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GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Substance Use Disorders: Neurobiology

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Faculty Disclosure

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Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders)



Addiction Is a Brain-Based Disorder

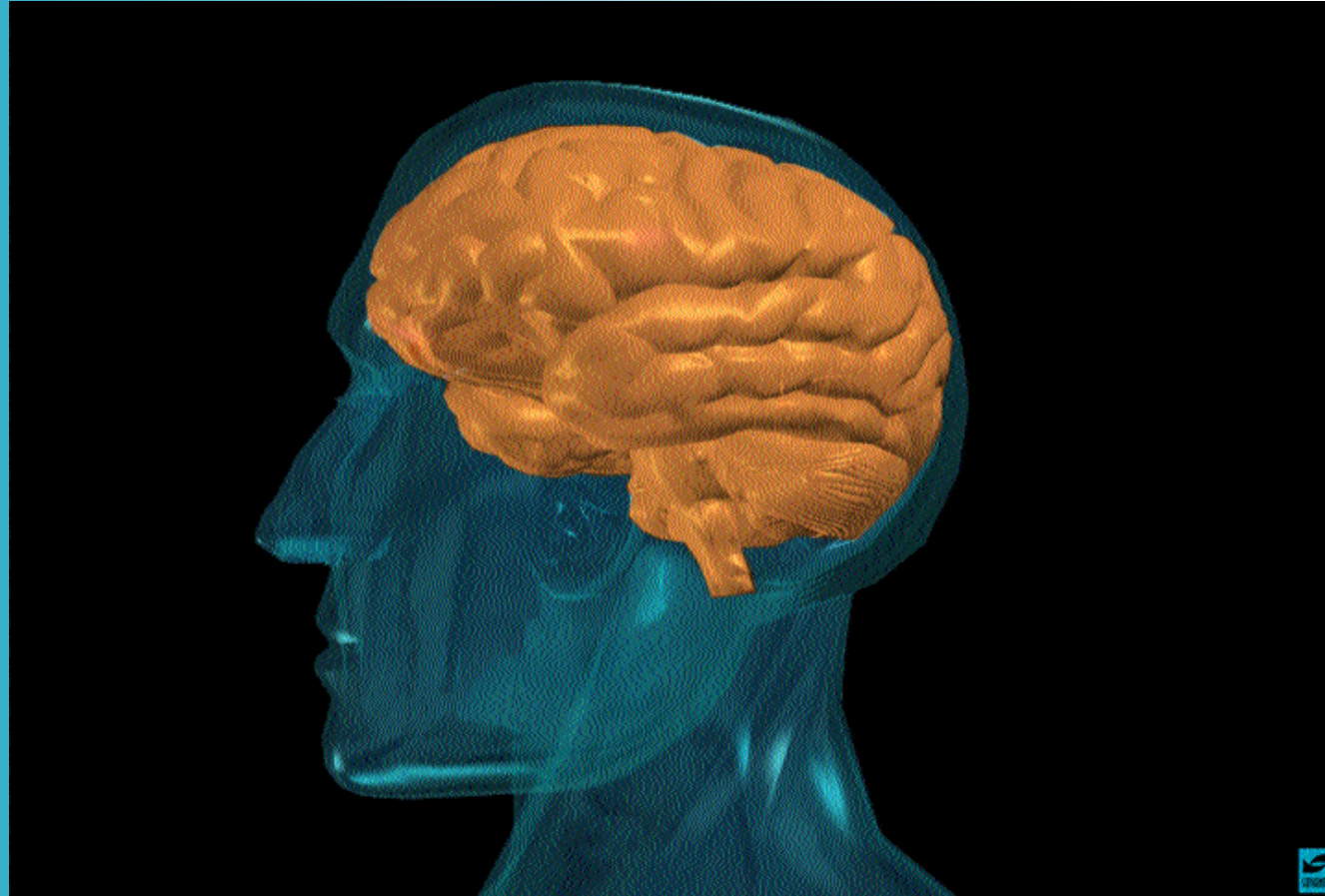


Photo courtesy of the NIDA Web site. From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana*.

Dan L. Longo, M.D., *Editor*

Neurobiologic Advances from the Brain Disease Model of Addiction

Nora D. Volkow, M.D., George F. Koob, Ph.D., and A. Thomas McLellan, Ph.D.

THIS ARTICLE REVIEWS SCIENTIFIC ADVANCES IN THE PREVENTION AND treatment of substance-use disorder and related developments in public policy. In the past two decades, research has increasingly supported the view that addiction is a disease of the brain. Although the brain disease model of addiction has yielded effective preventive measures, treatment interventions, and public health policies to address substance-use disorders, the underlying concept of substance abuse as a brain disease continues to be questioned, perhaps because the aberrant, impulsive, and compulsive behaviors that are characteristic of addiction have not been clearly tied to neurobiology. Here we review recent advances in the neurobiology of addiction to clarify the link between addiction and brain function and to broaden the understanding of addiction as a brain disease. We review findings on the desensitization of reward circuits, which dampens the ability to feel pleasure and the motivation to pursue everyday activities; the increasing strength of conditioned responses and stress reactivity, which results in increased cravings for alcohol and other drugs and negative emotions when these cravings are not sated; and the weakening of the brain regions involved in executive functions such as decision making, inhibitory control, and self-regulation that leads to repeated relapse. We also review the ways in which social environments, developmental stages, and genetics are intimately linked to and influence vulnerability and recovery. We conclude that neuroscience continues to support the brain disease model of addiction. Neuroscience research in this area not only offers new opportunities for the prevention and treatment of substance addictions and related behavioral addictions (e.g., to food, sex, and gambling) but may also improve our understanding of the fundamental biologic processes involved in voluntary behavioral control.

In the United States, 8 to 10% of people 12 years of age or older, or 20 to 22 million people, are addicted to alcohol or other drugs.¹ The abuse of tobacco, alcohol, and illicit drugs in the United States exacts more than \$700 billion annually in costs related to crime, lost work productivity, and health care.^{2,4} After centuries of efforts to reduce addiction and its related costs by punishing addictive behaviors failed to produce adequate results, recent basic and clinical research has provided clear evidence that addiction might be better considered and treated as an acquired disease of the brain (see Box 1 for definitions of substance-use disorder and addiction). Research guided by the brain disease model of addiction has led to the development of more effective methods of prevention and treatment and to more informed public health policies. Notable examples include the Mental Health Parity and Addiction Equity Act of 2008, which requires medical insurance plans to provide the same coverage for substance-use disorders and other mental illnesses that is provided for other illnesses,⁵ and the proposed bipartisan Senate legislation that

From the National Institute on Drug Abuse (N.D.V.) and the National Institute of Alcohol Abuse and Alcoholism (G.F.K.) — both in Bethesda, MD; and the Treatment Research Institute, Philadelphia (A.T.M.). Address reprint requests to Dr. Volkow at the National Institute on Drug Abuse, 6001 Executive Bld., Rm. 5274, Bethesda, MD 20892, or at nvolkow@nida.nih.gov.

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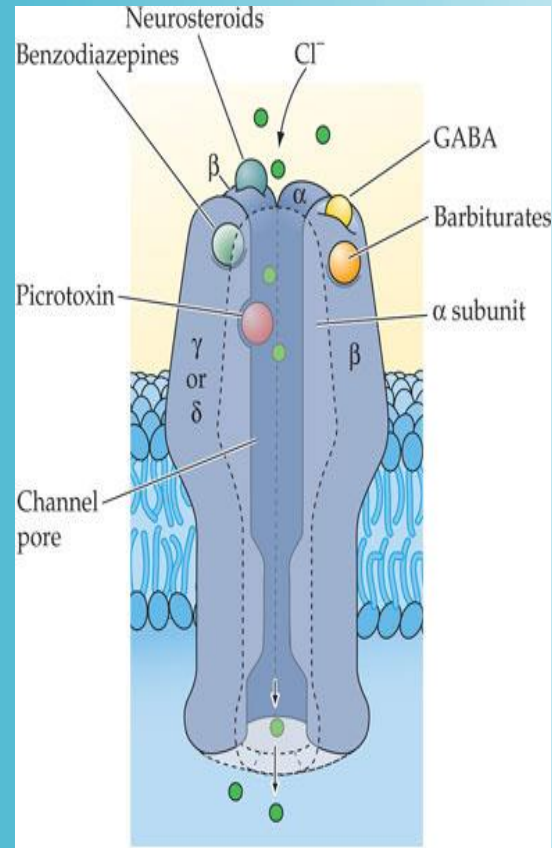
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Addiction Pharmacology

Substance	Mechanism of Action
Alcohol	GABA, opioid agonist; NMDA antagonist
Cocaine	Blocks re-uptake of dopamine
Amphetamines	Stimulate dopamine (norepinephrine) release
PCP, ketamine (Psychedelics)	NMDA antagonist
Opioids	Mu, delta, and kappa agonism
Cannabis	CB1 and CB2 agonist
MDMA	5HT release and re-uptake inhibition; mild DA and NE reuptake inhibition
LSD	5HT _{2a} agonism leading to increased glutamate?

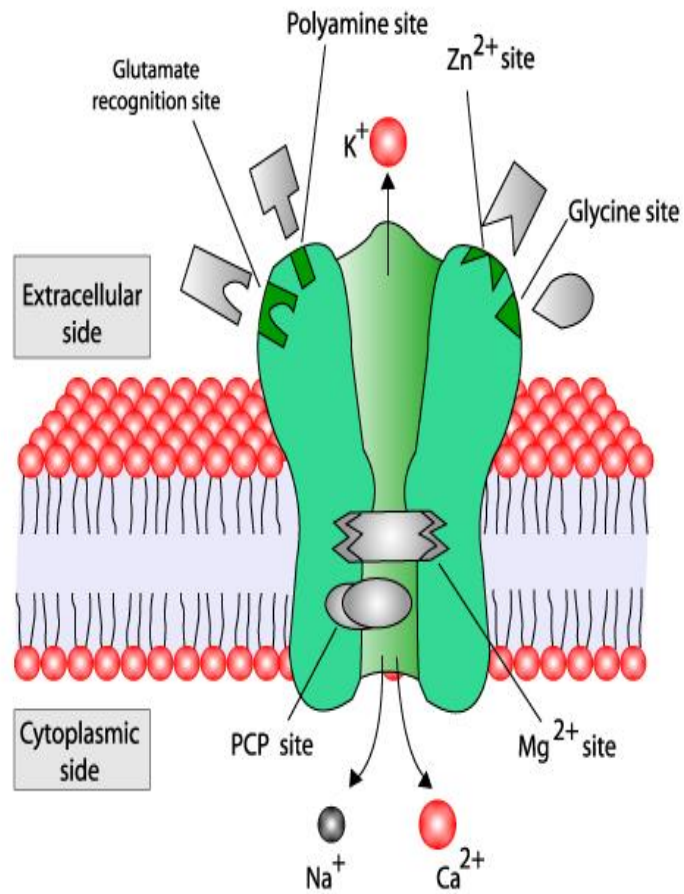
GABA Receptor



Barbiturates
Alcohol
Benzodiazepines
Anticonvulsants

Möhler, H. The rise of a new GABA pharmacology. *Neuropharmacol.* 2011;60:1042–1049.

Schematic representation of the NMDA (N - Methyl D- Aspartate) receptor complex



NMDA Receptor

Antagonists:
PCP (Phencyclidine)
Ketamine
Dextromethorphan
Memantine
Amantadine
Methadone

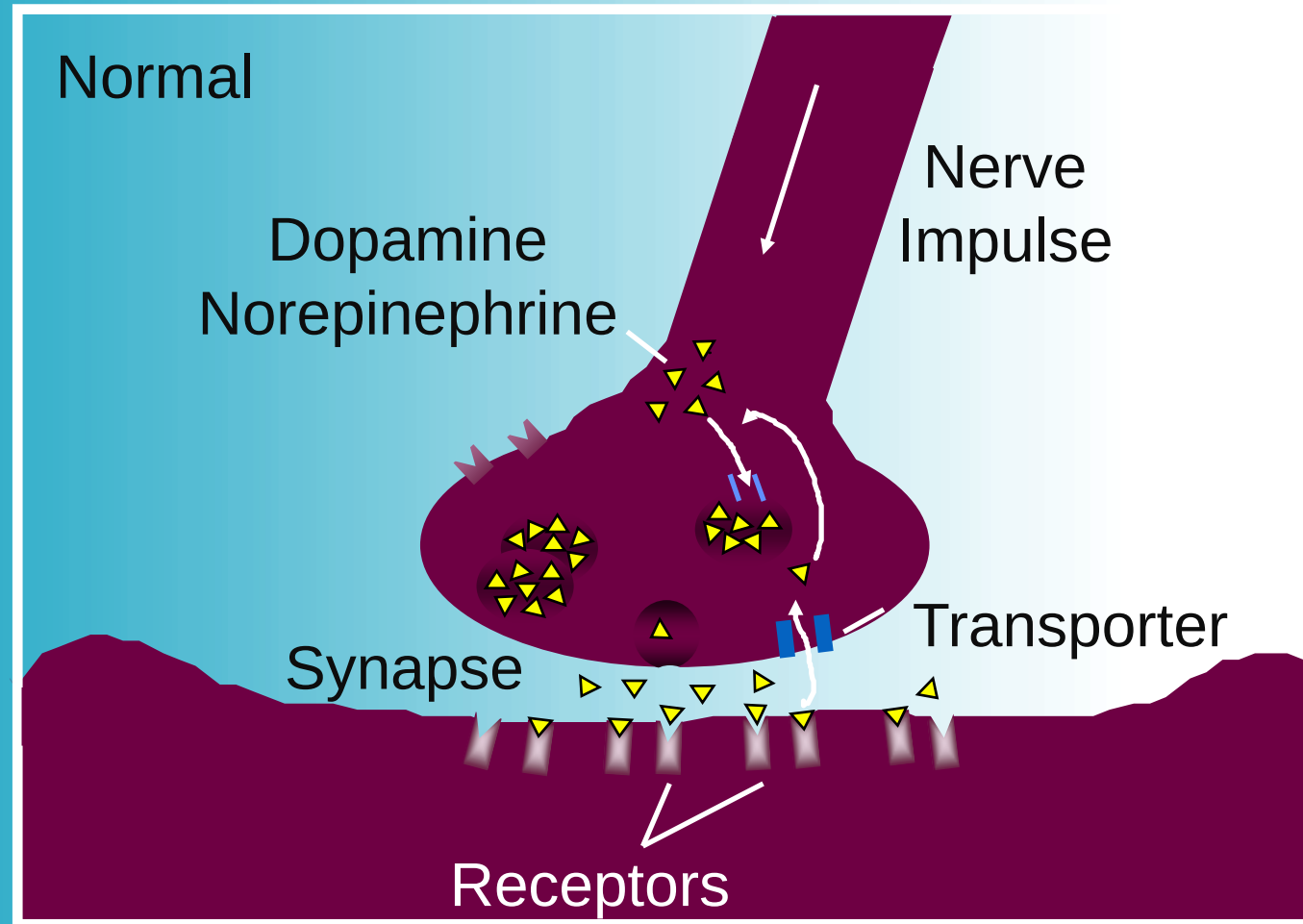


Psychedelics

Catecholamine Neurotransmission

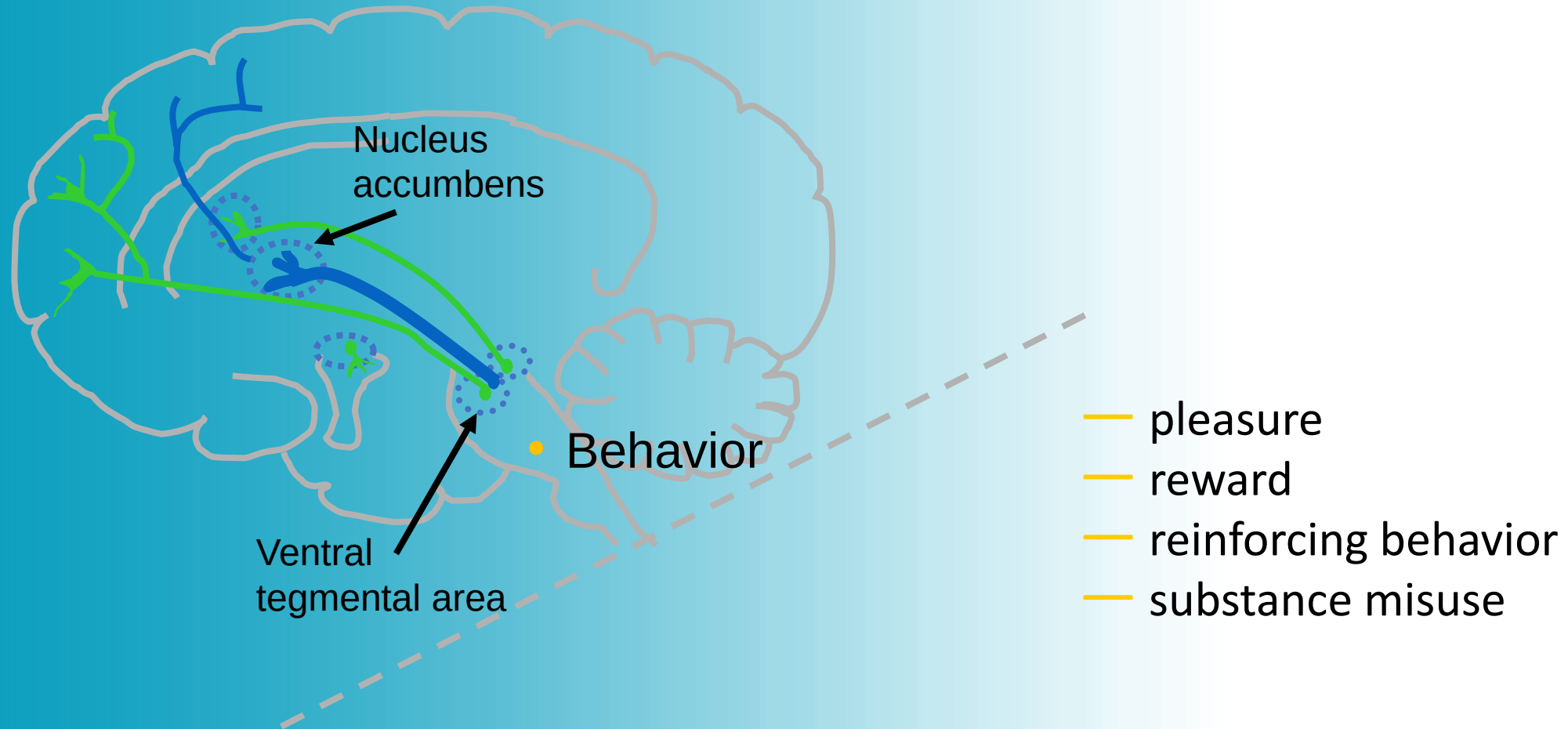


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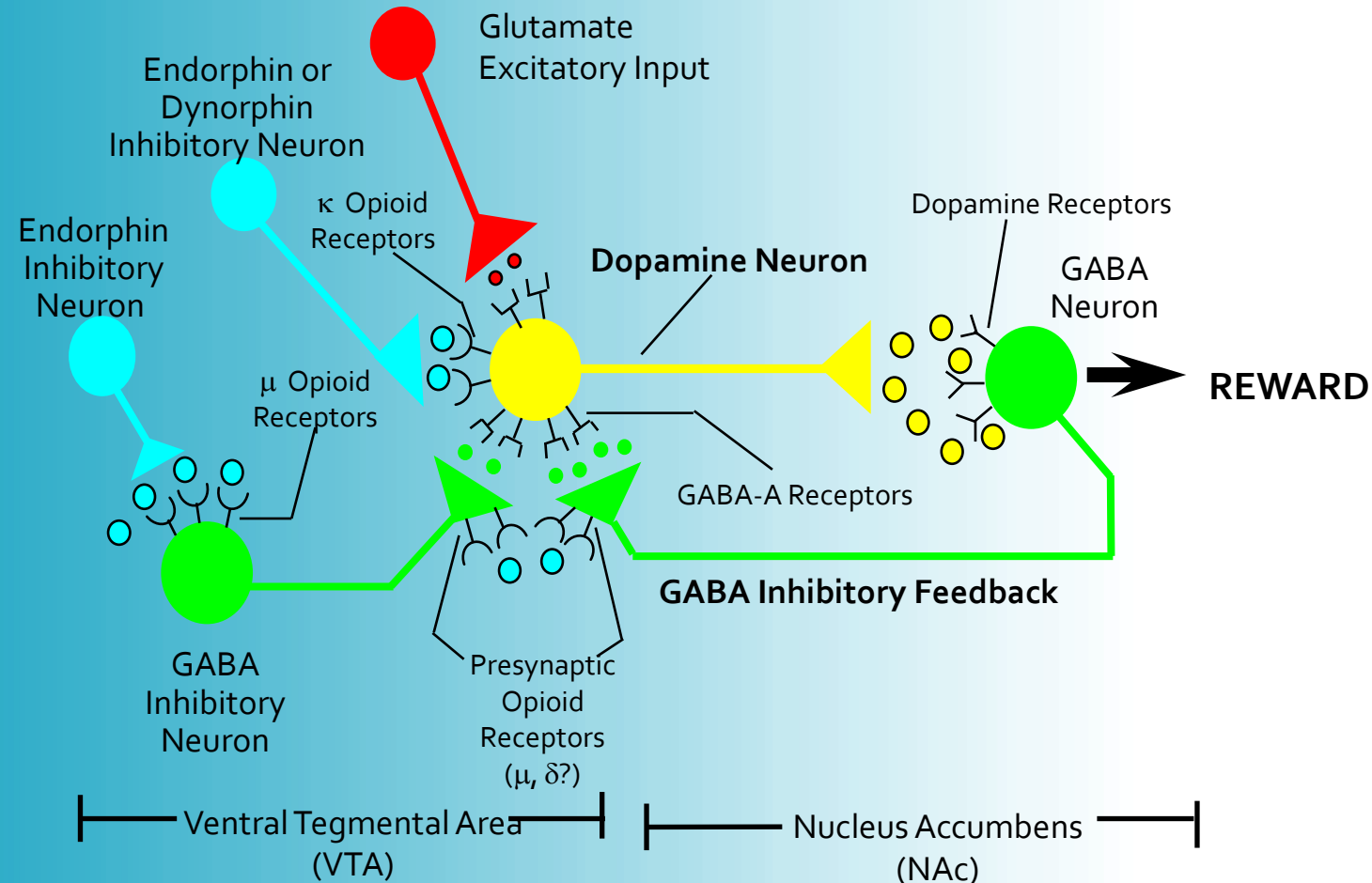




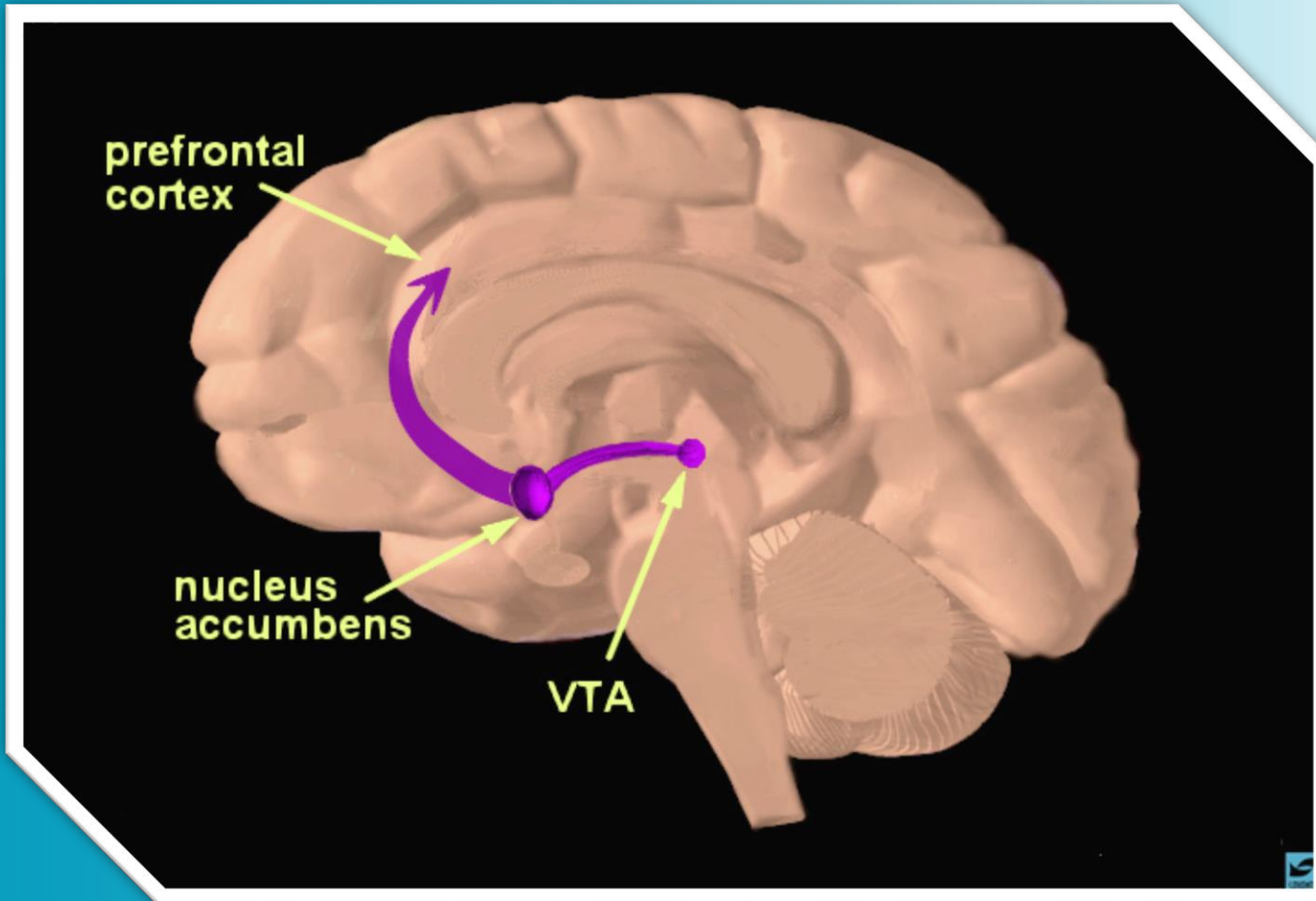
Dopamine Mesolimbic Pathway



Neurochemistry of Reinforcement



Neuroanatomy of Reinforcement



- The Ventral Tegmental Area (VTA)-nucleus accumbens pathway is activated by all drugs of dependence including alcohol
- This pathway is important not only in drug dependence, but also in essential physiological behaviors such as eating, drinking, sleeping, and sex

Photo courtesy of the NIDA Web site. From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana*.



Major Brain Circuits Involved in Addiction

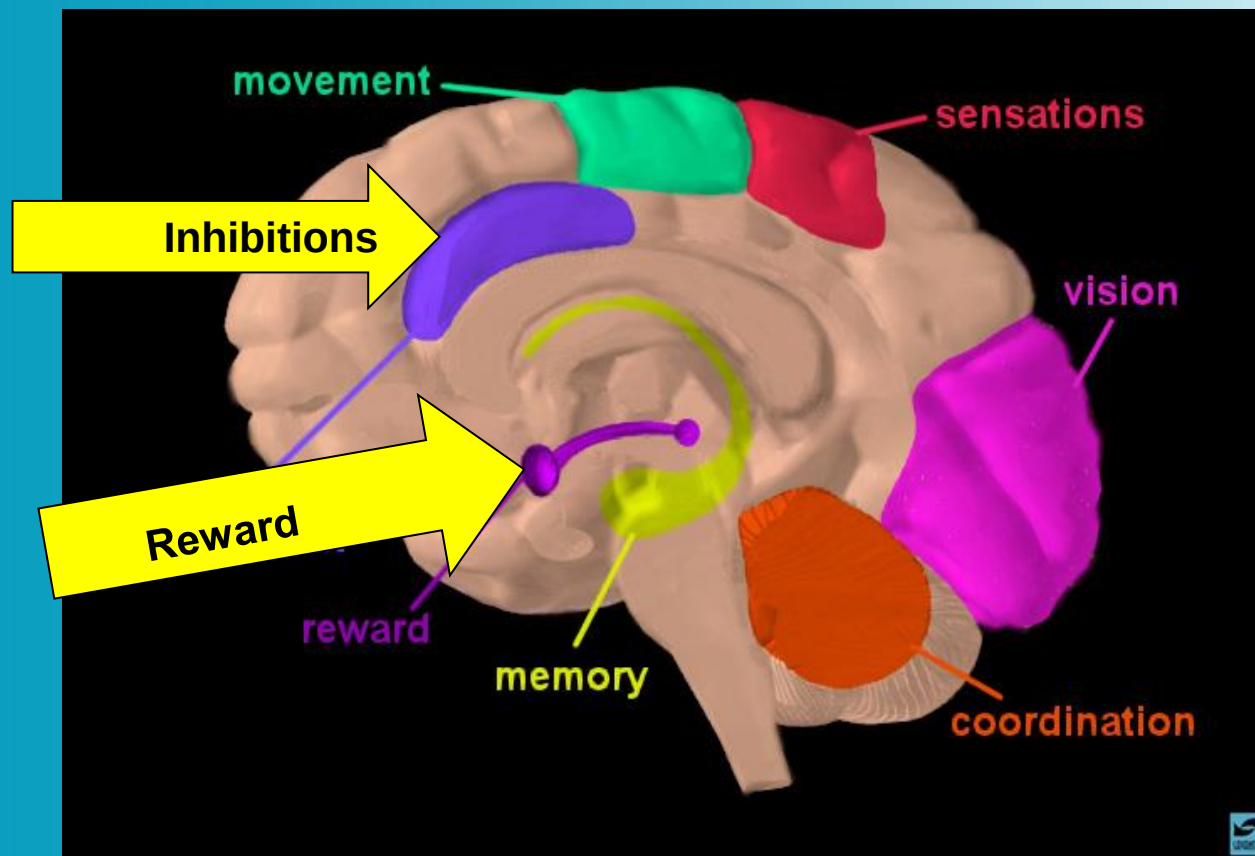


Photo courtesy of the NIDA Web site. From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana*.



The Story of Marijuana

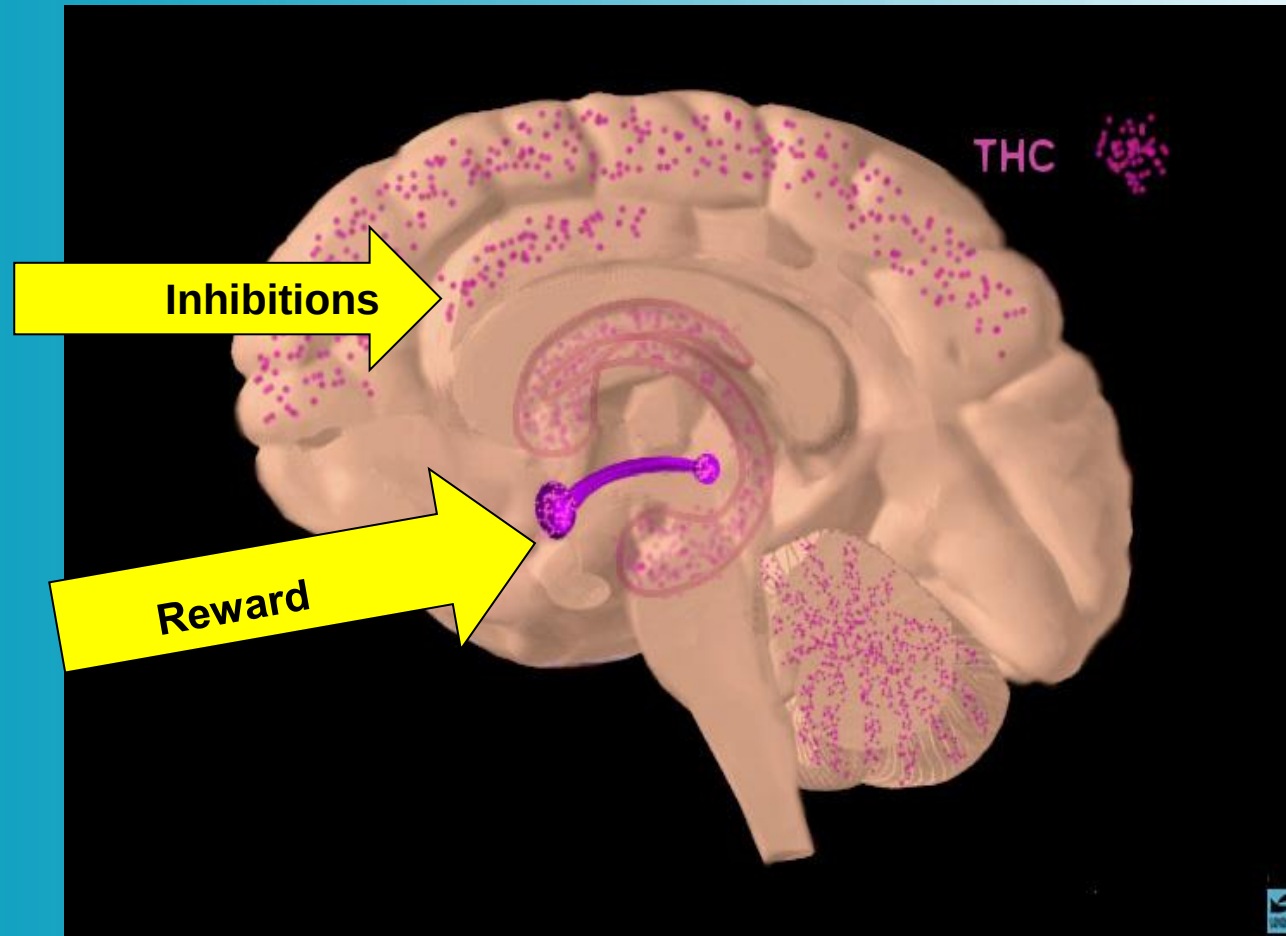
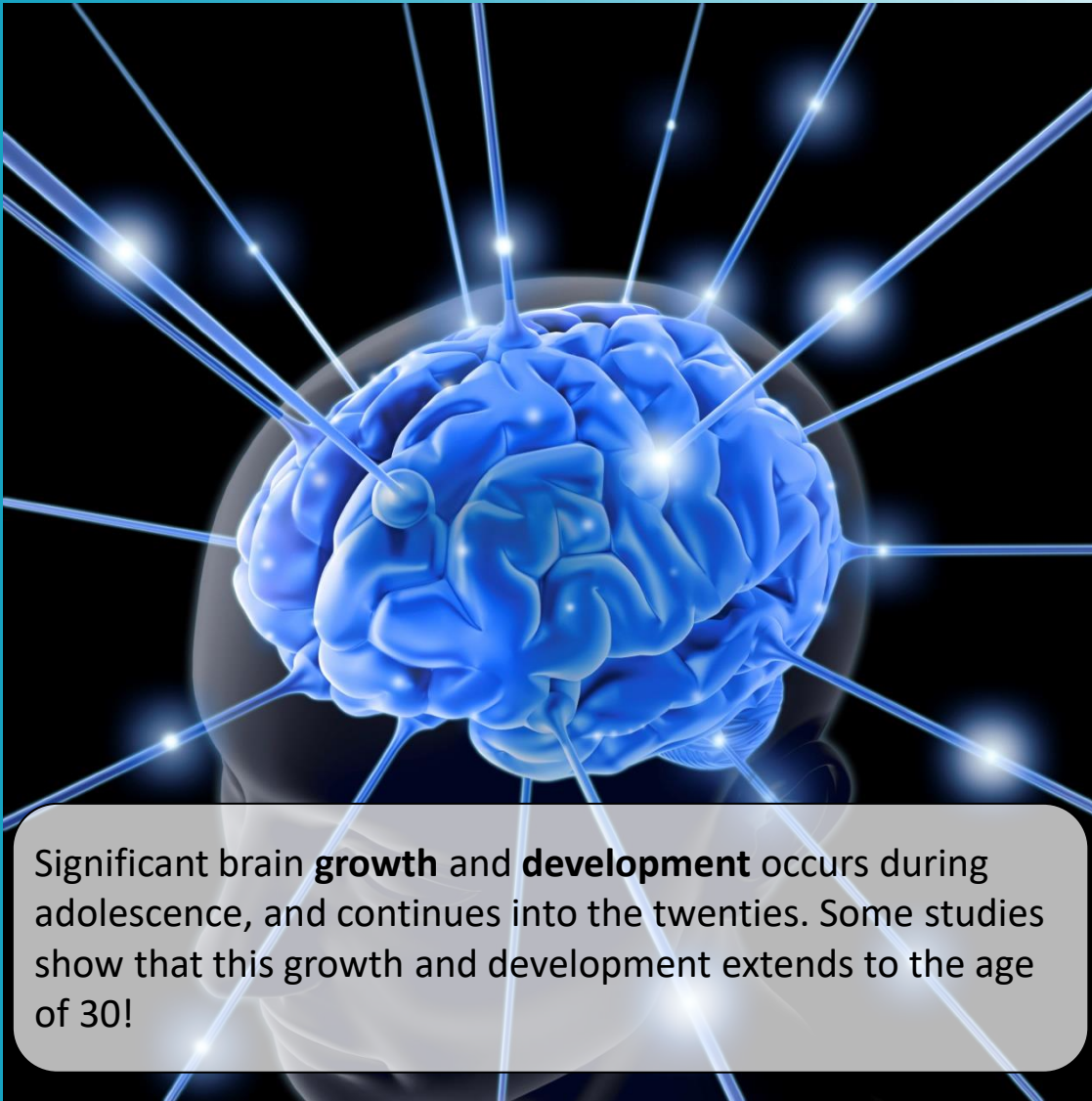


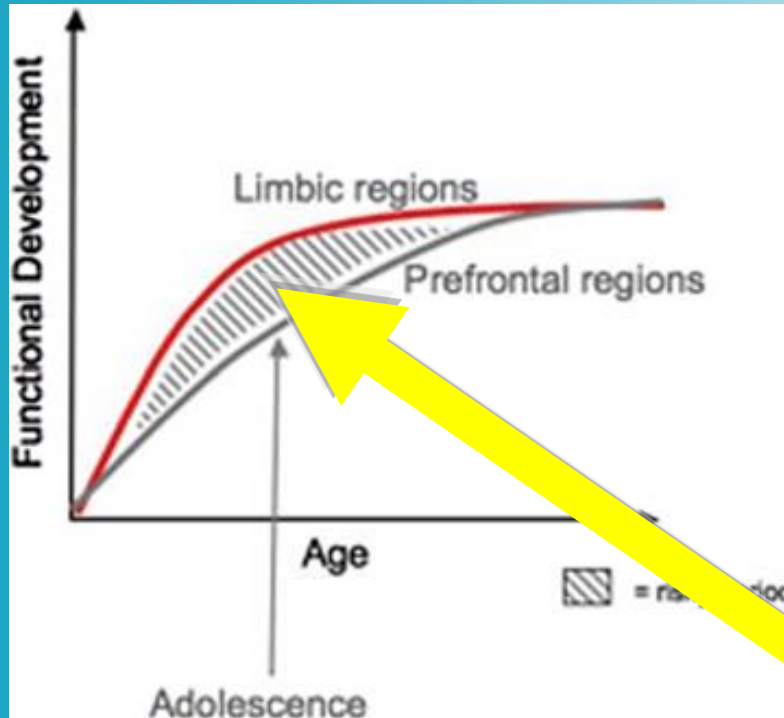
Photo courtesy of the NIDA Web site. From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana*.



Significant brain **growth** and **development** occurs during adolescence, and continues into the twenties. Some studies show that this growth and development extends to the age of 30!

Sowell, et al. 1999; Sowell, et al. 2001.

Does Dyssymmetry in Prefrontal Control of Limbic Regions Drive Young Peoples' Behavior?



Dysregulated Mood
(e.g. frustration, Irritability,
temper tantrums)

**Exaggerated with certain disorders such as Mood,
Substance Use, ADHD?**

Casey, et al. *J Am Acad Child Adolesc Psychiatry*, 2008;49:1189-201; Wilens, et al. *Drug Alc Dep*. 2013. Courtesy N Strang.



The Memory of Drugs

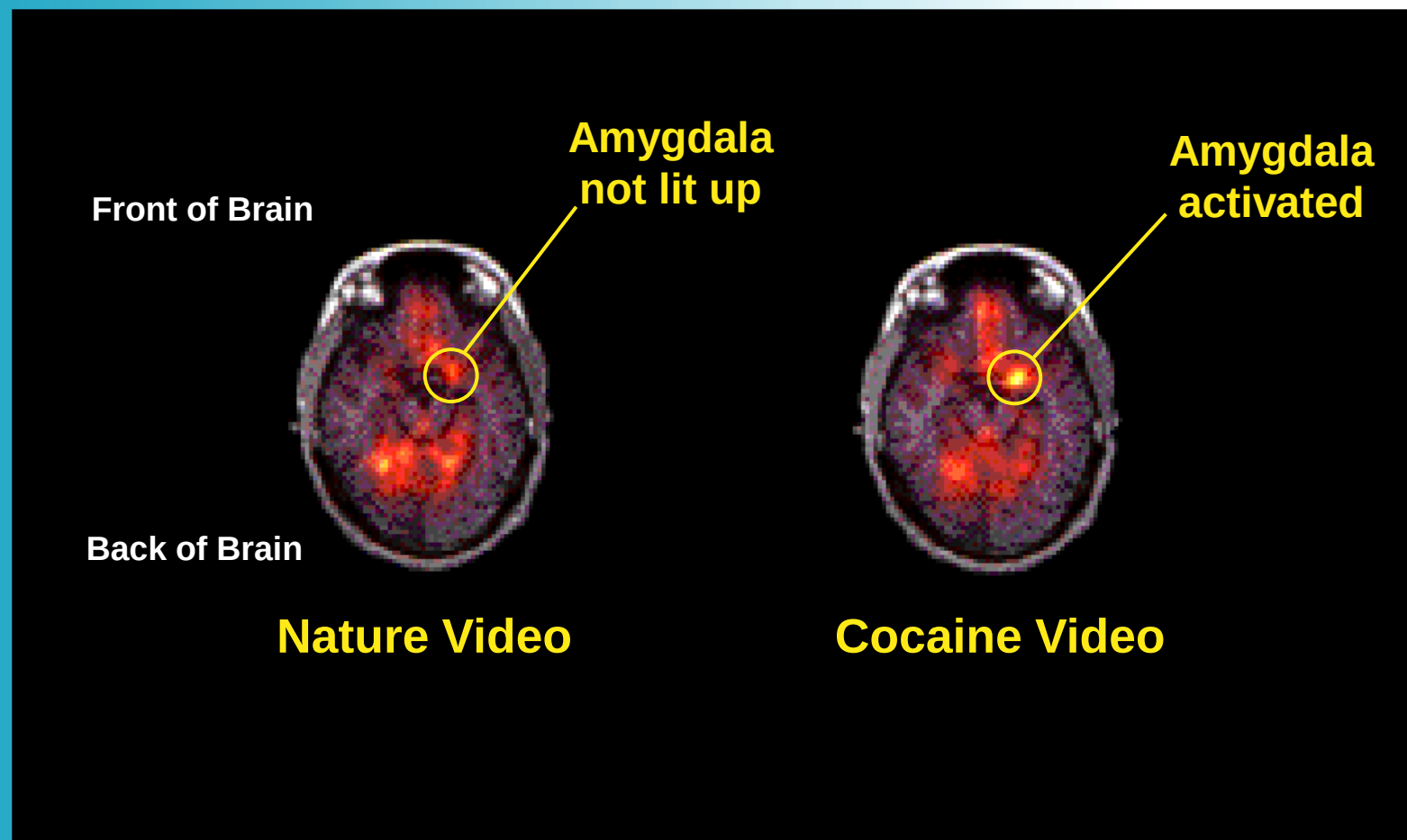


Photo courtesy of Anna Rose Childress, PhD.

Your Brain After Drugs

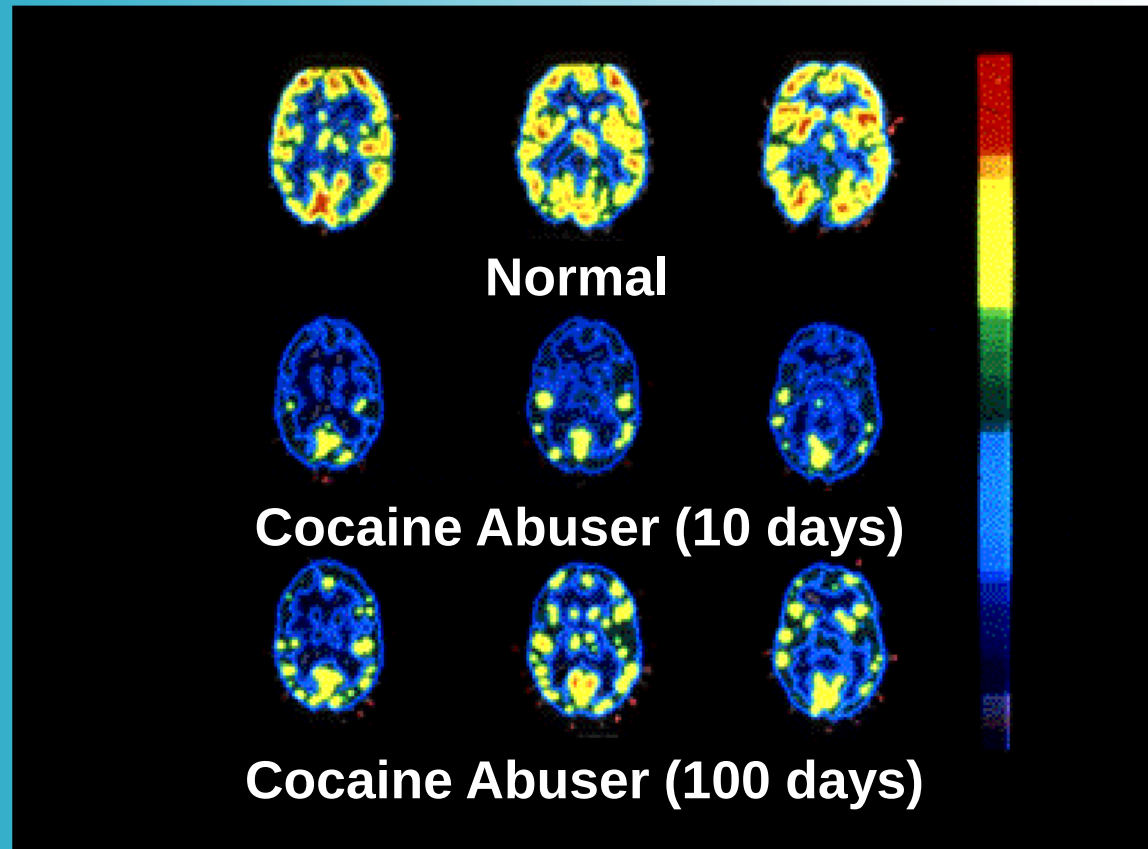


Photo courtesy of Nora Volkow, PhD. Volkow ND, Hitzemann R, Wang C-I, Fowler JS, Wolf AP, Dewey SL. Long-term frontal brain metabolic changes in cocaine abusers. *Synapse* 1999;11:184-190; Volkow ND, Fowler JS, Wang G-J, Hitzemann R, Logan J, Schlyer D, Dewey S, Wolf AP. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* 1993;14:169-177.



Drugs Have Long-Term Consequences

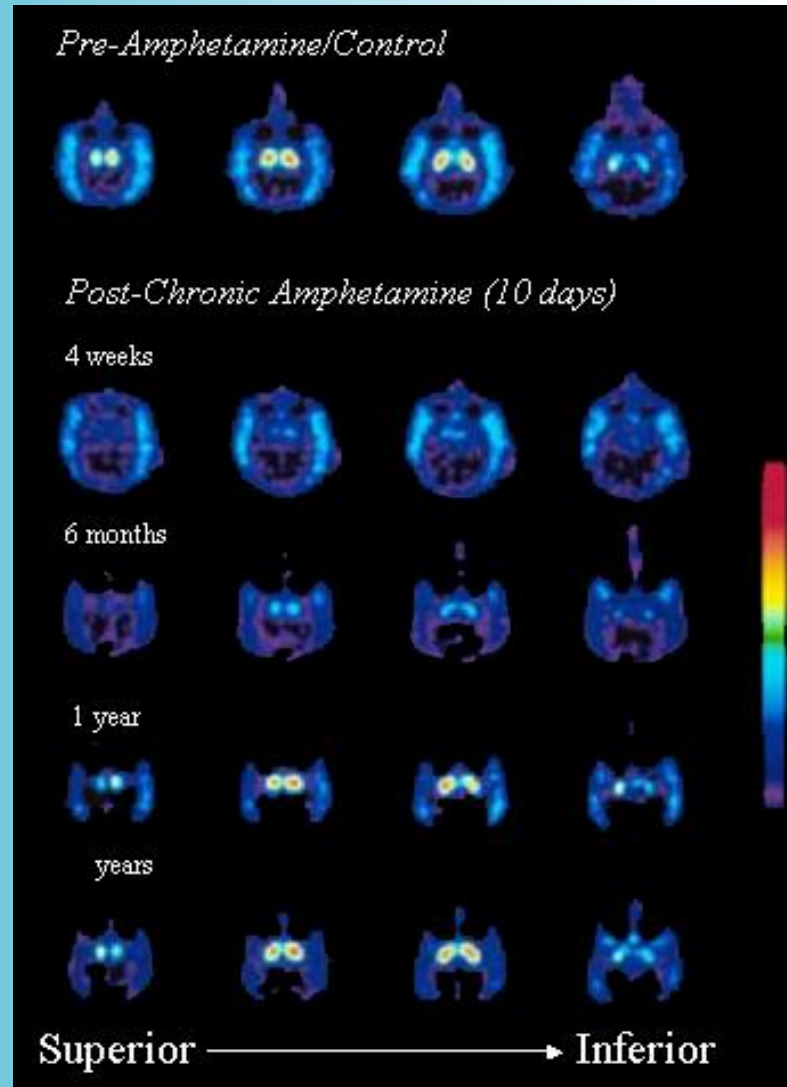


Photo courtesy of NIDA from research conducted by Melega WP, Raleigh MJ, Stout DB, Lacan C, Huang SC, Phelps ME.

Association of Cannabis Use During Adolescence With Neurodevelopment

Matthew D. Albaugh, PhD; Jonatan Ottino-Gonzalez, PhD; Amanda Sidwell, BS; Claude Lepage, PhD; Anthony Juliano, PsyD; Max M. Owens, PhD; Bader Chaarani, PhD; Philip Spechler, PhD; Nicholas Fontaine, BS; Pierre Rioux, MSc; Lindsay Lewis, PhD; Seun Jeon, PhD; Alan Evans, PhD; Deepak D'Souza, MD; Rajiv Radhakrishnan, MD; Tobias Banaschewski, MD, PhD; Arun L. W. Bokde, PhD; Erin Burke Quinlan, PhD; Patricia Conrod, PhD; Sylvane Desrivieres, PhD; Herta Flor, PhD; Antoine Grigis, PhD; Penny Gowland, PhD; Andreas Heinz, MD, PhD; Bernd Ittermann, PhD; Jean-Luc Martinot, MD, PhD; Marie-Laure Paillere Martinot, MD, PhD; Frauke Nees, PhD; Dimitri Papadopoulos Orfanos, PhD; Tomàs Paus, MD, PhD; Luise Poustka, MD; Sabina Millenet, PhD; Juliane H. Fröhner, MSc; Michael N. Smolka, MD; Henrik Walter, MD, PhD; Robert Whelan, PhD; Gunter Schumann, MD; Alexandra Potter, PhD; Hugh Garavan, PhD; for the IMAGEN Consortium

IMAGEN Multisite Study (8 sites)

N=799 children with scans and 5 year f/u

Mean age 14.4 yo (base) and 19 yo at f/u

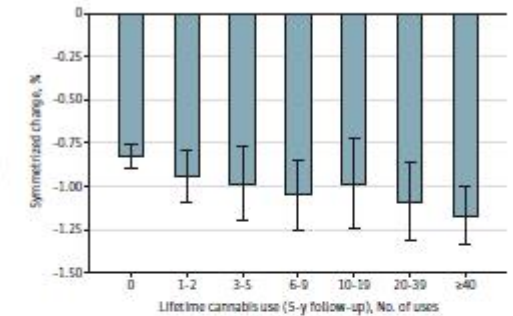
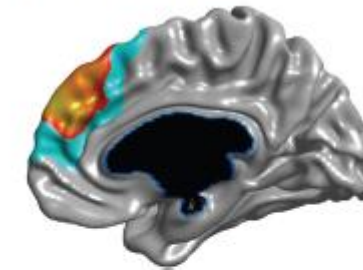
MRI imaging for cortical thickness development

Main findings

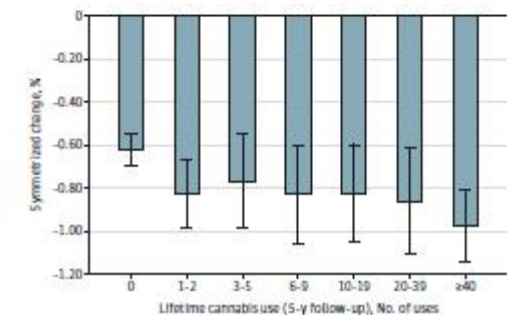
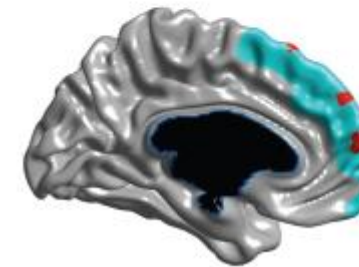
- No differences at baseline between cannabis users
- Age related thinning in cannabis use –dose response relationship
- Overlay in cortical thinning linked to CB1 receptor density (from other PET study)

Figure 3. Magnetic Resonance Imaging-Assessed Cortical Thinning at Varying Levels of Lifetime Cannabis Use

A Right dorsomedial prefrontal cluster



B Left dorsomedial prefrontal cluster





NEUROBIOLOGY OF OPIOID WITHDRAWAL

- HYPERACTIVITY OF NOR-ADRENERGIC NEURONS IN THE LOCUS COERULEUS
 - INCREASE BP, HR, RESPIRATIONS
 - INCREASE SWEATING, DIARRHEA
 - CLONIDINE & OPIATES REVERSE THESE EFFECTS
- INCREASED GABA EFFECTS: REDUCED DOPAMINE IN NUCLEUS ACCUMBENS
 - CAUSES DYSPHORIA, DEPRESSION, CRAVING
 - ONLY OPIATES REVERSE THESE EFFECTS

Slide courtesy of J Renner MD



Neurobiology of SUD: Summary

- **Competing neurocircuitry may result in, and/or be secondary to, SUD**
- **Adaptations occur at molecular and macro levels with SUD**
- **Brain recovery may link with clinical recovery—brain health recovery may take months with certain substances**
- **Therapeutics associated with brain biomarkers of SUD**