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Neurobiology of Addiction

Learning Objectives

- **To be able to:**
- Identify the anatomical areas of the brain involved in the reward pathway
- Outline the neurotransmitter systems which activate the reward pathway
- Identify the anatomical areas and receptors involved in activation from psychoactive drugs
- Identify the anatomical areas and receptors involved in the withdrawal from psychoactive drugs
- Understand concepts relating to the development of addiction

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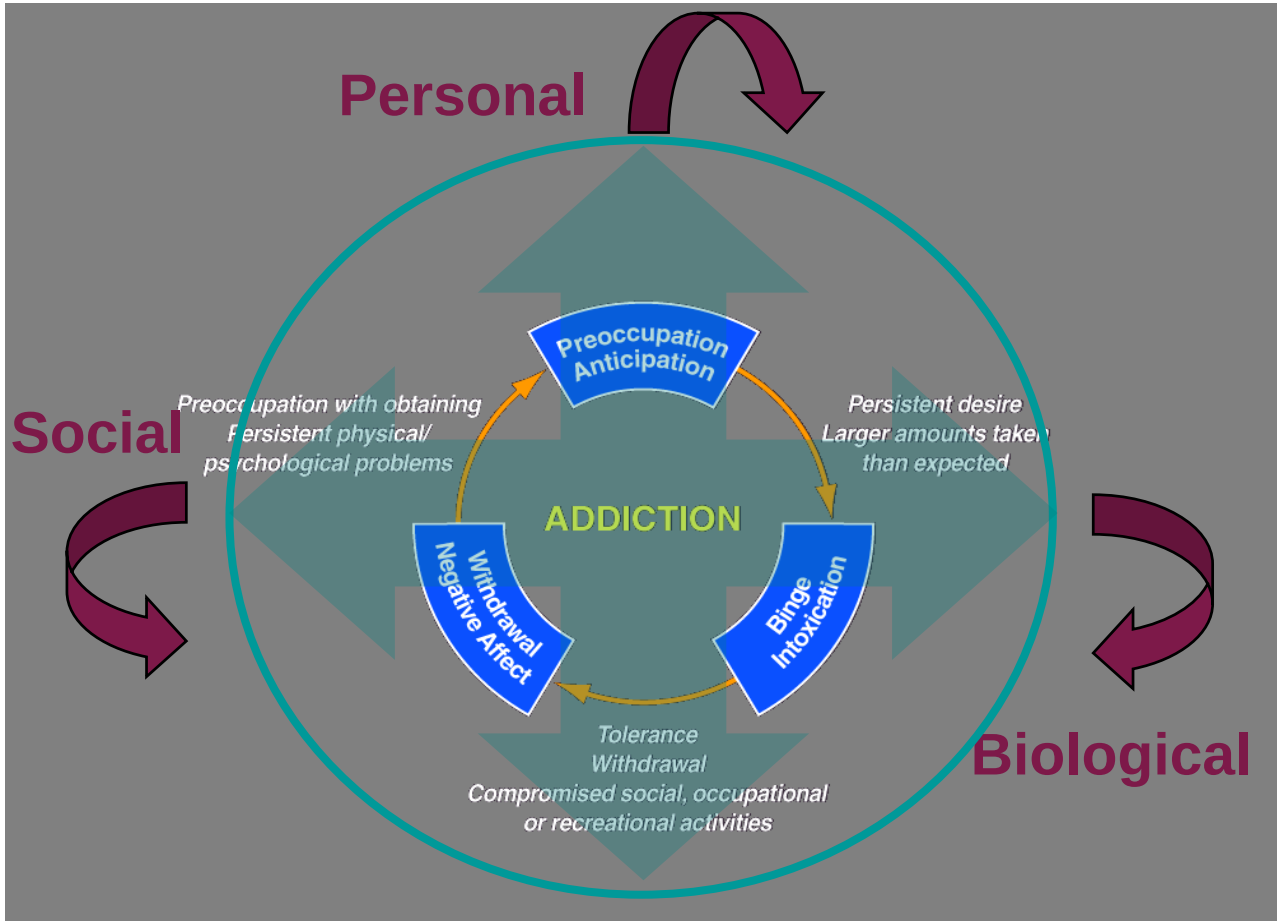
Addiction: General Concept



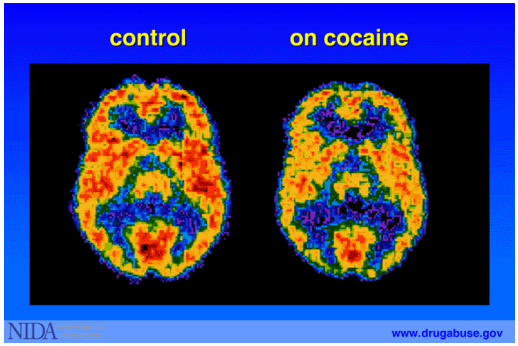
Koob & Moal (2006) Neurobiology of Addiction. Reprinted with permission

Addiction: Alcohol and Illicit Drugs

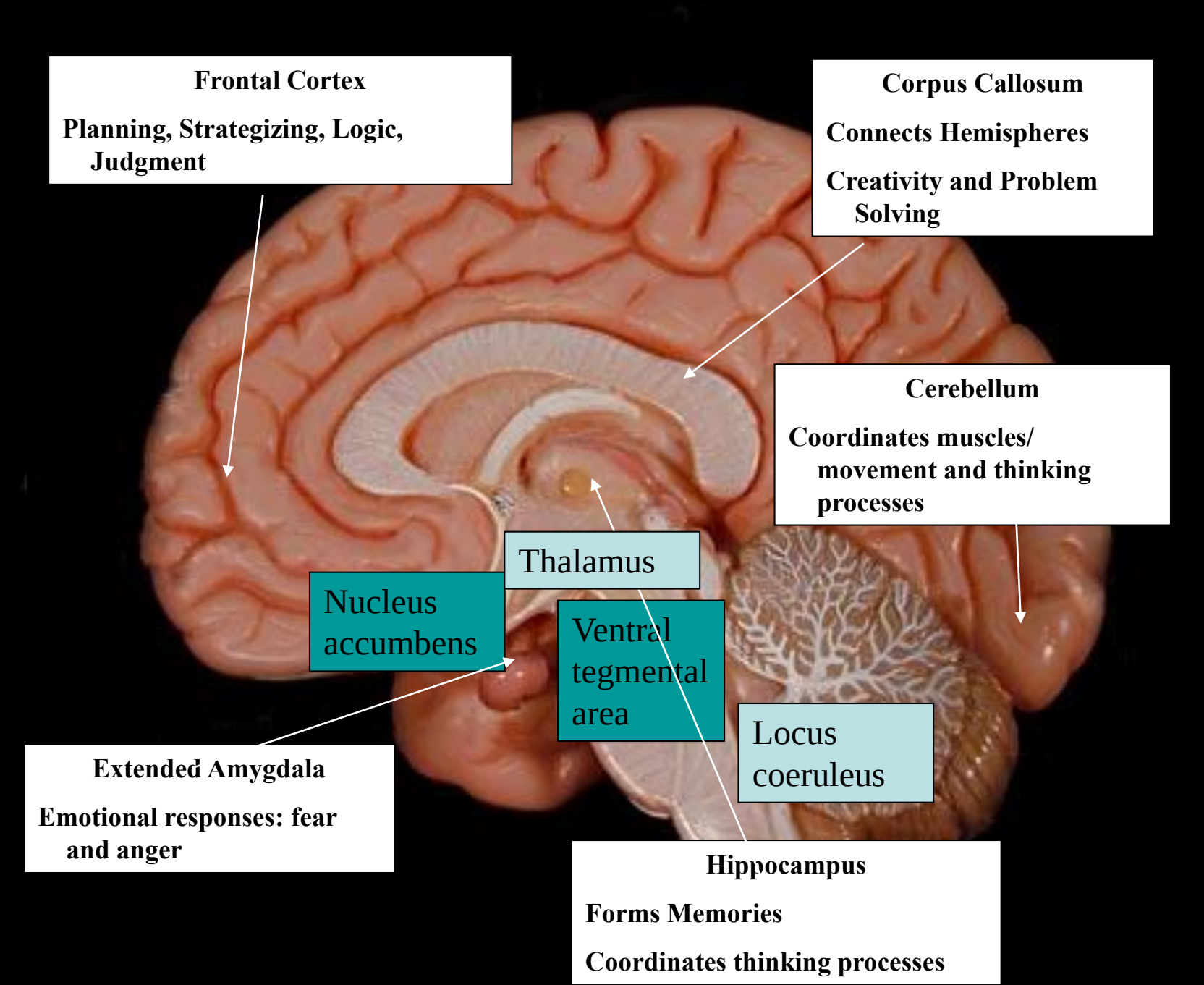
- Disease model: chronic, relapsing diseases of the brain
- ~ 6% meet the ICD-10 criteria for alcohol-use disorder
- ~ 2% meet the criteria for another ICD-10 drug disorder ***(1997 NSMHWB)***
- The risk of dependence is higher the earlier serious drinking begins
- Substantial co-morbidity with depression and anxiety disorders
- Incidence rate is higher in men than women

Neurobiology of Addiction: Intro

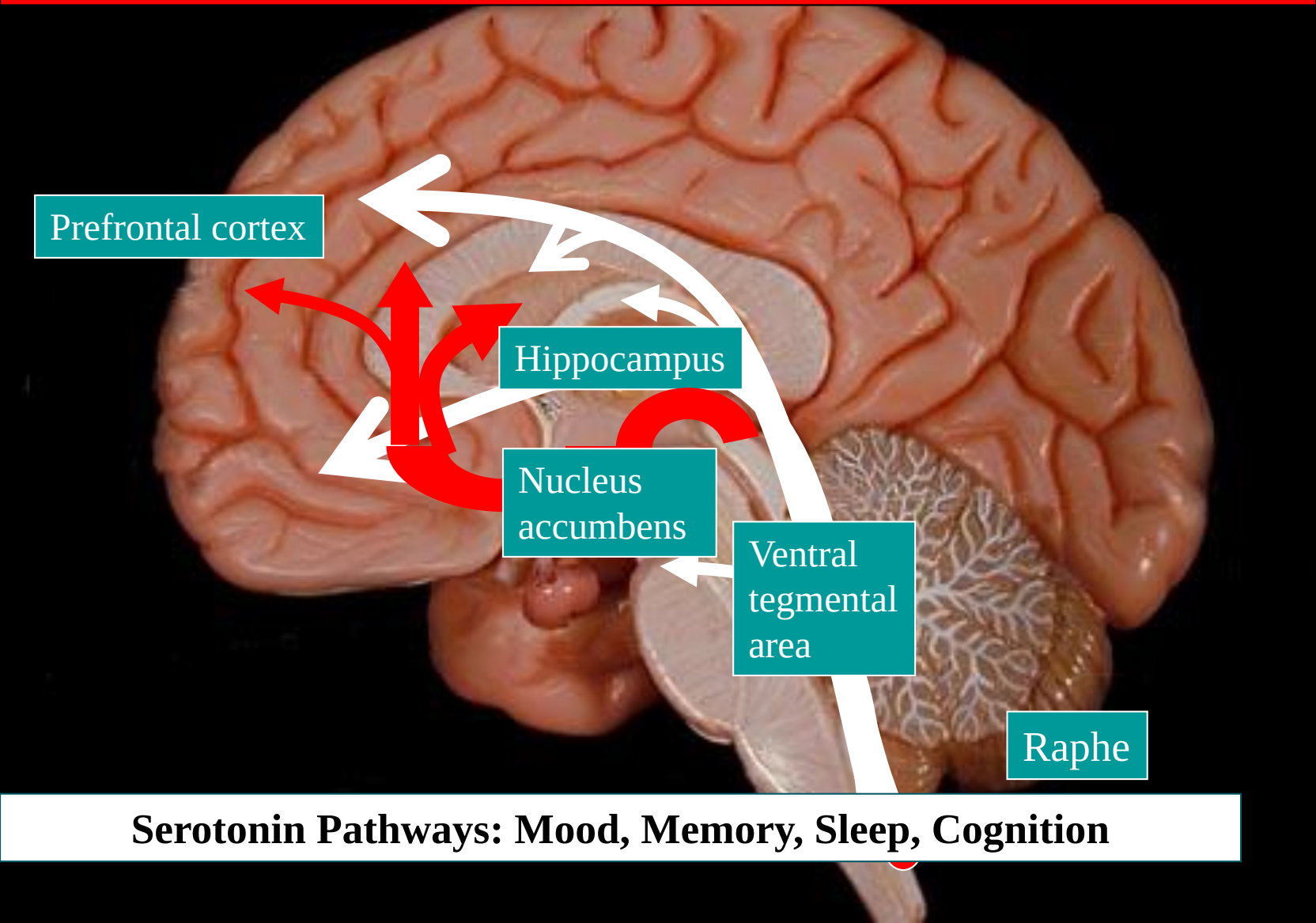
- Experimental research has provided a new understanding of addiction and its corresponding treatment
- Addictive drugs can be very damaging to personal, social and economic aspects of lives



- But have also provided an avenue for understanding brain function


Frontal Cortex
Planning, Strategizing, Logic, Judgment
Corpus Callosum
Connects Hemispheres
Creativity and Problem Solving
Cerebellum
Coordinates muscles/ movement and thinking processes
Thalamus
Nucleus accumbens
Ventral tegmental area
Locus coeruleus
Extended Amygdala
Emotional responses: fear and anger
Hippocampus
Forms Memories
Coordinates thinking processes

Dopamine Pathways: Reward, Pleasure, Euphoria, Motor Function, Decision making



Serotonin Pathways: Mood, Memory, Sleep, Cognition

Reward Pathway

- There is a axonal network in the brain labeled the ‘reward pathway’
- This reward pathway is activated by:
  - Food, water and sex, activities (such as sky diving, paragliding etc) and exercise

This reward pathway is also activated by drugs and alcohol

Reward Pathway

The following neurotransmitters act on the reward pathway:

Dopamine • Receptors: D1, D2 • Function: pleasure, euphoria, mood, motor function	**Serotonin** • Receptors: 5HT3 • Function: mood, impulsivity, anxiety, sleep, cognition
Cannabinoids • Receptors: CB1, CB2 • Function: Pain, appetite, memory	**Opioid peptides (Endorphins, Enkephalins)** • Receptors: Kappa, Mu, Delta • Function: pain

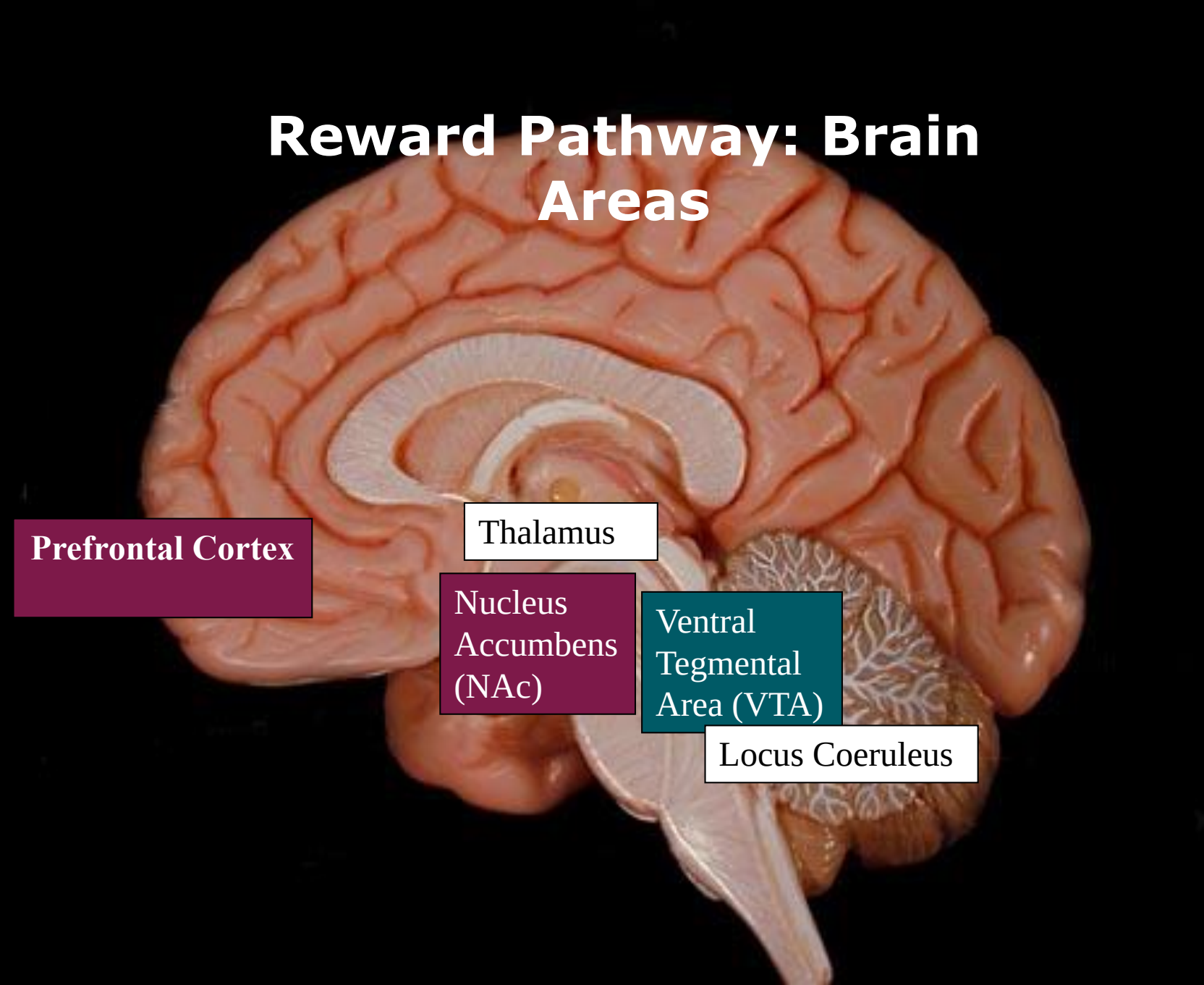
In all rewards, dopamine is the final activation chemical

Reward Pathway

Neurotransmitters and anatomical sites involved in the acute reinforcing effects of drugs of abuse

Dopamine Ventral tegmental area, nucleus accumbens	**Opioid Peptides** Nucleus accumbens, amygdala, ventral tegmental area
GABA Amygdala, bed nucleus of stria terminalis	**Glutamate** Nucleus accumbens

Reward Pathway: Brain Areas

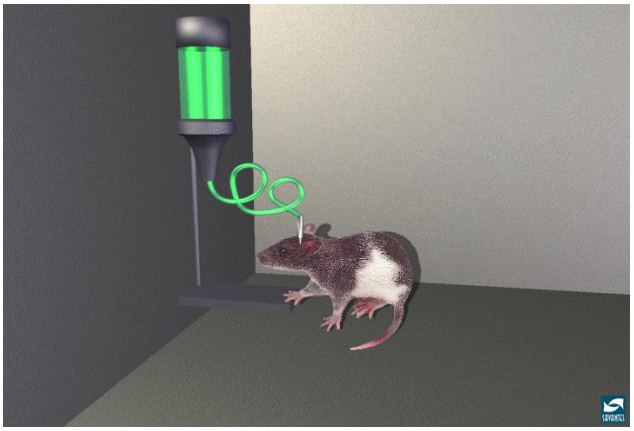


Reward Pathway: Experimental Research

- Self stimulation

Preclinical experiments have demonstrated that rats will bar press for stimulation of the VTA or NAc

Olds & Milner, 1954, J Comp Physiol Psychol, 47



Stimulation of Reward Pathway is Incredibly Powerful

Reward Pathway: Experimental Research

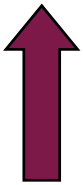
The potency of the stimulation will not fade and rodents will narrow their behavioural repertoire and ignore other priorities

- This behaviour can then be blocked
  - surgically by cutting the pathway from the VTA
  - chemically by administering dopamine antagonists

Reward Pathway: Experimental Research

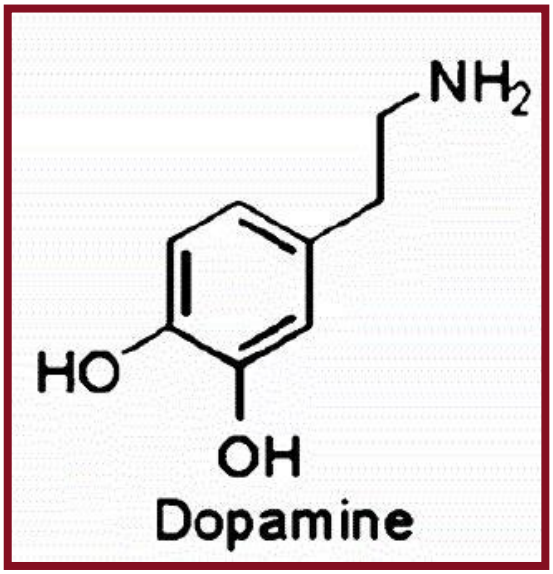
- Neuroimaging

Preclinical and clinical studies employing PET Scans and SPECT scans



increases in glucose and metabolism in the VTA and frontal cortex following *conditioned* stimuli (drug paraphernalia)

Reward Pathway: Dopaminergic Involvement



- Dopamine is released in the NAc following electrical stimulation
- Dopamine antagonists will block self-stimulation
- Dopamine agonists will be injected into the NAc by rodents (self-administration)
- Dopamine is released in the NAc following natural rewards

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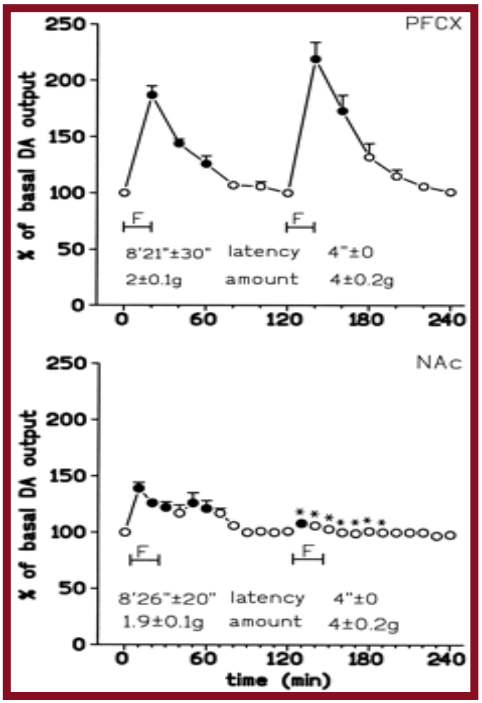
Natural Rewards: Dopaminergic Involvement



FOOD

Bassareo & Di Chiara, 1997,
Journal of Neuroscience 17(2):851-61.
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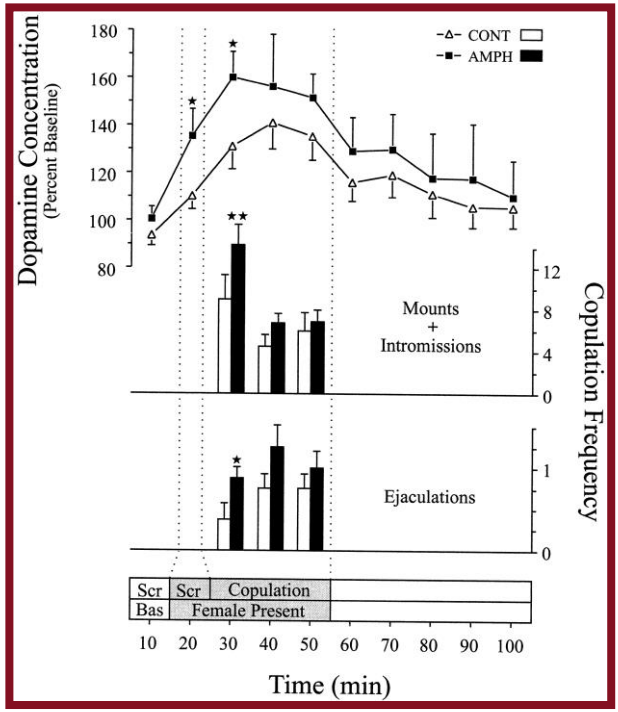

SEX

Fiorino & Phillips, 1999,
Journal of Neuroscience, 19 (1):456-63.
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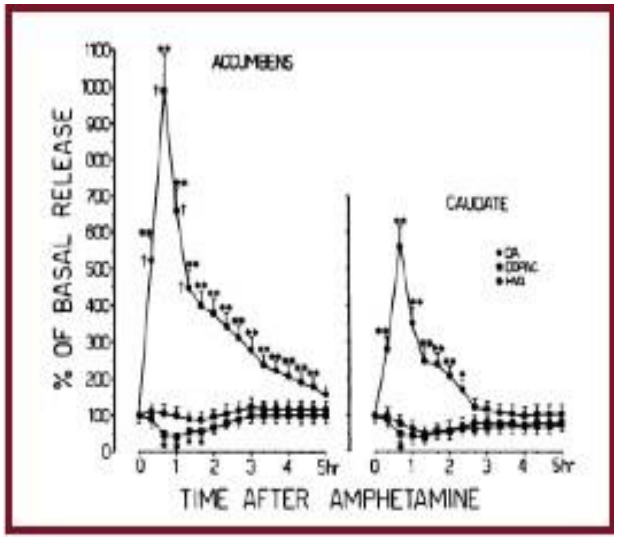
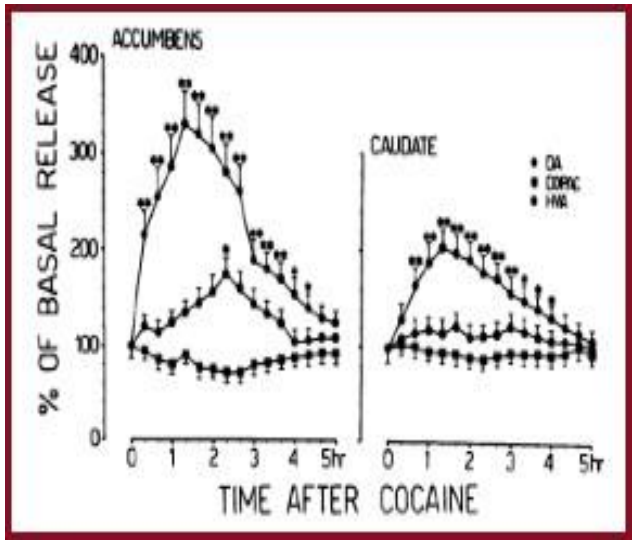
Drugs of Abuse: Dopaminergic Involvement

Self-administration: rodents bar press for amphetamine, cocaine, ethanol, nicotine



AMPHETAMINE



COCAINE

Di Chiara & Imperato, 1988, PNAS, 85 (14): 5274-8.
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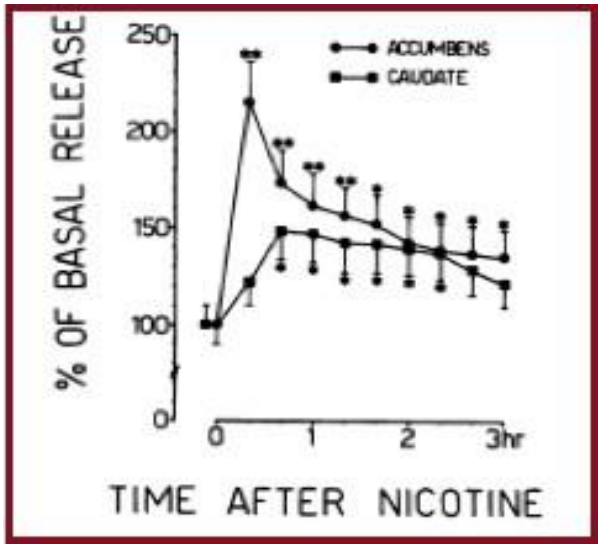
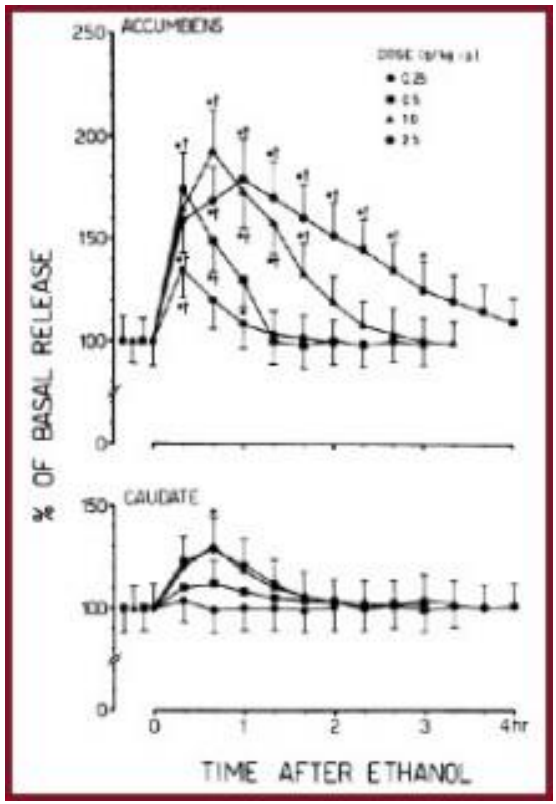
Drugs of Abuse: Dopaminergic Involvement



NICOTINE



ETHANOL

Di Chiara & Imperato, 1988, PNAS, 85 (14): 5274-8.
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Drug Action: Direct

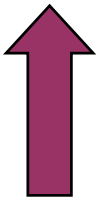
- Drugs of abuse may work via direct action on a receptor
- The magnitude of the effect will primarily depend upon the number of existing receptors

e.g. Dopamine agonists will bind directly to the dopamine receptors

Drug Action: Direct

e.g. Cocaine

- The mechanism of action for cocaine is via reuptake inhibition of dopamine
- Dopamine release is promoted via the protein responsible for the reuptake of dopamine (dopamine transporter; DAT)

Cocaine binds DAT =  *extracellular dopamine*

Drug Action: Cocaine

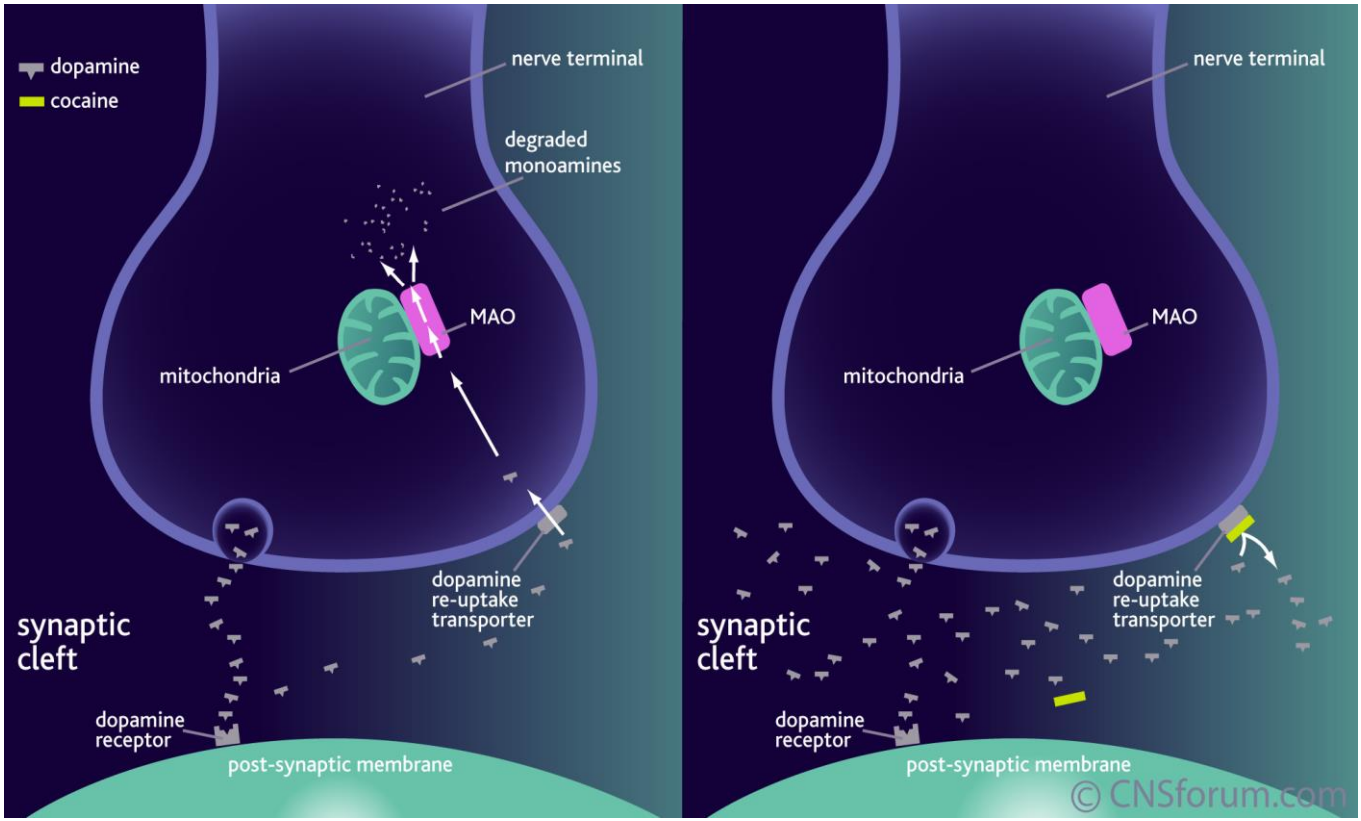


Image reproduced with permission from CNS Forum: www.cnsforum.com

Drug Action: Indirect

- Drugs of abuse may modulate dopamine via other receptor system and neurotransmitters that then modulate a different system

Downstream effects on dopamine from above systems

e.g. Alcohol

- Binds to subreceptors $GABA_A$: Dopaminergic activity is eventually increased in the VTA by inhibiting GABAergic interneurons
- Also binds to NMDA, endorphins, activates secondary messages and has direct serotonergic effects

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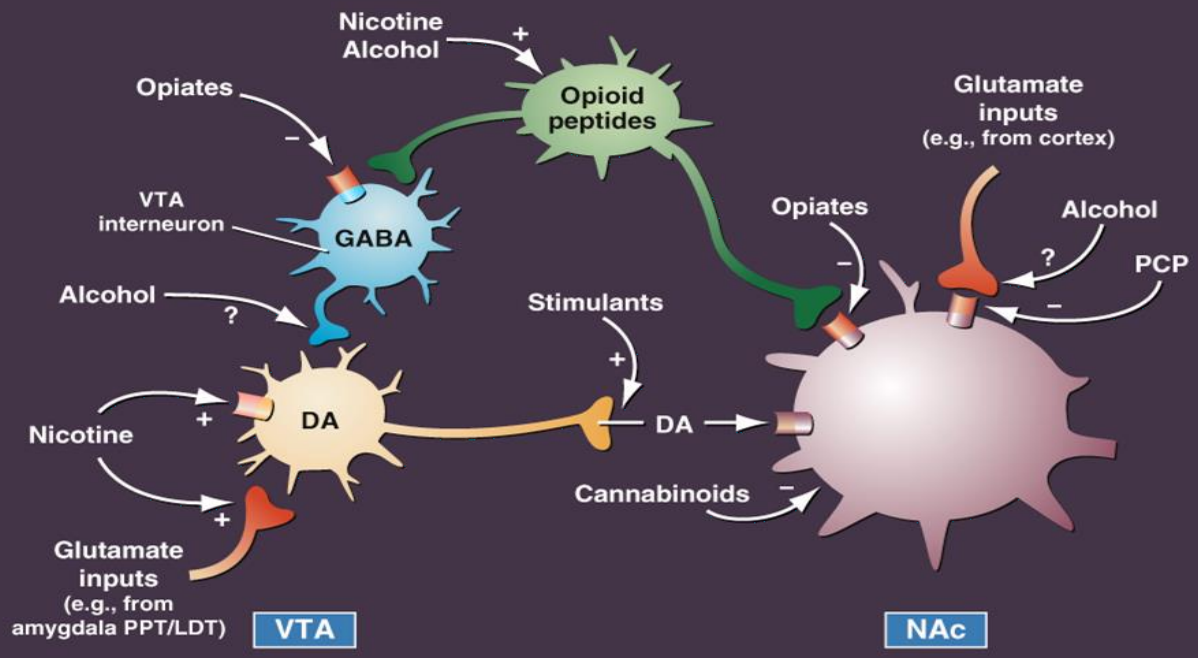
Drug Action & Reward Pathway

Converging actions of drugs of abuse on the ventral tegmental area (VTA) and the nucleus accumbens (NAc)



Reprinted with permission from Macmillan Publishers Ltd.; Nature Neuroscience, Nestler, 2005, Natl Neurosci, 8; http://www.nature.com/neuro/index.html

Drug Action & Reward Pathway

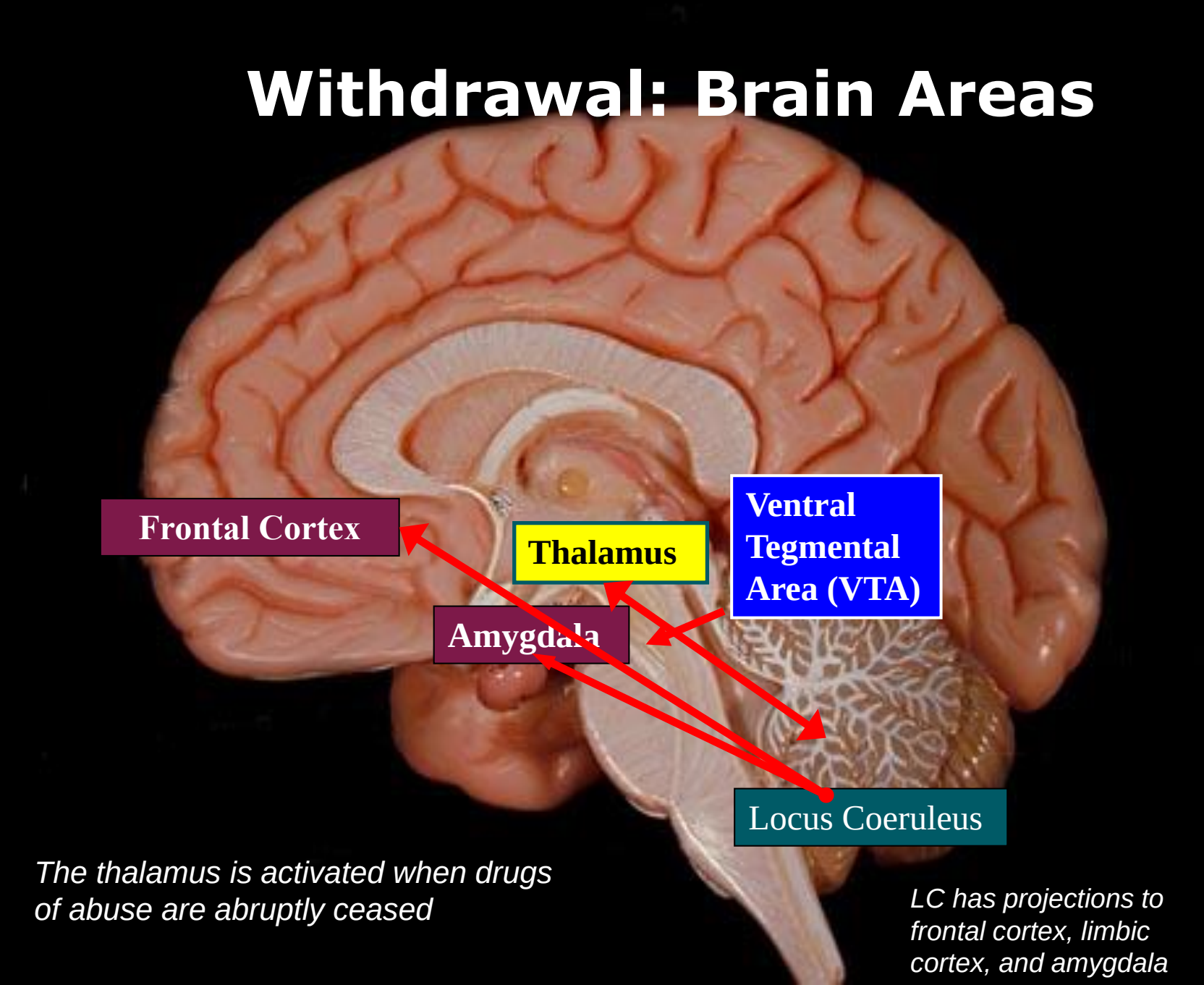
In summary:

Alcohol •Inhibit GABAergic neurons that project to dopaminergic neurons in the VTA	**Heroin** •Binds to opioid receptors that inhibit GABAergic neurons that project to dopaminergic neurons in the VTA
Cocaine •Blocks the function of DAT (by binding to the DAT and slowing transport)	**Nicotine** •Activates cholinergic neurons that project to dopaminergic neurons of the VTA

Withdrawal

- Following a physiological adaptation to the presence of an agent (e.g. drug of abuse), tolerance occurs
- Withdrawal is the result of an abrupt cessation of the drug
- This syndrome involves:
  - disturbance of the autonomic nervous system
  - activation of the thalamus
  - release of corticotrophin releasing factor (CRF)
  - activation of the locus coeruleus (LC)

Withdrawal: Brain Areas



The thalamus is activated when drugs of abuse are abruptly ceased

LC has projections to frontal cortex, limbic cortex, and amygdala

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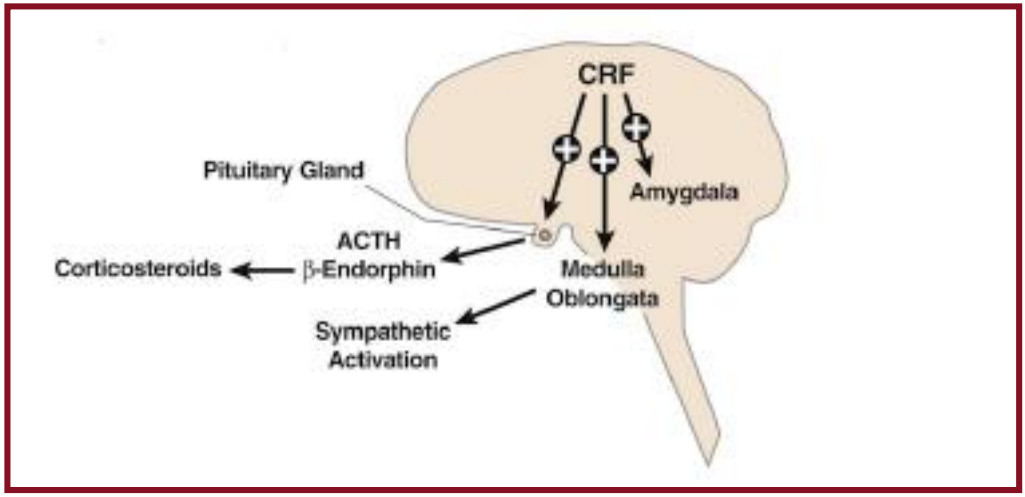
Withdrawal: Corticotrophin Releasing Factor (CRF) Involvement

The CRF system mediates the affective and somatic symptoms of drug withdrawal



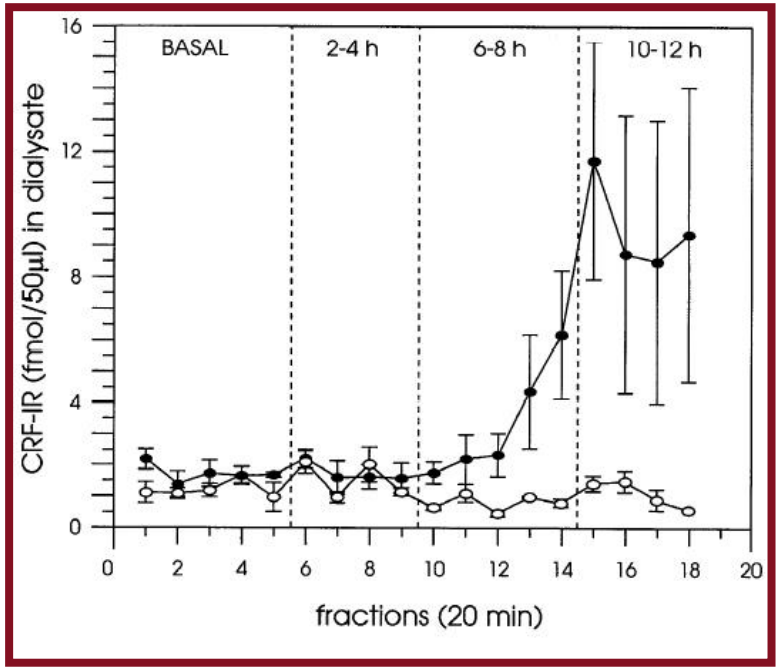
Koob, 2008, PNAS 105(26), 8809-10, Copyright 2008, National Academy of Sciences, U.S.A.

↑ Heart rate
Blood pressure
Blood glucose

↑ Response to stressors

Withdrawal: CRF Involvement

Extracellular CRF levels in the amygdala during withdrawal from ethanol



EtOH DEPENDENT

CONTROL

Pich et al, 1995, Journal of Neuroscience, 15(8):5439-5447
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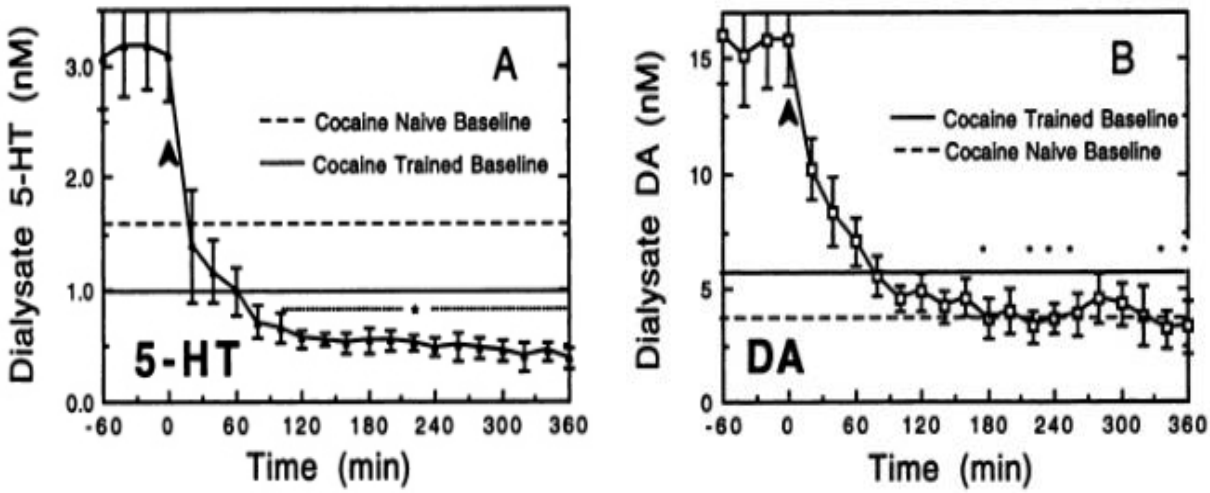
Withdrawal: DA & 5-HT Involvement

Extracellular DA and 5-HT in the Nucleus Accumbens During Cocaine Self-Administration and Withdrawal



Parsons et al (1995) J Pharmacol Exp Ther, 274.
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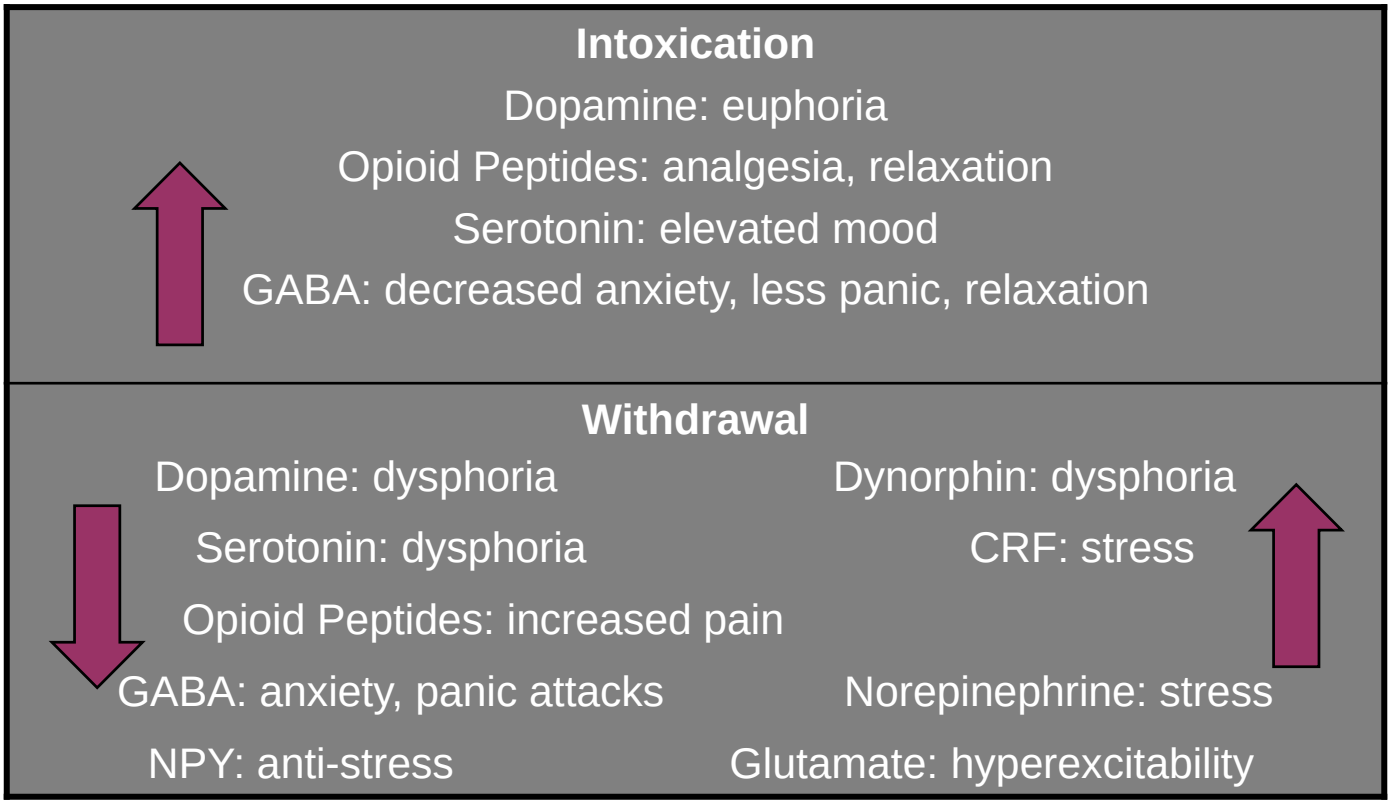
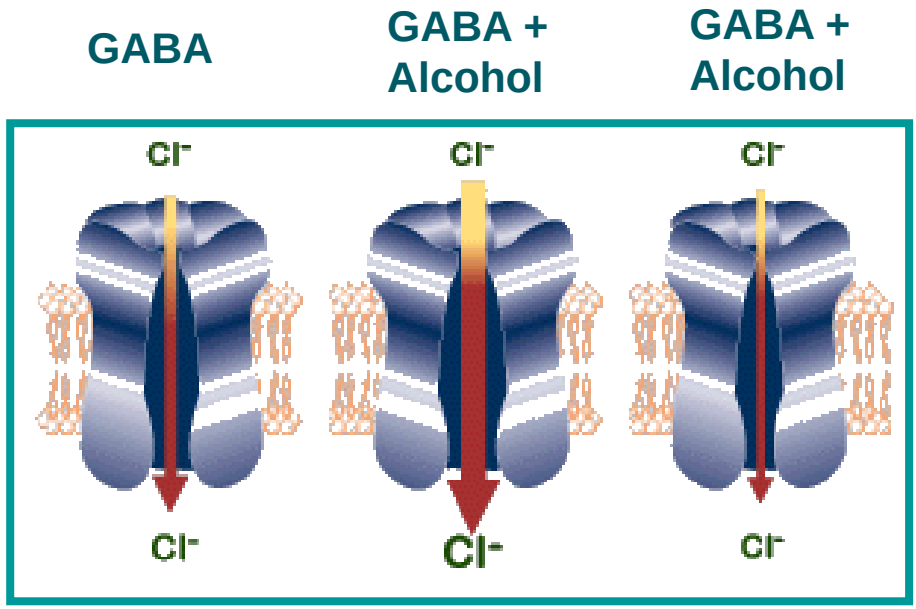
Intoxication & Withdrawal: Neurotransmitter Involvement



Patient feels dysphoric, irritable, depressed and angry

Withdrawal: Molecular Mechanisms

e.g. *Alcohol:* Representation of GABA receptor sensitivity



No Alcohol | Acute Intoxication | Chronic Intoxication

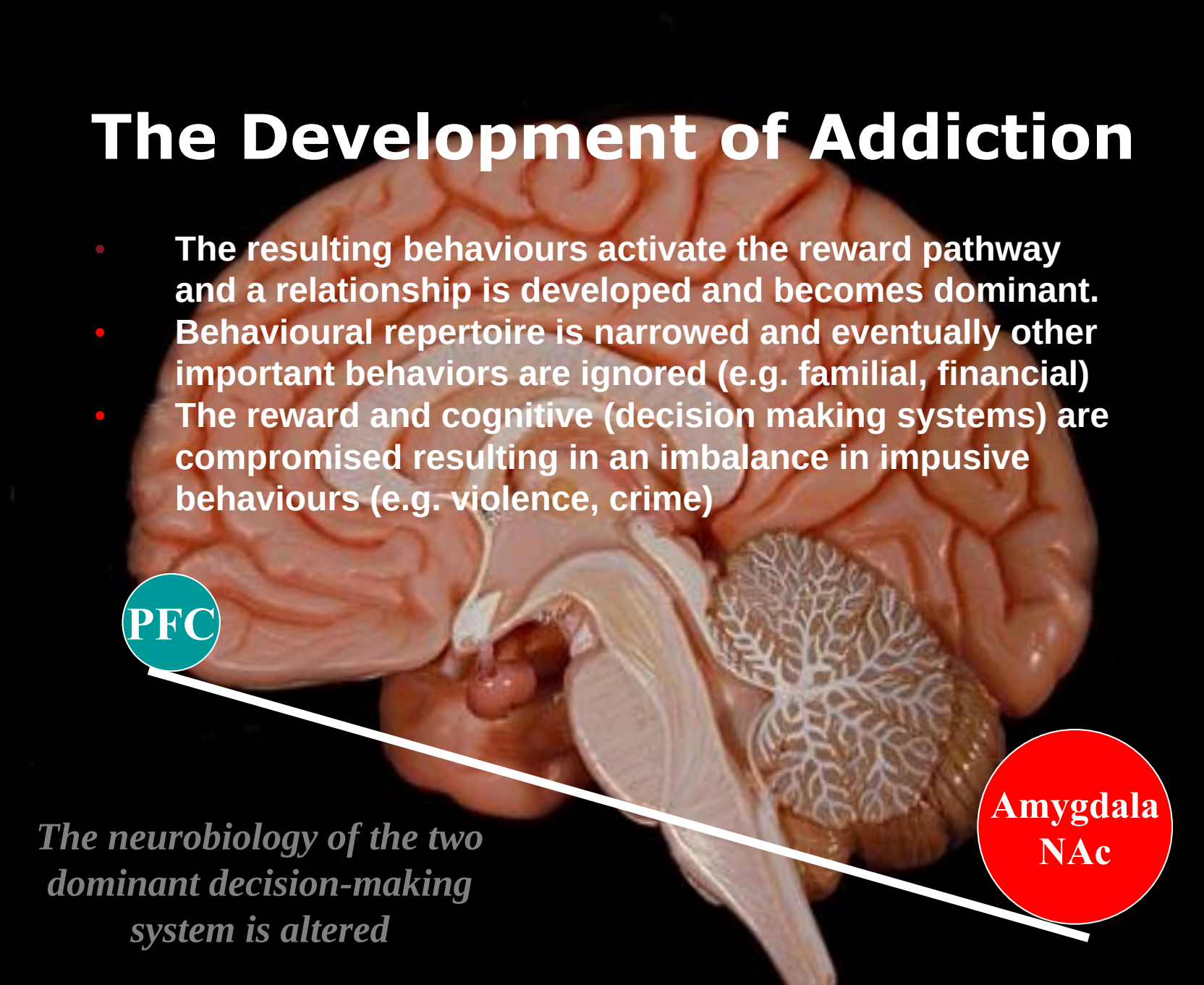
Adapted from Koob & Moal, 2006, reprinted with permission

The Development of Addiction

- The use of the drug of abuse is increased to maintain euphoria or to avoid dysphoria or withdrawal
- The number of receptors gradually increases to counter for the continual presence of the drug of abuse
- The amount of neurotransmitter gradually decreases through *depletion* and *feedback inhibition*
- The reinforcing properties of the drug are thus gradually decreased (tolerance)
- The need for drug to maintain this new homeostasis is therefore increased (dependence begins)

The Development of Addiction

- The resulting behaviours activate the reward pathway and a relationship is developed and becomes dominant.
- Behavioural repertoire is narrowed and eventually other important behaviors are ignored (e.g. familial, financial)
- The reward and cognitive (decision making systems) are compromised resulting in an imbalance in impusive behaviours (e.g. violence, crime)



The neurobiology of the two dominant decision-making system is altered

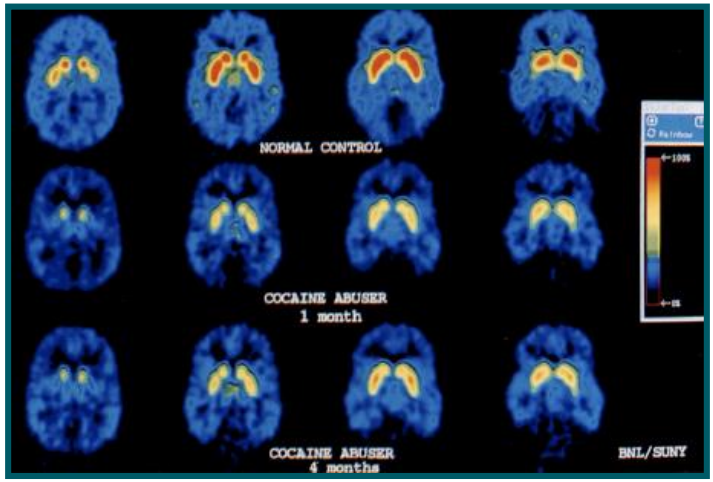
The Development of Addiction: Long Term Changes

There is evidence of prolonged drug abuse resulting in both structural and functional brain changes

Decreases in CREB transcription factor in NAc (and extended amygdala)

Decreases in metabolism in Orbito Frontal Cortex (OFC)

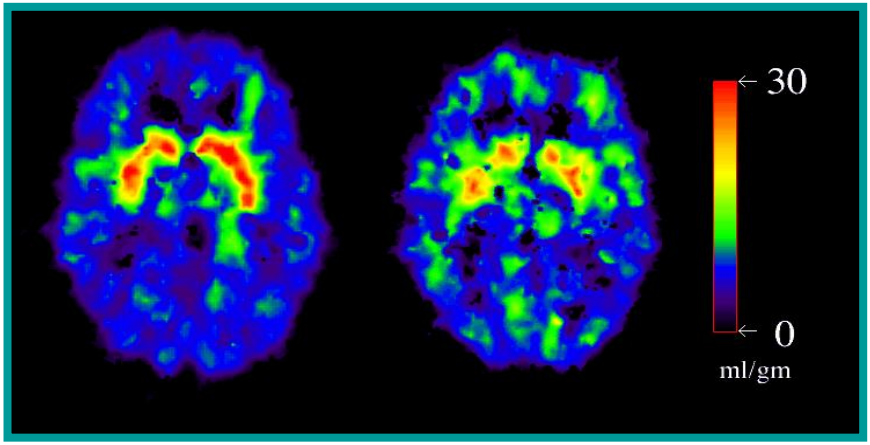
Decreases in dopamine D2 receptor binding (see figure below)



Volkow et al. Synapse 14 (2), 1993, pp. 169-177. © 1993 Synapse. Reprinted with permission of John Wiley & Sons, Inc.

The Development of Addiction: Long Term Changes

Dopamine transporter (DAT) binding following heavy methamphetamine (METH) use



Control METH user

Volkow et al. Am. J. Psychiatry 158(3), pp. 377-382, 2001
Reprinted with permission from the American Journal of Psychiatry (Copyright 2001). American Psychiatric Association.

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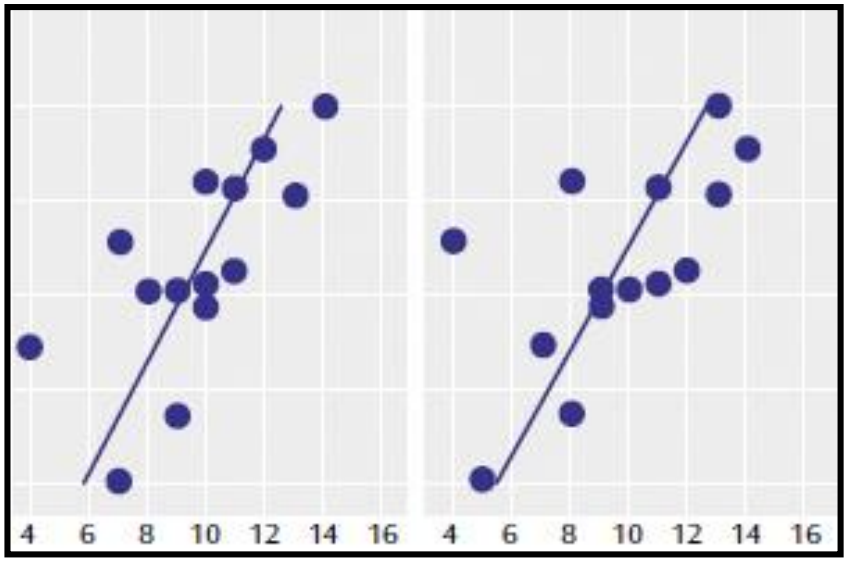
The Development of Addiction: Long Term Changes

Dependence of verbal memory on DAT

Striatal DAT Availability



Interference Recall Delayed Recall

Number of Words

Volkow et al. Am. J. Psychiatry 158(3), pp. 377-382, 2001
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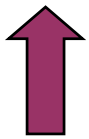
The Development of Addiction: Genetics

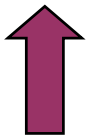
Inheritability has been found to range from 40-60%

Some variability between: gender and substances

Specifically:



4-fold increased risk in 1st degree relatives



4-fold increased risk also in adopted away children

The Development of Addiction: Genetics

Polymorphism is an altered base pair sequence
(altered mRNA = altered protein = altered function)

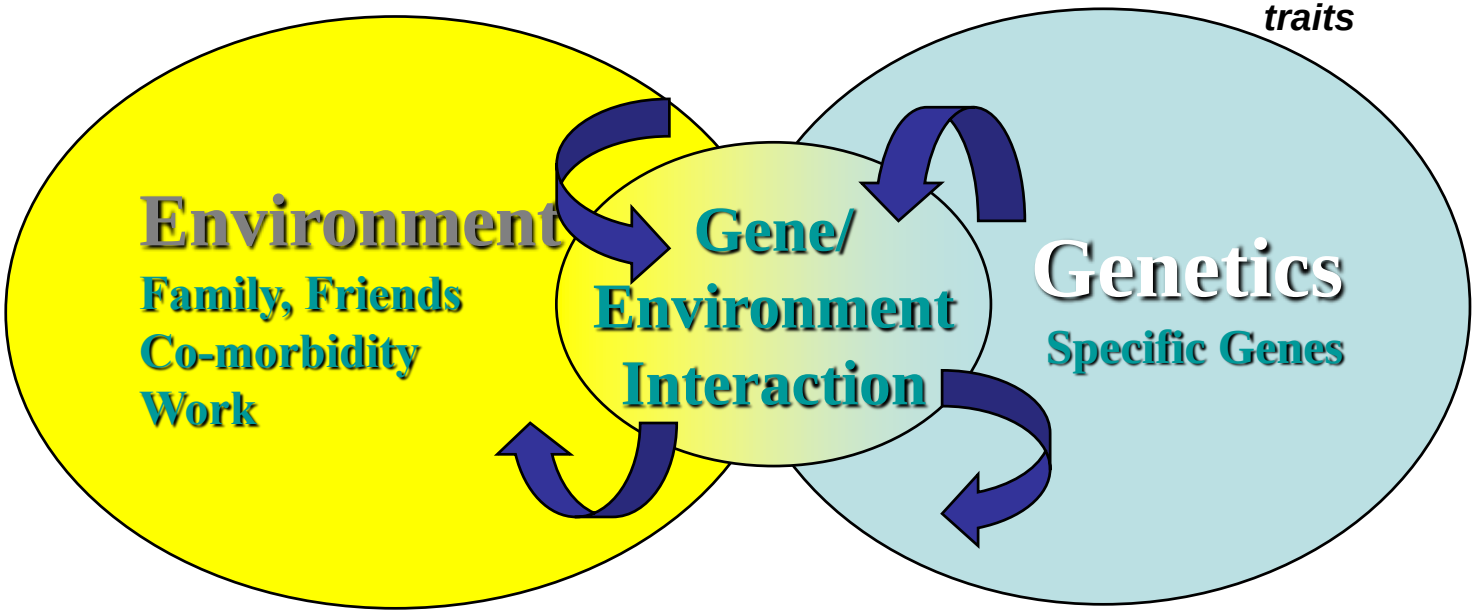
Polymorphisms may
- alter synthesis of dopamine
- alter neurotransmitter release

which may diminish function of prefrontal cortex and exaggerate amygdala

Functional consequences relating to addiction include altered: initial response to intoxication, tolerance development, withdrawal effects, psychiatric comorbidity

The Development of Addiction: Genetics

However, behaviors are complex genetic traits

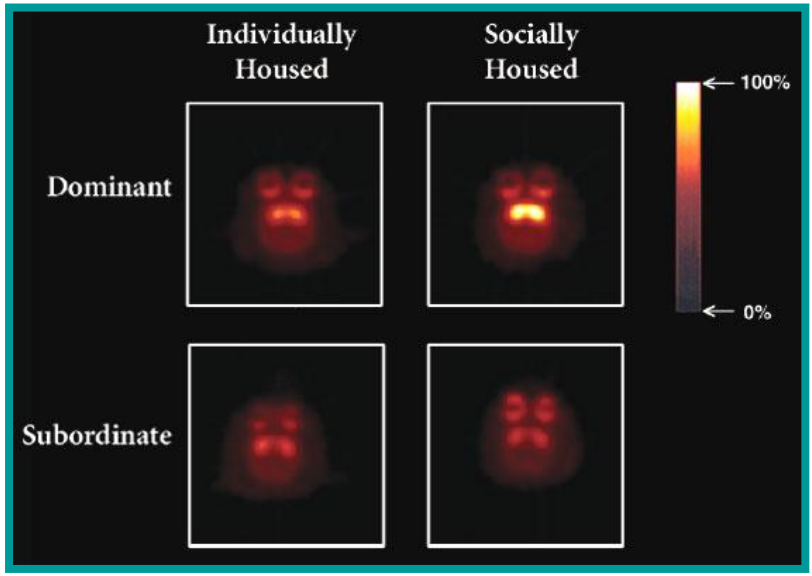


Genetics May Influence How Neurobiology Interacts With Environment

The Development of Addiction: Experimental Research

Social rank and vulnerability to drug use

Dominant monkeys socially housed revealed greater D2 receptor density



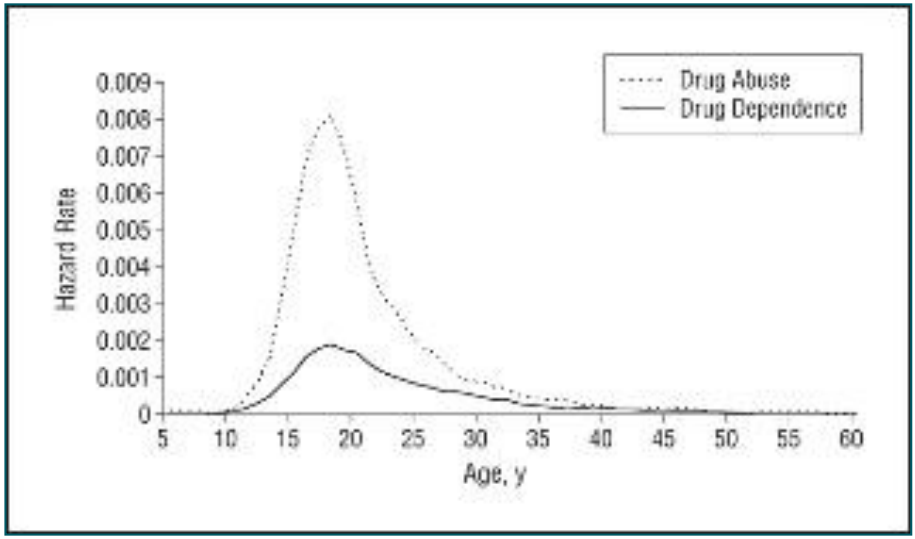
Subordinate animals more readily develop self-administration of cocaine

Reprinted by permission from Macmillan Publishers Ltd: Nature Neuroscience. Morgan et al. (2002) Nat Neurosci, 5 http://www.nature.com/neuro/index.html

Stress responses characterized during aggressive confrontation may have enduring neural and behavioral consequences.

The Development of Addiction: Adolescence

Drug and alcohol problems commence in adolescence



Compton et al, 2007, Arch Gen Psychiatry, 64.
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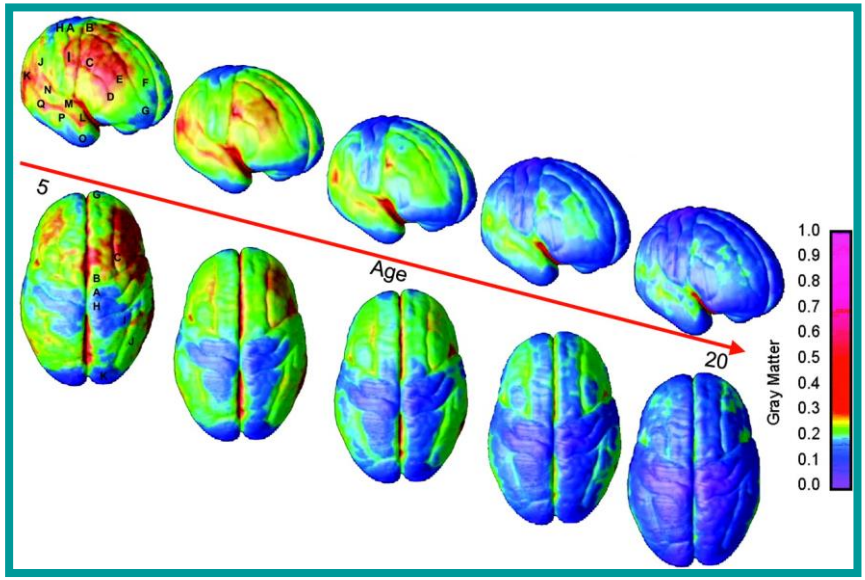
The Development of Addiction: Adolescence

Neuronal Development

- The back of brain matures first…
  - sensory and physical activities favoured over complex, cognitive-demanding activities
  - propensity toward risky, impulsive behaviors
    - group setting may promote risk taking
  - poor planning and judgment

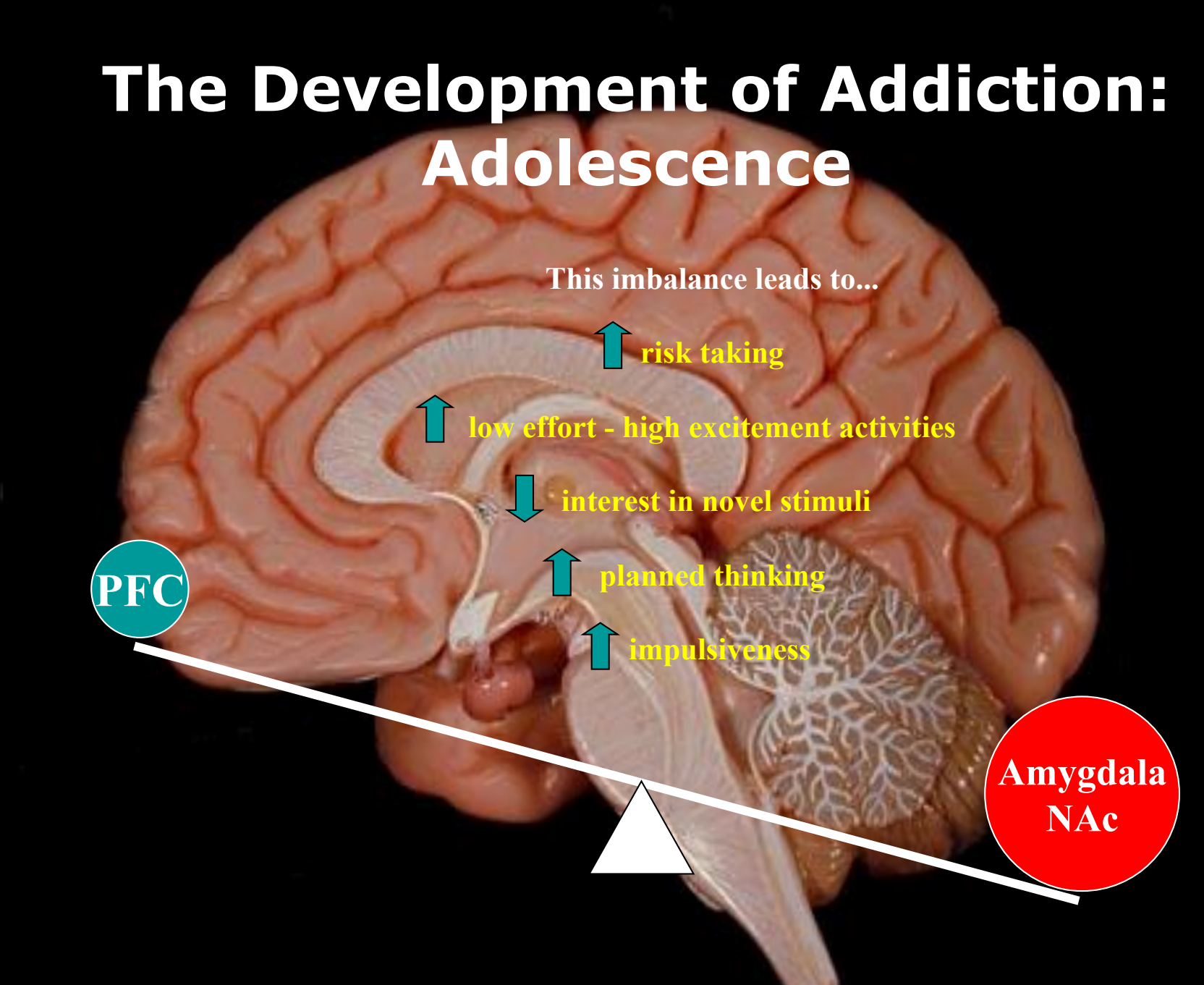
The Development of Addiction: Adolescence

Neuronal Development: Grey matter maturation moves from back to front

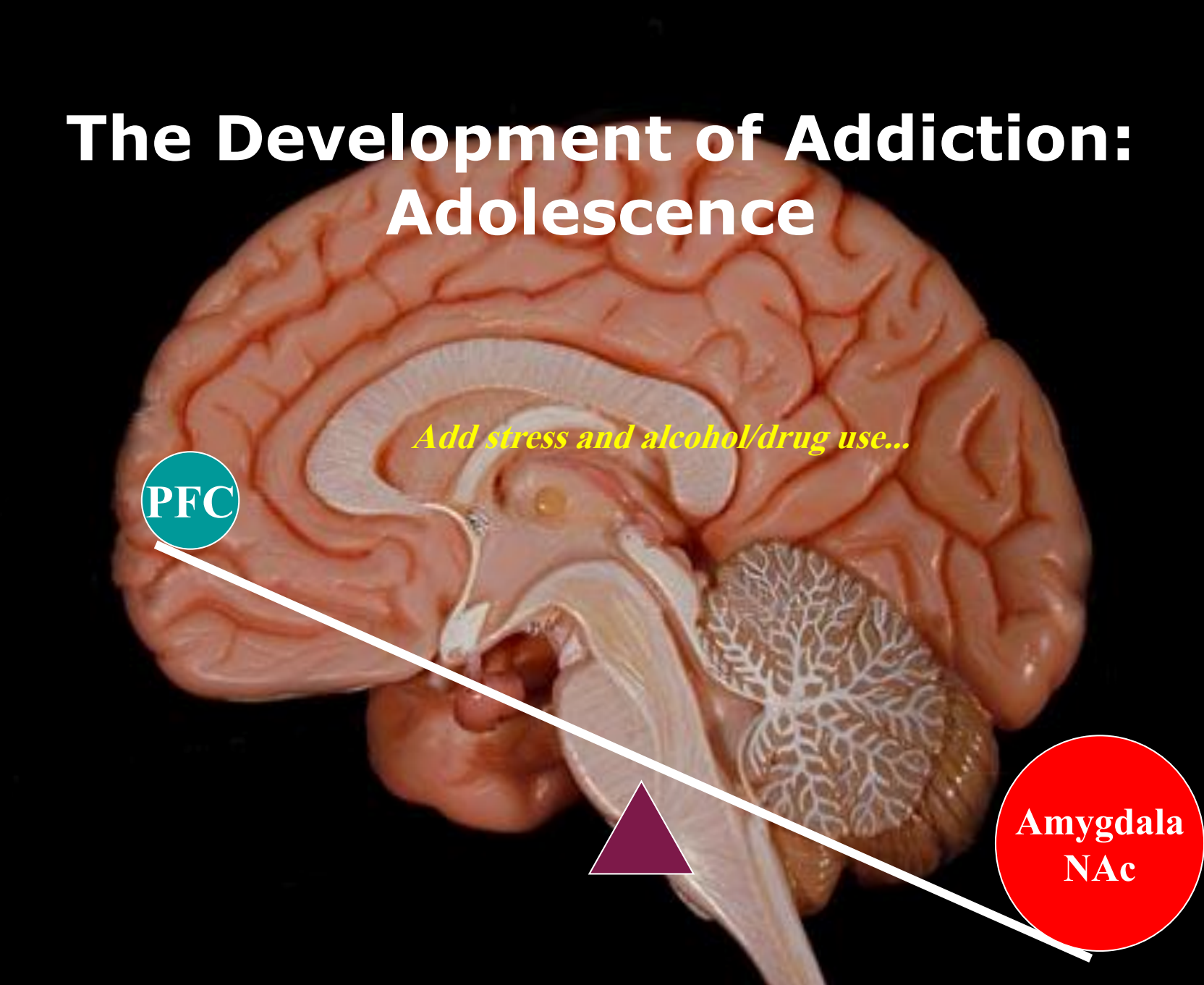


Gogtay et al (2004) PNAS, 101 (21). Copyright 2004, National Academy of Science, U.S.A.

The Development of Addiction: Adolescence



The Development of Addiction: Adolescence



Treatment of Addiction

These basic science discoveries have lead to the design of medications to treat addiction

Novel medications:

- Alcohol dependence:

  Naltrexone: blocks mu opioid receptor (reduces the rewarding effects of alcohol)

  Acamprosate: inhibits the release of glutamate thus decreasing excitation (withdrawal) that occurs during withdrawal

Treatment of Addiction

Novel medications continued:

- Heroin dependence:

Methadone, Buprenorphine: activate opioid receptors

- Tobacco dependence:

Nicotine gum/patch: activate nicotinic receptors

- Psychostimulant dependence:

Rimonabant: blocks cannabinoid receptors (CB1)

Addiction Is Multidimensional

- Addiction is influenced by many factors including biological (neurobiology), social (family, friends, work) and personal (psychological processes relating to addiction).

- Thus while the potential for addiction is related to neurobiology in some degree, situational (social circumstances) factors play a substantial role.

- Indeed, many people use alcohol and drugs and do not become addicted.

Neurobiology of Addiction: Brief Summary

- The classic anatomical areas of the brain involved in the reward pathway include the nucleus accumbens, ventral tegmental area and the prefrontal cortex
- Dopaminergic activity is the final chemical action in most behaviours relating to reward
- Drugs of abuse may work with receptors and transporters to directly or indirectly influence dopaminergic activity

Neurobiology of Addiction: Brief Summary Cont'd

- Withdrawal occurs following an abrupt cessation of drug of abuse following changes to the nervous system
- Addiction is the result of and results in lasting changes to neurocircuitry, cellular and molecular mechanisms

Case Study

- A 35 year old man comes into your practice. He states that he has been from drug-to-drug and asks you, “Dr, do I have a disease?”
- What do you tell the patient?
  - *Addiction is considered to be a brain disease in that drug exposure has likely induced some brain changes. Your brain is now in a state of “expectance” for various chemicals making it harder to say ‘no’ to drugs.*
  - *The pairing of pharmacotherapy and psychotherapy can help break this cycle by reducing withdrawal symptoms and implementing skills required for avoiding drugs.*
  - *Your ability to respond to treatment will depend on individual (such as motivation, genetics, age) and situational (work, support network) factors.*

The University of Sydney
Faculty of Medicine

NSW HEALTH

Author

Dr Kirsten Morley

Royal Prince Alfred Hospital &
University of Sydney