Reward and Addiction
Motivation is a theoretical construct, used to explain why people do what they do (e.g., the reasons for our actions, our needs, our desires).

What are we motivated toward?
• Survival (basic drives)
• Reward (enjoyment, success)

What influences motivation?
• Memory
  - past events, consequences
  - future outlook
• Executive functions
  - personality, interpretation
• Emotional state

Evidence suggests that motivated behavior involves coordinated communication between the prefrontal cortex, hypothalamus, and ("wanting") reward circuitry.
Reward is the positive/pleasurable consequence of an action, and it is a potent motivator. Rewards typically serve as reinforcements; that is, when presented after a behavior, they cause the probability of that behavior's occurrence to increase.

Primary (natural) rewards include those that are necessary for the survival of the species, such as sleep, thirst, food, temperature and sexual reproduction.

Secondary rewards include objects that derive their value from primary rewards (e.g., money can buy food).
Olds and Milner (1954) discovered that brain circuitry exists that reinforces behaviors. In particular, many species will administer brief bursts of weak electrical stimulation to specific sites in their own brains. This phenomenon is known as intracranial self-stimulation (ICSS), and the brain sites capable of mediating the phenomenon are called pleasure centers.
The mesotelencephalic dopamine system plays an important role in intracranial self-stimulation. Neurons project from the mesencephalon (midbrain) to the telencephalon.

The neurons in this system have their cell bodies in two midbrain areas:
- the substantial nigra (green)
- the ventral tegmentum (red)

Nigrostriatal pathway: substantia nigra neurons project to the dorsal striatum (degenerate in Parkinson’s disease)

Mesocorticolimbic pathway: ventral tegmental area neurons project to cortical and limbic sites, including the nucleus accumbens

The **mesocorticolimbic pathway** is the major “reward” pathway for ICSS and natural rewards (and site of action of addictive drugs). This circuit is involved in anticipatory pleasure (i.e., wanting or craving), as opposed to actual pleasure (i.e., liking). The latter circuit is unknown.
A simplified schematic of the major inputs to and outputs of the dopaminergic neurons in the ventral tegmental area (VTA). Glutamatergic excitatory inputs come from the prefrontal cortex (PFC; executive motivations) and lateral hypothalamus (LH; basic motivations). GABAergic inhibitory inputs arise from VTA interneurons and the nucleus accumbens (Nac). In turn, the VTA provides dopaminergic input to a variety of targets including the PFC and NAc.
The nucleus accumbens (NAc) receives direct dopaminergic input from the ventral tegmental area. Among its outputs, it indirectly excites the prefrontal cortex (via the ventral palladium (VP; part of the basal ganglia) and the dorsomedial nucleus of the thalamus).

The NAc appears to play a primary role in the anticipatory reward pathway. In particular, natural reinforcers (e.g., food) result in increased dopamine in the NAc, and lesions of the NAc (or ventral tegmental area) eliminate self-administration of addictive drugs (dopamine agonists).
Drug Use and Abuse

Drugs are taken for many reasons (e.g., medical, social).

Some drugs contain **psychoactive** chemicals that cross the blood brain barrier and alter the way nerve cells send, receive and process information, and thus affect behavior. In addition to their specific effects, many psychoactive drugs also over-stimulate the “reward circuit”.

Most any drug can be abused; that is, used at an inappropriate dose, period of time, or for a different purpose than that intended.

Drug addicts are those who continue to use a drug despite its adverse effects on their health and social life. Addiction and physical dependence (i.e., withdrawal symptoms) may occur together or separately.
Principles of Drug Action

**Drug administration:** the route affects the rate and degree to which the drug reaches its site of action.

- **Ingestion:** easy, but unpredictable
- **Injection:** fast and predictable, but need needle and potential for scar tissue, infection and overdose
- **Inhalation:** fast, but hard to regulate and may damage lung tissue
- **Absorption:** easy, but damage to nasal, oral and rectal mucosa

**Mechanisms of action:** once a drug enters the blood stream, it must pass through the blood-brain barrier to have its effects. Drugs influence the nervous system by altering the way nerve cells send, receive and process information.

**Drug metabolism and elimination:** the actions of most drugs are terminated by enzymes in the liver. Small amounts may also be excreted in bodily fluids (e.g., urine, sweat).
Tolerance

Drug tolerance is decreased sensitivity to a drug as a result of exposure to it. Drug tolerance can be shown in two ways: 1) a given dose has less effect; and 2) a larger dose is needed to produce the same effect. Tolerance is a shift in the dose-response curve to right. Tolerance can be metabolic in nature (less drug gets to the site of action) or functional (reduced sensitivity; fewer receptors or less responsive). Increased sensitivity to a drug is possible (called sensitization).
Withdrawal and Physical Dependence

After significant amounts of drug have been in the body for a period of time (e.g., days), its sudden elimination can trigger an adverse physiological reaction called withdrawal syndrome.

Withdrawal symptoms are the opposite of the drug’s effects. That is, the body has made changes to compensate for the drug’s presence and functions normally with the drug present.

Severity of withdrawal varies according to the drug and the pattern of use.
Commonly Abused Drugs: Tobacco

Psychoactive ingredient: nicotine

Addiction potential: high. About 70% of those who experiment with smoking become addicted. Only about 20% of attempts to quit are successful.

Health: smoker’s syndrome includes chest pain, labored breathing, wheezing, coughing, increased susceptibility to respiratory infections and lethal lung disorders (e.g., emphysema, cancer). Quitting typically results in major health benefits.

Effect on reward circuit: nicotine binds to acetylcholine receptors on dopaminergic neurons in the VTA. Channels opened, sodium flows in and depolarizes cell → increased release of dopamine in NAc.
Commonly Abused Drugs: Alcohol

Psychoactive ingredient: ethanol

Alcohol is classified as a depressant because at moderate-to-high levels it reduces neural firing (decreases release of glutamate, enhances GABA channels).

Health: severe alcohol withdrawal syndrome includes vomiting, convulsions and delirium tremens. Other ailments: Korsakoff’s syndrome, cirrhosis.

Effect on reward circuit: ethanol reduces the activity of voltage-dependent potassium channels in VTA neurons. As a result, the relative refractory period of VTA dopaminergic neurons is reduced, allowing them to fire more often. High rates in VTA neurons → increased release of dopamine in NAc.

Okamoto et al. 2006

Mereu et al. 1984
Commonly Abused Drugs: Marijuana

Psychoactive ingredient: THC (delta-9-tetrahydrocannabinol); over 80 others are present. *Cannabis sativa*: common hemp plant.

Addiction potential: low.

Health: high doses impair short-term memory and interfere with tasks involving multiple steps. Long-term: respiratory problems, no obvious permanent brain damage.

Effect on reward circuit: THC binds to CB1 (anadamide) receptors on GABAergic inputs in the VTA, reducing calcium influx and thus transmitter release. VTA dopaminergic neurons can thus fire more often → increased release of dopamine in NAc.

Note: artificial cannabinoids (e.g., Spice) are full agonists and can cause psychosis.
Commonly Abused Drugs: Amphetamines

Psychoactive ingredients: levo- and dextro-amphetamine

Addiction potential: high

Health: high doses impair short-term working memory and alter cognitive (executive) control.

Effect on reward circuit: competes with dopamine for “re”uptake in the NAc. Once inside the terminal button, it causes reuptake transporters to reverse their mode of operation. The net effect is to increase the level of dopamine in the NAc.
Psychoactive ingredient: cocaine. It is a stimulant, an appetite suppressant, and at low doses an anesthetic (nonspecific voltage-gated sodium channel blocker).

Addiction potential: high. Withdrawal is relatively mild.

Health: cocaine binges or sprees may lead to cocaine psychosis (unconscious, seizures, heart attack or stroke; looks like paranoid schizophrenia).

Effect on reward circuit: cocaine acts as a serotonin-norepinephrine-dopamine reuptake inhibitor [known as a triple reuptake inhibitor (TRI)]. Cocaine prevents dopamine reuptake in the NAc, thus high levels of dopamine persist.
Commonly Abused Drugs: Opiates

Psychoactive ingredient: morphine and codeine. Heroin is a semisynthetic morphine (greater penetration of the blood-brain barrier). Potent analgesics

Addiction potential: high. Addicts are drawn to use by the rush (acute state of euphoria) following IV injection. Tolerance and physical dependence.

Health: although opiates are highly addictive, direct health hazards are relatively minor. Indirect health hazards related to needle use.

Effect on reward circuit: opiates bind to endogenous opiate receptors on VTA GABAergic neurons, enhancing potassium efflux and thus reducing transmitter release. VTA dopamine neurons are disinhibited → increased release of dopamine in NAc.