

# THE POTENTIAL FOR ABUSE: ADDICTION

## STRESS OF PROLONGED SUBSTANCE ABUSE/ADDICTION ON BRAIN

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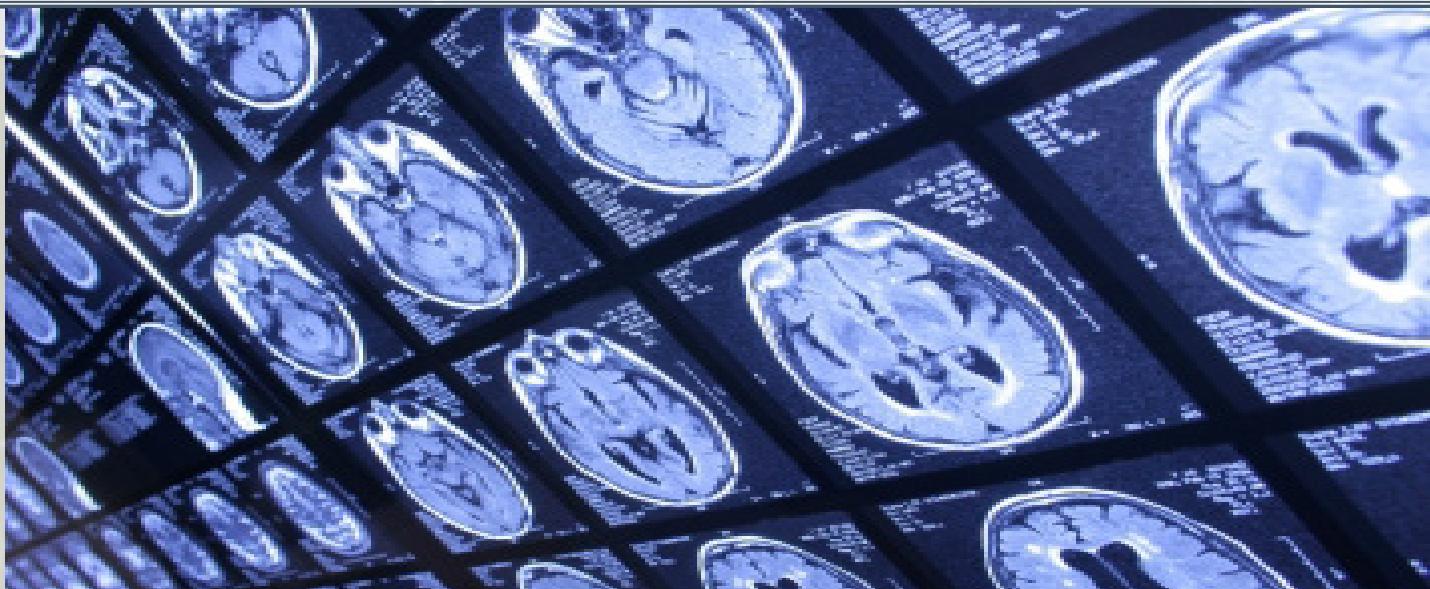


Figure 1. MRI scans of rat brains for a brain abnormalities study.

The U.S. Food and Drug Administration (FDA) defines abuse potential as a drug used for recreational use repeatedly and sporadically for 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 of potential abuse may in certain circumstances lead to addiction, more commonly referred to as substance dependence (FDA, 2010). Addiction is a chronic 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.

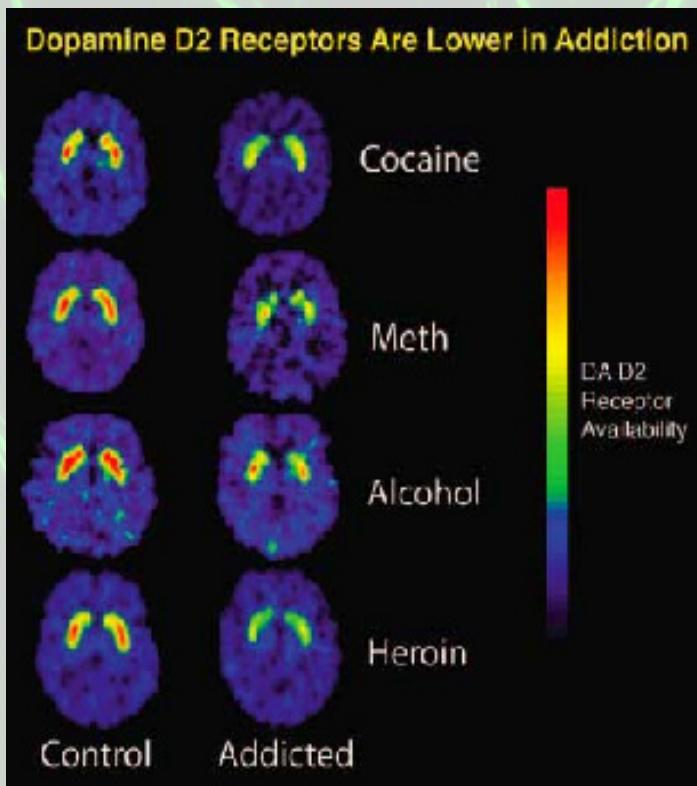
Dopamine, a neurotransmitter in the central nervous system associated with motor function, motivation, and pleasure is involved in the action of many drugs of potential abuse (Arias-Carrión, Stamelou, Murillo-Rodríguez, Menéndez-González, & Pöppel, 2010). Of the various dopaminergic pathways found in 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 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 and Milner conducted laboratory experiments in which they implanted electrodes in various

“A comparison of brain imaging pictures demonstrated that there is a significant difference between the brains of an addict as compared to a non-addict”

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 regularly and for a longer duration of time if they were allowed to do so (Olds & Milner, 1954). These studies indicated that the most sensitive areas of the brain that were able to produce the highest rewarding effects were also all connected through the neural pathway of the medial forebrain bundle (Olds & Milner, 1954).



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

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 various types of neurons that include a specific cluster of dopaminergic neurons that communicate foremost with the nucleus accumbens via the medial forebrain bundle (Hyman, 2005). Although the number of dopaminergic neurons housed in the VTA is minuscule 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, dopaminergic neurons are able to play a specialized role in influencing complex regions of the brain such as the reward system. The dopaminergic neurons of the VTA communicate with the medium spiny neurons of the nucleus accumbens (NAc) through synaptic connections that release dopamine neurotransmitters into the NAc (Hyman, 2005). The VTA- NAc circuit is involved in mediating the rewarding effects of both natural rewards and drugs of potential 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 the beneficial biological value of stimuli (Hyman, 2005). This structure conditions an individual to be able to associate 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).

Under normal conditions, the mesolimbic system of the brain reinforces positive behavior provides a positive reinforcement of behavior that is serves to be beneficial to an individual and species. The mesolimbic system creates a sense of pleasure and reward when an individual engages in behavior that pertains 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 positive reinforcement of pleasure results in this particular behavior to be repeated again. Similarly, all drugs of potential 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 of potential 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 increase in rewarding effects (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).

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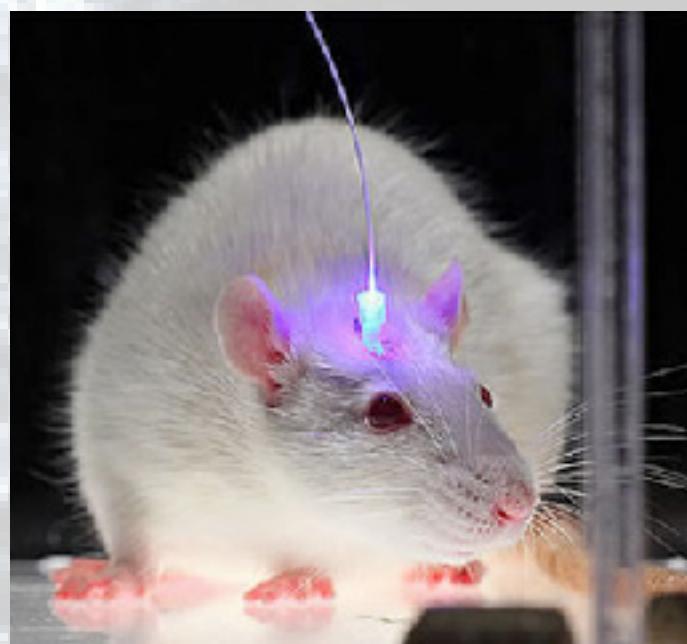
Further studies have illustrated that *in vivo* administration of different drugs of abuse results in a common increase in synaptic strength of dopamine neurons in the VTA-NAc circuit (Saal, Dong, Bonci, Malenka, 2003). A study compared five different drugs of abuse that differed in their molecular mechanisms 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 both being a psychoactive stimulant that increases dopamine concentrations within the brain (Saal, et al., 2003). These two drugs of potential abuse 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, (which acts on opioid receptors), nicotine's on nicotinic receptors, and ethanol's on various neurotransmitters (which acts on nicotinic receptors), and ethanol (that acts on various neurotransmitters) (Saal, et al., 2003). However, there were no apparent increases in the changes in synaptic adaptations on dopamine neurons with non-abusive drugs (Saal, et al., 2003).

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Although drug reward does play a role in drug addiction, it does not necessarily constitute the main underlying factor causing addiction. As a psychological disorder, addiction can also be attributed to various factors that can be influenced by environmental and genetic factors. However, the sense of euphoria and pleasure that is felt by self-administration of a drug can promote addiction by causing an individual to engage in repeated drug use (Chiara, 1999). Increased levels of dopamine release in response to salient stimuli such as drugs of abuse play a role in learning and motivation. Both addictive drugs and natural stimuli result in dopamine release that promotes an individual to engage in a certain behavior through positive reinforcement that is able to associate salient stimuli with a distinctive memory. However, the substantial release of dopamine from

drugs of abuse can overtime 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 a result of these decreased dopaminergic effects on the brain, an individual must increase dosage of a certain drug of abuse due to the tolerance that the brain has developed. 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).

Drugs of abuse can be potentially hazardous in their abilities to alter the brain in which natural stimuli become desensitized and behavior that once promoted survival is no longer reinforced. Although the linkage between drug reward and drug addiction is not entirely developed, there is evidence that supports that certain factors of drug reward 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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