Alcohol: Systems Biology

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Alcohol is Unique

Weak drug: intoxication at 10-50 mM

- Interacts with multiple signaling molecules
- Disrupts virtually all organ systems across the life span
- Effects in one organ system modify function of others

Metabolism yields 7 kcal/gm, toxic acetaldehyde, and reactive oxygen species.

- Replaces food calories; malnutrition; organ toxicity; cancer

Ubiquitous, socially acceptable, recreational drug used with health benefits by more than 120 million Americans.

- Moderate drinking decreases risk of heart disease, stroke, dementia

Alcohol Abuse and Dependence: 100,000 deaths; $200 Billion

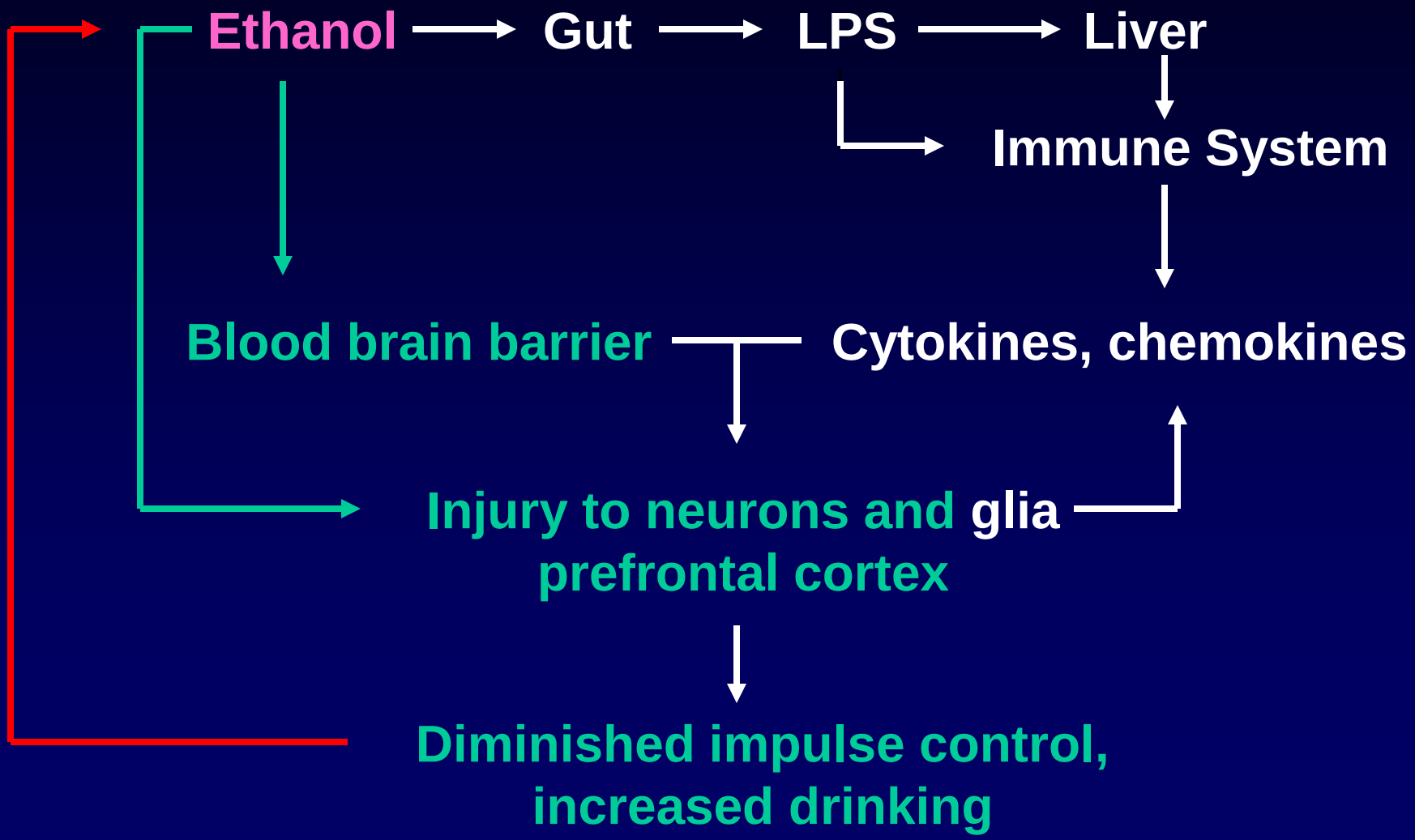
Abuse (Intermittent heavy use; binge drinking)

- Traffic fatalities (1/3); suicide (1/2); murders (1/2); sexual assault; risky sexual behavior; domestic violence; accidents; lost productivity; FASD; liver disease; stroke; intracerebral hemorrhage; pancreatitis; alcohol poisoning

Dependence (Regular heavy use).

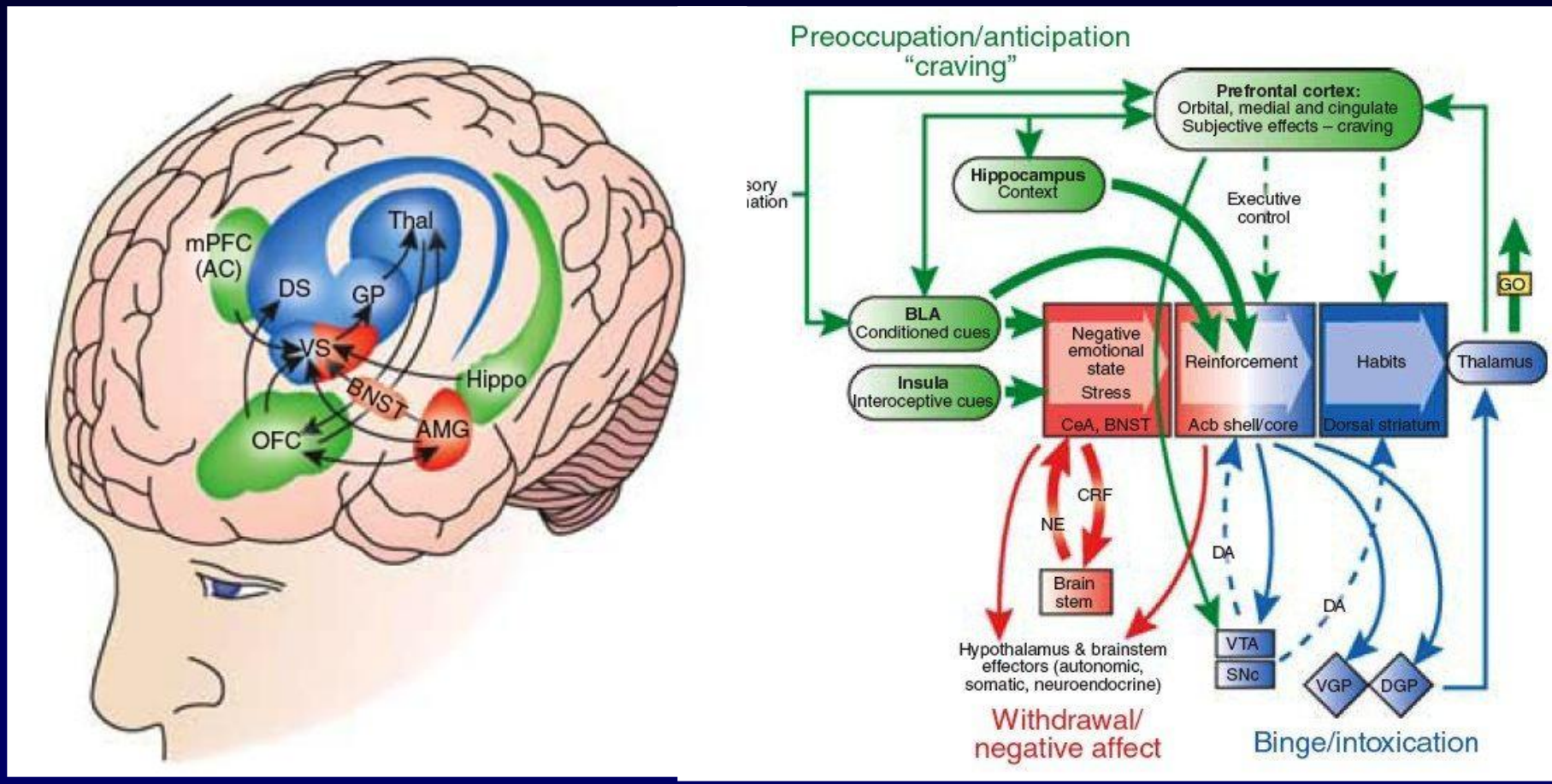
- FASD, dementia, neuropathy, cardiomyopathy, myopathy, cirrhosis, pancreatitis, gastritis; immunocompromise; cancer, alcohol withdrawal syndrome, seizures, and DTs

Organ Damage and Addiction are Impacted by Ethanol Effects on Multiple Organ Systems



Brain Circuits that Regulate Addictive Behavior

Koob and Volkow, Neuropsychopharmacology, 2009



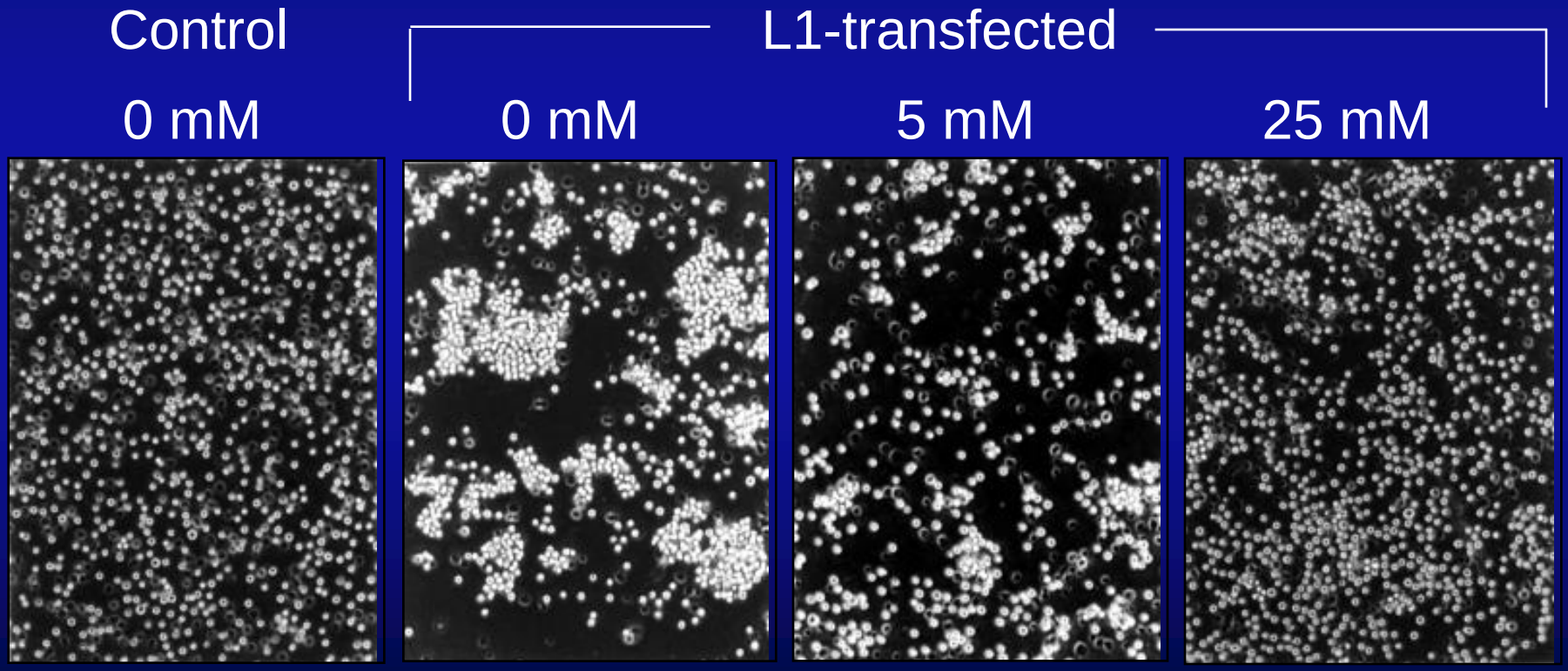
Fetal Alcohol Spectrum Disorders

- Deficient brain growth and dysmorphology
- Prenatal and/or postnatal growth retardation
- Facial dysmorphology

Most common non-genetic cause of mental retardation

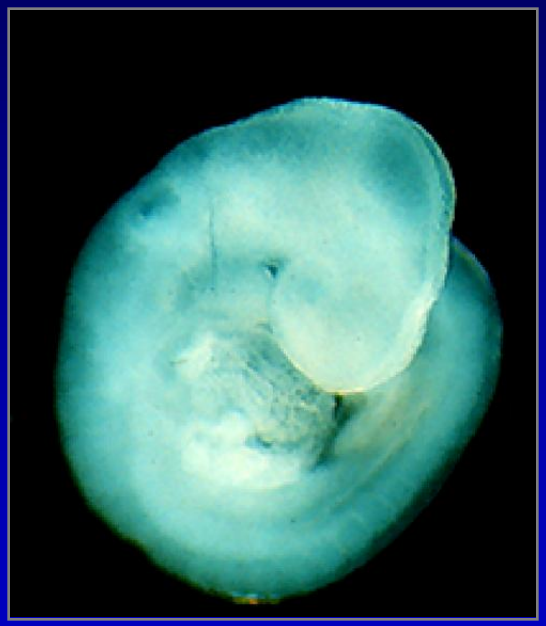
In-School Prevalence	
FAS:	0.2 - 0.7%
FASD:	2 - 5%

Ethanol inhibits cell adhesion in L1-transfected mouse L cells.

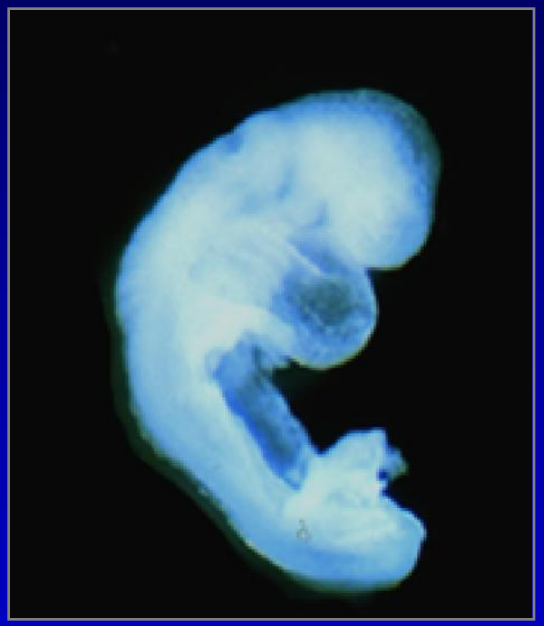


Ethanol does not inhibit cell adhesion in N-CAM transfected cells.

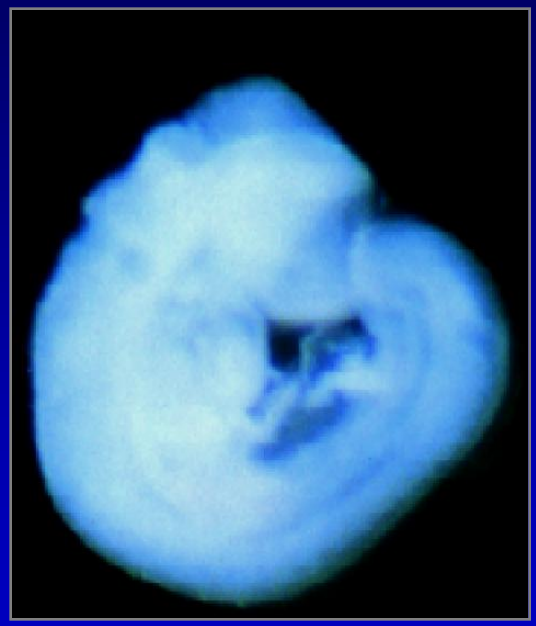
Drugs that block ethanol effects on L1 also prevent ethanol teratogenicity in mice



CONTROL

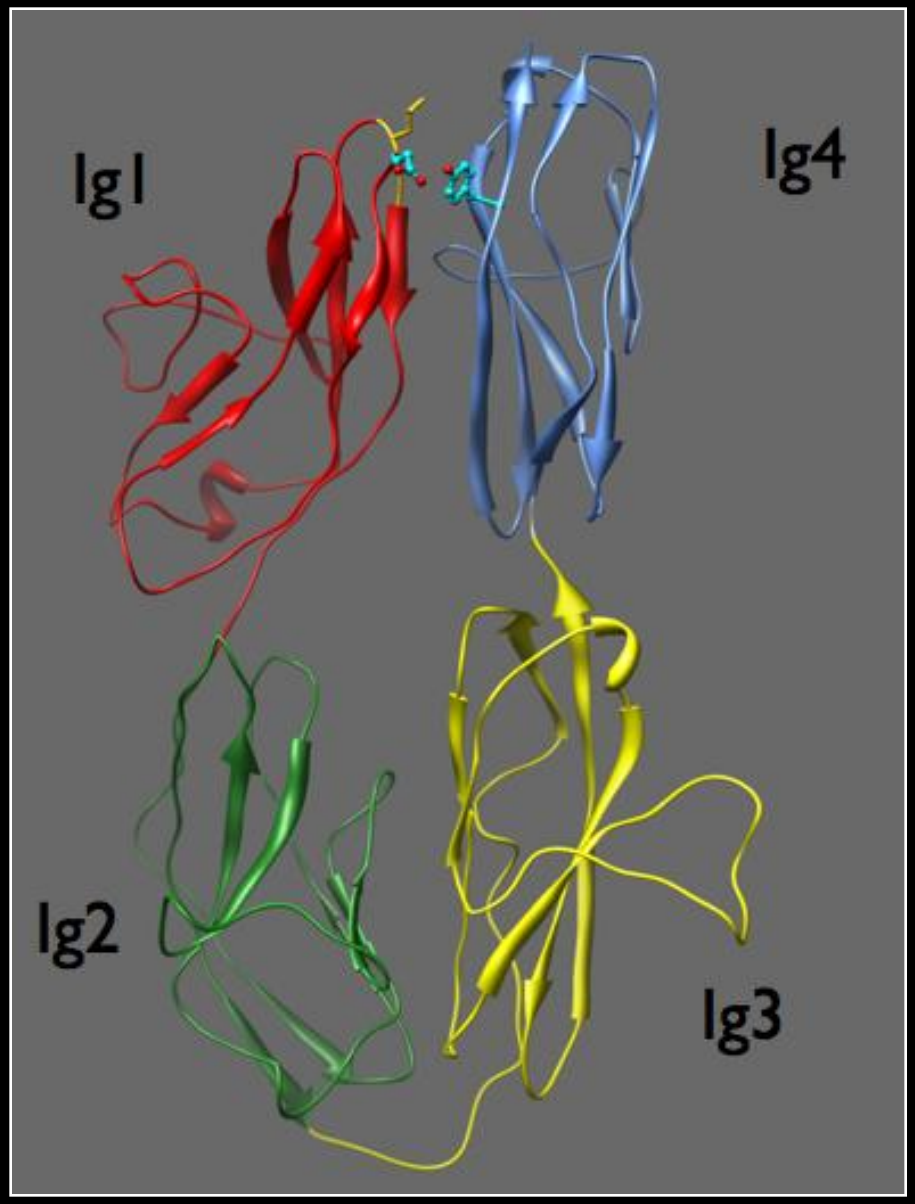


ETOH

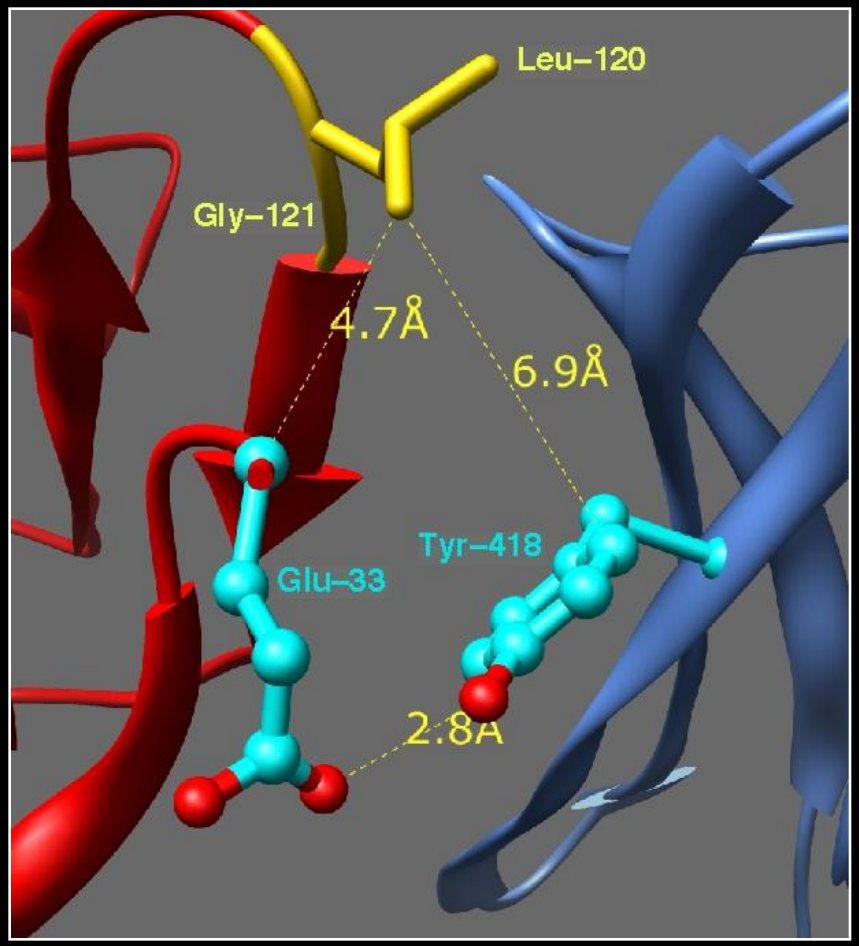


ETOH/OCT

Photos depict median number of somites per group.



Arevalo et al, PNAS, 2008



Photolabeling identifies a binding pocket for alcohol agonists and antagonists at the domain interface between Ig1 and Ig4, The two photolabeled residues, Tyr-418 and Glu-33, form a strong hydrogen bond between the Ig1 and Ig4 domains close to Leu-120 and Gly-121, at which mutation causes human disease similar to FAS.

Fetal Alcohol Spectrum Disorders: Spectrum of NIAAA Research

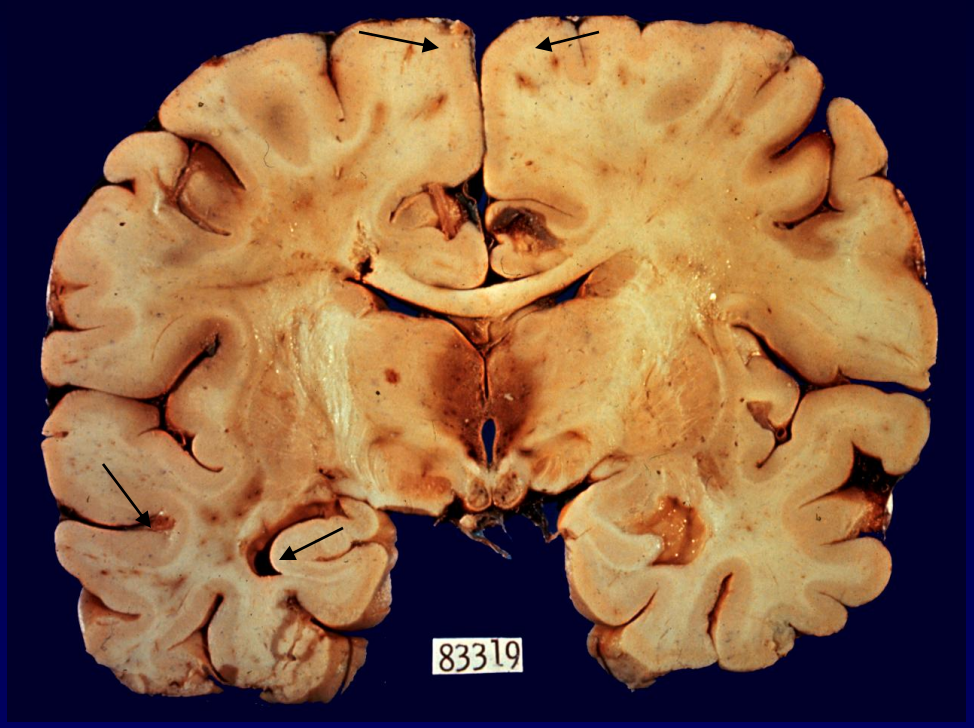
- Cellular and molecular mechanisms
- Genetic susceptibility and epigenetic modifiers
- Animal models: pathophysiology, dysmorphology, brain imaging, prevention, intervention
- Epidemiology: drinking pattern, prevalence
- Diagnosis: in utero ultrasound, 3D-facial imaging, brain imaging, cognitive and behavioral phenotype
- Prevention: Brief interventions pregnancy, nutrition, nutritional supplements (choline)
- Intervention: Cognitive, pharmacologic, policy

Brain Lesions in Alcoholics

- Alcohol Neurotoxicity
- Wernicke's encephalopathy: N,EN
- Hepatocerebral degeneration: L,EN
- Trauma: EI
- Fetal Alcohol Syndrome: EN, N
- Central Pontine Myelinolysis: N, EN, G
- Marchiafava-Bignami Syndrome: N, EN, G

N - nutritional; EN - ethanol neurotoxicity;
EI - ethanol intoxication
L - liver-brain toxcity; G - glial toxicity

Wernicke's Encephalopathy



Prevalence 0.8-2.8% of consecutive autopsies

- Alcohol replaces nutritive calories and causes nutrient malabsorption
- Brain lesions due to thiamine deficiency are potentiated by alcohol neurotoxicity
- Severe neurological impairment, including memory loss, oculomotor dysfunction, and gait ataxia

Concerns Regarding a Merger of NIAAA and NIDA

- Institute priorities drive funding, and funding drives science.
- An institute on addictions will prioritize research on addiction.
- The enormous public health burden from the non-addictive use of alcohol will not be adequately addressed, and research on the health benefits of alcohol will be orphaned.
- We will lose the highly integrated, systems approach of NIAAA that is necessary to understand the effects of alcohol use, abuse, and dependence at the molecular, genetic, cellular, organ, medical, psychological, social, and policy levels.

Concerns over Merger

There are no barriers to collaboration on addiction research that require a merger between NIDA and NIAAA.

There are no apparent scientific benefits to merger that could outweigh the enormous potential disadvantages.

PUBLIC HEALTH INSTITUTE

Alcohol Research Group

National Alcohol Research Center

Alcohol Health and Social Problems: Policy Research Status and Opportunities

Presentation to the
Substance Use, Abuse, and Addiction Working Group,
Scientific Management Review Board, NIH
September 23, 2009

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Presenter Disclosures

Thomas K Greenfield

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I am a grantee of NIAAA, a member of its Extramural Advisory Board, and serve on the Governing Council of the American Public Health Association

Overview of Topics covered in my written submission

- ***Generating new knowledge that leads to improved health outcomes***
- ***Linking alcohol consumption, patterns and problems***
- ***Alcohol's role in the burden of disease, both globally and nationally***
- ***Estimates of social costs, state and federal revenues and market controls***
- ***Studying alcohol externalities or harm to others, and drinking contexts***
- ***Effects of alcohol policy changes***

Prevention Policies

"[Prevention policies] are all policies that operate in a non- personalized way to alter the set of contingencies affecting individuals as they drink or engage in activities that (when combined with intoxication) are considered risky."[1]

"Alcohol policy is defined broadly as any purposeful effort or authoritative decision on the part of government or non-government groups to minimize or prevent alcohol-related consequences." [2]

[1]Moore & Gerstein (1981), p 53 *Beyond the Shadow of Prohibition*
[2]Babor et al. (2003), p 95 *Alcohol: No Ordinary Commodity*

Alcohol, Tobacco & Drugs Impose big Burdens:

Preventable Risks in the GBD, 2000 (% total DALYS)

Developing countries				Developed countries	
High mortality		Low mortality			
Underweight	14.9%	Alcohol	6.2 %	Tobacco	12.2 %
Unsafe sex	10.2 %	Blood pressure	5.0 %	Blood pressure	10.9 %
Unsafe water & sanitation	5.5 %	Tobacco	4.0 %	Alcohol	9.2 %
Indoor smoke (solid fuels)	3.6 %	Underweight	3.1 %	Cholesterol	7.6 %
Zinc deficiency	3.2 %	Body mass index	2.7 %	Body mass index	7.4 %
Iron deficiency	3.1 %	Cholesterol	2.1 %	Low fruit & vegetable intake	3.9 %
Vitamin A deficiency	3.0 %	Low fruit & vegetable intake	1.9 %	Physical inactivity	3.3 %
Blood pressure	2.5 %	Indoor smoke from solid fuels	1.9 %	Illicit drugs	1.8 %
Tobacco	2.0 %	Iron deficiency	1.8 %	Unsafe sex	0.8 %
Cholesterol	1.9 %	Unsafe water & sanitation	1.8 %	Iron deficiency	0.7 %

Ezzati M, Lopez A, Vander Hoorn S, Rodgers A, Murray CJL, CRA Collaborative Group. Selected major risk factors and global regional burden of disease. *Lancet* 2002; 360(9343):1347-1360

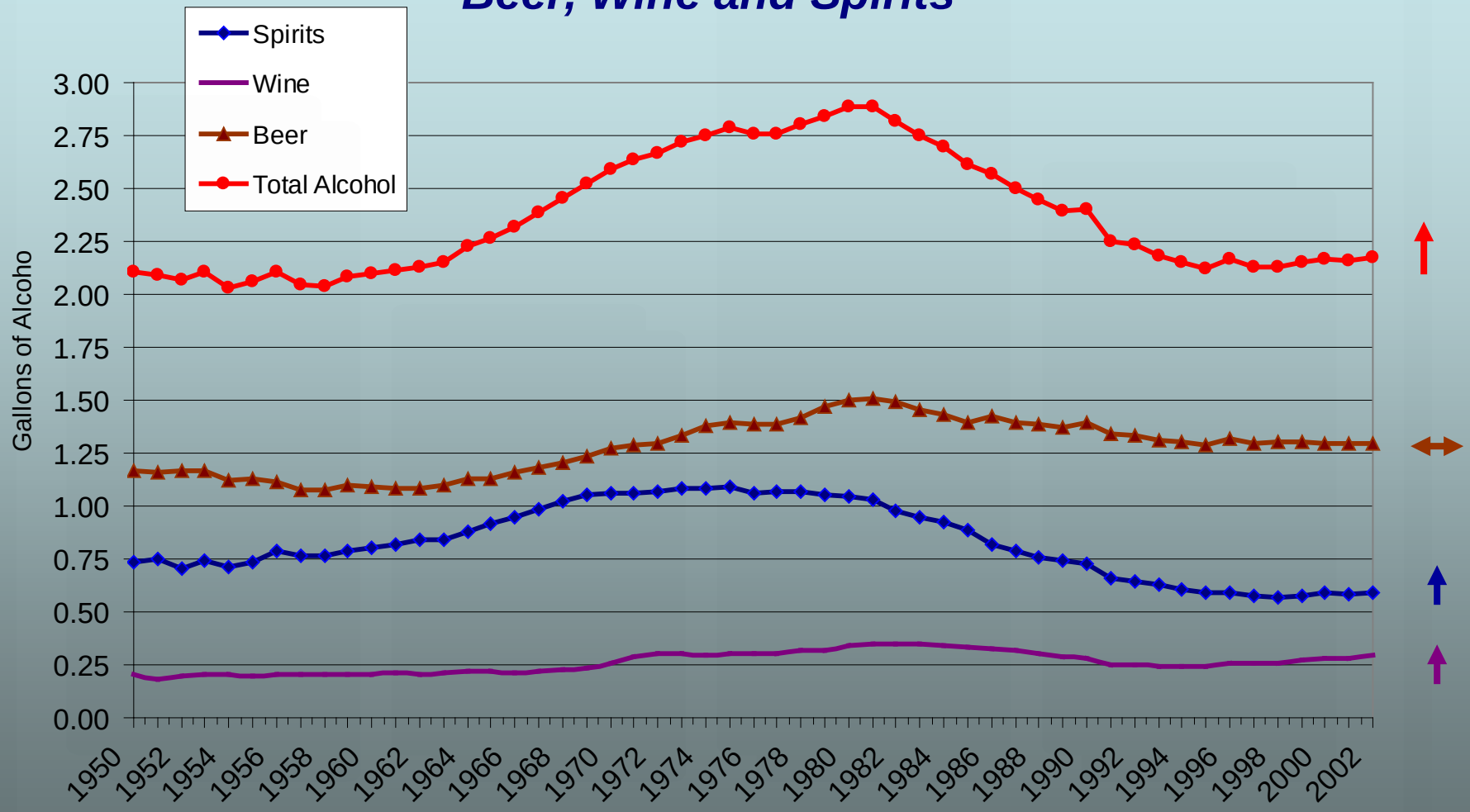
Alcohol-attributable burden of disease (in 1000 DALYs*) by sex and cause in 2004

	Men (%)*	Women (%)*	Total
Diseases for which alcohol has a detrimental effect			
Maternal and perinatal disorders (low birthweight)	64 (0·1%)	55 (0·5%)	119
Cancer	4732 (7·6%)	1536 (13·5%)	6268
Diabetes mellitus	0 (0·0%)	28 (0·3%)	28
Neuropsychiatric disorders	23 265 (37·6%)	3417 (30·1%)	26 682
Cardiovascular diseases	5985 (9·7%)	939 (8·3%)	6924
Cirrhosis of the liver	5502 (8·9%)	1443 (12·7%)	6945
Unintentional injuries	15 694 (25·4%)	2910 (25·6%)	18 604
Intentional injuries	6639 (10·7%)	1021 (9·0%)	7660
Total detrimental effects attributable to alcohol	61 881 (100·0%	11 349 (100·0%)	73 231
Diseases for which alcohol has a beneficial effect			
Diabetes mellitus	–238 (22·2%)	–101 (8·1%)	–340
Cardiovascular diseases	–837 (77·8%)	–1145 (91·9%)	–1981
Total beneficial effects attributable to alcohol	–1075 (100·0%	–1246 (100·0%)	–2321
All alcohol-attributable net DALYs	60 806	10 104	70 910
All DALYs	799 536	730 631	1530168
Percentage of all net DALYs attributable to alcohol	**7·6%**	**1·4%**	**4·6%**
CRA 2000 (for comparison)	6·5%	1·3%	4·0%

*** DALYS: disability-adjusted life-years**

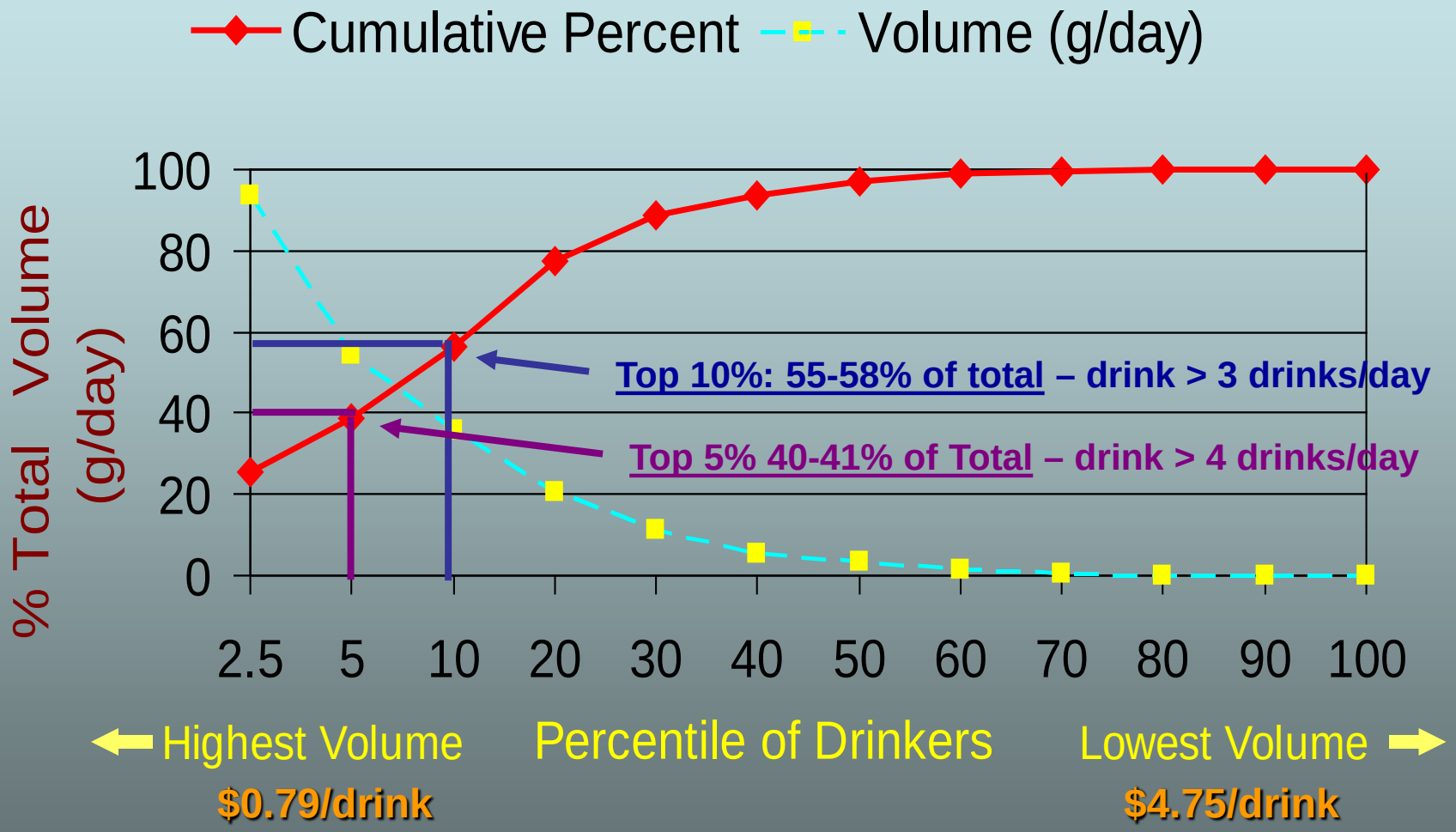
Source: Rehm et al, *Lancet* (2009)

U.S. Per Capita Consumption of Pure Alcohol from Beer, Wine and Spirits



Source: Kerr, Greenfield, Tujague, & Brown (2005)

Concentration of U.S. Alcohol Consumption



Sources: Greenfield & Rogers, *JSA*,1999; Kerr & Greenfield, *ACER*, 2007

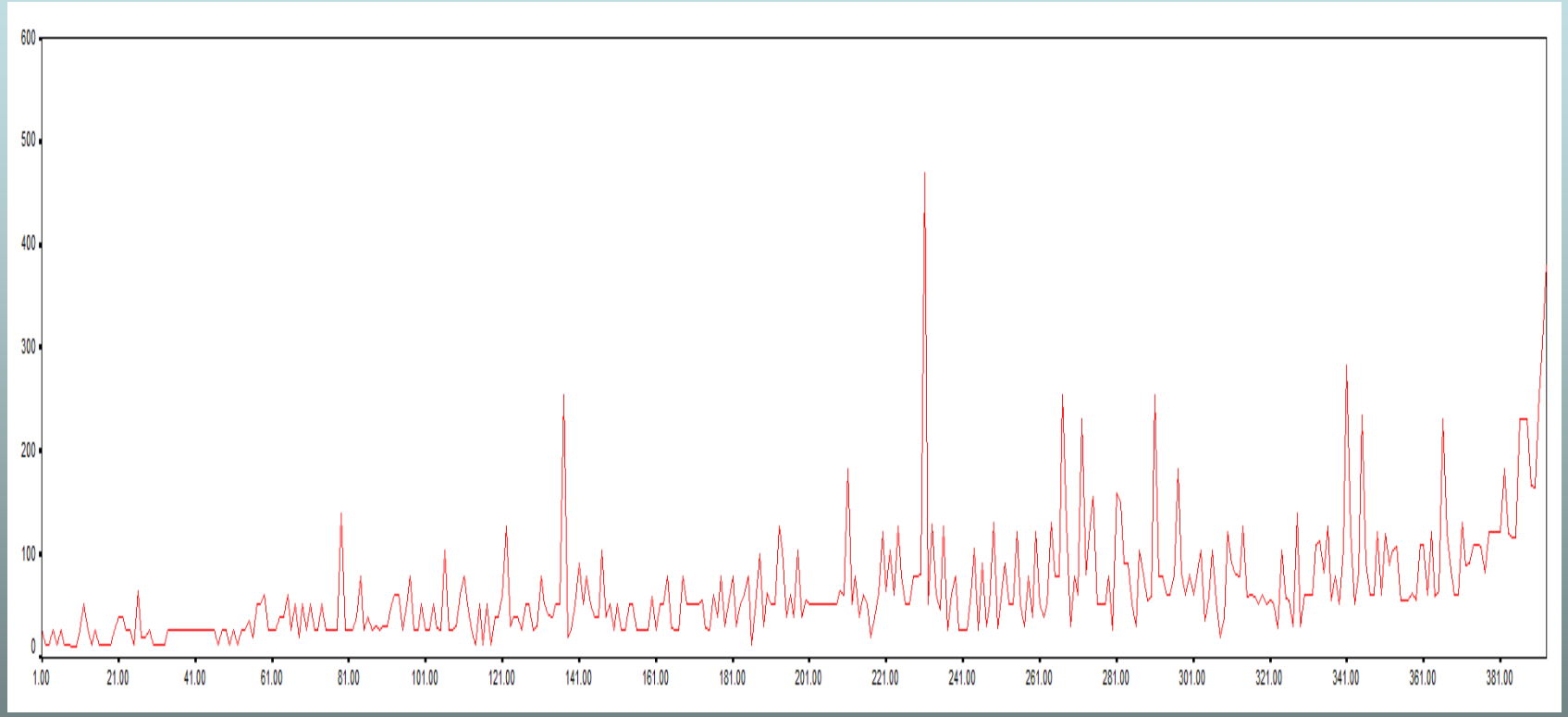
Concentration of Consumption and Heavy Drinking among Drinkers in the 2005 National Alcohol Survey

Of Drinkers:	Top 2.5%	Top 5%	Top 10%	Top 25%	Bottom 50%
Std. Drinks / Day	> 7.5	> 4.4	> 2.8	> 1.25	< 0.4
Percent Volume	28%	41%	55%	79%	5%
5+ Days	32%	47%	62%	81%	5%
	(24 - 39)	(40 - 54)	(56 - 67)	(77 - 85)	(3 - 5)
8+ Days	46%	62%	74%	88%	3%
	(37 - 55)	(54 - 70)	(67 - 80)	(85 - 92)	(2 – 4)
12+ Days	63%	74%	80%	90%	1%
	(53 - 74)	(65 - 83)	(71 - 88)	(85 - 96)	(.04 - 2)

(95% Confidence Intervals)

Source Kerr & Greenfield, *ACER*, 2007

Maximum for Urban Male n Goa, India
Ordered by Average Volume



Source: Greenfield et al. 1st Internat. Conf. on HIV and Alcohol in India, Mumbai, 2009

Summary of ethnic differences: Implications for Policy

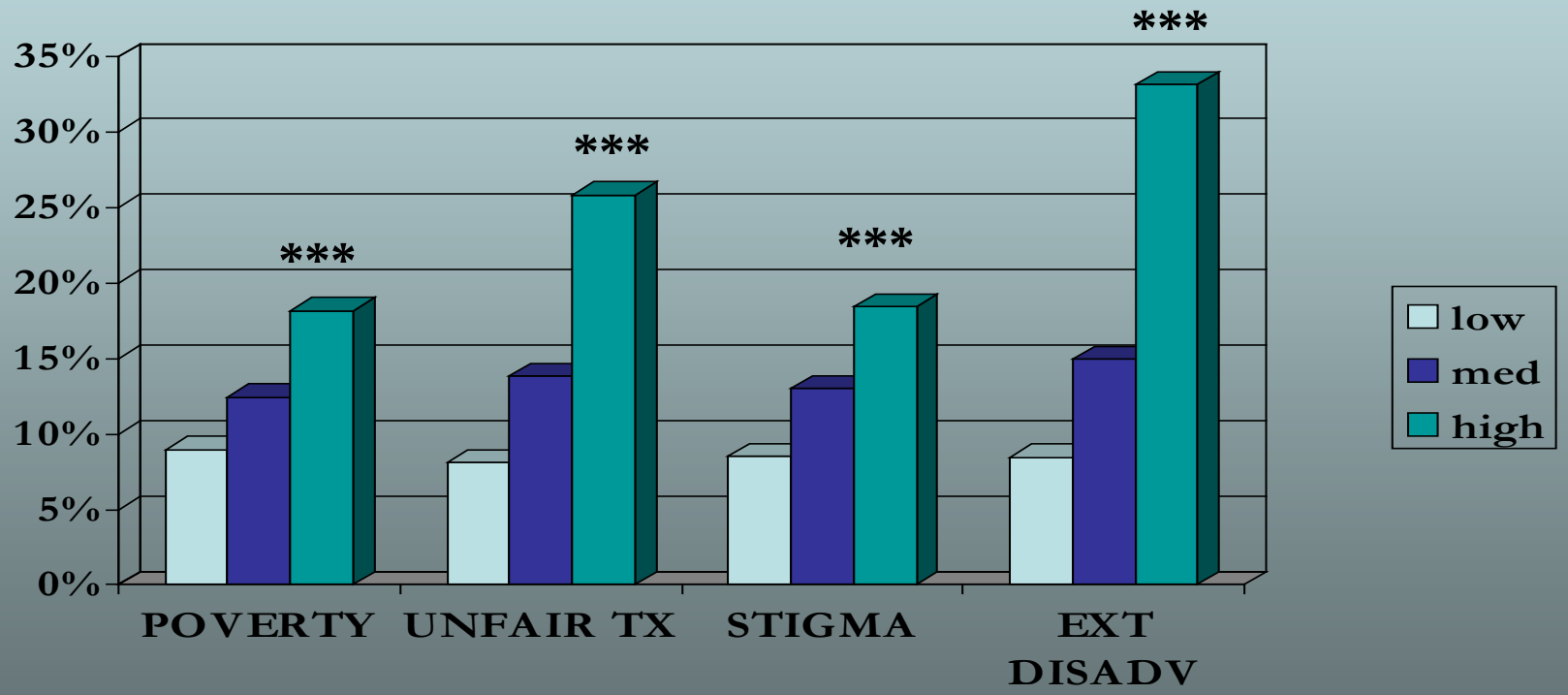
- **Longitudinal NAS surveys find later onset of AUDs for African Americans whose heavier drinking is delayed but lasts longer** (Caetano & Kaskutas, *JSA* 1995, *Sub Use/MisU*, 1996)
- **African American men consume more ethanol per drink (especially spirits and higher content malt liquors) with more variability in drink size, than whites** (Kerr, Patterson & Greenfield, *Addiction*, 2009)
- **Ethnic minorities with higher symptom severity show less treatment access than equivalent whites and experience more barriers** (Schmidt, Ye, Greenfield & Bond, *ACER*, 2007)
- **Social disadvantage (poverty, racial stigma, unfair treatment) exacerbate alcohol-related problems**

(Mulia, Ye, Zemore & Greenfield, JSAD, 2008)

Social disadvantage is associated with alcohol-related social & health problems

% reporting 1 or more tangible consequences

Note: Consequences = criminal justice, accidents, family, aggression, workplace or health problems

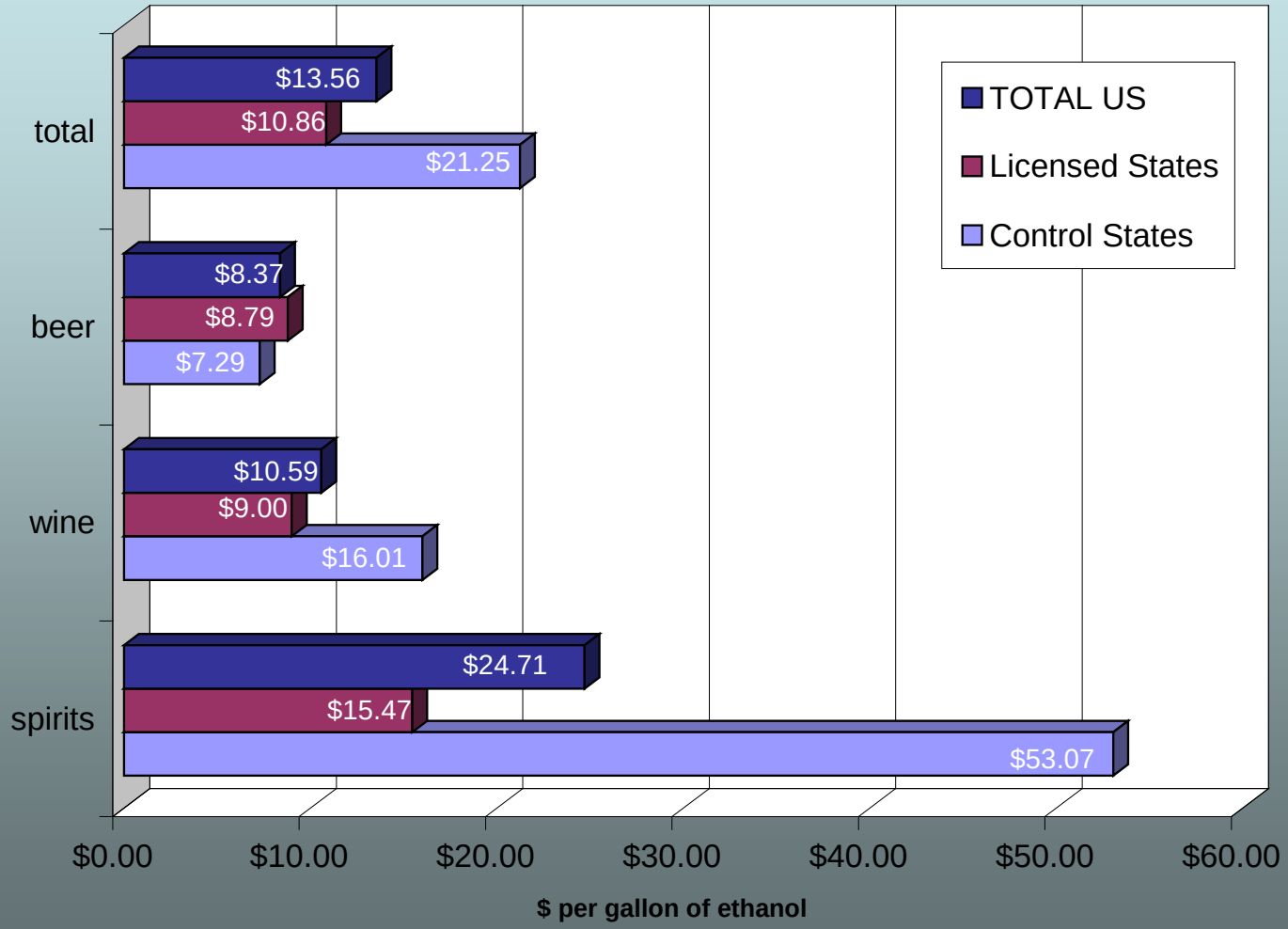


***p<.001

Source: Mulia, Ye, Zemore & Greenfield, *JSAD*, 2008

State Revenues per Gallon Ethanol in License and Control (Monopoly) States

Figure 2: Revenues per Ethanol Gallon by Beverage Type



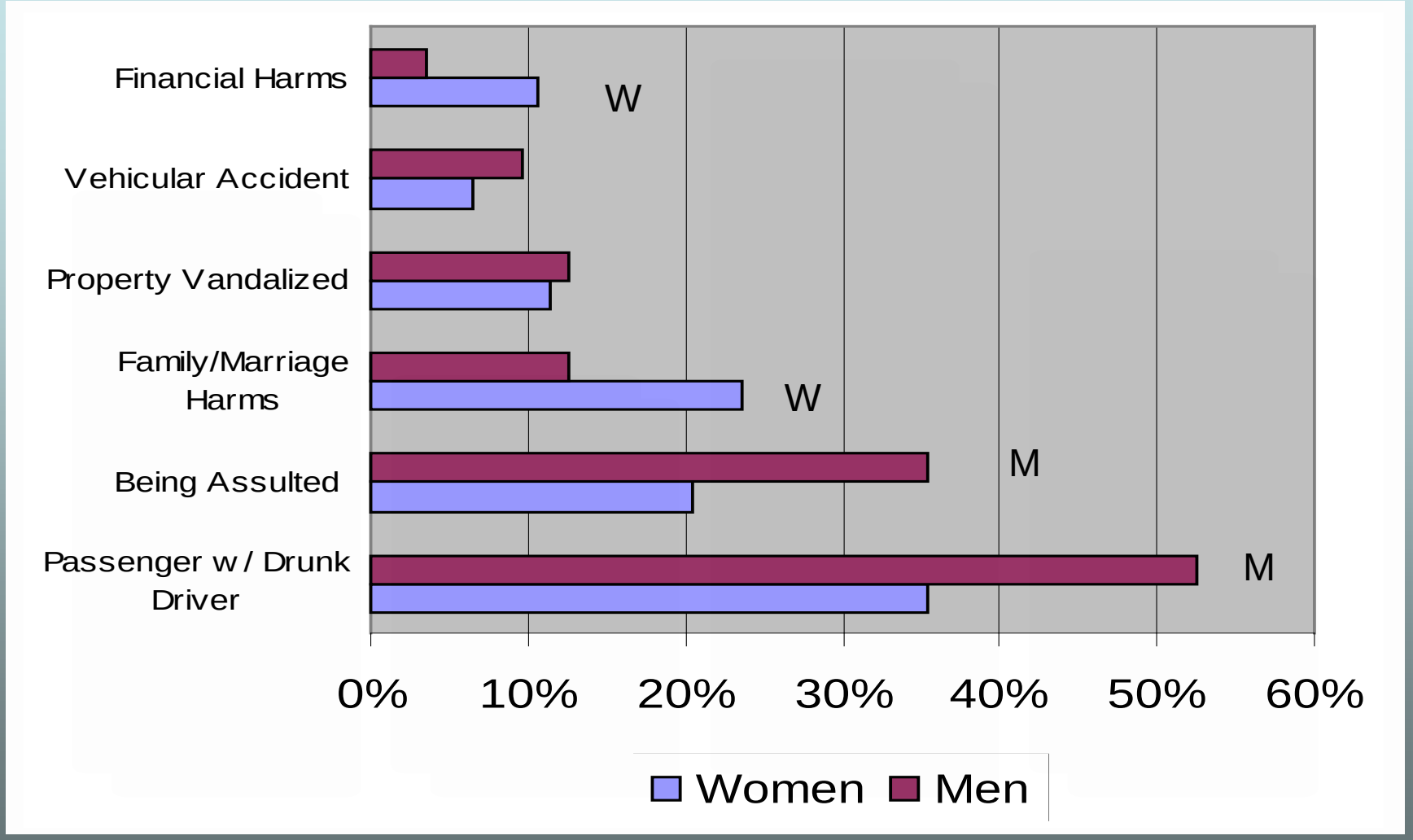
Source: National Alcohol Beverage Control Association (2009)

What has happened when retail monopolies have been privatized?

- **Research indicates direct state control over alcohol sales, both in the US and other countries reduces availability of the controlled beverage types (e.g., spirits) and reduces overall alcohol consumption**
- **Studies of effects of privatization imply that liberalization or elimination of state monopolies increases both consumption and (various types of) alcohol problems**
- **State alcohol regulators and ABC associations seek current policy data & evidence; NIAAA, with APIS and its ARCs provide a well-accepted source for such findings; not clear how a joint drug-alcohol IC would be regarded.**

Source: NABCA (2009) The effects of privatization of alcohol control systems

Externalities in 2005: Ever Harmed by Someone Else's Drinking?



Source: Greenfield APHA 2006 *(under review)*

Summary of Key Conclusions: 1

- Ongoing study of US trends and problem series is critical to identify the way policies work and interact, to help legislatures design evidence based policies and to examine their impact over time.
- NIAAA's portfolio of studies has helped us understand the etiology of ethnic/racial differences and services disparities; studies coming on line are now investigating reforms and fitting interventions to targets
- Human alcohol measurement has greatly advanced. Aggregate and individual measures have gained in precision for estimating ethanol exposure. Economic and time series analyses require precise measurement and this distinguishes alcohol from illicit drug studies
- In the last 25 years, NIAAA-supported policy analyses have demonstrated efficacy of environmental and policy strategies; sustainability analyses are now needed. Because these studies involve an array of state laws & systems they are best addressed in a dedicated IC.

Ratings of policy-relevant strategies and interventions

Policy - strategy	Effectiveness	Breadth of research support	Cross-cultural Testing	Cost to implement
Retail monopoly	+++	+++	++	Low
Restrict outlet density	++	+++	++	Low
Increase alcohol taxes	+++	+++	+++	Low
No service to intoxicated	+	+++	++	Moderate
Server liability	+++	+	+	Low
School programs	0	+++	++	High
Warning labels	0	+	+	Low
Min. legal purchase age	+++	+++	++	Low
'Zero tolerance' drivers <21	+++	+++	++	Low
Brief intervention-at risk	++	+++	+++	Moderate

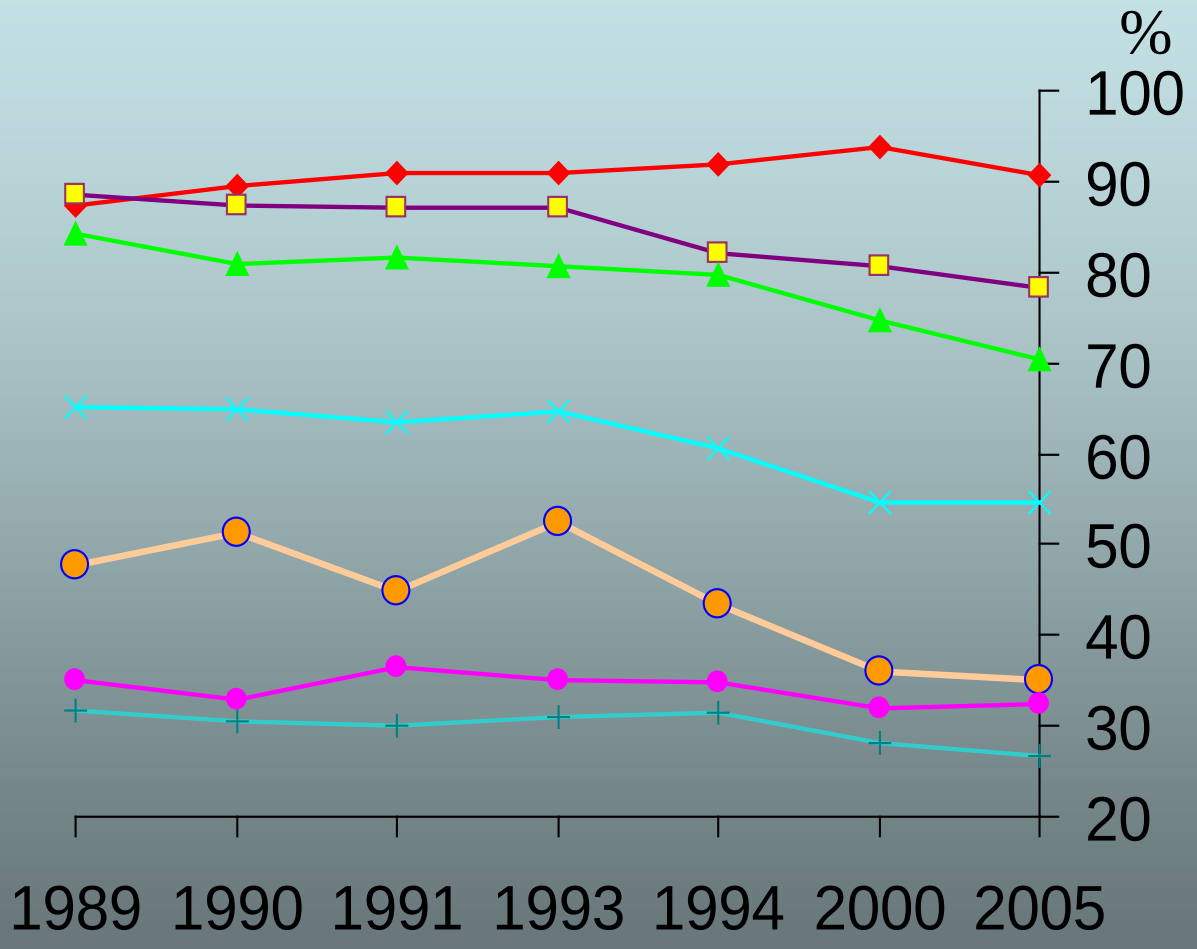
Source: Adapted from Babor et al, *Alcohol: No ordinary commodity* (Table 16.1), 2003

Key Points 2

- Public opinions about alcohol policies and prevention show erosion

- NIAAA is in the best position to focus efforts to mobilize research that will inform the public, Congress and the states on effective treatments and policies needed to address alcohol problems

Support Weakening for Stronger Alcohol Policies



- Warning Labels
- More Prevention
- Host Liability
- Counter Ads
- Increase Taxes
- Store Hours
- Drinking Age

Sources: Greenfield et al, *CDP* 2004; Greenfield et al, *CDP* in press

Final Key Points

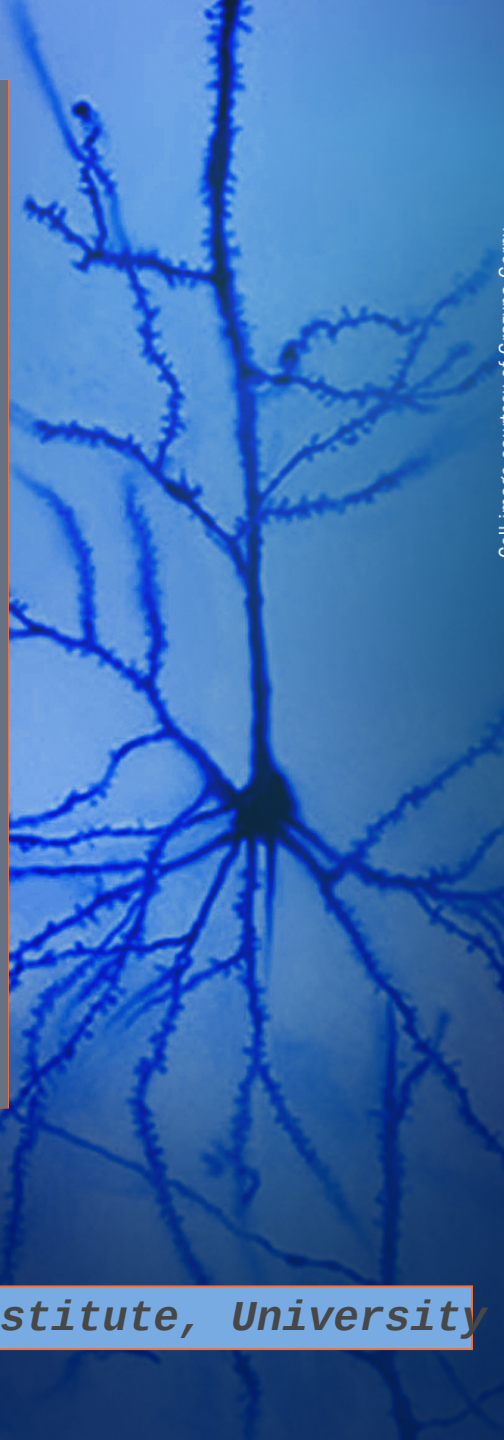
- The majority of drinkers drink moderately, but many exceed safe limits; on metrics of DALYs, injuries and externalities from hazardous drinking by younger people add much to the toll; dependent drinkers add most to mortality in late life.
- There is wide concern about loss of scientific momentum and disruption to the successful, multi-systems approach of NIAAA in a merged IC
- Alcohol's potential for both moderate and destructive use argue for a distinct, integrated, nuanced approach to guiding research, at which NIAAA has been highly effective. There are unique features of this model IC.
- State regulators and many public health leaders have serious concerns about the wisdom of mixing alcohol within a broader addictions framework and have expressed concern about such an untested structure

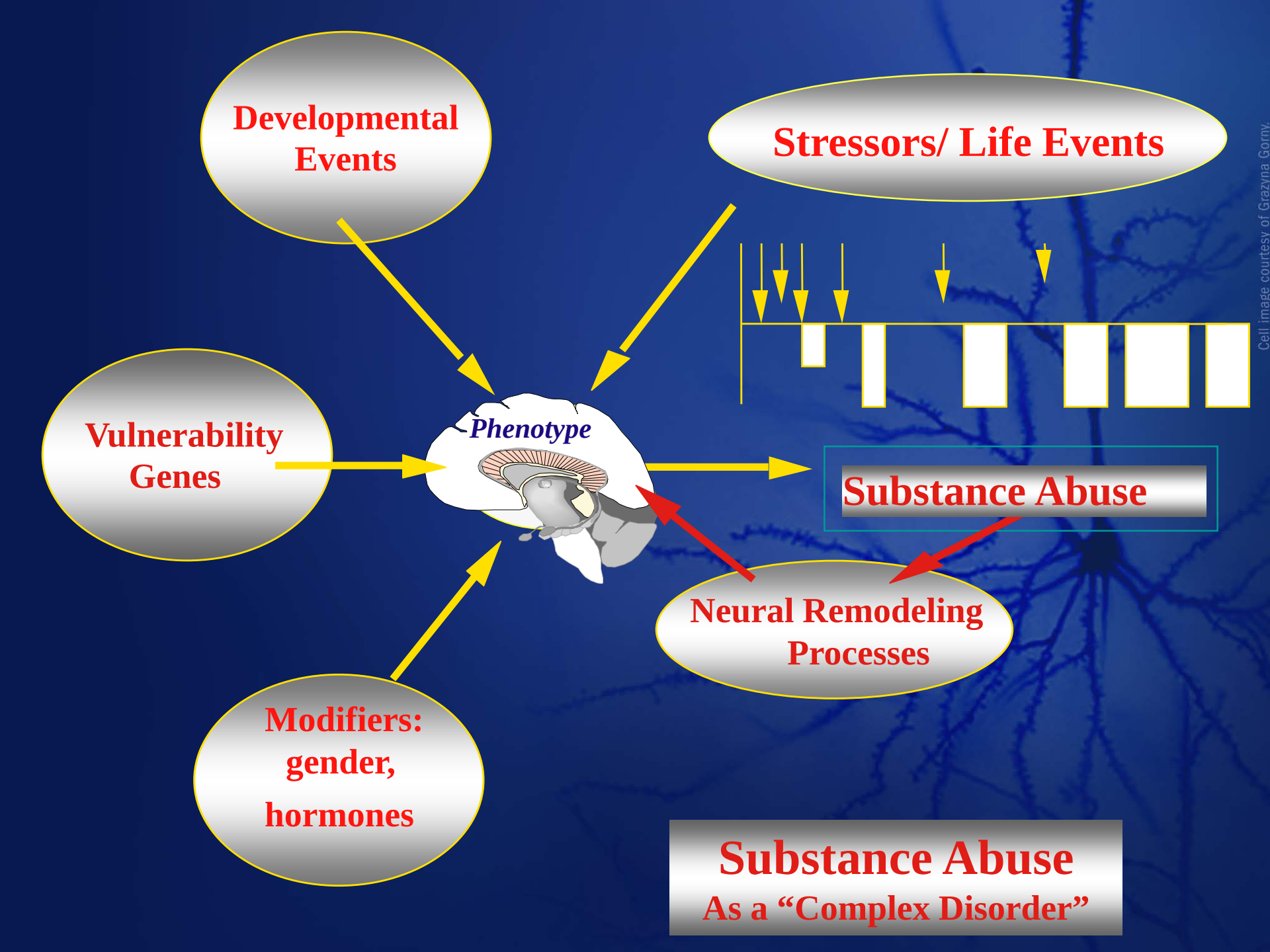
<tgreenfield@arg.org>

Substance Abuse:

Challenges and Opportunities

By
Huda Akil
U. of Michigan



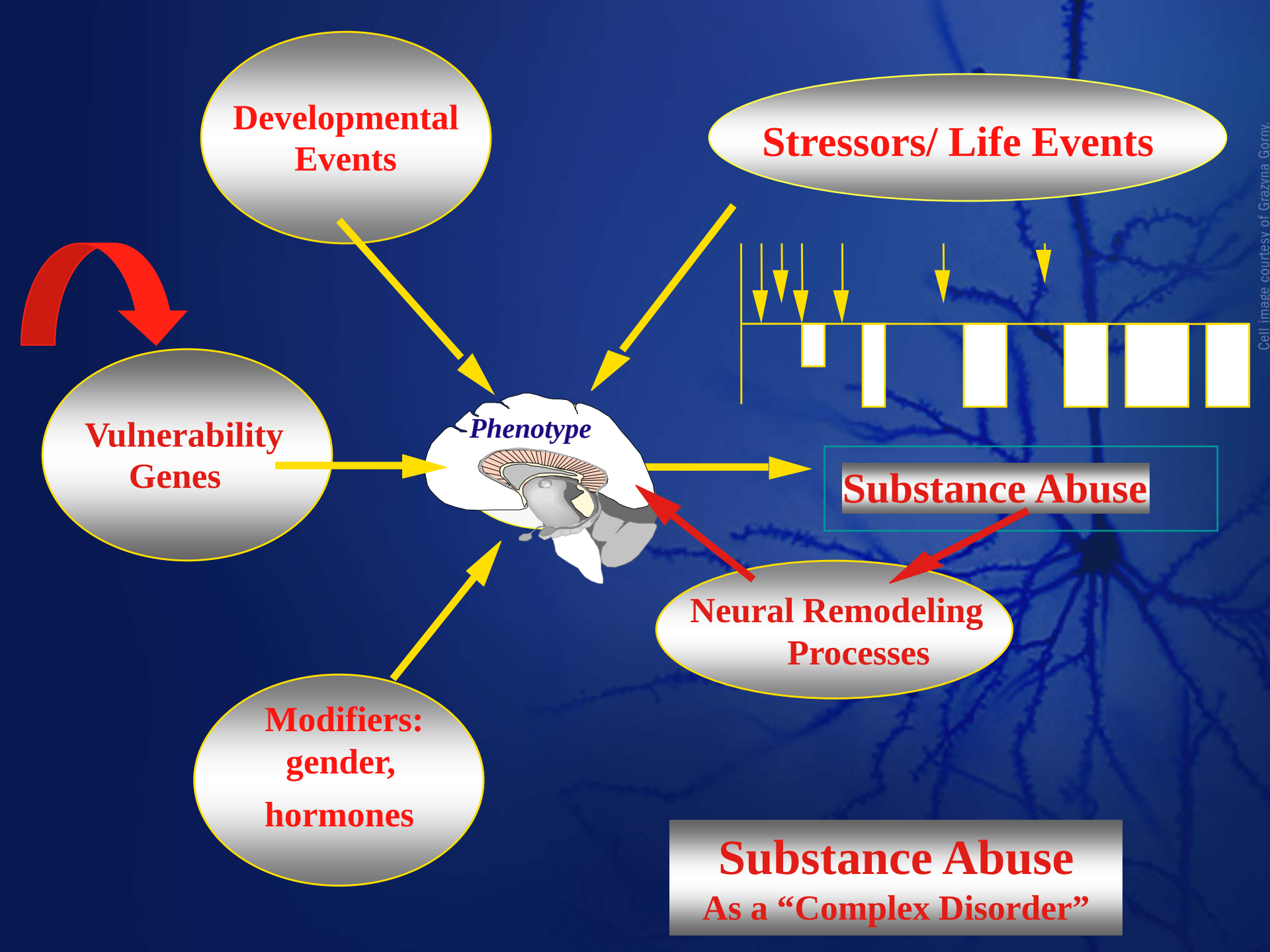

Developmental Events
Stressors/ Life Events
Vulnerability Genes
Phenotype
Substance Abuse
Neural Remodeling Processes
Modifiers: gender, hormones
Substance Abuse
As a "Complex Disorder"
Cell image courtesy of Grazyna Gorny.

Factors that Affect Various Phases of Addiction

Clinical and neurobiological studies indicate that different mechanisms are involved in the various phases of drug abuse

- ***-- Initial Willingness to Experiment with the Drug***
- ***-- Response to Drug Reward- How reinforcing it is***
- ***-- Rates of Extinction***
- ***-- Rates of Relapse***

Understanding these mechanisms will allow for specific strategies for prevention, treatment, and long term maintenance or relapse prevention in a more personalized approach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Cell image courtesy of Grazyna Gorny.

Conceptual Framework

- ***Externalizing Disorders*** are associated with “behavioral undercontrol” or “disinhibitory syndrome” and include Conduct Disorders, Attention Deficit Disorders, Antisocial Behavior and Substance Abuse.

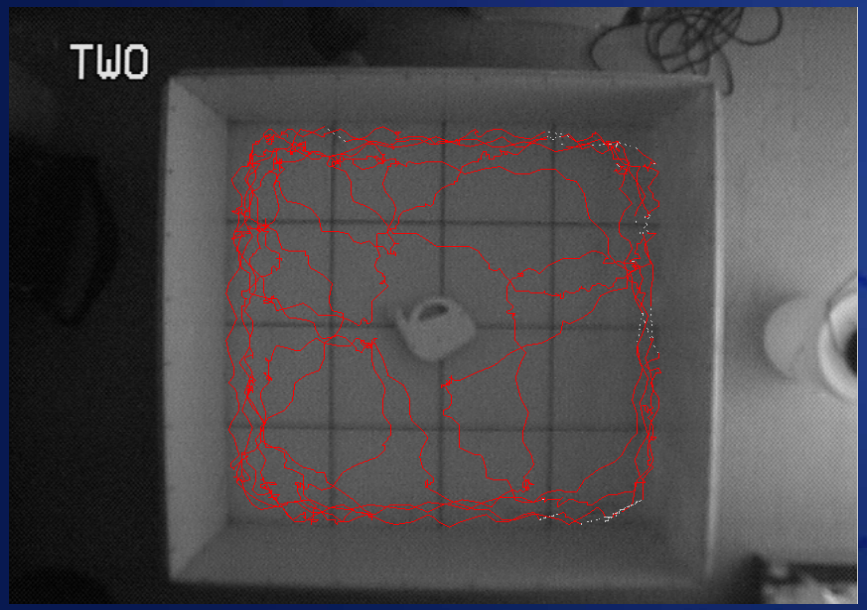
- Features of Externalizing Disorders include:
  - Novelty Seeking or Sensation Seeking
  - Impulsivity
  - Aggression

- ***“Internalizing Disorders”*** are associated with “behavioral overcontrol”. Include: Depression, Anxiety, Obsessive Compulsive Disorder, Somatic Disorders and Suicidal Behavior

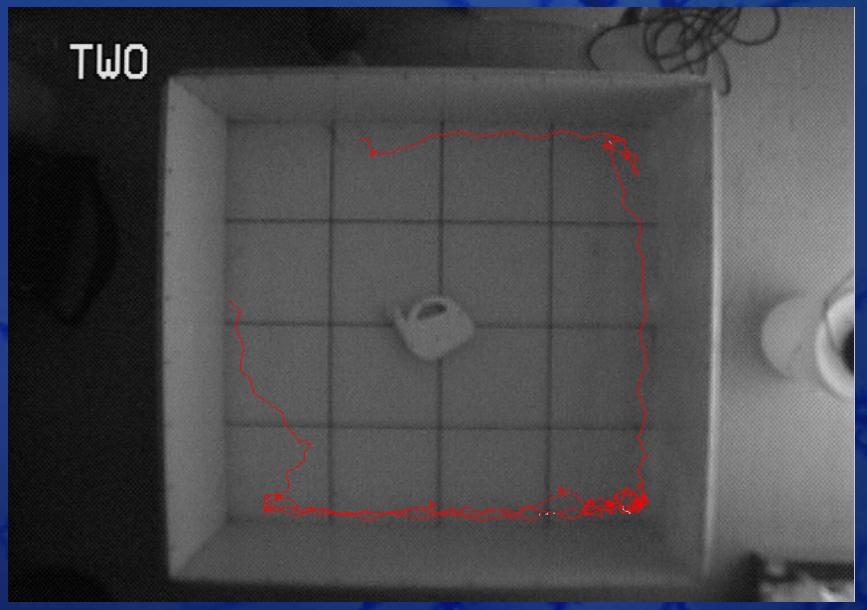
- Related to maladaptive thoughts and emotions

Meet the Rats!

High-Responder Rat (HR)

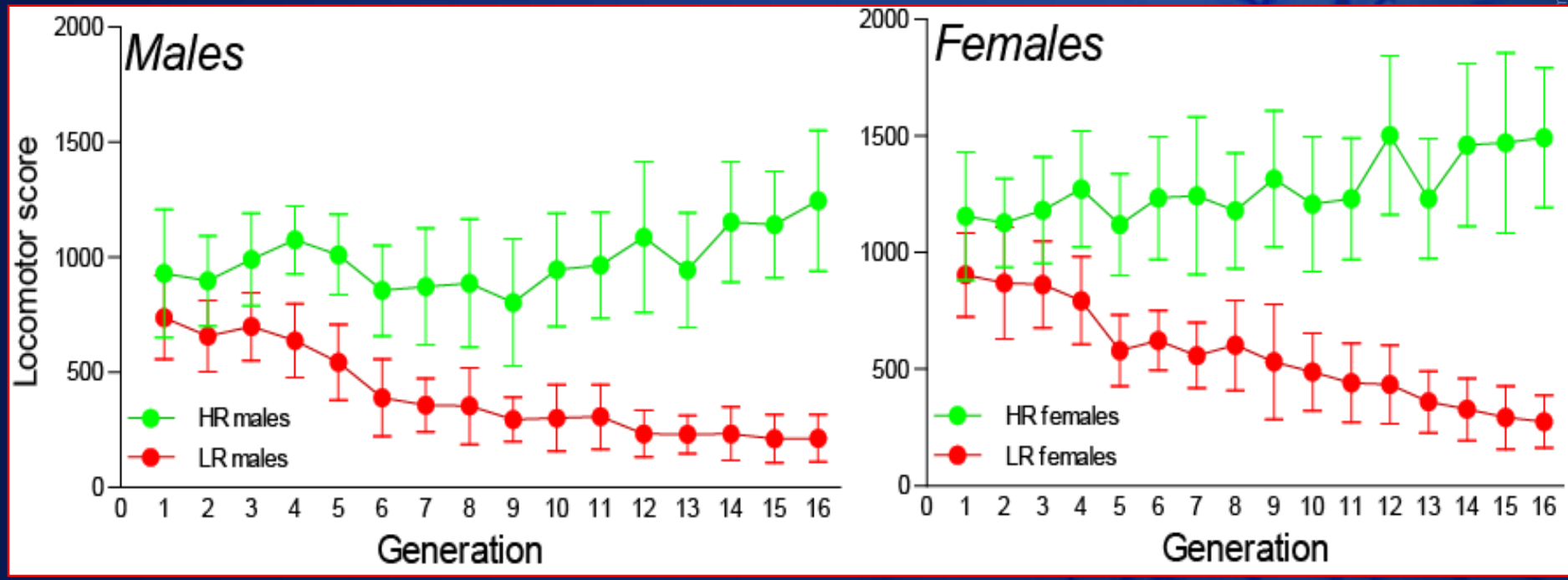


Low-Responder Rat (LR)



Clinton et al, 2005

Selective-Breeding for the HR and LR Traits in Males & Females



Modified from Stead, Clinton, et al. Behavior Genetics, 2006

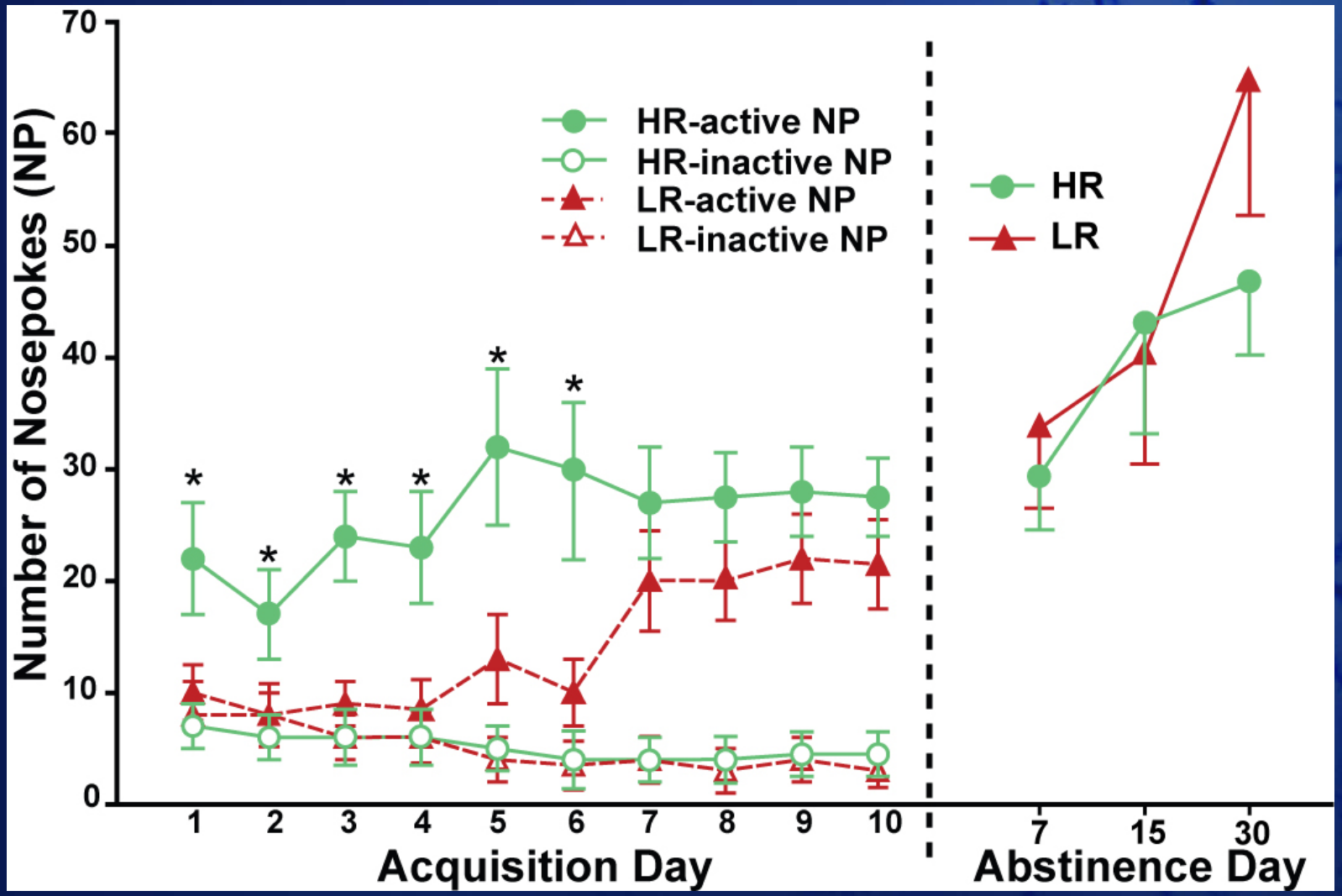
Broad ***behavioral characterization of HR/LR Bred Lines***

- Anxiety-Like Behavior
- Depression-Like Behavior
- Aggression
- Impulsivity
- Response to Environmental Cues

  (Sign- vs. Goal-Tracking)
- Behavioral response to drugs of abuse

- ***<u>NB</u>: No Differences in Learning & Memory***

Cocaine SA in HR vs. LR



Capriles et al 2006

Research Strategy

Use a combination of genomic and neuroscience approaches to discover:

a) Basal differences in animals with different propensity to drug use

b) Changes induced by the drug, or by triggers of drug-taking such as stress.

Tools Include:

Discovery Approach (e.g. Gene Expression Profiling)

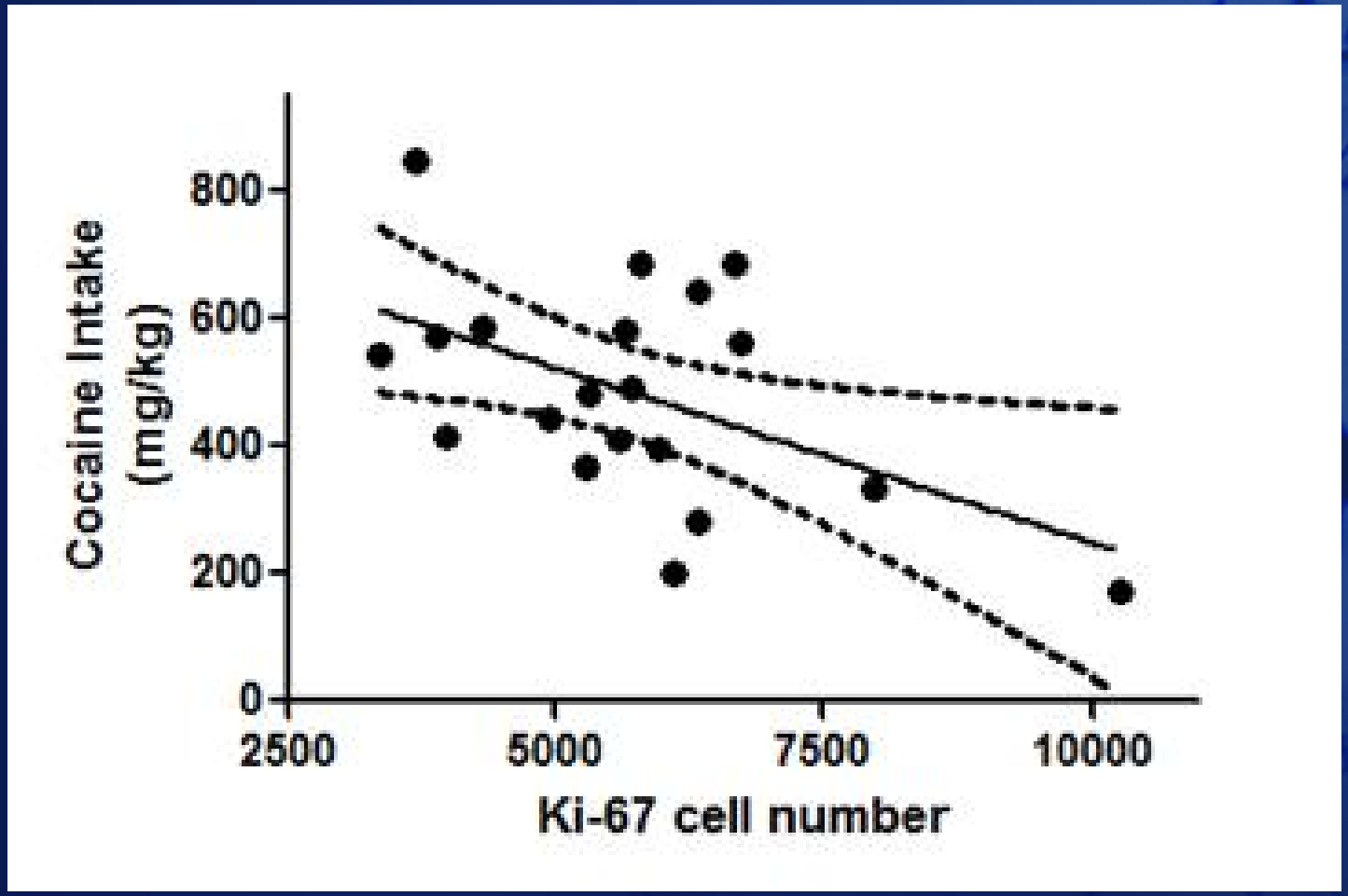
Anatomical Studies with Gene/Protein Expression

Epigenetic Studies

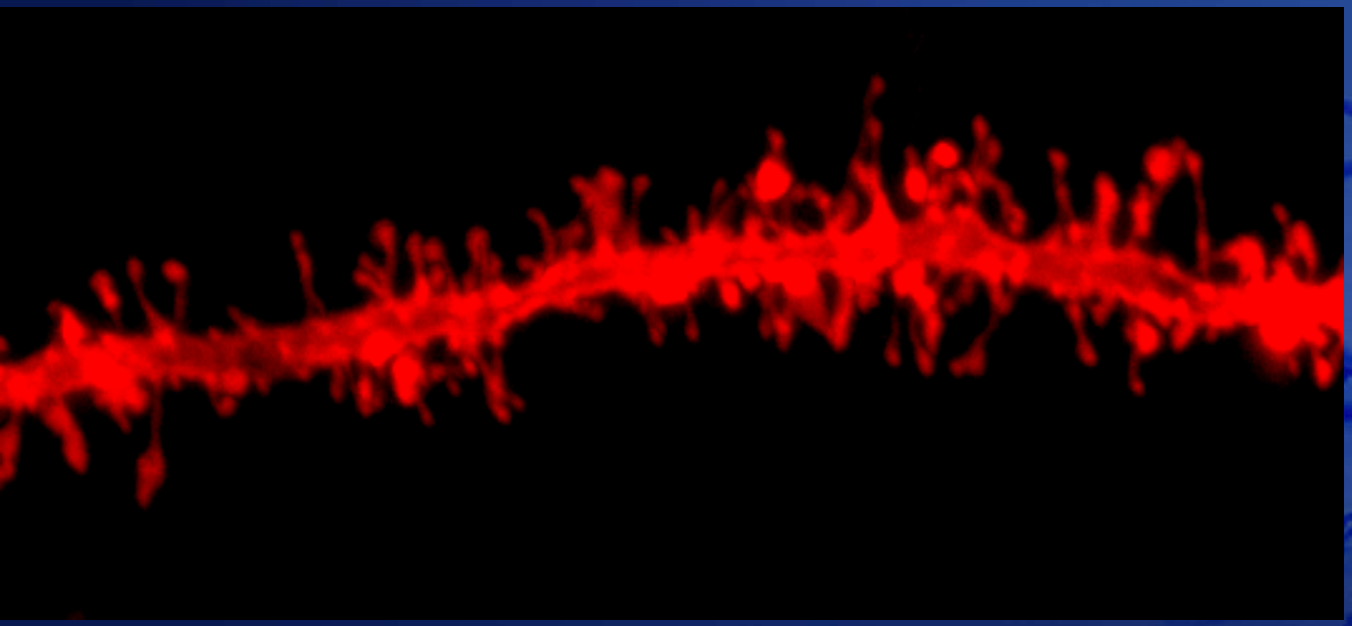
Neurogenesis Analyses

Morphological Studies

Extended Access to Cocaine Drives a Decrease in Hippocampal Cell Proliferation

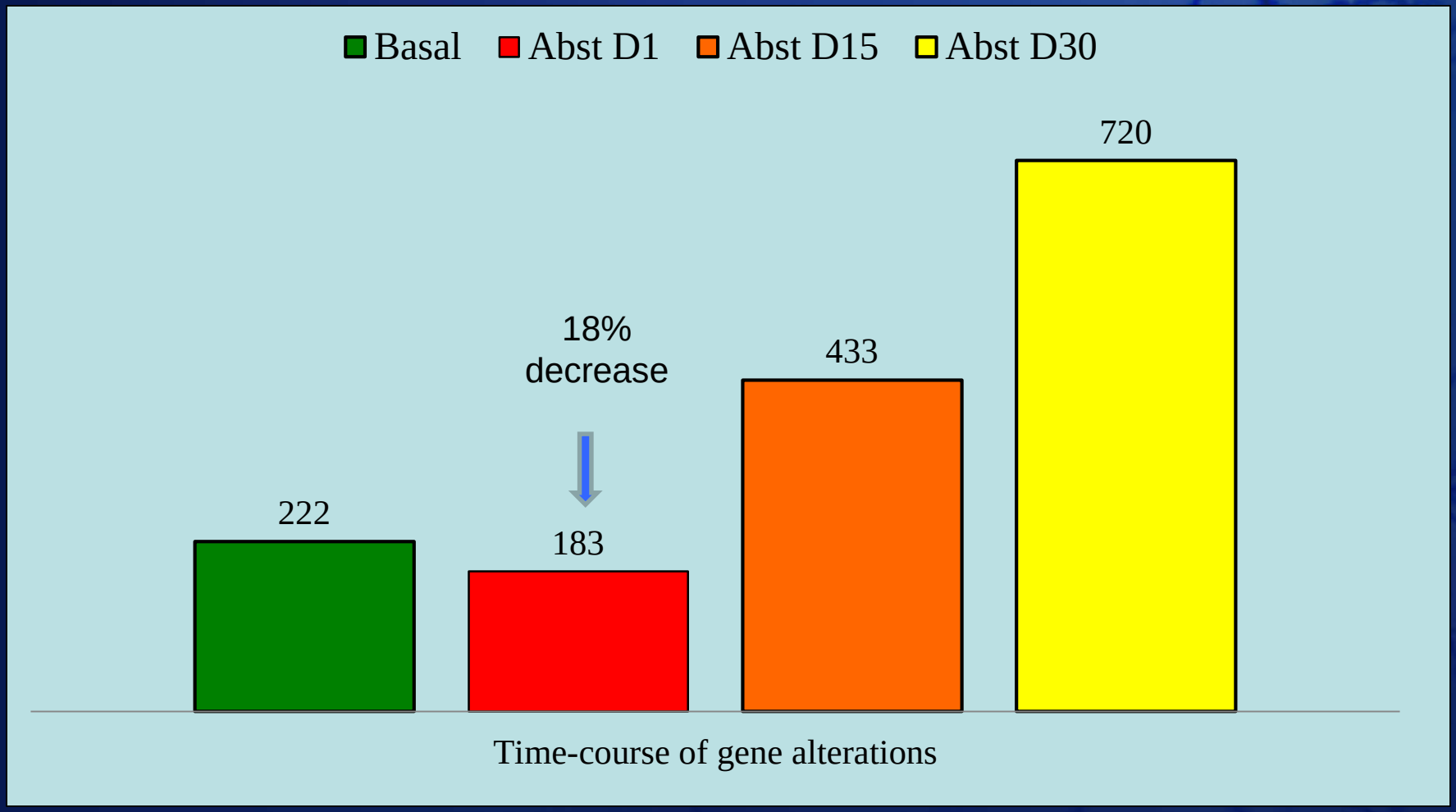


Effects on Morphology Beyond Neurogenesis



Basal Differences Seen Between HR and LR and Impact of Cocaine

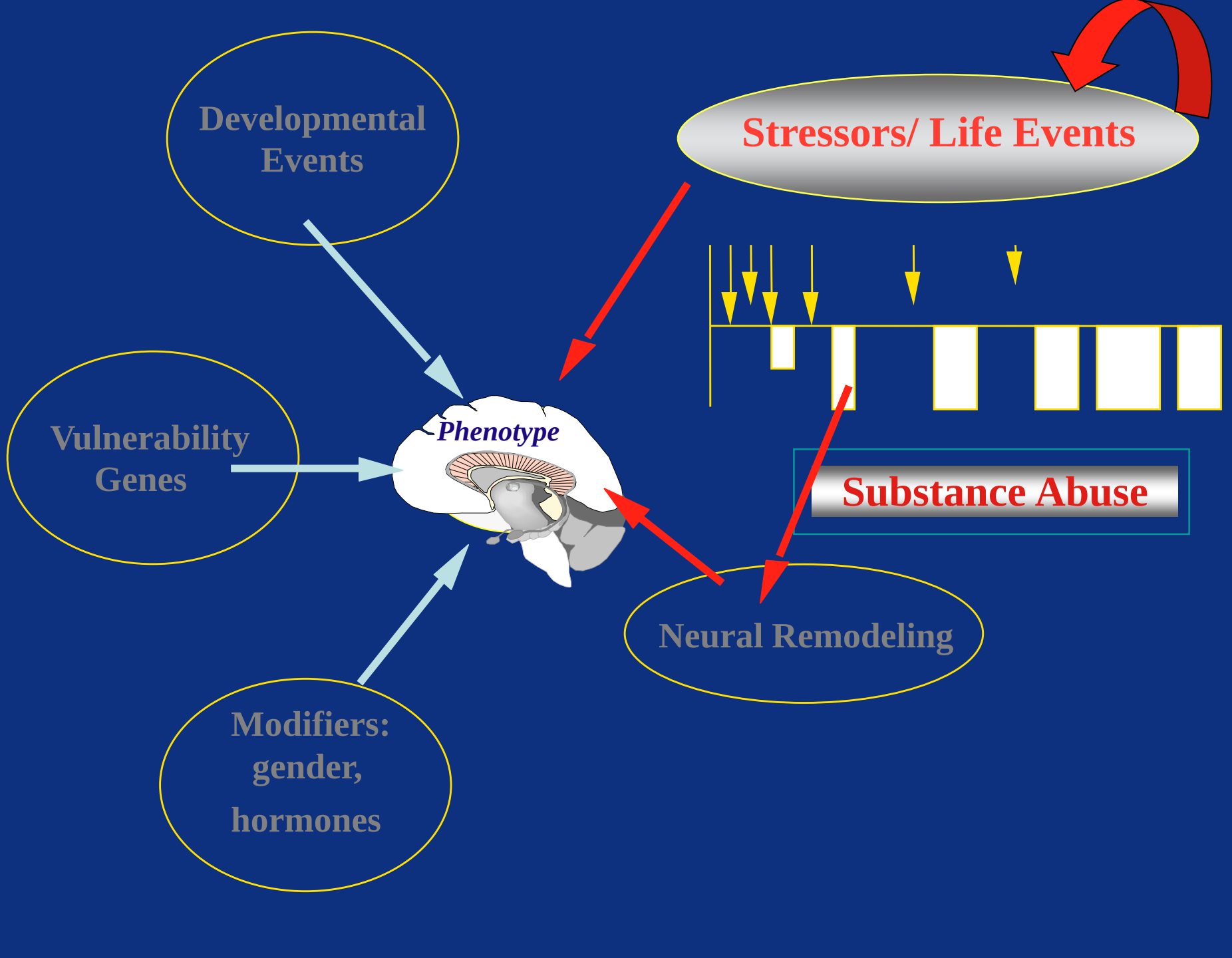
Abstinence Makes the Differences Grow Larger



Differences in Gene Expression Can be Due To:

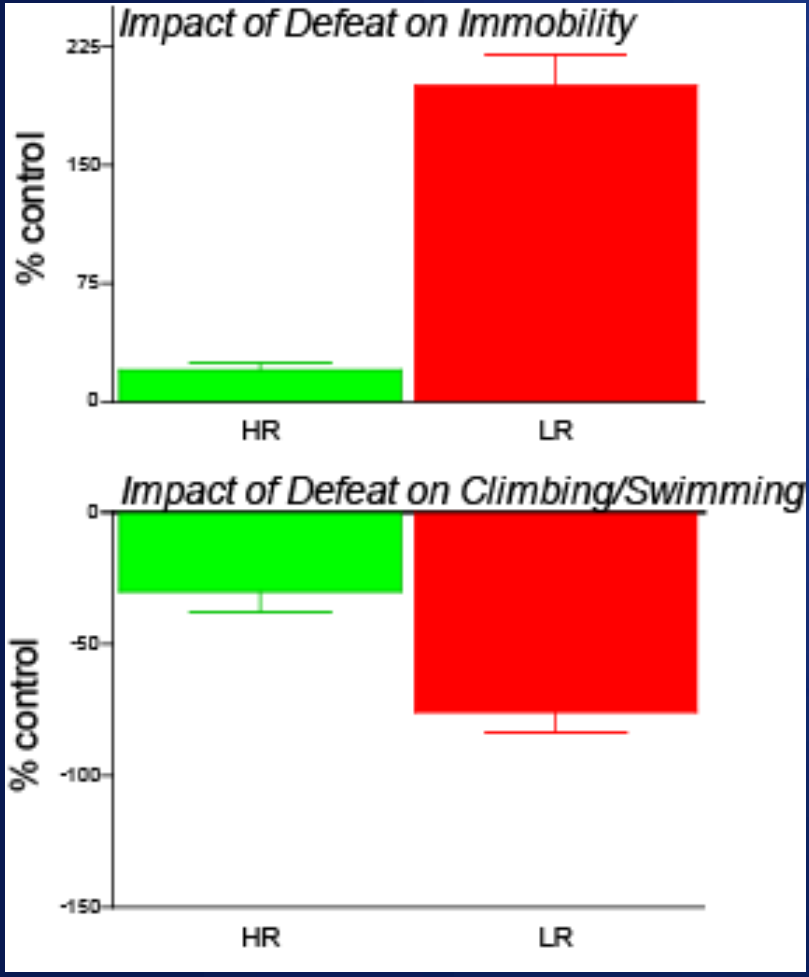
- Genetic Differences: SNPs, Insertions, Deletions
- Developmental Differences
- Regulatory Differences: Promoter Regulation
- Regulatory Differences: microRNAs
- Regulatory Differences: Epigenetics such as Methylation And Histone Acetylation.

Each Can Be Basal or In Response to the Drug or Interaction between the Two


Developmental Events
Stressors/ Life Events
Vulnerability Genes
Phenotype
Substance Abuse
Neural Remodeling
Modifiers: gender, hormones

The BEER doesn't fall far from the TRAILER

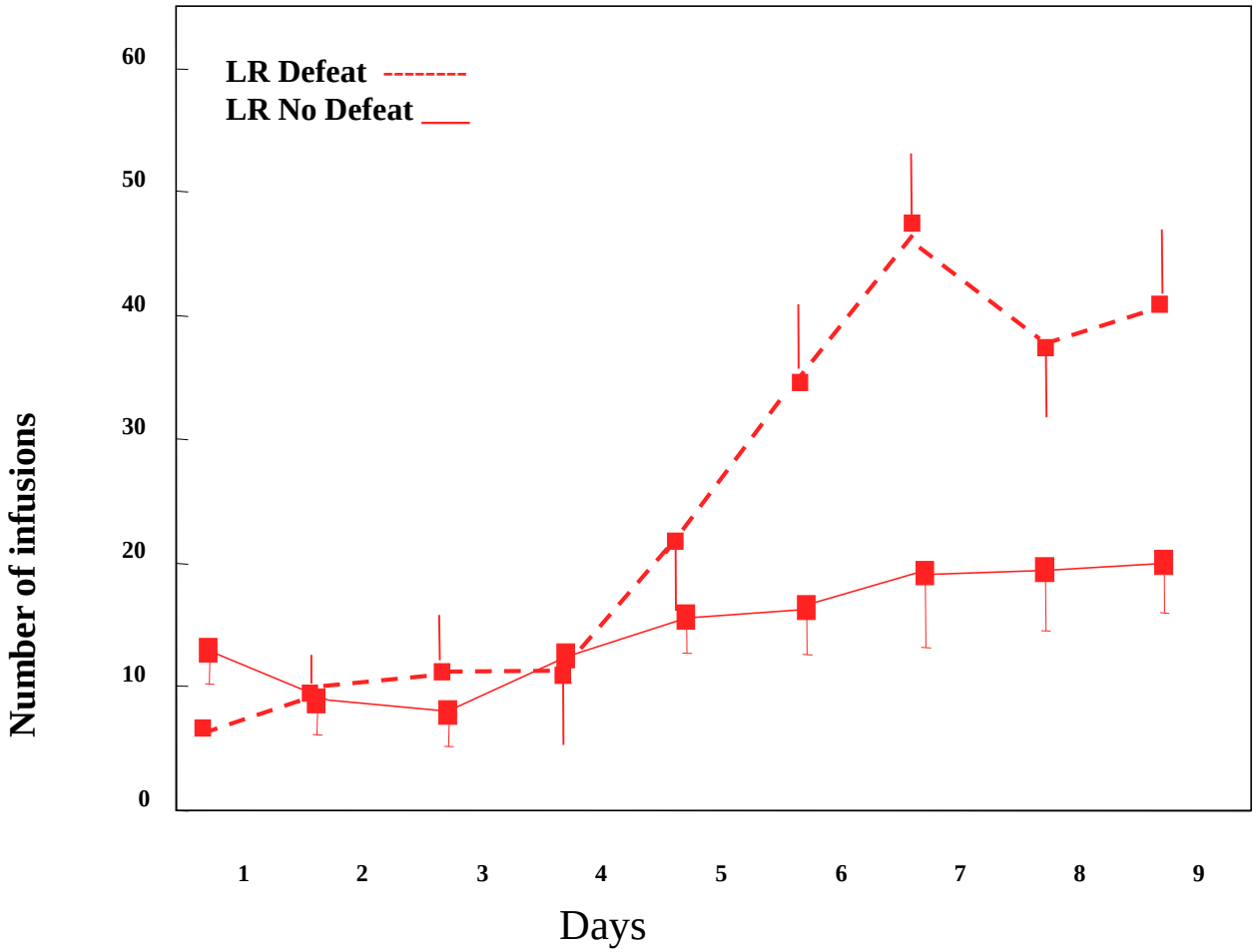
HR vs. LR response to Chronic Social Defeat



- We evaluated the impact of Social Defeat on depression-like behavior using the forced swim test (FST).
- Defeated LRs showed increased immobility (passive coping) and decreased climbing and swimming (data shown as % control).
- HR's performance was not dramatically affected by social defeat.

Clinton et al, 2008

Two Routes to Substance Abuse: Novelty-Seeking and Social Stress



Social Stress has little impact on Self-Administration in HRs

After Social Defeat, LRs and HRs take Equal Amount of Cocaine

Impact of Social Stress on HR vs. LR's

Social Stress Can have Differential Impact on the 2 groups:

- Social Defeat had a bigger impact on rendering LR's more HR-Like in terms of drug- seeking behavior

- Social Defeat further exacerbates the differences in "depressive behavior" between the two groups.

Two Paths to Substance Abuse: Molecular & Neural Mechanisms?

Can we begin to Uncover the Neural Changes that Might Drive the Drug Taking Behavior in Either Path?

Includes:

Gene Expression
Protein Changes
Epigenetic Changes
Changes in Neuronal Activity
Changes in Circuit Integration

HC: Microarray Analysis Reveals Differential Response in HR vs. LR to Social Defeat Stress

- ***Social Defeat had distinct effects in HR vs. LR Rats.***
- Changes in Gene Expression in LR particularly remarkable.
- These Altered Genes Include ***Growth Factors*** and Synaptic Molecules

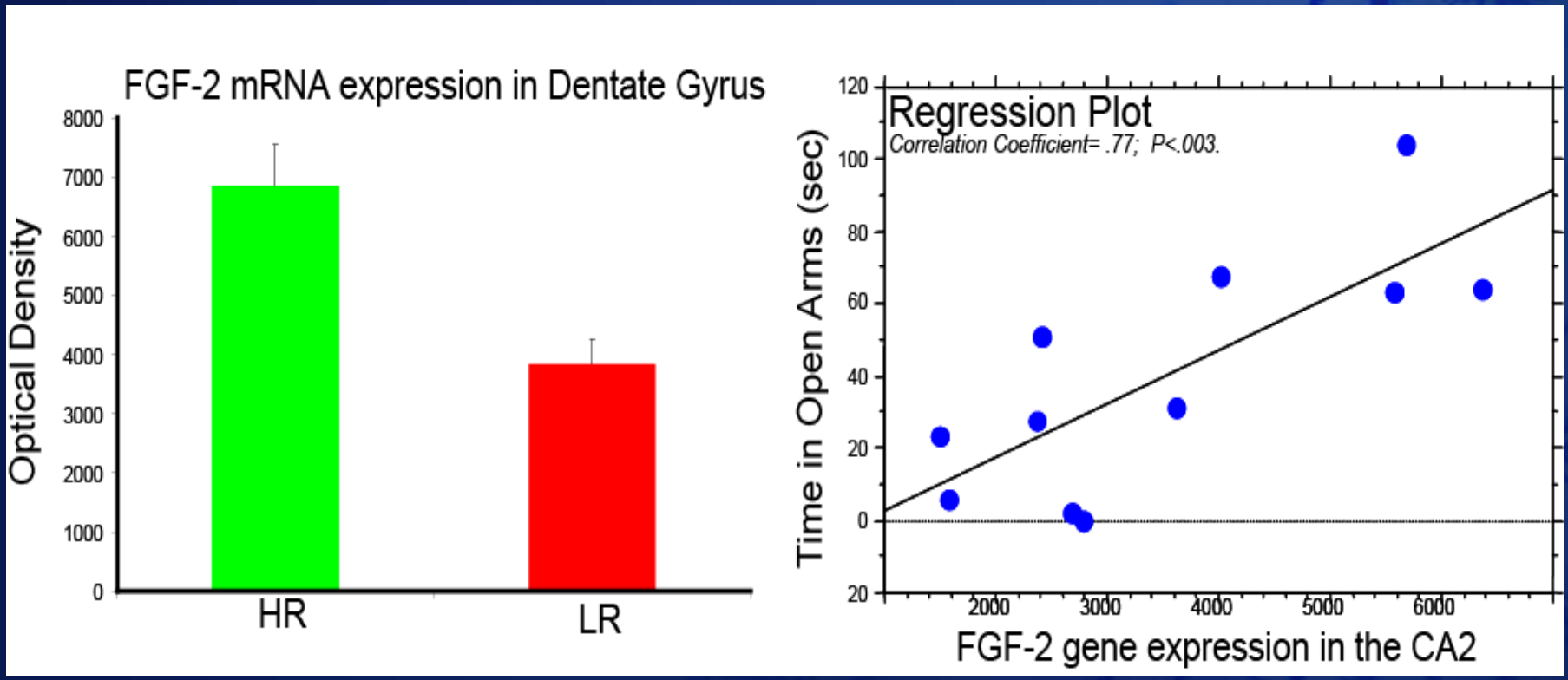
Hypothesis

Factors that Alter Brain Development and Structure May Play a Role as Antecedents to the HR-LR Phenotype, Response to Social Stress and to Substance Abuse Vulnerability.

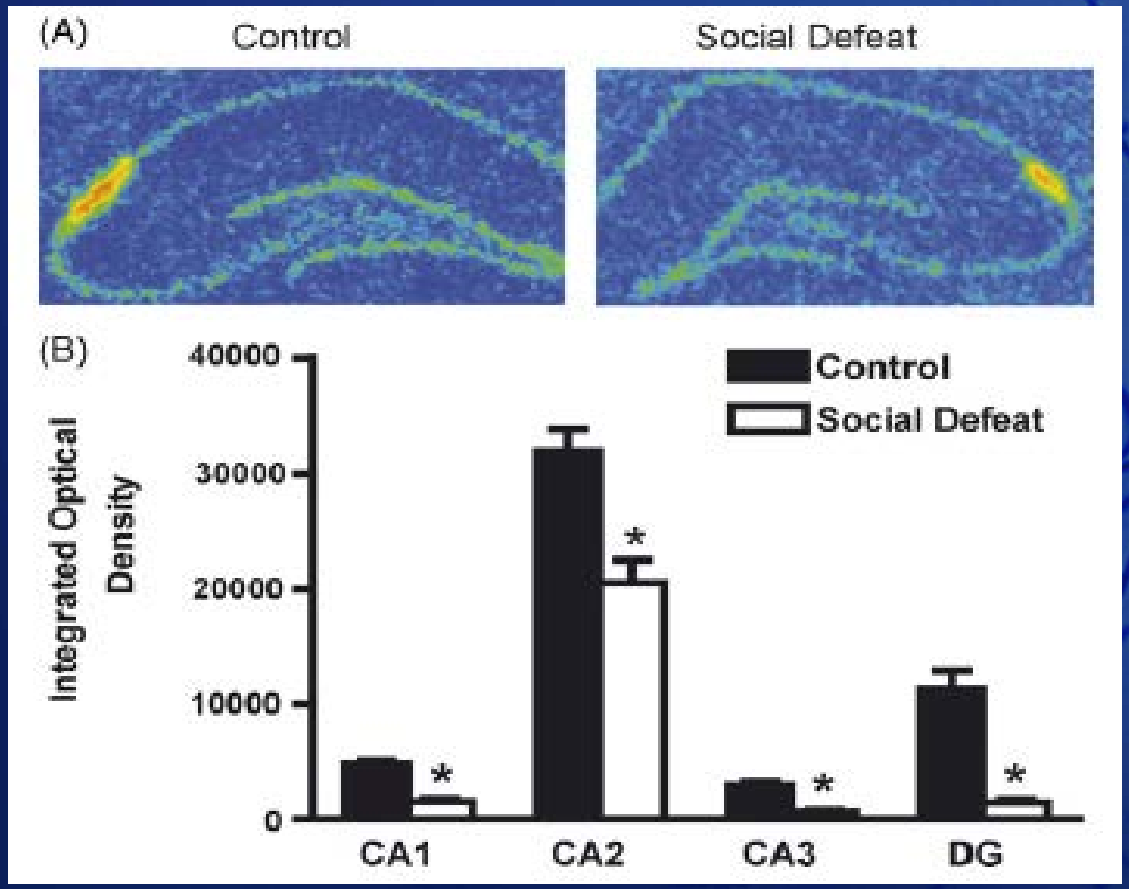
Concentrate on Factors that Appear to Affect Emotional Behavior.

Focus on the FGF Family- Highly Altered in Human Depression

Low FGF2 Levels associated with High Anxiety/Depressive Behavior



Social Defeat Decreases Expression of FGF2 and FGF R1: Parallels to Depressed Humans



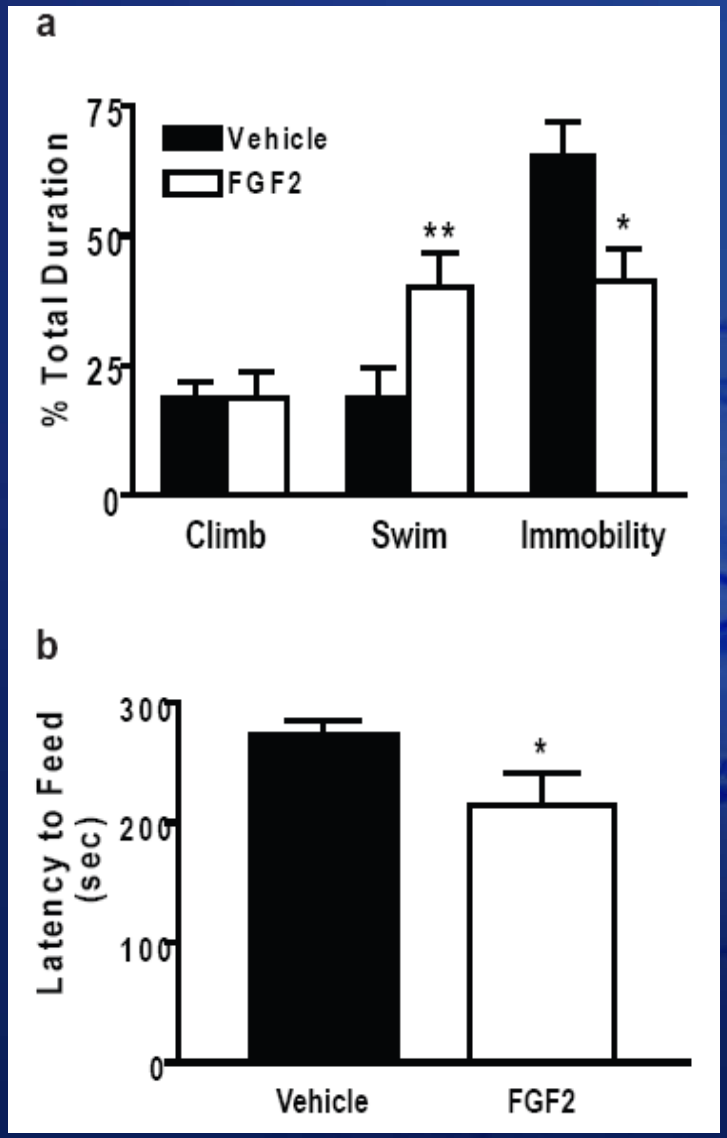
Following Four Days of Social Defeat.

Turner et al., 2008

Chronic Microinjections of FGF2 Decrease Depression-like Behavior, as Assessed by Two Independent Tests

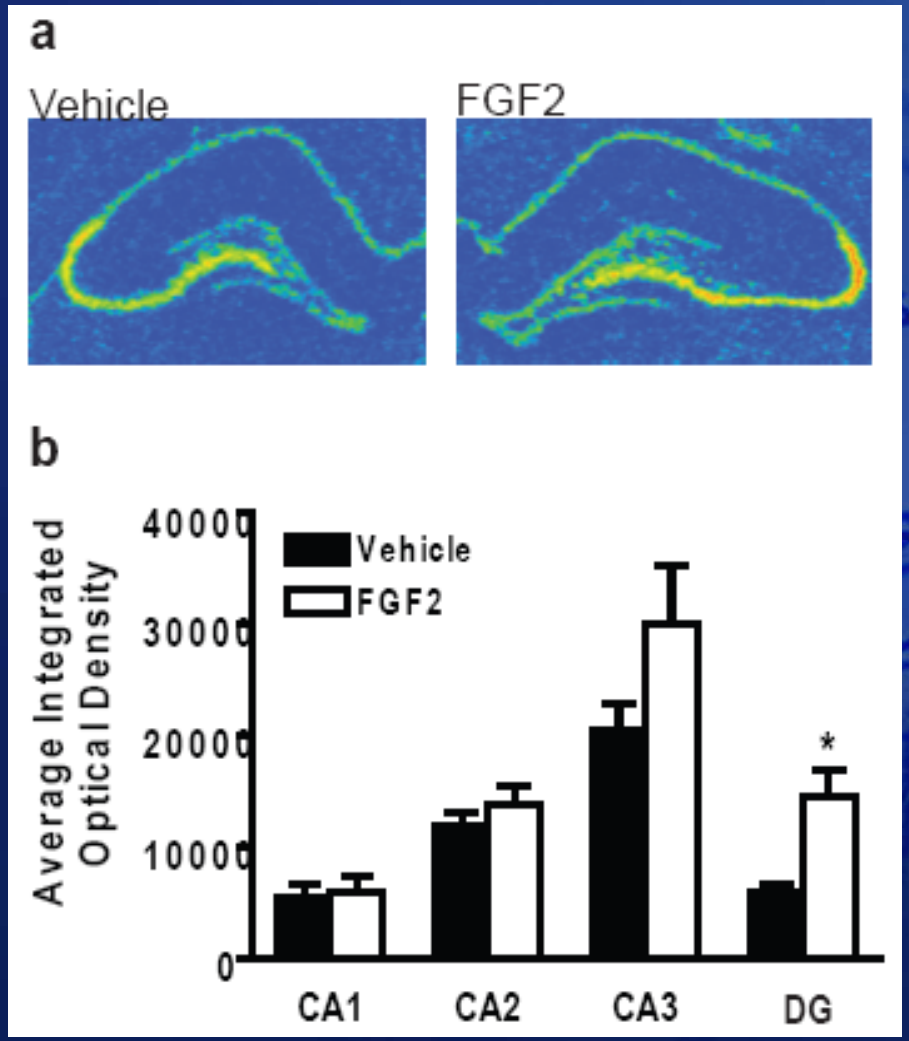
Forced Swim Test

Novelty-Suppressed Feeding



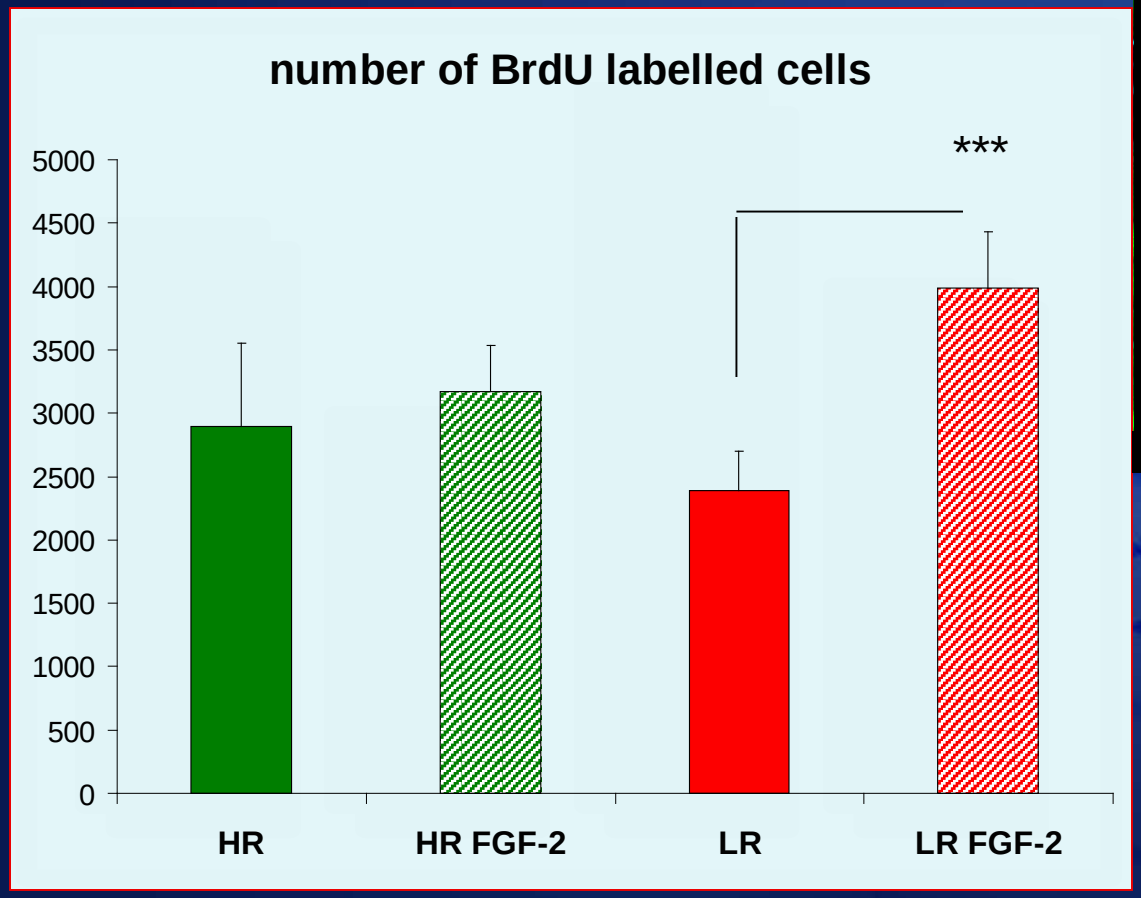
Turner et al., 2008

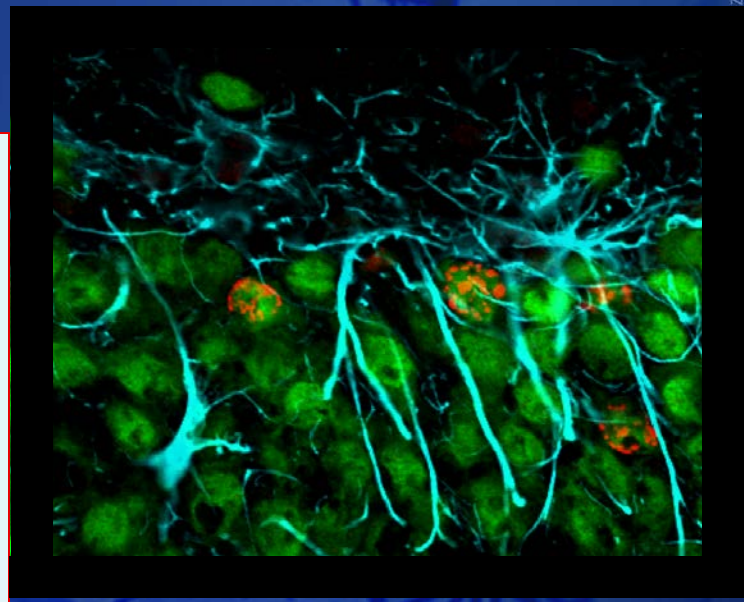
Microinjection of FGF2 Increases FGFR1 Gene Expression in the Dentate Gyrus



Turner et al., 2008

FGF-2 Administration Differentially Increases New Cell Survival in LR or High Anxiety Rats Only





Green = NeuN
Aqua = GFAP
Red = BrDU

Perez et al 2009

- *FGF-2 is Decreased by Social Defeat*
- *Exogenous FGF-2 can Change Affect, while Inducing its own Receptor*
- *Therefore FGF2 May Mediate the Effects of Social Defeat on Behavior.*
- *Cocaine induces FGF2 and FGF2 is Required for Sensitization*

Can Increased Cocaine Self-Administration in LRs be a Way to Offset the Impact the FGF2 Deficit Induced by a Combination of Genetic Predisposition and Impact of Stress?

Genetic Background, FGF2 and Social Defeat

Would Administering FGF2 after a chronic social stressor not only work as an antidepressant but also prevent the propensity to seek drugs?

Would that work only for LRs, who have natively low FGF2 and respond strongly to social defeat, but not for HRs, who have basally high FGF2?

Personalized Medicine for Rats!

Critical Future Direction:

BIOMARKERS!!

TRANSLATION INTO BIOMARKERS FOR HUMAN, NOT ONLY GENETIC VULNERABILITY BUT ALSO FOR FOLLOWING COURSE OF RESPONSE TO SUSBTANCE ABUSE AND RESPONSE TO POSSIBLE TREATMENT

BOTH CANDIDATE AND DISCOVERY APPROACHES

Cell image courtesy of Grazyna Gorny.

Consequences of Alcohol on End-Organ Pathology in Liver

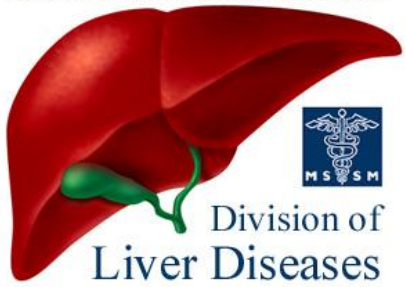
Perspectives on a Proposed NIAAA-NIDA Merger

Presentation to the SUAA Working Group of the SMRB
September 23, 2009

Scott Friedman, MD

- Fishberg Professor of Medicine & Chief, Division of Liver Diseases,
- Mount Sinai School of Medicine
- President, American Assn for the Study of Liver Diseases
- Member, NIAAA Advisory Council
- Grantee, NIAAA & NIDDK

The Mount Sinai School of Medicine



AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

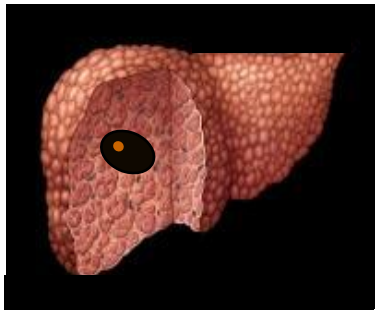
AASLD

Three Key Points

1. Overall impact of alcoholic liver disease and its distinct features
2. Unique role of NIAAA in integrating alcohol research
3. Direct impact of an NIAAA-NIDA merger

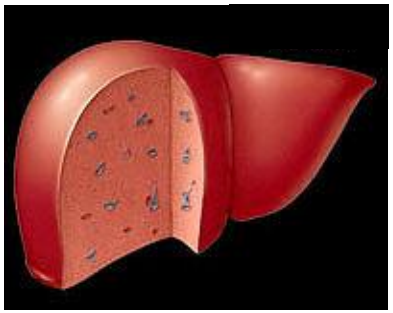
Impact of Alcoholic Liver Disease

Hepatocellular Carcinoma

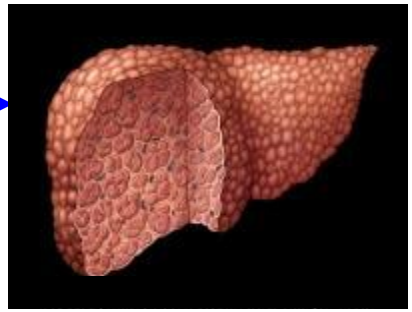


Alcoholic liver injury with fibrosis

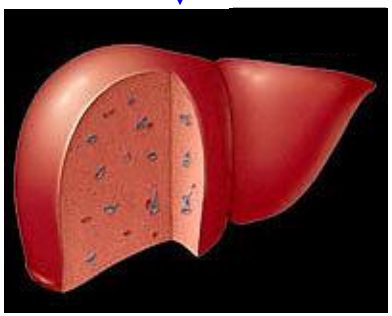
10-50 yrs



Normal liver



Cirrhosis



Liver Transplant

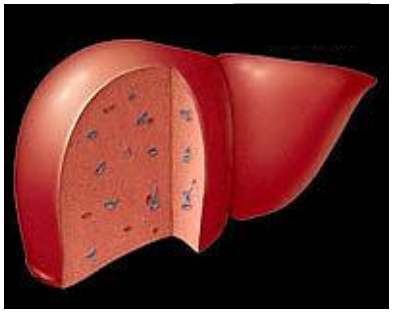
- **2 million Americans** suffer from alcoholic liver disease
- **30,000 deaths** from alcoholic liver disease each year

Impact of Alcoholic Liver Disease in the United States

- Alcohol use, together with hepatitis C (HCV) & hepatitis B (HBV) accounts for 70-90% of all cases of chronic liver disease in the Western world
- Up to 44% of patients with chronic HCV have a history of alcohol abuse
- Alcoholic liver disease accounts for ~ 20% of liver transplantations in the United States
- Alcohol abuse is an independent risk factor for liver cirrhosis and primary liver cancer (hepatocellular carcinoma)

Unique Features of Alcoholic Liver disease

- The liver is the main site of alcohol metabolism

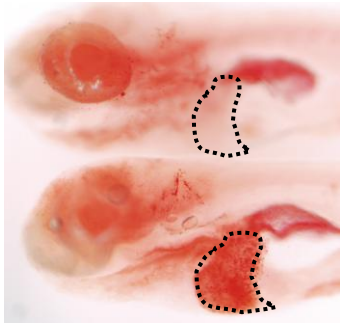
Ethanol →  ADH → *Acetaldehyde*

Cyp2E1 → ***Free radicals***

- Liver disease affects:
  - immunity
  - metabolism (protein, fat, and carbohydrate homeostasis)
  - bacterial clearance
  - drug detoxification

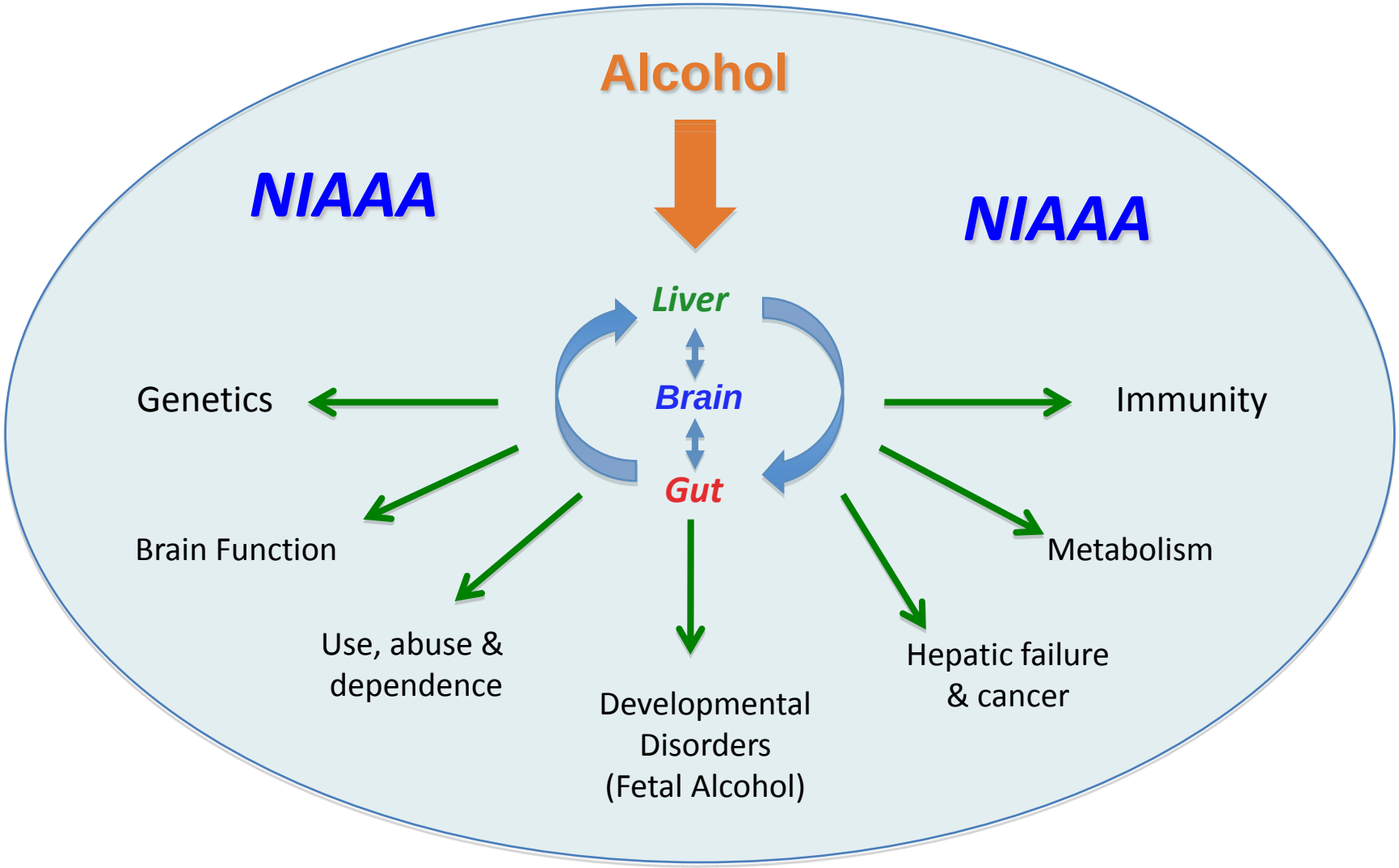
Milestones in Alcoholic Liver Disease
Leading to improved Health, supported by NIAAA

- Liver inflammation is precipitated by gut-derived pathogens due to altered intestinal permeability – relevant to ALL forms of liver disease
- Alcoholic liver injury results from 'multiple hits'
- Studies of alcoholic liver injury uncovered new pathways and models relevant to fatty liver from obesity and other etiologies:
  - Role of oxidant stress and disordered fat metabolism
  - New models, e.g., zebrafish



Work of K. Sadler-Edepli, PhD, NIAAA Grantee

The Multisystem and Inter-related Effects of Alcohol are Uniquely Integrated by NIAAA



Proposed NIAAA-NIDA Merger: *Concerns*

- NIAAA has successfully and uniquely integrated the study of alcohol's effects on behavior, physiology, & pathology
- Integrated study of multi-organ damage has not been a focus of NIDA; this critical perspective may wither following a merger
- The impact of alcoholic liver injury and collateral effects on the health of Americans are significant and merit dedicated support
- It is uncertain what will be gained by an NIAAA-NIDA merger, but likely that much will be lost

Presentation to the
NIH Substance Use, Abuse, and Addiction Working Group
Scientific Management Review Board
September 23, 2009

Alcohol Use in the U.S.: A Behavioral Perspective

Mark Goldman, Ph.D.
Distinguished Professor, Univ. of South Florida
Former Associate Director, NIAAA, 2003-2006

Considerations:

- (For humans) Behavior is biology actively interfacing with social/cultural environment to maximize evolutionary fitness
- In Western World, culture of alcohol use is pervasive
- Culture of alcohol use has uniqueness, and associated large public health burden
- Scientific organization should intimately understand and reflect uniqueness

- Like Darwin: Encourage cultural variation (among institutes), optimized to public health problem addressed
- Create more interplay (e.g., program officers on extended assignment to other institutes; not just NIAAA and NIDA)
- Create multi-institute working groups to explore behavioral overlap (e.g., other drugs, eating, resistance to healthy behaviors, personality problems, etc.), and perhaps find common remedies

Contextual/Cultural Behavioral Issues Faced by NIAAA

- **Legal (over 21); unique history (prohibition on/off)**
- **Encouraged in General Society (even <21)**
- **Legal industry exists, with extensive advertising**
- **Health and food benefits**
- **Social benefits (President's Beer Summit)**

Use is NORMATIVE, and woven into the fabric of U.S. culture across all ages and ethnicities.

Problems emerge for some from general use based on G/E interplay

G/E interplay

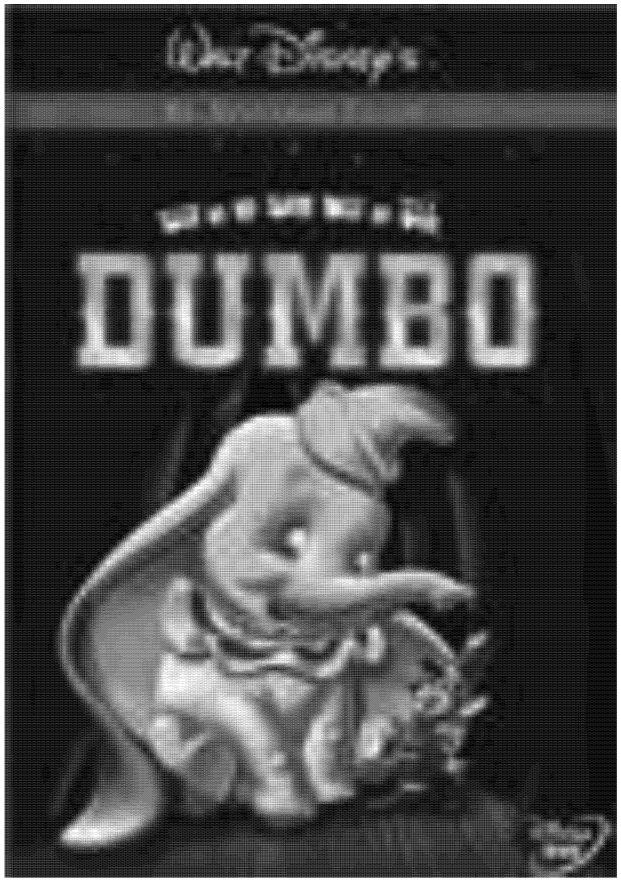
- Interaction
- Correlation (passive, active)
- Evocation (can escalate behavioral pattern)

Unique G/E interplay patterns related to alcohol culture in U.S.

Influences Developmental Pathways Over Lifespan

- Different behavioral patterns
- At different developmental periods
- Vulnerability, Resilience
- Oscillations, Exacerbations, Persistence, Desistence

Epigenesis influenced by unique U.S. alcohol culture


Walt Disney's
DUMBO

Example in one phase of development (Adolescence):

"…brain sculpting…(along with) certain adolescent-characteristic behaviors, including increases in risk-taking…and increased focus on social interactions with peers, are evident not only for human adolescents but also for their counterparts in other species." (p. S245)

Masten et al. (2008), Pediatrics

Risk-taking (a personality characteristic):

increase(s) the probability of reproductive success for male individuals of a variety of species, including humans…

facilitate(s)…emigration of sexually maturing adolescents away from genetic relatives" (p.245)

Masten et al. (2008), Pediatrics

Alcohol Response (Pharmacology) in Adolescents:

⇧ **social** facilitation.

⇩ aversive effects of acute alcohol intoxication (sedation, hangover, ataxia).

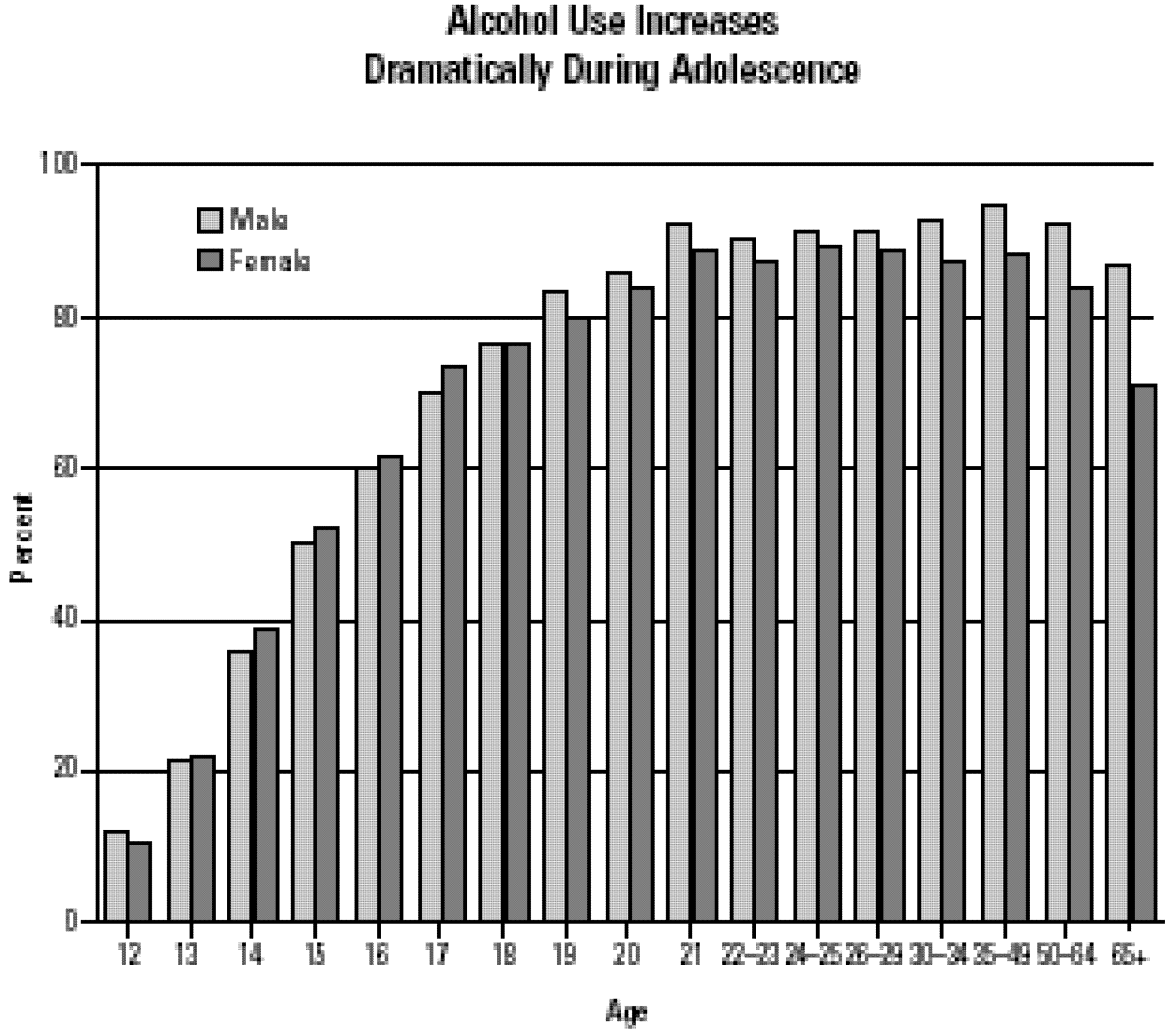


Figure 1: Percentage of Americans Who Have Ever Drunk Alcohol (A Whole Drink)

Source: SAMHSA data from 2005 National Survey on Drug Use and Health (NSDUH)

U.S. Drinking:

144 million Americans of all ages drink alcohol **(**65% of the U.S. adult population)

Of those, **126 million** do NOT have an Alcohol Use Disorder (87.5% of drinkers)

from NESARC

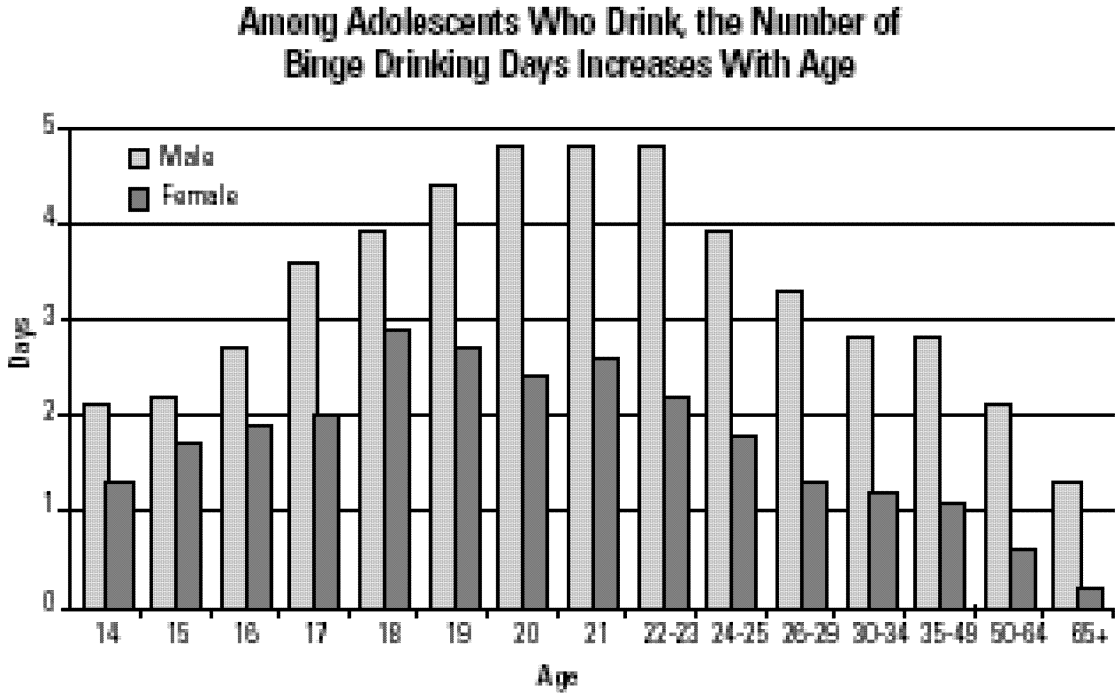


Figure 5: Number of Days in the Past 30 in Which Drinkers Consumed Five or More Drinks, by Age and Gender.

Source: SAMHSA data from 2005 NSDUH

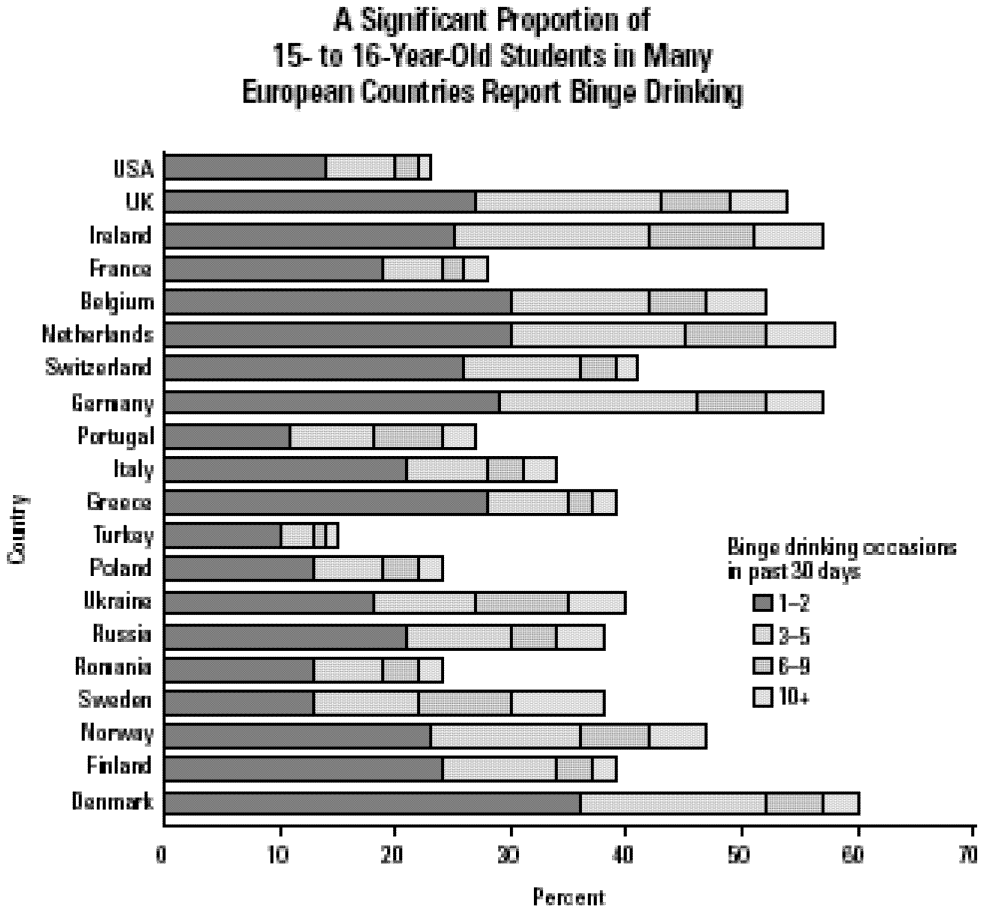


Figure 7: Percentage of European Students Ages 15–16 Who Have Engaged in Binge Drinking (5+ Drinks) Within the Past 30 Days.

Source: Hibell et al. 2004 (data from European School Survey Project on Alcohol and Drugs, 2003)

Despair grows over 'broken Britain'

Binge drinking teens, knife crime and teen pregnancies are signs "we've lost our way."

Associated Press

LONDON — Ahhh, Britain. The land of Shakespeare and the Beatles, Churchill and the Queen. Rolling green hills, groovy London shops, hip plaids splashed over raincoats and umbrellas.

Cut to the reality of 2009: the highest teen pregnancy rate in western Europe, a binge drinking culture that leaves drunken teens splayed out in the streets and rising knife crime that has turned some pub fights into deadly affairs.

Ahhh, Britain.

In the latest symbol of what some are calling "broken Britain," 13-year-old Alfie and his 15-year-old girlfriend Chantelle became parents last week. The news sparked a flurry of hand-wringing from the media — and even ordinary folk admitted it didn't help that Alfie barely looked 10, let alone 13, as he cradled his newborn daughter.

Associated Press

Teens drink alcohol on a street corner in Hebburn, England, Friday. The problem of youthful binge drinking shows up in a rise in liver disease among Britons in their 20s.

Alfie's father, who reportedly has nine or 10 children of his own, gamely promised to have a "birds and the bees" chat with his son to prevent him from producing a second child before he grows facial hair.

Somehow that was not reassuring.

Sir Bernard Ingham, once press secretary to former Prime Minister Margaret Thatcher, said people from across Britain's political spectrum are in despair over the country's social breakdown.

"It's an indication that we've lost our way, that people don't know the difference between right and wrong," he said of young Alfie. "The plain fact is society can't proceed on this basis. I think this is an indication of broken Britain."

Ingham said Britain's binge drinking and youth violence reflect the same general fall in standards and discipline.

"I think in time there will be a swing against this permissiveness," he said, noting a shift from British debauchery in the 18th century to Victorian straight-laced standards 100 years later.

Binge drinking has produced a rise in liver disease among Britons in their 20s and the unpleasant reputation of British "lager louts" at holiday resorts across Europe.

On any given night, London residents can see drunken teens staggering through the Underground subway system. Usually their friends help them, but sometimes collapsed teens are left on their own until police or transit staff intervene.

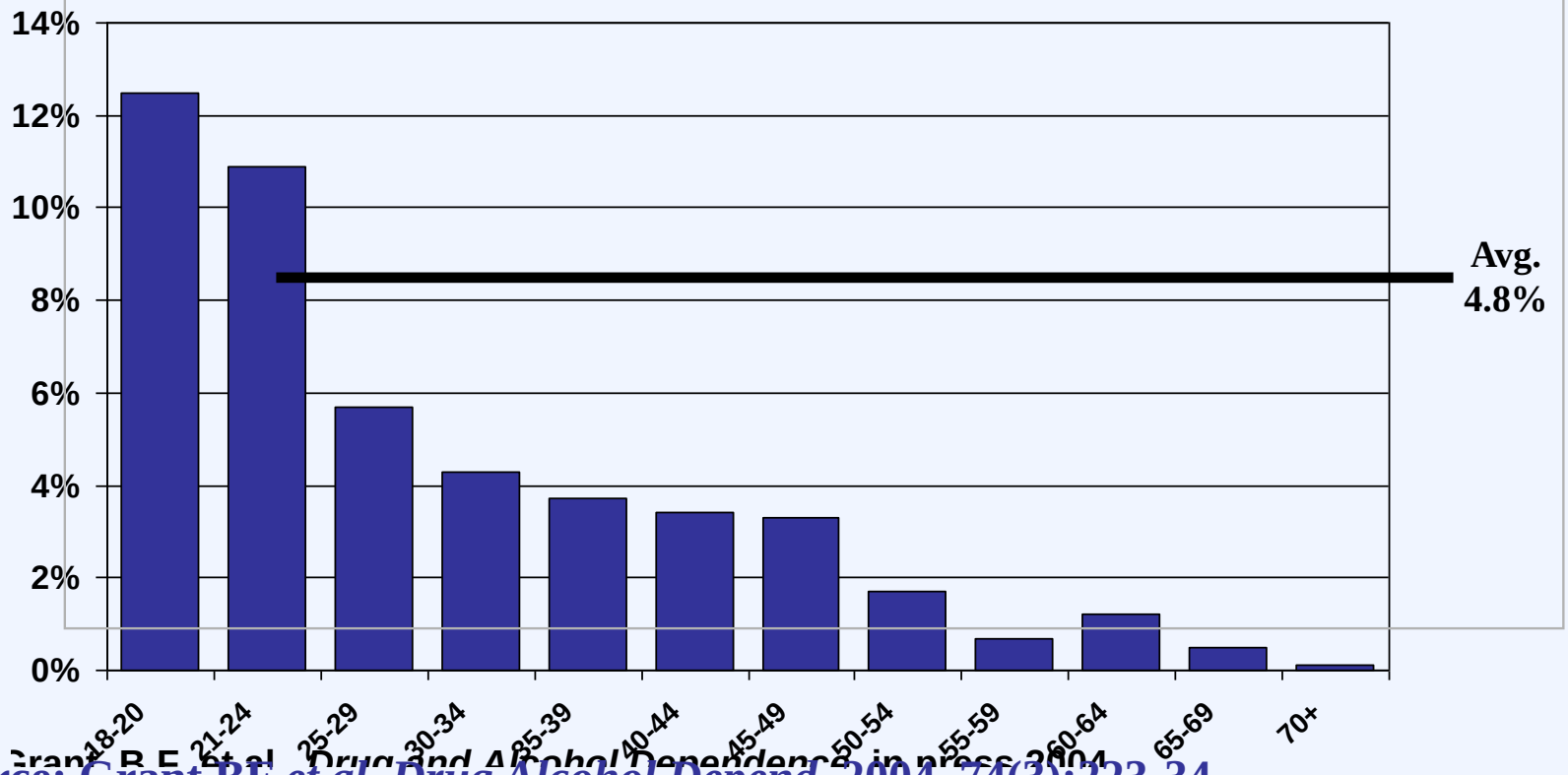
The rise in knife crime harkens back to the 1950s *West Side Story* era in the United States. The number of robberies carried out with knives rose 18 percent for the third quarter of 2008 compared with the year before, according to government figures released in January.

Associated Press, February 16, 2009

In adolescents, direct effects specific to alcohol (in U.S.):

- Annually, about 5,000 youth under 21 die from alcohol-related injuries (79,000 deaths across all ages, 1/3 fatal car crashes, ½ suicides/murders, 30% hospital admissions)
- Often a factor in physical and sexual assault and unintended sexual activity.

Prevalence of Past-year DSM-IV Alcohol Dependence: United States, 2001-2002



Source: Grant BF *et al. Drug Alcohol Depend.* 2004. 74(3):223-34.

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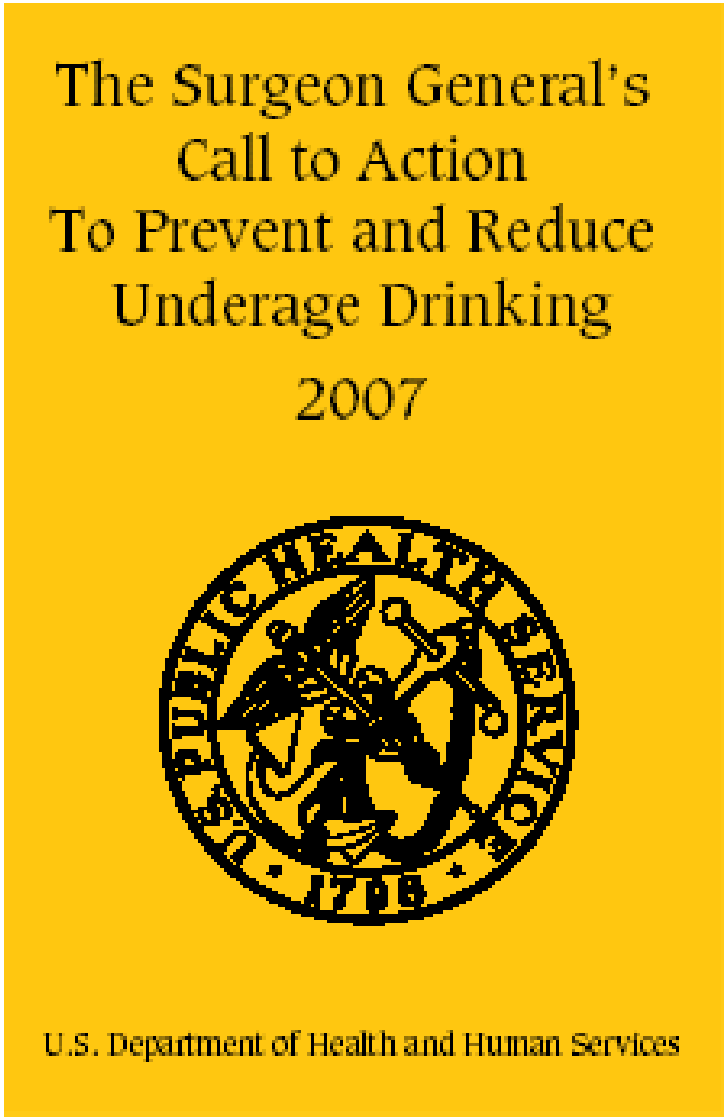
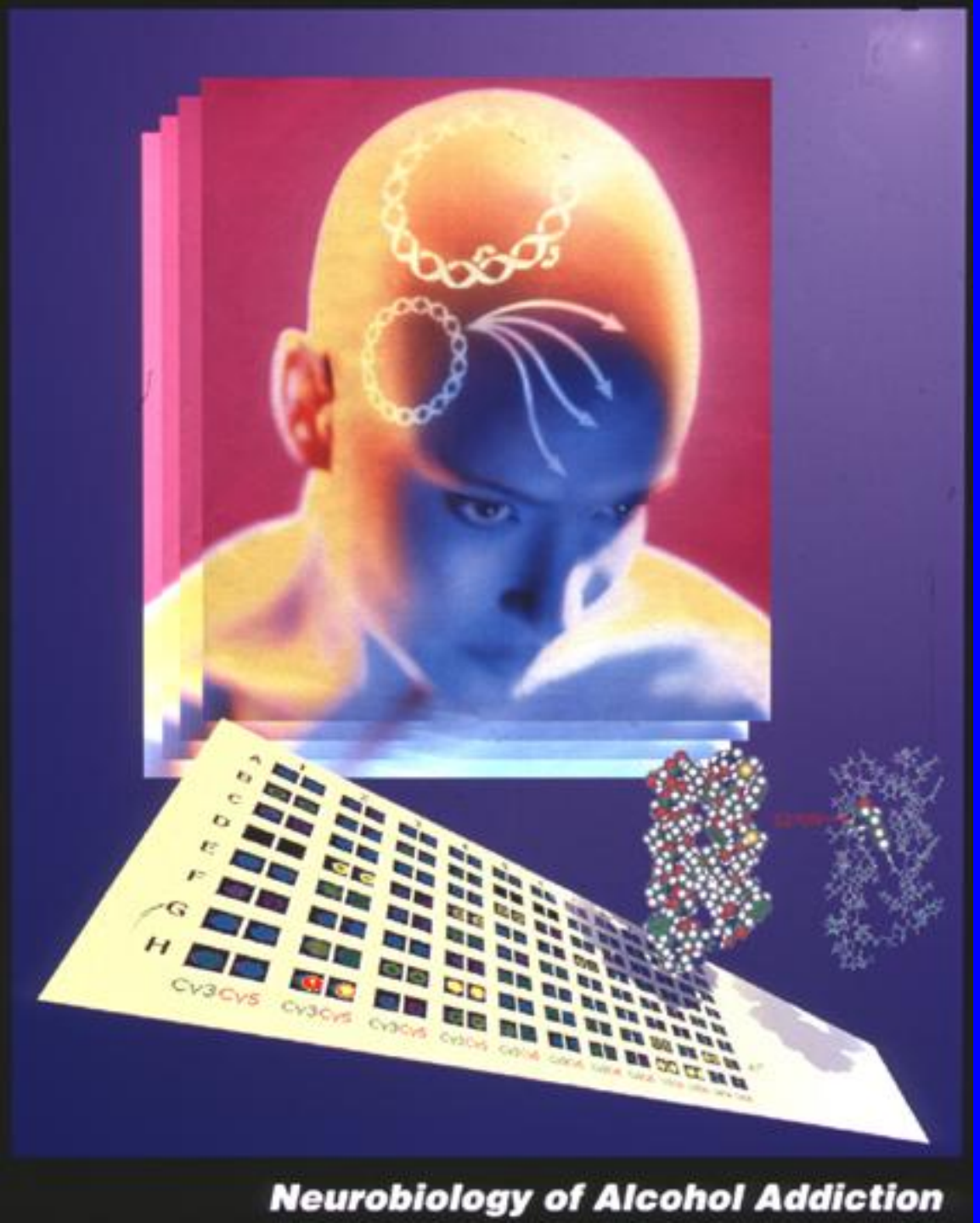


www.surgeongeneral.gov

The End

Thank you



Waggoner Center for Alcohol and Addiction Research

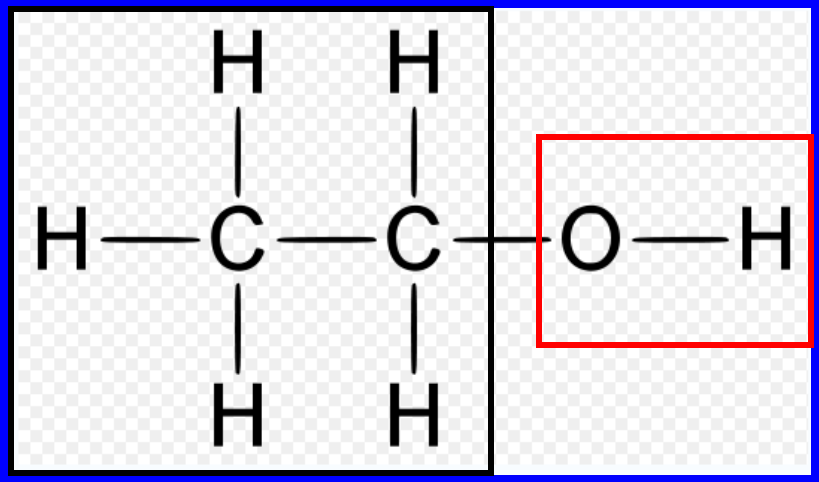
R. Adron Harris, Director

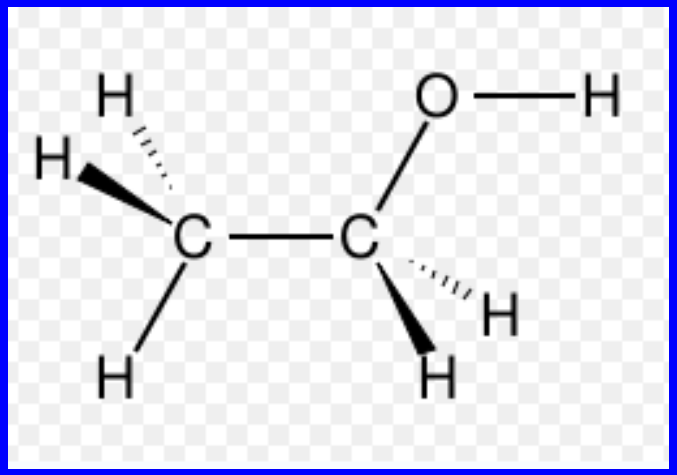
University of Texas Austin

Key Points

- Alcohol requires far higher blood levels than other drugs. As a result, it has more diverse molecular and cellular targets than other drugs
- The alcohol field has made excellent progress in molecular, behavioral and population genetics
- This work absolutely requires the integrated, multi-organ, systems approach which has successfully evolved within NIAAA

Ethanol



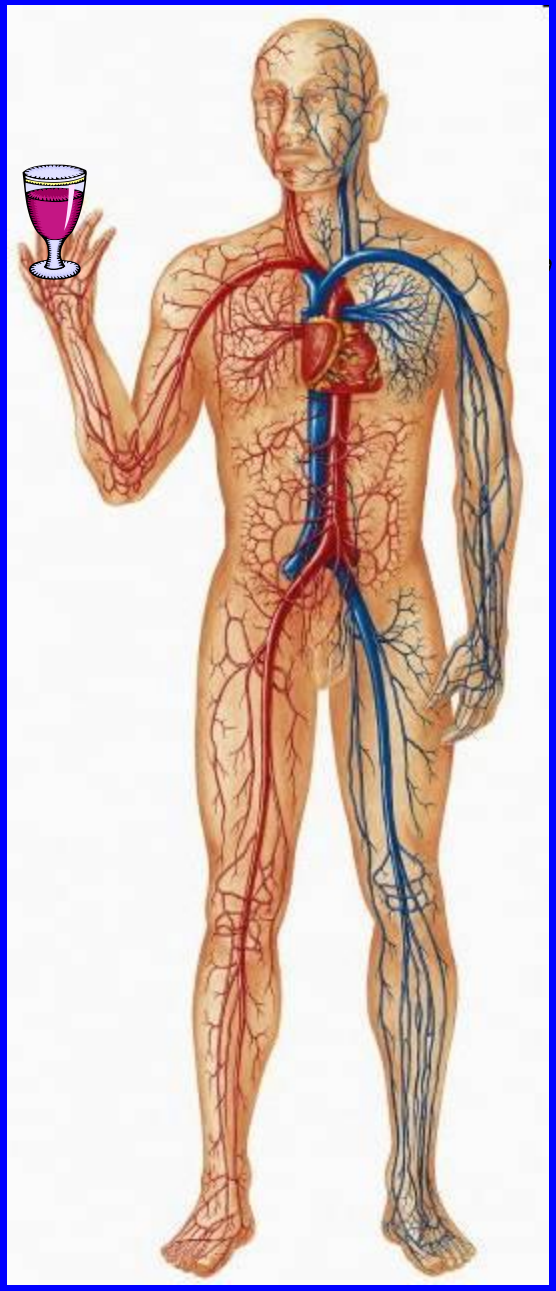


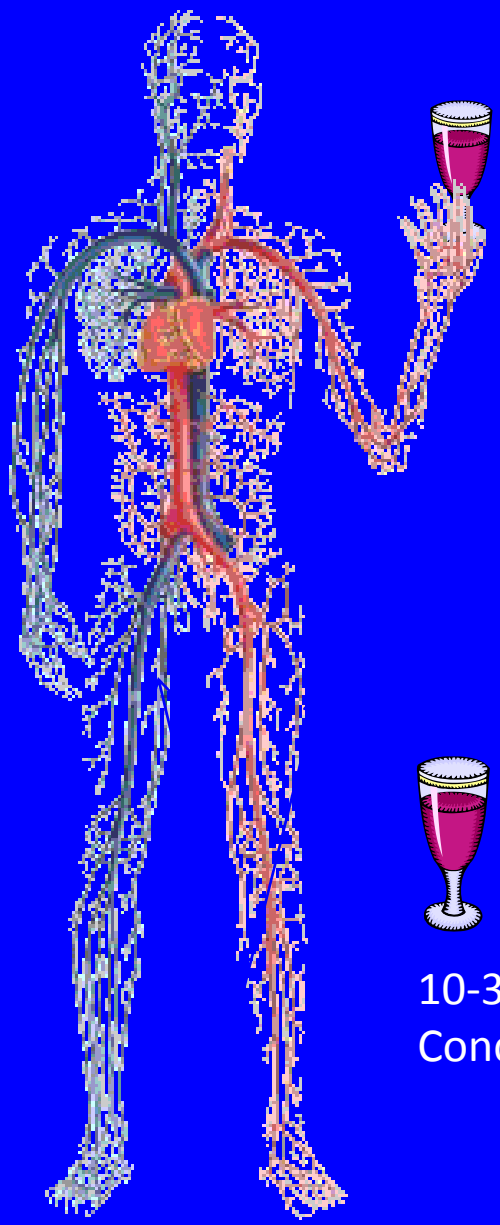
1. Small hydrophilic molecule. Low binding energy. Readily passes through biological membranes (timescale sec-min)
2. Interactions with biological targets
   a. Hydrogen bonding at –OH group
   b. Very weak hydrophobic interactions (-CH3 end of molecule)
   c. Results in low affinity (~mM) interactions with biomolecules

Driver's blood alcohol: 7.27

VILNIUS — Police were astonished by a breath test that registered 18 times Lithuania's legal alcohol limit for drivers. Police said Vidmantas Sungaila, 41, registered 7.27 grams per liter of alcohol in his blood repeatedly on different devices after he was pulled over Saturday for driving his truck down the center of a two-lane highway. Experts say anything above 3.5 grams per liter of alcohol in the blood is lethal for most people.

(A blood ethanol of 7.27 g/l is 158 mM)



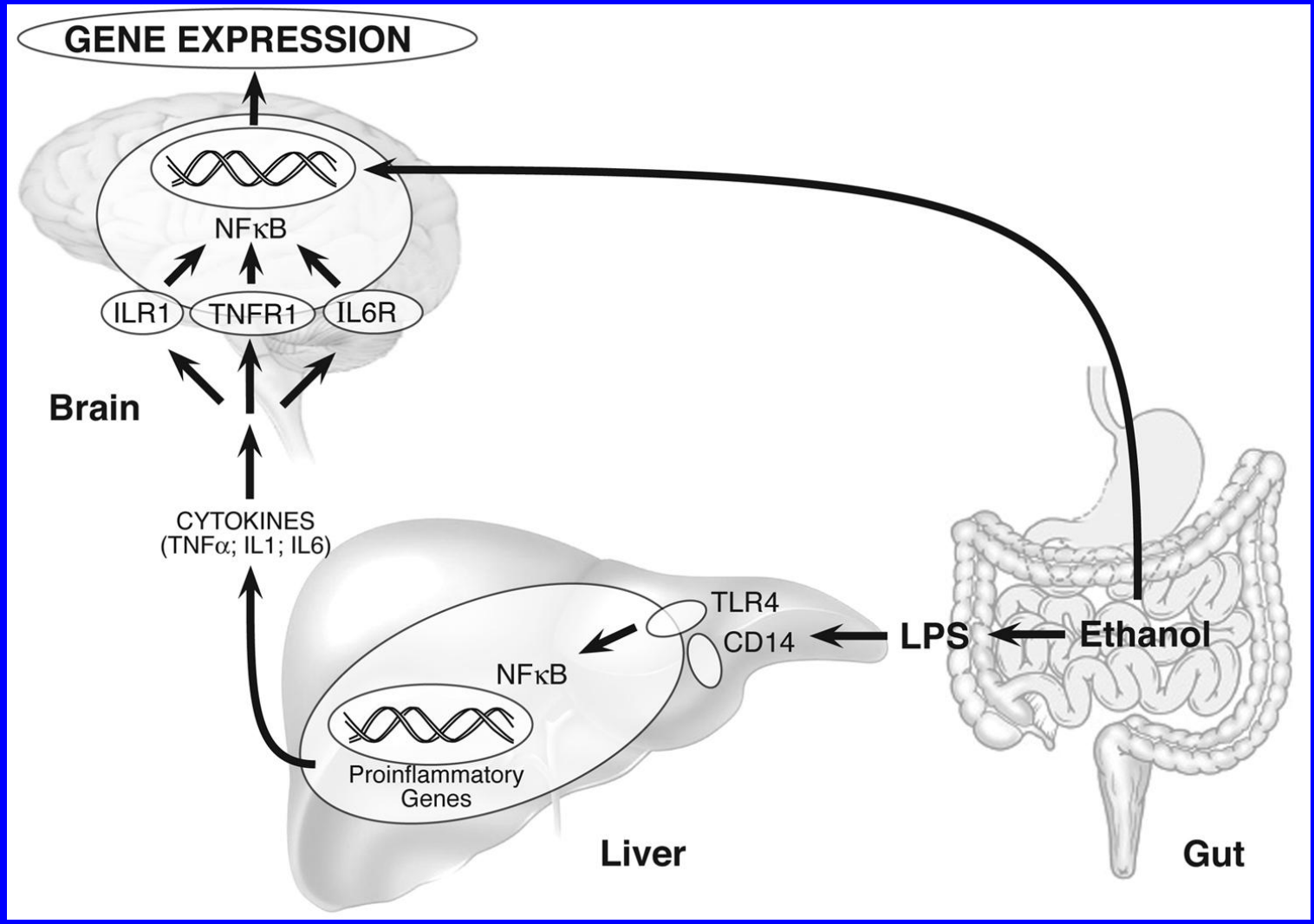


Wine has 2500 mM Ethanol

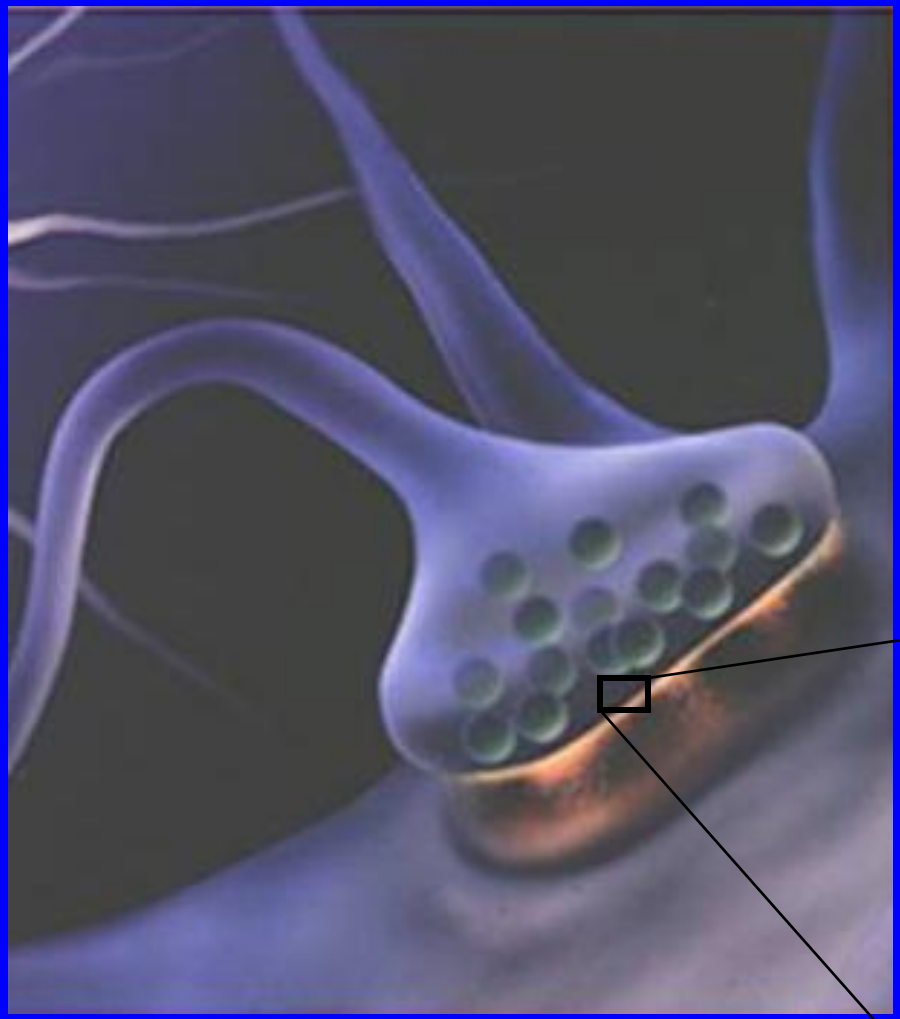
10-30 mM Blood Ethanol Concentration

The human gut contains an abundant bacterial flora. The inset shows a scanning electron micrograph of part of the small intestine, with bacteria shown in green. (Bajzer and Seeley)

Alcohol abuse causes bacterial toxins (LPS) to leak from gut and damage the liver and change gene expression in brain

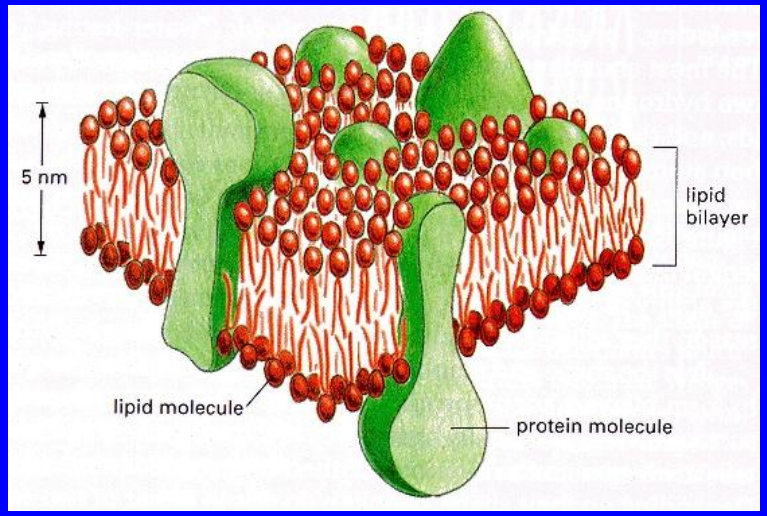


Synaptic Transmission: The Way Drugs Change Brain and Behavior

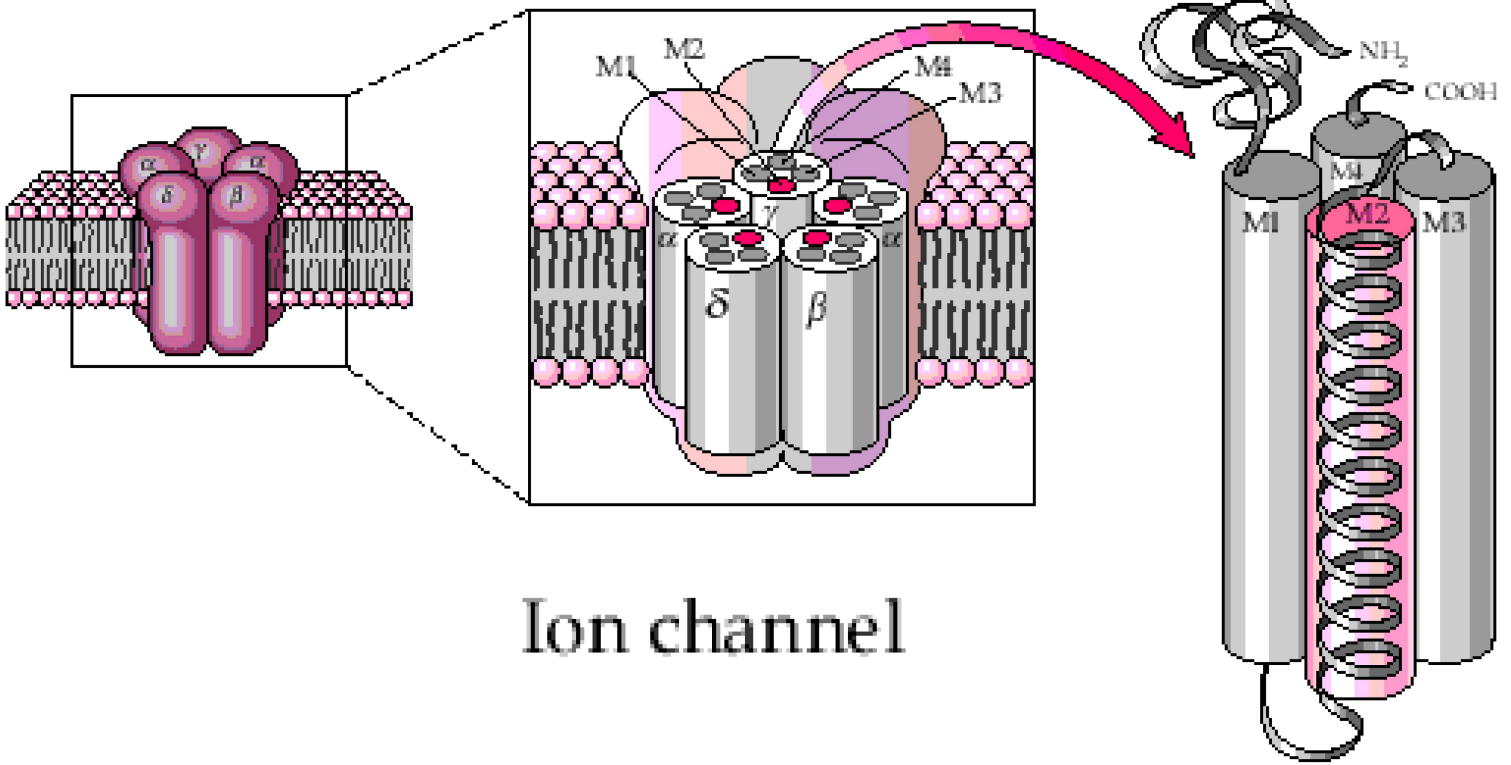


Chemical communication between neurons:

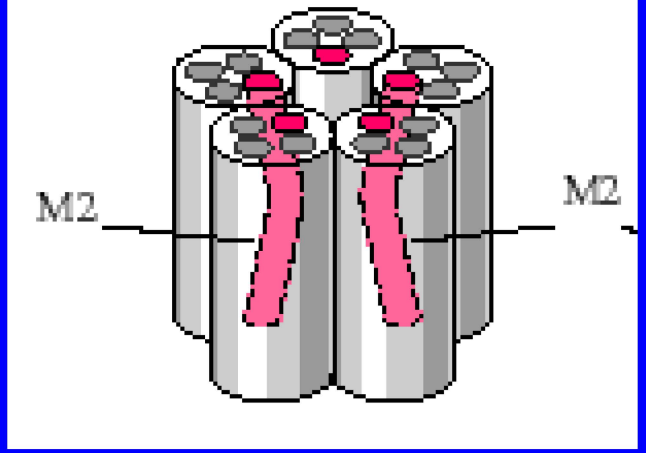
- Release of chemical messengers from one neuron
- Activation of specific proteins in the another neuron
- Excitation or inhibition of the neuron



Overall structure



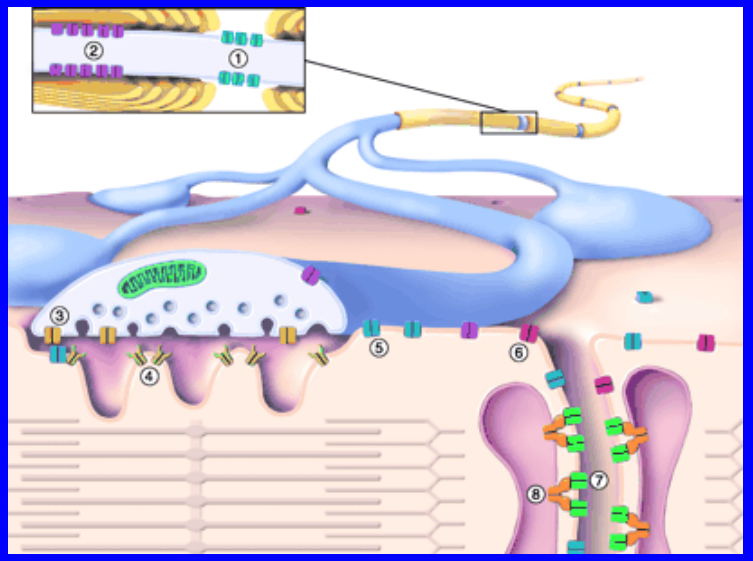
Ion channel



Nicotinic ion channel superfamily

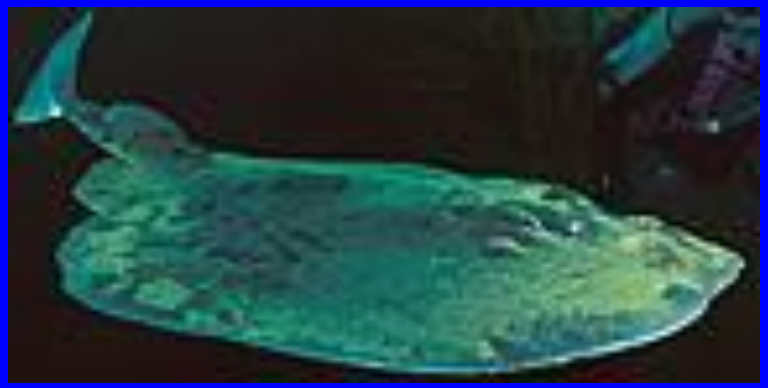
Cationic

- **Nicotinic Acetylcholine receptor (nAChR)**
- **5-HT_3 receptor**



Anionic

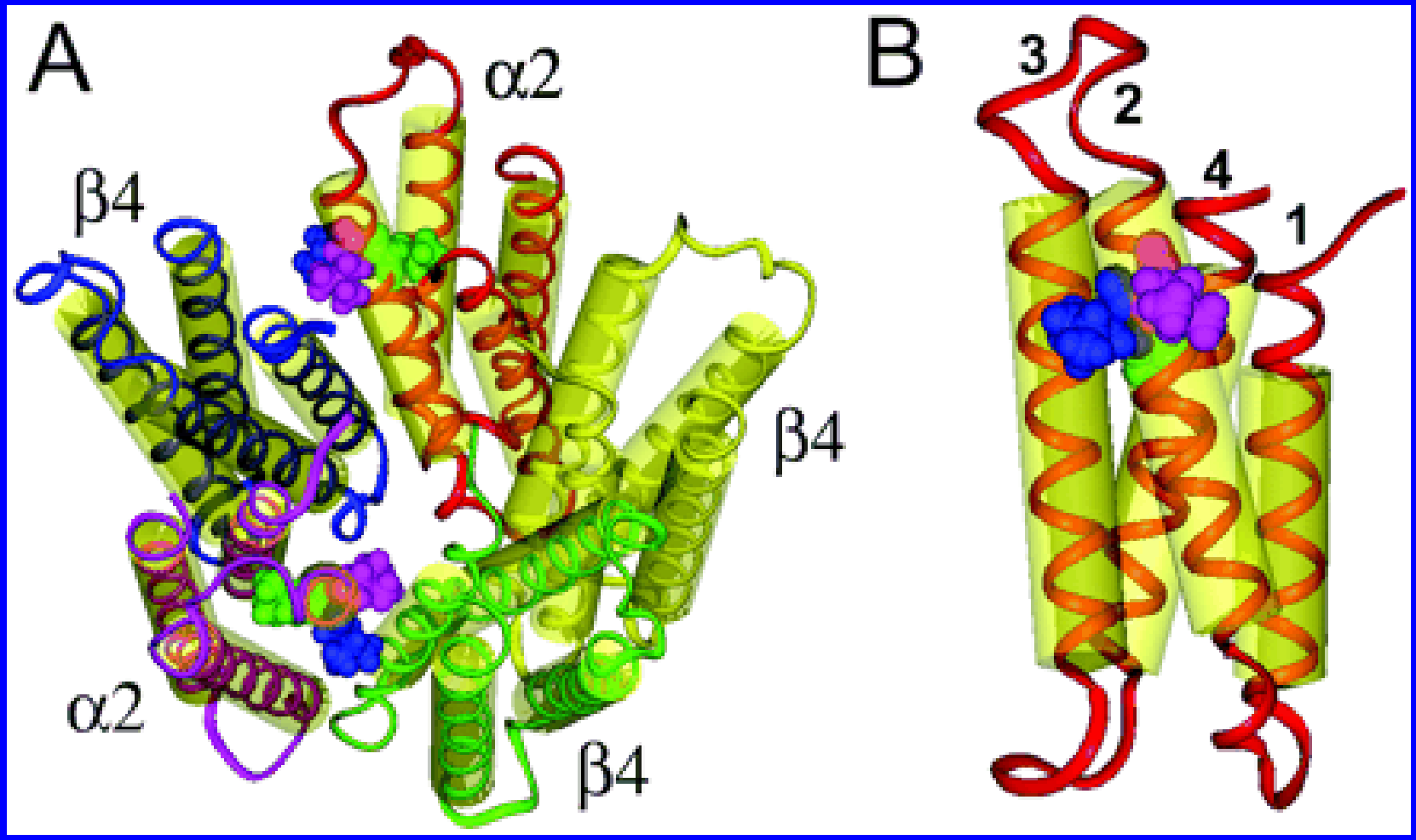
- **$GABA_A$ receptor**
- **$GABA_C$ receptor**
- **Glycine receptor**



Sites of Excitatory and Inhibitory Actions of Alcohols on Neuronal α2β4 Nicotinic Acetylcholine Receptors

C. M. Borghese, L. A. Henderson, V. Bleck, J. R. Trudell, and R. A. Harris

J Pharmacol Exp Ther. 2003 Oct;307:42-52.



Biol Psychiatry. 2009 July

Varenicline reduces alcohol self-administration in heavy-drinking smokers.

McKee SA, **Harrison EL**, **O'Malley SS**, **Krishnan-Sarin S**, **Shi J**, **Tetrault JM**, **Picciotto MR**, **Petrakis IL**, **Estevez N**, **Balchunas E**

Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut 06519, USA.
sherry.mckee@yale.edu

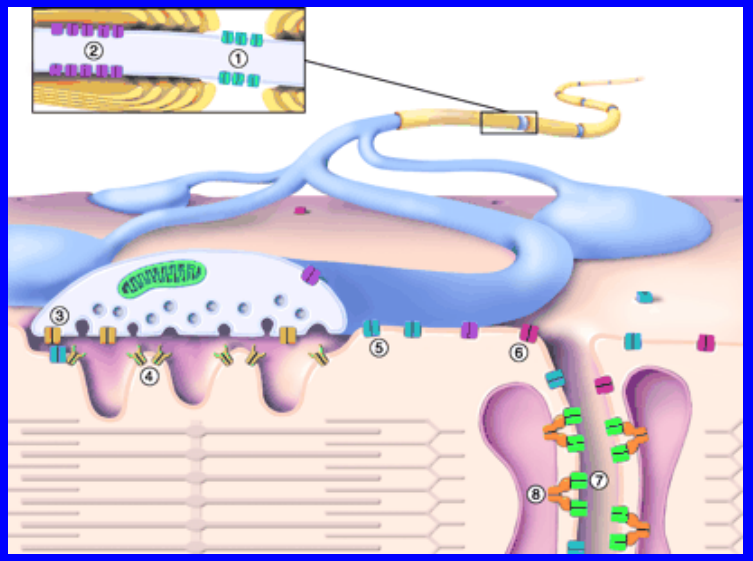
THE GENETIC BASIS OF ALCOHOL AND DRUG ACTIONS

EDITED BY
JOHN C. CRABBE, JR.
AND
R. ADRON HARRIS

Nicotinic ion channel superfamily
A role in genetics of human alcoholism?

Cationic

- Nicotinic Acetylcholine receptor (nAChR)
- 5-HT_3 receptor



Anionic

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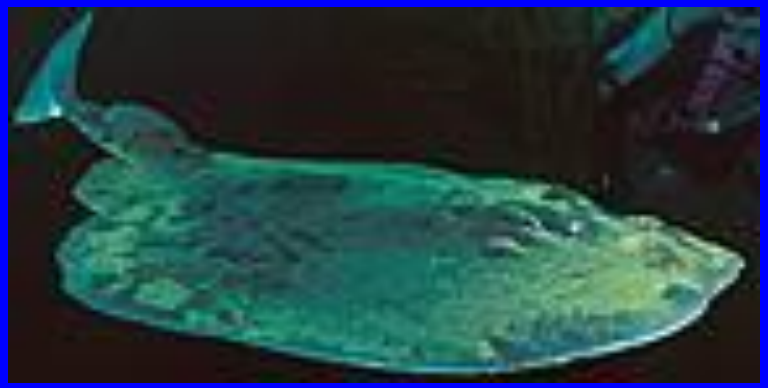
- $GABA_C$ receptor
- Glycine receptor



- *Neuropsychopharmacology* (2009)
- **_GABRG1_ and _GABRA2_ as Independent Predictors for Alcoholism in Two Populations**
- Mary-Anne Enoch, Colin A Hodgkinson, Qiaoping Yuan, Bernard Albaugh, Matti Virkkunen and David Goldman
- Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD

Summary

- Alcohol requires far higher blood levels than other drugs. As a result, it has more diverse molecular and cellular targets than other drugs
- The alcohol field has made excellent progress in molecular, behavioral and population genetics
- This work absolutely requires the integrated, multi-organ, systems approach which has successfully evolved within NIAAA

Thanks!

Effects of a Universal Prevention Program in First and Second Grade Classrooms on Young Adult Problem Outcomes: Implications for Research, Prevention and Treatment

Sheppard G. Kellam
Professor Emeritus JHU Bloomberg School of Public Health
AIR Center for Integrating Education and Prevention Research in Schools

NIH Scientific Management Review Board
Substance Use, Abuse, and Addiction Working Group
September 23 2009

The Developmental Epidemiology Strategy for Prevention Research

An integration of:

- Community epidemiology
- Life Course Development
- Preventive intervention randomized field trials

Developmental Epidemiology based Randomized Preventive Trials

- One of a set of current prevention research strategies
- Intervention is directed at early risk factor to reduce risk and improve developmental trajectories and outcomes
- Defining population helps control selection bias
- Periodic follow-up to determine impact on paths and outcomes—main effects and variation
- Allows study of who benefits and under what conditions

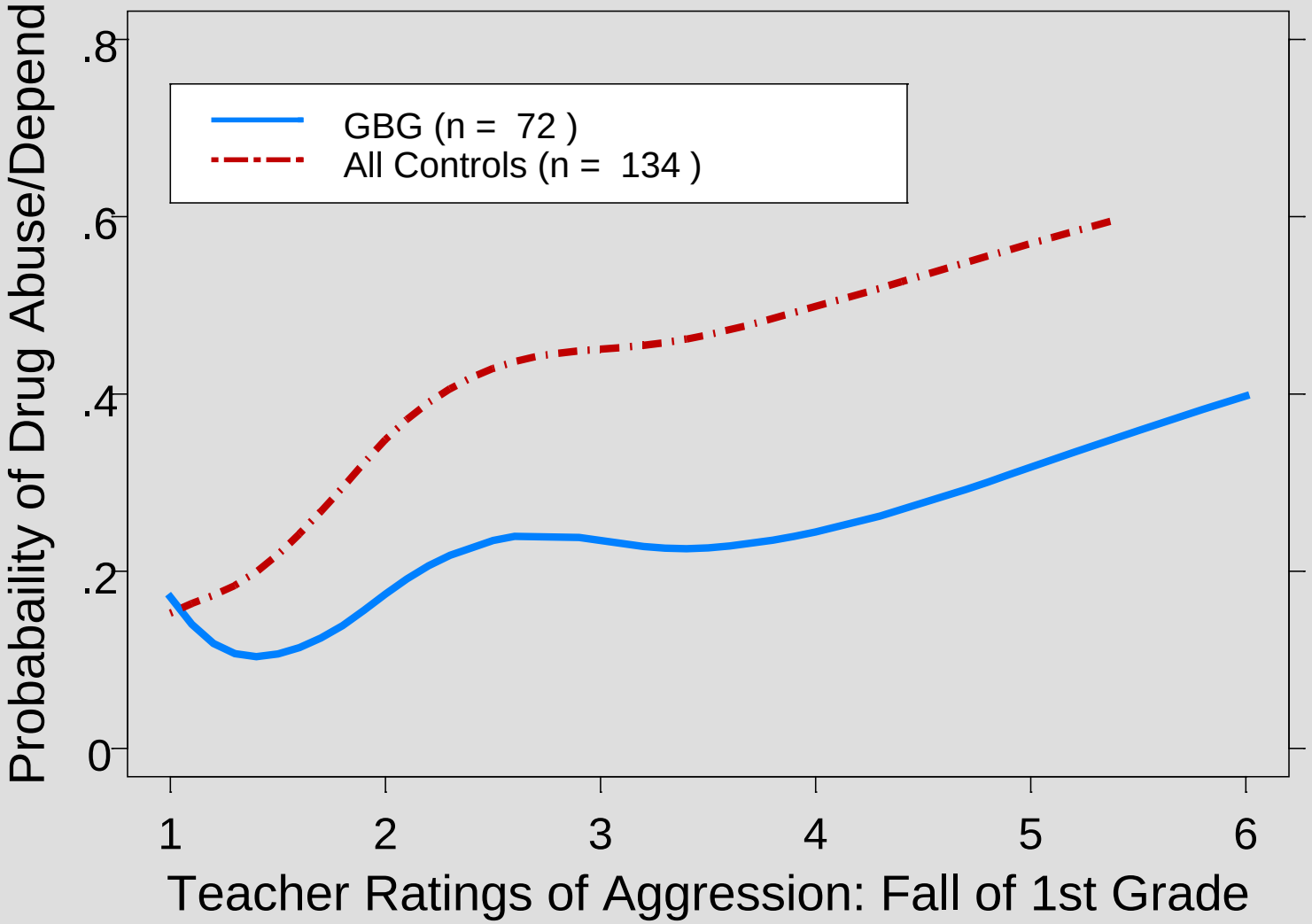
The Baltimore Education and Prevention Partnership

- The Baltimore City Public School System (BCPSS) has collaborated in 3 generations of education and prevention field trials.
- They were directed at helping children master key social task demands in 1st grade classroom.
- Interventions were tested separately, then together.
- The 1st generation will be our main focus today, where the Good Behavior Game (GBG) was tested by itself and the children, now young adults, were recently followed to ages 19-21.

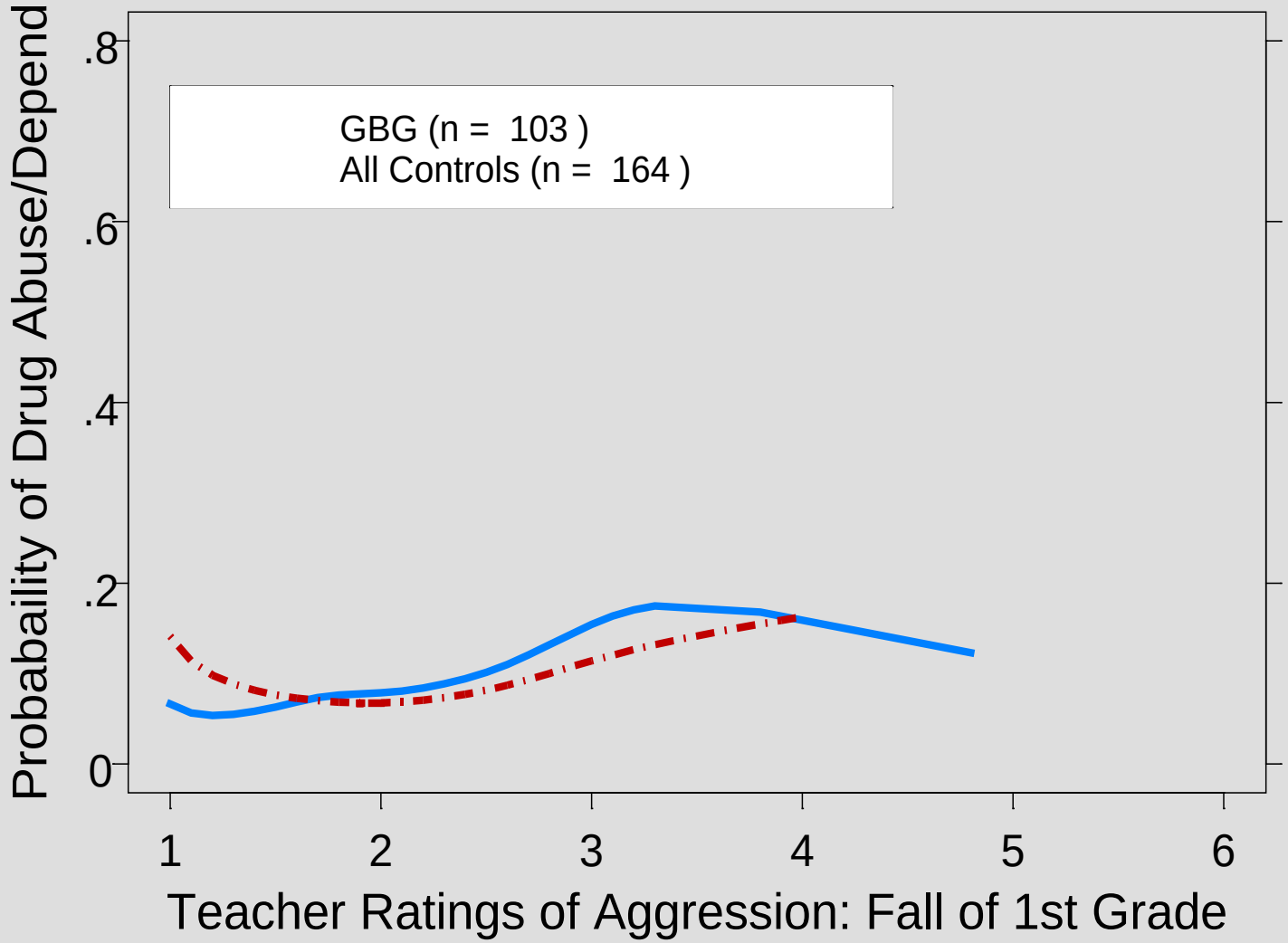
Goals of the Good Behavior Game (GBG)

- Provide teachers a classroom-wide method to socialize children into the role of student
- Reduce classroom aggressive, disruptive behavior among children to enhance classroom teaching and learning
- Prevent later drug abuse, delinquency, school failure and other problem outcomes

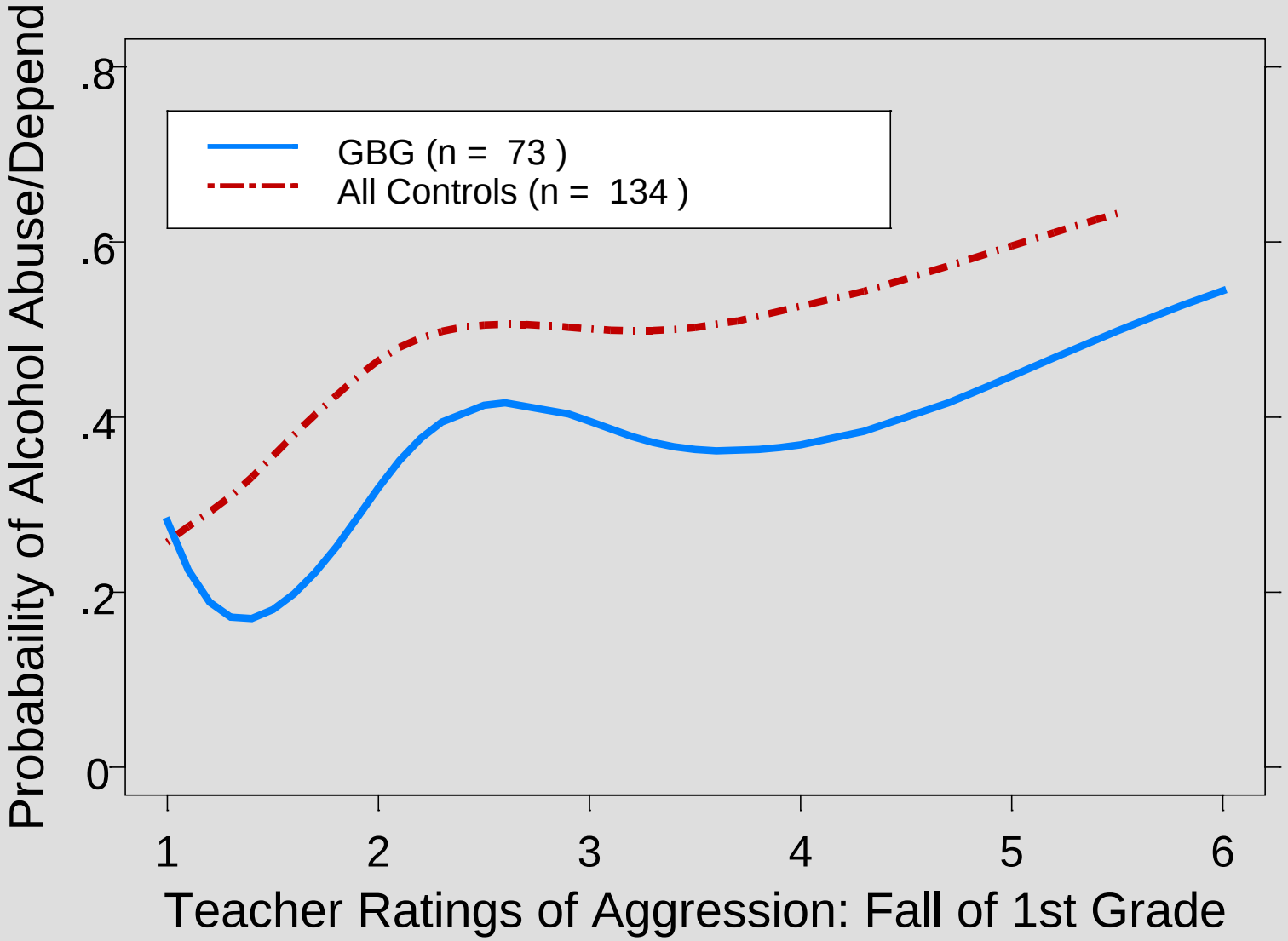
Drug Abuse or Dependence Disorders among Males in GBG Classrooms compared to Standard Classrooms by Level of First Grade Aggressive, Disruptive Behavior



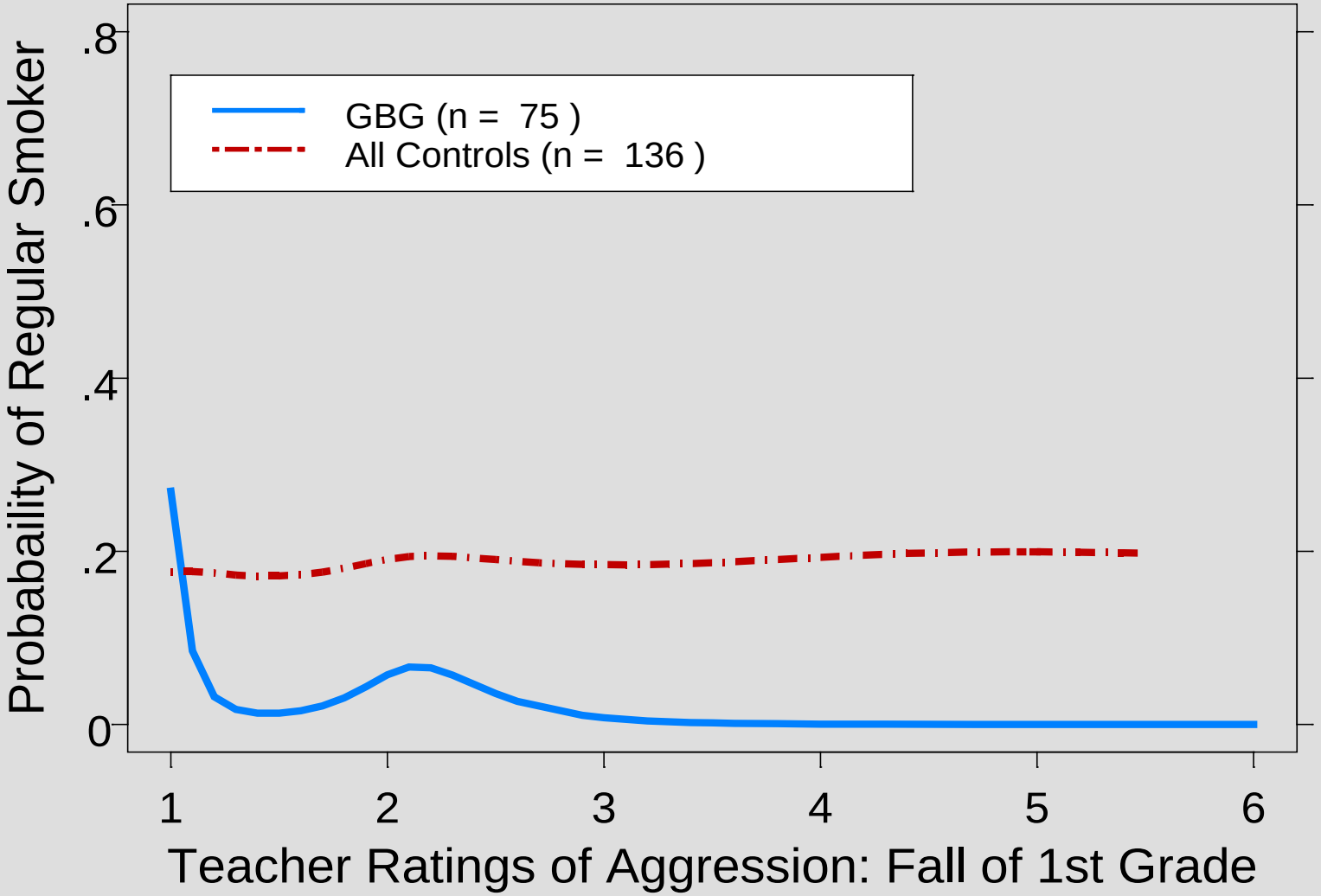
Drug Abuse or Dependence Disorders among Females in GBG Classrooms compared to Standard Classrooms by Level of First Grade Aggressive, Disruptive Behavior



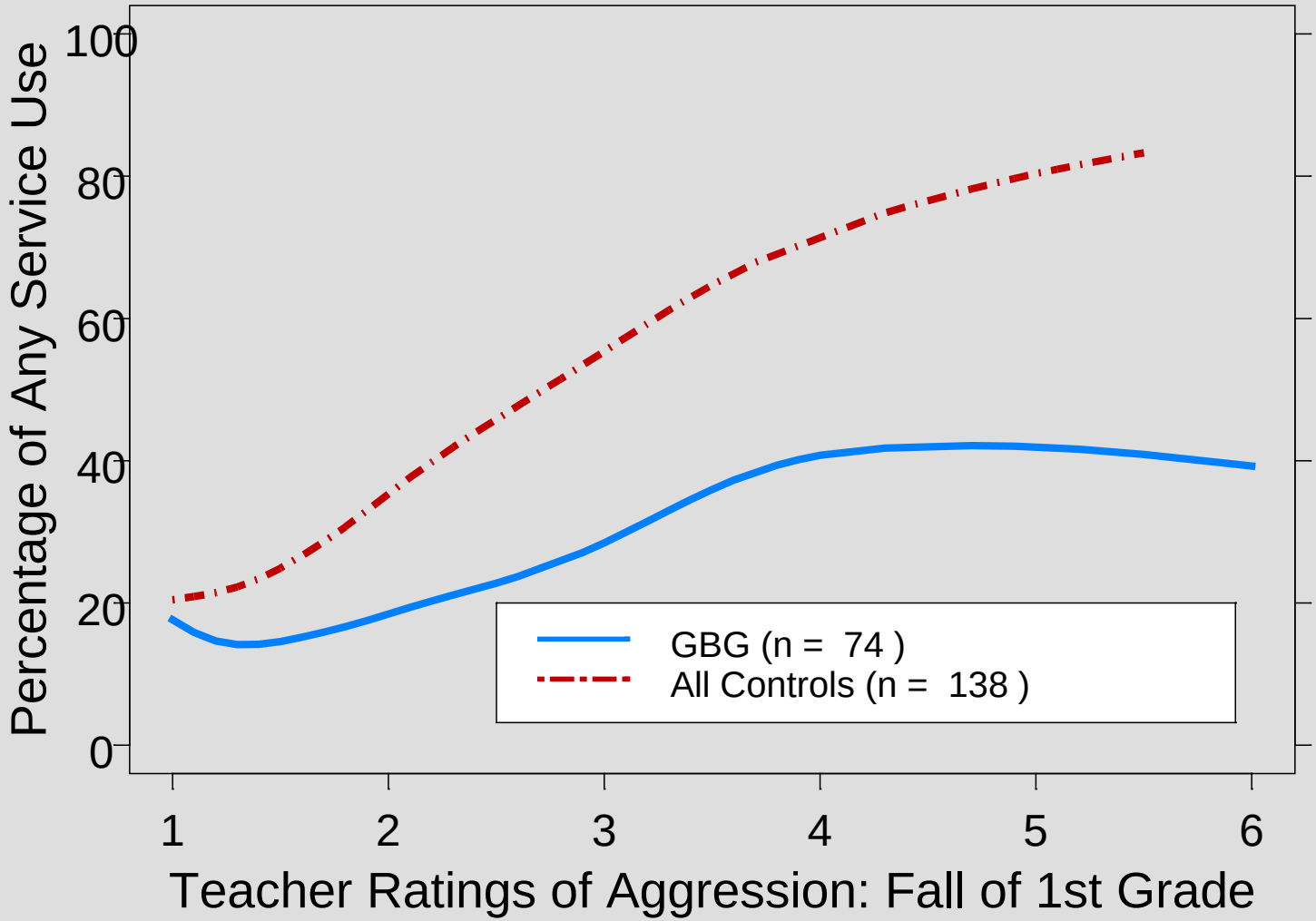
Alcohol Abuse or Dependence Disorders among Males in GBG Classrooms compared to Standard Classrooms by Level of First Grade Aggressive, Disruptive Behavior



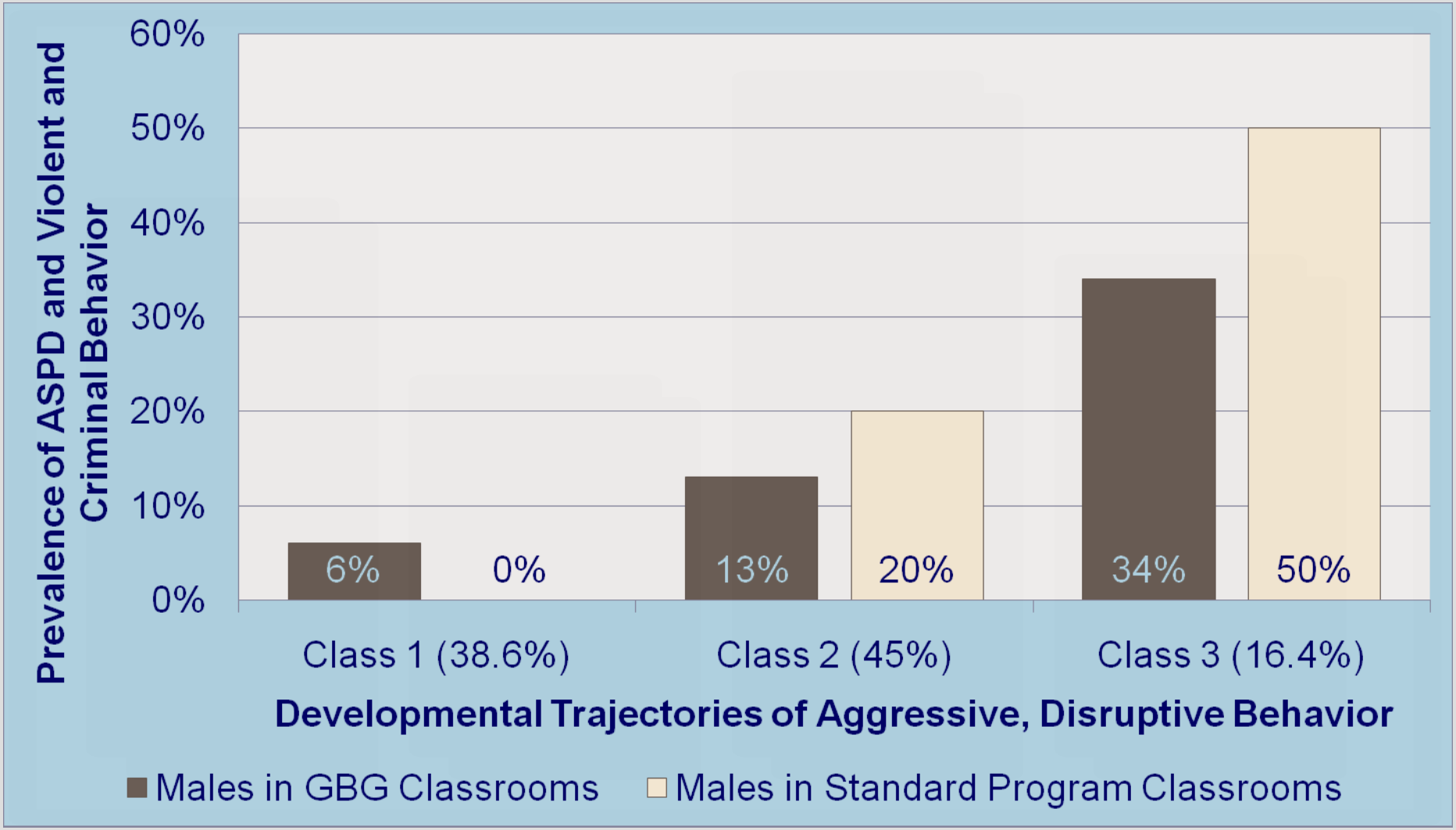
Regular Smoking among Males in GBG Classrooms compared to Standard Classrooms by Level of First Grade Aggressive, Disruptive Behavior



Impact of GBG done in 1st and 2nd Grades on Use of Services for Drug, Alcohol, Mental Health, and Behavioral Problems by Males Ages 19-21



ASPD and Violent and Criminal Behavior among Males

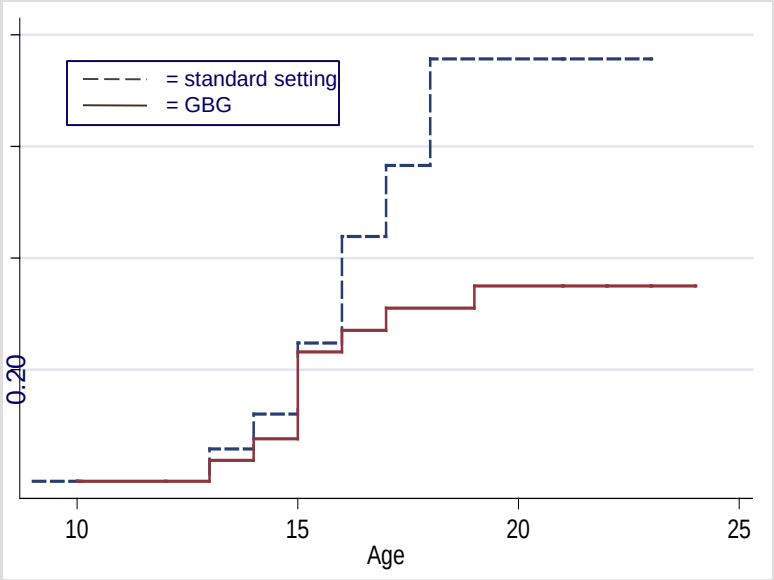


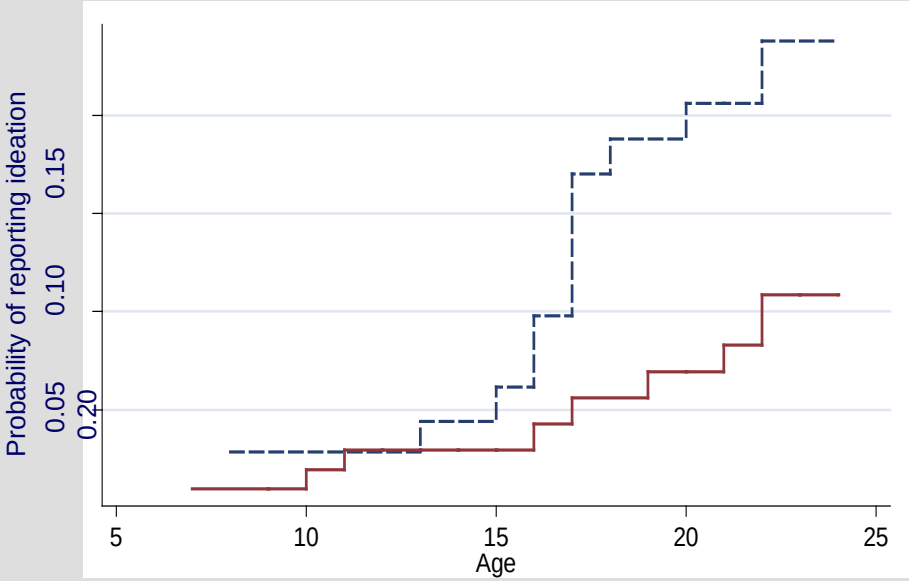
Suicidality

Females

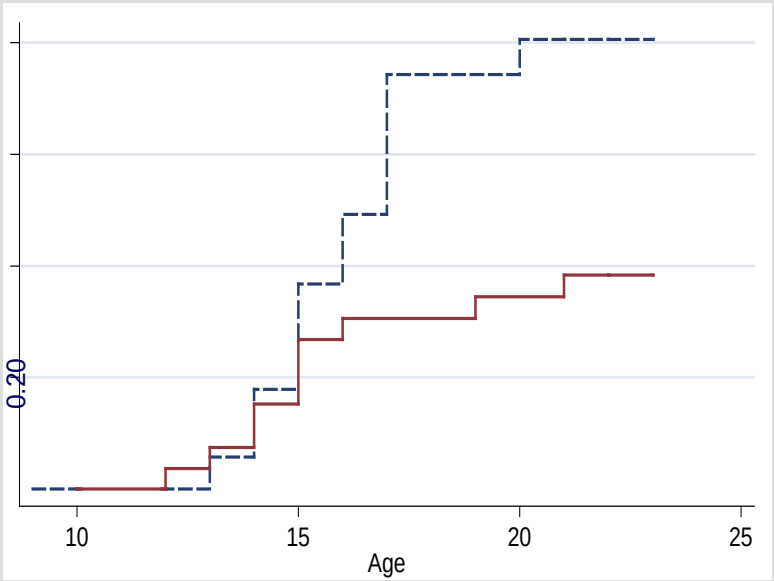
Males

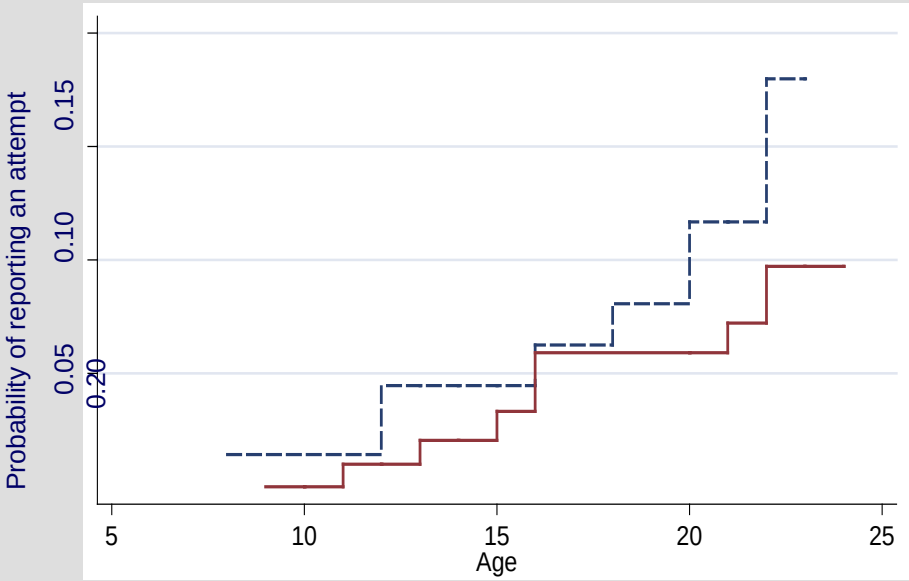
Ideation





Attempts





Inferences I: Scientific Integration not Scientific Silos

- An entire profile of later outcomes shared a common early risk factor

- The science structure must support research across the profile of outcomes in search of shared and unique etiologies and prevention strategies

Treatment Provider Perspective

NIH Scientific Management Review Board (SMRB)
Substance Use, Abuse, & Addiction Working Group (SUAA)

Herbert D. Kleber, M.D.
Professor of Psychiatry
Director, Division on Substance Abuse
Columbia University/NYSPI
email: hdk3@columbia.edu

September 23, 2009
National Institutes of Health

Problems with Treatment System

- Treatment needs
  - 23.1 million Americans need specialized treatment for substance abuse problems but only 2.3 million (10%) get it (NSDUH, 2008)
- "All Treatment works" – but inadequate data on whether that's for 5% or 50% & whom these individuals are
- Many (most?) treatment programs inadequately staffed & with large turnover (McLellan, et al.)
- Polysubstance abuse, especially alcohol, is the norm but clinical treatment trials tend not to include individuals with major alcohol problems
  - Alcohol use disorders (lifetime) range from 60-90% in drug use disorders (lifetime)

Clinical Experience

- As a clinician who's been in the substance abuse field for over 40 years, I get numerous referrals for treatment
- Patients include individuals with alcohol, cocaine, marijuana, and opioid problems; many are poly drug abusers
- I'm always happiest when the patient is primarily opioid dependent because we have such good medications to treat it. The next preference would be for alcohol because of available medications, next marijuana, and last cocaine
- Medications by themselves are often not adequate & various behavioral interventions & referral to 12-Step groups are an important part of the treatment experience

Advantages of Combining the Institutes

- Alcohol & other abused drugs tend to work on same systems
- Commonality of brain circuitry
  - e.g., cannabinoids & alcohol activate similar reward pathways & CB-1 receptors may regulate reinforcing effects of alcohol and mediate alcohol relapse
- A commonality of psychological & behavioral interventions, e.g., CBT, contingency contracting, motivational enhancement therapy

Advantages of Combining the Institutes

(Continued)

- Both deal with legal & illegal aspects of substance abuse
  - Underage drinking; DWI for NIAAA
  - Prescription opioid abuse; underage cigarette smoking for NIDA
- A combined institute could increase knowledge & improve treatment in these over-lapping areas
- Both institutes are dealing with chronic relapsing disorders which the treatment systems & their funding are woefully unprepared to deal with. A merger could improve this aspect of treatment

Advantages of Combining the Institutes

(Continued)

- Both NIDA & NIAAA have developed sophisticated & successful medication development programs
- Some medications can benefit both disorders
  - e.g., naltrexone for opioids & alcohol; disulfiram for cocaine & alcohol
- However, there appears to be limited cooperation & coordination between the intramural arms of the two institutes. Each has their strengths & weaknesses

Advantages of Combining the Institutes

(Continued)

- NIDA's Clinical Trials Network (CTN) would benefit from more emphasis on alcohol while NIAAA's clinical trials would benefit by more inclusion of polydrug abusers
- Likewise, NIDA's Criminal Justice Drug Abuse Treatment Studies could expand their reach to these dual-dependent populations & improve care to this under-served group
- The role that alcohol & other substances play in relapse for each disorder has been inadequately studied & a combined institute could improve relapse prevention for both

Panel Presentation III
Treatment/Relapse

Thomas Kosten MD

Waggoner Chair & Professor of Psychiatry, Pharmacology & Neuroscience

Associate Dean for Clinical Research

Baylor College of Medicine

Past President – American Academy of Addiction Psychiatry

Value Added by Merging NIDA and NIAAA

- Scientific overlap in vulnerability, mechanisms, use, prevention, and treatment of alcohol and other drug use
- Patients often abuse more than one substance and need treatment for all of them
  - 60% of tobacco smokers abuse alcohol
  - 85% of opiate addicts abuse alcohol
  - 90% of stimulant addicts abuse alcohol

Behavioral Interventions

- Most patients need concurrent behavioral treatment of both alcohol and other drugs
- **AND** Most behavioral therapies have great similarity across alcohol and other drugs of abuse
- Cognitive behavioral therapy
- Motivational enhancement therapy
- Contingency management therapy
- Counseling and group therapies
- Medication management therapies

Improved Clinical Trials

- Combined Institute for broadest approach to treating the multiple biological, behavioral, social, medical, and family factors in addiction
- Clinical trials of alcohol-polydrug abusers.
- NIDA's Drug Abuse Clinical Trials Network is currently unable to include alcohol-only arms
- Alcohol trials often do not measure smoking cessation, but 80% of alcoholics smoke

Medications Development

- Naltrexone and disulfiram are approved for alcoholism and show promise for drug addiction
- 85% of prescription opiate abusers also abuse alcohol, but buprenorphine effects on their alcohol abuse have not been examined
- Impact of even moderate use of alcohol (and tobacco) on relapse to other drug use has not been adequately addressed
- Pharmacogenetics – naltrexone and disulfiram

Institutional Cross-over Medications (NIDA & NIAAA)

- **Naltrexone** for opiates initially, then FDA approved for alcohol and potentially useful for methamphetamine
- **Disulfiram** for alcohol (aversive) and now 8 clinical trials showing efficacy for cocaine
- **Buprenorphine** for opiate addiction, and its mu opiate antagonism at anti-addiction doses may reduce comorbid alcohol abuse

Pharmacogenetic Cross-overs

- Naltrexone for alcohol appears more effective in patients with a common (30-50%) functional mu receptor polymorphism
  - ? Also for methamphetamine
- Disulfiram for cocaine appears more effective in patients without a common (40%) functional dopamine beta hydroxylase enzyme polymorphism that increases DA/NE ratio
  - ? Also for alcohol

Conclusions

- The science benefits from mutual enrichment of common brain pathways, shared medication efficacy, and overlapping pharmacogenetics
- All these drugs derange multiple organ systems beyond the brain – liver, lungs, heart, endocrine
- Behavioral treatments are quite similar across these abused substances
- Process addictions research in gambling, internet gaming, sex, food and other areas needs a coherent home to anchor its future contributions

A Plea for Synergism

- Addiction science is ripe for integration
- Behavioral and Pharmacological addiction treatment has substantial and successful overlap
- Integration & synergism is the transformative goal
- **NOT** Dis-integration or Dis-enfrancising productive research areas in either Institute
- We need a deliberate process for synergism, not cost saving or “efficiency”

Merger of NIH-NIDA & NIH-NIAAA?: Systems Science

Mary Jeanne Kreek, M.D.
Patrick E. and Beatrice M. Haggerty Professor
Head of Laboratory
The Laboratory of the Biology of Addictive Diseases
Senior Physician
The Rockefeller University

September 23, 2009
National Institutes of Health
Bethesda, MD

funded primarily by NIH-NIDA, NIH-NIMH, and NIH-CRR

Alcohol, Tobacco,
Opiates (Heroin & Prescription Medications),
Cocaine, Methamphetamine,
and Other Drugs of Abuse

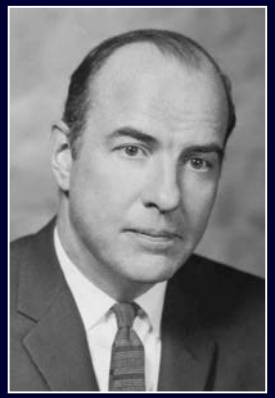
…are chemicals with reinforcing effects which may lead to abuse and specific addictions, chronic relapsing diseases with genetic and environmental, as well as drug-induced factors leading to their development.

Kreek, 2009

Development of Methadone Maintenance Treatment – 1964 Onward

Hypothesis (1964)

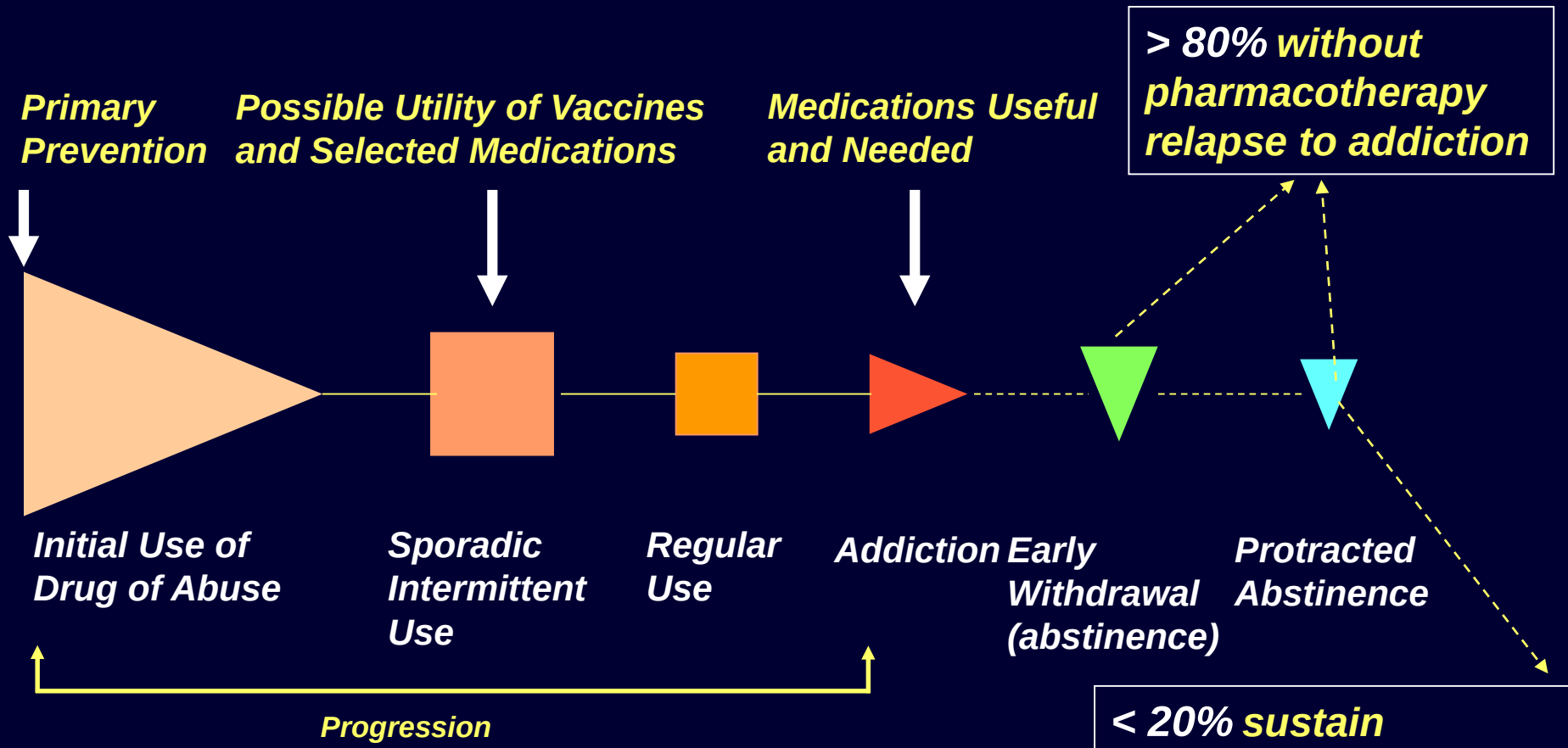
Heroin (opiate) addiction is a disease – a "metabolic disease" – of the brain with resultant behaviors of "drug hunger" and drug self-administration, despite negative consequences to self and others. Heroin addiction is not simply a criminal behavior or due alone to antisocial personality or some other personality disorder.



1964: Initial clinical research on development of treatment using methadone maintenance pharmacotherapy and on elucidating mechanisms of efficacy.

Dole, V.P., Nyswander, M.E. and Kreek, M.J.: Narcotic blockade. Arch. Intern. Med., 1966.

Natural History of Drug and Alcohol Abuse and Addictions

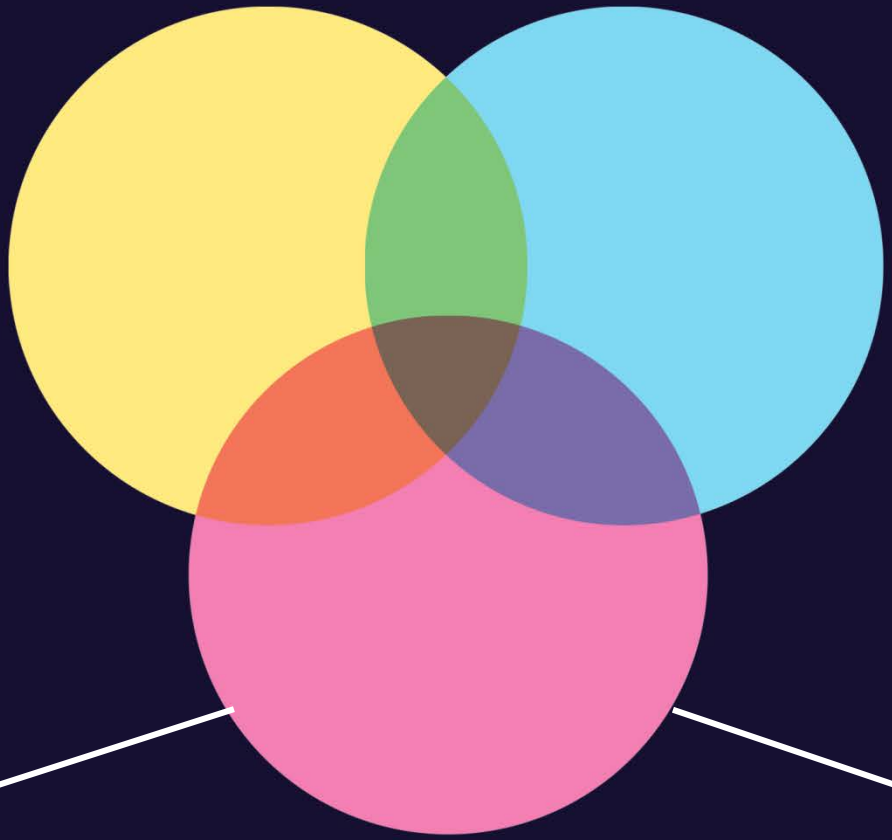


ADDICTION: ***Compulsive drug seeking behavior and drug self-administration, without regard to negative consequences to self or others (adapted from WHO).***

Kreek et al., Nature Reviews Drug Discovery, 1:710, 2002

Factors Contributing to Vulnerability To Develop a Specific Addiction

Use of the drug of abuse essential (100%)



Genetic (25-60%)
- DNA
- SNPs
- other polymorphisms

Environmental (very high)
- prenatal
- postnatal
- contemporary
- cues
- comorbidity
- stress-responsivity

- mRNA levels
- peptides
- proteomics

Drug-Induced Effects (very high)

- neurochemistry
- synaptogenesis
- behaviors

Kreek et al., 2000; Kreek et al., Nature Reviews Drug Discovery, 2005

Reinforcing or "Reward" Effects of Drugs of Abuse (Including Alcohol)

- Initial and early repeated exposure to a drug of abuse (including alcohol) may produce effects which are interpreted by the individual as "desirable" or "pleasurable", i.e., "rewarding".
- These effects may lead to "craving" or "hunger" for the drug, with resultant spontaneous activity or work for drug acquisition and self-administration.
- Primary brain regions which have been identified as the site of the "rewarding" effects of drugs of abuse are those rich in dopaminergic nerve terminals, especially the nucleus accumbens, amygdala, anterior cingulate and insula, and also the caudate and putamen.
- Each of these areas also has abundant receptors and peptides of the endogenous opioid system, including mu opioid receptor involved in reward, and kappa opioid receptors involved in countermodulation of reward.

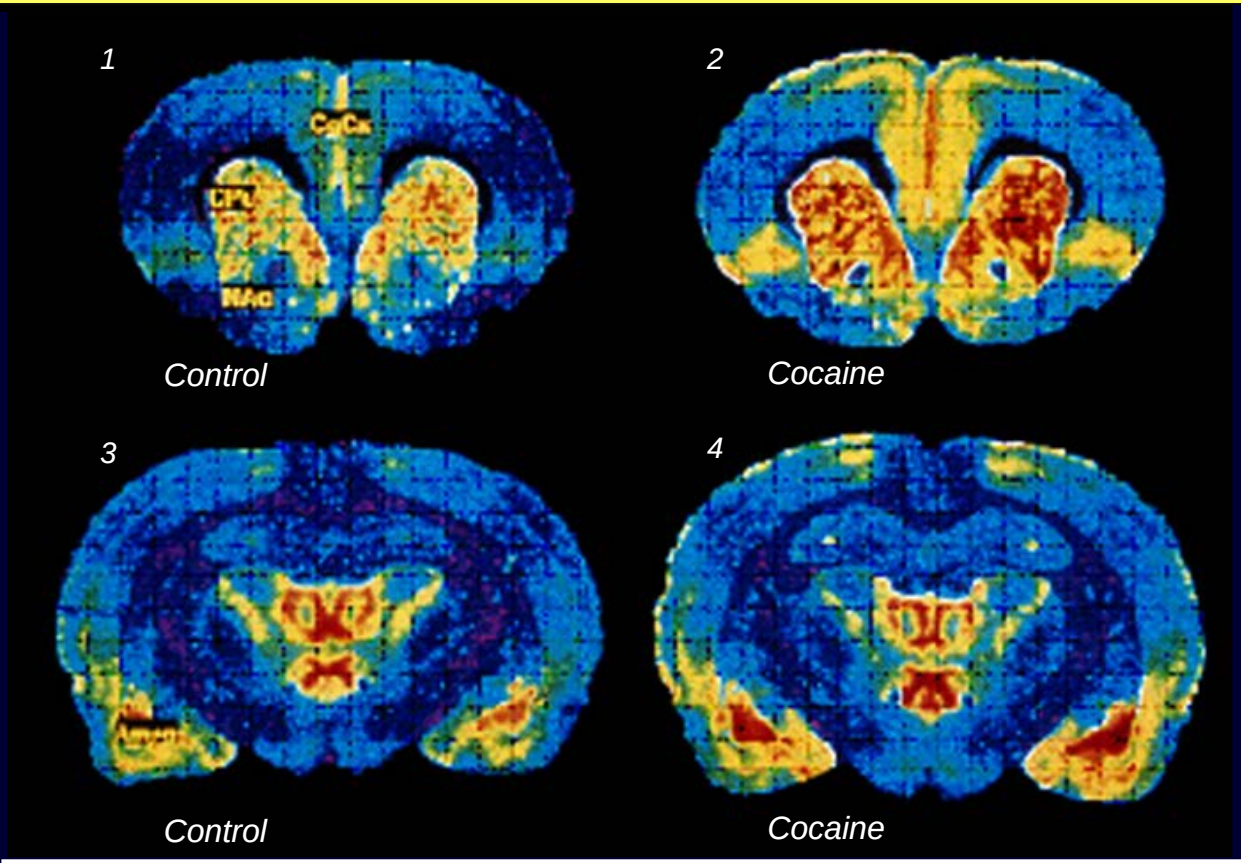
Kreek, 1987; 2008

Bidirectional-Translational Research: Novel and Conventional Animal Models

- **"Binge" Pattern Cocaine Administration Model:**
  Constant or Ascending Dose
  (mimics most common pattern of human use in addiction)
- **Intermittent Morphine (Heroin) Administration Model:**
  Constant or Ascending Dose
  (mimics most common pattern of human use in addiction)
- **"Binge" Pattern Oral Ethanol Administration Model:**
  (mimics common pattern of human excessive use)
- **Pump Methadone Administration Model:**
  (converts short-acting pharmacokinetic properties of opioid agonist in rodent to long-acting human pharmacokinetic profile)
- **Extended Access Self-Administration Without or With High-Dose Drug** (Cocaine or Opiate)

Kreek et al., 1987; 1992; 2001; 2005

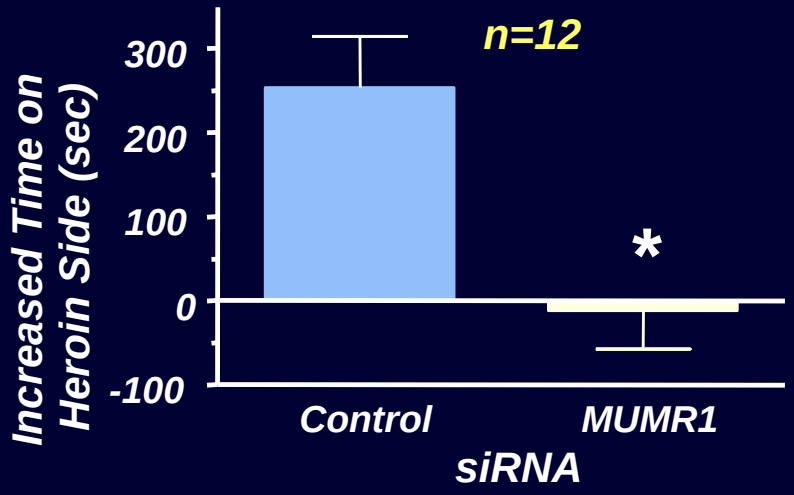
REWARD — Mu Opioid Receptor-Endorphin System: Chronic Cocaine in Rat Increases Mu Opioid Receptor Density, But With No Increase in Mu Endorphins

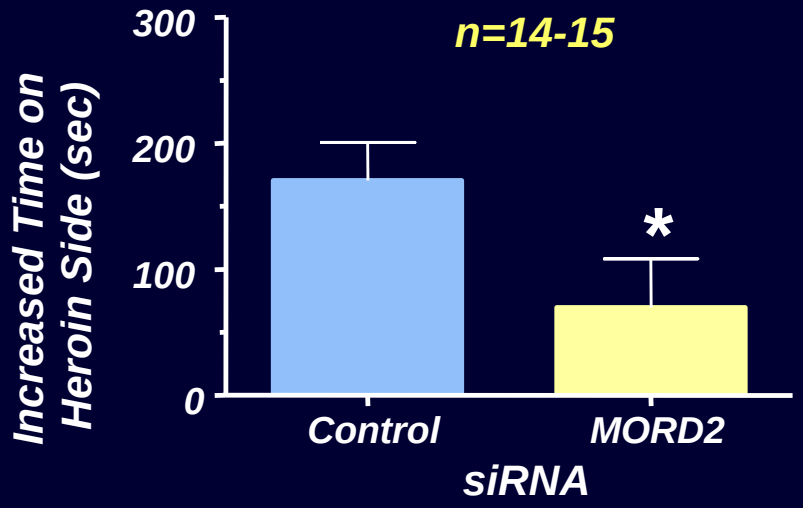


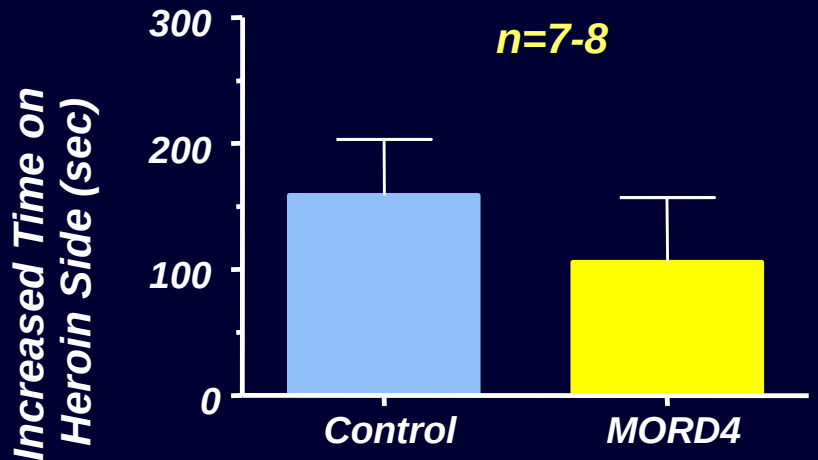
Relative "endorphin deficiency" develops and persists for an extended time.

Unterwald et al., Brain Res., 584:314 1992; Unterwald et al., NeuroReport, 5:1613, 1994; Unterwald et al., Brain Res. 900:103, 2001

Effects of SiRNAs Directed at the Mu Opioid Receptor mRNA and Instilled Specifically in the Substantia Nigra and Ventral Tegmental Area of Mouse Brain Blunts or Ablates Heroin-Induced Conditioned Place Preference







siRNAZhang et al, Neuroscience 158, 474–483., 2009

Mu Opioid Receptor Knock-Out Mice

- No morphine or other mu agonist analgesia
- No heroin or morphine self-administration
- No heroin or morphine induced conditioned place preference
- Attenuated self-administration of cocaine
- Attenuated self-administration of alcohol

[Different knock-out constructs and multiple research groups, including Kieffer, Uhl, Yu. Pintar, Loh, with, e.g., Maldonado, Pasternak, Hoellt, Roberts]

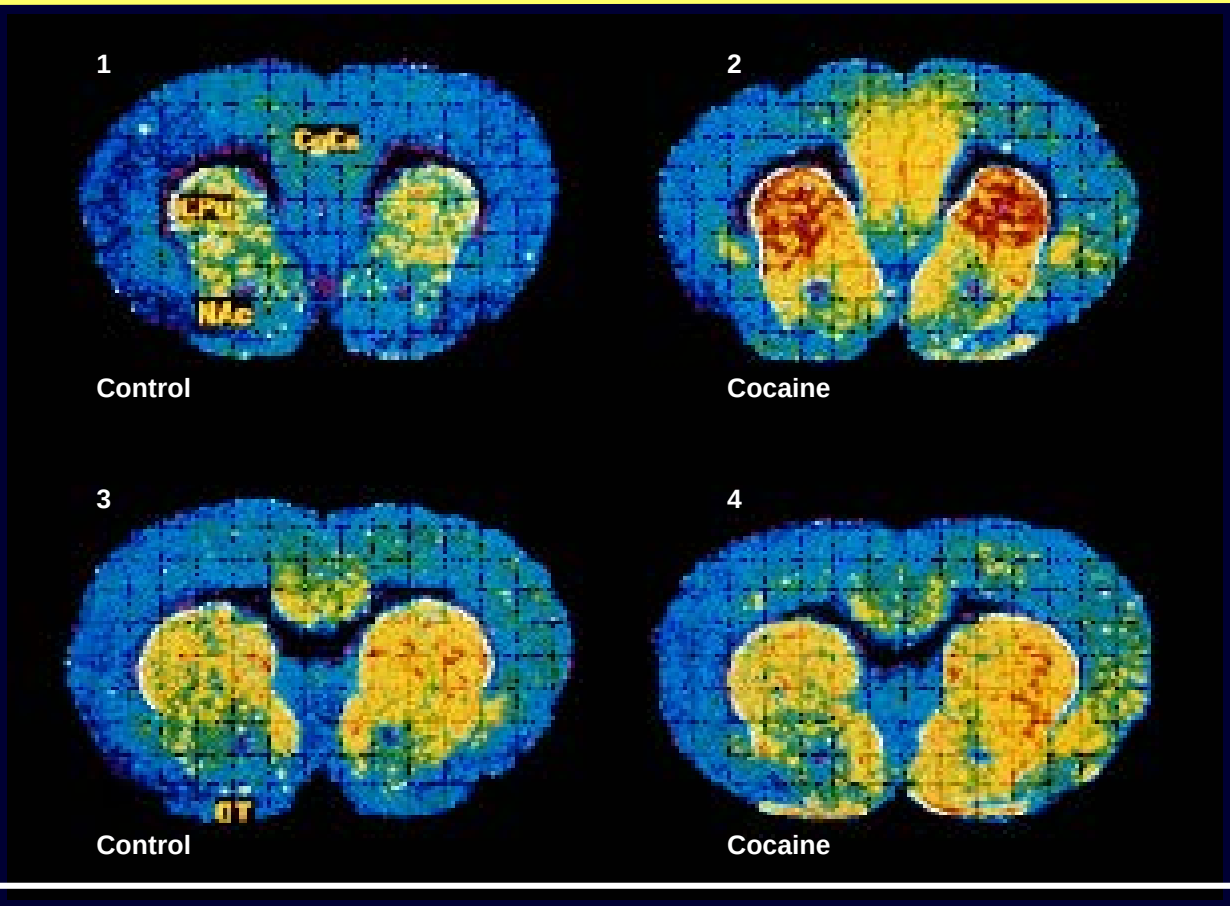
Reviewed in Kreek et al., Nature Reviews Drug Discovery, 1:710-726, 2002

Mu Opioid Agonist, Partial Agonist and Antagonist Pharmacotherapies: Alcoholism and Cocaine Addiction, as well as Heroin and Other Opiate Addiction Treatment

Heroin and Other Opiate Additions	*Alcoholism*	*Cocaine Addiction*
Methadone	*Naltrexone*	*? Naltrexone*
Buprenorphine	*Nalmefene*	*? Buprenorphine*
		? Methadone

Kreek, 2009

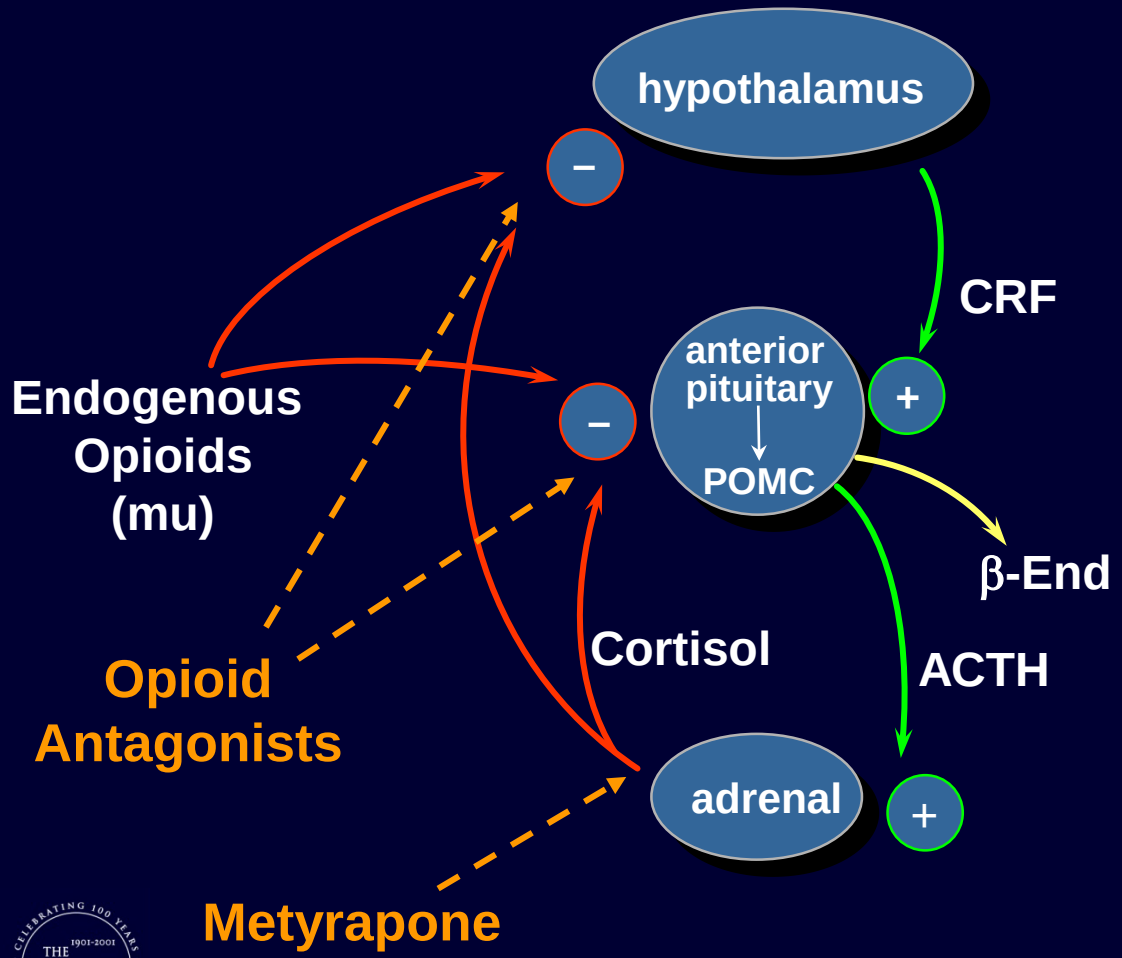
COUNTERMODULATION – Chronic Cocaine Increases Kappa Opioid Receptor Density in Rat, But Kappa Opioid Receptor Directed "Dynorphins" Also Increase



Dynorphin Acting at the Kappa Opioid Receptor Lowers Dopamine Levels and Prevents Surge After Cocaine

Spangler et al., Mol. Brain Res., 38:71, 1996;
Unterwald et al., NeuroReport, 5:1613, 1994

Hypothesis — Atypical Responsivity to Stressors: A Possible Etiology of Addictions



Atypical responsivity to stress and stressors may, in part, contribute to the persistence of, and relapse to self-administration of drugs of abuse and addictions. Such atypical stress responsivity in some individuals may exist prior to use of addictive drugs on a genetic or acquired basis, and lead to the acquisition of drug addiction.

Kreek, 1972; 1981; 1982; 1984 … 2008

Heroin, Cocaine, and Alcohol Profoundly Alter Stress Responsive Hypothalamic-Pituitary-Adrenal (HPA) Axis: Normalization during methadone treatment

- Acute effects of opiates
- Chronic effects of short-acting opiates (e.g., heroin addiction)

} Suppression of HPA Axis (decrease levels of HPA hormones)

- Opiate withdrawal effects *
- Opioid antagonist effects
- Cocaine effects *
- Alcohol effects

} Activation of HPA Axis (increase levels of HPA Hormones)

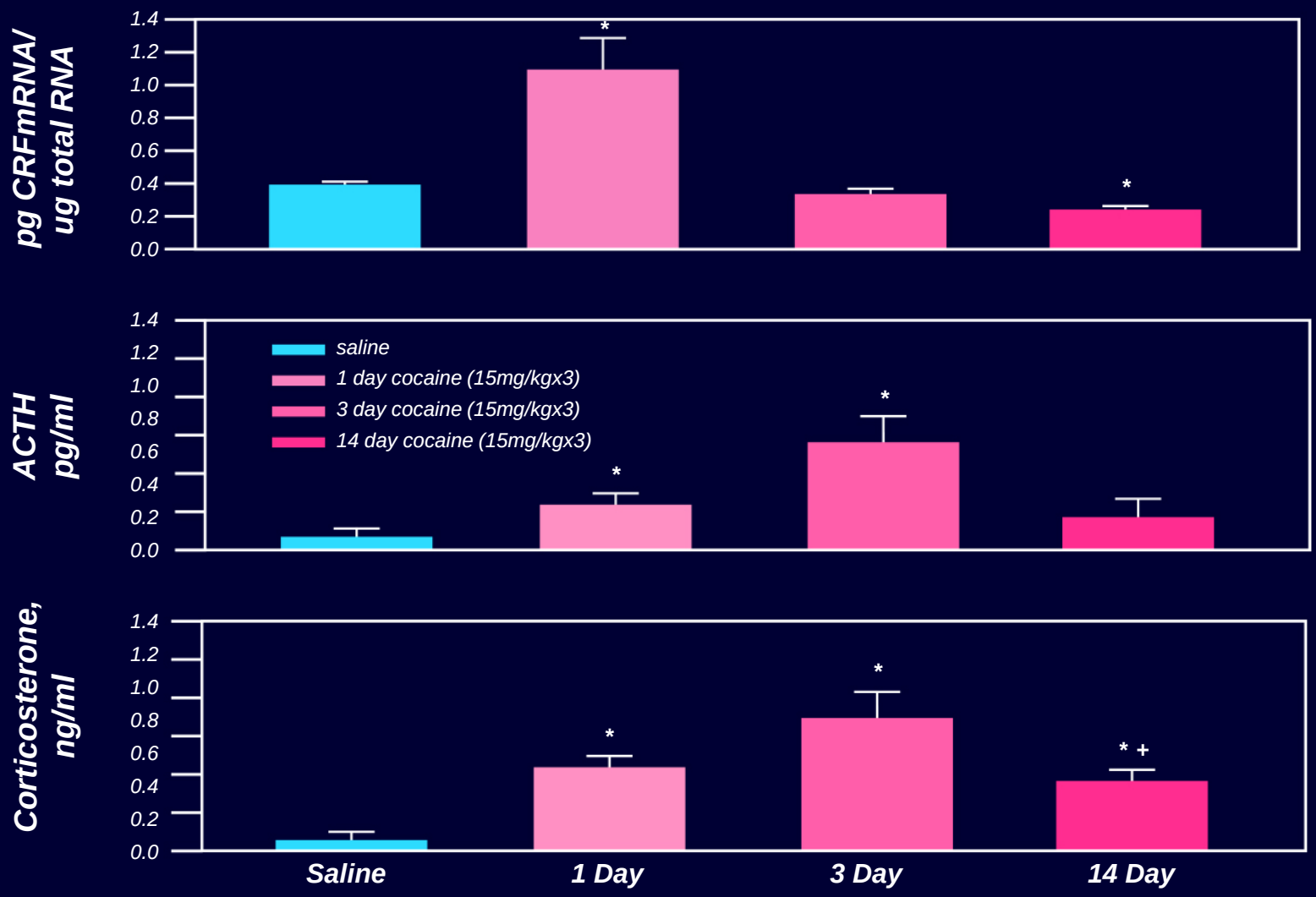
- Chronic effects of long-acting opiate (e.g. methadone in maintenance treatment)

Normalization of HPA Axis

* Our challenge studies have shown that a relative and functional "endorphin deficiency" develops.

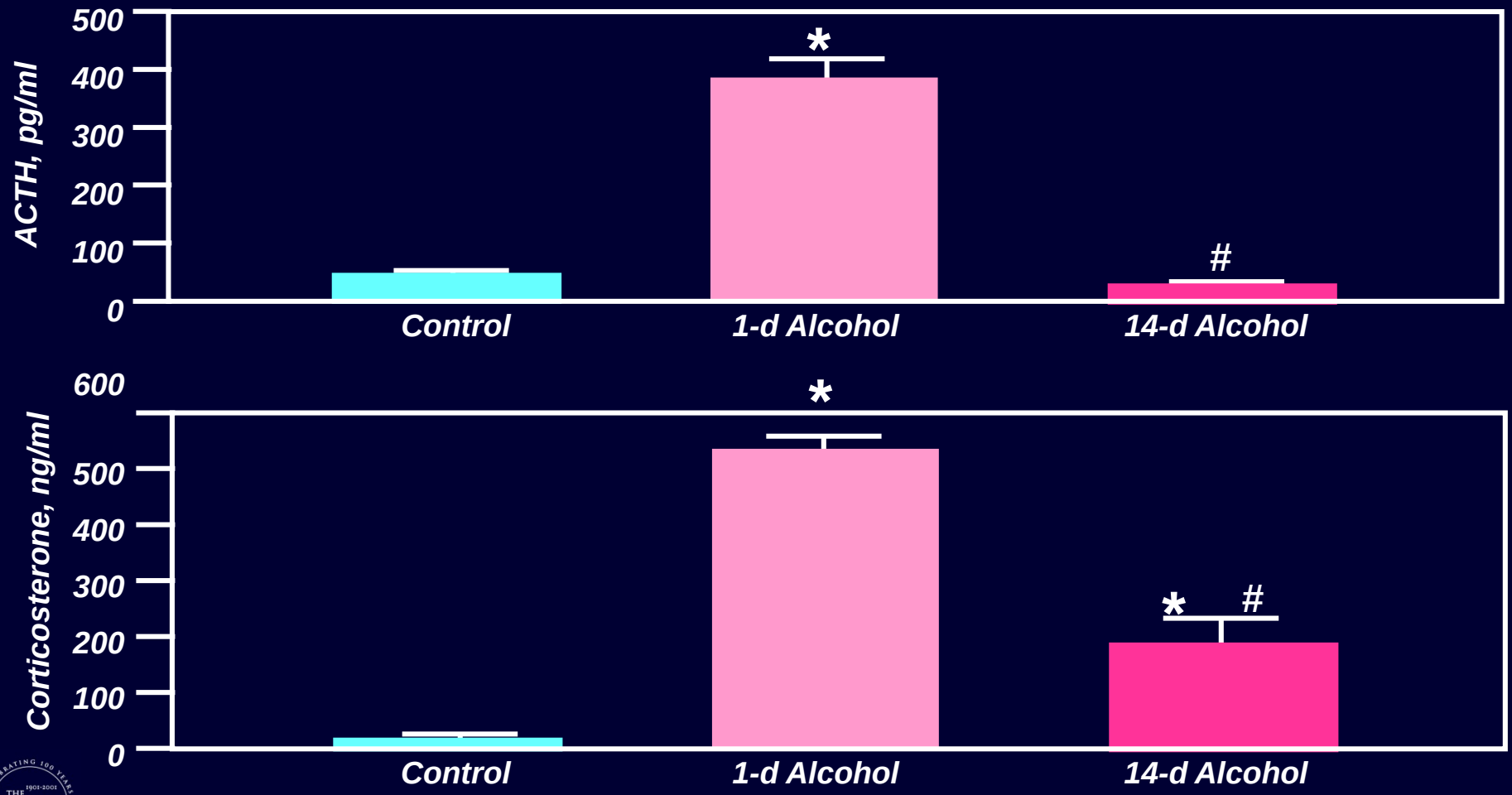
Kreek, 1972; 1973; 1987; 1992 … 2008

“Binge” Pattern Cocaine Administration Effects on CRF mRNA Levels in Rat Hypothalamus and Plasma Levels of ACTH and Corticosterone



Zhou et al., 1996

Effect of Acute and Chronic Binge Pattern Alcohol Administration (1.5g/kg, h x 3/day) on Plasma ACTH and Corticosterone in Rats



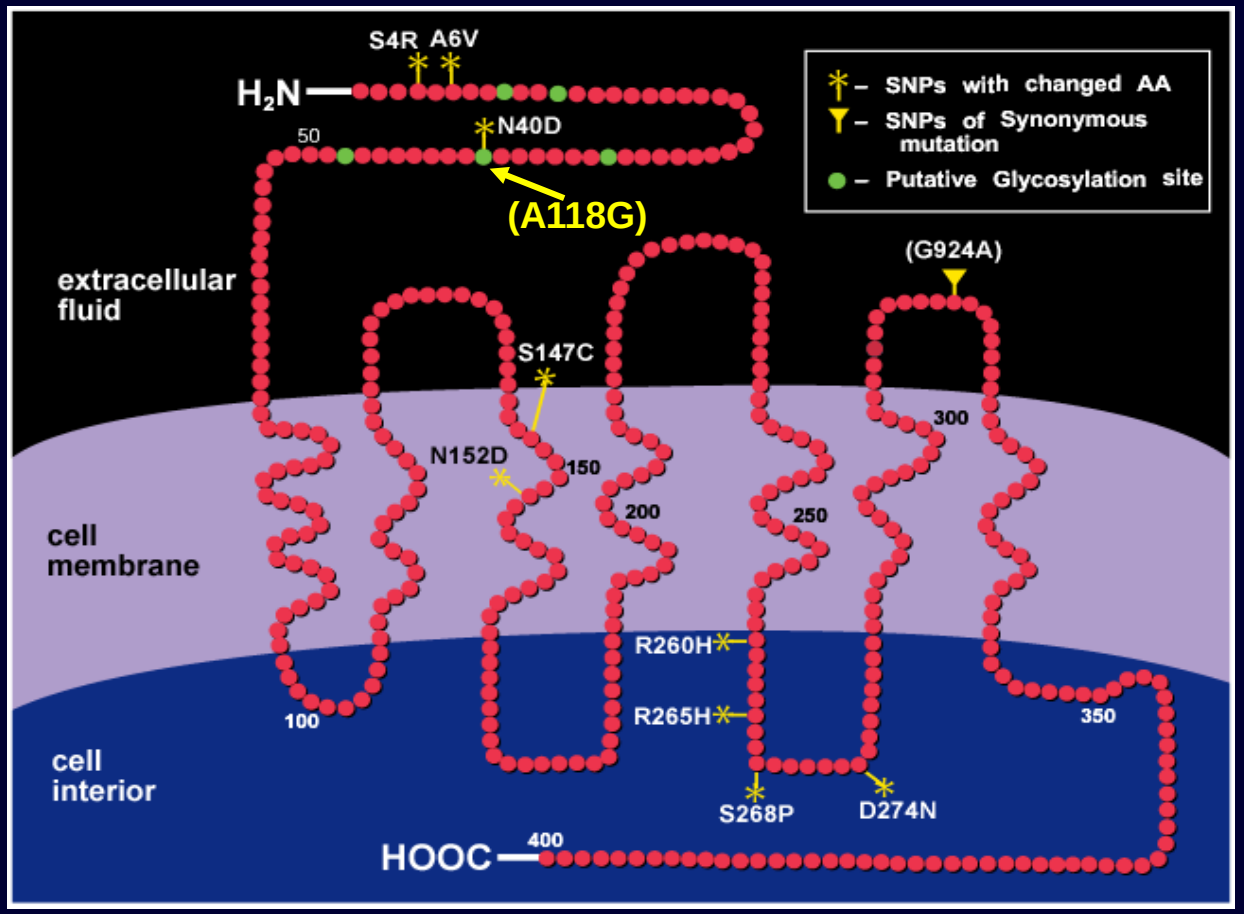
Zhou, Franck et al, 2000

Genetic Variants of the Mu Opioid Receptor: Single Nucleotide Polymorphisms in the Coding Region Including the Functional A118G (N40D) Variant

HYPOTHESIS

Gene variants:

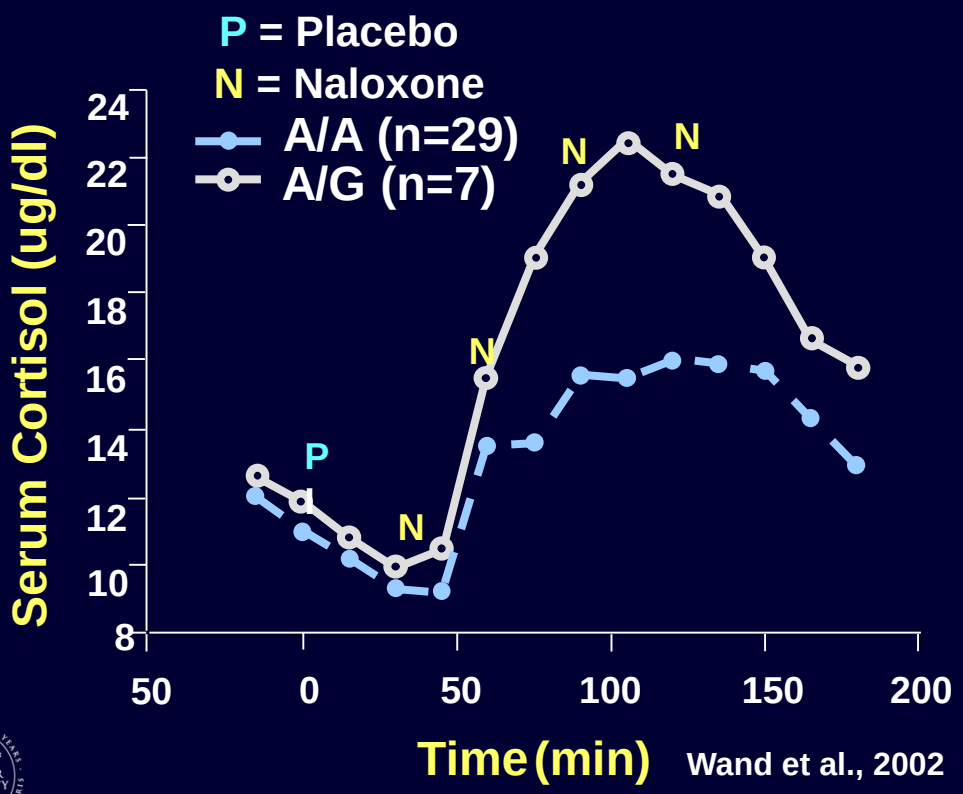
- **Alter physiology "PHYSIOGENETICS"**
- **Alter response to medications "PHARMACOGENETICS"**
- **Are associated with specific addictions**



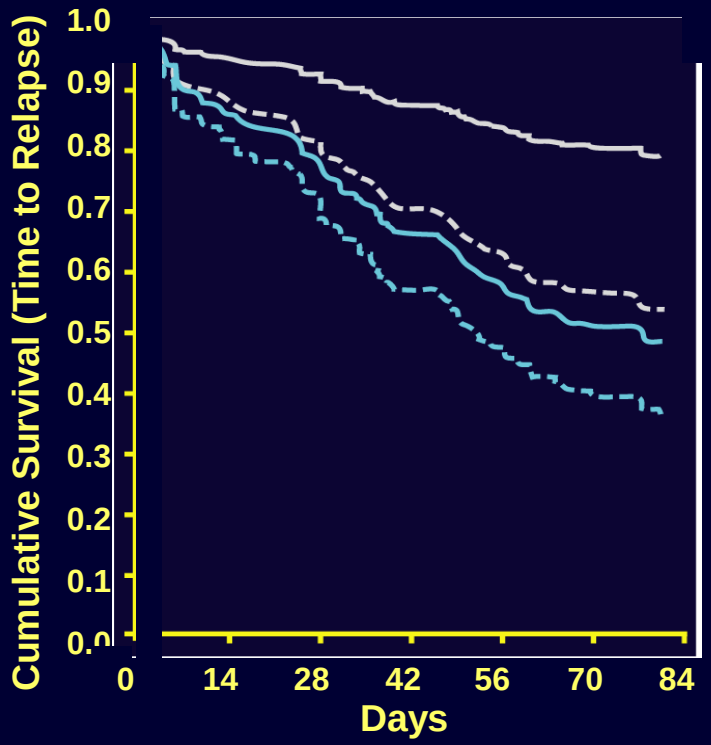
Bond, LaForge… Kreek, Yu, PNAS, 95:9608, 1998

"Physiogenetics" and "Pharmacogenetics" Related to A118G Variant of Human Mu Opioid Receptor Gene – Altered Stress Responsivity

Basal plasma levels of cortisol significantly higher in persons with the A118G variant.
Bart et al., 2006



Wand et al., 2002



Naltrexone/ A/G, G/G (n=23)
Naltrexone/ A/A (n=48)
Placebo/ A/G, G/G (n=18)
Placebo/ A/A (n=41)

Oslin et al., 2003

Association Between a Functional Polymorphism in the mu Opioid Receptor Gene and Opiate Addiction in Central Sweden

Genotype	All Subjects		Swedish with Both Parents Swedish	
	Controls (n=170)	Opiate Dependent (n=139)	Controls (n=120)	Opiate Dependent (n=67)
A/A	147 (0.865)	98 (0.705)	104 (0.867)	46 (0.687)
A/G	21 (0.123)	39 (0.281)	15 (0.125)	19 (0.283)
G/G	2 (0.012)	2 (0.014)	1 (0.008)	2 (0/030)

RR = 2.86 $\chi^2_{(1)}$= 13.403 P = 0.00025* RR = 2.97 $\chi^2_{(1)}$= 8.740 P = 0.0031*

	Opiate Dependent (n=139)	Control (n=170)
G/G; A/G	41	23
A/A	98	147
118G Allele Frequency	0.155	0.074

Thus, in the entire study group in this central Swedish population,
Attributable Risk due to genotypes with a G allele in this population: 18%
Attributable Risk due to genotypes with a G allele in Swedes w/ Swedish parents: 21%
(with confidence interval ranges from 8.0 to 28.0%)

Bart G , Heilig M, LaForge KS… Ott J, Kreek MJ, et al., Molecular Psychiatry, 9:547-549, 2004

Association Between a Functional Polymorphism in the mu Opioid Receptor Gene and Alcoholism in Central Sweden

	Swedish with two Swedish parents		Non-Swedish without Swedish Parents	
	Alcohol Dependent (n=193)	Control (n=120)	Alcohol Dependent (n=196)	Control (n=50)
A118	158	104	141	43
A118G, G118G	35	16	55	7

OR=1.92 $\chi^2_{(1)} = 7.18$, p = 0.0074

	Alcohol Dependent (n=389)	Control (n=170)
G/G; A/G	90	23
A/A	299	147
118G Allele Frequency *	0.125	0.074

* Overall 118G Allele Frequency = 0.109

Thus, in the entire study group in this central Swedish population:
Attributable Risk due to genotypes with a G allele: 11.1%
(with confidence interval ranges from 3.6 to 18.0%)

Bart G , Kreek MJ, LaForge KS… Ott J, Heilig M, et al., Neuropsychopharmacology, 2005

BUT… Major Budget Concerns!!!

NIH – and Congress – must see any merger of NIH-NIDA and NIH-NIAAA as a move to enhance science and thus, ultimately, healthcare in the very costly areas of the addictive diseases, and not as a "cost saving" strategy.

BUDGET:

1 + 1 must = 2 (or 3), NOT 1.2 or 1.5!

Kreek, 2009

Alcohol Treatment

Stephanie O'Malley, Ph.D.
Professor of Psychiatry
Yale University School of Medicine

September 23, 2009

Co-morbidity of Alcohol and Other Drugs

- With the exception of nicotine dependence, psychiatric co-morbidity has greater co-morbidity with alcohol dependence.

- Even nicotine dependence occurs in a minority of those with alcohol use disorders.
  - 34.5% of those with past year alcohol use disorder meet current criteria for nicotine dependence
  - 22.8% of those with past year nicotine dependence meet current criteria for an alcohol use disorder

Psychiatric and Other Drug Co-Morbidity: Gaps in Research?

- Initial studies of new medications for alcohol often exclude *current dependence* on other drugs (except nicotine), major psychiatric disorders, and the medically ill.
- Similarly, alcohol dependent patients are typically excluded from initial studies of drug dependence
- Promising findings in one area are rapidly followed up in patients with other drug use, psychiatric co-morbidity or medical illness

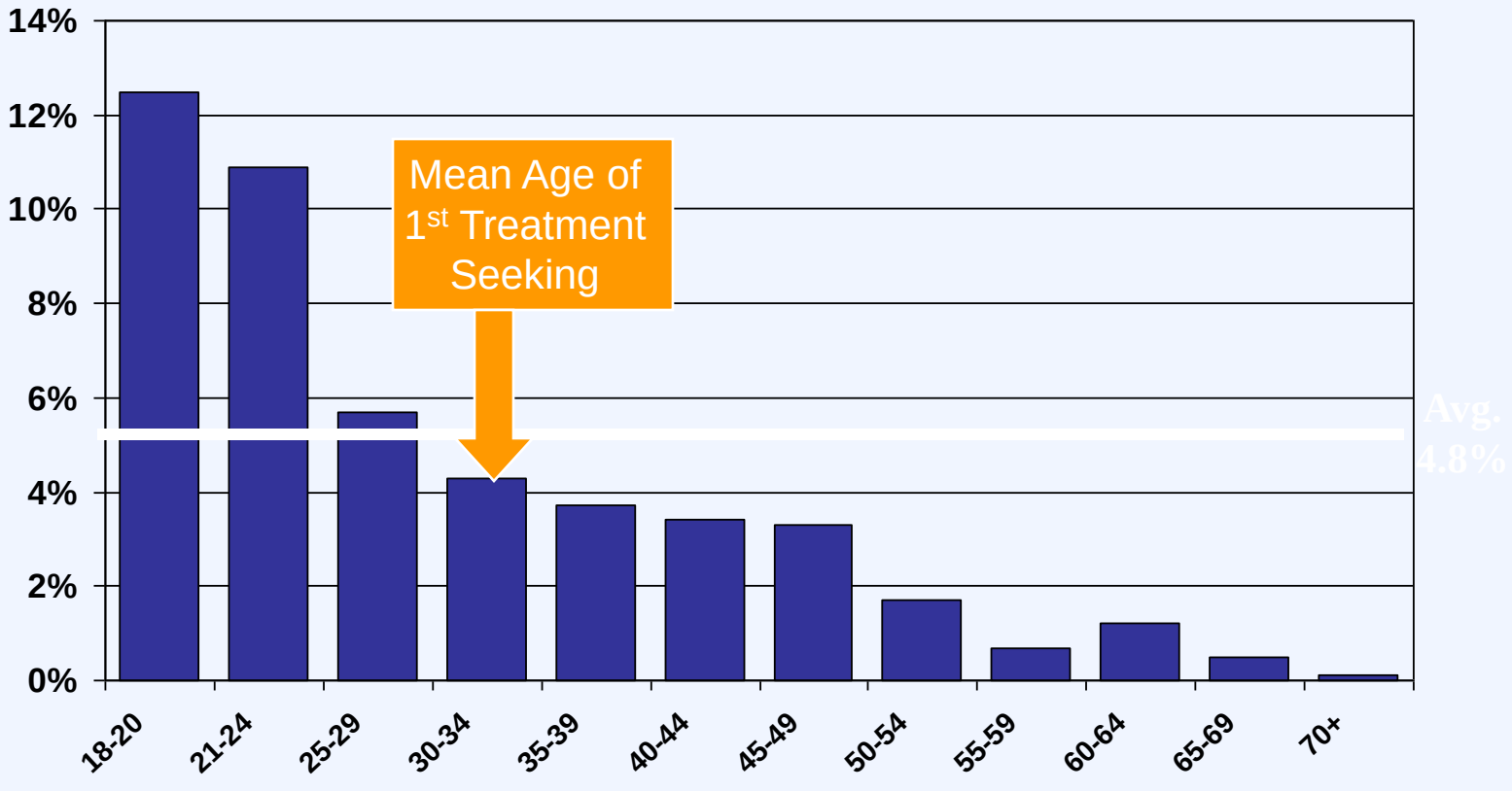
Varenicline

- Approved for smoking cessation based on drug company research in smokers without substantial co-morbidities in May 2006
- Status of Research in 2009
  - 24 grants on CRISP
  - 114 studies on Clinical Trials.gov
  - Populations and Indications Expanded
    - Alcohol dependence, methamphetamine, cocaine
    - Patients with schizophrenia, bipolar illness, ADD, depression
    - Head and neck cancer, other medical co-morbidities

Goals of Treatment

- Treatment of drug abuse has the primary goal of abstinence, a shared goal for those with significant alcohol dependence
- However, other goals may be appropriate for the larger group of hazardous drinkers.
- The development of treatments that help heavy drinkers reliably maintain safe drinking limits will be attractive to patients and should have large public health benefits

Prevalence of Past-year DSM-IV Alcohol Dependence: United States, 2001-2002



Source: Grant BF *et al. Drug Alcohol Depend.* 2004. 74(3):223-34.

College Students Are More Interested in Reducing than Quitting Drinking

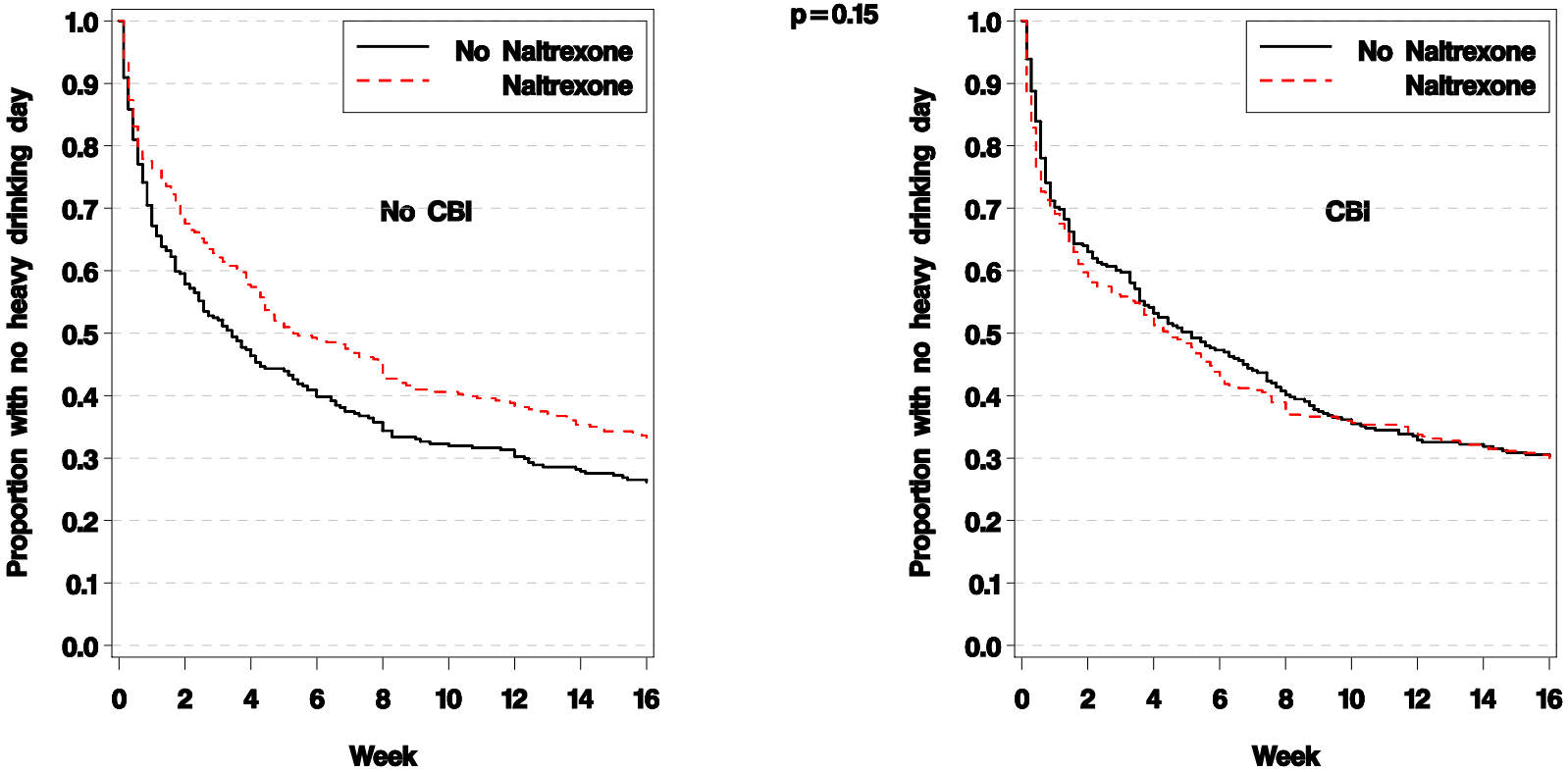
	Large Public University		Private University	
	Cut-down	Stop	Cut-down	Stop
Maybe – Definitely	13.8%	5.7%	14.3%	6.3%
N	2233	2219	321	316

Corbin, unpublished data; Epler, Sher & O'Malley, *Journal of College Health*, In Press

Naltrexone Shows Modest Effects on Return to Heavy Drinking in Alcohol Dependent Patients with Medical Management

MM Only

MM + Behavioral Therapy



The COMBINE Study (Anton et al, 2006)

Does NIAAA's Integrated Focus on All Aspects of Alcohol Benefit Treatment?

- Research on alcohol toxicity has informed the specification of "safe limits" for drinking and brief interventions that draw links between these harmful health effects and advice to reduce drinking
- The US Preventive Services Task Force recommends screening and brief interventions for unhealthy alcohol use for adults, including pregnant women, in primary care centers.

USPSTF, 2004,
http://www.ahrq.gov/clinic/3rduspstf/alcohol/alcomisrs.htm

Does NIAAA's Integrated Focus on All Aspects of Alcohol Benefit Treatment?

- Research on the mechanisms alcohol's effects on organ pathology could ultimately lead to new treatments for hazardous alcohol use.
- NIAAA Report to the Advisory Council on "Gut-Liver-Brain Interactions in Alcohol-Induced Pathogenesis" is an exemplar

Current Organizational Structure

- Examples of collaborations between NIAAA and NIDA
  - Transdisciplinary Tobacco Use Research Centers
  - Interdisciplinary Consortium on Stress, Self-Control and Addiction
  - Workgroups formed by either Institute typically invite program staff and extramural investigators from the other institute
- Treatment researchers focused on alcohol follow the work of their colleagues in drug abuse and vice versa

Benefits of an Institute Focused on Alcohol

- Systems biology approach to studying the effects of alcohol drinking on health and disease is an important strength made possible by having an Institute devoted to all aspects of alcohol use, abuse and dependence.

- This integrated approach promotes exchange of ideas and collaborations across disciplinary boundaries that would be unlikely to occur otherwise

Presentation to the NIH Scientific Management Review Board

September 24, 2009

Linda J. Porrino

Department of Physiology and Pharmacology

Wake Forest University School of Medicine

Wake Forest University School of Medicine

College on Problems of Drug Dependence

- CPDD is the largest organization devoted to research on substance abuse. Also serves as an interface with academic, government, and industrial organizations with the goal of advancing research, treatment and prevention.
- Over 700 members
- Annual meeting attended by 1500 participants
- Represent researchers in chemistry, genetics, pharmacology, clinical pharmacology, treatment, prevention, epidemiology, policy
- Represent those who study illegal drugs, prescription drugs, legal drugs

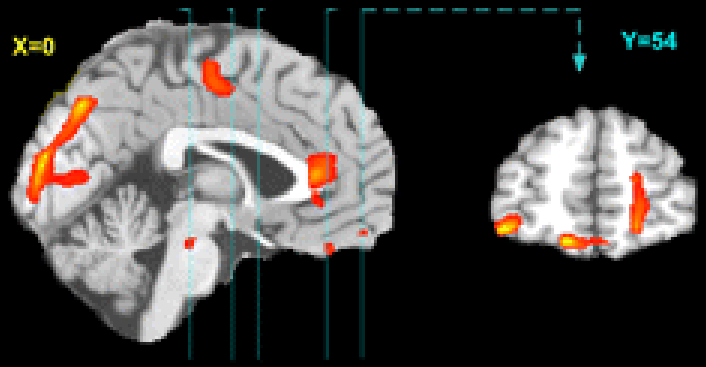
Other Qualifications

- Chair, Department of Physiology and Pharmacology
  - Centers from both NIDA and NIAAA
  - 23 researchers who have funding from one or both institutes
- Investigator with current research support from both institutes

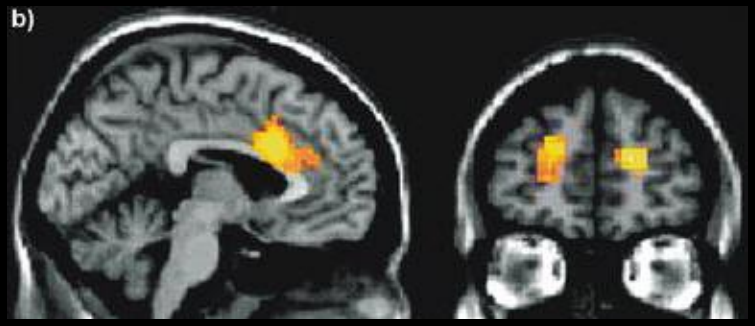
Relapse

- Desire or need to obtain a drug months or years after last use. Often accompanied by feelings of craving
- Arguably the most debilitating long-term effect of addiction to drugs of abuse.
- Animal models of reinstatement - return to drug use precipitated by exposure to
  - Environmental stimuli or cue-induced
  - Pharmacological stimuli or drug-induced
  - Stress or stress-induced

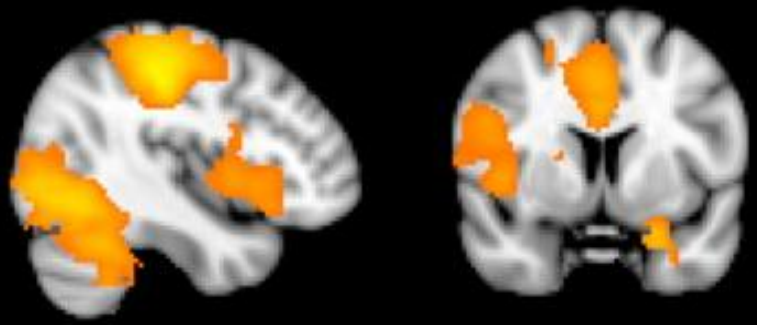
Circuits



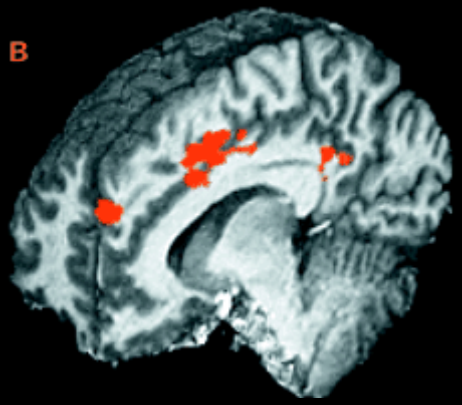
Nicotine



Alcohol



Marijuana

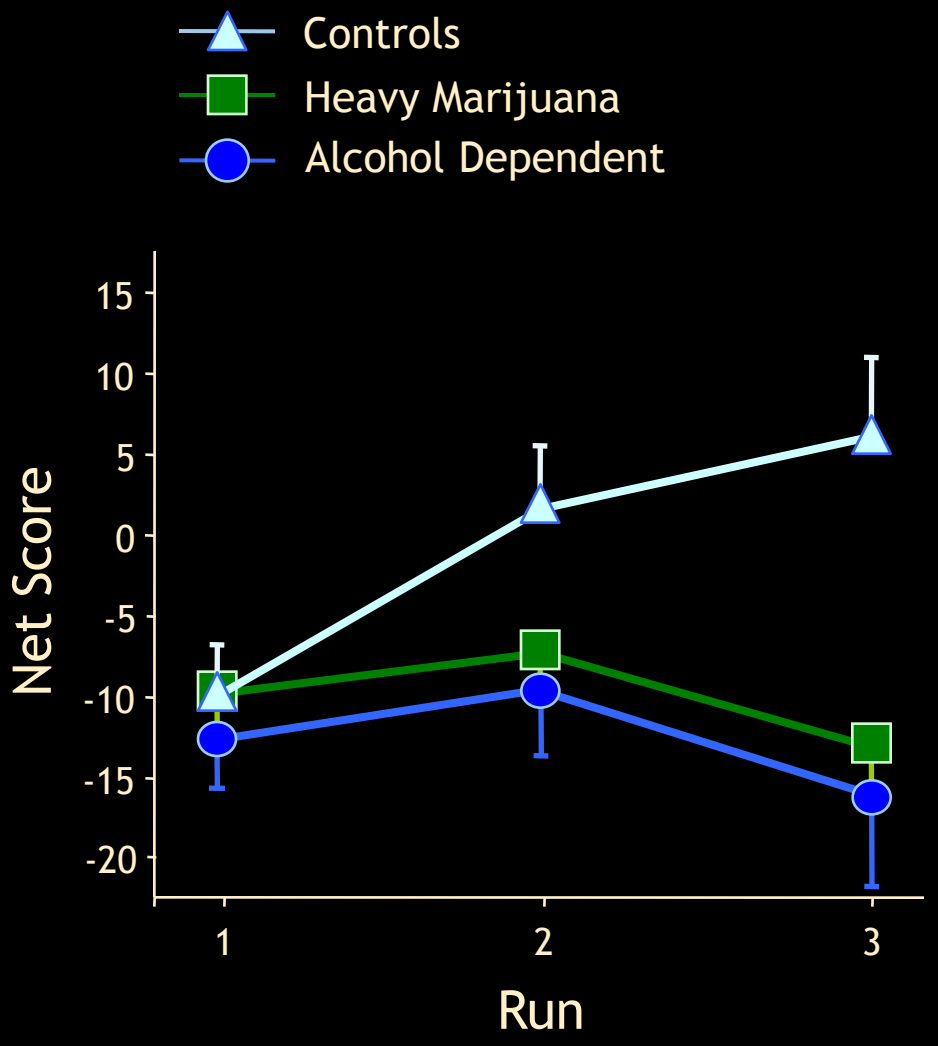


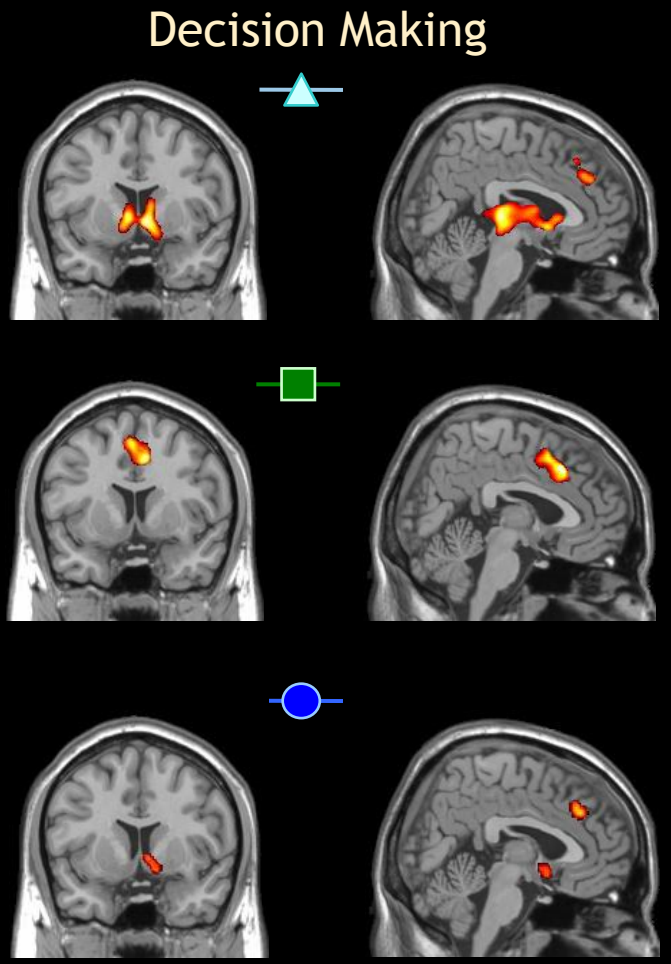
Cocaine

Pharmacological Interventions

System	Drug	Alcohol	Stimulants
Opioid	Naltrexone	✓	✓
GABA	Topirimate Baclofen	✓✓	✓✓
Glutamate	mGluR2/3 agonist mGluR5 antagonist	✓✓	✓✓
Cannabinoid	CB1 antagonist	✓	✓

Dependent Drug Users: Abnormal Behavior and Brain Function





* $p < .05$

Is the merger of NIAAA and NIDA a good idea?

Pros

- Similarities of the basic science and genetics
- Encourage research on interactions –key for treatment
- Impact on our understanding of the trajectory of drug use
- Greater impact of a single larger institute

Cons

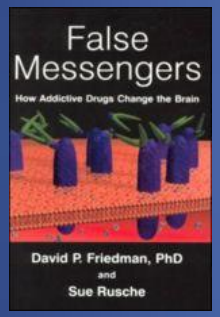
- Budget limitations could reduce research on **any** drug
- Reduce impact of treatment and prevention for any drug from either portfolio
- Less money for research

Why Families Support the Merger of the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism

Sue Rusche
President and CEO, National Families in Action
Atlanta, Georgia

National Families in Action's Programs

Addiction Studies Program



False Messengers

Original Parent Movement

Parent Corps Pilot Program

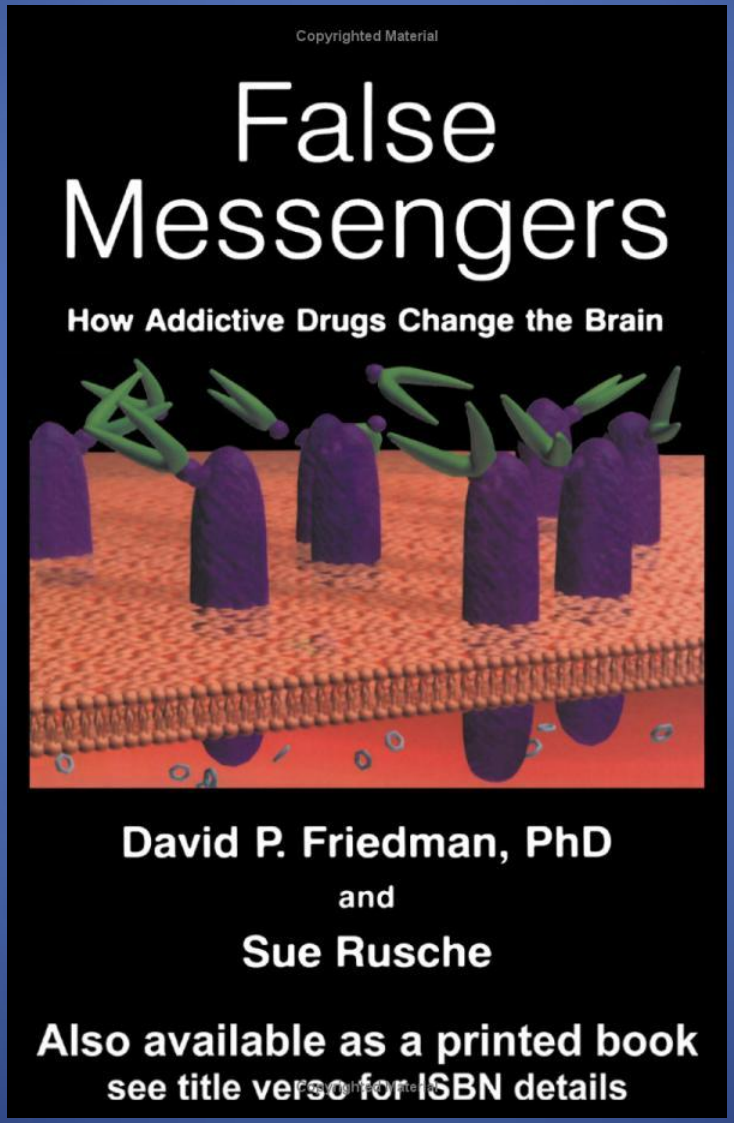
National Parents Corps Act of 2009

Addiction Studies Program

with Wake Forest University School of Medicine

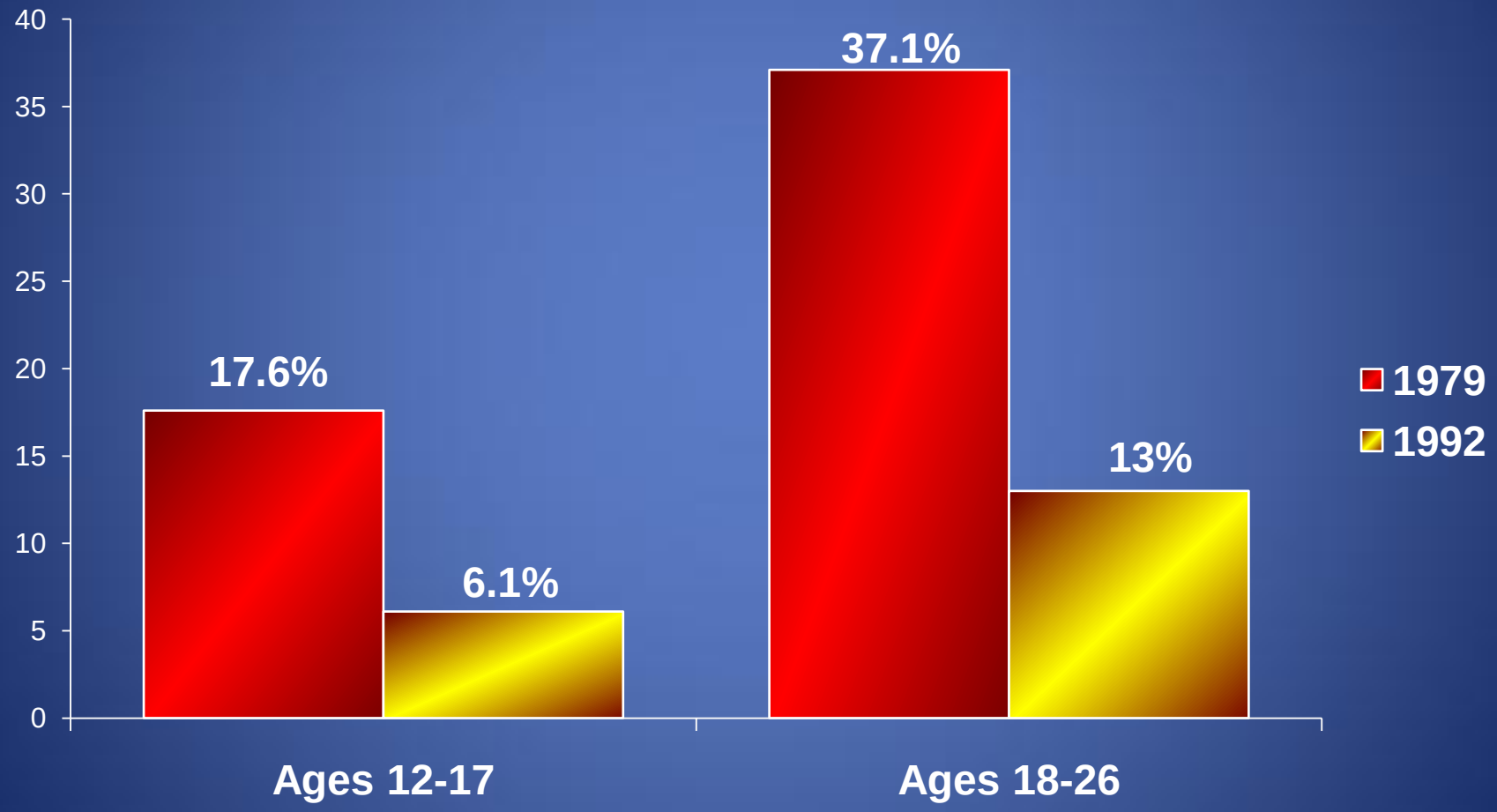
- Journalists Program
  - Provide a basic understanding of the science that underlies drug abuse and addiction
    - Print, broadcast, & electronic journalists
- States Program
  - Help states strengthen their drug policies based on evidence-based programs
    - State legislators and executive branch leaders

False Messengers



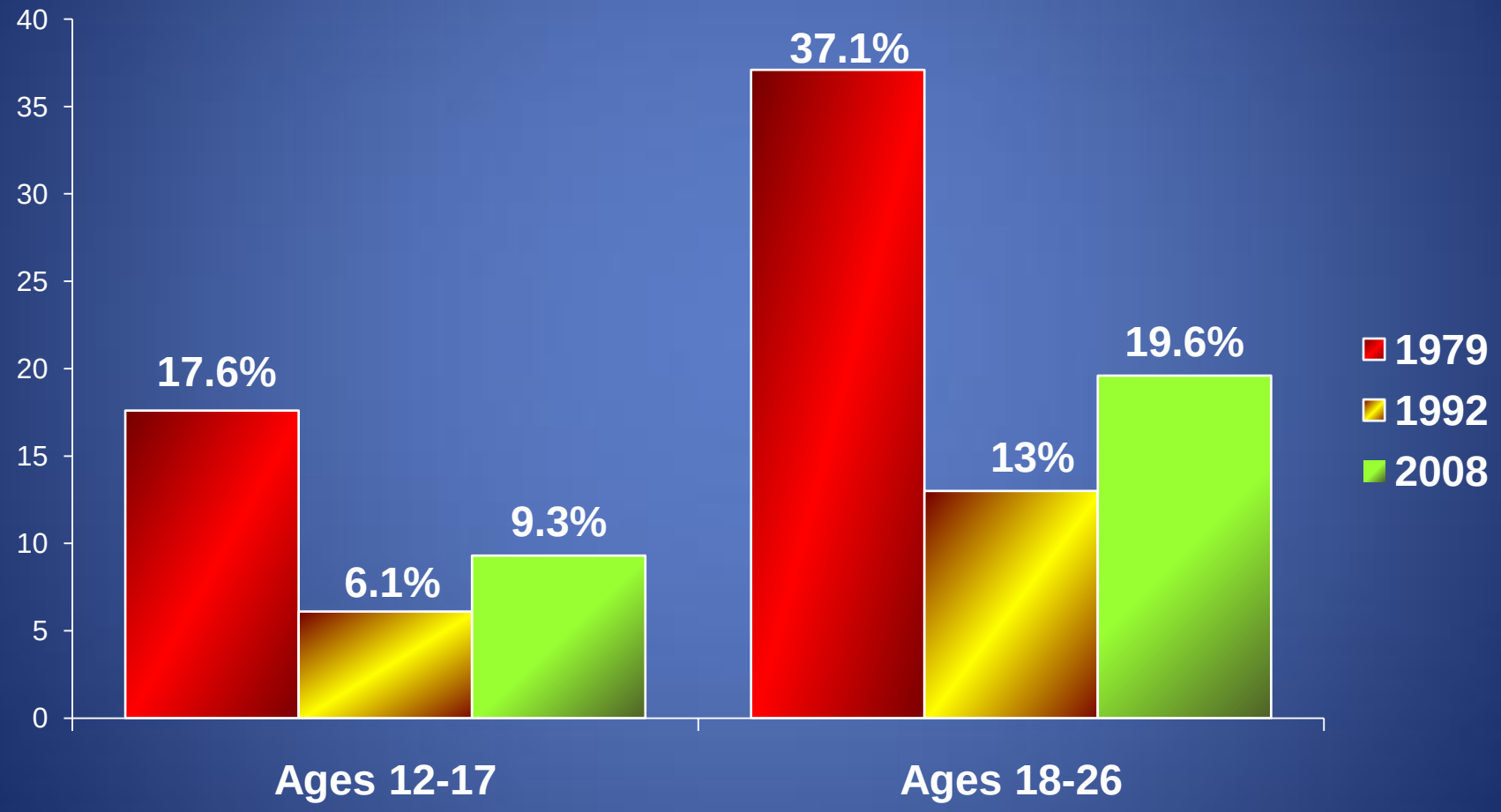
Original Parent Movement

Past month drug use, 1979-1992



Original Parent Movement

Past month drug use, 1979-2008



Parent Corps Pilot Program

Created Parent Corps

To institutionalize original parent movement

Modeled after Peace Corps (Peace Corps for parents)

$4.2 million grant 3-year pilot program (2003-2006)

First Annual Parent Corps Conference, Atlanta, Georgia, June 2005

19 middle schools or high schools in nine states:

California
Colorado
Connecticut
Georgia
Illinois
Kansas
North Carolina
South Carolina
Wisconsin

Parent Corps model

One salaried Parent Leader per school

- Works with other parents in his/her child's school

Nonprofit partners

- Recruit Parent Corps schools, Parent Leaders

National Families in Action

- Hires & trains Parent Leaders
- Manages & supervises Parent Leaders day-to-day

What do Parent Leaders do?

Recruit and educate parents

Disseminate information

Assess and address parents' concerns

Host meetings, trainings, workshops

Mobilize parents

- To make homes, school, and surrounding community healthy and safe for adolescents
- Reduce commercial pressures that exploit teens

Recruiting parents

Ana Gonzalez, Osborne Parent Leader, recruits parents into the Parent Corps as part of Osborne High School Parent Corps activities.

Parent Corps Pilot Program

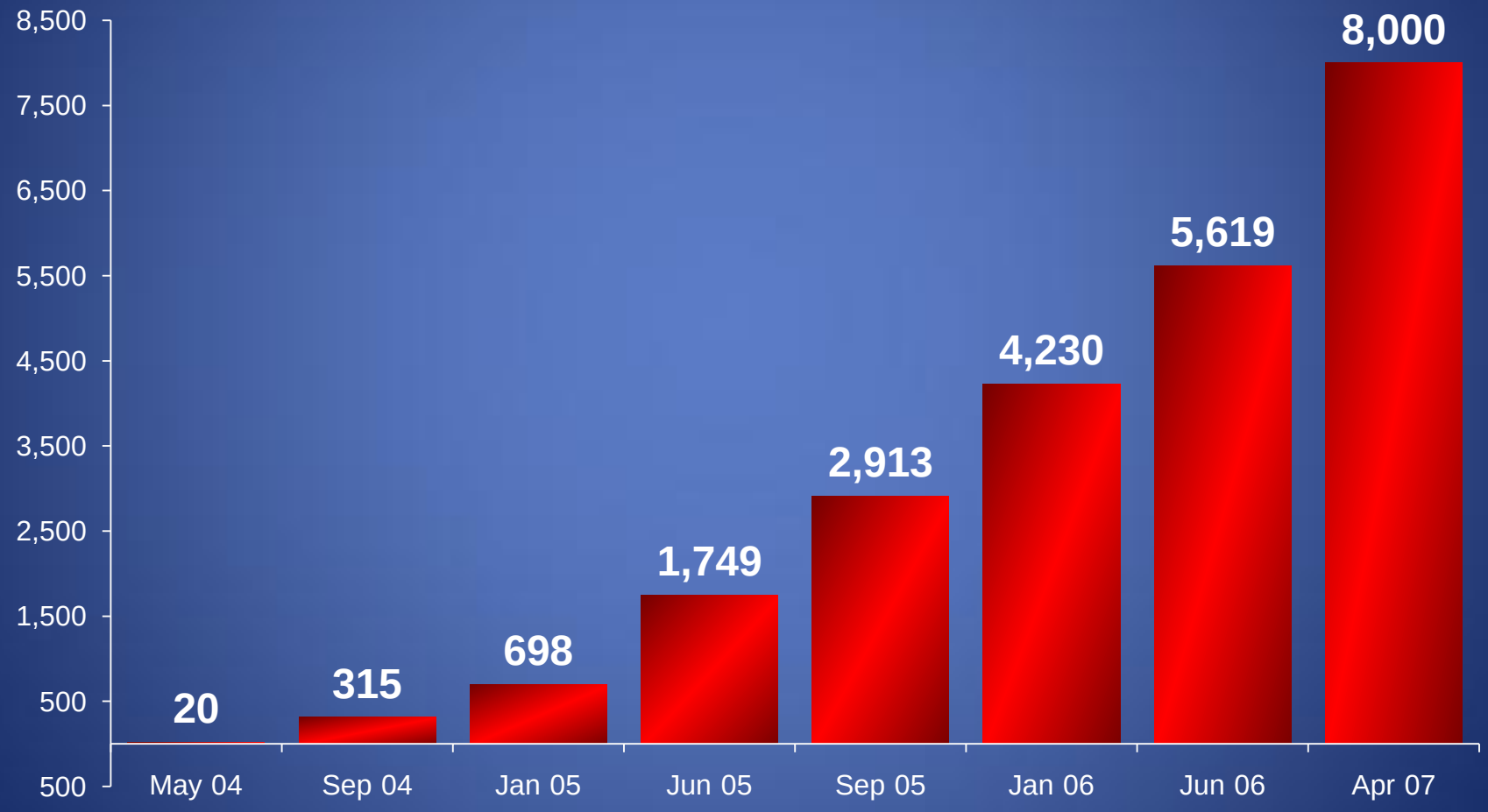
Educating, training, and mobilizing parents

Sharing Best Practices at the First Annual Parent Corps Conference, Atlanta Georgia, June 2005

Parent Corps Pilot Program Results

Parent Corps parent membership

(19 schools in 9 states)



Parent Corps school principals

- Positive communications from parents doubled
- Student attendance increased
- Grades increased
- Discipline problems decreased
- Drop-out rates decreased

Six Parent Corps school principals address Second Annual Parent Corps Conference in Washington D.C., June 2006.

The Parent Corps builds

a delivery system that reaches into the heart of the family to protect adolescents from harm.

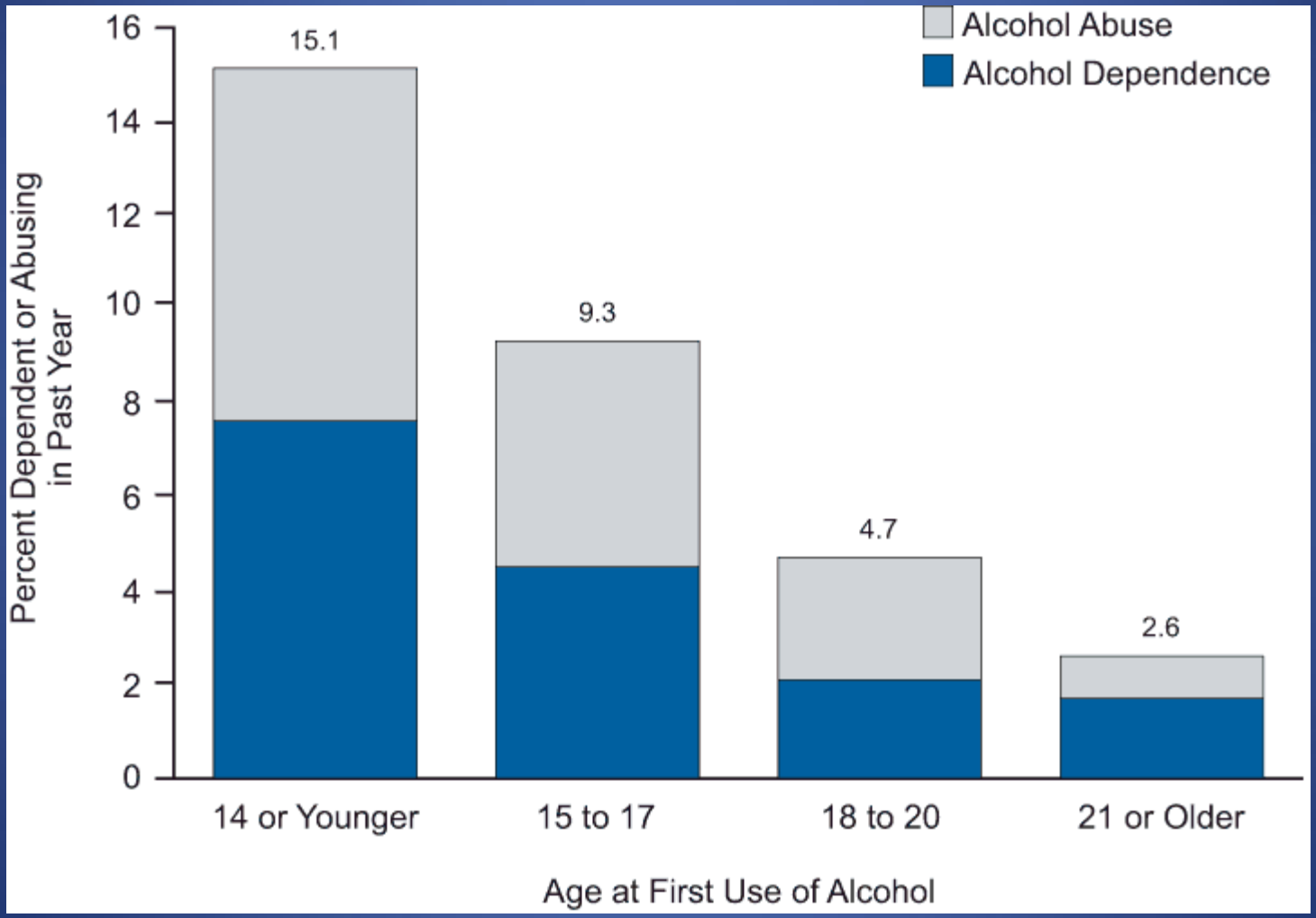
Dinner workshop for parents at Suzanne Middle School Parent Corps and Walnut High School Parent Corps, Walnut, California.

H.R. 3075

The National Parents Corps Act of 2009

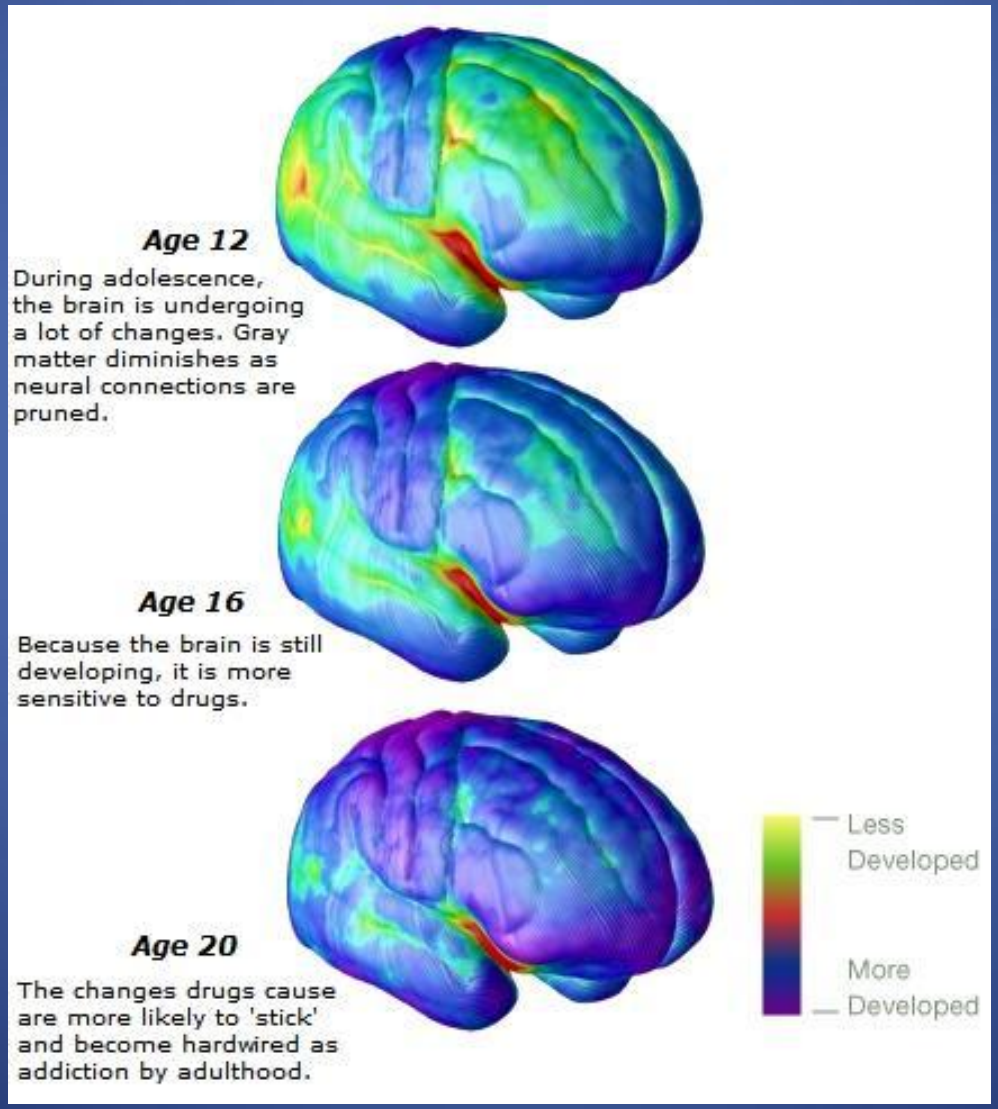
- Sponsored by Congressman John Lewis
- H.R. 3075 will establish a national Parent Corps program for all states, based on results of Parent Corps pilot program
- For more information or to ask your Congress person to cosponsor H.R. 3075, contact: Jamila Thompson, 202-225-3801 or Jamila.thompson@mail.house.gov

Addiction begins in childhood. The earlier adolescents start, the more likely they will develop addiction.



Alcohol dependence or abuse in the past year among adults aged 21 or older, by age at first use of alcohol
2008 National Survey on Drug Use and Health

Their developing brains make them more vulnerable to making poor decisions and, possibly, to developing addiction.



Gogtay et al., 2004. Proceedings of the National Academy of Sciences 101:8174 8179.

Once adolescents initiate use, they don't use just drugs OR just alcohol . . .

NIDA Portfolio

- Marijuana
- Cocaine
- Other Illicit Drugs
- Prescription Drugs
- Nicotine
- Inhalants

NIAAA Portfolio

- Wine
- Liquor
- Beer

They use everything!

There are many good reasons to merge NIDA and NIAAA.

- We think the most important reason is to end the artificial barrier between alcohol and other addictive drugs.
  - Journalists report on both alcohol and other drug problems
  - States cope with both alcohol and other drug problems
  - Families struggle with both alcohol and other drug problems

- It makes sense for a single institute to reflect what is going on in the real world. . .

for the sake of all our children.

NIDA

IS

WONDERFUL

CLINICAL BACKGROUND

- 31 YRS DIRECTOR OF VA PROGRAM
  - 20,000 OP VISITS/YR
  - 350 IP/YR
  - TEACH
    - Med Students
    - Psychiatry
    - Family Practice
- 8 YRS DIRECT PRIVATE PROGRAM
  - IP
  - OP
  - Adults & Teens
- CHAIR DSM IV SUD; MEMBER DSM V

MY CONCERN

HOW MERGER AFFECTS:

- TREATMENT
- PREVENTION
- RESEARCH
- TEACHING

KEY QUESTIONS

- WHERE'S THE BEEF?
- HOW DOES CHANGE HELP ME:
  - KEEP PEOPLE HEALTHY?
  - HELP PATIENTS IMPROVE?
- WHAT'S THE DOWNSIDE?
  - (AKA: THE IMPACT ON ME/MINE?)

HOW TO MAKE DECISIONS

- DATA!
- LOGIC
- EXPERIENCE

ALCOHOL: NOT JUST ANOTHER DRUG

- ✓ LEGAL
- ✓ PREVALENCE:
  - USE
  - UNHEALTHY USE
  - PROBLEMS
  - ABUSE/ DEPENDENCE
- ✓ AFFECTS MOST:
  - SYSTEMS
  - MED ILL
  - PSYCH ILL
- ✓ IMPACTS:
  - ALL AGES
  - BOTH SEXES
  - ALL GROUPS

LOGIC/EXPERIENCE I

NIH

- IN THE BEGINNING:
  2 INSTITUTES
- MERGER IN ADAMHA
- NOW 2 INSTITUTES

SOCIETIES

- RSA FOR ALCOHOL
- CPDD FOR DRUGS
  NEVER MEET TOGETHER
  NEVER MERGE

LOGIC/EXPERIENCE II

- WHERE'S THE BEEF?

  TOO MANY INSTITUTES?

  MONEY?

  BIGGER IS BETTER?

LOGIC/EXPERIENCE III

EFFECTS ON MY PATIENTS

ASSETS (?)

SAVE $

↑ EFFICIENCY

↑ IMAGE

LIABILITIES

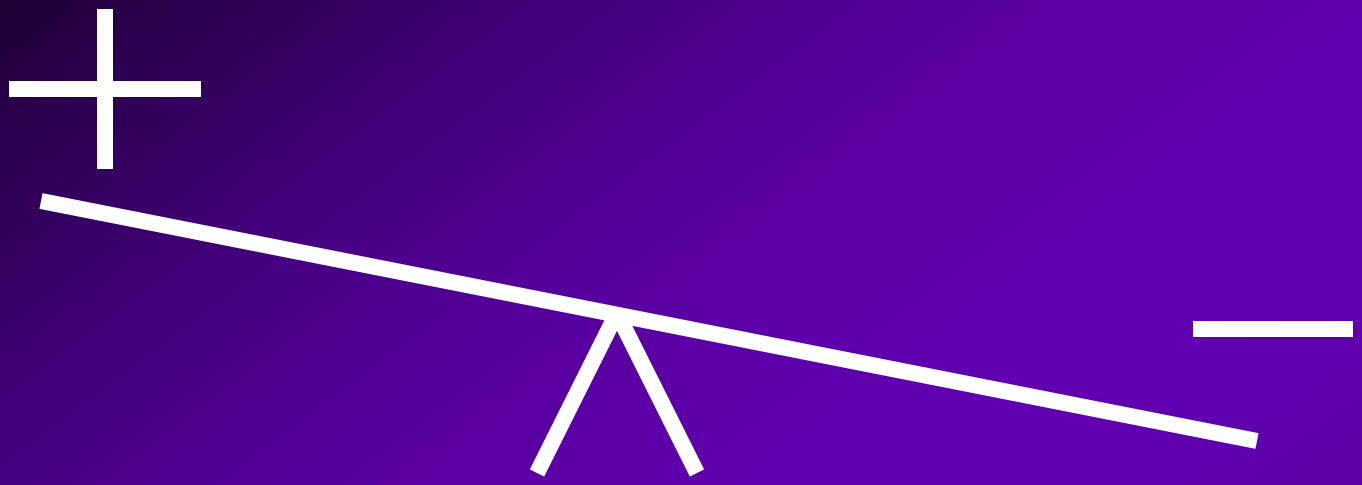
ALCOHOL NOT FOCUS

↓ DATA ON USE/MISUSE

↓ DATA ON BODY SYSTEMS

↓ TEACH HEALTHFUL USE

↑ RELUCTANCE TO ID/GET Rx



MAJOR LOSS

A DEDICATED, FOCUSED INSTITUTE

- **THE MOST PREVALENT**
- **LEGAL**
- **CONTROL OF USE IN MANY**
- **COMPLEX, UNIQUE ISSUES**

KEY QUESTIONS

- WHERE'S THE BEEF?
- HOW DOES CHANGE HELP ME:
  - KEEP PEOPLE HEALTHY?
  - HELP PATIENTS IMPROVE?
- WHAT'S THE DOWNSIDE?
  - (AKA: THE IMPACT ON ME/MINE?)

Medical Complications Alcohol and Drug Abuse

David Vlahov, Ph.D., R.N.
New York Academy of Medicine

Merger

Merger –

combining two interests into one;

no new entity is created.

Consolidation:

combining separate companies into single one.

creates a new entity.

Benefit ?:

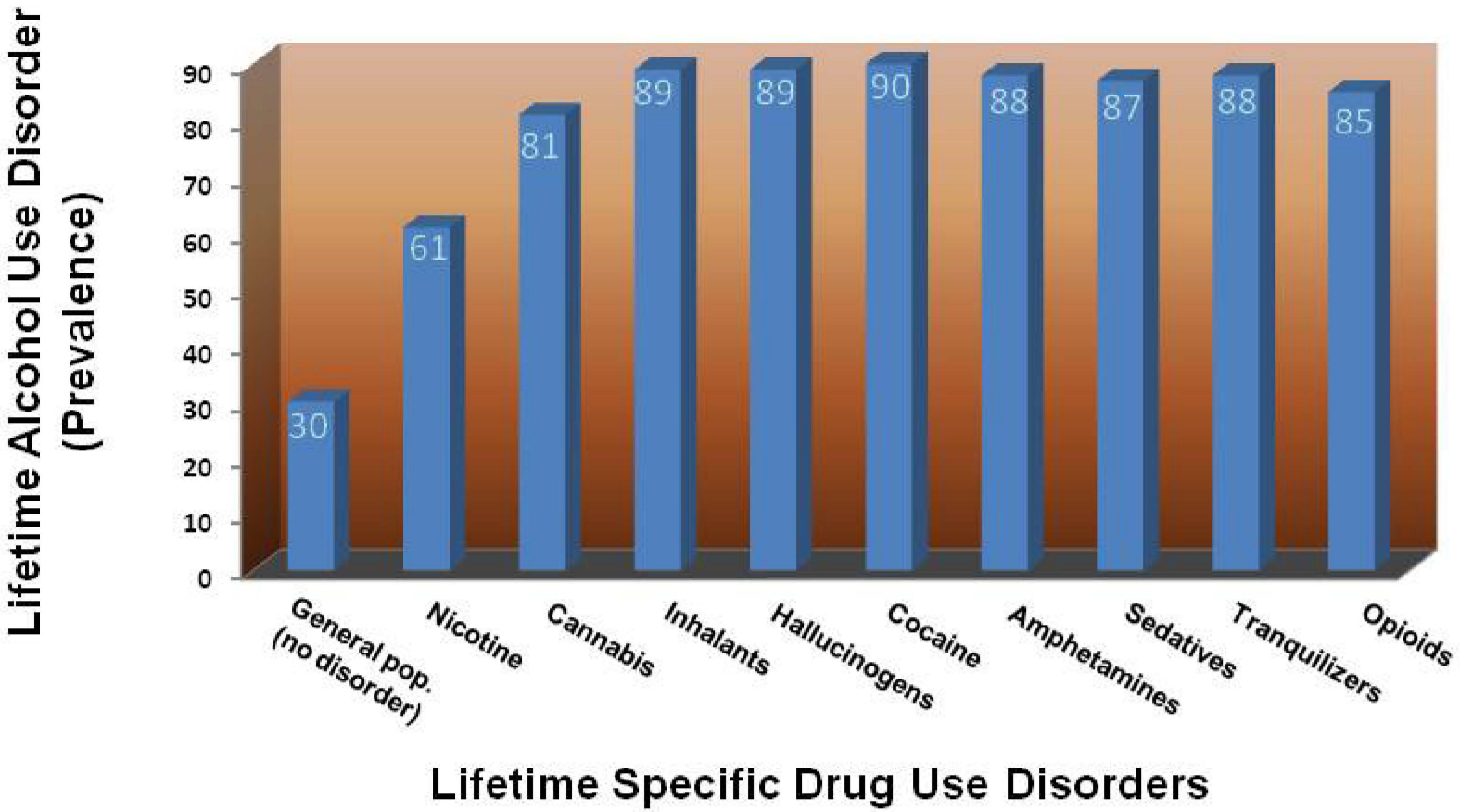
- Synergy – stronger than each alone.
- Efficiency – shared resources

UNODC Definition of “Drug”

- The definition of the word drug proposed by the World Health Organization (WHO) refers to **all psychoactive substances**, i.e., "..any substance that, when taken into a living organism, may modify its perception, mood, cognition behaviour or motor function."

- **This distinction includes alcohol, tobacco and solvents** and excludes medicinal, non-psychoactive substances**.**

Alcohol Use Disorders are Common Among Persons with Drug Use Disorders



Special analysis NESARC study (N=43,081) Conway, Compton, and Brodsky, June 2009 (unpublished)

Adverse Consequences for Tobacco, Alcohol and Illicit Drug Use

- Major Causes of Death
- Multiple Organ Systems

Annual Causes of Death in the United States, 2005

Tobacco	**435,000**
Poor Diet and Physical Inactivity	365,000
Alcohol	**85,000**
Microbial Agents	75,000
Toxic Agents	55,000
Motor Vehicle Crashes	26,347
Adverse Reactions to Prescription Drugs	32,000
Suicide	30,622
Incidents Involving Firearms	29,000
Homicide	20,308
Sexual Behaviors	20,000
All Illicit Drug Use, Direct and Indirect	**17,000**

Organ Systems Affected

- Central Nervous System - depressant,
- Hepatotoxic – Liver,
- Pancreatitis – acute, chronic, diabetes
- Metabolic – Hypoglycemia, Vitamin deficiencies
- Hollow Organ - Esophagitis, Gastritis, Nutritional deficiencies
- Alcoholic Myopathy – muscle weakness, pain, atrophy.
- Alcohol Cardiomyopathy -
- Endocrine – Testicular atrophy, feminization
- Psychosocial toxicity – depression, self esteem

Adverse consequences for Polydrug Abuse

- **Animal models are needed that include alcohol and/or nicotine as well as other drug exposure, given their high rates of co-occurrence and the need to better elucidate their toxicity and common mechanisms.**

- **Clinical studies** are needed on drug abusing sub-groups with potential health vulnerabilities, such as individuals who do not drink to excess, but who also take illicit drugs. Our current knowledge gap in this area could have serious health consequences for the likely majority of drug abusers who are mixing substances.

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Pancreas: Cigarette smoke enhances ethanol-induced pancreatic injury.

- Anesthetized rats – cigarette smoke administered alone or in combination with intravenous alcohol infusion. Controls: saline or alcohol alone.
- Cigarette smoke potentiated the impairment of pancreatic capillary perfusion caused by ethanol, and both the number of rolling leukocytes and myeloperoxidase activity levels were increased compared to ethanol or nicotine administration alone.
- Smoking a contributing factor in the development of alcohol induced pancreatitis in the rat model.

Hartwig et al., 2000

Cardiovascular: Cocaine and Alcohol

- Dogs (n=6) administered cocaine alone or in combination with ethanol. Monitored.
- **Cocaine clearance decreased with prior administration of alcohol**.
- Ethanol did not change concentration effect relationship of cardiovascular response to cocaine administration.
- **Conclude: alcohol does not directly enhance the cardiovascular effects of cocaine.**

Laizure SC, Parker RB, 2009

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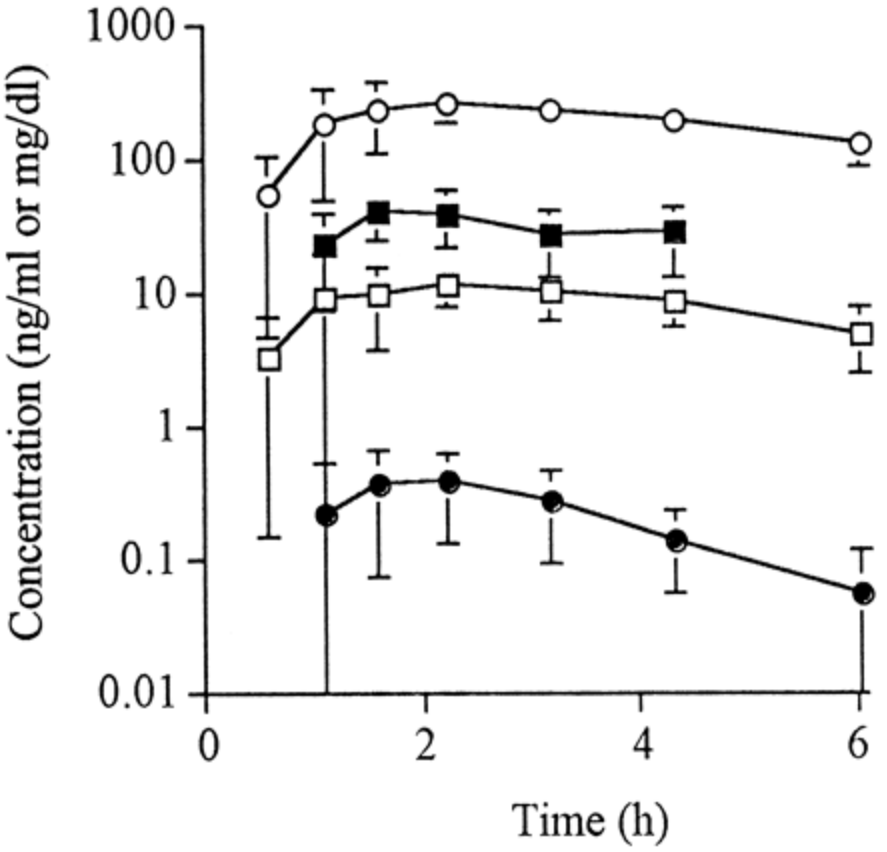
Ethylphenidate formation in human subjects after the administration of a single dose of methylphenidate and ethanol.



1. **Fig. 3.** *Plasma concentration versus time profiles for methylphenidate (white square); ethylphenidate (black circle); ritalinic acid (hollow circle); and ethanol (black square) (mg/dl) in six healthy subjects after oral administration of methylphenidate (20 mg) followed 30 min later by ethanol (0.6 g/kg, consumed over 15 min).*

Markowitz JS, et al. . 2000

Esophageal Cancer: Interaction of tobacco and alcohol

- 830 case subjects and 1779 control subjects in a pooled analysis from 5 case control studies.
- Alcohol and tobacco alone were strongly related to the risk of esophageal cancer, even in the absence of the other exposure.
- A history of simultaneous exposure to cigarette smoking and alcohol drinking had a strong multiplicative effect on risk.
- **Concomitant exposure to heavy alcohol drinking and black-tobacco smoking identified the group with the highest risk for developing esophageal cancer (odds ratio = 107).**

Castellsague, 1999

Head and Neck Cancer – Interaction of Alcohol and Tobacco

- International Head and Neck Cancer Epidemiology Consortium
- Analyzed individual-level pooled data from 17 European and American case-control studies (11,221 cases and 16,168 controls).
- A **greater than multiplicative joint effect between ever tobacco and alcohol use was observed for head and neck cancer risk** (ψ = 2.15; 95% confidence interval, 1.53-3.04). The Population Attributable Risk for tobacco or alcohol was 72% (95% confidence interval, 61-79%) for head and neck cancer.

Hashibe, 2009

Lip Cancer: Combined Effects of Alcohol and Tobacco

- Case-Control (general population)
- **Variables** **Odds Ratios**:
  - Interaction alcohol and cigarettes= 23.6
  - Sun Exposure = 11.9
  - Skin reaction and sporadic warts = 4.4
  - Light (hazel/gray) eyes = 3.5

Perea-Milla Lopez, et al., 2003

Hepatocellular Carcinoma:
Multiplicative Interaction: Tobacco and Alcohol

- 333 incident cases of HCC; 360 controls
- **Variables** **Odds ratios**
  - Cigarettes (>/= 2ppd) = 2.5
  - Alcohol (>40 glasses/wk) = 1.9
  - **Both** **= 9.6**

Kuper H , et al., 2000

Hepatitis C Related Liver Fibrosis Progression among HIV+ and HIV- Injection Drug Users.

- Of **116 HCV+ IDUs** with paired liver biopsies (median: 4 years apart), the sample was 28% HIV+, 95% African American, 82% male and median age was 42 years. 51% were current IDU, 60% used alcohol

- Compared with the initial biopsy, the median progression rate (fibrosis units/year) was 0.11 (range -0.68 to 1.42), and did not significantly differ by HIV status. FP occurred in 21%.

- **A trend was seen with greater FP with increased alcohol use and with increased IDU at study visits**.

- Paired biopsies were scored from 0 to 6 according to the modified histologic activity index (MHAI). FP was defined as an increase in fibrosis score of = 2 units.

Wilson, 2004

Prenatal Alcohol Use, Tobacco and Perinatal Outcomes.

- Preterm labor
- Low birth weight
- Growth restriction, Small for Gestational Age

occurred more frequently in women who drank and smoked during pregnancy. This **increased odds ratio was more than the sum of the effects of either smoking or drinking**.

(Aliyu et al, 2009; Odendaal HJ, 2009)

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EXPLORE: Multivariate analysis of HIV seroconversion: Drug and alcohol use

Drug	N at baseline	No. of infections	**Hazard ratio***	95% CI
Heavy alcohol**	419	41	1.87	1.24, 2.81
Amphetamines	527	67	1.93	1.41, 2.64
Alcohol or drugs before sex	2952	205	1.57	1.08, 2.27

* REF = no, light or moderate use of alcohol; no speed use; no use before sex

** Heavy alcohol = 4+ drinks every day or 6+ drinks on a typical day

NIAAA-NIDA Merger

Opportunities for scientific synergies