Prenatal nicotine exposure induces sex-dependent changes in dopamine pathways in adolescent brain

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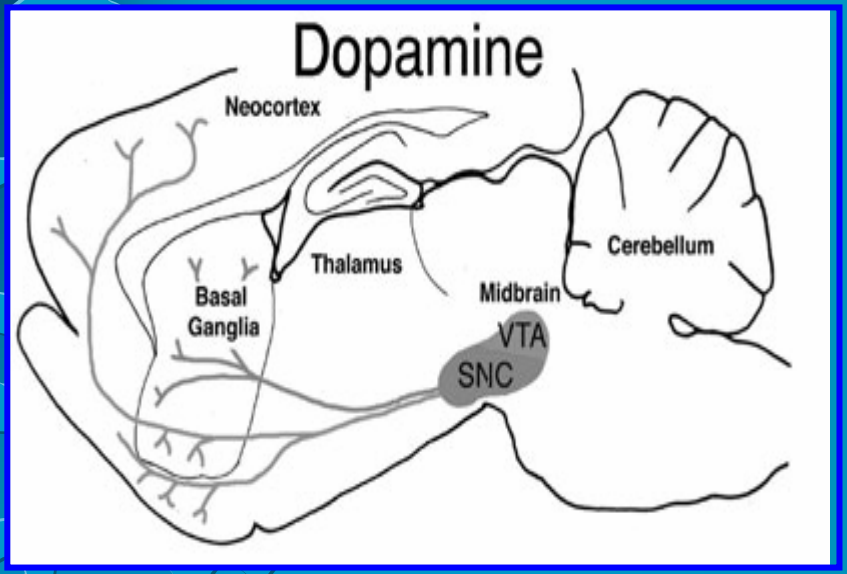
Brain dopamine system



- Locomotion
- Motivated behavior
- Reward
- Drug abuse

Hypothesis

Nicotine exposure during sensitive developmental periods induces long-term dysfunction of dopamine transmission

Two sensitive periods for maturation of dopamine systems

Fetal

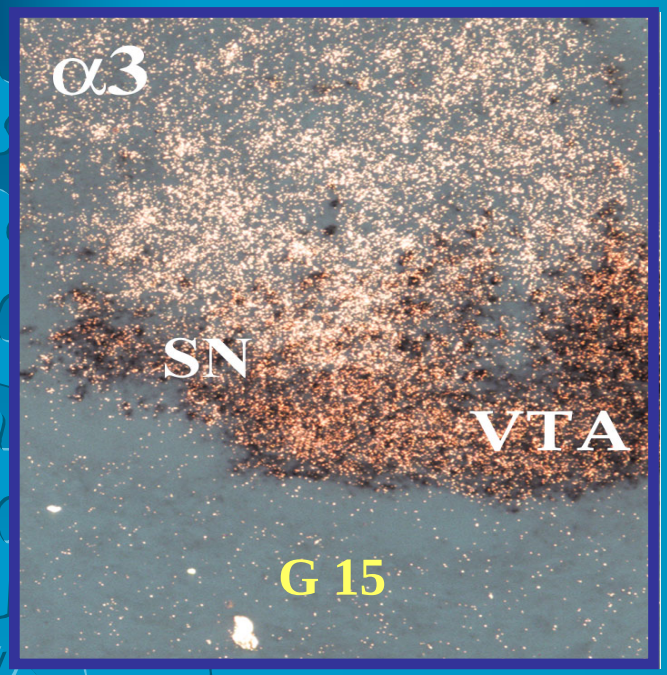
Adolescence

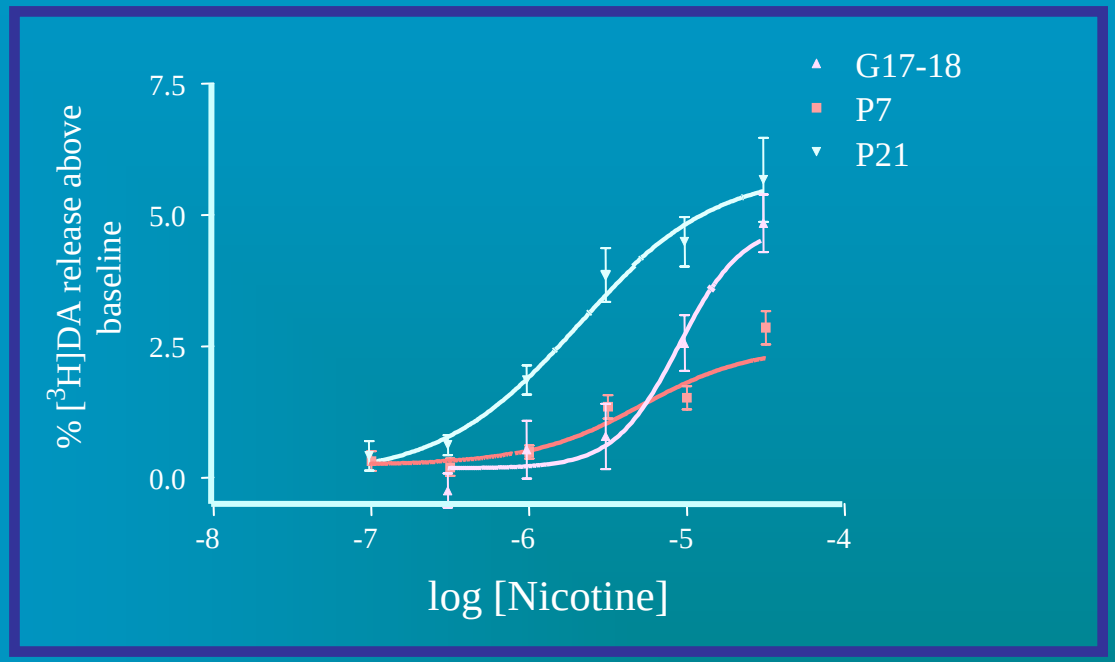
Maternal smoking associated with increased incidence of:

- ADHD
- Conduct disorder
- Drug abuse
- Obesity

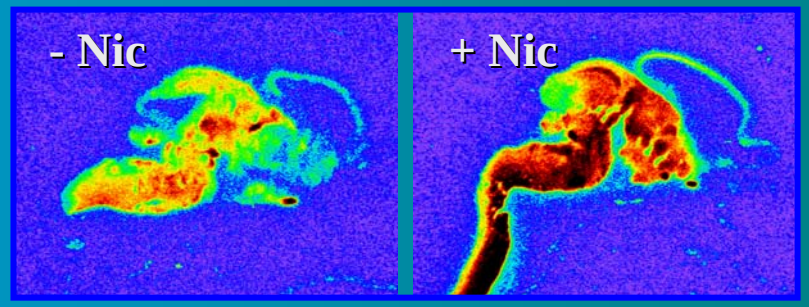
Possible involvement of DA dysfunction?

Early appearance of functional nicotinic receptors on fetal DA neurons





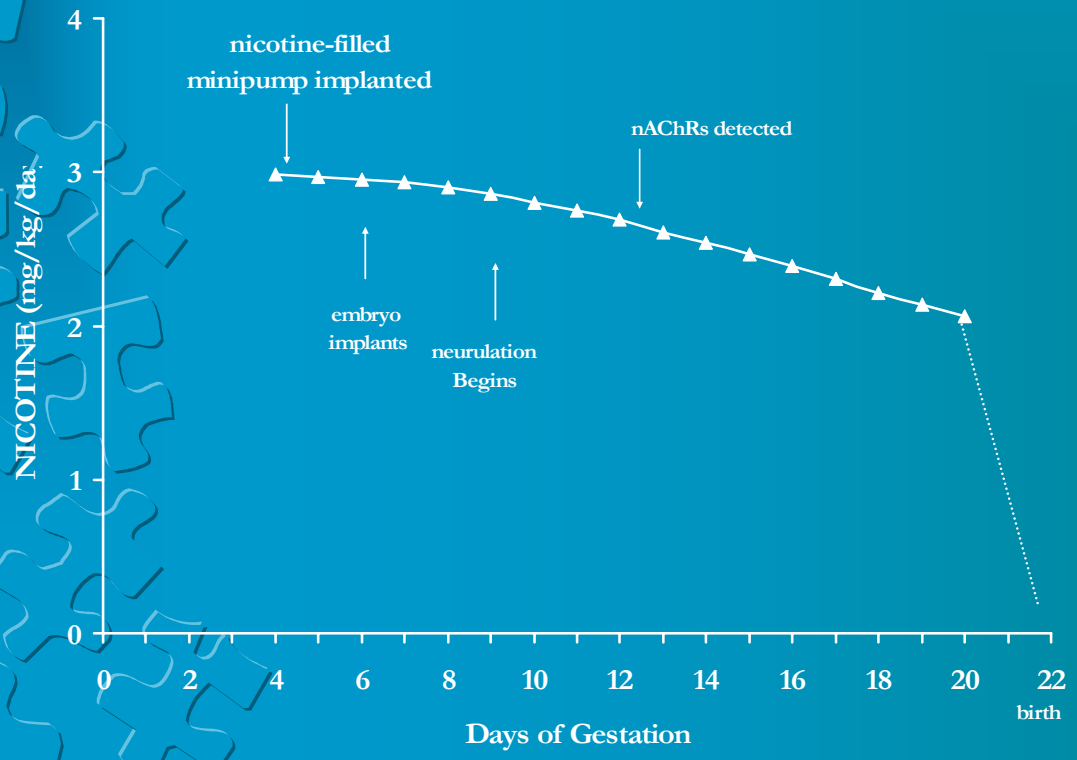
Chronic gestational nicotine (GN) exposure increases fetal nicotinic receptor binding



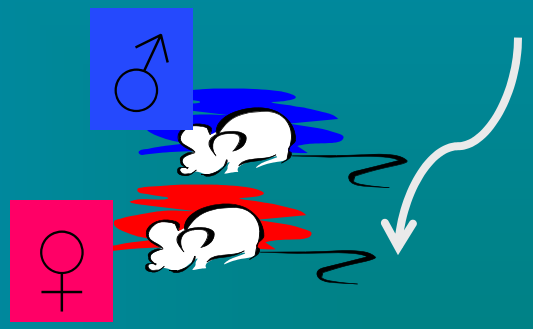
Gestational drug treatment and rearing

Dam arrives (G2)

Minipump implanted (G4) saline or nicotine (3 mg/kg/day)

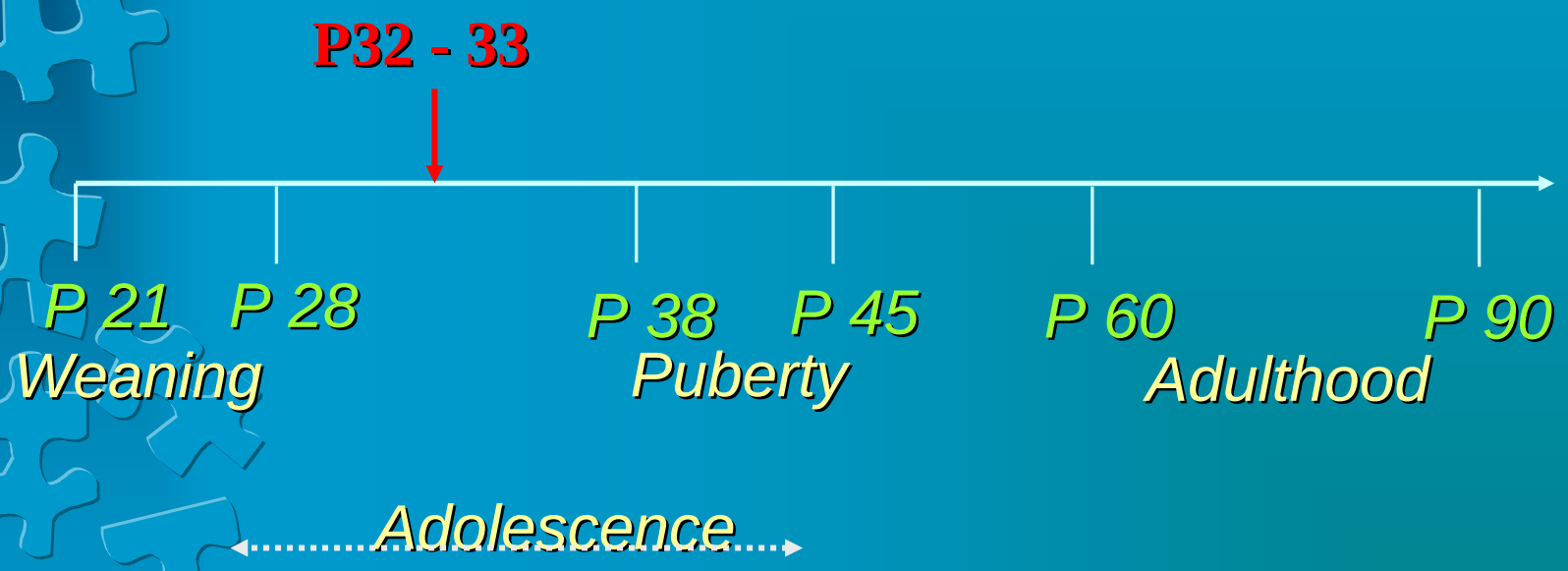


Pups switched to surrogate dam (P0)



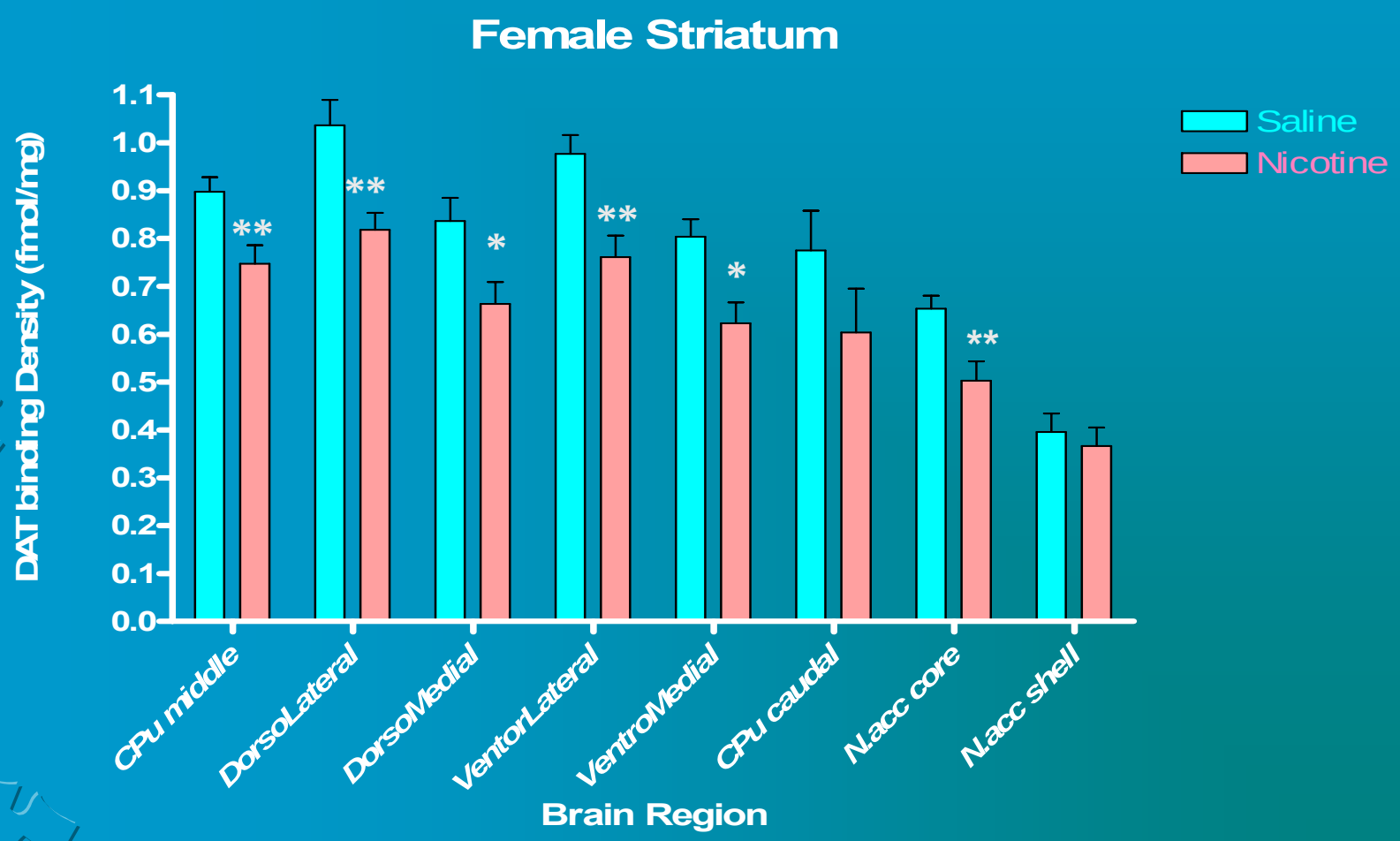
Pups weighed daily and weaned at P21

The effects of GN treatment were studied during adolescence

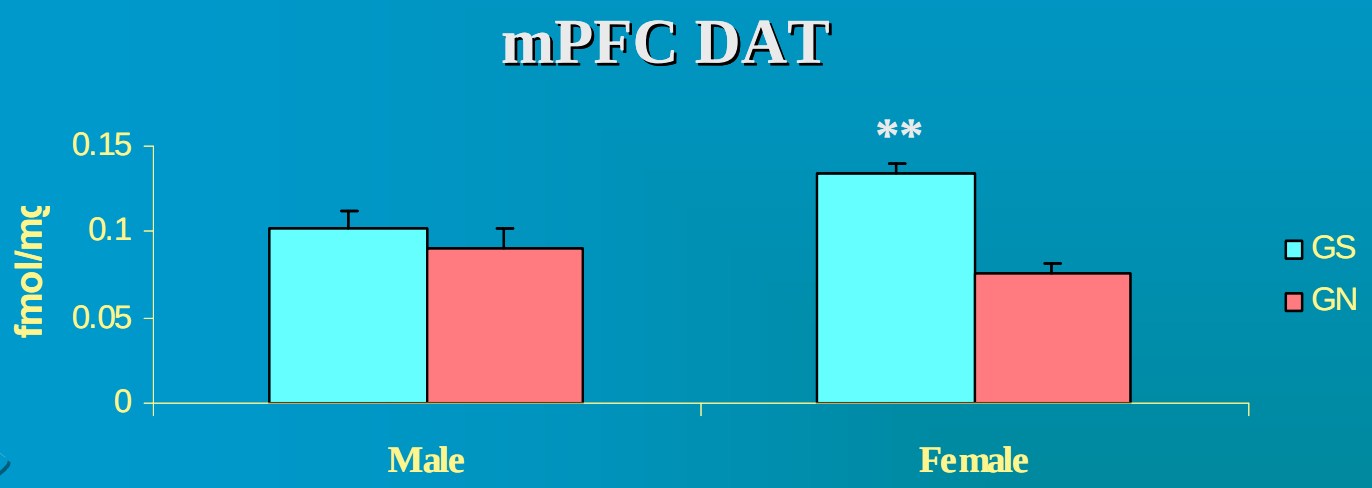


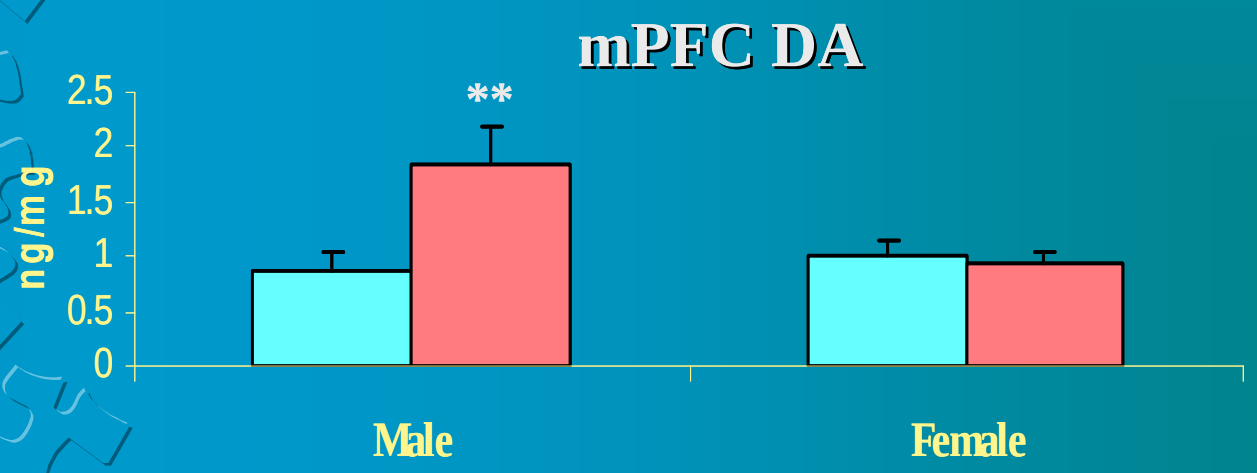
- **Biochemical analyses**
- **Behavioral effects of cocaine**

Gestational nicotine (GN) decreases DAT levels in female striatum

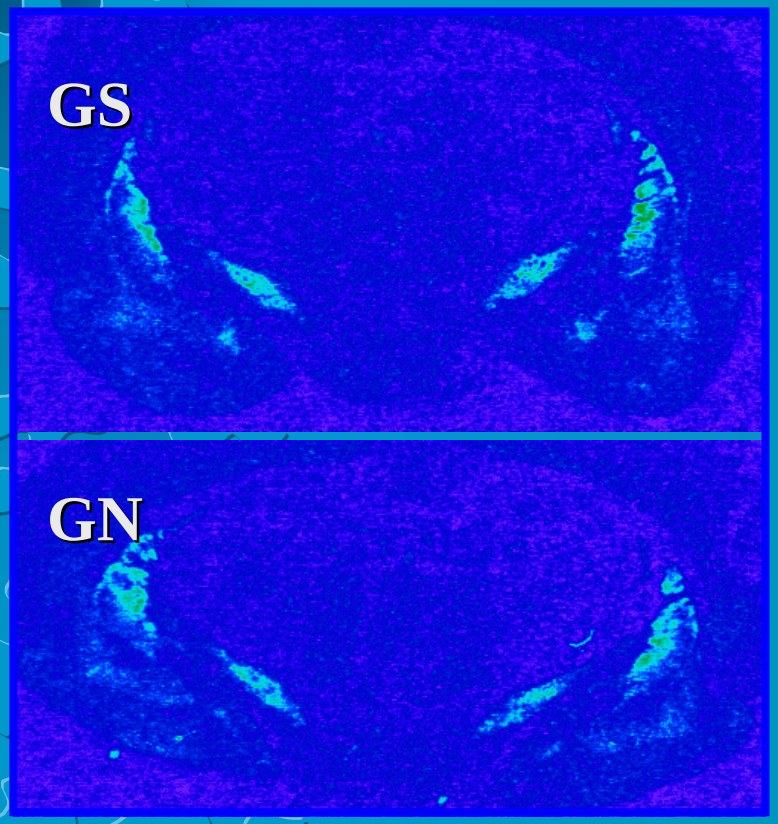


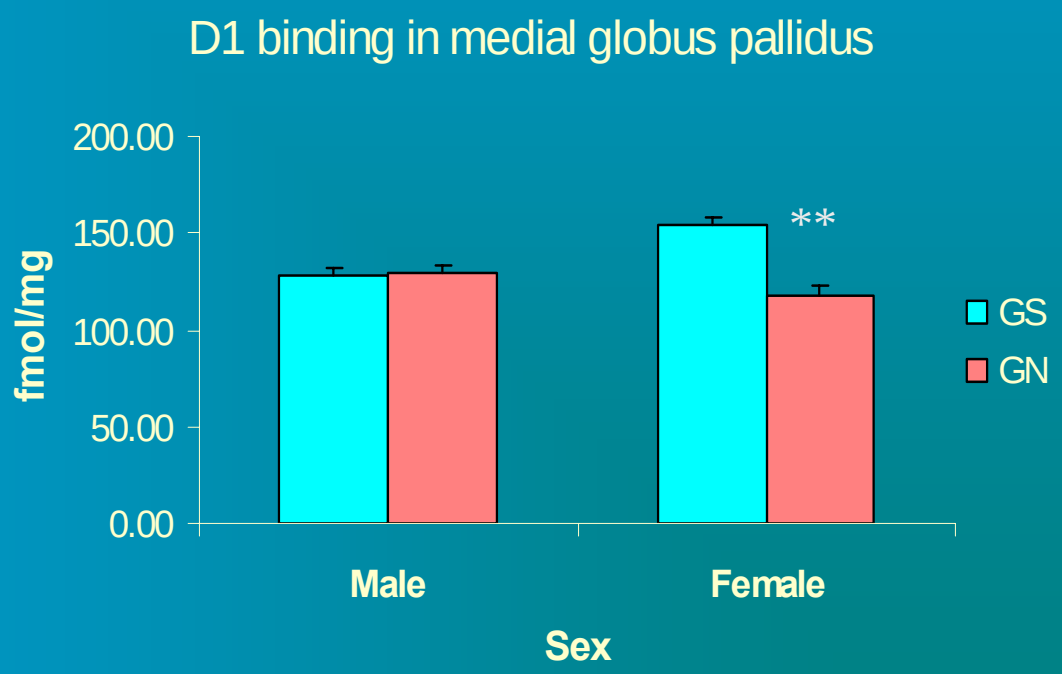
GN treatment alters prefrontal cortex DAT and DA in a sex-dependent manner



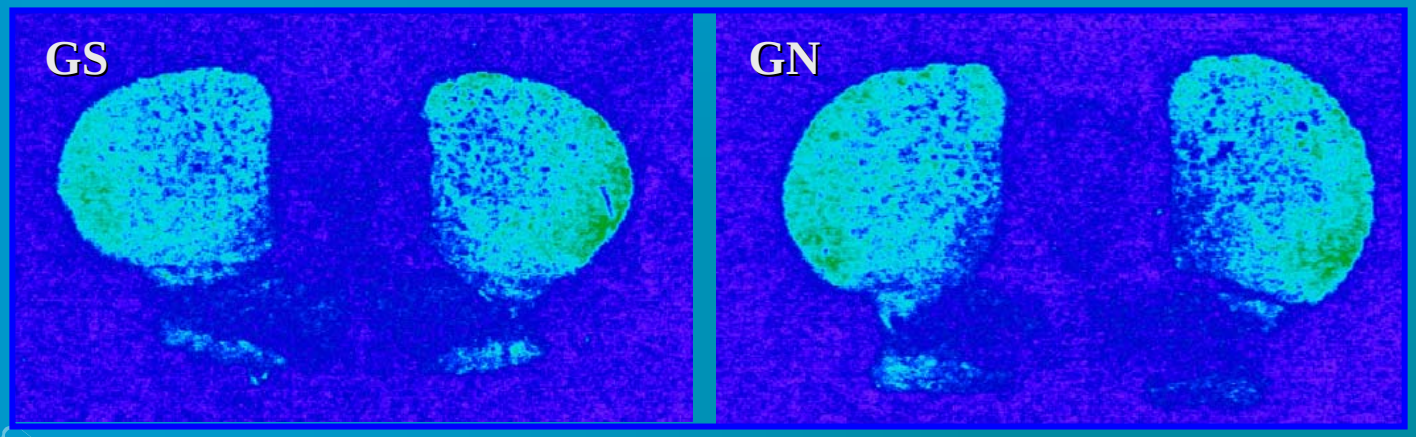


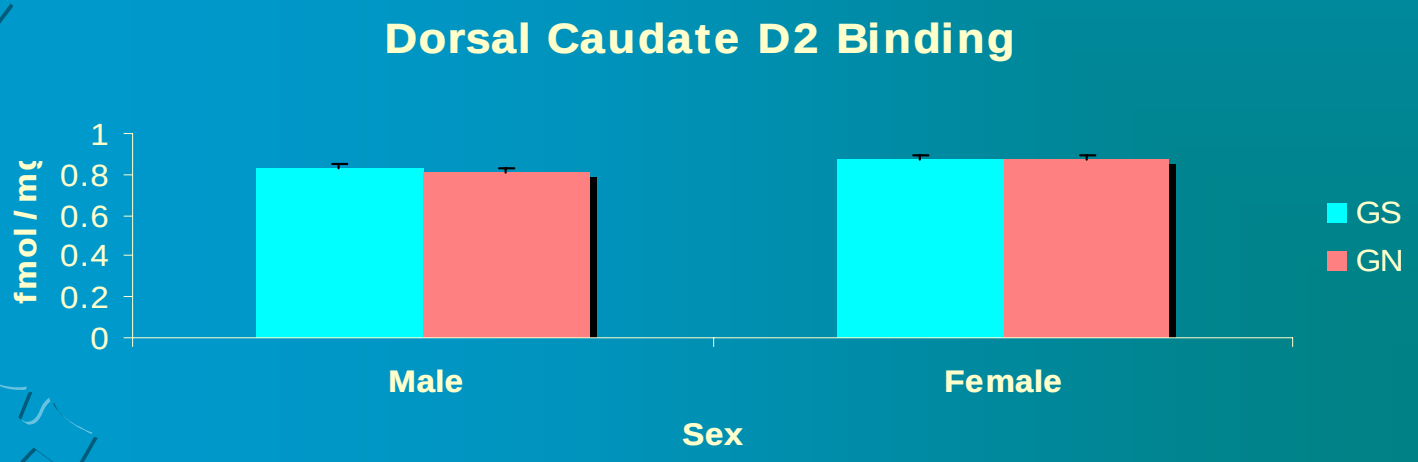
GN treatment alters D1 binding only in the medial globus pallidus



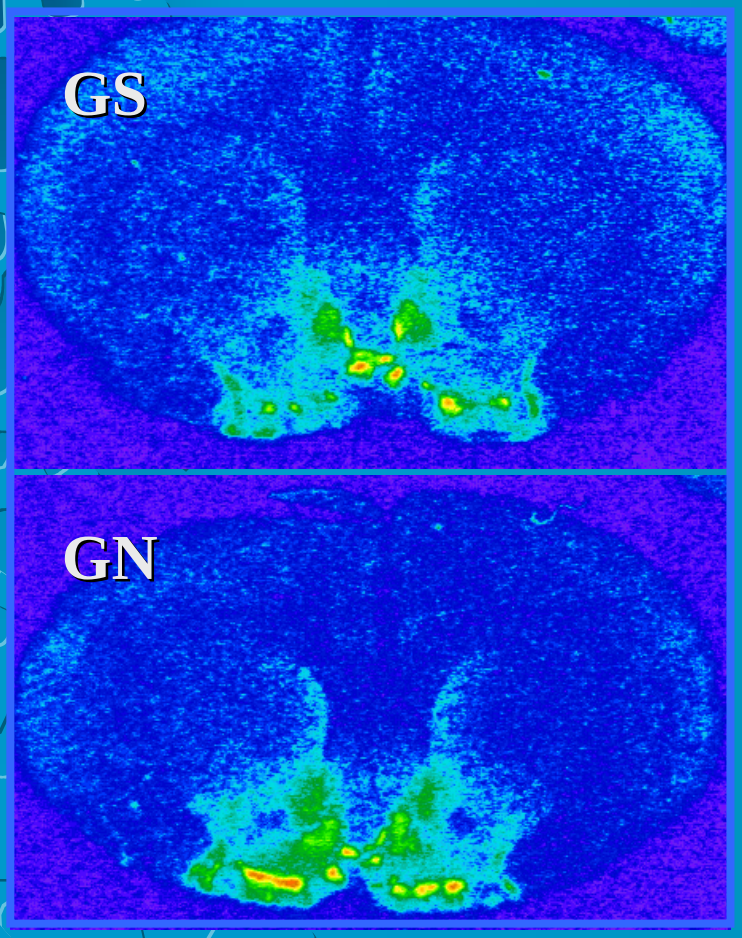


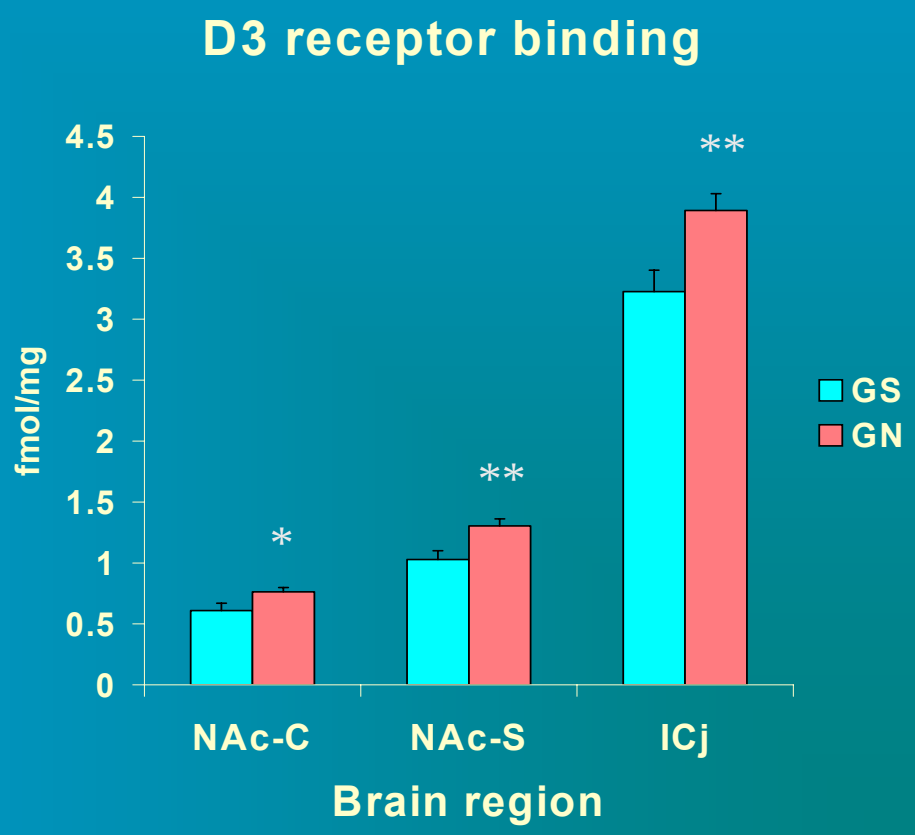
GN treatment does not affect D2 binding



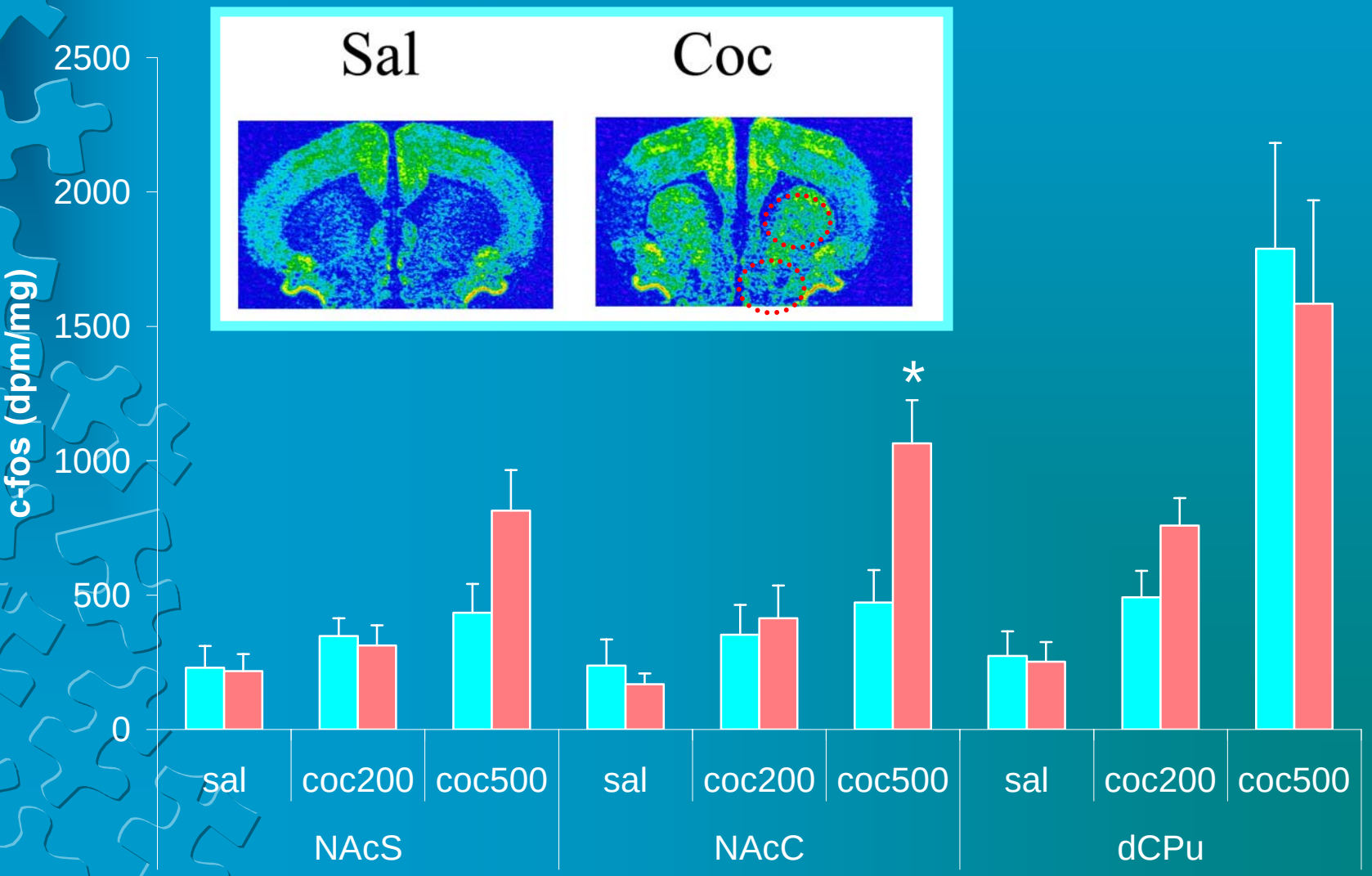


GN treatment increases D3 receptor binding in both males and females

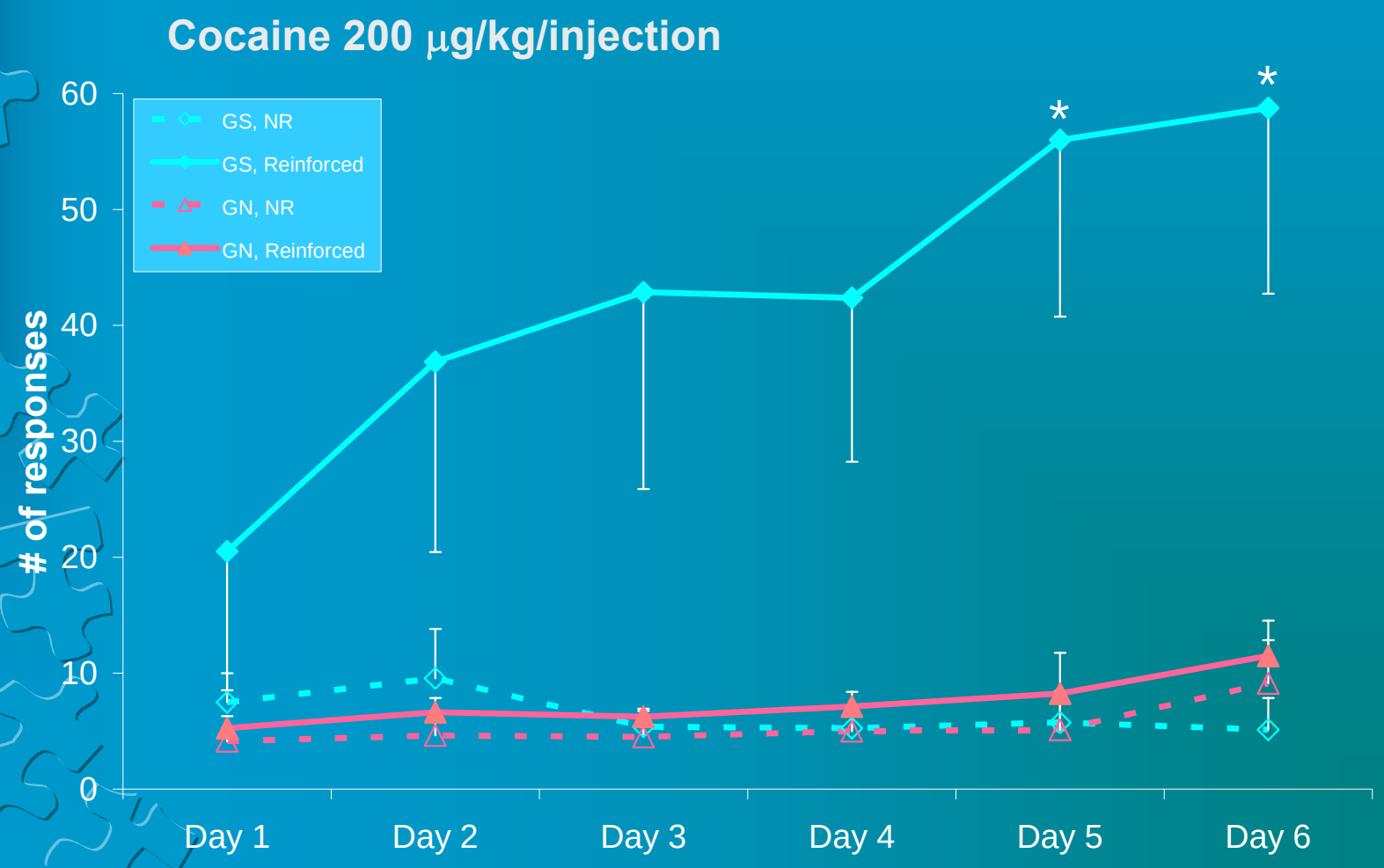




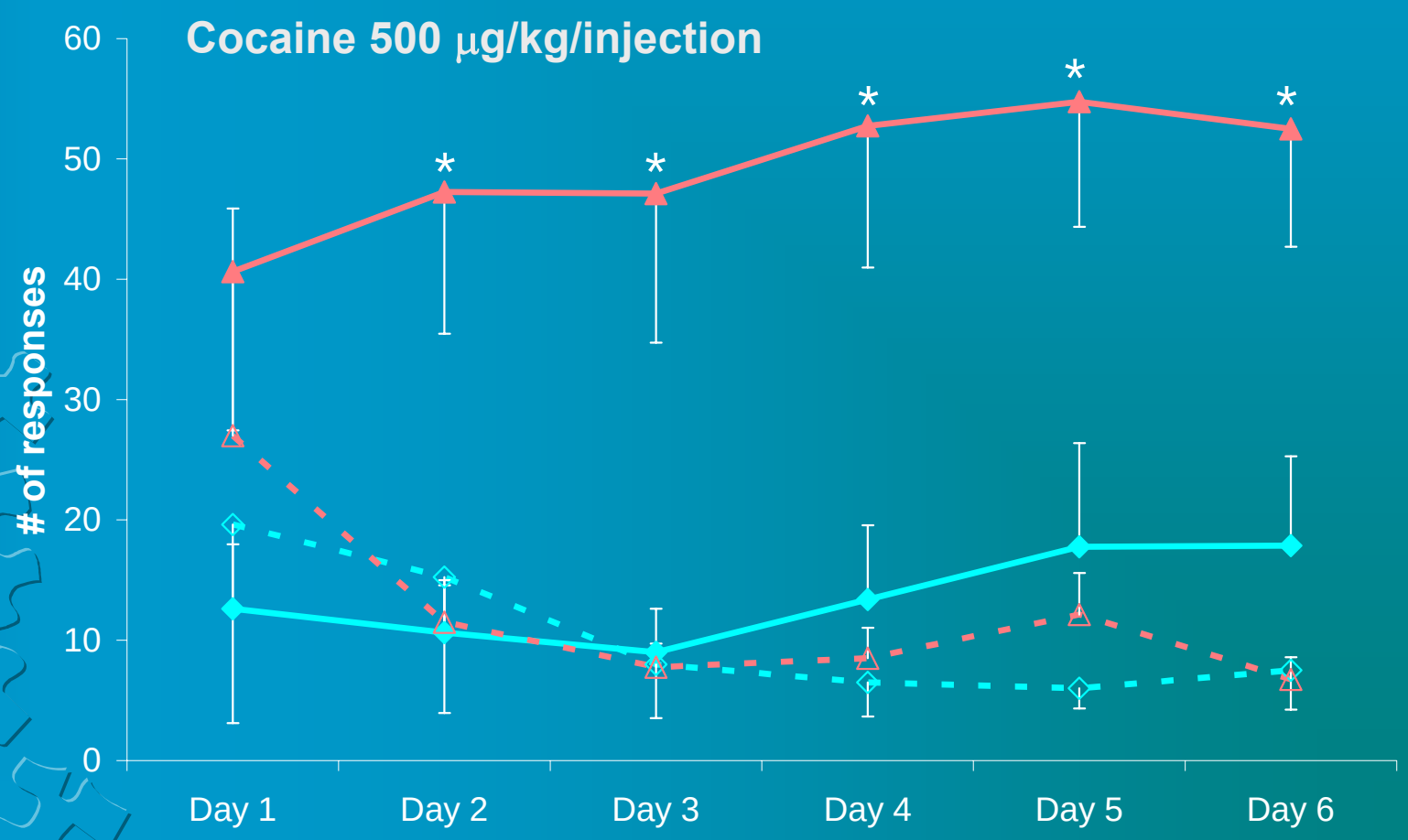
GN increases cocaine-induced neuronal activation in nucleus accumbens



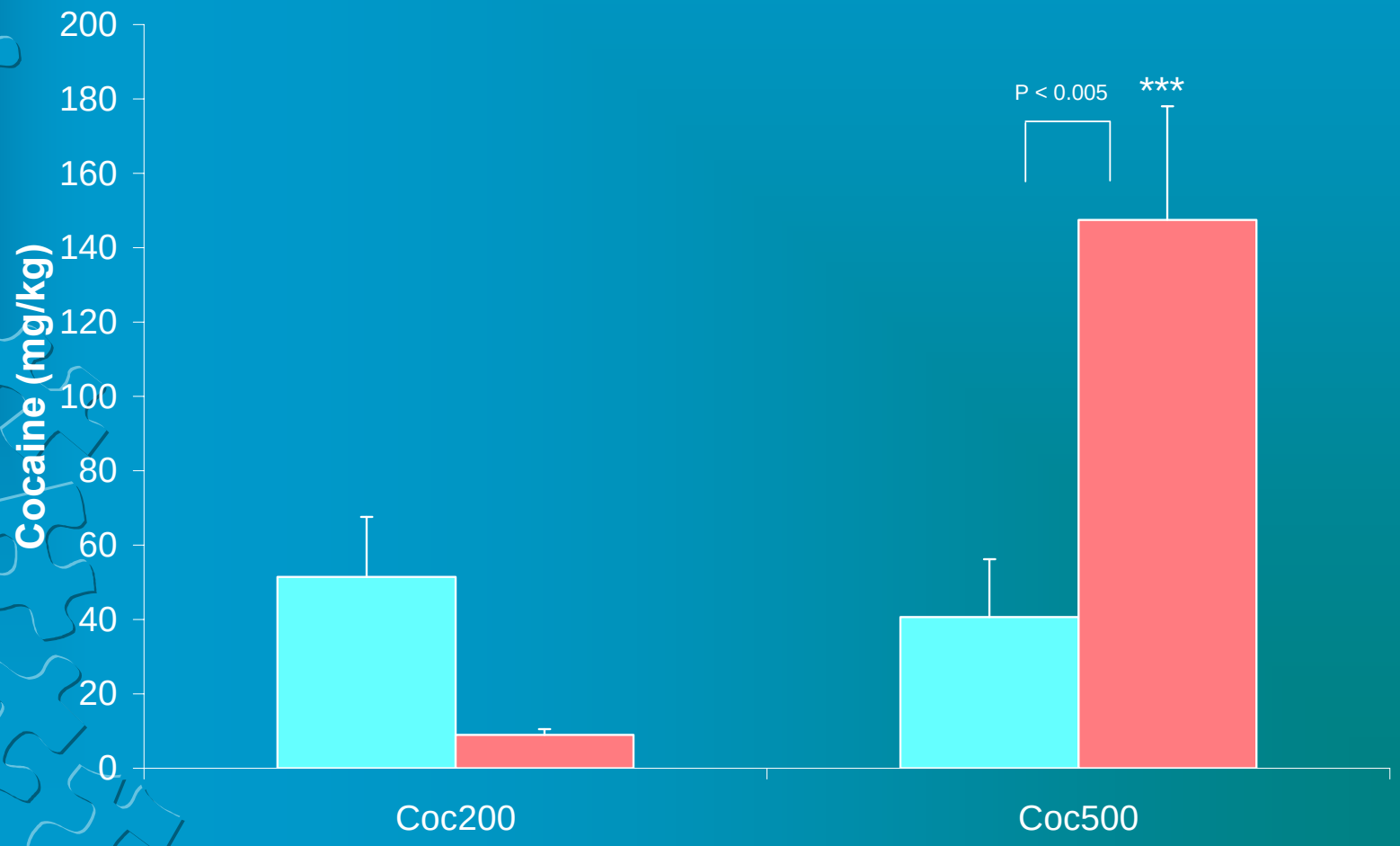
GN treatment decreases sensitivity to the rewarding effects of low dose cocaine



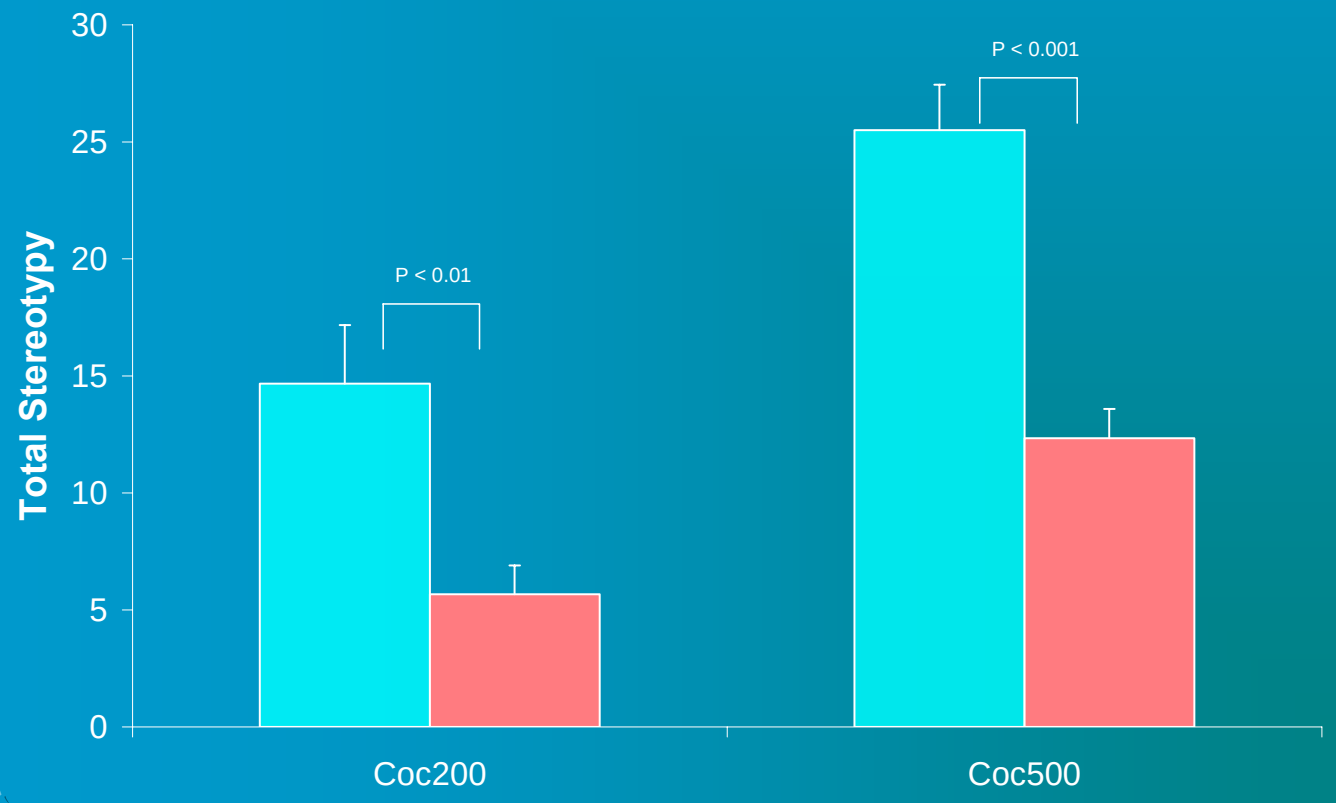
GN increases self-administration of a higher dose of cocaine



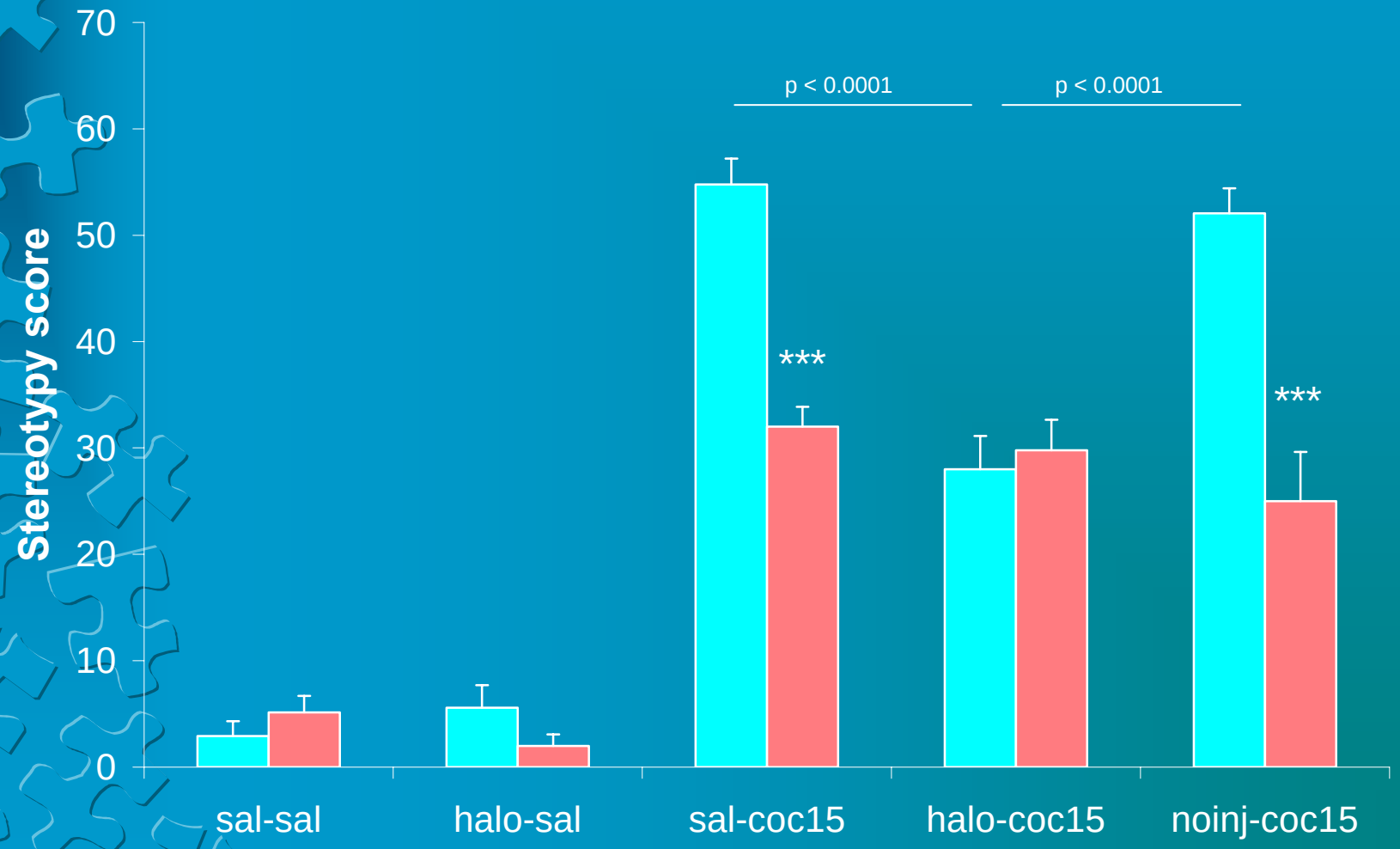
GN increases total cocaine intake



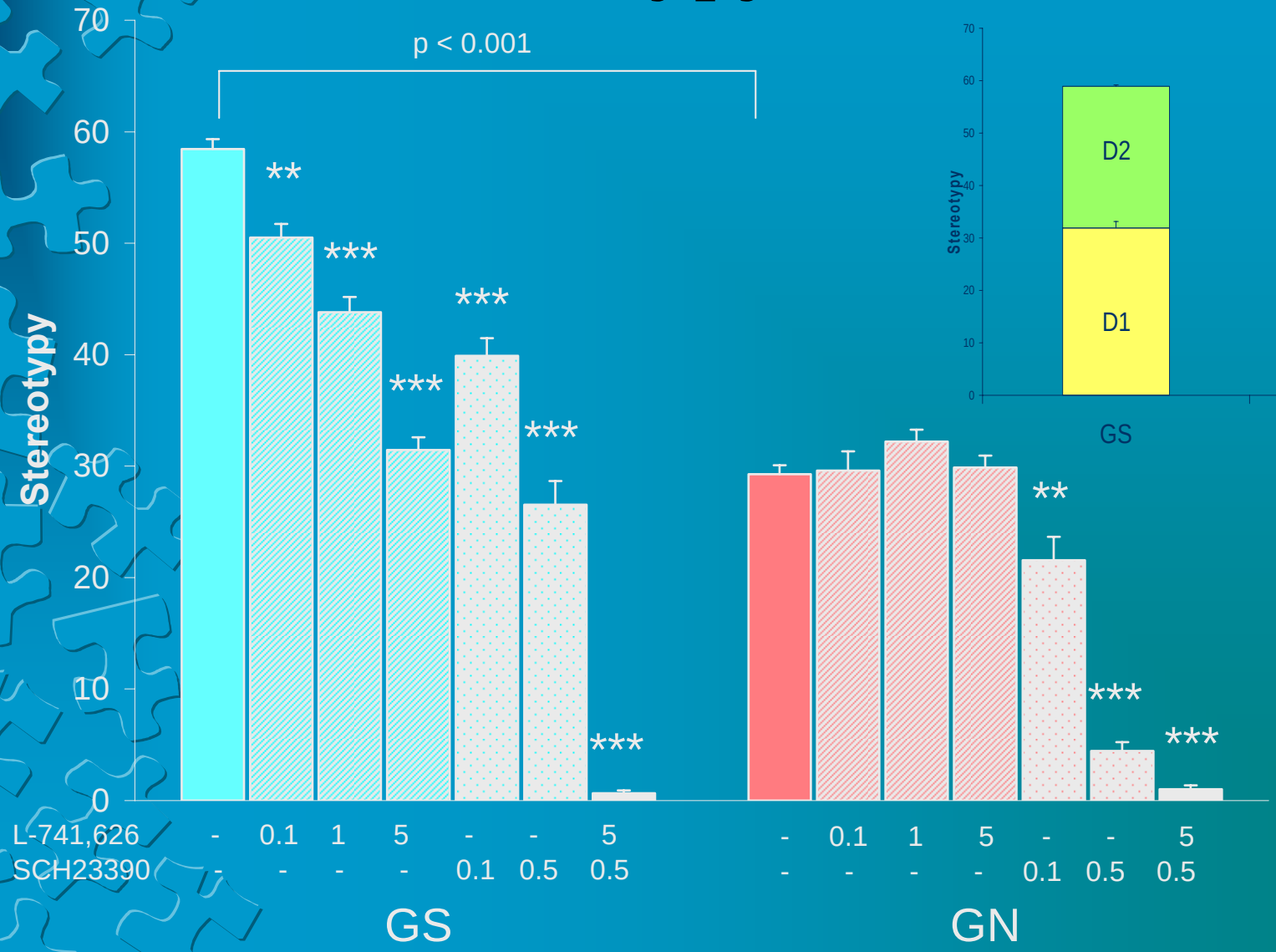
GN decreases cocaine-induced stereotypy



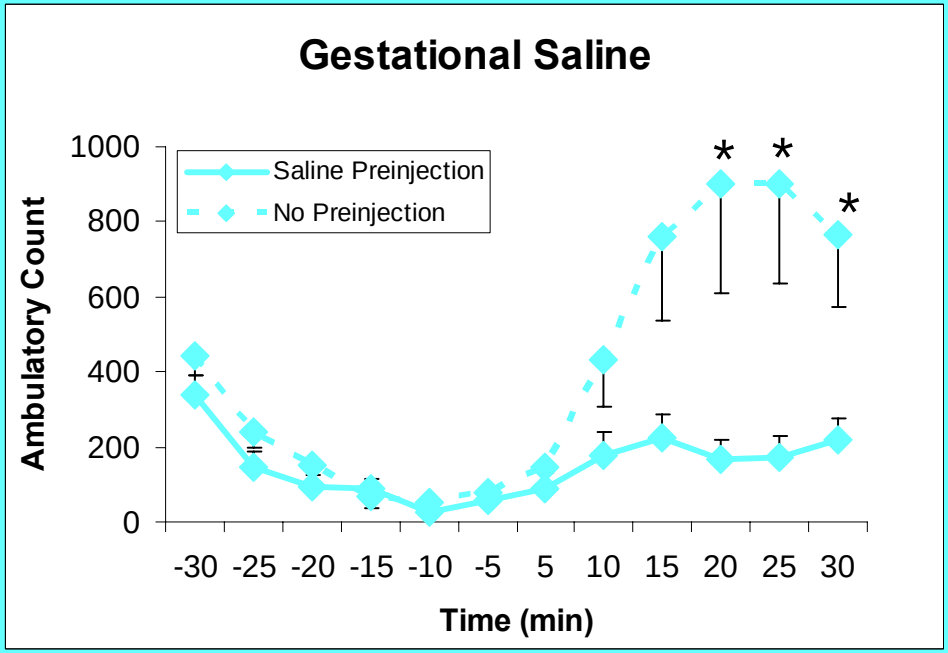
Haloperidol blocks cocaine-induced stereotypy in GS but not GN rats

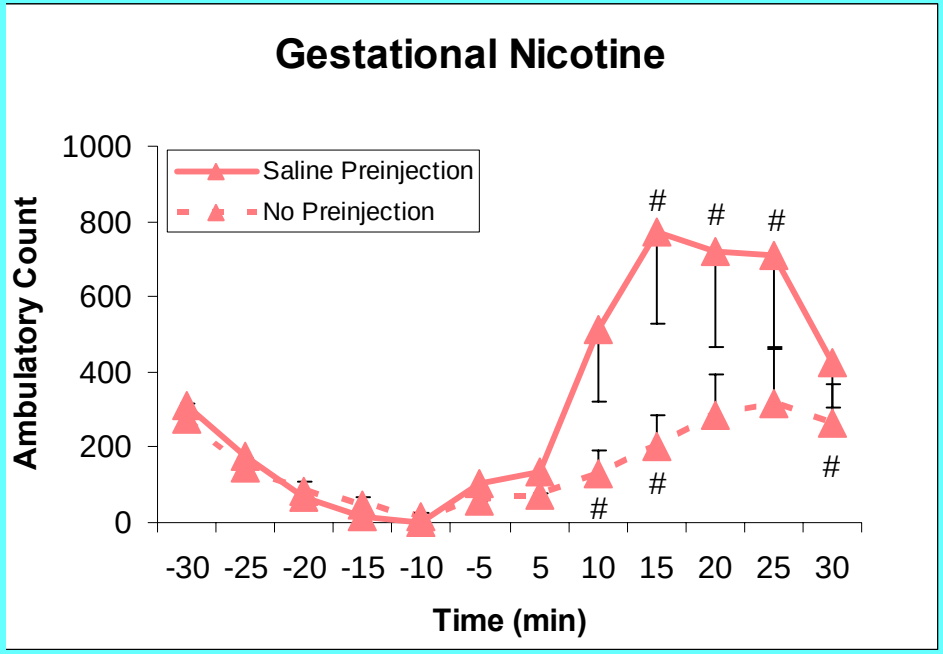


Loss of a D2 receptor mediated stereotypy in GN rats

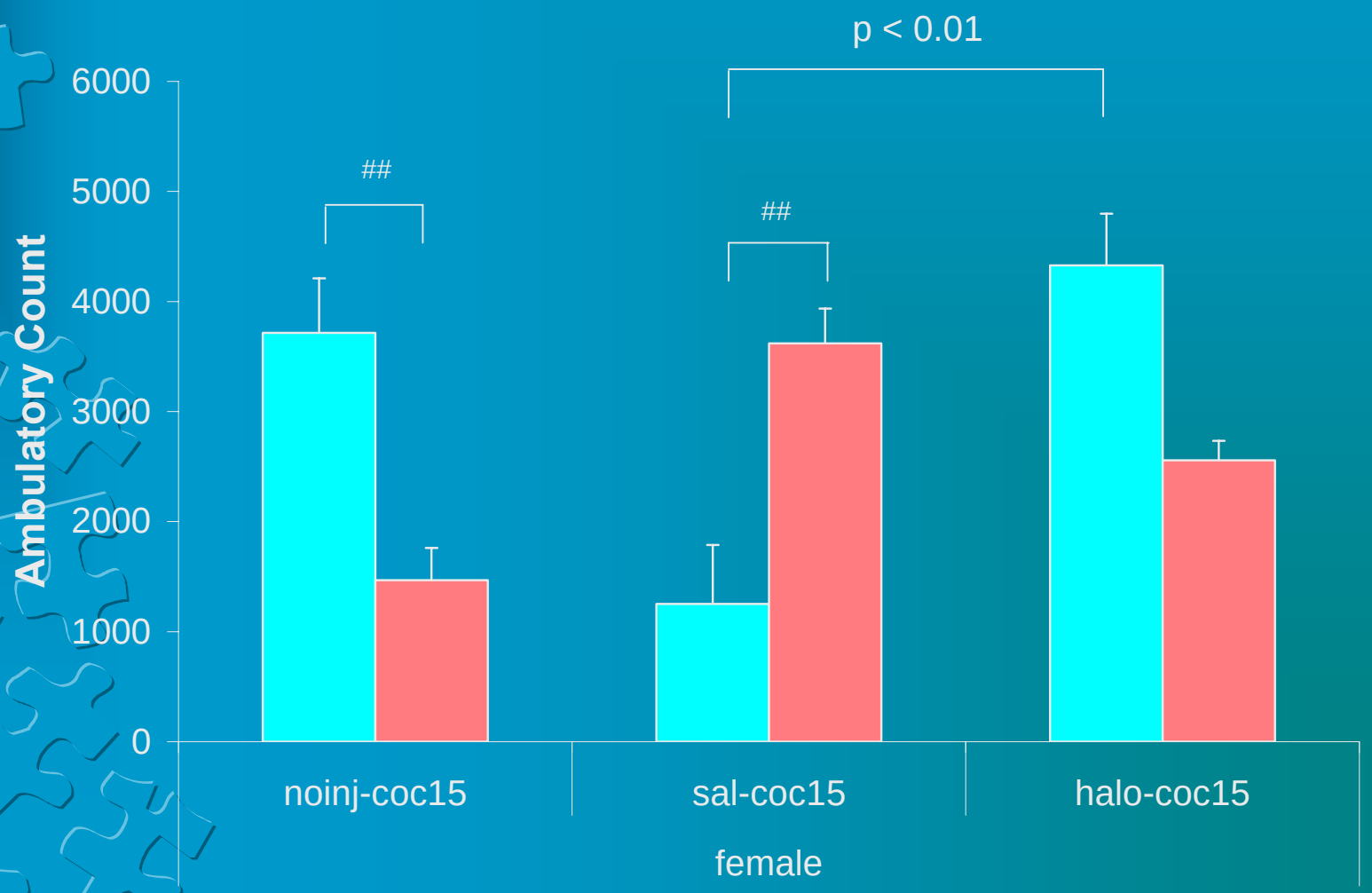


Prior stress has different effects on cocaine-induced locomotor activity in GS and GN females

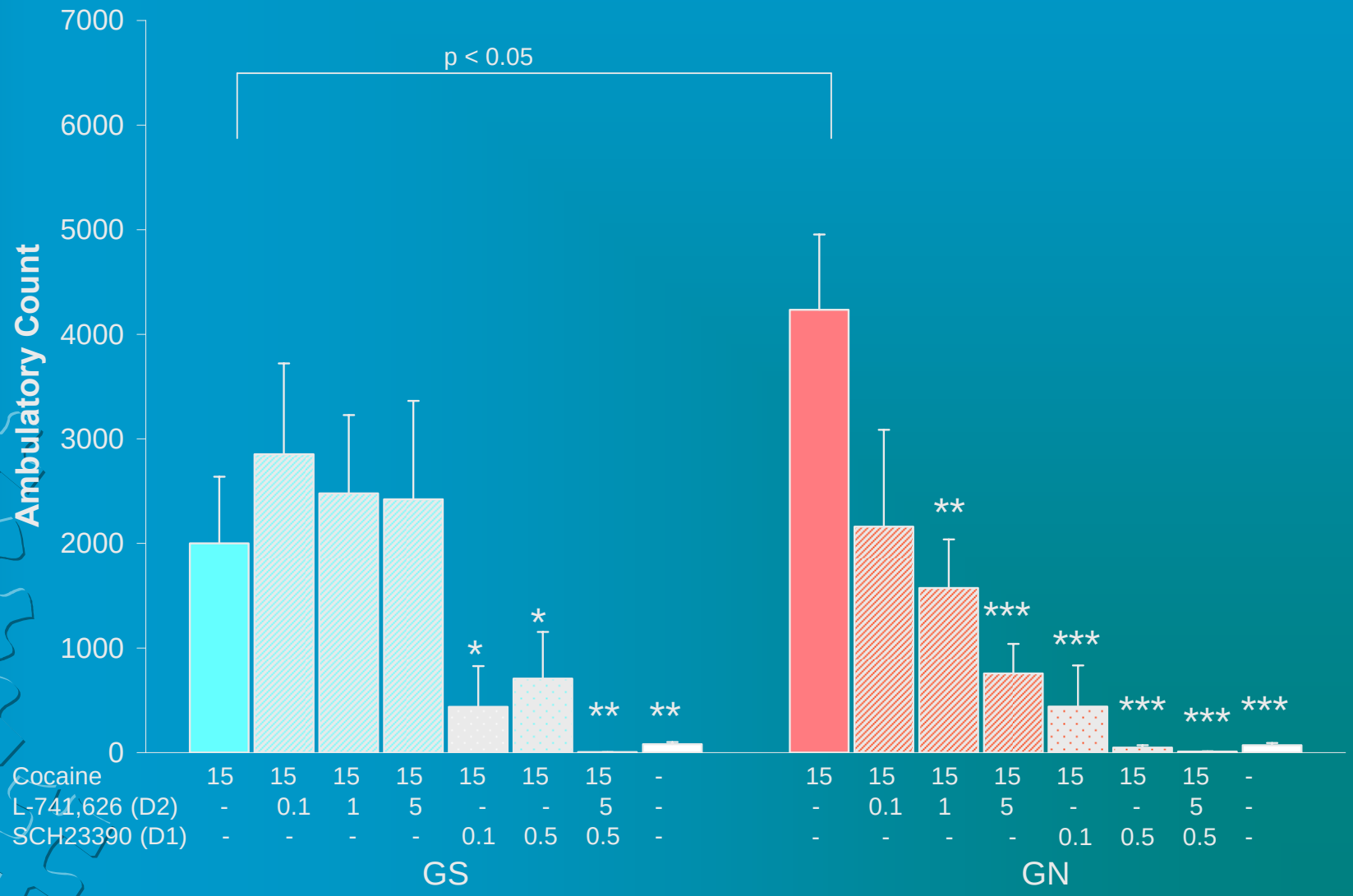




Haloperidol reverses stress-induced decrease in cocaine locomotion in GS females



Both D1 and D2 receptors mediated cocaine-induced locomotion in GN rats

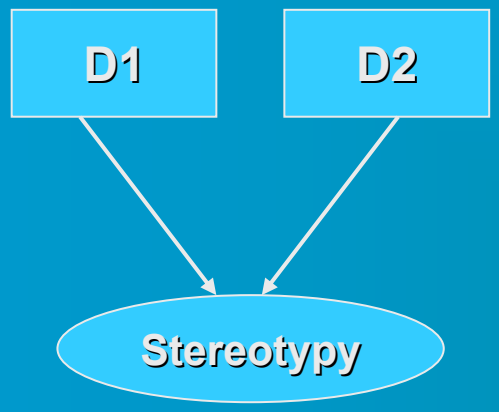


Gestational nicotine treatment results in the following changes in adolescence:

- Sex-dependent alterations in biochemical markers of DA function
- Increased threshold for cocaine self-administration, with an increase in total intake
- Complex changes in locomotor behavior

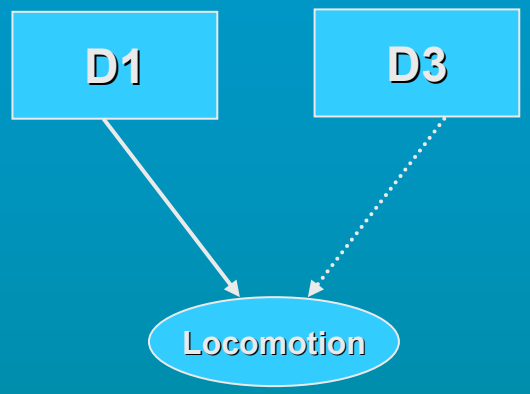
GS

Males + Females



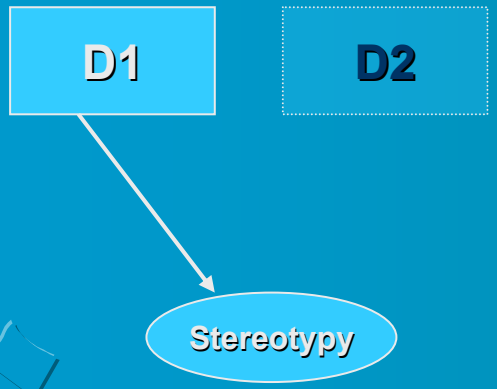
GS

Females + stress



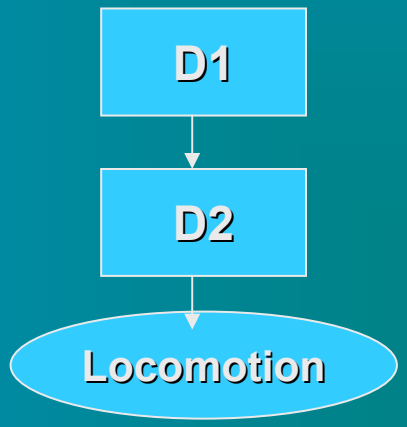
GN

Males + Females



GN

Females + stress



Thanks…….

to the Leslie Lab

and the National Institute on Drug Abuse