Fall 2017

Cocaine and the Dopamine Hypothesis of Addiction

Grace Gibson
Elizabethtown College, gibsong@etown.edu

Cocaine and the Dopamine Hypothesis of Addiction

FYS100C: Gotta Have It: Exploring the Science of Addiction

Grace Gibson

Dr. Hagan

Abstract

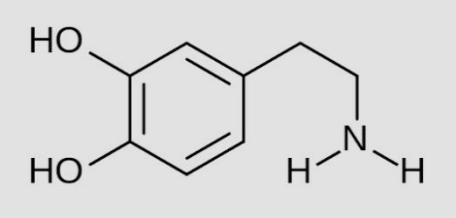
Dopamine is the primary neurotransmitter associated with addiction. Among the drugs that impact dopamine function, cocaine notably causes long-term blunting of dopamine release. The "blunted-dopamine hypothesis" explains the behaviors of addiction via cocaine's blunting effects. In a non-addicted brain, dopamine acts in the midbrain reward system to regulate pleasure and related emotions. The brain responds to rewarding stimuli by mobilizing dopaminergic neurons to release dopamine, causing the pleasure associated with eating, gambling, and drug use. Notable structures involved in dopamine pathways are the dorsal and ventral striata, the nucleus accumbens (a part of the ventral striatum), and the ventral tegmental area, where high concentrations of dopamine receptors are located. Though different dopamine receptor types impact addiction in different ways, D_1 receptors are most involved in cocaine addiction.

Amphetamine and other stimulants directly cause the brain to release dopamine. By increasing the rate at which neurons generate action potentials and the intensity of the action potentials generated, amphetamine significantly increases dopamine levels in the striatum. Amphetamine is therefore highly useful in the field of dopamine research, as researchers can directly induce dopamine release with their application. Cocaine also increases dopamine levels within the striatum by inhibiting the dopamine active transporter, the protein that removes dopamine from the synaptic cleft after it has been released. Dopamine levels are therefore greater following a cocaine-mediated dopamine release. These changes to dopamine function over time facilitate the changes to neurobiochemistry that promote cocaine addiction.

Introduction: Dopamine, the Brain, and Addiction

Though addiction involves the complex "molecular choreography" of thousands of biochemical components, none is more renowned for its involvement than the neurotransmitter dopamine. Figure 1 shows the structure of dopamine, an endogenous molecule derived from the amino acid tyrosine (*Biosynthesis* section, para. 1). Dopamine acts as a neural signaling molecule, a neurotransmitter, that plays a critical role in the brain's "reward system" (Washington, 2017, para. 1).

Figure 1: Structure of Dopamine

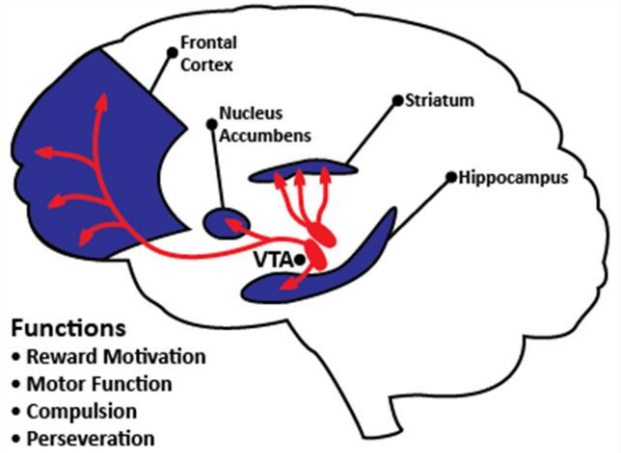


Note: Adapted from Washington, M. T. (2017). Dopamine. In AccessScience. McGraw-Hill Education.

Like all neurotransmitters, dopamine is produced and released by neurons and causes its specific response by binding to dopamine receptors on other neurons (Washington, 2017, *Biosynthesis* section, para. 1; *Release from Neurons* section, para. 1). The dopamine reward system facilitates "incentive salience", which creates feelings of "want" and desire, and operant conditioning, specifically positive reinforcement (Nutt et al., 2015, p. 305). By inciting pleasure in response to positive (i.e. rewarding) stimuli, dopamine inspires repeated consumption of substances that cause pleasure (e. g. food) and repeated practice of activities that do the same (e. g. sex, gambling; Di Chiara & Bassareo, 2007, p. 72).

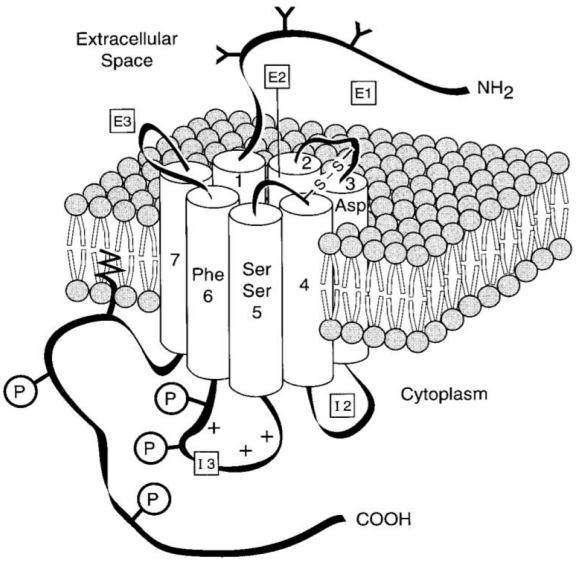
The system that controls reward, and therefore many aspects of addiction, spans many parts of the brain, involving diverse brain structures and varied ligands (Washington, 2017, *Role in Behavior* section, para. 1). Dopamine is therefore not the sole neurotransmitter through which the reward system acts. However, dopamine is notable as the "chief" neurotransmitter because rewarding stimuli elicit a release of dopamine (Nutt, Lingford-Hughes, Erritzoe, and Stokes,

Figure 2: Dopamine pathways in the brain



Note: Adapted from Organically in Tune. (2014). The organic effects of dopamine and the brain's reward system.

Figure 3: Dopamine transporter



Note: Adapted from Ritz, M. C., Lamb, R. J., Goldberg, S. R., & Kuhar, M. J. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science,* (4819), 1219-1223.

2015, p. 305). Cocaine, an addictive drug associated with long-term changes in dopamine pathways, acts most significantly within the dorsal and ventral striatum, the latter of which contains the nucleus accumbens (NAc; Singer & Robinson, 2014, para. 1; Washington, 2017, *Role in Behavior* section, para. 1). The ventral tegmental area (VTA), as the origin of dopamine, is also important to addiction because dopamine activity is modulated by this region (Singer & Robinson, 2014, *Brain and neuronal activity* section, para. 1). Figure 2 shows the location of dopamine pathways in the brain, including the striatum, the NAc, and the VTA.

Dopamine interacts with neurons that contain dopamine receptors; this is the factor that forms dopamine pathways from disparate neurons. An example of a dopamine receptor can be seen in figure 3. All dopamine receptors are

transmembrane proteins, but they are not homogeneous. There are five classes of dopamine receptor, each with unique properties and distributions throughout the brain, though they can be broadly grouped according to similarities in structure and function (Missale, Nash, Robinson, Jaber, and Caron, 1998, p. 191).

The habitual nature of activities associated with dopamine release is important to maintaining homeostasis. However, changes to dopamine pathways resulting from long-term drug abuse can also promote addiction. Substances such as cocaine and amphetamine can interact with specific receptors on dopaminergic neurons, causing an increase in the amount of dopamine found in the striatum (Nutt et al., 2015, p. 305). Amphetamine plays an important role in dopamine testing because it causes dopaminergic neurons to release dopamine; it is therefore used in multiple studies to induce dopamine release (Martinez et al., 2003). Cocaine, on the other hand, inhibits the transporter involved in dopamine uptake, resulting in a greater buildup of dopamine in the striatum (Wu, Reith, Kuhar, Carroll, & Garris, 2001).

Long-term cocaine abuse is associated with significant physiological changes to dopamine pathways. In the brains of those addicted to cocaine, dopamine release via the VTA into the striatum may be diminished; this is the so-called “blunted dopamine hypothesis” (Volkow et al., 2014, p. 1041). According to this hypothesis, physiological changes to the addict’s brain promote less dopamine activity in response to rewarding stimuli; this greatly decreases dopamine release. Addiction and its attendant behaviors therefore persist as the addict attempts to elicit the dopamine-driven pleasure.

Direct measure of the action of dopamine molecules can be difficult, requiring inventive solutions to obtain quantitative data. One common practice in the field of dopamine research is to introduce a radioactive ligand that selectively binds to dopamine receptors. Images generated by

positron emission tomography (PET scans) can then monitor the radioligand's interaction with receptors in the brain. By comparing binding of the radioligand before and after a dopamine-releasing process, such as a drug administration, scientists can indirectly measure dopamine release via the amount of radioligand molecules displaced from dopamine receptors. A lower amount of bound radioligand signals a higher amount of bound dopamine.

Locations of Dopamine and Drug Action

Dopamine pathways are not contained within one specific section of the brain; they span many areas and involve various neural structures. Because not all dopamine pathways mediate reward, only a specific subset of dopamine pathways is implicated in reward and therefore in addiction. In a now-seminal work in the field of neural signaling, Olds and Milner (1954) mapped out the brain location on which rewarding stimuli act, now relevant as the area of action for stimulant drugs. Performing their modelling in rats, the researchers constructed electrodes that electrically stimulated various areas of a rat's brain when the rat pressed a lever (p. 419). They then left the rats to their own devices for periods of several hours, allowing the animals to press the lever as they chose (p. 420). All rats were given a percentage score that denoted the amount of time they spent pressing the lever. Based upon the definition of a rewarding stimulus—one that promotes continual behavior to achieve the effects of the stimulus—a higher amount of time pressing the lever signaled reward-seeking behavior (Nutt et al., 2015, p. 305). Preservation and examination of the rat brains showed that the electrodes that stimulated the center of the forebrain (the septal region) were activated most frequently (Olds & Milner, 1954, p. 421). Figure 4 (see following page) details the percentage of time rats spent pressing the lever to stimulate various areas of the brain. Voltages vary because each rat's voltage was determined

Figure 4: Time Spent by Rats Eliciting Electrical Stimulation

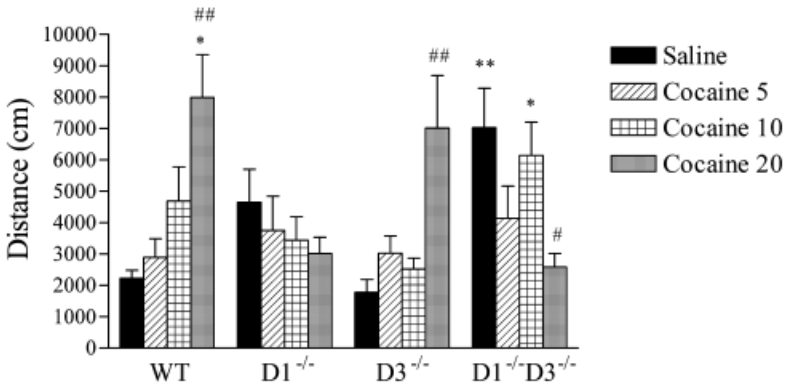
Animal's No.	Locus of Electrode	Stimulation Voltage r.m.s.	Percentage of Acquisition Time Spent Responding	Percentage of Extinction Time Spent Responding
32	septal	2.2–2.8	75	18
34	septal	1.4	92	6
M-1	septal	1.7–4.8	85	21
M-4	septal	2.3–4.8	88	13
40	c.c.	.7–1.1	6	3
41	caudate	.9–1.2	4	4
31	cingulate	1.8	37	9
82	cingulate	.5–1.8	36	10
36	hip.	.8–2.8	11	14
3	m.l.	.5	0	4
A-5	m.t.	1.4	71	9
6	m.g.	.5	0	31
11	m.g.	.5	0	21
17	teg.	.7	2	1
9	teg.	.5	77	81

Note: Adapted from Olds, J. & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology, 47*(6), 419-427.

separately—each one is the voltage at which behavioral changes are just noticeable. Acquisition refers to the time during which pressing the lever led to electrical stimulation; extinction refers to the time when the lever produced no stimulation. The extinction period acted as a control period, during which the rats' behavior was evaluated in the presence of no stimulus. The septal region was clearly stimulated most frequently during acquisition, from 75 to 92 percent of the time. The rats' repeated stimulation of this area was a pattern of behavior associated with a rewarding stimulus. The study therefore concluded that the brain's center for reward was most likely located in the center of the forebrain (p. 425). Later research, including that of Martinez et al. (2003), confirmed this area as both the center of dopamine activity and the target for physiological effects of addictive drugs. Today, this area is known to contain the VTA and the adjoining dorsal and ventral striatum (containing the NAc), the areas where drug use incites increased dopamine release.

Another important aspect of dopamine pathways is the type of receptors present. The D_1-like receptors, consisting of the D_1 and D_5 receptors, are activators of the protein adenylyl cyclase (AC; p. 195). AC catalyzes formation of a secondary signaling molecule, adenosine 3',

Figure 5: Movement of cocaine-treated mice



Note: Adapted from Karasinska, J. M. et al. (2005). Deletion of dopamine D1 and D3 receptors differentially affects spontaneous behaviour and cocaine-induced locomotor activity, reward and CREB phosphorylation. *European Journal of Neuroscience, 22*(7), 1741-1750.

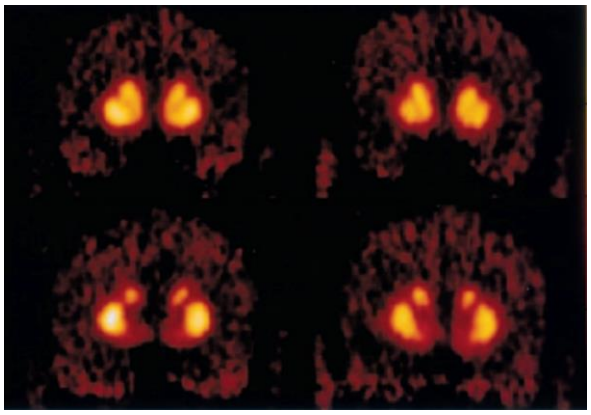
5'-cyclic monophosphate (cAMP), to transduce a signal (p. 190, 195). The D_2-like receptors, consisting of D_2, D_3, and D_4 receptors, inhibit AC to prevent transduction (p. 190, 195). The D_4 and D_5 receptors are not widespread within the striatum and are therefore not of importance to understanding dopamine pathways located there (Missale et al., 1998, p. 199). Among the remaining three receptor types, D_1 receptors appear to be most significant to cocaine effects (p. 1741). Karasinska, George, Cheng, and O'Dowd (2005) evaluated cocaine-induced behavioral changes in mice lacking D_1 receptors, D_3 receptors, and both D_1 and D_3 receptors. Wild-type mice with normal receptor expression were included as controls. Figure 5 reveals the horizontal movement of mice treated with varying doses of cocaine: 5, 10, and 20 milligrams per kilogram of mass. The wild-type mice (WT) exhibited clear increases in movement after cocaine administration; this is the expected effect of cocaine in mice. The mice lacking D_1 receptors exhibited a slight decrease to movement, while the mice lacking D_3 receptors showed inconsistent responses: movement increased for 5 and 20-milligram doses and decreases for the 10-milligram dose. Mice lacking both receptor types also exhibited decreased movement for all doses. The study concluded that though absence of both receptor types caused changes to the mice's responses, mice lacking D_1

receptors deviated most from the controls (Karasinska et al., 2005, p. 1748). This conclusion determines that D_1 receptors are most greatly implicated in the brain's response to cocaine, though D_3 receptors (and other D_2-like receptors) are also involved.

Amphetamine Causes Dopamine Release

To study the magnitude of a dopamine release, a dopaminergic neuron must be induced to release the neurotransmitter via application of a specific substance. Cocaine is often the study of such trials because it decreases the amount of dopamine released in the brains of cocaine addicts. Many trials that test cocaine's blunting effect produce controlled dopamine release via administration of amphetamine or similar compounds.

Figure 6: PET scans before and after amphetamine

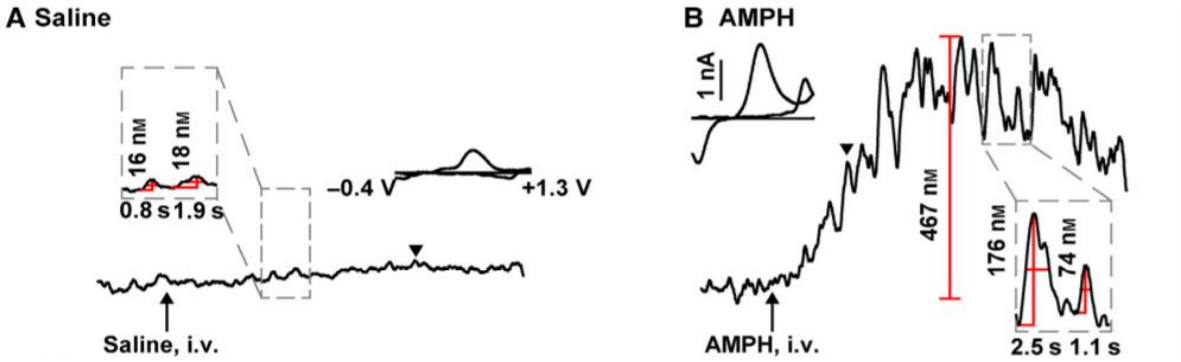


Note: Adapted from Martinez, D. et al. (2003). Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of The International Society of Cerebral Blood Flow and Metabolism, 23*(3), 285-300.

Martinez et al. (2003) demonstrated the dopamine-releasing effect of amphetamine in human brains. This study used the radioligand [^{11}C]raclopride, a radioactively-labelled molecule that binds selectively to dopamine receptors, to monitor binding of dopamine. Subjects underwent PET scans before and after amphetamine administration, both with [^{11}C]raclopride present (p. 286). The PET scans, shown in figure 6, show binding of [^{11}C]raclopride before amphetamine (left) and after amphetamine (right). Lighter

colors represent lower concentrations of bound [^{11}C]raclopride; the top and bottom rows show results in the same subject from slightly different views. The PET scans qualitatively revealed a lower amount of [^{11}C]raclopride binding within the striatum and surrounding regions, i.e., areas containing dopamine receptors, after amphetamine administration (p. 290). Researchers were also able to quantitatively determine reductions to dopamine receptor availability: the least-impacted region of the dopamine pathway had a mean drop in availability of 6.1 percent, while the most-affected region experienced a mean drop of 16.1 percent (p. 291). Fewer available receptors indicated greater interaction between dopamine and its receptors and therefore a greater concentration of dopamine (p. 289). Martinez and colleagues concluded that amphetamine causes dopamine release (2003, p. 292).

Figure 7: Voltage in dopaminergic neurons treated with saline solution and amphetamine



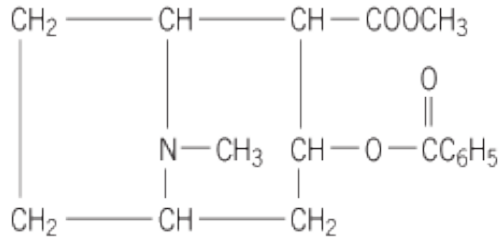
Note: Adapted from Covey, D. P. et al. (2016). Amphetamine elevates nucleus accumbens dopamine via an action potential-dependent mechanism that is modulated by endocannabinoids. *European Journal of Neuroscience, 43*(12), 1661-1673.

The method of amphetamine's dopamine-increasing effect in the NAc of rat brains was explored in a study by Covey, Bunner, Schuweiler, Cheer, and Garris (2016, p. 1662). The results of this study are shown in Figure 7. Monitoring electrical activity with fast-scan cyclic voltammetry (FSCV) allowed researchers to evaluate action potentials, or signals that induce a

neuron to release its neurotransmitter. The researchers affixed microelectrodes to the VTA and NAc regions, known to be areas of drug-induced dopamine release, to monitor electrical activity in those regions (p. 1662). The graph on the left in figure 7, labelled “A”, represented electrical activity in the brain when treated by saline solution; this was a control trial. It revealed only small changes to voltage within the neuron of interest, specifically those within the VTA and NAc. The graph on the right, labelled “B”, revealed greater changes in voltage after administration of amphetamine. The peaks in voltage represent action potentials generated by the dopaminergic neuron. A neuron’s pattern of generating action potentials is called burst firing; it can be seen from this study that amphetamine increases dopamine levels by increasing the burst-firing rate of dopaminergic neurons. Additionally, action potentials generated after amphetamine application were greater in intensity. Therefore, the method by which amphetamine increases dopamine levels in the NAc is by increasing the rate and intensity of action potentials generated by dopaminergic neurons.

Cocaine Increases Dopamine Levels in the Midbrain

Figure 8: Structure of cocaine

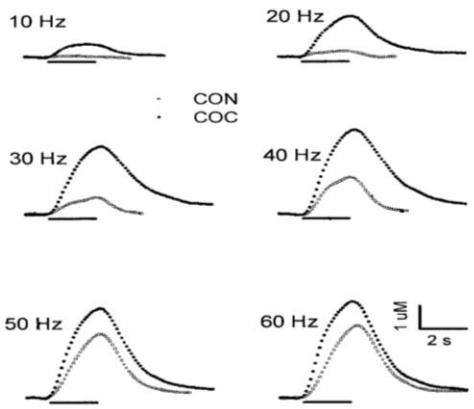


Note: Adapted from Weil, Andrew T. (2014). Cocaine. In AccessScience. McGraw-Hill Education.

The physiological changes associated with dopamine blunting originate with cocaine’s effects upon striatal dopamine levels. Increased dopamine levels, resulting from cocaine’s ability to inhibit dopamine uptake, cause the neuroadaptations that limit dopamine release in long-term cocaine users.

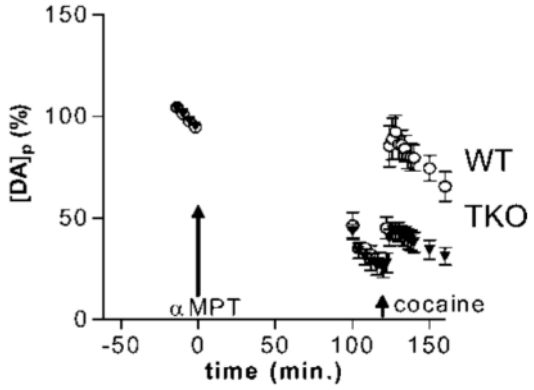
Figure 8 shows the structure of cocaine. This specific structure allows cocaine to competitively inhibit the dopamine active transporter, preventing dopamine uptake and causing high levels of dopamine to build up in the striatum (Ritz, Lamb, Goldberg, and Kuhar, 1987, p. 237). This phenomenon was tested by Wu et al. (2001) using voltammetry in rats. Electrodes were implanted in areas of the ventral striatum (p. 6339). Some of the electrodes measured electrical activity; others stimulated the brain to induce dopamine release. Figure 9 shows the results of the study; closed circles (forming darker-colored lines, the upper of the two lines for each trial) represent cocaine trials and open circles (lighter-colored, lower) represent control trials. Each graph shows the concentration of dopamine over time as either a saline solution (control) or cocaine was administered. While the overall pattern of concentration remains constant, dopamine levels in the striatum increase more with cocaine present. The same pattern in dopamine concentration was observed at varying frequencies, with a more pronounced effect at lower frequencies. Researchers also quantitatively determined the rate of dopamine uptake throughout the trials with the readings obtained through electrical measurement and found that dopamine uptake rates decreased significantly in cocaine trials (p. 6339, 6342). The study concluded that cocaine increases striatal dopamine levels via inhibition of the dopamine active transporter, the agent of dopamine uptake (p. 6345).

Figure 9: Dopamine releases with and without cocaine present



Note: Adapted from Wu, Q. et al. (2001). Preferential increases in nucleus accumbens dopamine after systemic cocaine administration are caused by unique characteristics of dopamine neurotransmission. *The Journal of Neuroscience, 21*(16), 6338-6347.

Figure 10: Dopamine increases in mice's striata after cocaine administration



Note: Adapted from Venton, B. J. et al. (2006). Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve pool. *Journal of Neuroscience, 26*(12), 3206-3209.

In addition to inhibition of the dopamine transporter, cocaine can also increase dopamine levels by inducing release of reserve dopamine. Figure 10 shows dopamine concentration increases in the striatum of mice following administration of cocaine (Venton et al., 2006). Dopamine concentration, [DA]p (%), is given as a percentage of pre-cocaine dopamine concentration. Preceding administration of cocaine is administration of α-methyl-p-tyrosine (AMPT), a substance that inhibits the enzyme tyrosine hydroxylase to severely reduce the mice's ability to produce dopamine from tyrosine. AMPT therefore ensures that released dopamine originates from stored reserves. Open circles, labelled as "WT" (wild-type), represent mice with normal production of the protein synapsin. Filled triangles, labelled as "TKO" (triple knock-out), represent mice in which production of synapsin has been halted via suppression of three synapsin genes. Because synapsin is the structural protein that mobilizes vesicles of dopamine to be placed into reserves, mice lacking synapsin lack sufficient stored dopamine (p. 3207). In this study, researchers implanted microelectrodes into the middle of the forebrain and used FSCV to locate dopaminergic signals (p. 3208). One set of microelectrodes measured the continuing electrical activity of the neurons; another set administered electrical stimulation at a level experimentally determined to release maximum dopamine (p. 3208). Several induced dopamine releases were performed first without cocaine, then with cocaine present. Cocaine

administration to both WT and TKO mice increased dopamine release levels, though the increase was significantly greater in WT mice (p. 3208). Because mice without significant reserves had a lower cocaine-induced dopamine release, the study concluded that cocaine elevates dopamine levels by releasing dopamine from reserve vesicles.

Cocaine Use Causes Dopamine Blunting

The dopamine-releasing effects of amphetamine and other stimulants and the dopamine-increasing effect of cocaine converge in studies that examine cocaine's effect on dopamine release. Based on such studies, a primary physiological effect of cocaine addiction has been determined to be decreased dopamine release in response to rewarding stimuli.

Figure 11: Change in binding potential (BP) of [^{11}C]raclopride before and after induced dopamine release in control and cocaine-addicted subjects

	Healthy Subjects (N=24)		Cocaine-Dependent Participants (N=24)		Group Differen
Functional and Anatomical Subdivision	Mean Change (%)	SD	Mean Change (%)	SD	(%)
Limbic striatum (ventral striatum)	-12.4	9.0	-1.2	7.3	11.2
Associative striatum	-6.7	5.7	-2.6	6.6	4.1
Precommissural dorsal caudate	-4.6	6.2	-2.8	7.8	1.8
Precommissural dorsal putamen	-8.7	7.0	-1.0	6.5	7.7
Postcommissural caudate	-6.9	7.8	-6.3	10.7	0.6
Sensorimotor striatum: postcommissural putamen	-14.1	7.8	-4.3	7.5	9.8
Striatum	-9.5	5.9	-3.0	6.5	6.5

Note: Adapted from Martinez, D. et al. (2007). Amphetamine-induced dopamine release: Markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. *The American Journal of Psychiatry, 164*(4), 622-629.

Martinez et al. (2007) compared controlled dopamine release in two different groups of volunteer subjects: 24 active cocaine users and 24 non-cocaine-addicted controls. All regions where [^{11}C]raclopride binding was examined were within the striatum, the center of dopamine activity. Figure 11 shows the percent change in binding potential (BP) of [^{11}C]raclopride before

and after application of amphetamine, used to induce dopamine release; "SD" is the standard deviation. BP is the ratio of ligands bound to receptors to free ligands; a lower BP indicates fewer ligands bound to receptors. Lower BP, as expressed by the negative results of every trial, indicated decreased binding of [^{11}C]raclopride to dopamine receptors: [^{11}C]raclopride was displaced from the receptors following amphetamine administration due to an increase in striatal dopamine levels (p. 1041). However, the decrease in BP was significantly greater in the controls than in either "cohort" of cocaine abusers, indicating a greater amount of dopamine release in control subjects. The study concluded that dopamine release in cocaine addicts was greatly diminished compared to that in non-addicts. A second study by Volkow et al. (2014) used nearly identical methods and came to the same conclusion; these results were not an isolated incident.

This is how cocaine addiction develops: repeated instances of cocaine use markedly increase dopamine levels. As time and usage progress, the brain adapts to higher dopamine levels in the striatum through physiological changes. The result of these changes is the blunting of dopamine release in response to rewarding stimuli. Drug-taking behaviors persist as the affected individual attempts to elicit the pleasurable response of a dopamine release, now diminished by the drug use that he or she continues to pursue.

Conclusion

Mapping out any brain activity is a complex and laborious task; dopamine pathways are no exception. It has taken numerous studies to pinpoint the location of dopamine action in the brain and to connect that action to its roles in pleasure, reward, and conditioning. The neural reward system, in which dopamine is the essential element to reward response, was first sequenced to the midbrain by Olds and Milner (1954), who determined that rats self-stimulate

this area of the brain more than other areas when left to their own devices. Subsequent research has specified the involvement of the VTA, the ventral striatum (including the NAc), and the dorsal striatum in dopamine pathways.

Dopamine pathways are connected by neurons containing dopamine receptors. As elucidated by Ritz et al. (1987), there are five types of dopamine receptor, categorized by their structure and function into two larger subgroups: the D_1-like receptors and the D_2-like receptors. While D_1, D_2, and D_3 receptors are all found within the areas of dopamine activity and all appear to have an influence in cocaine addiction, D_1 receptors appear to be the most significant (Karasinska et al., 2005).

As a neurotransmitter, dopamine functions by binding to its specific receptors on neurons and thereby transmitting a signal to that neuron. This signaling is mediated by action potentials, or electrical signals, transmitted the length of neurons. Amphetamine has a notable effect upon the action potentials generated by dopaminergic neurons; namely, it increases them. Administration of amphetamine has been shown to increase the rate at which dopaminergic neurons generate action potentials and the intensity of those action potentials, causing the neurons to release more dopamine (Covey et al., 2016). Amphetamine is therefore a highly useful drug in dopamine research because it induces dopamine release.

Cocaine, too, increases dopamine levels in the midbrain. By inhibiting the dopamine transporter, cocaine prevents normal uptake of dopamine and ensures that dopamine levels in the ventral and dorsal striata are elevated (Wu et al., 2001). Due to this effect, cocaine has long-term impacts upon the brain's ability to release and receive dopamine. Known as the blunted dopamine effect, the brains of those addicted to cocaine experience a much-decreased release of dopamine when stimulated (Martinez et al., 2007; Volkow et al., 2014).

The progression of cocaine addiction is clearly marked by neurobiochemical alterations dopamine pathways. It is unsurprising that dopamine, as the neurotransmitter most involved in the brain's reward system, also plays a key role in the effects of cocaine, an addictive drug associated with rewarding effects. The blunted-dopamine hypothesis explains that cocaine addiction persists due to the drug's long-term impact on dopamine pathways, i.e., its ability to reduce dopamine release. Cocaine therefore alters the brain's ability to perceive pleasure and reward, a change that impacts several aspects of the addict's life.

References

Covey, D. P., Bunner, K. D., Schuweiler, D. R., Cheer, J. F., & Garris, P. A. (2016). Amphetamine elevates nucleus accumbens dopamine via an action potential-dependent mechanism that is modulated by endocannabinoids. *European Journal of Neuroscience, 43*(12), 1661-1673. doi:10.1111/ejn.13248 http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=c9h&AN=116236397&site=eds-live

Di Chiara, G. & Bassareo, V. (2007). Reward system and addiction: What dopamine does and doesn't do. *Current Opinion in Pharmacology, 7*(1), 69-76. doi:10.1016/j.coph.2006.11.003 https://www.researchgate.net/publication/6624736_Di_Chiara_G_Bassareo_V_Reward_system_and_addiction_what_dopamine_does_and_doesn%27t_do_Curr_Opin_Pharmacol_7_69-76

Karasinska, J. M., George, S. R., Cheng, R., & O'Dowd, B. F. (2005). Deletion of dopamine D1 and D3 receptors differentially affects spontaneous behaviour and cocaine-induced locomotor activity, reward and CREB phosphorylation. *European Journal of Neuroscience, 22*(7), 1741-1750. doi:10.1111/j.1460-9568.2005.04353 http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=c9h&AN=18417942&site=eds-live

Martinez, D., Slifstein, M., Broft, A., Mawlawi, O., Hwang, D., Huang, Y., ... Laruelle, M. (2003). Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *Journal of Cerebral Blood Flow and Metabolism: Official*

Journal of The International Society of Cerebral Blood Flow and Metabolism, *23*(3), 285-300. Retrieved from http://journals.sagepub.com/loi/jcb http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=mdc&AN=12621304&site=eds-live

Martinez, D., Narendran, R., Foltin, R. W., Slifstein, M., Hwang, D., Broft, A., & ... Laruelle, M. (2007). Amphetamine-induced dopamine release: Markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. *The American Journal of Psychiatry*, *164*(4), 622-629. doi:10.1176/appi.ajp.164.4.622 http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2007-07328-017&site=eds-live

Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., & Caron, M. G. (1998). Dopamine receptors: From structure to function. *Physiological Reviews*, *1*(78), 189-225. Retrieved from http://physrev.physiology.org/content/78/1/189.short

Nutt, D. J., Lingford-Hughes, A., Erritzoe, D., & Stokes, P. A. (2015). The dopamine theory of addiction: 40 years of highs and lows. *Nature Reviews. Neuroscience*, *16*(5), 305-312. doi:10.1038/nrn3939 http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=mdc&AN=25873042&site=eds-live

Olds, J. & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology, 47*(6), 419-427. doi:10.1037/h0058775 http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=1955-06866-001&site=eds-live

Ritz, M. C., Lamb, R. J., Goldberg, S. R., & Kuhar, M. J. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science*, (4819), 1219-1223. Retrieved from http://www.jstor.org/stable/1699528?seq=1#page_scan_tab_contents http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edsjsr&AN=edsjsr.1699528&site=eds-live

Singer, B. F. & Robinson, T. E. (2014). Incentive-sensitization disease model of addiction. In *AccessScience*. McGraw-Hill Education. doi:10.1036/1097-8542.YB140377 https://www.accessscience.com:443//content/incentive-sensitization-disease-model-of-addiction/YB140377

Venton, B. J., Seipel, A. T., Phillips, P. E. M., Wetsel, W. C., Gitler, D., Greengard, P., … Wightman, R. M. (2006). Cocaine increases dopamine release by mobilization of a synapsin-dependent reserve pool. *Journal of Neuroscience, 26*(12), 3206-3209. doi:10.1523/JNEUROSCI.4901-04.2006 http://www.jneurosci.org/content/26/12/3206.full

Volkow, N. D., Tomasi, D., Wang, G., Logan, J., Alexoff, D. L., Jayne, M., & ... Du, C. (2014). Stimulant-induced dopamine increases are markedly blunted in active cocaine abusers. *Molecular Psychiatry, 19*(9), 1037-1043. doi:10.1038/mp.2014.58 http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=mdc&AN=24912491&site=eds-live

Washington, M. T. (2017). Dopamine. In AccessScience. McGraw-Hill Education. doi:10.1036/1097-8542.203330 https://www.accessscience.com:443//content/dopamine/203330

Wu, Q., Reith, M. A., Kuhar, M. J., Carroll, F. I., & Garris, P. A. (2001). Preferential increases in nucleus accumbens dopamine after systemic cocaine administration are caused by unique characteristics of dopamine neurotransmission. *The Journal of Neuroscience, 21*(16), 6338-6347. Retrieved from http://www.jneurosci.org/content/jneuro/21/16/6338.full.pdf http://ezproxy.etown.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2001-11079-012&site=eds-live