

Pharmacology For the Addiction Professional  
The Neuroscience of Addiction 2014:  
The Anti-Reward Brain System – Part 2



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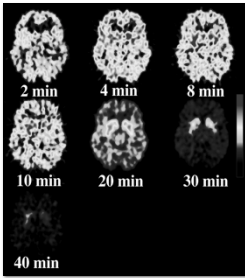
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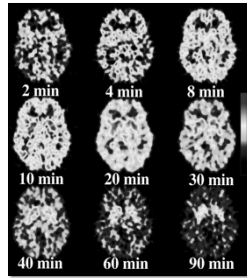
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**Pharmacokinetics in Human  
Brain**

**[<sup>11</sup>C]Cocaine**



**[<sup>11</sup>C]Methylphenidate**



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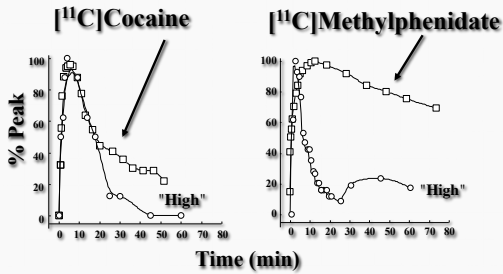
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**Relationship Between Drug  
Pharmacokinetics and the “High”**



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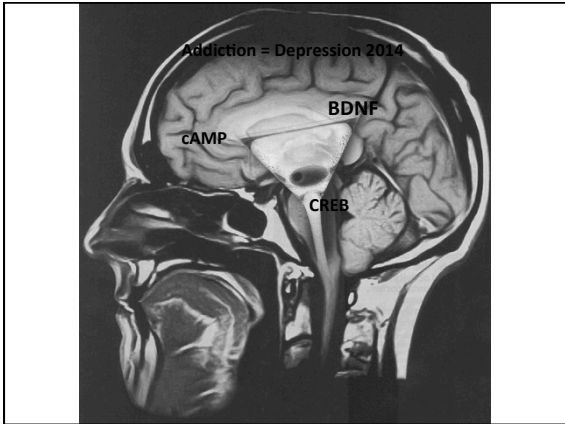
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### Definitions

- cAMP- Cyclic adenosine monophosphate used for intracellular signal transduction
- BDNF- Brain-derived neurotrophic factor-encourage the growth and differentiation of new neurons and synapses.
- CREB-(cAMP Response Element Binding)-neuronal plasticity and long-term memory formation in the brain.

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### Serotonin (5-HT) and Fear

**5-HT strongly implicated in emotional behavior:**

- 5-HT synapses targeted by mood-altering drugs
- SSRIs effective against panic, anxiety & depression
- 5-HT<sub>1A</sub> partial agonists are effective anxiolytics
- 5-HT<sub>1A</sub> knockout mice exhibit increased fear/anxiety
- 5-HTT knockout mice exhibit increased fear/anxiety

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### Brain Derived Neurotrophic Factor and neuronal plasticity

- increases cortical neuron survival
- sculpts glutamate innervation patterns
- increases synaptic efficacy of glutamate
- modulates LTP in hippocampus
- expression increased during spatial memory
- expression increased by antidepressant treatments
- **genetic associations: Alzheimers Disease, Parkinson's Disease, bipolar disorder, schizophrenia, addictions ?????**

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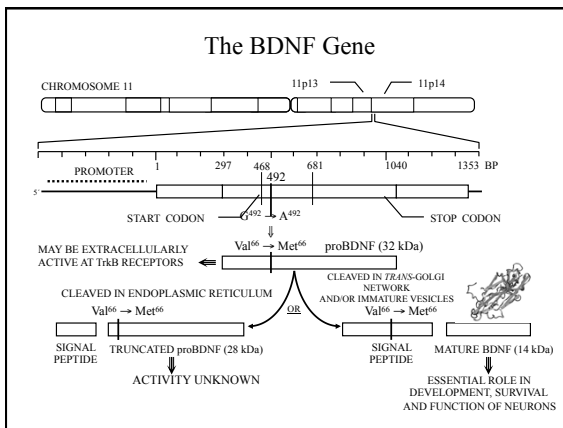
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This is your brain



This is your brain  
Thanks to balanced  
BDNF



Think of it like fertilizing and pruning your rose bushes

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## Molecular Biology of Addiction:

### Addiction is a form of drug-induced neural plasticity

- Upregulation of cAMP pathway
  - Occurs in response to chronic administration of drugs
  - Resulting activation of transcription factor CREB (cAMP response element-binding)
  - Both mediate aspects of tolerance and dependency
- Induction of another transcription factor,  $\Delta$  FosB
  - Exerts opposite effects
  - May contribute to sensitized responses to drug exposure

Ref: Nestler, Eric - Molecular Biology of Addiction. Am J of Addictions 10:201-217, 2001

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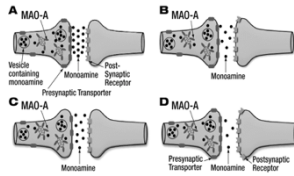
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## THE RECEPTOR SENSITIVITY HYPOTHESIS

- Supersensitivity and up-regulation of post-synaptic receptors leads to depression
- Suicidal and depressed patients have increased 5HT- $\alpha_2$  receptors




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## Basis for Plasticity: Summary

- Drugs enter the brain and bind to an initial protein target
- Binding perturbs synaptic transmission which in turn cause the acute behavioral effects of the drug
- Acute effects of the drug do not explain addiction by themselves

Ref: Nestler, Eric - Molecular Biology of Addiction. Am J of Addictions 10:201-217, 2001

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Ref: Nestler, Eric - Molecular Biology of Addiction. Am J of Addictions 10:201-217, 2001

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- Addiction produces a change in brain structure and function (adaptation to the drug)
- molecular and cellular changes in particular neurons alter functional neural circuits
- This leads to changes in behavior consistent with addicted states
- Addiction is therefore a form of drug induced neural plasticity

Ref: Nestler, Eric - Molecular Biology of Addiction. Am J of Addictions 10:201-217, 2001

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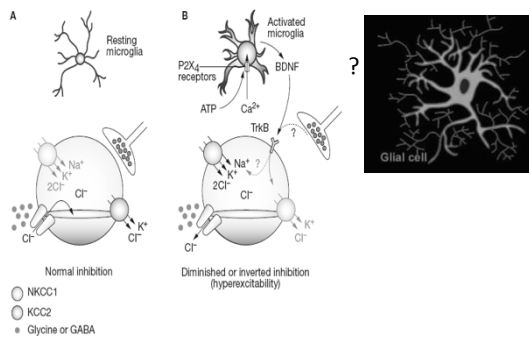
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### The Neurochemistry of Recovery and Discovery




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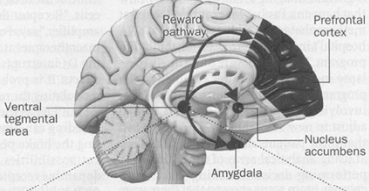
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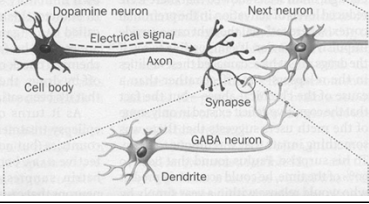
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**What happens in the brain**

1. We feel good when neurons in the reward pathway release a neurotransmitter called dopamine into the nucleus accumbens and other brain areas.



2. Neurons in the reward pathway communicate by sending electrical signals down their axons. The signal is passed to the next neuron across a small gap called the synapse.



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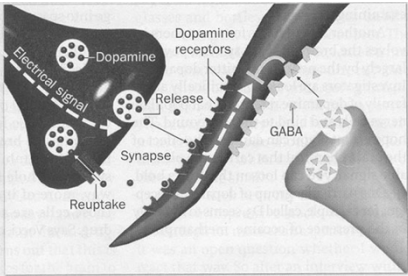
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3. Dopamine is released into the synapse, crosses to the next neuron and binds to receptors, providing a jolt of pleasure. Excess dopamine is taken back up by the sending cell. Other nerve cells release GABA, an inhibitory neurotransmitter that works to prevent the receptor nerve from being overstimulated.



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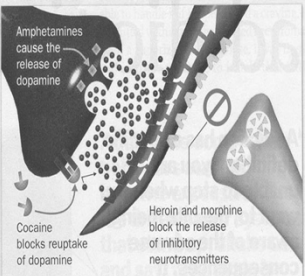
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4. Addictive substances increase the amount of dopamine in the synapse, heightening the feeling of pleasure. Addiction occurs when repeated drug use disrupts the normal balance of brain circuits that control rewards, memory and cognition, ultimately leading to compulsive drug taking.



Source: National Institute on Drug Abuse (NIDA)  
TIME Diagram by Karolina Divil, Meg Massey and Joe Lertbe

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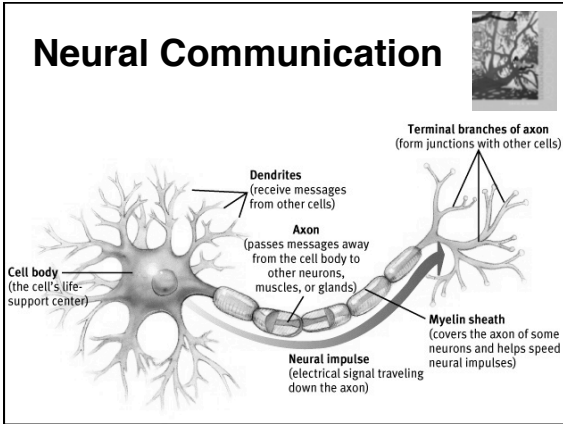
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### Neural Communication

- Action Potential
  - a neural impulse; a brief electrical charge that travels down an axon
  - generated by the movement of positively charged atoms in and out of channels in the axon's membrane
- Threshold
  - the level of stimulation required to trigger a neural impulse

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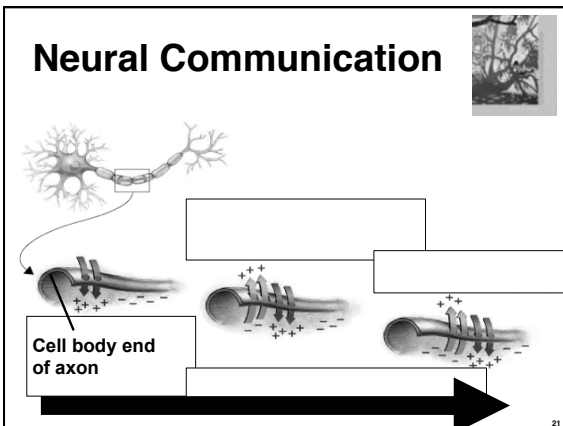
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## Neural Communication



- Synapse [SIN-aps]
  - junction between the axon tip of the sending neuron and the dendrite or cell body of the receiving neuron
  - tiny gap at this junction is called the *synaptic gap* or *cleft*
- Neurotransmitters
  - chemical messengers that traverse the synaptic gaps between neurons
  - when released by the sending neuron, neurotransmitters travel across the synapse and bind to receptor sites on the receiving neuron, thereby influencing whether it will generate a neural impulse

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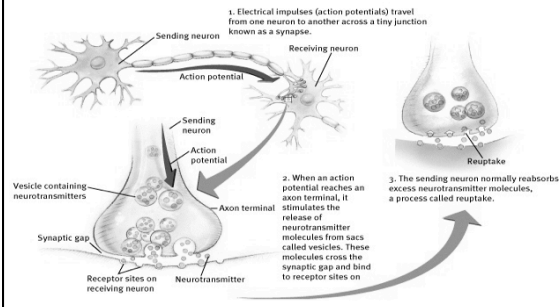
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## Neural Communication



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## Neural Communication



Serotonin Pathways

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Dopamine Pathways

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# Neural Communication



TABLE 2.1  
SOME NEUROTRANSMITTERS AND THEIR FUNCTIONS

Neurotransmitter	Function	Examples of Malfunctions
Acetylcholine (ACh)	Enables muscle action, learning, and memory	Undersupply, as ACh-producing neurons deteriorate, marks Alzheimer's disease
Dopamine	Influences movement, learning, attention, and emotion	Excess dopamine receptor activity linked to schizophrenia; starved of dopamine, the brain produces the tremors and decreased mobility of Parkinson's disease
Serotonin	Affects mood, hunger, sleep, and arousal	Undersupply linked to depression; Prozac and some other antidepressant drugs raise serotonin levels
Norepinephrine	Helps control alertness and arousal	Undersupply can depress mood
GABA (gamma-aminobutyric acid)	A major inhibitory neurotransmitter	Undersupply linked to seizures, tremors, and insomnia
Glutamate	A major excitatory neurotransmitter; involved in memory	Oversupply can overstimulate brain, producing migraines or seizures (which is why some people avoid MSG, monosodium glutamate, in food)

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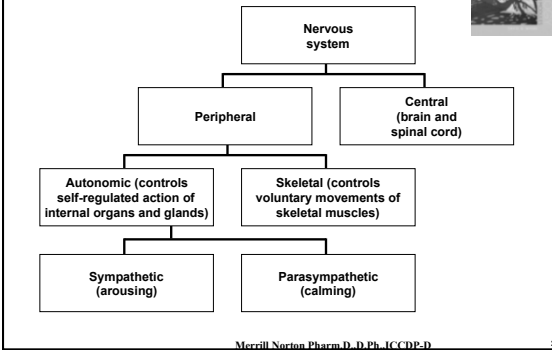
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# The Nervous System



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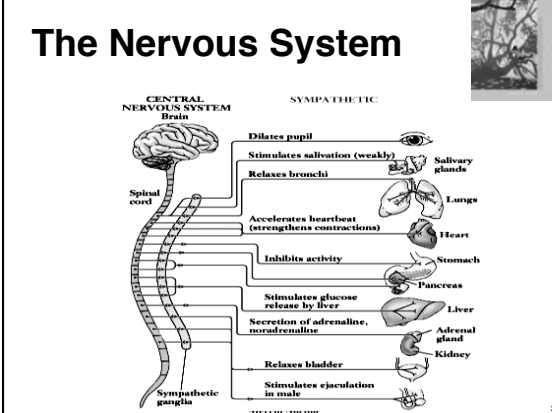
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# The Nervous System



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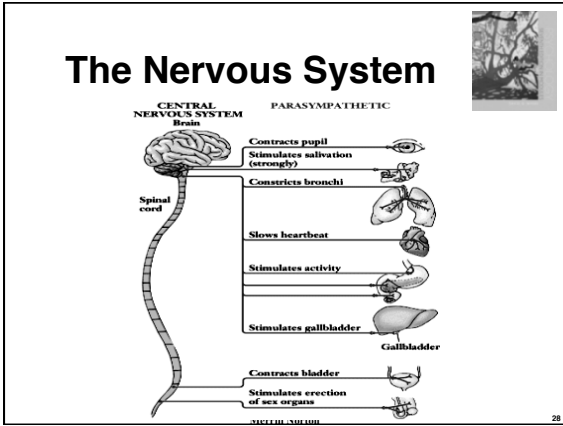
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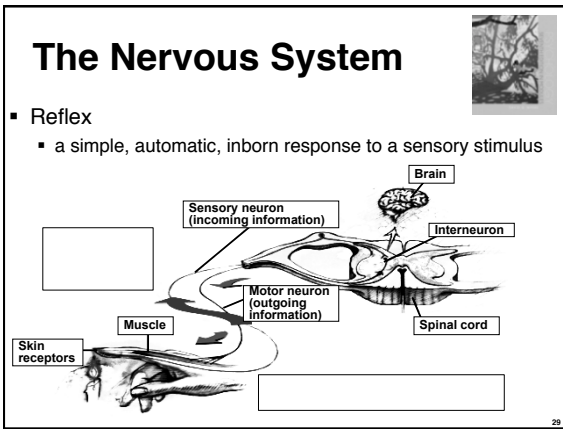
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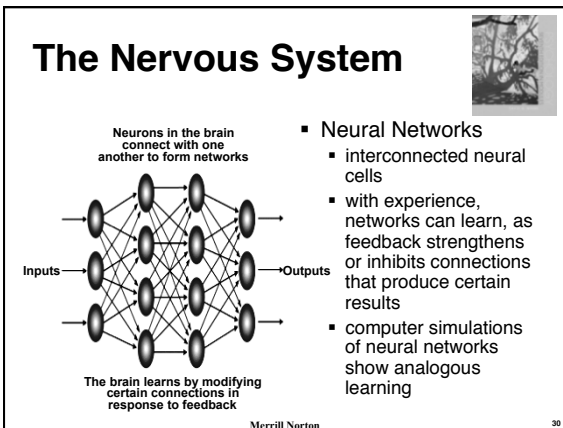
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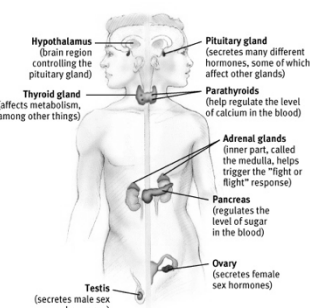
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## The Endocrine System



- **Endocrine System**
- the body's "slow" chemical communication system
- a set of glands that secrete hormones into the bloodstream

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## Major Classes of Psychoactive Chemicals

- **CNS Depressants**
- **CNS Stimulants**
- **Narcotics**
- **Hallucinogens**
- **Cannabis**
- **Solvents/ Inhalant**
- **Steroids**
- **Psychotropics**

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## CENTRAL NERVOUS SYSTEM (CNS) STIMULANTS SUMMARY

<ul style="list-style-type: none"> <li>• <i>Pharmacological Actions effects</i></li> <li>• Constricted blood vessels decreased vessel tone</li> <li>• Increased blood pressure decreased pressure</li> <li>• Increased energy Fatigue</li> <li>• Increased strength</li> <li>• Euphoria Depression, anxiety</li> <li>• Increased alertness concentrating</li> <li>• Decreased appetite</li> </ul>	<p><i>Withdrawal</i></p> <p>Normal or</p> <p>Normal or</p> <p>Weakness</p> <p>Trouble</p> <p>Increased</p>
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**NARCOTICS**

- *Naturally Occurring* - Codeine, Morphine, Opium
- *B. Semi-synthetic* - Dilaudid, Heroin, Hydrocodone, Percodan , Oxycontin
- *C. Synthetic* – Buprenorphine, Demerol, Fentanyl, Methadone

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**NARCOTIC SUMMARY**

- Symptoms of users - Drowsiness, lethargy, euphoria, slurred speech, bobbing head (nodding), flushing of skin of face, neck, chest, pinpoint pupils, constipation, and nausea. The duration of psychoactive chemical effect varies from 3-6 hours for Codeine to 12-36 hours for methadone.
- How used - Injected - (I.V. or “skin popping”)
- Orally or Smoked (Opium)
- Physical dependence - YES (Very Rapid)
- Psychological dependence - YES (High Degree)
- Tolerance - YES (Very Rapid)

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**HALLUCINOGENS**

- Examples
- LSD, MDSA, MDMA (Adam, Ecstasy), MDEA (EVE), MBDB, DMT, STP, Mescaline, Psilocybin, etc.
- Spice
- Bath Salts
- Salvia

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**HALLUCINOGENS SUMMARY**

- Physical and Mental Effects
- Distortions in perception;
- Euphoria;
- Impaired short-term memory;
- Increased pulse;
- Disturbed judgement;
- Withdrawal and tolerance;
- Method of ingestion;
- Specific effects of PCP;
- Severe adverse effects possible:
  - Anxiety reaction;
  - Depression;
  - Schizophrenia-like episode, usually paranoid; sometimes long-lasting and difficult to treat;
  - Accidents;
  - “Flashbacks”
  - Extremely low effective dose;
  - Taken sporadically.

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**CANNABIS: MARIJUANA, HASHISH**

- (Cannabis Sativa and Indica) Called Pot, Reefer, Dope, Weed, or Grass. Usually a mixture of the leaves, flowering tops, stems and seeds of the cannabis plant. The plant contains about 60 cannabinols to which the intoxicating properties are attributed.
- Tetrahydrocannabinol, or THC, is the most prevalent and most potent of the cannabinols found in the marijuana plant. The potency of marijuana is usually measured by the concentration of THC in the plant, cigarette or extract. There has been a dramatic increase in the potency of marijuana confiscated over the last 15 years.

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**CANNABIS SUMMARY**

- Concentrations of THC
  - Marijuana- (4-8 % THC)
  - Hashish (up to 12% THC)
  - Hash Oil (up to 30% THC)
- Symptoms of users—Altered time sense (time appears slow), reddening of the eyes, confusion, paranoia, increased appetite, mood swings, drowsiness, vision may seem sharper and sounds may seem more distinct, increased reaction time, increased heart rate.
- How used
  - When smoked—Onset of effect is within minutes, peak intensity is within 70 minutes, decline is within 2 hours, clearing of the effects within 6 hours.
  - When eaten—Only 1/3 to 1/4 of THC reaches the blood stream. Onset is from 30-120 minutes; duration of effect is 8-12 hours.
- Physical dependence—Suggested
- Psychological dependence—YES
- Tolerance—Plasma half-life of THC is shorter in chronic users than in non-users. Users tend to increase daily intake by shortening the interval between highs or by increasing total numbers of cigarettes used.
- Withdrawal symptoms—Irritability, restlessness, nervousness, insomnia, dysphoria.

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**SOLVENTS AND INHALANTS**

- Organic Solvents (hydrocarbons) are industrial solvents and aerosol sprays
- Volatile Nitrates
- Nitrate “poppers” are used to enhance sexual behavior performance. It is now a prescription substance. Butyl and Isobutyl, “Locker Room”, “Rush”, “Bolt”, “Quick Silver” and “Zoom” are used to enhance sexual pleasure.
- Nitrous Oxide

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**STEROIDS (Anabolic)**

- These psychoactive chemicals are male hormones that increase muscle mass. Names are: Testosterone, Dianabol. Effects include: elevated mood, aggressiveness, high risk of injury because muscle mass is all that increases while tendon strength remains the same; masculinization of women (body hair and baldness), feminization of males (atrophy of the gonads), and liver cancer. These compounds are currently on the Control Substance Schedule III listing.

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**OVER-THE-COUNTER PSYCHOACTIVE CHEMICALS**

- Allergy Treatment Products/Cough/Cold Remedies containing Caffeine, Codeine, Pseudoephedrine derivatives.
- Antidiarrheal products containing Paregoric.
- Antitussives containing Codeine and Pseudoephedrine.
- Sedatives and Sleep Aids/Appetite Suppressants containing Codeine and Pseudoephedrine .
- Appetite Suppressants/Diet Control Medications containing Caffeine, Codeine, Psuedoephedrine and Phenylephrine derivatives.

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**USE OF PHARMACEUTICALS**

- These are some precautions that will help avert problems with prescribed psychoactive medications:
- Avoid any medications that contain alcohol such as prescription cough syrups, liquid vitamin supplements, and any other preparations containing alcohol.
- Avoid any medications that contain any central nervous system stimulants such as prescription appetite suppressants and antihistamines.
- Avoid any medications that contain a narcotic that is used for pain relief or as an anti-diarrheal.
- Avoid any medications that contain a central nervous system depressant used for anxiety or as a sedative-hypnotic.

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**CENTRAL NERVOUS SYSTEM (CNS) DEPRESSANTS**

- *Alcohol*- Ethyl alcohol, Ethanol (Beer, Liquors, Wine)
- *B. Barbiturates*- Amytal, Butabarital, Nembutal, Phenobarbital, Seconal
- *C. Benzodiazepines*- Valium, Librium, Ativan, Serax, Xanax, Tranxene, Klonopin
- *D. Other CNS Depressants*- Ambien, Lunestra, Sonata

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**CENTRAL NERVOUS SYSTEM DEPRESSANT SUMMARY**

- **Physical and Mental Effects**
- Tolerance
- Generally useful only for brief therapy
- **Other effects**
- Varying lengths of action and medical uses
- Withdrawal
- Potentiation with other depressants
- Release inhibition, hostility, agitation
- Depression, brain damage with chronic use
- Habituation
- Neuroadaptation

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### CENTRAL NERVOUS SYSTEM STIMULANTS

- *Amphetamines* (Synthetic)-d,l amphetamine, Dextroamphetamine, Methamphetamine
- *B. Naturally Occurring-* Caffeine, Cocaine, Nicotine
- *C. Synthetic Agents Like Amphetamines* - Methylphenidate, Phentermine HCl

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### Natural Rewards

- Food
- Sex
- Excitement
- Comfort

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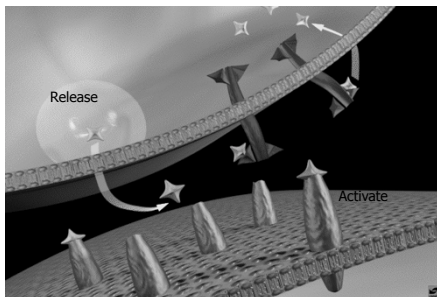
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### Dopamine Spells REWARD



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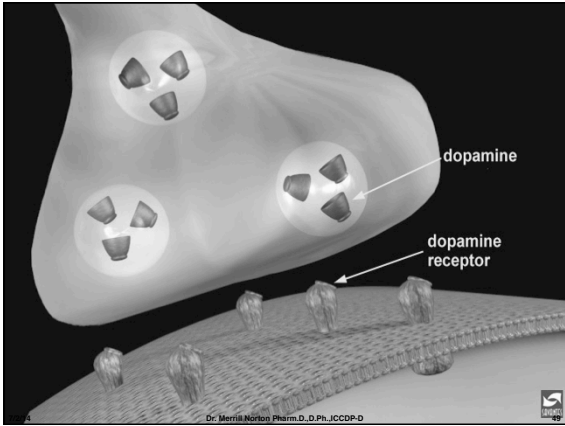
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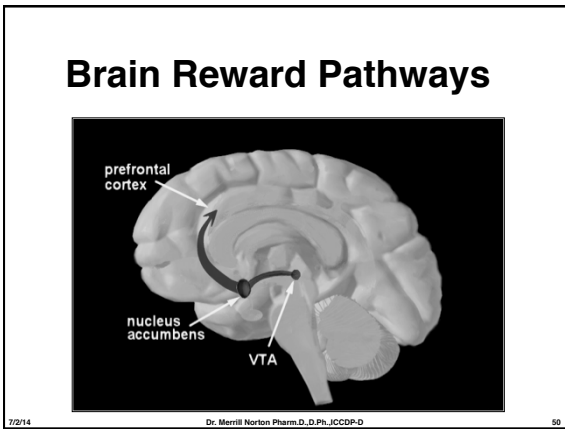
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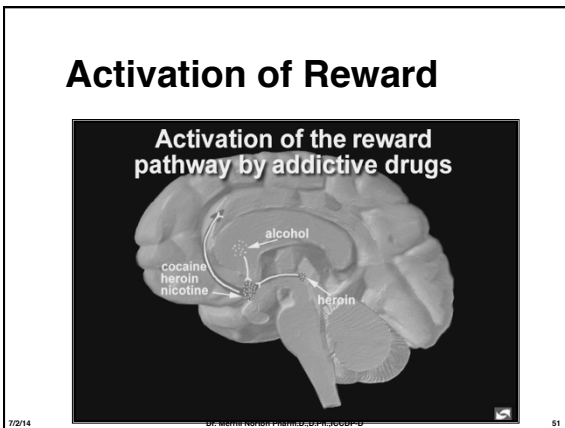
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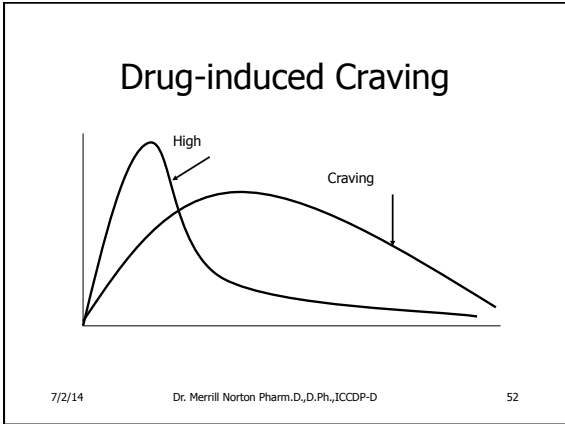
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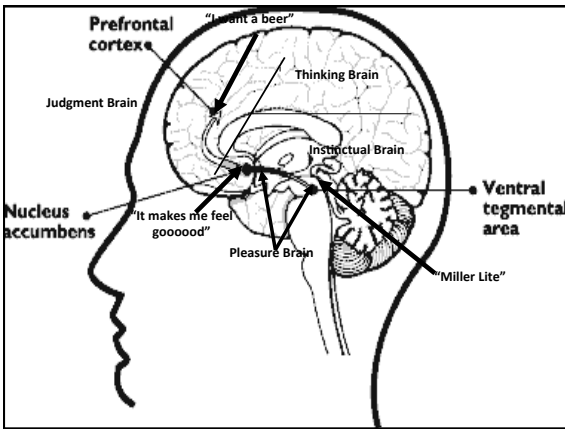
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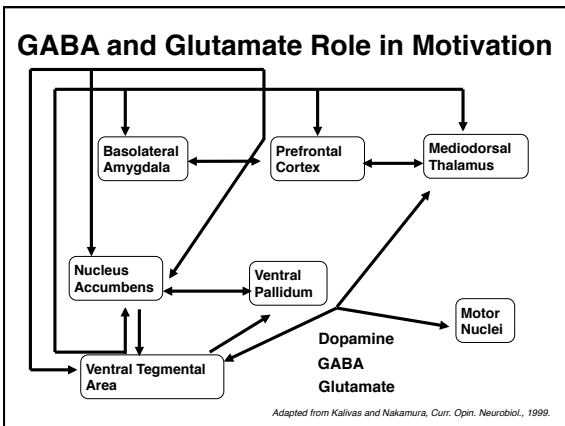
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