

REWARD AND REINFORCEMENT I

Neural basis of appetitive behavior and motivation

“Every animal habitually persists in each act which gives pleasure- and desists from each act which gives pain...” Herbert Spencer, 1872

General Principles

The modern concept of motivation derives from the historical desire to account for the needs and drives that govern the strength and direction of our behaviors. The ancient Greeks talked about instincts and hedonism (pleasantness and unpleasantness), and Plato believed that reason was in the head, but that courage was in the chest and appetite in the abdomen. We now know of course that instincts and basic biological drives for food, water, sex, warmth and shelter, attachment and affection, are firmly grounded in the brain!

There is a central neural system that mediates motivational states, reinforcement and reward, and hedonic (or pleasurable) experience. James Olds, at McGill University, discovered this “reward” system during his studies on rat brain arousal in the 1950s. Olds mistakenly placed stimulating electrodes in a part of the limbic system and found that rats would press a lever for electrical stimulation, almost nonstop, except for sleep. Research on human subjects, many years ago, also revealed that electrical stimulation of some parts of the brain (somewhere in the hypothalamus) produced a feeling of quasi-orgasmic sexual arousal. This system appears to mediate not only biological reinforcement, but also the rewarding effects of drugs of abuse. This system, therefore, is involved in some of the motivated behaviors absolutely necessary for survival of the individual (such as the procurement and ingestion of food that is motivated through the state known as hunger; finding and ingesting water through thirst) or for the survival of the species (sex, maternal behavior, defense of a territory). Many motivated behaviors have the property of leading to reward and reinforcement. For example, if an organism is motivated by hunger to eat food, the consumption of food is perceived as a positive affective experience and is rewarding. Most often, the experience of a rewarding state will result in an **increase** in appetitive responses, such as food-seeking behavior. In this specific case, food is considered the reinforcer.

Unfortunately, humans have developed or discovered substances (psychoactive drugs) that readily and powerfully activate this reward/reinforcement system. As a result, it is difficult for humans to control their intake of these substances. Likewise, the intake of some foods (usually sweet and rich) results in activation of this system, which also makes control of the intake of these foods difficult and may lead to eating disorders and obesity. Given the importance of these problems (alcohol and other drug abuse, eating disorders, and obesity) in clinical experience, it is important to understand current concepts of the underlying mechanisms of motivation, reward and reinforcement.

Examples

Consider a newborn baby. How do babies spend most of their time? Sleeping, eating, crying and cuddling. Babies come into the world with many innate mechanisms for motivated behavior, and for getting their basic needs attended to. For example, they respond differentially to substances with different tastes. The initial taste of sweet results in a facial expression appearing markedly more positive than other expressions. Other studies demonstrate that sweet is associated with an **increased** force of sucking and a **rise** in heart rate. Clearly, a newborn baby is capable of discerning what it likes and responds in a manner that **increases** procurement of that substance. Similarly, we spend much of our lives trying things out, deciding whether or not the result was positive, and repeating those behavioral responses that lead to positive results. Before examining the neurobiology of motivated behavior, some basic psychological terms need to be introduced to help us understand the processes of reward and reinforcement.

One of the most important theoretical developments in psychology was the “**law of effect**,” formulated by E.L.Thorndike, in the early part of the 20th century. This law stated that the **reward of success** is “stamped in” stimulus-response associations, while **punishments** or other negative consequences stamped them out. This idea may sound familiar, as it formed the empirical basis for the work of the famous psychologist B.F. Skinner. Skinner believed that all behavior was shaped by positive or negative events.

A behavioral act often results in consequences that lead to an increase or decrease in the subsequent frequency of that behavior. This is called **instrumental** (also called “operant”) **conditioning**, which was first described by the legendary behaviorist psychologist, B. F. Skinner. In a typical “Skinner box”, there is a lever that a rat can press and a food pellet is delivered. The rat learns to press the lever as a result of being reinforced. This basic paradigm can be generalized to explain virtually all learning that is more complex than an instinctive response. The basic idea, of course, is that behavior that is followed by **positive** events will continue and strengthen, while behavior followed by negative events, will decline and eventually fade away. In operant conditioning, there are three basic variables. First, of course are the **behavior** (e.g. lever pressing) and the **consequence** (e.g. food pellet). A third, equally important, but perhaps not so obvious variable is the **discriminative stimulus**, which signals that the behavior and reinforcement contingency is in effect (the sight of the bar, the context of the box, etc.) Note that the sensory system detects a discriminative stimulus, and due to the reinforcer, the discriminative stimulus is associated with a given behavior. Thus, learning in the case of instrumental conditioning is the association of a stimulus with a behavior.

While we will return to this point later, it is important to emphasize that dopamine is very important in the acquisition of instrumental responses. In fact, drugs that block dopamine receptors in the nucleus accumbens (to be discussed soon!) **inhibit** the acquisition of instrumental responses.

As alluded to earlier, those consequences resulting in a subsequent **increase** of the probability of the behavior are termed **positive** reinforcers. A **negative** reinforcer increases a behavior that **relieves** a negative state. Finally, those consequences that subsequently **decrease** the occurrence of the behavior are termed **punishments**. Examples of positive and negative reinforcers as well as punishment are shown in Table 1.

Behavioral response	Consequence	Subsequent Behavior
Sucking liquid	Obtain sweet	Increased sucking
Lever press	Shock	Decreased level pressing
Talking to attractive person	Increased attention from person results in pleasant, aroused state	Increased talk
Use of painkiller for pain	Relief of pain	Increased use of painkiller
Talk to doctor	Doctor nods/asks questions	Increased reporting
Talk to doctor	Dr. flips through chart and gets your name wrong	Decreased reporting

Table 1. Consequences of various behavioral responses and their effects on subsequent responding.

The consumption of sweets, or talking to an attentive attractive person or attentive doctor is considered **positively** reinforcing. In all of these instances, the consequences result in a positive internal state that will increase the subsequent frequency of sucking or talking. An electric shock would be a punishment of a lever press because after the organism pressed the lever and experienced the shock, lever pressing would **decrease** in frequency. The inattentive doctor acts as a **punisher** because it decreases reporting. The relief of pain (negative state) after taking a painkiller may result in increased use of the painkiller. In this example, pain relief is a **negative** reinforcer because it increases the use of the painkiller to reduce a negative state.

Factors influencing the effectiveness of a reinforcer

Numerous factors influence the process of reinforcement. These include the schedule of reinforcement, the availability of reinforcers, the extinction process, and individual differences.

The schedule of reinforcement

Continuous reinforcers are consequences that are always paired with the occurrence of the behavior. For example, an experimenter provides a sweet food pellet to a rat for **each** lever press. In the early acquisition phase, continuous reinforcers are quite effective in “stamping in” the behavior. **After acquiring a behavior**, animals including humans will work very hard for even intermittent reinforcement. For example, many humans play slot machines which deliver random, intermittent reinforcement. Rats will press a lever many hundred of times for only an occasional injection of cocaine. The **immediacy** of the consequence (or potential reward) also influences its reinforcing or punishing qualities. The rapid effects of intravenous or smoked drugs on brain function are believed to underlie their potent reinforcing qualities as compared to orally ingested drugs, which must first be absorbed from the GI tract.

The availability of other reinforcers

The presence or absence of alternative reinforcers in the environment influences the likelihood of any stimulus becoming established as a reinforcer. For example, the availability of a sweet solution to a rat will dramatically decrease its lever pressing for drug reinforcers. It is believed that providing alternative social reinforcers to kids in impoverished environments may decrease their risk of using drug reinforcers.

Extinction

Sometimes, the reinforcer/reward no longer occurs after the occurrence of a behavioral response. Consequently, the probability of the behavior will decline in frequency. This process is known as **extinction**. For example, a rat presses a bar in its cage and nothing happens. Neither a positive or a negative condition exists for the rat. The rat presses the bar again and again nothing happens. The rat's behavior of pressing the bar is weakened by the consequence of not experiencing anything positive or stopping anything negative.

Behavioral responses rewarded for a long period of time or with a **very potent reward** may take a longer to extinguish. For example, a gambler who is lucky at the slots on the first gambling trip might be found several years later still pulling the lever and remembering that big first night.

Individual Differences

Individuals differ in their sensitivity to various reinforcers/rewards. Some individuals have initially positive (or at least less negative) responses to drugs or alcohol while others find these substances aversive. Animals can be bred to be very sensitive to the rewarding effects of alcohol, drugs, or to intracranial electrical stimulation. Perhaps differences in response to rewards/reinforcers are due to neurobiological differences among individuals. In one study, the responses to alcohol by sons of alcoholics were examined. Although the sons were not yet alcoholic, they showed less "**negative**" **responses** to alcohol exposure such as **cortisol increases** or **postural sway**. People may also differ in their ability to tolerate a long delay between the behavior and the presentation of a reinforcer.

Reinforcement has a neurobiologic basis

The importance of dopamine in reinforcement was introduced earlier. The neuroanatomy and neurochemistry of positive reinforcement is relatively well understood, at least in terms of basic mechanisms. The neural circuitry most closely linked to positive reinforcement is the “**mesocorticolimbic dopaminergic (DA) system.**” This system is composed of several brain stem and forebrain nuclei that include the **ventral tegmental area (VTA)**, **nucleus accumbens (N. Acc.)**, **prefrontal cortex**, **amygdala**, **hippocampus** and the **septum**. The **VTA** (Fig. 1) is a region in the midbrain that lies close to the substantia nigra pars compacta and, like pars compacta, contains **dopaminergic** cell bodies that project rostrally. The **nucleus accumbens**, which is located in the base (ventral) of the forebrain just ventral and medial to the head of the caudate and the putamen (Fig. 2), is one of the primary terminal projection sites of VTA/DA cell bodies. In addition, the **prefrontal cortex** receives direct projections from the VTA. This mesocorticolimbic DA system does not exist in isolation. At each level, it has critical connections to other brain regions, particularly basal ganglia and limbic structures.

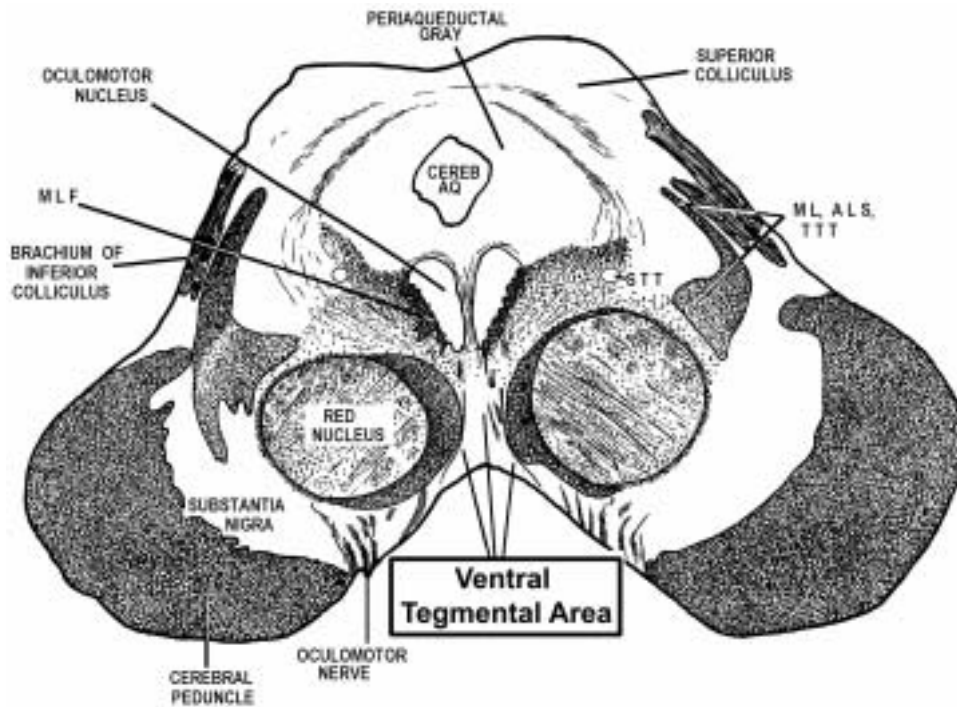


Fig. 1 Ventral tegmental area in the human brain.

Fig. 2. Location of nucleus accumbens in the human forebrain.

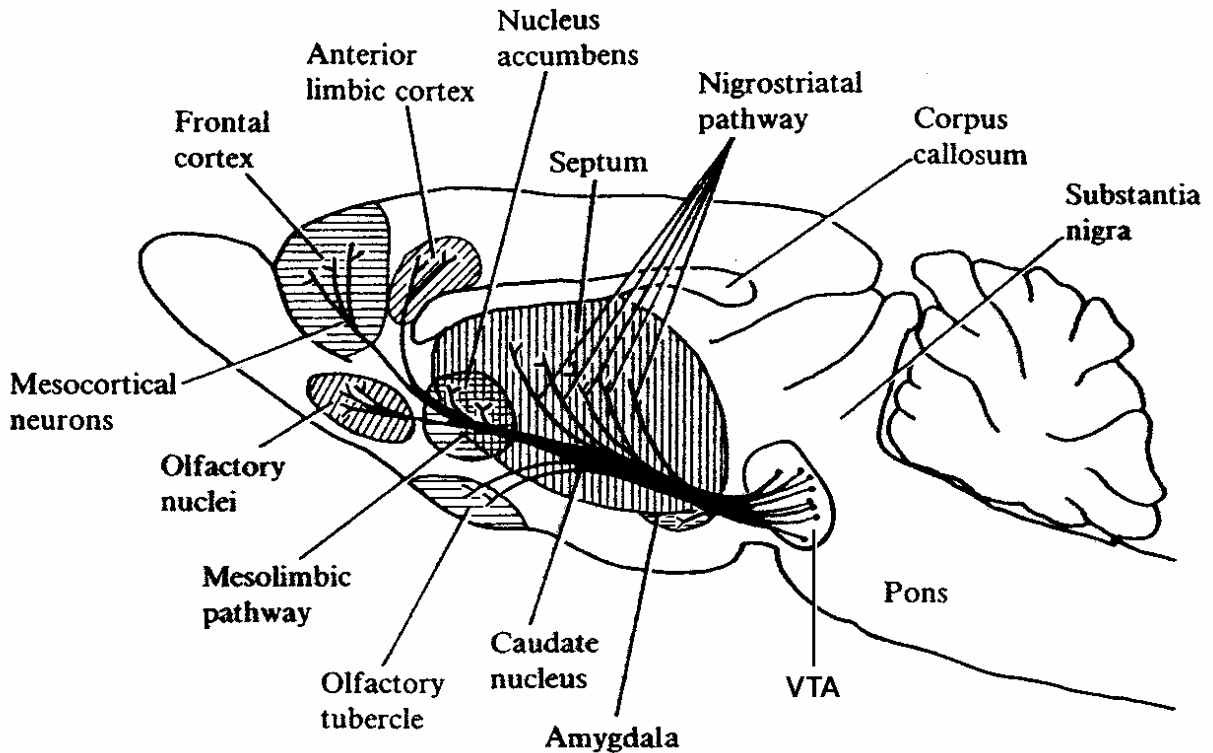
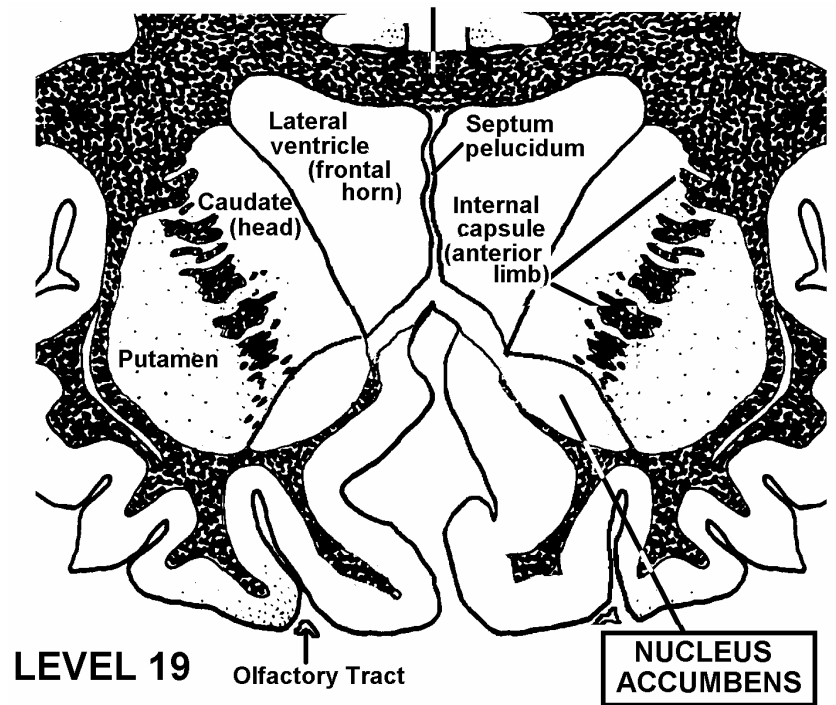


Fig. 3. Schematic of rat brain mesocorticolimbic dopamine system (sagittal view). This system plays a major role in mediating the rewarding effects of natural (e.g., food, water) and artificial (e.g., drugs) reinforcers. Dopamine cell bodies located in the VTA project their fibers to forebrain sites including the **nucleus accumbens**, **prefrontal cortex**, **amygdala** and **hippocampus**. The release of dopamine, especially in the **nucleus accumbens**, mediates positive reinforcement. Modified from Ungerstedt, 1974.

Dopamine is involved in positive reinforcement

A variety of data, both in animals and humans, implicate an involvement of **dopamine** (DA) in the positive reinforcement process, especially in relation to the mesocorticolimbic DA system, and the nucleus accumbens in particular. Recall from your study of Parkinson's disease that the caudate and putamen (more dorsal aspects of the striatum), which are innervated by the substantia nigra pars compacta, are related to motor functions. In contrast, the more ventral regions (which includes the **nucleus accumbens**) seem more aligned with **reward** and **motivational** functions. What is the evidence for this notion?

As noted earlier, electrical stimulation of certain brain sites (e.g., the hypothalamus) is positively rewarding, as demonstrated by the observation that rats will repeatedly press a lever (up to 6,000 times per hour) to deliver electrical current to certain brain sites. At effective hypothalamic sites for reinforcement, the electrical current stimulates a descending pathway from the prefrontal cortex to the VTA. Such stimulation activates the mesocorticolimbic system (press lever [behavior]--feels good [consequence] —press lever again). Of course a rat will also repeatedly press the same lever if the stimulating electrode is in the VTA and in fact the VTA is one of the “hot spots” for electrical brain stimulation. If DA is removed from the mesocorticolimbic system via a lesion, or the rats are given DA blockers, the rats will no longer engage in lever-pressing for brain stimulation.

Studies using *in vivo* microdialysis (measurement of neurotransmitters in the extracellular fluid of a specific brain region) have shown that ingestion of food, water, and sweet solutions (i.e., natural reinforcers) is accompanied by **increases** in extracellular DA concentrations in the nucleus accumbens (see Fig. 4). This finding is interpreted to reflect the activation of the ascending VTA-DA pathway. Sexual stimuli (i.e., a mate) and mating behavior are also associated with marked **increased** in DA release in the nucleus accumbens (Fig. 5).

Research in human subjects has revealed that comparable electrical brain stimulation is associated with profoundly pleasurable effects. For obvious ethical reasons, research with human subjects has been very limited. However, the available data suggest that the principles learned from animal experimentation are valid for human subjects; studies of electrical stimulation of reward pathways in humans provide direct evidence that stimulation that is reinforcing in animals is both reinforcing and intensely pleasurable in humans.

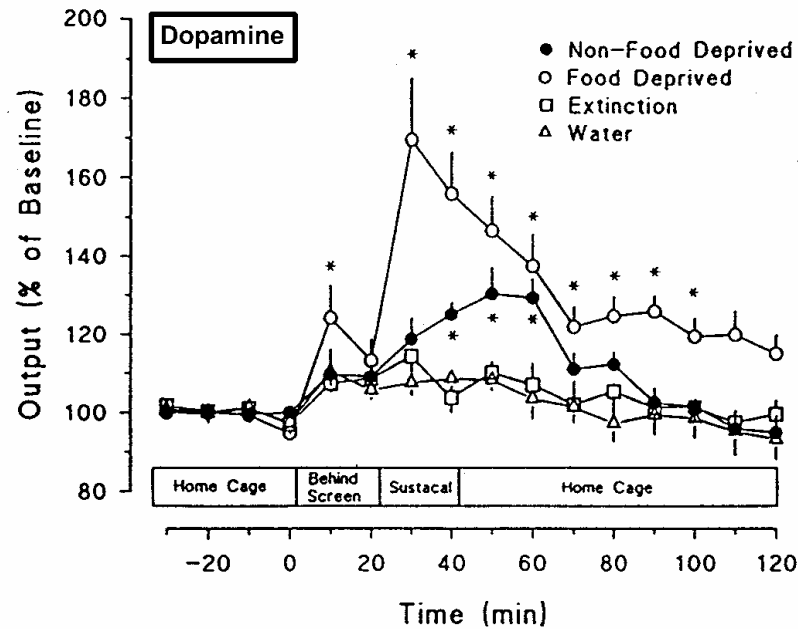


Fig. 4. A microdialysis experiment that allows the monitoring of extracellular dopamine levels within the nucleus accumbens during ongoing feeding behavior. Behavior was monitored in several groups of rats, all of which had previous training with a highly palatable sweet liquid food (“Sustacal”). There was a hungry group, a group that was not food deprived, and two control groups: the “extinction” group (nothing in the tube on the test day) and the water group (water instead of Sustacal). The rats were first monitored in the home cage, then put in the cage where they normally received the sweet food. Twenty minutes later a screen was removed and they were allowed access to the drinking tube. Dopamine was markedly increased during feeding, and the effect was magnified in the hungry group. Even the anticipation of food in the hungry group activated dopamine.

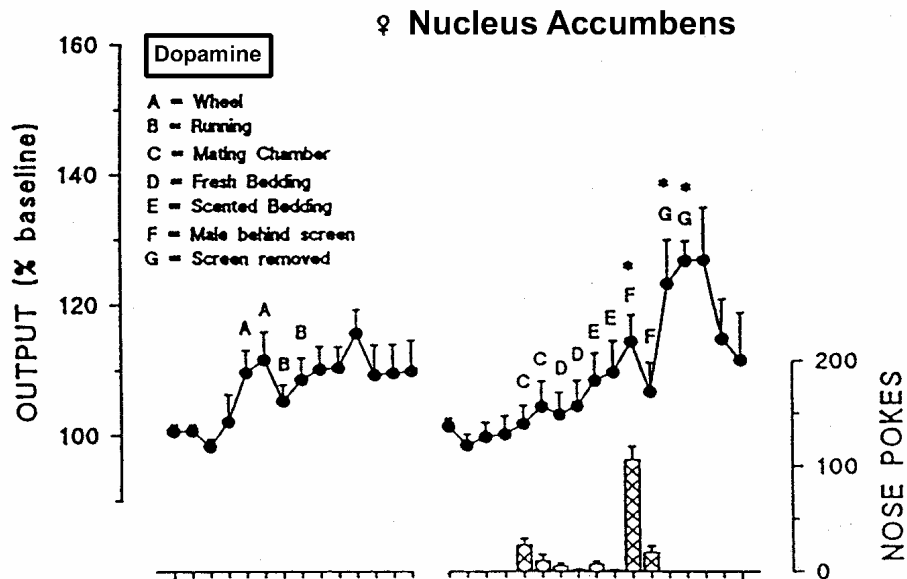
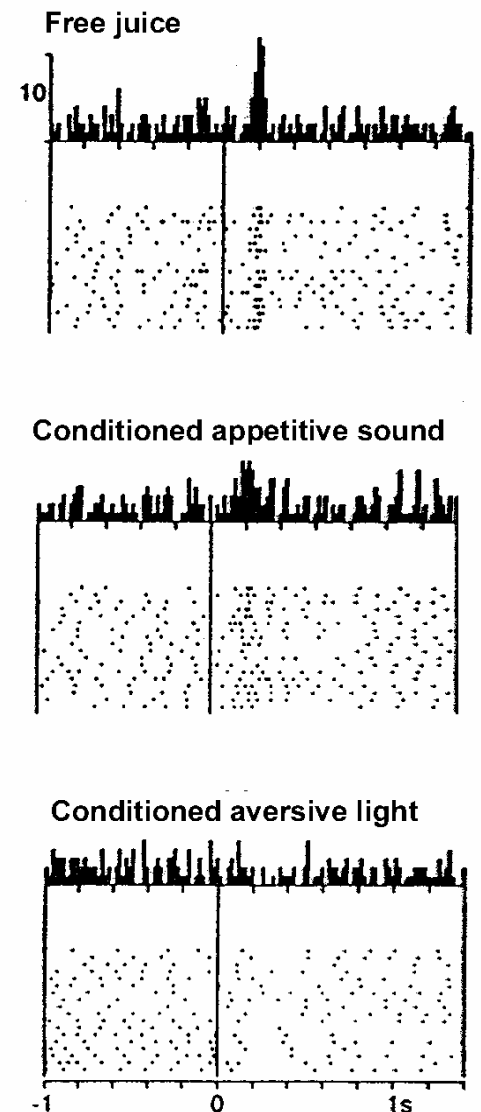


Fig. 5. In this experiment, rats were monitored for extracellular dopamine with a microdialysis probe in the nucleus accumbens. Sexually experienced male rats were tested under various conditions: motor activity (wheel running), anticipation of mating, and access to the female and copulation. Basal dopamine levels are shown at 100%. Dopamine is somewhat **enhanced** during motor activity, but is increased much more during the sexual cues (olfactory and visual). From Damsma et al., 1992.

An additional important and interesting hypothesis is that DA release is associated not only with primary reinforcing stimuli, such as food for a hungry animal, or a male rat for a female in heat, but also with **conditioned** stimuli (remember the experiments on Pavlov's dog in the Emotion chapter). Such stimuli are previously neutral stimuli which have become rewarding by virtue of being associated with the availability or delivery of reward (the conditioned response in "Pavlov's dog"). Thus, environmental stimuli such as the room, lights, sounds, or smells can become potent signals of impending reward (of course, such stimuli can be negative signals if they are predictive of aversive or unpleasant events). It is believed that DA may play an important role in learning about stimuli **predictive** of reward. For example, recording experiments in awake monkeys have shown that DA neurons in the VTA fire in response to both primary and conditioned rewarding stimuli (see Fig. 6). That is, the DA cells **increase** their firing when a monkey is given some juice (unconditioned stimulus like the meat powder in Pavlov's dog) **and** also after hearing a sound (conditioned stimulus) that they know will be followed by a reward (juice) if they just reach for it. In contrast, DA cells do **not** increase their firing when a conditioned stimulus (a light) comes on that they have learned will be followed by an irritating puff of air (an aversive stimulus).

How does the VTA receive information about the external and internal environment? The afferent inputs to the VTA are complex and arise from many regions, but several candidates are the **locus coeruleus**, **pedunculopontine nucleus** (a primarily cholinergic cell group in the pons that was not discussed in the brain stem lectures), **amygdala**, and **prefrontal cortex**. Indeed, processed sensory and emotional information could reach the VTA via the prefrontal inputs (as mentioned earlier, this pathway is reciprocal, since the VTA also projects to the prefrontal cortex).

Fig. 6. Selective activation of dopamine neuron by primary and conditioned appetitive stimuli, in an electrophysiological recording experiment in a behaving monkey. Neuronal activity increased after a drop of free juice (top) and after a conditioned sound eliciting a reaching movement for juice reward (middle). Activations were absent after a conditioned light in air-puff avoidance trials (bottom) the figure shows neuronal activity from one midbrain dopamine neuron. Each dot denotes the time of a neuronal impulse, and each line of dots shows one trial. The stimulus was presented at time 0 (the vertical line in the middle of each plot). This experiment demonstrates that midbrain DA neurons may code both natural rewards and environmental cues that signal reward, but are unlikely to code learned aversive stimuli. From Mirenowicz and Schultz et al., 1996.



Opiates and the VTA

Although dopamine is important for many aspects of motivated behavior, other neurochemical systems may also play a role. For example, the brain contains its own "morphine-like" substances, termed endogenous **opioids**. There are several types of opioid compounds, such as **enkephalins**, **endorphins**, and **dynorphins**, which are found in various cell groups (especially in the hypothalamus) and pathways throughout the brain. These opiate pathways can directly turn on VTA cells and thus cause release of DA in nucleus accumbens. By mechanisms now being studied, opiate pathways can also cause the release of DA in nucleus accumbens via direct input to this nucleus. For instance, there are opiate receptors on GABA processes that terminate on VTA terminals. The direct opiate pathway blocks the release of GABA on these VTA terminals in nucleus accumbens and thus causes the release of DA. Opiates can also be injected into the blood stream (heroin) and reach opiate receptors on VTA cells and the GABA processes in the nucleus accumbens.

Opioids may regulate food intake and the affective response to **sweet** taste. It is proposed that opioid activity in the brain is stimulated by the sensory properties of food and determines the hedonic evaluation of food and drink. That is, when we eat something sweet the endogenous opioid circuits turn on and dopamine levels rise (endorphins probably contribute to the warm inner glow induced in chocaholics). There is evidence that endogenous opioid circuits terminating in the **nucleus accumbens** may be particularly involved in modulating **palatability** and **taste preferences**. Infusion of opioids directly into the accumbens, which results in an increase in the firing of nucleus accumbens neurons (euphoria), makes rats that are not hungry feed voraciously, particularly high fat or sweet food (palatable). Humans given the **opiate blocker naltrexone** during food consumption state that their perception of hunger hasn't changed, but that the "food doesn't taste as good" (no associated dopamine euphoria). Infusion of naltrexone into the nucleus accumbens of a rat **reduces** consumption of highly palatable/appetizing food (again, no associated DA euphoria).

Opioids in other limbic areas, such as the **amygdala** and **hypothalamus** may regulate emotional responses in relation to stress. Opioid peptides are released in response to threat or danger (part of stress response). The resultant analgesia may protect the organism from pain until it can escape. **Activation** of opiate receptors also appears to **reduce anxiety**. For example, administration of opiates to infant monkeys suppresses the signs of distress observed when they are separated from their mothers. Thus, taking opiates may help to alleviate stressful psychological states, and thus be rewarding, by acting on the brain's own "coping" system. In summary, activation of opioid systems, in a variety of brain regions, appears to be associated with states of positive affect.

Clinical correlates

Binge eating problems and eating disorders: parallels to substance abuse problems

An important observation from animal studies is that deprivation of one reinforcer such as food results in increased intake of alternative reinforcers. Rats that are maintained on 80% of their normal body weight will **increase** their lever pressing for drug rewards. Similarly, rats with a history of lever pressing for a sweet solution will increase lever pressing for drugs following deprivation of the sweet solution. Also, recent work here at the UW has shown that rats with a **strong** preference for sweet solutions or sweet-fat foods are more likely to develop preferences for morphine or alcohol. These phenomena suggest that the same systems underlying food intake may be affected by drugs of abuse, and that there are individual differences in sensitivity or desire for rewarding substances.

Another example illustrates the effects of dieting on binge eating and increased intake of alcohol and drug use. Binge eating occurs in 25-30% of obese people presenting to weight loss programs and in a sizable minority of college girls in the general population. Binge eating is characterized by the intake of a large amount of food in a short period of time. In addition, binge eaters feel a loss of control. Interestingly, the majority of people with this behavioral syndrome report that their binge eating started after a period of dieting or was worsened after dieting. Dieting can be generally defined as the attempt to refrain from eating food, particularly highly palatable, calorically-dense food. In other words, dieting is the attempt to deprive oneself of a natural reinforcer.

Women who diet most severely are more likely to not only binge eat, but to also drink heavily, smoke, and use marijuana. Furthermore, intake of large quantities of food and drugs appear to be reciprocally related because binge eating may increase during abstinence of alcohol. Thus, both animal and human studies suggests a strong linkage between deprivation of one reinforcer (food) and intake of other reinforcers: decreased use of a potent reinforcer appears to make control over other reinforcers more difficult.

Problem Solving

1. Which of the following statements is **TRUE**?
 - A. opiate-related pathways are functionally related to the ventral tegmental area (VTA)
 - B. opiate-related pathways are functionally related to nucleus accumbens
 - C. dopamine is released by the axon/terminals of VTA cells
 - D. endorphins are released by the axons/terminals of VTA cells
 - E. three of the above are **TRUE**

2. Which of the following associations is **TRUE**?
 - A. dopamine—VTA
 - B. norepinephrine--LC
 - C. epinephrine—adrenal medulla
 - D. endogenous opioids---turn on VTA
 - E. all of the above are **TRUE**

3. The neural circuitry thought to mediate positive reinforcement:
 - A. includes the nucleus accumbens
 - B. can be turned on by stimulating descending inputs to the VTA that run through the hypothalamus
 - C. includes cell bodies within the ventral tegmental area
 - D. is functionally related to endogenous opioid circuits
 - E. all of the above are **TRUE**

4. The mesocorticolimbic reward system:
 - A. originates in the substantia nigra
 - B. is thought to release dopamine into the nucleus accumbens in response to conditioned stimuli
 - C. innervates the ruber-duber and the dorsal striatum
 - D. is activated only by thinking about sex
 - E. the cortical part is related to visual cortex

5. The opioid peptide system:
 - A. includes enkephalins, endorphins, and dynorphins
 - B. decreases the intake of palatable foods
 - C. increases anxiety by acting at pain receptors
 - D. when blocked by a pharmacological antagonist, increases the sensation of hunger
 - E. inhibits the mesocorticolimbic pathway

6. Deprivation of a reinforcer:
- A. causes opiate release in the medulla oblongata
 - B. increases sensitivity to other reinforcers
 - C. does not affect control over other reinforcers
 - D. decreases responsiveness to other reinforcers
 - E. all of the above are **TRUE**
7. Which of the following is an example of positive reinforcement?
- A. when you talk to your doctor, she / he ignores you
 - B. when you take some Advil and it relieves your pain
 - C. when you eat a dessert and it makes you sick
 - D. when you tell a joke and people laugh
 - E. when you play with a baby and he / she cries
8. An example of negative reinforcement is:
- A. taking cocaine for its euphoriant properties
 - B. taking heroin to reduce withdrawal symptoms
 - C. pressing a lever for food
 - D. being shocked for pressing a lever
 - E. none of the above is/are **TRUE**
9. The VTA (ventral tegmental area) projects to:
- A. prefrontal cortex and nucleus accumbens
 - B. nucleus accumbens and locus ceruleus
 - C. hippocampus and motor cortex
 - D. striatum and raphe nucleus
 - E. nucleus accumbens and the ruber/duber/sluber
10. A VTA dopamine neuron could expect to be activated:
- A. when the animal is presented with a loud noise
 - B. when the animal is presented with food
 - C. when the animal is awake but resting
 - D. when the animal is presented with a stimulus previously paired with food
 - E. B and D are **TRUE**

11. Which of the following statements is **TRUE**?

- A. there is **no** relationship between deprivation of one reinforcer and intake of other reinforcers
- B. injections of opioids into the VTA decrease a rat's consumption of fatty food
- C. approximately 25-30% of obese people in weight loss programs are binge eaters
- D. consequences resulting in a subsequent increase of the probability of the behavior are termed negative reinforcers
- E. two of the above are **TRUE**

12. Which of the following statements is **TRUE**?

- A. sexual stimuli are associated with marked decrease in dopamine release in the nucleus accumbens
- B. an inattentive doctor acts as a negative reinforcer because you won't go back to see him soon
- C. injection of an opiate blocker into nucleus accumbens will result in rats eating voraciously
- D. the nucleus accumbens lies lateral to the lenticular nucleus (globus pallidus and putamen)
- E. **none** of the above statements is **TRUE**

13. Stephan and Cody were two mentally disabled boys who seldom **smiled** at other people. Dr. Hopkins used a procedure in which he would take them for walks, and if they smiled at passers by, he would give them some pieces of M & M's candy. This procedure caused Stephan and Cody to smile much more often than they had before.

- A. this is an example of negative reinforcement
- B. this is an example of punishment
- C. the consequence is smiling
- D. the behavior is receiving the candy
- E. this is an example of positive reinforcement

Answers:

- | | |
|----------------|-------|
| 1. E (A, B, C) | 10. E |
| 2. E | 11. C |
| 3. E | 12. E |
| 4. B | 13. E |
| 5. A | |
| 6. B | |
| 7. D | |
| 8. B | |
| 9. A | |