HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 4 (2022)

The Central Mechanisms by Which Illicit Drugs Lead to Addiction

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Introduction

Drug addiction is a persistent and extremely harmful brain disorder. Addiction has been a prevailing issue throughout the world as the effect it has on individuals can be highly detrimental to one's health. The most recent data available from the United Nations Office against Drugs and Crime stated that in 2013, 246 million people used psychoactive drugs at least once over the course of a year (UNODC, 2015). In the DSM-5, the Diagnostic and Statistical Manual of Mental Disorders, addiction is defined as a 'substance-use disorder' which places importance on the idea of compulsive drug-seeking behaviors rather than the characteristics and symptoms of drug dependence (Lüscher, Robbins, Everritt, Para. 2). Addictive behavior is characterized regardless of negative economic, social, and health consequences that an individual engages in. Addicted Individuals spend great amounts of time and effort in order to obtain drugs that are not readily available. In the absence of the drug, this compulsive drug-seeking leads to maladaptive or harmful decisions despite the negative repercussions.

Drug addicts begin taking drugs for their positive effect on mood as well as their confidence and self-esteem, but once addiction takes place, drug addicts continue to take drugs to avoid negative states which can grow to be quite severe. These negative states are psychological dependencies that affect emotional and cognitive states including stress and withdrawal symptoms. Additionally, repeated drug-taking incurs physiological changes in the central nervous system, as well as other stress and withdrawal and tolerance-related symptoms. When an individual develops tolerance to the drugs they are taking, they begin to need more of it in order to achieve the same effect as when they first started taking the drug. This occurs because of pharmacodynamic effects such as receptor desensitization and internalization. Pharmacokinetic tolerance is when an adaptive homeostatic response is produced and the drug receptors become inhibited, which decreases the pharmacological effect. Withdrawal consists of both physiological and emotional effects that someone undergoes when reducing or stopping the intake of the substance they are addicted to. In physiological withdrawal, with repeated use of the drug, one's body decreases the number of receptors that the drug binds in order to cause its effect. Thus, when there is no drug in the system, there are fewer receptors available than prior to drug use and it becomes difficult to maintain normal activity.

Withdrawal not only has physiological effects as seen above but also includes emotional symptoms like sadness. However, it's important to remember that this is a result of the physiological symptoms of withdrawal, eg. receptor desensitization or internalization. In psychological withdrawal, individuals face shame about taking drugs, especially if they know they shouldn't because they have a problem. Both withdrawal and tolerance are directly correlated to the physiological changes that someone experiences when they are addicted.

When one becomes physiologically dependent on a drug, there are many changes to the nervous system. There are multiple brain areas involved in the development and recurrence of drug addiction, but perhaps the most well-known is the reward system. The reward pathway is a midbrain region that consists of the ventral tegmental area (VTA) and the nucleus accumbens (NAc) (Figure 1). After decades of research, it is well established that many illegal drugs cause the VTA to release dopamine in the NAc. This ability to cause the release

of dopamine in the reward pathway is theorized to be the primary cause of what makes a substance addictive. Dopamine release is known to regulate motivation and learning. Illicit drugs that increase the release of dopamine, such as Cocaine and Meth, both do so in the reward pathway. The cells become overstimulated by this increased dopamine release, which leads to feelings of pleasure and exhilaration.

This theory regarding dopamine release and its relationship with addiction is well accepted, however, illicit drugs that are thought to be dangerous do not only affect the dopaminergic system. In addition, there is an entire class of drugs called hallucinogens that only affect the serotonergic system. There is currently a debate in the field about whether drugs that affect serotonin can be addictive and if they should be regarded as schedule 1 drugs, or drugs with a high potential of abuse and no accepted medical use. This is of particular importance right now as there is continuous research that shows how hallucinogens have a number of beneficial effects due to serotonin. In particular, serotonin is responsible for emotions and judgment in the brain. It provokes intense feelings of happiness and well-being. However, there is a high potential for abuse, and many side effects including nausea, vomiting, and headache. This research paper discusses a plethora of drug theories and their potential for them in the future.

Drug Theories and When Is One Determined to Be Addicted

Currently, about 246 million people around the world have used an illicit drug (Ouzir, 2016). The reasons for use include the sensations of pleasure, to reduce symptoms of withdrawal and other effects of substance usage, or even curiosity. There have been many theories found around the etiology of addictive behaviors which focus on neurobiological, environmental, psychopathological, behavioral, and other general aspects of addiction (Ouzir, 2016). In the past, psychoactive substances have been used for medicinal purposes as well as in rituals and ceremonies (Lang, 2004). Additionally, evolutionary biologists even stated that many plants have evolved to have the ability to synthesize secondary metabolites or small organic molecules produced by an organism which is not necessary for their growth, development, or reproduction (Monfil 2014), such as nicotine and morphine which are psychoactive drugs derived from plants. Due to the emergence of substances in agriculture, these drugs are available in higher quantities. This accelerated the rate of drug addiction even more. Drug addiction has an extremely detrimental effect on the health and behavior of individuals as well as social development. This repeated usage of drugs leads to tolerance, many of the times, which is when a larger dose is needed to maintain the initial drug responsiveness, which then leads to dependence (APA, 2000; Wise and Koob, 2014). Researchers even observed that animals in many environments, wild, domesticated, and captive, ingest psychoactive plants which allowed them to conclude that the usage of psychoactive drugs may be a common behavioral trait in animals (Siegel, 2005). Many animal-lab studies conducted regarding addiction supported the idea that these mammals also demonstrate signs of compulsive drug-seeking and drug-taking behaviors (Campbell and Carroll, 2000). This idea also raises questions about whether or not illicit drugs act on specific areas of the brain. As a result of this hypothesis, many studies, and claims regarding the dopaminergic pathway or the brain reward system in the development of drug dependence (Wise, 2002). Additional studies have shown that natural activities such as sexual activity, food, and positive social interaction can activate the reward system.

Another theory is that addiction to all schedule 1 drugs increases dopamine, or DA, transmission in the same parts of the brain as reward processing. Often, drugs induce neural dopamine release in high levels, which causes the reward system to become flooded with it (Bressan and Crippa, 2005; Kelley and Berridge, 2002). The dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and the shell of the nucleus accumbens (NAcc) begin to excite due to the addictive drugs (Nestler, 2005).

Another recently growing theory is regarding the serotonin (5-HT) system. Evidence illustrates that this system is implicated in the vulnerability and establishment of drug-use-associated behaviors and the maintenance of addiction (Müller and Homberg, 2015; Kirby et al., 2011; Müller et al., 2010). Depending on the type

of drug, the extracellular 5-HT activity, and 5-HT receptor functions are changed when the drugs are administered. As stated above, serotonin receptors influence biological and neurological processes such as aggression, anxiety, learning, memory, and even sleep.

The goal of this research paper is to determine the central mechanisms by which illicit drugs lead to addiction and compulsive drug-seeking behavior. Furthermore, this paper aims to investigate the specific contributions of the dopaminergic and serotonergic systems to addictive behavior.

Dopamine

Dopamine and the Reward System

Dopamine is an important neurotransmitter that plays a vital role in reward and motivation in the brain. The dopaminergic system, or the part of the brain responsible for making stimuli and initiating behaviors, is important for both survival and reproduction. Dopamine is made in the midbrain region better known as the reward pathway. In the reward pathway, the production of dopamine takes place in the Ventral Tegmental Area (VTA). From there, it is released into the nucleus accumbens (NAc). This pathway is important for, as stated previously, reward and motivation. When dopamine is released in a process, we are more motivated to do these behaviors and seek out the stimuli.

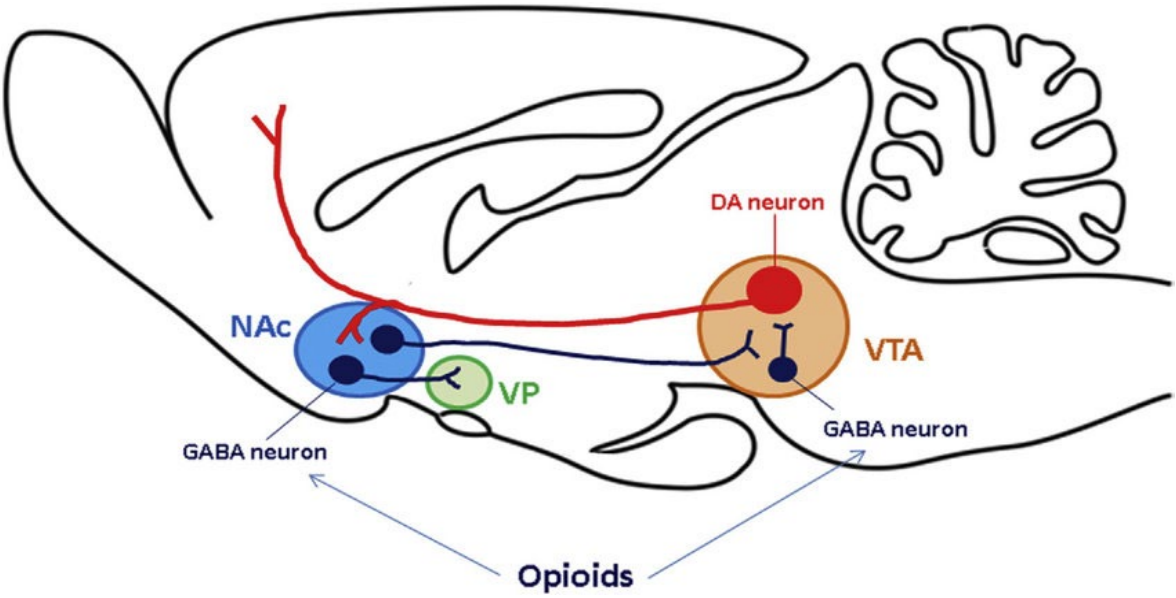

Figure 1. A diagram of the dopamine reward system. DA neurons: red, GABA interneurons: dark blue (Li, 2016).

We experience an urgent need for food when we are hungry. When one eventually finds that food, it triggers their reward system and this stimulus causes a release of dopamine from the VTA to NAc. Dopamine rewards us with the pleasurable feeling you experience with food, water, and sex. We, as humans, also experience a desirable need for sex. This is because reproduction is important for evolution and to pass down our genes, which is the goal of each species. The brain's reward system rewards food and sex as they both help us survive.

As the reward system is a very important system in our brain, it also has vulnerabilities. This region has been exploited greatly by very readily available drugs. High levels of dopamine are found in the reward systems, specifically, the NAc, when these illicit drugs are used since the dopamine is released in immense amounts (Bressan and Crippa, 2005; Kelley and Berridge, 2002). The individual, therefore, experiences the feelings of reward much quicker and at a more intense degree. Over time, the drugs become less rewarding and the craving for the drugs get greater. Overall, the amount of dopamine released from natural stimuli is much more controlled than when one takes drugs. The dopaminergic reward pathway is very important for our survival, however, addictive drugs misuse this and hijack these important pathways, which thus leads to addiction.

Dopamine Drugs and Their Effects

There are many different drugs that affect dopamine in the body and they all work in different ways. Normally, inhibitory neurons are active in our synapse which inhibits the release of dopamine. Anandamide, a neurotransmitter that plays a role in pain, depression, and appetite, activates cannabinoid receptors to turn off the release of the inhibitory neurotransmitters, therefore allowing dopamine to be released again. When one consumes marijuana, THC, the active ingredient, mimics Anandamide and binds to the cannabinoid receptors which allows dopamine to be released into the synapse.

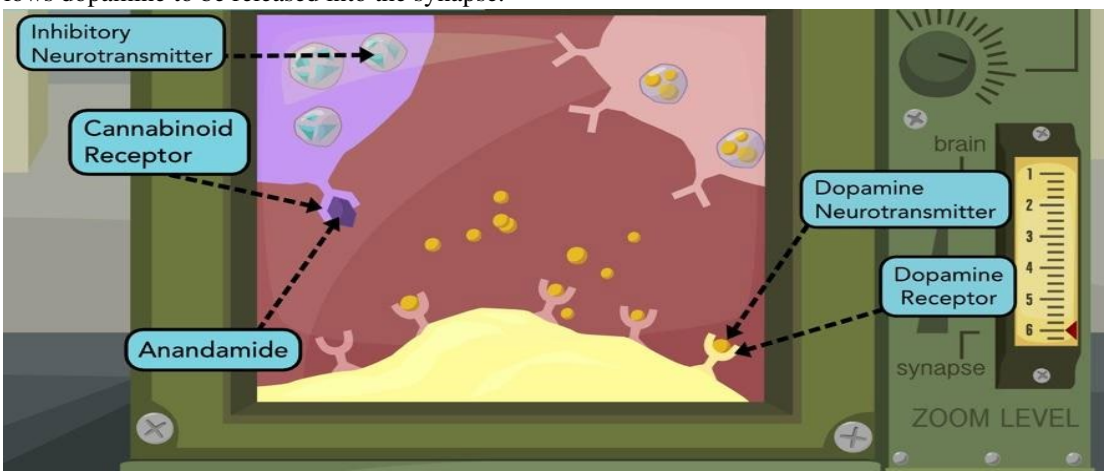

Figure 2. When activated by Anandamide, the release of inhibitory neurons is turned off by the receptors which prevents the release of dopamine (University of Utah, 2006).

When activated by Anandamide, the release of inhibitory neurons is turned off by the receptors which prevent the release of dopamine (University of Utah, 2006).

Methamphetamine, another illicit drug that affects the dopaminergic system, does so by mimicking the natural Dopamine in our bodies. Therefore, Methamphetamine is allowed into the dopamine transporters and begins to enter the dopamine vesicles. As a result of this, dopamine is forced out. This excess of Dopamine leads to transporters' reverse, in which the dopamine of this membrane transporter proteins is moved in the opposite direction. Therefore, dopamine is pumped out of the cell and into the synapse. The postsynaptic cells become overstimulated by the excess dopamine trapped in the synaptic cleft, where it is allowed to repeatedly bind to the postsynaptic dopamine receptors.

Cocaine also traps dopamine in the synaptic cleft. It binds to the dopamine transporters which prevents dopamine from being removed from the synapse. The dopamine builds in the synapse and continues to bind to the postsynaptic receptors over and over again. This overstimulates the cell. While all of these different drugs

act by distinct mechanisms, they all have the same final effect, which is an increase in dopamine in the reward pathway.

Serotonin

Serotonin and the Effect of Hallucinogens

Serotonin is a neurotransmitter that especially plays an important role in the central nervous system. Serotonin plays a large role in the regulation of many activities such as mood, emotions, and appetite. Serotonin has many wide-ranging functions and is necessary for our bodies to function. Our body uses serotonin to send messages between nerve cells and enables them to communicate with others. Serotonin, also known as 5-HT, is involved in cortical function. 5-HT stimulates excitatory and inhibitory neurons in GABA interneurons. This is why when one ingests drugs such as Hallucinogens, they experience many changes in reality. Hallucinogens, which affect the serotonergic systems, such as lysergic acid diethylamide, more commonly known as LSD, have proven to alter human consciousness, emotion, and cognition. It is also proven that LSD regulates the activity of midbrain neurons which contain 5-HT, or serotonin, which helped determine that the serotonergic systems in the CNS are why LSD has the psychoactive effects it does (Giménez, 2019). 5-HT binds to specific cell membrane receptors which mediate the physiological functions when hallucinogens are taken. Hallucinogens mimic the actions of serotonin and bind to receptors, which alters the shape and structure of these receptors. It is currently accepted that hallucinogens interact with 5-HT2A receptors, also known as serotonin 2A receptors, that generate these effects. "When activated, the receptors cause neurons to fire in an asynchronous and disorganized fashion, putting noise into the brain's system" (Ross, 2020). This leads to the psychedelic experience when one takes hallucinogens such as magic mushrooms. Although hallucinogens do not necessarily bind with these receptors, it has been found that 5-HT2A receptors must be activated in order to generate the behavioral response that hallucinogens are proven to produce.

Currently, there is no evidence to show that serotonergic drugs are addictive like drugs that affect the dopamine system are. There is, however, been continuous research regarding the benefits of serotonergic drugs. This includes research on using hallucinogens such as LCD for medical uses such as curing alcoholics. An article written by a renowned author Michael Pollan, the Trip Treatment, states that psychedelics were tested on alcoholics, individuals with OCD, depressives, schizophrenics, etc., and the results reported were positive. However, research was halted as the Controlled Substances Act was signed determining psychedelics as Schedule 1 drugs that prohibited their use. Currently, psilocybin is being tested by researchers to treat anxiety, addiction, and even depression. The effects of psilocybin are proven to be very similar to those of LSD but are not as disapproved of in society. One of the most influential early studies which proved psilocybin can be used was the Good Friday experiment which was conducted by Walter Pahnke in 1962. In this double-blind experiment, twenty students were given a capsule of white powder. Ten of these contained psilocybin and ten contained a placebo. Eight of the ten students who received psilocybin reported a 'mystical experience' whereas the control group experienced feelings of 'peace', determining that psilocybin has effects that could impact the medical industry forever (Pollan, 2015). Since then, there have been a plethora of experiments that have proved that psilocybin can, indeed, be used for medical purposes in the future. "After nearly five hundred administrations of psilocybin, the researchers have reported no serious negative effects" (Pollan, 2015). This is said to be due to the actions of serotonin 2A receptors on GABA neurons which reduce brain activity in those areas.

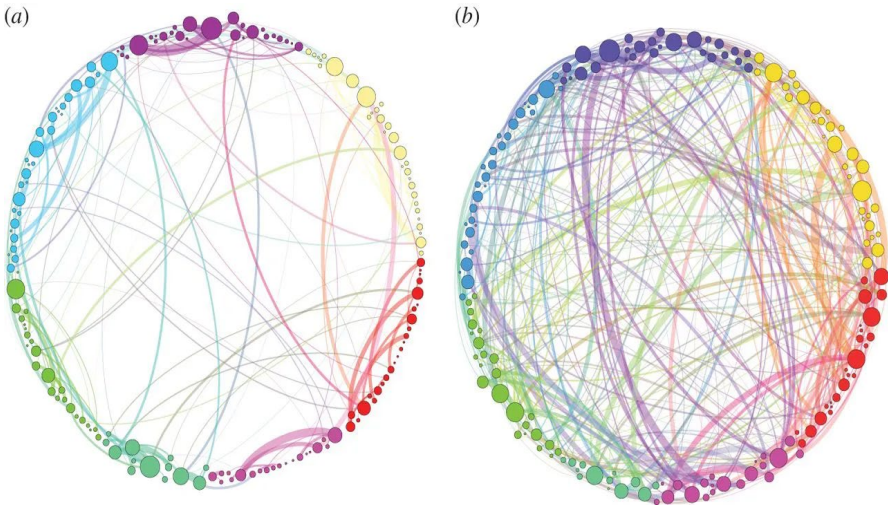

Figure 3. The image on the left is of the human brain on a placebo, and the image on the right is of a brain on psilocybin (Illing 2018).

Serotonin Illicit Drugs and Their Effects

One drug that deals with Seratonin is Ecstacy. Similar to dopamine, serotonin transmitters are responsible for removing serotonin molecules from the synaptic cleft. Ecstasy mimics serotonin, however, it is taken up much quicker and this interaction alters the serotonin transporter. Serotonin is then forced out and leaves lots of excess serotonin in the synapse, allowing it to bind to the receptors many times, leading to overstimulation of nearby cells. This excess release of serotonin is one cause of the mood-elevating effects many individuals undergo. MDMA, another name for ecstasy, affects the serotonergic pathways responsible for mood, sleep, perception, and appetite. LSD exclusively deals with serotonin.

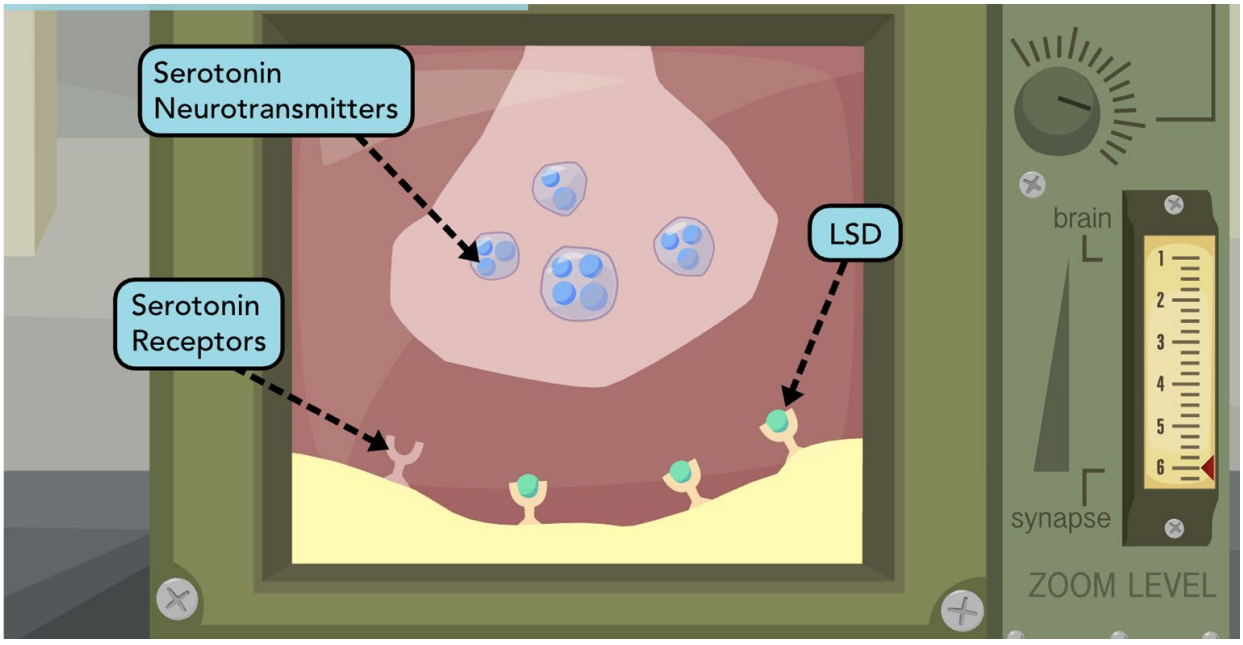

Figure 4. LSD resembles serotonin chemically and binds to serotonin receptors, thus elicits its effects (University of Utah, 2006).

This is because it resembles serotonin chemically and binds with the receptors in the place of serotonin. However, it only reacts with particular receptors, sometimes inhibiting the amount of serotonin and other times exciting it.

The History of Hallucinogens, Why They Became Illegal

Hallucinogens, including naturally occurring chemicals such as psilocybin, and synthetic compounds, like LSD, demonstrate alterations of human consciousness, emotion, and cognition. The Hallucinogenic effects of LSD and the idea that LSD and serotonin share chemical and pharmacological profiles led to the claim that biogenic amines like serotonin are involved in the psychosis of mental disorders (López-Giménez and González-Maeso, 2018). In order to understand why hallucinogens became illegal, it is also important to know their history. Psychedelics, which are a class of hallucinogenic drugs that produce changes in perception, mood, and cognitive processes. Psychedelics might be the oldest class of pharmacological agents that are known to man today (López-Giménez and González-Maeso, 2018). For example, psilocybin mushrooms were used by the Aztecs for healing as well as in religious and divinatory rituals. These psilocybin mushrooms were called *teonanacatl* at the time, meaning "god's flesh" (Ott and Bigwood, 1978; Schultes and Hofmann, 1979). The Hindu holy book, Rig Veda, mentions the use of *Soma,* which is a sacred substance that induced higher levels of consciousness. The use of psychedelics during many religious practices makes us aware that these substances can be mind-altering. The first synthetic hallucinogen, LSD, was discovered in 1935, by Albert Hoffman, while researching for an analeptic agent. When he became accidentally exposed to the drug, he began to experience hallucinations. In 1947, the drug was put on the market as named "Delsid" (Forrest, 2020). Psychiatrists used this drug in psychotherapy as it was believed to help the patient access repressed emotions. There were also many human experiments conducted with LSD, however, these studies were conducted without the consent of the participant in many of the cases. LSD use increased greatly in the late 1950s and early 1960s due to the increased popularity in the media. Additionally, individuals such as Timothy Leary who advocated strongly for psychedelic drugs helped bring experimentation rates to the highest they ever were in the 1960s. As the usage of these drugs increased, more and more adverse reactions began to be reported. Due to a plethora of health concerns, the government banned LSD in 1966. Illicit use and research continued, however. As of now, LSD is considered a schedule 1 drug.

Addiction Research in The Lab

Animal Studies

In order to test many of the theories scientists have made regarding addiction, many individuals test on animals in the lab such as mice and rats. Researchers study on mice and rats rather than other animals as they are very similar to humans genetically (Ball, 2016). Since the animal in the lab cannot communicate with us in order to tell the scientists what they are experiencing, they instead monitor behavioral protocols in order to figure out whether or not the drug works on them and if they feel 'euphoric'. One method which researchers use in order to test on these animals is the conditioned-place preference test.

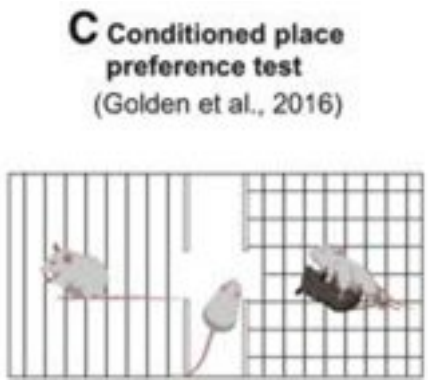

Figure 5. Animals are given the choice between two environments (Golden et al., 2016).

In this test, the animals are given a choice from two different environments. One of the environments, a conditioned stimulus, is put along with a motivationally rewarding stimulus, the unconditioned stimulus. In the other environment, the animals are given a neutral stimulus, or saline administration (Leong, 2018). In other words, one side of the chamber is paired with a drug whereas the other is saline. The behaviors are demonstrated by the amount of time the animal spends in each of the chambers on test day. Researchers found that cocaine-associated cues, or the drug paired chamber, maintained effectiveness for a long period of time (Mueller and Stewart, 2000; Reichel and Bevins, 2008). Another highly used method to test behavior in the lab is called Intravenous (IV) Drug Self- Administration.

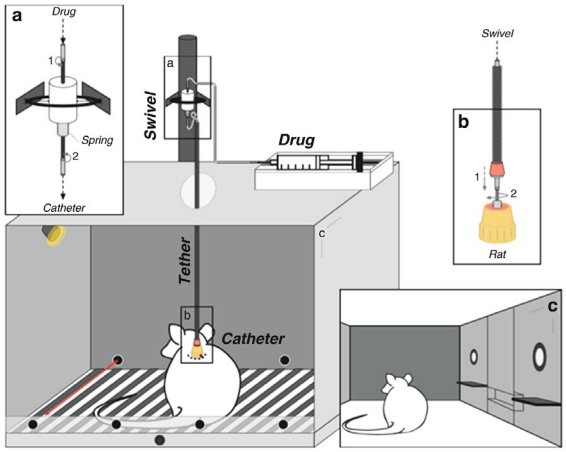

Figure 6. Intravenous Drug Self- Administration through catheters and tethers which allow the subject to choose when to administer the drug (Allain, 2020).

This method uses operant conditioning, for example, a lever, key peck, etc., to receive an outcome or drug administration. In this model, animals are taught how to press a lever which results in an IV infusion of a drug in the catheter (Leong, 2018). The test subjects are either given the substance on schedules of reinforcement, including fixed ratio and variable ratio schedules. In a variable ratio schedule, the animal gets the drug when they want and when they press the lever. In a fixed ratio, the animal has to work hard in order to get the reward they wanted. The test subjects are proven to become time-dependent in the incubation of drug cravings in the test explained above. Rats experience abstinence for 1-8 weeks after they faced the maintenance phase (Grimm, Hope, Wise, & Shaham, 2001). When the animals face abstinence they are either placed back in their home cages, in a different environment than the one in which they administered the drug, or handled daily. “The extent and degree of relapse varies as a function of the time since the last drug experience (Grimm et al., 2001; Tran-Nguyen et al., 1998), and generally increases over time, and thus has been coined “incubation” (Grimm et al., 2001) of drug craving” (Leong, 2018).

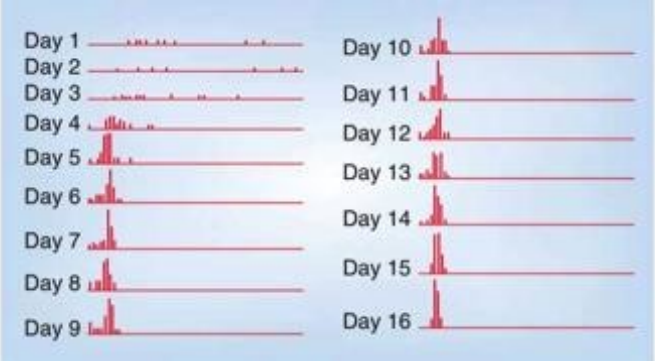

Figure 7. Example of variable ratio schedule: Interval histograms from rat lever- pressing for cocaine. The narrowing of interresponse times over days' show compulsiveness developed to cocaine.

Human Studies

Human studies are very difficult to conduct as there are many limitations around it and it is very controlled. Many of the studies one can conduct on animals cannot be done on humans such as manipulating brain surgery. Therefore, animal studies have been conducted in place of these. Animals are good research subjects as they are biologically similar to humans. They also have very short life cycles so they can be studied throughout their whole life span. Animal research has helped us make breakthroughs in many areas, especially in medicine. Millions of lives have been saved or improved as a result of these studies.

There is, however, still a need to conduct some studies on humans. One study conducted examined the effects of MDMA, or ecstasy, compared to the stimulant methamphetamine (MA). This study focused on two measures of social behavior in healthy young adults. This study used a four-session, within-subjects, double-blind design in which young adults received a placebo, 0.75 mg/kg MDMA, 1.5 mg/kg MDMA, or 20 mg of methamphetamine (MA) in randomized order (Bershad, 2019). The participants in the study were given behavioral tasks, in which researchers recorded their behaviors. They recorded positive results of the experiment as both doses of MDMA and the dose of MA induced a "high feeling". This is the most common example of research that is conducted on humans. Their behavior is studied in order to verify or fail to verify a hypothesis.

Should Serotonergic Drugs Be Used as Treatment?

Researchers have discovered many applications for psychedelic therapy and there is a large potential for them in the future. There are, however, many side effects as hallucinogens can produce profound mind-altering effects. These psychedelic drugs have a large promise in the treatment of a wide variety of mental health conditions such as addiction and depression. Current trials on these drugs have demonstrated improvement in tested individuals and are determining the applications and effectiveness of psychedelic drugs on specific conditions, however further research is needed before they can be available to the public.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

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