The Habenula and Nicotine Withdrawal: From Mouse to Human

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The Godfather

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Introduction

- Complications from tobacco smoke are the number one cause of death in developed countries (~20%)

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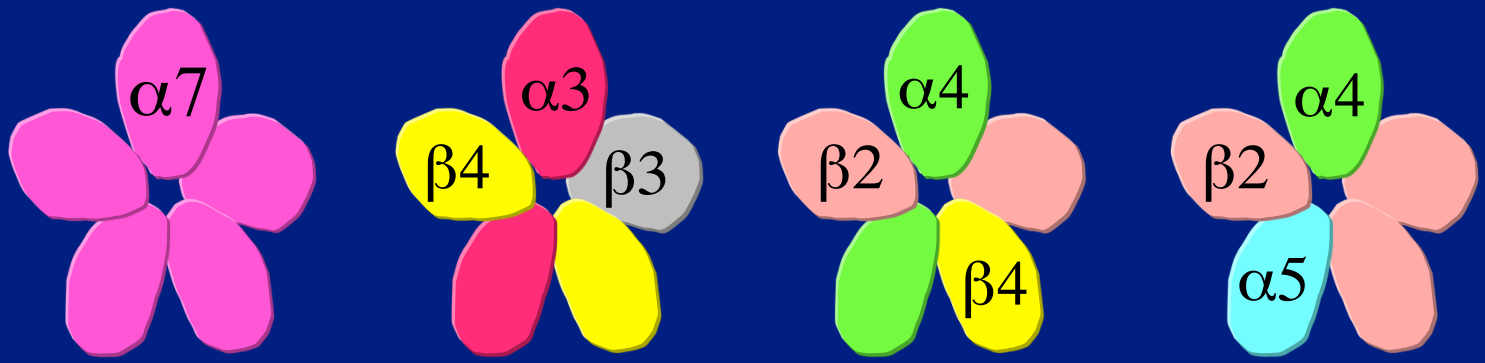


…etc.

Why do you smoke?

"I just can't quit" — Withdrawal

"If I am anxious I'll smoke" — Anxiety

"It makes me feel sharper" — Cognitive

Why did you start smoking?

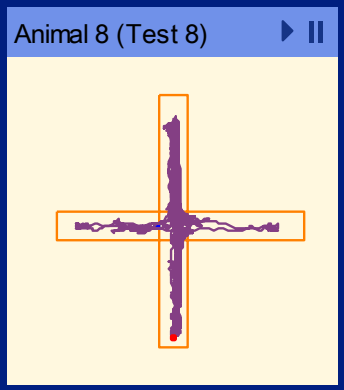
"All my friends were smoking"

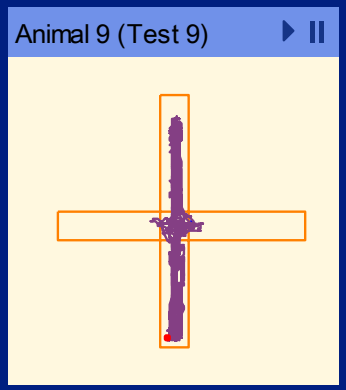
"It was cool" — Social component

Humphrey Bogart

Ingrid Bergman

Elevated Plus Maze to Study Anxiety-Related Behavior in Rodents





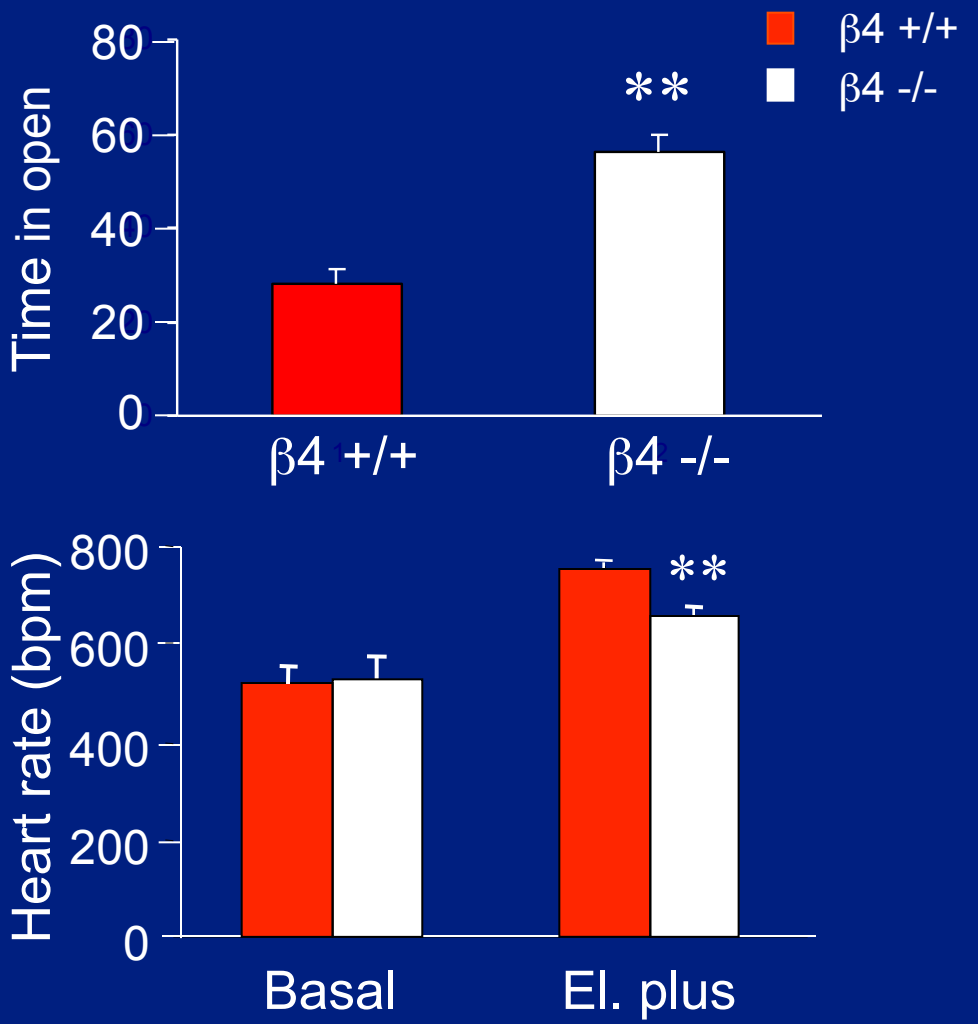
Less anxious-like mouse

More anxious-like mouse

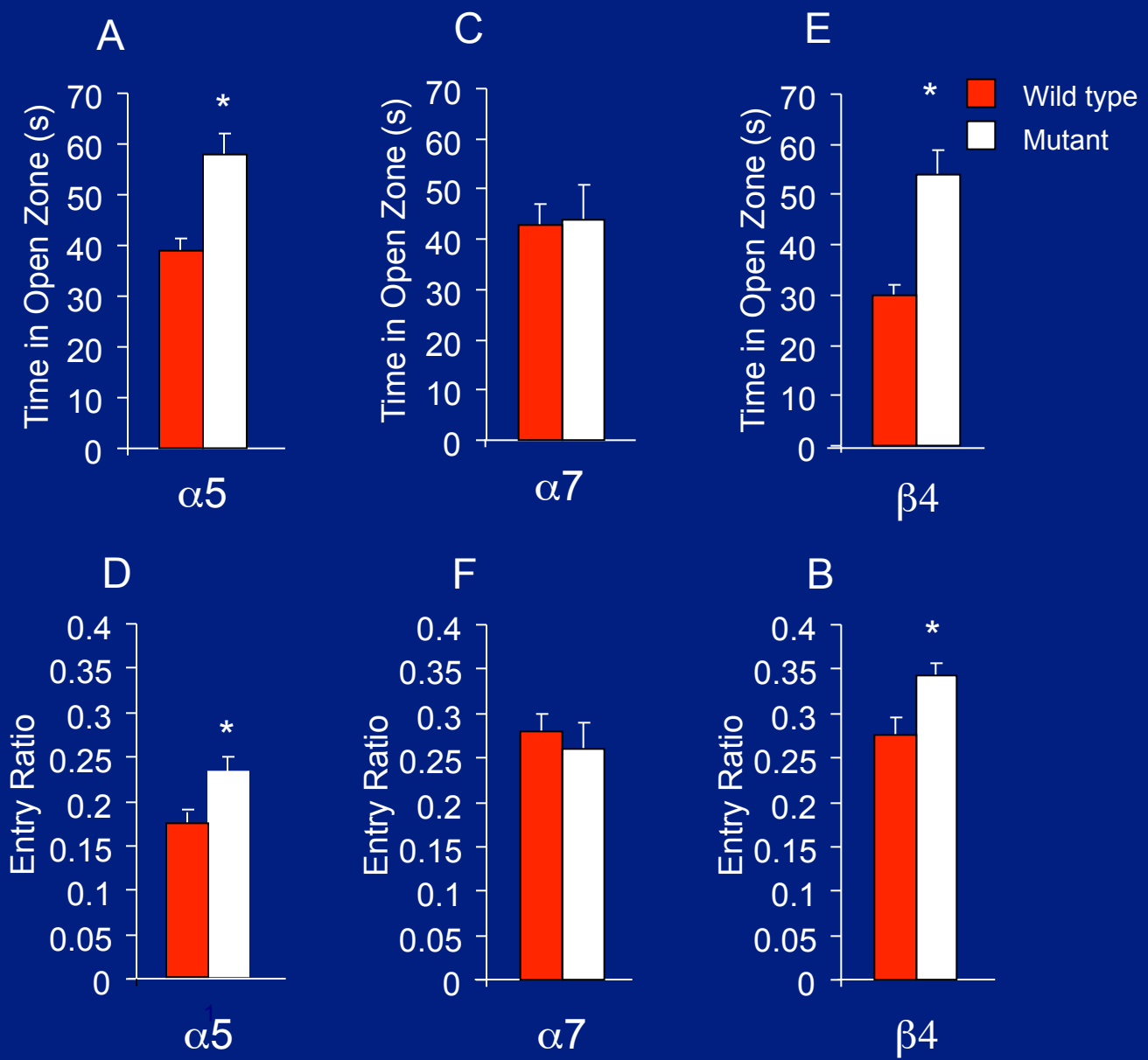
Validation: drugs like benzodiazepines that are tranquilizers in humans increase open arm exploration in rodents

β4 -/- mice behave as less anxious in the elevated plus maze

If I' m anxious, I' ll smoke



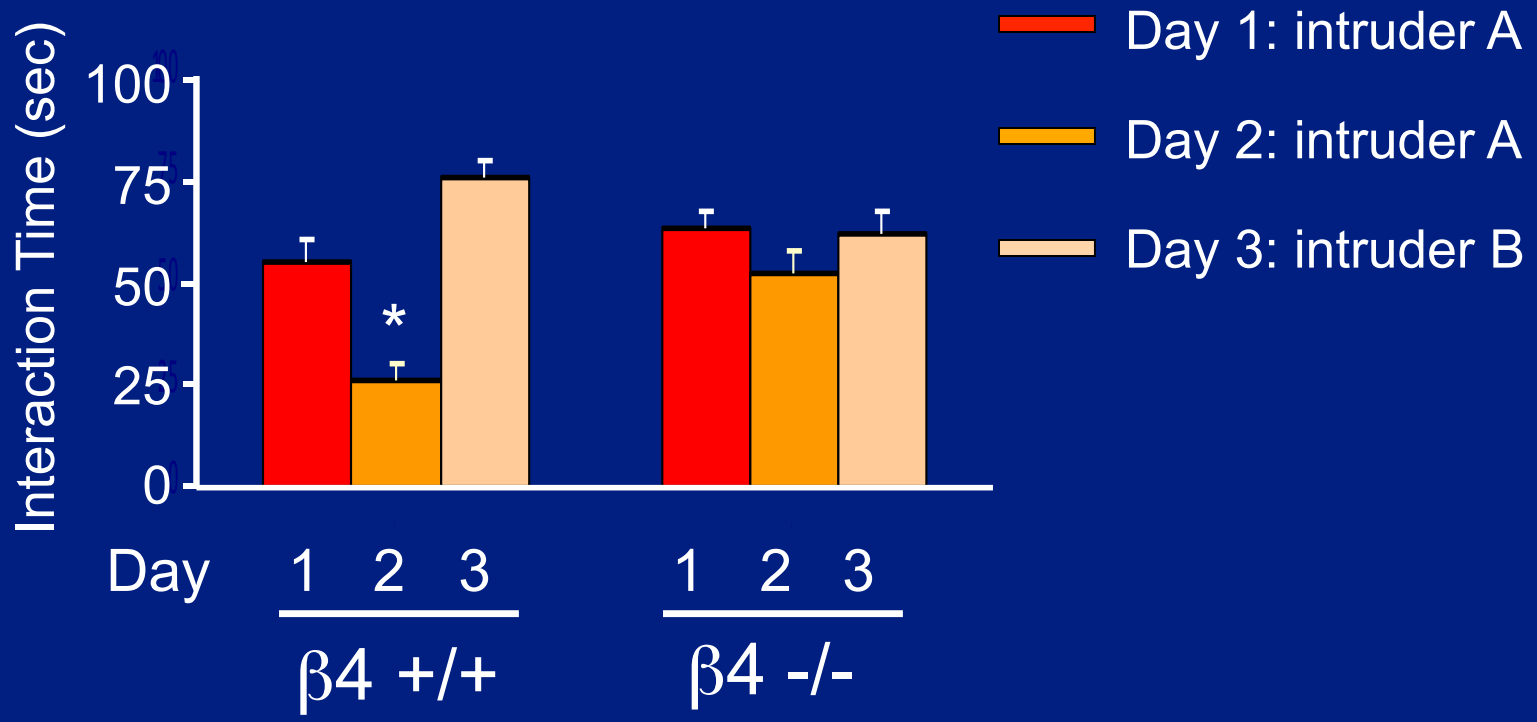
β4 -/- and α5 -/- mice behave as less anxious in the elevated plus maze



β4 -/- mice show abnormal social behavior: Intruder test

Cognitive and social component

2 min interaction of adult resident with smaller intruder

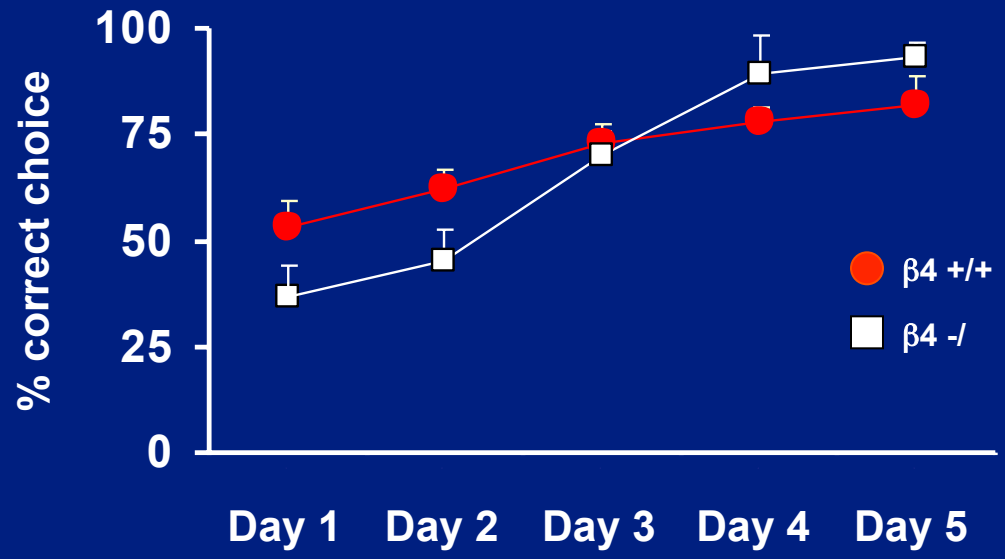


Non-social olfactory memory was normal

β4 -/- mice show abnormal social behavior. Normal non-social memory

Cognitive and social component

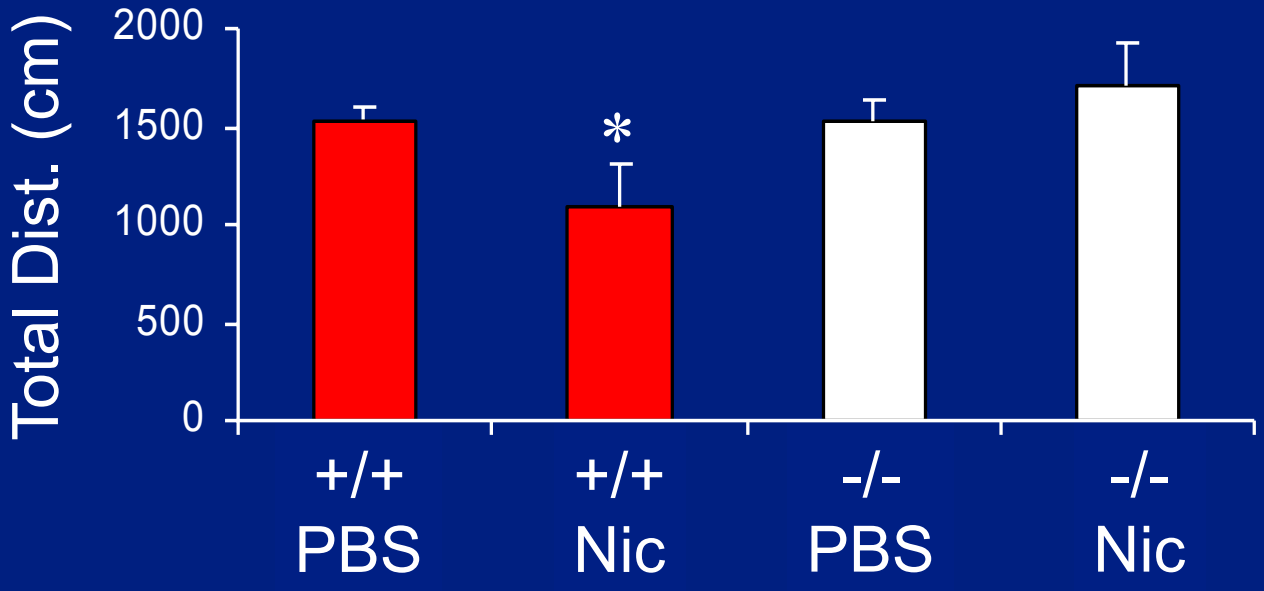
Mice were trained to find chocolate under sand mixed with different scents. For each of 3 pairs of scents, one predicted chocolate and one did not.



β4 -/- mice are resistant to the hypolocomotive effects of nicotine

The effect of the first cigarette predicts later risk for tobacco addiction

Nic 0.5 mg/Kg (ip)

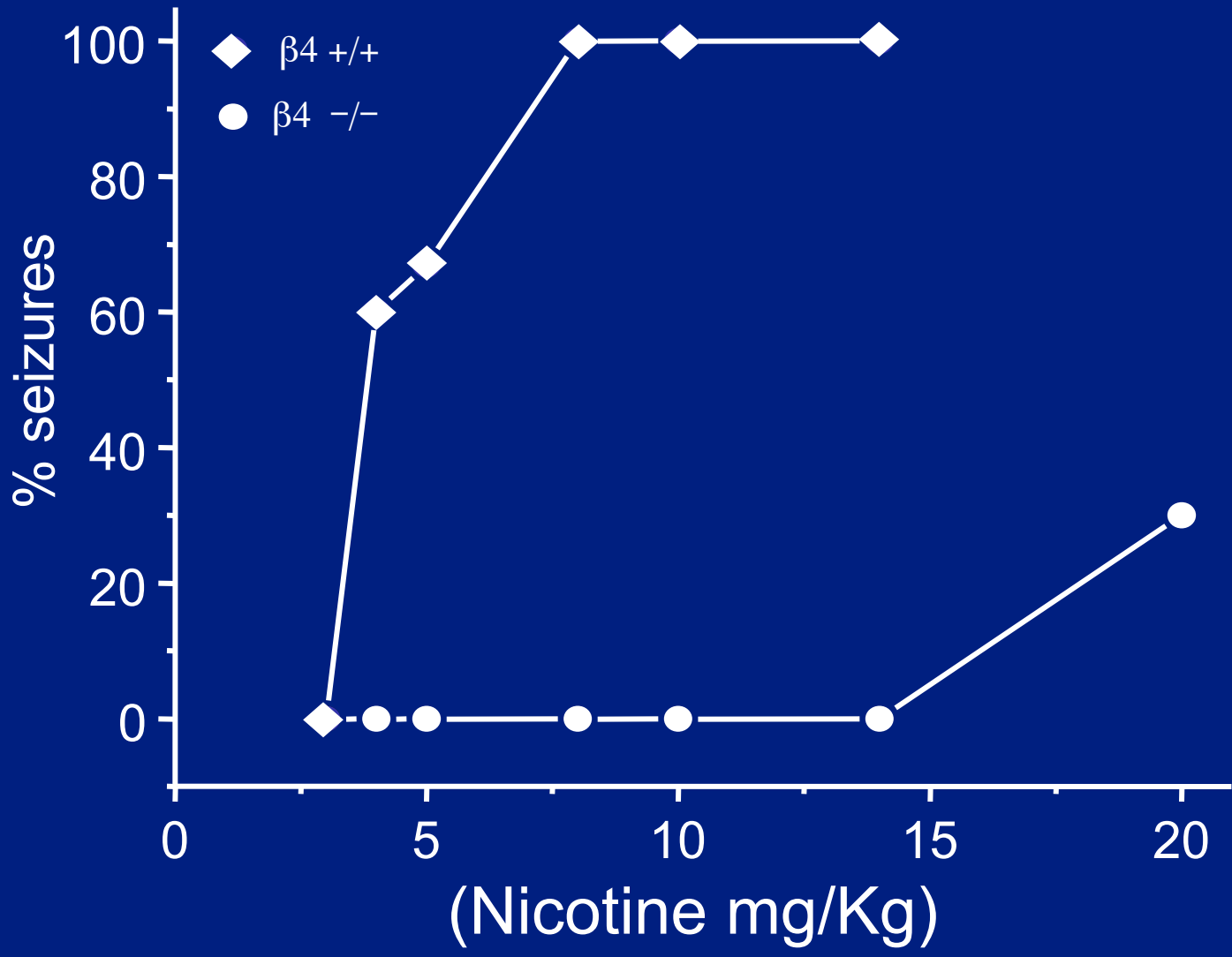


β4 -/- mice are less sensitive to nicotine-induced seizures

The effect of the first cigarette predicts later risk for tobacco addiction

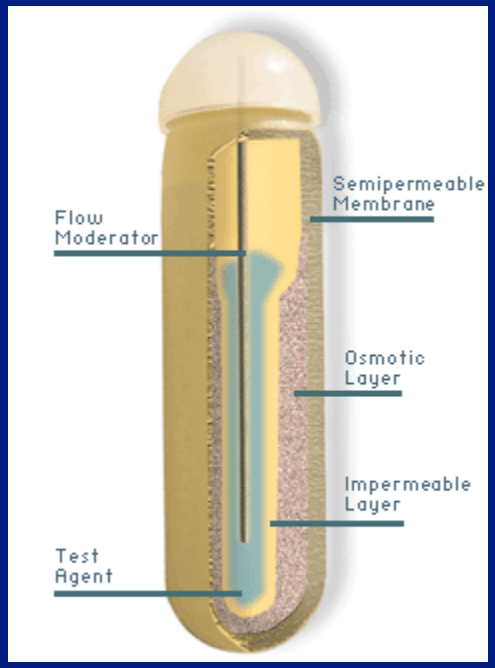
Nicotine (ip)

Observe 5’



Nicotine withdrawal in the mouse

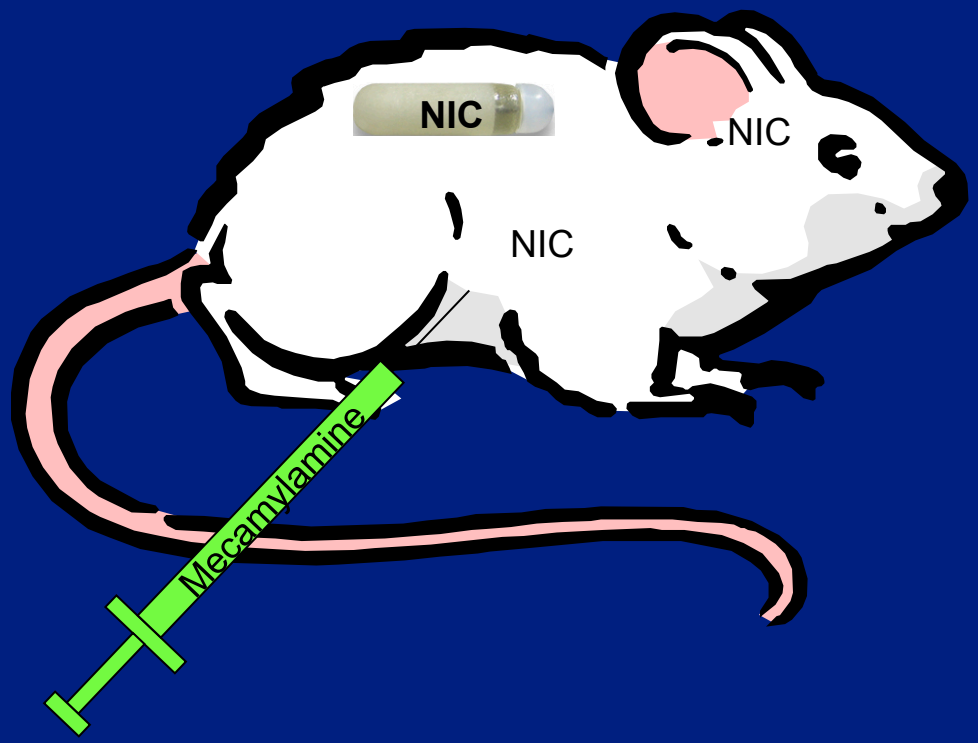
The osmotic minipump



Delivers drug sc continually for 2 weeks

Nicotine withdrawal in the mouse

I just can't quit

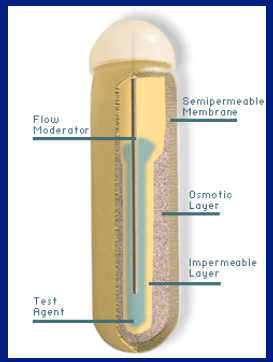


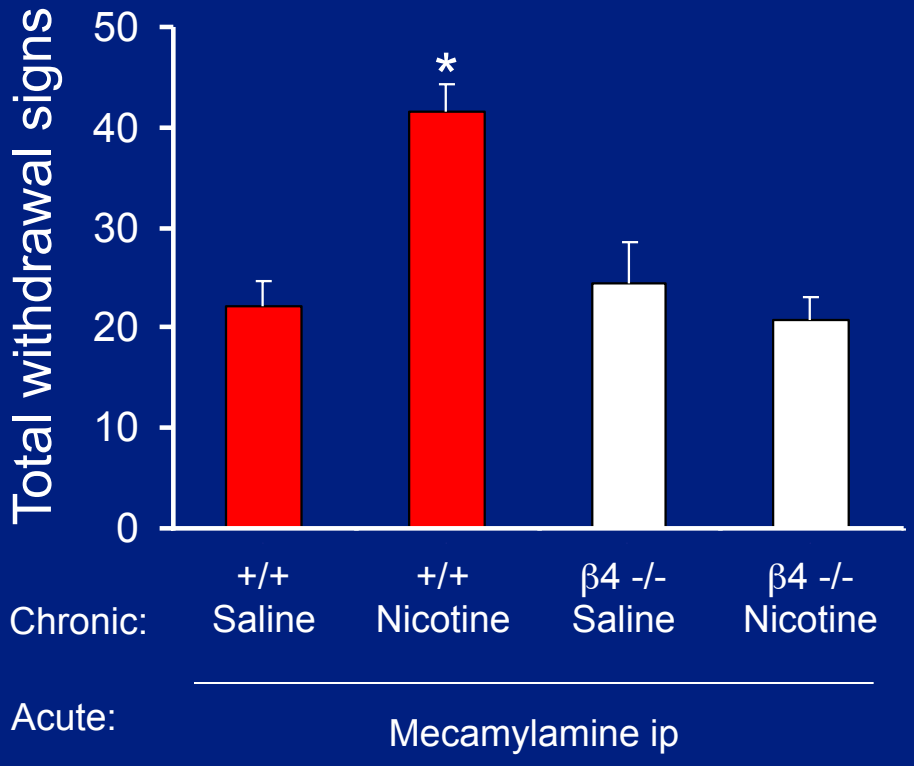
Withdrawal signs

Increased shaking
Increased grooming
Increased scratching

The β4 subunit is necessary for nicotine withdrawal

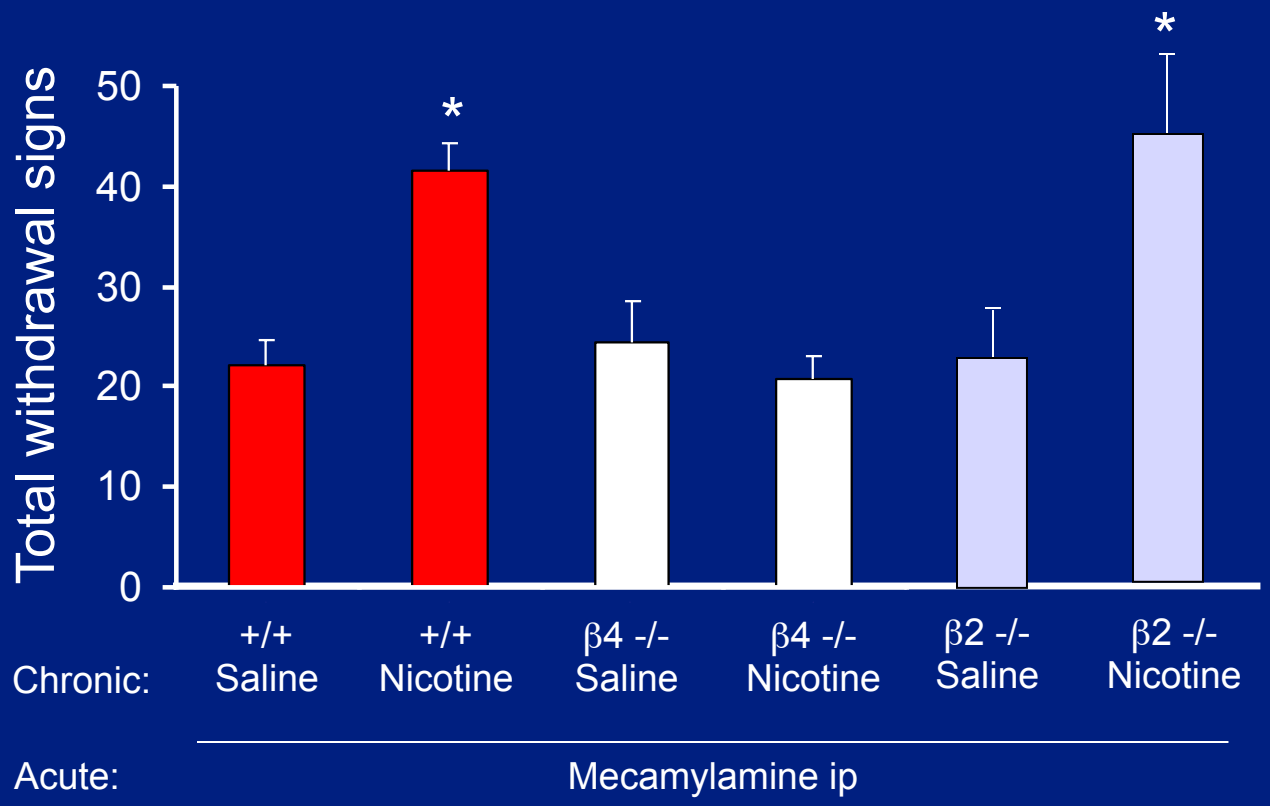
I just can't quit



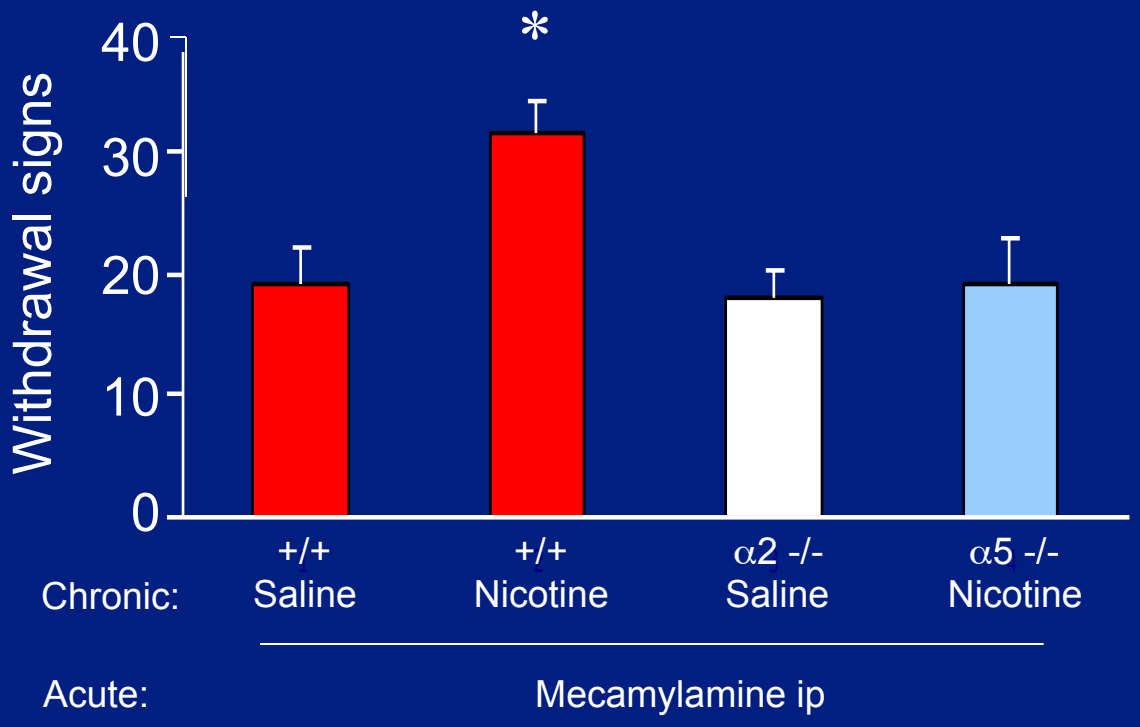


The β4 (but not the β2) subunit is necessary for nicotine withdrawal

I just can't quit

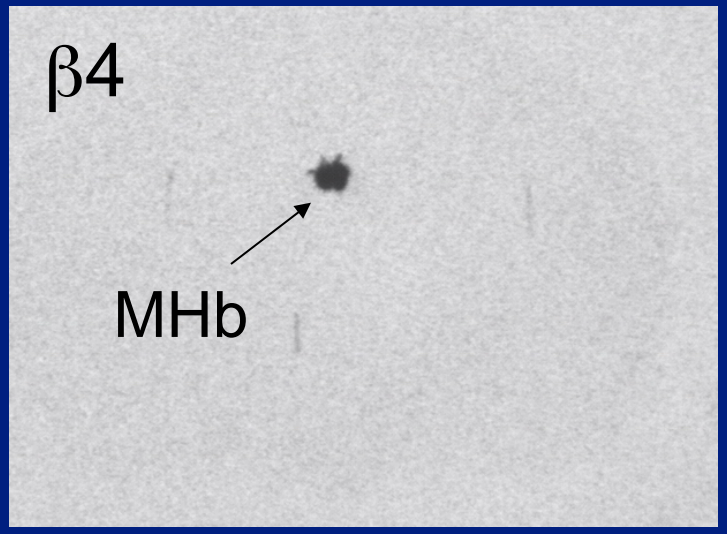


The α2 and α5 subunit are also necessary for nicotine withdrawal

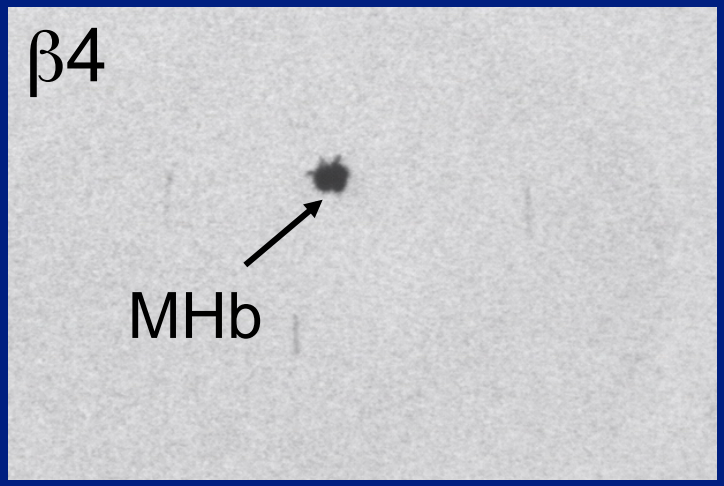


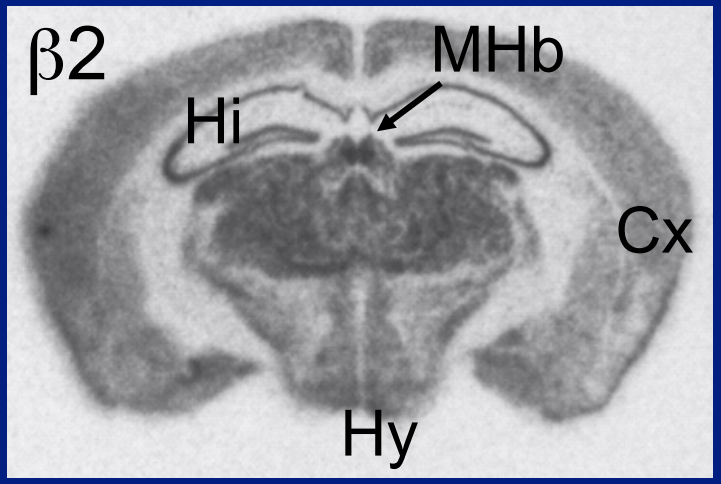
Where in the brain does all this happen?

β4 mRNA in the CNS



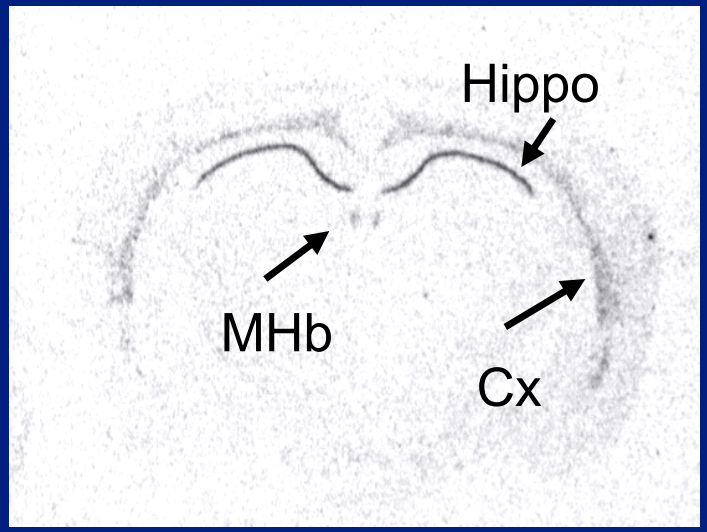
β4 and β2 mRNA in the CNS

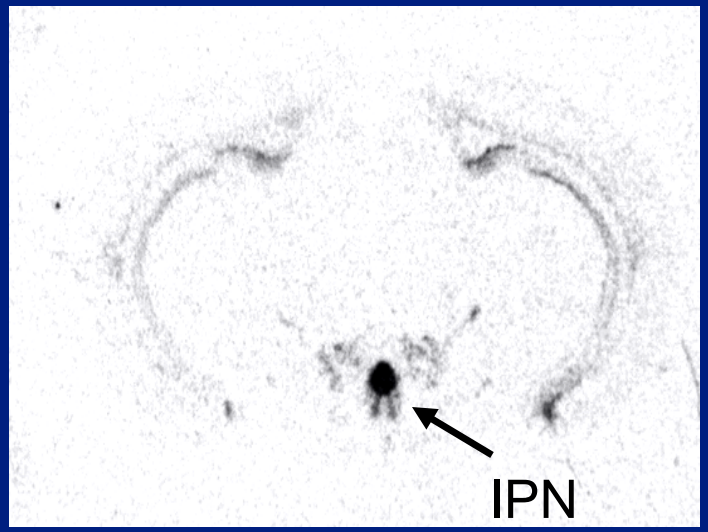




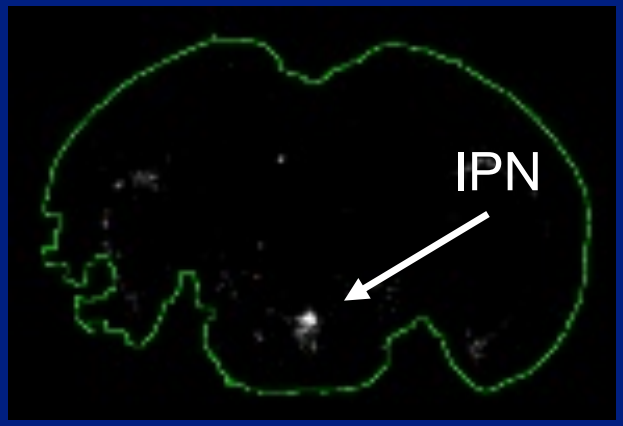
α5 and α2 nAChR subunit expression pattern

α5





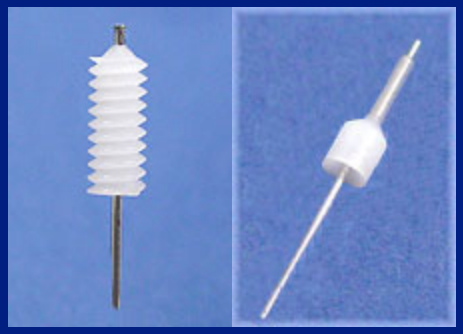
α2

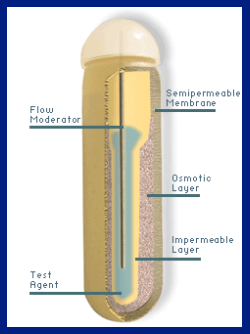


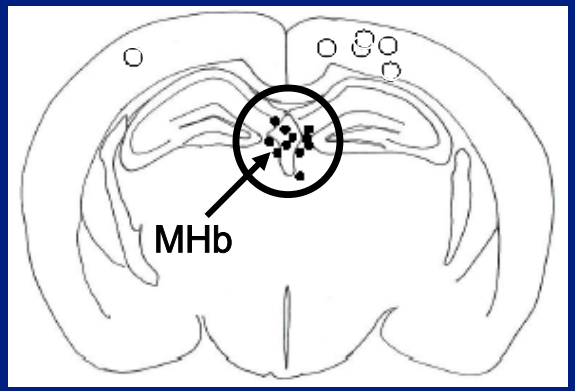
From the Allen atlas
www.brain-map.org

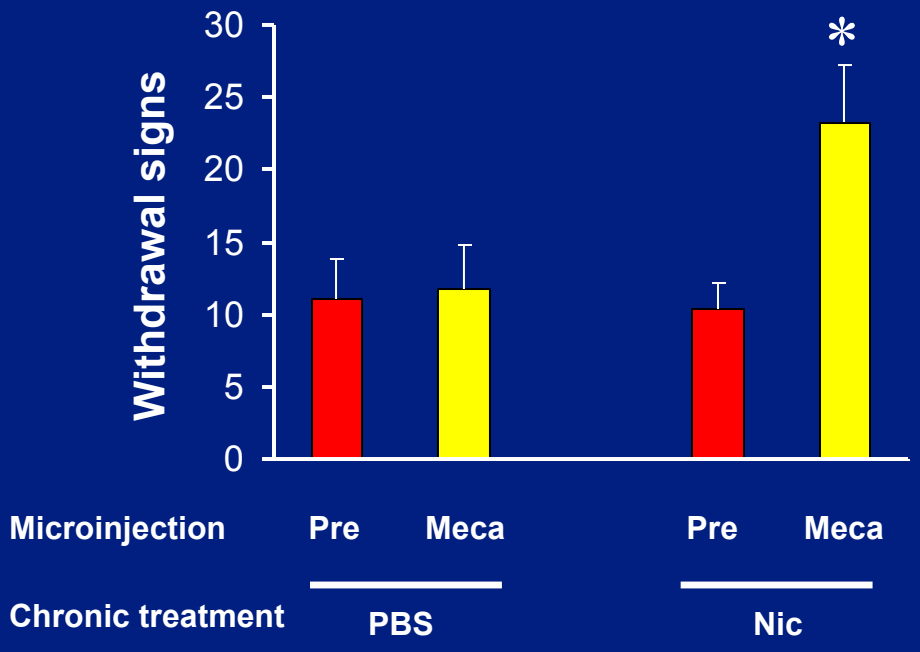
Microinjection of mecamylamine in the habenula is sufficient to precipitate nicotine withdrawal

I just can’t

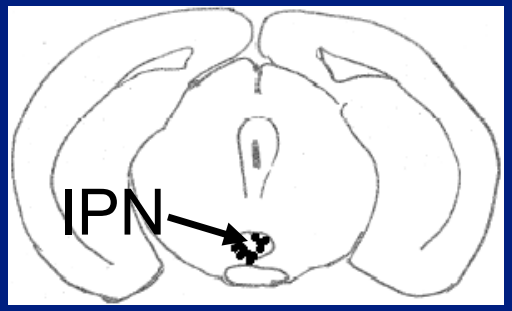


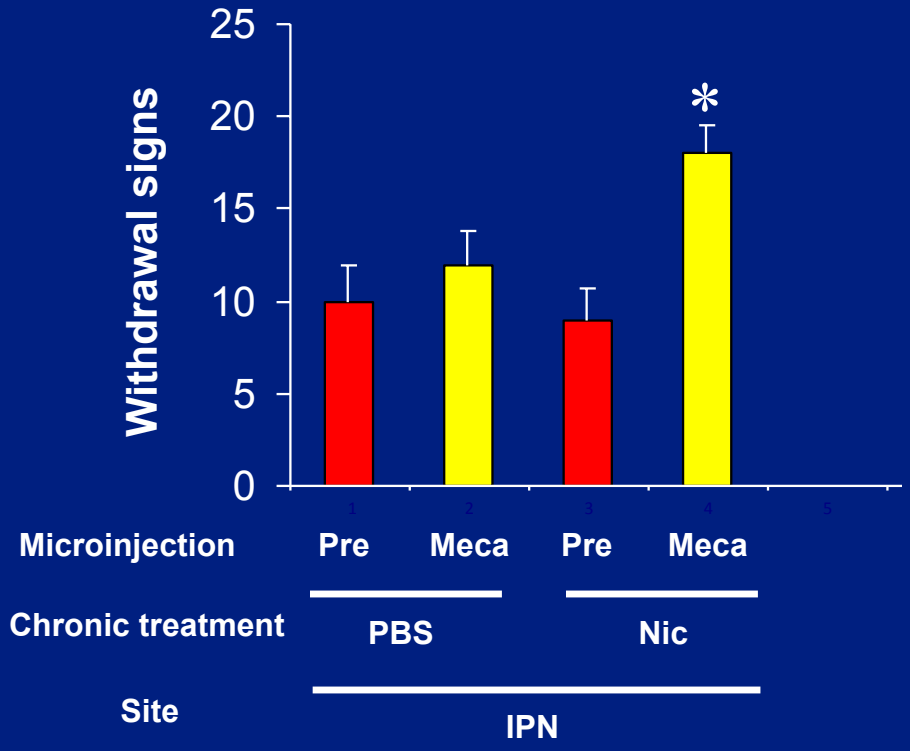






Microinjection of mecamylamine in the habenula or IPN, but not cortex, is sufficient to precipitate nicotine withdrawal





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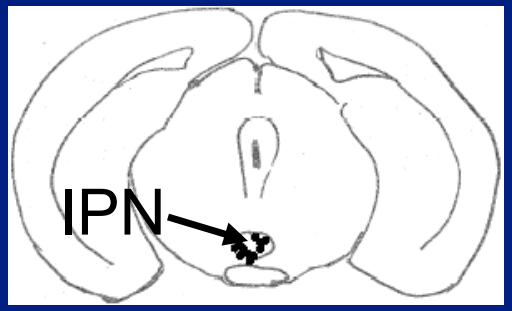
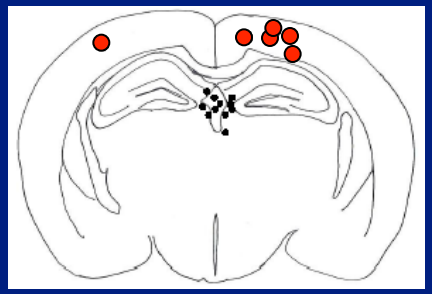
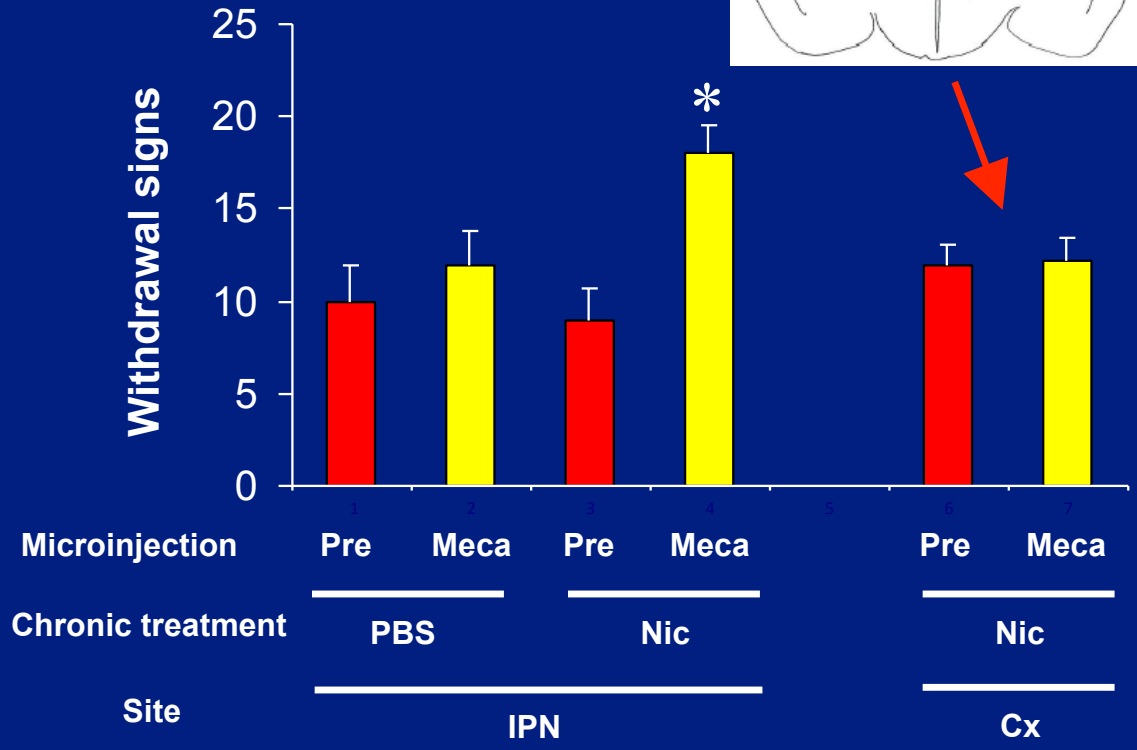






If you ask a mouse "How do you feel?"

Happy

Confused

Upset

Sad

Excited

Appalled

Anxious

Confident

Horrified

Joyful

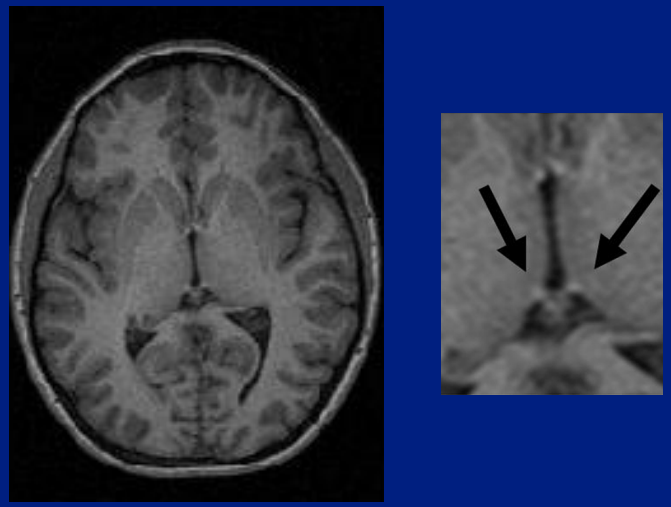
Worried

Bored

Is any of this relevant to human health?

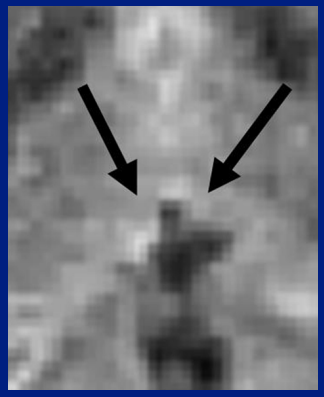
Can we see the habenula on fMRI?

Structural



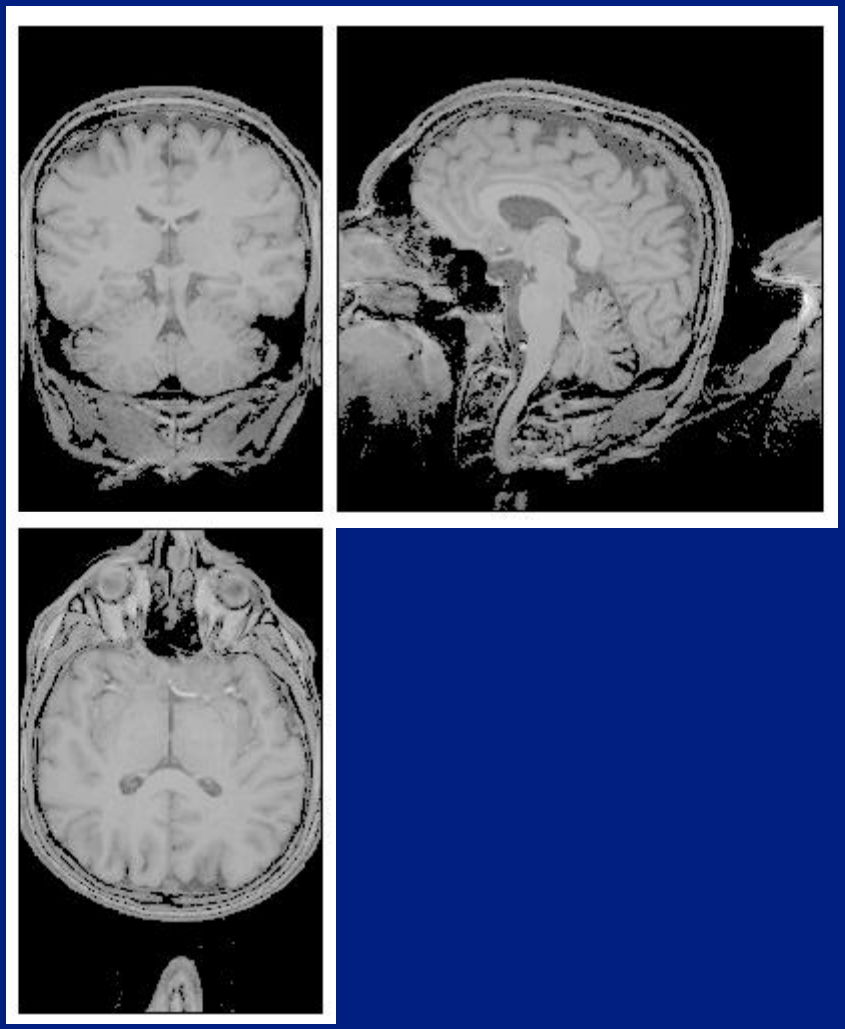
10 minutes in the MRI
voxel is 1 x 1 x 1 mm

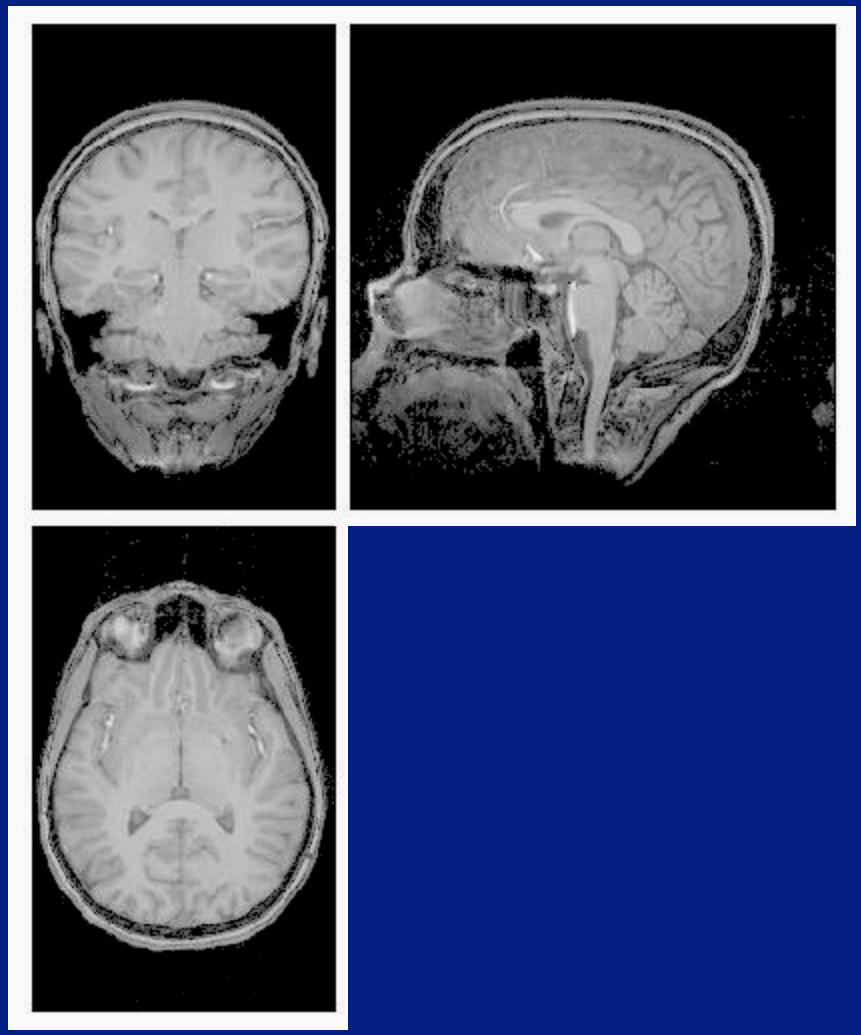
functional



2 sec per slice in the MRI
voxel is 3 x 3 x 4 mm

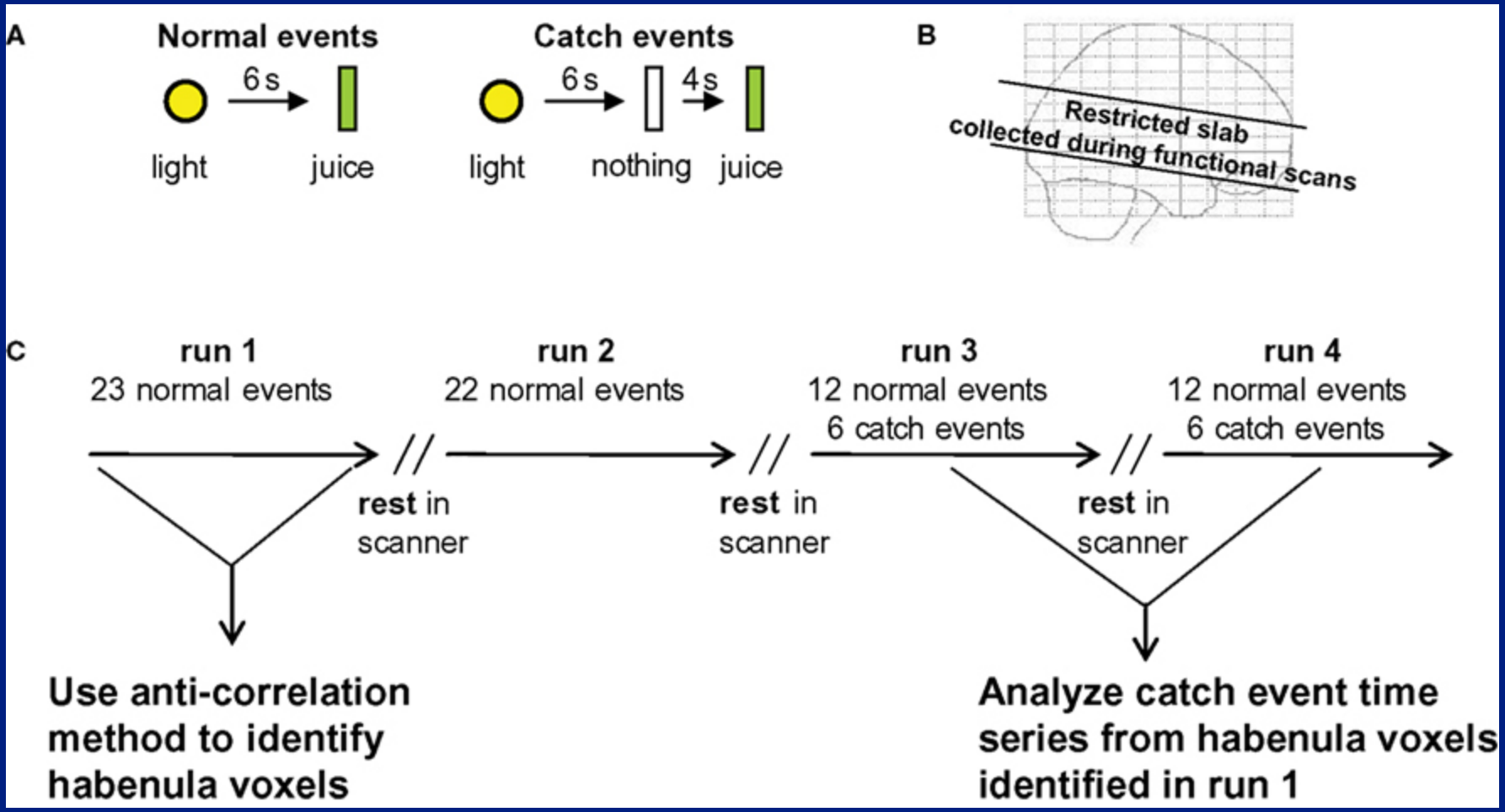
All humans are different



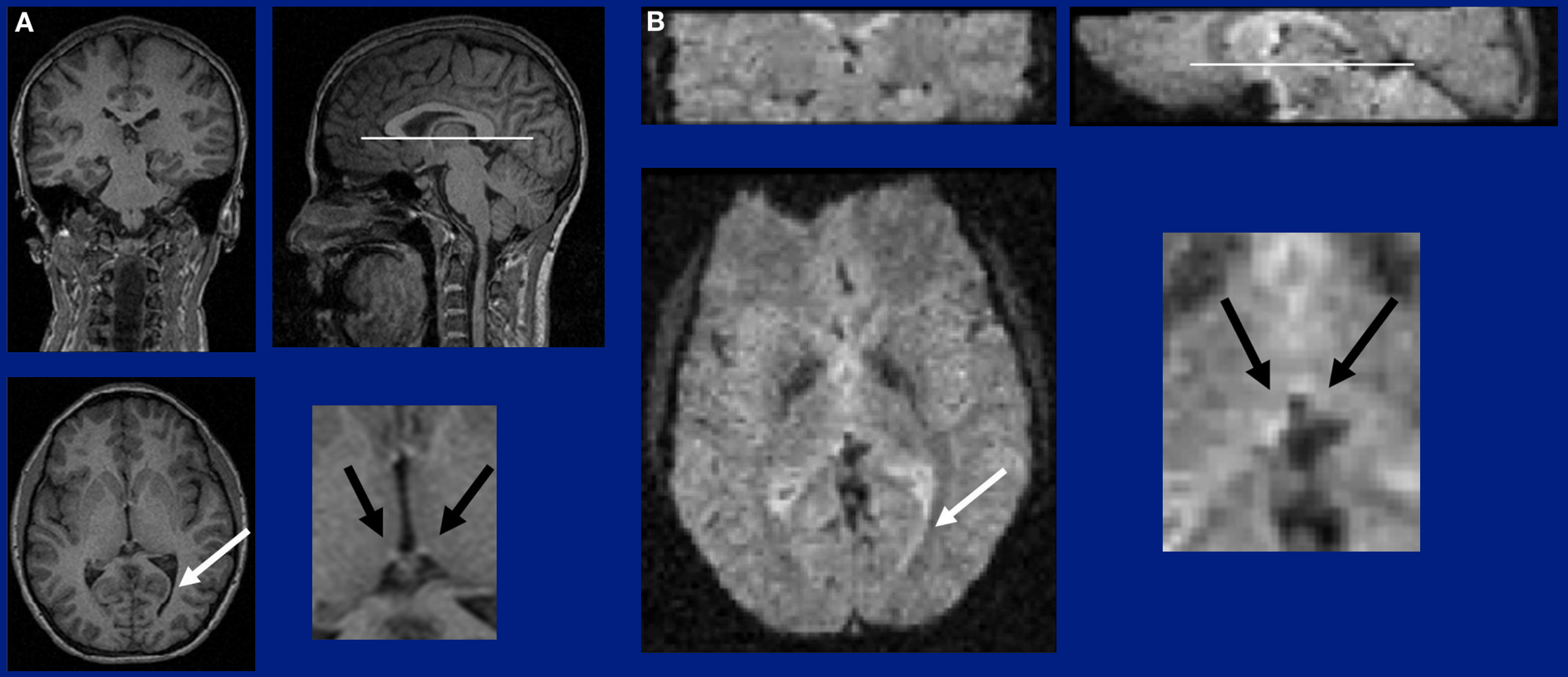


It is easy to identify the habenula in structural MRI, but a brain-by-brain analysis may be needed to see functional activity

Passive learning with juice reward

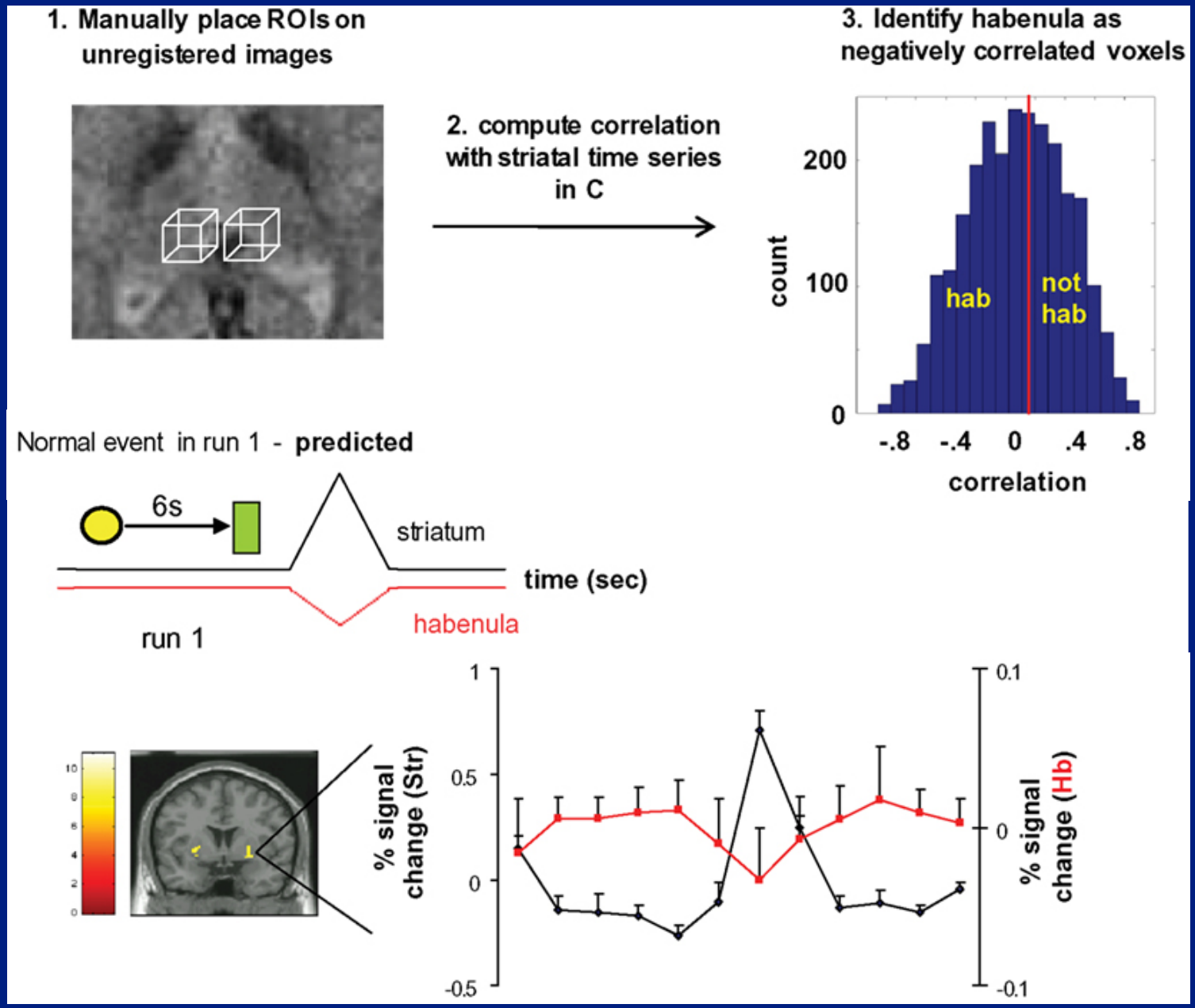


Manual co-registration

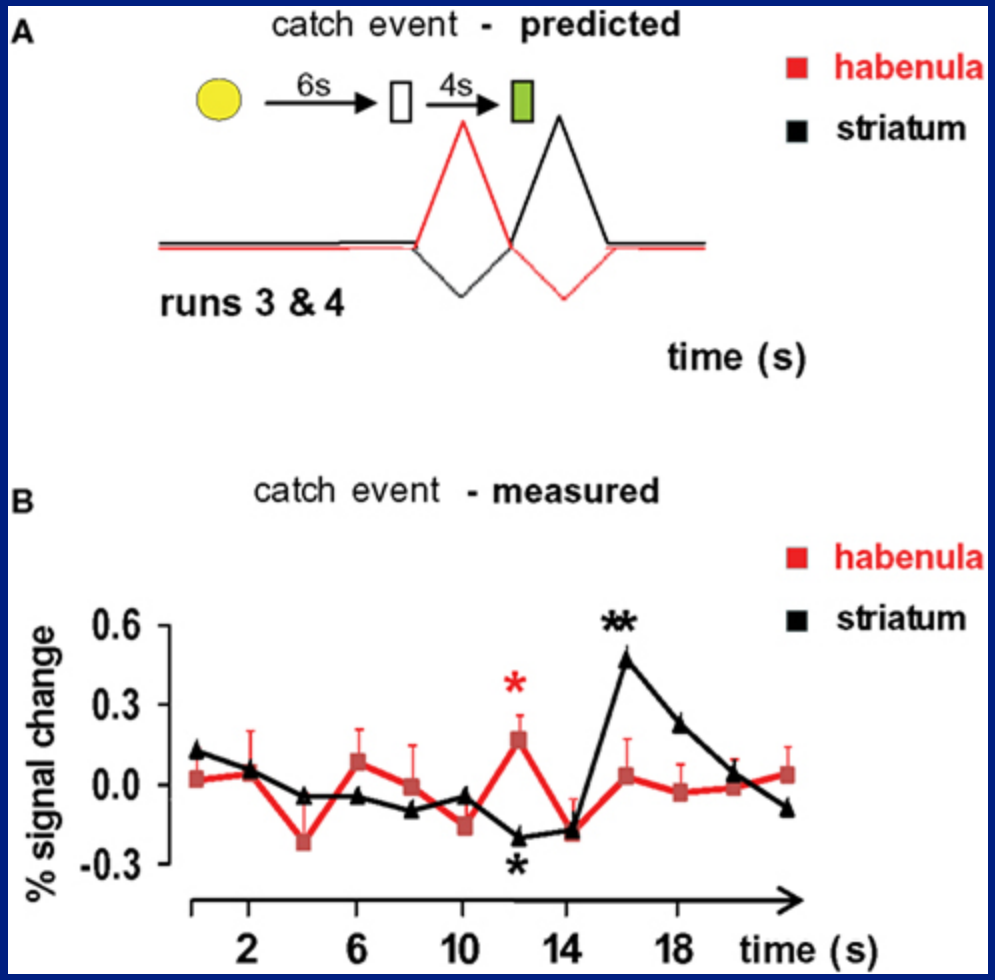


For each of 50 subjects, we manually co-registered structural and functional images, and manually defined coordinates for the right and left habenulae

Anticorrelation approach to identify Hb voxels



Negative prediction errors activate the habenula



Summary

β4 subunit-containing nAChRs in the medial habenula might be critical mediators of several effects of nicotine and related behaviors.

β4 -/-, α5-/-, and α2 -/- mice:

- Behave as less anxious than wild type littermates (β4 and α5 -/-)

- Display social amnesia (β4 -/-)

- Are insensitive to acute nicotine (β4 -/-, α5 -/-, and α3)

- Do not show nicotine withdrawal symptoms (β4 -/-, α2 -/-, α5 -/-)

Summary 2

- Blocking nAChRs in the habenula or ipn precipitates nicotine withdrawal in "addicted" mice

- The human habenula activates during "disappointment"

GWAS showed that SNPs in α5 (and α3, β4) account for smoking risk in humans.

Speculation: Is drug withdrawal a state of continuous disappointment due to habenula hyperactivation?

Current work

- Human habenular activation in non-smokers, sated smokers and smokers in withdrawal.

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