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# The Potential for Abuse: Addiction

## Stress of Prolonged Substance Abuse/Addiction on the Brain

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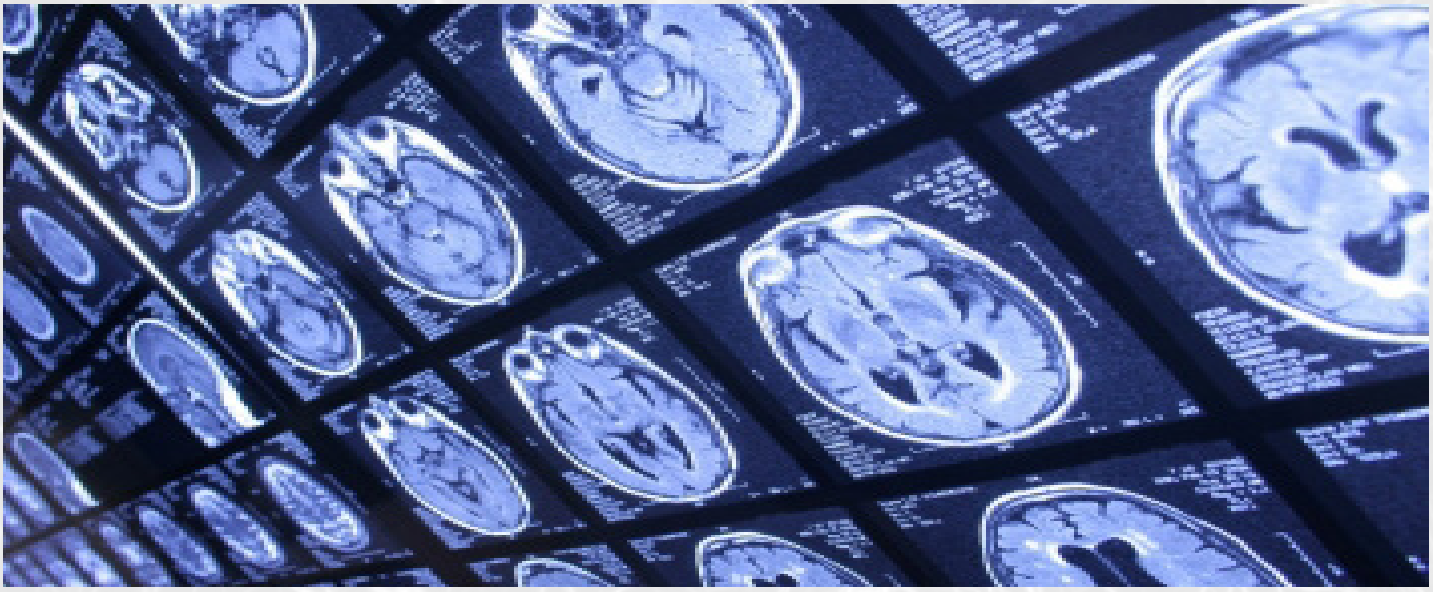

**Figure 1.** MRI scans of rat brains for a brain abnormalities study.

The U.S. Food and Drug Administration (FDA) states that drugs that have a high potential for abuse are frequently used for their recreational purposes, in lieu of any medical use that may apply, due to the positive psychoactive effects that are produced on the central nervous system (FDA, 2010). These drugs include, but are not limited to, opioids, nicotine, amphetamine, ethanol, and cocaine (FDA, 2010). Drugs with a high potential for abuse may in certain circumstances lead to addiction, more commonly referred to as substance dependence (FDA, 2010). Continuous use of these kinds of drugs disrupts the brain, allowing an individual to build a tolerance to the drug that is characterized by a compulsive behavior to administer higher doses in an attempt to produce similar outcomes of euphoria (FDA, 2010). An extended use of these substances results in an increase in tolerance as well as an increase in the potential for addiction. Addiction is a chronic relapsing disorder characterized by a compulsive use of substances despite the adverse consequences involved (FDA, 2010). Recent studies indicate that addiction may be a chronic brain disease caused by abnormalities in the mesolimbic system.

The brain reward system was comprehensively studied by Olds and Milner (1954) who first identified the regions of the brain in which direct electrical stimulation produced a positive reinforcing effect (Olds & Milner, 1954). Olds and Milner conducted laboratory experiments in which they implanted electrodes in various regions in the rat's brains and allowed the rats to self-administer their own electrical stimulation with a lever (Olds & Milner, 1954). They found that in the areas of the brain in which electrical stimulation was most rewarding, the rats stimulated themselves in these areas most frequently and for a longer duration of time (Olds & Milner, 1954). These studies indicated that the areas of the brain that were able to produce the highest rewarding effects were all connected through the neural pathway of the medial forebrain bundle (Olds & Milner, 1954). The neural circuitry that is contained within the medial forebrain bundle produces these rewarding effects with the release o dopamine upon stimulation.

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Dopamine, a neurotransmitter in the central nervous system associated with motor function, motivation, and pleasure is the neurotransmitter released when many drugs with a high potential for abuse cross the blood brain barrier into the brain and act on the mesolimbic system. (Arias-Carrión, Stamelou, Murillo-Rodríguez, Menéndez-González, & Pöppel, 2010). Of the various dopaminergic

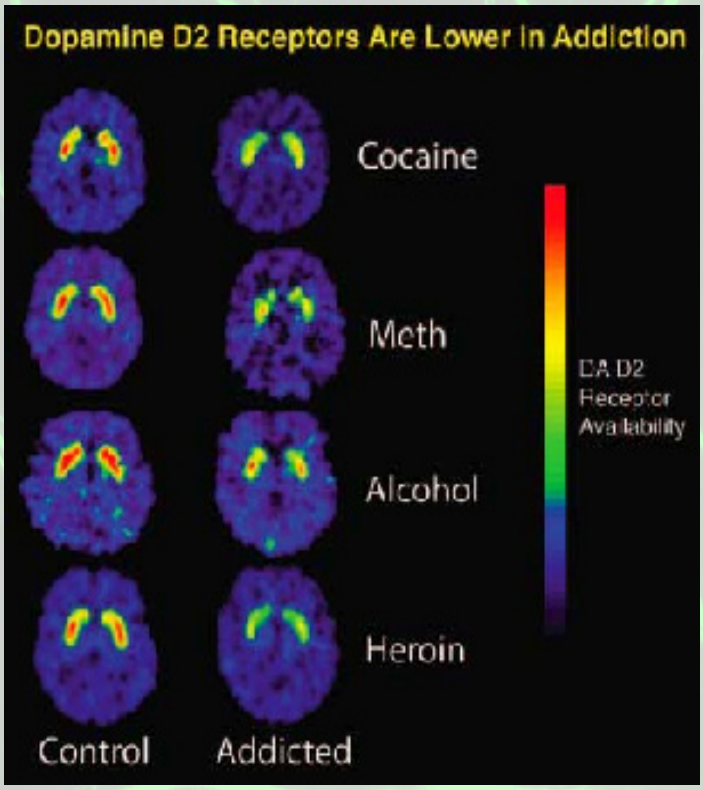


**Figure 2.** PET scans of human brain showing addictive substances and their consequences

pathways found in the body, the mesolimbic dopamine system in particular plays a crucial role as the "pleasure center" of the brain by reinforcing rewarding behavior (Hyman, 2005). This pathway contains dopaminergic neurons along which signals are carried from one region of the brain to another.

The mesolimbic pathway begins in a region of the midbrain referred to as the ventral tegmental area (VTA) that connects to the limbic system through projections to the nucleus accumbens, amygdala, hippocampus, and medial prefrontal cortex (Hyman, 2005). The VTA is composed of a cluster of dopaminergic neurons that communicate with the nucleus accumbens via the medial forebrain bundle (Hyman, 2005). Although the number of dopaminergic neurons housed in the VTA is miniscule compared to other regions of the brain, these individual neurons run extensively throughout the brain, with axonal lengths approximating 74 cm and synaptic connections containing roughly 500,000 terminals (Arias-Carrión, et. al., 2010). As a result of their extensive length, dopaminergic neurons are able to function in various regions of the brain, such as the mesolimbic reward system. The dopaminergic neurons of the VTA communicate with the neurons of the nucleus accumbens (NAc) through voltage changes that release dopamine neurotransmitters into synapses containing dopamine receptors, D1 and D2 receptors, located on the dendrites of the medium spiny neurons (MSNs) of the NAc (Hyman, 2005). The NAc is composed of an outer shell as well as an inner core (Hyman, 2005). The outer shell of the NAc is the region in the brain that individuals will actively self-administer electrical stimulations to (Hyman, 2005). The VTA- NAc circuit is involved in mediating the rewarding effects of both natural rewards and drugs with a high potential for abuse (Hyman, 2005). The amygdala is another structure within the limbic system that interacts with the VTA-NAc pathway through neural circuitry. Located in the temporal lobe anterior to the hippocampus, the amygdala functions in regulating emotions and is associated with conditioned learning involving a conditioned response to an external stimulus (Hyman, 2005). This structure conditions an individual to classify an external stimulus as either rewarding or aversive (Hyman, 2005). The VTA also interacts with a nearby structure known as the hippocampus, located in the temporal lobe's medial portion. The hippocampus plays a crucial role in memory, adaptive behavior, and the maintenance of homeostasis (Nestler, n.d.). Lastly, the medial prefrontal cortex of the brain functions in decision making related to a reward or aversive stimuli (Hyman, 2005). Deregulation of the medial prefrontal cortex is characterized by a loss of control and compulsive behavior (Hyman, 2005).

Under normal conditions, the mesolimbic system of the brain reinforces positive behavior that is beneficial to an individual and species. The mesolimbic system creates a sense of pleasure when an individual engages in naturally rewarding behaviors that pertain to water, food, exercise, or reproduction (Nestler, n.d.). These naturally rewarding stimuli activate the mesolimbic system, resulting in a release of dopamine neurotransmitters in the shell of the nucleus accumbens (Hyman, 2005). This influx of dopamine creates a sense of pleasure, resulting in a positive reinforcement where an individual repeats a certain behavior to receive the same euphoria. Similarly, all drugs with a high potential for abuse also act directly on the mesolimbic pathway by releasing dopamine and producing the same sense of pleasure (Arias-Carrión, et al., 2010). However, drugs with a high potential for abuse differ from natural stimuli due to their ability to release a more substantial concentration of dopamine into the extracellular space of the nucleus accumbens, resulting in an overstimulation of the brain (Volkow, Fowler, Wang, Swanson, 2004). In essence, the brain adapts to the over stimulating effects of these drugs through homeostatic mechanisms that result in the production of tolerance, in which an individual is forced to increase dosage of a drug in order to receive the same effects (Volkow, et al., 2004).

Further studies have illustrated that in vivo administration of different drugs with a high potential for abuse results in an increase in synaptic strength of dopamine neurons in the VTA-NAc circuit (Saal, Dong, Bonci, Malenka, 2003). A study compared five different drugs with a high potential for abuse that differed in their molecular mechanisms within the brain: cocaine, amphetamine, morphine, nicotine, and ethanol (Saal, et al., 2003). First, cocaine and amphetamine were compared together due to similarities they share as psychoactive stimulants that increase dopamine concentrations within the brain (Saal, et al., 2003). These two drugs were found to both increase excitatory transmission onto dopamine neurons (Saal, et al., 2003). Similar results were found in morphine's effect on opioid receptors, nicotine's on nicotinic receptors, and ethanol's on various neurotransmitters (Saal, et al., 2003). However, no significant changes were observed concerning synaptic strengths of dopamine neurons with non-abusive drugs (Saal, et al., 2003).

Although the biological basis of drug reward is important in understanding the mechanisms of drug addiction within the brain, it does not necessarily constitute the main underlying factor leading to drug addiction. As a psychological disorder, addiction can also be attributed to various factors that include genetics as well as environmental cues. The pleasurable effects associated with drugs with a high potential for abuse promote addiction by positively reinforcing the behavior of self-administration that leads an individual to consume that particular drug again (Chiara, 1999). In addition, increased levels of dopamine release in response to salient stimuli such as the context in which drugs with a high potential for abuse appear also play a role in learning and motivation (Chiara, 1999). Both addictive drugs and natural stimuli result in dopamine release that leads an individual to be able to associate an environment with a distinctive memory. However, the substantial release of dopamine from drugs with a high potential for abuse can result in neurobiological changes in the brain that alter the thresholds in which natural stimuli and drug stimuli are able to activate dopamine release (Volkow, et al., 2004). Brain imaging studies have indicated a decrease in the release of dopamine and the number of dopamine receptors in the mesolimbic pathway associated with an addicted individual (Volkow, et al., 2004). As the levels of dopamine decrease, an individual becomes desensitized to natural stimuli that once were salient and the sense of pleasure subsides (Volkow, et al., 2004). With the memories stored in the amygdala and hippocampus, an individual may attempt to recreate these euphoric feelings through compulsive use of drugs despite the negative consequences involved (Volkow, et al., 2004).

"However, no significant changes were observed concerning synaptic strengths of dopamine neurons with non-abusive drugs (Saal, et al., 2003)."

Drugs with a high potential for abuse can be potentially hazardous in their abilities to alter the brain. These drugs impact the brain in such a way that an individual becomes desensitized to natural stimuli and behavior that once promoted survival. These natural stimuli no longer become positively reinforced through dopamine release, influencing an individual to engage in compulsive self-administration of drugs despite the adverse consequences on health. Recently, there has been growing evidence that dopamine may not play as great of a role as it was perceived to play in drug reinforcement (Wise, 2004). For instance, drugs such as morphine and nicotine illustrate dopamine-independent as well as dopamine-dependent rewarding effects (Wise, 2004). Although the relationship between the rewarding effects of drugs and drug addiction is not entirely developed, there is evidence that certain factors of drug reward such as the direct release of dopamine on the mesolimbic system have the potential to lead to addiction (Pierce, 2005).

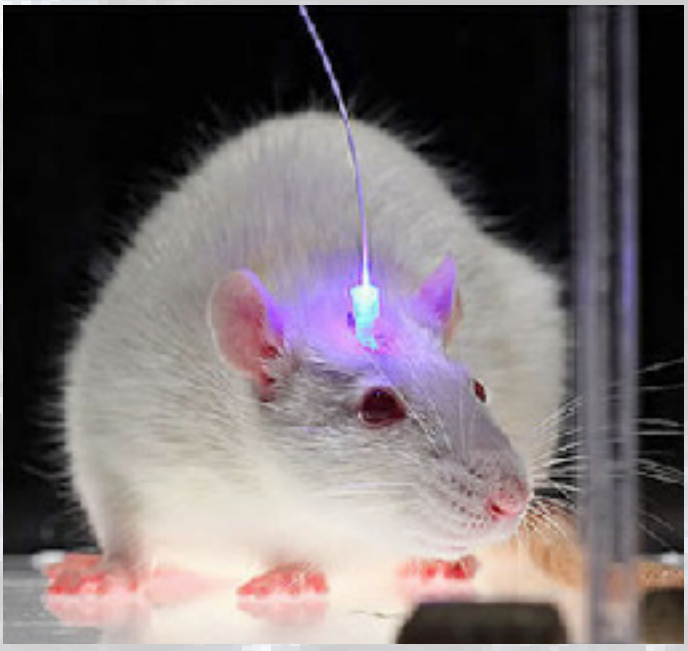

**Figure 3.** A rat with a fiber-optic cable, which applies a laser signal to the brain to stimulate specific brain cells.

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