FACULTY OF MEDICINE

Neurobiology of Addiction

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Neuroadaptational View of Addiction: Behavioural Sensitization

- Definition: Repeated exposure to a substance results in progressive and enduring enhancement of the motor stimulant effect induced by that substance.

  Intermittent Exposure → Behavioural sensitization

  Continuous Exposure → Tolerance

- Use results in a shift in incentive salience state depending on how well a drug induces behavioural sensitization.

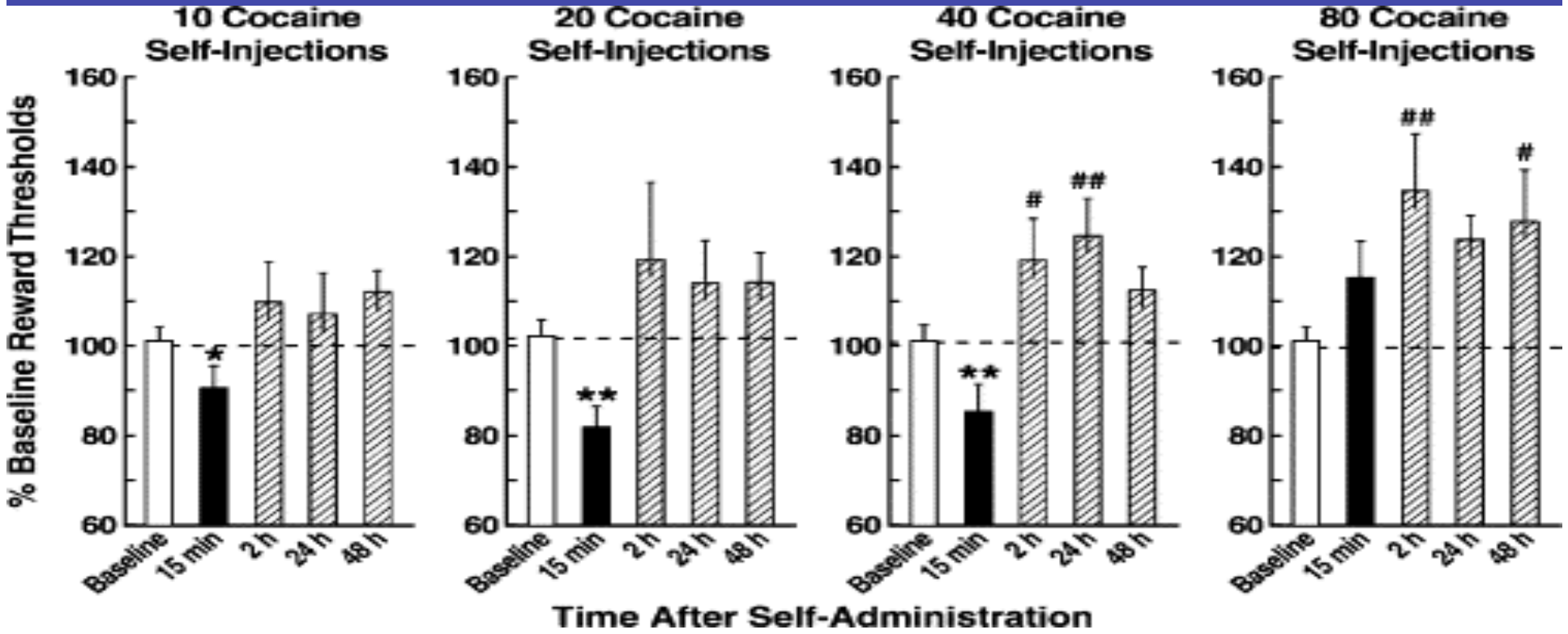
  Shift from drug ***Liking*** → Drug ***Wanting*** (or ***Craving***)

- Associative learning links enhanced incentive value to substance-related visuospatial and emotional stimuli

Koob GF, Le Moal M. Neurobiology of Addiction 2006

Neuroadaptational View of Addiction: Homeostatic Changes

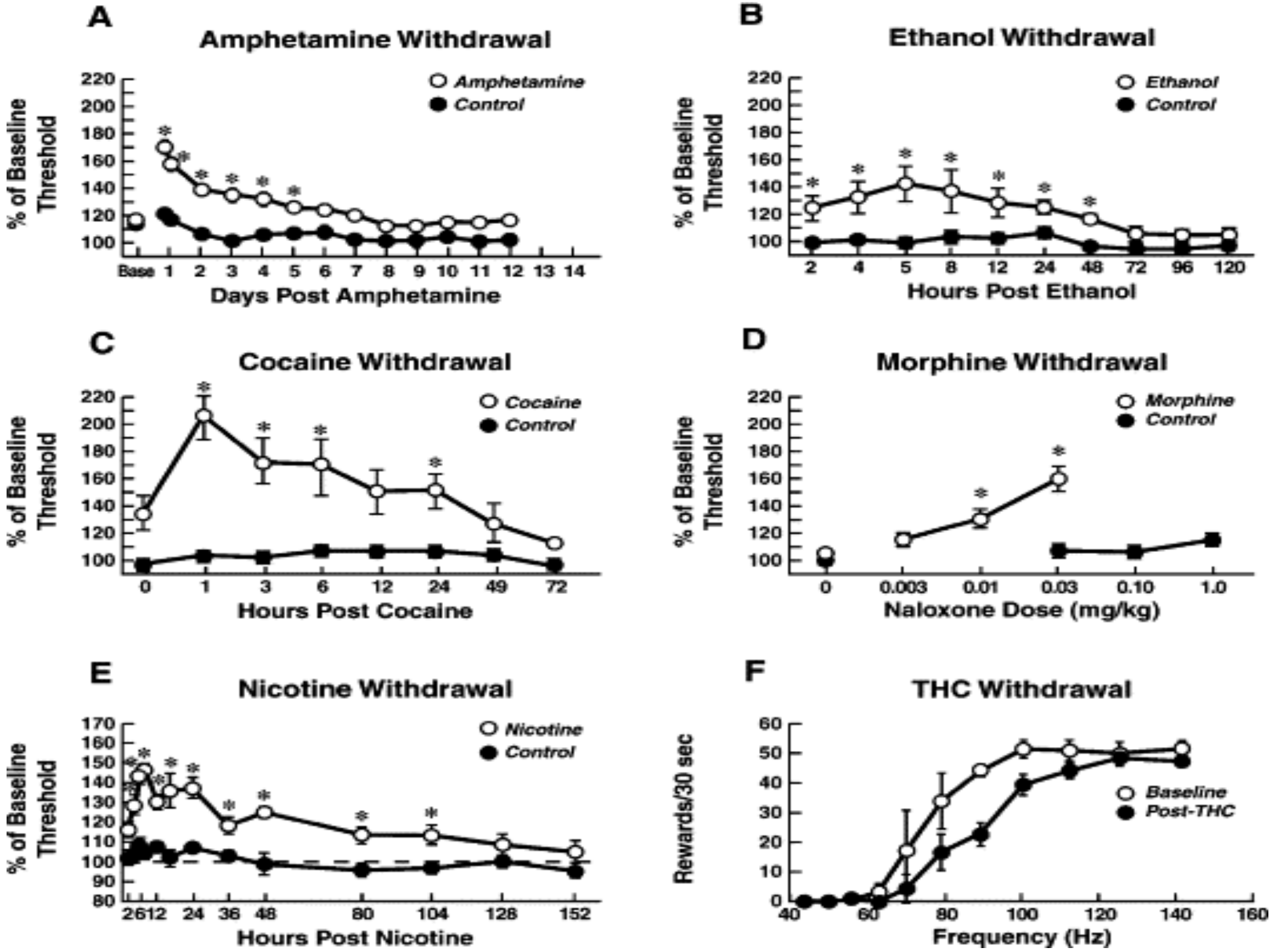
- Counteradaptive hypothesis: Initial acute effects of the substance are counteracted by homeostatic changes mediating primary drug effect.
- Reward thresholds elevate at a rate dependent on the substance's ability to produce a reward response.

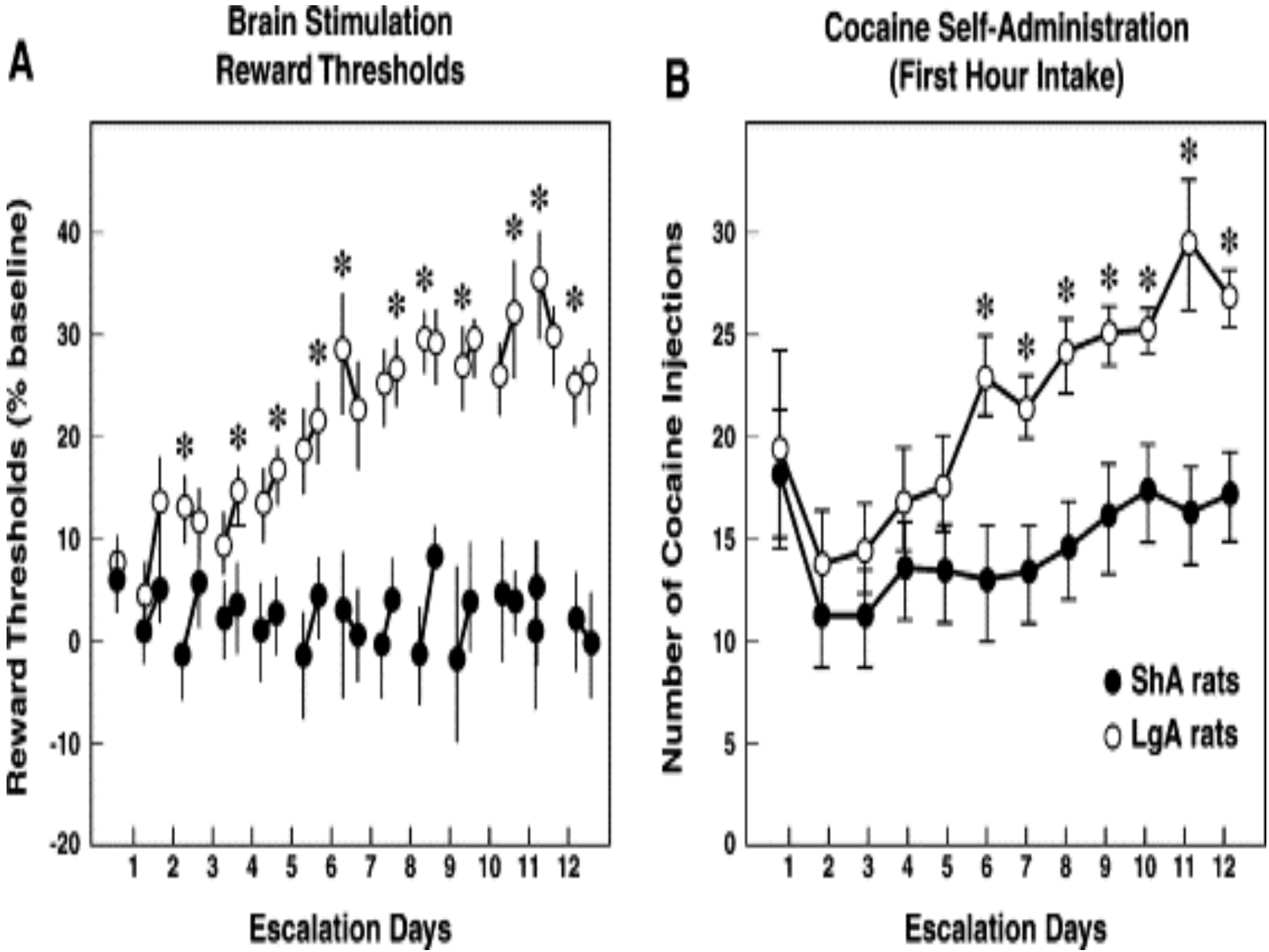


Elevation of Reward Thresholds:

- Results in chronic shift in homeostatic set point
- Addiction development
  - **Vulnerabilities & Protective factors:**
    - Psychosocial
    - Temperament & Personality
    - Genetics (DA polymorphism, ADH, ALDH)
    - Co-morbidity
    - Early Exposure
- Source of other self-regulation failures – mood, anxiety, perception
- Persistent vulnerability to relapse

Koob GF, Le Moal M. Neurobiology of Addiction 2006


A
Amphetamine Withdrawal
% of Baseline Threshold
Amphetamine
Control
Base 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days Post Amphetamine
B
Ethanol Withdrawal
% of Baseline Threshold
Ethanol
Control
2 4 5 8 12 24 48 72 96 120
Hours Post Ethanol
C
Cocaine Withdrawal
% of Baseline Threshold
Cocaine
Control
0 1 3 6 12 24 49 72
Hours Post Cocaine
D
Morphine Withdrawal
% of Baseline Threshold
Morphine
Control
0 0.003 0.01 0.03 0.10 1.0
Naloxone Dose (mg/kg)
E
Nicotine Withdrawal
% of Baseline Threshold
Nicotine
Control
2612 24 36 48 80 104 128 152
Hours Post Nicotine
F
THC Withdrawal
Rewards/30 sec
Baseline
Post-THC
40 60 80 100 120 140 160
Frequency (Hz)


A
Brain Stimulation
Reward Thresholds
Reward Thresholds (% baseline)
40
30
20
10
0
-10
-20
1 2 3 4 5 6 7 8 9 10 11 12
Escalation Days
B
Cocaine Self-Administration
(First Hour Intake)
Number of Cocaine Injections
30
25
20
15
10
5
0
ShA rats
LgA rats
1 2 3 4 5 6 7 8 9 10 11 12
Escalation Days

Addiction Liability Relates to: Drug Type, Dose & Mode of Use

- Drug Type: Volatility, lipid solubility, bioavailability, and ability to activate DA
  - Cannabis & Alcohol → 10% of regular users develop dependence
  - Cocaine & Amphetamine → 10% of initial users develop dependence
- Increased dose → Increased addiction liability
- Mode of Use Addiction Liability: The more rapidly a drug is delivered to its site of action, the greater the reinforcing effect.
  1. Intravenous or smoked (bypass venous system)
  2. Intranasal
  3. Oral
  4. Transdermal

Karan LD et al. Pharmacokinetic and Pharmacodynamic Priniciples. In: Principles of Addiction Medicine, 3rd Ed. ASAM 2003:83-100

Alcohol Pharmacology:

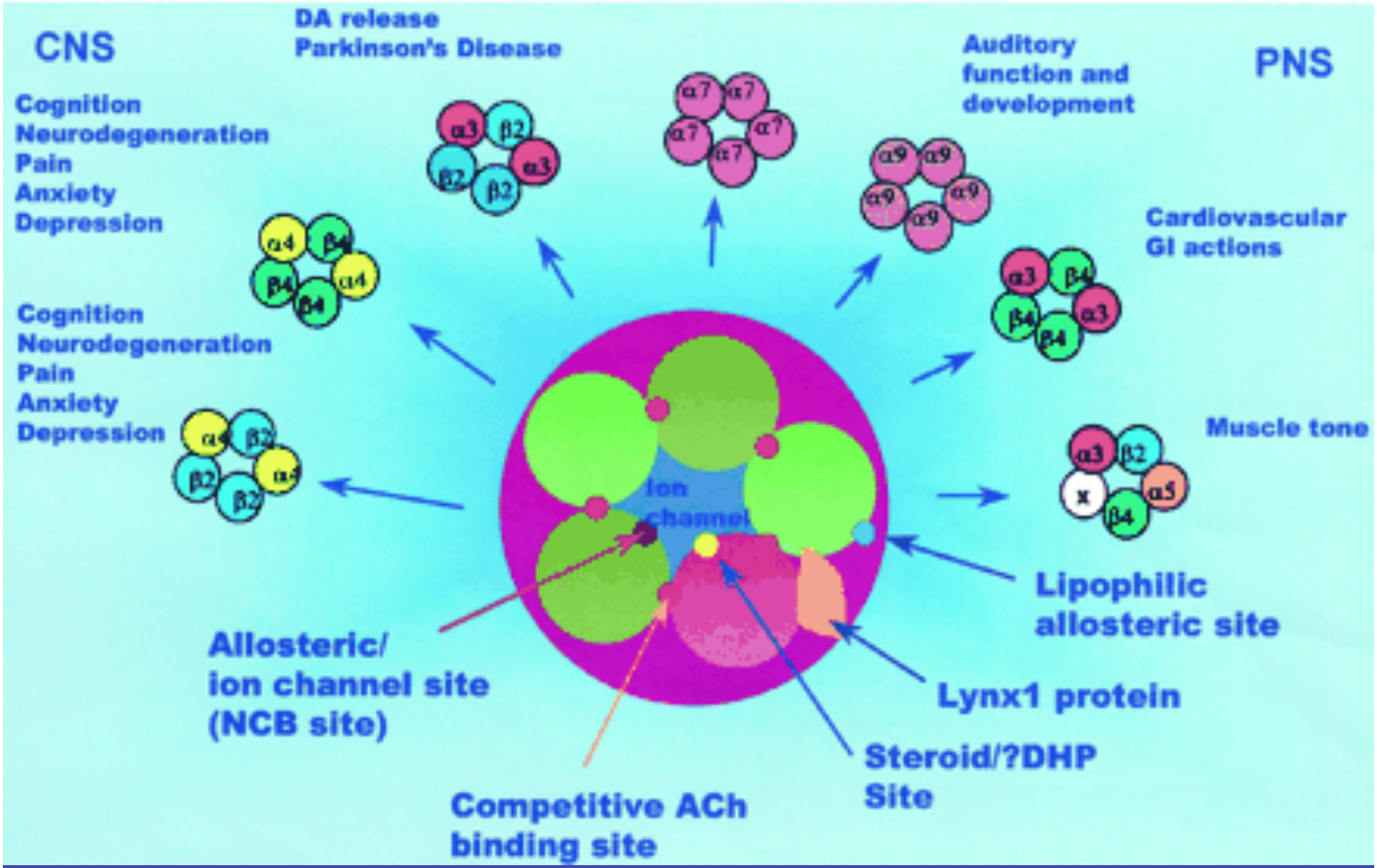
- **ALCOHOL** → Alcohol Dehdrogenase (ADH) → **ACETALDEHYDE** → Acetaldehyde Dehydrogenase (ALDH) → **ACETONE**
- Zero order kinetics (ADH saturated at low levels)
- Lipophilic action increasing membrane fluidity now discounted as basis of action
- Opioid receptor gene (OPRM1) found in 15-25% of people may mediate response to naltrexone (87% vs 49%)
- Disulfiram acts via ALDH inhibition
- Best genetic data links ADH and ALDH polymorphisms to likelihood for dependence

Alcohol Pharmacology:

- Acts via ligand-gated ion channels:

	ACUTE	WITHDRAWAL/ CHRONIC	MEDS?
• NICOTINIC ACh Receptor	Stim. And Inhibition	Uncertain	?
• DOPAMINE [Reward]	Stim. Release,	DECREASE	D3
• OPIOIDS PEPTIDES	Stim. Release	?	NALTREXONE
• GABA-A [Inhibition]	Stim. [Anxiolytic], Incr. DA	INHIBITION	TOPIRAMATE
• GLUTAMATE [Excitation]	Inhibition, Incr. DA	ACTVATION	ACAMPROSATE
• 5-HT3 SEROTONIN	Stim.	INHIBITION	ONDANSETRON

Major Putative Native Neuronal nAChR Subtypes:



Nicotine releases ACh, NE, DA, S, glutamate, and GABA

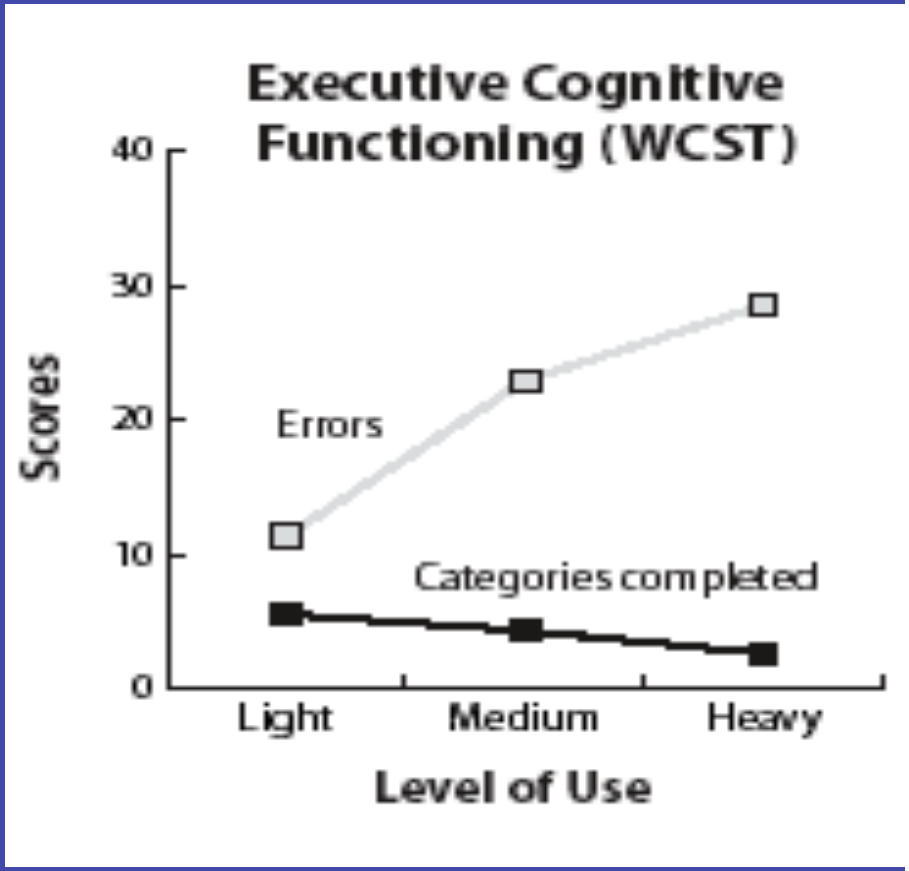
Mechanism of Action for Cannabis:

- Acts via CB1 (brain) & CB2 (immune system) G-protein linked receptors inhibiting adenylyl cyclase
- CB1 receptors mediate neuropsychiatric effects:
  - Basal ganglia & Cerebellum (molecular layer) - movement
  - Hippocampus & cortex - memory
  - Ventromedial striatum & nucleus accubens – addiction liability
- Neurotransmitter effects:
  - Acetylcholine – decreases activity esp. in hippocampus
  - NMDA receptors – inhibits activity
  - GABA – increases activity
  - Dopamine – increases activity in striatum and mesolimbic tissues & stimulates release in nucleus accumbens via disinhibition of GABAergic tonic inhibition

Martin BR. Neurobiology of Marijuana. Textbook of Substance Abuse Treatment, 3rd Ed, 2004:47-54.

Neuropsychological Effects of Cannabis:

- Acute/sub-acute (from 48-72 hours to 1 week) impairment of:
  - Verbal and visual memory
  - Executive functioning
  - Psychomotor speed
  - Manual dexterity
- Severity of use correlates to effects
- No evidence of long-term cognitive deficits with sustained abstinence



Bolla KI et al. *Neurology* 2002;59:1337-1343

Pope HG Jr, Yurgelun-Todd D. *JAMA* 1996;275:521-527

Opiods:

- Primary effects at **mu**, kappa and delta opioid receptors
- Opioid agonist mediated inhibition of GABA neurons results in disinhibition and activation of dopaminergic neurons
- Heroin shortest half-life
- More rapid pain tolerance than respiratory tolerance
- Withdrawal primarily mediated via noradrenergic system
  - **Locus cereleus**
  - **Role of clonidine (centrally mediated presynaptic alpha-2 receptor agonist)**

Borg L, Kreek MJ. The Pharmacology of Opioids. Principles of Addiction Medicine, 3rd Ed, 2003.

Critical Role of Dopamine:

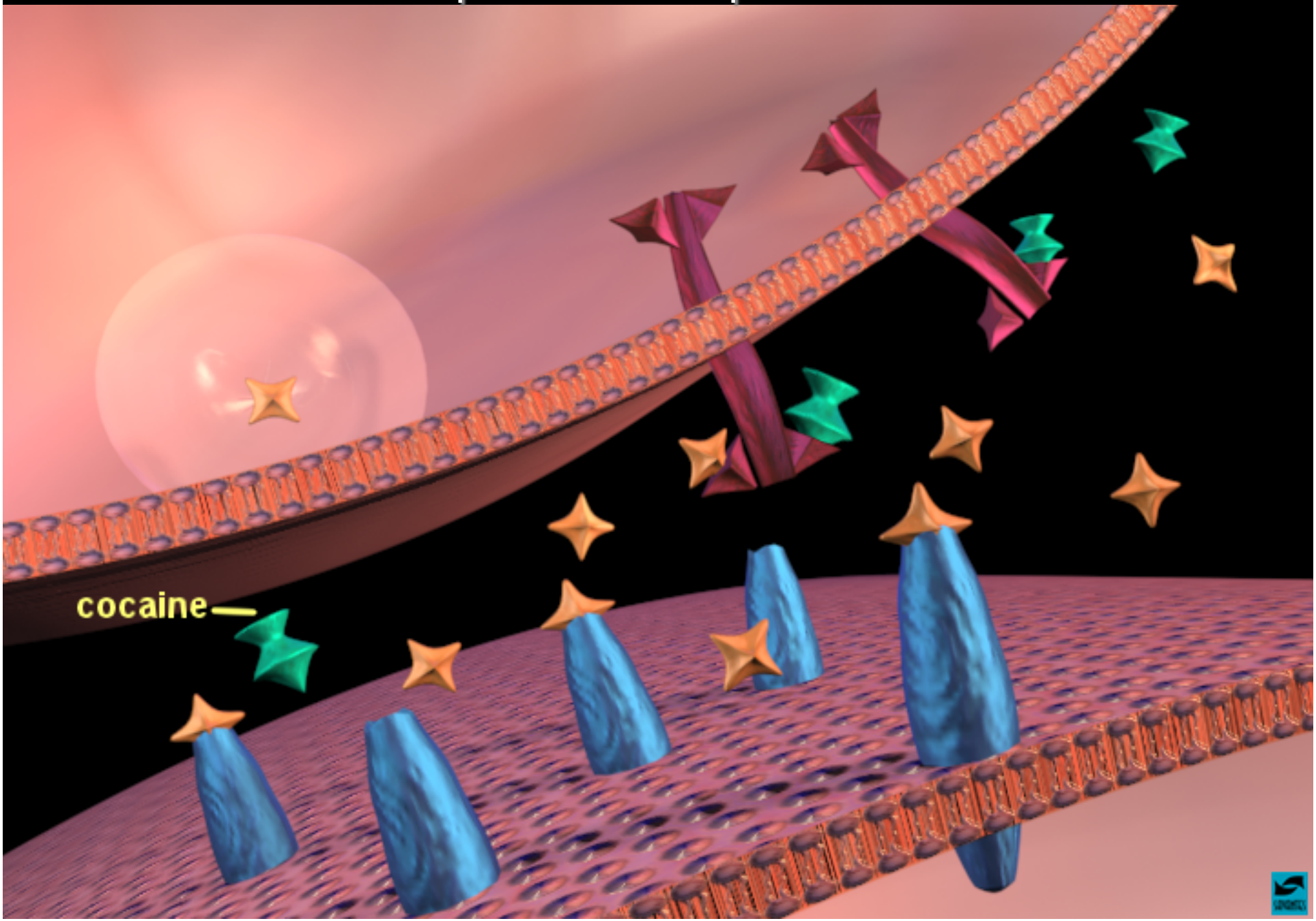
- Extended dopamine reward pathway activated by all substances of dependence
  - Hallucingoens like LSD primarily serotonergic - minimal dependence
- Dopamine critical for:
  - **Mood**
  - **Reward Experience & Expectation (esp. D3)**
  - **Motivation & Attention**
  - **Memory Salience**
    - links substance use with emotional and visuospatial cues
    - Classic and operant conditioning of behaviour
- Primary role in the development of dependence, but less so in relapse and persistence of behaviour

COCAINE

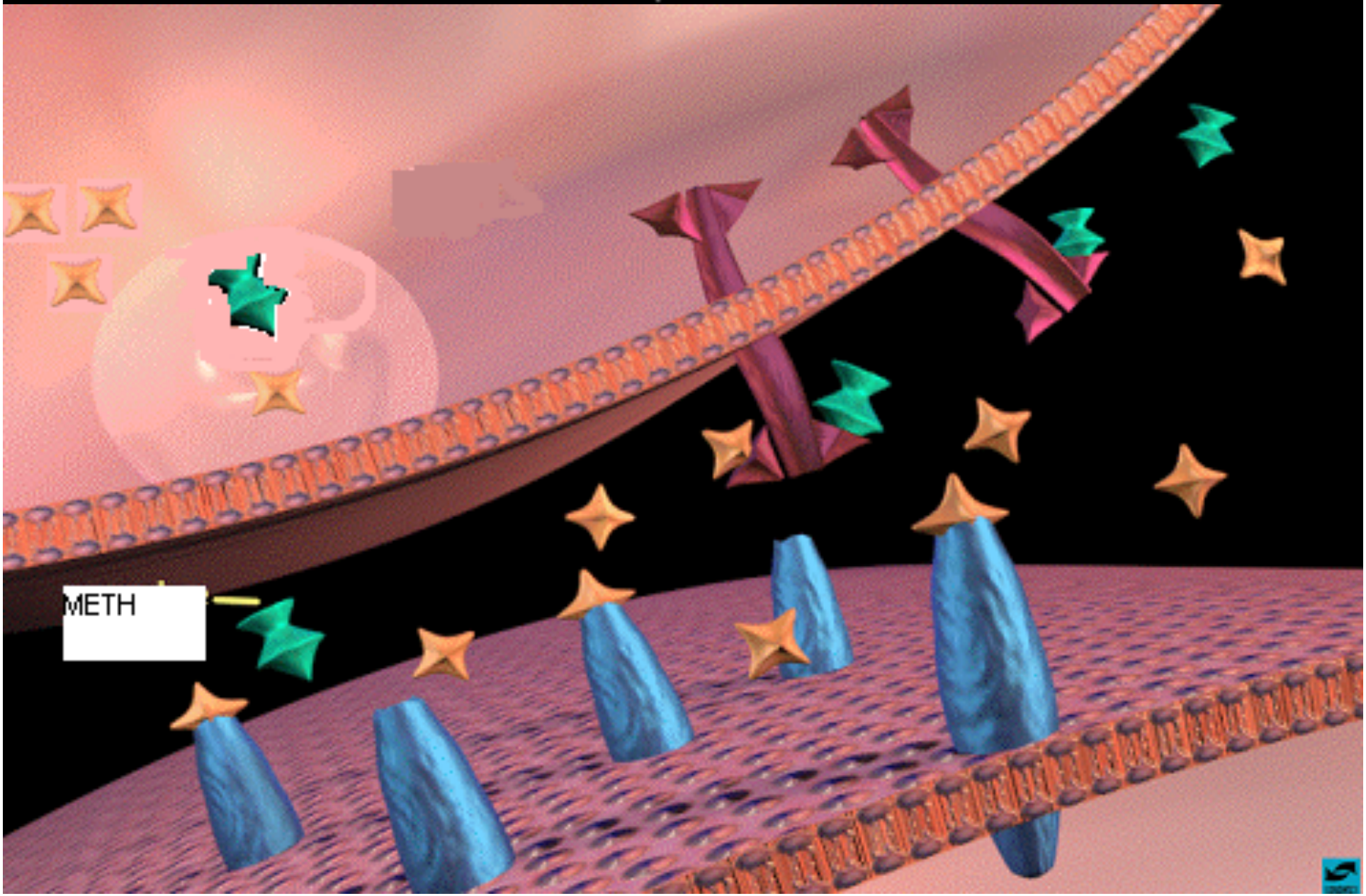
Inhibits Reuptake of Dopamine + Norepinephrine

+Heroin: Speed-Ball

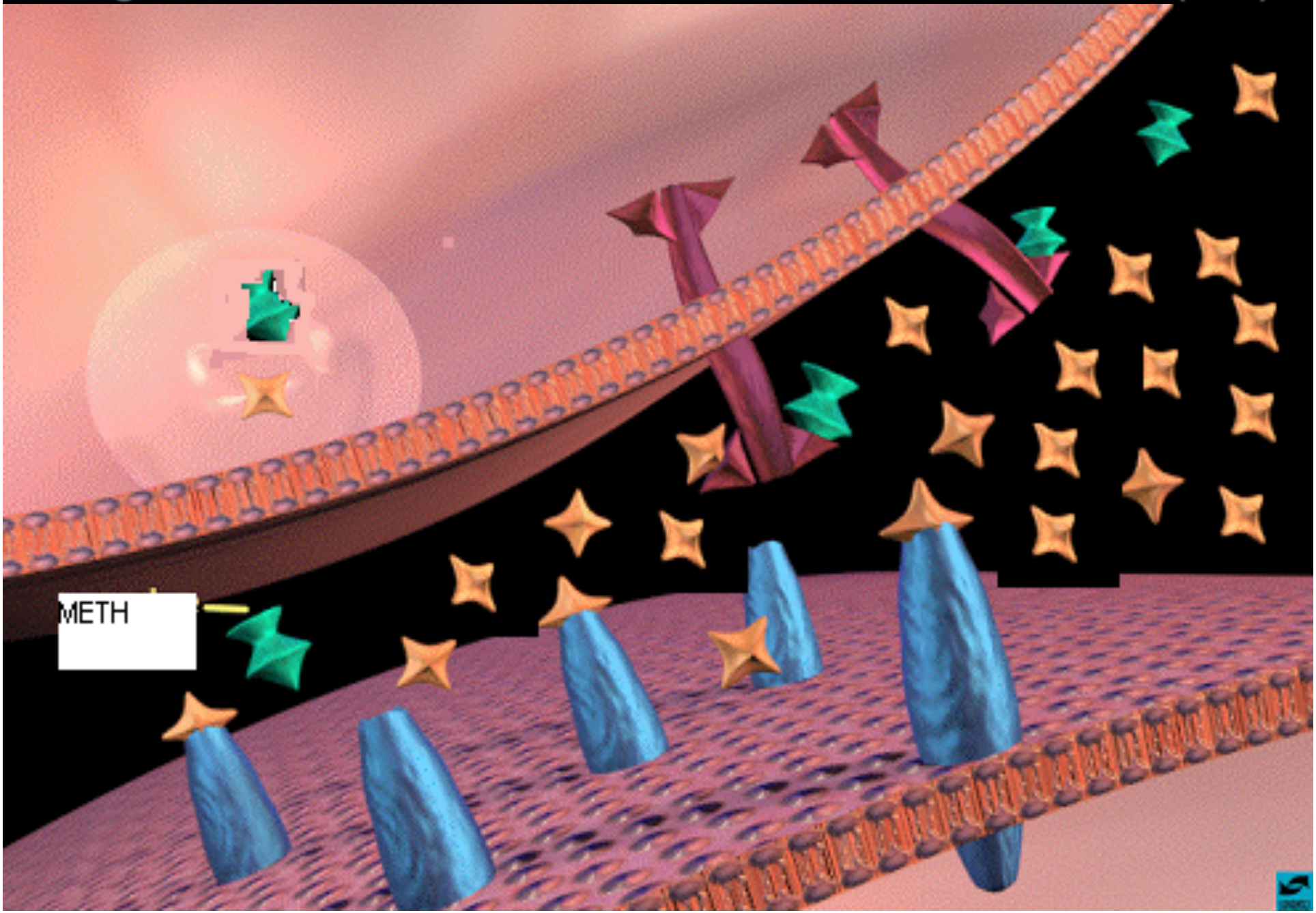
Cocaine limits dopamine re-uptake



Meth: Vesicular monoamine transporter 2 (VMAT2), enhanced membrane transport



Net greater efflux of monoamine neurotransmitters (DA)



Psychopharmacology of Methamphetamine:

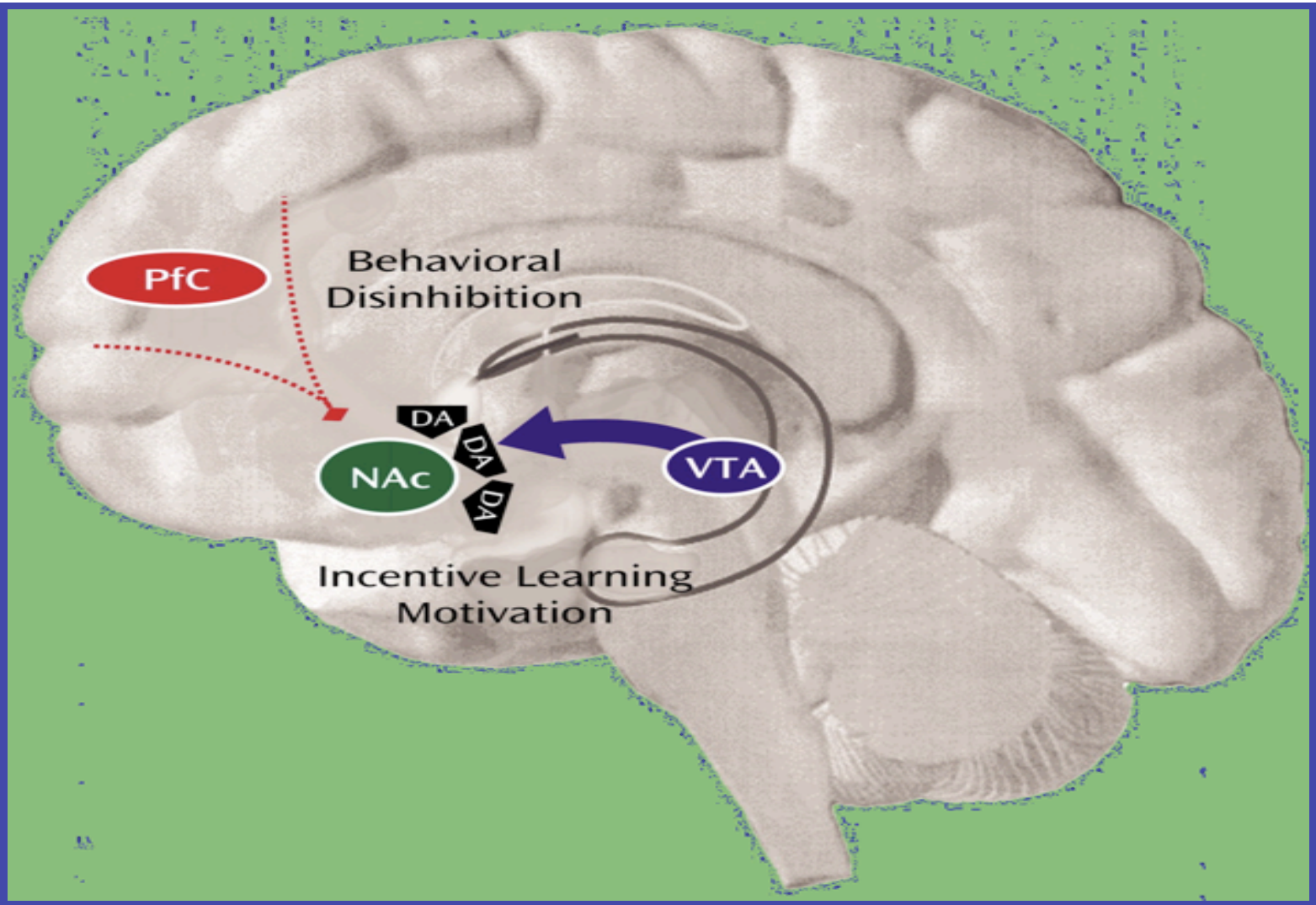
- Physical effects (sympathetic): hypertension, tachycardia, hyperthermia, tachypnea, vasoconstriction
- Acute psychological effects: euphoria, enhanced energy, increased alertness/attentiveness, increased speed of processing, feelings of enhanced physical and emotional capacity, decreased ability to filter information, increased libido
- Elimination half-life: 8 – 13 hours
- Greater lipid solubility than amphetamine
- Drug screen positive for 48-72 hours (high false positive rate)

Cobb Scott J et al. Neuropsychol Rev 2007;17:275-297

Chronic Effects of Methamphetamine Use:

- Cardiovascular effects: pulmonary HTN, aortic dissection, MI, CVAs, hypertensive crisis.
- "Meth Mouth"
- HIV & Hepatitis C (risky IV use and sexual patterns)
- Antisocial behaviour and violence
- Psychosis – usually short-term (< 10 days), but 1/3 may have symptoms up to 1 month esp. those with polymorphism at hDAT1 gene and/or noradrenergic hyperactivity may develop persistent psychoses
- Depression & Suicide (esp women, IV users) – crash phase, alterations in amygdala activity, persistent hypodopaminergic state during early/mid abstinence
- ADHD – cause or consequence?

Cobb Scott J et al. Neuropsychol Rev 2007;17:275-297
Ujike H, Sato M. Ann NY Acad Sci 2004;1025:279-287
London ED et al. *Arch Gen Psychiatry* 2004;61:73-84
Ujike H etal. Pharmacogenomics J 2004;3:242-7
Jaffe C et al. J Addict Dis 2005;24:133-152
Iyo M et al. Ann NY Acad Sci 2004;1025:288-295



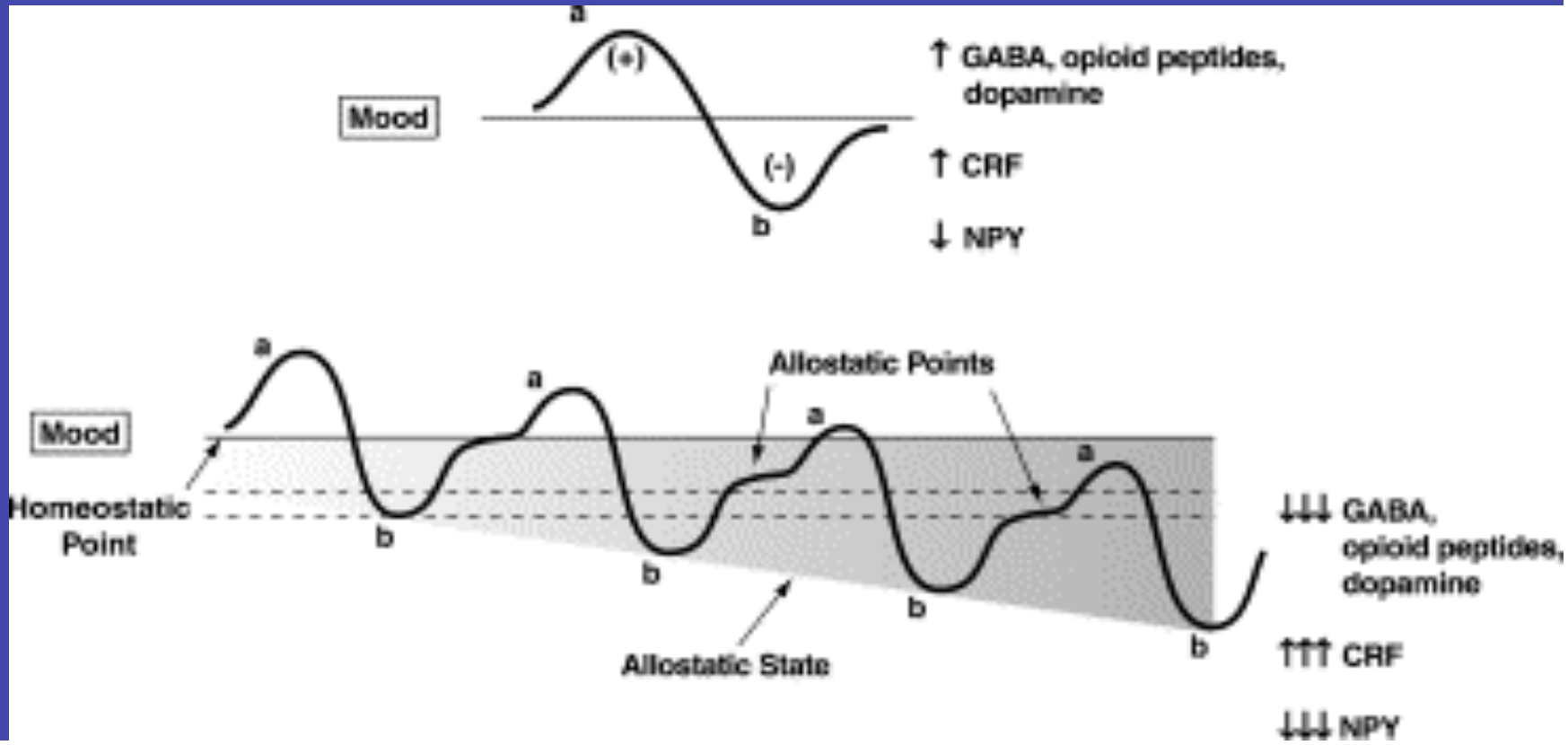
- Dopamine reward pathway activated by substances of abuse in a greater and sustained fashion than natural rewards resulting in substance use behaviour taking on persistent and preferential importance

Self D. *Am J Psychiatry* 2004;161:223

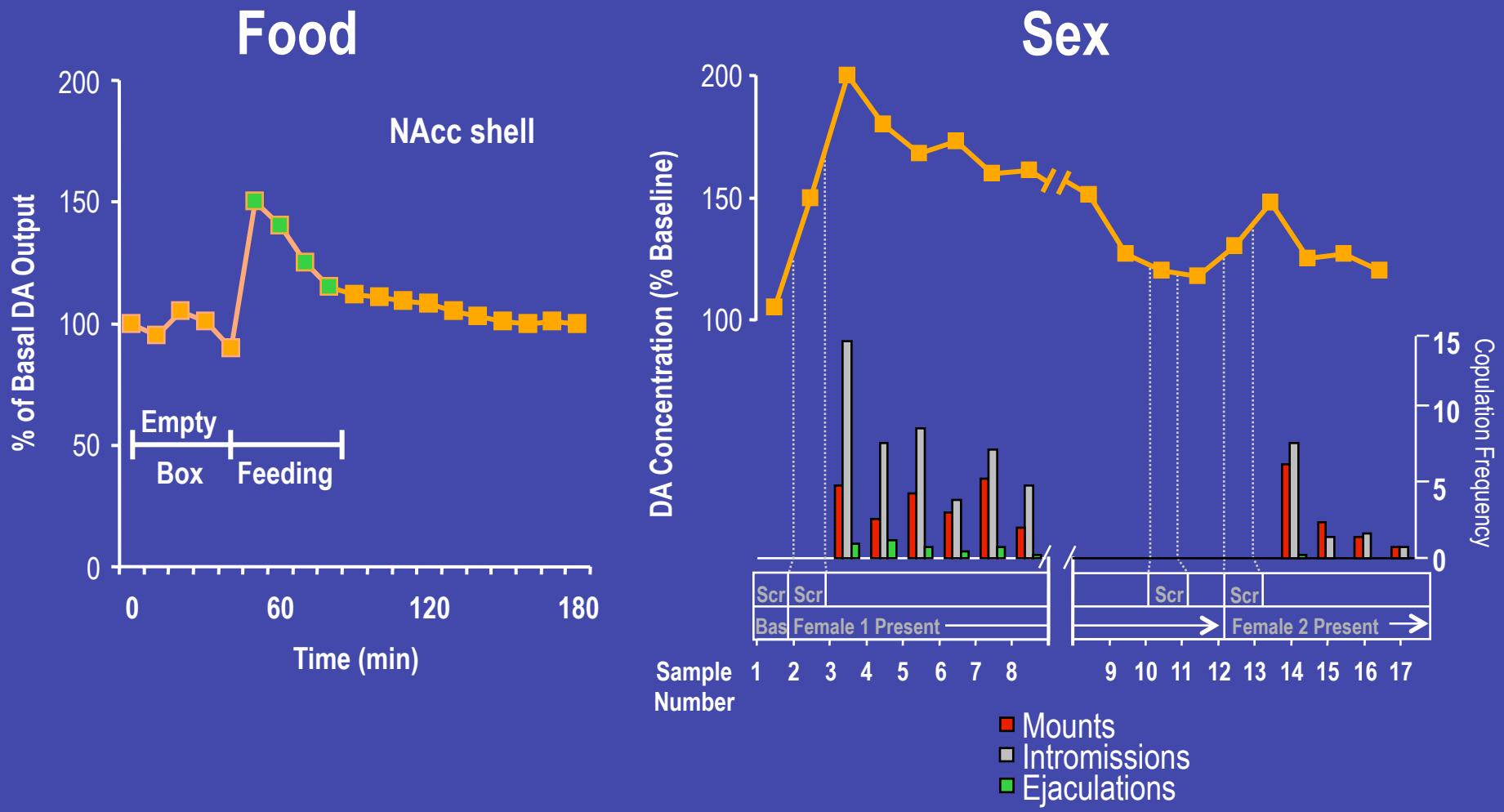
Kalivas P, Volkow ND. Am J Psychiatry 2005;162:1403-1413

Allostatic Change

- Chronic deviation of the regulatory system from its normal (homeostatic) operating level



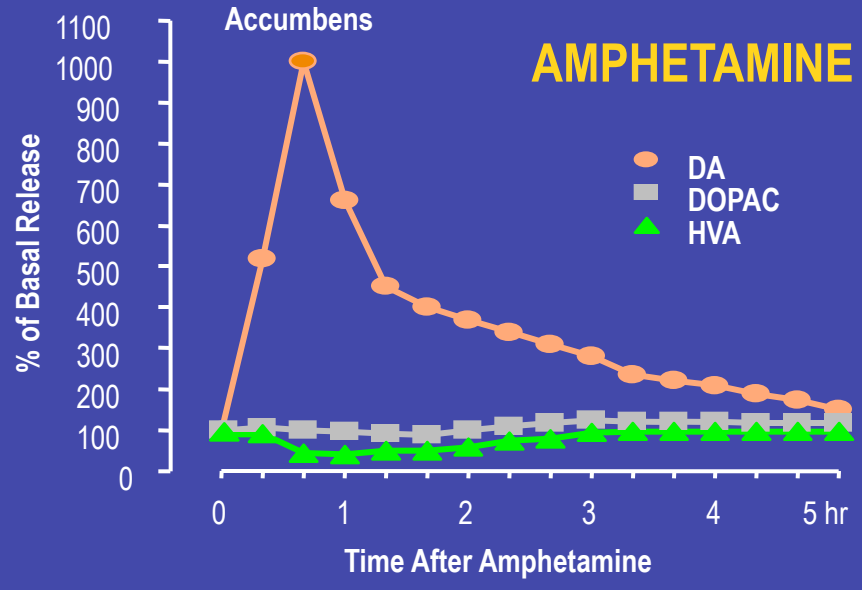
Dopamine Activation With Natural Rewards

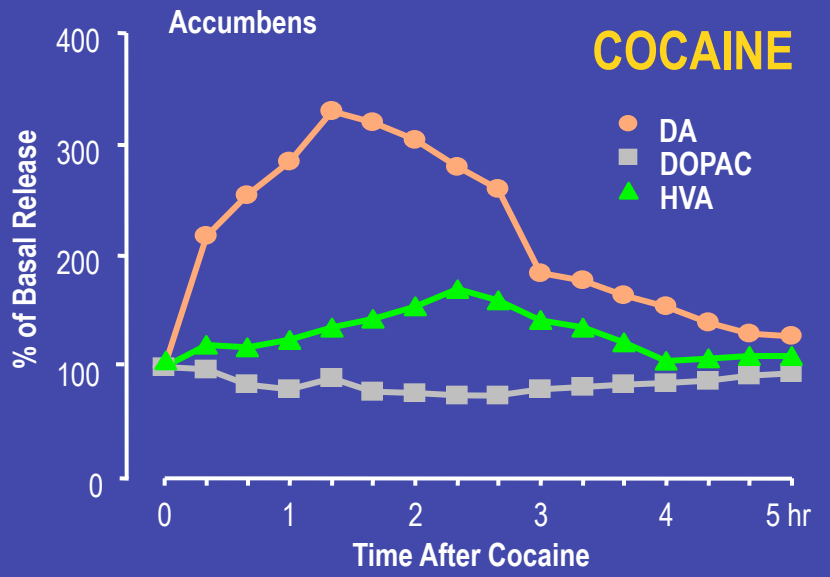


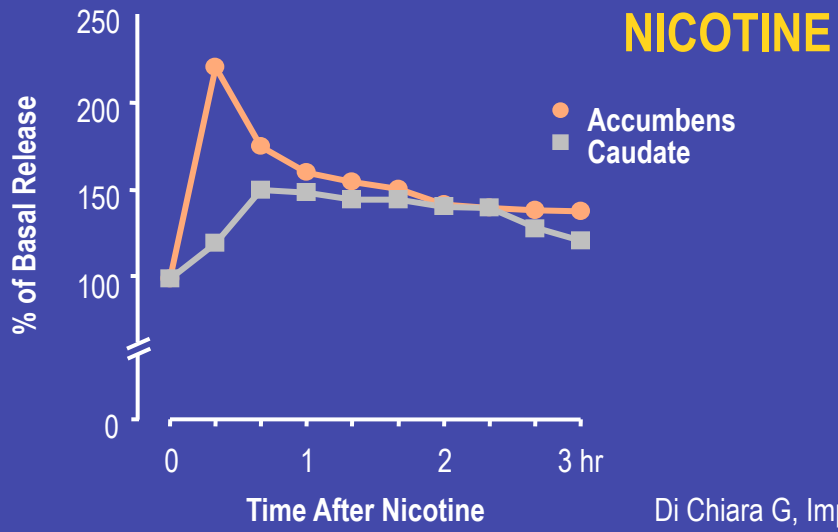
Bassareo V, Di Chiara G. Neurosci Letter 1999;89:637-641

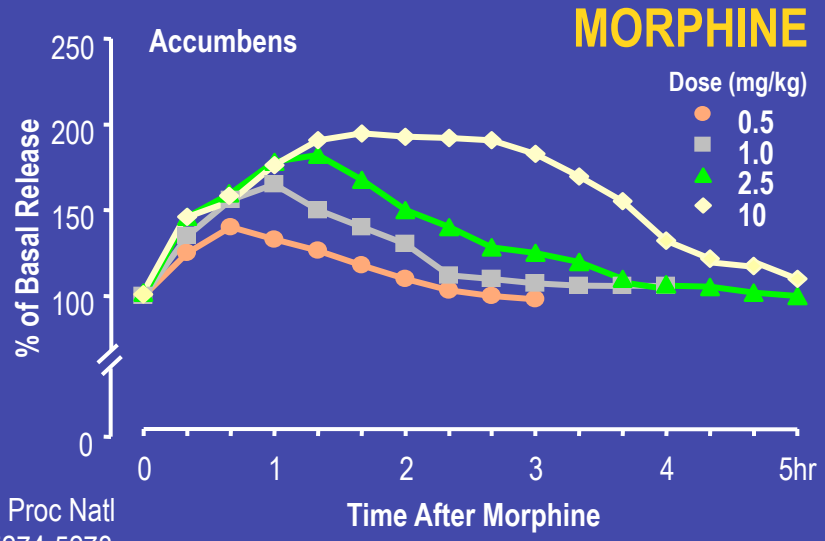
Fiorino DF, Phillips AG. J Neurosci 1999;19:456-463

Dopamine Activation with Substance Use



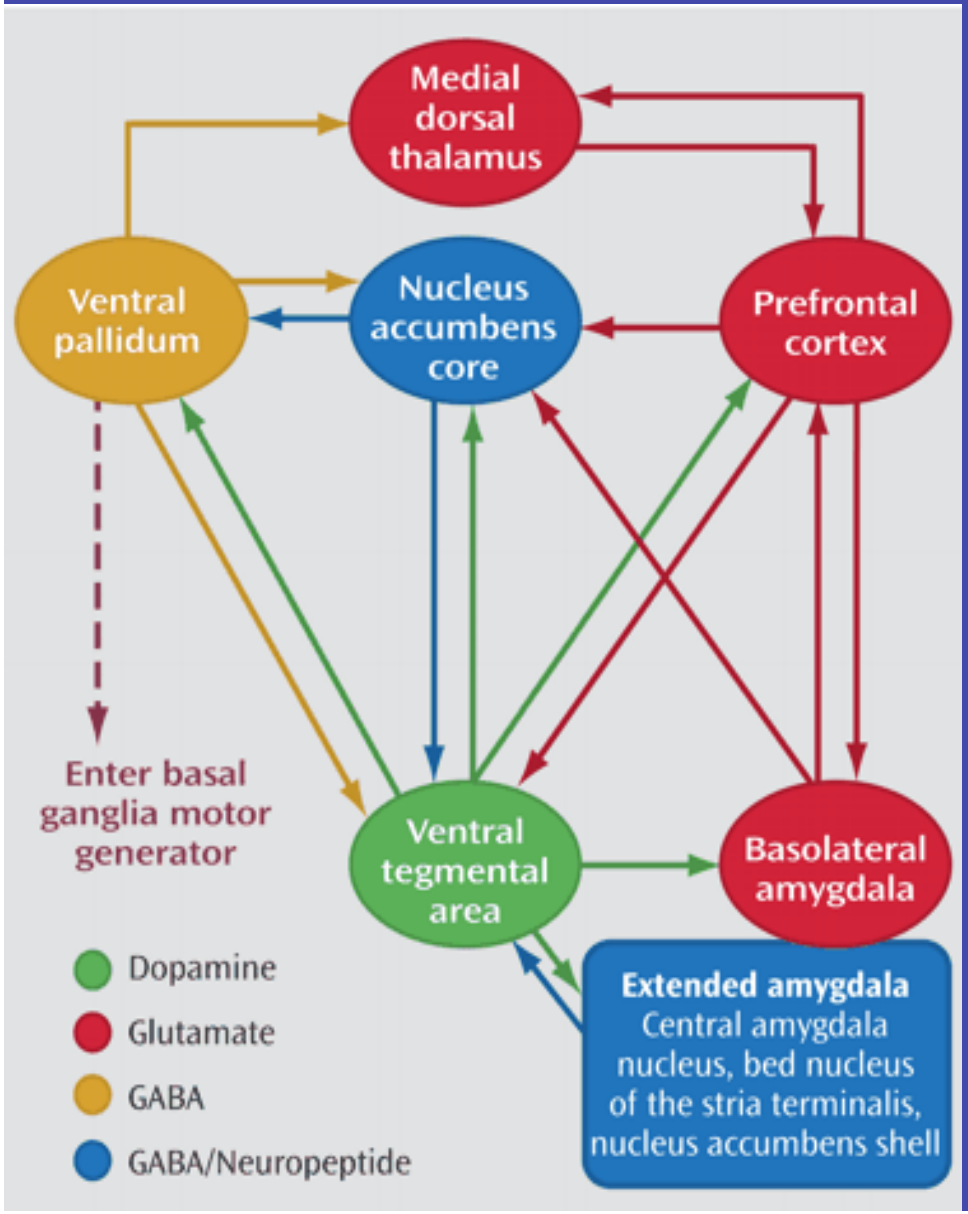






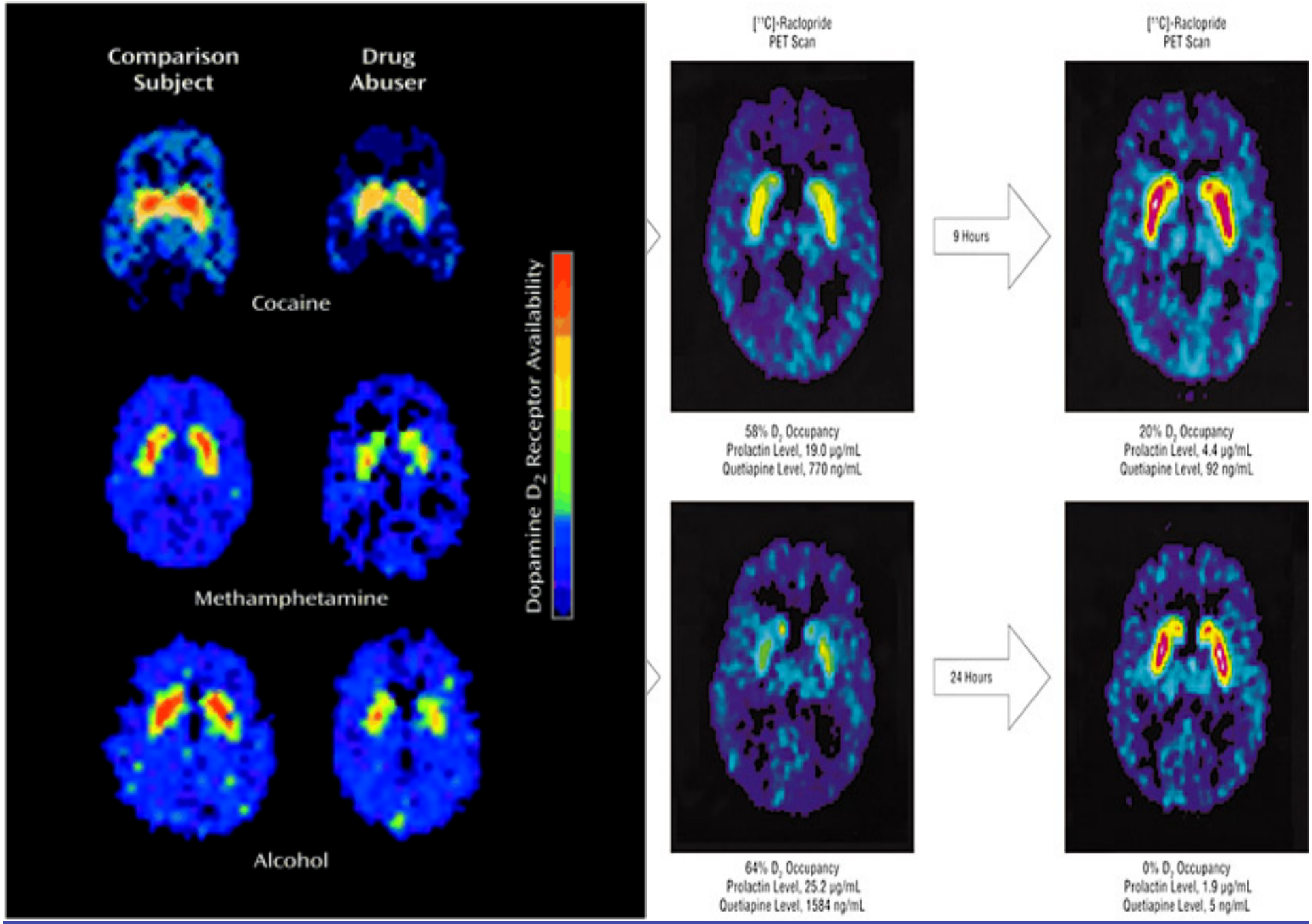
Di Chiara G, Imperato A. Proc Natl Acad Sci USA 1988;85:5274-5278

Current Understanding of Substance Use Disorders



- Activation of dopamine reward pathways with exposure to addictive substance
- Reward expectancy coded in prefrontal cortex and hippocampus/ amygdala by dopamine activation
- Cues for addictive substance promote activation of prefrontal cortex
- Decreased dopamine activity with exposure to addictive substance once dependent

Kalivas P & Volkow N. Am J Psychiatry 2005



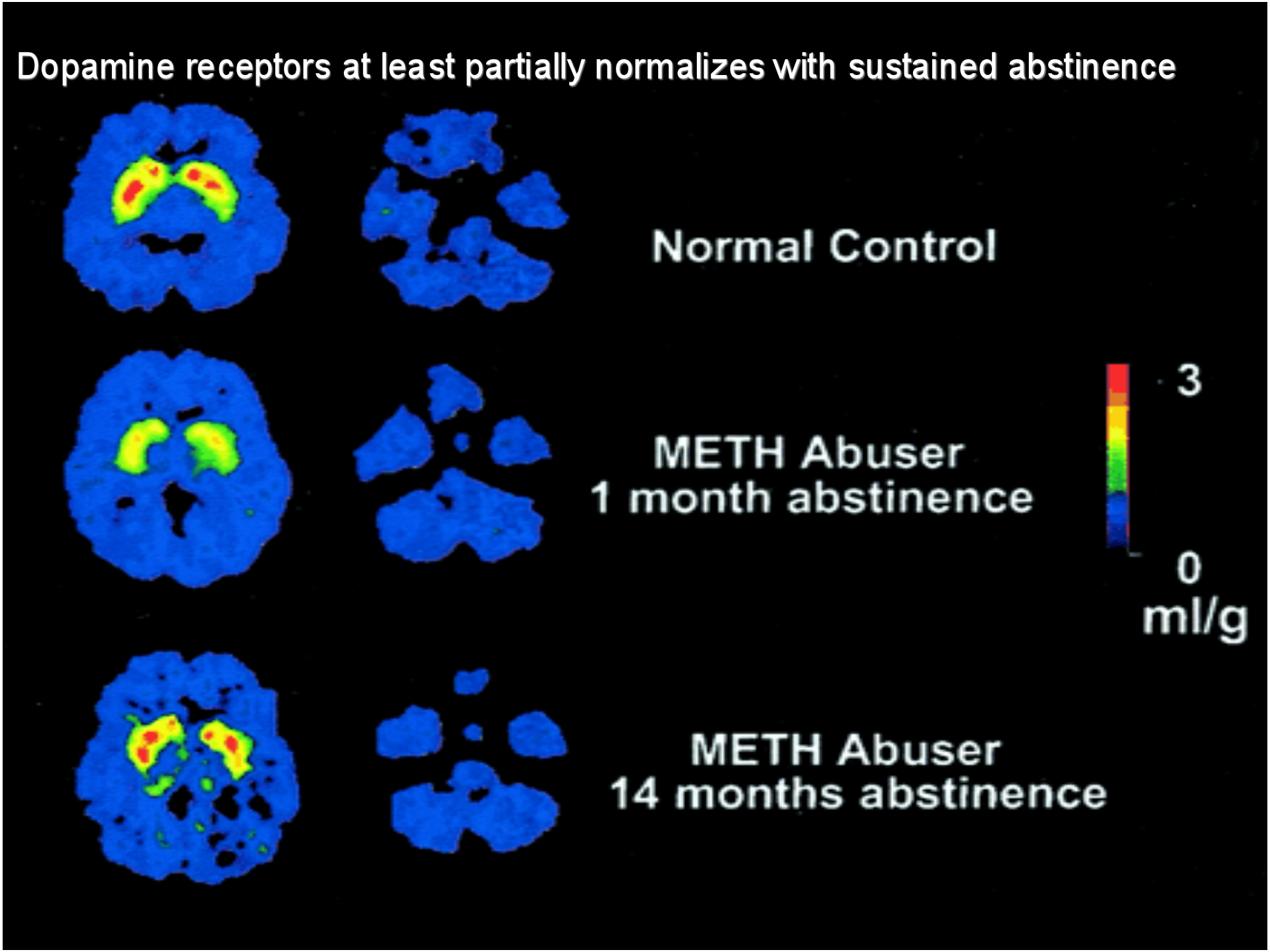
Goldstein RZ & Volkow ND. Am J Psychiatry 2002

Kapur, S. et al. Arch Gen Psychiatry 2000;57:553-559.

Neuropsychological Effects of Chronic Methamphetamine Use (DA Deficit State):

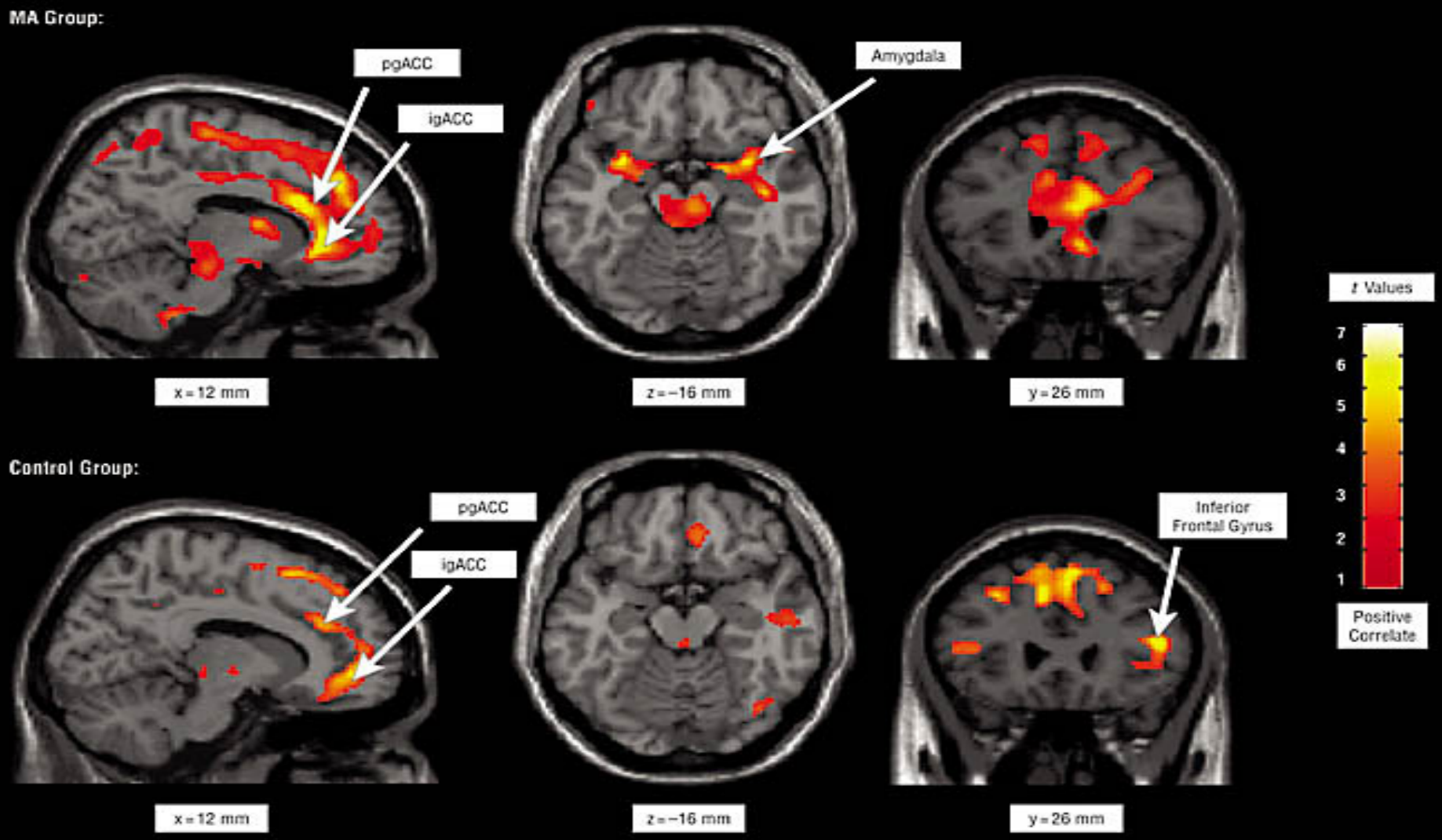
- Decreased episodic memory & learning – deficient executive aspects of encoding & retrieval (frontostriatal)
- Decreased cognitive set shifting & response inhibition (frontal)
- Impulsive choices (medial frontal)
- Slowed information processing speed (striatal)
- Impaired attention, working memory (ACC, DLPFC)
- Unclear if duration & severity of use correlates with findings, ? neurotoxicity?
- Symptoms persist with complete abstinence for up to 9 months with inhibition and episodic memory last to recover (if it occurs)

Cobb Scott J et al. Neuropsychol Rev 2007;17:275-297



Volkow ND et al. J Neuroscience 2001;21:9414-8

Positive Covariation Between Regional Cerebral Glucose Metabolic rate (rCMRglc) and Beck Depression Inventory (BDI) Score in the Methamphetamine (MA) Abusers (n = 18) and in Controls (n = 17)



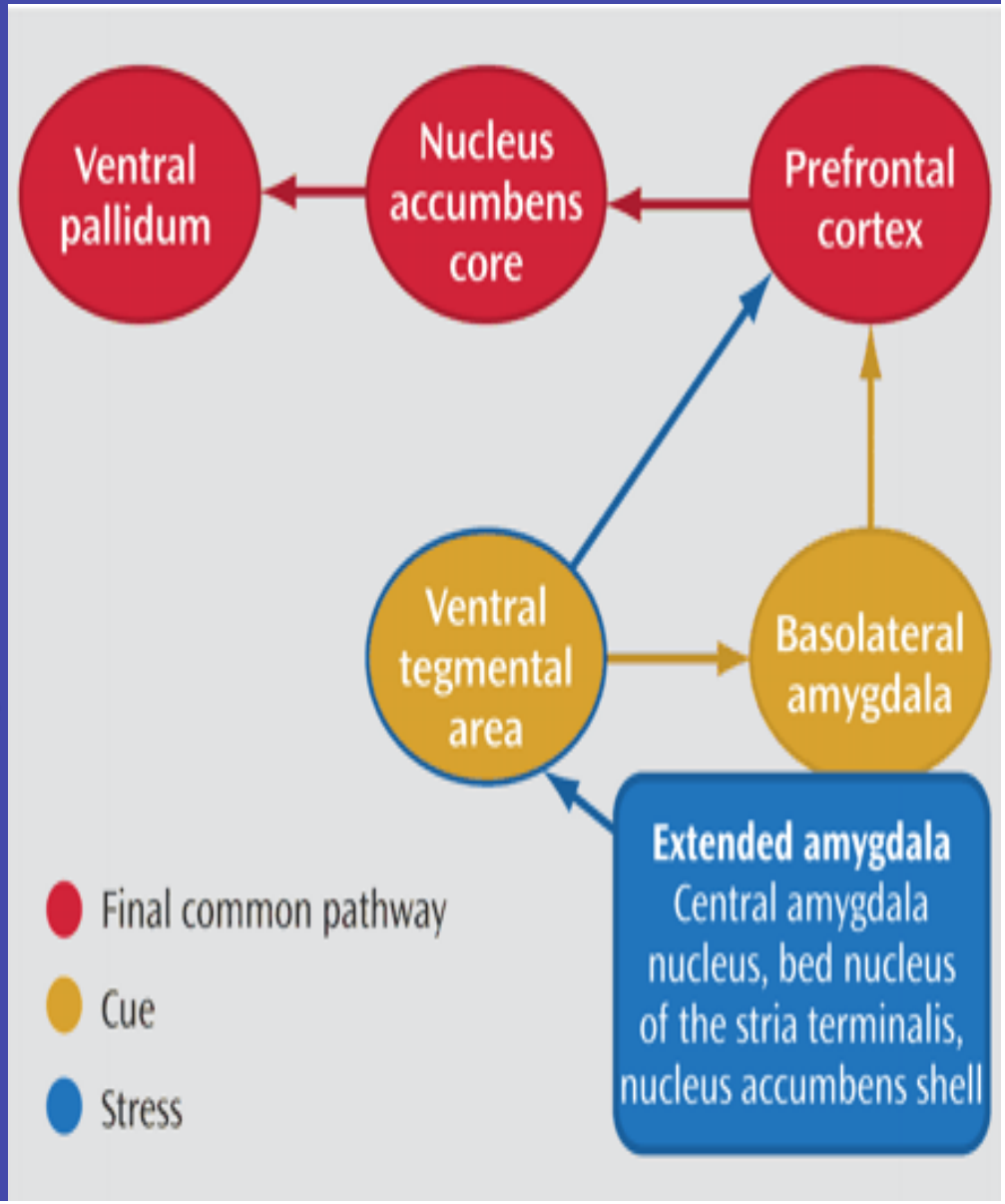
London ED, et al. *Arch Gen Psychiatry* 2004;61:73-84

Role of Other Neurotransmitters:

- **Norepinephrine/Epinephrine** (Opioids)
  - Mood
  - Stress Response
  - Withdrawal
- **Glutamate** (Stimulants)
  - Cues
  - Drug Exposure & DA modulation
  - Exicitoxicity
- **GABA** (Alcohol, Benzodiazepines)
  - Drug Exposure & DA modulation
- **Serotonin** (Hallucinogens)
  - DA modulation
  - Mood & Anxiety

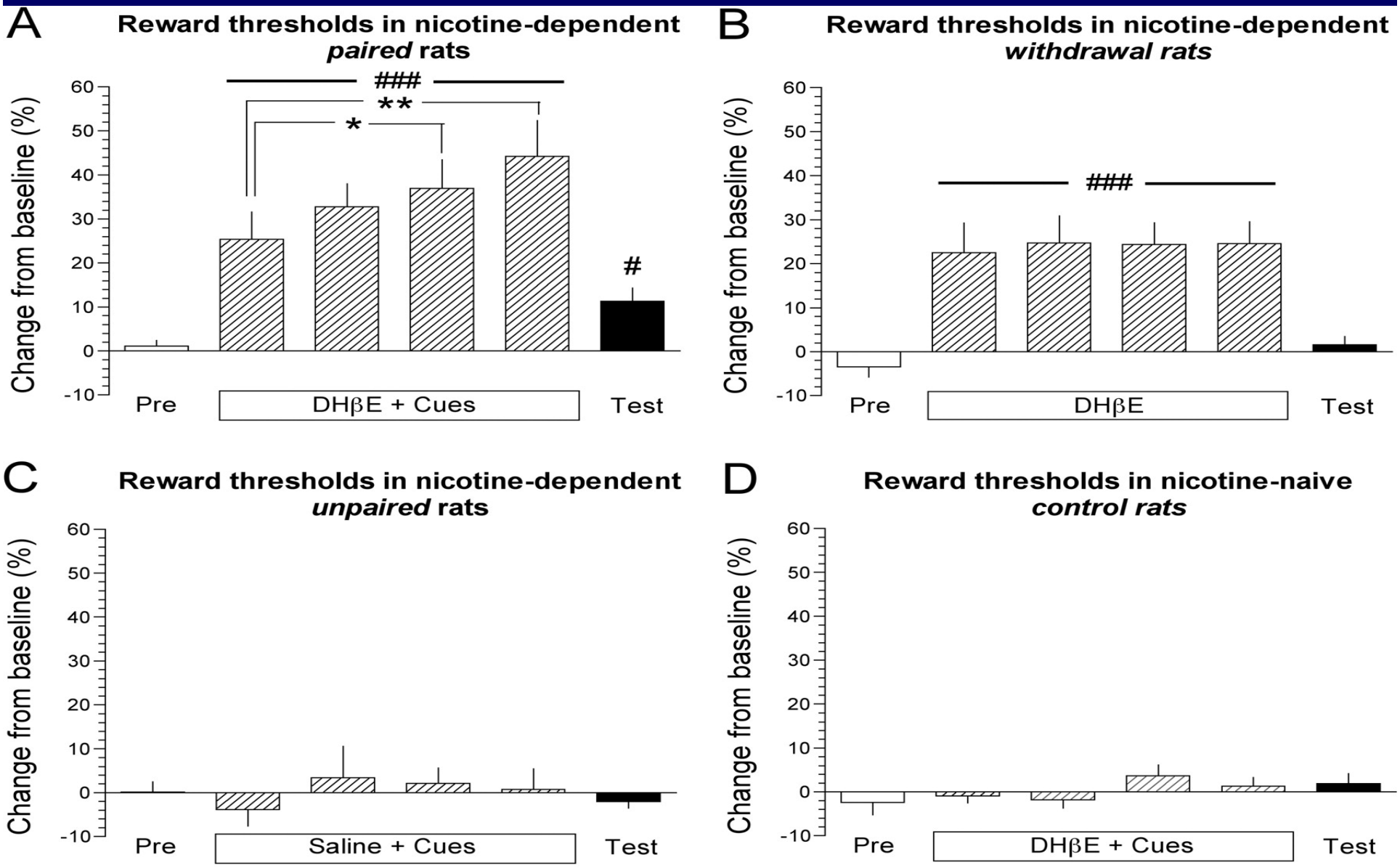
Pathways for Relapsing to Substance Use

- Stress including anxiety & depression result in increased amygdala activity (CRF, NE)
- Cues activate glutamatergic pathways including prefrontal cortex leading to cascade effect
- Low dose or other substance use re-initiates use via D3 pathway



Kalivas P & Volkow N. Am J Psychiatry 2005

Conditioned nicotine withdrawal decreased the activity of brain reward systems



Kenny, P. J. et al. J. Neurosci. 2005;25:6208-6212

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Rational Pharmacotherapy for Addiction?

- **Few evidence based pharmacotherapy options !**
- **Naltrexone:** opioid antagonism blocking high
- Acamprosate: GABA, glutamate modulation
- **Disulfiram:** inhibits aldehyde dehydrogenase
- **Modafanil:** 2 positive RCTs for cocaine dependence
- D2 Antagonists, SSRIs & other antidepressants: primarily negative trials
- Bupropion: partially blocks dopamine uptake (methamphetamine, nicotine)
- **Varenicline** (nicotine)
- Anticonvulsants: withdrawal, GABA modulation of DA activity (topiramate: alcohol, cocaine)
- Baclofen (cocaine, smoking)
- **Methadone, Buprenorphine** (opioids)

Tihonen J et al. Am J Psychiatry 2007;164:160-2.
Vocci FJ, Appel NM. Addiction 2007;102:96-106
Barr AM et al. J Psychiatry Neurosci 2006;31:301-313
Elkashef A et al. Addiction 2007;102:107-113.
Ling W et al. Curr Psychiatr Reports 2006;8:345-354