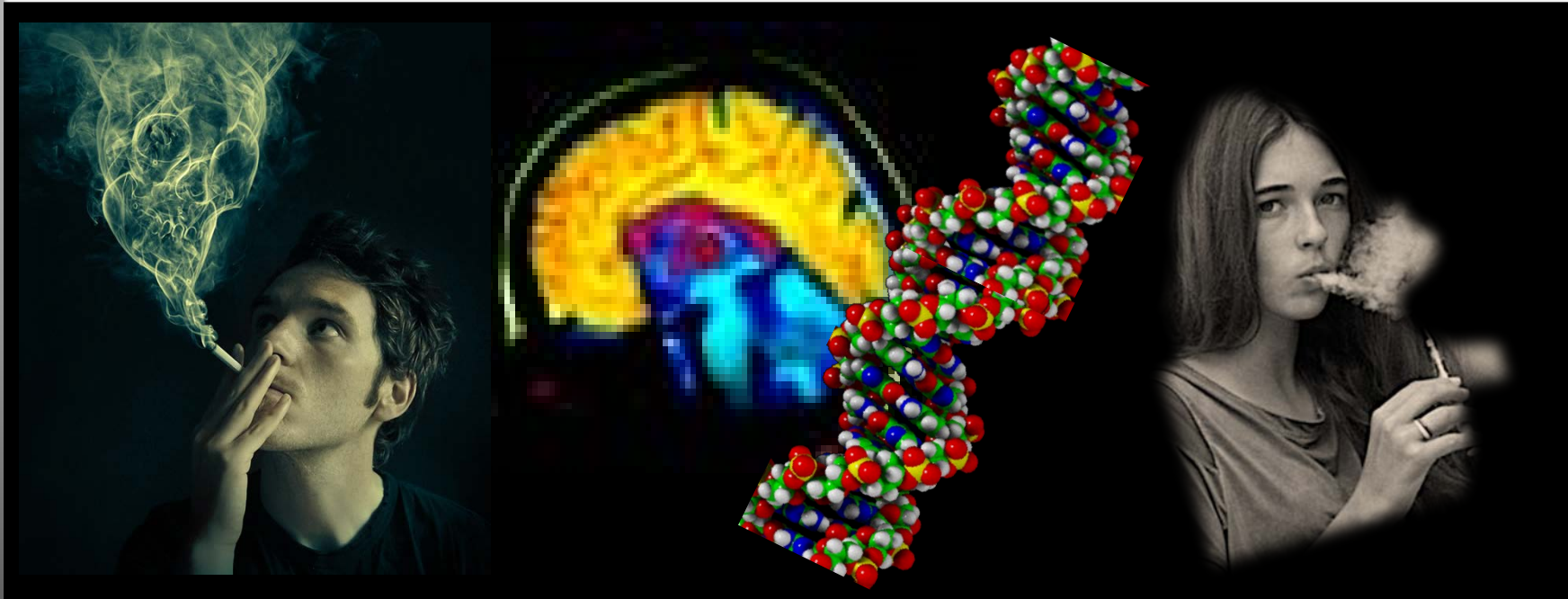


Tobacco Research at NIDA: *Basic Science, Prevention, Treatment and Regulatory Science*



October 27, 2015

Susan Weiss , PhD

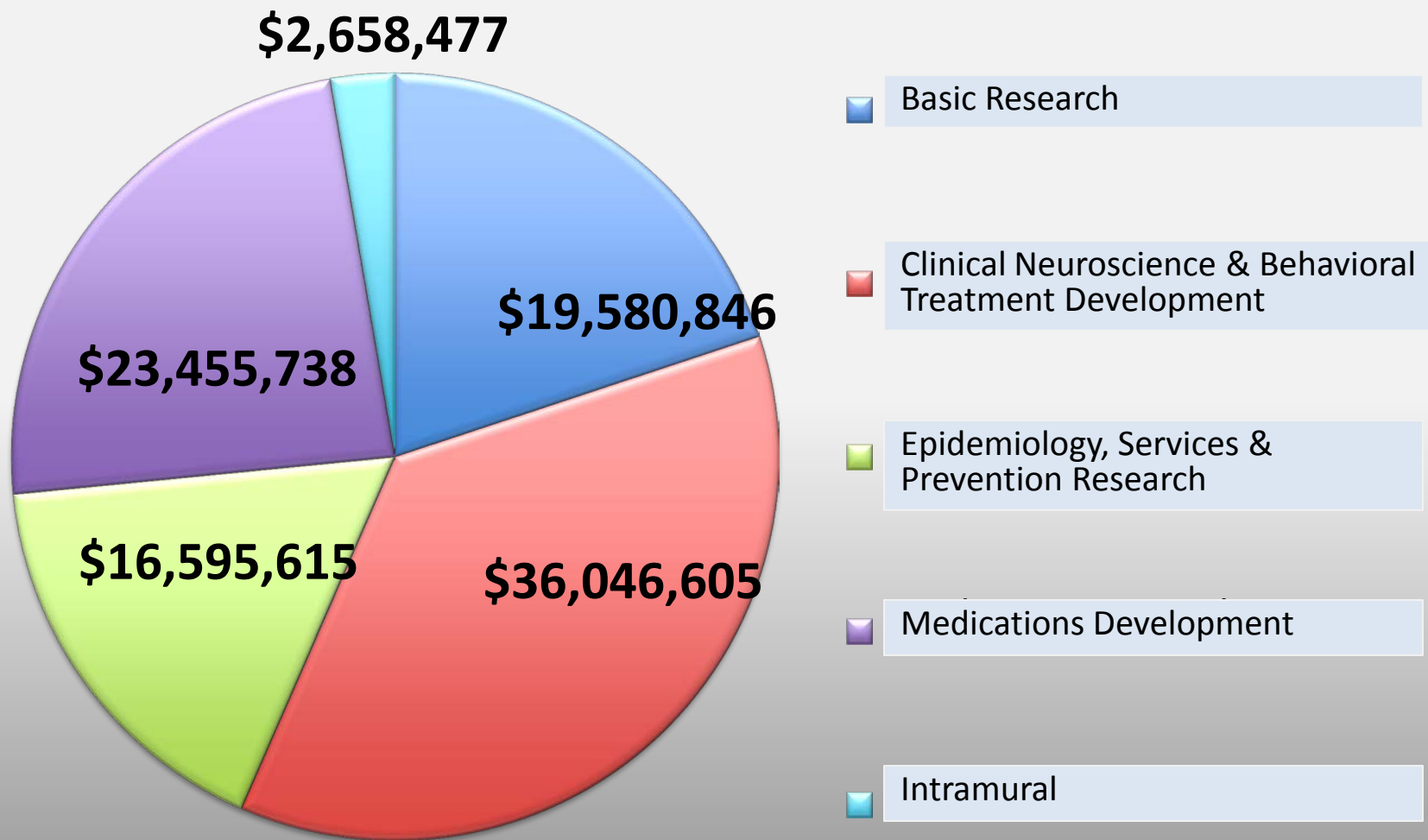
Director

Division of Extramural Research



National Institute
on Drug Abuse

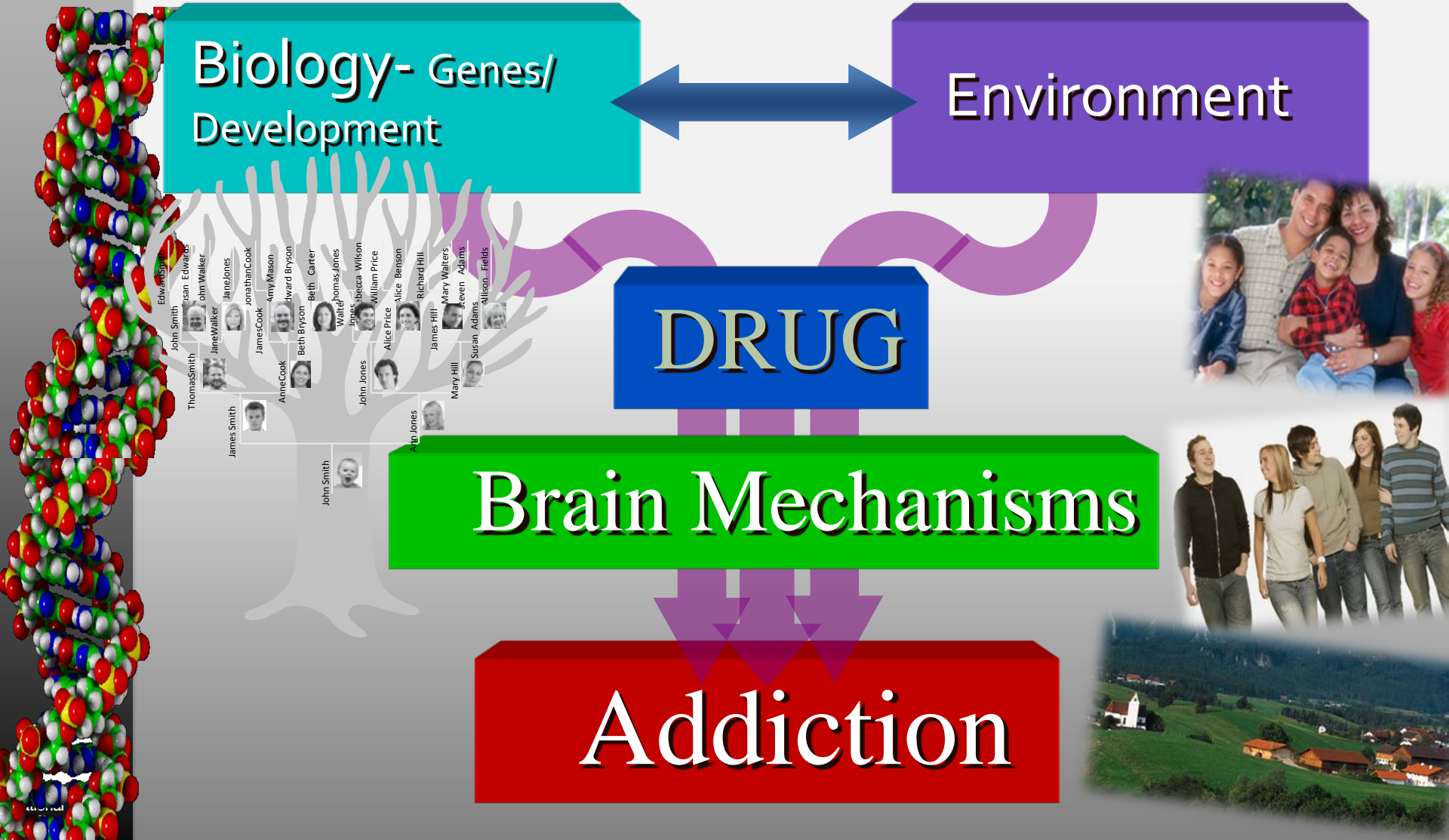
NIDA FY 2014 Tobacco Grants (294, \$101M)*



* Does NOT include FDA/CTP supported grants and contracts



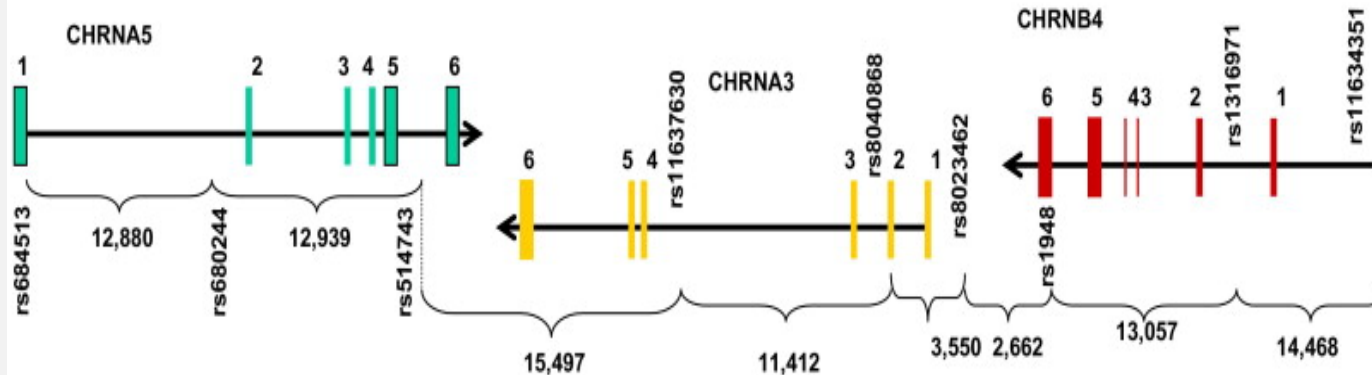
Addiction and Other Psychiatric Diseases Involve *Multiple Factors*



Themes for NIDA Research

- Basic Science
 - ✓ Genetics (understanding impact of genetics on vulnerability to smoking-related morbidity/mortality)
 - ✓ Biomarkers of vulnerability
- New Delivery Systems (ENDS)
- Medications Development
- Behavioral and Integrated Treatments
- Vulnerable Populations (e.g., youth, pregnant women, mental illness)
- Prevention (ABCD)
- Integrated Tobacco Surveillance and Regulatory Studies (MTF, PATH, and others)

Convergent Results Support CHRNA5/A3/B4 Gene Cluster Association with Nicotine Dependence



Human Molecular Genetics, 2007, Vol. 16, No. 1 24–35
 doi:10.1093/hmg/ddl441
 Advance Access published on December 7, 2006

Novel genes identified in a high-density genome wide association study for nicotine dependence

Biological Psychiatry

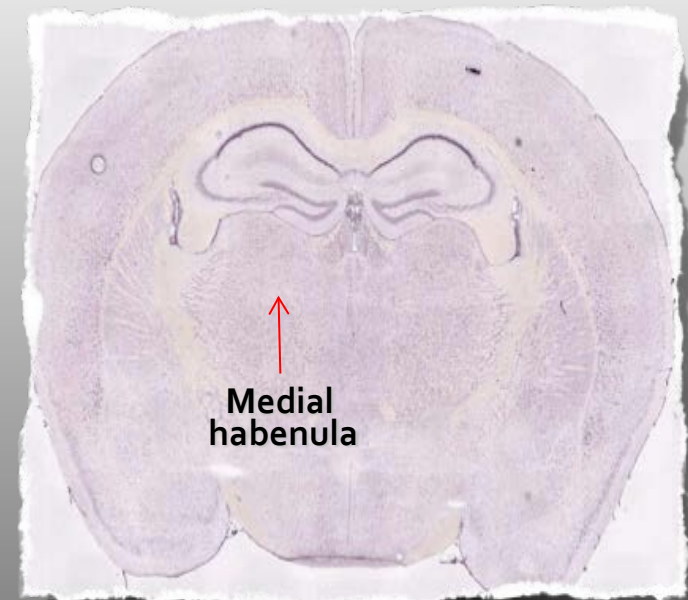
The CHRNA5/A3/B4 Gene Cluster Variability as an Important Determinant of Early Alcohol and Tobacco Initiation in Young Adults

Molecular Psychiatry (2008), 1–6
 © 2008 Nature Publishing Group. All rights reserved 1359-4184/08 \$30.00
 www.nature.com/mp

IMMEDIATE COMMUNICATION

α -5/ α -3 nicotinic receptor subunit alleles increase risk for heavy smoking

$\alpha 5$, $\alpha 3$, $\beta 4$, have a high concentration in habenula and interpeduncular nucleus

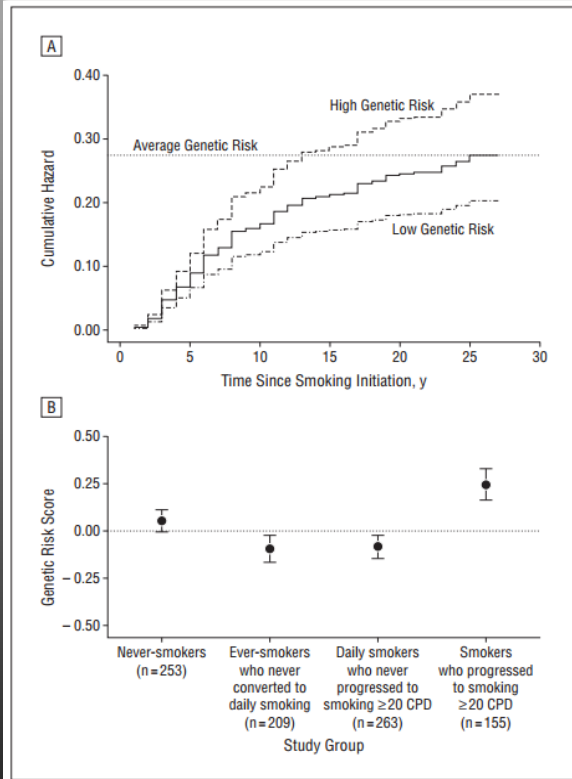


Medial habenula



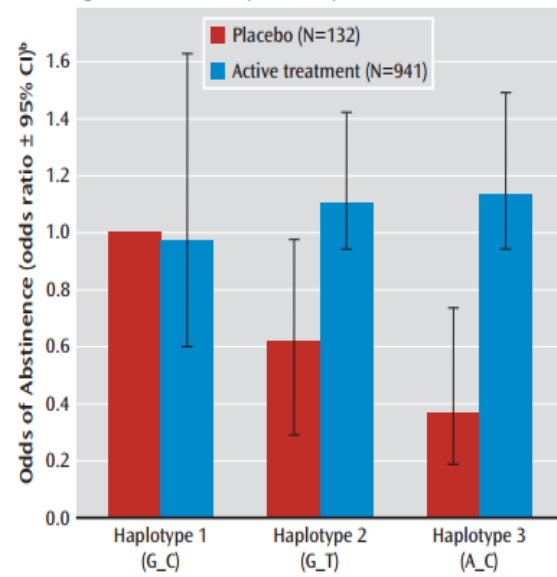
Genes Affect Risk for Smoking Progression, Odds of Quitting and Whether Medications May Help

Polygenic Risk and the Developmental Progression to Heavy, Persistent Smoking and Nicotine Dependence

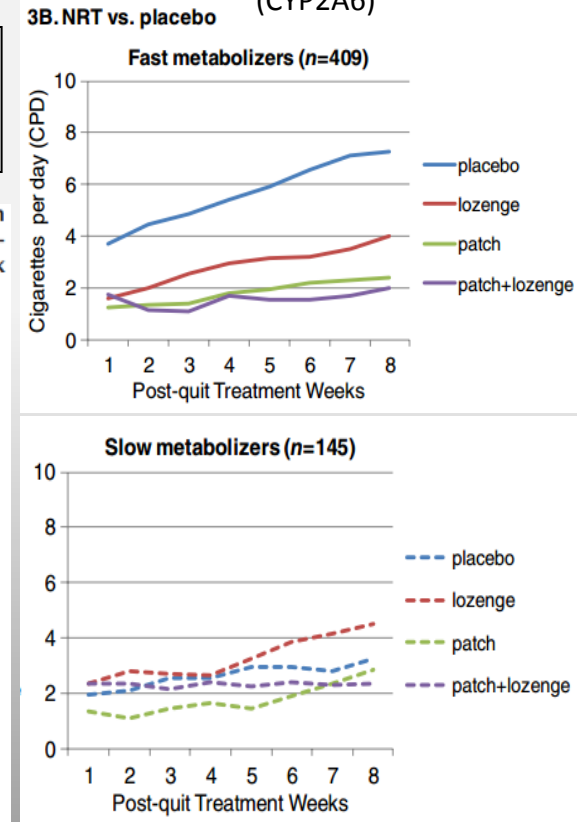


Interplay of Genetic Risk Factors (*CHRNA5-CHRNA3-CHRNB4*) and Cessation Treatments in Smoking Cessation Success

FIGURE 1. Effect on Endpoint Abstinence of Interaction Between Treatment and Haplotype in Nicotinic Receptor Gene Cluster *CHRNA5-CHRNA3-CHRNB4* in an 8-Week Smoking Cessation Trial (N=1,073)^a



Pharmacotherapy effects on smoking cessation vary with nicotine metabolism gene (*CYP2A6*)



	Placebo	NRT lozenge	NRT patch	NRT lozenge+patch
Fast Metabolizers	72	98	108	131
Slow Metabolizers	27	42	40	36



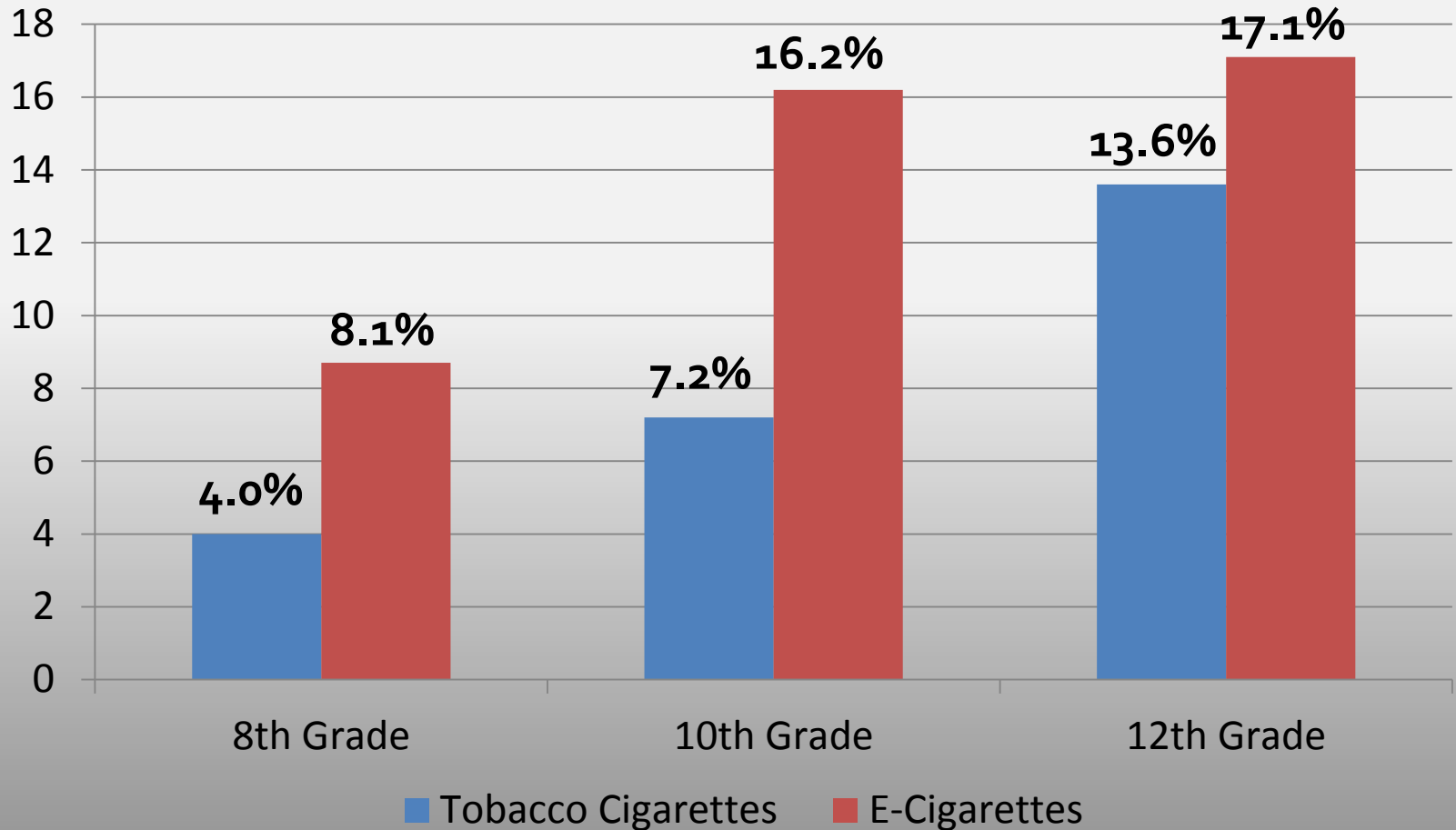
Source: *Belsky DW, et al., JAMA Psychiatry 70: 534-42, 2013

Source: *Chen LS et al., Am J Psychiatry 169: 735-42, 2012

Source: *Chen LS et al., Addiction 109: 128-37, 2013

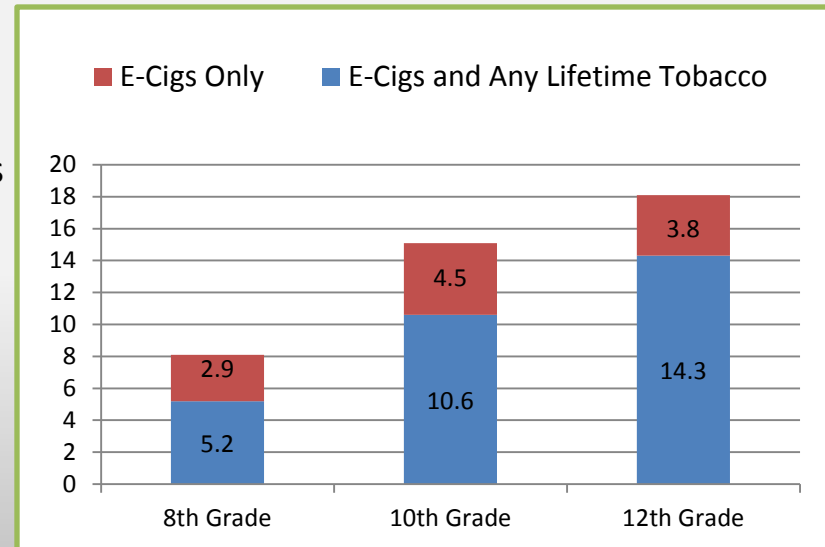
More Youth in USA Using E-Cigarettes Than Tobacco Cigs

Past Month Use of E-Cigs vs. Traditional Cigarettes in the 2014 Monitoring the Future Study of 8th, 10th and 12th Grade Students in USA



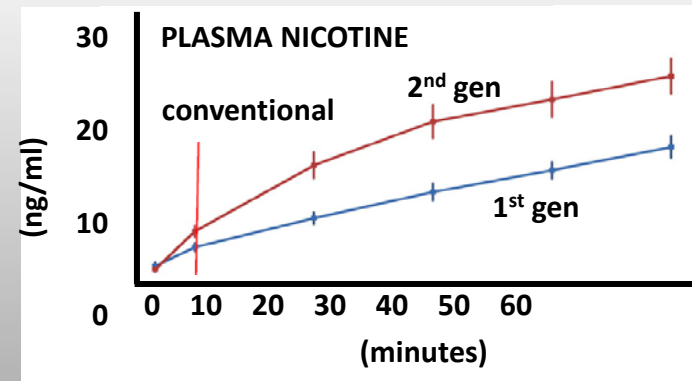
Current Trends and Statistics

- **Who is using e-cigarettes?**
 - Use doubling every year since 2010
 - High school kids use e-cigarettes more often than combustible cigarettes in the last 30 days (MTF and NYTS)
 - 25-55 % of kids that used e-cigarettes in past 30d had *never used combustibles* (MTF)
 - In adults, dual use with combustibles most common scenario
 - Is this temporary until e-cigarettes routinely deliver combustible levels of nicotine?
 - Regular vapers who quit combustibles generally use higher power devices likely to deliver highest levels of nicotine



E-Cigarette Aerosol Contents

- **Long-term safety of aerosol inhalation is unknown**
 - Many constituents are “Generally Recognized as Safe” (GRAS) for food, **BUT** lung inhalation bypasses first pass metabolism
 - Some compounds same as in tobacco smoke: acrolein, formaldehyde
 - Generally substantially lower toxin levels (9-450x) than in tobacco smoke
- **Variable voltage devices can alter the aerosol**
 - Higher voltage produces higher temps, more nicotine in aerosol
 - This may also increase levels of toxic compounds: e.g., formaldehyde
 - Under certain conditions, levels near those of conventional cigarettes
- **E-cigarette aerosol is less complex than tobacco smoke**
 - ≈ 5000 compounds in tobacco smoke
 - ≈ 70 known carcinogens in tobacco smoke
 - Many fewer compounds in e-cigarette aerosol



Source: Goniewicz et al, 2014; Kosmider et al, 2014

E-Cigarettes and Policy Implications

(Federal, State, Local Level)

- **2009 Family Smoking Prevention and Tobacco Act (Tobacco Control Act)**
 - FDA currently regulates cigarettes, cigarette tobacco, roll-your-own tobacco and smokeless tobacco products (e.g., limits sale, distribution, advertising, establishes product standards)
 - Newly proposed (2014) regulations include e-cigarettes, cigars, pipe tobacco and some dissolvables; final rule expected June 2015 (*still waiting*)
- **E-cigarette regulatory action mostly taking place on the State and local-level**
 - ~41 States restrict sale of e-cigarettes to minors; 18 states have laws regulating use (e.g., in state buildings, schools, public places/transport)
 - Local laws on e-cigarette parallel combustible tobacco product regulations
 - e.g., Montgomery (MD) County Council voted to ban e-cigarette (e-hookah, e-pipe and vape pens) use in public places and increase taxes on products
- **Currently minimally regulated**
 - Over 250 e-cigarette brands in U.S.; thousands of e-juice flavors

Current NIH E-Cigarette Funding, FY15

	NIDA		NCI		NHLBI	
Total Grants	19		11		2	
	FDA	NIH/IC	FDA	NIH/IC	FDA	NIH/IC
	15	4	8	3	1	1
Total \$\$	\$13,623,174		\$7,482,757		\$625,287	

*Additional NIDA: SBIR Contract (NJOY) - \$330,428; portions of PATH and MTF

Most Common Research Areas

- **How are devices being used/dual use** (Eissenberg)
- **Abuse liability** (Rose)
- **Nicotine delivery characteristics** (George)
- **Role of flavors** (Krishnan-Sarin)
- **User perceptions/advertising** (O'Connor)
- **Safety of constituents** (Talbot)
- **Natural history studies of use** (Carpenter)
- **Animal/in vitro models** (Robinson)



Research Questions in Need of Answers

- **Youth use of e-cigarettes relative to combustible**
 - Role in long term e-cigarette use and/or nicotine addiction
 - Which products most common for initiation?
 - Are e-cigarettes a gateway to combustible?
- **Prevalence of alternative drug use in e-cigarettes**
 - E-cigarette cartomizers filled with marijuana extracts are a standard medicinal marijuana product
 - Use of other substances routinely mentioned in blogs/chat rooms
- **What is the addictive potential of e-cigarettes?**
- **Need to determine role in cessation and harm reduction**
 - Useful tool for nicotine cessation?
 - What are real risks and benefits versus combustible?
 - Likelihood of initiation/addiction by adults?
 - Role for special populations such as schizophrenia, heavy smokers



Therapies for Smoking Cessation

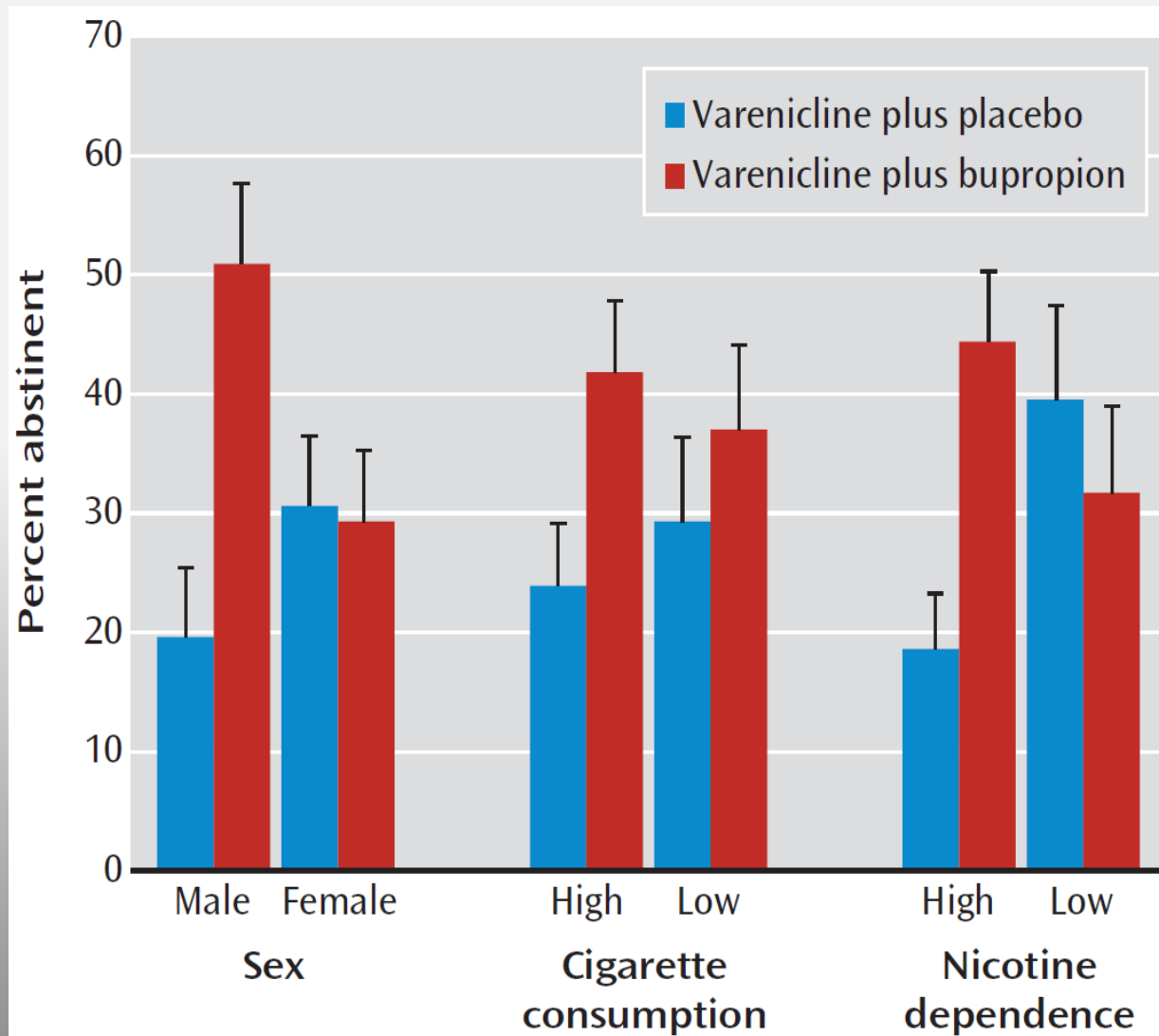
- **7 FDA approved first-line pharmacotherapies:**
 - 5 NRT and 2 non-NRT
- **Cessation treatment has limited efficacy after 6 months**
Only 20% using pharmacotherapy are abstinent for more than a year.

Treatment	Abstinence Rate at 6 mo, %
Self-help and Quitline	8.5% and 12.7%
Counseling alone	14.6%
* Varenicline (2mg/day and 1 mg/day)	33.2% and 25.4%
* Bupropion SR	24.2%
* Nicotine patch	23.4%
Medication and counseling	27.6%

Source: * *Treating Tobacco Dependence in Light of the 2008
US Department of Health and Human Services Clinical Practice Guideline*

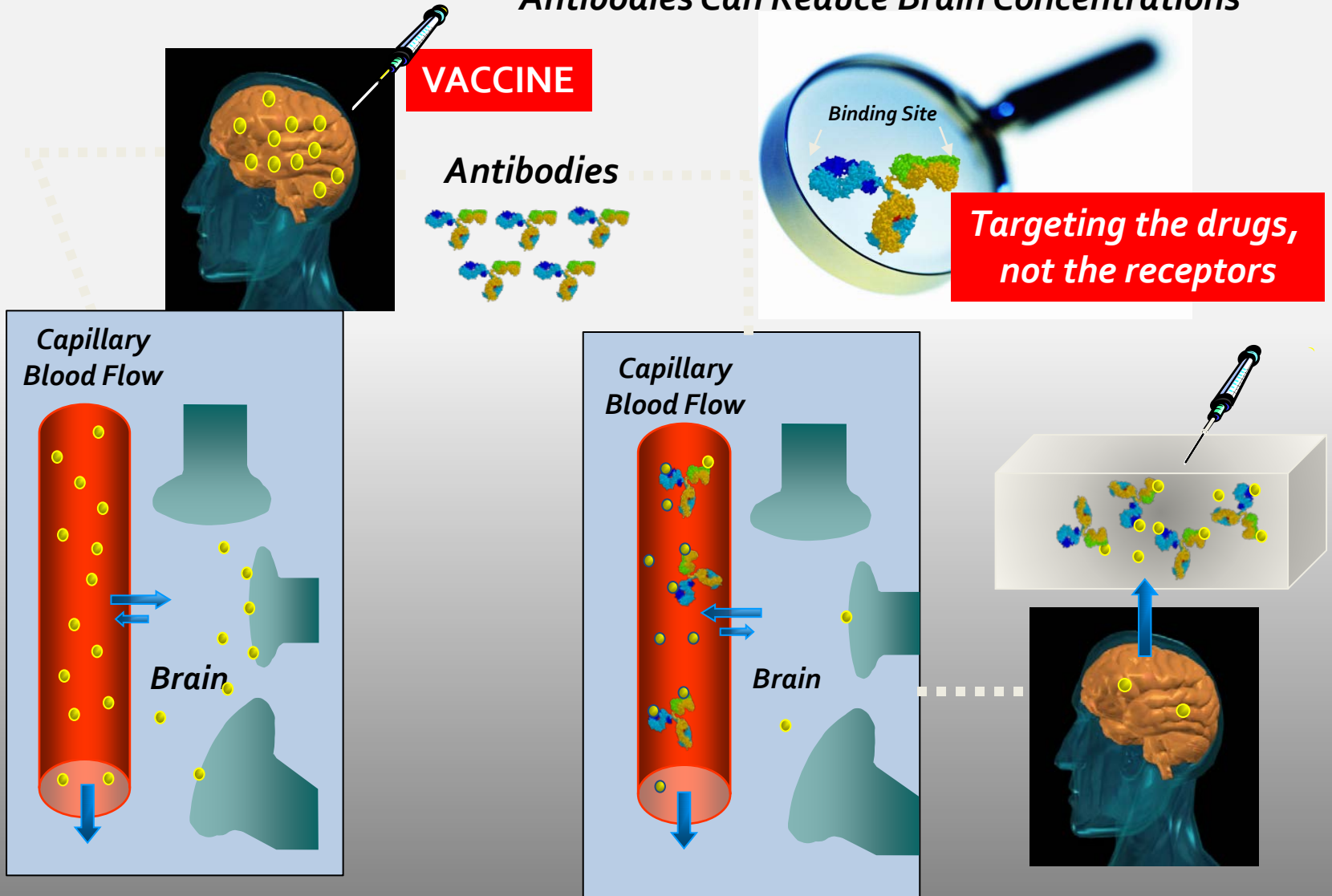


Varenicline & Bupropion SR Combination Therapy for Smoking Cessation

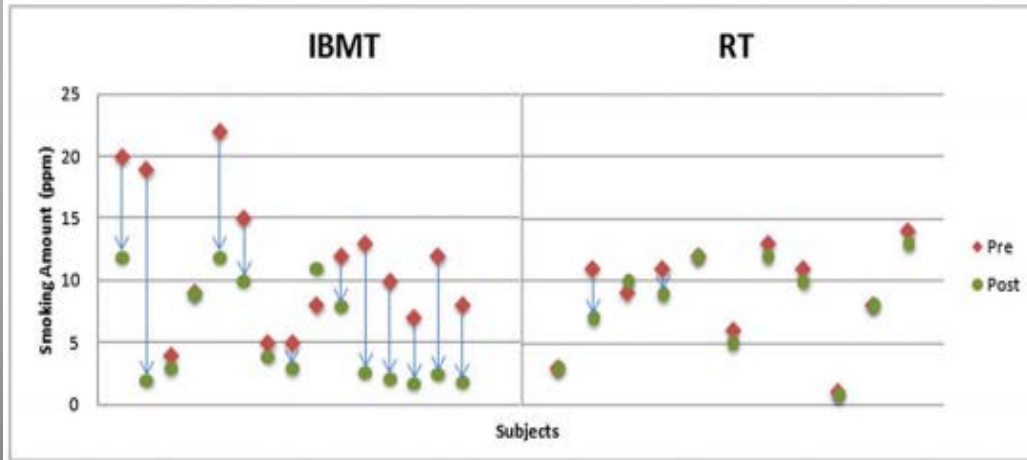


Immunotherapies for Addiction Treatment (i.e., Vaccines)

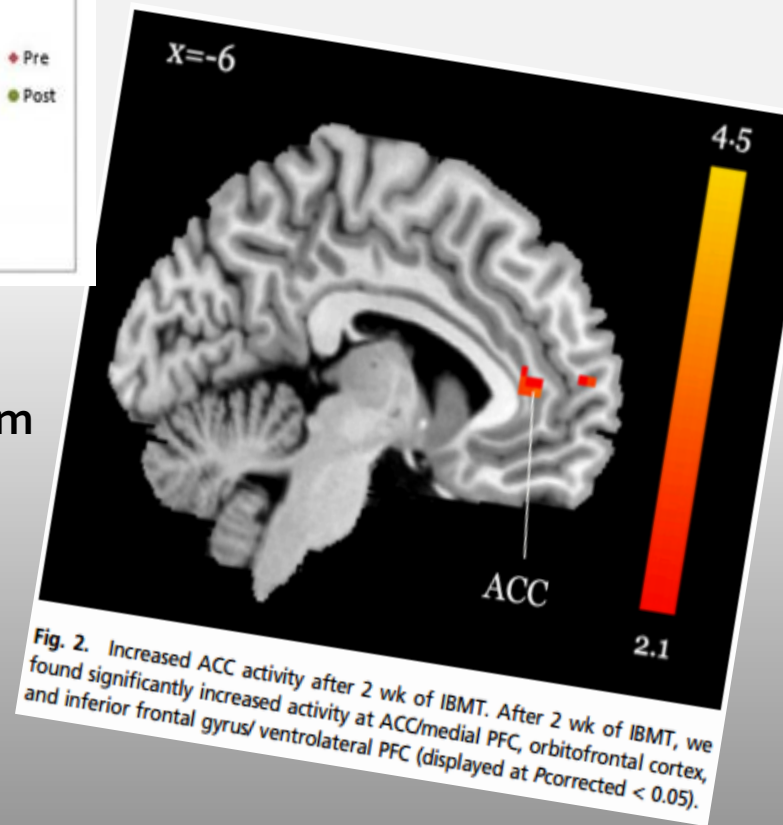
Antibodies Can Reduce Brain Concentrations



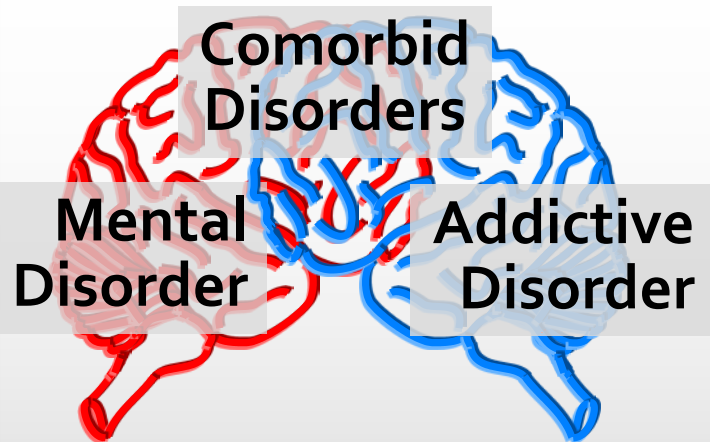
Mindfulness Meditation for Smoking Cessation



- Individuals received
 - integrative-body-mind training, a form of mindfulness meditation
 - generalized relaxation training
- IBMT reported reductions in smoking, withdrawal symptoms and cravings for cigarettes
- Positively associated with activity in brain areas associated with self-control and decision-making



Source: Tang et al PNAS 2013;110:13971



COMORBIDITY

Smoking Epidemiology

Non-Ill Population:	23%*
Alcoholism:	56.1% (current); 43.5% (lifetime)**
Drug Addictions:	67.9% (current); 49% (lifetime)**
Schizophrenia:	70-85%***
Depression:	44.7% (current); 36.6% (lifetime)**
Anxiety:	54.6% (current); 46% (lifetime)**
PTSD:	44.6% (current); 45.3% (lifetime)**
ADHD:	41-42% (adults)****
	19-46% (adolescents)****

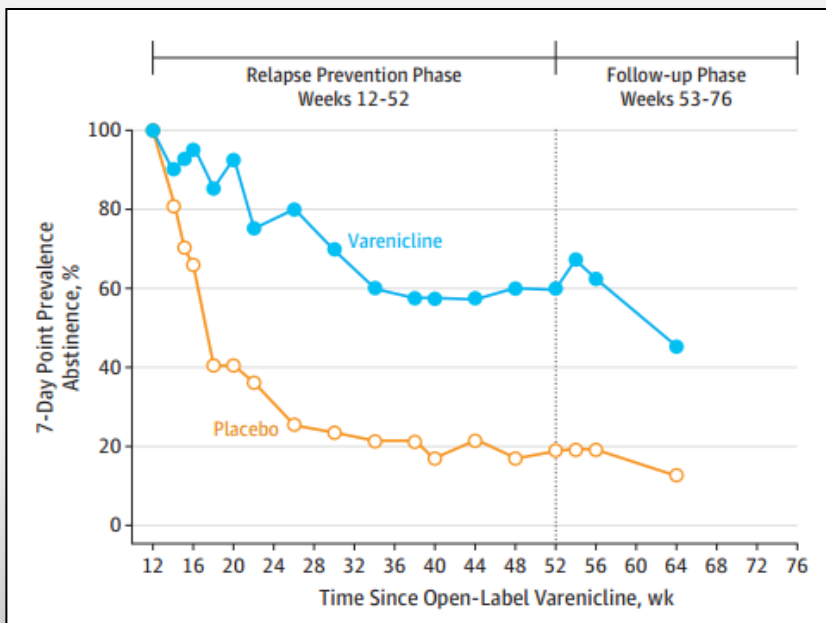
*Source: *2010 National Survey on Drug Use and Health, SAMHSA 2011.*

*Source: **Lasser et al., JAMA 2000; 284(20): 2606-2610.*

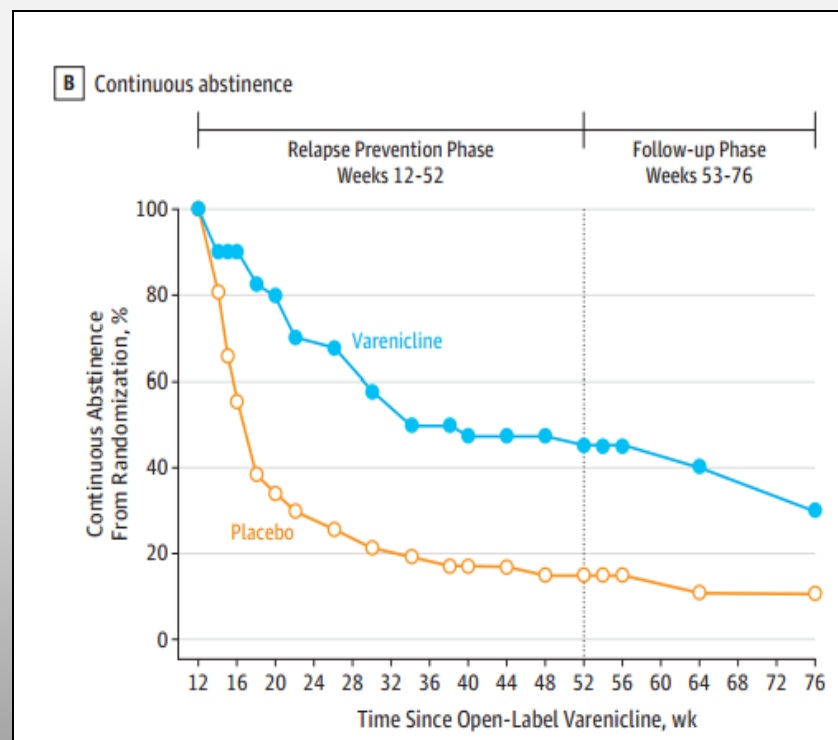
*Source: ***Ziedonis et al., Nic and Tob Res Dec 2008; 10(12): 1691-1715.*

*Source: ****McLernon et al., Ann NY Acad Sci 2008; 1141: 131-147.*

Maintenance pharmacotherapy+ CBT can help individuals with Serious Mental Illness stay smoke-free



Maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates for individuals with serious mental illness after 1 year of treatment and at 6 months after treatment discontinuation



Source: *Evins et al., [Maintenance Treatment with Varenicline for Smoking Cessation in Patients with SCZ and Bipolar Disorder](#), JAMA 311: 143-54, 2014

Regulatory Science in Action

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Randomized Trial of Reduced-Nicotine Standards for Cigarettes

Eric C. Donny, Ph.D., Rachel L. Denlinger, B.S., Jennifer W. Tidey, Ph.D., Joseph S. Koopmeiners, Ph.D., Neal L. Benowitz, M.D., Ryan G. Vandrey, Ph.D., Mustafa al'Absi, Ph.D., Steven G. Carmella, B.A., Paul M. Cinciripini, Ph.D., Sarah S. Dermody, M.S., David J. Drobes, Ph.D., Stephen S. Hecht, Ph.D., Joni Jensen, M.P.H., Tonya Lane, M.Ed., Chap T. Le, Ph.D., F. Joseph McClermon, Ph.D., Ivan D. Montoya, M.D., M.P.H., Sharon E. Murphy, Ph.D., Jason D. Robinson, Ph.D., Maxine L. Stitzer, Ph.D., Andrew A. Strasser, Ph.D., Hilary Tindle, M.D., M.P.H., and Dorothy K. Hatsukami, Ph.D.

Source: *N Engl J Med* 2015;373:1340-1349.

Perspective:

Reduced-Nicotine Cigarettes — A Promising Regulatory Pathway

Michael Fiore, M.D., M.P.H., M.B.A., and Timothy Baker, Ph.D.



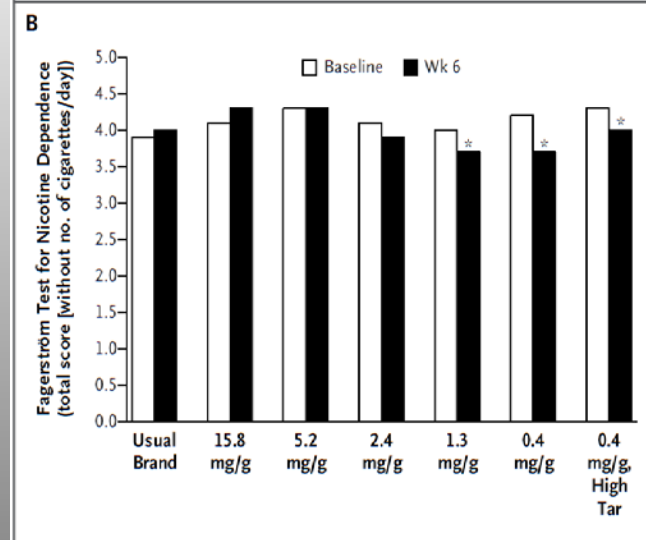
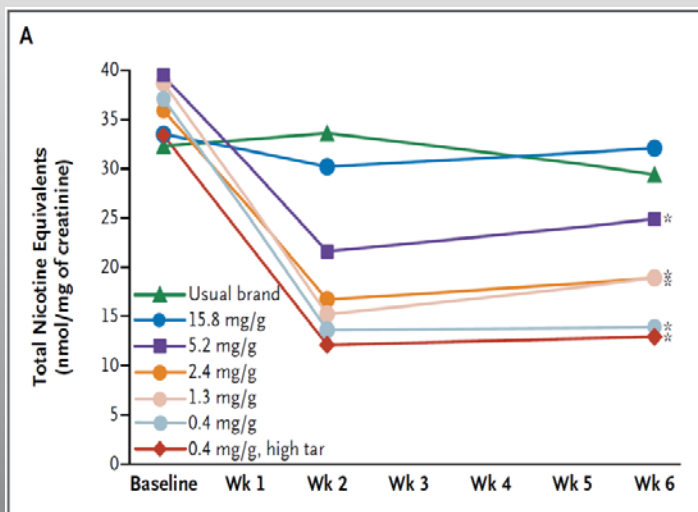
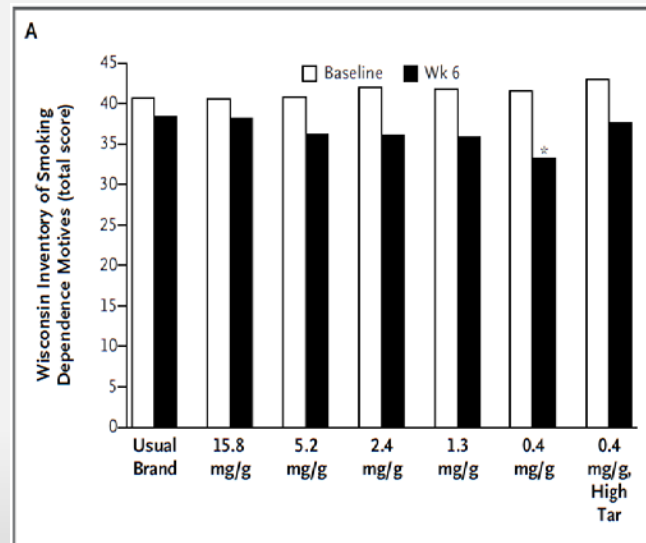
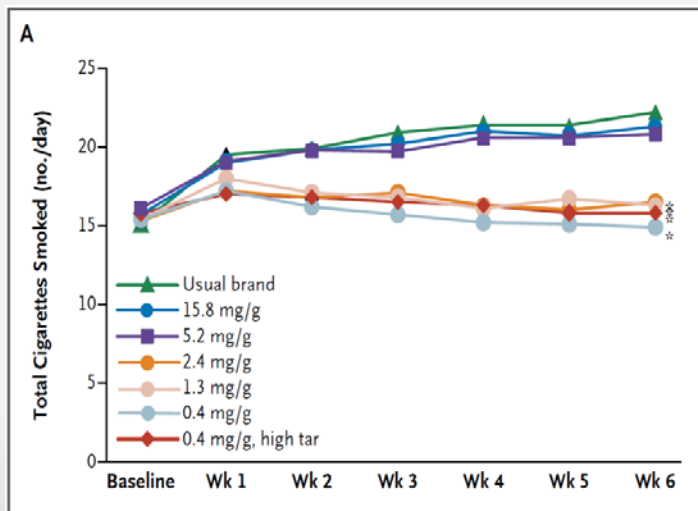
The NEW ENGLAND
JOURNAL of MEDICINE

Source: *N Engl J Med* 2015;373:1289-1291.



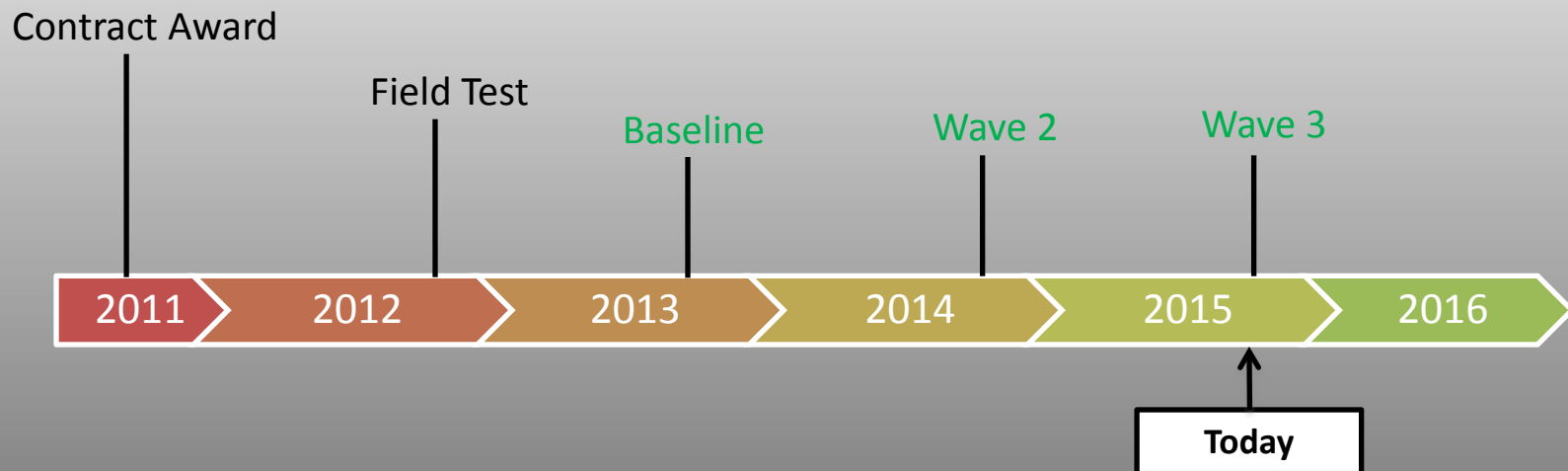
National Institute
on Drug Abuse

Regulatory Science: Randomized Trial of Reduced-Nicotine Standards for Cigarettes



Population Assessment of Tobacco and Health (PATH) Study

- National, longitudinal cohort study of ~46,000 users of tobacco products and those at risk for tobacco use ages 12 and older in the U.S.
- Funded by the Center for Tobacco Products, FDA.
- ***Results from this study will help inform the impact of FDA regulatory authority over tobacco products, and help to inform future activities.***



PATH Study Domains *(examples)*

- Baseline Sample 45,971 total (32,320 age 18+; 13,651 age 12-17)
- Outcomes
 - Tobacco Product Use including Dual Use, Switching, New Products
 - Tobacco Use Behaviors including Initiation, Cessation/Quitting, Relapse
 - Health Outcomes
- Mediators/Moderators
 - Demographics
 - Knowledge, Attitudes, Beliefs, and Risk Perceptions
 - Tobacco Addiction
 - Peer, Environmental, Contextual influences
 - Mental Health/Substance Abuse Co-morbidities

PATH Next Steps

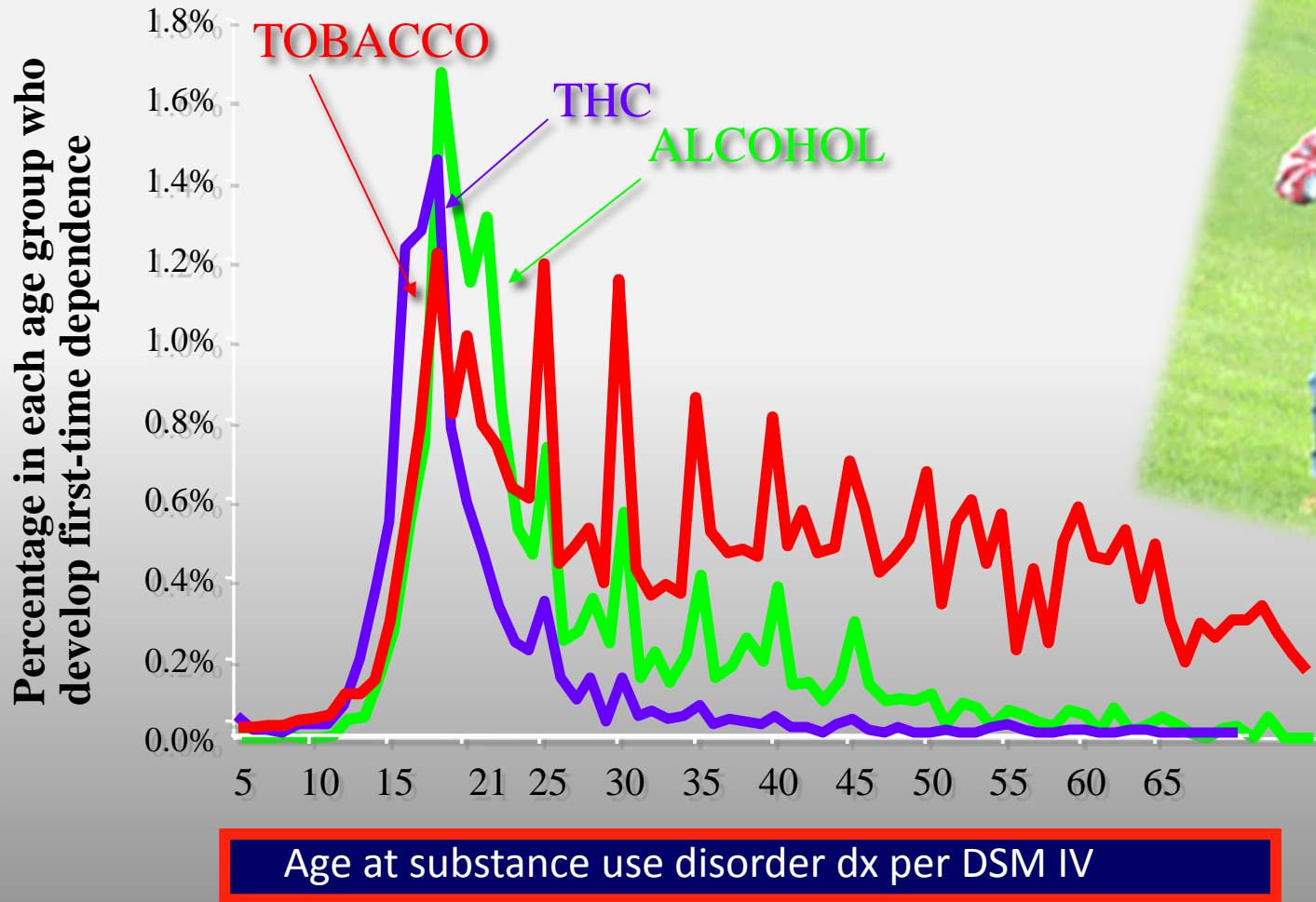
- Data collection ongoing
- Selected analysis ongoing
- Accelerated efforts to have the PATH Study be a resource to the scientific community while ensuring highest data quality
- More Information: [PATHstudyinfo.nih.gov](https://pathstudyinfo.nih.gov)

Adolescent Brain Cognitive Development (ABCD): A Longitudinal Study

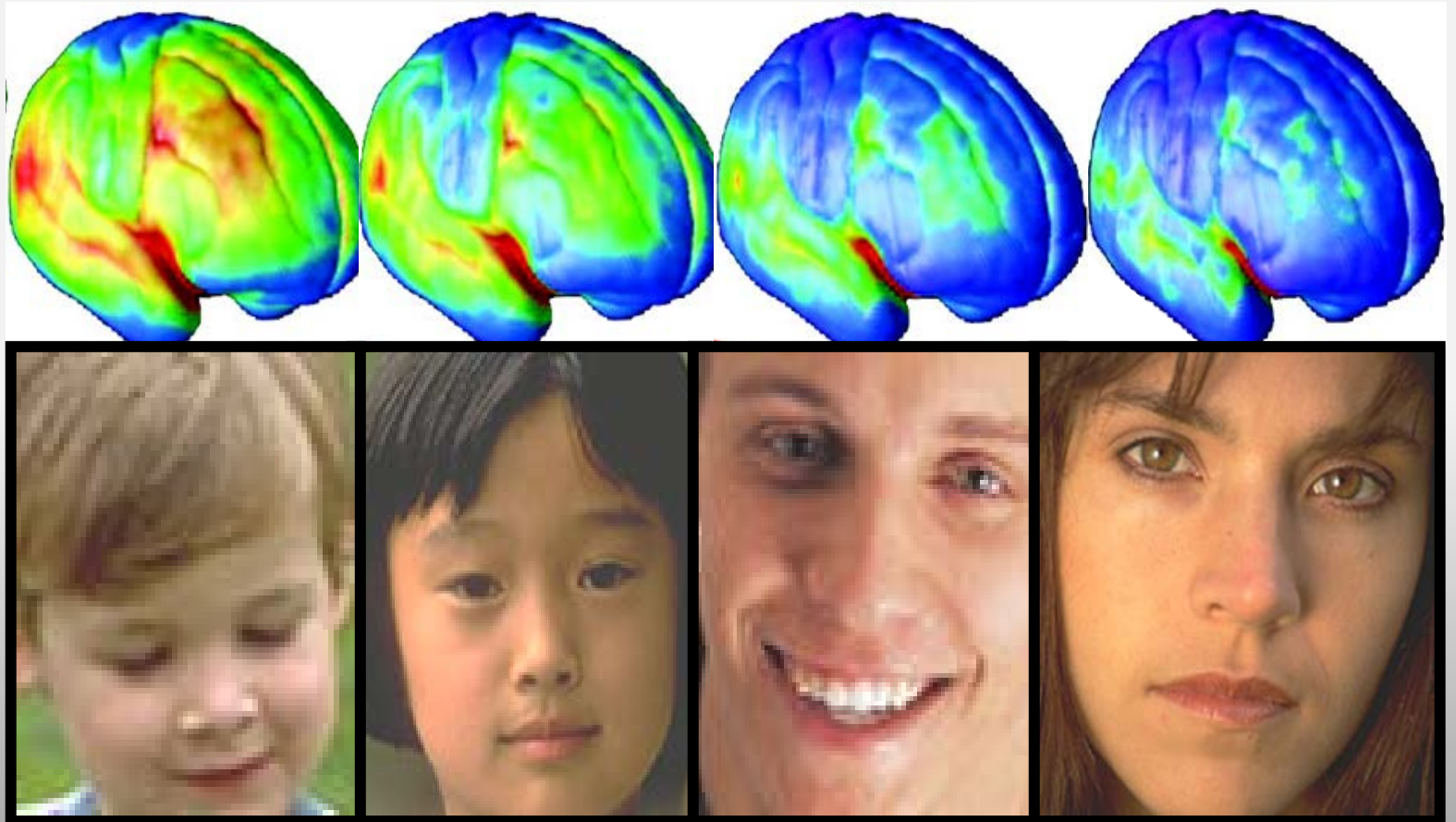
Ten year longitudinal study of 10,000 children from age 10 to 20 years to assess effects of substances on individual brain development trajectories



Adolescence is the period of greatest vulnerability for Substance Abuse & Addiction



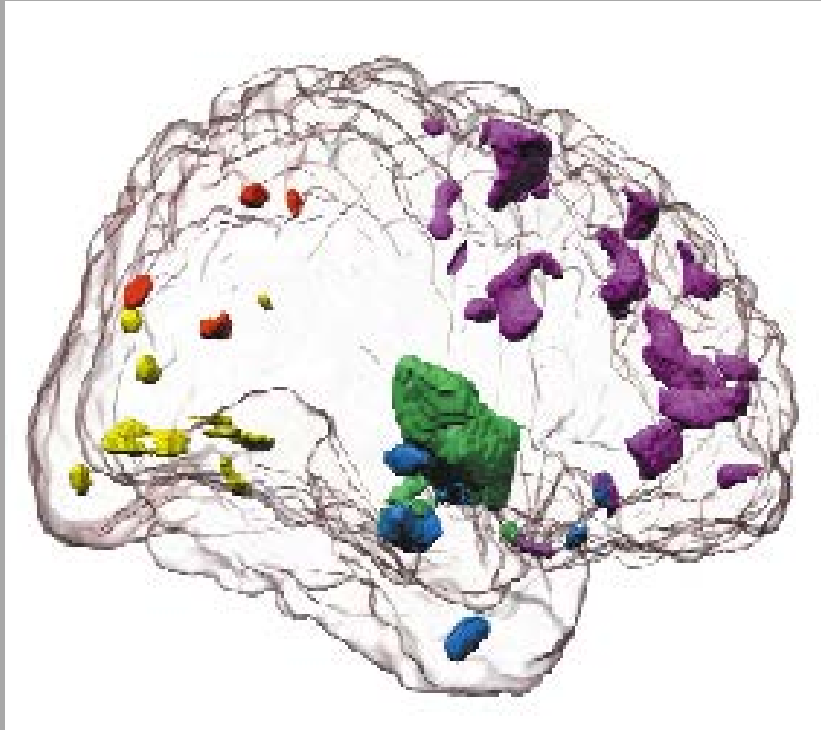
Adolescent Brains Are Still Developing



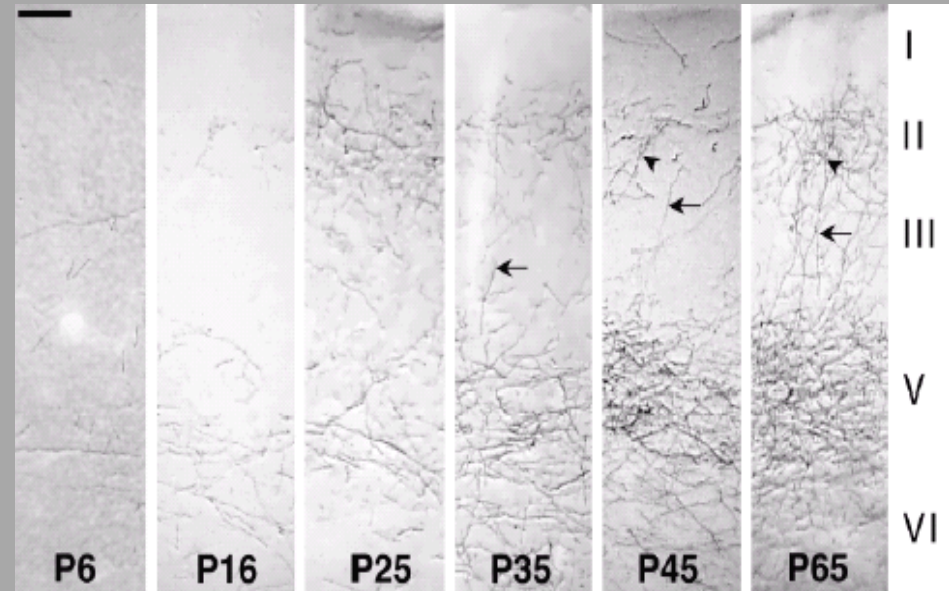
Source: Gogtay, Nitin et al. (2004) Proc. Natl. Acad. Sci. USA 101, 8174-8179



Frontal Brain Connections are Among the Latest to Mature



Brain areas where volumes are smaller in adolescents than young adults



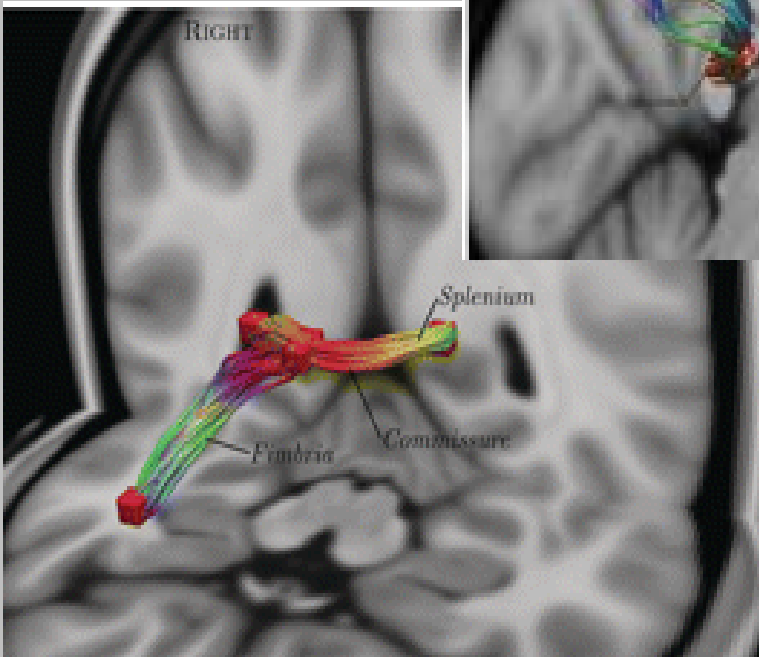
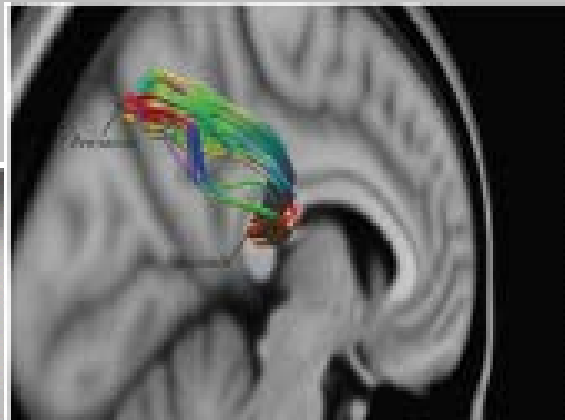
*During Adolescence the
COGNITION EMOTION
Connection is Still under
Development*

Source: Sowell, E.R. et al., *Nature Neuroscience*, 2(10), pp. 859-861, 1999

Source: Cunningham, M et al., *J Comp Neurol* 453, pp 116-130, 2002.

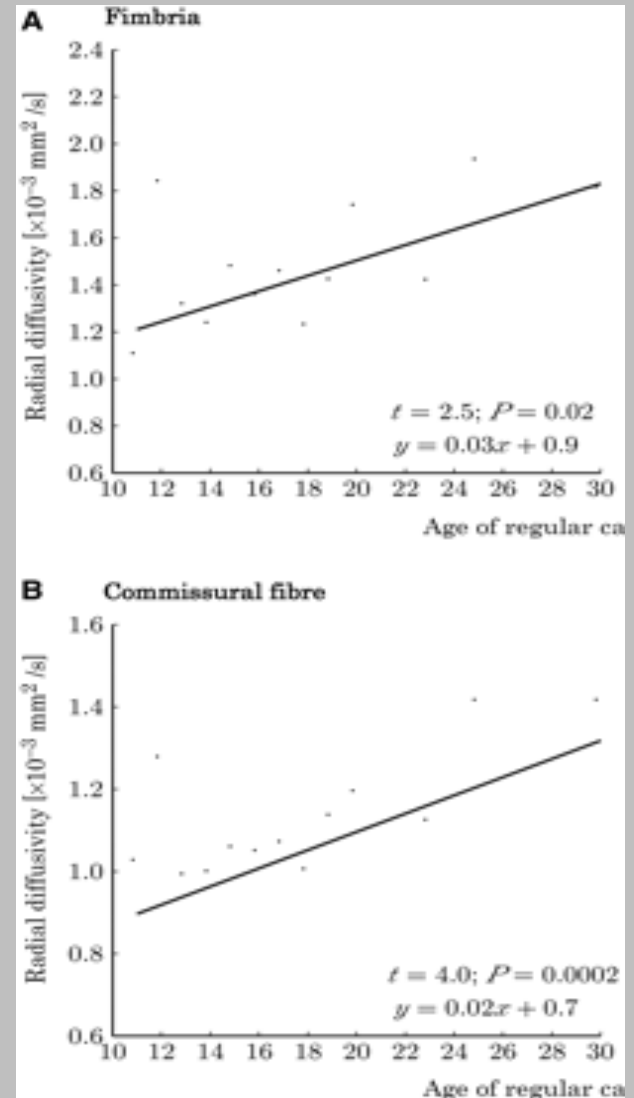
Increasing Evidence that Early Cannabis Use Alters Brain Structure: Cannabis Decreases Axonal Fiber Connectivity

Precuneus to splenium



Fimbria of hippocampus, hippocampal commissure and Splenium

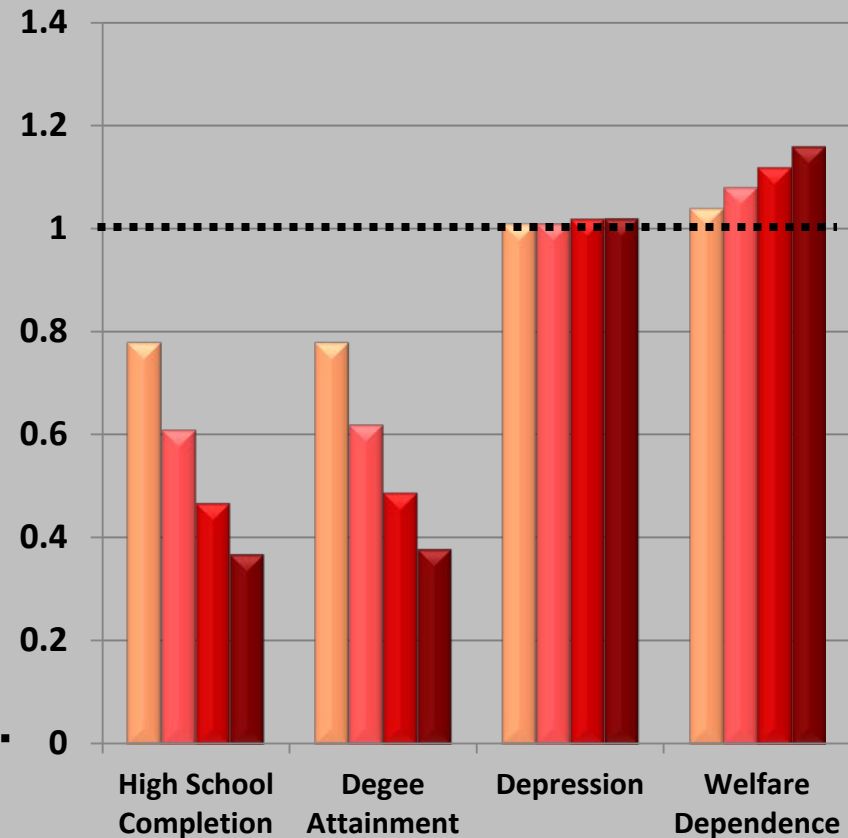
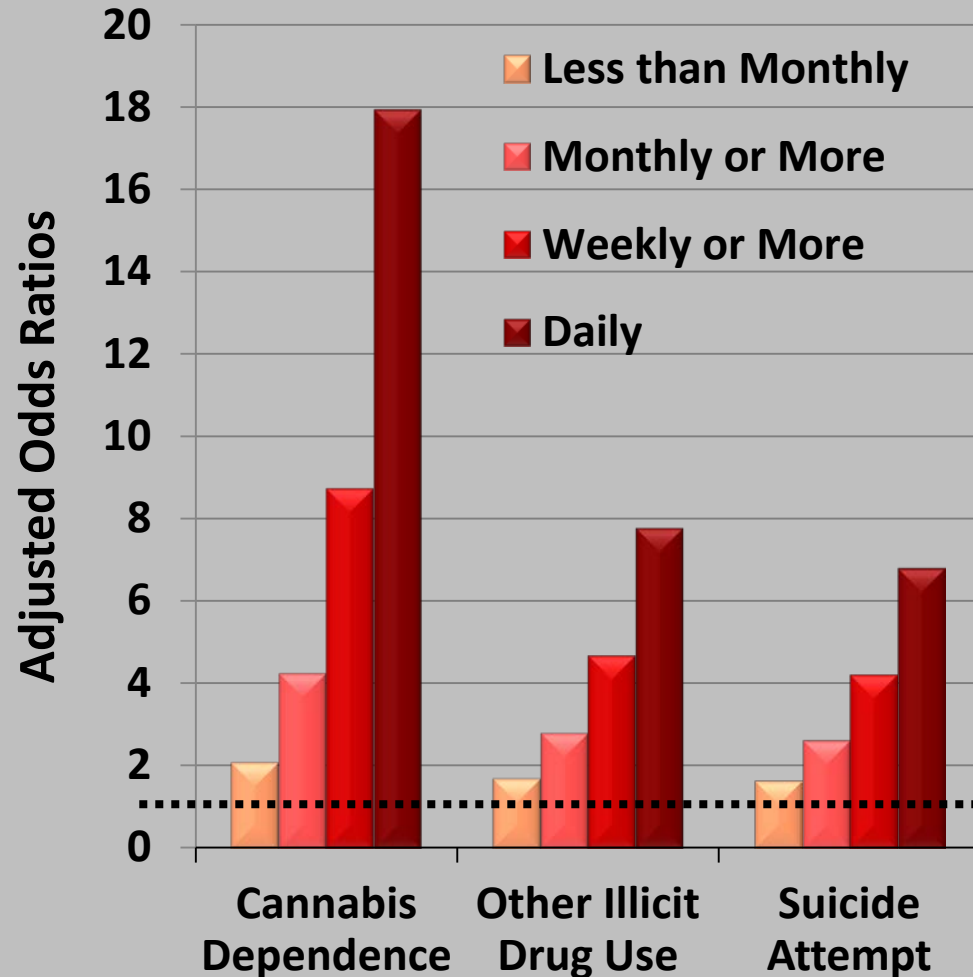
Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).



Source: Zalesky et al Brain 2012.

Adverse Psychiatric/Education/Social Outcomes as a Function of Frequency Of Cannabis Use Before Age 17 (at age 30; n=2500-3700)

Consistent and dose-response associations were found between frequency of adolescent cannabis use and adverse outcomes

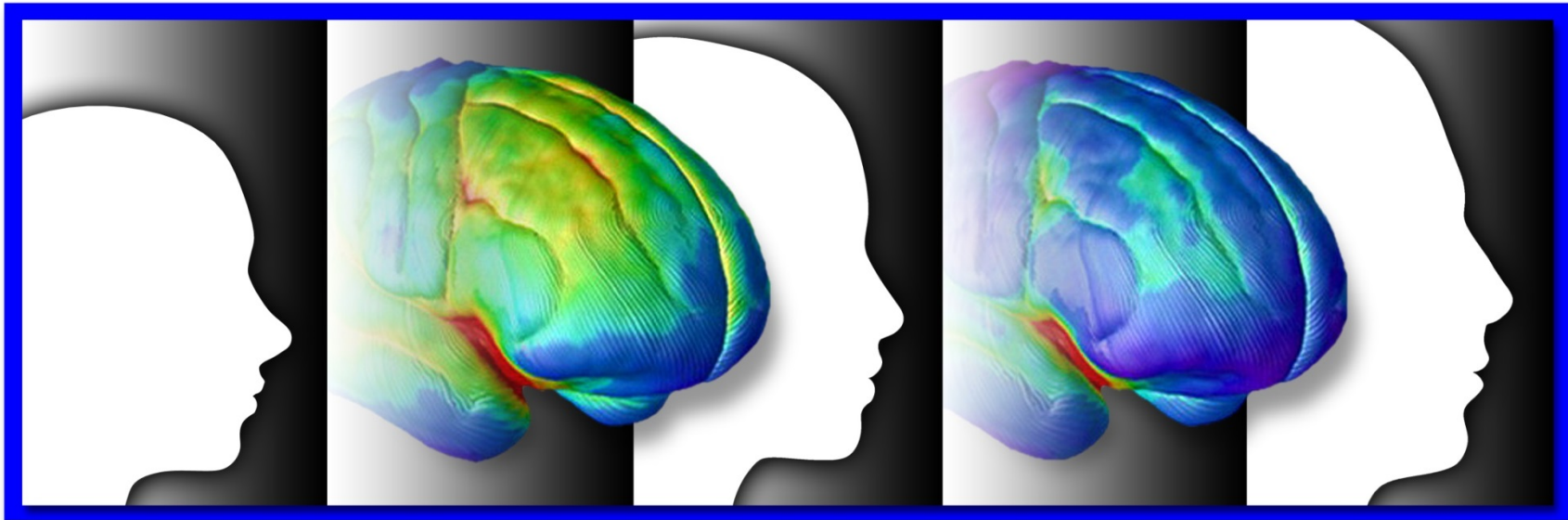


Source: Silins E et al., *The Lancet* September 2014.

ABCD Study

NIDA, NIAAA, NCI, NICHD, NIMH, NIMHD, OBSSR, NINDS

Ten year longitudinal study of 10,000 children from age 10 to 20 years to map individual trajectories of human brain development and to evaluate how it is influenced by genetics and environment, most notable drugs (including nicotine, marijuana, and alcohol), and by mental illnesses.



Adolescent Brain Cognitive Development

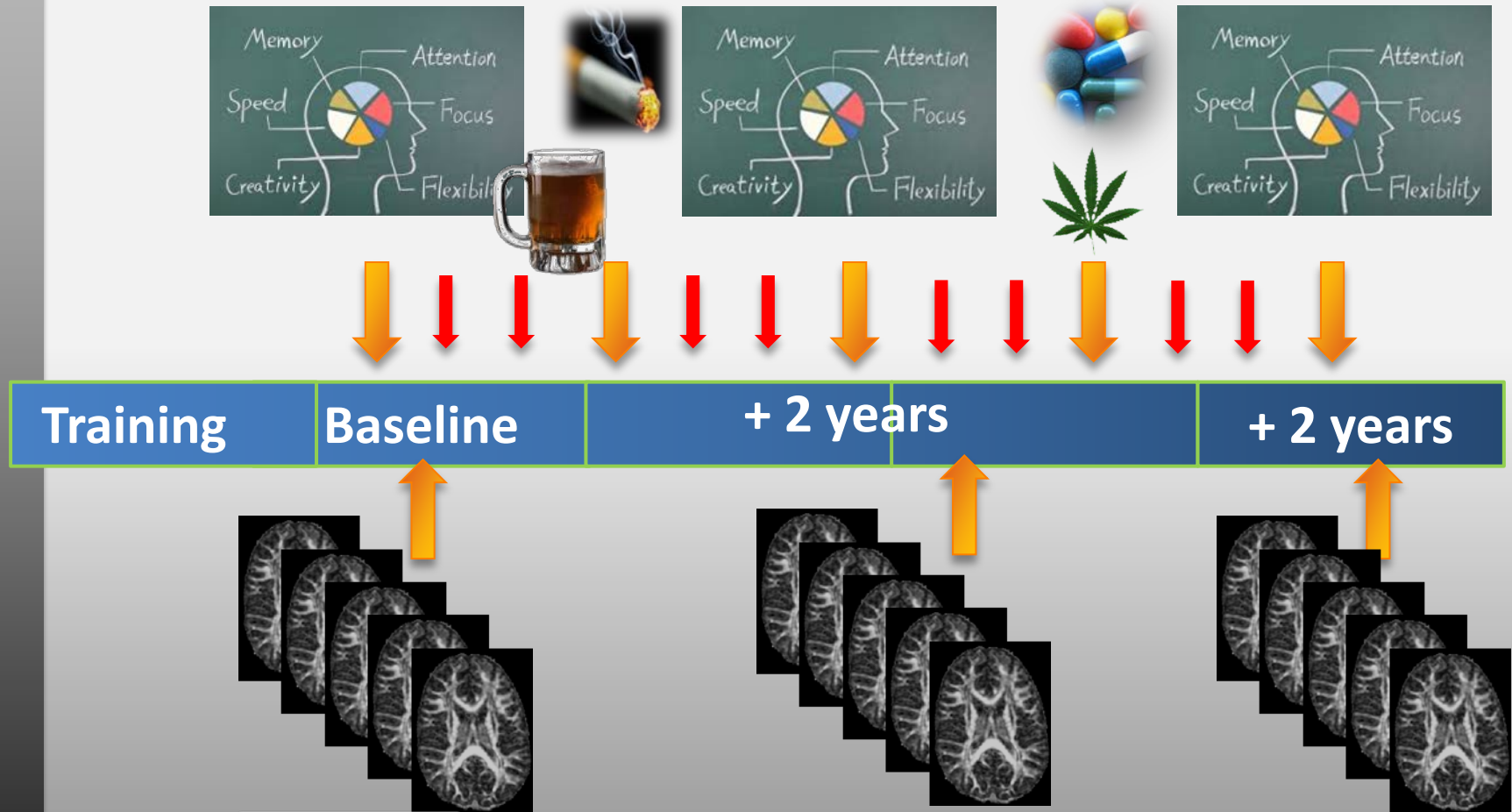


Central Research Questions

- What is the impact of diverse patterns of use of marijuana, alcohol, nicotine and other substances on the structure and function of the developing brain, as revealed by brain imaging?
- What are the consequences of substance use on physical health, psychosocial development, information processing, learning, memory, academic achievement, motivation, emotion regulation, and other behaviors?
- How does substance use affect the expression of psychopathology, including substance use disorders, and how does the emergence of psychopathology influence drug use?
- What factors (prenatal, genetic, epigenetic, neurobiological, psychosocial, family history, head trauma, others) influence substance use and its consequences during development?
- In what way does use of each substance contribute to the use of others (gateway interactions)?

Timeline:

- 1) Biennial Imaging;
- 2) Annual In-person assessments;
- 3) Semi-annual or Quarterly web-based surveys

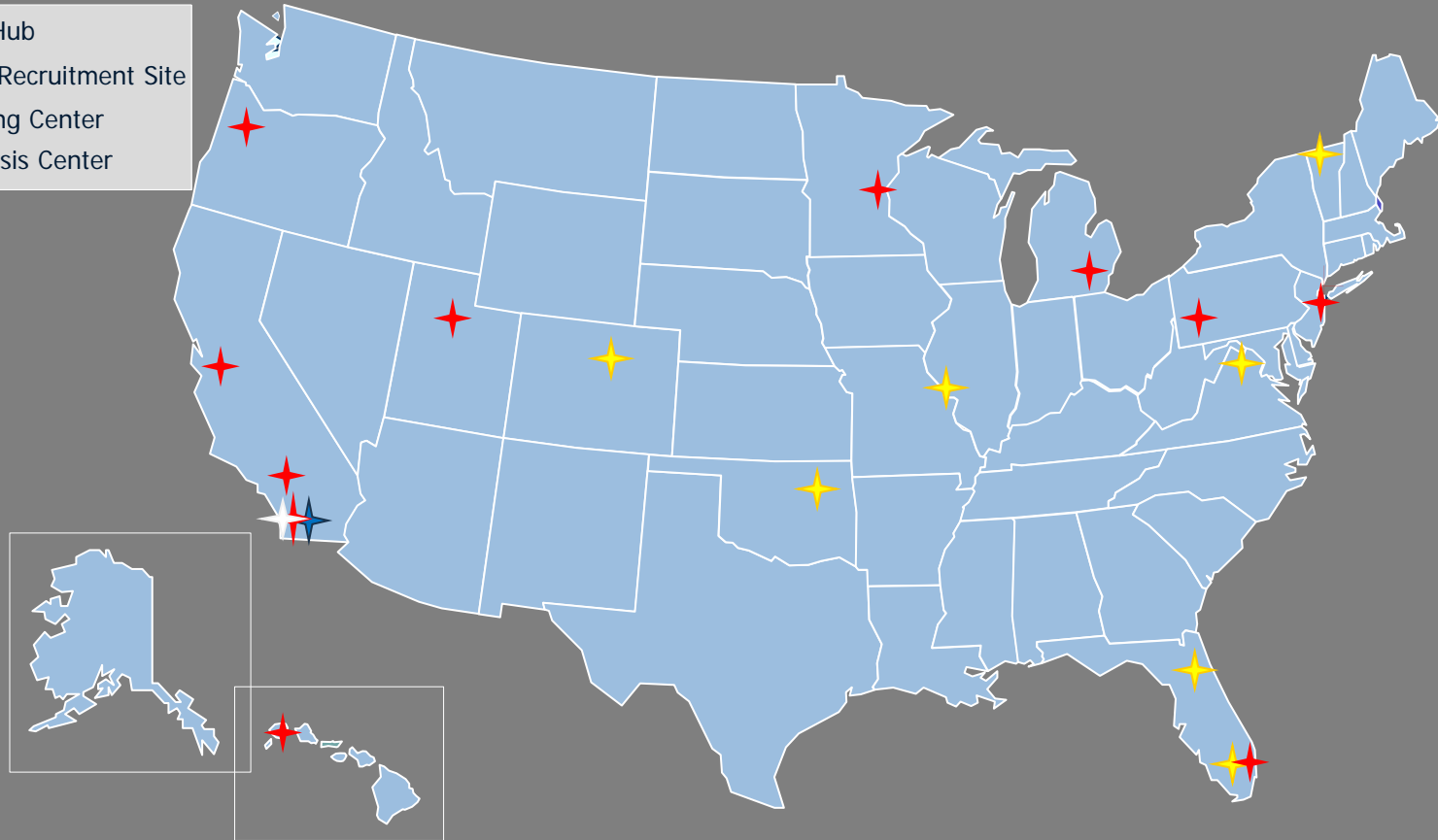


Measures

Substance use, Cognition, Emotion, Mental Health, Physical health, Executive Function, General Intelligence, Environment, Biospecimens: Genetics, Epigenetics

Adolescent Brain Cognitive Development Study Sites

- Research Hub
- Additional Recruitment Site
- Coordinating Center
- Data Analysis Center



Coordinating Center
T. Jernigan/S. Brown
University of California
San Diego

Data Analysis & Informatics Center
A. Dale
University of California
San Diego

T. Ernst
University of Hawaii
at Manoa

B. Nagel
Oregon Health &
Science University

I. Colrain
SRI International
Menlo Park, CA

E. Sowell
Children's Hospital of
Los Angeles

S. Tapert
University of California
San Diego

D. Yurgelun-Todd
University of Utah

W. Iacono
University of
Minnesota

M. Heitzeg
University of Michigan

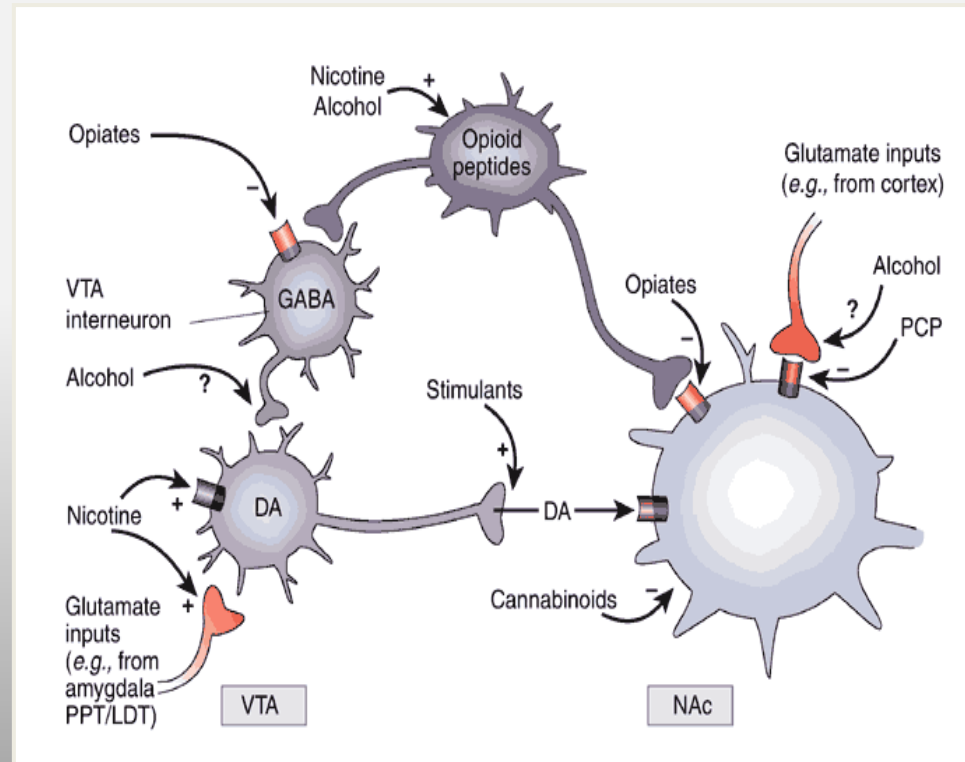
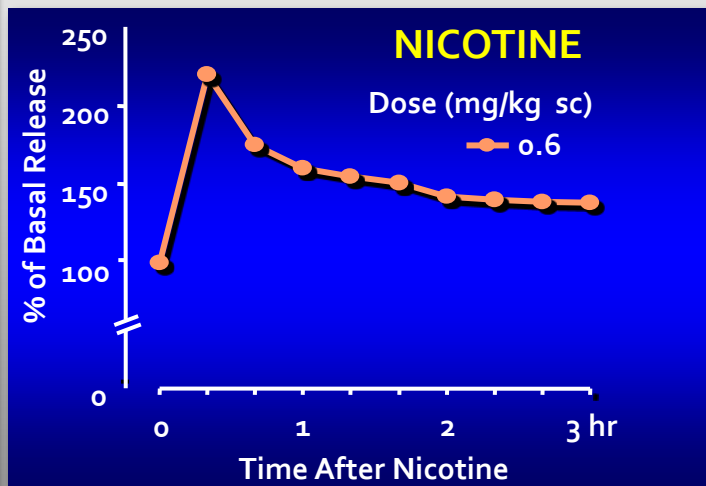
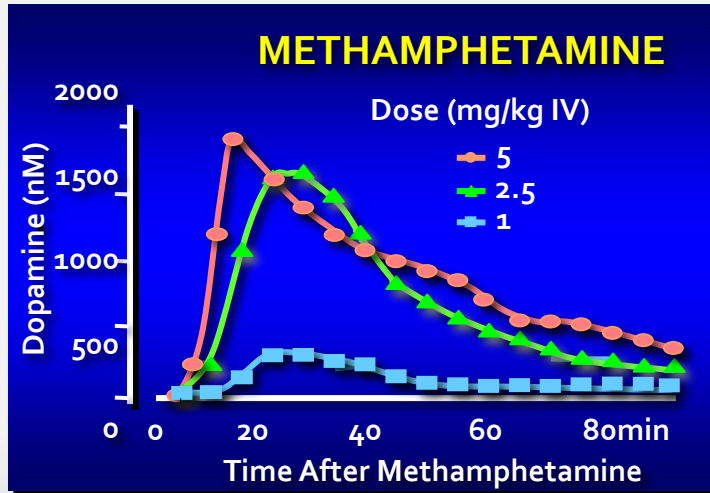
D. Clark
University of
Pittsburgh

B. Casey
Weill Medical College
of Cornell University

R. Gonzalez
Florida International
University



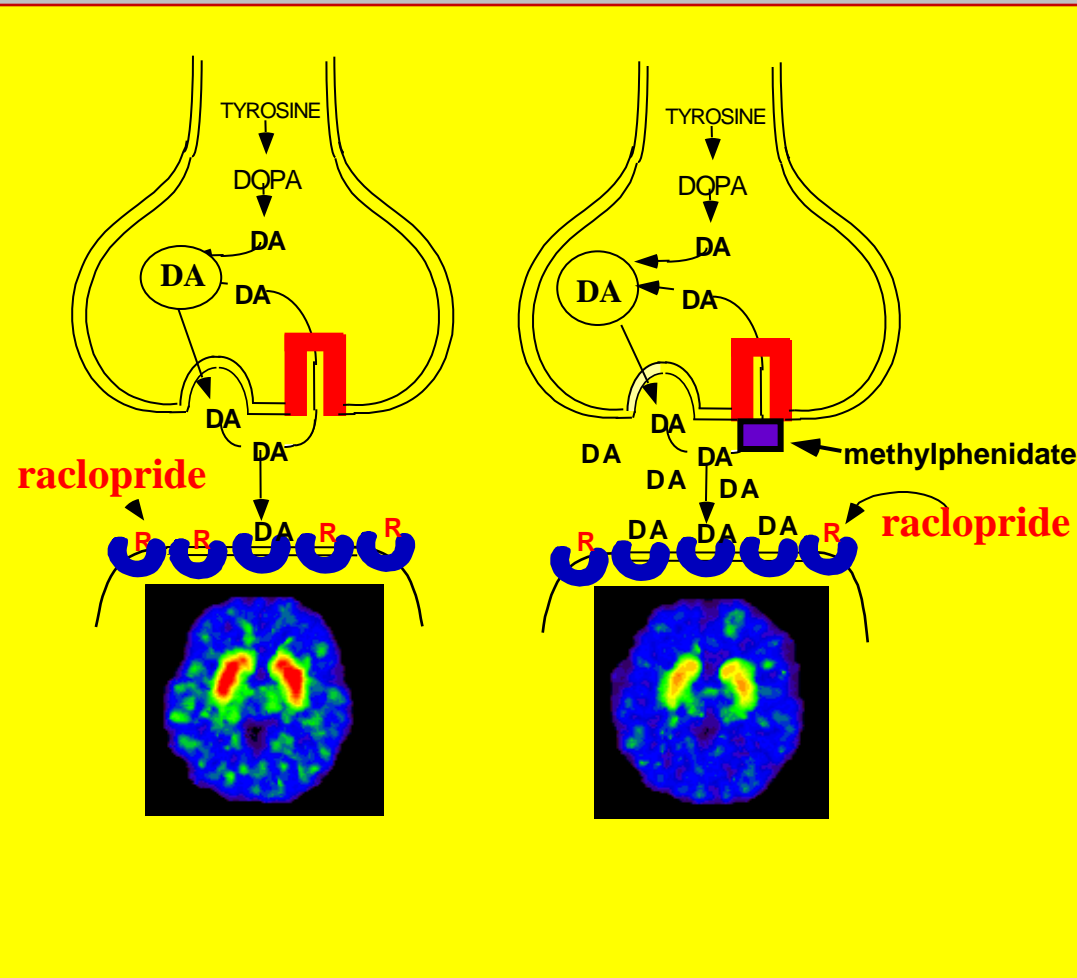
All Drugs Abused by Humans Raise Brain Dopamine Levels in the Nucleus Accumbens



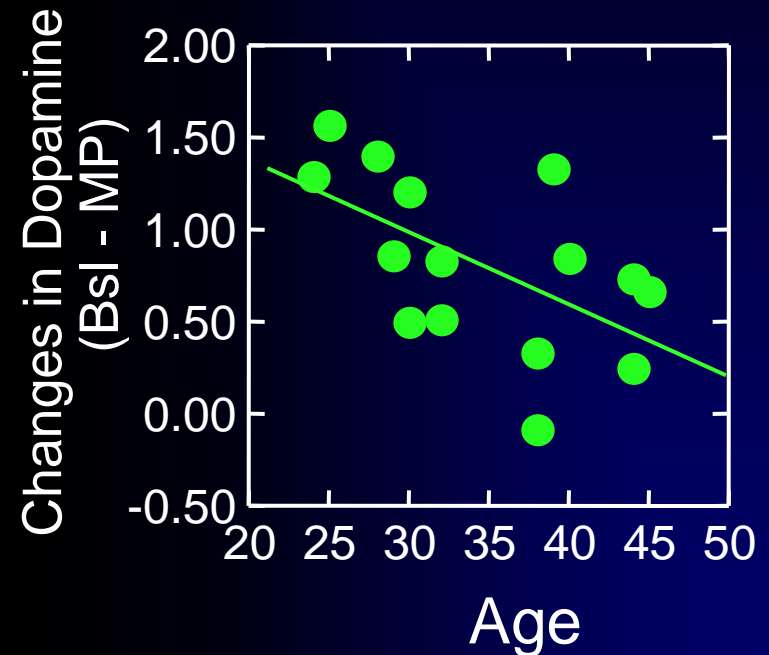
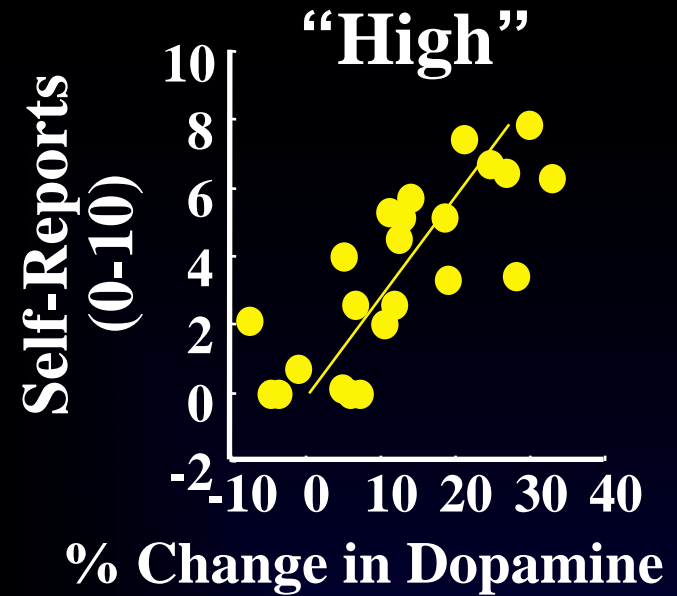
Source: Di Chiara et al.

Source: Nestler, Nature Neurosci, 2005

DA and Drug Reinforcement and Age Effects



DA increases are associated with drug rewarding effects and decrease with age



DOPAMINE D₂ RECEPTORS

Decrease with Age in the Human Brain

DOPAMINE D₂ RECEPTORS

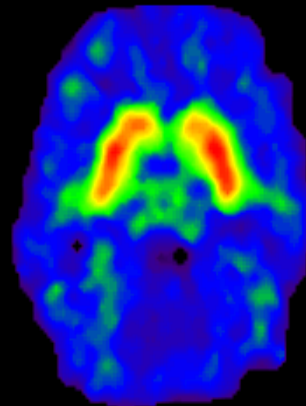


Prenatal 7

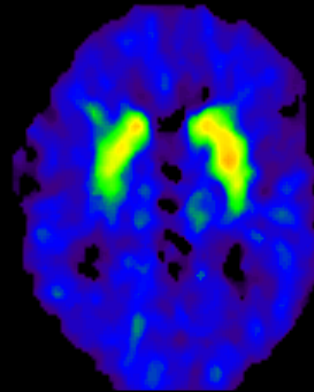


ADULT

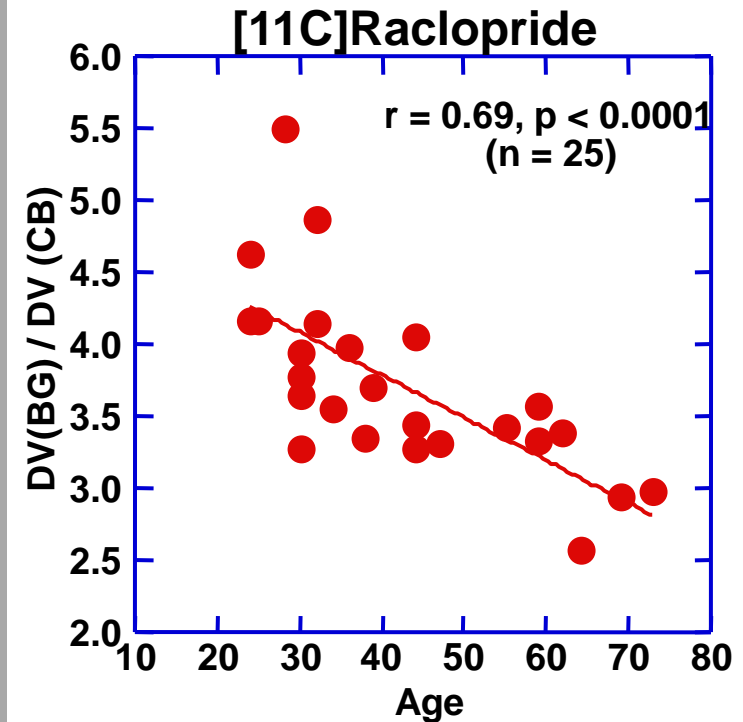
Source: GENSAT



24 year old

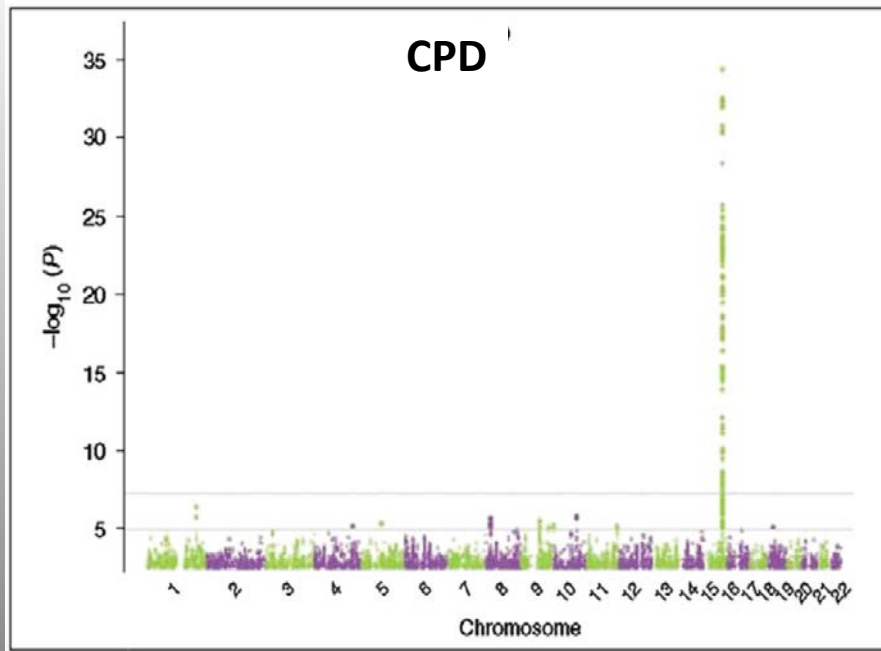
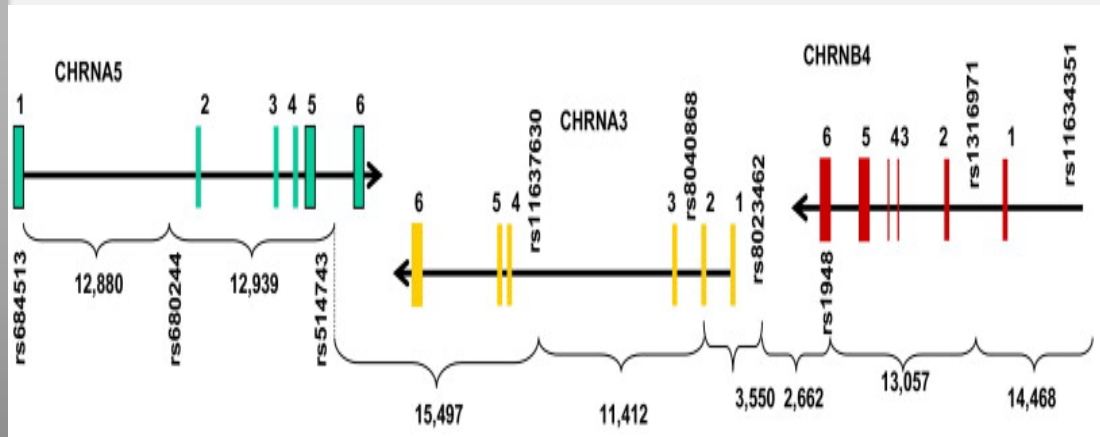


86 year old



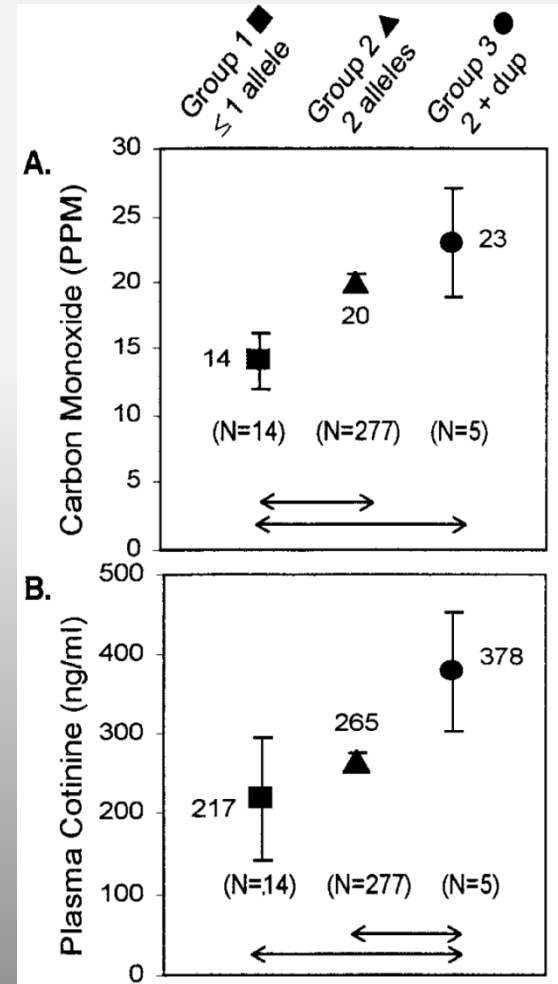
Gene Variants and Nicotine Dependence

CHRNA5/A3/B4



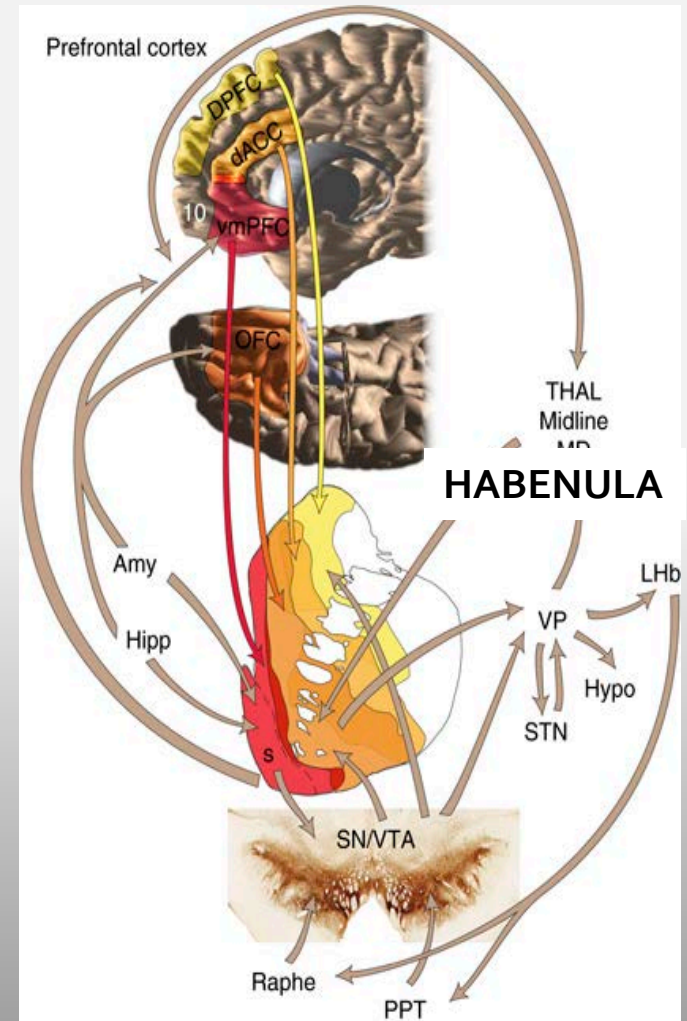
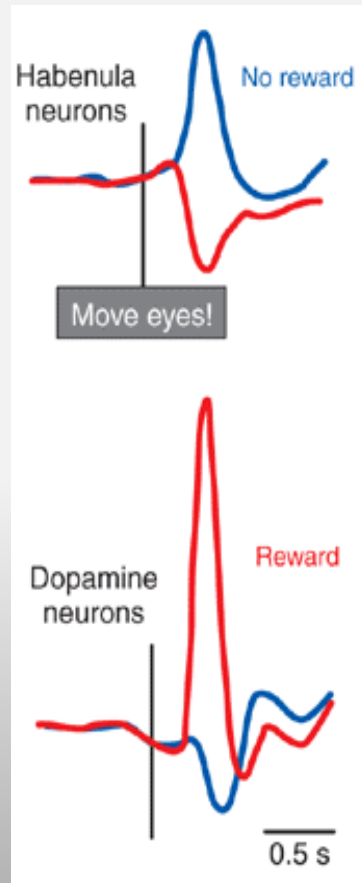
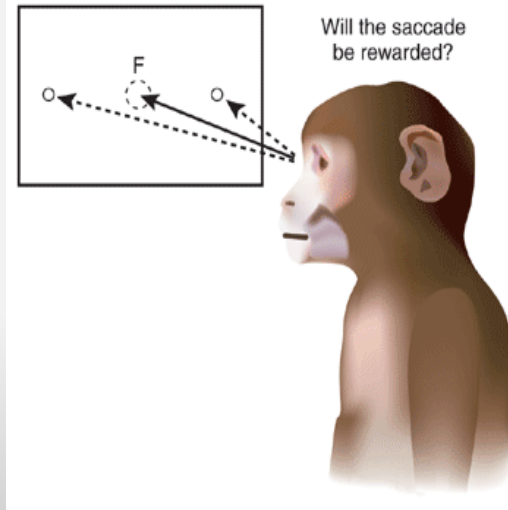
Source: TAG Nature Genetics 2010;42(5):441

CYP2A6



Source: Rao et al Mol Pharm 2000;58:747

Habenula and Negative Reward



Habenula neurons increased firing for NO REWARD and decreased firing for REWARD

Dopamine neurons increased firing for REWARD and decreased firing for NO REWARD.

Source: Kimura et al., Nature Neuroscience 2007.

Habenula inhibits dopamine neurons
 Habenula communicates negative reward signals to dopamine neurons



E-cigarette Activities at NIDA

- **Types of research grants or contracts (including supplements)**

Type	R01	F31	P50	R21	K01	Supplements	Contracts
#	11	2	3	5	1	4	5

- **Funding source (of the e-cig component)**

◆FDA: 19

◆IC: 12

- **Major focus of research topic from IC perspective**

◆Content & safety of e-liquid and aerosol

◆Nicotine PK

◆Abuse Liability

◆How are devices used

- **Type of study**

◆Animal research: 2

◆Clinical research: 20

◆Cellular research: 4

◆Cohort/epidemiology: 2

- **Other activities**

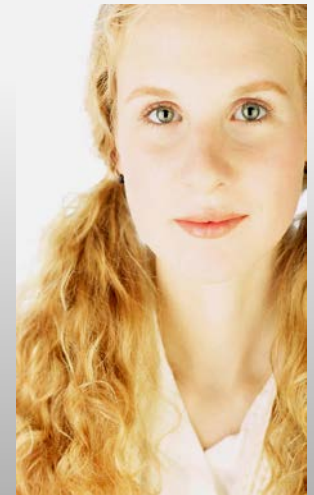
– Development of standardized research e-cigarette

– Large Surveys of tobacco product use including ecigs

- Monitoring the Future (MTF)

- Population Assessment of Tobacco and Health (PATH)

Although Adolescents are
in their Prime Physically,
Morbidity and Mortality Doubles
As A Result of Behavioral Changes
that Occur During the Transition from
Childhood to Adolescence



*What Makes This Time One of
Increased Risk?*

Types of Electronic Nicotine Devices

Disposable e-cigarette



NJOY, White Cloud,
Greensmoke

Rechargeable e-cigarette



Markten, Mystic,
blu, VUSE

**Pen-style, medium-sized
rechargeable e-cigarette**



eGo,
Totally Wicked

**Tank-style, large-sized
rechargeable e-cigarette**

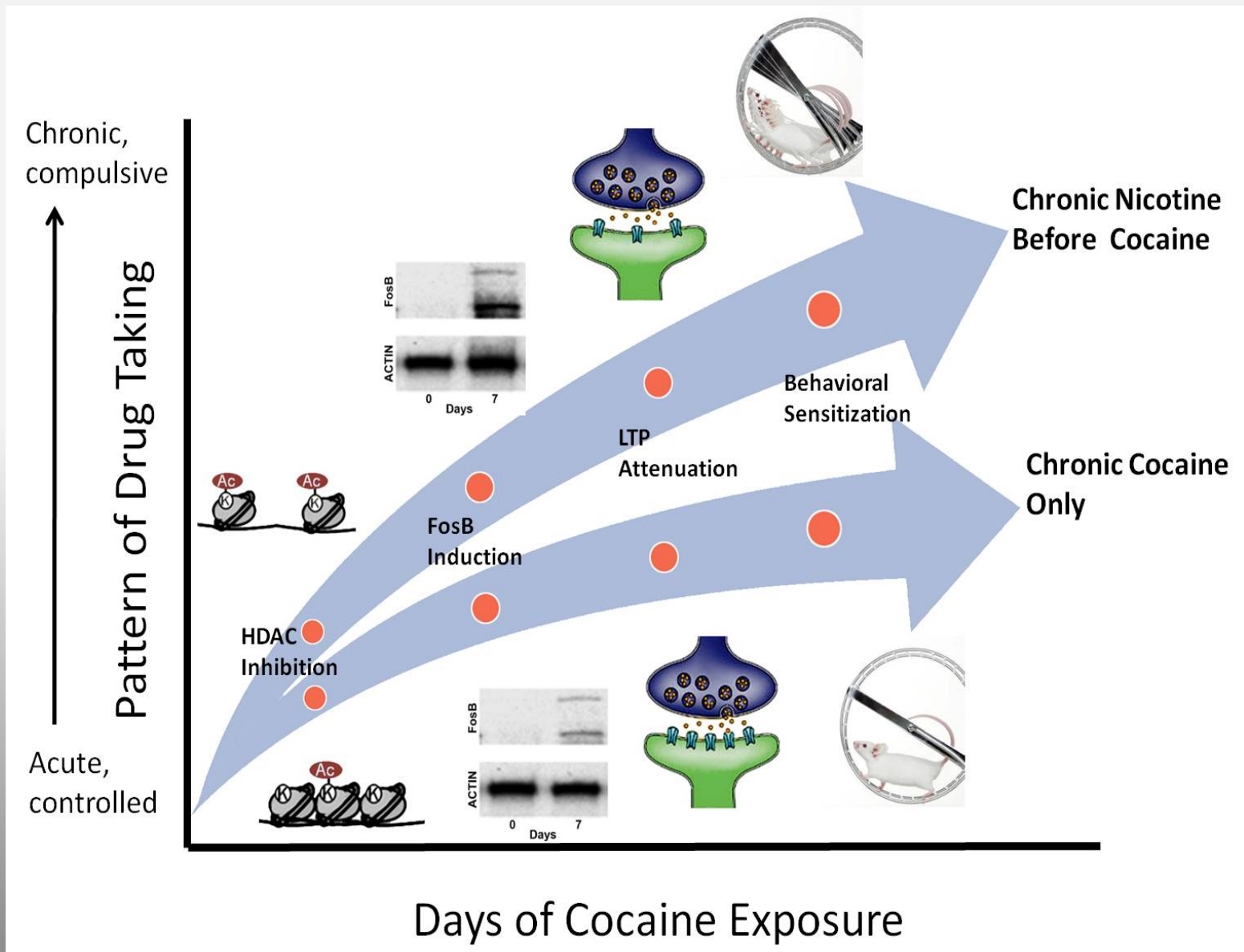


Volcano Lavatube

Sealed device
or cartridge

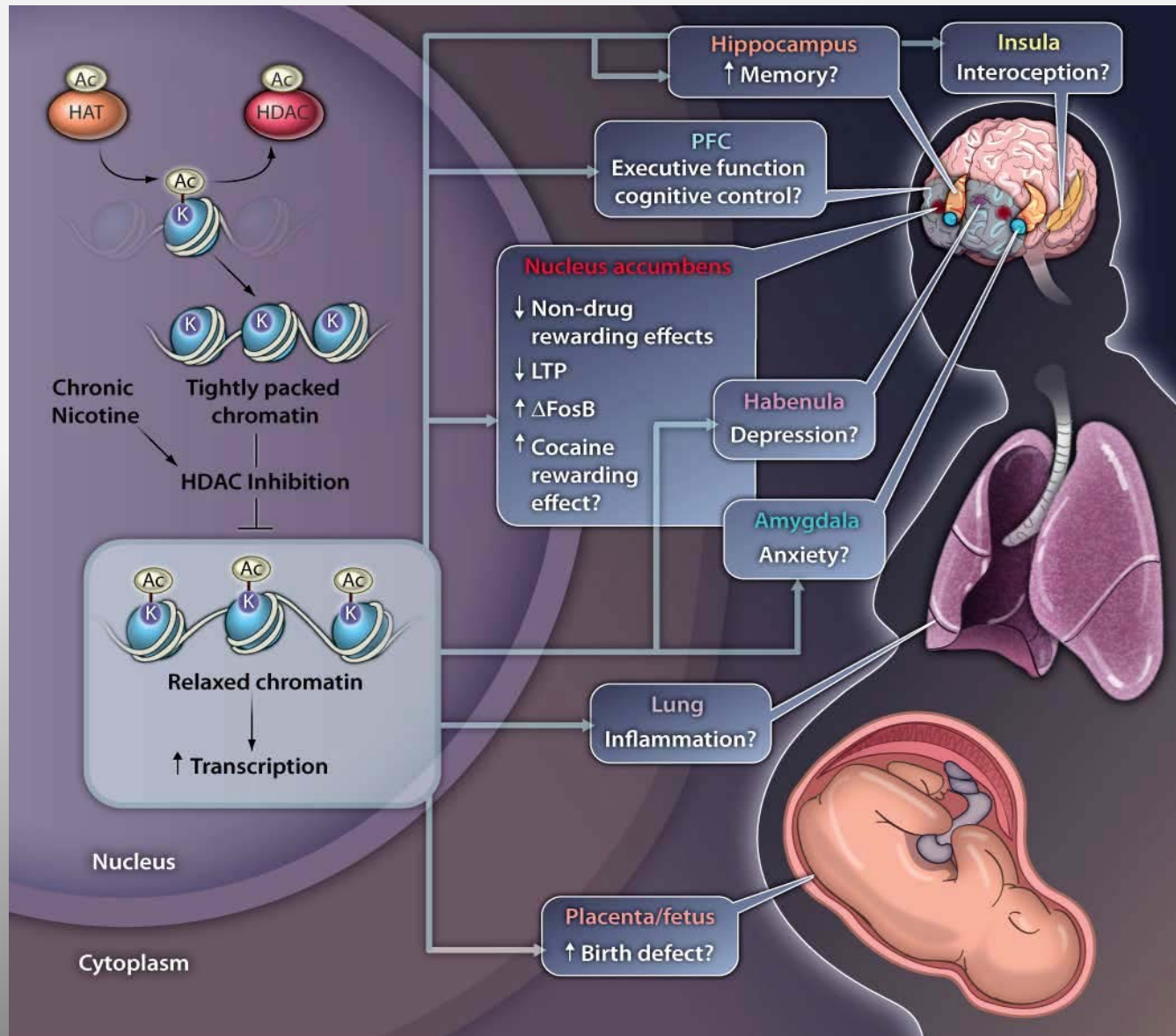
User adds liquid
to device

Gateway Effects of Nicotine?



Source: Levine A. et al., *SciTransl Med.* 2011.

Epigenetic Changes: Wide Ranging Impact



Source: Volkow ND, *SciTransl Med* 2011;3:107ps43-107ps43