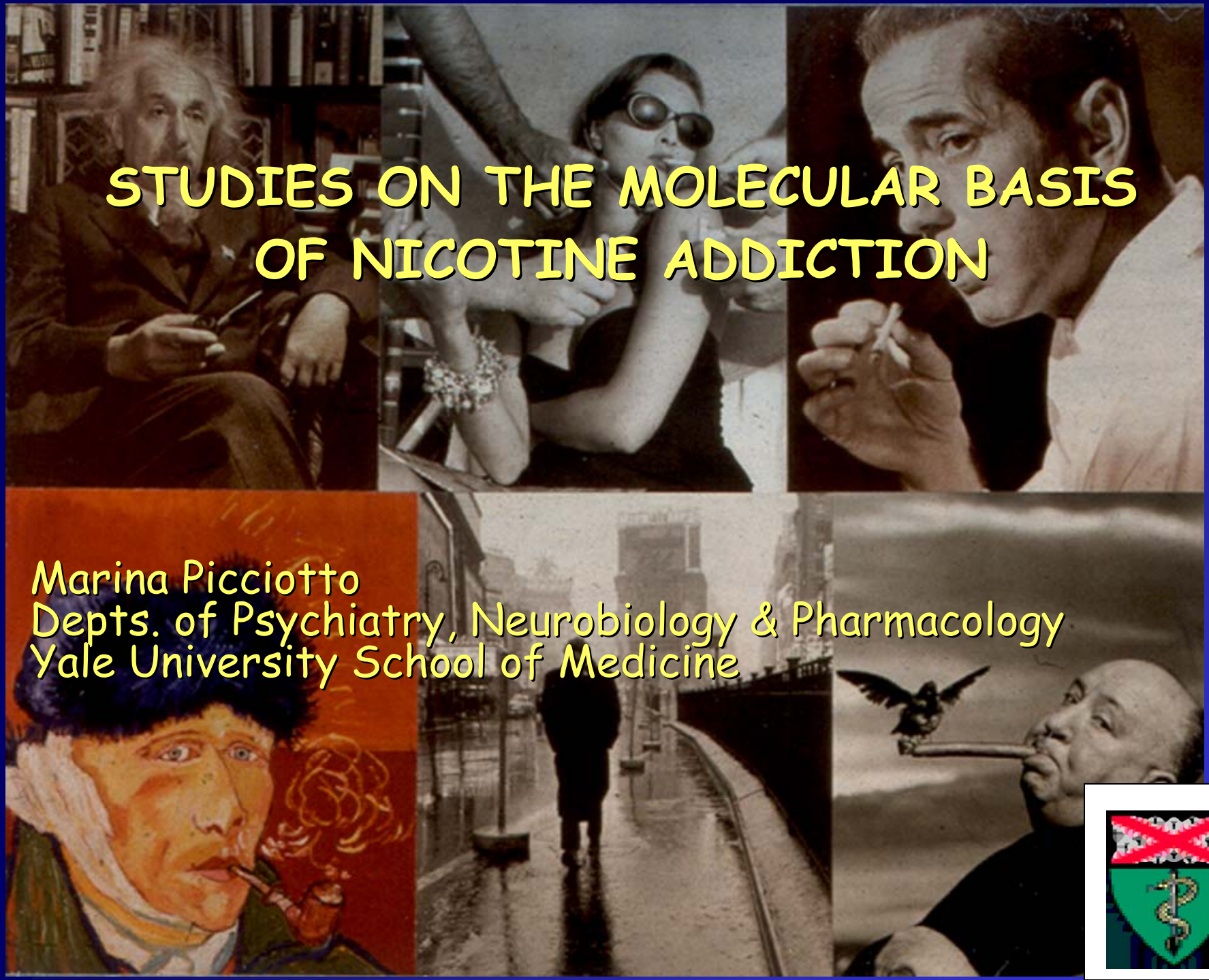
STUDIES ON THE MOLECULAR BASIS OF NICOTINE ADDICTION



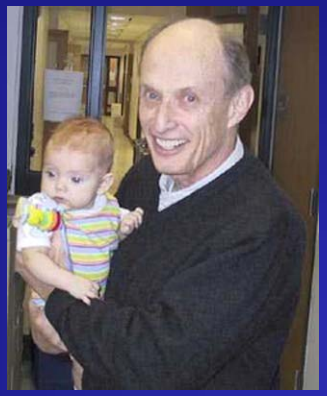
Marina Picciotto
Depts. of Psychiatry, Neurobiology & Pharmacology
Yale University School of Medicine

The Waletzky Family

Jacob Waletzky

My Mentors

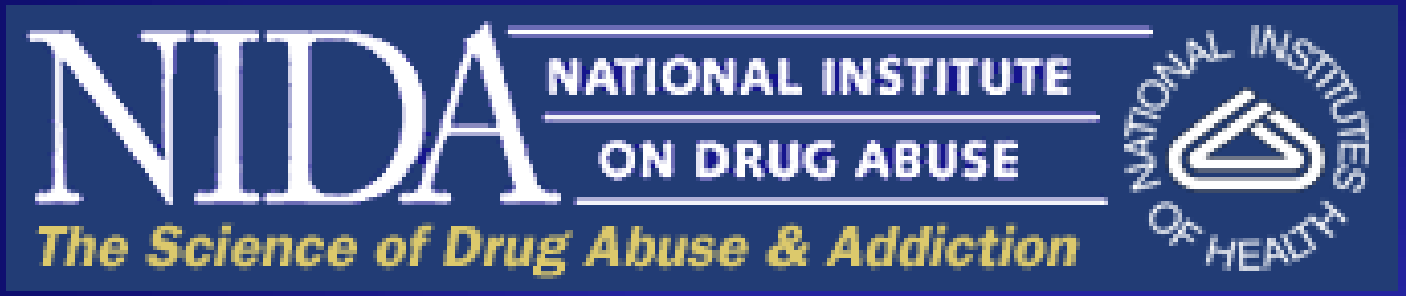
R Scheller



P Greengard

J-P Changeux

NIDA


NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE
The Science of Drug Abuse & Addiction
NATIONAL INSTITUTES OF HEALTH

Current lab members

Yuki Asaka
Amine Bahi
Christian Brabant
Emily Einstein
Nadia Gavrilova
Christopher Heath
Yonwoo Jung
Helen Kamens
Jérémie Lavaur
Diane Lendroth
Yann Mineur

Past lab members

Nii Addy
Bob Beech
Darlene Brunzell
Barbara Caldarone
Ali Harrist
Jessica Hawes
Sarah King
Roopa Narasimhaiah
Reba Rabenstein
Oli Somenzi
Tanya Stevens
Rebecca Steiner
Nataly Uboha
Vanna Zachariou

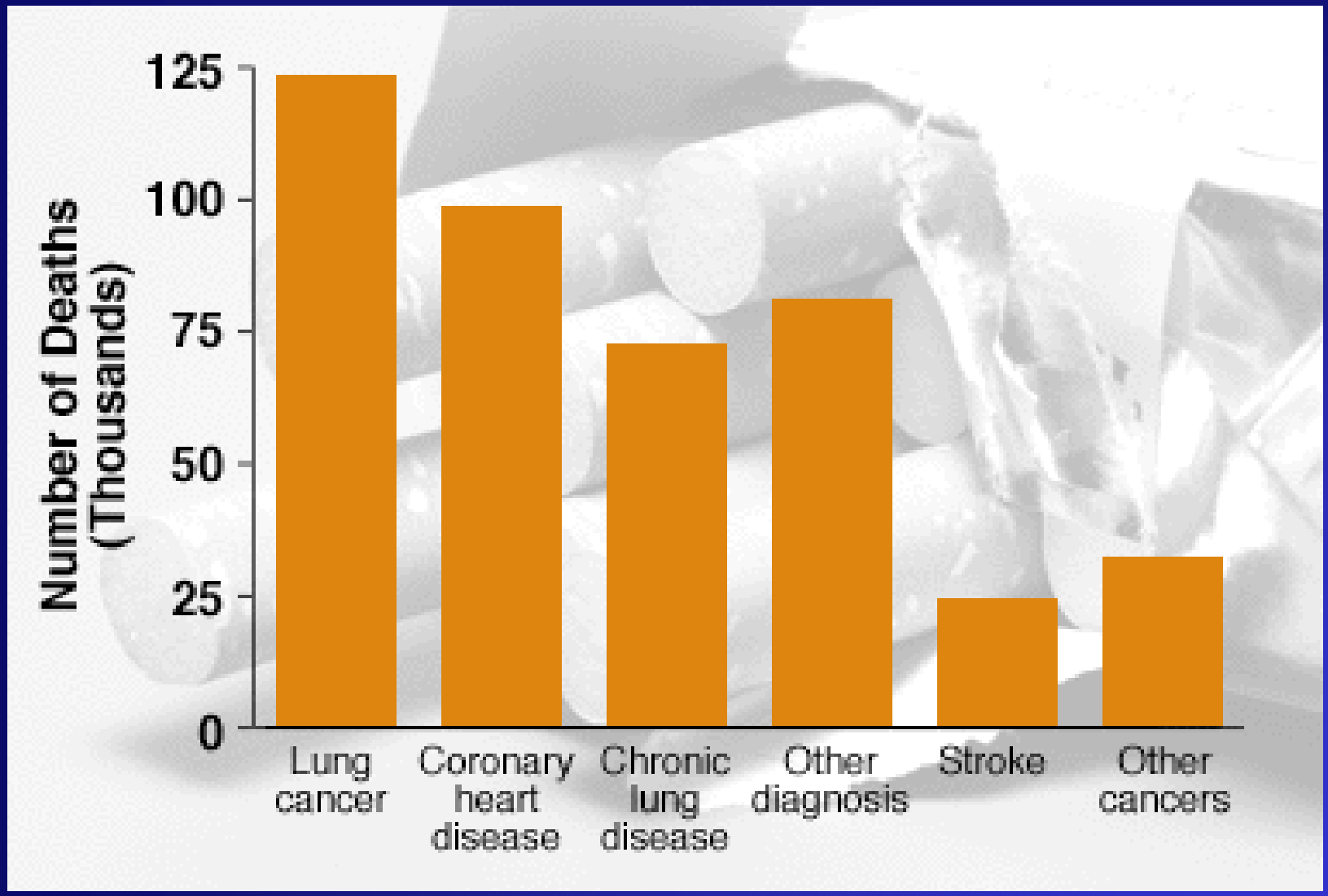
Collaborators

Steve Buka
J-P Changeux
Clement Lena
Al Collins
Sharon Grady
Michael Marks
Ron Duman
Sam Newton
Reiko Fitzsimonds
Tony George
Stephanie O'Malley
Julie Staley
Michele Zoli

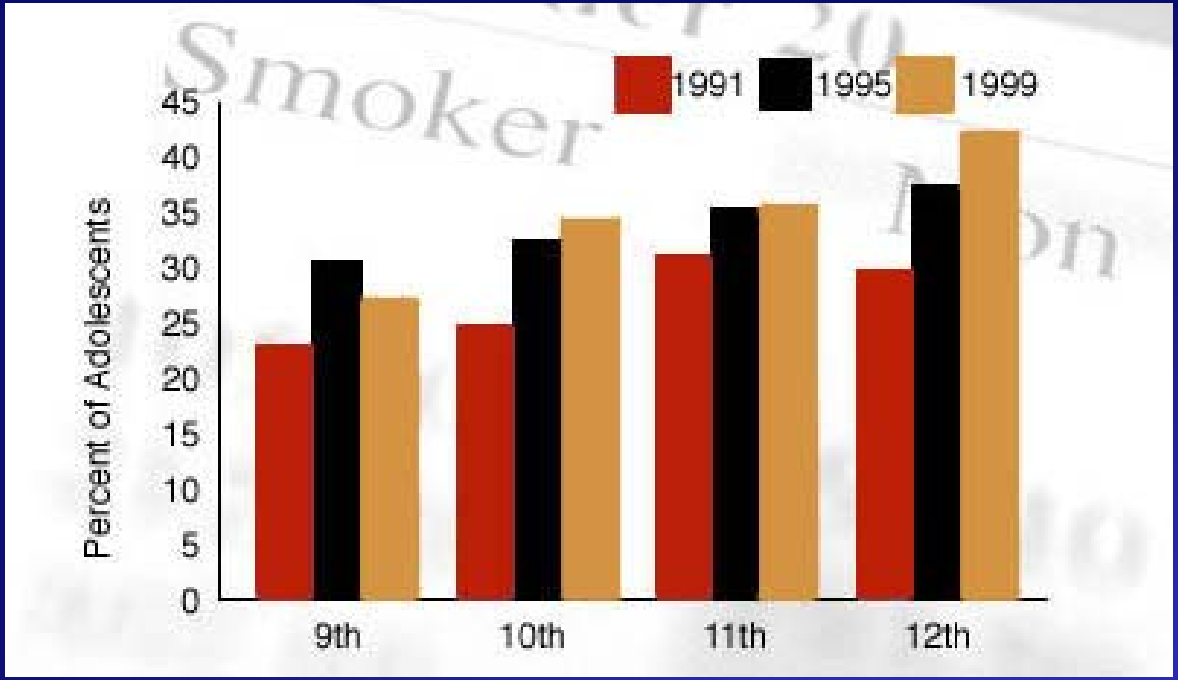
Funding

NIDA TTURC
NIMH NARSAD

Smoking is still the leading cause of death in the developed world



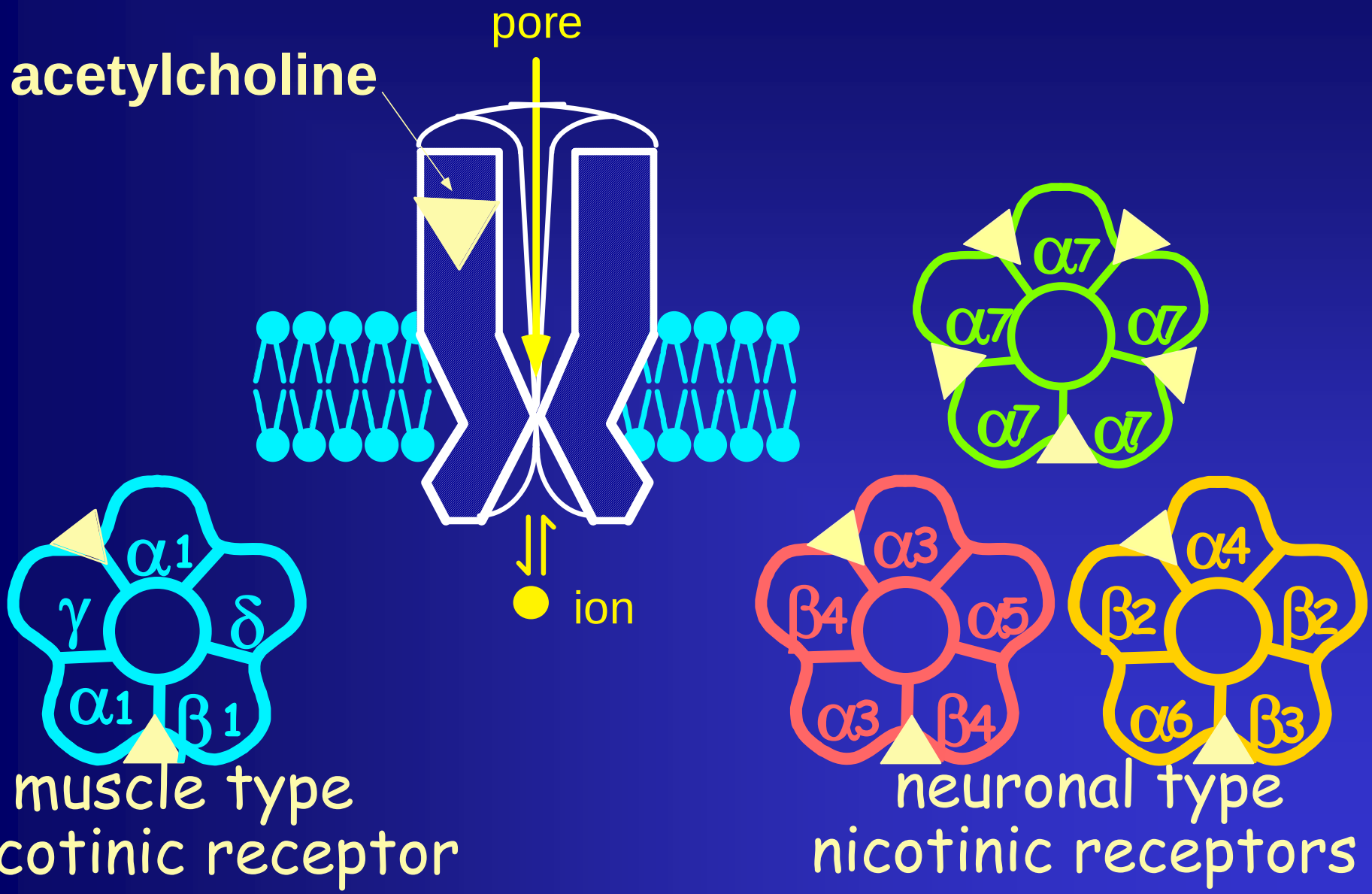
The majority of smokers start as adolescents



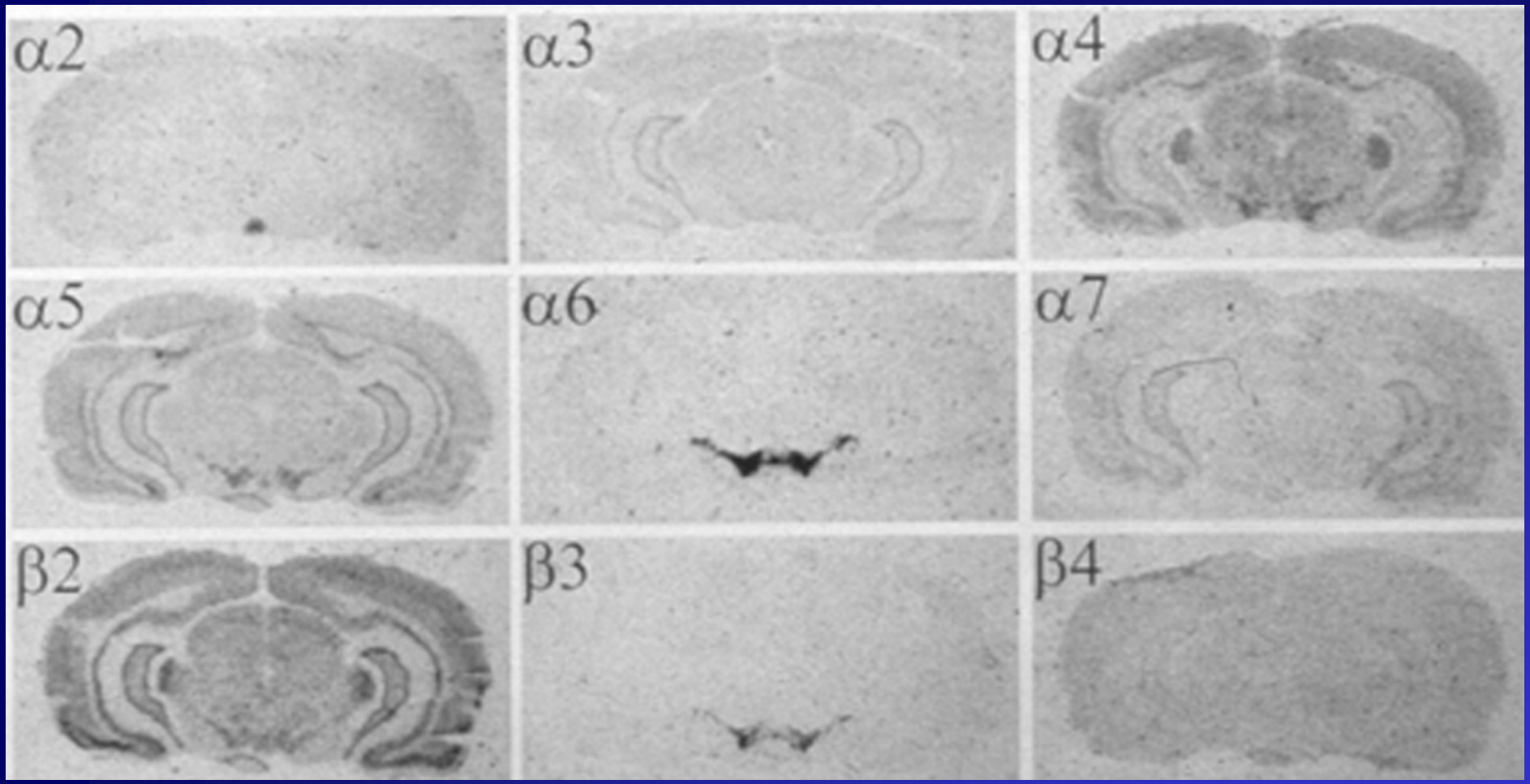
Maternal and adolescent smoking have long-lasting effects on behavior (Jacobsen).

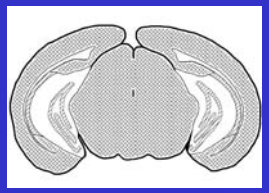
Nicotine can accelarate maturation of *GABA* neurons (Berg) and potentiate synaptic plasticity during critical periods of development (Metherate, King).

Structure of nicotinic ACh receptors



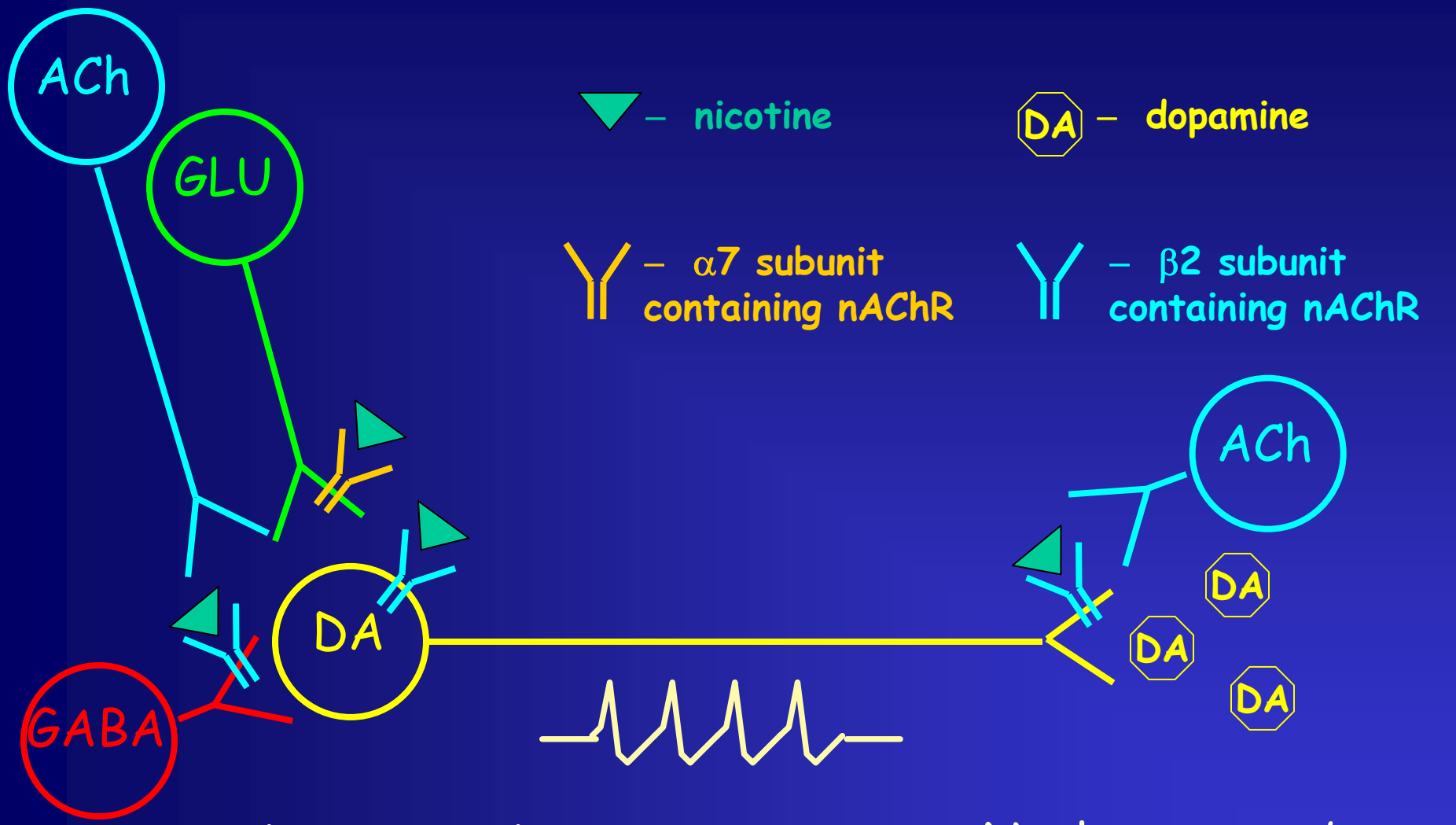
Nicotinic subunit in situ - VTA



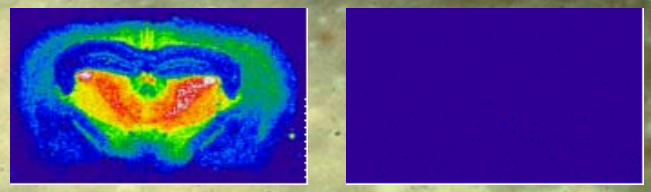


Zoli, unpublished

Nicotine regulation of the DA system

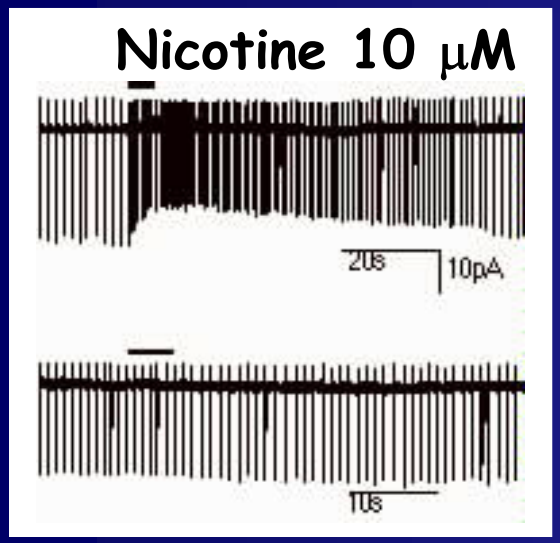


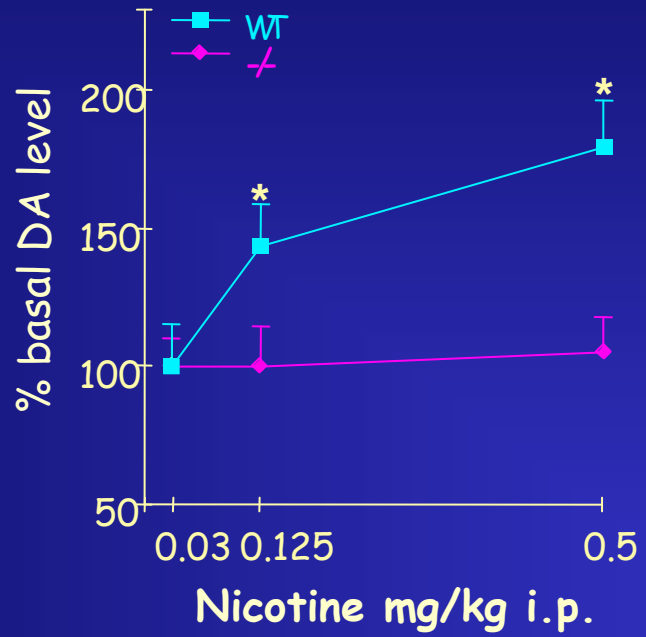
Acetylcholine receptors containing the β2 subunit are involved in the reinforcing properties of nicotine

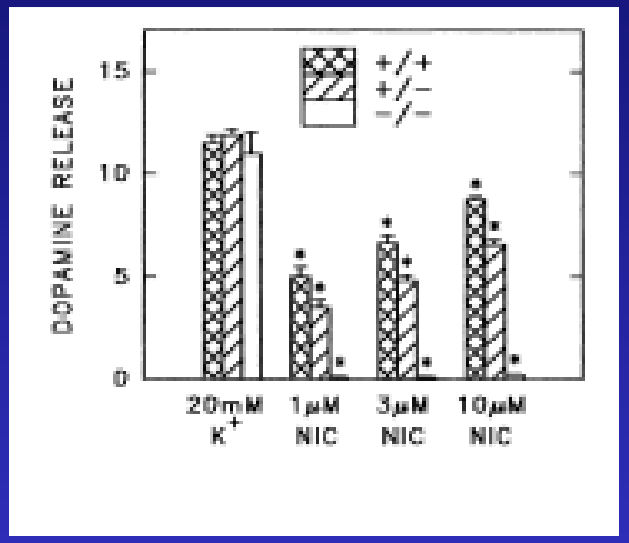


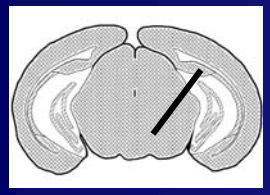
WT KO

Nicotine does not stimulate dopamine release in β2-/- mice...





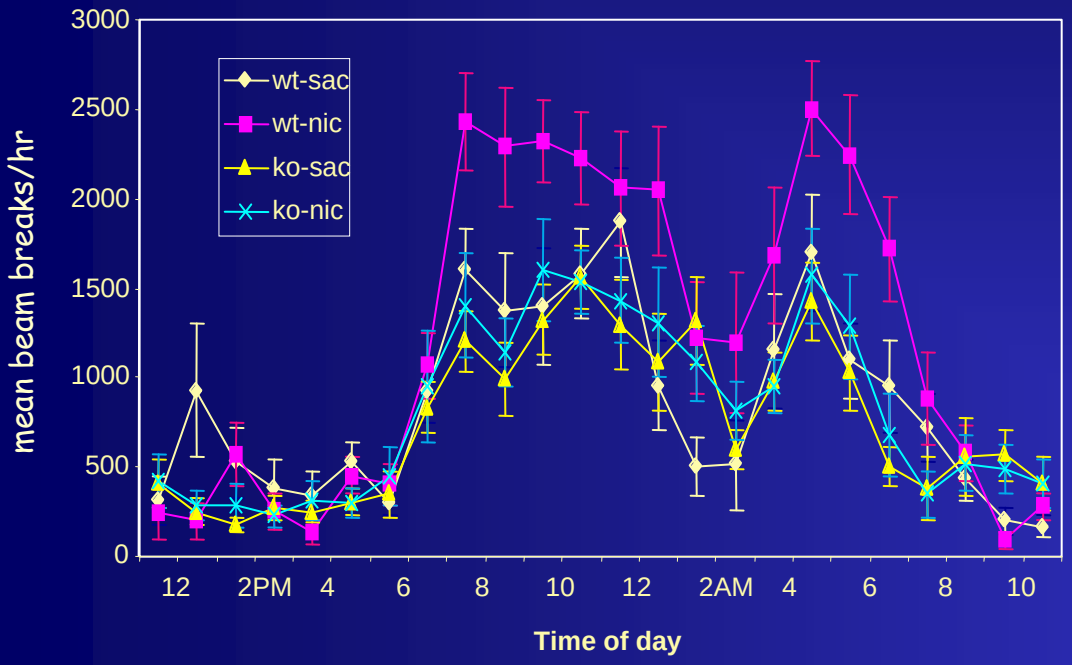




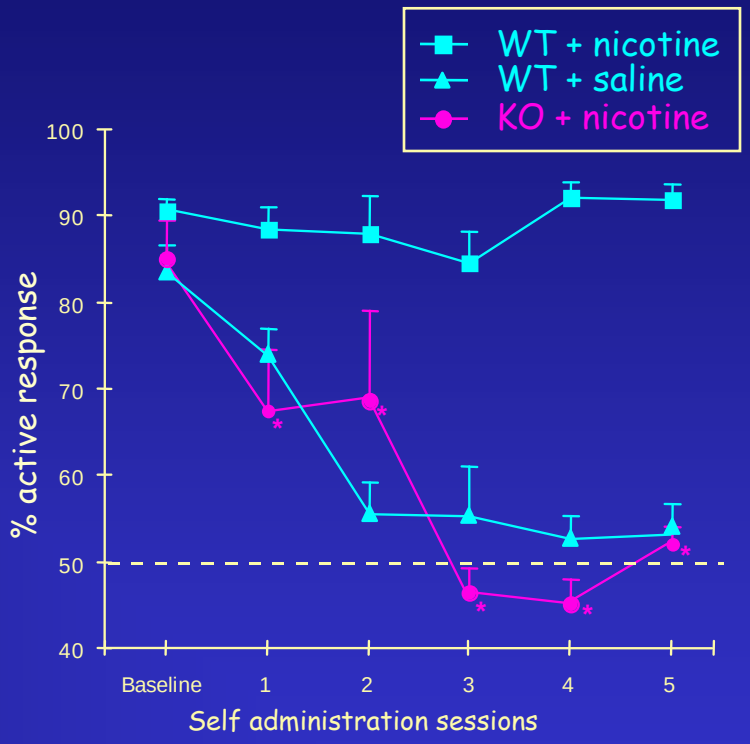
Picciotto et al, Nature, 1998

Grady et al, J Neurochem, 2001

…and is not reinforcing

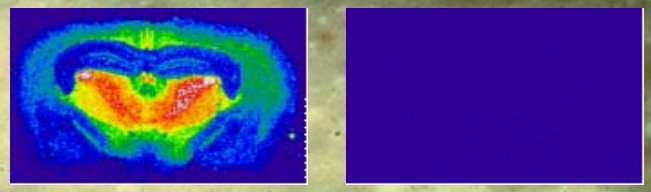


King et al, Neuropharm. 2004



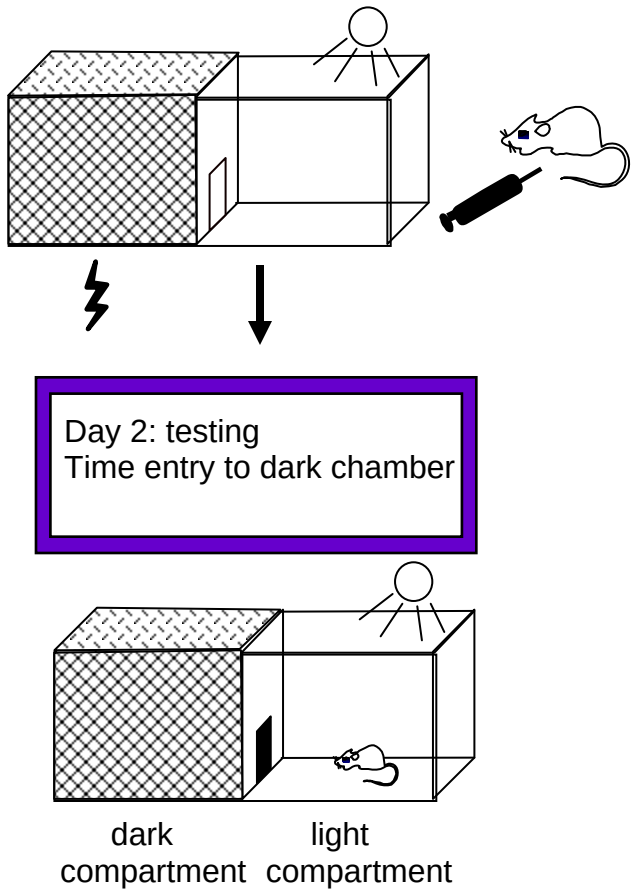
Picciotto et al, Nature, 1998

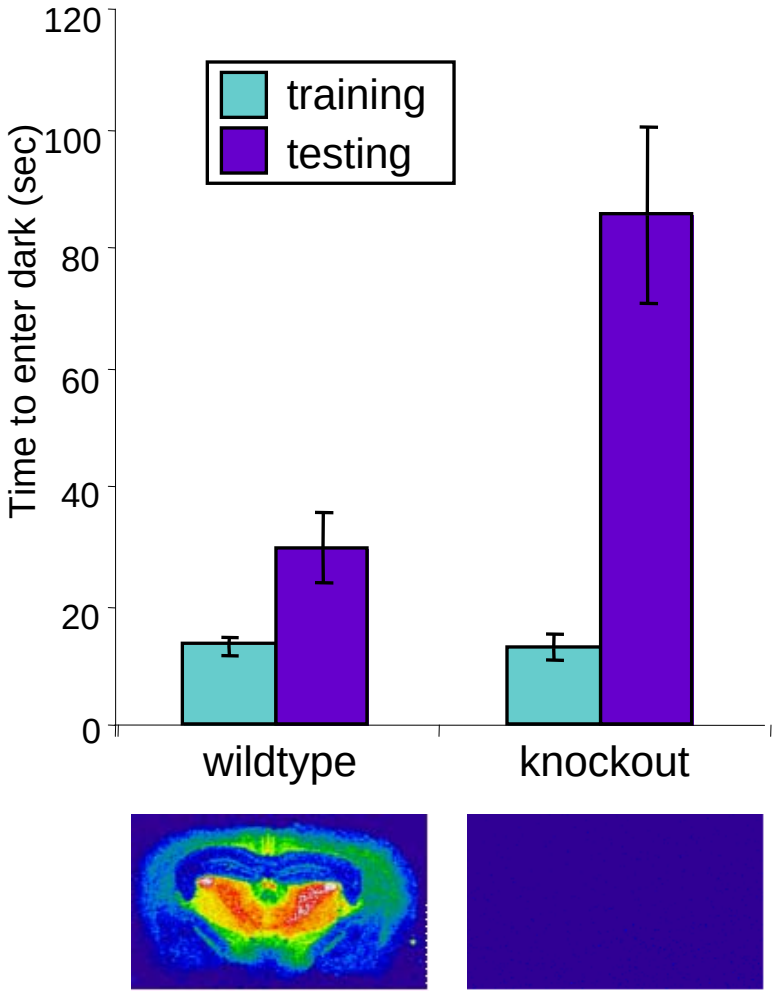
Abnormal avoidance learning in mice lacking functional high-affinity nicotine receptor in the brain



WT KO

Constitutive β2 subunit knockout results in hypersensitive passive avoidance learning



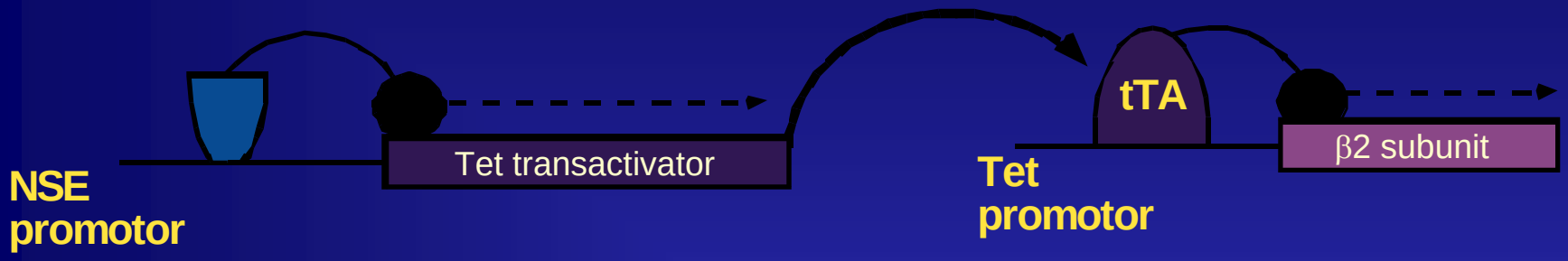


Picciotto et al, Nature, 1995

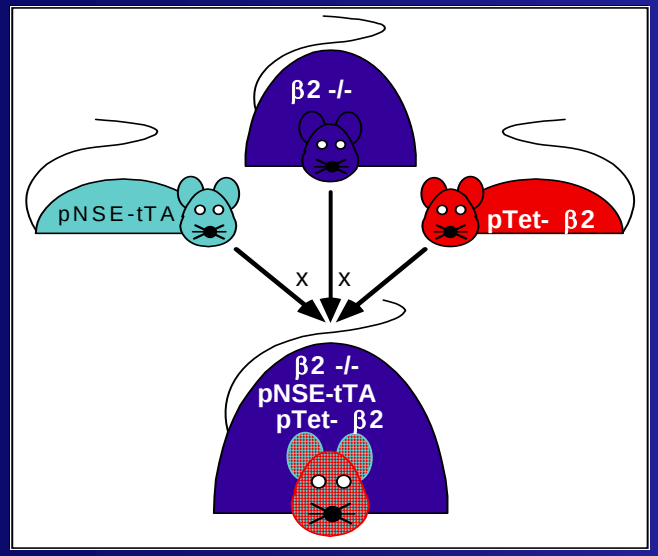
Questions to be answered:

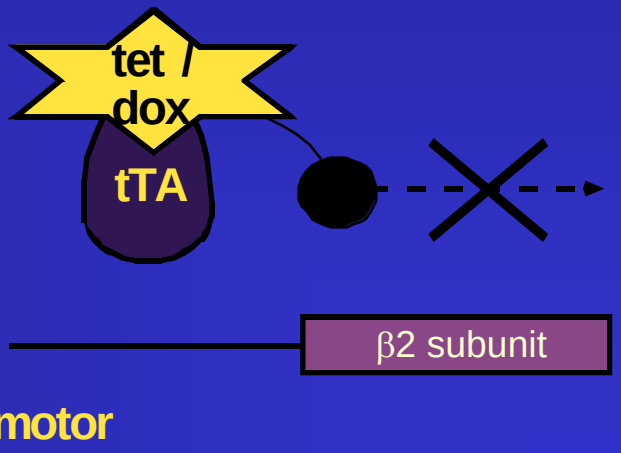
- Where in the brain is this happening?
- When during development are nAChRs necessary for this effect?
- What are the effects of nicotine on this behavior?

Inducible region specific expression

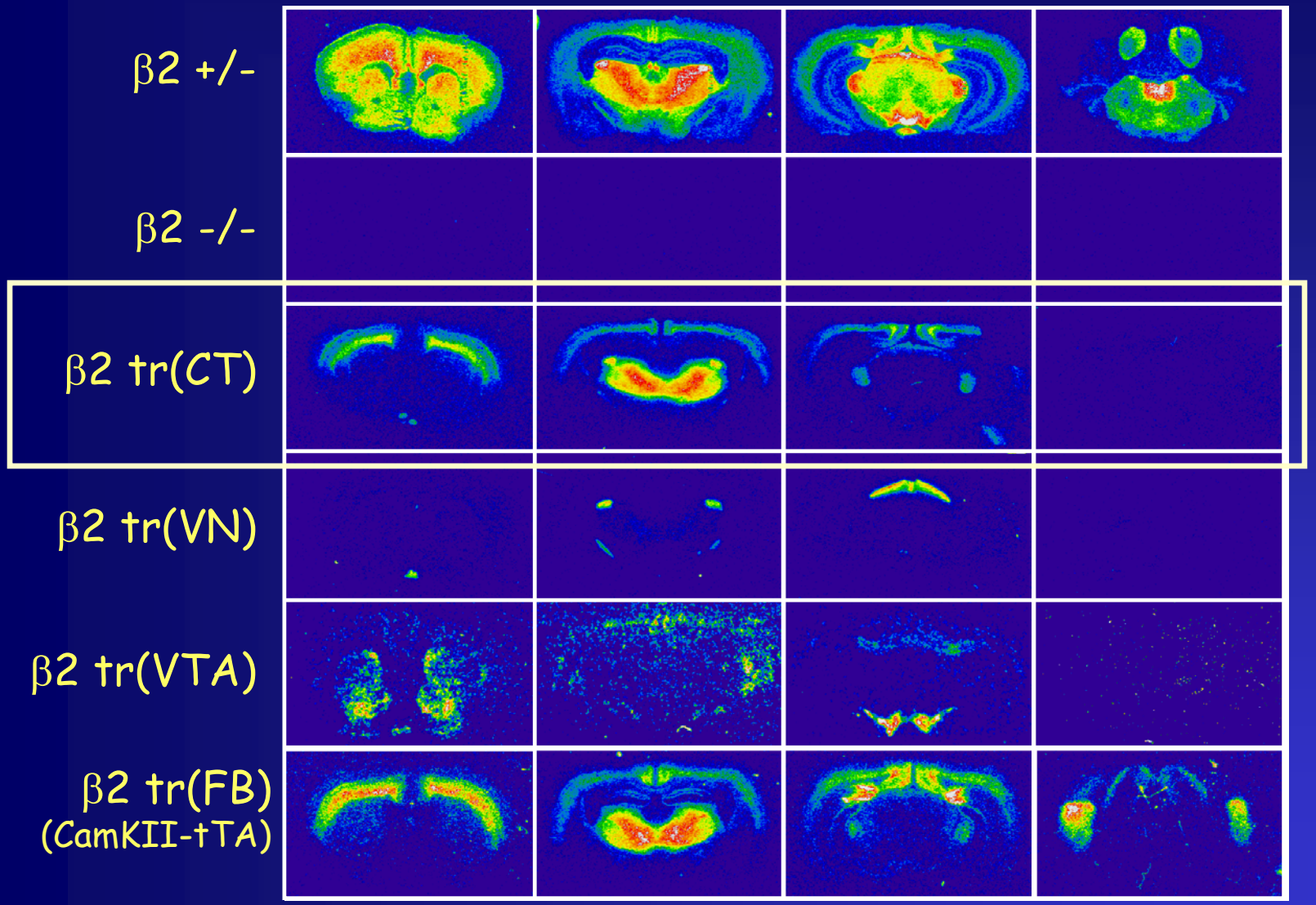


Temporal-control of gene expression

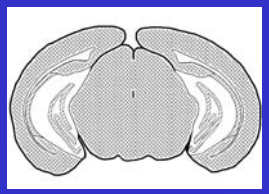




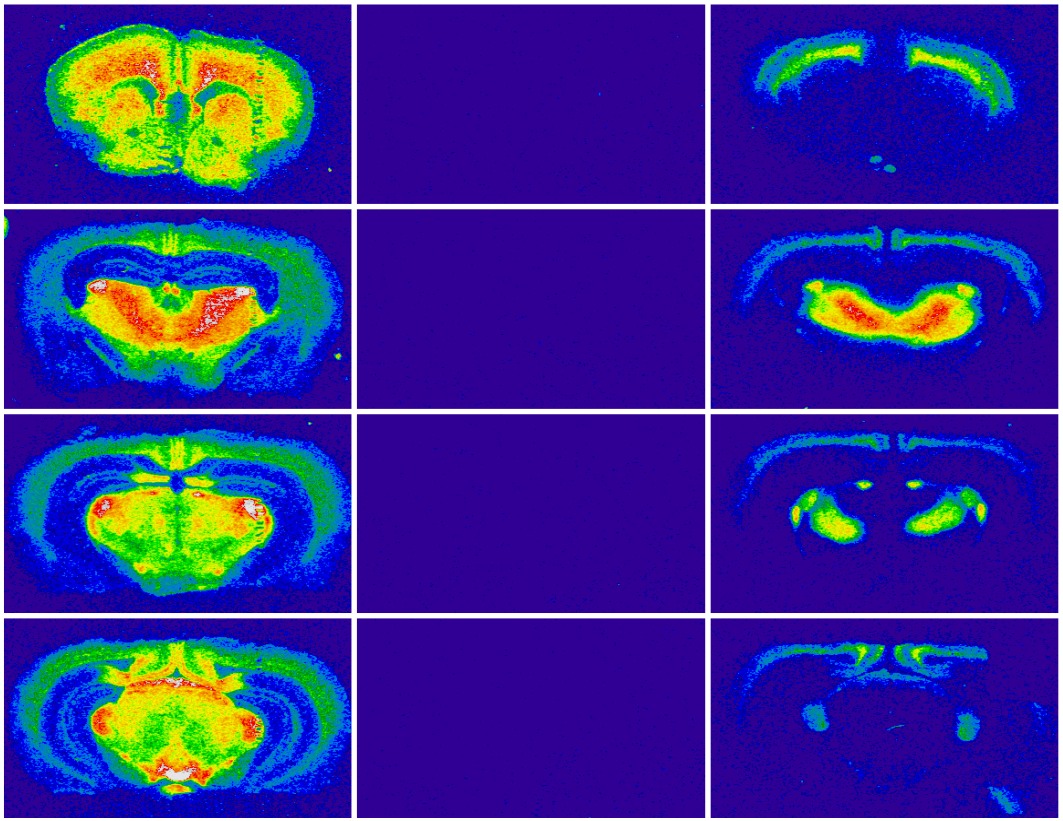
Region-specific gene expression



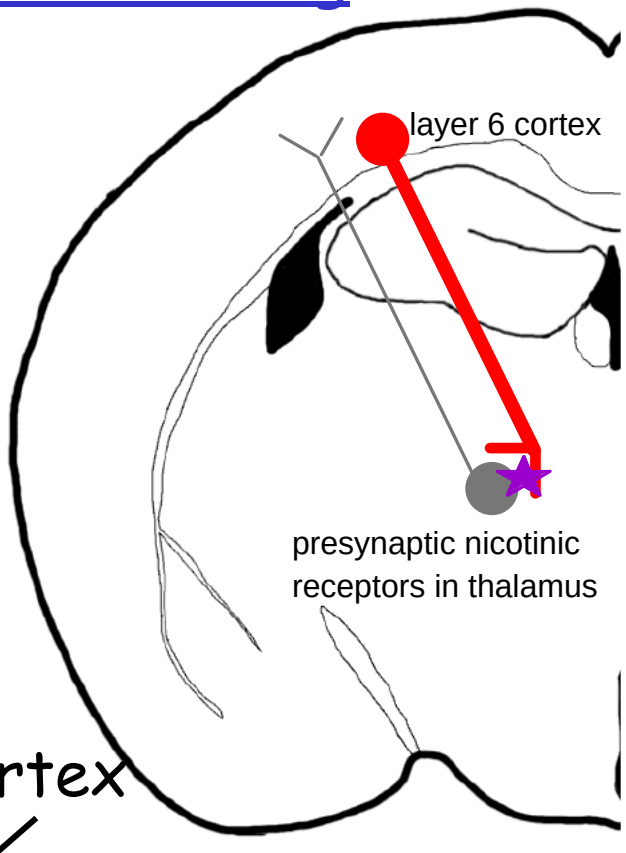
King et al, J. Neurosci., 2003



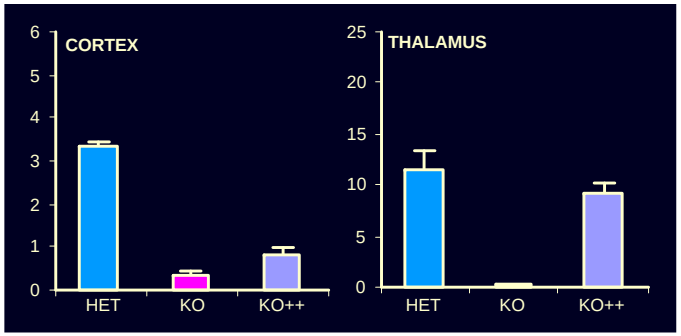
wildtype β2 knockout transgenic



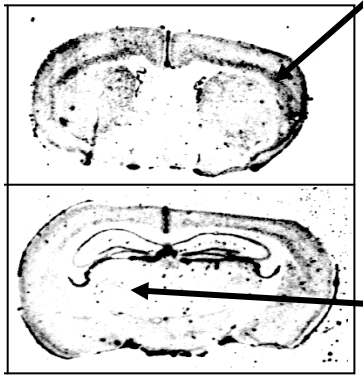
Nicotine binding



Rubidium efflux

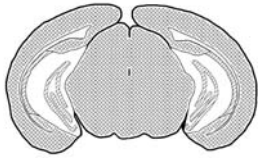


cortex



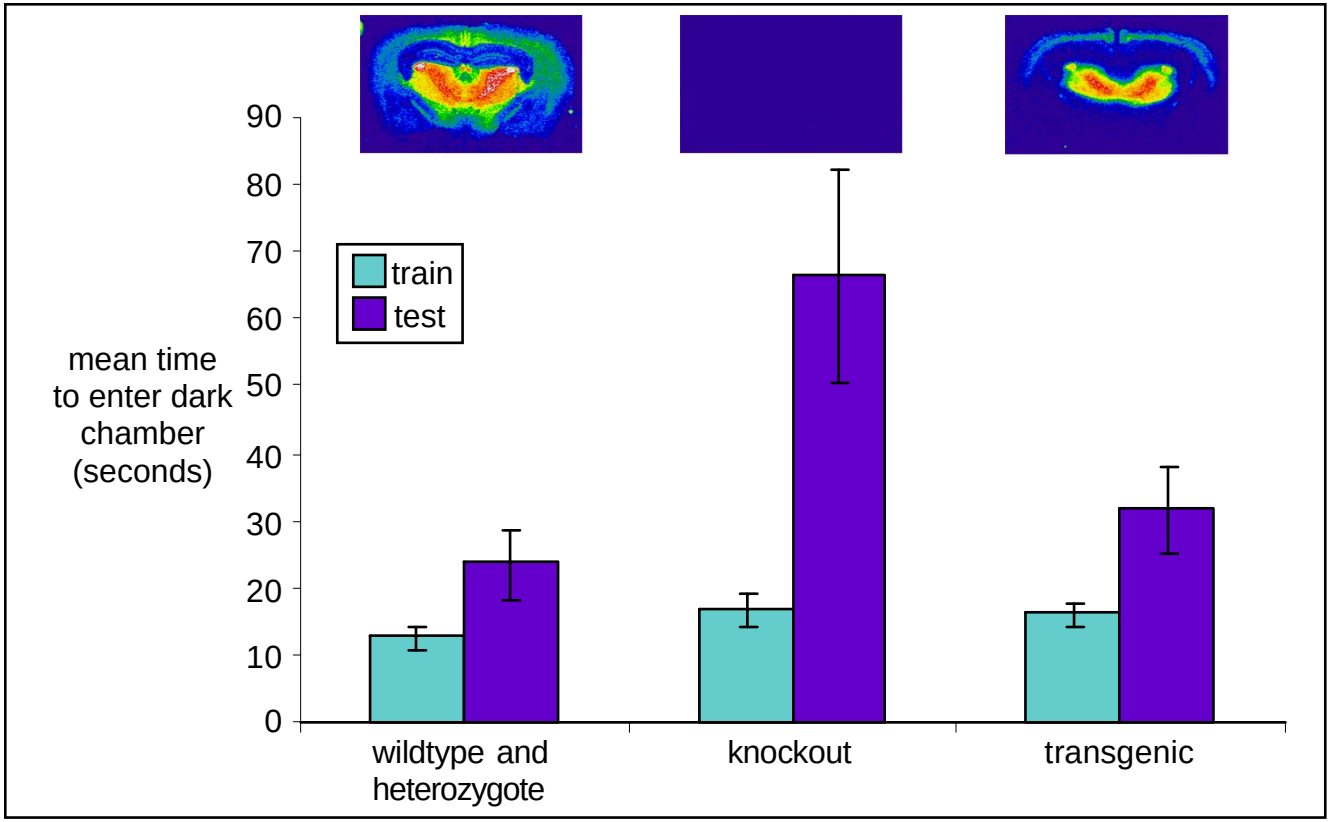
in situ hybridization

thalamus



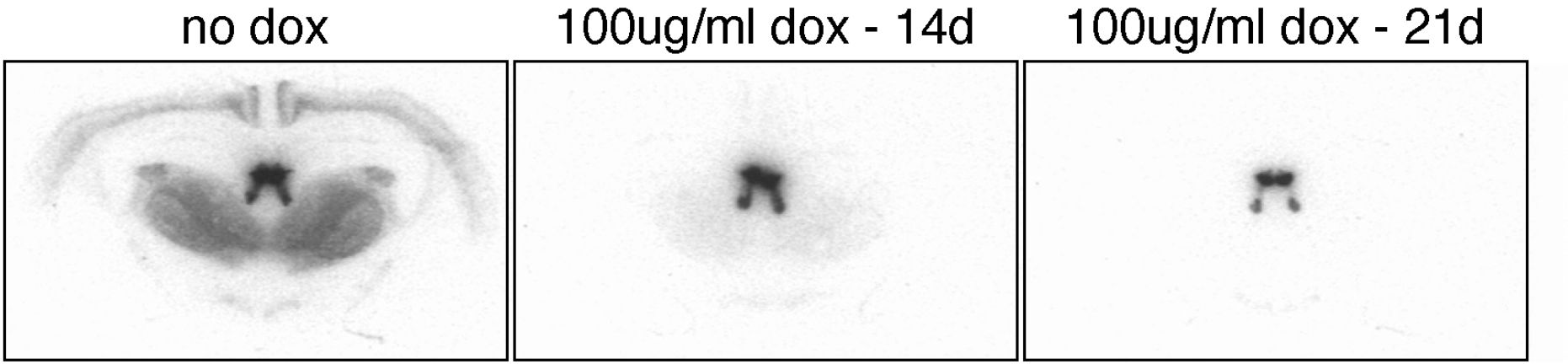
King et al, J. Neurosci., 2003

Corticothalamic expression of β2 nAChRs rescues adult passive avoidance

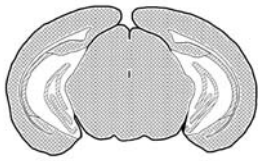


King et al, J. Neurosci., 2003

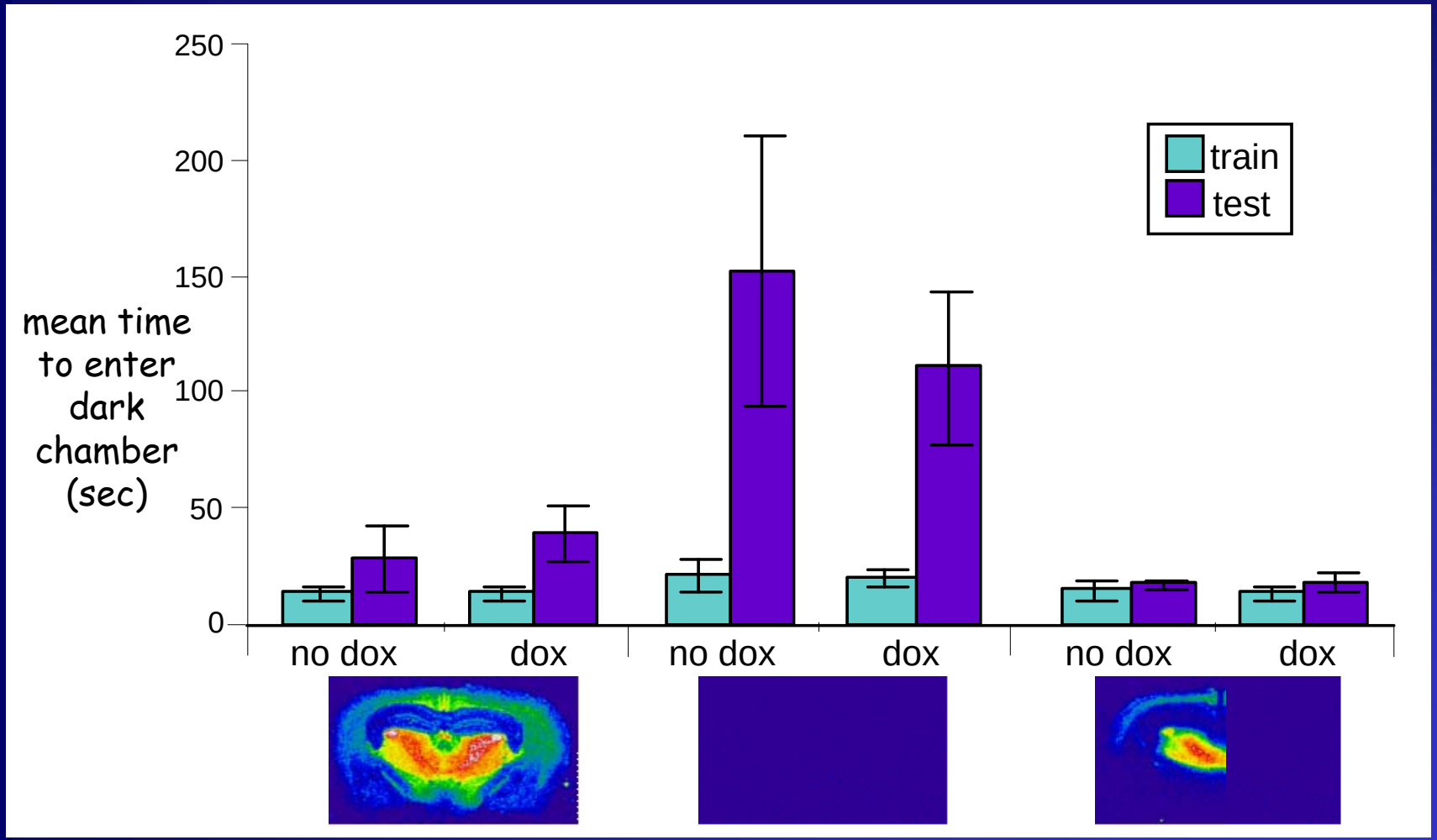
Temporally-controlled gene expression



King et al, J. Neurosci., 2003

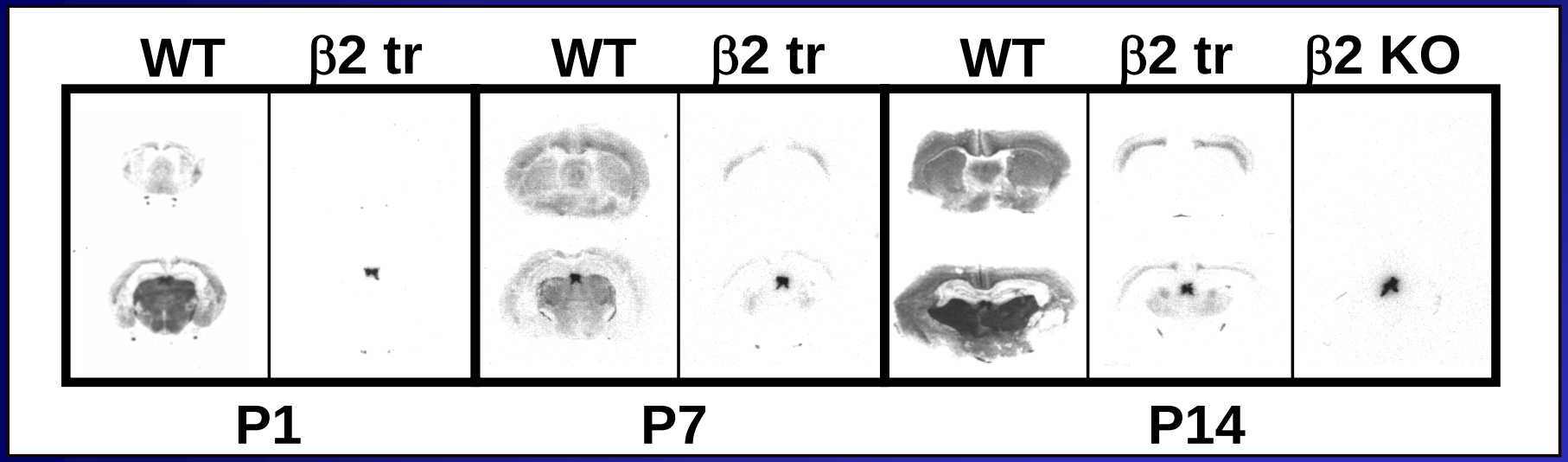


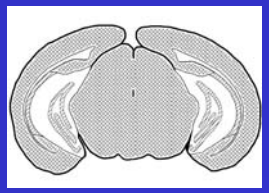
Passive avoidance behavior depends on presence of β2 nAChRs during development



King et al, J. Neurosci., 2003

The β2 nAChR transgene is expressed in corticothalamic efferents after P7





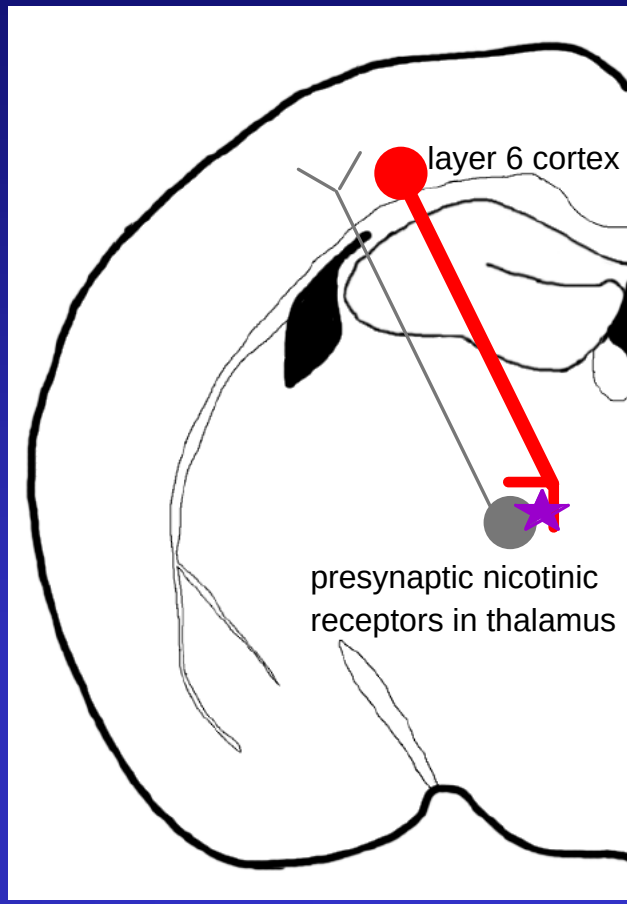
Sarah King

Synaptic maturation in cortex and thalamus occurs in the second postnatal week (rodent) or 3rd trimester (human).

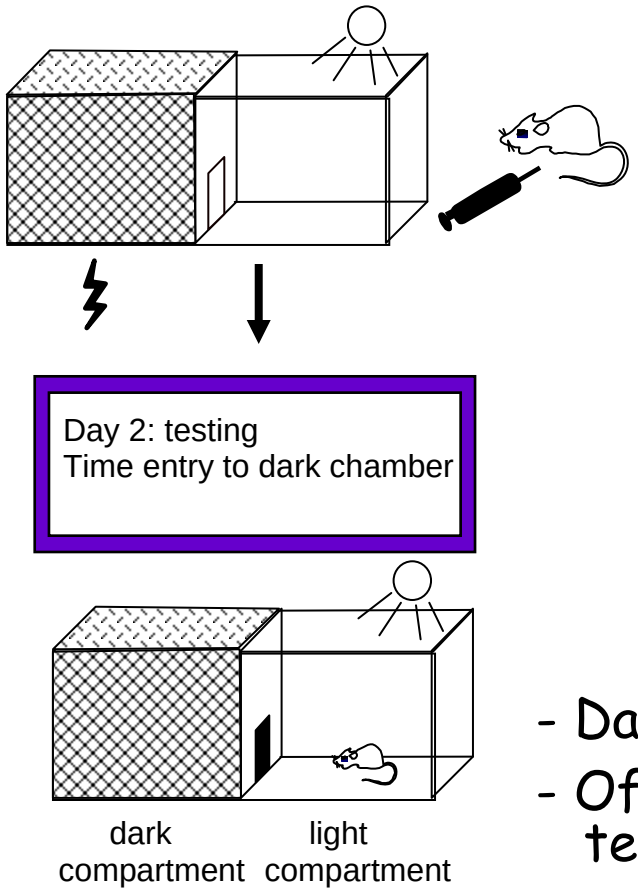
Chronic nicotine treatment during this critical period:

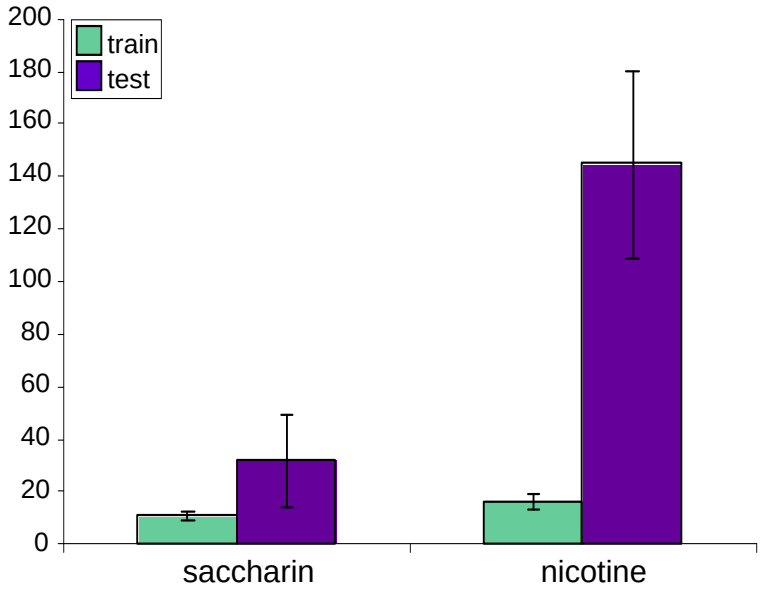
-Enhances NMDA receptor-mediated transmission in neocortex of rats (Aramakis and Metherate 1998).

-Increases NR2A mRNA in auditory cortex layer 6 and decreases NR2B in medial geniculate (auditory thalamus) (Hsieh et al. 2002).



Nicotine during development results in hypersensitive passive avoidance in adulthood

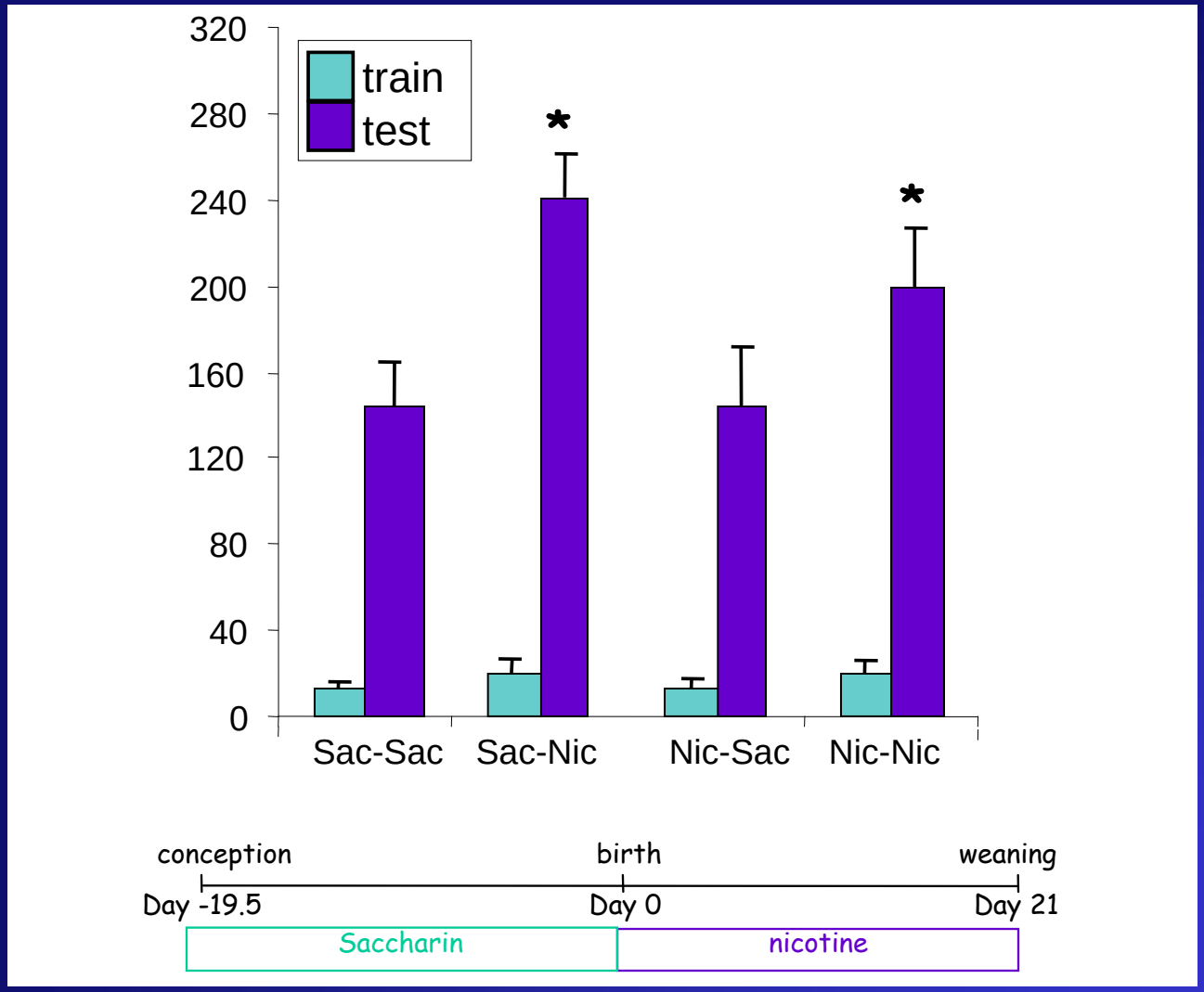




- Dams 200 ug/ml nicotine in drinking water
- Offspring weaned on water (3 - 4 weeks), tested as adults (3 - 5 months).

King et al, submitted, 2008

Nicotine affects PA learning when administered only posnatally



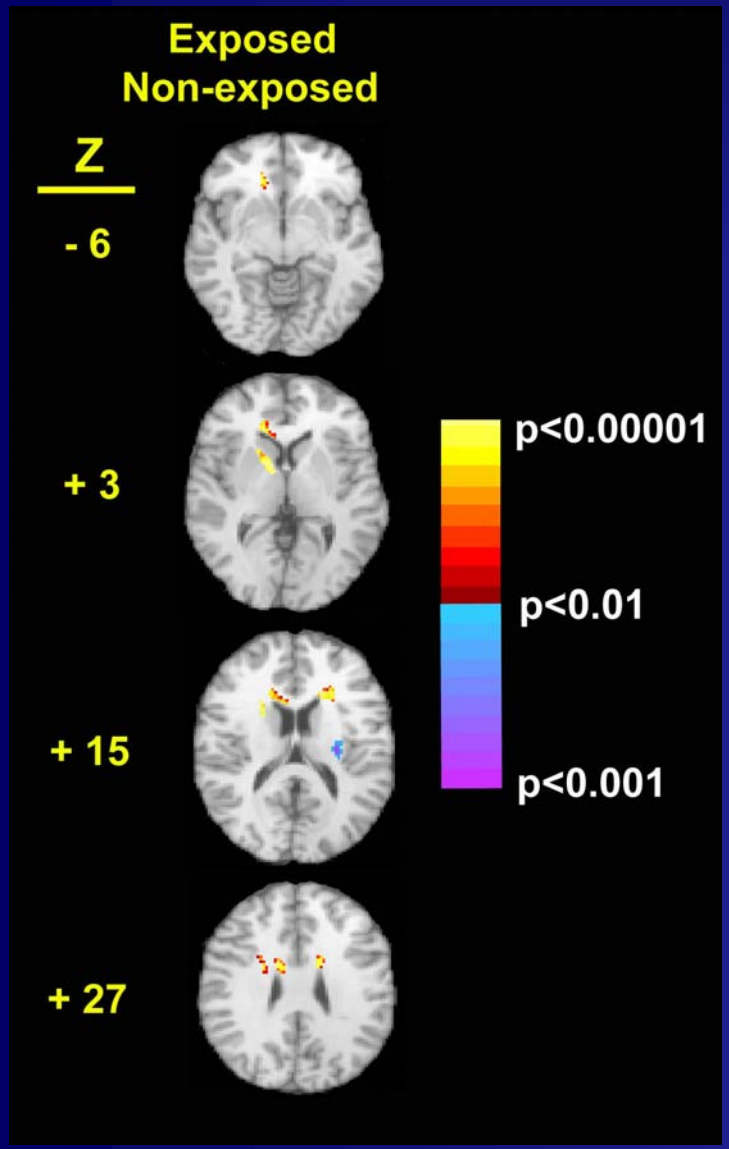
King et al, submitted, 2008

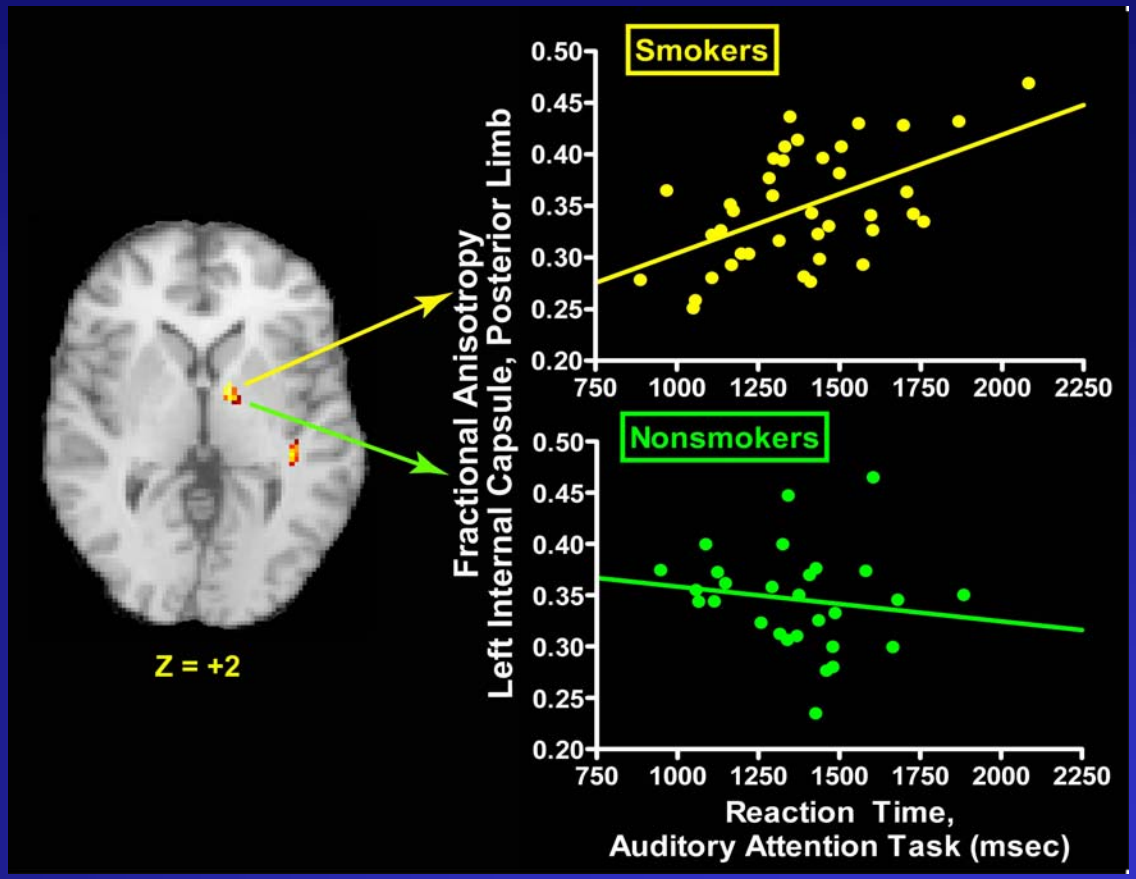
Developmental nicotine exposure in humans is linked to:

- ADHD
- Conduct disorder
- Altered auditory processing
- Lower IQ
- Increased likelihood of smoking

(Ernst et al., 2001; Wakschlag et al., 2002)

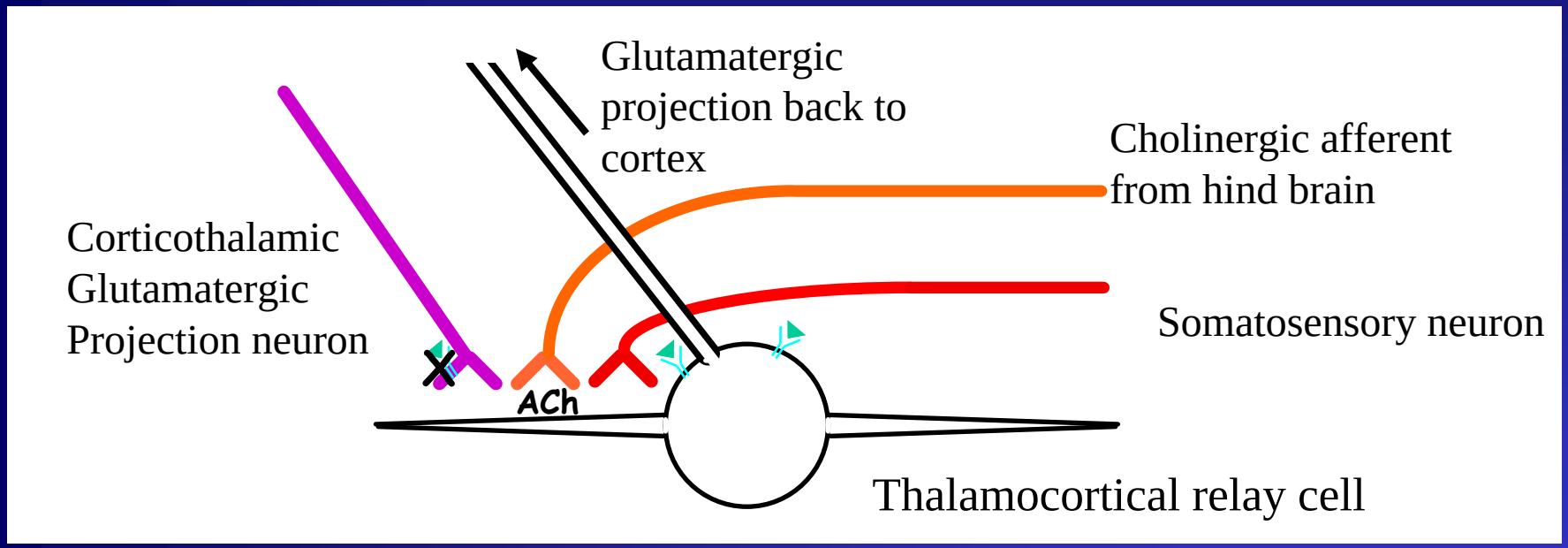
Developmental smoke exposure increases white matter maturation in internal capsule





Jacobsen et al, J Neurosci, 2007

What we think is happening



Summary

- Both perinatal nicotine exposure and β2* nACHR KO result in hypersensitive passive avoidance in adulthood
- Expression in corticothalamic efferents rescues this defect in KO mice
- nAChR signaling may be critical for maturation of corticothalamic glutamate synapses