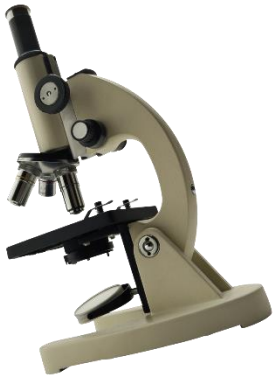
Timothy E. Wilens, M.D.
Center for Addiction Medicine and Child Psychiatry Service

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY



Substance Use Disorders: Neurobiology

Massachusetts General Hospital

MASSACHUSETTS GENERAL HOSPITAL
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Faculty Disclosure

Timothy Wilens, M.D. has served as a consultant, or has received grant support from the following:

- Otsuka, NIH (NIDA), Ironshore, Vallon
- Licensing agreement with Ironshore (Before School Functioning Questionnaire)
- Clinical care: MGH, Bay Cove Human Services, Gavin/Phoenix, National Football League (ERM Associates), Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge), MGH Comprehensive Clinical Psychiatry (Elsevier), MGH Psychopharmacology and Neurotherapeutics (Elsevier)

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

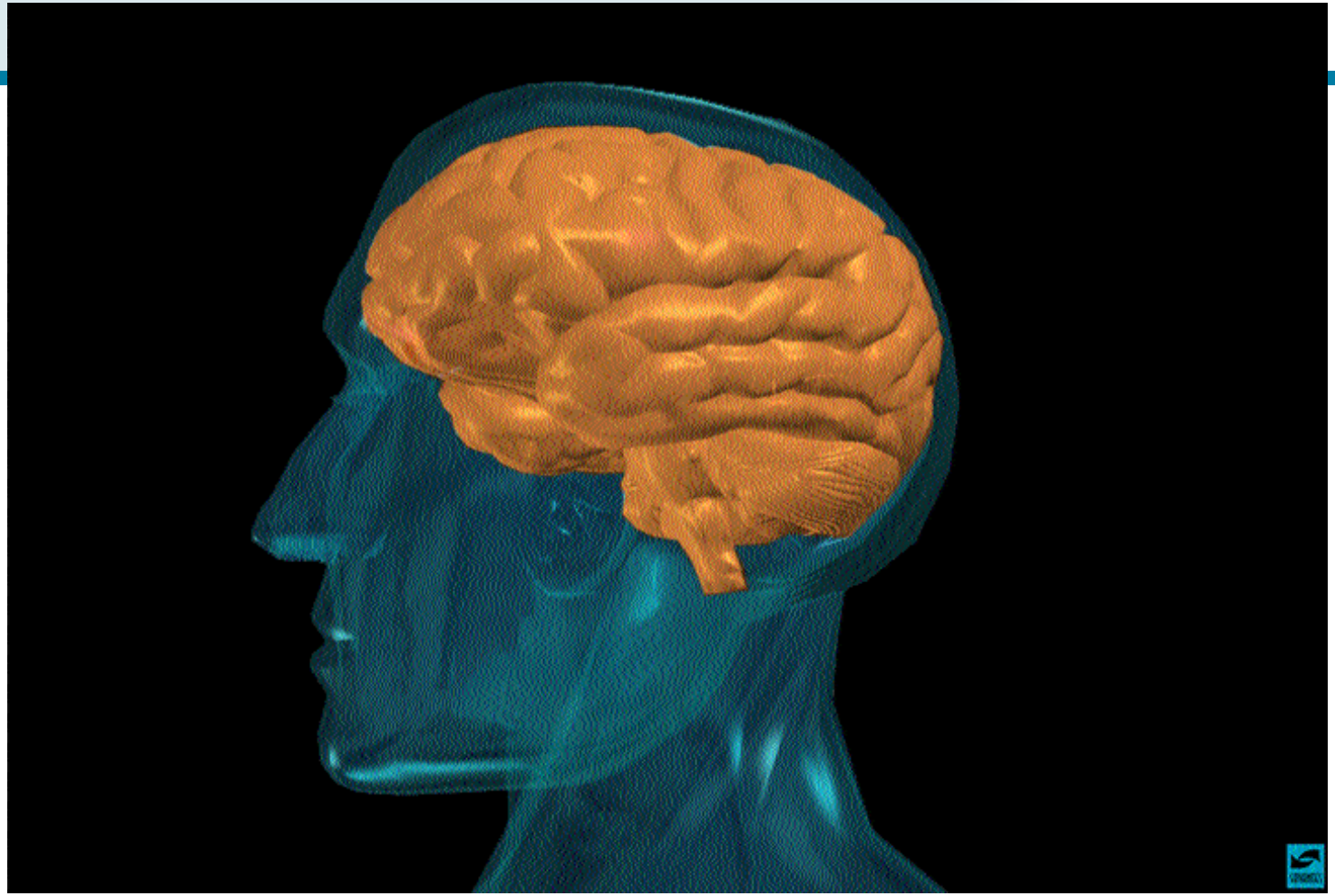

Photo courtesy of the NIDA Web site. From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.*

REVIEW ARTICLE

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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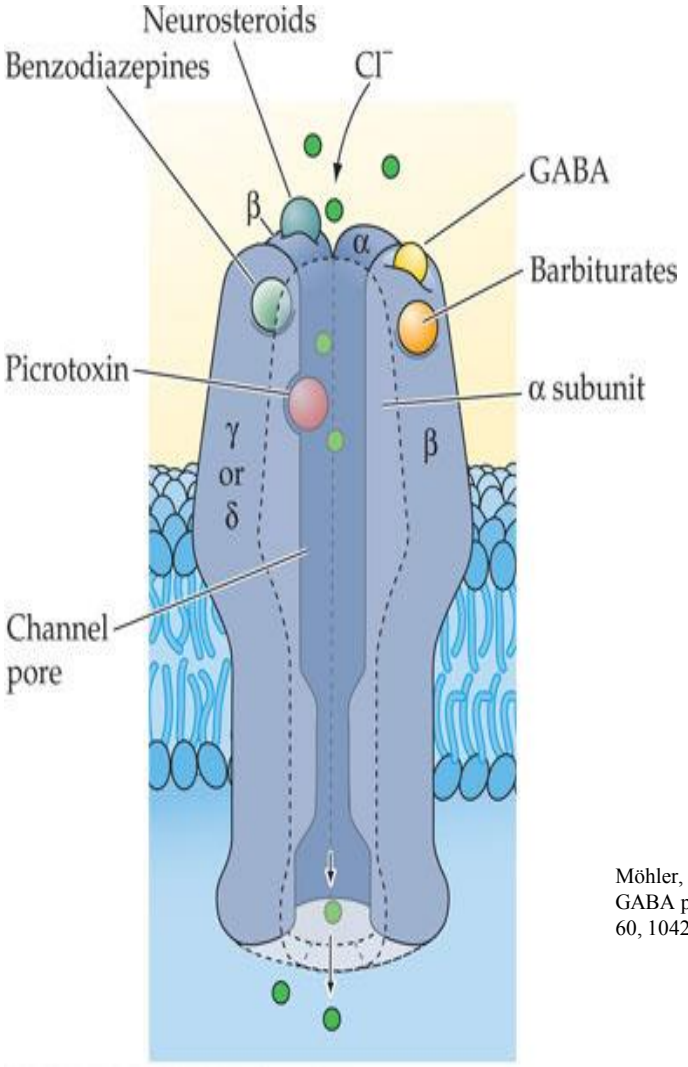
Addiction Pharmacology

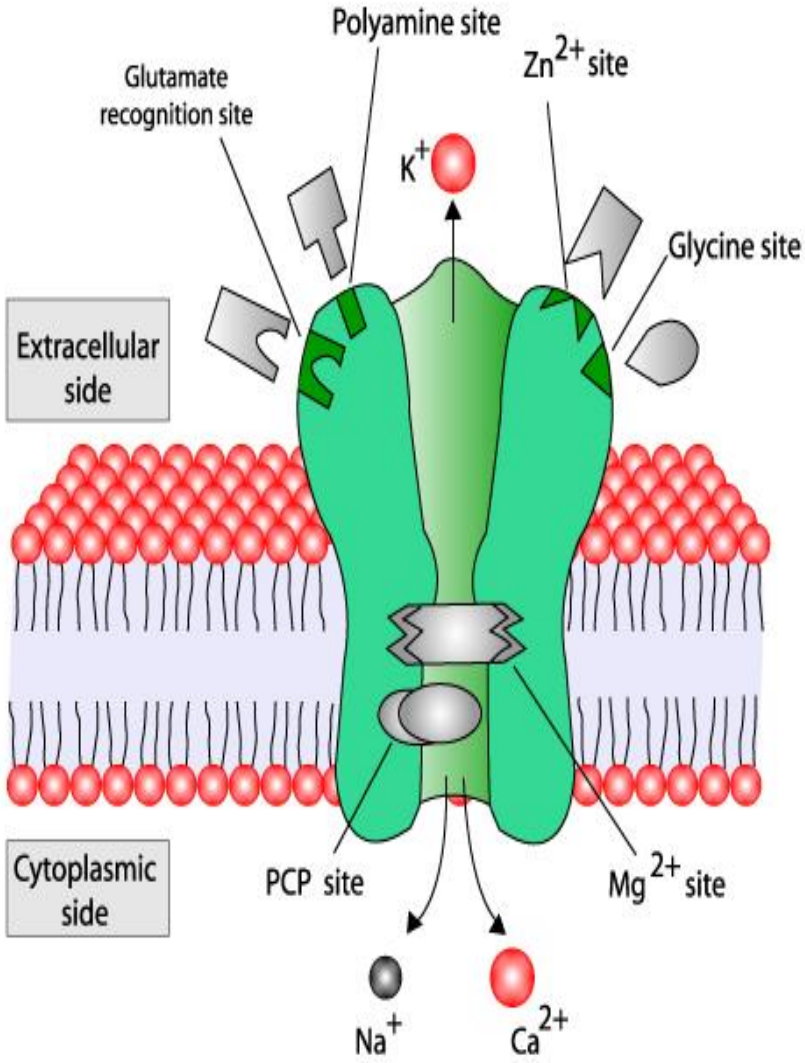
Substance	Mechanism of Action
Alcohol	GABA, opioid agonist; NMDA antagonist
Cocaine	Blocks re-uptake of dopamine
Amphetamines	Stimulate dopamine release
PCP, ketamine	NMDA antagonist
Opioids	Mu, delta, and kappa agonism
Cannabis	CB1 agonist
MDMA	5HT release and re-uptake inhibition; mild DA and NE reuptake inhibition
LSD	5HT2a agonism leading to increased glutamate?

GABA Receptor

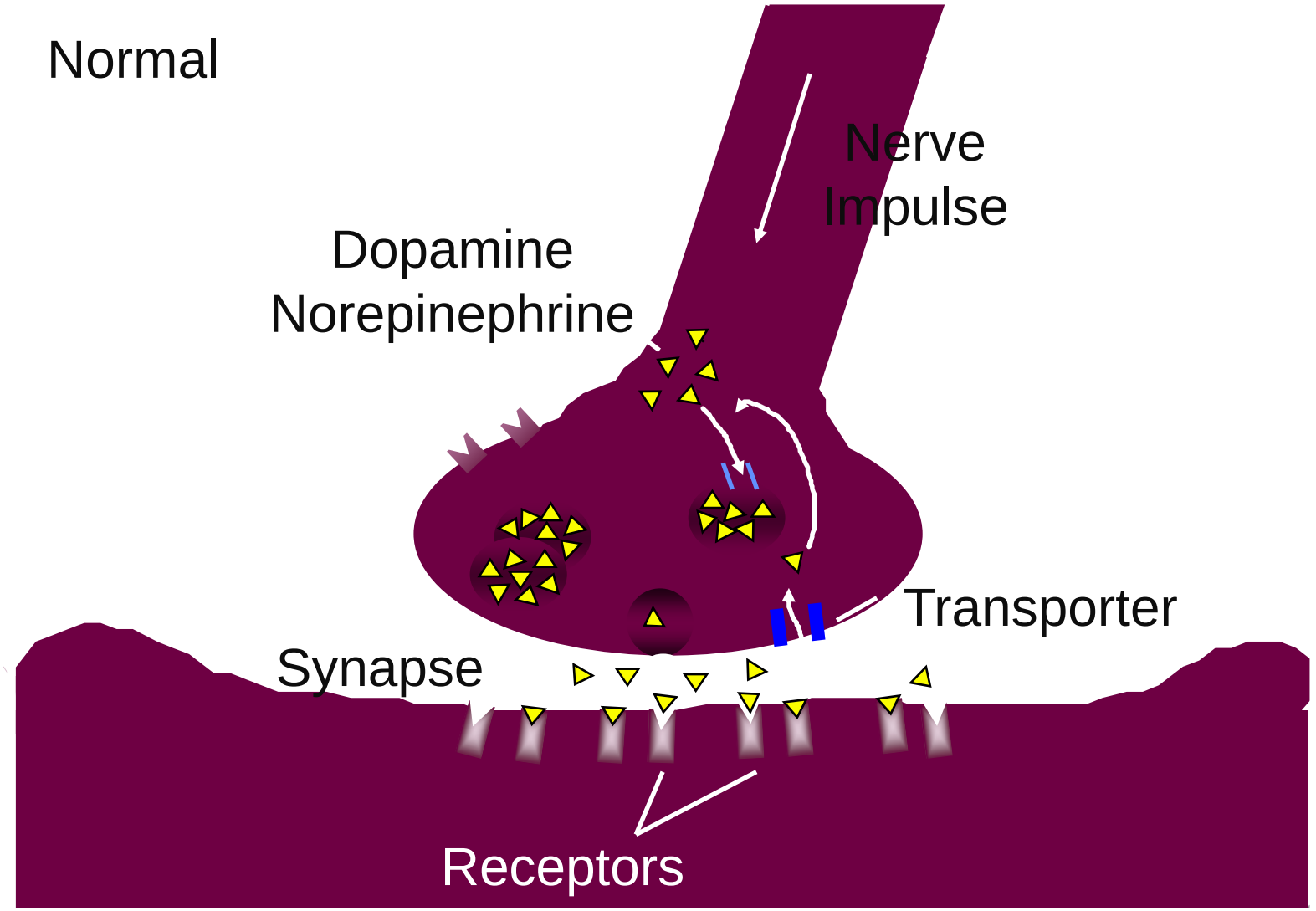


Möhler, H. (2011). The rise of a new GABA pharmacology. Neuropharmacol., 60, 1042–1049.

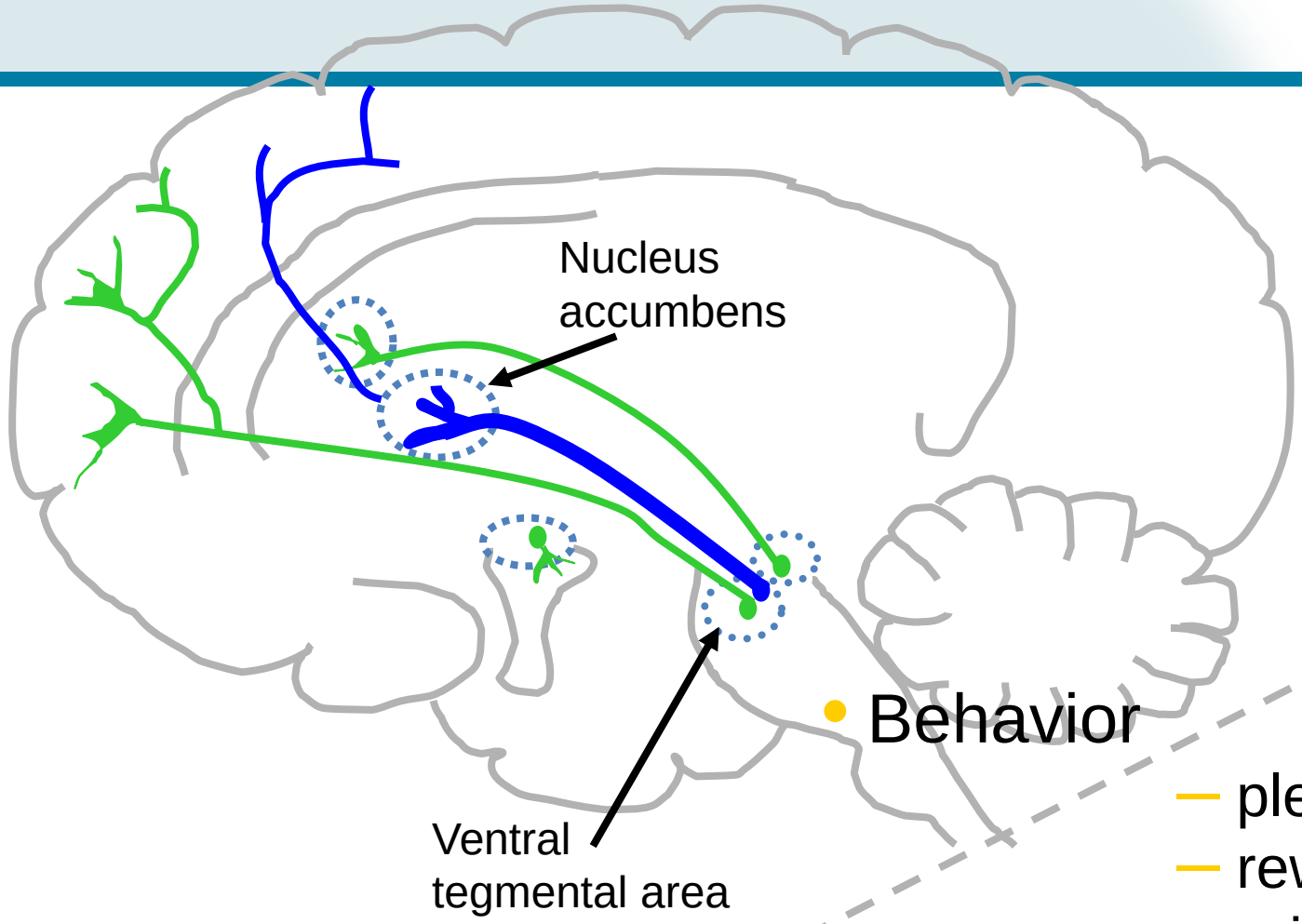
Schematic representation of the NMDA (N - Methyl D- Aspartate) receptor complex



Catecholamine Neurotransmission

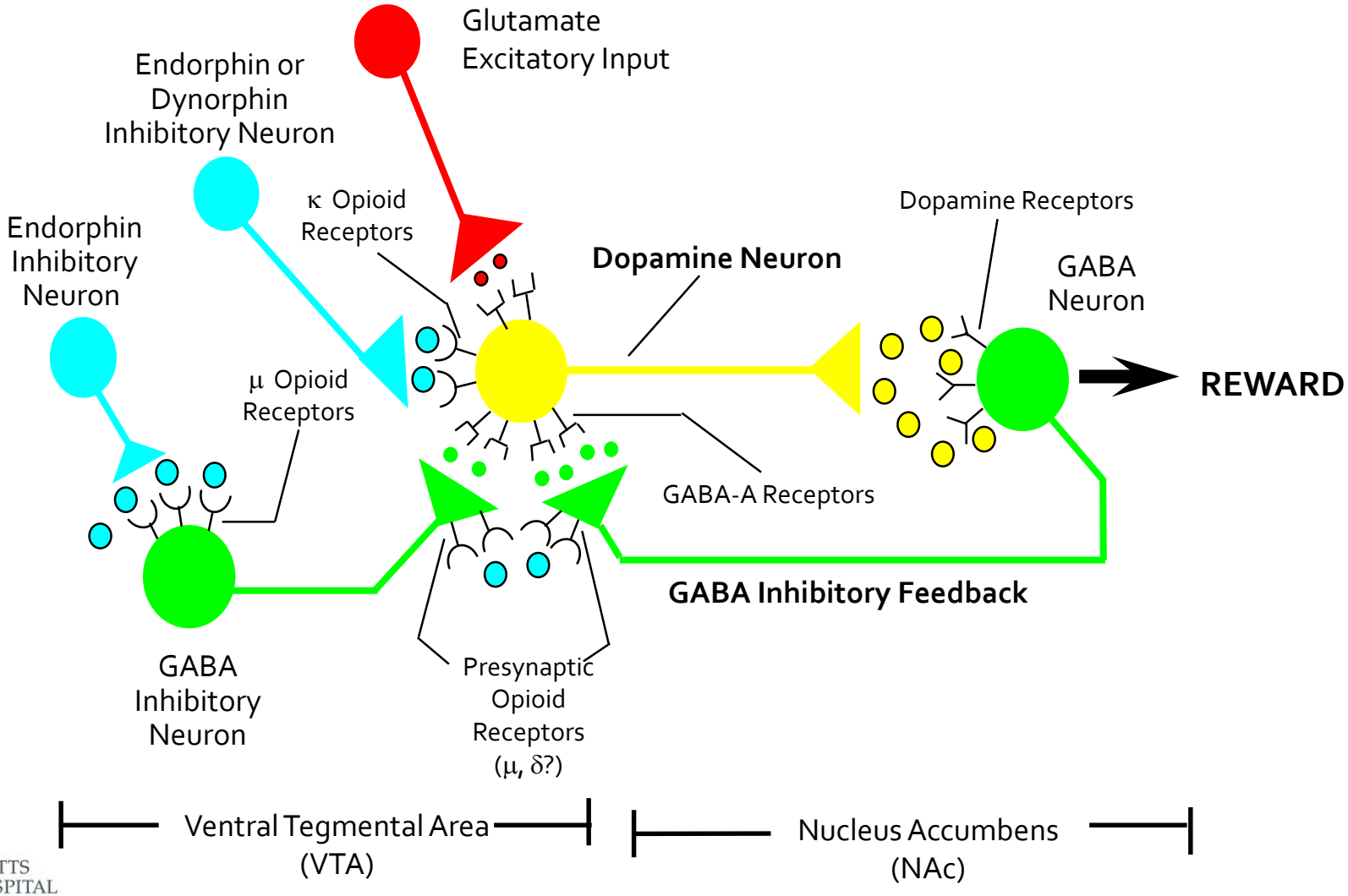


Dopamine Mesolimbic Pathway

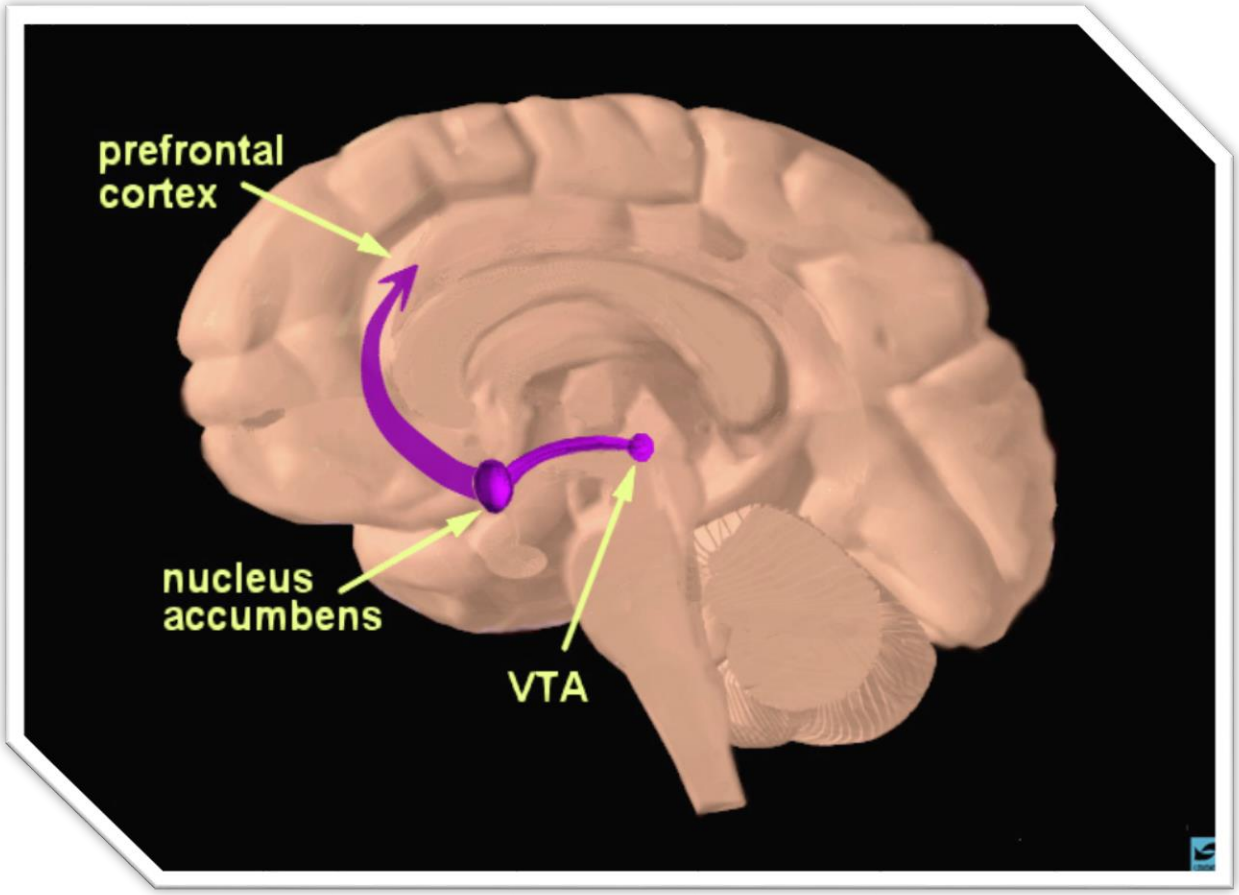


- Behavior
  - pleasure
  - reward
  - reinforcing behavior
  - substance misuse

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

Major Brain Circuits Involved in Addiction

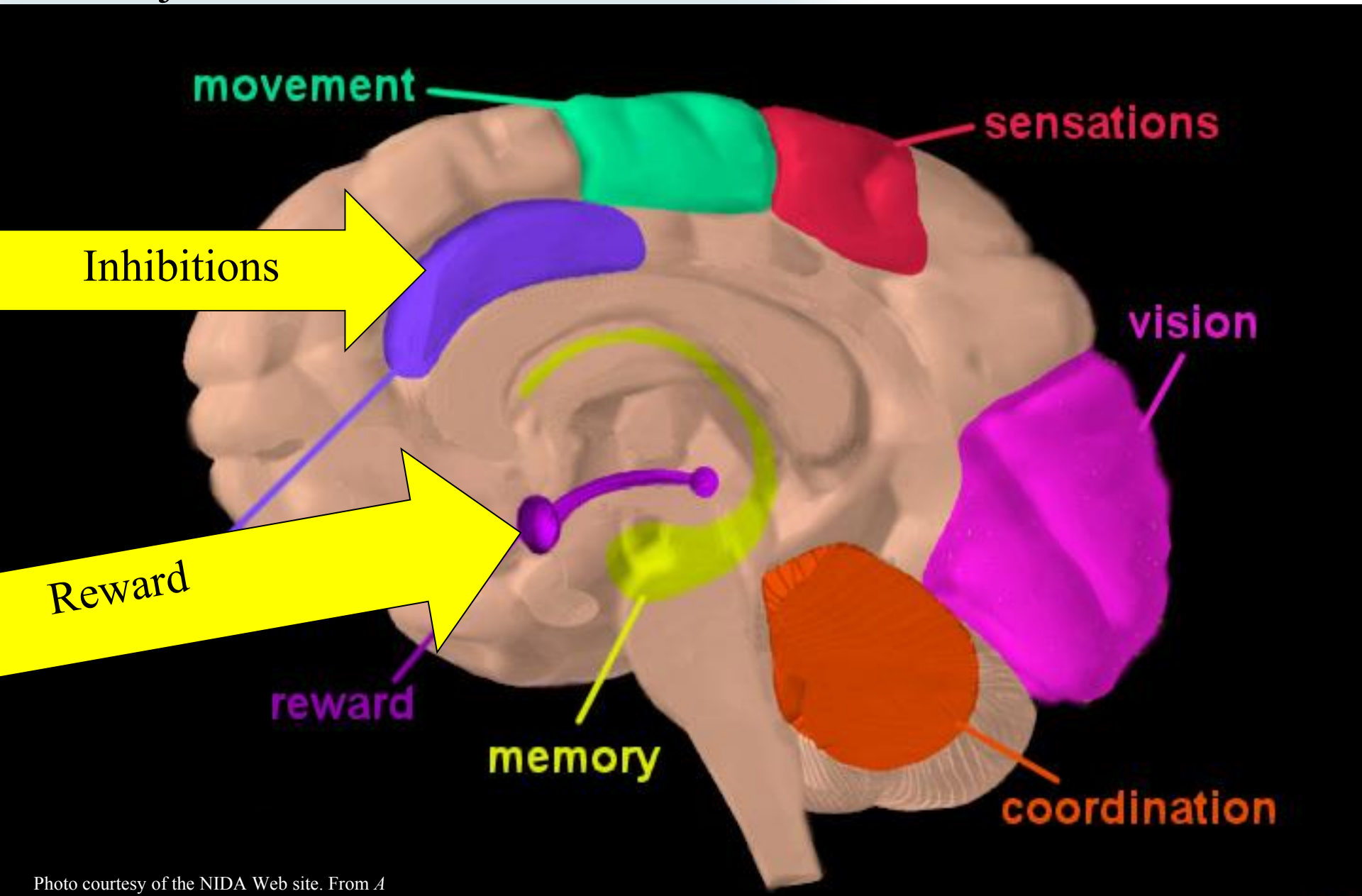


Photo courtesy of the NIDA Web site. From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.*

The Story of Marijuana

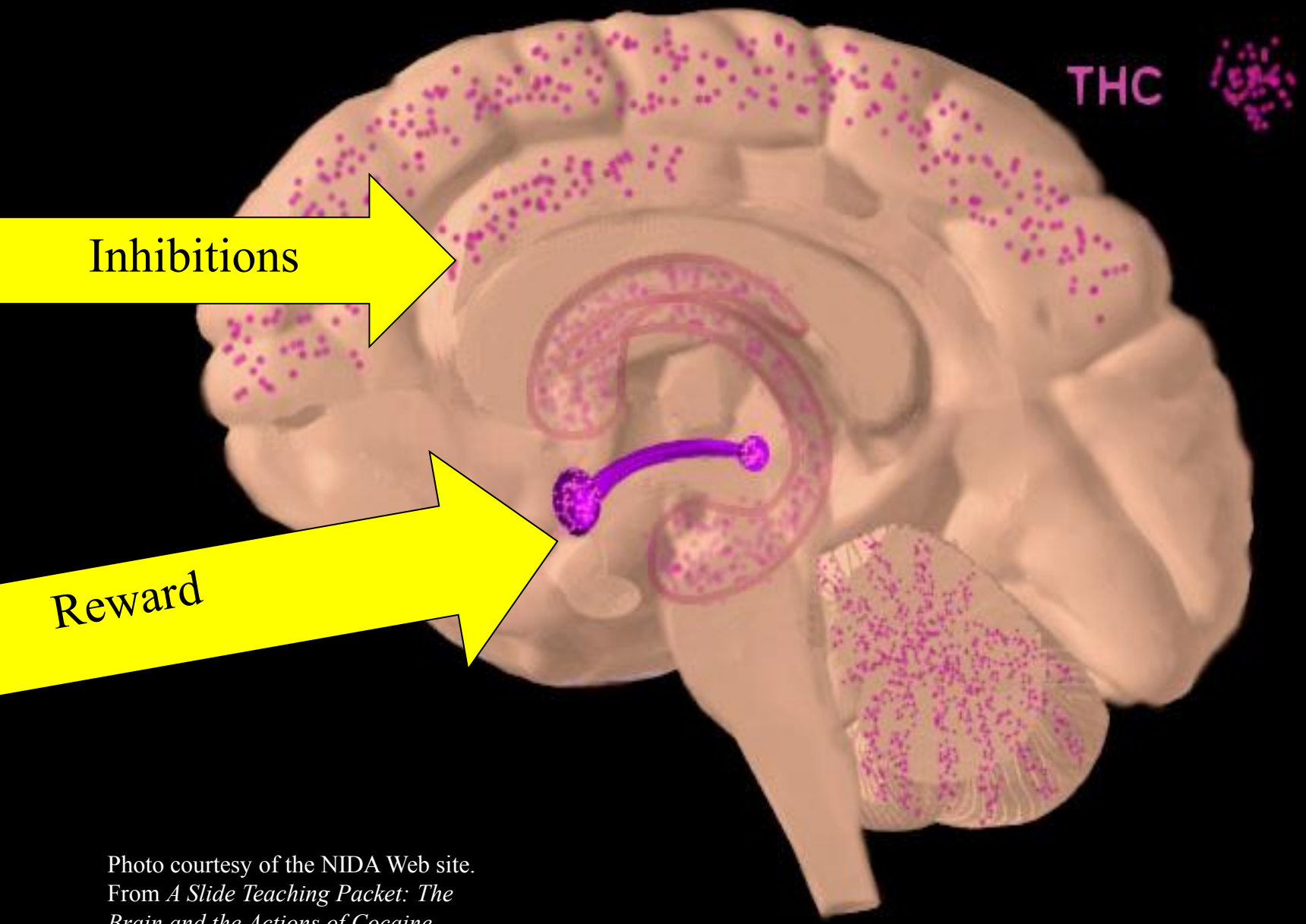
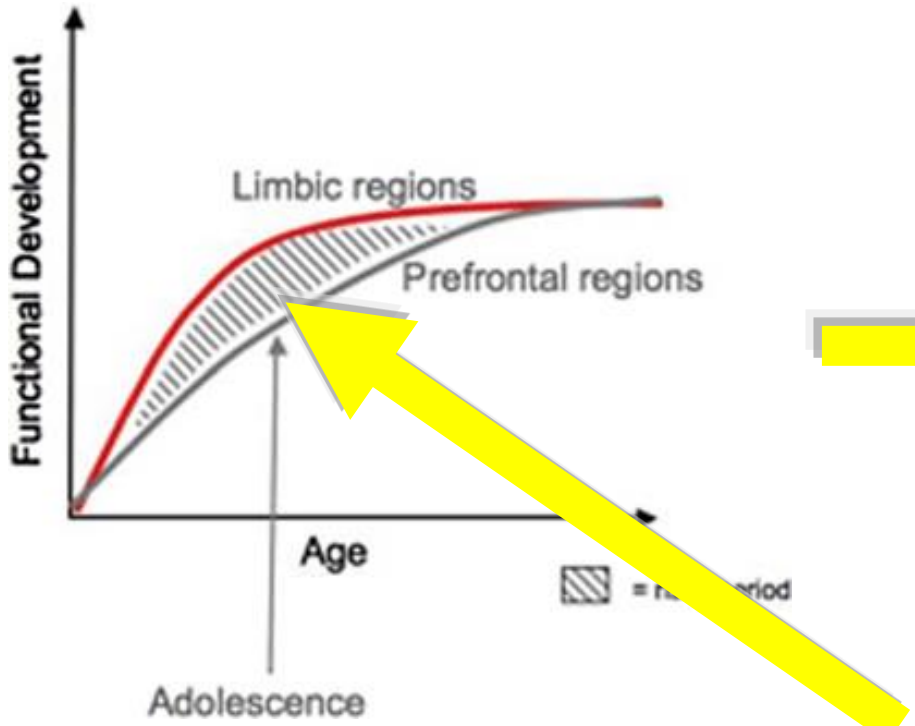


Photo courtesy of the NIDA Web site.
From *A Slide Teaching Packet: The Brain and the Actions of Cocaine, Opiates, and Marijuana.*

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 TAY behavior ?



Dysregulated Mood

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

Exaggerated with certain disorders such as Mood, Substance Abuse, 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

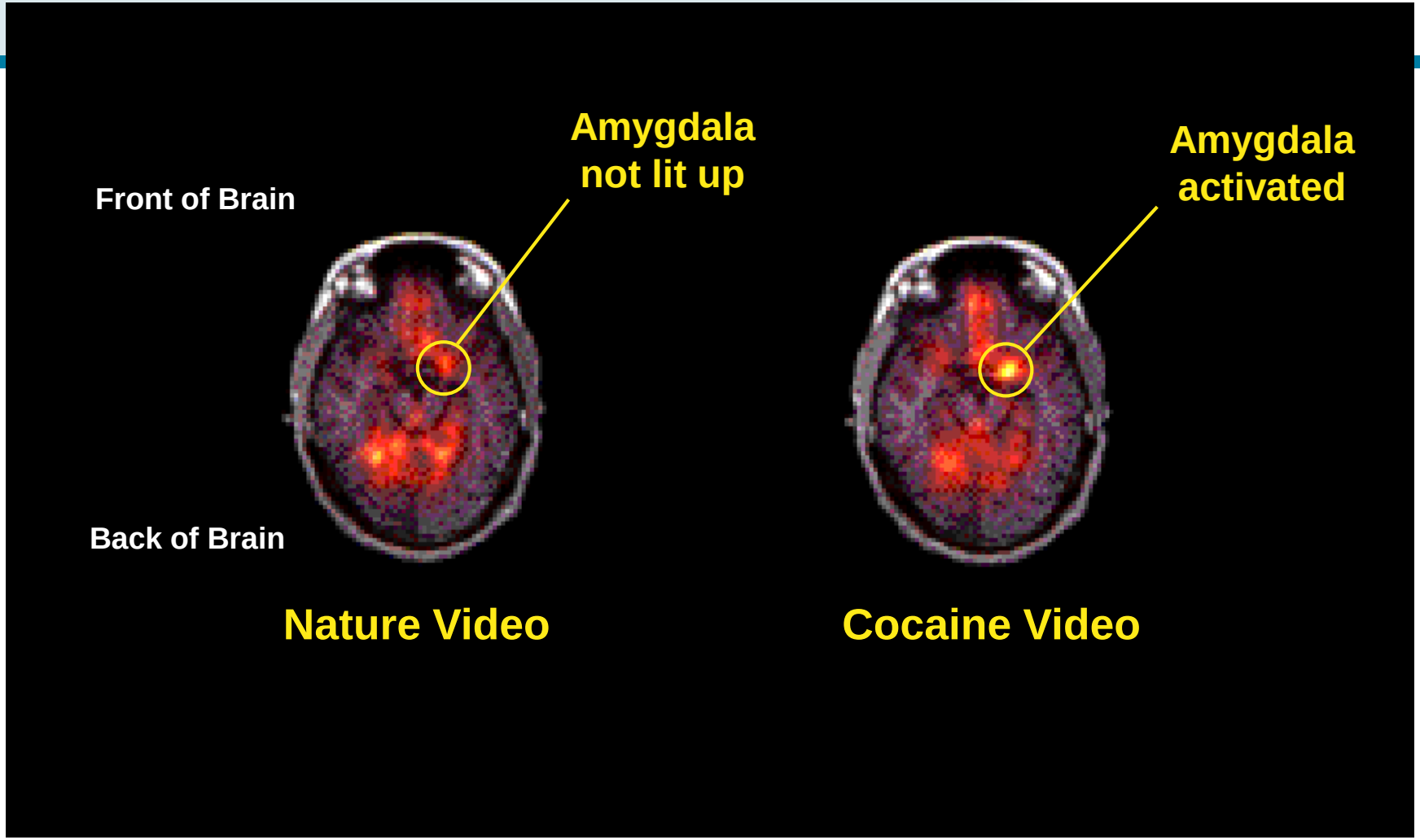
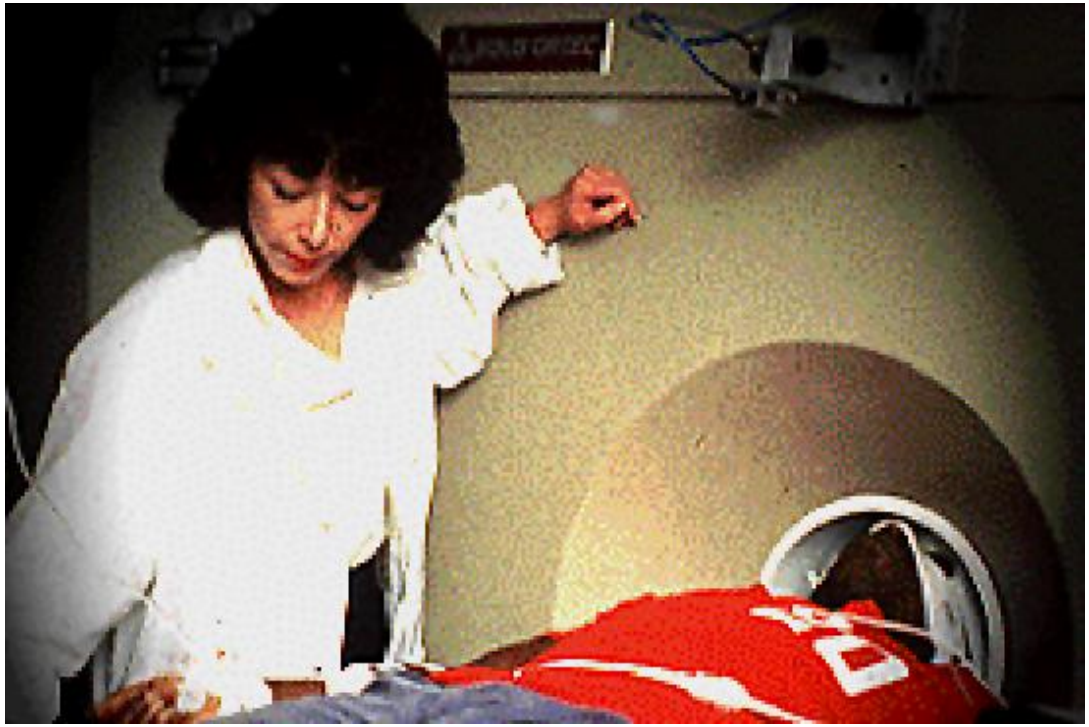


Photo courtesy of Anna Rose Childress, Ph.D.

Positron Emission Tomography (PET) And Brain Recovery from SUD



Your Brain After Drugs

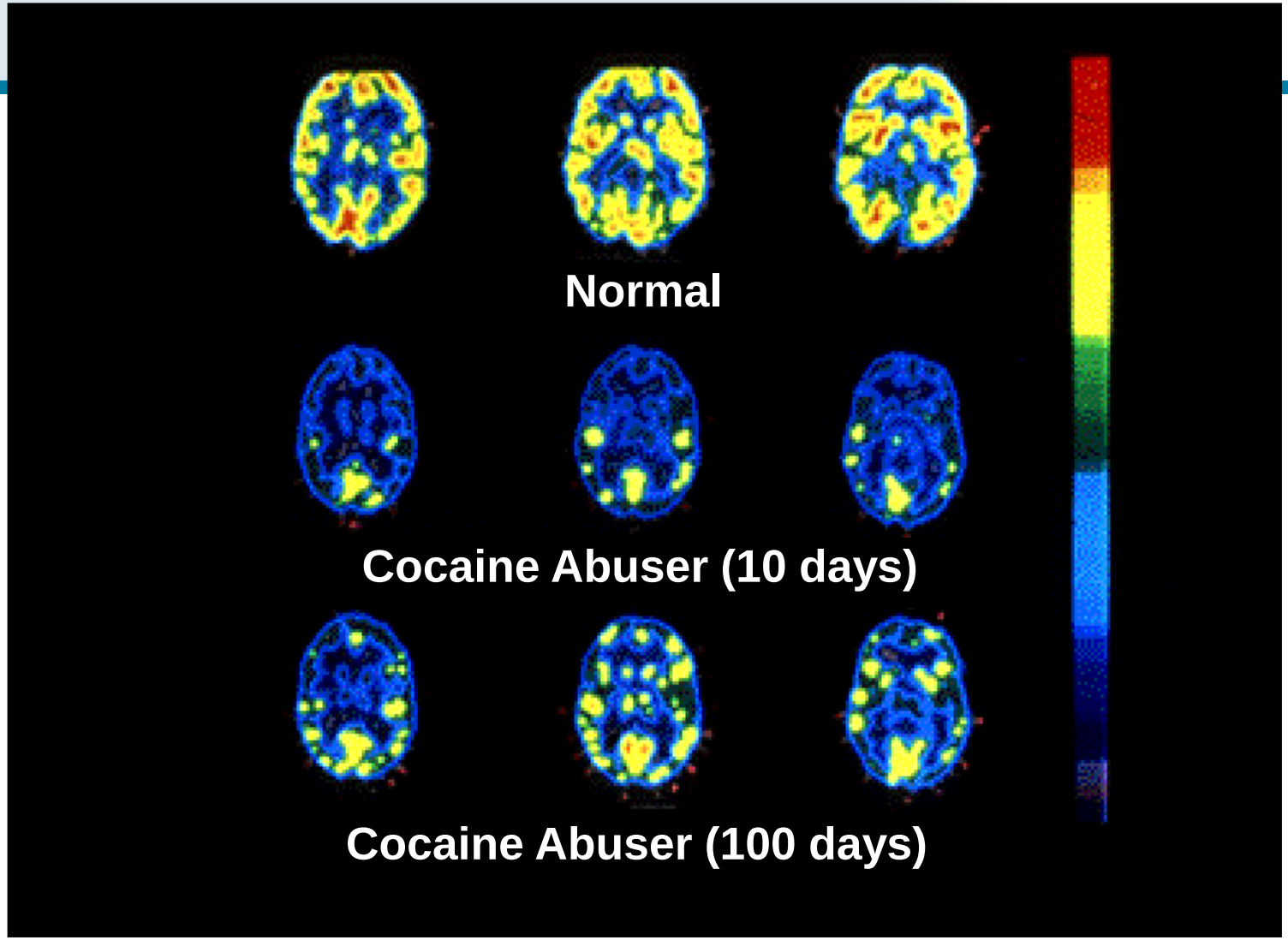


Photo courtesy of Nora Volkow, Ph.D. Volkow ND, Hitzemann R, Wang C-I, Fowler IS, Wolf AP, Dewey SL. Long-term frontal brain metabolic changes in cocaine abusers. *Synapse* 11:184-190, 1992; Volkow ND, Fowler JS, Wang G-J, Hitzemann R, Logan J, Schlyer D, Dewey 5, Wolf AP. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse* 14:169-177, 1993.

Drugs Have Long-term Consequences

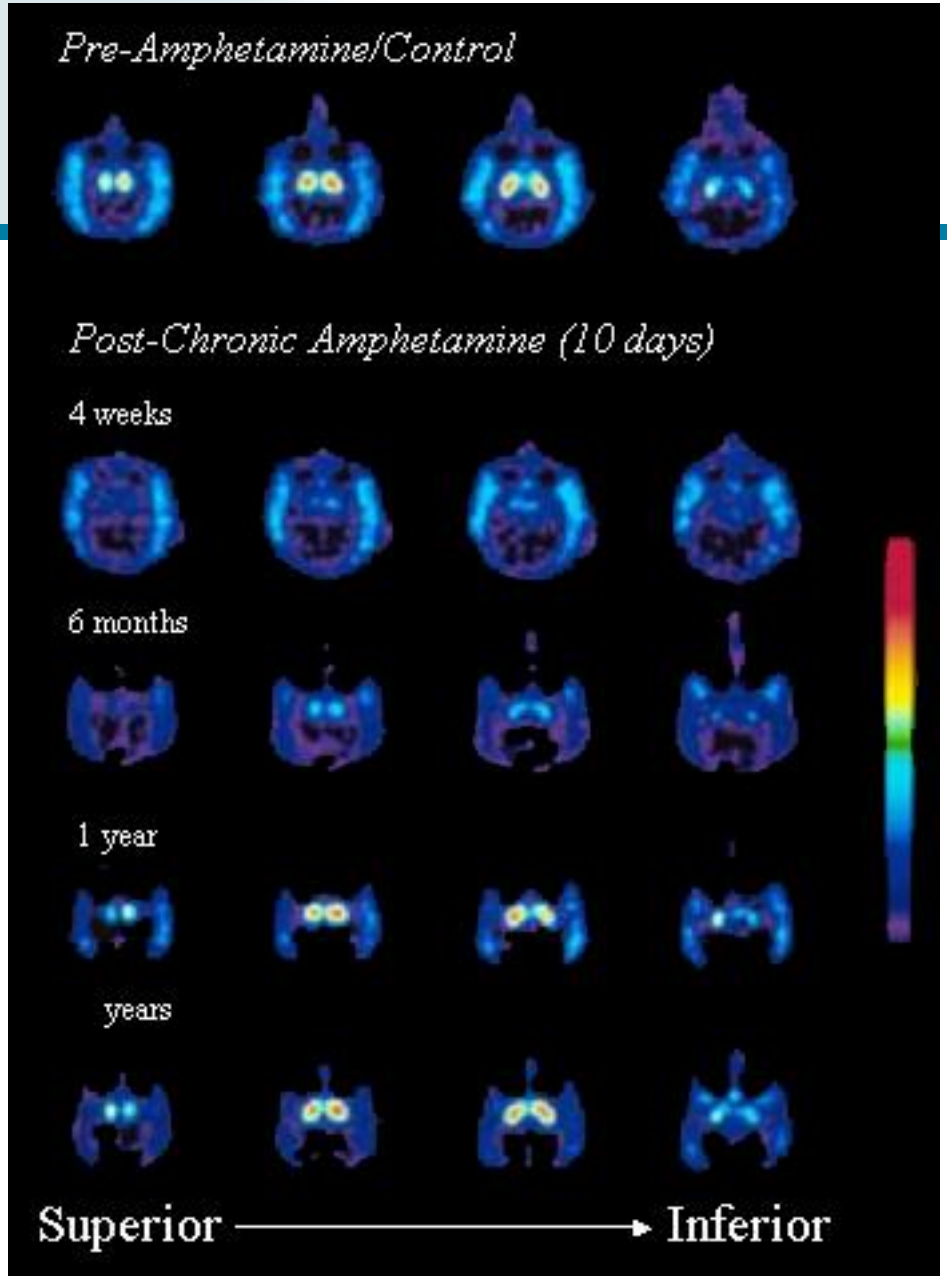


Photo courtesy of NIDA from research conducted by Melega WP, Raleigh MJ, Stout DB, Lacan C, Huang SC, Phelps ME.

NEUROBIOLOGY OF OPIOID WITHDRAWAL

- HYPERACTIVITY OF NOR-ADRENERGIC NEURONS IN THE LOCUS COERULEUS
  - INCEASE 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

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**

Questions?