National Institute on Drug Abuse (NIDA)

The Neurobiology of Drug Addiction

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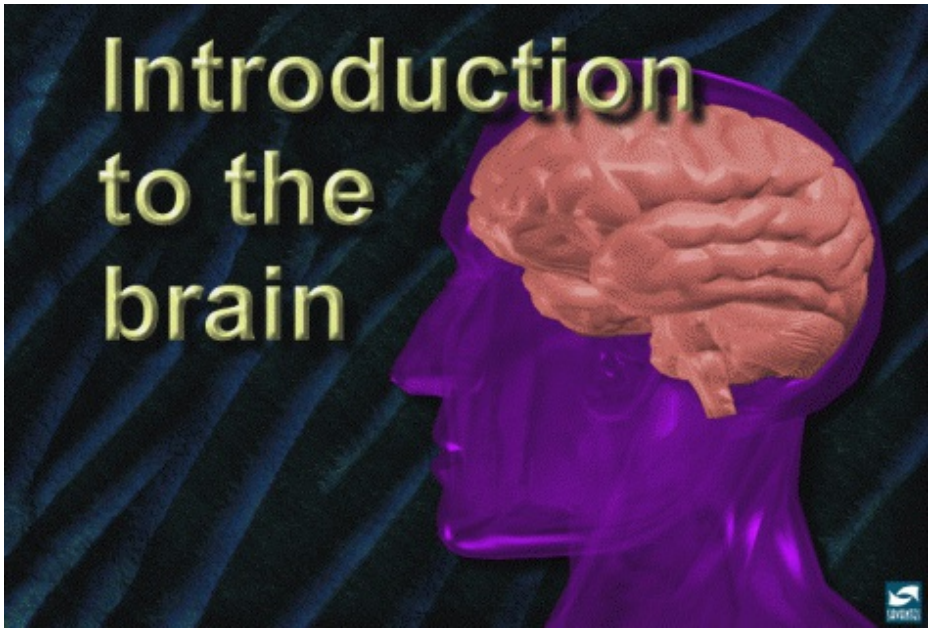
Background Information for the Presenter

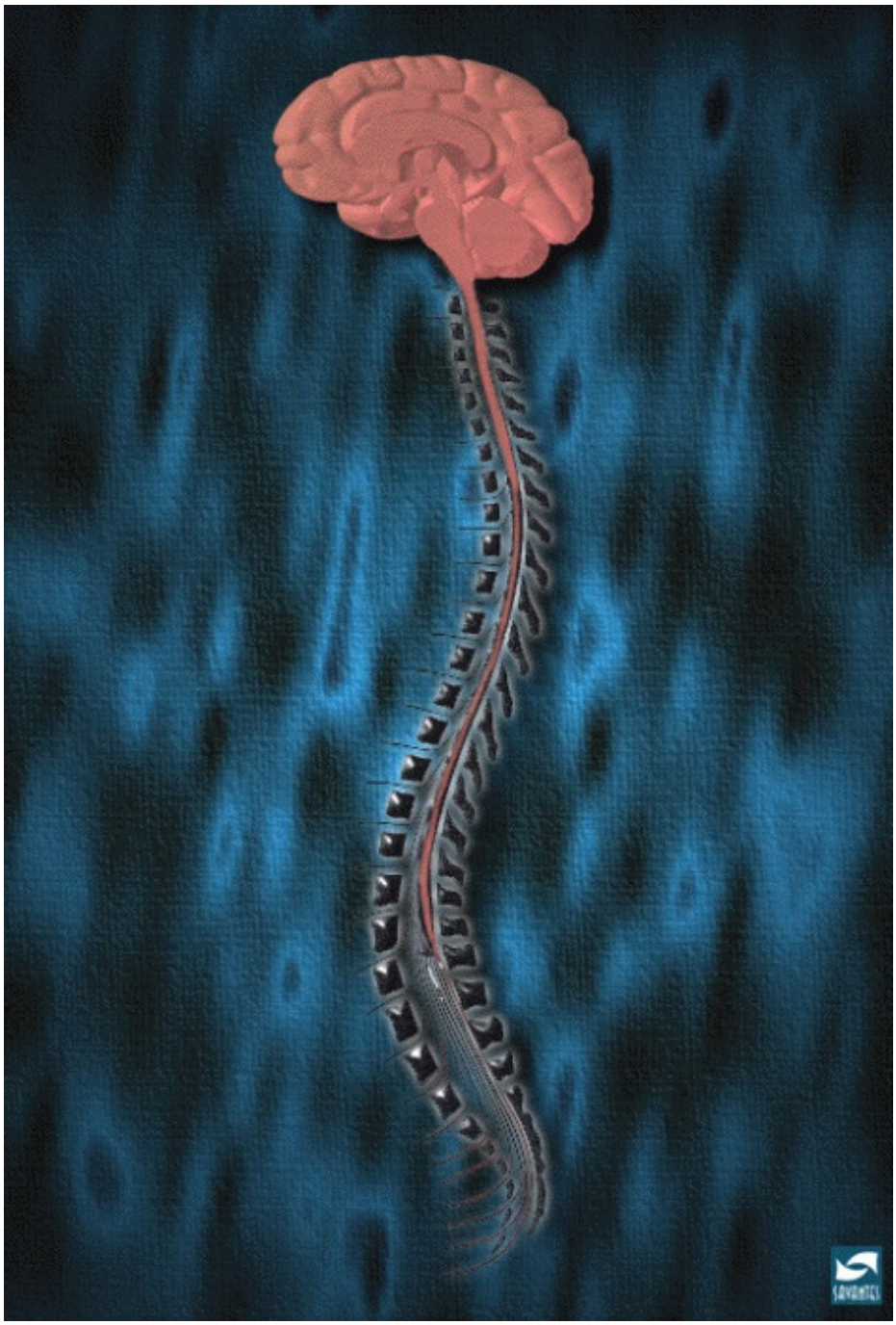
Section I: Introduction to the Brain

1: Introduction



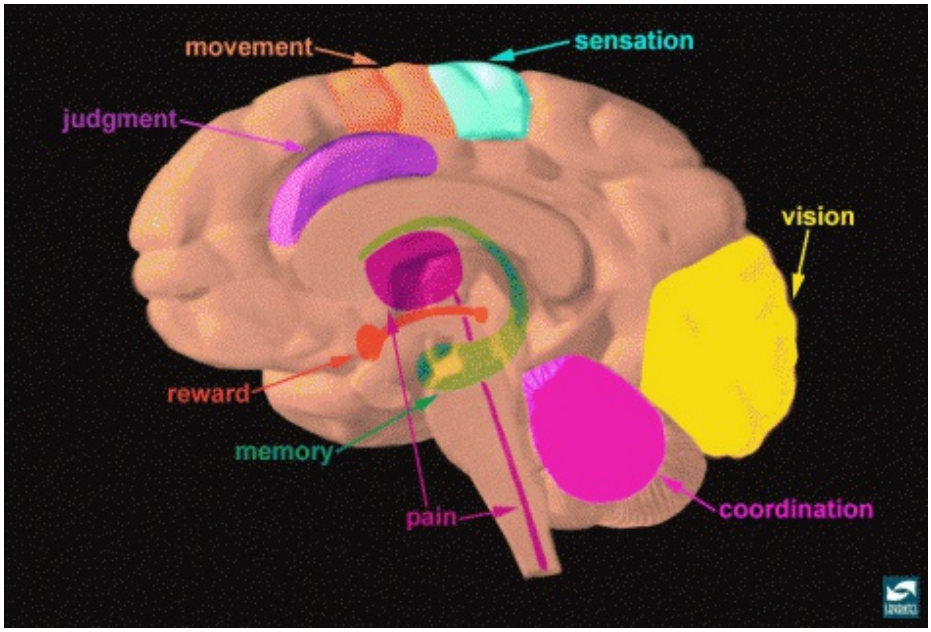
Introduce the purpose of your presentation. Indicate that you will explain how the brain basically works and how and where drugs such as heroin and cocaine work in the brain. Tell your audience that you will discuss the concept of "reward" which is the property that is characteristic of many addictive drugs.

2: The brain and spinal cord



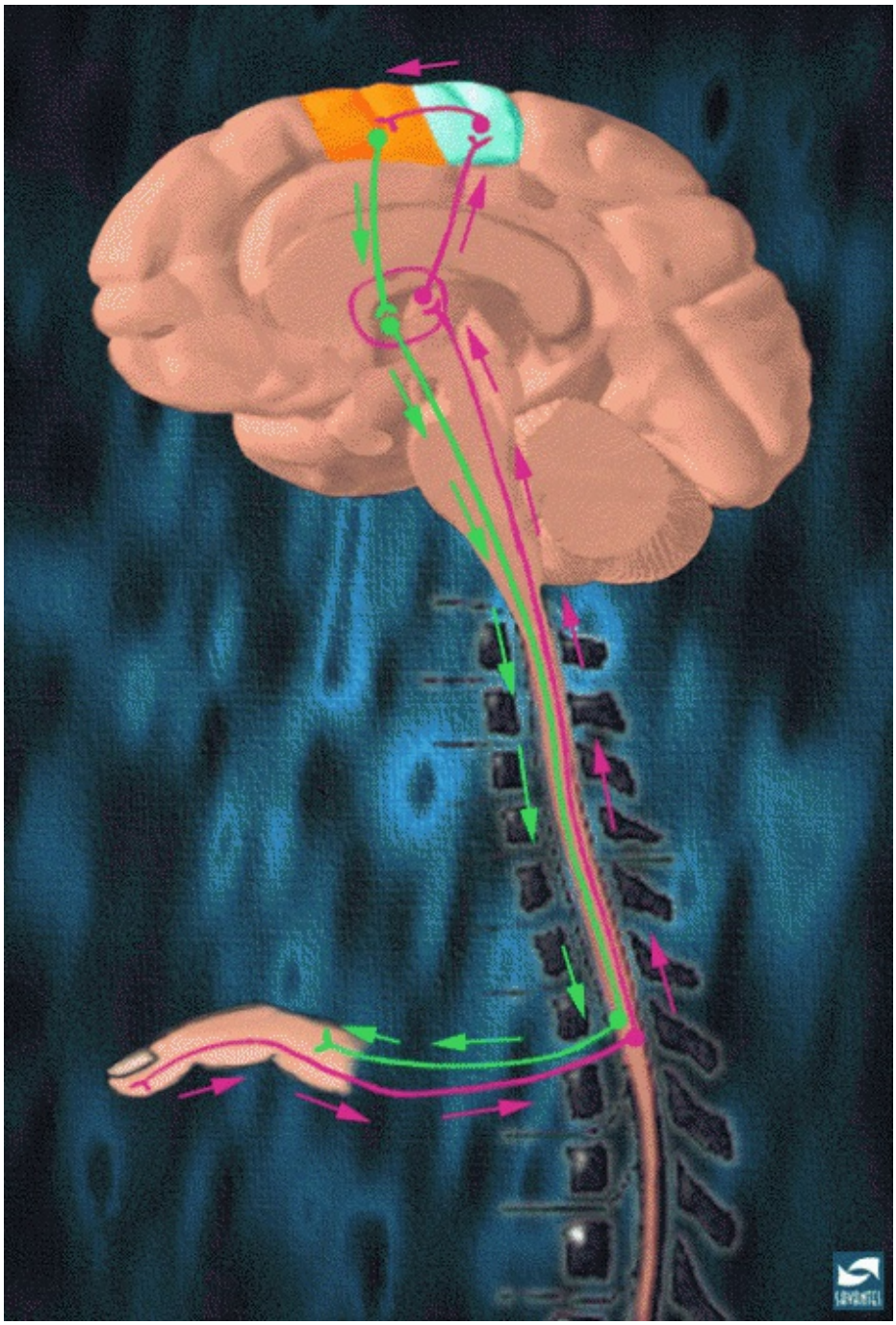
The central nervous system is composed of both the brain and the spinal cord. Describe the brain as a functional unit; it is made up of billions of nerve cells (neurons) that communicate with each other using electrical and chemical signals.

3: Brain regions and neuronal pathways



Certain parts of the brain govern specific functions. Point to areas such as the sensory (orange), motor (blue) and visual cortex (yellow) to highlight their specific functions. Point to the cerebellum (pink) for coordination and to the hippocampus (green) for memory. Indicate that nerve cells or neurons connect one area to another via pathways to send and integrate information. The distances that neurons extend can be short or long. For example, point to the reward pathway (orange). Explain that this pathway is activated when a person receives positive reinforcement for certain behaviors ("reward"). Indicate that you will explain how this happens when a person takes an addictive drug. As another example, point to the thalamus (magenta). This structure receives information about pain coming from the body (magenta line within the spinal cord), and passes the information up to the cortex. Tell the audience that you can look at this in more detail.

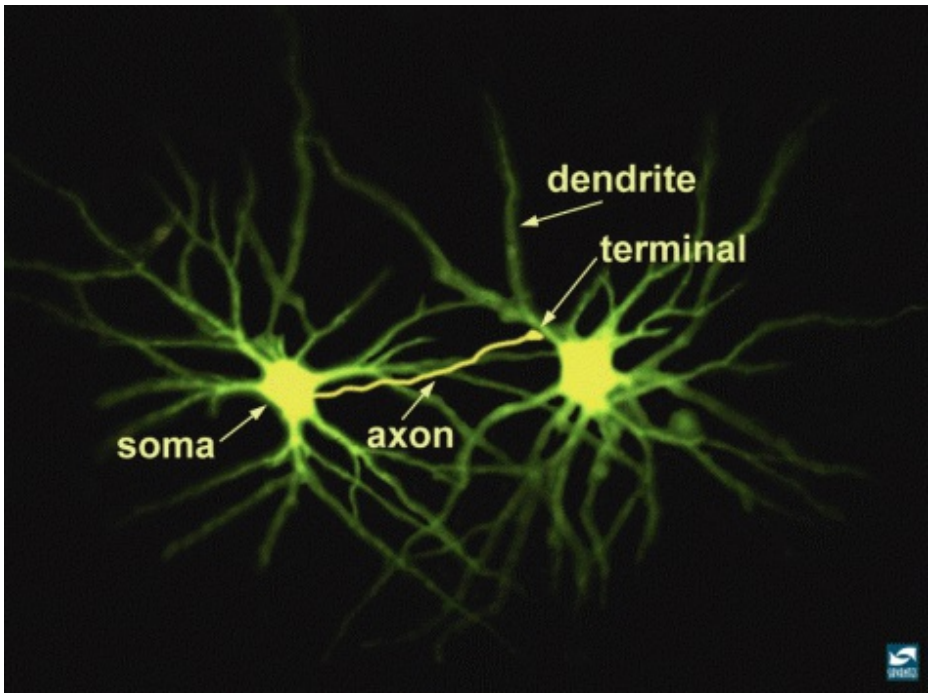
4: Pathway for sensation of pain and reaction to pain



This is a long pathway, in which neurons make connections in both the brain and the spinal cord. Explain what happens when one slams a door on one's finger. First, nerve endings in the finger sense the injury to the finger (sensory neurons) and they send impulses along axons to the spinal cord (magenta pathway). Point to each part of the pathway as you explain the flow of information. The incoming axons form a synapse with neurons that project up to the brain. The neurons that travel up the spinal cord then form synapses with

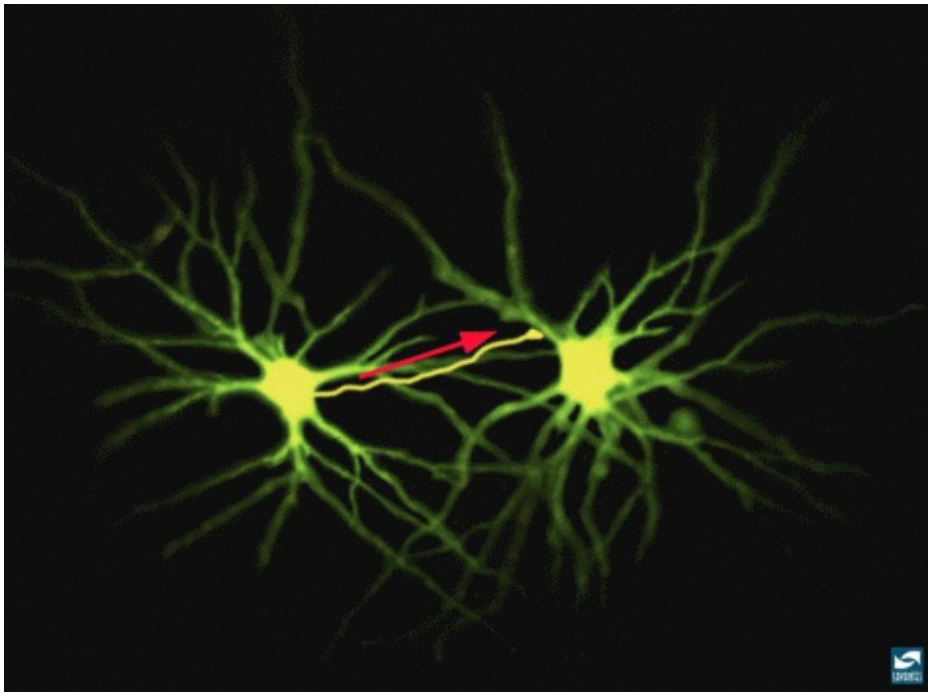
neurons in the thalamus, which is a part of the midbrain (magenta circle). The thalamus organizes this information and sends it to the sensory cortex (blue), which interprets the information as pain and directs the nearby motor cortex (orange) to send information back to the thalamus (green pathway). Again, the thalamus organizes this incoming information and sends signals down the spinal cord, which direct motor neurons to the finger and other parts of the body to react to the pain (e.g., shaking the finger or screaming "ouch!").

5: Neuronal structure



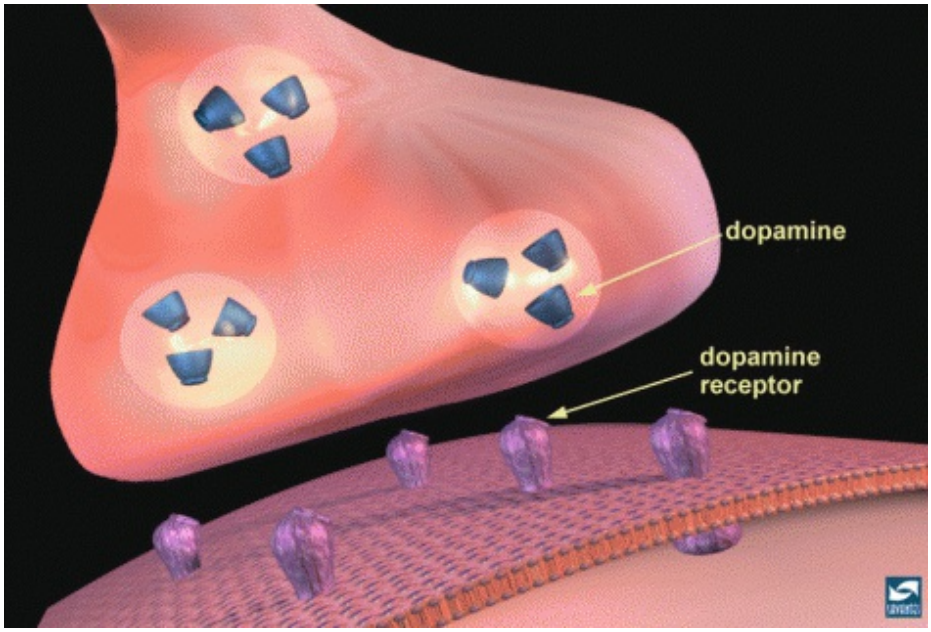
Indicate that these pathways are made up of neurons. This image contains real neurons from the thalamus. They have been filled with a fluorescent dye and viewed through a microscope. Describe the anatomy of a neuron: point to the cell body (soma), dendrites, and axon (marked with text). At the end of the axon is the terminal, which makes a connection with another neuron. [Note: the axon has been drawn in for clarity, but actually, the axons of these neurons travel to the cerebral cortex.]

6: Impulse flow



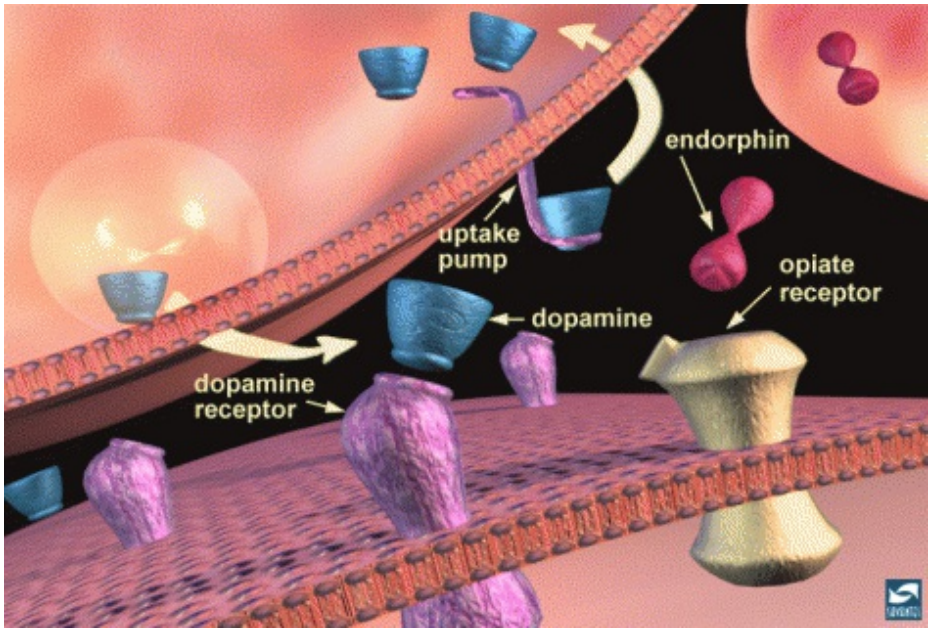
Explain the normal direction of the flow of information (electrical and chemical). An electrical impulse (the action potential) travels down the axon toward the terminal. Point to the terminal. The terminal makes a connection with the dendrite of neighboring neuron, where it passes on chemical information. The area of connection is called the synapse. Although the synapse between a terminal and a dendrite (shown here) is quite typical, other types of synapses exist as well. For example, a synapse can occur between a terminal and a soma or axon.

7: The synapse and synaptic neurotransmission



Describe the synapse and the process of chemical neurotransmission. As an electrical impulse arrives at the terminal, it triggers vesicles containing a neurotransmitter, such as dopamine (in blue), to move toward the terminal membrane. The vesicles fuse with the terminal membrane to release their contents (in this case, dopamine). Once inside the synaptic cleft (the space between the two neurons) the dopamine can bind to specific proteins called dopamine receptors (in pink) on the membrane of a neighboring neuron. This is illustrated in more detail on the next image.

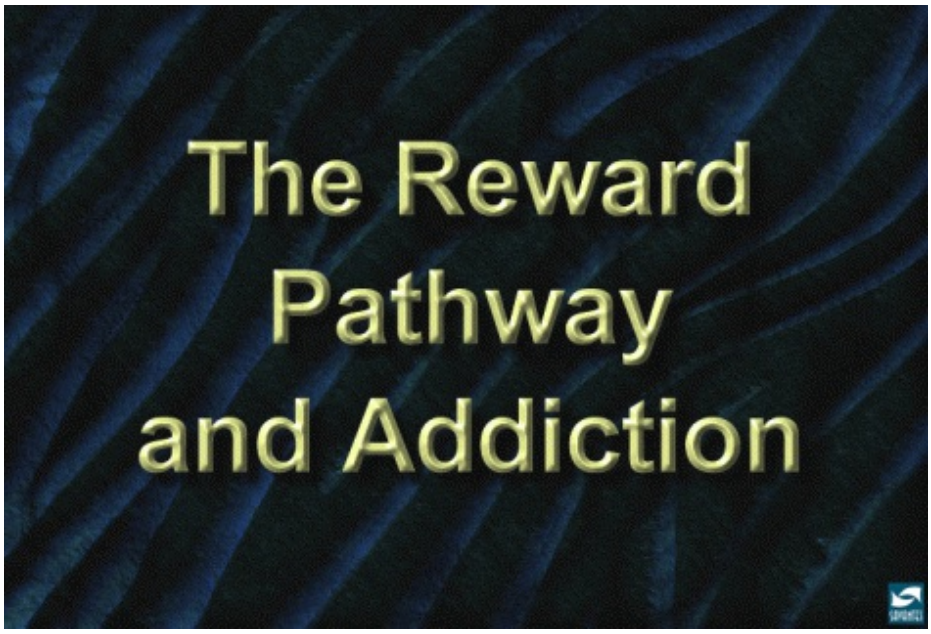
8: Dopamine neurotransmission and modulation by endogenous opiates



Using the close-up of a synapse, continue using dopamine for your example of synaptic function. Explain that it is synthesized in the nerve terminal and packaged in vesicles. Reiterate the steps in neurotransmission. Show how the vesicle fuses with the membrane and releases dopamine. The dopamine molecules can then bind to a dopamine receptor (in pink). After the dopamine binds, it comes off the receptor and is removed from the synaptic cleft by uptake pumps (also proteins) that reside on the terminal (arrows show the direction of movement). This process is important because it ensures that not too much dopamine remains in the synaptic cleft at any one time. Also point out that there are neighboring neurons that release another compound called a neuromodulator. Neuromodulators help to enhance or inhibit neurotransmission that is controlled by neurotransmitters such as dopamine. In this case, the neuromodulator is an "endorphin" (in red). Endorphins bind to opiate receptors (in yellow) which can reside on the post-synaptic cell (shown here) or, in some cases, on the terminals of other neurons (this is not shown so it must be pointed out). The endorphins are destroyed by enzymes rather than removed by uptake pumps

Section II: The Reward Pathway and Addiction

1: The reward pathway and addiction

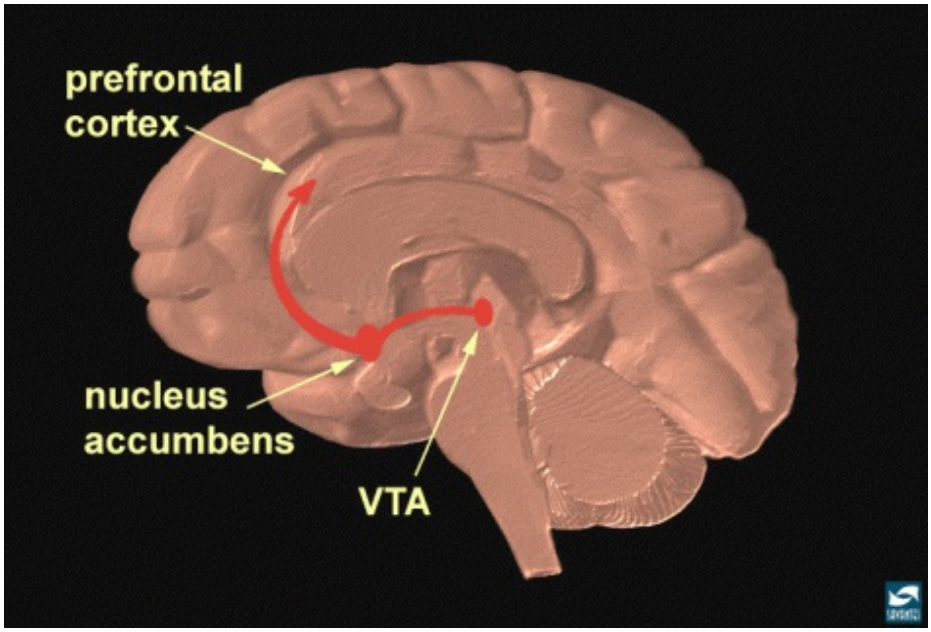


Introduce the concept of reward. Humans, as well as other organisms engage in behaviors that are rewarding; the pleasurable feelings provide positive reinforcement so that the behavior is repeated. There are natural rewards as well as artificial rewards, such as drugs.

2: Natural rewards

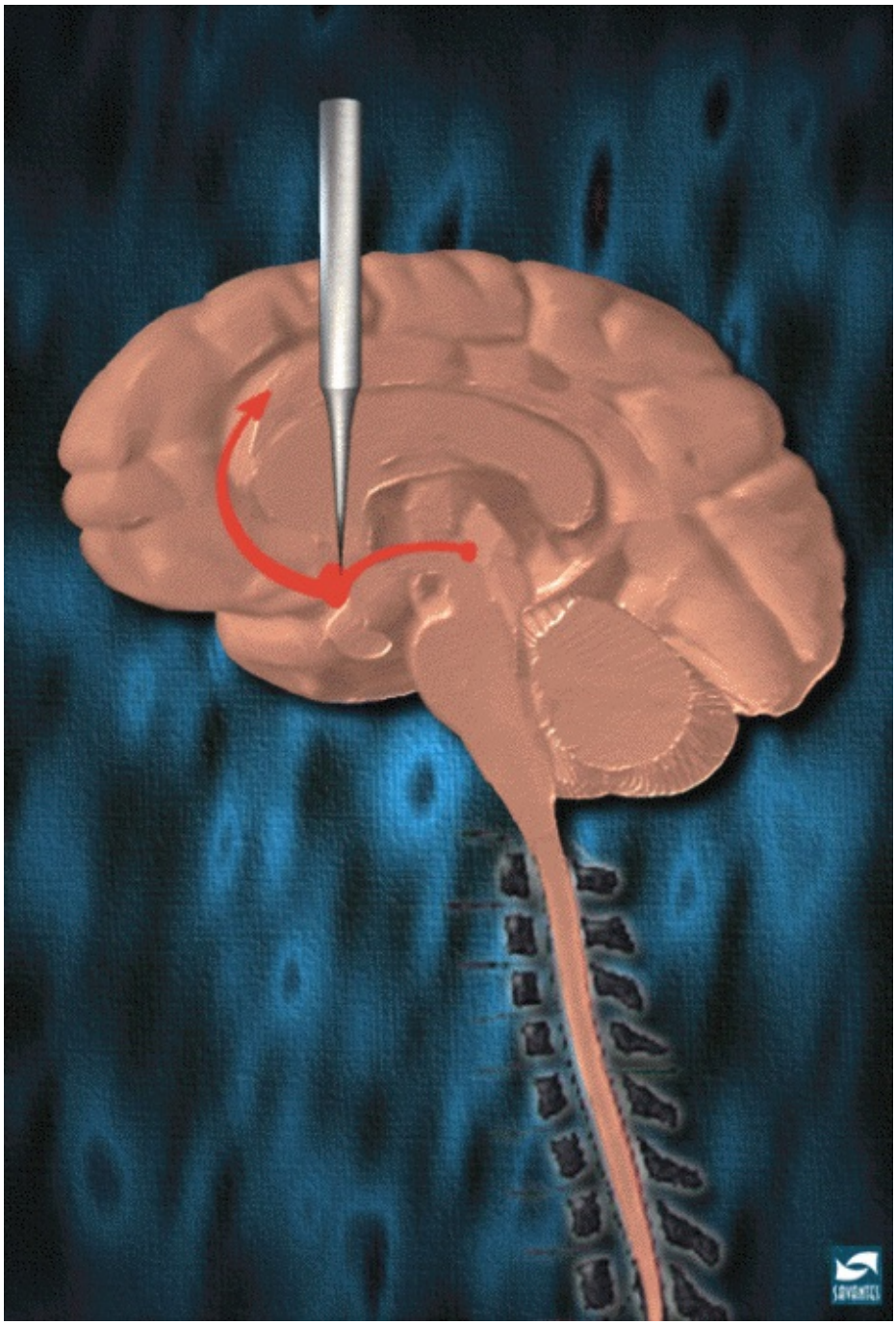
Natural rewards such as food, water, sex, and nurturing allow the organism to feel pleasure when eating, drinking, procreating, and being nurtured. Such pleasurable feelings reinforce the behavior so that it will be repeated. Each of these behaviors is required for the survival of the species. Remind your audience that there is a pathway in the brain that is responsible for rewarding behaviors. This can be viewed in more detail in the next image.

3: The reward pathway



Tell your audience that this is a view of the brain cut down the middle. An important part of the reward pathway is shown and the major structures are highlighted: the ventral tegmental area (VTA), the nucleus accumbens, and the prefrontal cortex. The VTA is connected to both the nucleus accumbens and the prefrontal cortex via this pathway and it sends information to these structures via its neurons. The neurons of the VTA contain the neurotransmitter dopamine, which is released in the nucleus accumbens and in the prefrontal cortex (point to each of these structures). Reiterate that this pathway is activated by a rewarding stimulus. [Note: the pathway shown here is not the only pathway activated by rewards, other structures are involved too, but only this part of the pathway is shown for simplicity.]

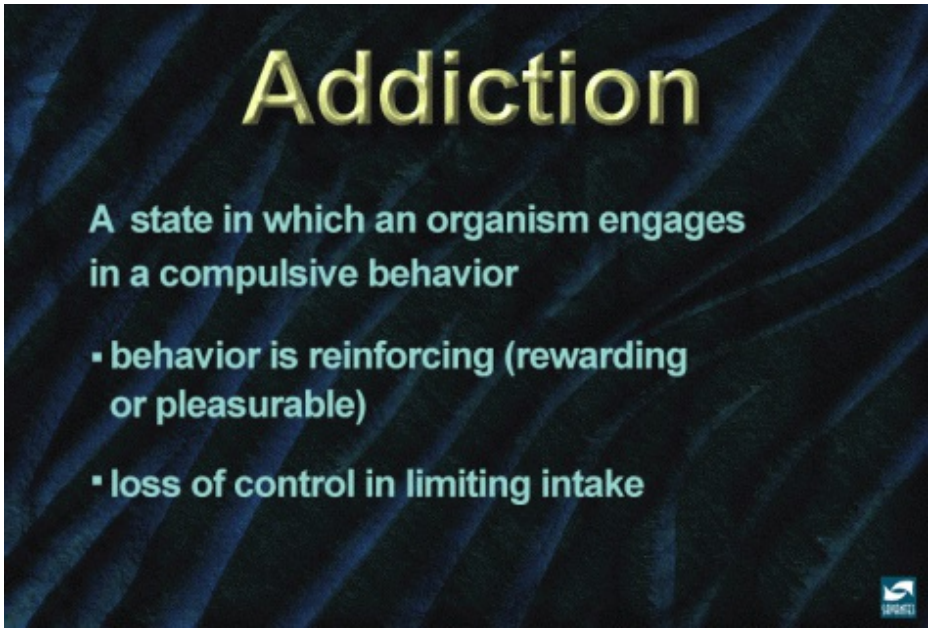
4: Activation of the reward pathway by an electrical stimulus



The discovery of the reward pathway was achieved with the help of animals such as rats. Rats were trained to press a lever for a tiny electrical jolt to certain parts of the brain. Show that when an electrode is placed in the nucleus accumbens, the rat keeps pressing the lever to receive the small electrical stimulus because it feels pleasurable. This rewarding feeling is also called positive reinforcement. Point to an area of the brain close to the nucleus accumbens. Tell the audience that when the electrode is placed there, the rat

will not press the lever for the electrical stimulus because stimulating neurons in a nearby area that does not connect with the nucleus accumbens does not activate the reward pathway. The importance of the neurotransmitter dopamine has been determined in these experiments because scientists can measure an increased release of dopamine in the reward pathway after the rat receives the reward. And, if the dopamine release is prevented (either with a drug or by destroying the pathway), the rat won't press the bar for the electrical jolt. So with the help of the rats, scientists figured out the specific brain areas as well as the neurochemicals involved in the reward pathway.

5: Addiction

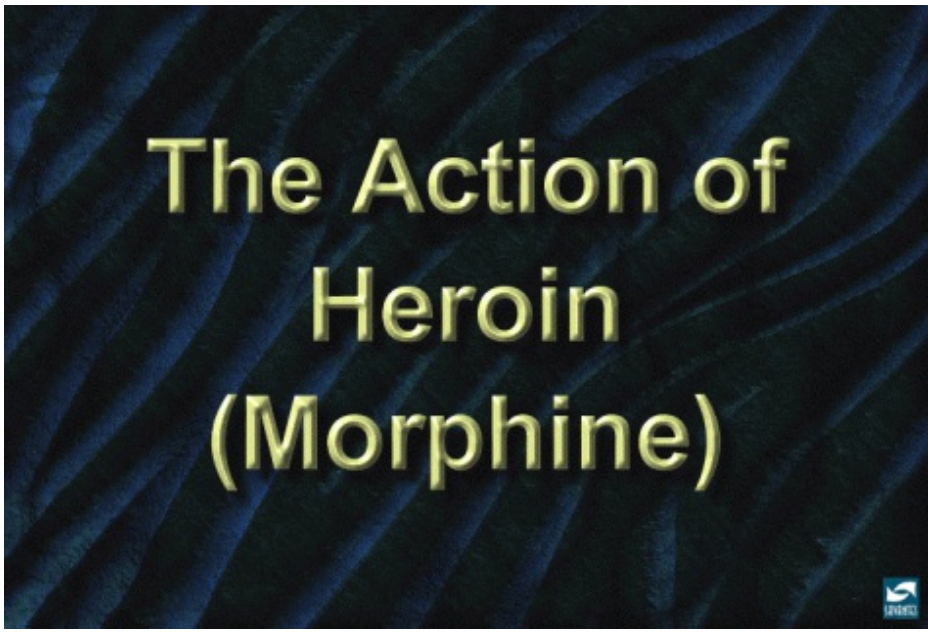


Now that you have defined the concept of reward, you can define addiction. Addiction is a state in which an organism engages in a compulsive behavior, even when faced with negative consequences. This behavior is reinforcing, or rewarding, as you have just discussed. A major feature of addiction is the loss of control in limiting intake of the addictive substance. The most recent research indicates that the reward pathway may be even more important in the craving associated with addiction, compared to the reward itself. Scientists have learned a great deal about the biochemical, cellular, and molecular bases of addiction; it is clear that addiction is a disease of the brain. State that you will provide two examples of the interaction between drugs that are addictive, their

cellular targets in the brain, and the reward pathway.

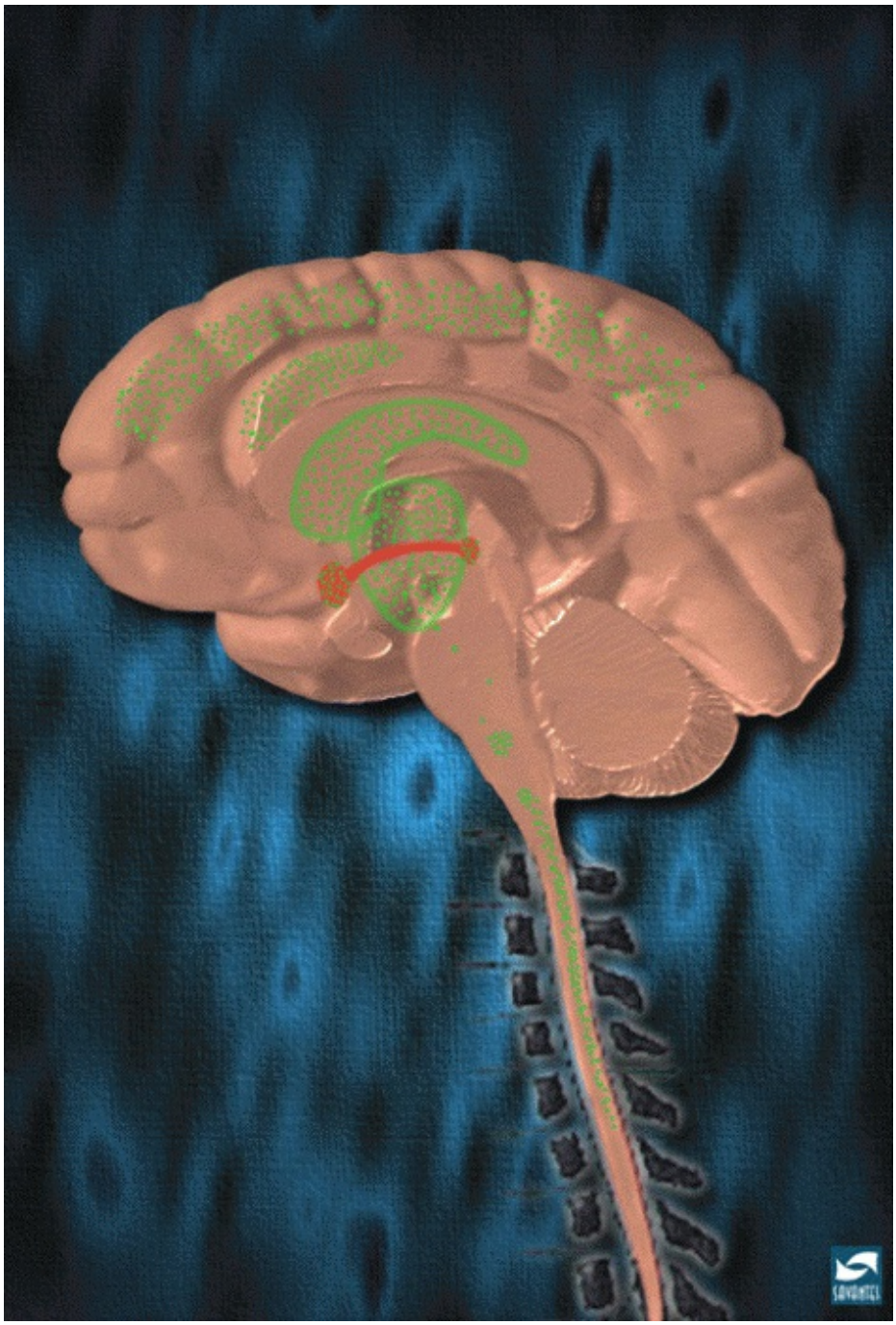
Section III: The Action of Heroin (Morphine)

1: The action of heroin (morphine)



Heroin is an addictive drug, although not all users become addicted. Environment and the personality of the user are important in producing addiction. Heroin produces euphoria or pleasurable feelings and can be a positive reinforcer by interacting with the reward pathway in the brain. Indicate that you will explain how this happens.

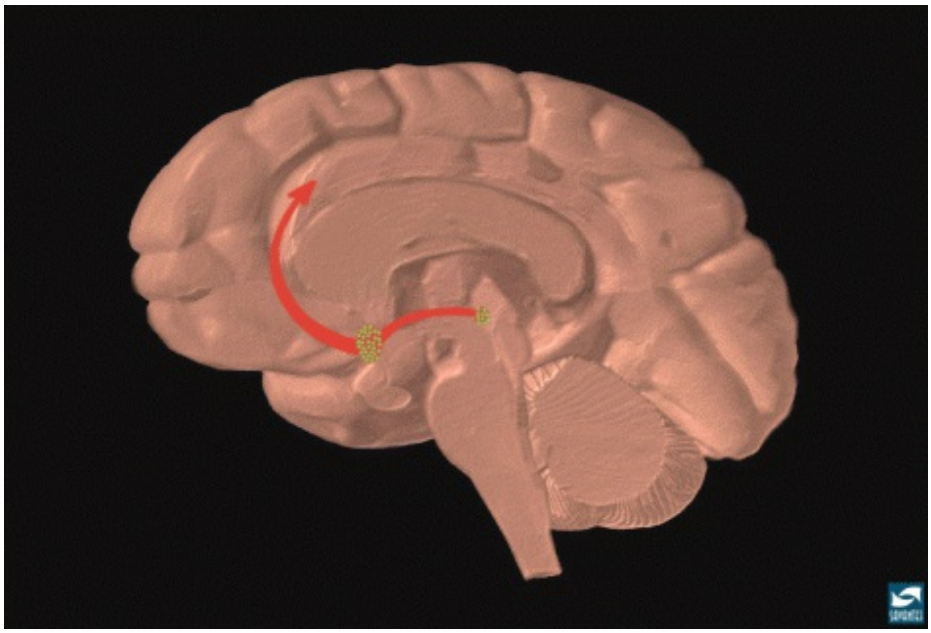
2: Localization of opiate binding sites within the brain and spinal cord



When a person injects heroin (or morphine), the drug travels quickly to the brain through the bloodstream. Actually, heroin can reach the brain just as quickly if it is smoked (see description of image #25). Abusers also snort heroin to avoid problems with needles. In this case, the heroin doesn't reach the brain as quickly as if it were injected or smoked, but its effects can last longer. Once in the brain, the heroin is converted to morphine by enzymes; the morphine binds to opiate receptors in certain areas of the brain. Point to the areas where

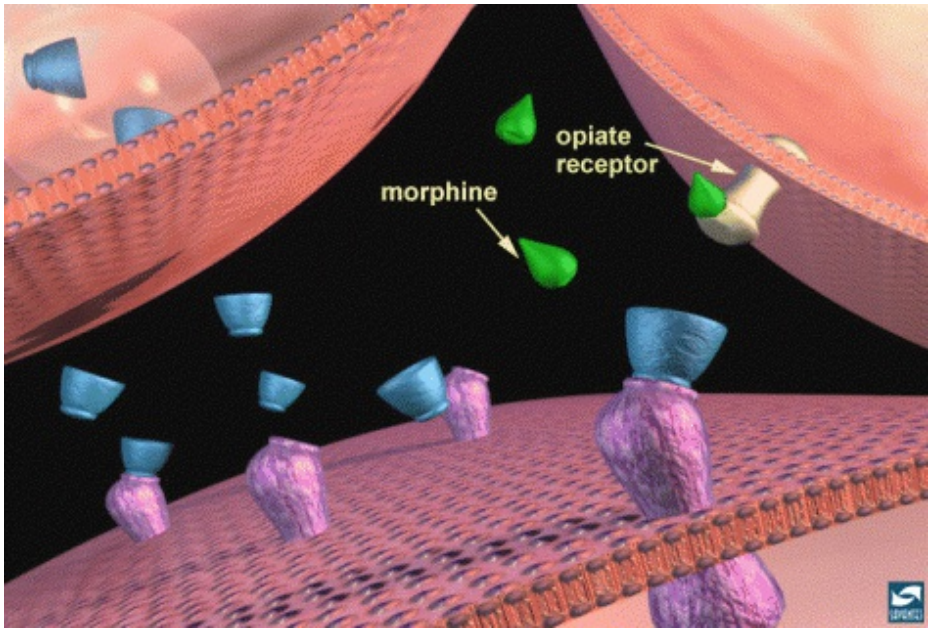
opiates bind (green dots). Part of the cerebral cortex, the VTA, nucleus accumbens, thalamus, brainstem, and spinal cord are highlighted. Show that the morphine binds to opiate receptors that are concentrated in areas within the reward pathway (including the VTA, nucleus accumbens, and cortex). Morphine also binds to areas involved in the pain pathway (including the thalamus, brainstem, and spinal cord). Binding of morphine to areas in the pain pathway leads to analgesia (loss of pain).

3: Morphine binding within the reward pathway



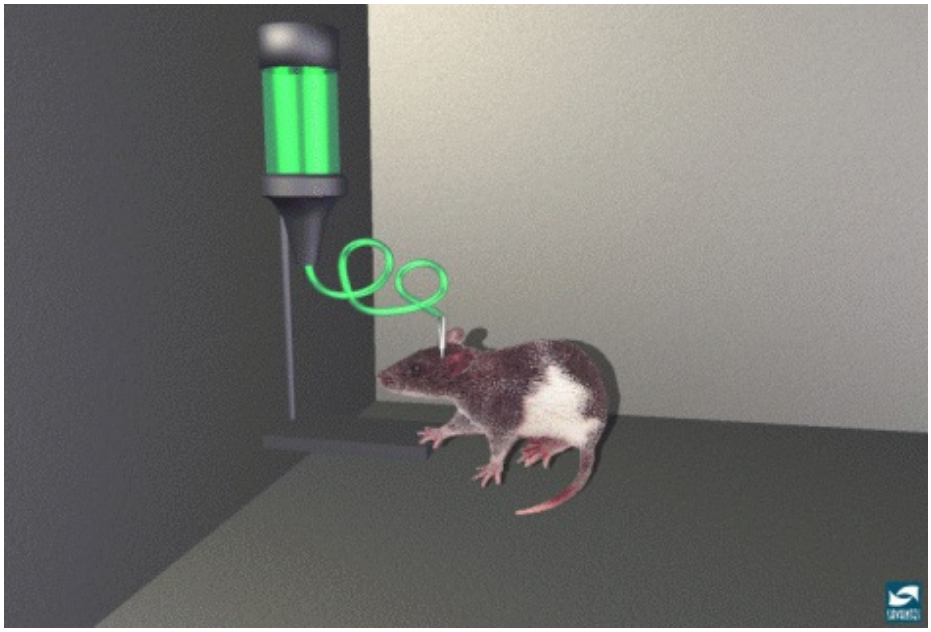
Reiterate that morphine binds to receptors on neurons in the VTA and in the nucleus accumbens. This is shown here within the reward pathway. Indicate that you will show how morphine activates this pathway on the next image.

4: Opiates binding to opiate receptors in the nucleus accumbens: increased dopamine release



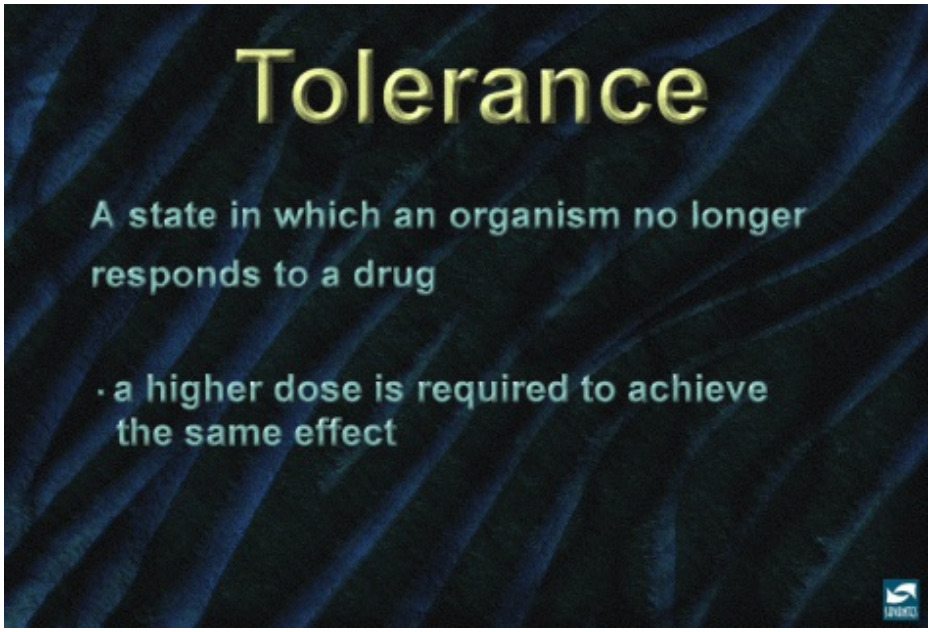
This is a close-up view of a synapse in the nucleus accumbens. Three types of neurons participate in opiate action: one that releases dopamine (on the left), a neighboring terminal (on the right) that contains a different neurotransmitter (probably GABA for those who would like to know), and the post-synaptic cell that contains dopamine receptors (in pink). Show that opiates bind to opiate receptors (yellow) on the neighboring terminal and this sends a signal to the dopamine terminal to release more dopamine. [In case someone asks how, one theory is that opiate receptor activation decreases GABA release, which normally inhibits dopamine release, so dopamine release is increased.]

5: Rats self-administer heroin



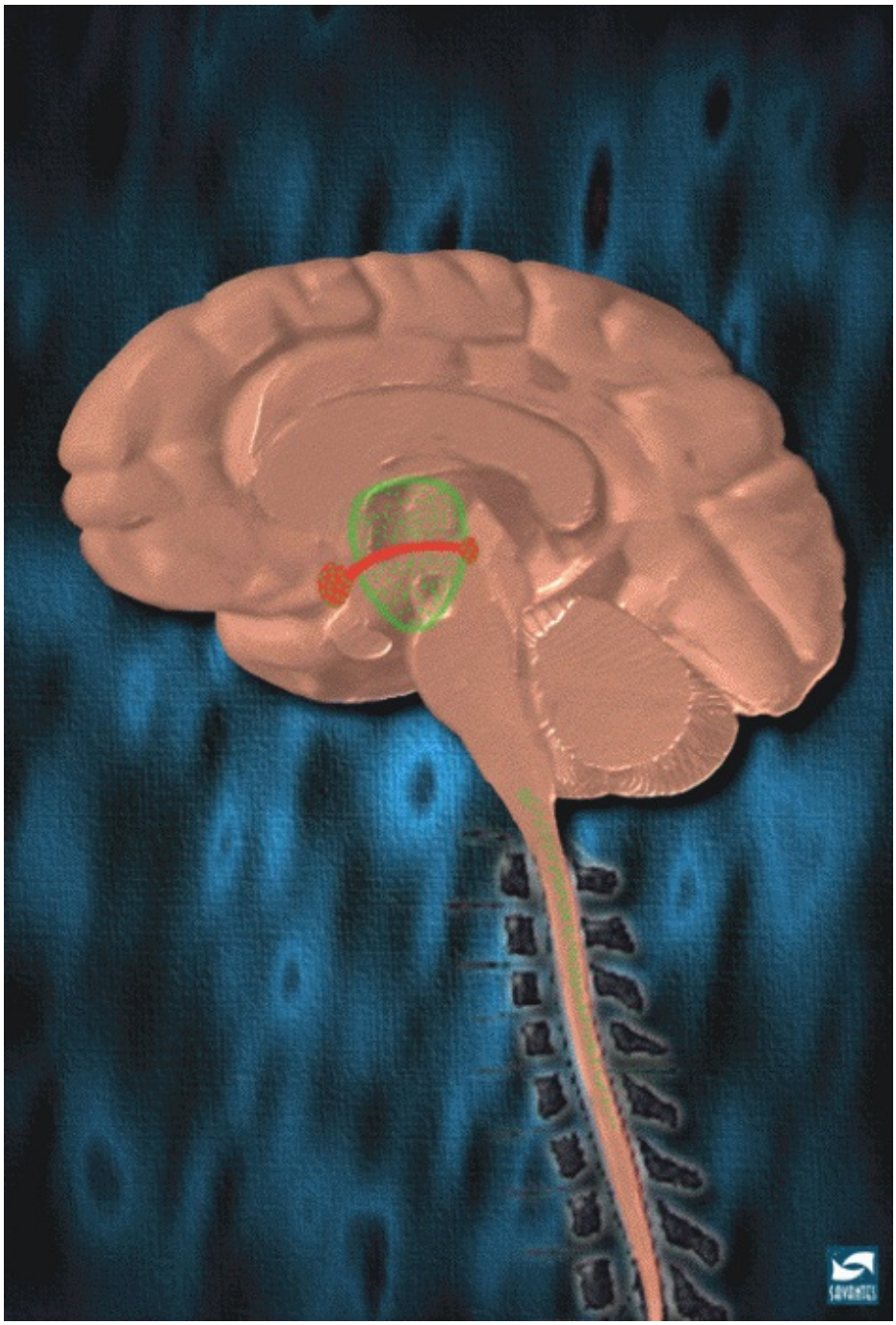
Just as a rat will stimulate itself with a small electrical jolt (into the reward pathway), it will also press a bar to receive heroin. In this image, the rat is self-administering heroin through a small needle placed directly into the nuclues accumbens. The rat keeps pressing the bar to get more heroin because the drug makes the rat feel good. The heroin is positively reinforcing and serves as a reward. If the injection needle is placed in an area nearby the nucleus accumbens, the rat won't self-administer the heroin. Scientists have found that dopamine release is increased within the reward pathway of rats self-administering heroin. So, since more dopamine is present in the synaptic space, dopamine-dependent neurotransmission is augmented, causing the activation of the reward pathway.

6: Definition of tolerance



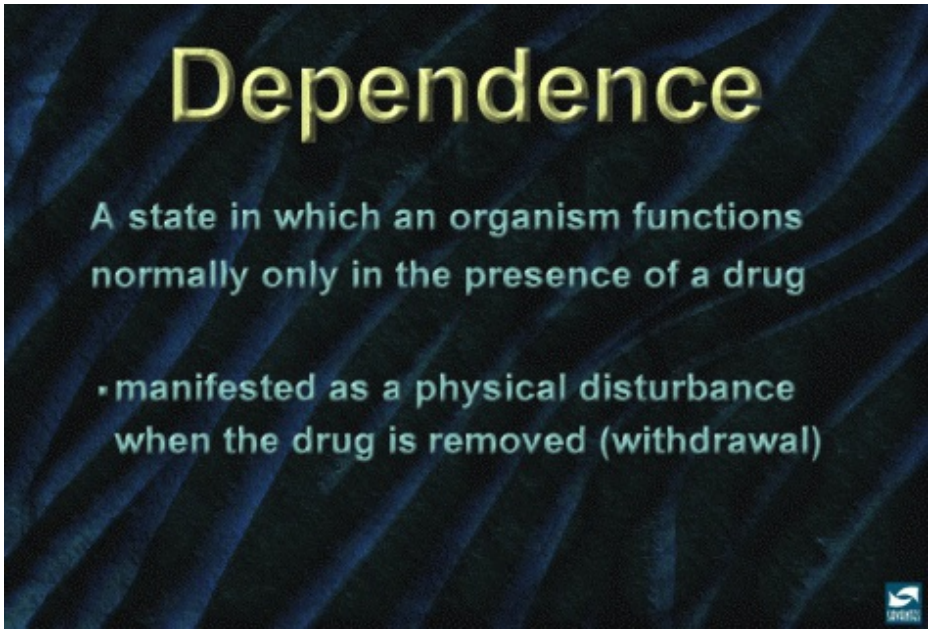
When drugs such as heroin are used repeatedly over time, tolerance may develop. Tolerance occurs when the person no longer responds to the drug in the way that person initially responded. Stated another way, it takes a higher dose of the drug to achieve the same level of response achieved initially. For example, in the case of heroin or morphine, tolerance develops rapidly to the analgesic effects of the drug. [The development of tolerance is not addiction, although many drugs that produce tolerance also have addictive potential.] Tolerance to drugs can be produced by several different mechanisms, but in the case of morphine or heroin, tolerance develops at the level of the cellular targets. For example, when morphine binds to opiate receptors, it triggers the inhibition of an enzyme (adenylate cyclase) that orchestrates several chemicals in the cell to maintain the firing of impulses. After repeated activation of the opiate receptor by morphine, the enzyme adapts so that the morphine can no longer cause changes in cell firing. Thus, the effect of a given dose of morphine or heroin is diminished.

7: Brain regions mediating the development of morphine tolerance



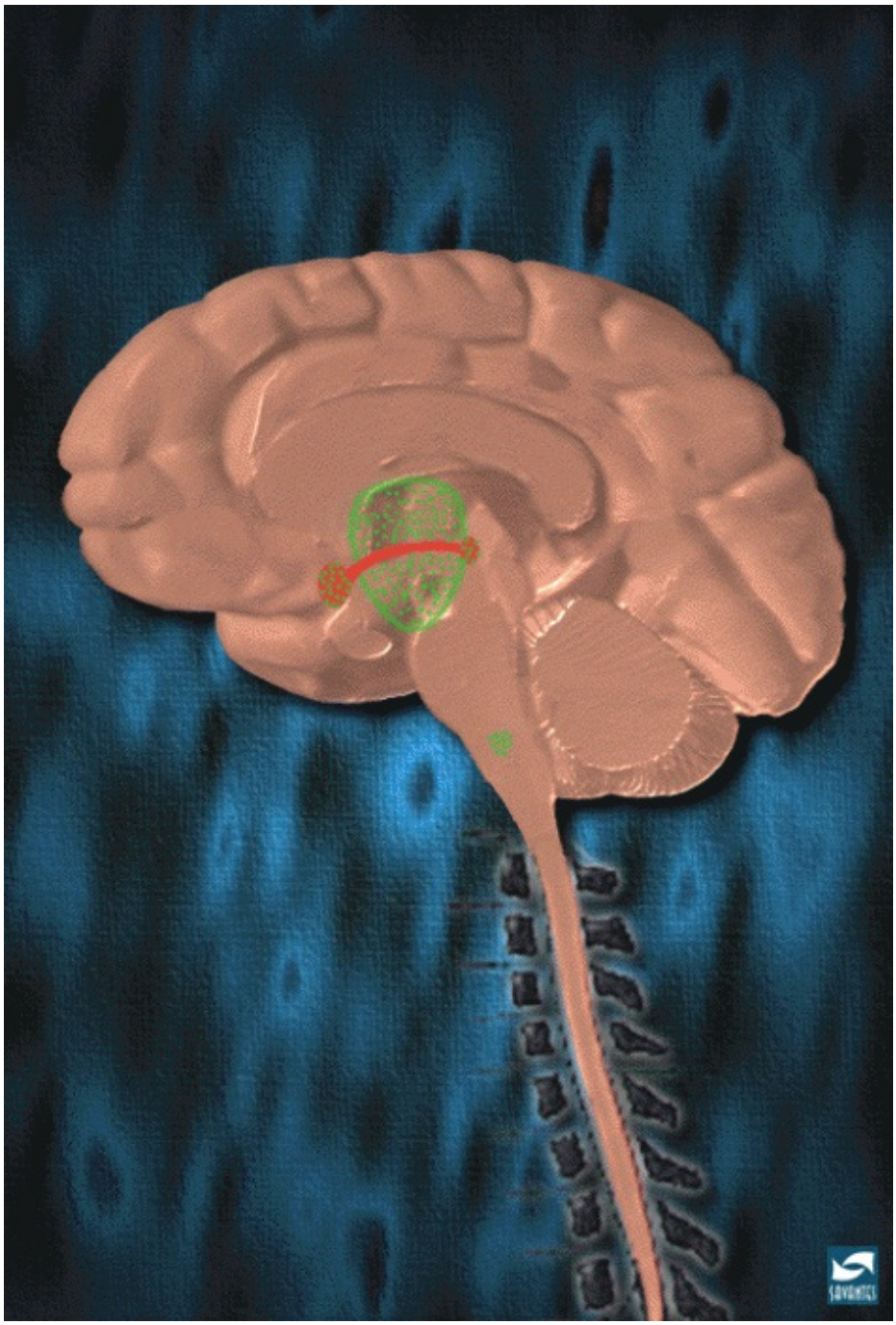
The development of tolerance to the analgesic effects of morphine involves different areas of the brain separate from those in the reward pathway. Point to the two areas involved here, the thalamus, and the spinal cord (green dots). Both of these areas are important in sending pain messages and are responsible for the analgesic effects of morphine. The parts of the reward pathway involved in heroin or morphine addiction are shown for comparison.

8: Definition of dependence



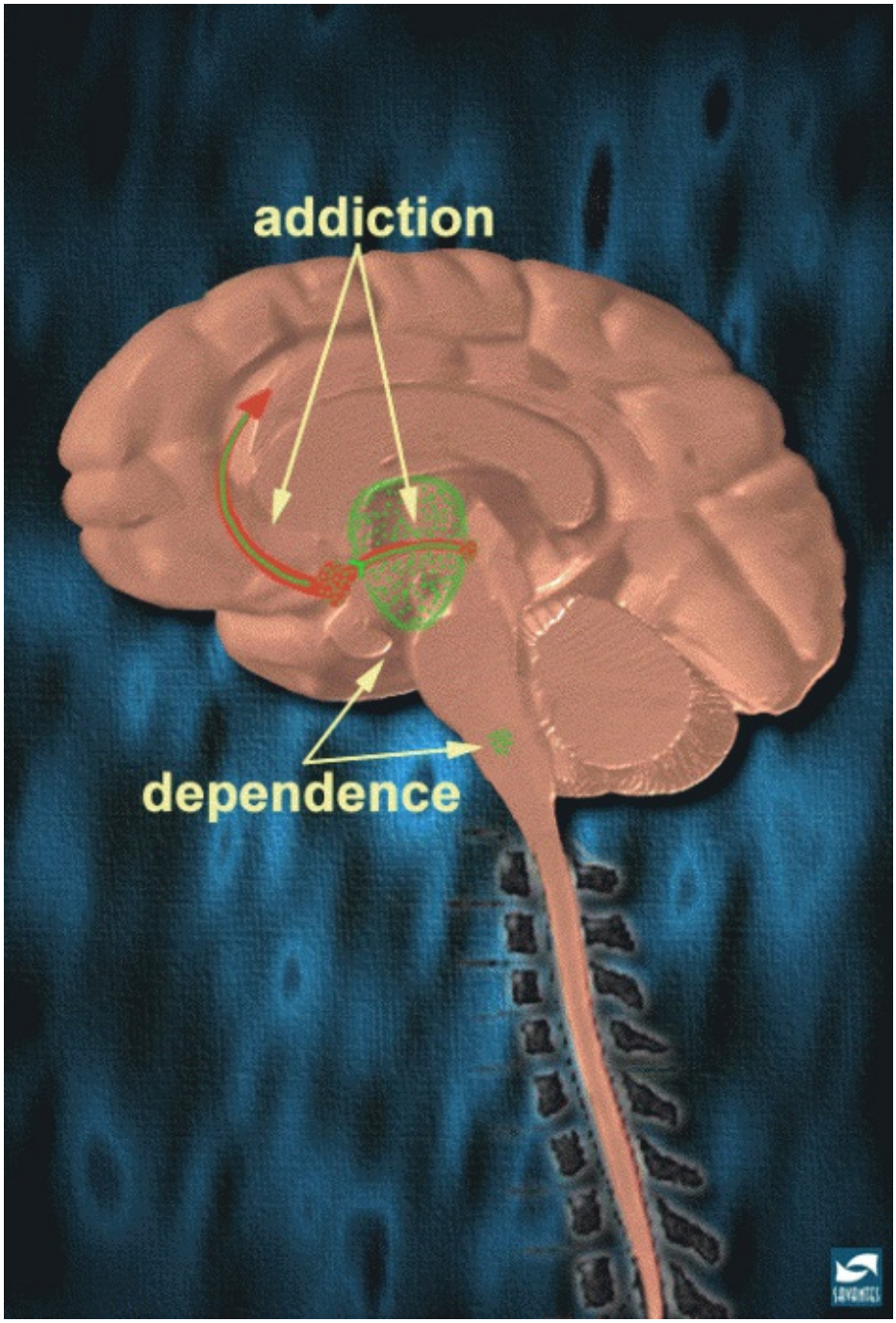
With repeated use of heroin, dependence also occurs. Dependence develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug. When the drug is withdrawn, several physiologic reactions occur. These can be mild (e.g., for caffeine) or even life threatening (e.g., for alcohol). This is known as the withdrawal syndrome. In the case of heroin, withdrawal can be very serious and the abuser will use the drug again to avoid the withdrawal syndrome.

9: Brain regions mediating the development of morphine dependence



The development of dependence to morphine also involves specific areas of the brain, separate from the reward pathway. In this case, point to the thalamus and the brainstem (green dots). The parts of the reward pathway involved in heroin or morphine addiction are shown for comparison. Many of the withdrawal symptoms from heroin or morphine are generated when the opiate receptors in the thalamus and brainstem are deprived of morphine.

10: Addiction vs dependence



As you have just explained, different parts of the brain are responsible for the addiction and dependence to heroin and opiates. Review the areas in the brain underlying the addiction to morphine (reward pathway) and those underlying the dependence to morphine (thalamus and brainstem). Thus, it is possible to

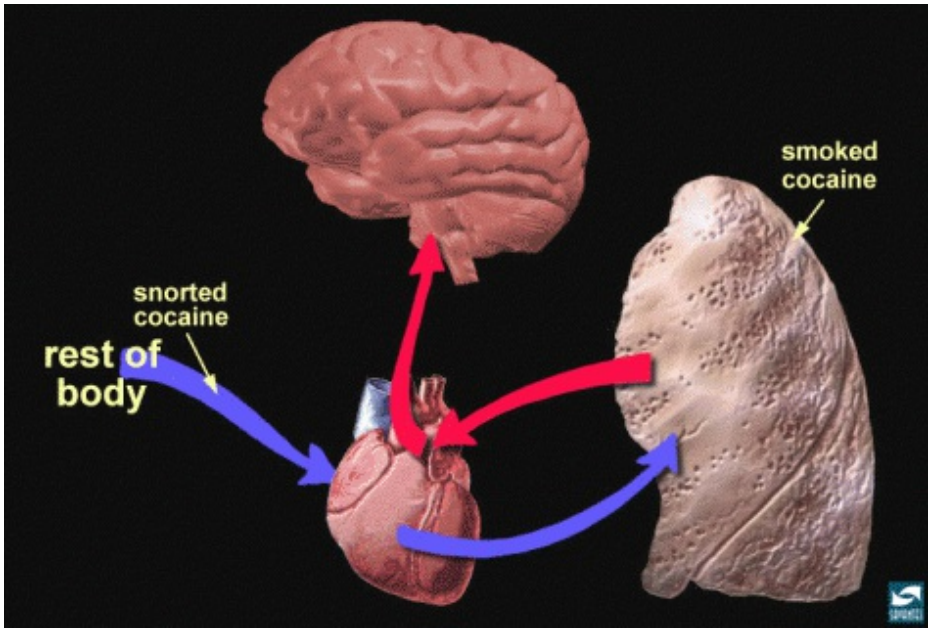
be dependent on morphine, without being addicted to morphine. (Although, if one is addicted, they are most likely dependent as well.) This is especially true for people being treated chronically with morphine, for example, pain associated with terminal cancer. They may be dependent - if the drug is stopped, they suffer a withdrawal syndrome. But, they are not compulsive users of the morphine, and they are not addicted. Finally, people treated with morphine in the hospital for pain control after surgery are unlikely to become addicted; although they may feel some of the euphoria, the analgesic and sedating effects predominate. There is no compulsive use and the prescribed use is short-lived.

Section IV: The Action of Cocaine

1: The action of cocaine

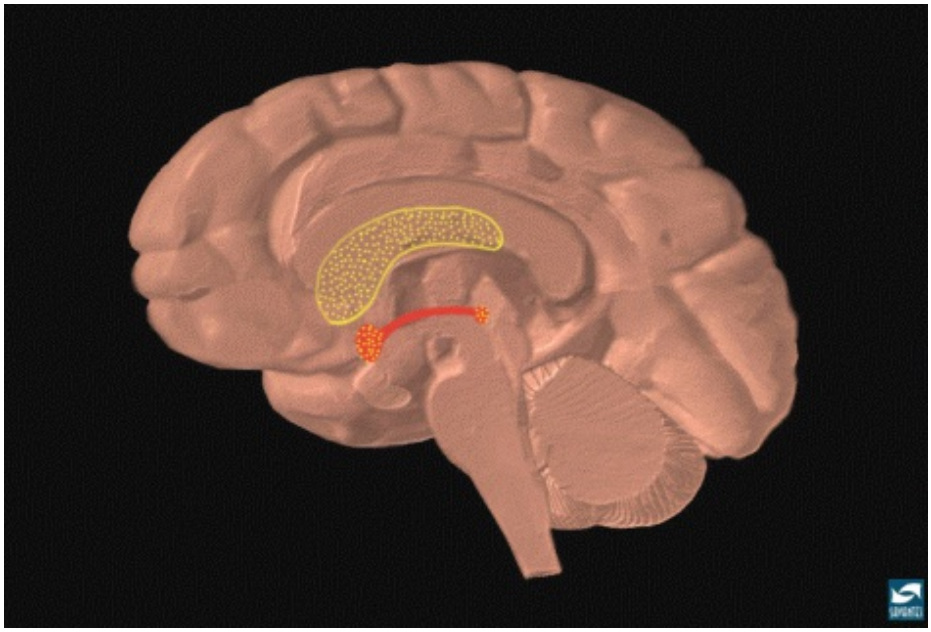
Cocaine is also an addictive drug, and like heroin, not all users become addicted. However, with the advent of crack cocaine (the freebase), the rate of addiction to cocaine has increased considerably.

2: Snorting vs smoking cocaine: different addictive liabilities



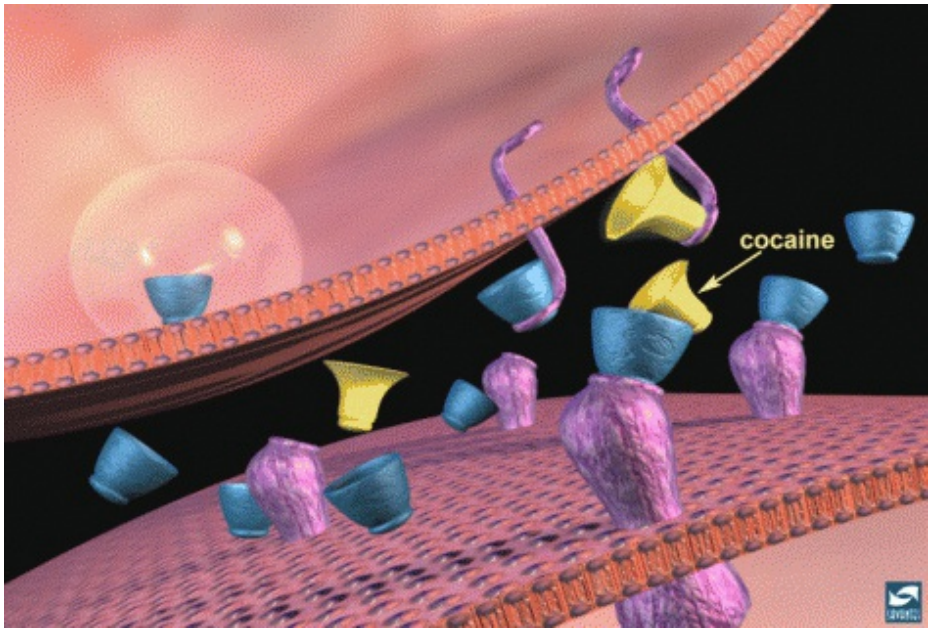
Historically cocaine abuse involved snorting the powdered form (the hydrochloride salt). When cocaine is processed to form the freebase, it can be smoked. Heating the hydrochloride salt form of cocaine will destroy it; the freebase can be volatilized at high temperature without any destruction of the compound. Smoking gets the drug to the brain more quickly than does snorting. Show the audience why this happens. Snorting requires that the cocaine travels from the blood vessels in the nose to the heart (purple arrow), where it gets pumped to the lungs (purple arrow) to be oxygenated. The oxygenated blood (red arrows) carrying the cocaine then travels back to the heart where it is pumped out to the organs of the body, including the brain. However, smoking bypasses much of this, the cocaine goes from the lungs directly to the heart and up to the brain. The faster a drug with addictive liability reaches the brain, the more likely it will be abused. Thus, the time between taking the drug and the positive reinforcing or rewarding effects that are produced can determine the likelihood of abuse.

3: Localization of cocaine "binding sites"



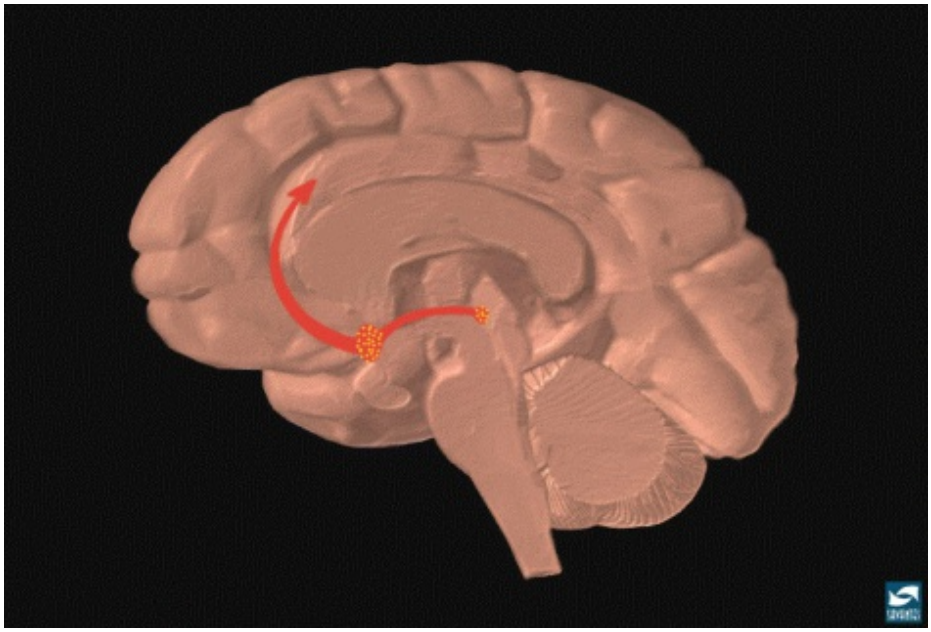
When a person smokes or snorts cocaine, it reaches all areas of the brain, but it binds to sites in some very specific areas. These are highlighted with the yellow dots: the VTA, the nucleus accumbens, and the caudate nucleus (the largest structure). Point out that cocaine binds especially in the reward areas that you have just discussed. The binding of cocaine in other areas such as the caudate nucleus can explain other effects such as increased stereotypic (or repetitive) behaviors (pacing, nail-biting, scratching, etc..)

4: Dopamine binding to receptors and uptake pumps in the nucleus accumbens: the action of cocaine



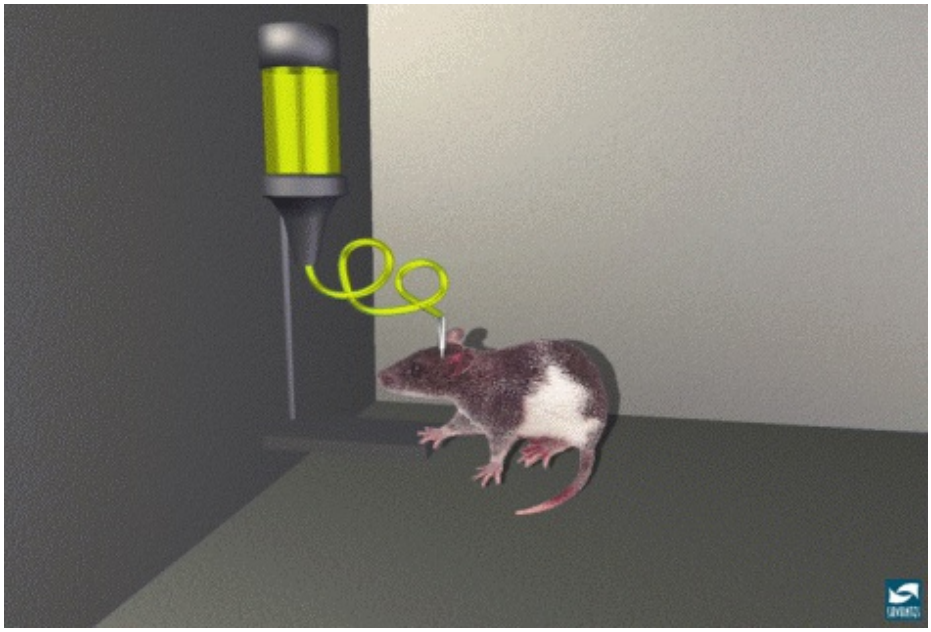
Explain that cocaine binds to sites in areas of the brain that are rich in dopamine synapses such as the VTA and the nucleus accumbens. Review dopamine transmission in the close-up of a synapse in the nucleus accumbens. Point to dopamine (inside the terminal) that is released into the synaptic space. The dopamine binds to dopamine receptors and then is taken up by uptake pumps back into the terminal. Now show what happens when cocaine is present (yellow). Cocaine binds to the uptake pumps and prevents them from transporting dopamine back into the neuron terminal. So more dopamine builds up in the synaptic space and it is free to activate more dopamine receptors. This is the same effect that you showed in an earlier image with morphine, where morphine increased dopamine release from the terminal to produce more dopamine in the synaptic space.

5: Cocaine dependence and activation of the reward pathway



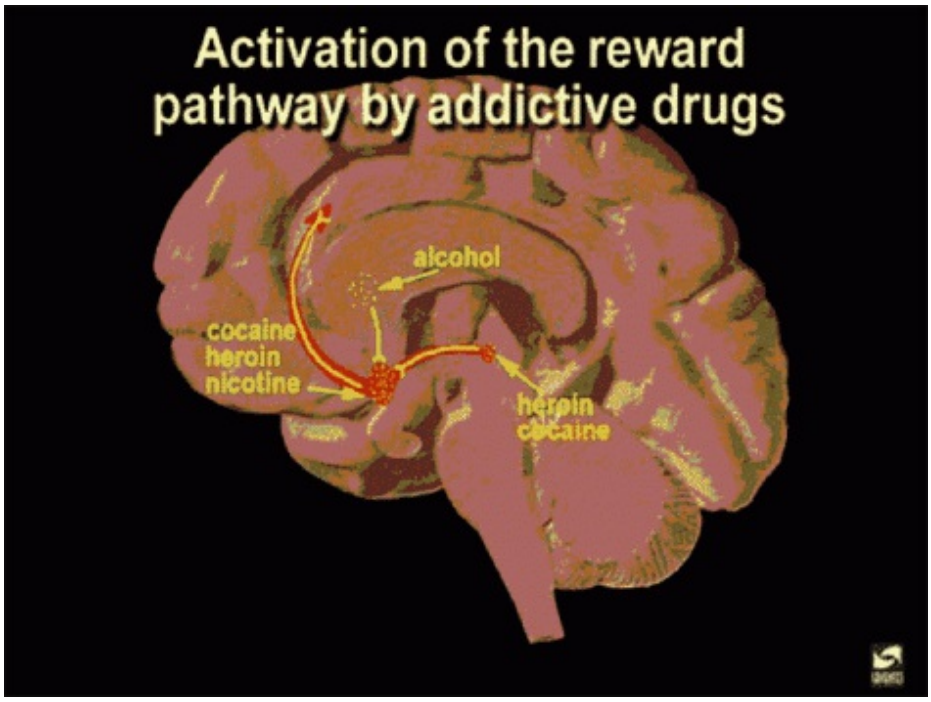
Review where cocaine binds within the reward pathway (the VTA and the nucleus accumbens). As a result of cocaine's actions in the nucleus accumbens (point to the dots of cocaine in the VTA and nucleus accumbens), there are increased impulses leaving the nucleus accumbens to activate the reward system. This pathway can be activated even in the absence of cocaine (i.e., during craving). Indicate that with repeated use of cocaine, the body relies on this drug to maintain rewarding feelings. The person is no longer able to feel the positive reinforcement or pleasurable feelings of natural rewards (i.e. food, water, sex)--the person is only able to feel pleasure from the cocaine. Thus the user becomes dependent and when the cocaine is no longer present, anhedonia (inability to feel pleasure) and depression emerge as part of a withdrawal syndrome. To avoid this, the user goes back to the cocaine. Unlike the example for morphine, cocaine addiction (i.e., craving) and dependence (i.e., anhedonia) both involve structures in the reward pathway.

6: Rats self-administer cocaine



Scientists have measured increased dopamine levels in the synapses of the reward pathway in rats self-administering cocaine. Just as they did for heroin, rats will press a bar to receive injections of cocaine directly into areas of the reward pathway such as the nucleus accumbens and the VTA. Again, if the injection needle is placed near these regions (but not in them), the rat will not press the bar to receive the cocaine. The ability of rats to self-administer cocaine is an excellent predictor of the addictive potential of this drug.

7: Summary: addictive drugs activate the reward system via increasing dopamine neurotransmission



In this last image, the reward pathway is shown along with several drugs that have addictive potential. Just as heroin or morphine and cocaine activate the reward pathway in the VTA and nucleus accumbens, other drugs such as nicotine and alcohol activate this pathway as well, although sometimes indirectly (point to the globus pallidus, an area activated by alcohol that connects to the reward pathway). Although each drug has a different mechanism of action, each drug increases the activity of the reward pathway by increasing dopamine transmission. Because of the way our brains are designed, and because these drugs activate this particular brain pathway for reward, they have the ability to be abused. Thus, addiction is truly a disease of the brain. As scientists learn more about this disease, they may help to find an effective treatment strategy for the recovering addict.

Background Information for the Presenter

Objectives

The objective of the teaching packet is to illustrate to the audience the basic function of the brain, the neurobiological basis for addiction and the actions of heroin and cocaine. The packet is arranged in 4 sections. The first section introduces the brain and presents some basic neurobiology, the second introduces the reward pathway and the third and fourth present the mechanism of action of heroin and cocaine and how each affects the reward system.

Before Using the Teaching Packet

- Know your target audience. Be prepared to adjust your presentation depending on the degree of education and training of your audience.
- Read the narrative script and practice the presentation. Be prepared to define any word used in the presentation. If you need additional information, several reference materials are also included at the end.

General Instructions

- The presentation should take approximately 30-40 minutes (without questions).
- Use the narrative text as a guide, it need not be repeated word-for-word.

Additional Reference Material

1. G. Hanson and P.J. Venturelli. Drugs and Society, Jones and Barlett Publishers, Boston, 1995.
2. O. Ray and C. Ksir. Drugs, Society, and Human Behavior, Mosby, St. Louis, 1996.

3. R.R. Levine, C.A. Walsh and R.D. Schwartz. Pharmacology: Drug Actions and Reactions, Parthenon Publishing Group, New York, 1996.

For additional information about NIDA, contact us.