Innovations in Pharmacotherapy and the Use of Vaccines in Treatment of Addiction

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Topics

- Addiction Process and Brain Pathways: Relevance to Pharmacotherapy targets
- Pharmacotherapies: Current State of Affairs
- New and Emerging: Immunotherapies
- Future Directions and Final Thoughts

Addiction: A Brain Disorder

- Like mental illness, drug addiction is a brain disease (not just a brain disease, but it is that).
- Characterized by compulsive and, at times, uncontrollable drug craving and drug seeking.
- These behaviors stem from drug-induced changes in brain structure and function.
- Changes occur in some of the same brain areas that are disrupted in other mental disorders.
- The neuroscience of addiction has provided a platform for pharmacotherapy developments related to addictions treatment.

A Word From Our Sponsor...

His Holiness, The Pope, enjoyed the invigorating properties of coca wine. Leo XIII carried a personal hipflask to fortify himself in time of need. A grateful Pope awarded a Vatican gold medal to its distinguished originator, the Corsican-born pharmacist and businessman Angelo Mariani. Mariani had a keen eye for the benefits of celebrity-endorsement.

Substance Dependence: A Brain-based Motivational Disorder

- Apart from the negative health "side-effects", addiction itself represents a behavioural (motivational) disorder.
- Addiction is characterized by dysregulation of motivational processes.
- Motivational systems in the brain are disrupted following short and long term exposure to drugs of abuse.

"Susan, this might be just the wine talking, but I think I want to order more wine."

Alterations in The Brain's Reward/Motivation System:

at the Core of Brain Dysfunction in Substance Dependence

*-drug use (e.g. **reward**, conditioning, sensitization, tolerance)*
-environmental factors (e.g. externally-derived stress)
-more extreme neurobiological conditions inherent to the individual (e.g. mental illness)

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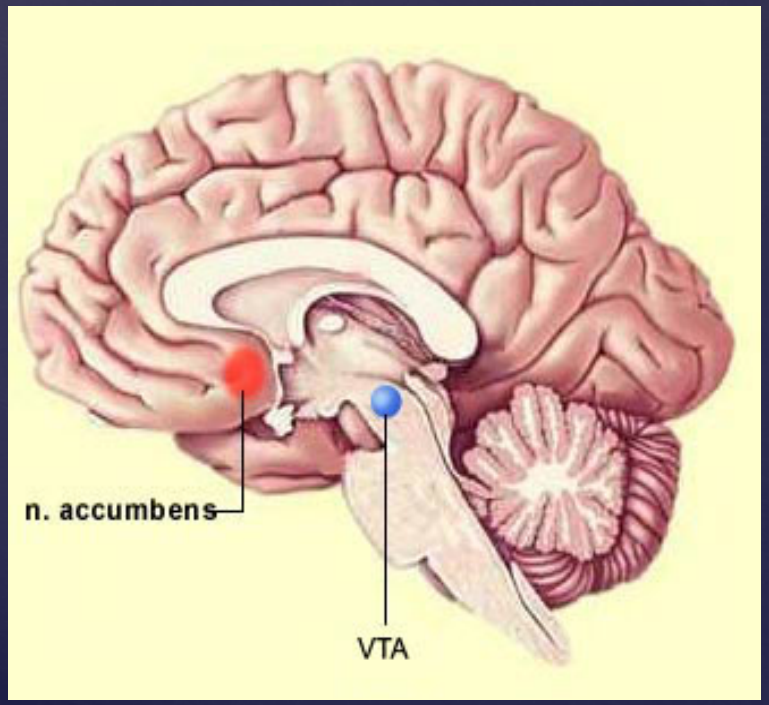
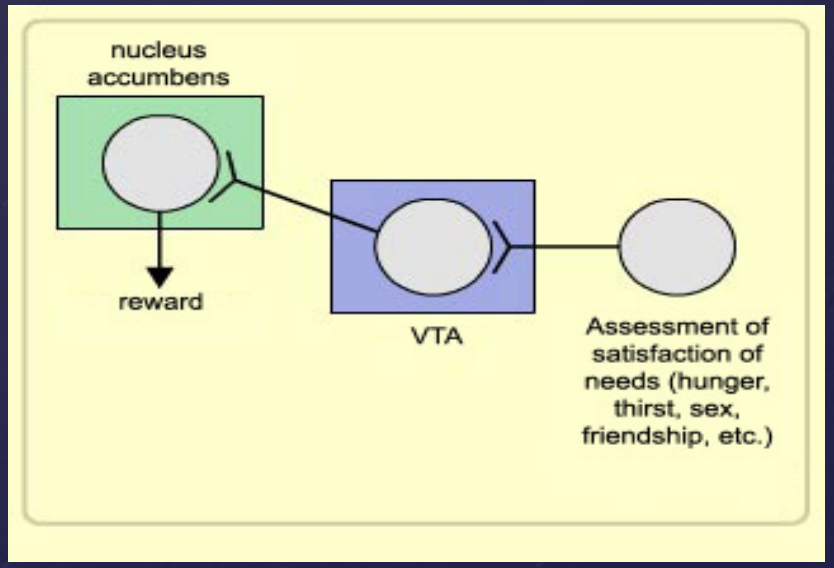
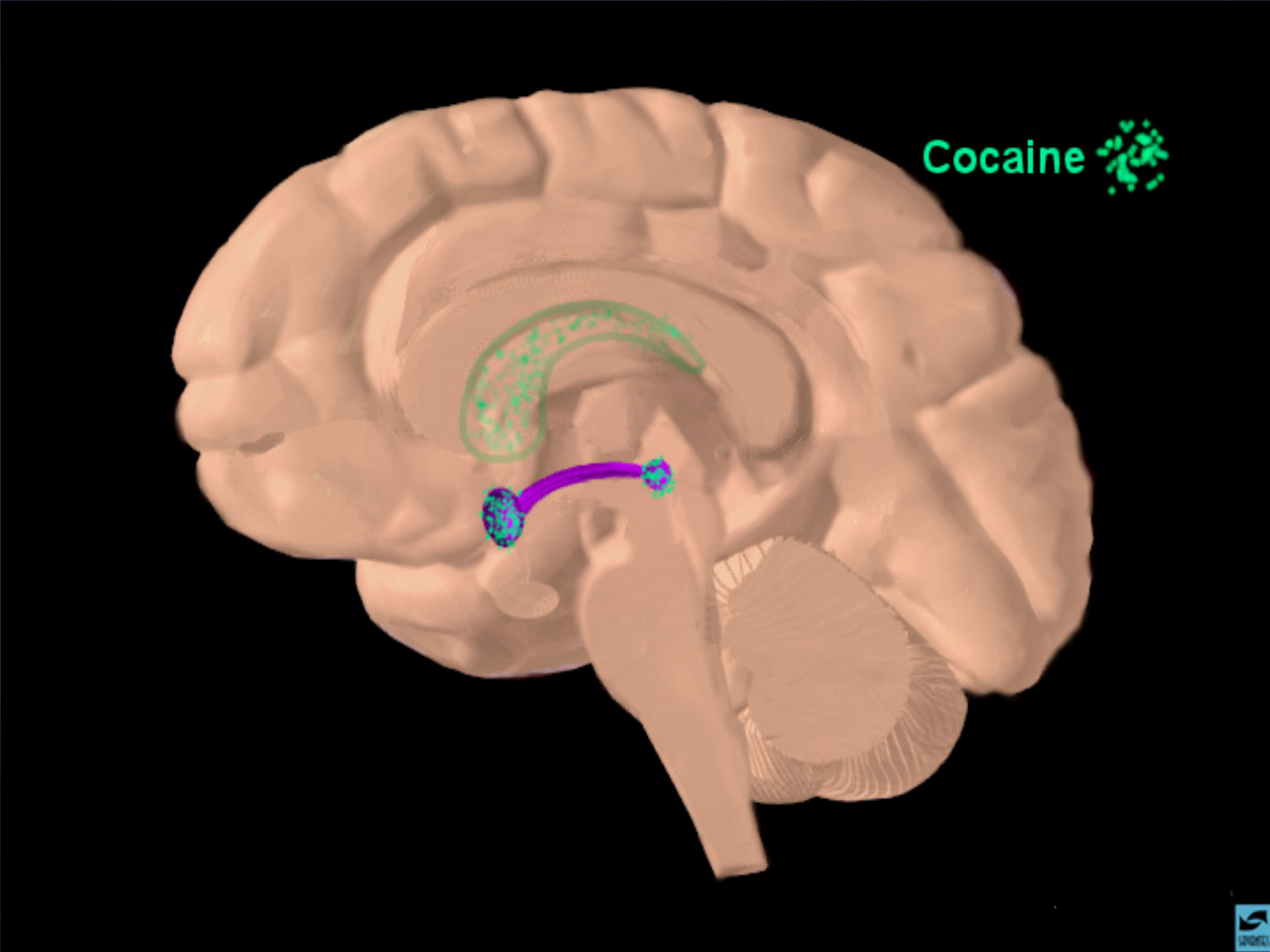
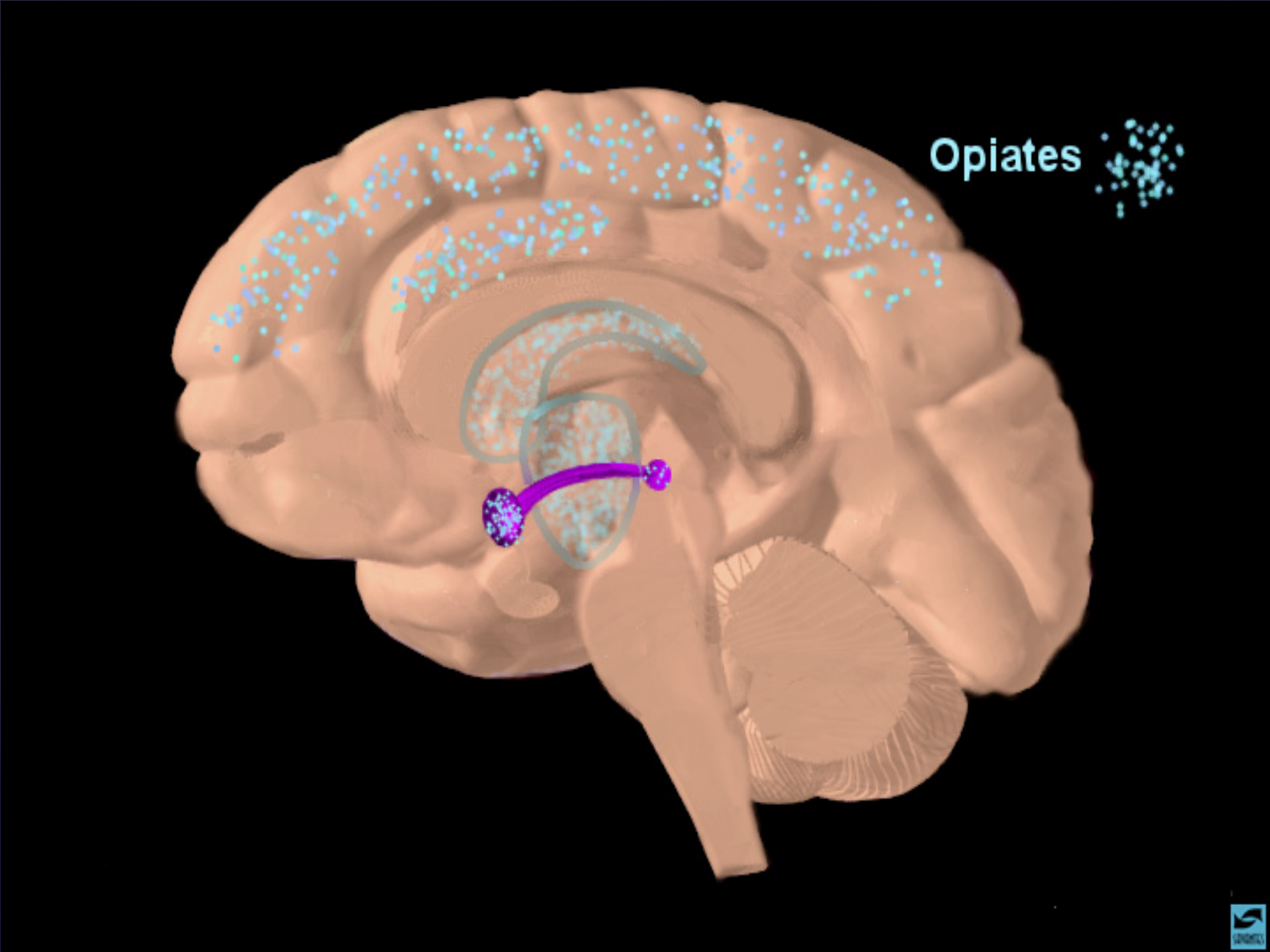
A common pathway for different drugs of abuse?

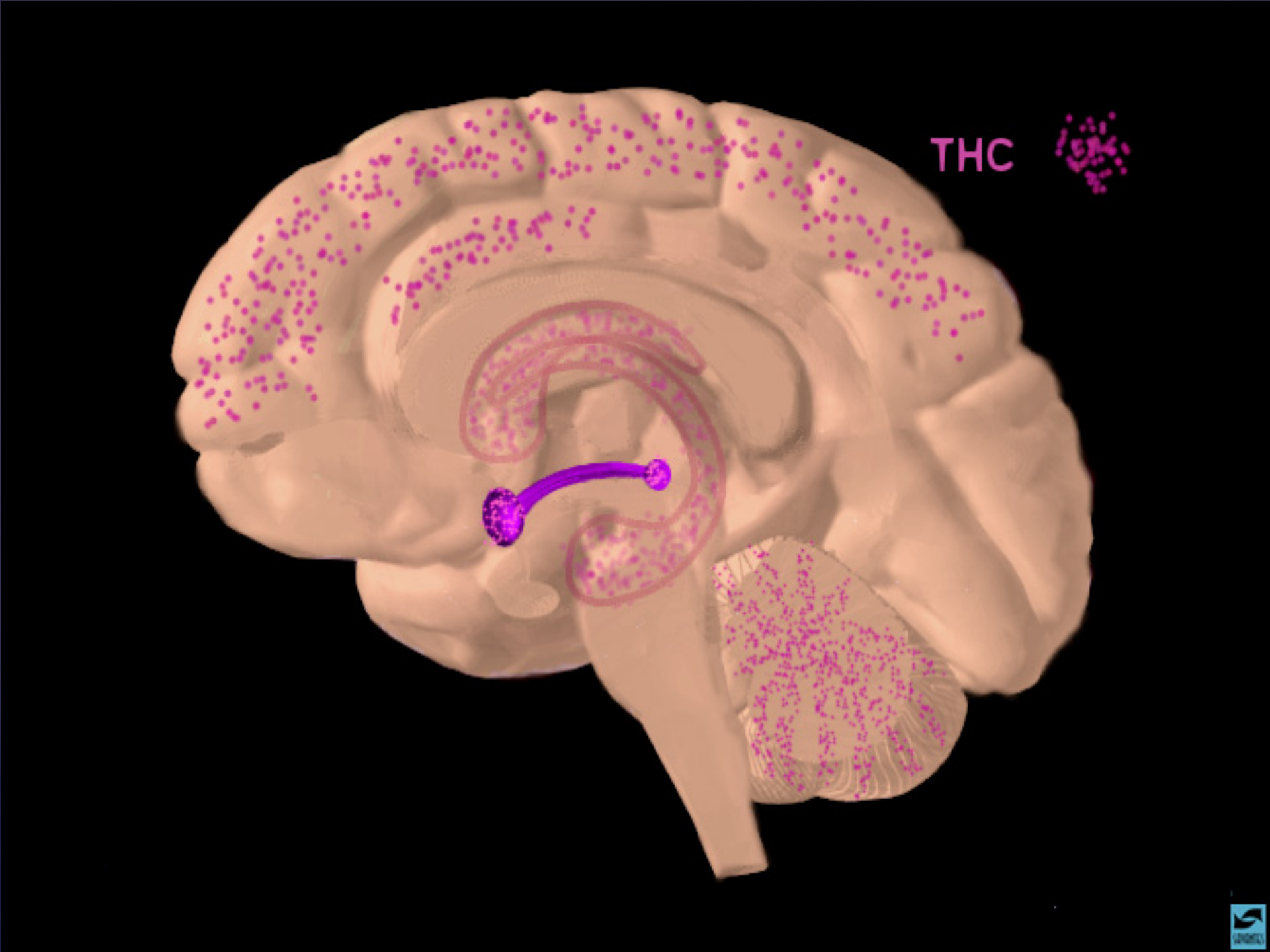
Brain Reward Circuitry and the Mesolimbic Dopamine system



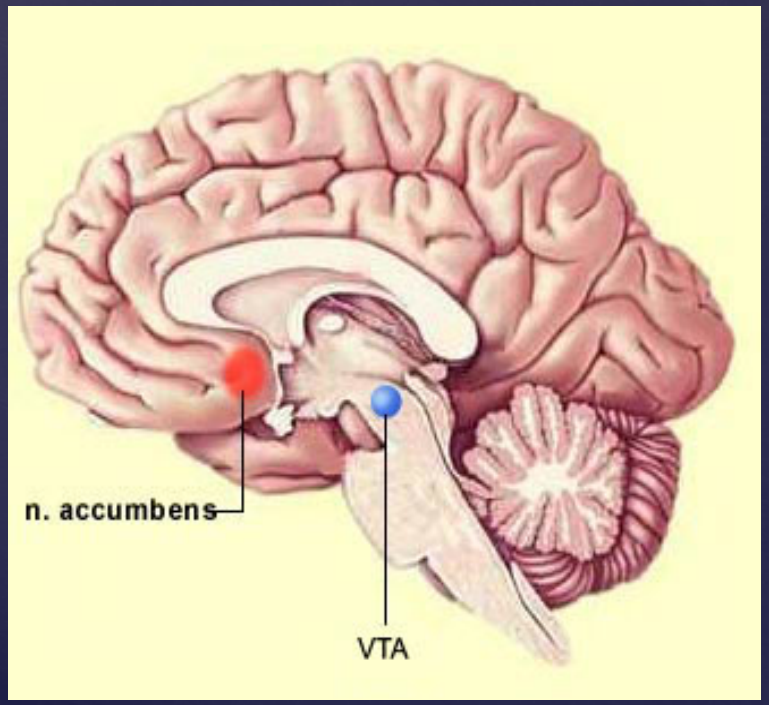


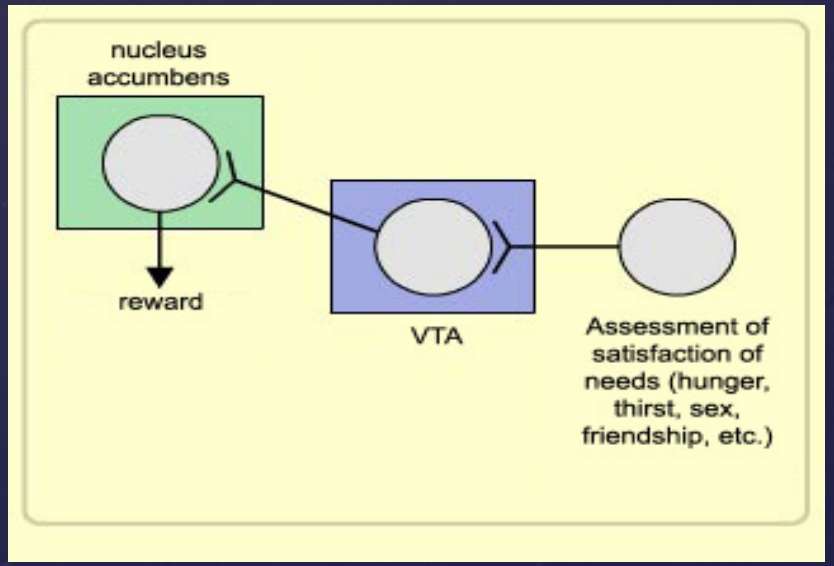

Cocaine


Opiates


THC

Brain Reward Circuitry and the Mesolimbic Dopamine system: A common pathway for different drugs of abuse.





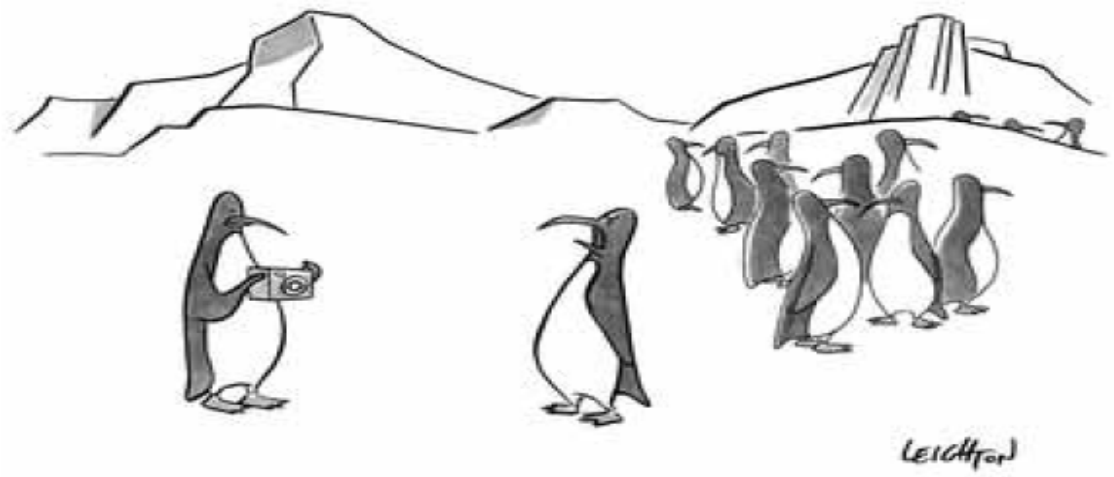
but……dependence is more than drug reward

Reward (Acute Effects)

- Approach Behavior
- Hedonic Reactivity
- Assignment of Positive Valence to Stimuli
- Conditioning and sensitization

Drug Dependence (long term effects)

- Maladaptive Reward Functioning
- Anticipatory Arousal
- Relapse/Craving
- Sensitivity to Drug-Related Cues
- Generalization of Drug-Related Cues
- Exaggerated Mental Preoccupation
- Tolerance
- Withdrawal



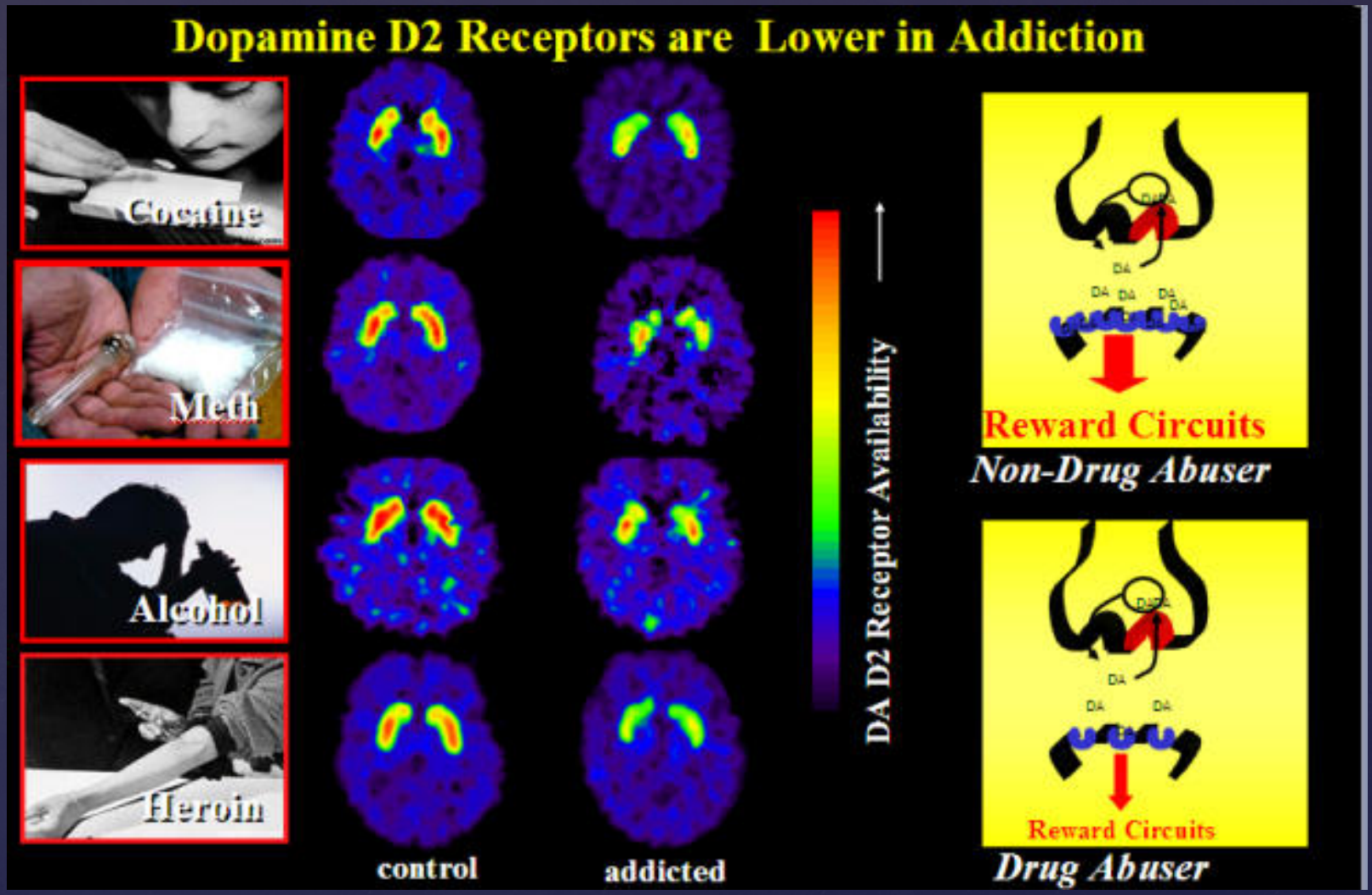
"Why on earth would you spring for color film?"

Robert Leighton (1/9/2006)

Addiction-linked Brain Changes in People:

Evidence from Human Neurobiology--Positron Emission Tomography (PET)

Long term and repeated drug use induce changes in brain that are very different from short term acute effects



The use of PET scans to assess the effect of drug abuse on the brain has opened new horizons to understanding how the brain works.

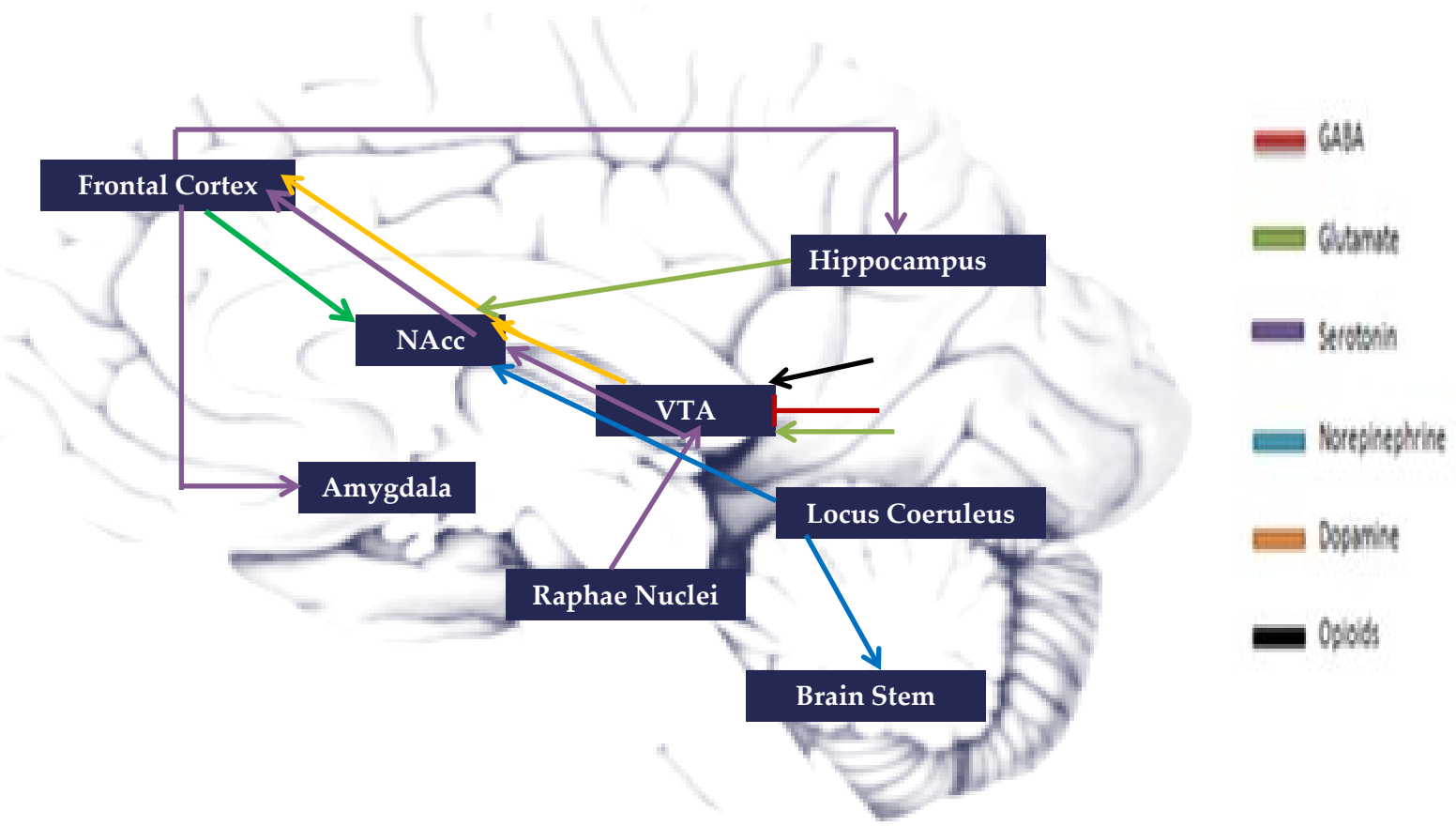
Potential Process Targets for Treatment

1. **Early:** Initiation and reward systems
2. **Mid:** Reinforcement and conditioning processes
3. **Late:** Later stages of the drug dependence
   - *focus of current Pharmacotherapies-*
     - Extinction-based approach (e.g. antagonists)
     - Substitution-based approach (e.g. agonists, partial agonists)
     - Craving and affect targeted treatments
     - Aversion-based approaches
     - Withdrawal management

Neurochemical Targets for Past and Recent Pharmacological Treatments

- Nicotine receptors (Ach)
- GABA
- NMDA receptors (Glutamate)
- Serotonin
- Norepinephrine
- Dopamine
- Opioids

Neuroanatomical Context of Pharmacotherapies



Dopamine (DA) Agonist-based Treatments

- Function : increase DAergic activity to reduce the harm and weaken the addiction

- Goal: reduce strength of craving and decrease the severity of withdrawal symptoms

  - Selegiline - DAergic agonist (2000s as stop-smoking aid)
  - Modafinil – DAergic agonist (2000s for withdrawal)
  - Bupropion - DAergic agonist (Zyban approved in 1997)

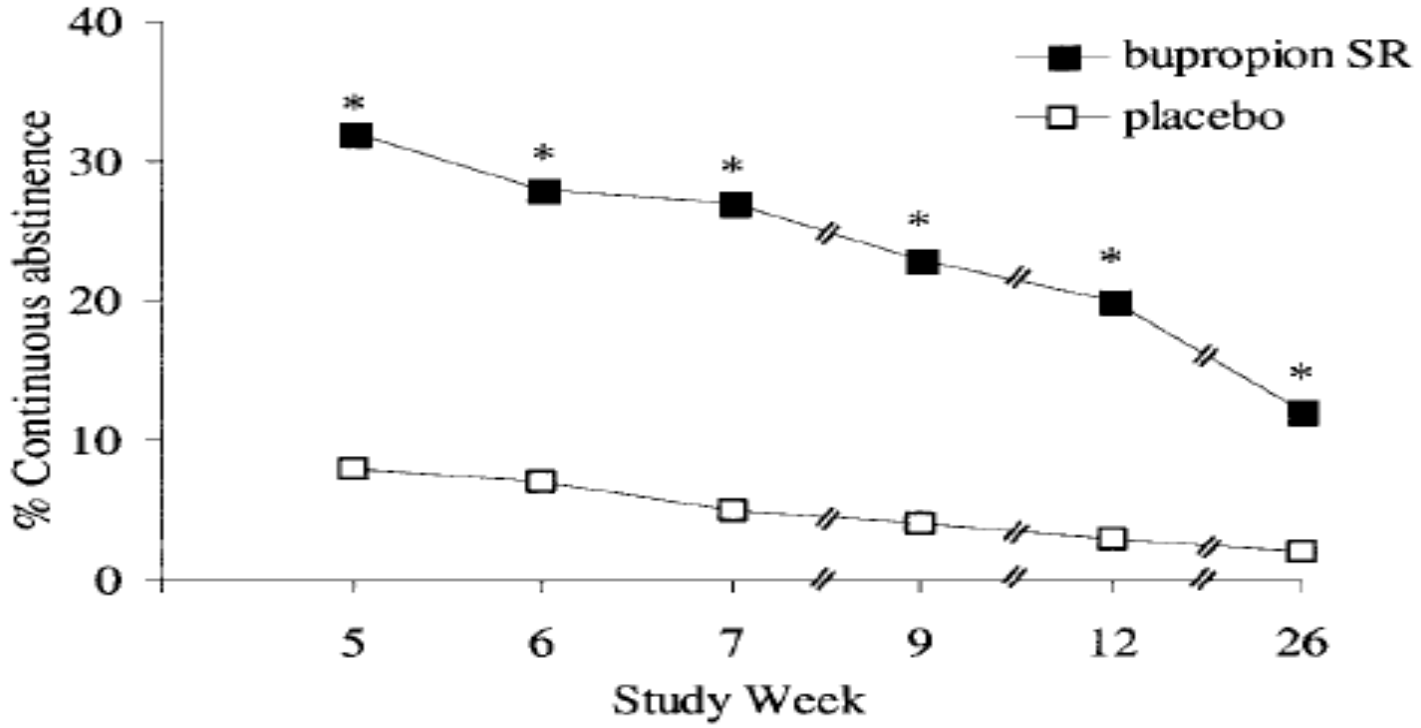


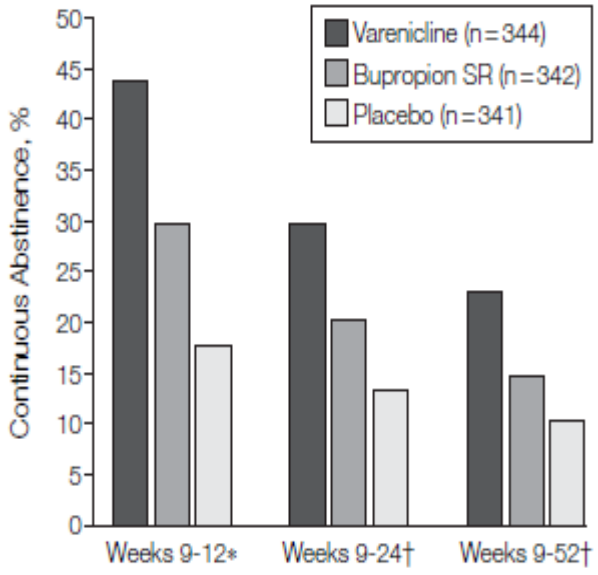
Fig 1. Continuous abstinence from the start of week 4 through each clinic visit during the treatment phase and through the follow-up visit at week 26. At each clinic visit, continuous abstinence was significantly higher (*$P < .001$) in participants receiving bupropion SR than the abstinence in the corresponding participants treated with placebo.

Gonzales et. al, *Clin . Pharmacol. Ther.* 2001

Pharmacological Treatments Targeting Nicotinergic systems

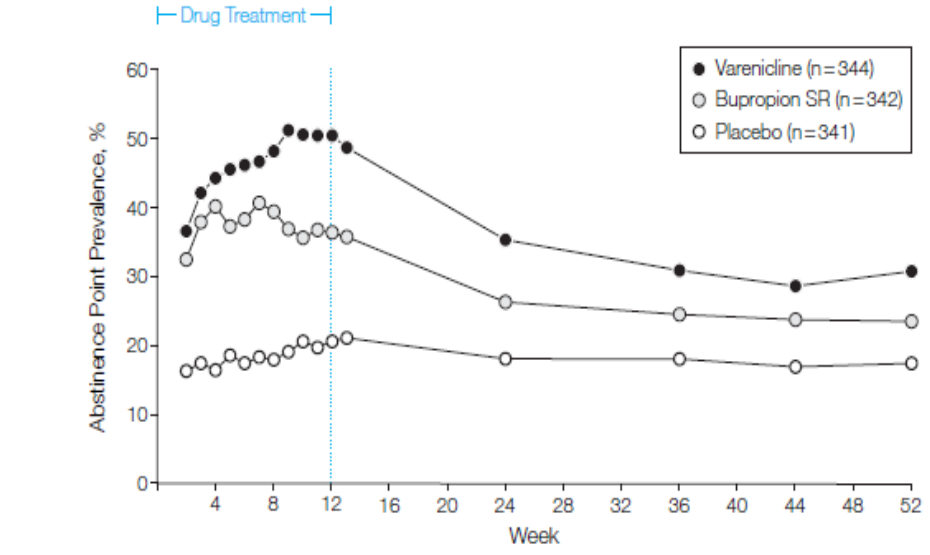
- Mecamylamine – nicotinic Ach receptor antagonist (earliest article on addiction cxn -1990s; important to craving and reward
- Varenicline – nicotinic receptor partial agonist (2006); important to craving and reward

Figure 2. Continuous Smoking Abstinence Rates



*Carbon monoxide level confirmed at clinic visits.
†Clinic and telephone visits.

Figure 3. Smoking Abstinence Point Prevance Verified by Carbon Monoxide Level at 7 Days

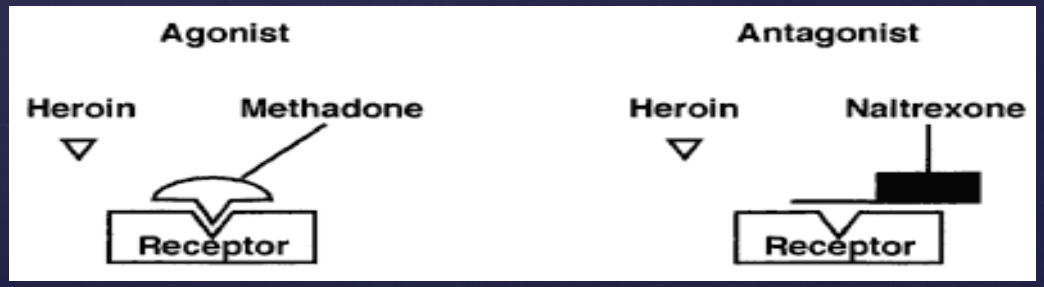


Bupropion SR indicates sustained-release bupropion.

Jorenby et. al, JAMA 2006

Pharmacological Treatments Targeting Opioid systems

- Significant to reward-blocking and long-term maintenance
  - Methadone – agonist (1960s)
  - Naloxone, Naltrexone- antagonists (1960s, 1994)
  - Buprenorphine, Suboxone - partial agonists (1980s, 2002)



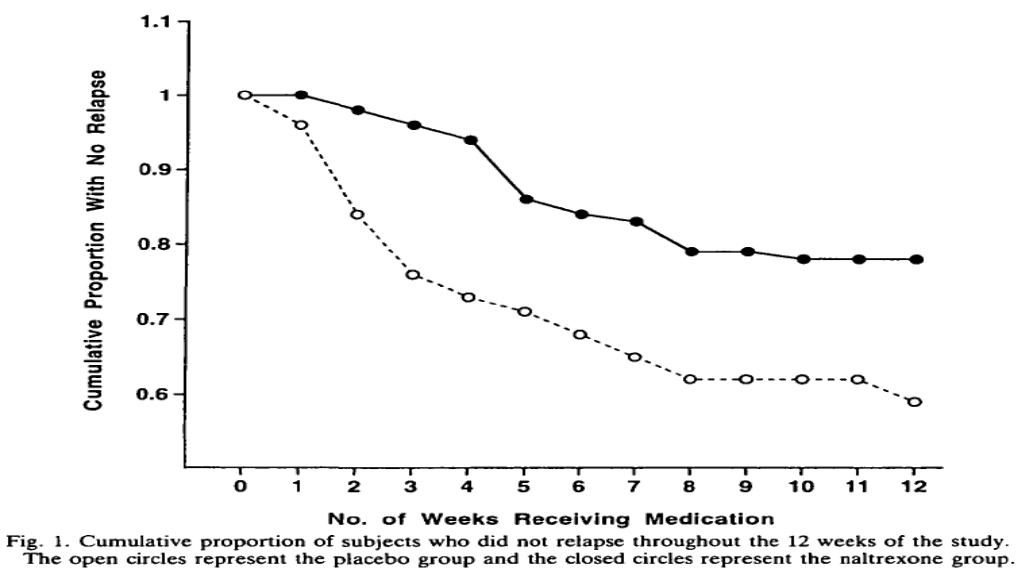
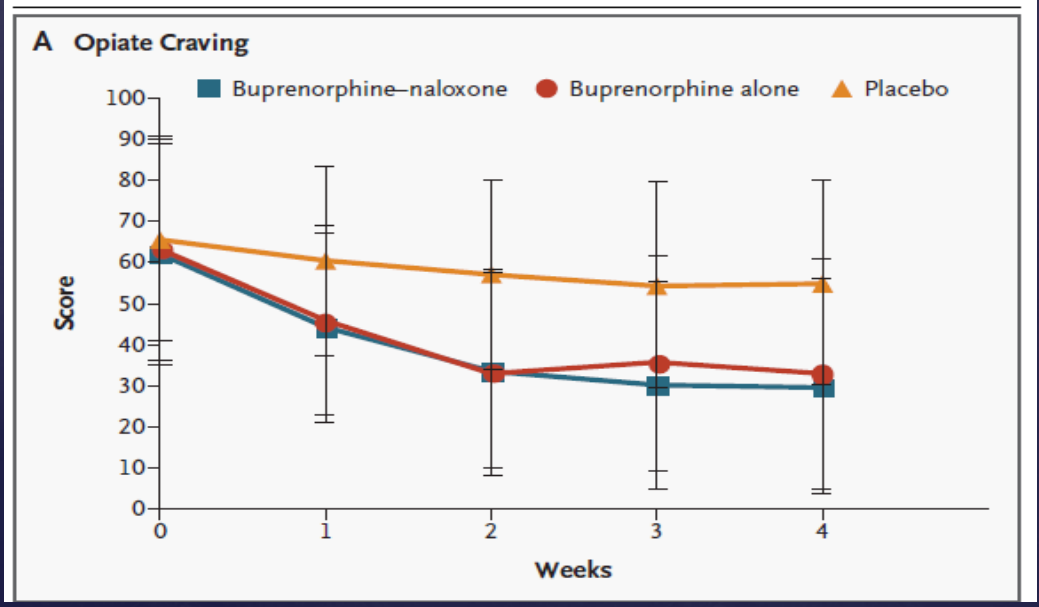
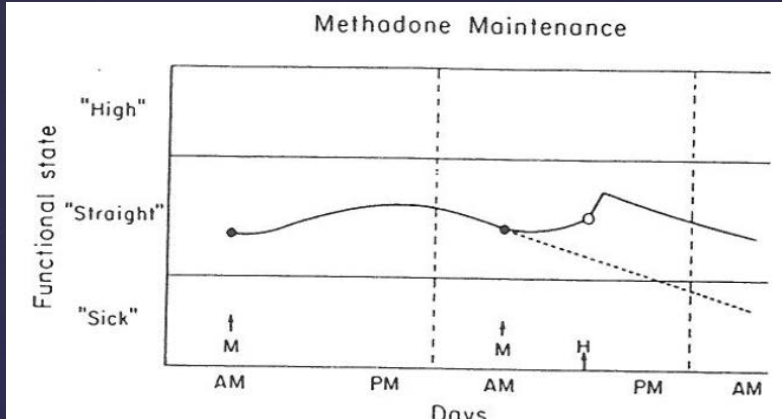


Fig. 1. Cumulative proportion of subjects who did not relapse throughout the 12 weeks of the study. The open circles represent the placebo group and the closed circles represent the naltrexone group.

Volpicelli, Volpicelli, & O'Brien, *Alcohol & Alcoholism* 1995



Fundala et. al, *N Engl J Med* 2003



Functional state of a patient blockaded with methadone (a single oral dose each morning). The effect of an intravenous injection of heroin in the blocked patient is shown in the second day. The dotted line (-----) indicates the course if methadone is omitted.

FIG. 2.—Stabilization of patient in state of normal function by blockade treatment. A single, daily, oral dose of methadone prevents him from feeling symptoms of abstinence ("sick") or euphoria ("high"), even if he takes a shot of heroin.

Dole, Nyswander, & Kreek, *Trans. Assoc. Am. Phys.* 1966

NMDA/ GABA/ MA-based Treatments

- **NMDA** (*N*-methyl-D-aspartate) is an amino acid derivative which binds to specific NMDA receptors-- associated with the excitatory neurotransmitter, GLUTAMATE
  - Activates mesolimbic DA ; conditioning, learning and memory

- **GABA** (γ- Aminobutyric acid) is an inhibitory neurotransmitter that acts to oppose excitatory neurotransmitters, such as glutamate;
  - Inhibits mesolimbic DA

- The **monoamines**, dopamine (DA) , serotonin (5HT) & norepinephrine (NE)
  - important to craving, arousal and reward processes

GABA and Glutamate-related Treatments

- **Acamprosate –** NMDA agonist/GABA agonist ; important to relapse prevention (1989)
- **Vigabatrin –** GABA transaminase inhibitor; increases GABA, reward-blocking (1980)
- **Tiagabine –** GABA reuptake inhibitor; increases GABA, reward-blocking (2000)
- **Topiramate –** AMPA antagonist; increases GABA, relapse prevention (2000)
- **Valproic acid –** GABA transaminase inhibitor; increases GABA

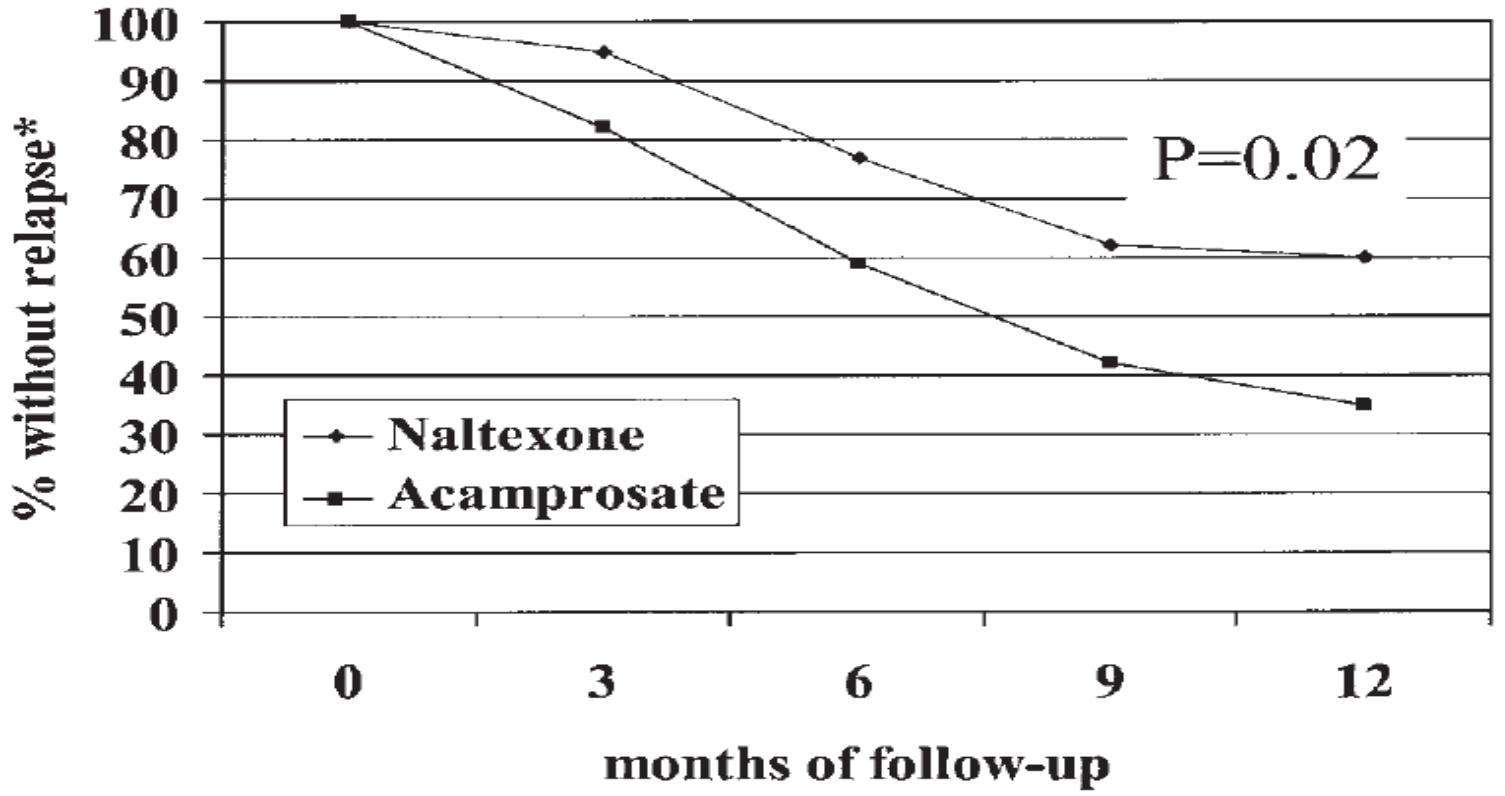
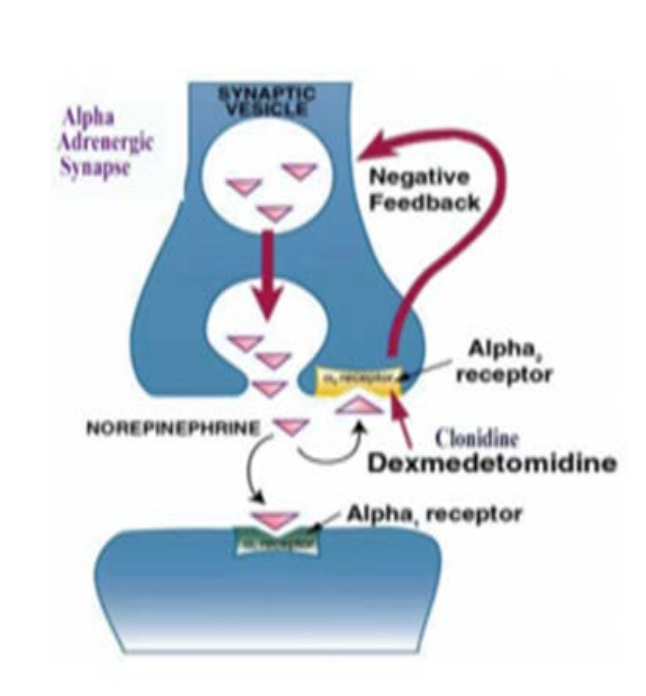


Fig. 2. Survival analysis to first relapse.
◆, naltrexone; ■, acamprosate. *Five or more drinks per day.

Rubio, Jimenez-Arriero, Ponce & Palomo, Alcohol & Alcoholism 2001

Withdrawal Management-based Treatment



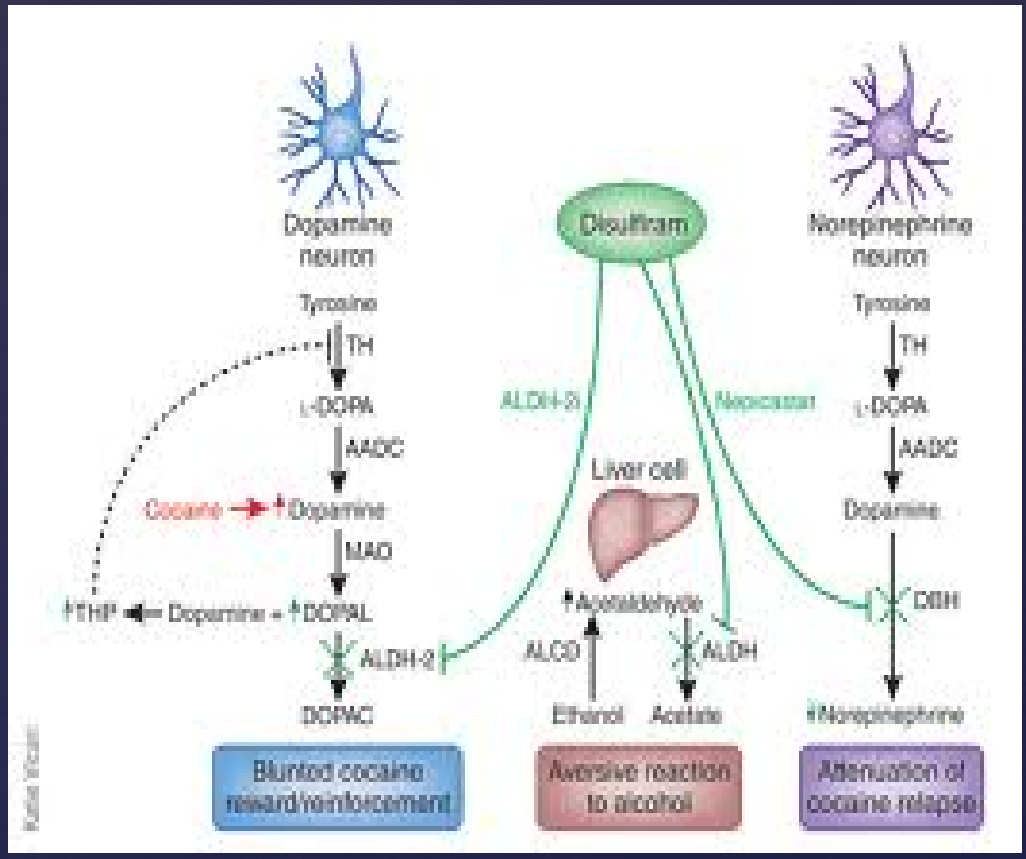
Clonidine

- Medication primarily for high blood pressure, anxiety and pain
- Used in treatment of alcohol, opiate and nicotine abuse
- Acts on alpha-2 (α_2) adrenergic receptors in the brain to decrease blood pressure and suppress NE release
- Used to alleviate withdrawal symptoms associated with detoxification; decreases sweating, anxiety, heart rate, blood pressure and restleness

Aversion – based Treatment

Disulfiram

- Increases alcohol sensitivity such that consumption results in negative, unpleasant bodily reactions (e.g. high blood-pressure, sweating, vomiting)
- Recently found to play a role in cocaine abuse treatment as it inhibits DA breakdown ; too much DA causes increased blood pressure and anxiety, among other symptoms



Weinshenker, *Nature*, 2010

New and Emerging….

The Economist

Combating addiction

Can a vaccine stop drug abuse?

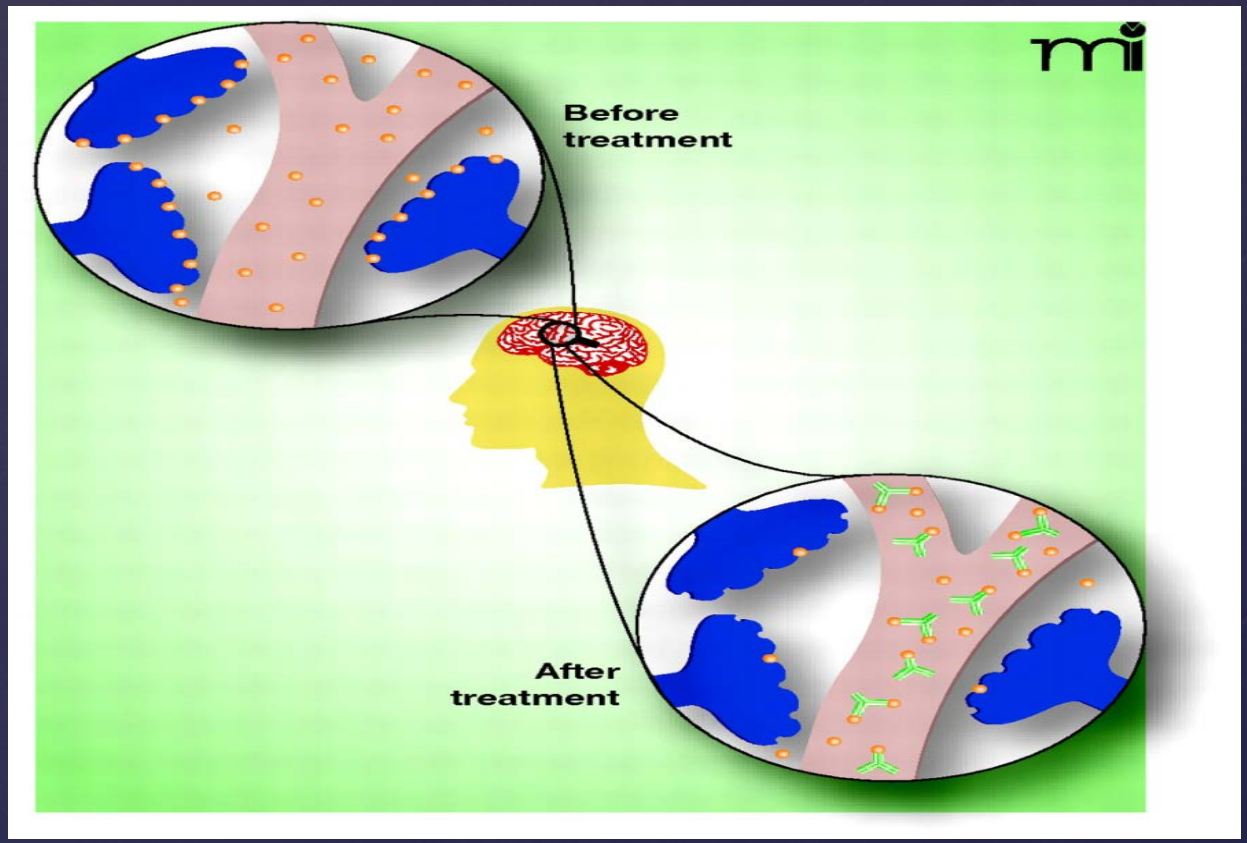
It may be possible to vaccinate people against addictive drugs

May 19th 2011 |From the print edition

Emerging Approaches: Immunotherapies

- A vaccine is a chemical conjugate molecule that stimulates an immunological response in the body
- A large carrier protein forms a platform for a molecule (hapten) to attach to: the molecule represents an analog of the drug of abuse.
- Because the molecules representing drugs of abuse are typically small in size and flexible, they generally go undetected by the body and may not stimulate an immune response.
- Immunotherapy approach aims to create vaccines that allow the immune system to recognize the drug molecule and create an immune response
- The immune response would be characterized by inactivation of the drug effect, and a "remembering" by the immune system for future defense

Designing Immunotherapies to Thwart Drug Abuse



Depiction of the mechanism by which a drug-specific antibody protects the brain from adverse health effects. When drugs of abuse are self-administered, the drug (yellow circles, "Before") rushes from the bloodstream (in gray) across the blood-brain barrier into the brain where it binds to sites of action (blue terminals) that produce euphoria. "After Treatment" with a high affinity anti-drug antibody (Y-shaped object), drug entry into the brain is restricted and rapid antibody-induced redistribution occurs which blocks or reduces the rewarding pharmacological effects. (Peterson et al, 2009)

Vaccines

- **Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone-Maintained Patients**
- **A Randomized, Double-blind, Placebo-Controlled Efficacy Trial**
- **Bridget A. Martell, MD, MA; Frank M. Orson, MD; James Poling, PhD; Ellen Mitchell, RN; Roger D. Rossen, MD; Tracie Gardner, PhD; Thomas R. Kosten. MD**
- *Arch Gen Psychiatry.* 2009;66(10):1116-1123.
- ***Conclusions Attaining high (≥43 µg/mL) IgG anticocaine antibody levels was associated with significantly reduced cocaine use, but only 38% of the vaccinated subjects attained these IgG levels and they had only 2 months of adequate cocaine blockade. Thus, we need improved vaccines and boosters.***

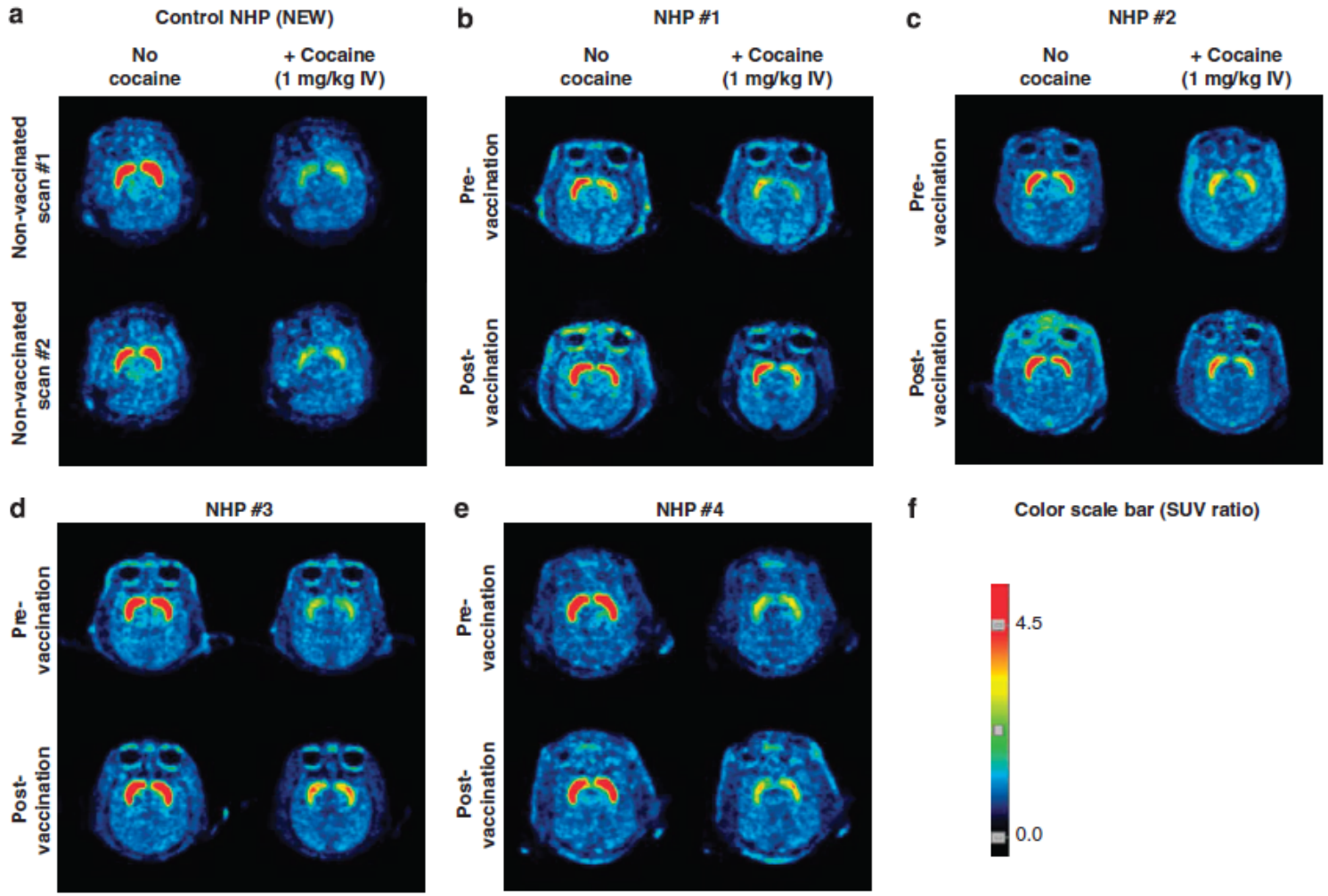


Figure 2 [^{11}C]PE2I-PET images before and after dAd5GNE vaccination with and without cocaine administration. The images display the standard uptake value (SUV) of cortical and subcortical areas normalized to the SUV of the reference region, cerebellum. (a) Control, non-vaccinated. (b–e) Vaccinated, correspond to nonhuman primates (NHP) #1–4. For each panel, top left—pre-vaccination without cocaine; top right—pre-vaccination with cocaine; bottom left—post-vaccination without cocaine; and bottom right—post-vaccination with cocaine. In all panels, the cocaine dose was 1 mg/kg. (f) The color scale bar representing the SUV ratio (scale 0.0–4.5) for all images.

Maoz et. al, *Neuropsychopharmacology* 2013

Summary

- Pharmacotherapy development strategies build on neuroscientific knowledge of reward systems
  - Limited new pharmacological targets in recent years
  - Modest efficacy
- Existing pharmacotherapies target systems that have been known for some time (NMDA, AMPA and nicotine-based treatments most recently emerged)
- Immunotherapies are the most recently explored emerging target and represent a paradigm shift

Additional Considerations

- ***Developmental*** : targeting different mechanisms associated with stages of addiction development (i.e. early vs late intervention)
- ***Developmental*** : youth and early detection/intervention
- ***Comorbidity*** and concurrent disorders: parallel systems
- ***Individual variability*** (genetic and epigenetic considerations)
- Intersection between ***community-based programs*** and emerging immunotherapeutic approaches requires integration
- ***Polydrug use*** and immunotherapy limitations

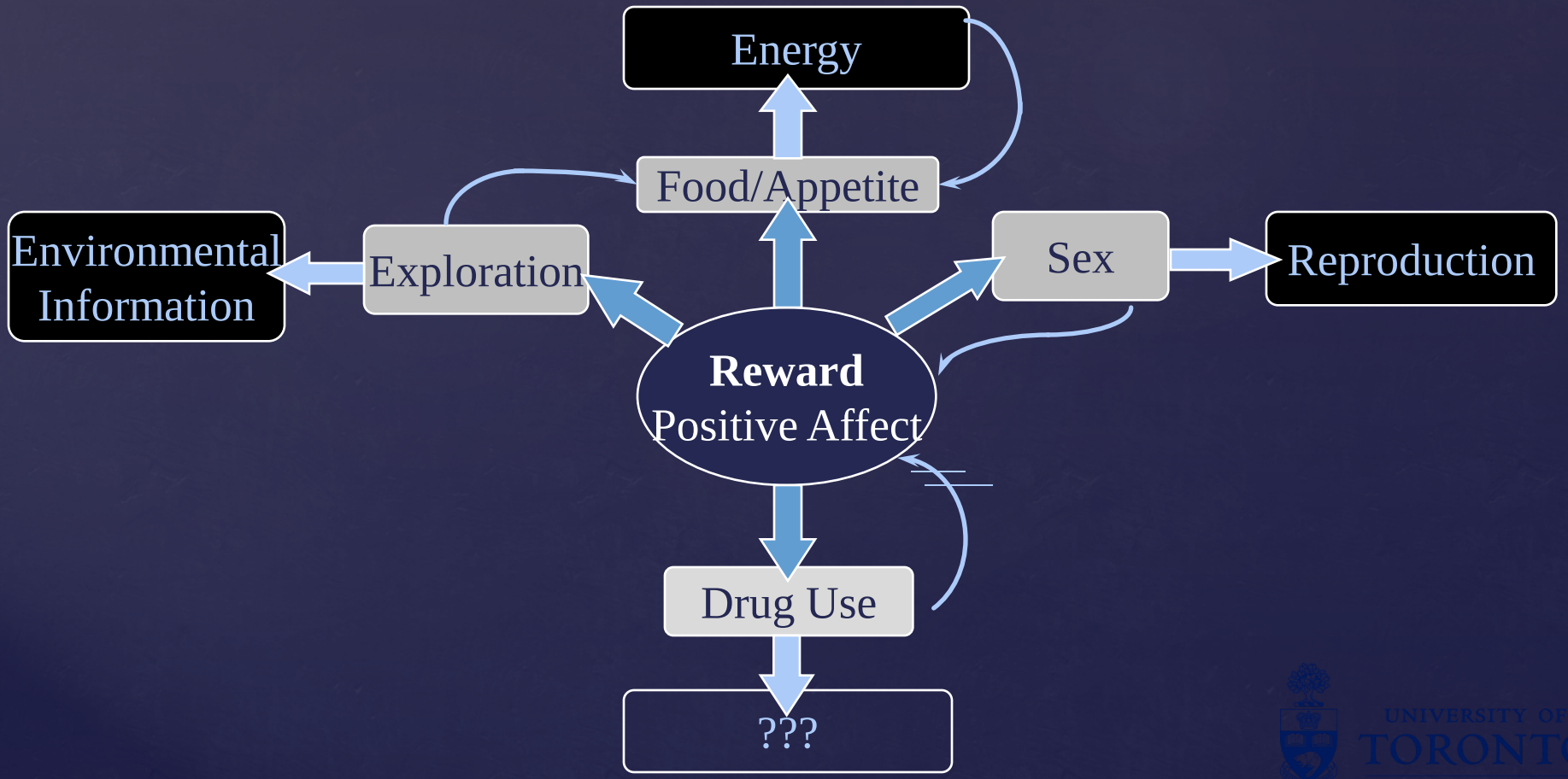
THANK YOU

Addiction Process Targets for Current Pharmacotherapies

- Current Pharmcotherapies largely target later stages of addiction process

- Approaches include:
  - Extinction-based approach (e.g. antagonists)
  - Substitution-based approach (e.g. agonists)
  - Craving and affect targeted treatments
  - Aversion-based approaches
  - Withdrawal management

Drug of abuse access, and interfere with **("hijack")**, brain reward systems that are ***essential for the expression of normal motivated behaviour.***



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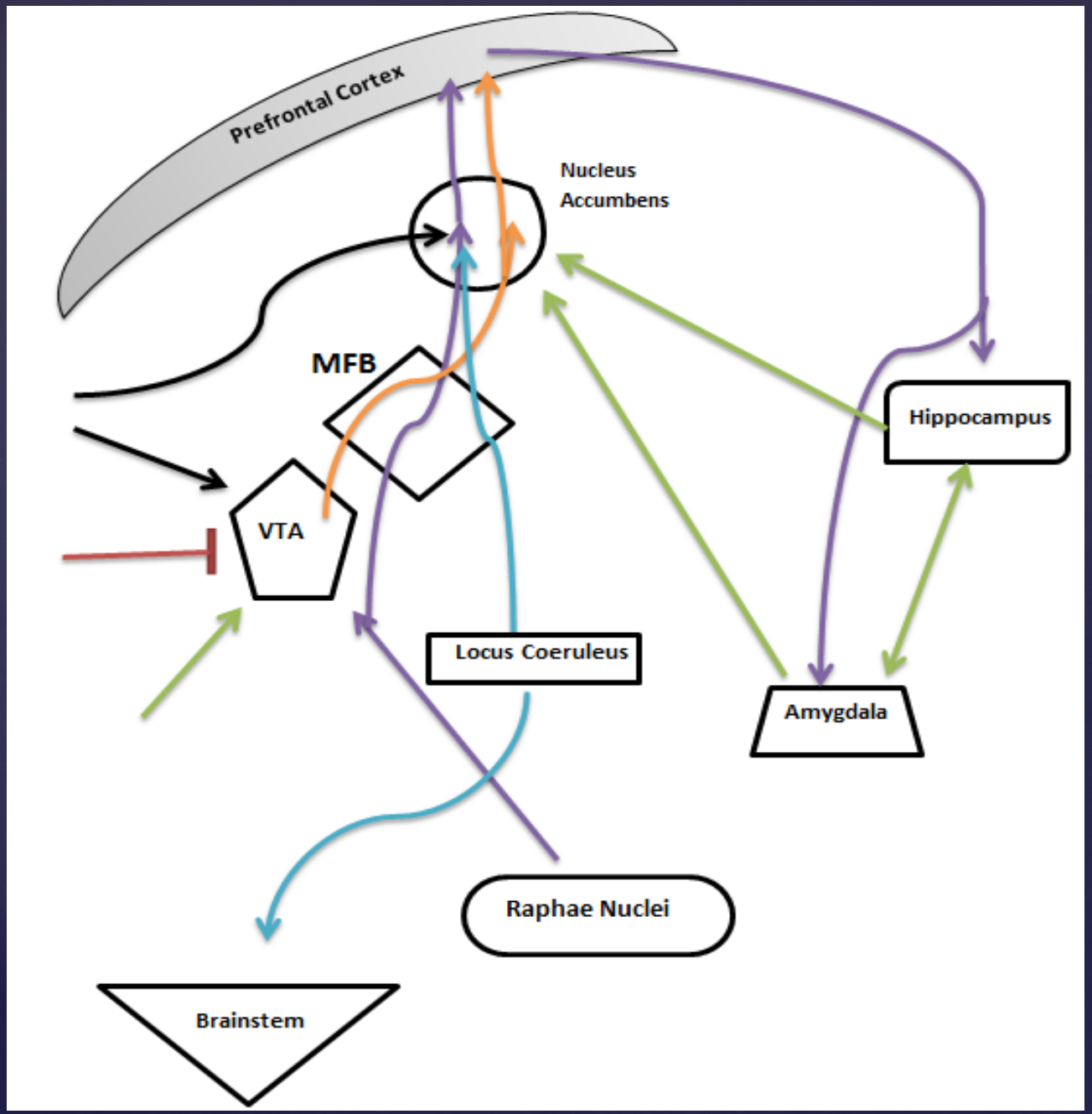
Prefrontal Cortex
Nucleus
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VTA
Hippocampus
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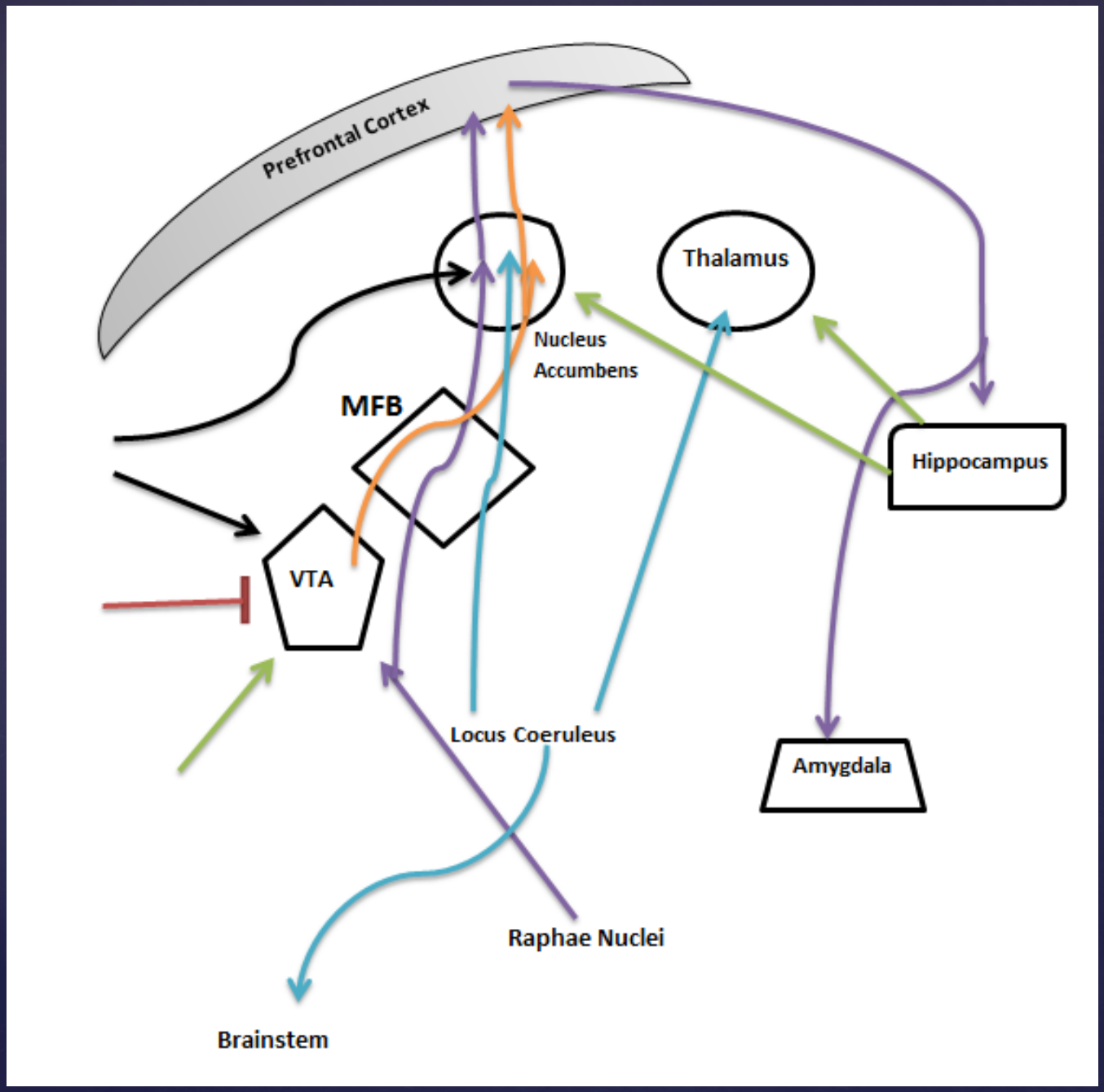
Serotonin
Norepinephrine
Dopamine
Opioids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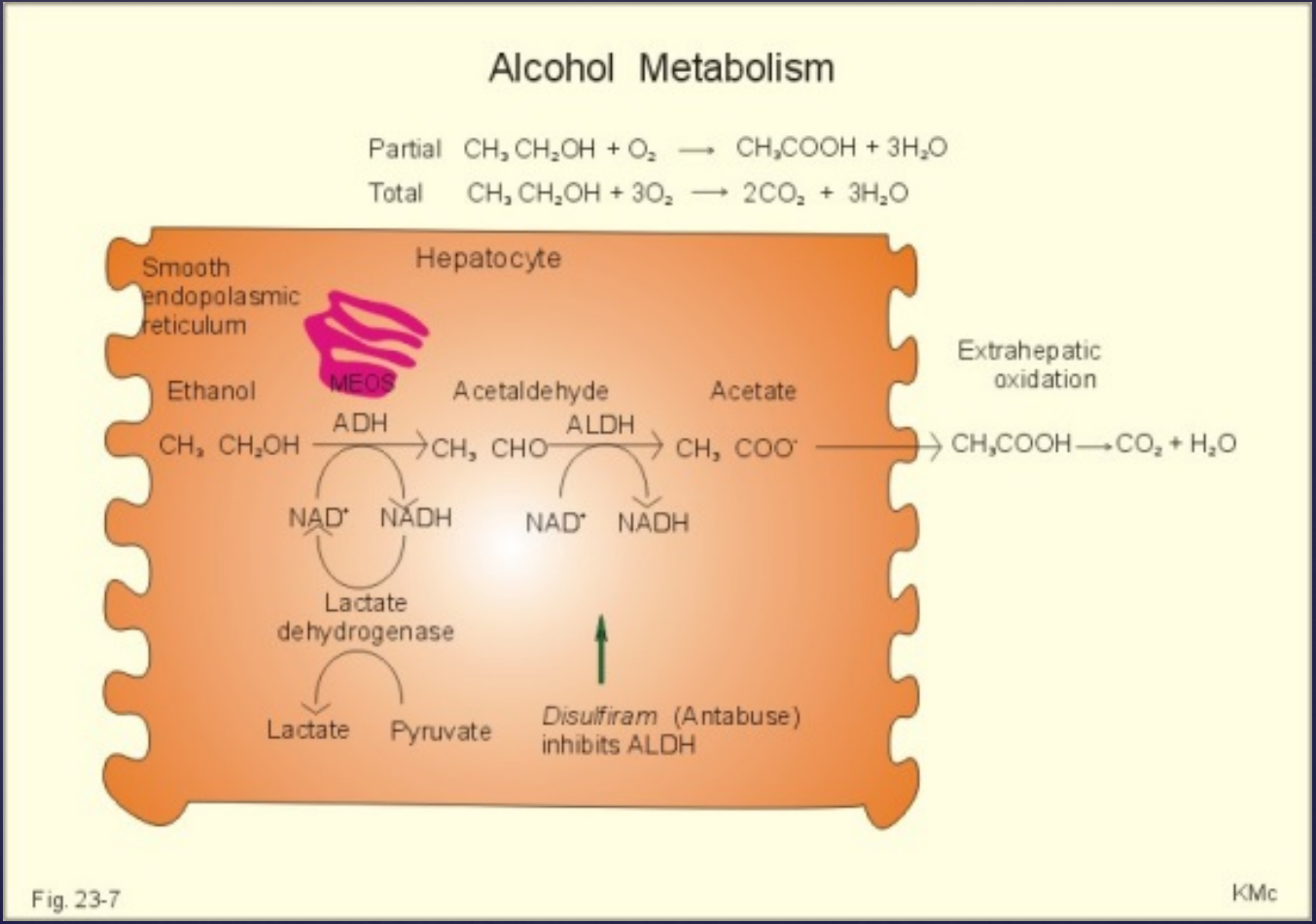
GABA
Glutamate
Serotonin
Norepinephrine
Dopamine
Opioids

- ** For your knowledge



- Need results slide with data from the Bridget et al vaccine study

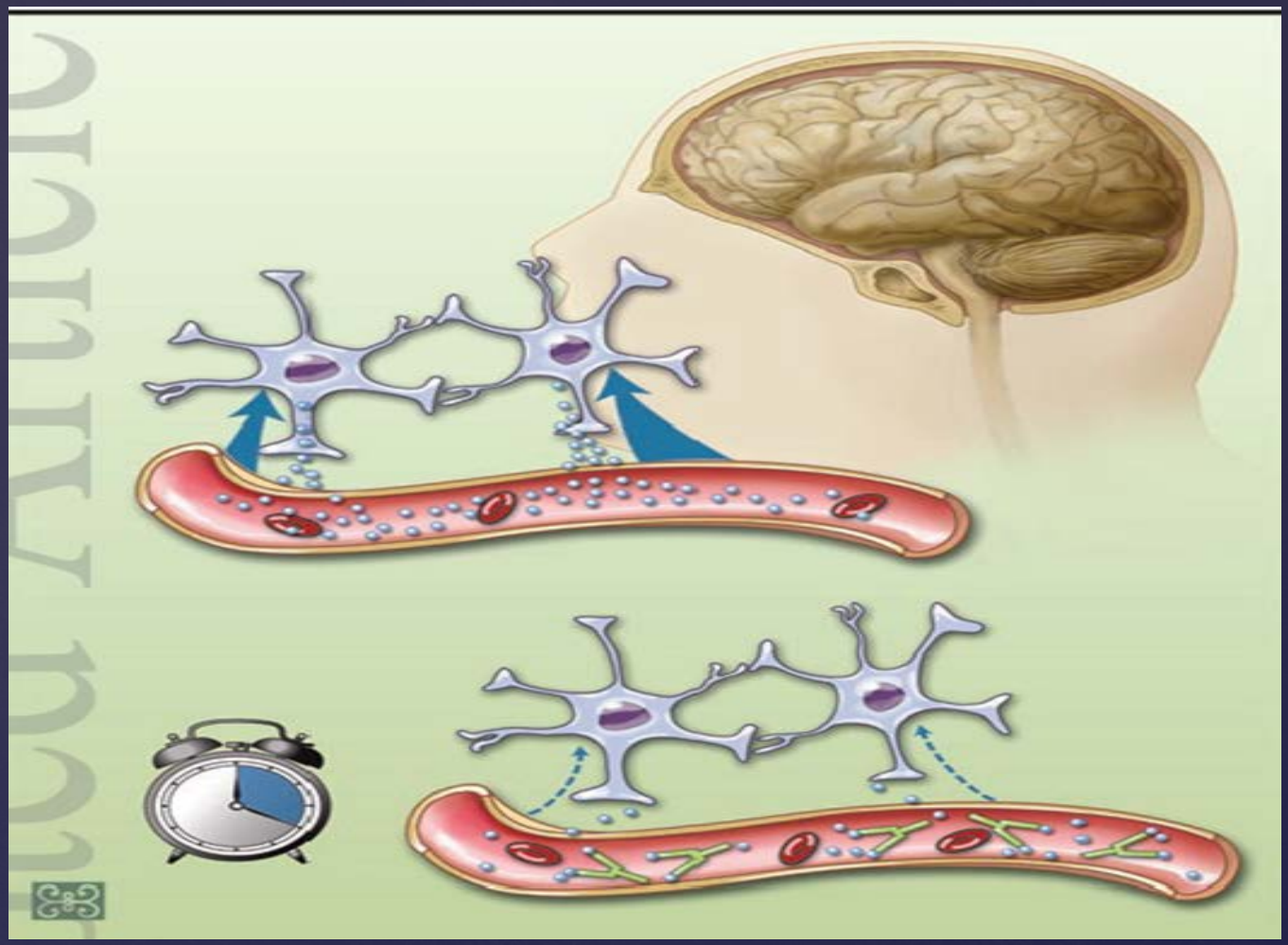


Figure 2 Mechanism of action of a vaccine against cocaine addiction. In the absence of the vaccine, cocaine is readily absorbed at the blood–brain barrier and thereby enters the brain. In the brain, the drug causes reinforcement of pleasurable effects, or the "high" associated with cocaine. If a vaccine is administered, it stimulates the production of antibodies against cocaine. Subsequently, if cocaine is taken, the antibodies bind to the drug and sequester it in the blood circulation. This antibody–drug binding prevents the cocaine from rapidly leaving the blood vessels and entering the brain, thereby reducing the drug's euphoric effects.

Kosten, Domingo, Orson & Kinsey, *British Journal of Clinical Pharmacology* 2013

Neurochemical and Behavioural Targets for Past and Recent Pharmacological Treatments

Monoamine systems

- Selegiline - DAergic agonist (2000s as stop-smoking aid)
- Modafinil – DAergic agonist (2000s for withdrawal)
- Buproprion - DAergic agonist (Zyban approved in 1997)

GABA/NMDA systems

- Acamprosate – GABA agonist (1989)
- Vigabatrin – GABA transaminase inhibitor (earliest article found on addiction cxn - 1980)
- Tiagabine – GABA reuptake inhibitor (1980s-90s was created; earliest article found on addiction cxn – 2000)
- Topiramate – AMPA antagonist (glutamate) (1979; earliest article found on addiction cxn - 2000)
- Valproic acid - GABA transaminase inhibitor

Opioid systems

- Methadone – agonist (1960s)
- Naloxone, Naltrexone- antagonists (1960s, 1994)
- Buprenorphine, Suboxone - partial agonists (1980s, 2002)

Nicotinergic

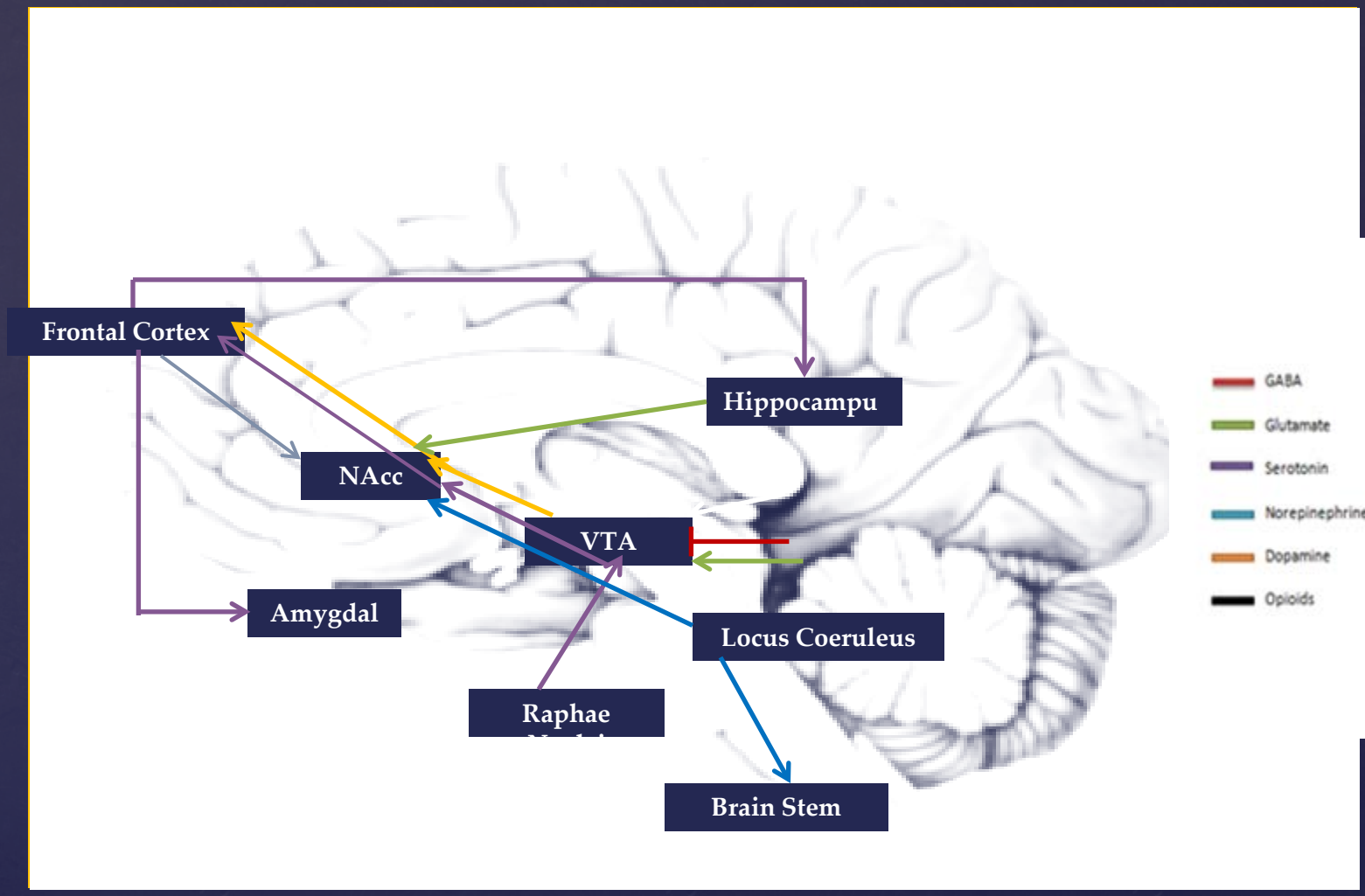
- Mecamylamine – nicotinic ACh receptor antagonist (1990s)
- Varenicline – nicotinic receptor partial agonist (2006)

5. Withdrawal management

- Clonidine – adrenergic agonist (1980s)

6. **Alcohol metabolism**

- Disulfiram -enzymatic target (1950s)


Frontal Cortex
Hippocampu
NAcc
VTA
Amygdal
Locus Coeruleus
Raphae
Brain Stem
GABA
Glutamate
Serotonin
Norepinephrine
Dopamine
Opioids

Neurochemical Targets for Past and Recent Pharmacological Treatments

- **Monoamine systems**
- **Opioid systems**
- **Ach systems**
- **GABA/NMDA systems**
- **Withdrawal management**
- **Alcohol metabolism**

Addiction--
Stages of Brain related changes

1. ***Exploration and drug activation*** of brain reward systems

2. In the beginning, ***sensitization*** of Brain Reward systems (i.e. increased dopamine) and beginning of development of association with drug relate cues: progressively enhanced rewarding value of drugs

3. In the **longer term**, effects of sustained increases in dopamine release leads to the opposite **– down-regulation – the brain adapts**

4. The long term effects of drug use are facilitated by **drug related cues** and by **chronic stress**

5. Changes in baseline dopamine function – the new normal (brain requires drug to achieve normal state – a **homeostatic** mechanism)

6. More drug use to counter the psychological effects of downregulation…. Leads to more downregulation… leads to more profound effects & downward spiral.

Neuroanatomical Context: Pharmacotherapies