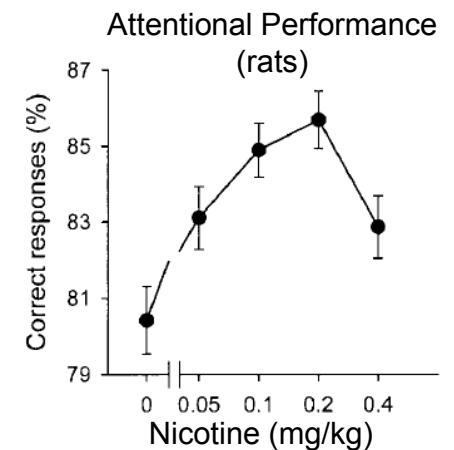
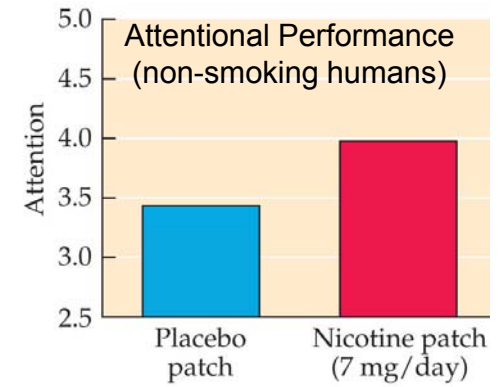


## Reward Circuits and Drug Addiction (III) Ch.4

- Commonly Abused Drugs
  - High Addictive Potential (nicotine, opioids, psychostimulants)
- (Older) Theories of Addiction
- Dopamine contribution to drug taking, addiction
- **PLEASE FILL OUT YOUR TEACHING EVALUATIONS!**

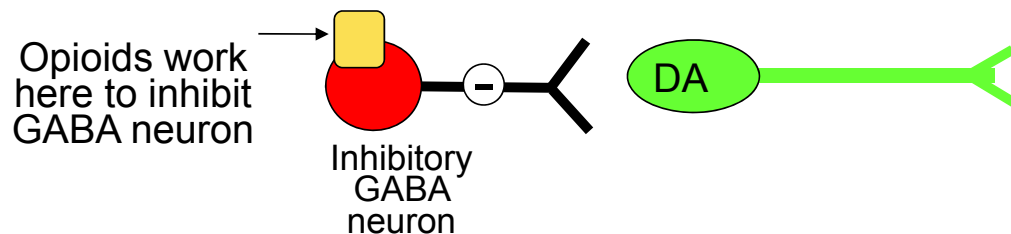
## Nicotine (II)

- About 70% of people who experiment with smoking become addicted.
  - Compare vs alcohol (10%) or heroin (30%).
- ~ 20% of all attempts to quit are successful for <2 years
- Multiple health hazards with chronic use (primarily from the smoke)
- Its not ALL bad: **nicotine** has been shown to:
  - Improve **attention**/cognition in normal subjects (both smokers AND non-smokers)
  - Also improves cognition in individuals with Alzheimer's or schizophrenia
  - Decrease risk of Parkinson's
- Drugs are being developed to produce beneficial effects of nicotinic stimulation



# Opiates (I)

- High addictive potential; originally used ~ 4000 B.C.
  - In order of potency; fentanyl > heroin > morphine > methadone > codeine
  - The rush: when taken I.V., initial wave of intense abdominal orgasmic pleasure that evolves to serene drowsy euphoria
  - First rush entices the user to do more, tolerance builds up, higher doses needed to get similar effect; never as good as 1st rush
- Act as agonists for “endogenous opioid” receptors
  - **Enkephalin and endorphin** are 2 common endogenous opioid peptides- generally *inhibit* neural activity
  - Endogenous opioids mediate numerous functions (analgesia, emotional regulation, sensory/motor integration)
  - Receptors in the accumbens mediate pleasurable aspects of natural rewards (e.g.; sweet/fatty tastes)
  - Opioid receptors are on GABA neurons in the VTA. Activating these receptors inhibit GABA neurons, disinhibits dopamine neurons



## Opiates (II)

- **Withdrawal:** 6-12 hrs after last dose, ↑ restlessness. watery eyes, nose, sweating followed by a fitful sleep for several hours
  - Opioids depress CNS function; opioid withdrawal is rebound hyperactivity.
  - The symptoms are typically worst on the 2nd-3rd day and disappear by the 7th day
- **Long-term health consequences:** Main risks of the I.V. user is risk of O.D. (either due to using street drugs of unknown potency or conditioned tolerance effects) and use of second-hand needles

**TABLE 11.2** Acute Effects of Opioids and Rebound Withdrawal Symptoms

Acute action	Withdrawal sign
Analgesia	Pain and irritability
Respiratory depression	Panting and yawning
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Tranquilization	Fearfulness and hostility
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupil constriction	Pupil dilation
Hypothermia	Hyperthermia
Drying of secretions	Tearing, runny nose
Reduced sex drive	Spontaneous ejaculation
Flushed and warm skin	Chilliness and “gooseflesh”

- Other health consequences of long-term use are relatively minor: constipation, pupil constriction, menstrual irregularity, reduced libido
- Recent work suggest that **long-term cognitive deficits** are associated with chronic heroin abuse

## Psychostimulants (Cocaine, Amphetamines)

- High addictive potential

- **Psychological effects:** increased self-confidence, alertness, energy, makes people friendly and talkative
- **Physiological effects:** motor activation (fidgety), ↓ appetite, ↓ need for sleep, ↑ arousal, ↑ cardiovascular tone

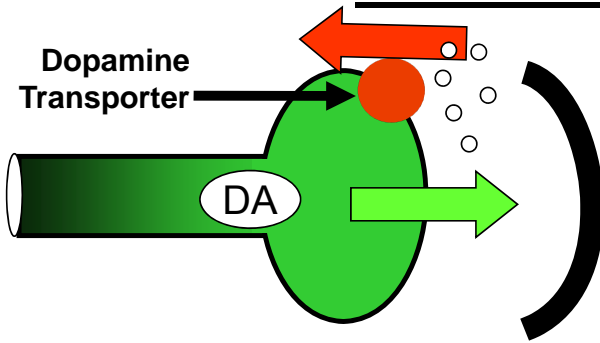
- Addicts typically abuse in “sprees”; binges where high levels of intake are maintained for 1-3 days

- Sprees end when \$\$\$ runs out or toxicity develops

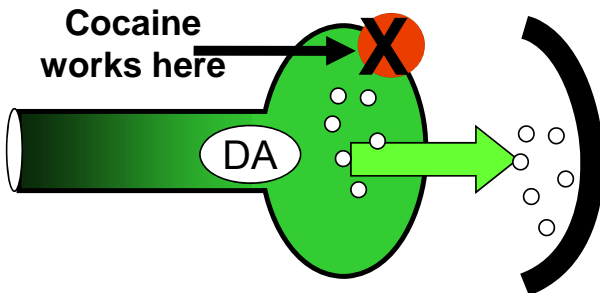
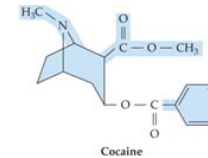
- **Withdrawal:** “the crash” - fatigue, increased appetite, depression, anhedonia, anxiety, irritability, sometimes agitation or extreme suspicion. Also accompanied by increase drug craving.
  - Withdrawal symptoms tend to be more prominent with amphetamines (particularly methamphetamine) vs cocaine
  - Many times, **physical** withdrawal symptoms are not as visibly apparent as they are for other drugs



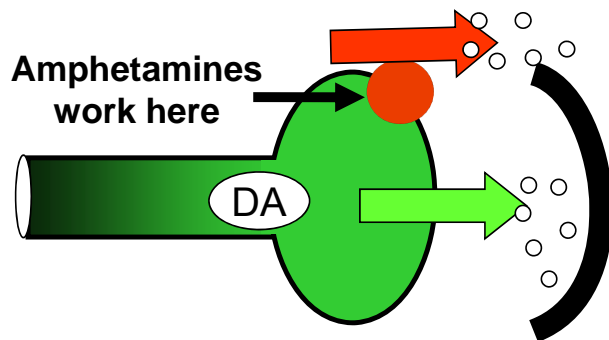
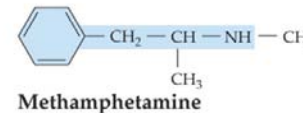
# Actions of Cocaine and Amphetamines



**Normal DA transmission:** DA is released by presynaptic terminal, but is quickly taken back by the DA transporter



**Cocaine:** blocks the DA transporter, so DA that has been released stays out a lot longer

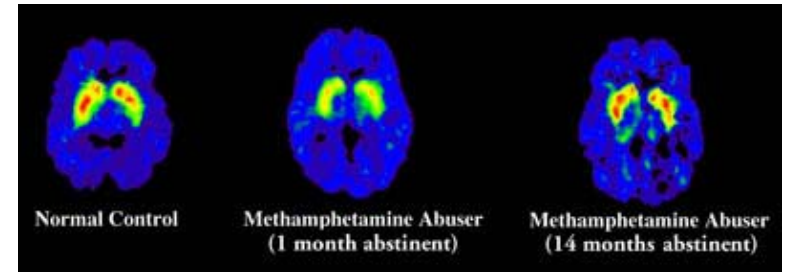


**Amphetamines: Reverses** the DA transporter, so more DA is released and stays out a lot longer

**-Both work on multiple monoamine systems (NE, 5-HT), but reinforcing effects mediated via by actions on DA**

# Psychostimulant Toxicity

- Numerous adverse consequences with long-term use
  - Psychosis, seizures, brain damage to monoamine system, strokes, heart attacks
- Brain damage may be the result of strokes (vasoconstriction via ↑ noradrenaline release) or DA-induced toxicity (too much of a good thing)
- Many stimulant abusers display deficits in cognitive functions mediated by the PFC, which can persist for years after drug abstinence.



Cocaine Abuse Will Affect You Mentally and Physically



The addict after and before the meth addiction

## Psychostimulants- Therapeutic Effects

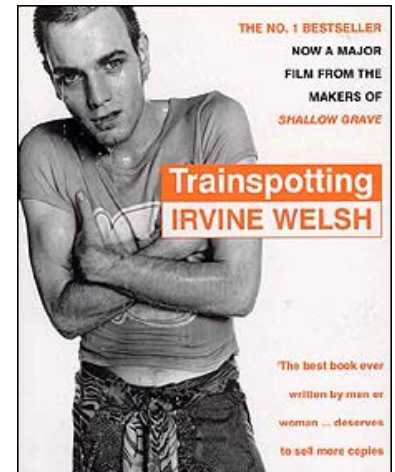
- At lower doses (ie: those used for recreational use) psychostimulants like d-amphetamine (Adderall™) or methylphenidate (Ritalin™) have therapeutic benefits
- **Powerful stimulant:** promotes wakefulness
  - Amphetamine given to WW II military personnel to reduce their need for sleep
  - Still prescribed in for some type of sleep disorders like narcolepsy
  - One key side effect = reduces R.E.M. sleep
- **Cognitive enhancer:** enhances multiple forms of cognition
  - Attention, working memory, memory encoding
  - Enhances cognitive function in healthy human subjects and in certain psychiatric disorders (ADHD, schizophrenia)
  - Many of these effects are though to be mediated by enhancing DA and noradrenaline activity in the prefrontal cortex
  - However, enhancement of these functions comes at the sacrifice of other functions (e.g.; creative thought)





# Theories of Drug Addiction (I)

- **Physical Dependence Model:** Drug taking is driven by desire to reduce withdrawal symptoms
  - **Problems:** Addicts often relapse when withdrawal symptoms have passed; some drugs do not have severe withdrawal symptoms (i.e.: cocaine)
  - Detoxified addicts (drugs eliminated from system) still remain addicted
  - Treatments used to curb withdrawal (e.g. nicotine patch) are not 100% effective
- **Note:** some emotional effects of drug withdrawal (depressed mood, reduced motivation, irritability) may persist for some time after **physical** withdrawal symptoms have ceased- this may *contribute* to persistence of addiction.

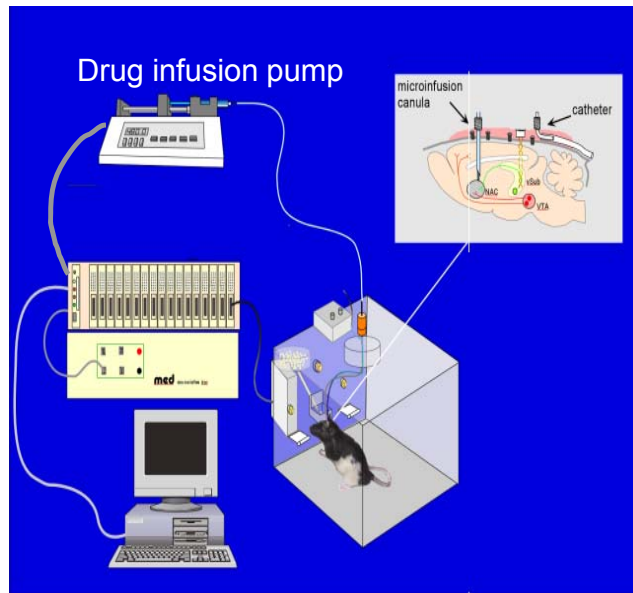


## Theories of Drug Addiction (II)

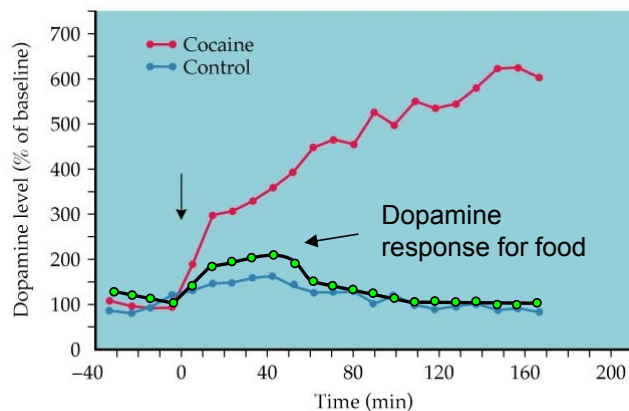
- **Positive Reward Model:** addicts take drugs for the pleasurable feelings
  - **Problem:** addicts can continue to seek/take drugs even if they are no longer giving as good a “rush” they have felt in the past (i.e.: tolerance to the hedonic effects have occurred)
  - Some drugs (eg; nicotine) do not give as much of a euphoric rush as other drugs (eg: heroin) but can be just as addictive



# Dopamine and Animal Models of Drug Reward



- REDUCING DA TRANSMISSION **reduces/ abolishes** self administration for most drugs
  - **Blocking DA** receptors also **disrupts** formation of **conditioned place preference** for drugs
- Responding for drugs of abuse is associated with **↑** DA release in the accumbens
- DA release is also increased by consumption of ***natural rewards and/or presentation of reward-associated cues***
  - However, magnitude of DA release by drugs of abuse can be greater/prolonged than that induced by natural rewards



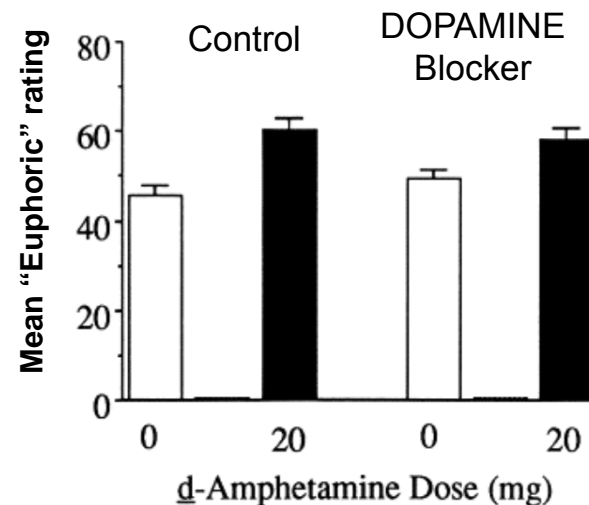
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➤ **So, drugs of abuse activate the brain's natural reward learning pathways, but to a much greater degree**

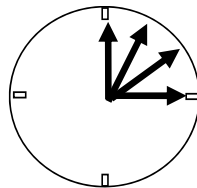
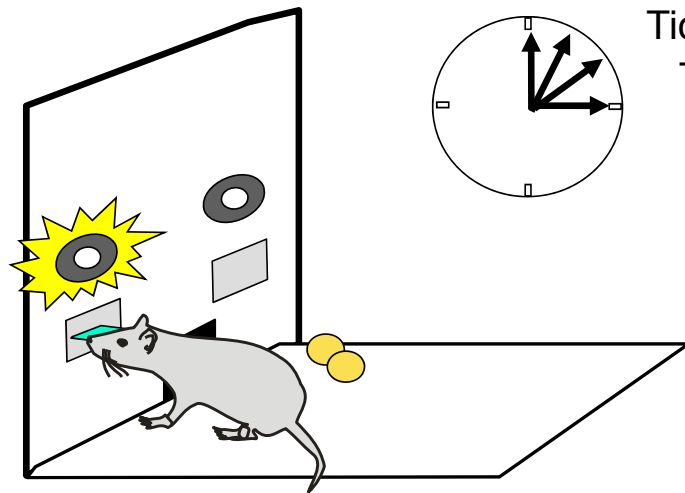
## Dopamine and Drugs of Abuse- what it's not

- So, rewards are pleasurable, rewards increase dopamine release, so dopamine is pleasure?
  - Note that “Reward” has 2 components
    - “**Liking**” = pleasurable, hedonic effects of rewards
    - “**Wanting**” = craving, willingness to work for rewards
- **Study: *Blockade of dopamine receptors in humans does not alter subjective ratings* of drug euphoria**
  - It is now relatively well-accepted (by *most* scientists) that dopamine is **not involved** in the pleasurable effects of drugs of abuse (or natural rewards)
- Dopamine more involved in the preparatory/approach behaviours associated with rewards and conditioned stimuli, NOT their pleasurable effects
  - Endogenous opioids (e.g.: endorphins) play a role in pleasurable aspects of rewards
- **So, dopamine helps get you to the good things in life (wanting), but doesn't seem to be involved in you liking them**

Dopamine antagonism does not affect reported euphoria induced by amphetamine



# Dopamine and Approach Towards Reward-Related Stimuli



Tick...

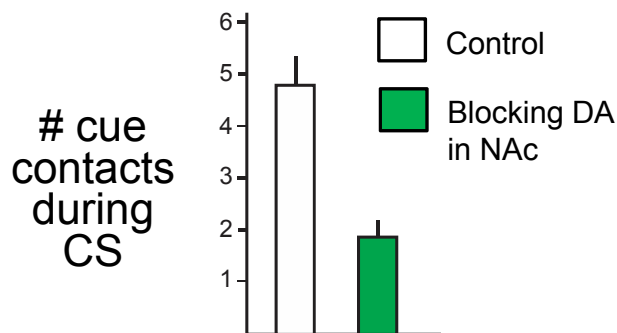
Tick...

Tick...

**Pavlovian Approach** (Autoshaping): Cue comes on, predicts food delivery 10 s later

→ Food ALWAYS delivered, regardless of whether animal interacts with lever

→ Over training, animals start to approach/press/bite lever while waiting for food to be delivered – cue becomes attractive, elicits approach



→ Blocking NAc DA receptors **reduce approach to cue** (but DOES NOT disrupt approach/consumption of food reward)

➤ **So, dopamine promotes behaviors directed towards reward-related stimuli**