2009

Nicotine dependence treatment: A translational research approach

Caryn Lerman
University of Pennsylvania

Nicotine Dependence Treatment: A Translational Research Approach

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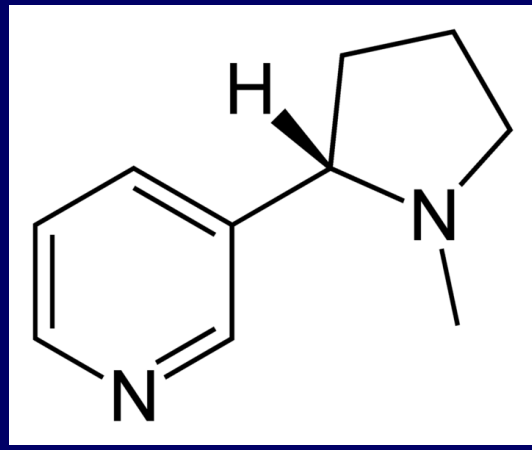
Transdisciplinary Tobacco Use Research Center
UPENN



Disclosure Information

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Grant Support: National Institutes of Health

Employee of: University of Pennsylvania

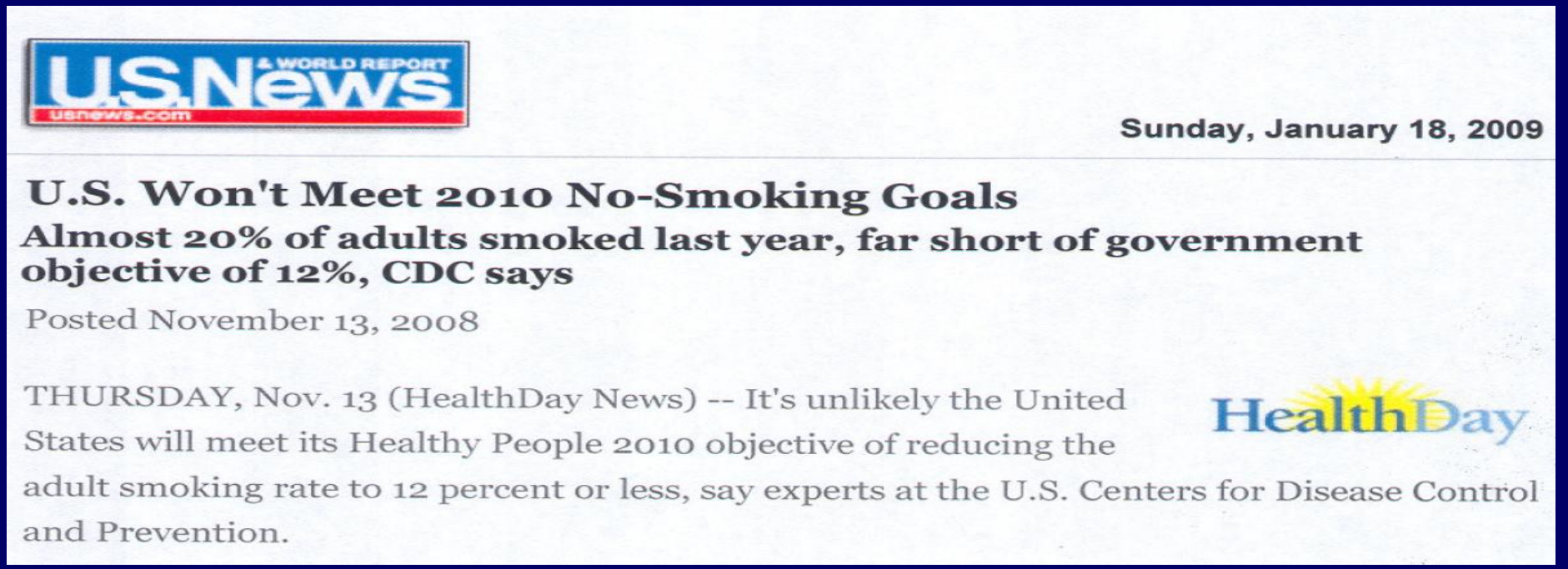
Off Label use discussed: naltrexone, tolcapone

Why Study Tobacco Use?

- **Tobacco use is the leading cause of PREVENTABLE death in the U.S.**
- **Each day > 4,000 youth ages 12-17 start smoking cigarettes**
- **Each year >400,000 Americans die from tobacco smoking**
- **High comorbidity with alcohol and drug dependence**

Source: 2006-7 AMA-RFS Public Health Committee

Our Challenge



U.S.News & WORLD REPORT
usnews.com

Sunday, January 18, 2009

U.S. Won't Meet 2010 No-Smoking Goals

Almost 20% of adults smoked last year, far short of government objective of 12%, CDC says

Posted November 13, 2008

HealthDay

THURSDAY, Nov. 13 (HealthDay News) -- It's unlikely the United States will meet its Healthy People 2010 objective of reducing the adult smoking rate to 12 percent or less, say experts at the U.S. Centers for Disease Control and Prevention.

- **1 in 5 Americans is tobacco dependent.**
- **Current FDA-approved medications are successful for only 1 in 3 smokers.**

An Investment in Nicotine Dependence Medication Development

Academic scientists can (and should) contribute to the development of safe and effective medications for nicotine dependence

Lerman et al. Nature Reviews Drug Discovery, 2007

Tobacco Use Research Center P50 (1999-)

Scientific Mission

To translate discoveries in neuroscience, pharmacology, and genetics to improve treatment for nicotine dependence

Translational Research Examples

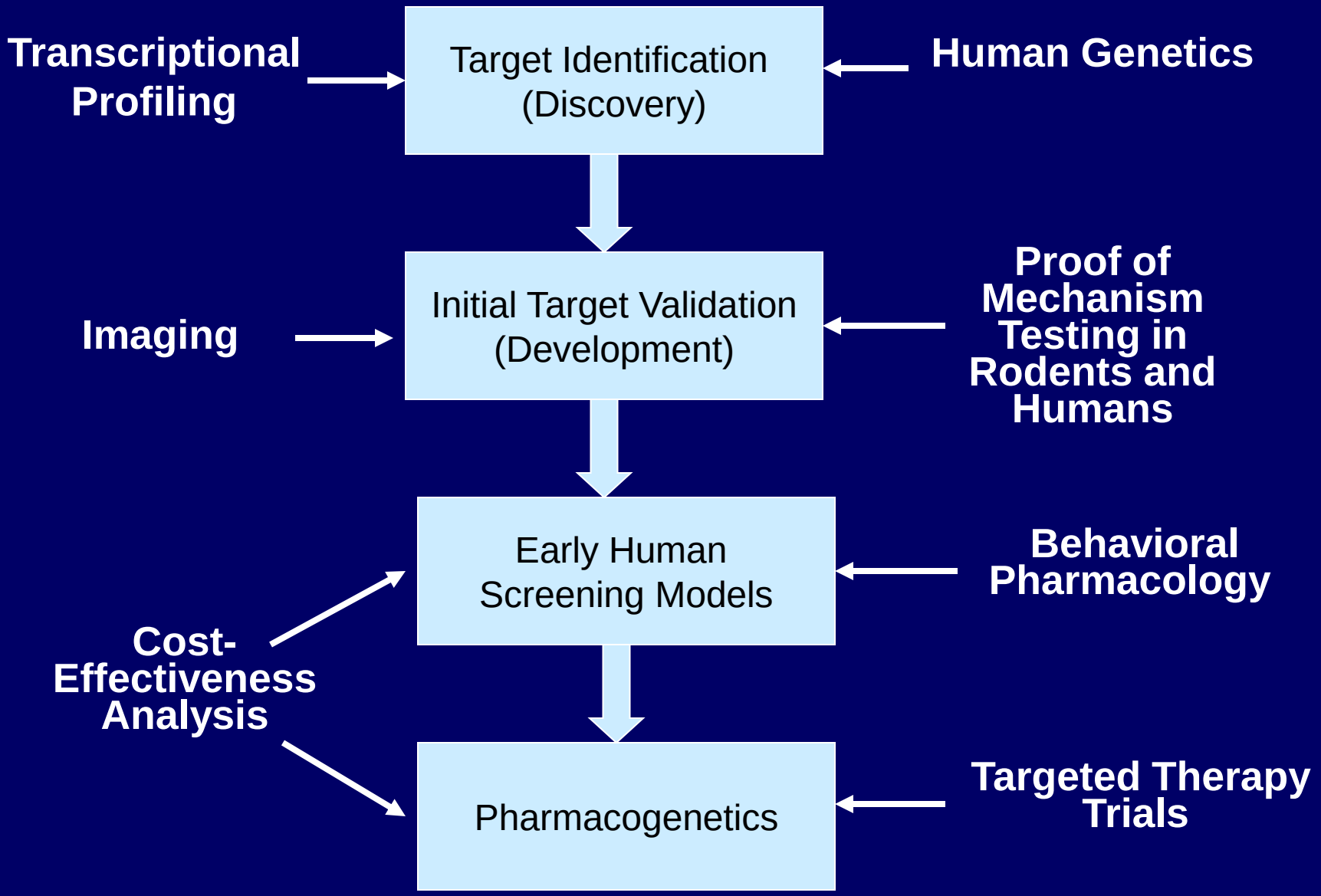
Laboratory to the clinic and back

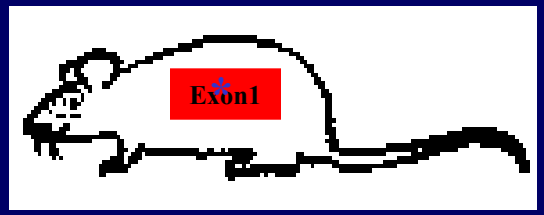
- **Opioid genetic mechanisms in nicotine reward and relapse**
- **COMT as a novel therapeutic target for nicotine dependence**

Laboratory to the clinic to the community

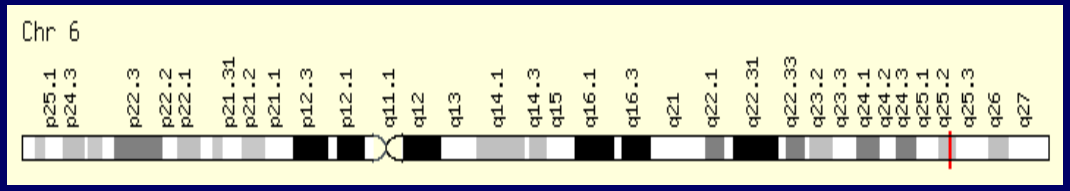
- **Nicotine metabolite ratio as a biomarker of relapse risk and therapeutic response**

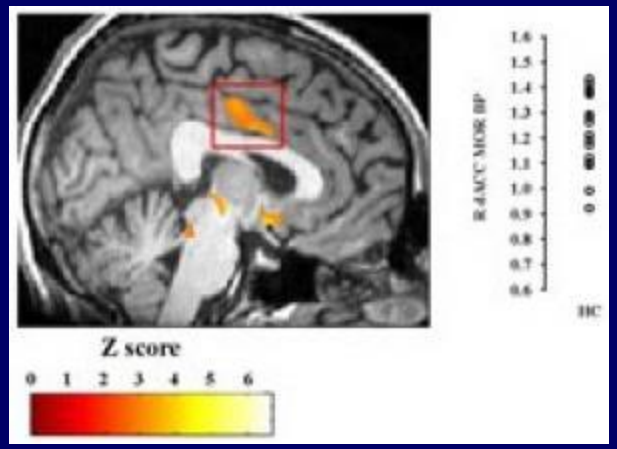
Drug Development for Tobacco Dependence



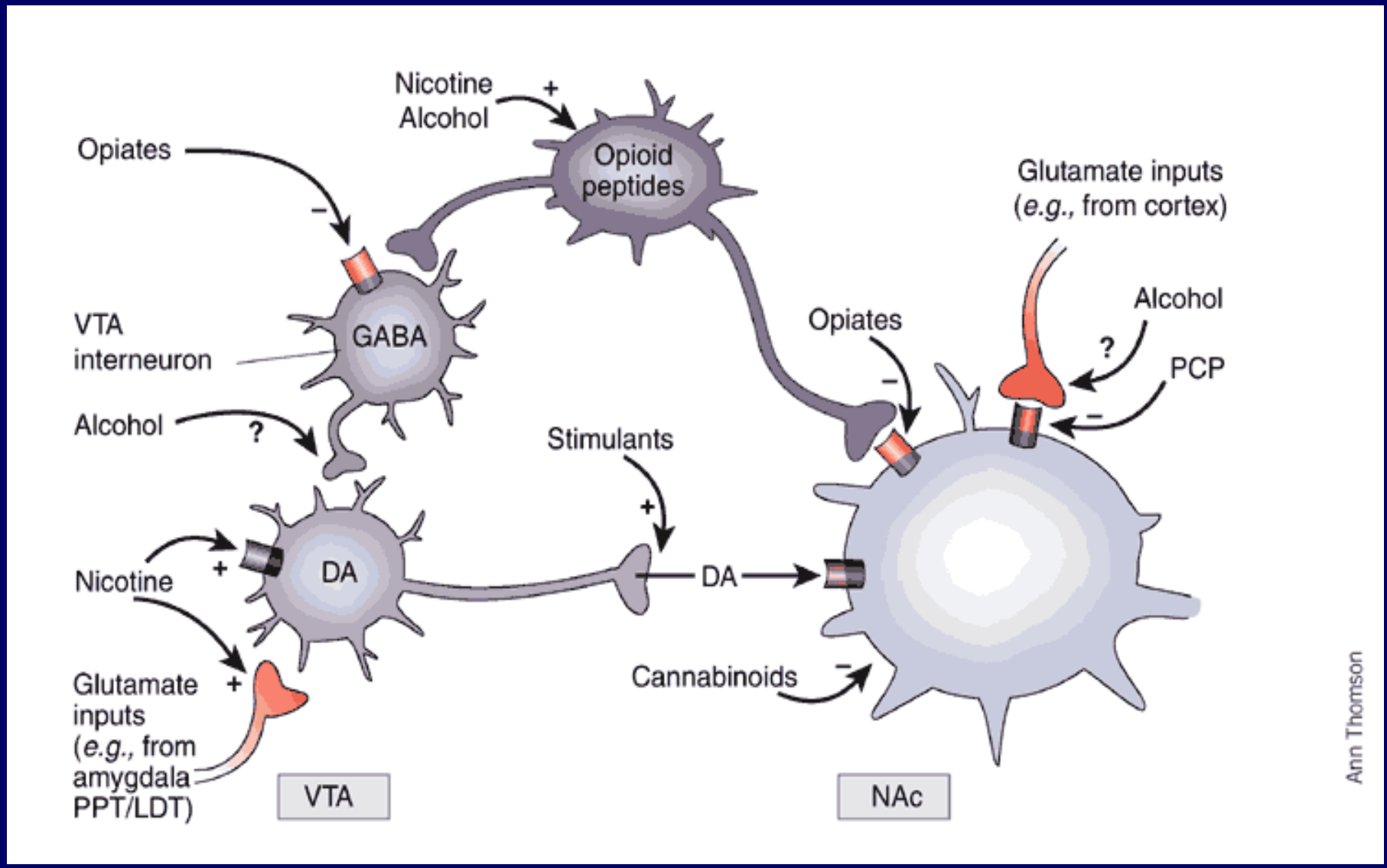


Opioid genetic mechanisms in nicotine reward and relapse





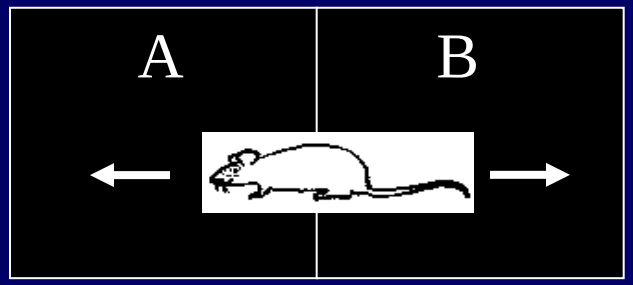
Opioid Mechanisms in Nicotine Reward



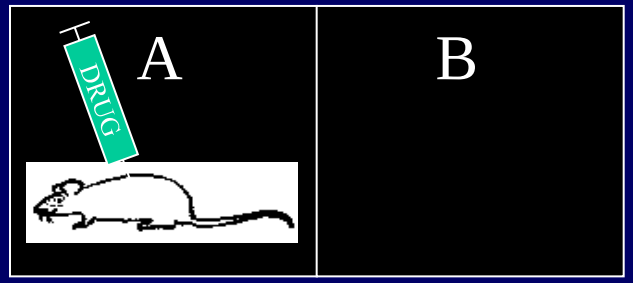
Eric Nestler

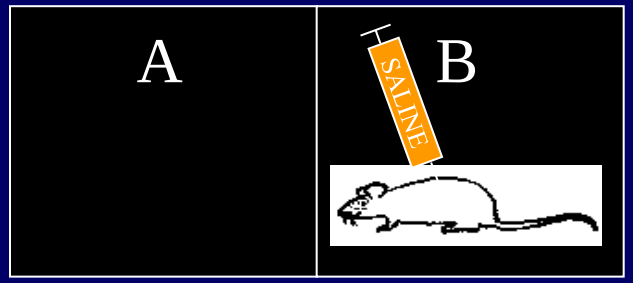
Mouse Model of Nicotine Reward

Day 1

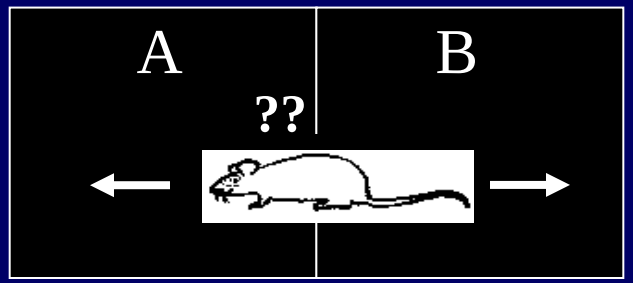


Pairing Days 2-8





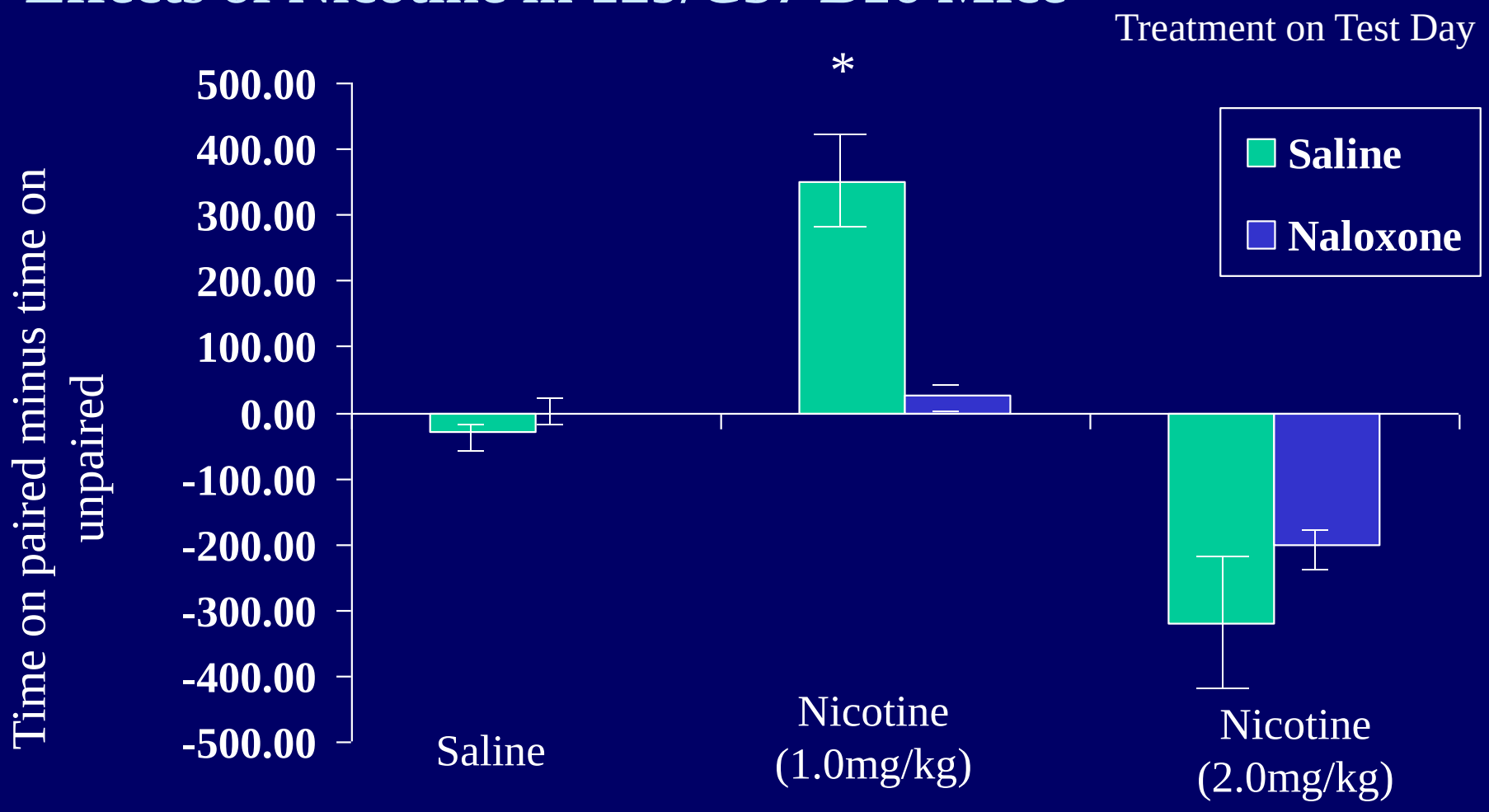
Test Day



Test Day

Work by Julie Blendy

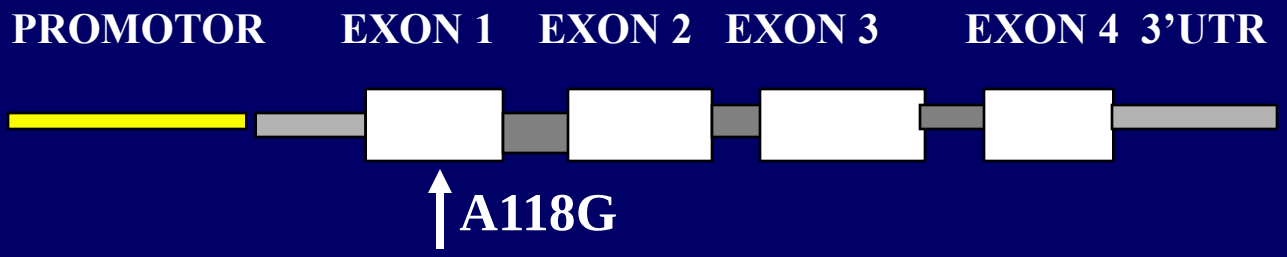
Naloxone on Test Day Blocks Conditioned Rewarding Effects of Nicotine in 129/C57 B16 Mice



*p<.05

Walters et al, Neuron, 2005

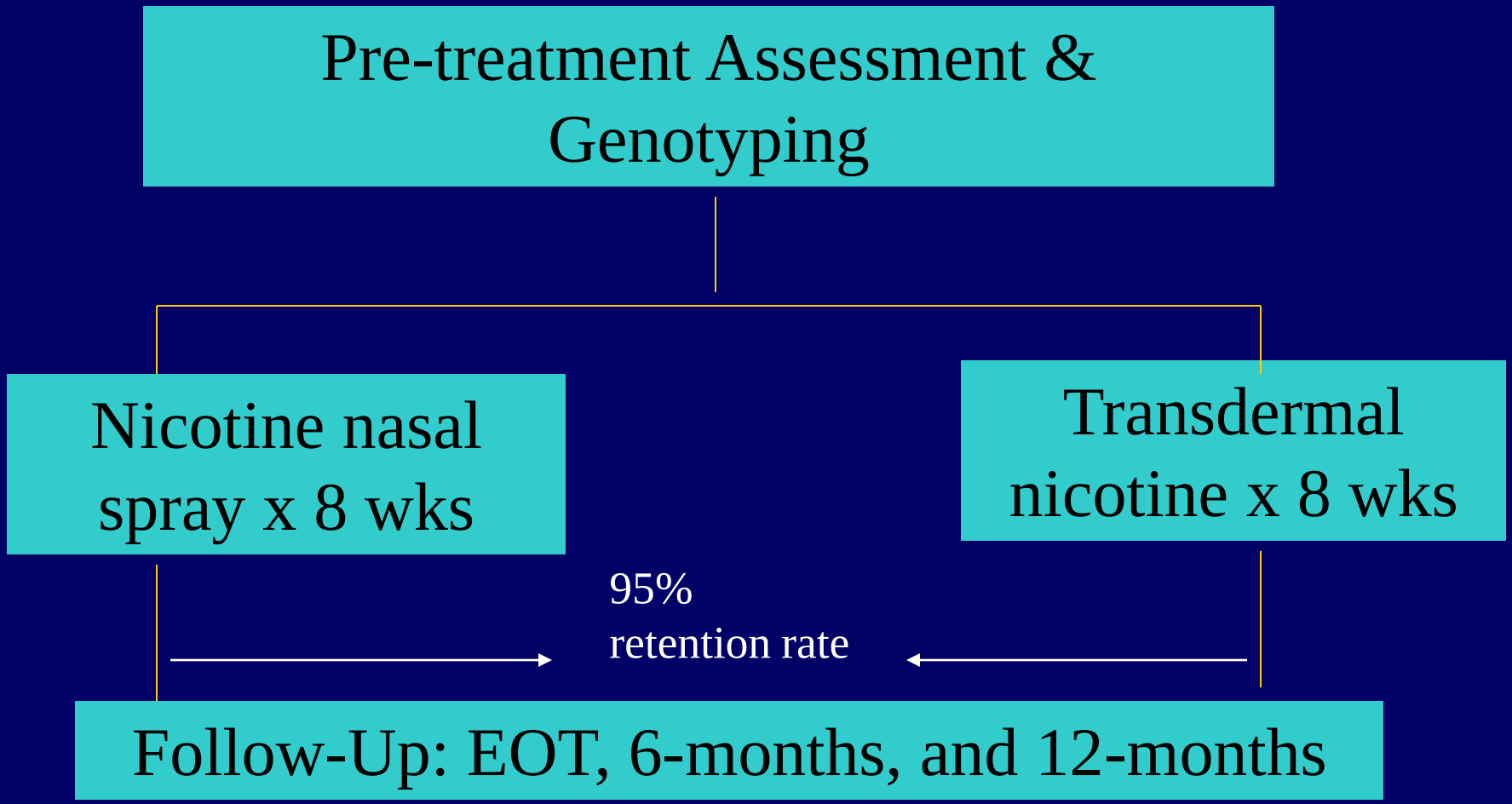
The Human OPRM1 Gene



- **The human OPRM1 gene includes a common Exon 1 Asn40Asp (A118G) mis-sense single nucleotide polymorphism (SNP).**
- **G allele associated with reduced mRNA expression and protein levels (Zhang et al)**
- **Present in 25-30% of persons of European ancestry**

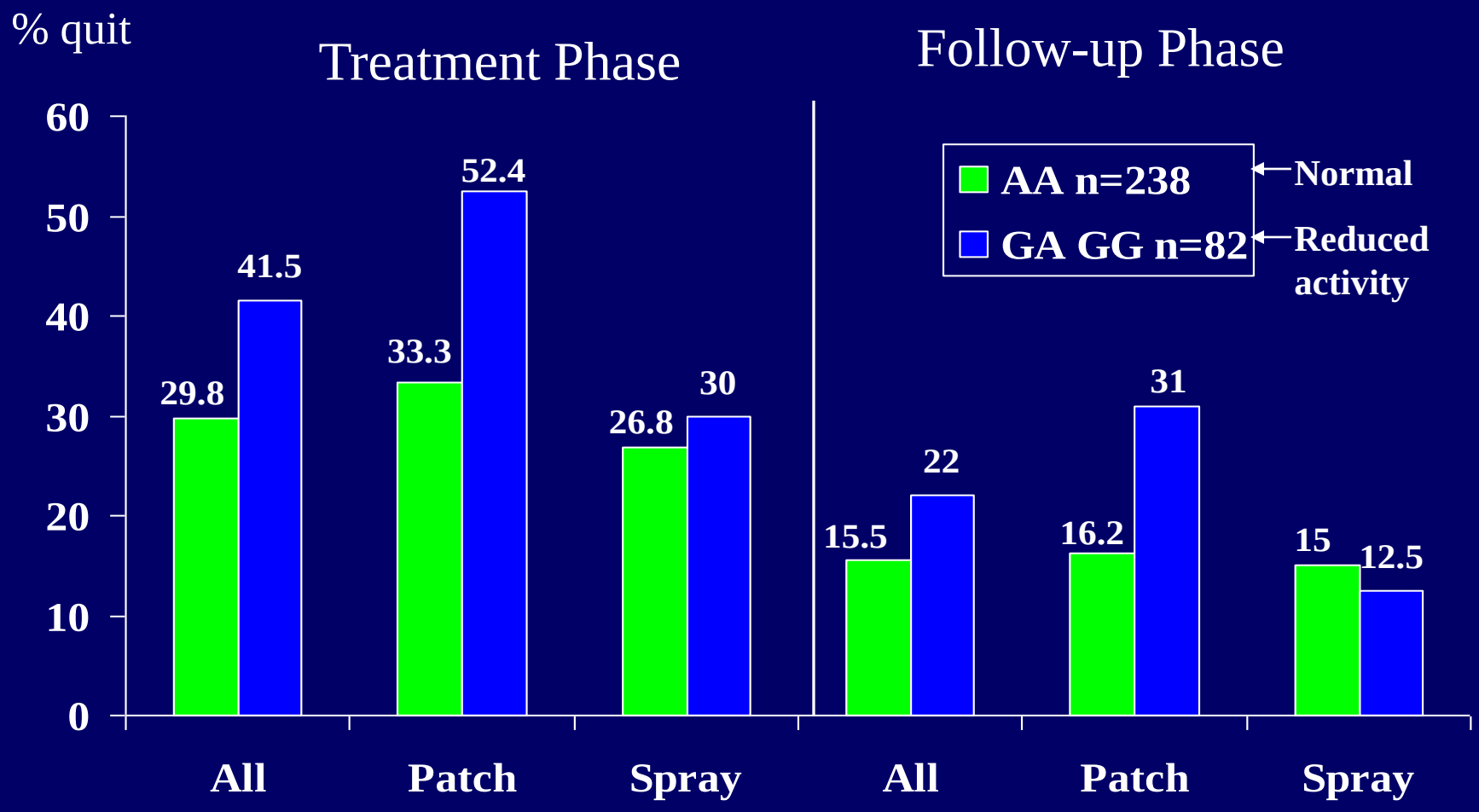
Hypothesis: Smokers with G allele will have a lower liability to relapse in smoking cessation treatment

Open Label Pharmacogenetic Trial of NRT (n=600*)



*European ancestry only (n=420)

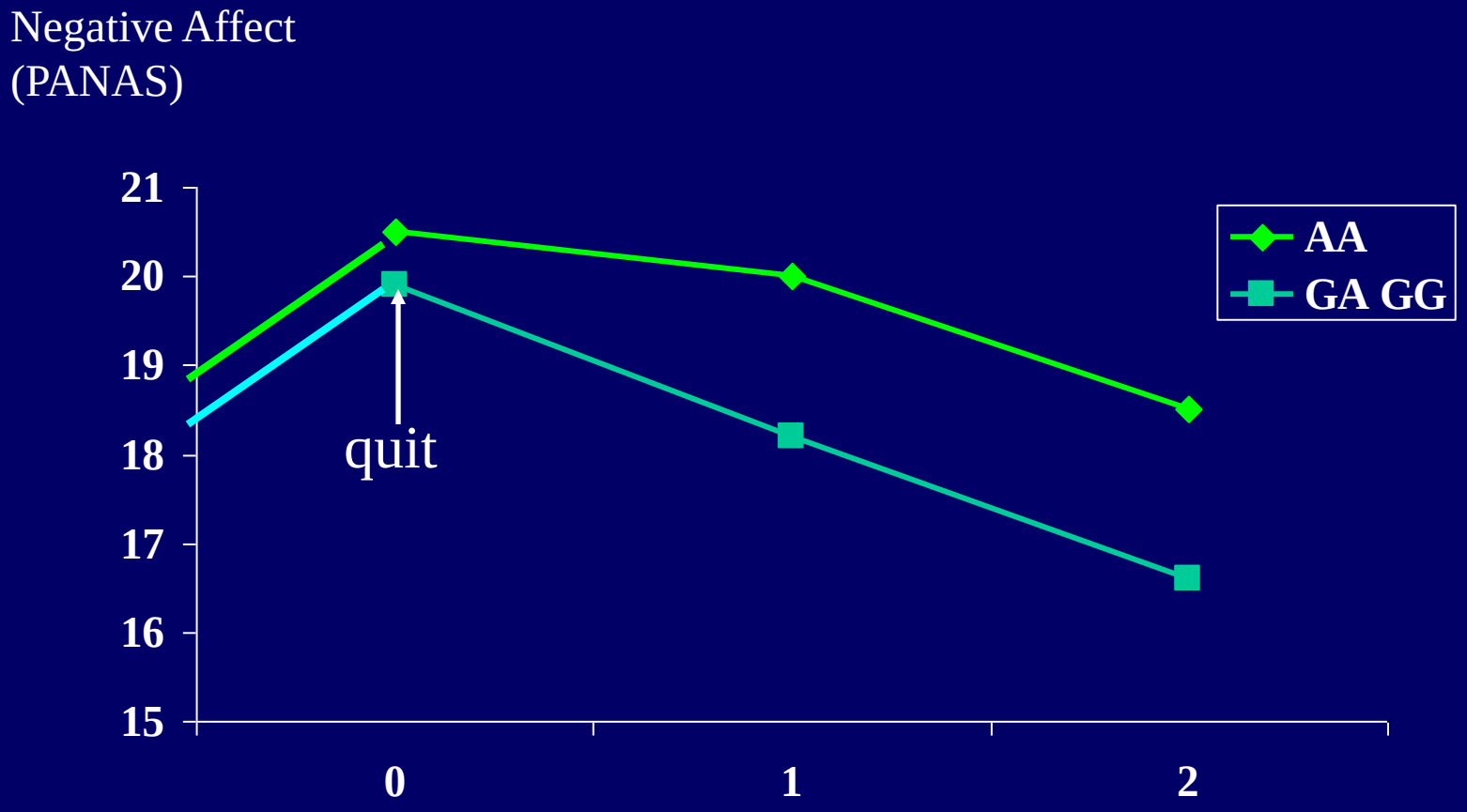
OPRM1 Asn40Asp Variant is Associated with Response to Nicotine Replacement Therapy



OR= 1.9, p=.01

Lerman et al., *Pharmacogenomics J*, 2004

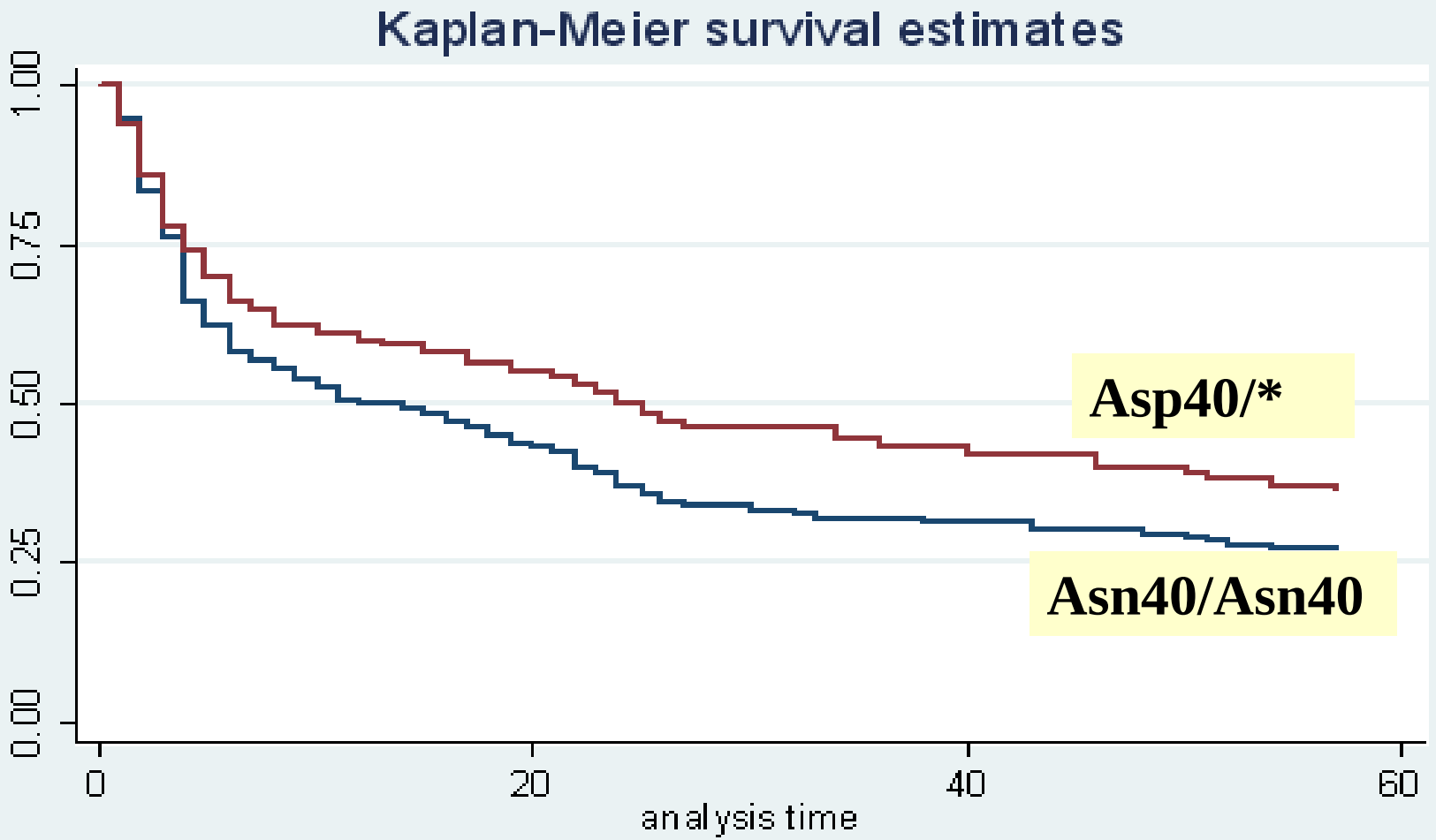
Smokers with Asp40 Variant Report Greater Reductions in Negative Affect During NRT



p=<.001 in linear regression model

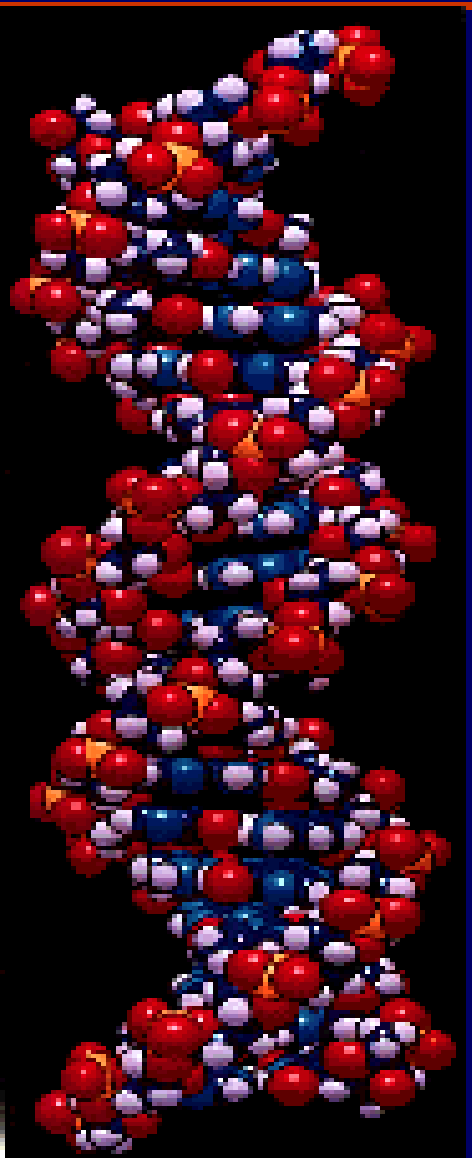
Lerman et al., Pharmacogenomics J, 2004

Independent Validation in Nicotine Patch Trial (21mg x 8 weeks; n=351)



HR=0.74 [.55-.98] p=.039

What is the Mechanism of Enhanced Therapeutic Response in Smokers with the OPRM1 Asp40 (G) allele?

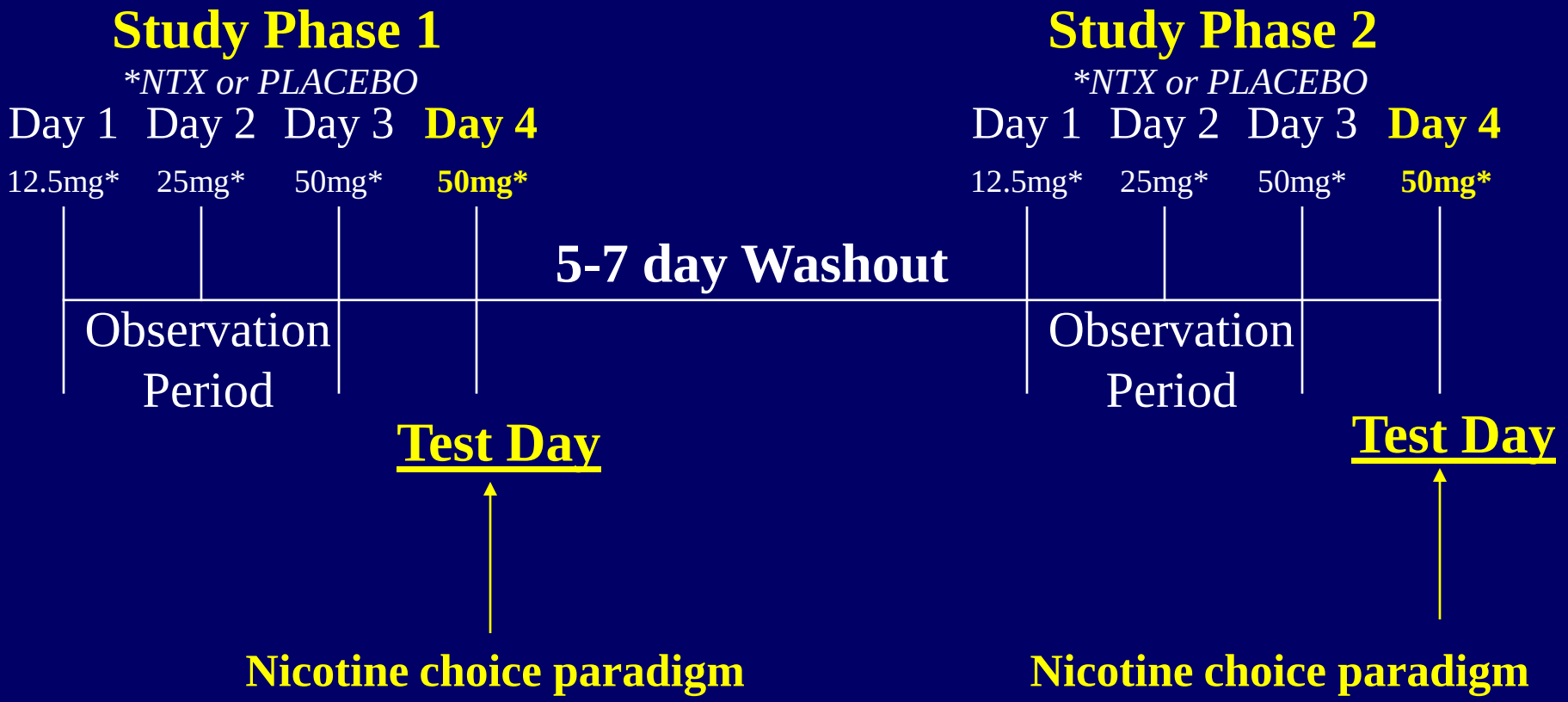


1. Do carriers of the OPRM1 G allele (loss of function) exhibit reduced nicotine reinforcement?

2. Does naltrexone reduce nicotine reinforcement—particularly in smokers with OPRM1 G allele?

3. Are females more sensitive to opioid system effects on nicotine reward?

Within Subject Design



N=30 Asn40/Asn40

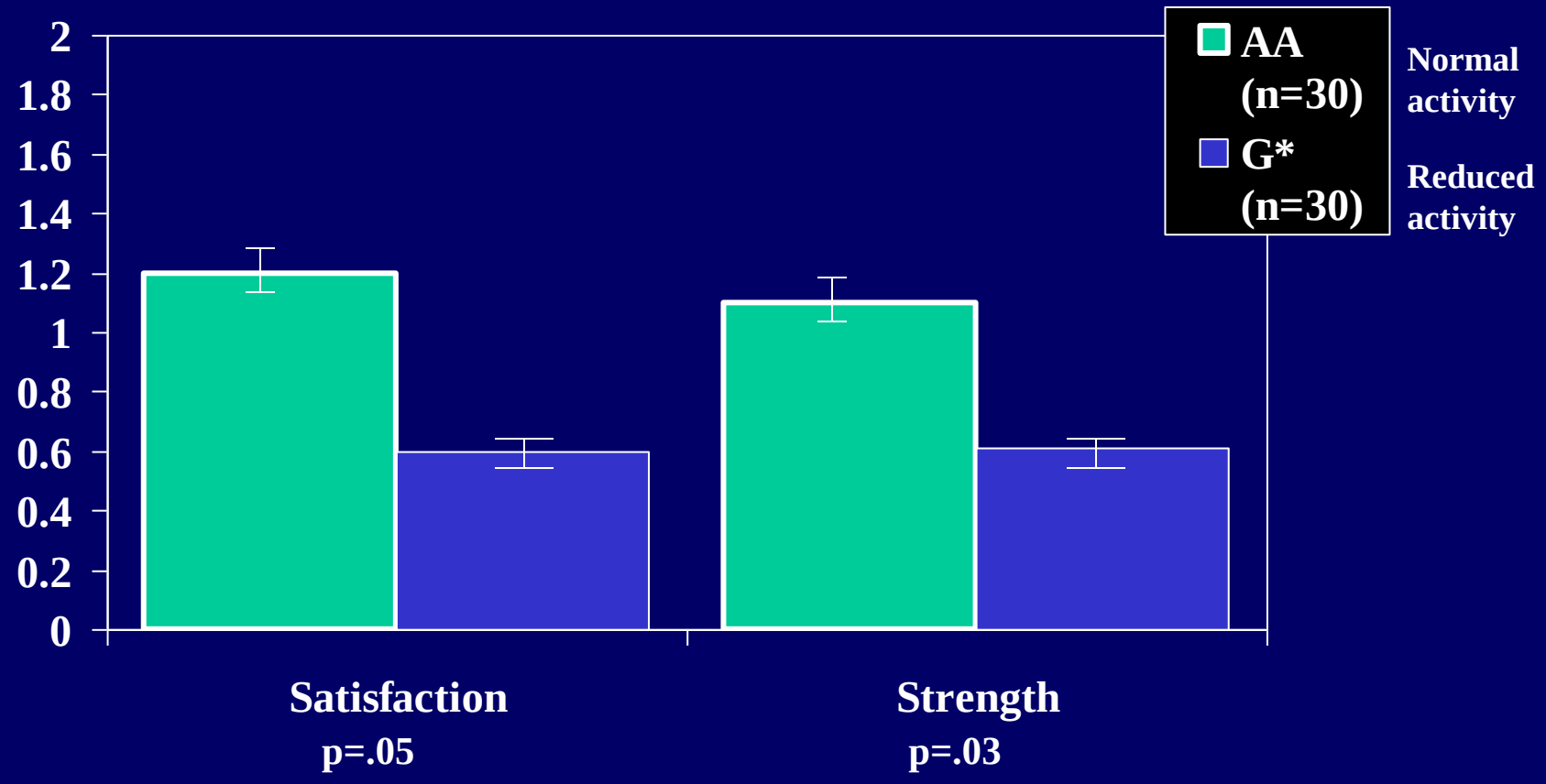
N=30 Asp40/*

Human Model of Nicotine Reward

- 2 hour deprivation period (to standardize exposure without inducing serious withdrawal symptoms)
- Initial (blinded) exposure to 4 puffs of Quest cigarettes: denic. (.05 mg) vs nic. (.6 mg)
- Assess subjective effects
- Self-administer 4 puffs from either cigarette at 30 minute intervals in 6 trials over a 3-hour period
- Outcome measure is number of nicotine puffs chosen out of 24 = relative reinforcing value of nicotine

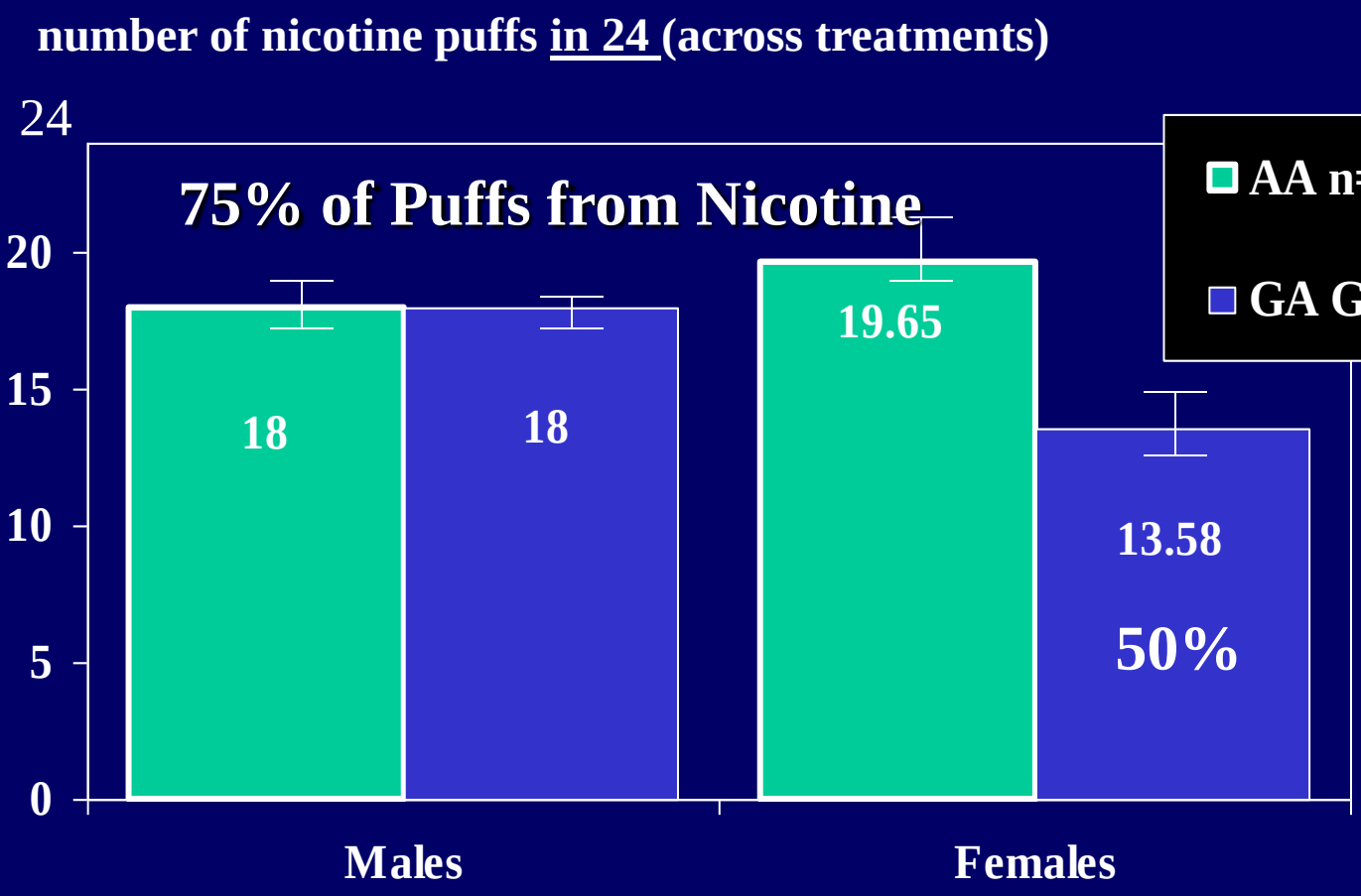
Reduced Activity OPRM1 Allele is Associated with Reduced Nicotine Reward

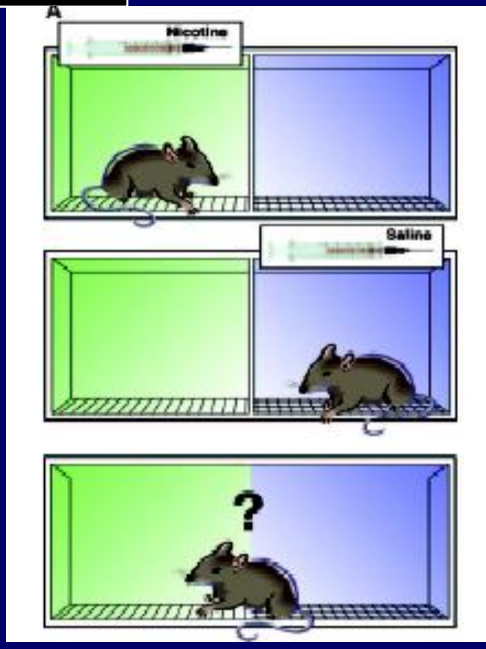
Subjective Ratings (nicotine minus denicotinized cigarette)



Ray et al. *Psychopharmacology*, 2006

OPRM1 Genotype Predicts Nicotine Reinforcement in Females but not in Males

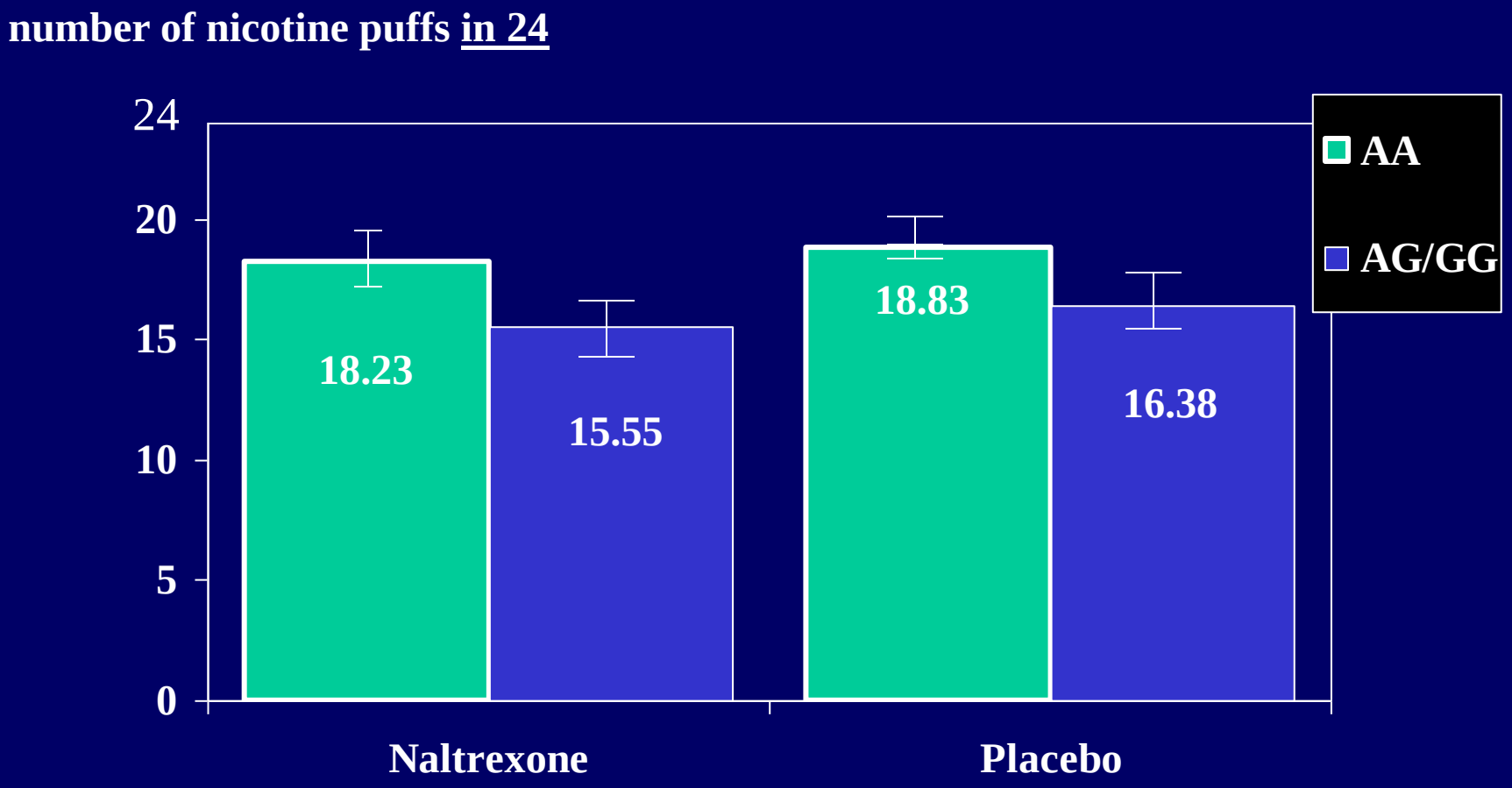




P (genotype by gender interaction)=.036

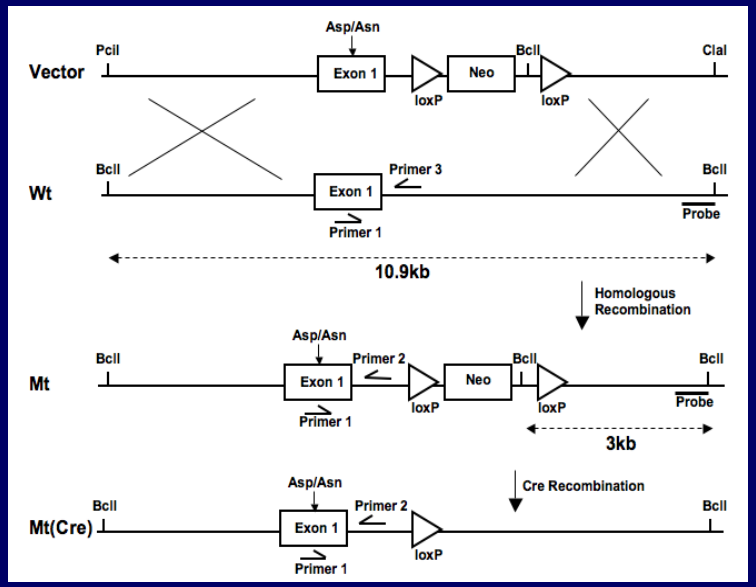
Ray et al. *Psychopharmacology*, 2006

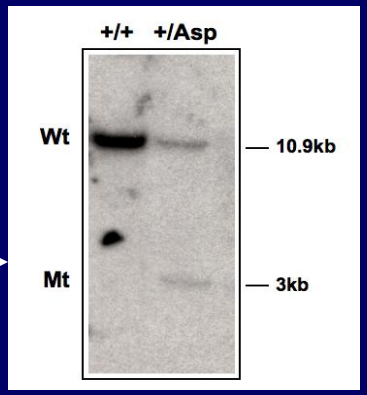
Naltrexone Does Not Reduce Nicotine Reward or Interact with OPRM1 Genotype

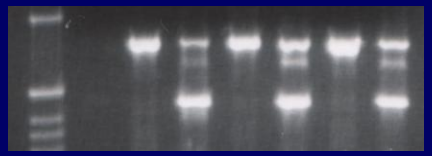


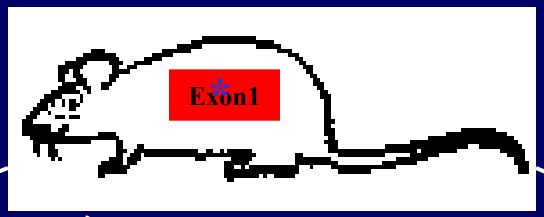
Ray et al. *Psychopharmacology*, 2006

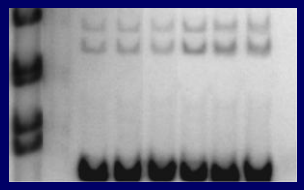
Using Targeted Genetic Mutations in the Mouse to Understand Human OPRM1 SNP (Blendy)



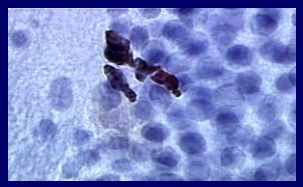








Molecular



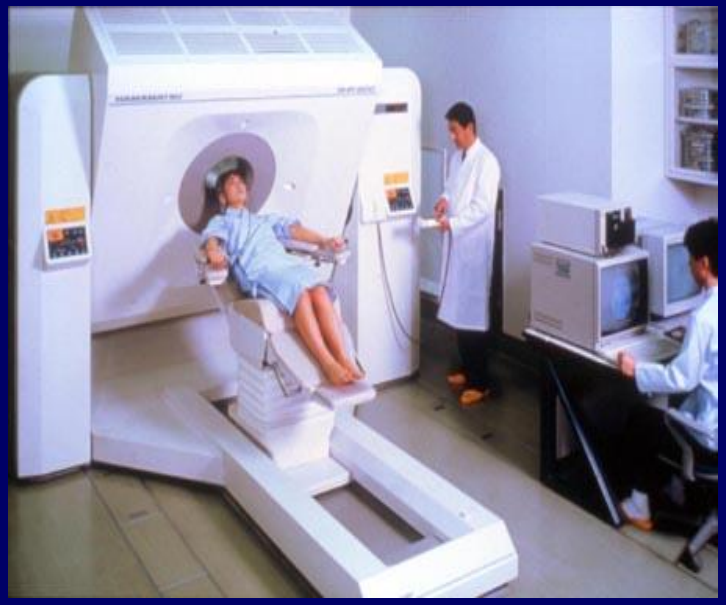
Cellular

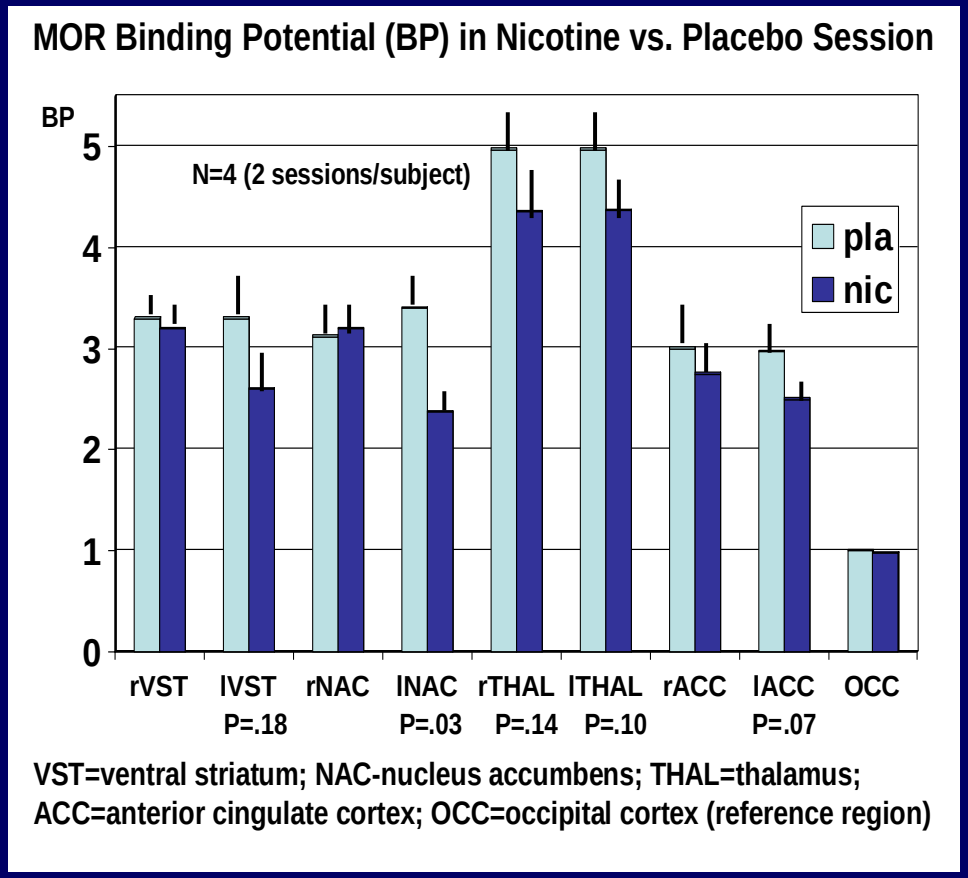
Imaging

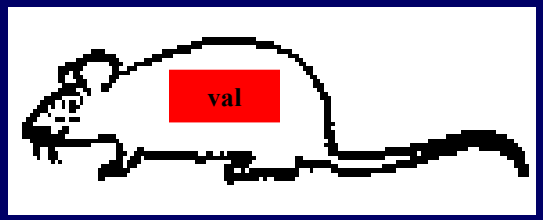
Behavioral

Examine MOR Binding as Mechanism for Observed *OPRM1* Association with Nicotine Reward

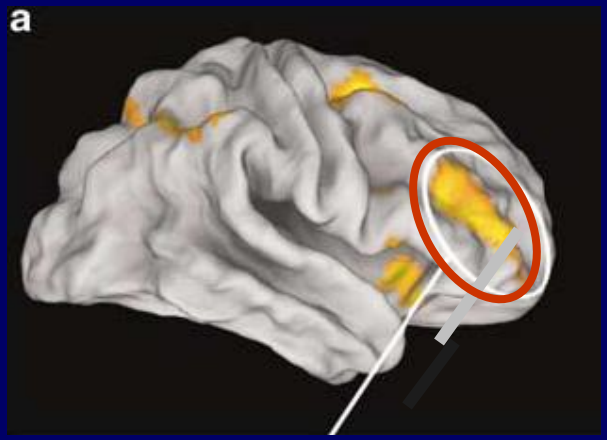
2x2 Factorial Design: (1) nicotine vs. denic cig (within subject); (2) *OPRM1* genotype (stratified by sex)



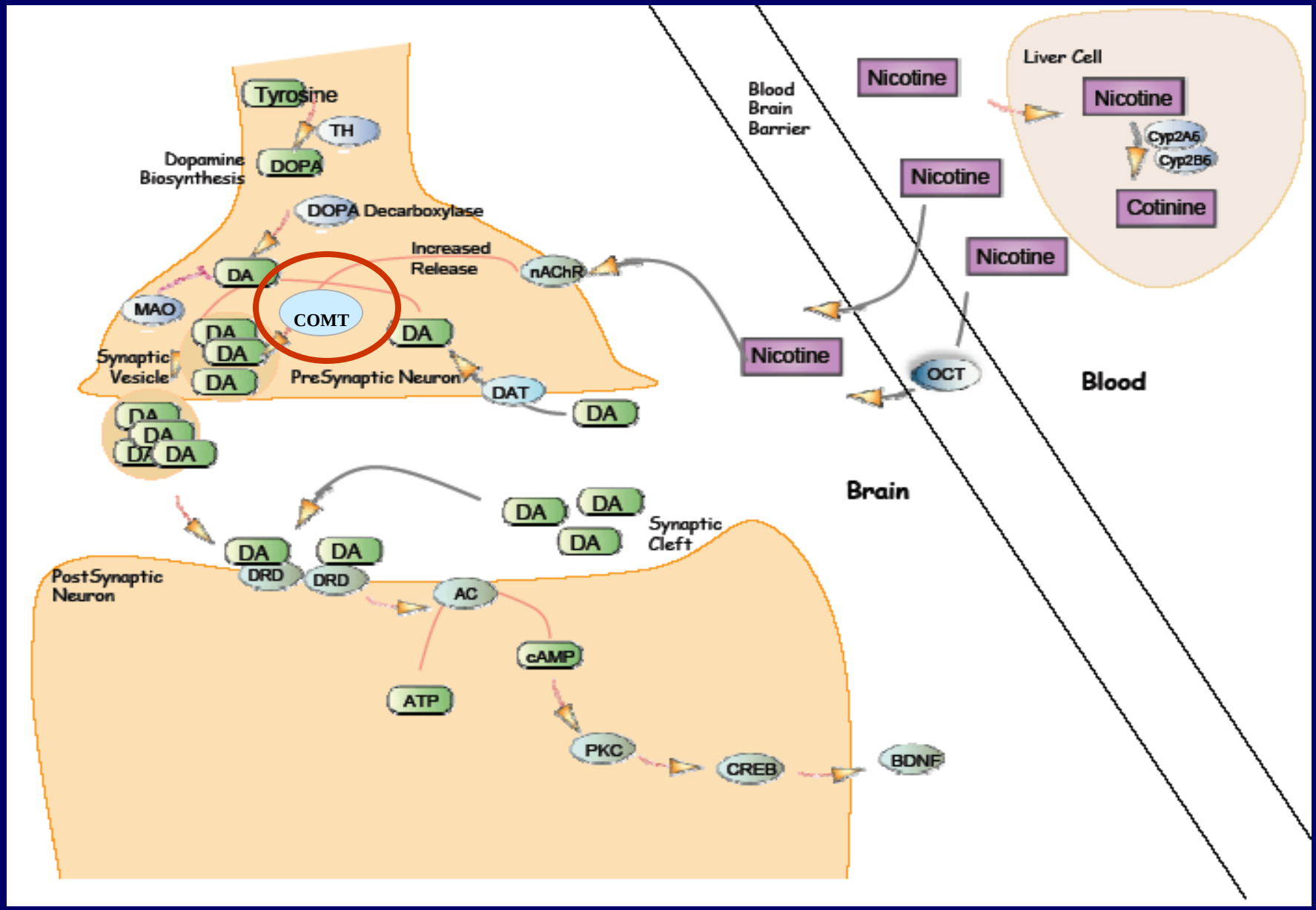




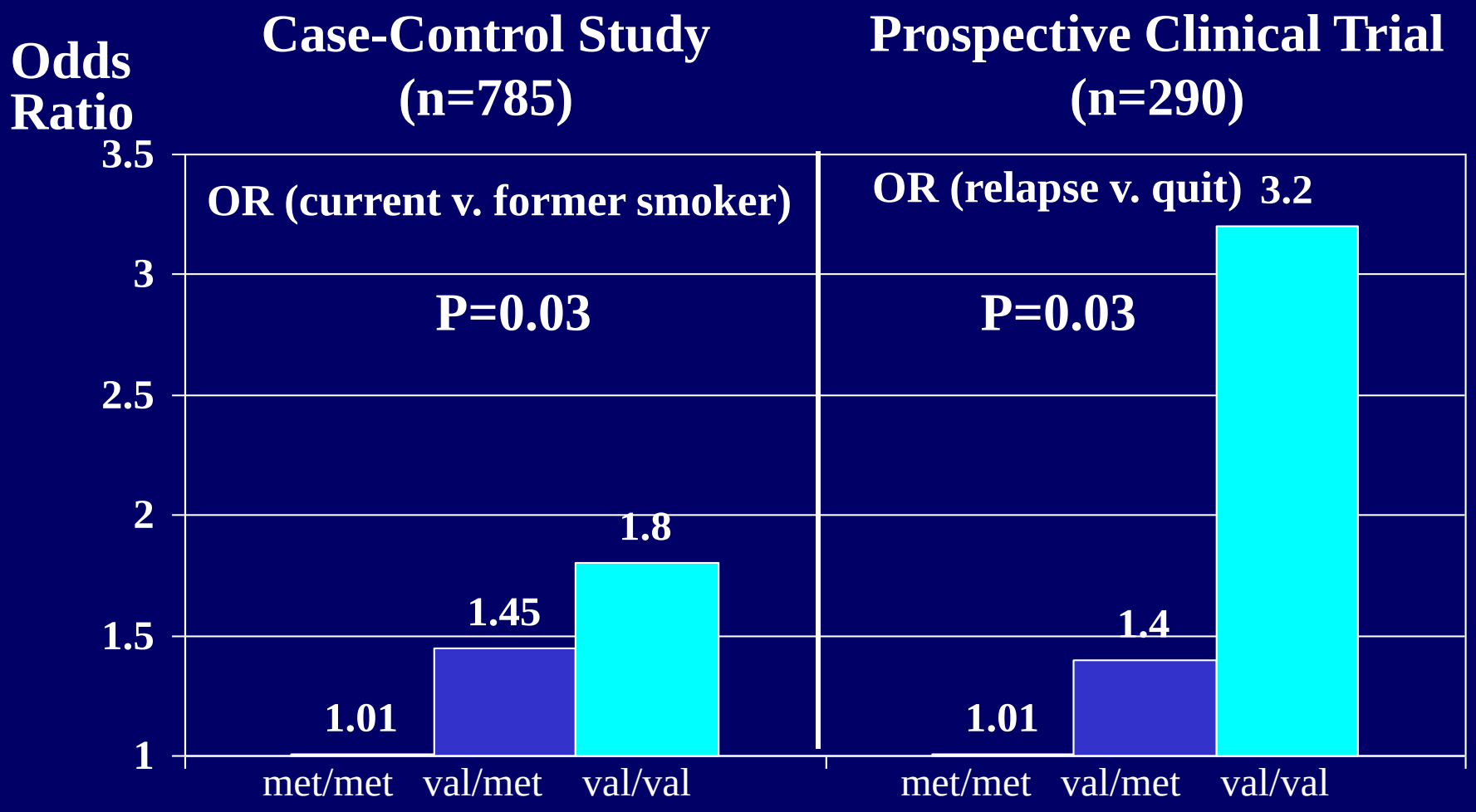
COMT as a novel therapeutic target for nicotine dependence



Nicotine-related Brain Reward Pathway



COMT val^{158}met Polymorphism Predicts Smoking Relapse in Independent Studies



Colilla et al., Pharmacogenetics and Genomics, 2005

COMT is a Potential Therapeutic Target

- **Methylation enzyme involved in the inactivation of dopamine**
- **Common functional val^{158}met variant (1 in 4 are val/val)**
- **Val allele is associated with an increase in COMT activity and corresponding decrease in dopamine in frontal cortex**
- **Carriers of the val allele exhibit deficits in cognitive function**

Hypothesis: Nicotine deprivation will produce cognitive deficits in smokers with val/val genotypes, an effect that may prompt smoking relapse to reverse deficits.

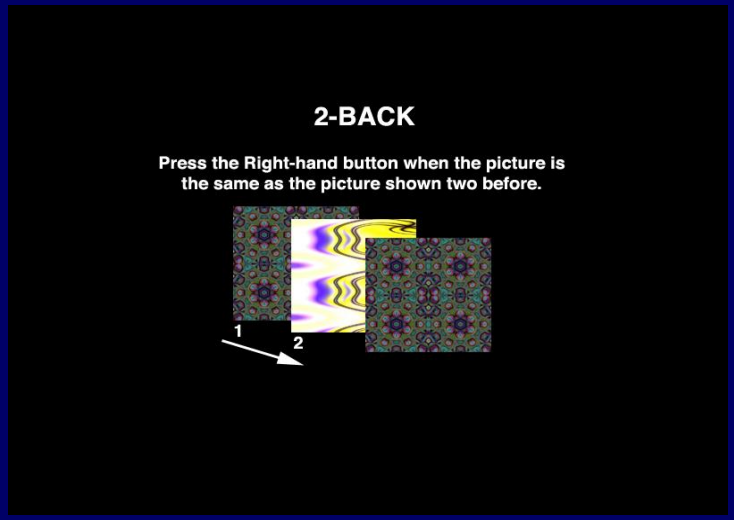
Imaging-Based Target Validation

Prospective genotyping

met/met: n=11

val/met: n=12

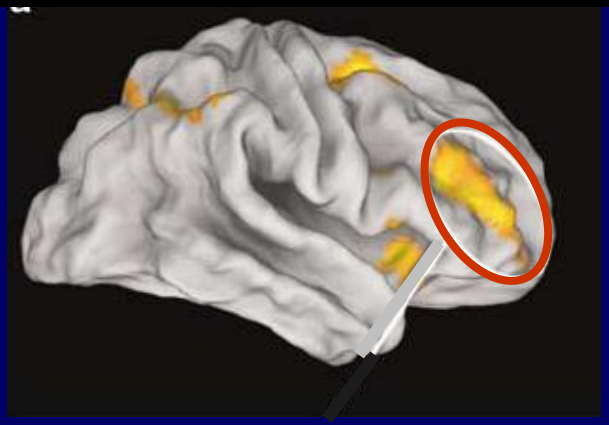
val/val: n=10



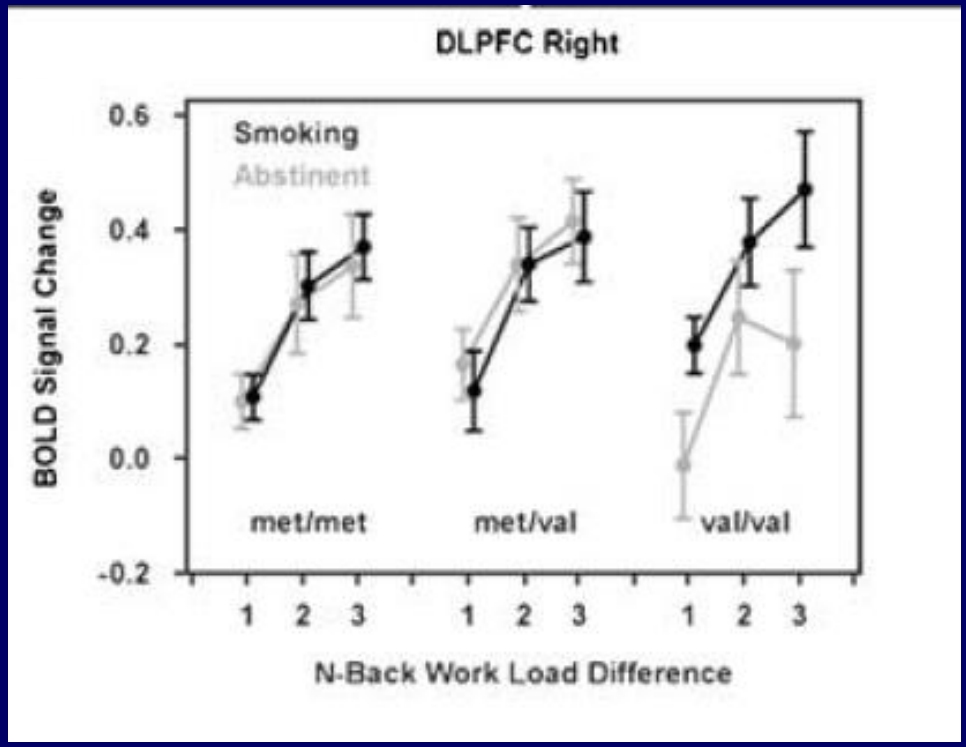
Smokers scanned on two occasions (counterbalanced): (1) smoking as usual vs. (2) >14 hrs. abstinent (confirmed with CO)

Brain Signature of Abstinence Effect on Cognitive Function in *COMT* val/val group

Dorsolateral prefrontal cortex



Genotype x abstinence effect (p=0.0005)



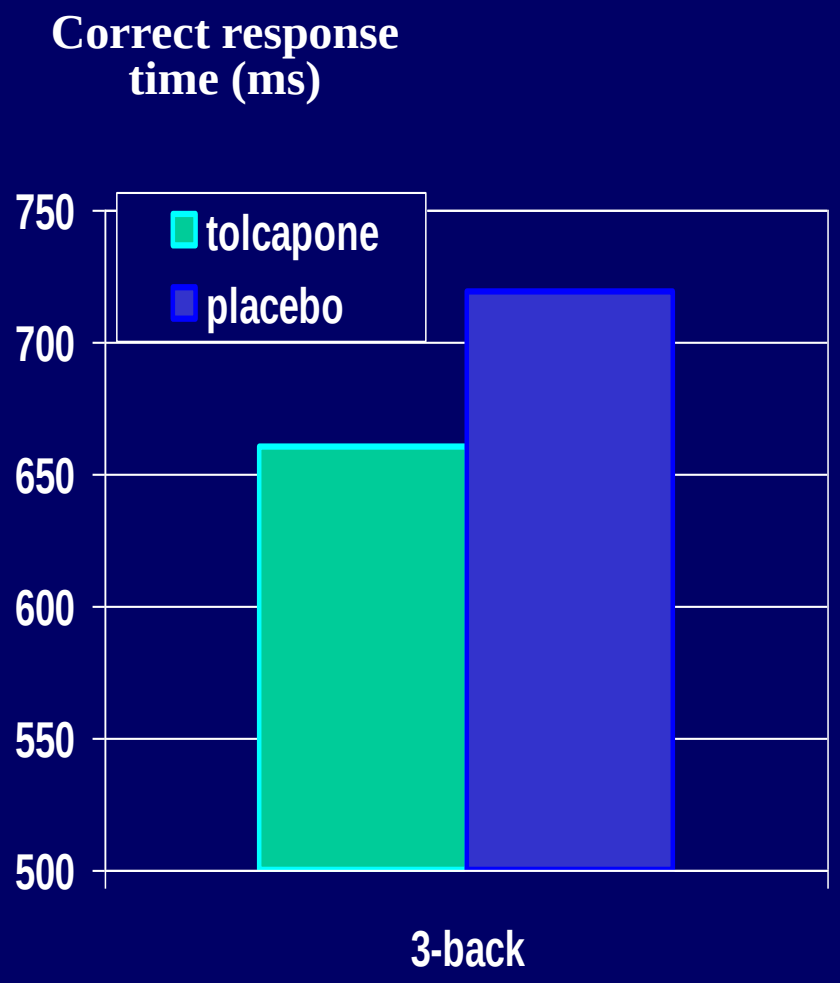
- **Brain activation in smokers with val/val genotypes is reduced in abstinence during performance of difficult cognitive task**
- **Reduced activation is liked with slower performance in val/val group at higher task difficulty (p=0.03)**

Loughead* et al, *Molecular Psychiatry, 2009

Tolcapone as a "Tool Compound" for Proof of Mechanism Study

- Inhibitor of COMT in central nervous system
- FDA-approved for the treatment of Parkinson's Disease
- Cognitive enhancing effects

Phase I Safety Study of Tolcapone in Smokers



COMT val/val group

- Short-term (7-day) treatment with tolcapone 200mg t.i.d. is safe and well tolerated by smokers
- Tolcapone (v. placebo) decreased speed of performance in val/val group at high task difficulty
- No effect of tolcapone in met/met group

Phase II Study of Tolcapone in Smokers

Reversal of abstinence-induced cognitive deficits by tolcapone will provide "proof of mechanism"

PLACEBO/TOLCAPONE®

Day 14 – 27
WASH-OUT

TOLCAPONE®/PLACEBO

Medication run up

Day 1 - 9

Day 10 - 13

Medication run up

Day 28 - 37

Day 38 - 41

3.5 days mandatory abstinence (CO confirmed)

3.5 days mandatory abstinence

fMRI Scan

fMRI Scan

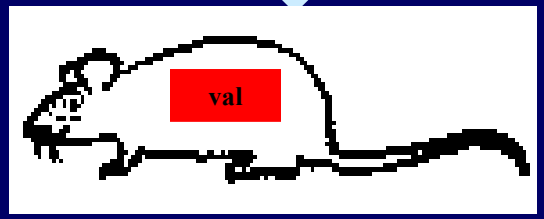
Summary: COMT

COMT val allele is risk factor for nicotine dependence

Cognitive deficits are a core symptom of dependence and predict relapse

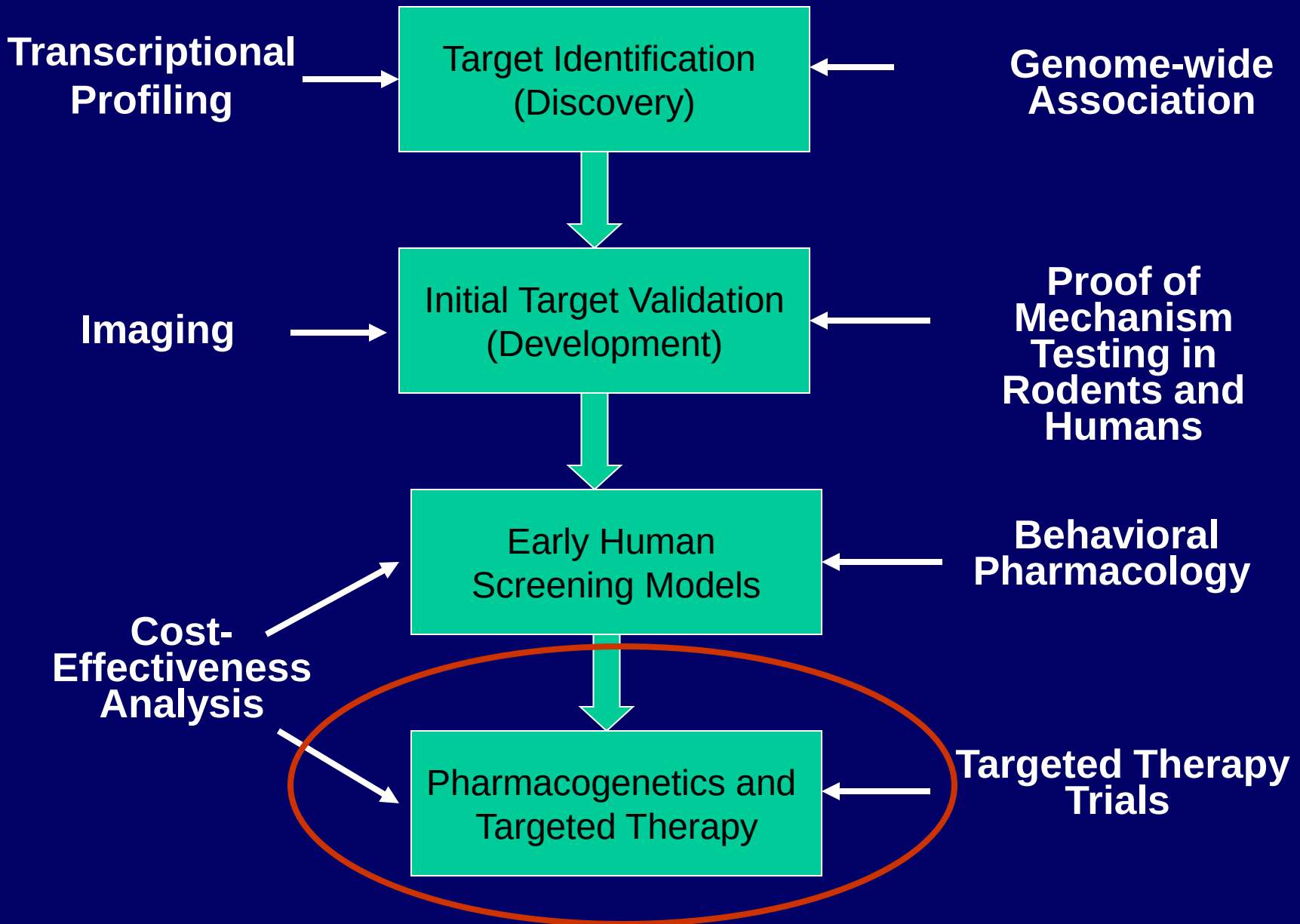
Smokers with val/val genotype have altered brain function and cognitive deficits in abstinence

Proof of mechanism experiments (tolcapone)

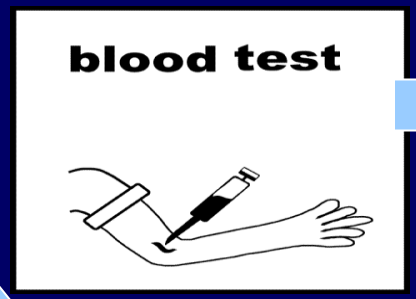


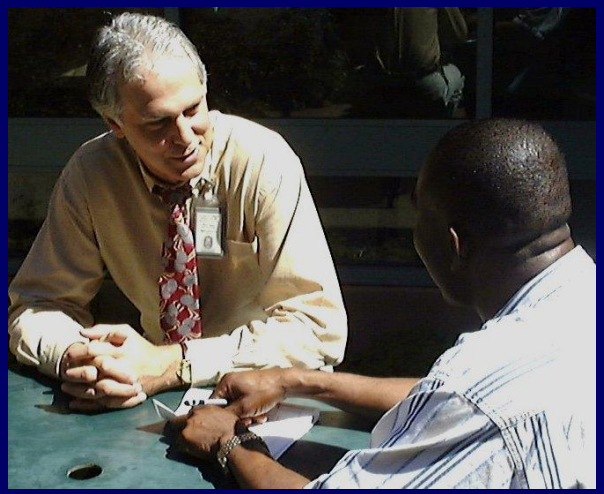
Convergent genetic and pharmacologic evidence would support COMT as a therapeutic target for tobacco dependence

Drug Development for Tobacco Dependence

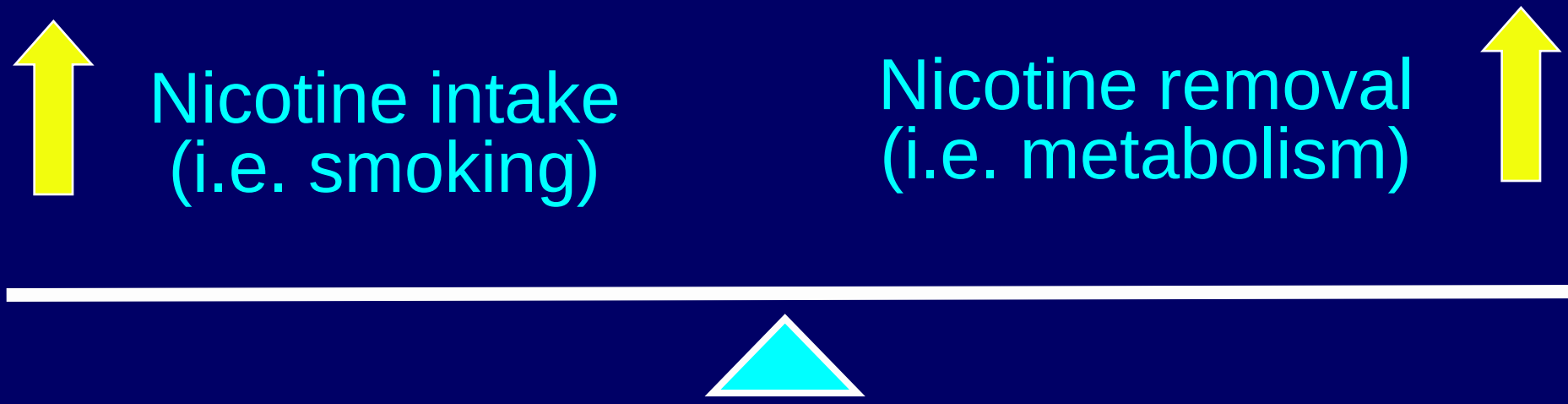


Targeted Therapy for Tobacco Dependence

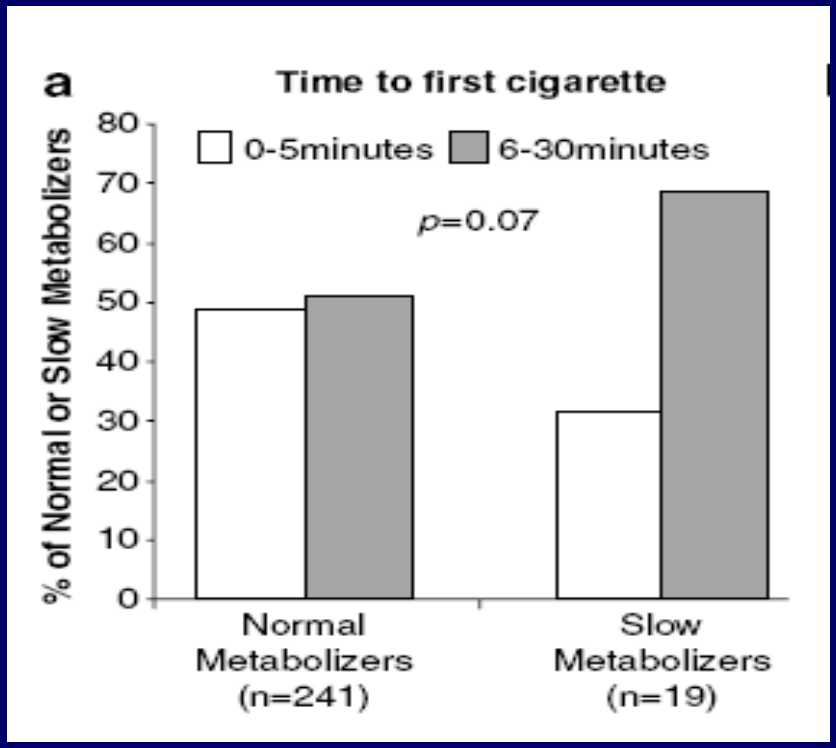




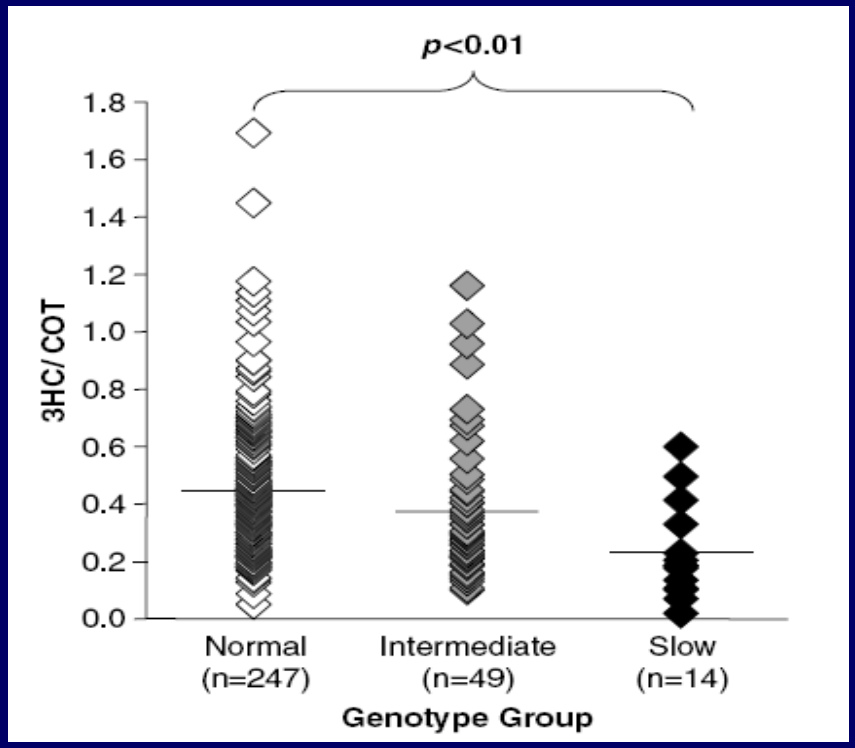
Nicotine Dependent Smokers Alter Smoking to Maintain Nicotine Levels:



CYP2A6 Gene Mutations Alter Dependence Phenotypes



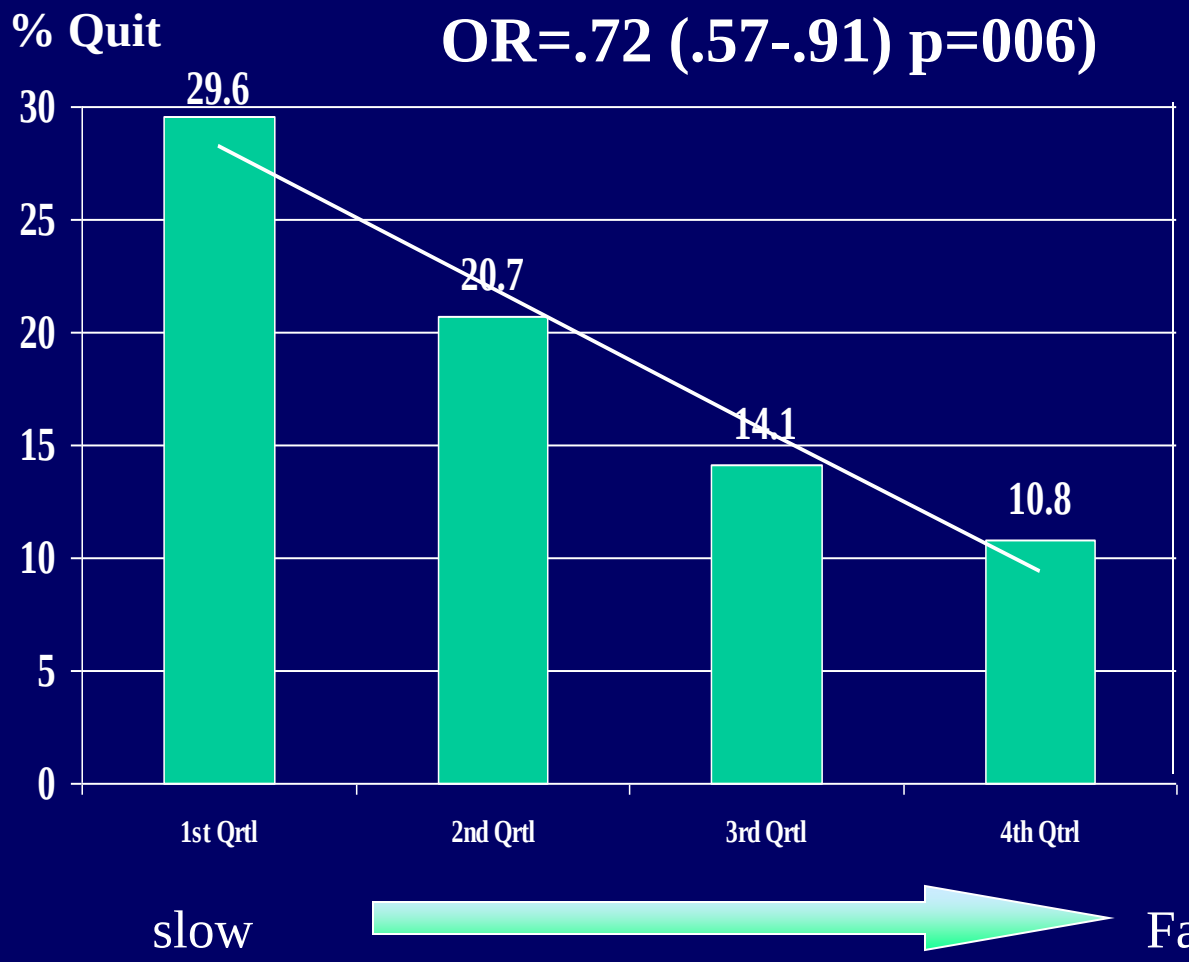
Genetically slow metabolizers smoke fewer cigs/day and are less dependent



CYP2A6 genotype alters enzyme activity and metabolite ratio

Malaiyandi et al., Molecular Psychiatry, 2006

Nicotine Metabolite Ratio Predicts Therapeutic Response to Nicotine Patch (n=480)

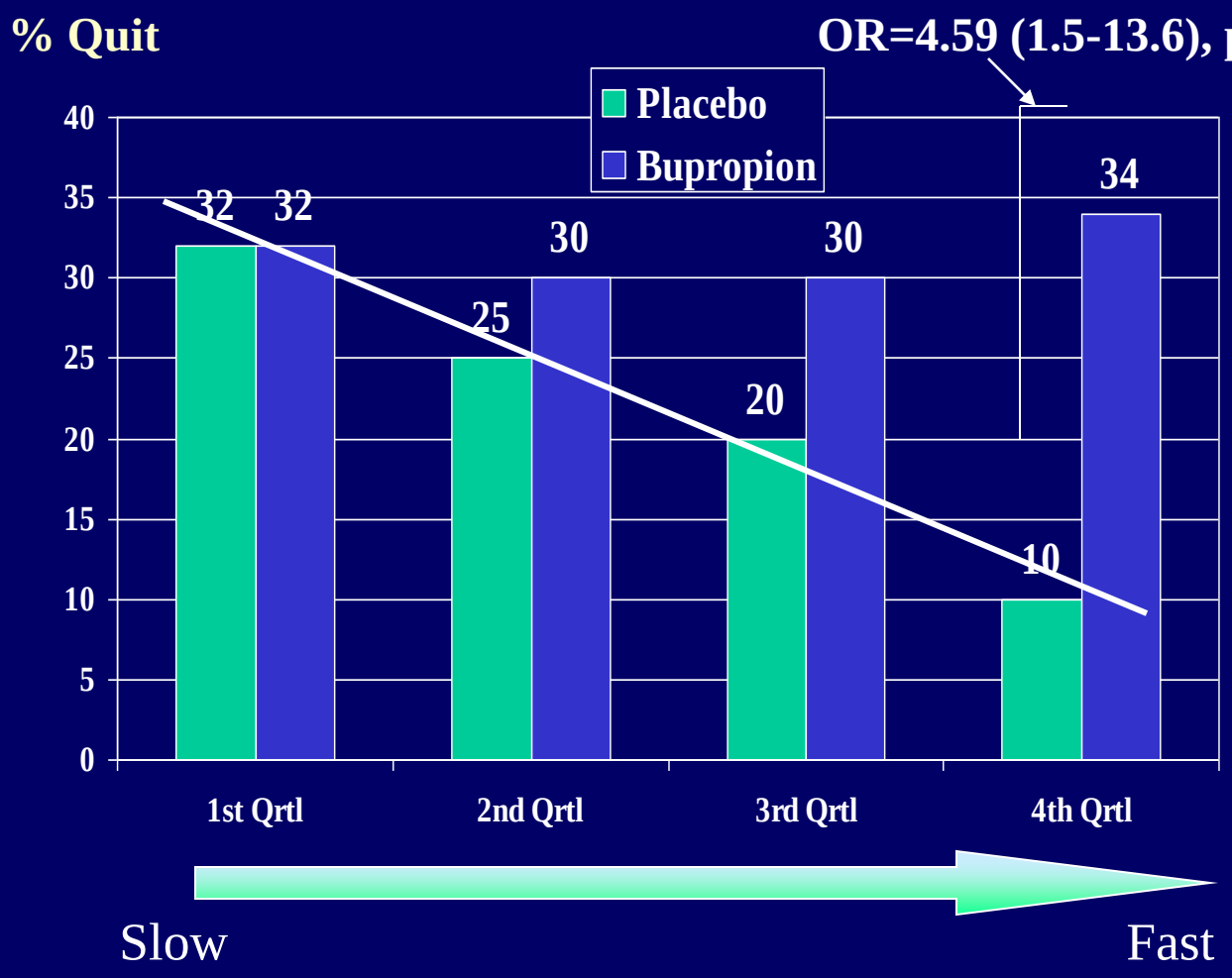


- 30% reduction in quit rates with increasing metabolic rate
- Reduction in plasma nicotine levels from patch
- Findings replicated

Is this specific to nicotine replacement therapy?

Lerman et al., Clinical Pharmacology & Therapeutics, 2006

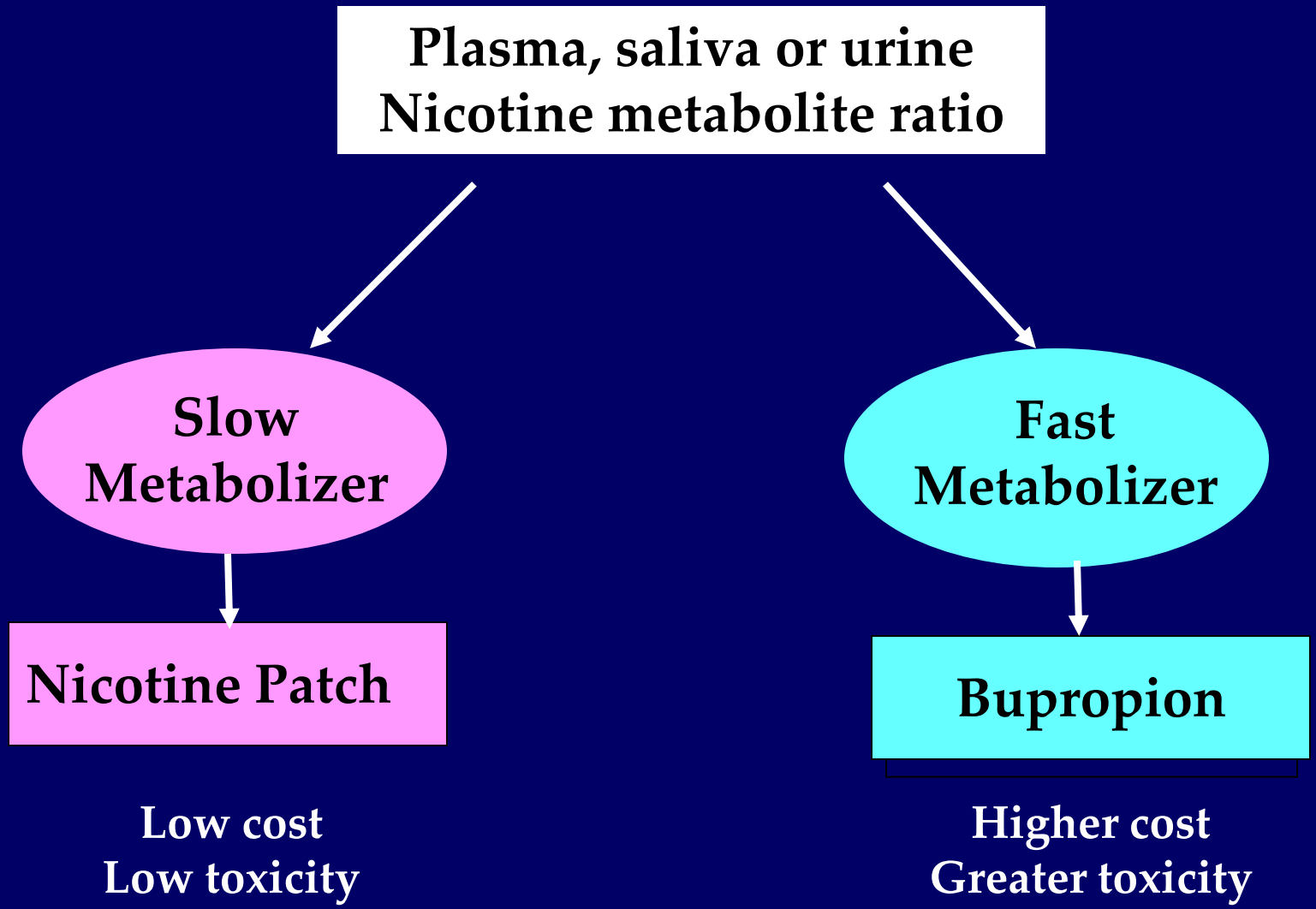
Nicotine Metabolite Ratio Predicts Therapeutic Response to Bupropion (n=414)



- **Decreased quit rates also observed with placebo**
- **Increased liability to relapse in fast metabolizers is reversed by bupropion**
- **Fast metabolizers are candidates for bupropion**

Patterson et al., Clinical Pharmacology & Therapeutics, 2008

Algorithm for Use of Nicotine Metabolite Ratio to Personalize Smoking Cessation Treatment



Summary: Nicotine Metabolism

CYP2A6 gene linked with dependence phenotypes

Nicotine metabolite ratio is a stable measure of CYP2A6 activity

Genetically slow metabolizers respond well to transdermal nicotine; fast metabolizers respond well to bupropion

Targeted therapy based on nicotine metabolite ratio is cost-effective

Evidence from prospective targeted therapy trial will support translation to practice

Test kit in development through industry collaboration

Summary and Implications

- **Genetics and neuroimaging provide powerful new tools for probing the biological basis of nicotine dependence**
- **A better understanding of biology will lead to better treatments and tests to personalize treatment to individual smokers**
- **Reductions in tobacco use will have a significant public health impact**

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Nicotine Opioid Interactions

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Tyndale (U. Toronto), Benowitz (UCSF)

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