Using Cognitive Neuroscience Methods to Interrogate the Neurobiology of Addiction

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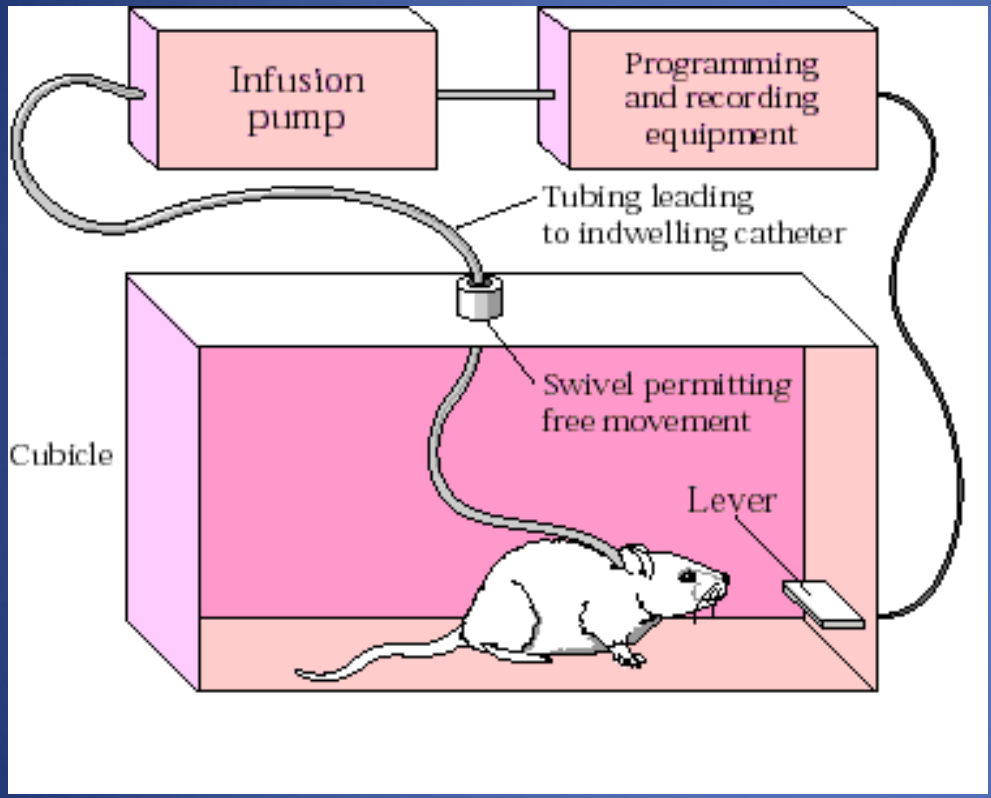
Alcoholism is a major and *underserved* public health problem

Illness	Prevalence	Approved Medications
Schizophrenia	**1.3%**	**20**
Mood Disorders	7.1%	31
Anxiety Disorders	16.4%	10
Substance Abuse	**9.8%**	Opiates: 4, Alcohol: 4* Stimulants/Other: 0 **Total: 6***

Data from SAMHSA & NIMH (Sept. 2005)

**** Naltrexone*** is approved for alcohol *and* opiate addiction

Bottom-up approach:



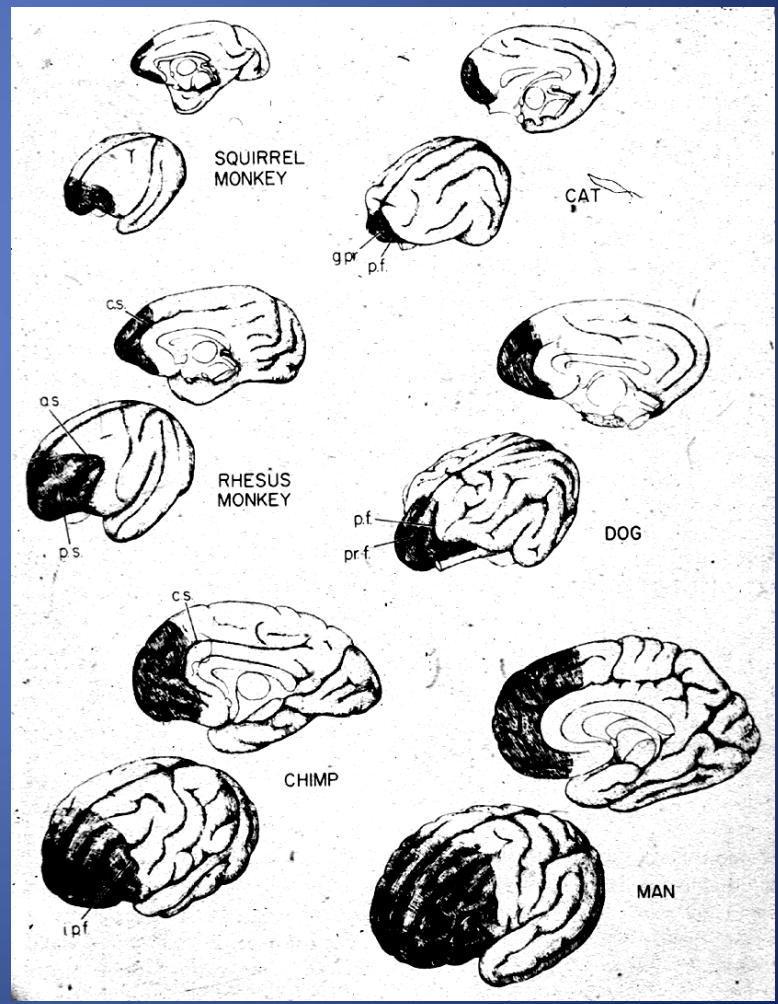
Based on animal models of addiction:
e.g. drug self-administration

Identify interventions that reduce drug self-administration > pursue clinical trials

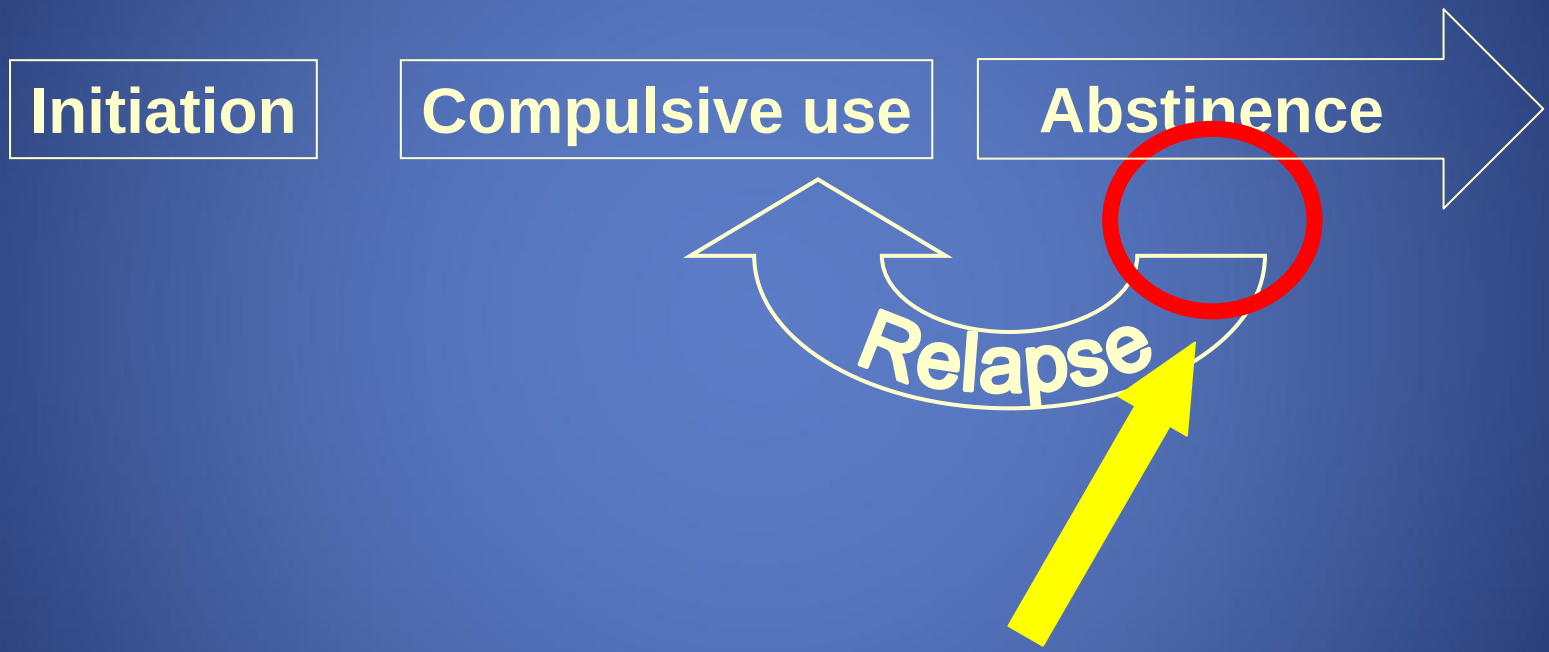
Why use a top-down approach?

The prefrontal cortex

- key target of drugs of abuse
- the seat of executive control; *addiction = loss of control*
- most developed in humans



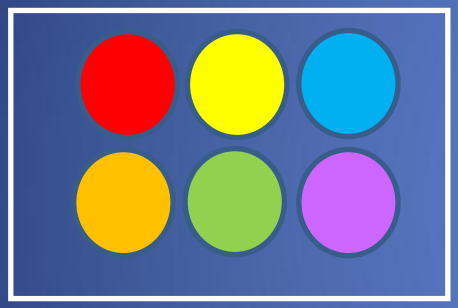
Role for cognitive neuroscience



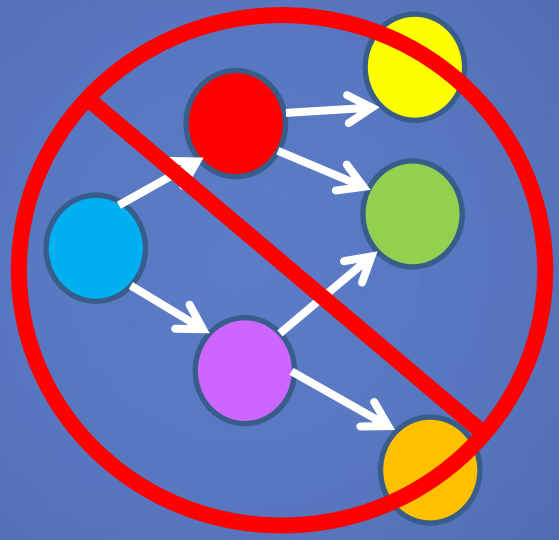
Cognitive mechanisms of this transition?

Utility of intermediate phenotypes

Addictive disorders are complex



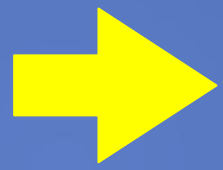
Sub-traits



We have not found "the" addiction gene

Classes of *cognitive* intermediate phenotypes relevant to relapse

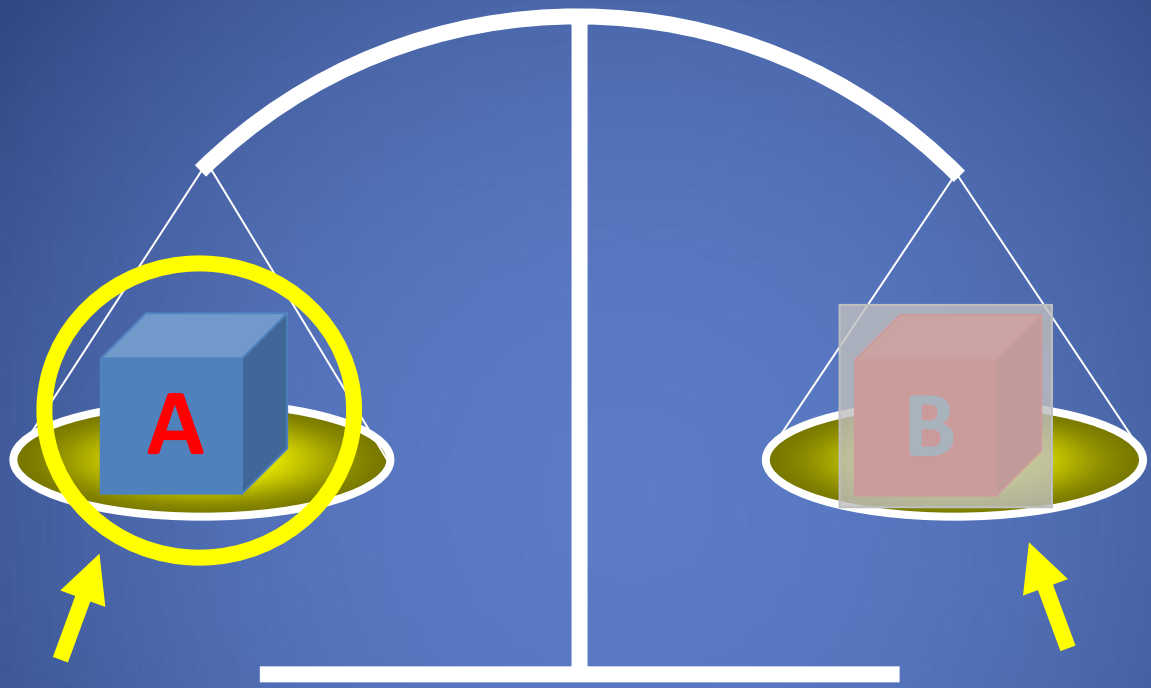
Stimulus Processing



Associative Learning

Response Selection

Immediate reward preference



Best short-term choice

Best long-term choice

“Now” > *“Later”*

Relationship to alcoholism?

Impulsive Choice Ratio

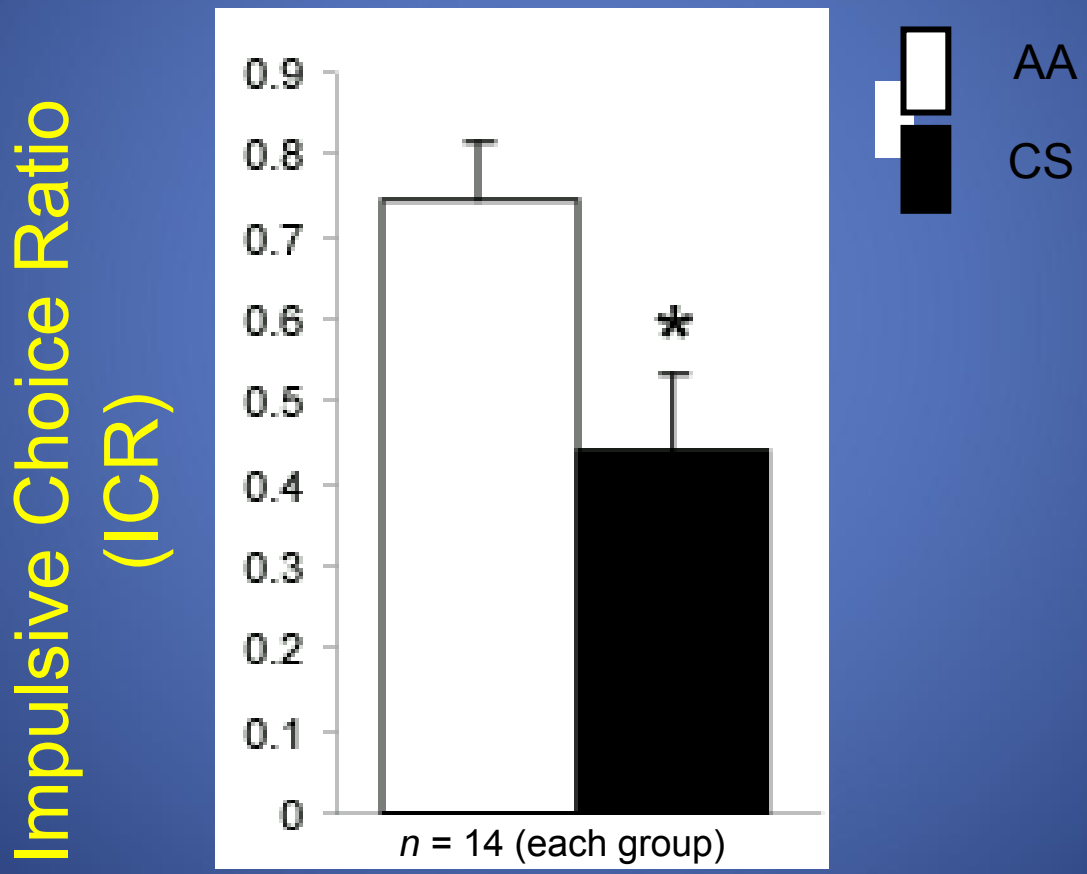
Index of cognitive impulsivity:

ratio of impulsive choices across all WANT trials

ICR = Sooner/(Sooner + Later)

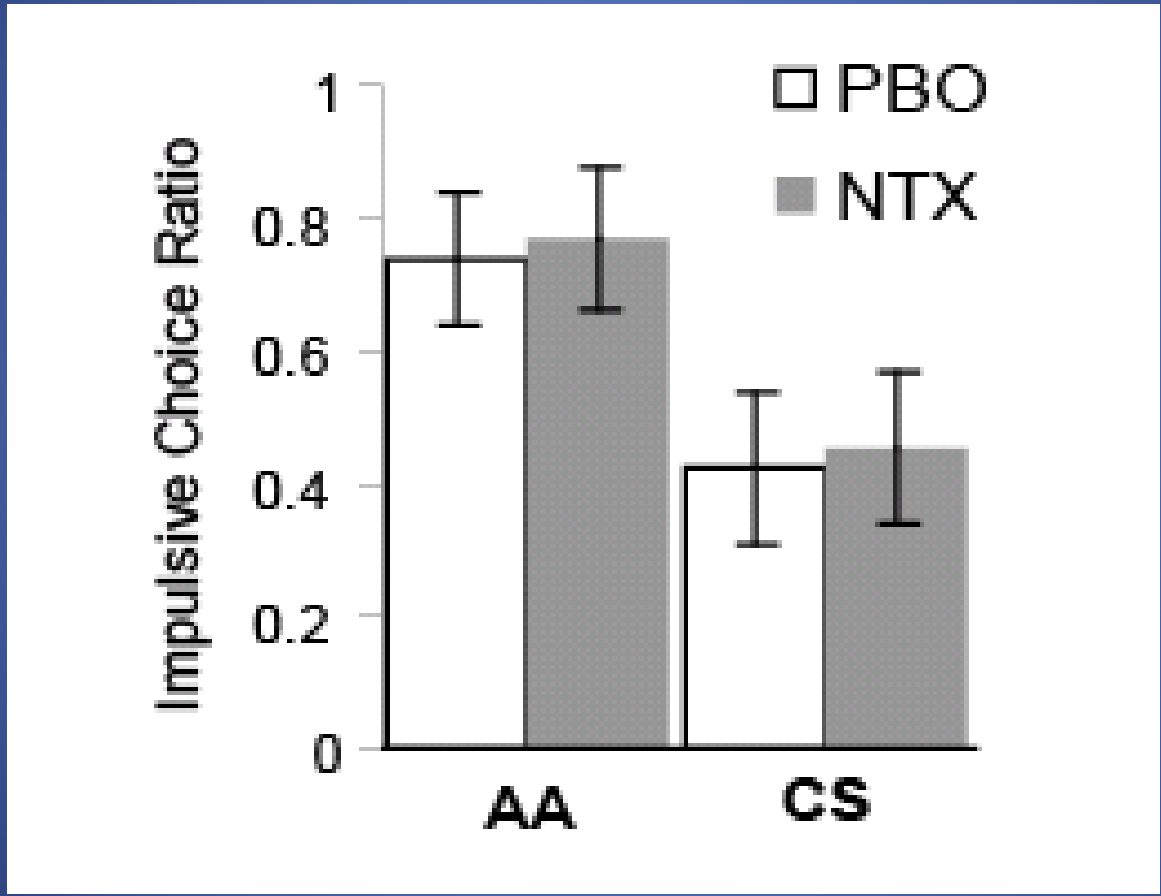
Zero ratio
=
No impulsive choices

Alcoholics (AA) choose the smaller-sooner option more often than controls (CS)



Mitchell JM, Fields HL, D'Esposito M, Boettiger CA (2005) *Alcoholism Clinical & Experimental Research* **29:** 2158-2169

NTX effect on impulsive choice

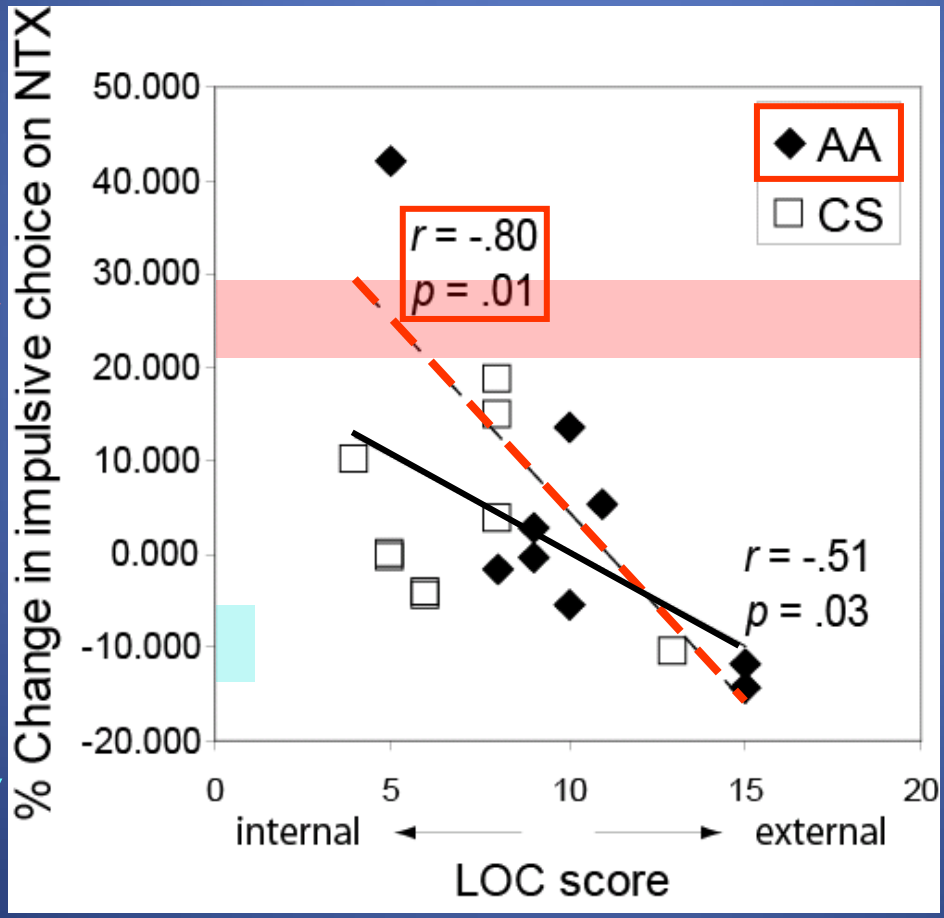


Mitchell JM, Tavares VC, D'Esposito M, Fields HL, Boettiger CA (2007) *Neuropsychopharmacology* **42:** 439

LOC predicted NTX's effect on ICR

More impulsive choices

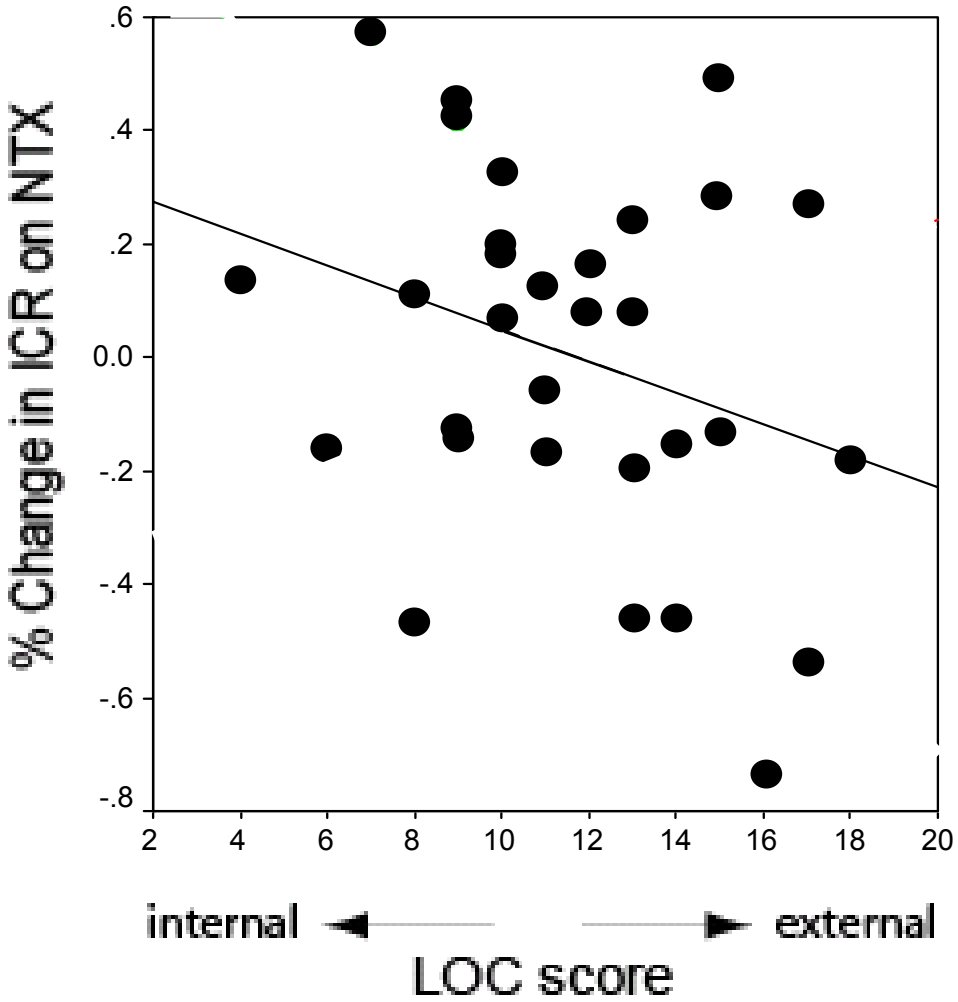
Fewer impulsive choices



Relationship stronger in AA group

Mitchell, et al. (2007) *Neuropsychopharmacology* **42:** 439

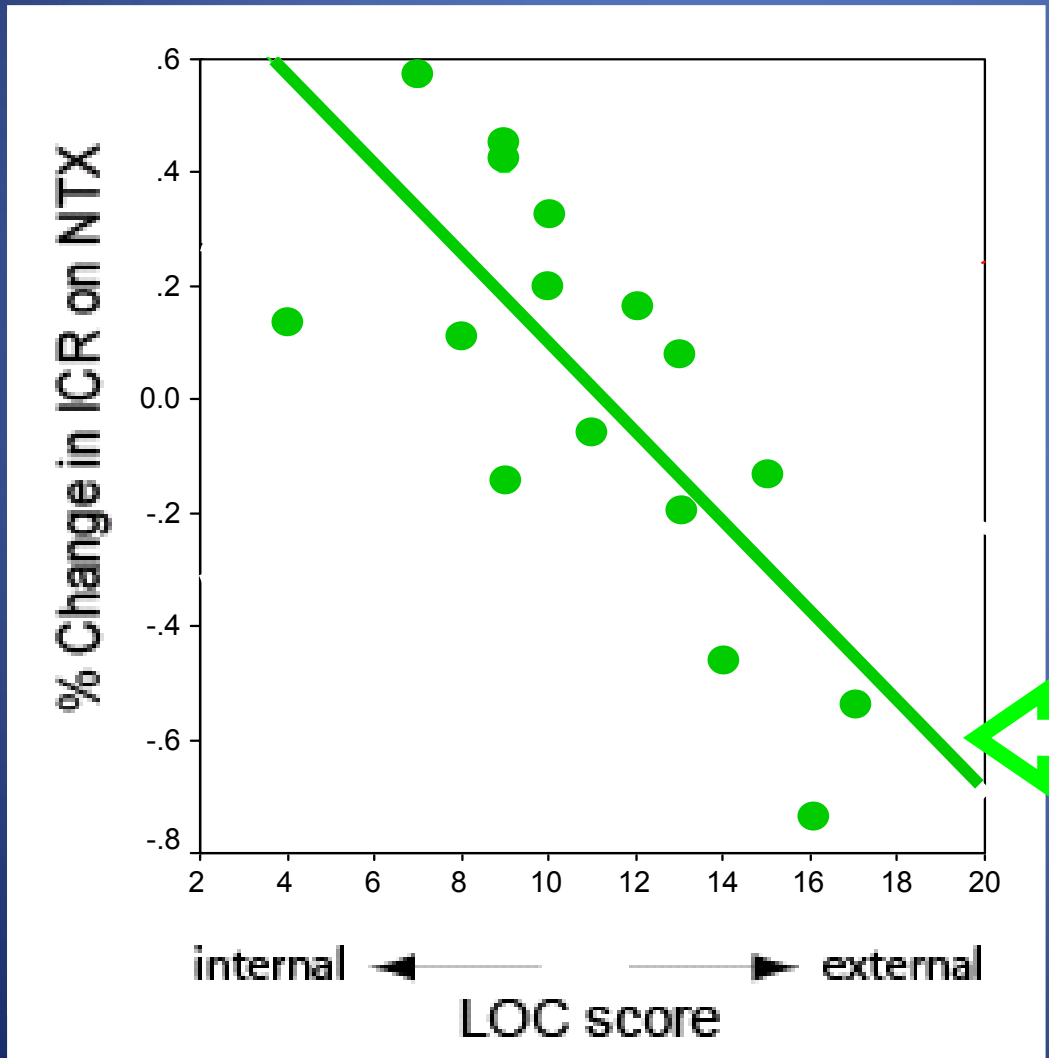
LOC result replicated in a separate group of control subjects



r=.37, p=.04

Altamirano et al (2006) Society for Neuroscience

LOC is a robust predictor of NTX response in people with a family history of alcoholism



FH+

Effect driven by FH+ subjects

r=.75, p=.001

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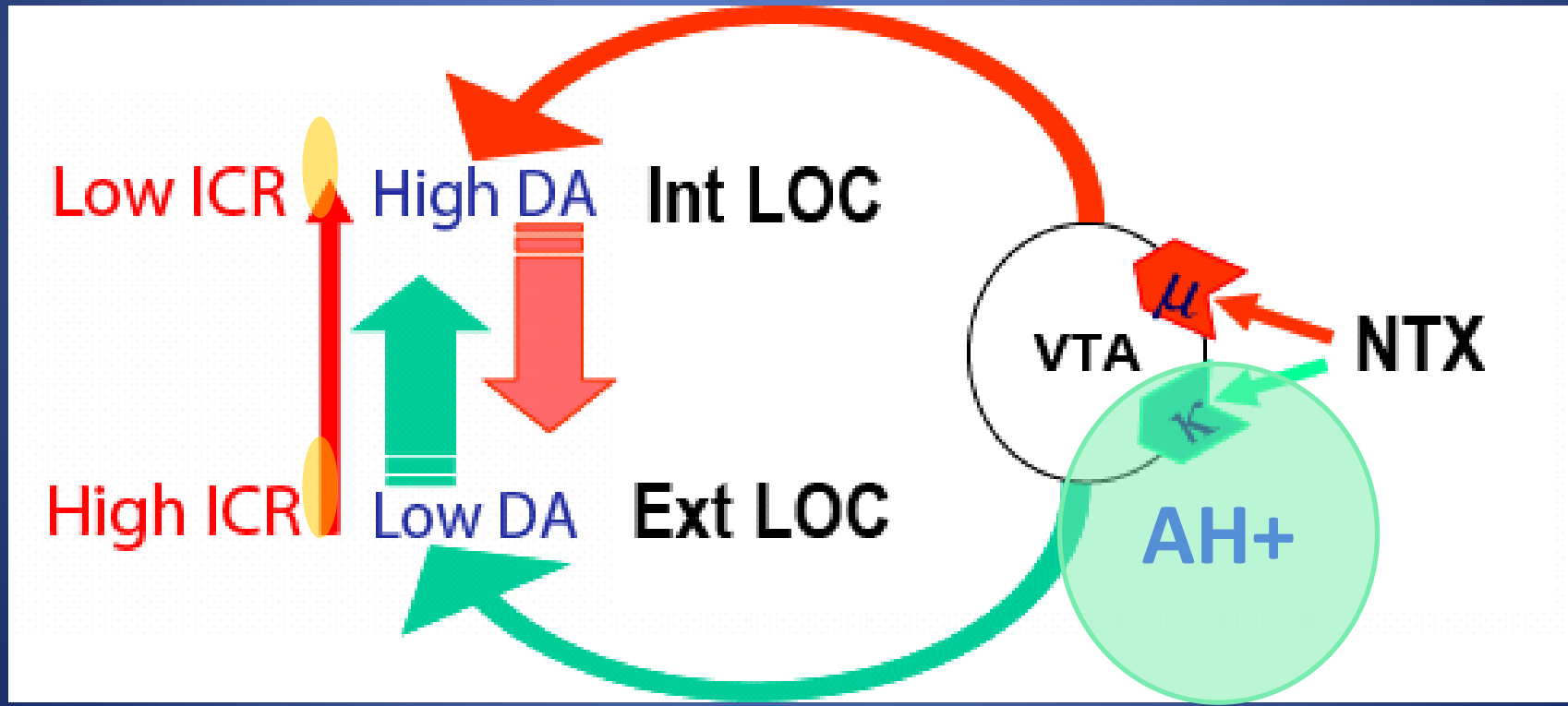
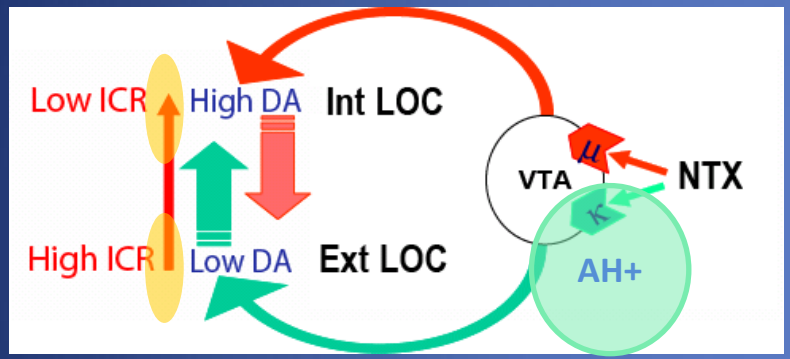
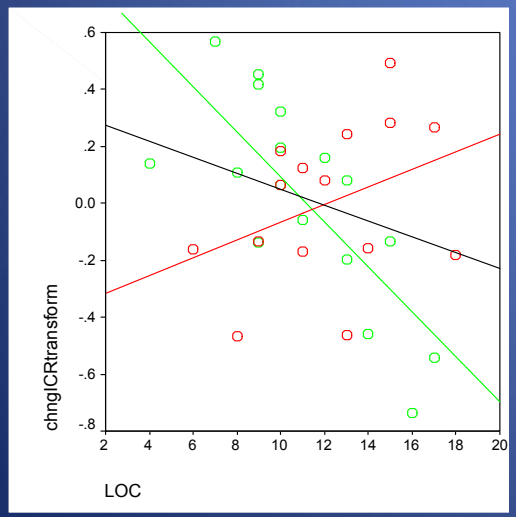
Baseline opioid and dopamine signaling may determine NTX's effect on impulsive choice

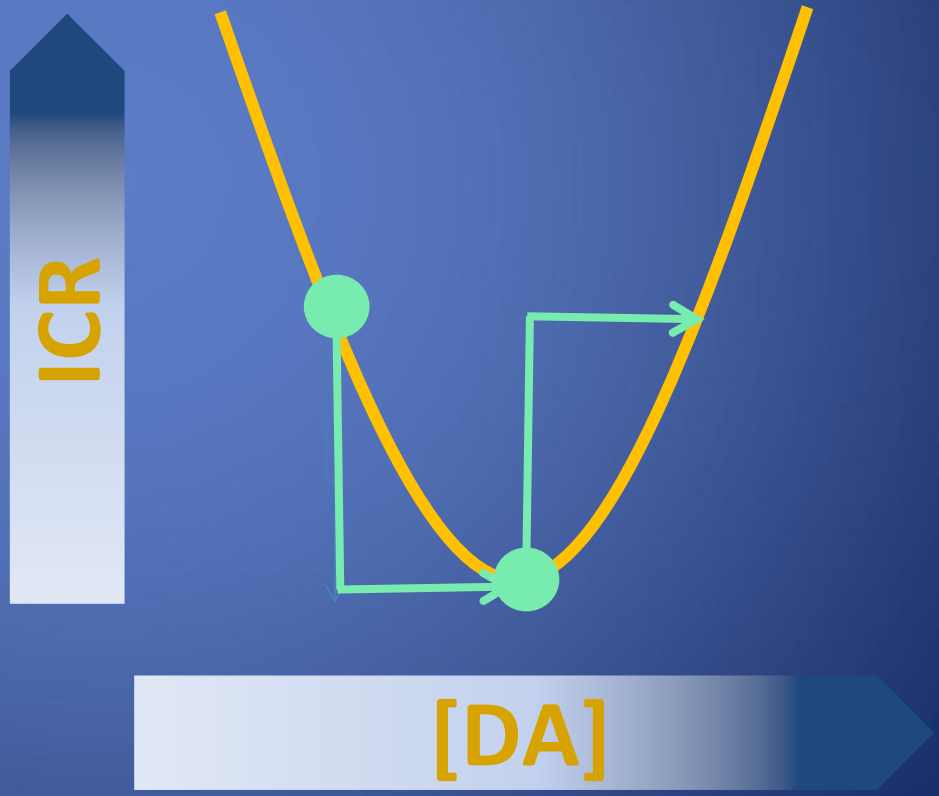


Mitchell, et al. (2007) *Neuropsychopharmacology* **42:** 439

Baseline opioid and dopamine signaling may determine NTX's effect on impulsive choice







Conclusion

Baseline frontal dopamine predicts NTX's effect on decision-making behavior *especially in those with a family history of alcoholism*

Current Studies

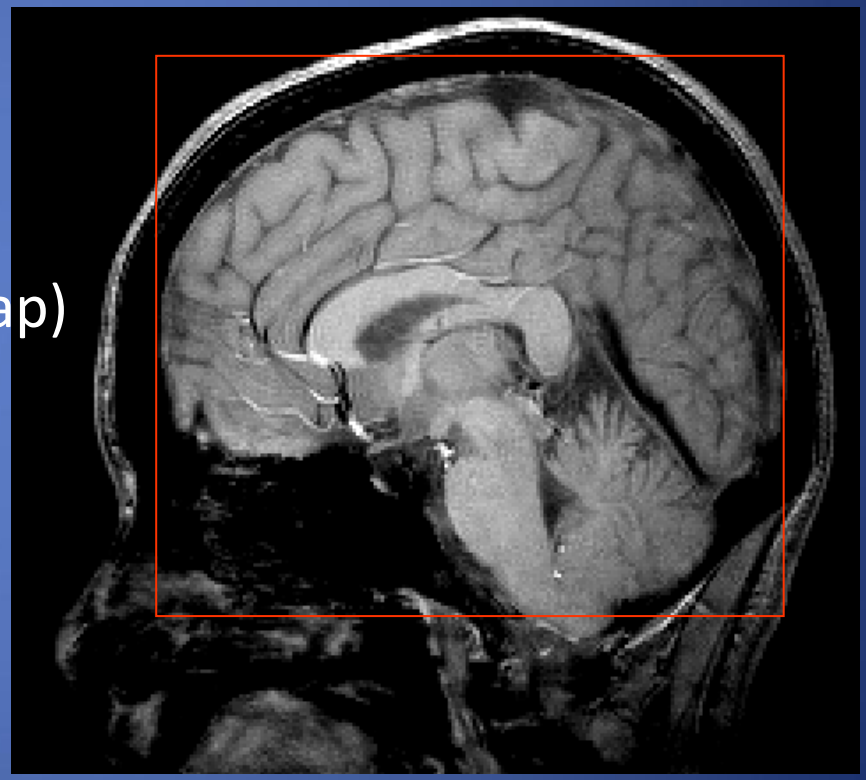
- Testing the effect of dopaminergic manipulations on decision-making
- Determining whether NTX-induced changes in decision-making predict clinical outcome

fMRI study of immediate reward bias

19 subjects (8 females)
Right-handed

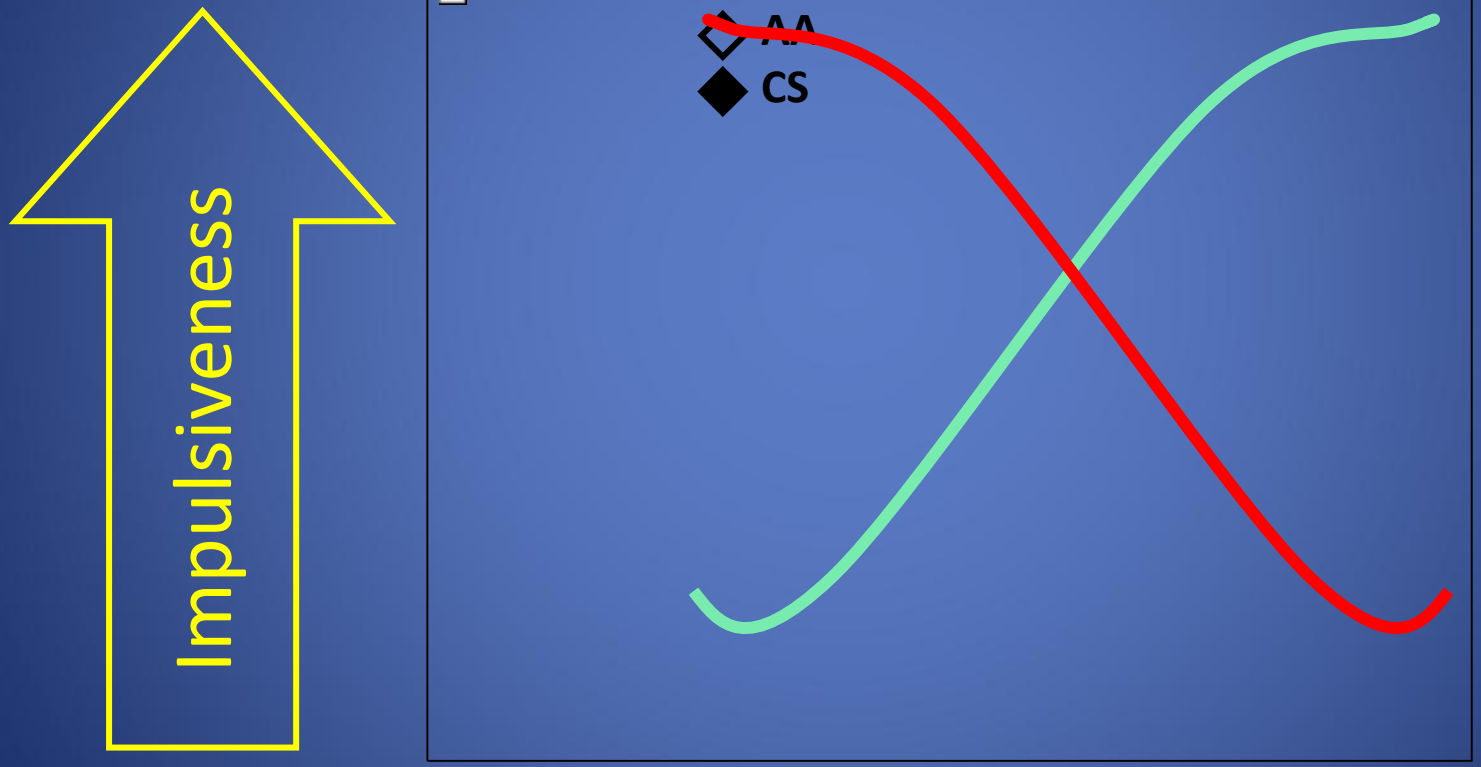
4 Tesla Varian Inova MR Scanner

FOV 224 X 224 mm
64 X 64 matrix size
40 3.5mm coronal slices (0.5mm gap)
TR = 2200 ms
TE = 28 ms
Flip Angle = 20 degrees
1-shot EPI
k-space sampled from – to +



Analysis in SPM2 & SnPM

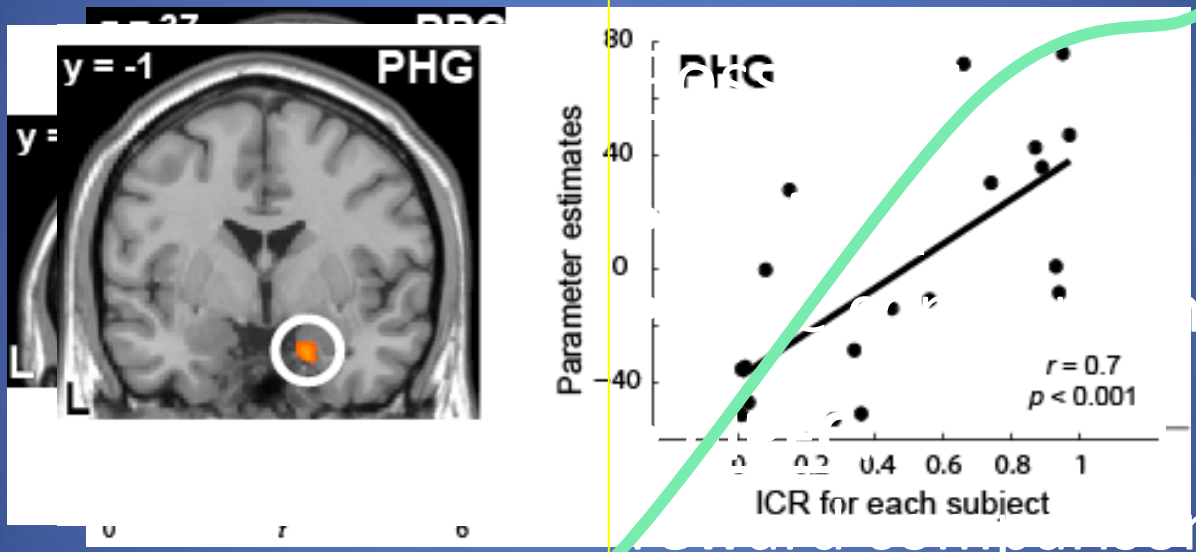
Despite significant group differences, choice behavior spanned a continuous range



Boettiger CA, et al. (2007) *Journal of Neuroscience* **27:** 14383

More active during decision-making in those biased toward *'Now"*

fMRI signal



- **Peri-amygdala**: affect-based decision-making

Impulsivity

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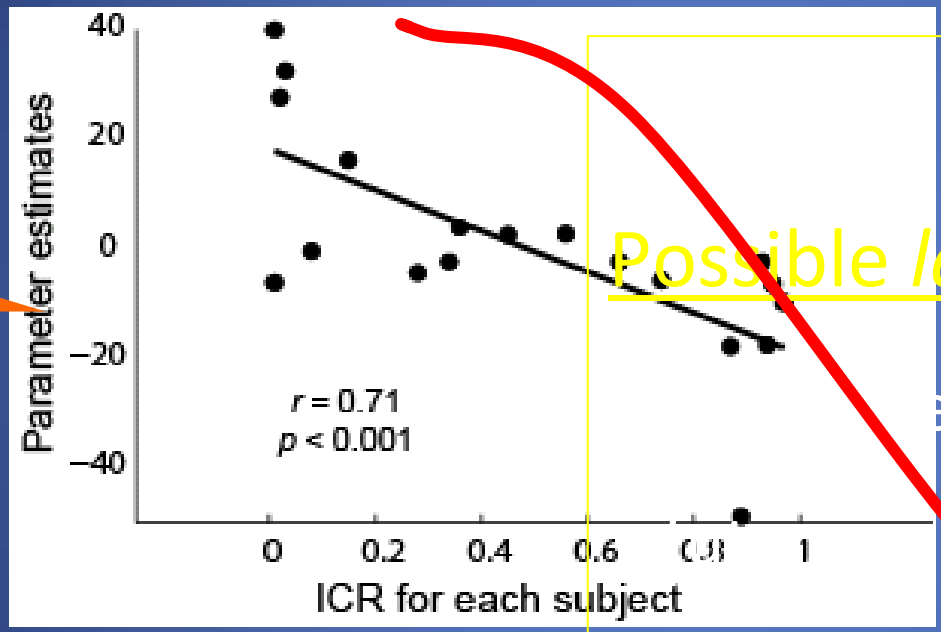
More active during decision-making in *"Later"* biased choosers

OFC fMRI signal

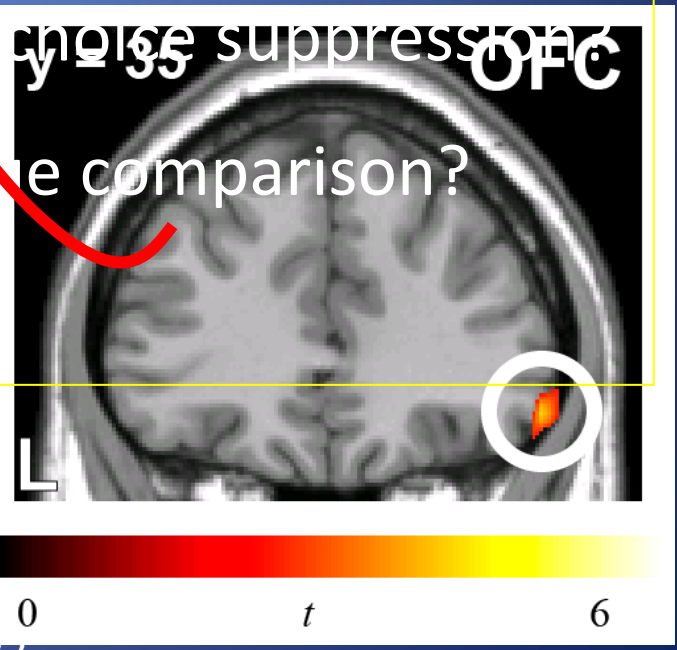


Impulsivity

Possible *lat*OFC roles:

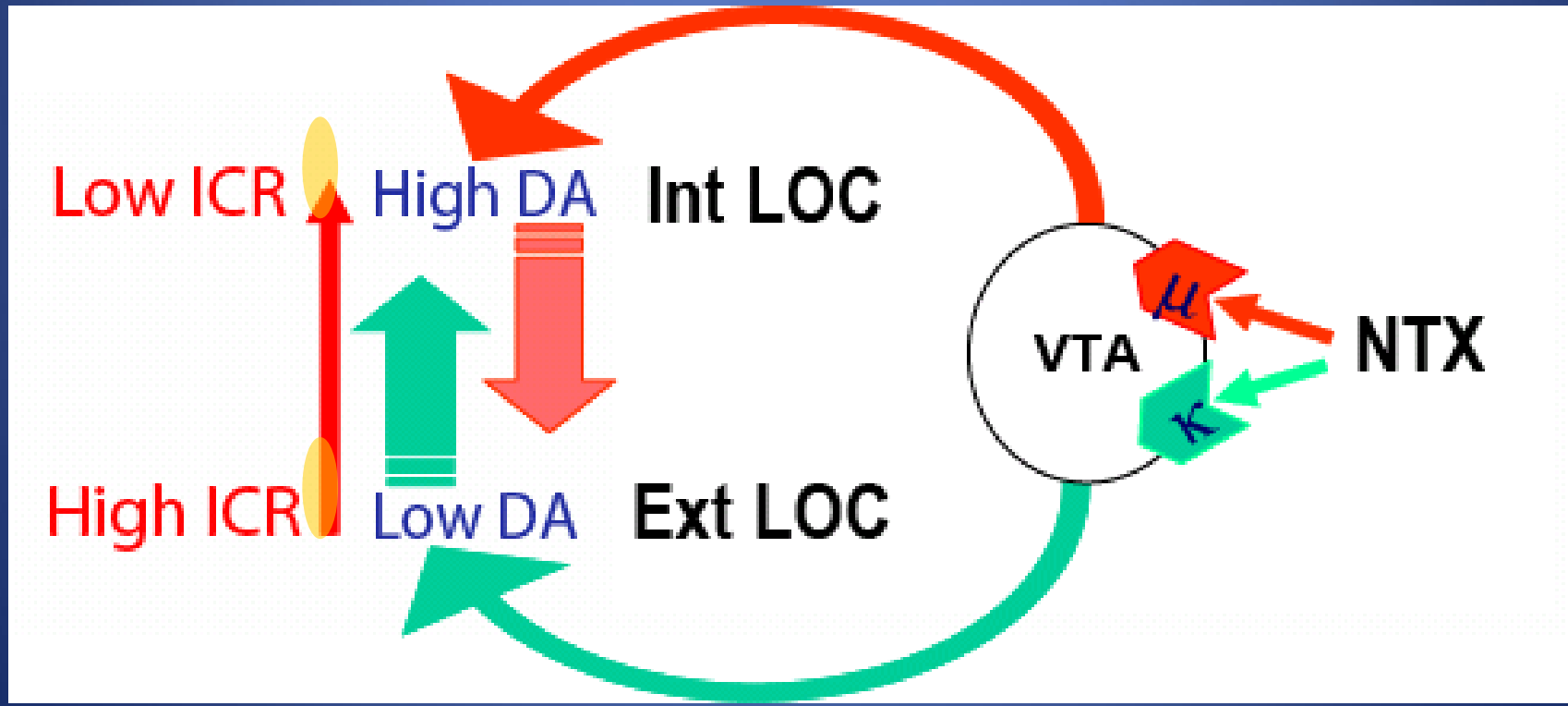
choice suppression?

e comparison?



Boettiger CA, et al. (2007) *Journal of Neuroscience* **27:** 14383

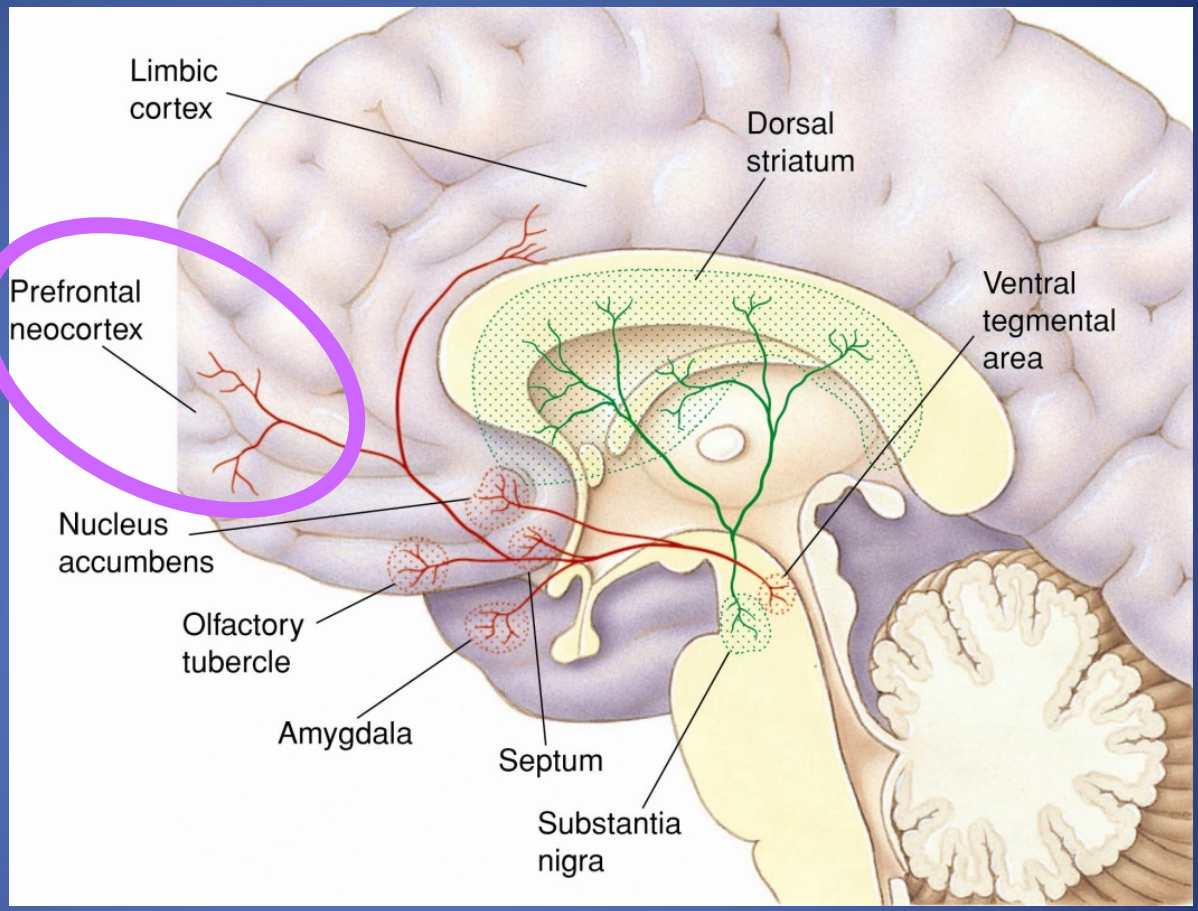
Baseline opioid and dopamine signaling may determine NTX's effect on impulsive choice



Mitchell, et al. (2007) *Neuropsychopharmacology* **42:** 439

COMT regulates frontal DA

Dopamine transporter is sparse in the cortex

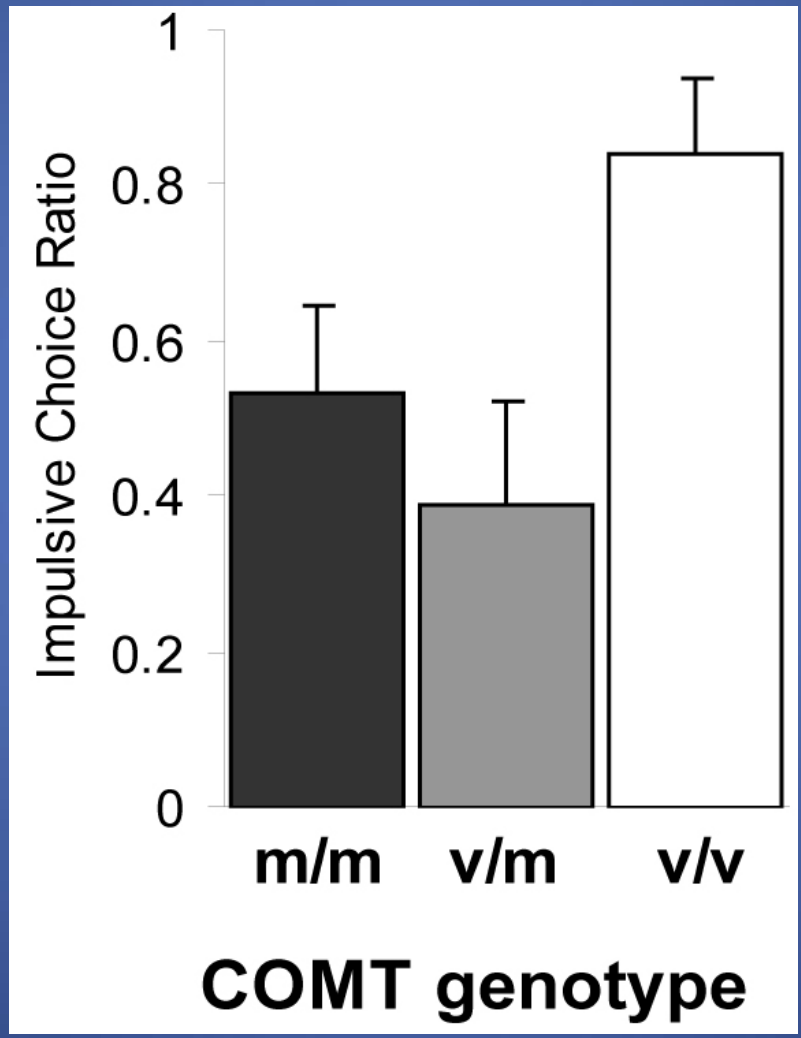


Both variants (Val & Met) are common in the population

Met variant is ***hypoactive*** →

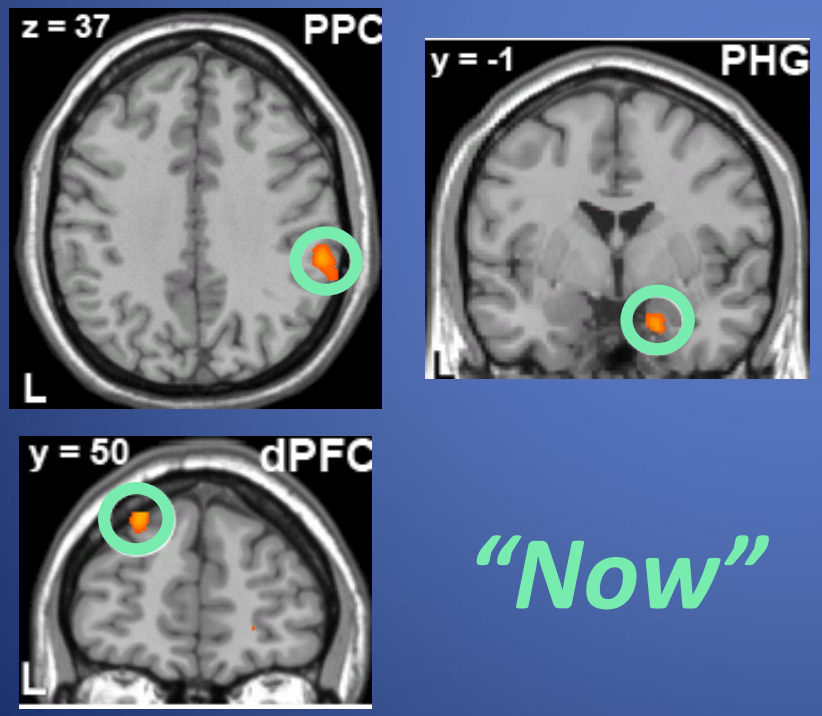
results in elevated cortical dopamine

COMT Val158Met genotype predicts choice behavior

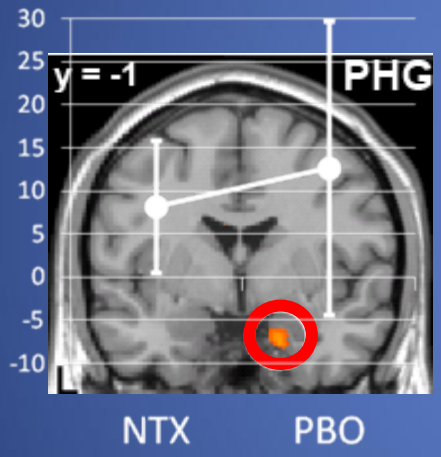


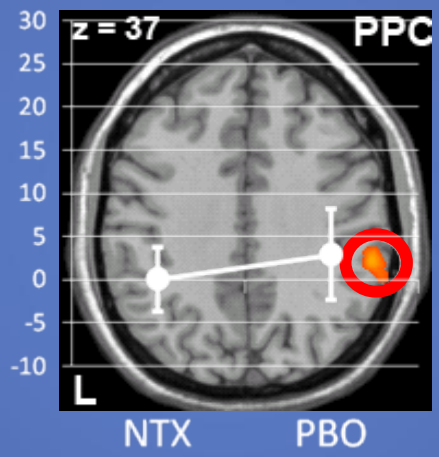
Boettiger CA, et al. (2007) *Journal of Neuroscience* **27:** 14383

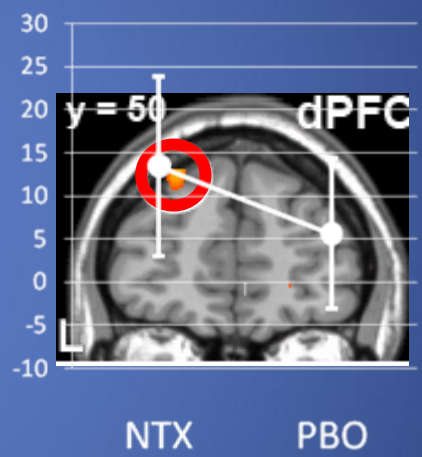
Does NTX alter activity in these areas during *Now* vs. *Later decisions*?



NTX effects during *Now* vs. *Later decisions*:

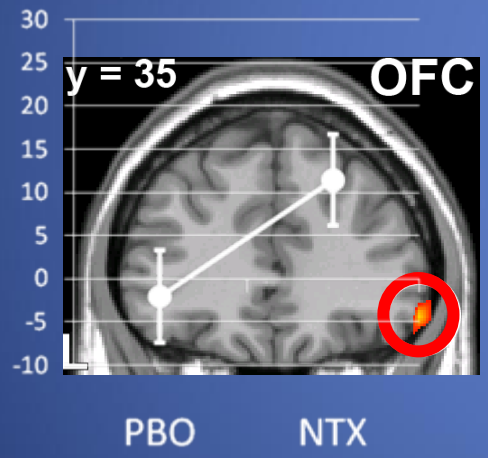






No effect in "Now" areas

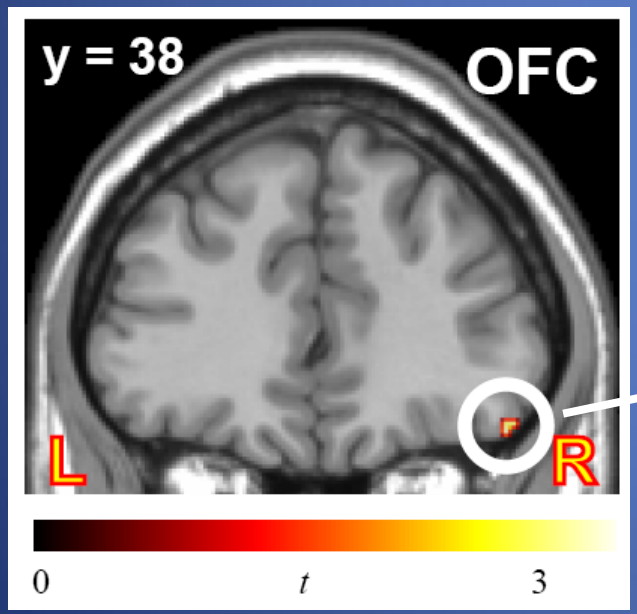
NTX effects during *Now* vs. *Later decisions*:

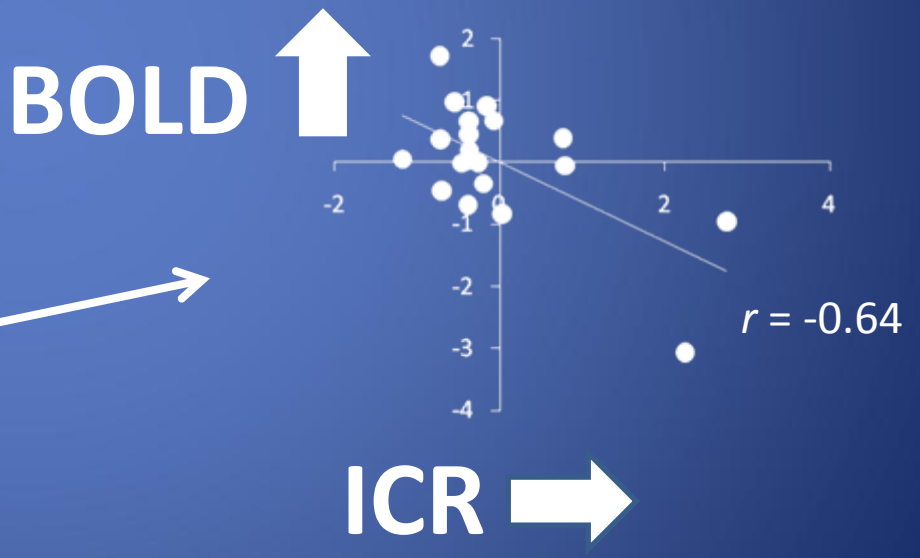


Naltrexone significantly elevates BOLD in "Later" areas

NTX effects in the OFC predicted

NTX effects on choice:





Boettiger CA, et al. (2009) *Pharmacology, Biochemistry & Behavior* (2009)

Summary:

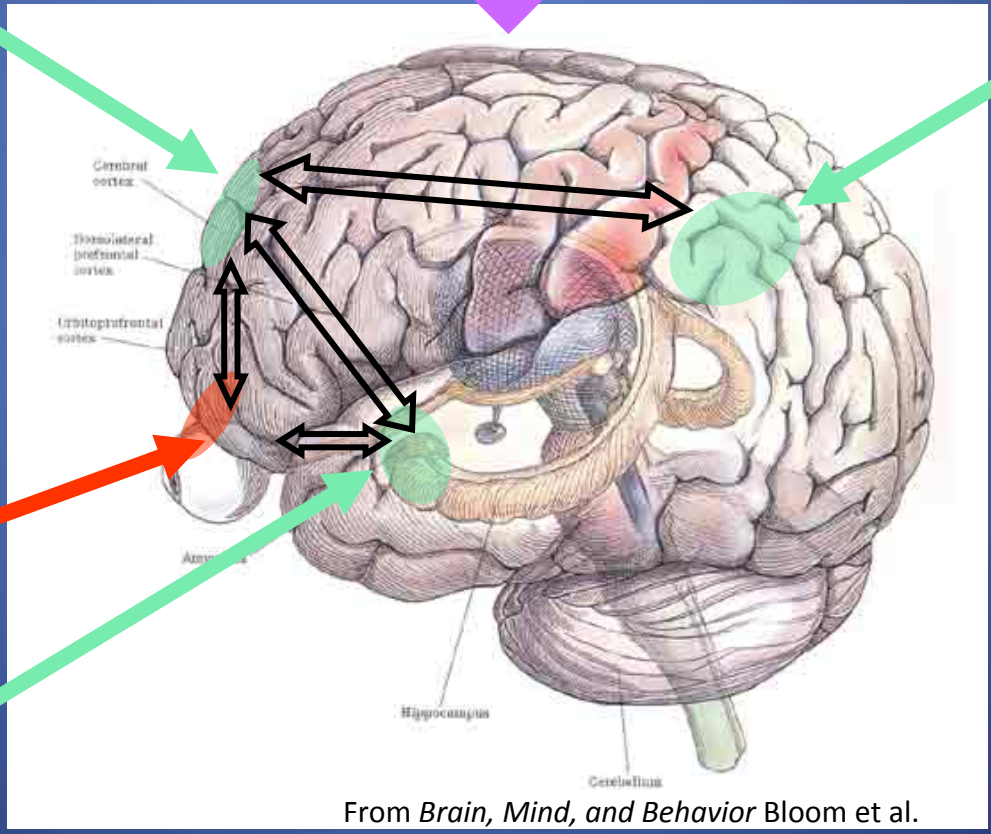
Add NTX

Dorsolateral Prefrontal Cortex

Parietal Cortex

Orbitofrontal Cortex

Amygdala



From *Brain, Mind, and Behavior* Bloom et al.

Conclusions

- NTX may support long-term decisions by increasing OFC activity during decision-making
- OFC activity during *Now/Later* decisions may be a surrogate therapeutic target

Future Directions

- Do NTX-induced changes in OFC function during decision-making predict clinical outcome?
- Development of immediate reward bias: a pre-existing risk trait or consequence of alcohol abuse?
- Neurobiology of attentional bias towards addiction cues

Acknowledgements

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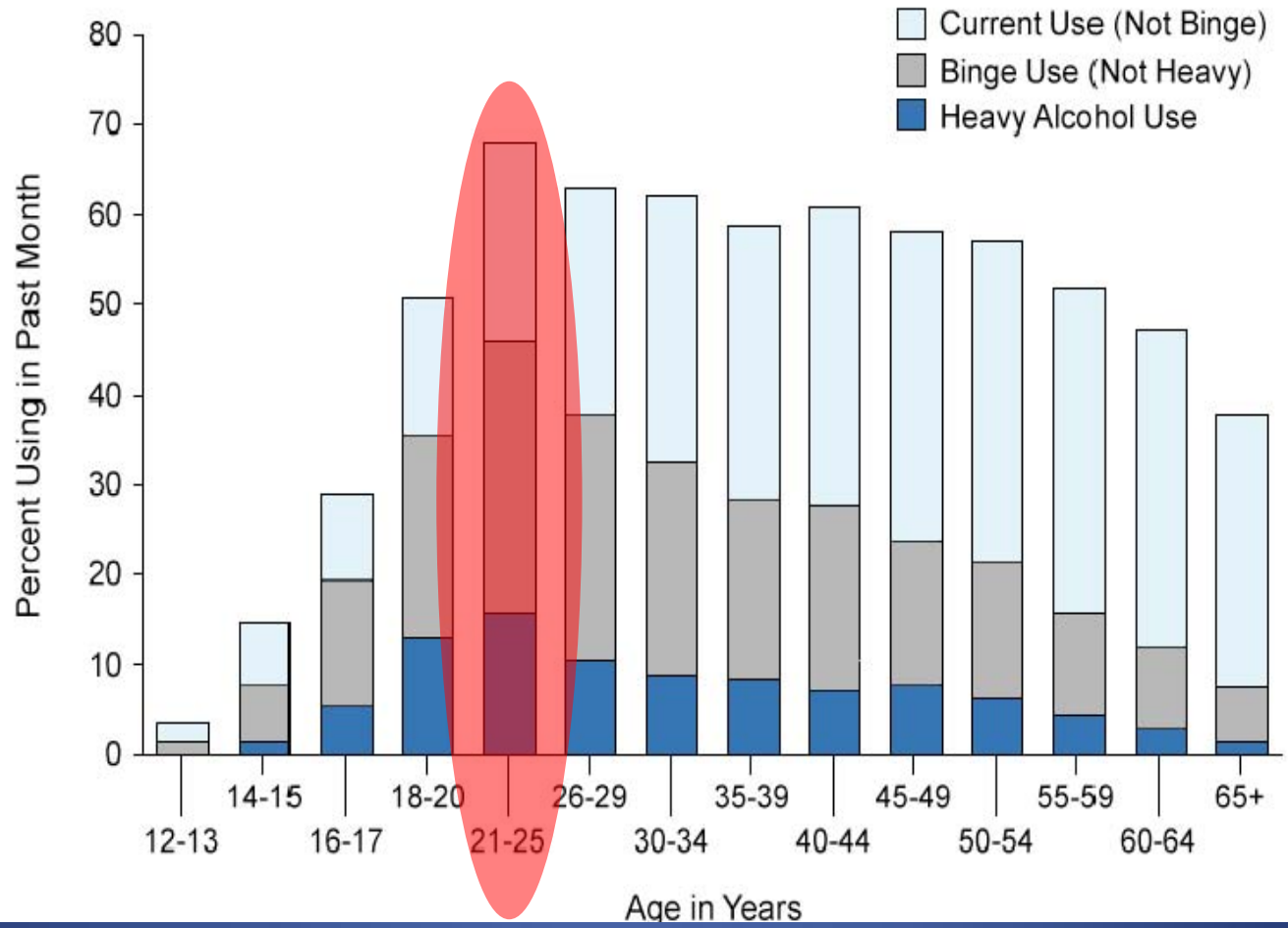
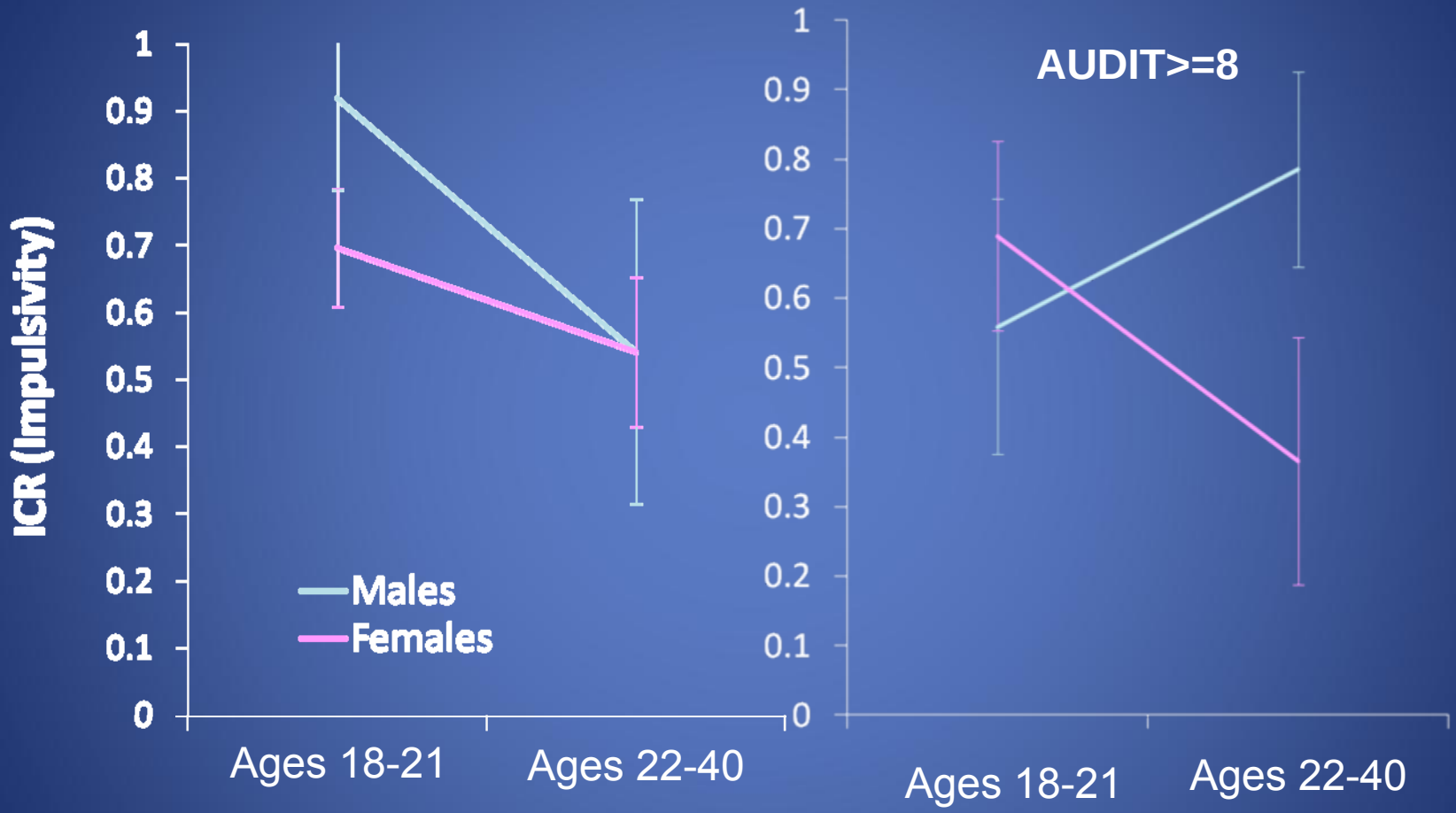
U.S. Department of Defense – Wheeler Center for the Neurobiology of Addiction

Drinking patterns in young adults (SAMHSA, 2007)

Figure 3.1 Current, Binge, and Heavy Alcohol Use among Persons Aged 12 or Older, by Age: 2007

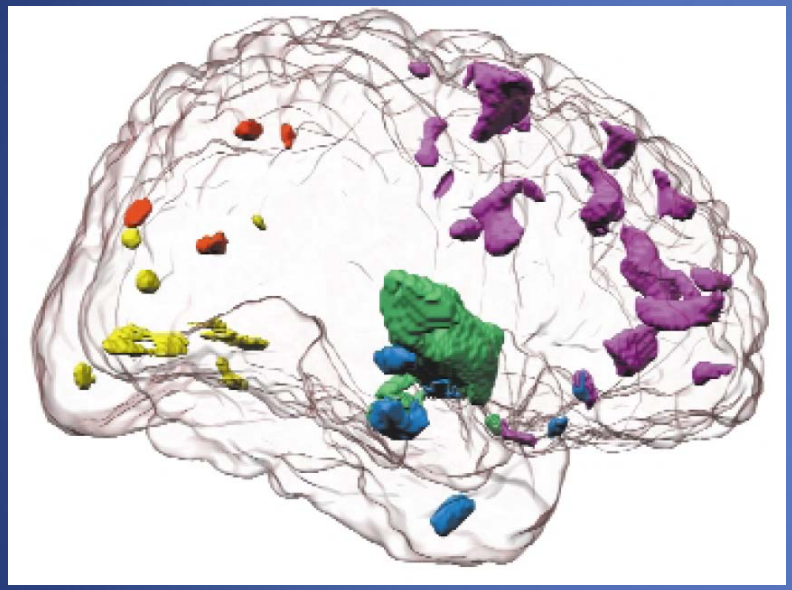


Late adolescents discount like sober alcoholics!

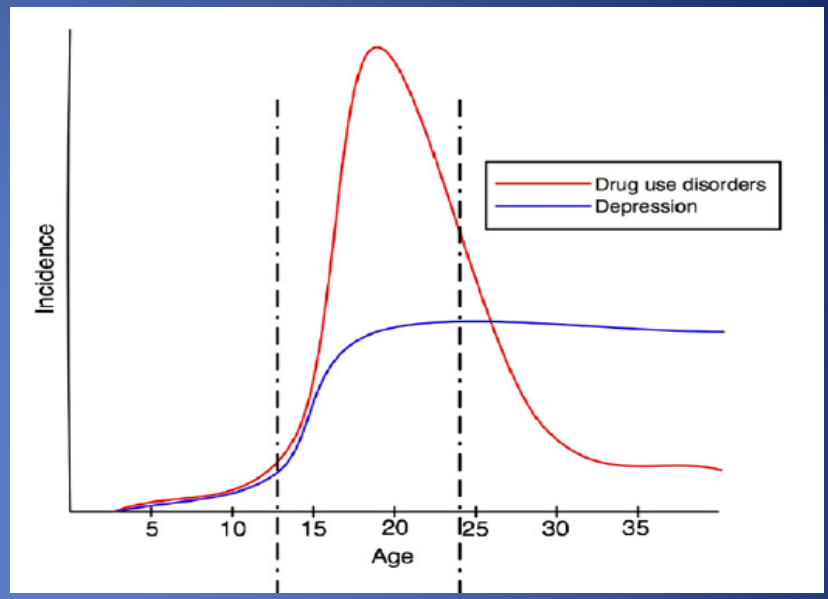


Smith, Freeman-Daniels & Boettiger (2010) Research Society on Alcoholism

Frontal Development as an Explanation for immediate reward bias of Late Adolescents?

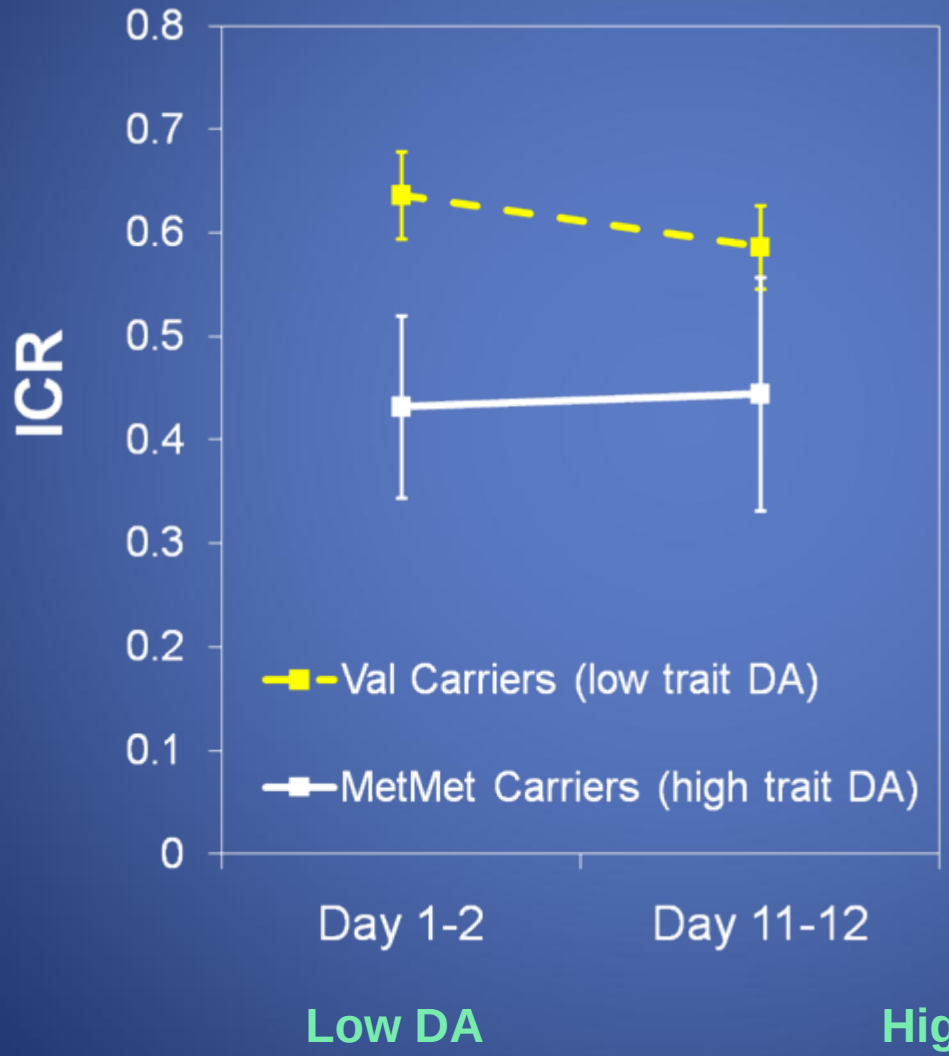


Sowell et al., 1999



Davey et al., 2008

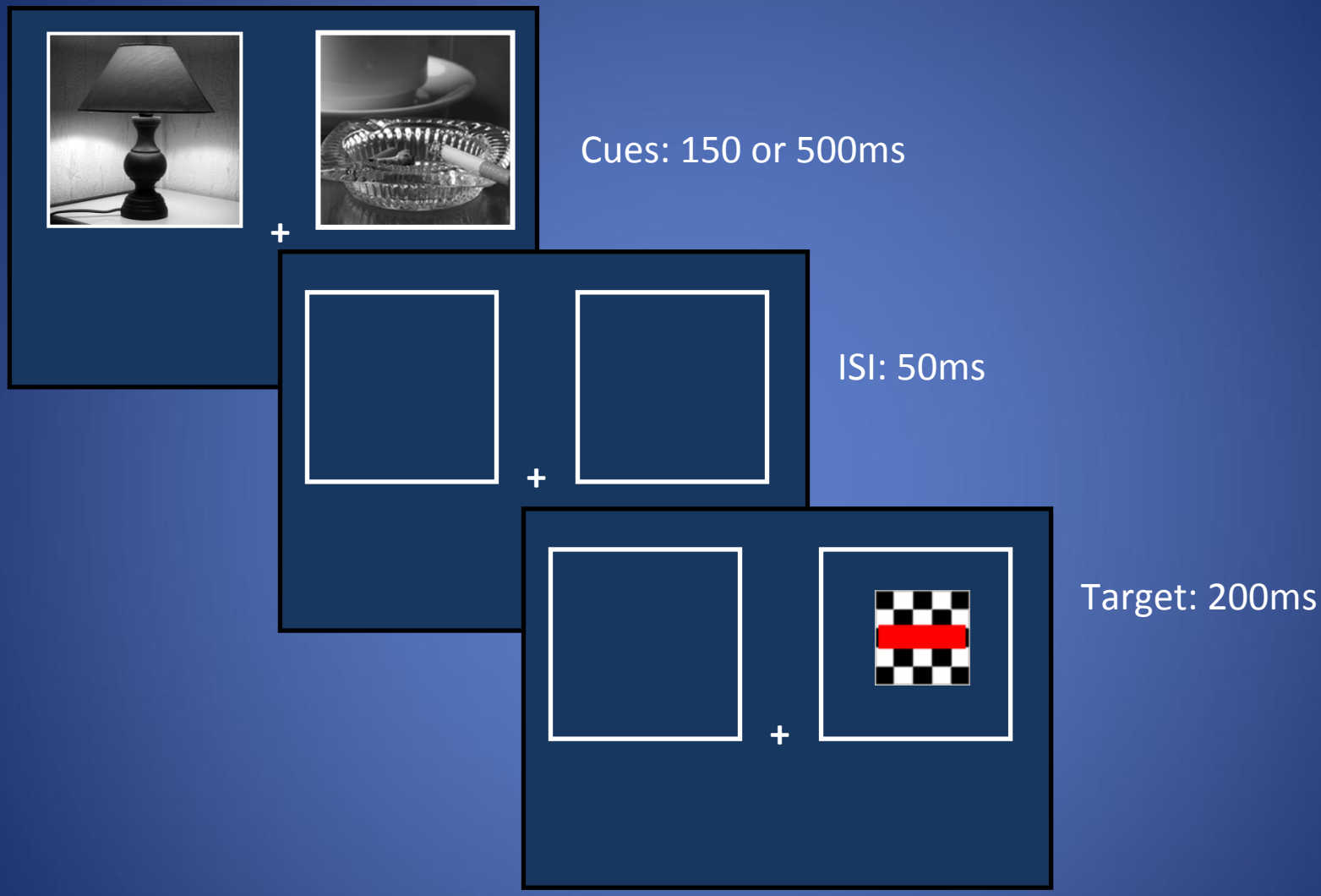
Cycle day affects immediate reward bias in females



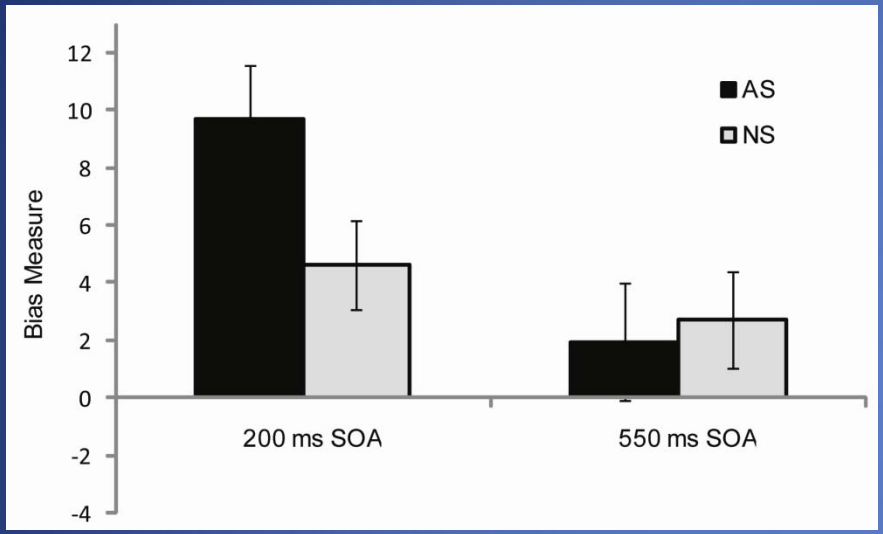
Cycle effect interacts with COMT genotype

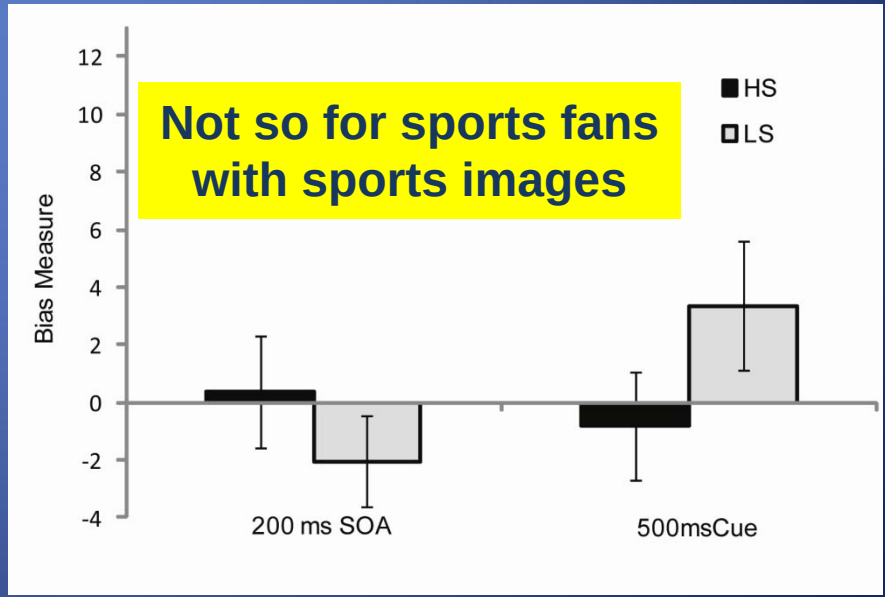
Smith & Boettiger (2010) Cognitive Neuroscience Society

Spatial cuing



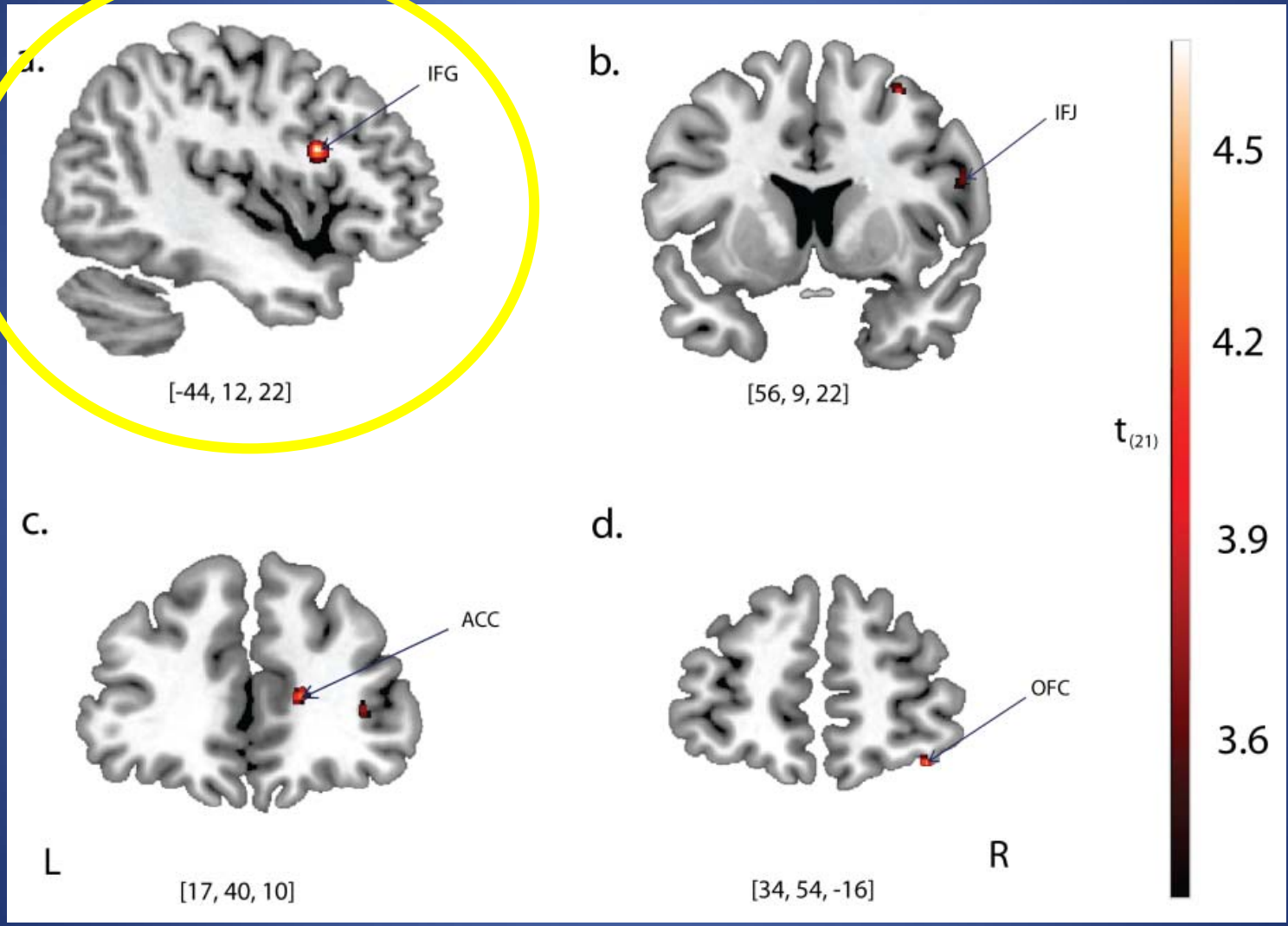
Smokers' attention is reflexively captured by smoking images





Chanon & Boettiger (in press) Psychopharmacology

Novel biomarkers of nicotine addiction



Chanon & Boettiger (2010) Cognitive Neuroscience Society

Delay Discounting Task: single trial

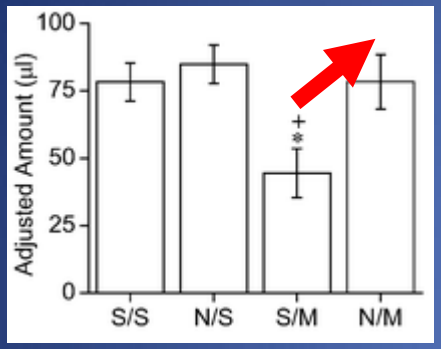
$100
6 MONTHS

+

$70
TODAY

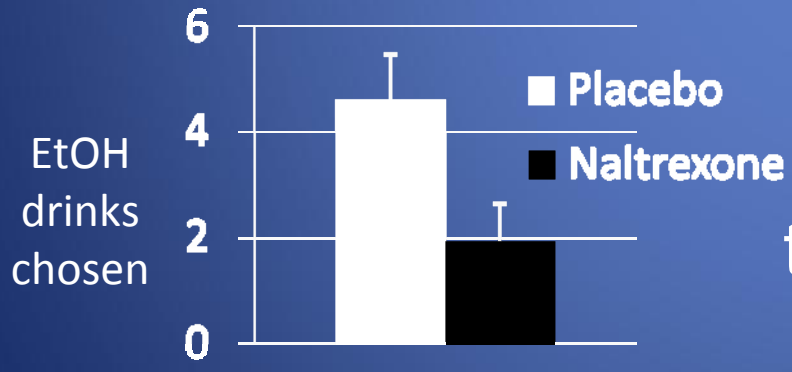
WANT ?

Naltrexone may reduce immediate reward bias



Reduces impulsive choice in a rat model

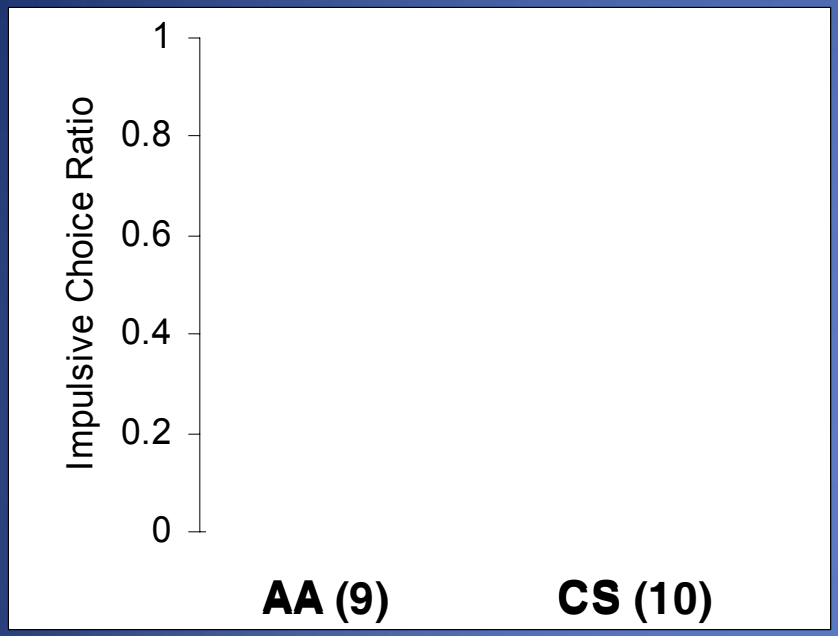
Kieres AK, et al. (2004) *Psychopharmacology* **173:** 167



Shifts preference from immediate alcohol reward to delayed monetary reward in a lab bar setting

from: O'Malley SS, et al. (2002) *Psychopharmacology* **160:** 19

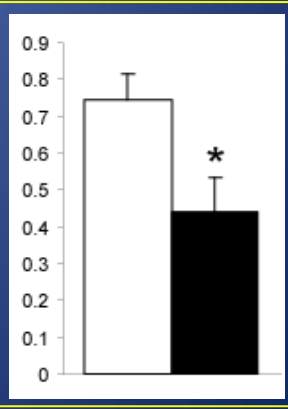
fMRI subjects: behavioral results



Sober alcoholics chose *Now* over *Later* more frequently

Boettiger CA, et al. (2007) *Journal of Neuroscience* **27:** 14383

Decision-making behavior during fMRI similar to our previous behavioral study

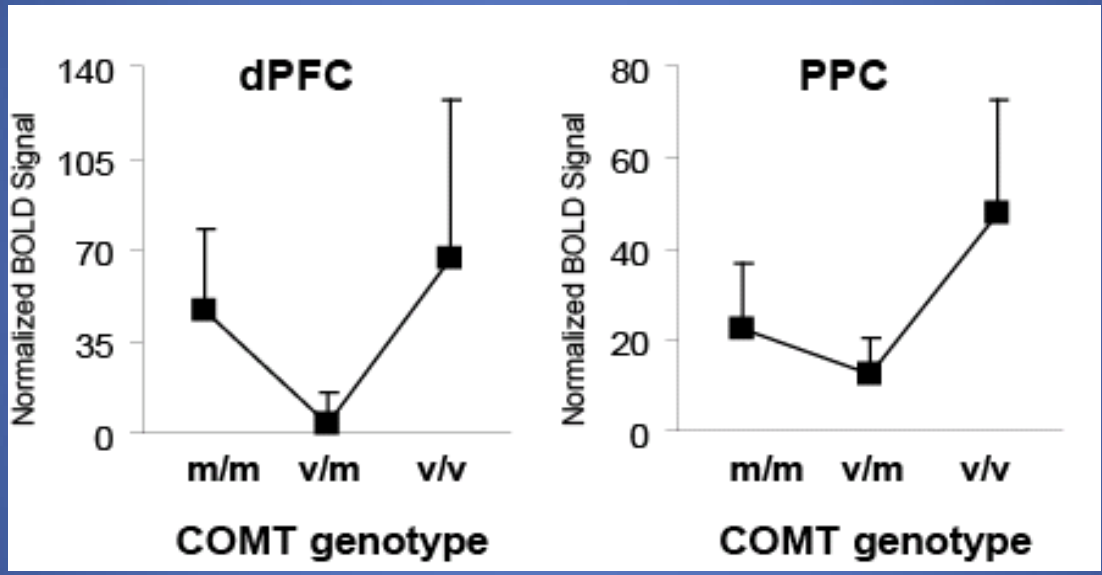


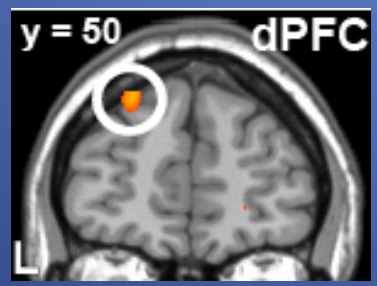
Mitchell JM, et al. (2005) *Alcoholism Clinical & Experimental Research* **29:** 2158

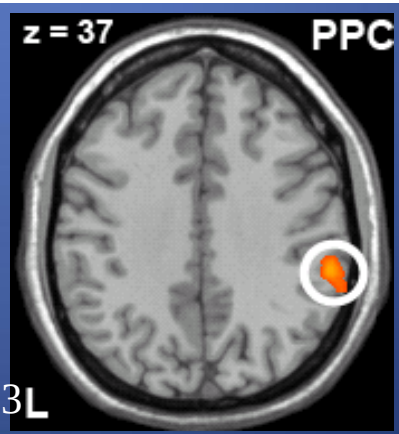
Brain areas in which decision-making activity correlates with *Now* vs. *Later* preference?

1. Decision-making Contrast: (WANT – CON)
2. Regression: ICR vs. Decision-making Contrast

COMT Val158Met genotype predicts activity during decision-making in the dPFC & PPC







Boettiger CA, et al. (2007) *Journal of Neuroscience* **27:** 14383

Butte County California:

ReVia® (NTX) Project for repeat DUI offenders

	Antabuse	NTX
Time to any new crime		
Drug/alcohol related new crimes (%)		