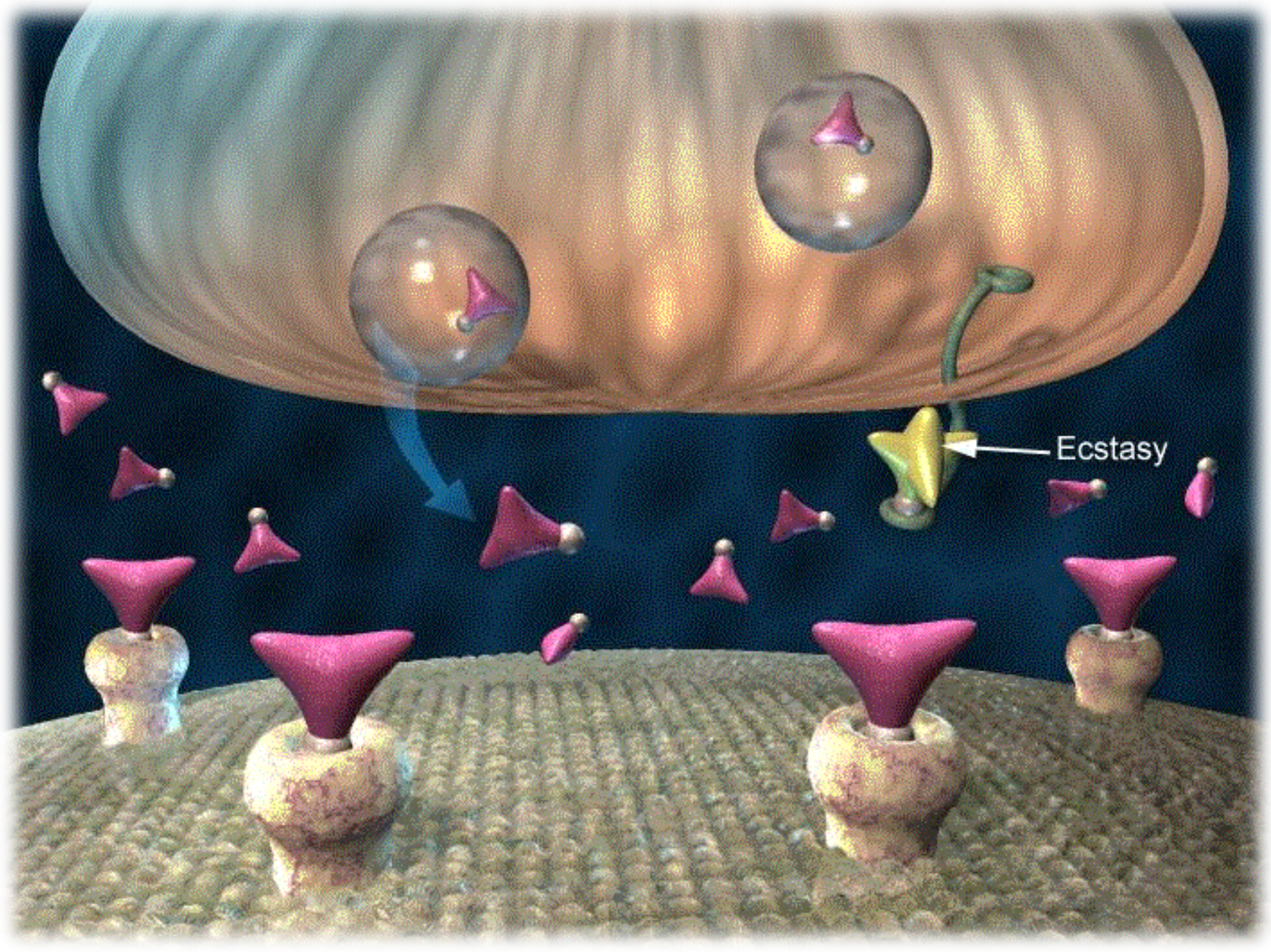
Drugs, Behaviour, and Neurotransmitters



Psychostimulants

Indirect DA agonists: cocaine, amphetamine, methamphetamine, methylphenidate (Ritalin)

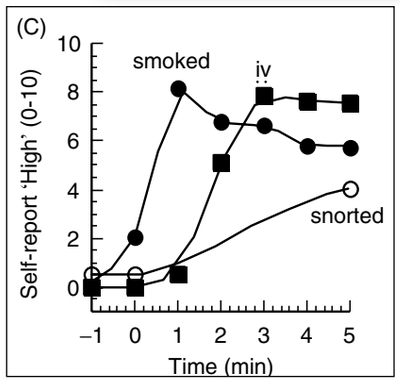
Non-DA-agonists: caffeine, nicotine, scopolamine

We will discuss only the indirect agonists

Psychostimulants

Cocaine

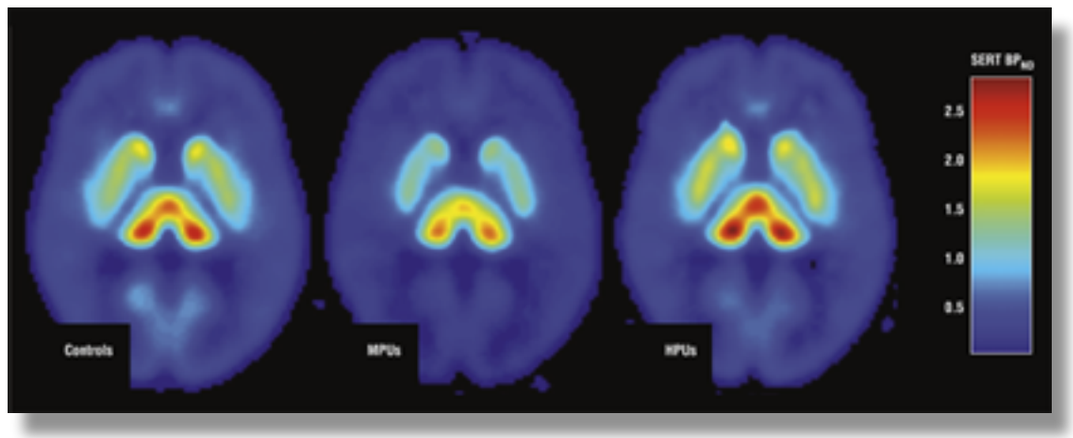
- Found in the leaves of the coca shrub
- Schedule II drug (it has medical use as local anesthetic)
- Cocaine HCl, can be taken orally, intranasally (snorting), or IV. As free base (crack - baking soda; freebase cocaine - ammonia & ether), can be smoked
- Physiological effects: Increases heart rate and blood pressure, appetite suppressant
- Behavioural/subjective effects: "High" - Mood elevation, euphoria, heightened energy, great self-confidence. Sometimes a brief "Rush" - great pleasure (like intense orgasm). Also, hyperactivty, increased sexual interest, increased aggressiveness
- Interestingly, the stimulant effect is much smaller in well-functioning, motivated subject



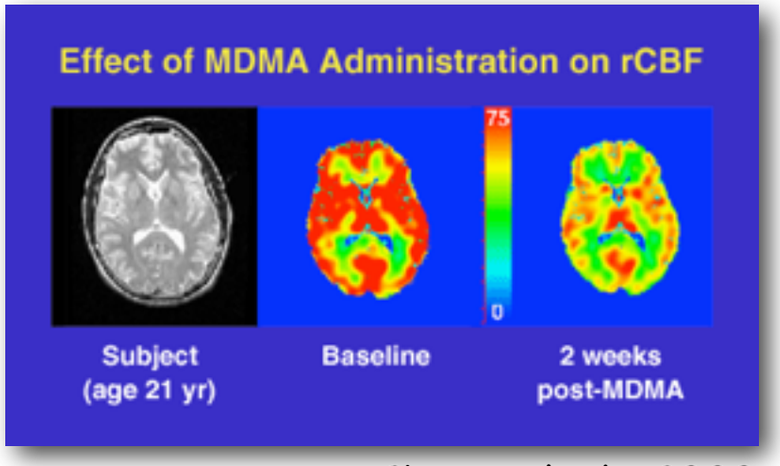
Psychostimulants

Amphetamines

- Synthetic psychostimulants. There are some plant compounds with similar molecular structure (e.g., khat)
- Methamphetamine (meth, speed) and MDMA (Ecstasy) are also members of the same family
- A schedule II drug
- Can be taken orally (tablets) or IV.
- Physiological, behavioural and subjective effects are very similar to cocaine's
- Neurotoxicity: high for methamphetamine (maybe MDMA?)



Erritzoe et al., 2011



Chang et al., 2000

Psychostimulants

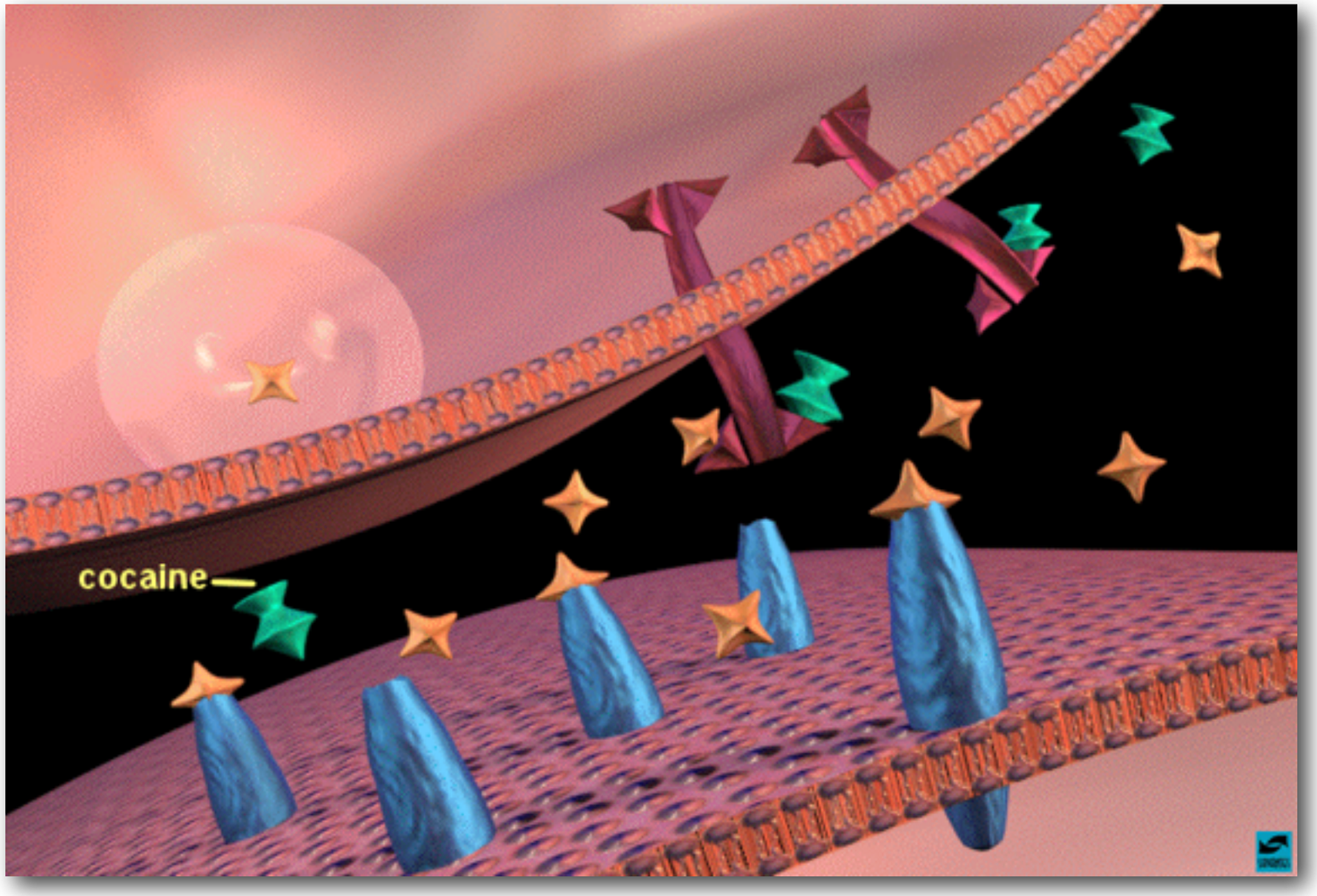
Cocaine & Amphetamine

- Both tolerance and sensitization can develop with chronic use
- Compulsive use leads to **binge** stage
- Withdrawal (Gawin & Kleber, 1986): Phase 1 - **Crash** (up to 4 days), Phase 2 - **withdrawal** (up to 10 weeks), Phase 3 - **extinction** (indefinitely?)

Psychostimulants – Mechanism of action:

Cocaine

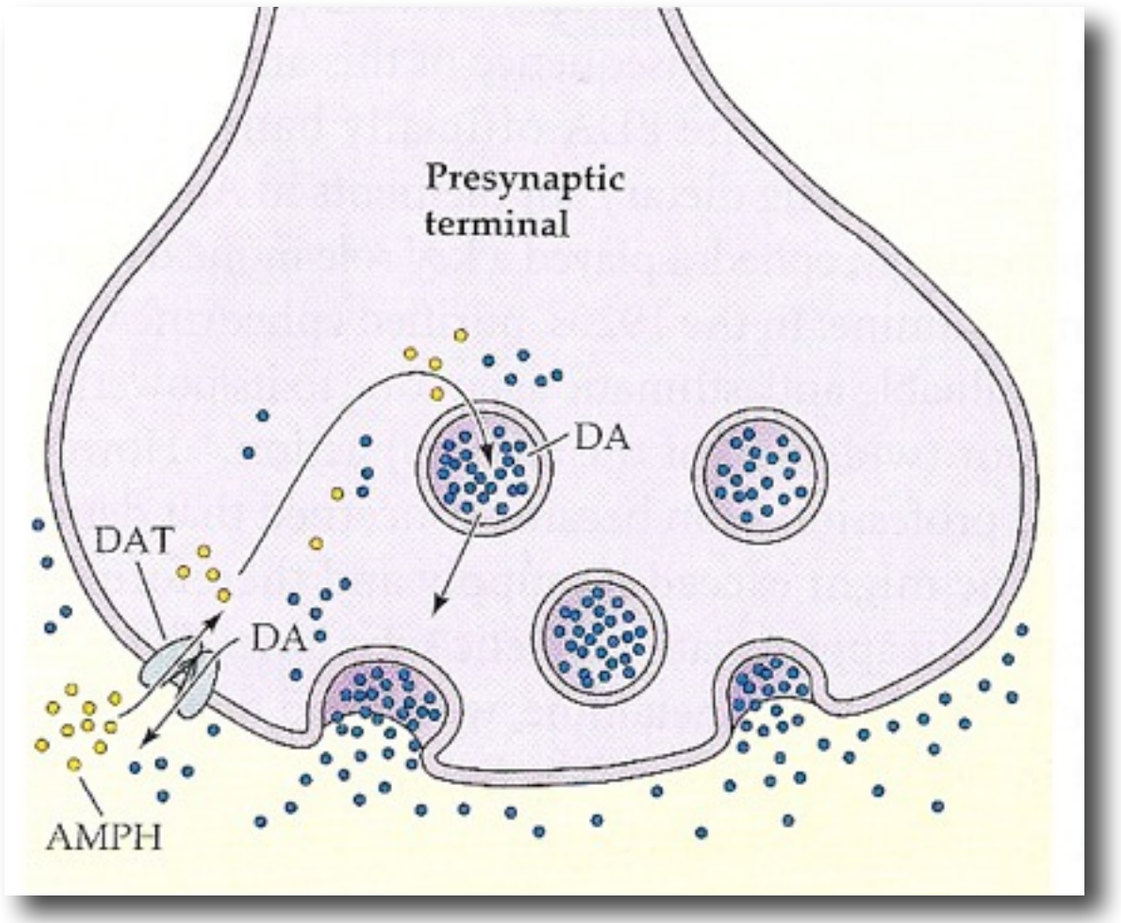
- Acts by blocking the reuptake of DA, NE, and 5-HT. Cocaine blocks 5-HT reuptake most effectively. However, cocaine's effects on locomotor activity, reinforcement, and addiction are mediated by the DA system.



Psychostimulants: Mechanism of action:

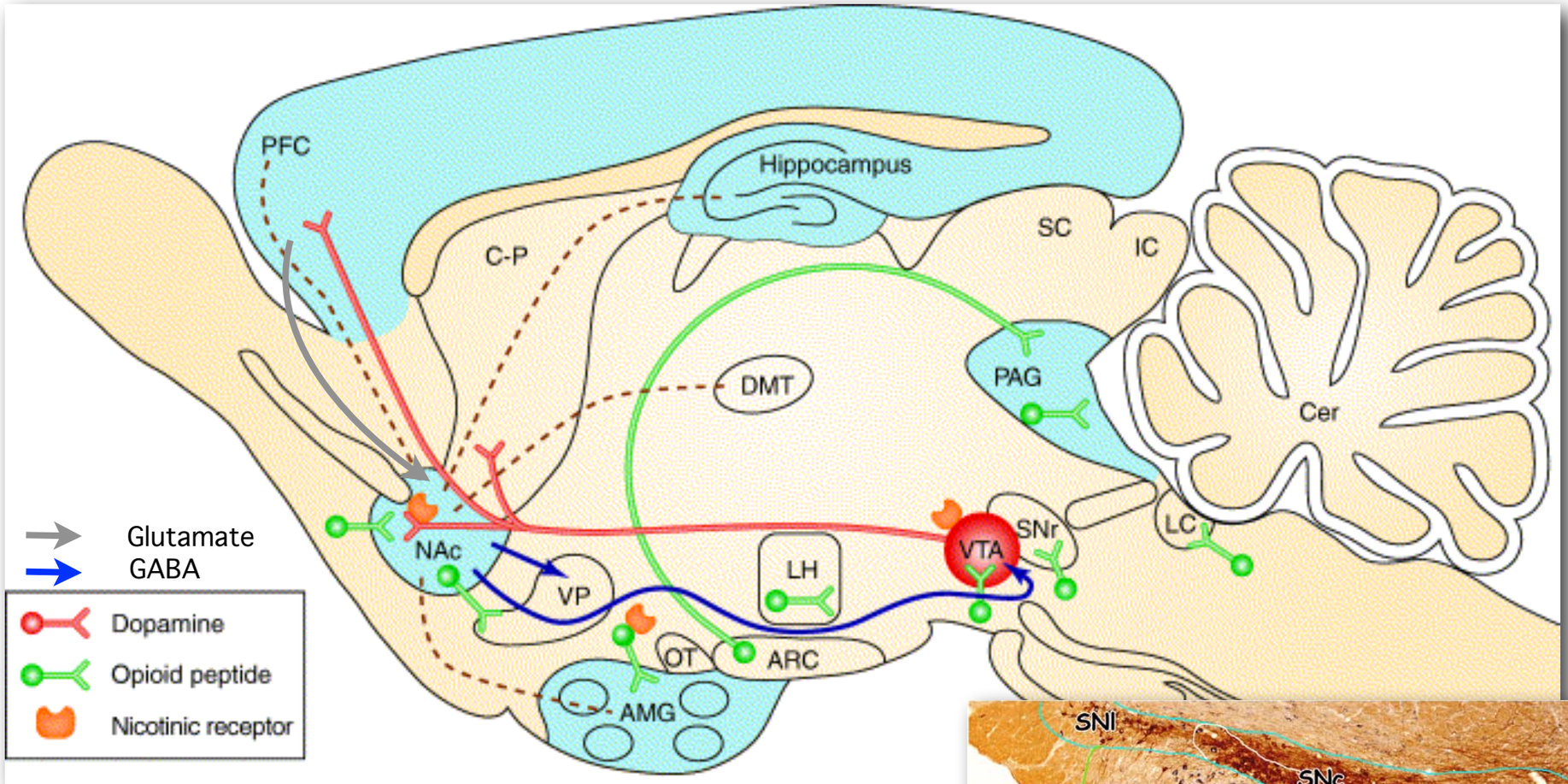
Amphetamine

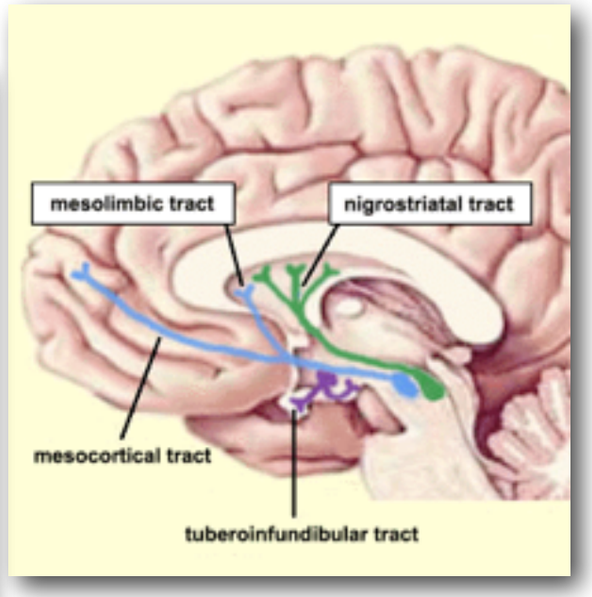
- Similar to cocaine, acts by blocking the reuptake of DA, NE, and 5-HT, and the effects on locomotor activity, reinforcement, and addiction are mediated by the DA system. Blocks DA reuptake most effectively. However, it also releases DA from the vesicles and reverses DAT.

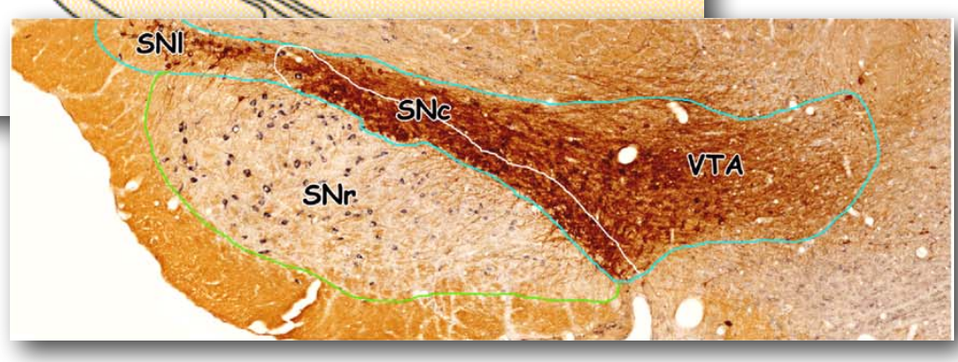


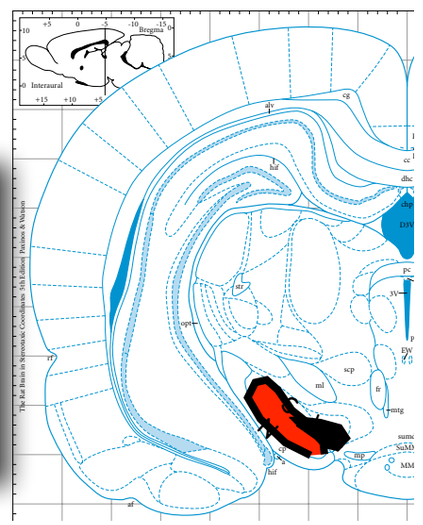
The DA System

- Two major neuronal pathway from the mid-brain to forebrain and cortex:
  - Nigrostriatal [substantia nigra (SN) to dorsal striatum (caudate putamen)]
  - Mesocorticolimbic [ventral tegmental area (VTA) to ventral striatum (nucleus accumbens), olfactory tubercle, frontal cortex (but also septum, amygdala, and hippocampus)





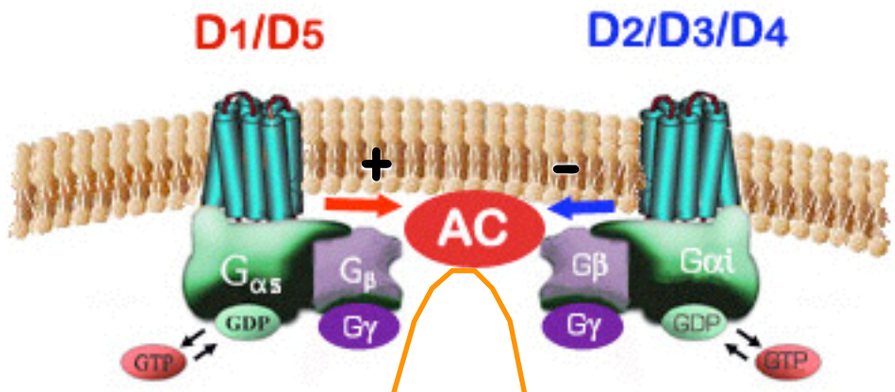




The DA System

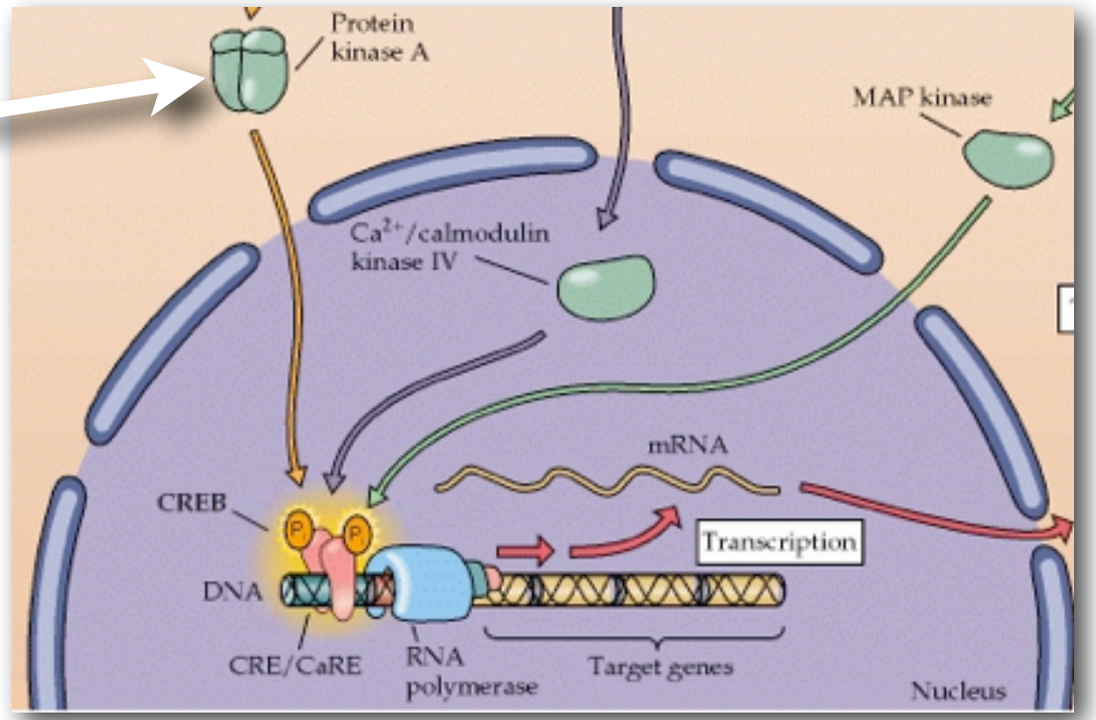
DA receptors:

- Two subtypes: D1-like and D2-like



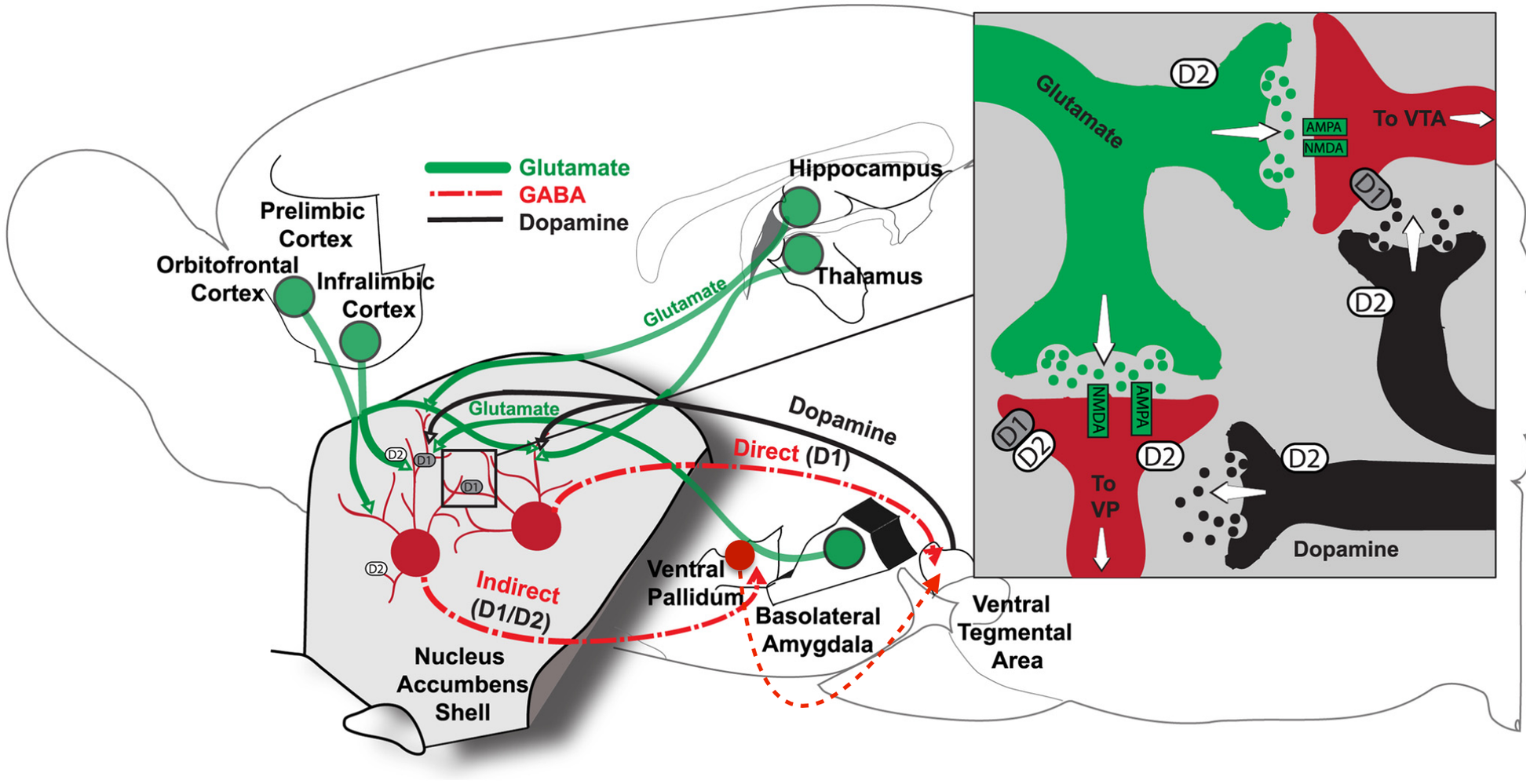
ATP

cAMP



The DA System

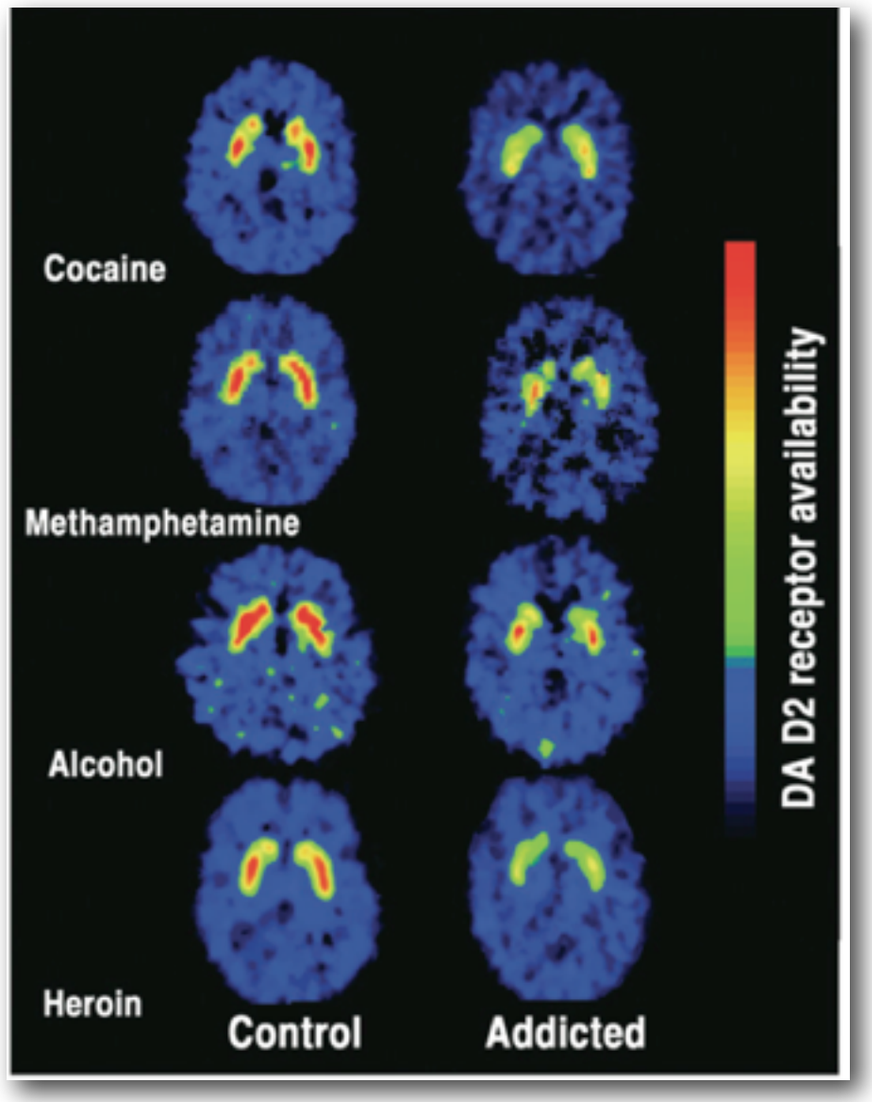
Mesocorticolimbic circuits



The DA System

Adaptations in the DA system following chronic drug use:

- Reduction in DA D2 receptors in the striatum



PET scans in abstinent drug abusers - [^{11}C]raclopride
(from Volkow & Wise 2005)

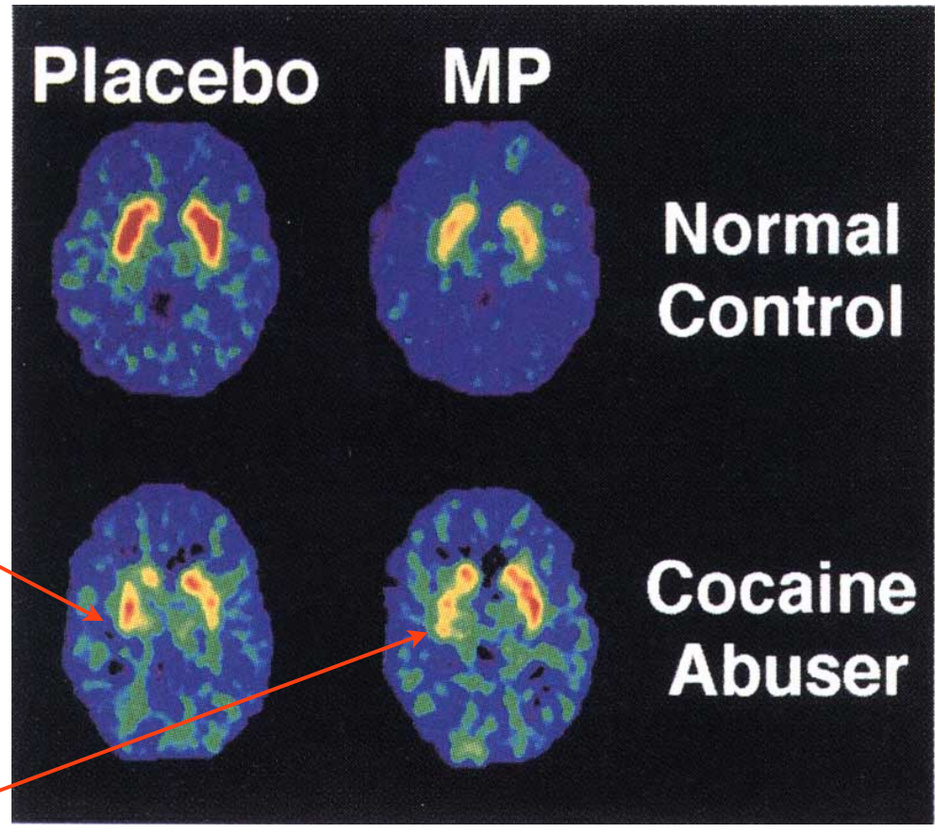
The DA System

Adaptations in the DA system following chronic drug use:

- Lower DA release in addicts

Lower baseline D2 availability

Reduced DA release following MP



PET scans in abstinent drug abusers following methylphenidate (Ritalin) administration (i.v.) (from Volkow et al., 1997)

The DA System

Adaptations in the DA system following chronic drug use:

- Sensitization of DA release with repeated exposure (Boileau et al. 2006)

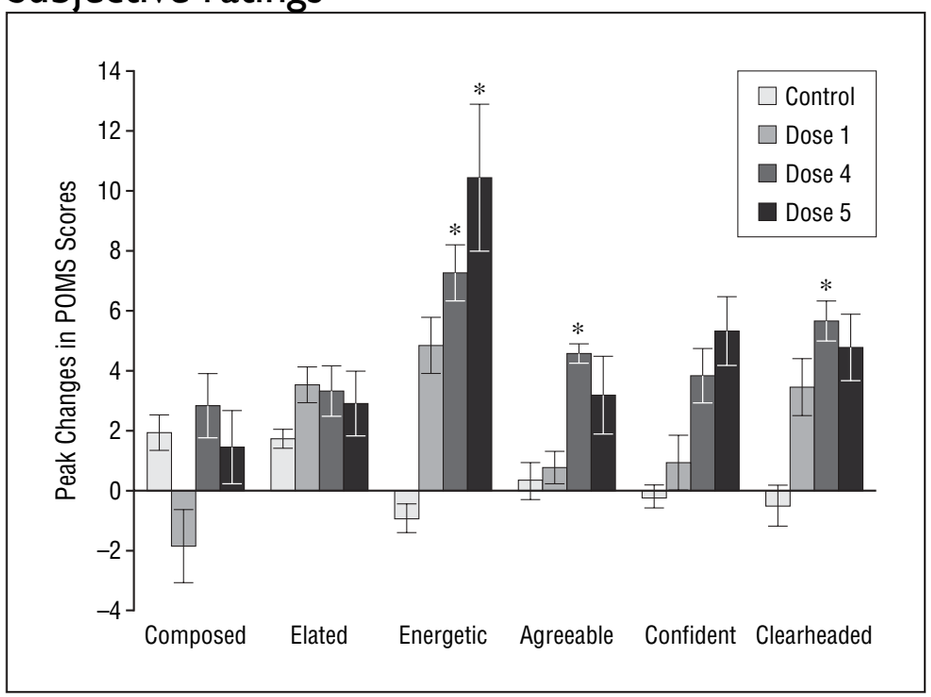
- 10 healthy adults
- Sensitization procedure: 3 repeated amphetamine (AMPH) exposures (0.3 mg/kg, by mouth); ~ 2 days apart

Table. Experimental Design

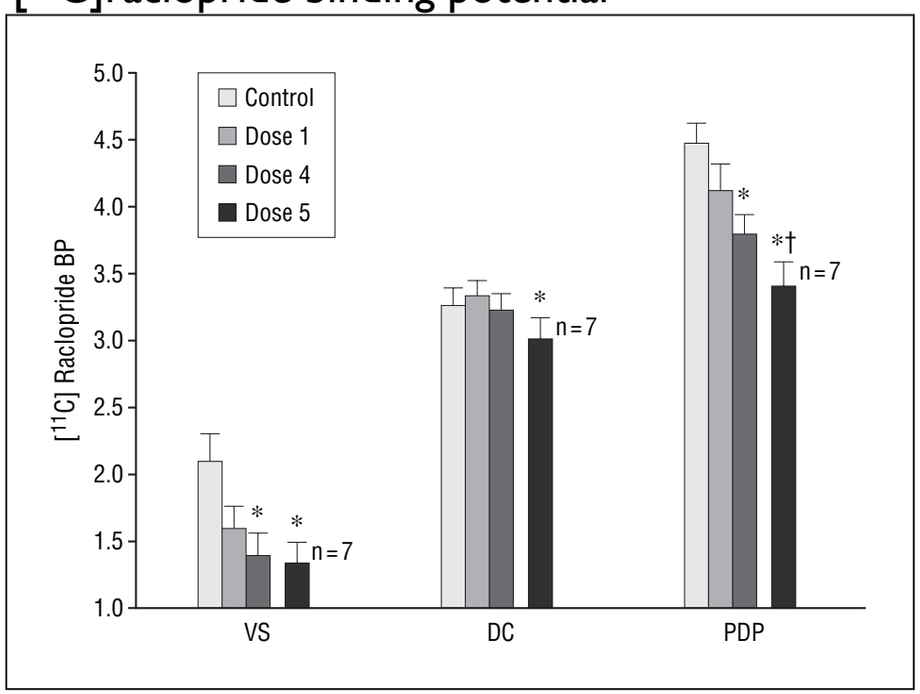
Sensitization Study (n = 10)*							
0 or >22 d	**1 d**	**3 d**	**5 d**		**21 d**		**1 y**
PET baseline+	PET AMP	Sham AMP	Sham AMP	14-d latency	PET AMP	Approximately 1-y latency	PET AMP

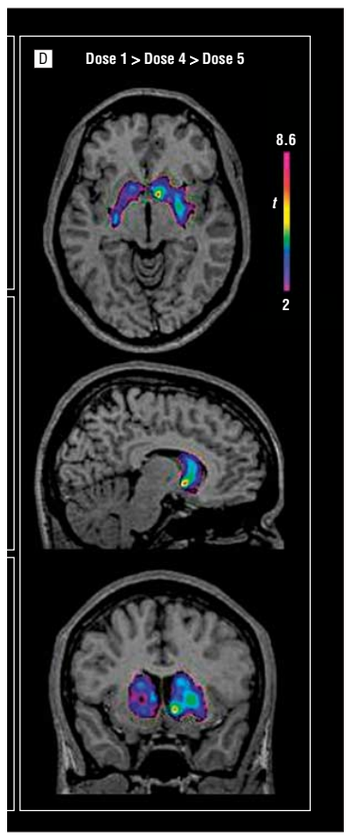
Control Study (n = 6)						
0	**1 d**	**3 d**	**5 d**		**21 d**	**22 d**
PET baseline	AMP	AMP	AMP	14-d latency	PET baseline	AMP

Subjective ratings



[^{11}C]raclopride binding potential





Opiates

- Also known as opioids
- **Opium**, the extract of the poppy plant is the source for the opiate family of drugs
- The active ingredients: **morphine**, **codeine**, and **thebaine**
- Opium can be smoked or eaten, morphine is usually injected
- **Heroin** is 2-4 times more potent than morphine and acts faster (and is a Schedule I drug)
- Heroin is taken IV, snorted, or injected under the skin ("skin popping")
- Heroin is converted (rapidly) into 6-monoacetylmorphine (3-10 times more potent than morphine) and then (slowly) to morphine in the brain and blood
- Fentanyl (synthetic, 80x more potent than morphine); Oxycodone/Oxycontin (semisynthetic, 1-4x morphine potency)

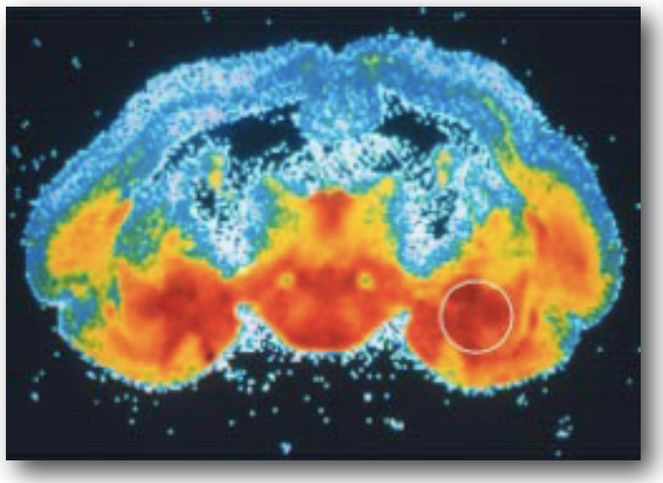
Opiates

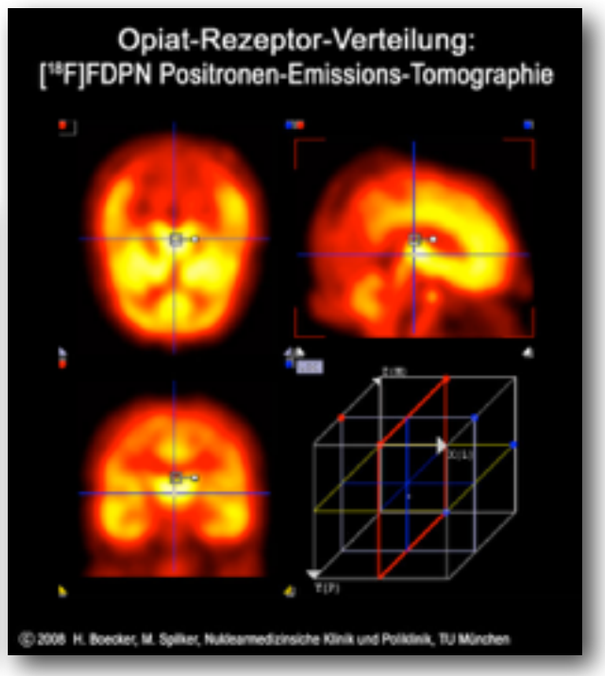
- Physiological effects: Decreased BT, suppressed cough reflex (and breathing center), nausea, decreased gastro-intestinal secretion and motility, constricted pupils, coma
- Behavioural/subjective effects: at low doses - analgesia; higher doses - euphoria "high" ⟶ "nod" ⟶ "being straight"
- Some effects on cognitive function with chronic use (related to neurotoxicity?)
- Some effects show tolerance - analgesia, euphoria, sedation, lethal dose. Expressed as weaker effect and shorter duration
- Patterns of use: "Chippers"; Marginal subjects; Addicted
- Withdrawal: Physical and affective symptoms. Physical symptoms peak 36-48 hr after last dose and linger up to 72 hr. Most symptoms will be over within 7-10 days

Opiates

Mechanism of action:

- Three major types of opiate receptors: μ, δ, κ
- Different distribution in the brain, different affinity to opiate peptides, and somewhat different function. The μ opiate receptor seems to be the most critical for the rewarding effects of opiates.
- Metabotropic, open K^+ channels, close Ca^{2+} channels, inhibit adenylyl cyclase activity - Reduced excitability of the neuron

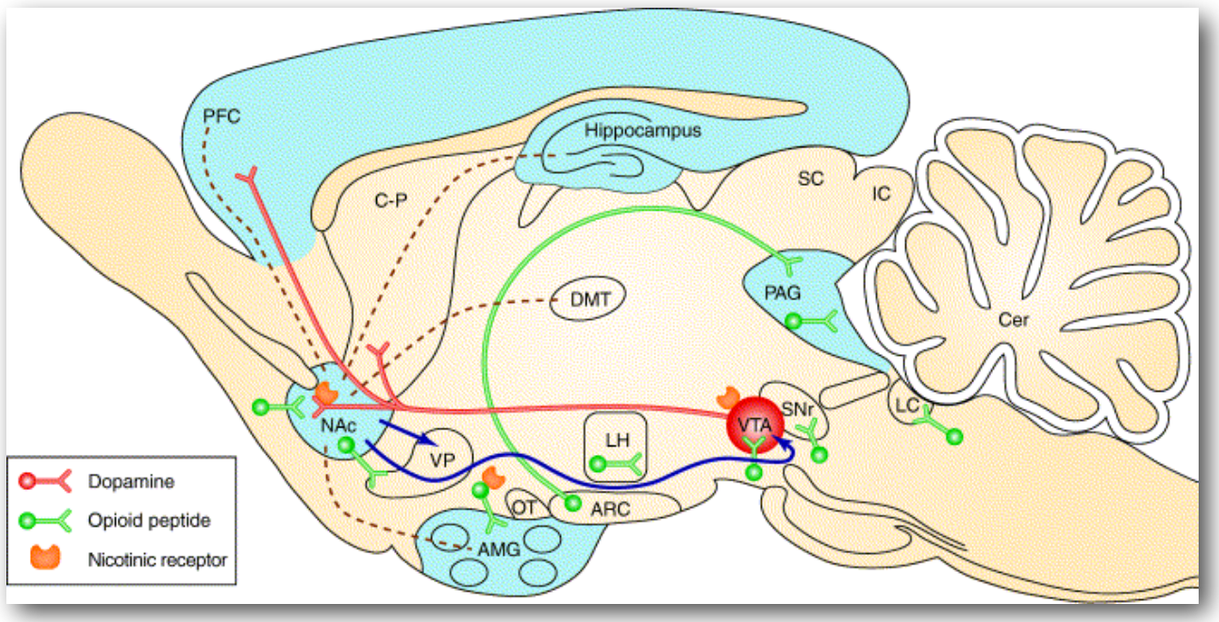


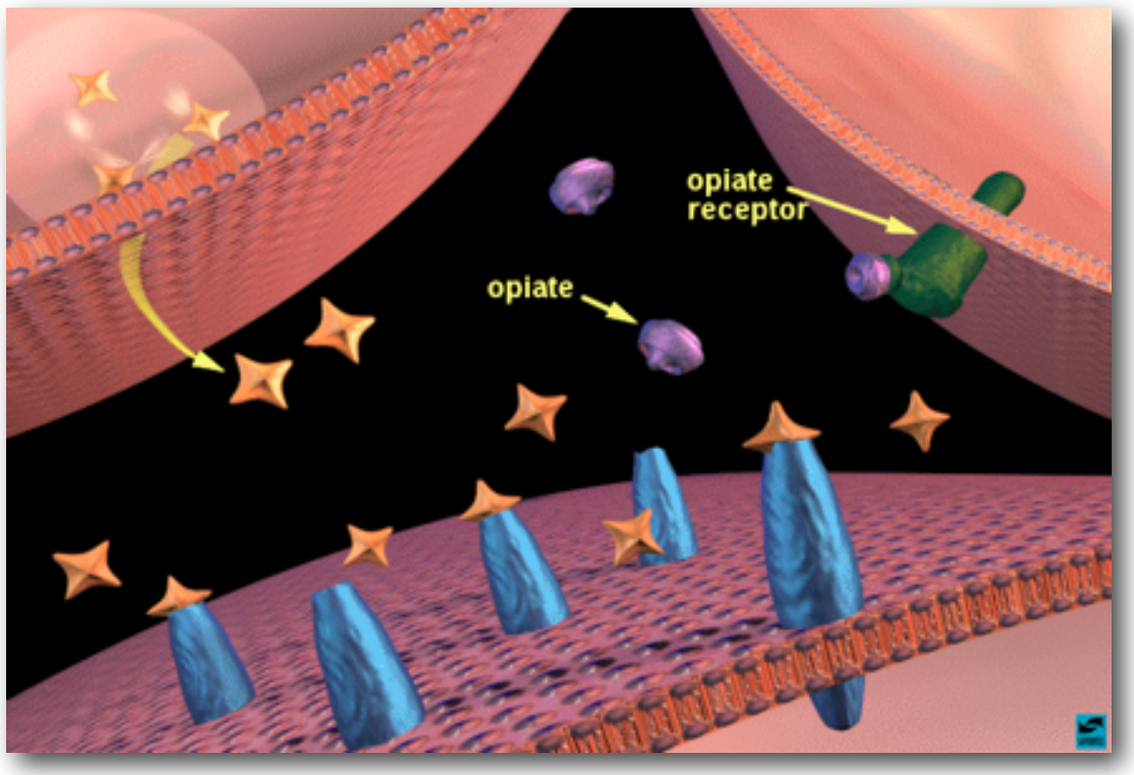


Opiates

Mechanism of action:

- DA-dependent and DA independent mechanisms.
- DA seems to be critical for some, but not all, of the rewarding effects of opiates
- Opiate reward-related DA transmission is affected by removal of GABA inhibition





Cannabinoids

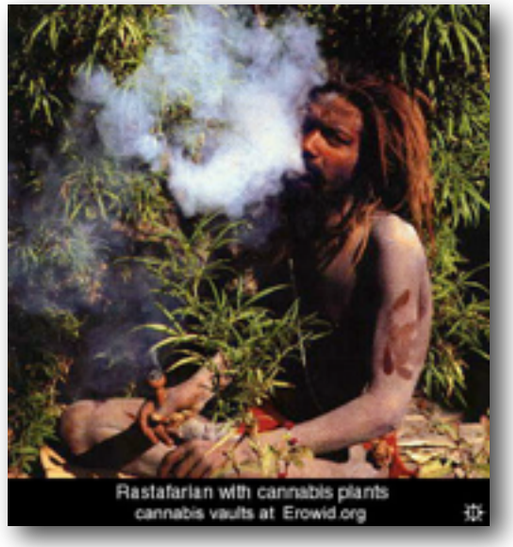
- Found in cannabis plants (e.g. Cannabis sativa)
- Schedule I drug (schedule II in Canada; might change...)
- Distributed as marijuana or hashish. Usually smoked ("joints", "bongs", chillum), but can be eaten (weed cookies, brownies...)
- The psychoactive ingredient:

  Δ^9-6a-10a-trans-tetrahydrocannabinol (THC)

- Physiological effects: Increased heart rate and blood pressure. Increases hunger. Some suppression of the immune system
- Behavioural/subjective effects:
  - Low to moderate doses - "Buzz", "High", "Stoned", "Come down"
  - High doses: Psychedelic effects, sometimes hallucinations

Cannabinoids

- Some cognitive and motor impairments
- Chronic use may lead to "amotivational syndrome"
- Tolerance: Readily develops for most behavioural/ subjective effects, but not to the orexigenic effects
- Addiction potential: Although at first thought to be minimal, there is an increasing number of reports on subjects that meet the DSM criteria and seek help
- Withdrawal: Not easy to describe (clinically). May include decreased appetite/weight lose, irritability, anxiety, sleep disturbance, aggression, depressed mood. Can last a couple of weeks



Cannabinoids

Mechanism of action:

- Endocannabinoids: Enandamide, 2-AG
- Two types of receptors: CB1 and CB2
- Activation of CB1 can inhibit the release of many neurotransmitters (GABA, glutamate, NE, 5-HT…)
- Endocannabinoids act as retrograde messengers
- Reinforcing effect of THC mediated by DA and opiates in the VTA and NAc. DA-independent mechanisms?