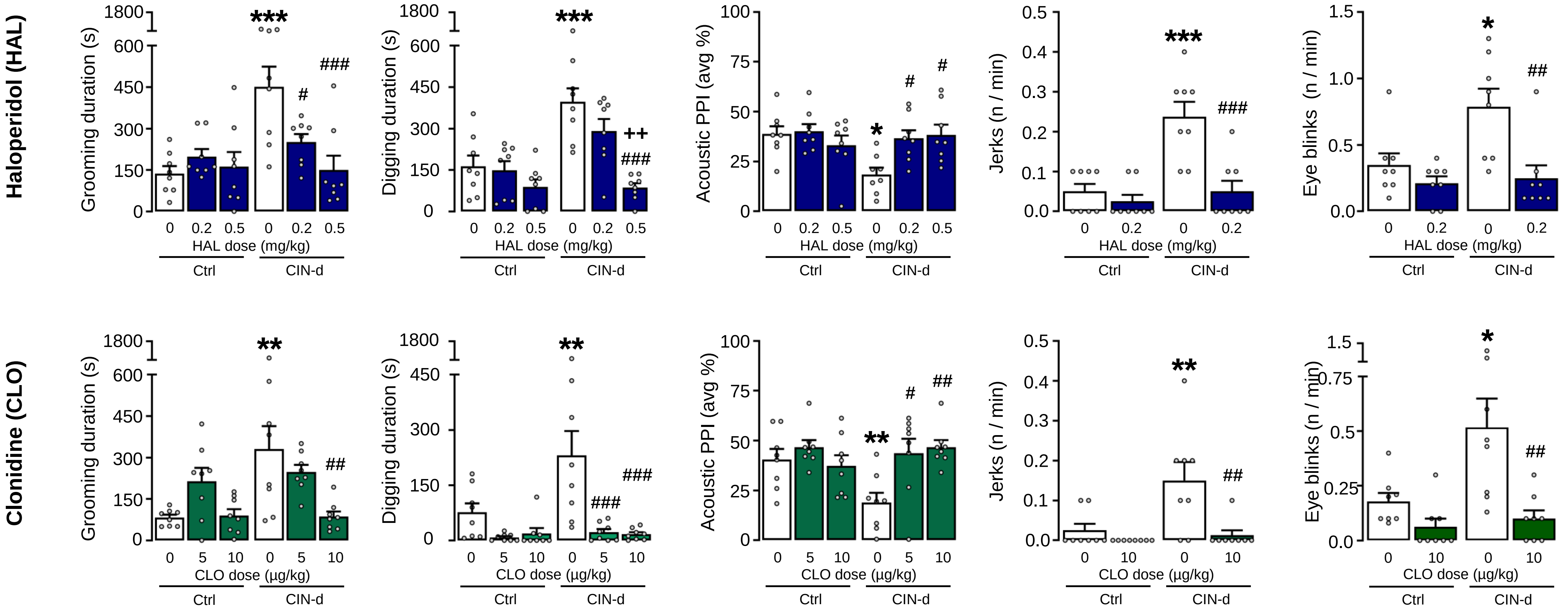



Grooming stereotypies


Tic-like jerks

**Cadeddu *et al*, Neuropsychopharmacology, 2023**

# CIN-d mice are sensitive to hallmark TS therapies

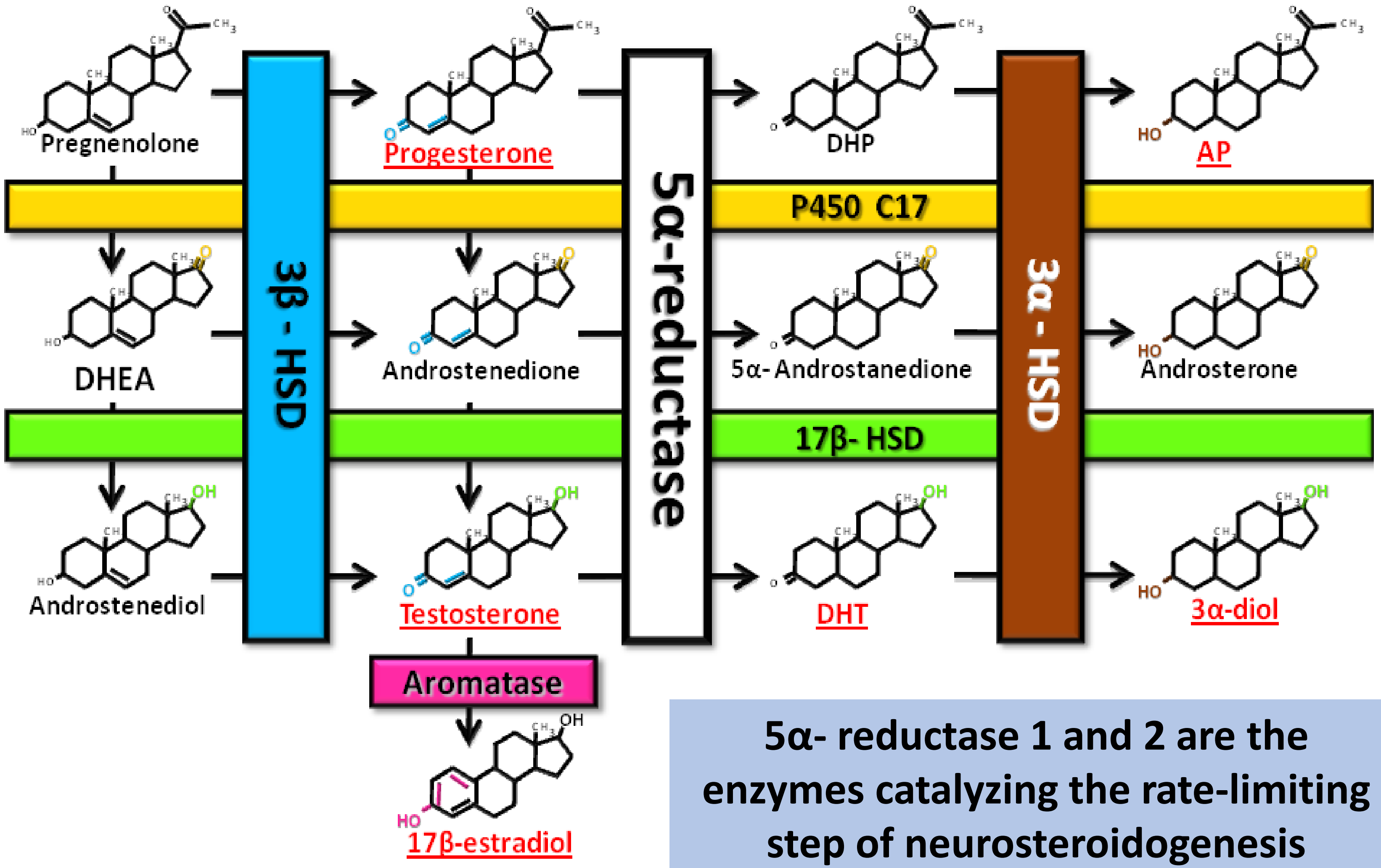



Cadeddu *et al*, Neuropsychopharmacology, 2023

# Can we use animal models to develop new treatments?

| New therapeutic targets | New putative treatments |
|---|---|
| Neurosteroids - allopregnanolone | Isoallopregnanolone & Finasteride |
| $M_4$ muscarinic receptors | Xanomeline, $M_4$ PAMs |
| $5\text{-}HT_{2A}$ serotonin receptors | Pimavanserin |
| Cannabinoids | ? |
| GABA-A receptors (α6) | DK-I-56-1 |

# Neurosteroids: important mediators of stress response

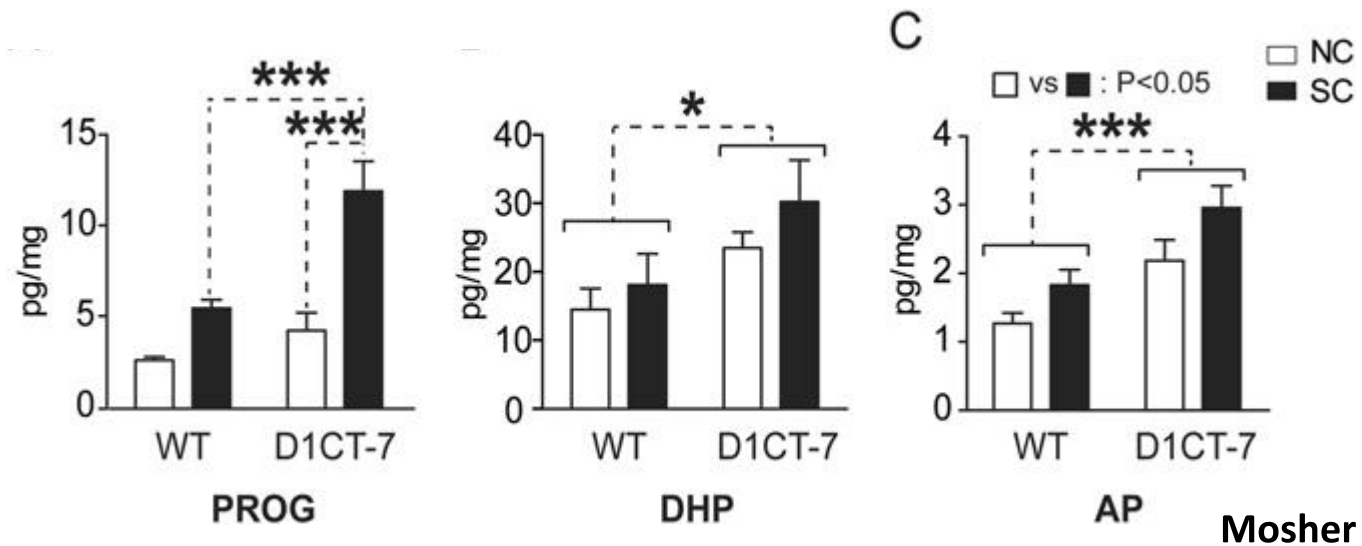



**5α- reductase 1 and 2 are the enzymes catalyzing the rate-limiting step of neurosteroidogenesis**

**Adapted from Paba, Frau, Devoto, Marrosu, Bortolato, Curr Pharm Des. 2011**

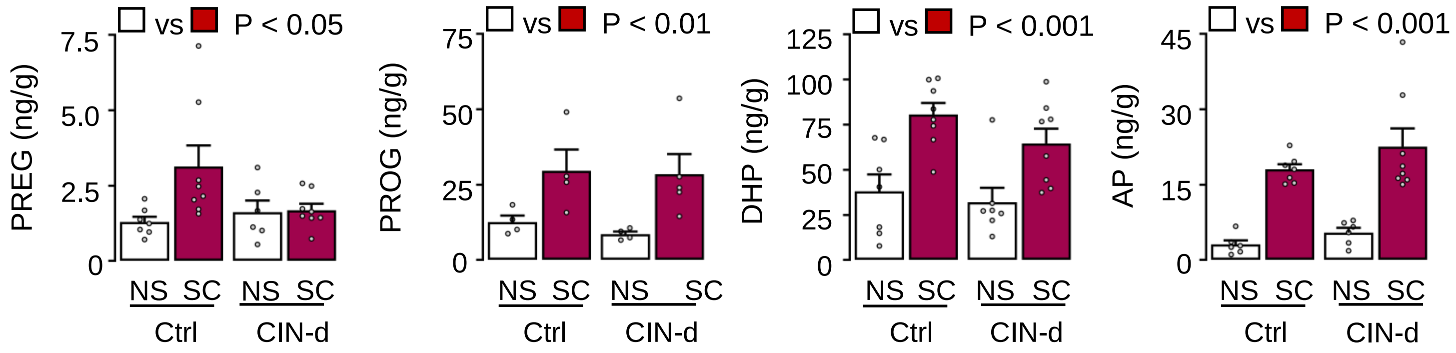
# Stress increases allopregnanolone in the PFC of mice

D1CT-7



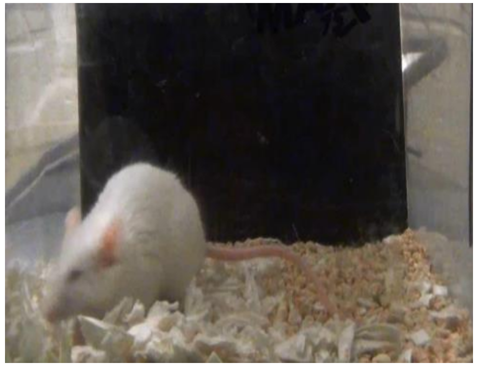

Mosher *et al*, Sci Rep, 2017

CIN-d



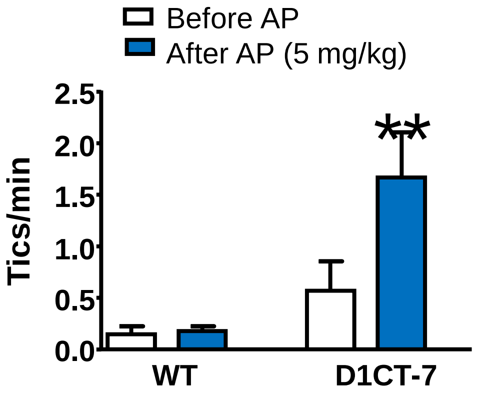

Cadeddu *et al*, Neuropsychopharmacology, 2023

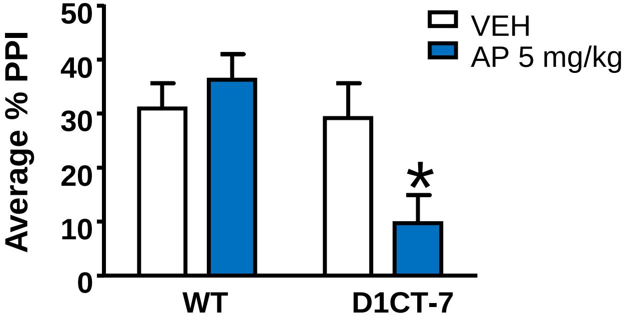
# Allopregnanolone produces TS-like manifestations in mice



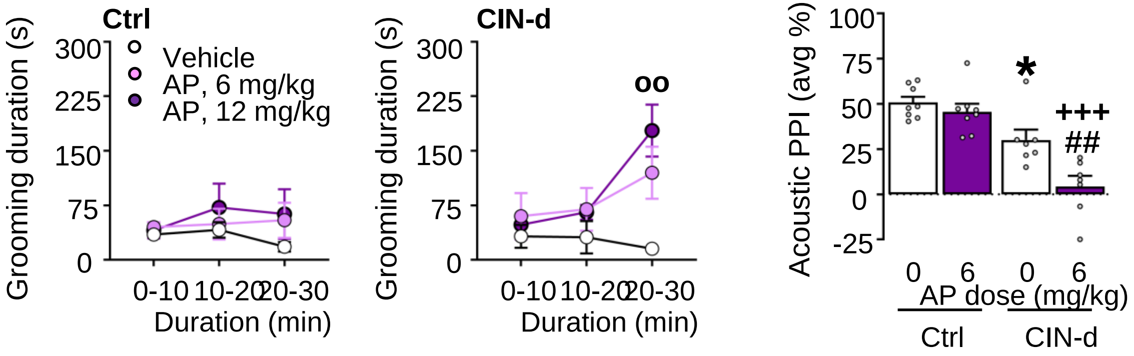
Before AP

After AP

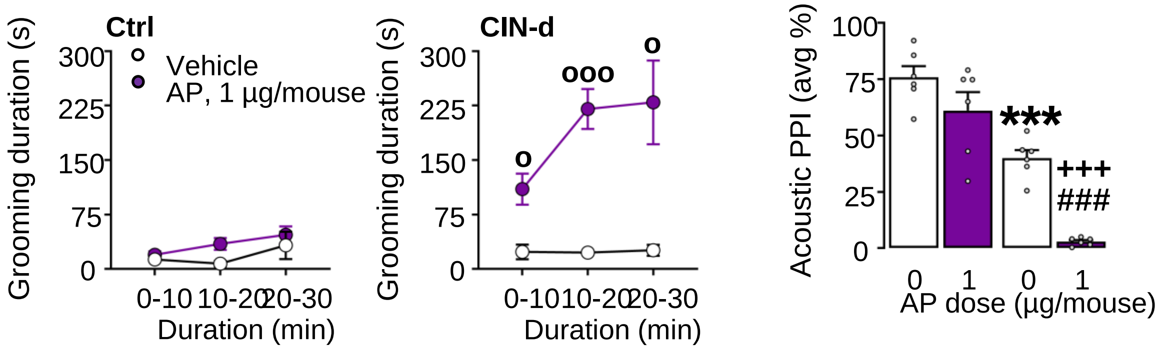



Mosher et al, 2017

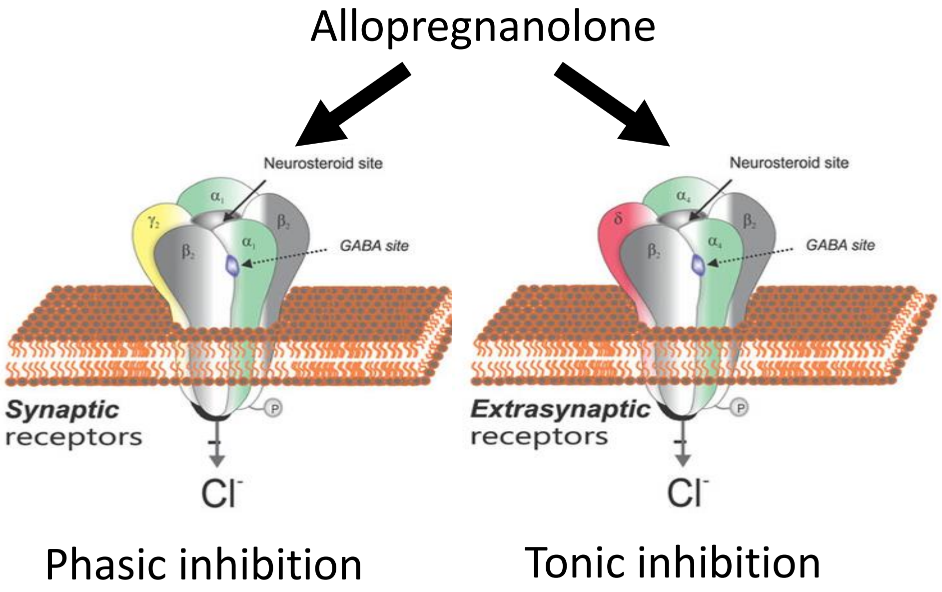


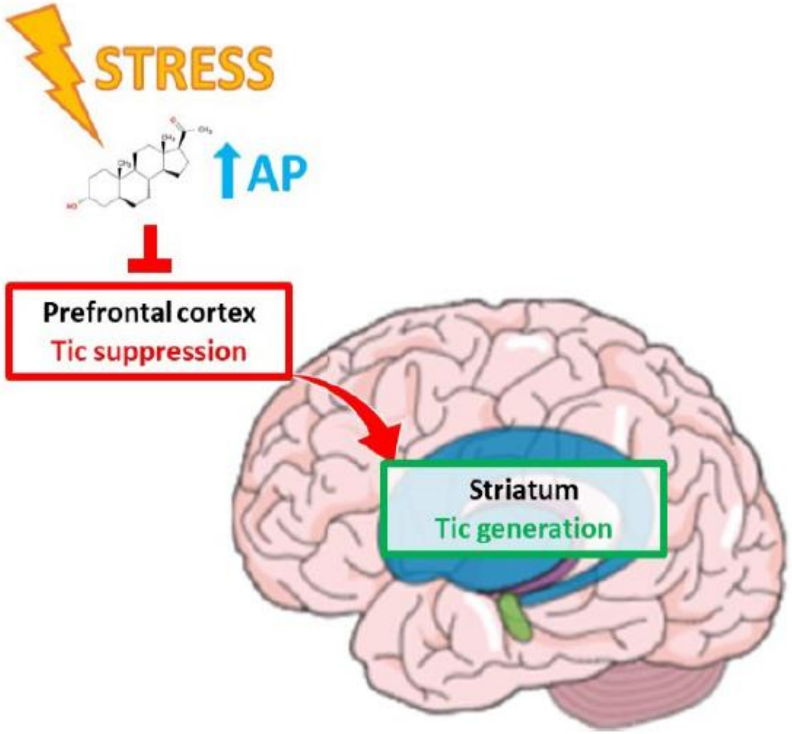

AP-systemic




AP-mPFC

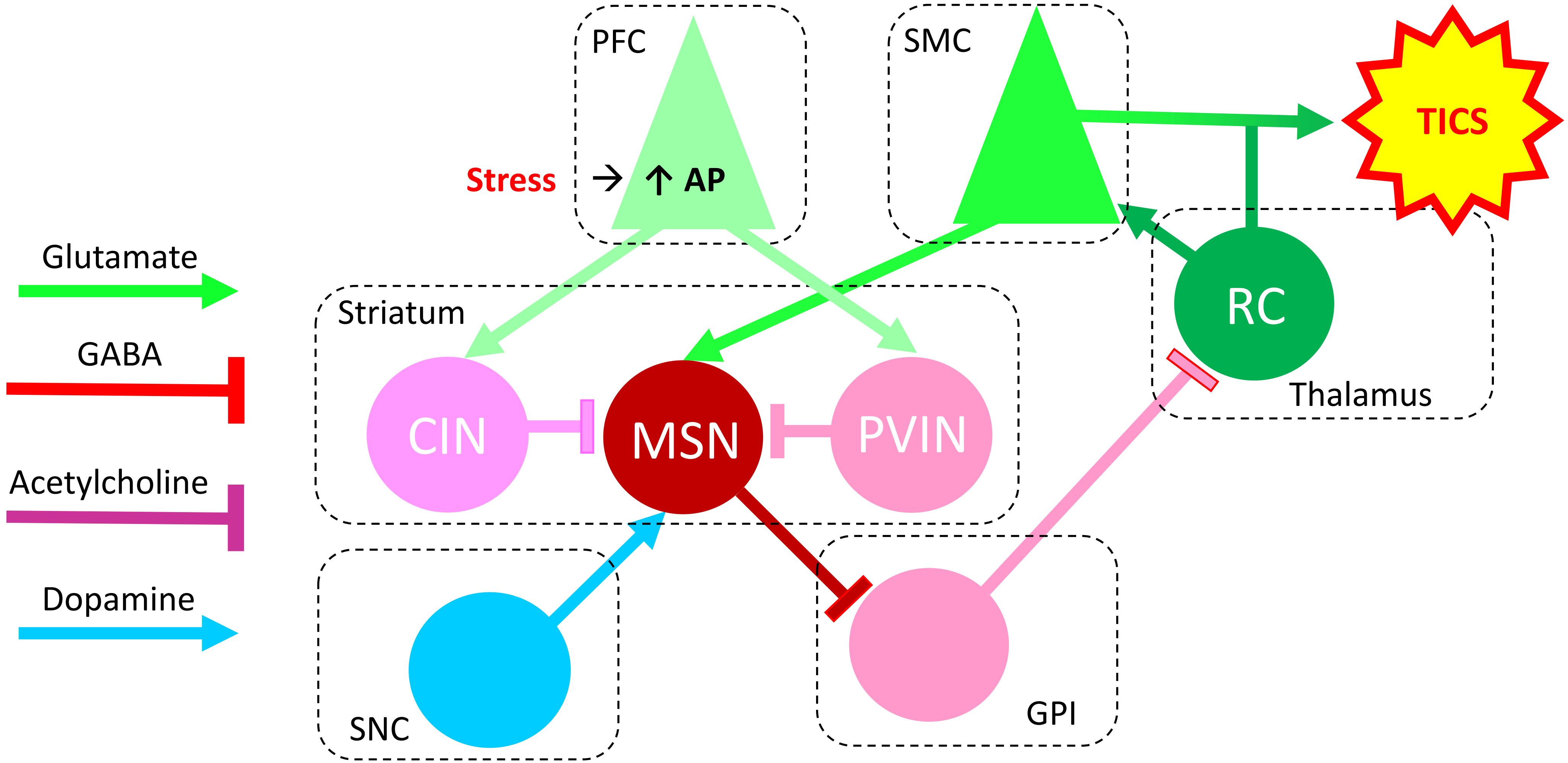
# Allopregnanolone activates GABA-A receptors



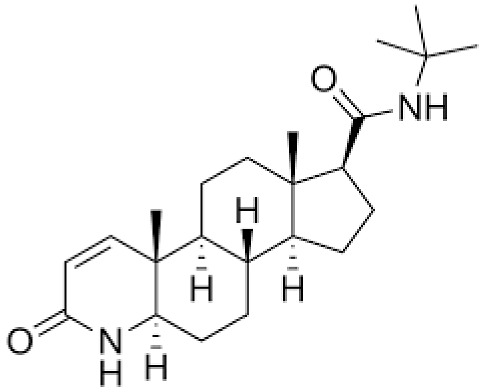

AP inhibits PFC functions by **activating GABA-A receptors → lower ability to suppress tics**

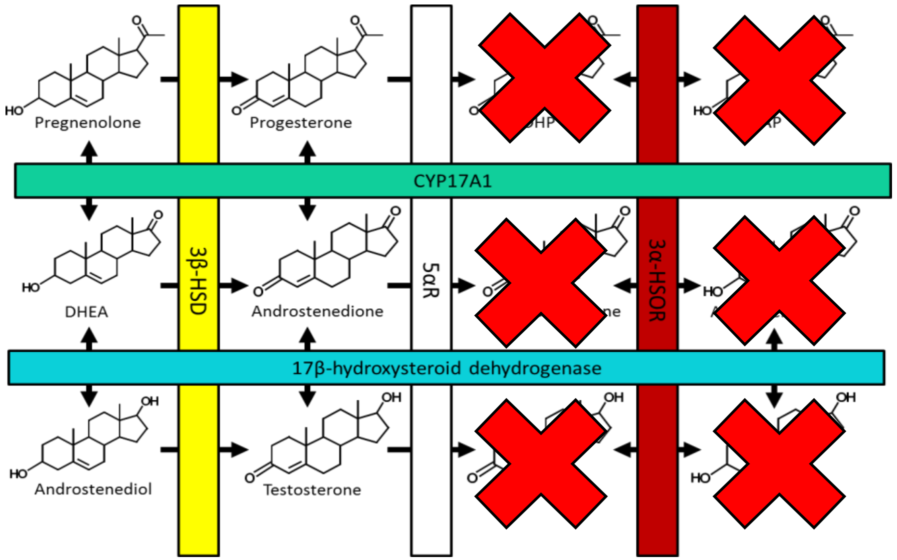
# Stress reduces tic control via allopregnanolone



# FINASTERIDE

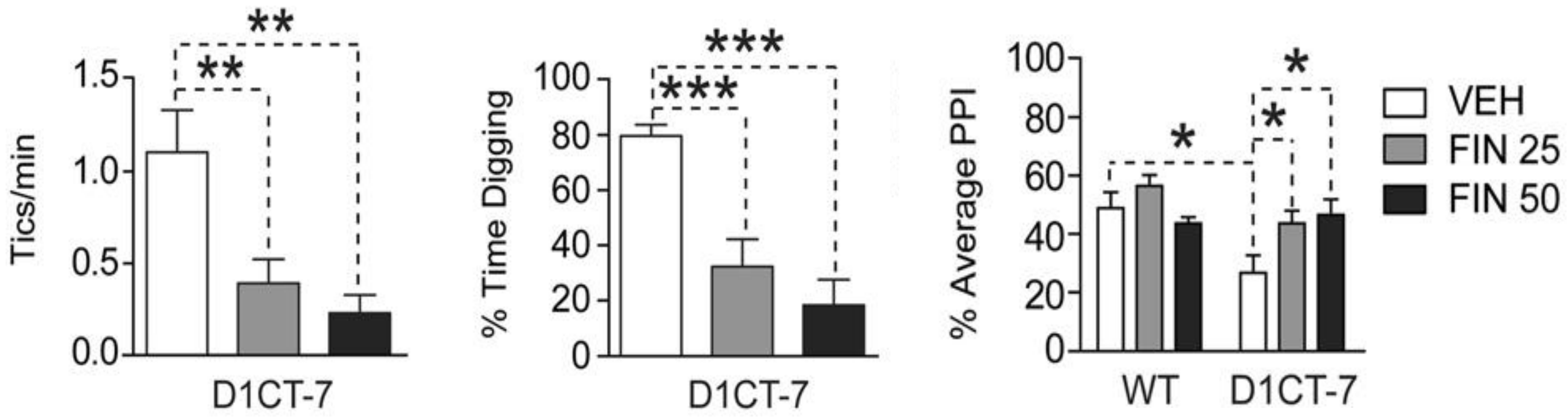
- Approved by FDA for treatment of benign prostatic hyperplasia and alopecia in humans
- By blocking 5α-reductase, finasteride reduces the synthesis of several neuroactive steroids
- Finasteride also dramatically reduces AP synthesis in the PFC



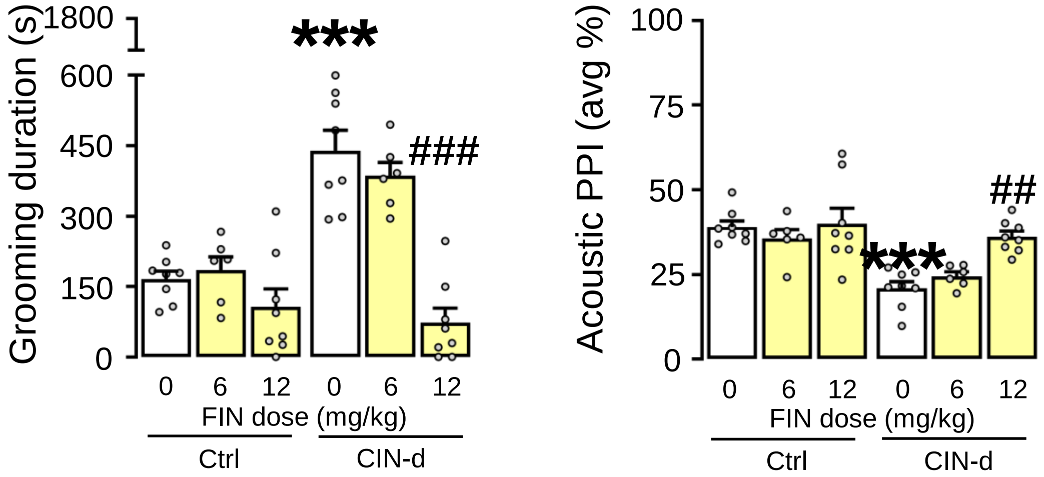
# Finasteride reduces TS-related behaviors in mice

**D1CT-7**



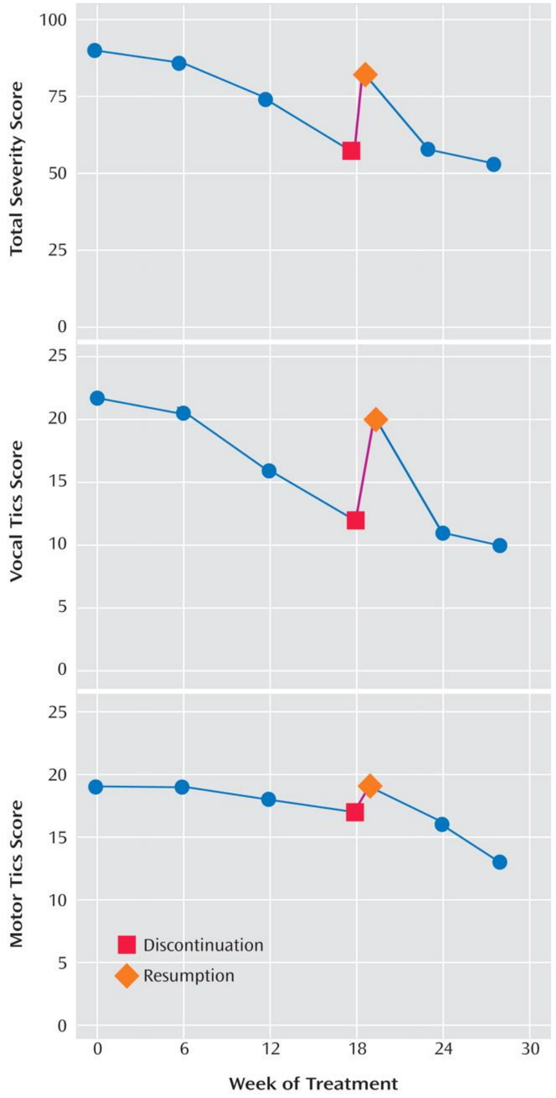

**Mosher *et al*, Sci Rep, 2017**

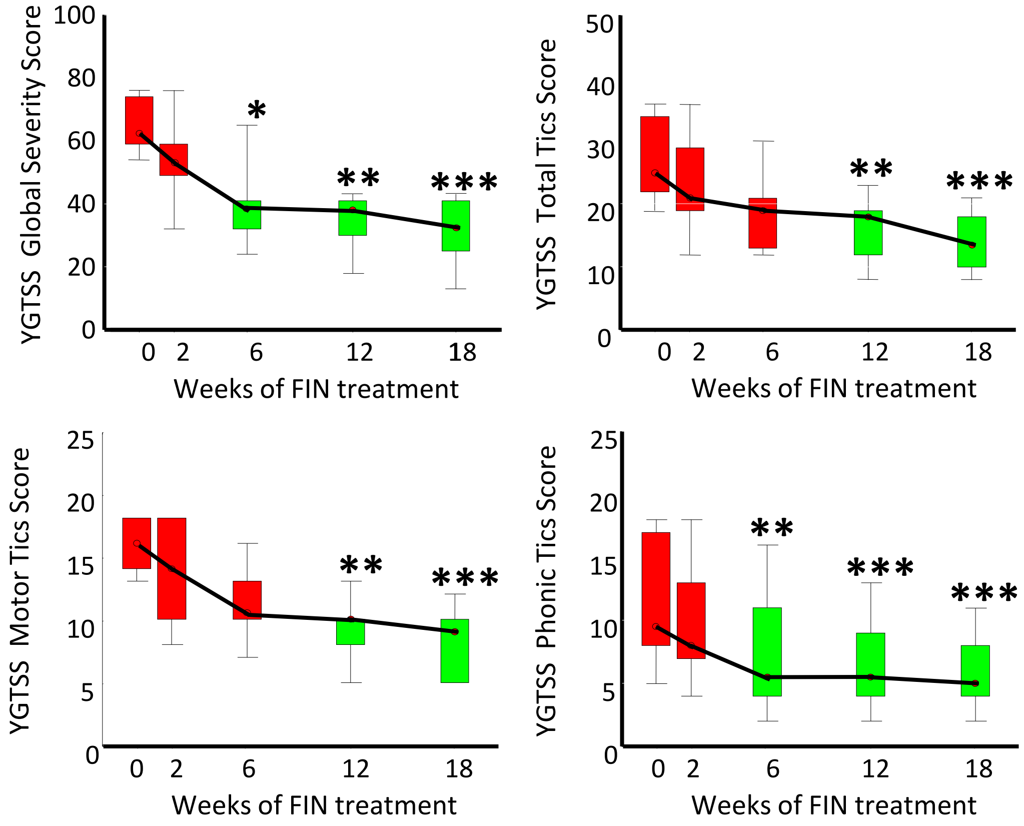
**CIN-d**




**Cadeddu *et al*, Neuropsychopharmacology, 2023**

# Finasteride reduces tics in treatment-refractory TS patients



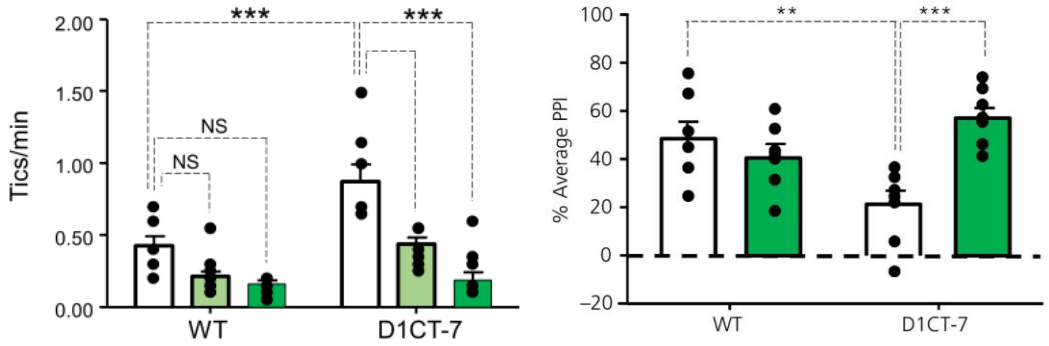




**Bortolato et al, 2007, *Am J Psych***

**Muroni, Paba, Marrosu, Bortolato, 2011, *Mov Disord***

# The AP antagonist isoallopregnanolone (isoAP) reduces tic-like behaviors

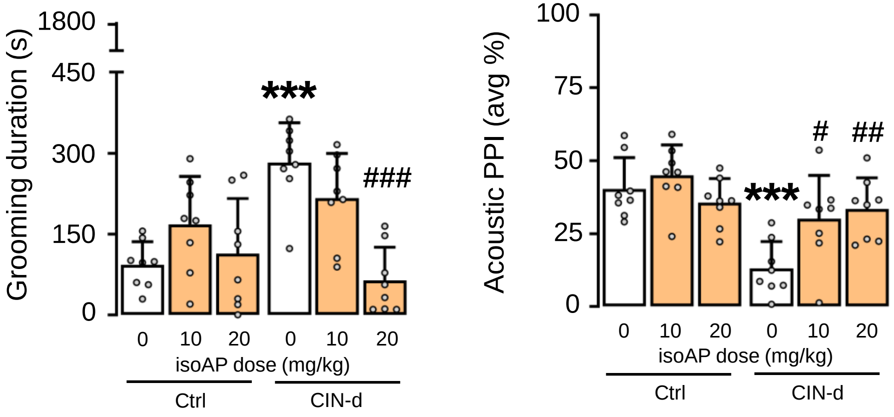
**D1CT-7**



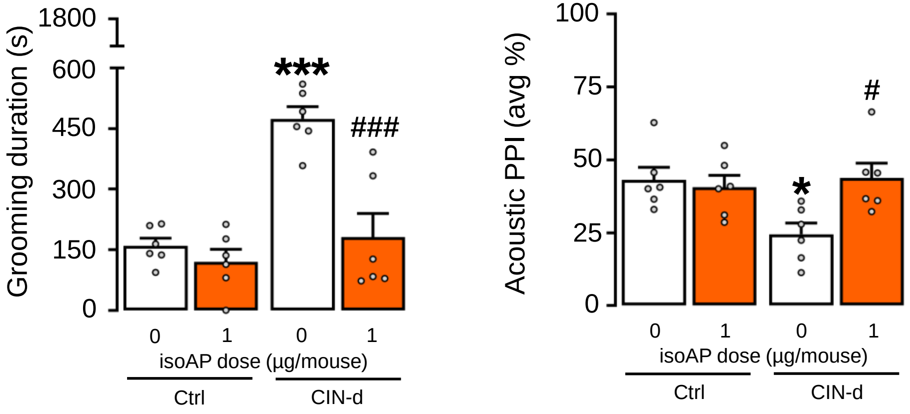

Vehicle (SC)
IsoAP (5 mg/kg, SC)
IsoAP (10 mg/kg, SC)

**Cadeddu et al., 2020, J Neuroendocrinol**

**CIN-d**




isoAP systemic



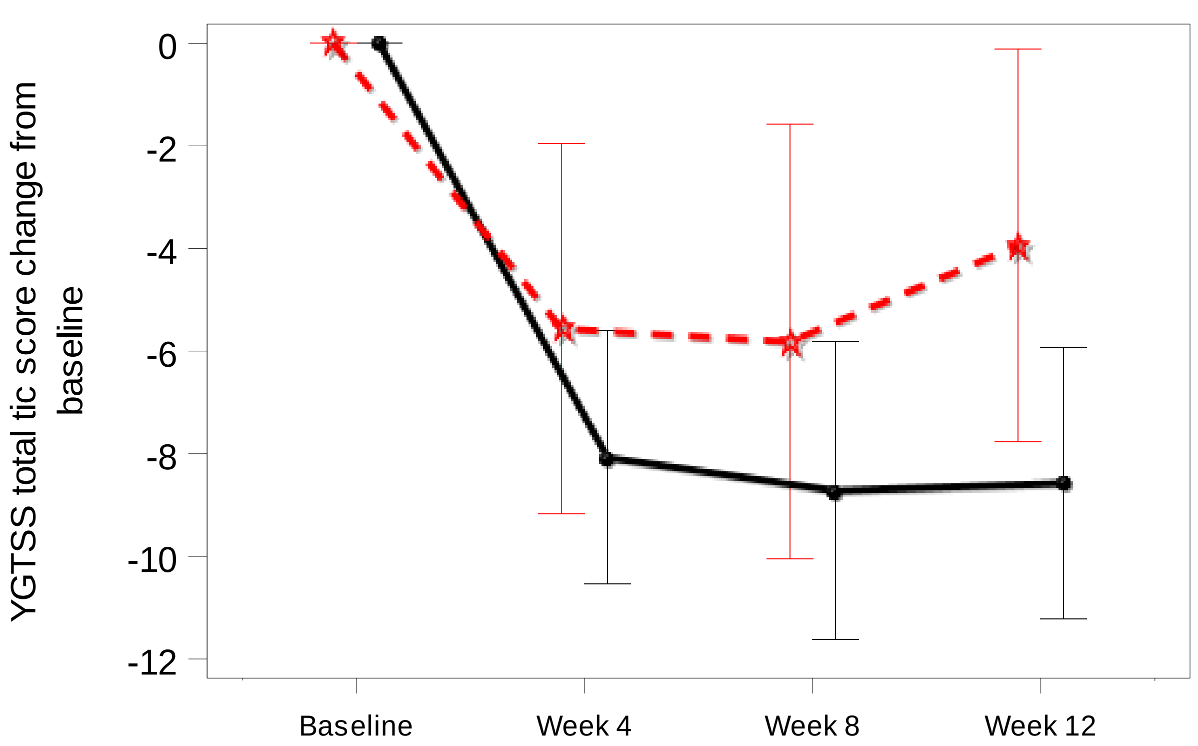

isoAP mPFC

**Cadeddu et al., 2023, Neuropsychopharmacology**

TIC CON

# Isoallopregnanolone (sepranolone) reduces tic severity in TS

YGTSS total tic score change from baseline, pediatrics and adults (mITT)




12 w

p=0.051 active vs SoC

| mITT population | Sepranolone + SoC | SoC |
|---|---|---|
| | N =17 | N=9 |
| Week 4 | -8.07 | -5.56 |
| Week 8 | -8.72 | -5.81 |
| Week 12 | -8.57 | -3.94 |
| PP population | N=10 | N=5 |
| Week 4 | -10.72 | -2.95 |
| Week 8 | -11.82 | -4.35 |
| Week 12 | -9.92 | -3.95 |

mITT

Patients having taken at least 6 doses per 4 weeks

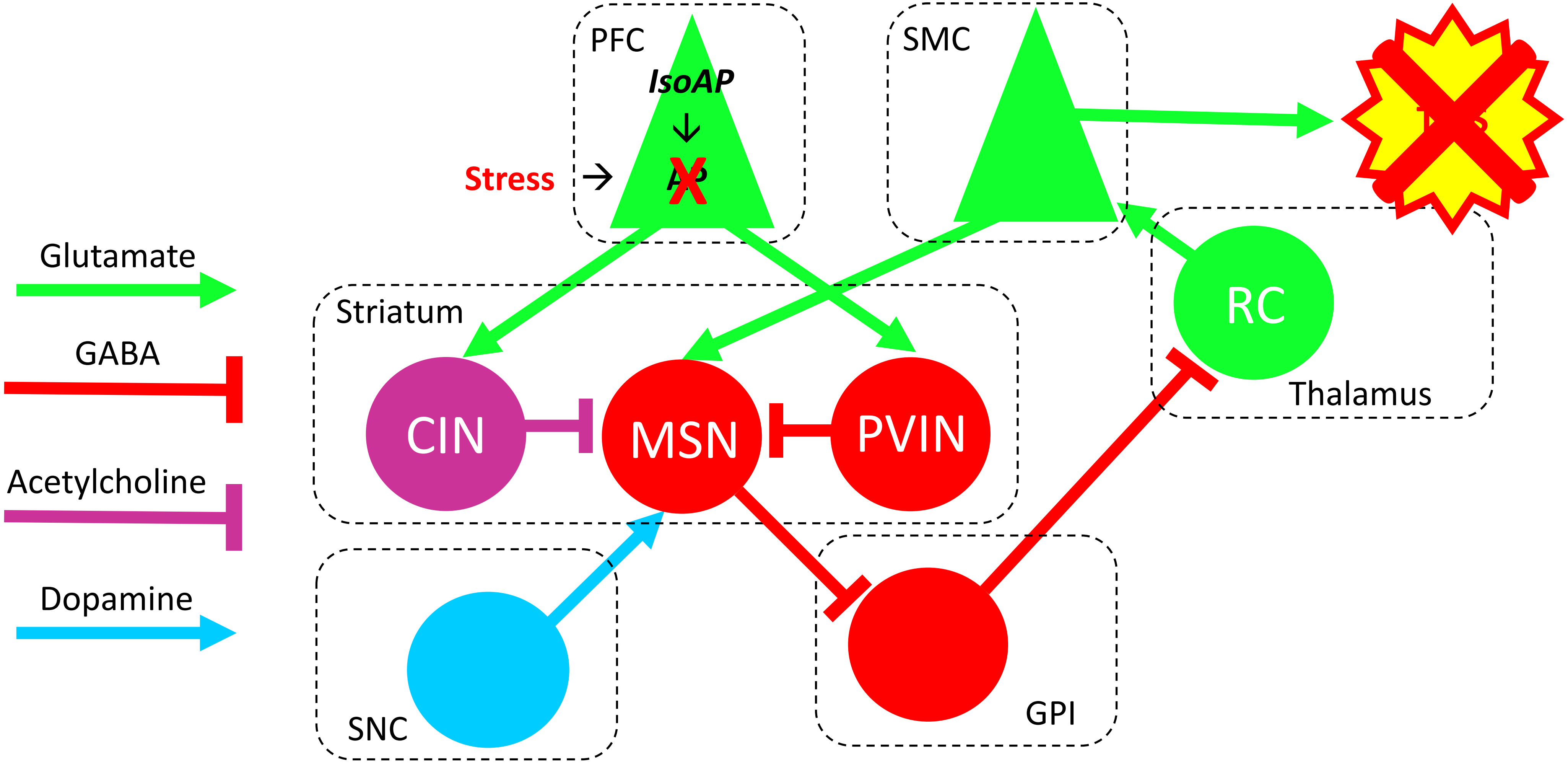
Per-protocol (PP)

Patients having taken all doses as planned and all visits within predefined visit window

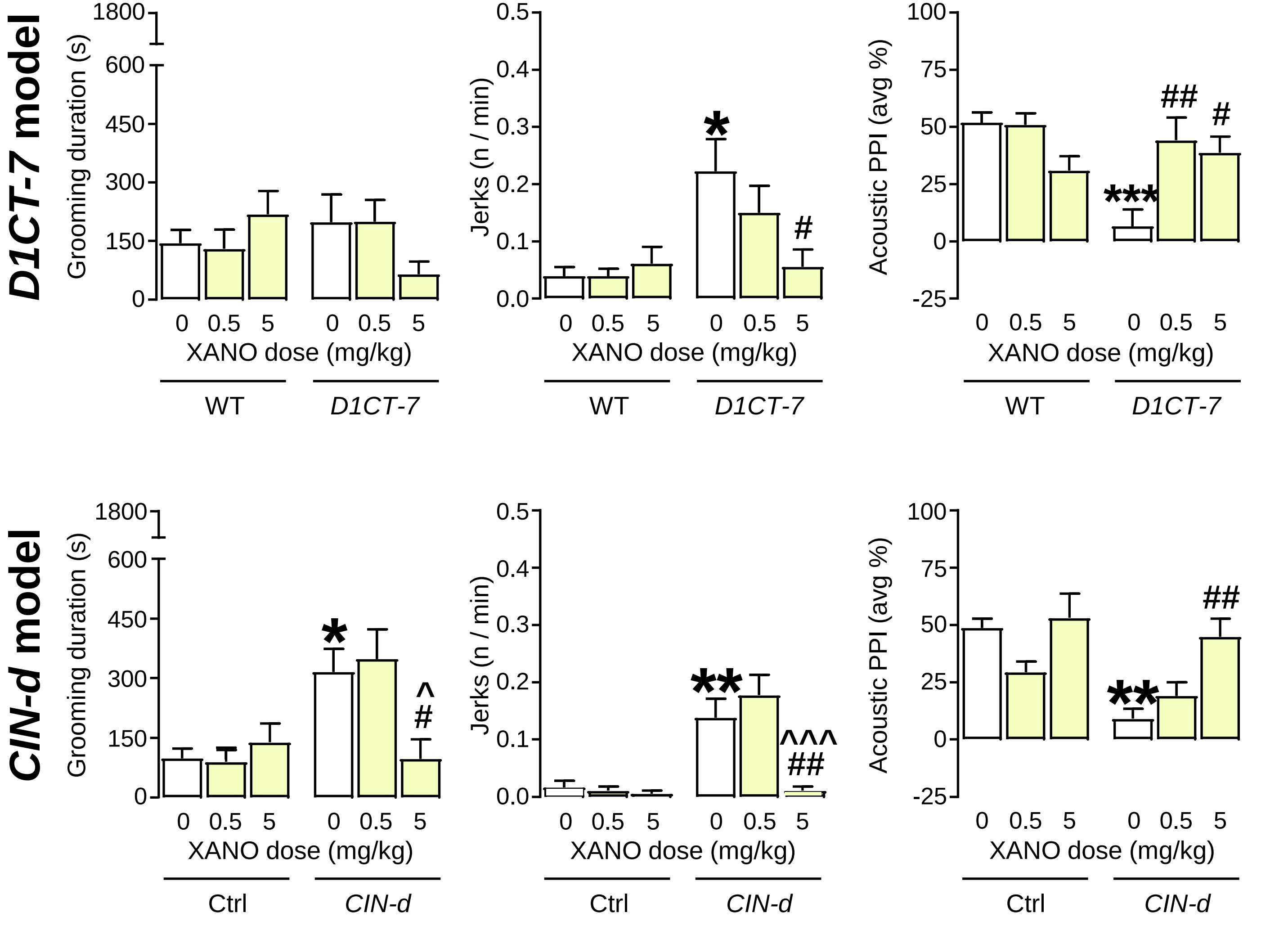
From: Heidi Biernat and Nanette Debes

TIC CON

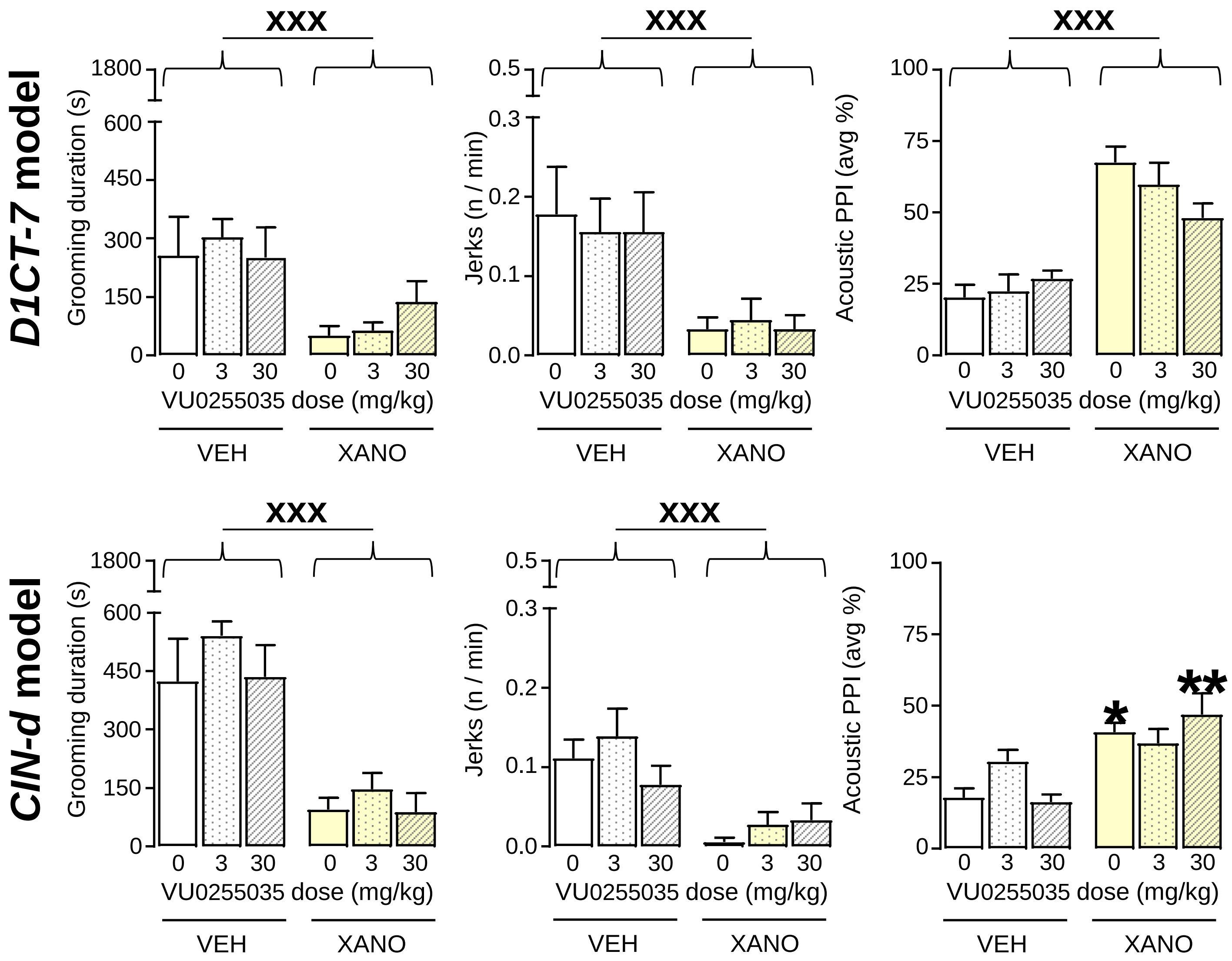
# IsoAP and finasteride suppress tics by restoring PFC function



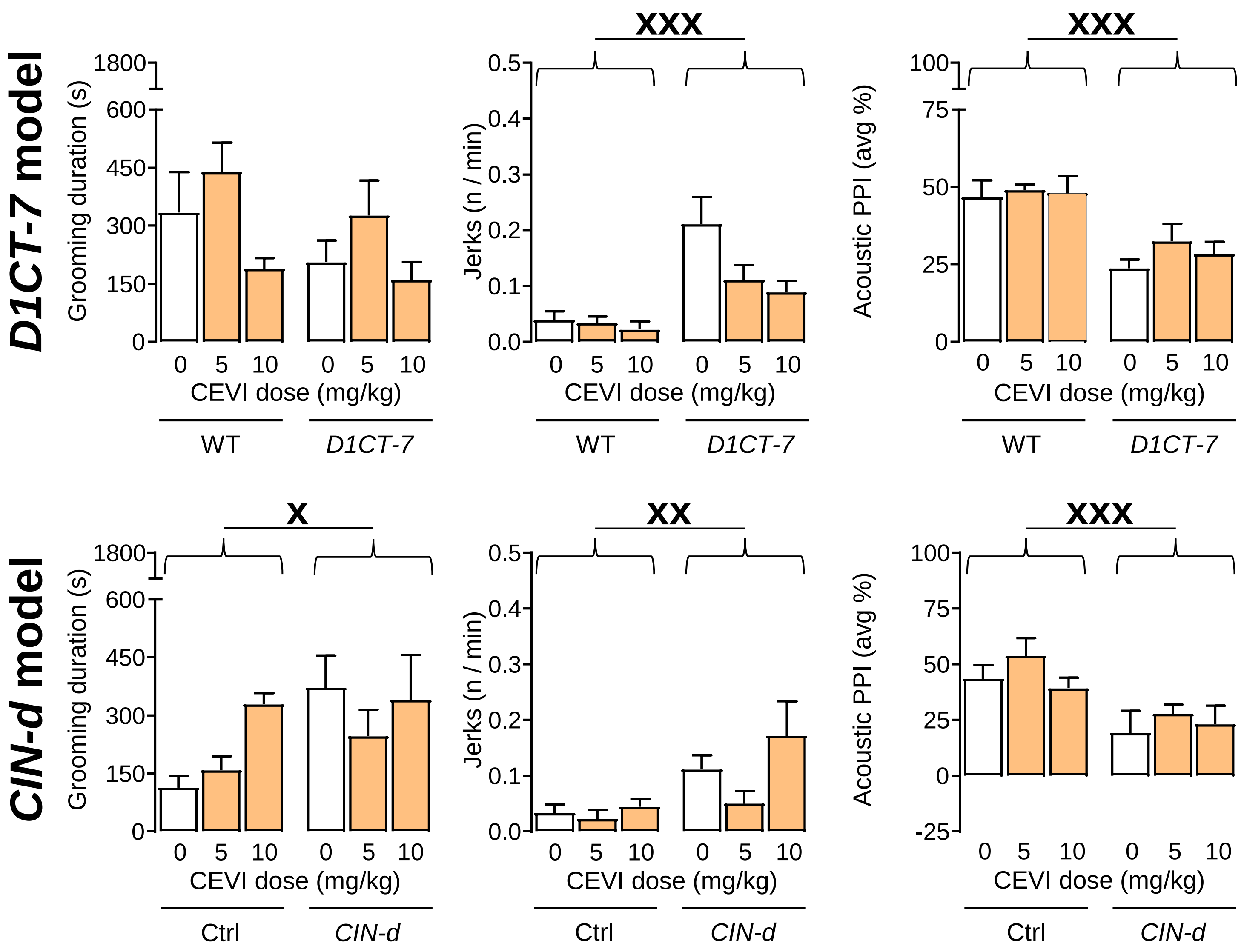
# The M1/M4 agonist xanomeline reduces TS-related responses in mice



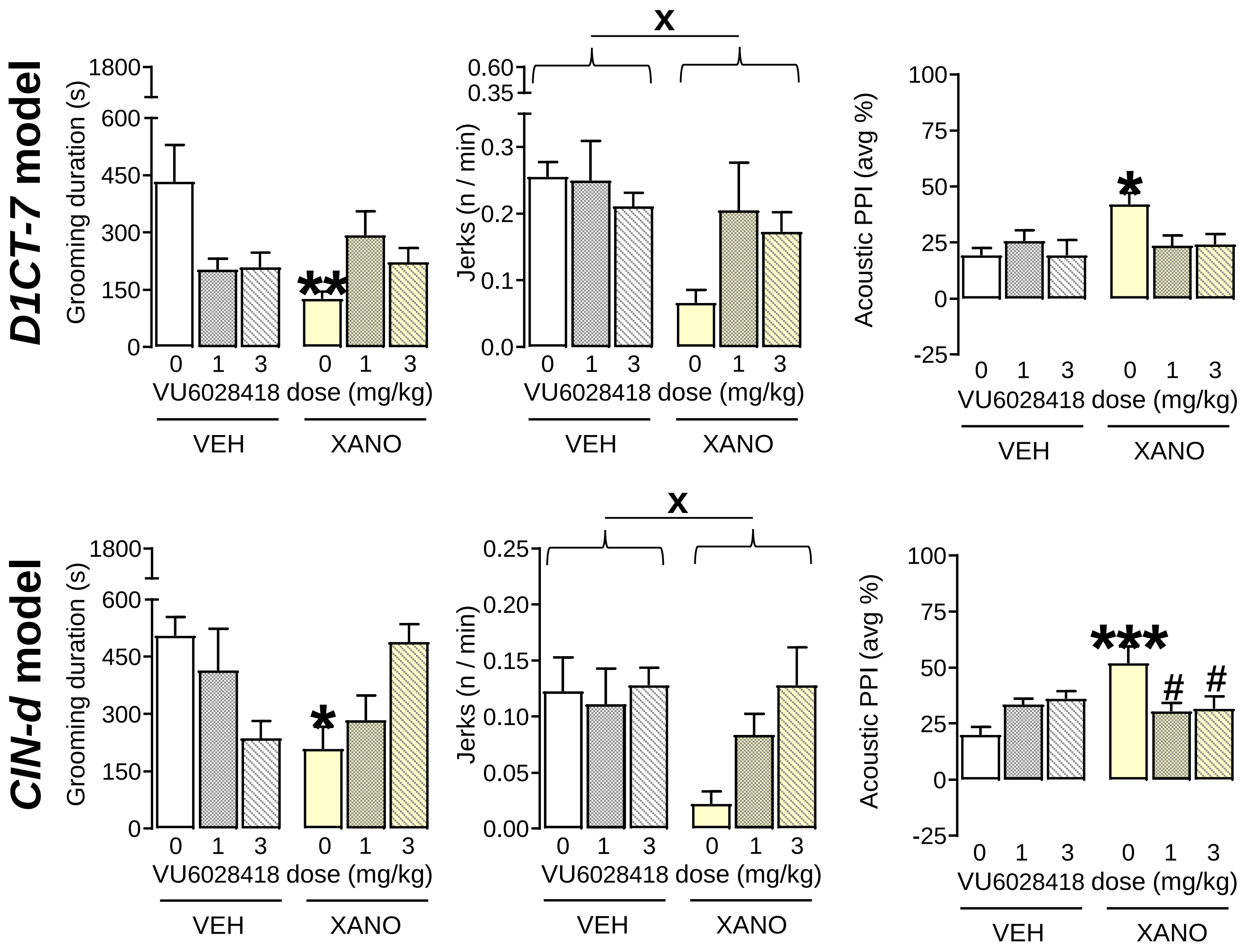
# The M1 antagonist VU0255036 does not counter the effects of xanomeline



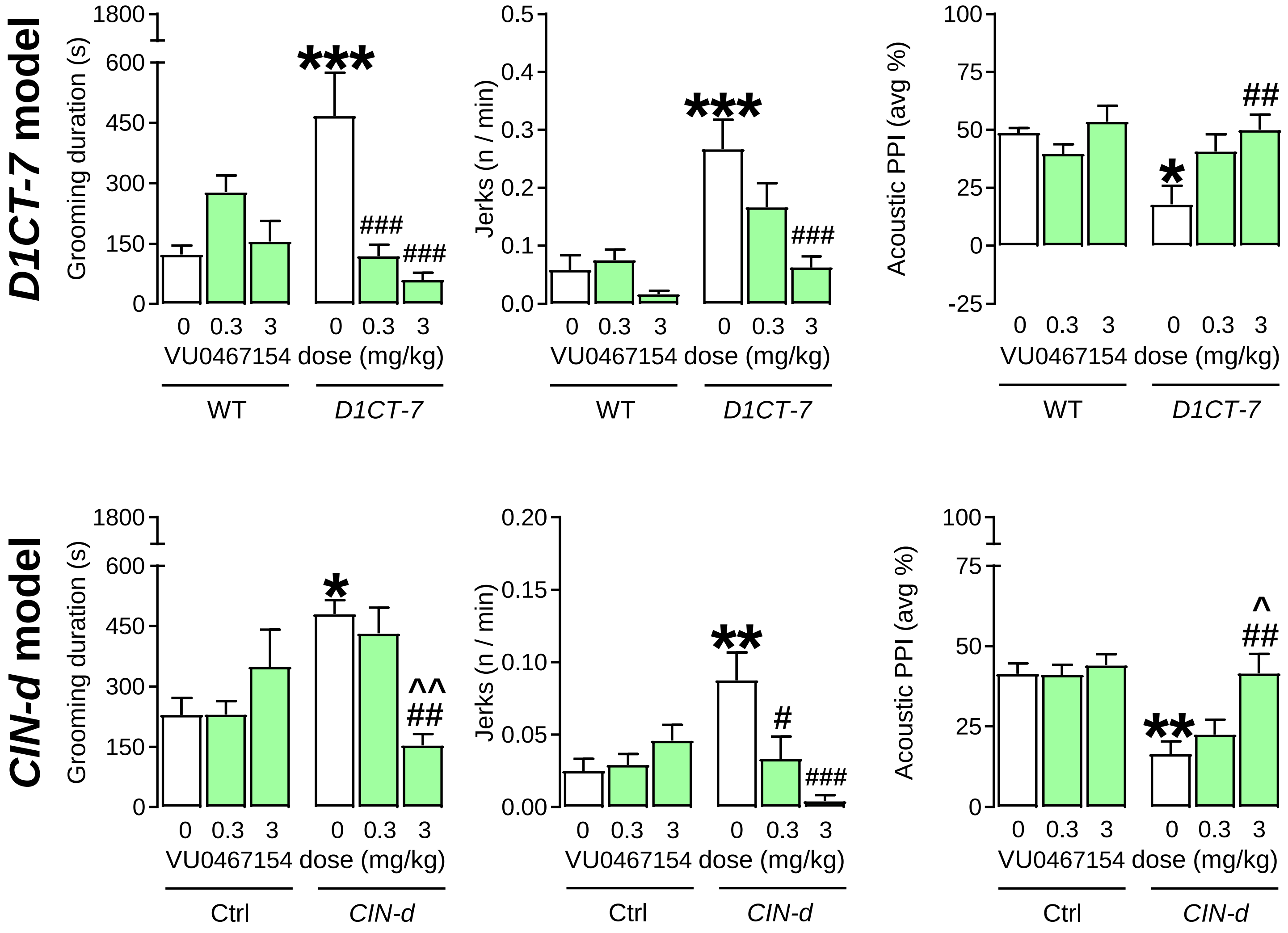
# The M1 agonist cevimeline does not reduce TS-related responses in mice



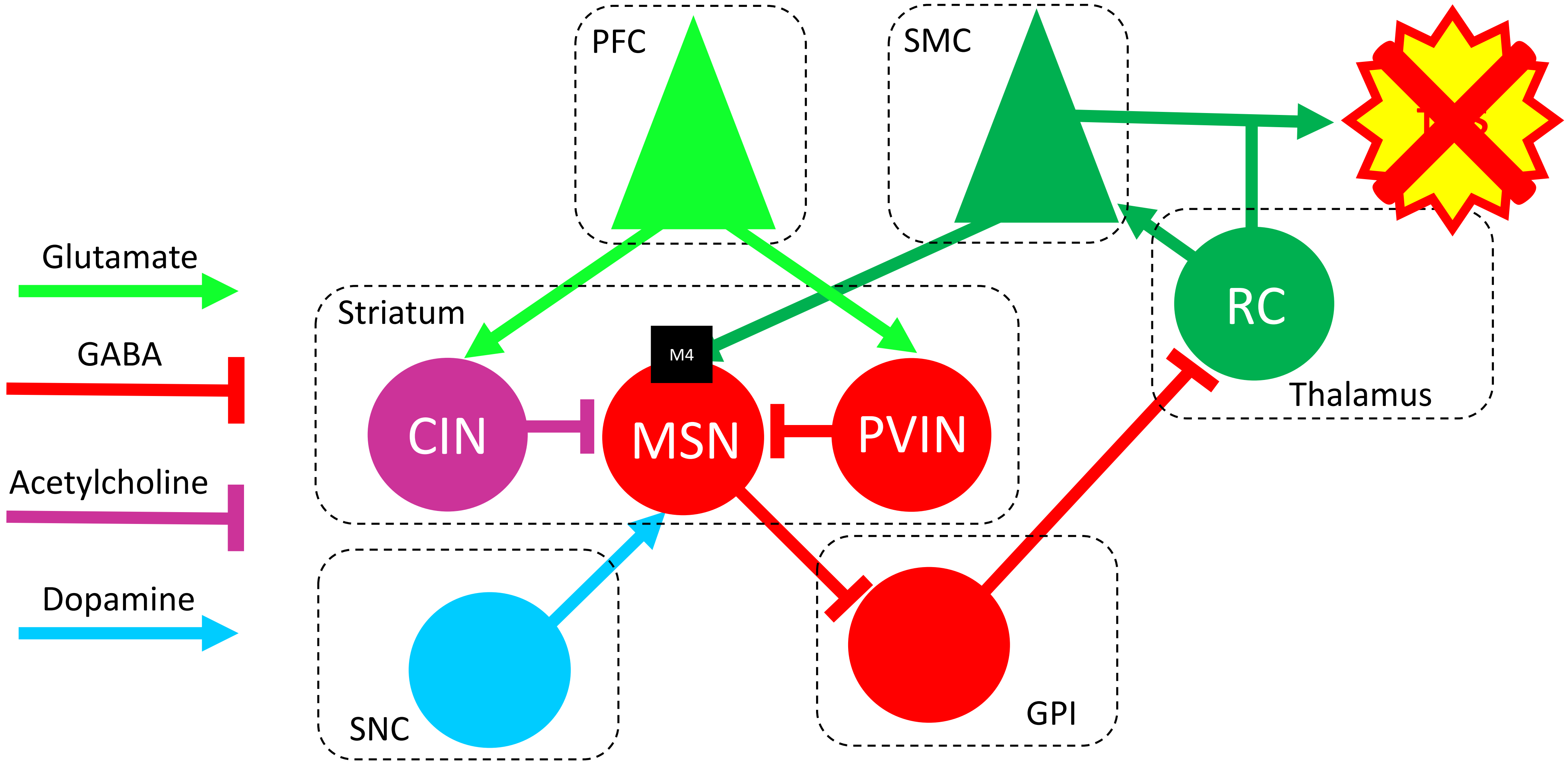
# The M4 receptor antagonist VU6028418 reverses the effects of xanomeline



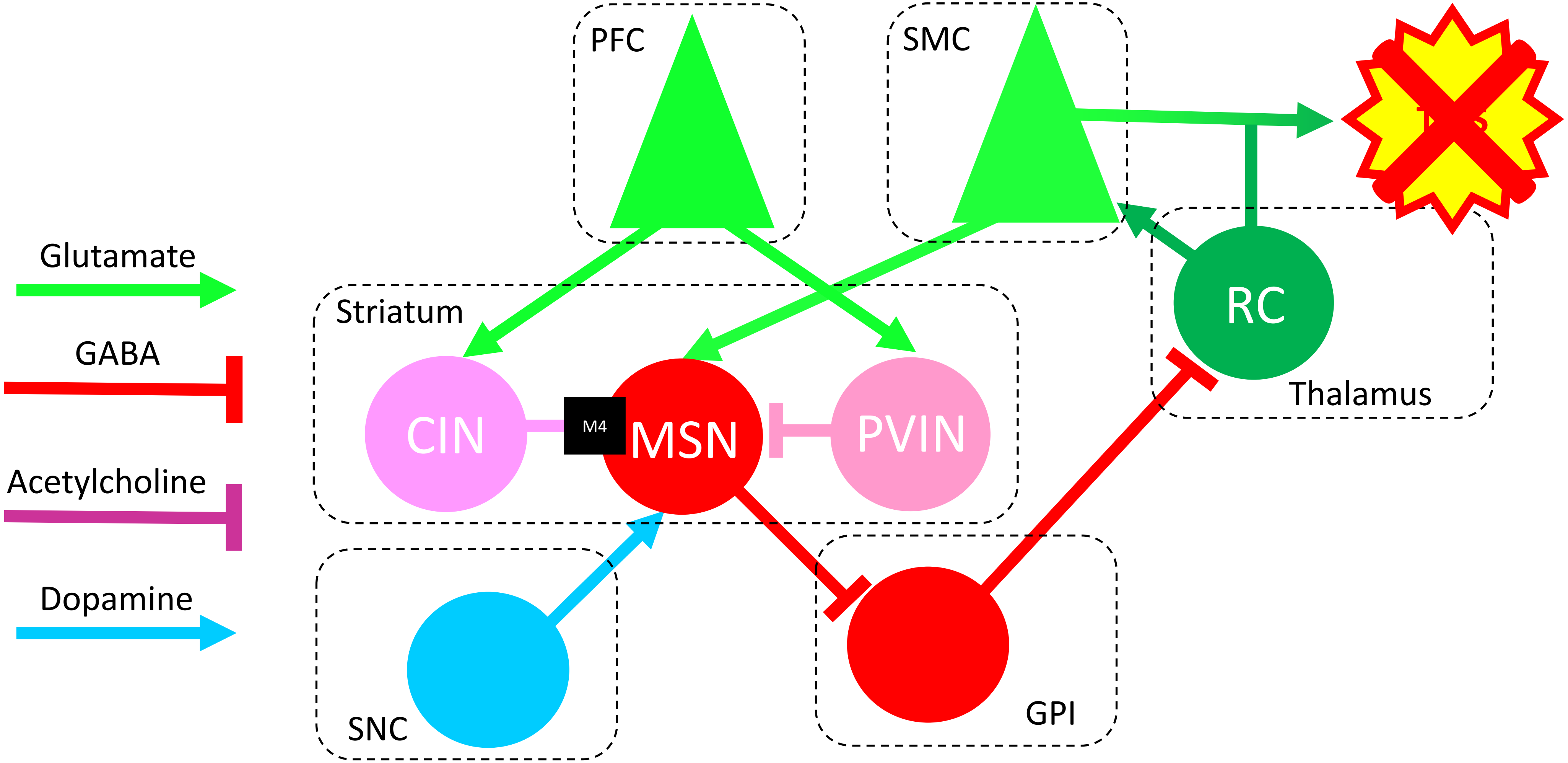
# The M4 positive modulator VU0467154 reduces TS-related responses in mice



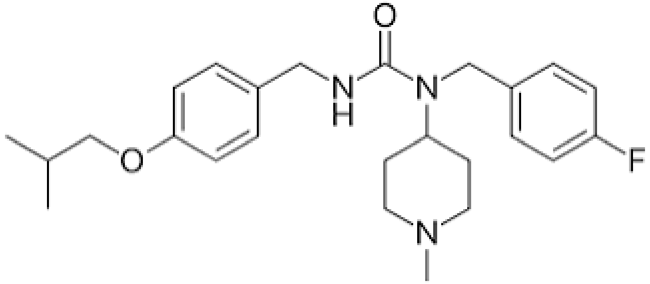
# M4 activation counters the effects of corticostriatal activation

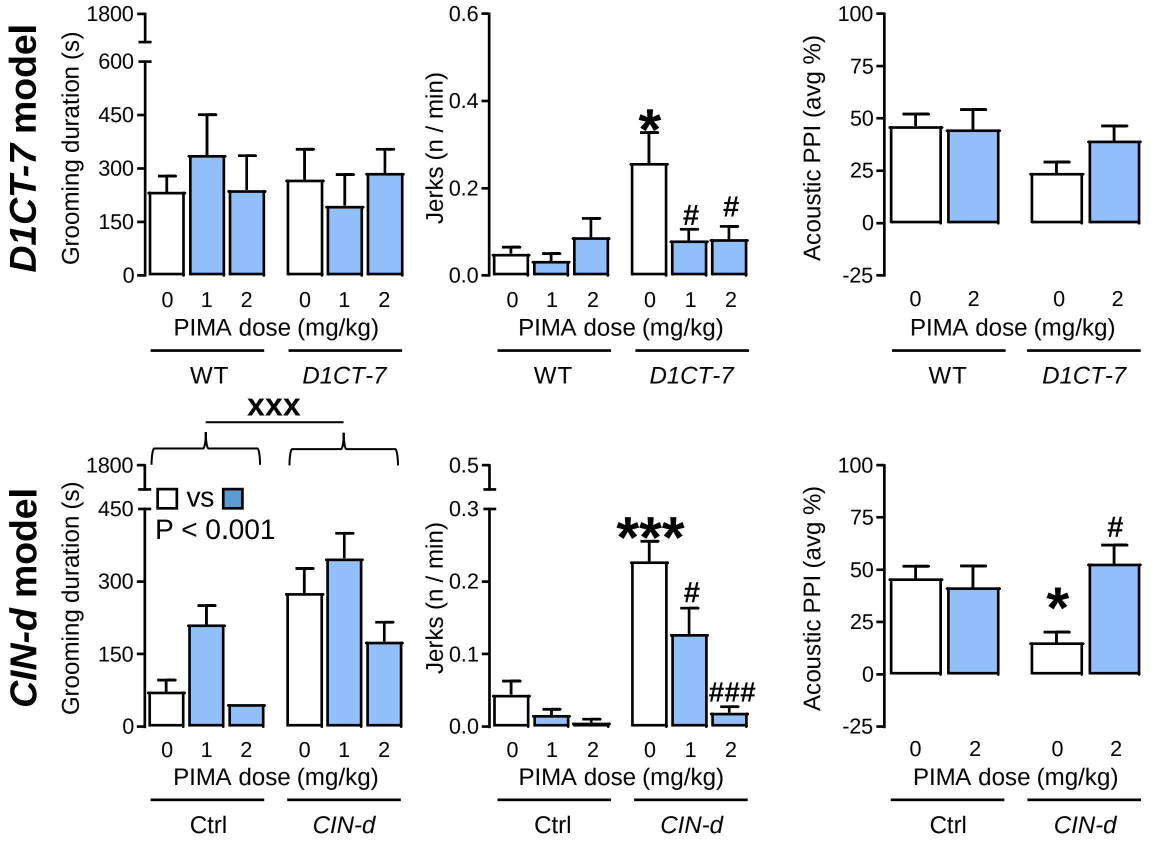


# M4 activation offsets the effects of low striatal acetylcholine



# The 5HT2A antagonist pimavanserin reduces TS-related responses in mice



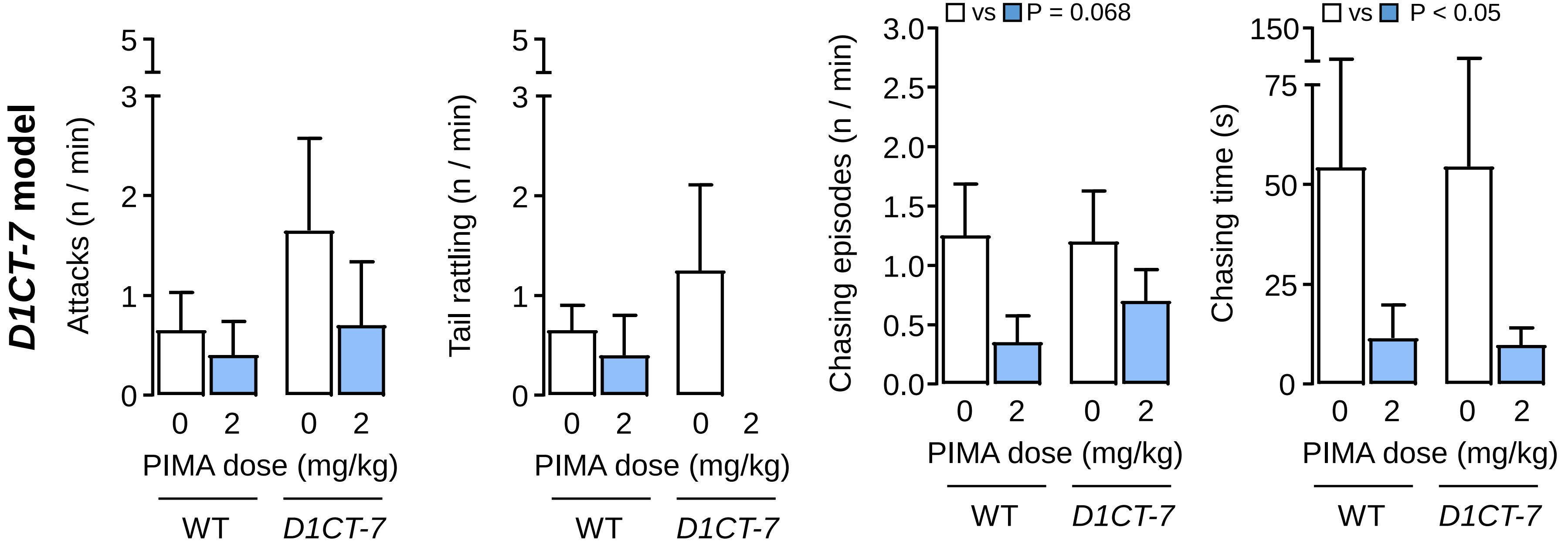



Approved in 2016 for psychosis in Parkinson's disease

5-$HT_{2A}$ receptors are overexpressed in the cortex of TS Patients (Haugbøl et al., 2007)

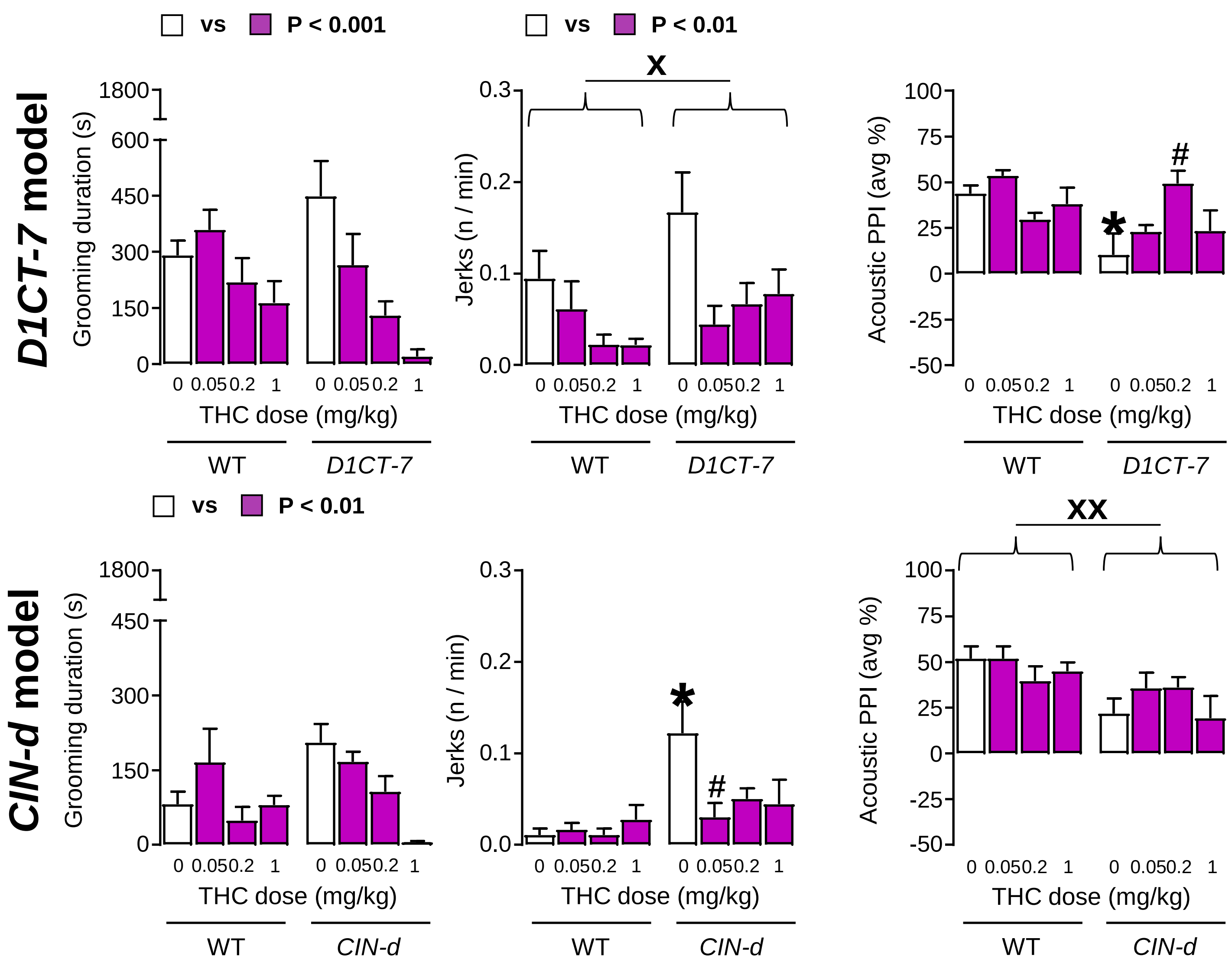
In a pilot study, pimavanserin reduced tics in TS patients (Billnitzer and Jankovic, 2021)

# Pimavanserin also reduces aggression in D1CT-7 mice




Given the association of coprophenomena with aggression, we speculate that these data may signify that pimavanserin may be particularly appropriate for high-severity TS individuals with coprolalia and copropraxia

# THC reduces some TS-relevant phenotypes in a dose- and model-dependent fashion



# 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
- Using different models of TS, we showed that stress may exacerbate symptoms via increased synthesis of the neurosteroid **allopregnanolone**
- Therapies that reduce allopregnanolone synthesis (such as **finasteride**) or signaling (such as **isoallopregnanolone**) have a promising therapeutic effect in TS
- Using the same strategy, we found that **$M_4$ activators** and **5-$HT_{2A}$ antagonists** may be new putative therapeutic strategies for tic disorders

TIC CON

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