THE NEURAL MECHANISMS OF REWARD AND ADDICTION
- A Review of the Role of Dopamine in Cocaine Addiction

Bachelor Degree Project in Cognitive Neuroscience
Basic level 22.5 ECTS
Spring term 2018

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Between stimulus and response there is a space. In that space is our own power to choose our response. In our response lie our growth and our freedom.

- Viktor E. Frankl (Volkow & Baler, 2014)
Abstract
Cocaine is known for its severe addictive properties and still, there is no effective treatment for cocaine addiction. Cocaine is a powerful chemical substance. It enters the brain rapidly and cause abnormal high levels of dopamine. Dopamine is found to be the neural correlate for reward. Addictive drugs, such as cocaine, are reported to be rewarding and initially generate many dimensions of positive effects. However, repeated cocaine use are associated with both structural and functional abnormalities in several brain regions, especially in areas responsible for voluntary control. Loss of control gives way to compulsive consumption and craving for more cocaine stimulation. These neuronal changes and negative symptoms tend to occur gradually, while the tolerance increases. The addicted individual has to enhance the dose in order to obtain the desired effect, which is; becoming physically dependent of a substance. Also, dysregulation of reward circuitries causes decreased sensitivity to natural rewards leading to increased interest in cocaine-related reward stimulation. The abstinence usually last for long time, even years, after self-administration, which makes addicts highly sensitive to relapse. Up to date, effective therapeutic interventions and pharmacological treatments are limited. Neurostimulation techniques such as DBS have shown positive results in regulation of dopaminergic excitability. Though, more research in the complexity of dopamine and mesolimbic areas is well needed, in order to better understand the neural basis of cocaine addiction and be able to offer evidence-based treatments. This thesis will provide an overview of the neuronal impact of cocaine on the dopaminergic reward circuitries in the brain.

Keywords: neural communication, dopamine, reward, addiction, cocaine
Table of Contents

Abstract ........................................................................................................................................... 3

1. Introduction .................................................................................................................................. 5

2. Neural Communication ................................................................................................................. 6
   2.1 Neurons ................................................................................................................................... 7
   2.2 Glia Cells ................................................................................................................................. 7
   2.3 Synaptic Transmission ............................................................................................................. 8
   2.4 Neurotransmitters .................................................................................................................. 10

3. Reward Systems .......................................................................................................................... 13
   3.1 What is reward? ..................................................................................................................... 13
   3.2 Areas and Pathways ............................................................................................................... 14
   3.3 Phases of Reward ................................................................................................................... 14
   3.4 Conscious vs. Unconscious Reward ...................................................................................... 16

4. Cocaine Addiction ....................................................................................................................... 17
   4.1 Homeostasis .......................................................................................................................... 17
   4.2 Expression and Symptoms ....................................................................................................... 18
   4.3 Neural Basis of Addiction ....................................................................................................... 20
   4.4 Neural Changes ...................................................................................................................... 21
   4.5 The Cycle of Addiction ........................................................................................................... 22
   4.6 Drug Relapse .......................................................................................................................... 24
   4.7 Cocaine .................................................................................................................................. 25

5. Discussion ..................................................................................................................................... 28

References ......................................................................................................................................... 33
1. Introduction

Cocaine is one of the most prominent drugs of abuse, as well as the strongest pharmacological reinforcer ever discovered (Morrison, 2014). The World Drug Report (2017) observed that the production, trafficking, the number of users and reported drug overdose cases have increased markedly the recent years. Cocaine abuse has become a substantial public health problem, resulting in various social, psychological and medical problems. This illegal drug affects the brain rapidly by increasing the levels of dopamine and modify its receptors. Dopaminergic neurons are the most prominent in the brain and are highly involved in reward processes. Cocaine and rewarding stimuli activates the same dopamine circuitries, however, cocaine activates the brain more intensely and long-term use could lead to a disruption of the dopamine reward systems. But what is the actual role of dopamine in reward processes and cocaine addiction? How exactly does cocaine addiction impact the dopaminergic circuitries? The aim of this thesis is to answer these questions.

Millions of interconnected neurons in the central nervous system are well organized in order to generate the complex neurochemistry and behaviours of ours (Kandel, et al., 2013). Dopamine and its receptors are crucial for normal brain function and are involved in several important physiological processes, including reward. Reward and pleasure are essential for a normal extent of human wellbeing (Berridge & Kringelbach, 2008). Rewarding stimuli activate neural circuits, including dopaminergic mesolimbic circuitry, which primarily motivates us to maintain contact with certain environmental stimuli (Volkow & Morales, 2015). Food, sex and social interactions are examples of natural rewards in our everyday life (Berridge & Kringelbach, 2008). In contrast to drug-related reward, dopamine neurons decrease their response from natural rewards, and the motivation to continue intake is usually reduced as a result.

Initially, drug experimentation is usually a voluntary behaviour including pleasurable experiences; that is, it is rewarding. Persistent consumption, however, will cause dysregulation of the reward system stability and disturb the brain’s capacity for voluntary control and gradually change into abstinence symptoms of negative affect. Due to the drug’s pharmacological properties, it introduces molecular changes in mesolimbic structures, including nucleus accumbens (NAc), which promotes motivational behaviour for continued drug intake. These neural changes gradually alter various systems and psychological functions, and result in numerous negative symptoms of addiction such as increased tolerance, craving and drug dependence. Drug dependence refers to a state where systems in the brain adapt to the drug consumption and alters their reward set point, which leads to failure in maintaining
dopaminergic reward activity within an original range of reinforcement (Koob & Moal, 1997; Koob, 2001). This could even result in reduced interest and activated dopamine neurons as response to natural rewards.

It is clear that cocaine has negative mental and physical effects on our brain. However, the link between cocaine and dopamine, and its neurochemical consequences on the brain should be better understood of the general public. This essay could have potential relevance for the understanding of the complexity of dopaminergic communication and rewarding processes in relation to cocaine addiction, and possibly inspire the required research of eventual treatments.

Initially, neural communication will be explained in detail, in order to highlight the complexity of synaptic transmission, that is neurotransmitters and their signals. This will be of an importance for the overall understanding of the following sections of the thesis, since neurochemistry is the foundation for rewarding processes as well as addictive disorders. The reward circuitries, more specifically the mesolimbic pathway, will then be clarified and put in relation to dopamine, that is the primary neurotransmitter involved in reward processing. Following this, the thesis will present the neuronal aspects of addiction and cocaine. Cocaine influence the levels of dopamine in the brain and repeated consumption is associated with structural and functional changes in dopaminergic reward systems. Today, there is no effective treatments for cocaine addiction, but eventual treatments that require more research will be presented. In the end, the complexity of neural communication of reward circuitries is discussed. Also, the potent neurochemical consequences of cocaine addiction will be provided. Lastly, suggestions for future research are and its limitations are considered.

One final note; as many neuronal circuitries, the reward systems are regulated by numerous interacting brain-body signals, such as hormones and neurotransmitters. Dopamine often modulates other neurotransmitter systems in its neurochemical signalling. Since it is not possible to cover all molecular and cellular aspects involved in reward processing, this thesis will primarily be focusing on dopamine, dopaminergic neurons and their receptors in relation to reward and cocaine addiction.

2. Neural Communication

Neurons are the cells in the brain that receive, analyse and transmit information. They transfer information between each other, but also to non-neuronal cells such as those found in muscles, glands and organs (Gazzaniga, Ivry, & Mangun, 2016). The brain is built up of neurons (and glia, more on which below), more specifically \(10^{11}\) neurons, which are
organized into thousands of different types. However, neurons with similar functional properties can act differently depending on the way they are interconnected. The interconnections of neurons result in the complex behaviour of human beings (Kandel, et al., 2013). There are two primary classes of brain cells, namely neurons and glia cells, which will be briefly reviewed below.

2.1 Neurons

The structure of a neuron typically consists of four fundamental parts; a cell body, dendrites, an axon and presynaptic terminals. The cell body includes the standard mechanisms found in all human body cells, such as protein-and energy producing structures, DNA, cytoplasm and other intracellular organelles (Kandel, et al., 2013). Unlike other cells, however, neurons carry physiological properties beneficial for rapid processing and transmission of information.

The dendrites are responsible for receiving information from other neurons and can vary in structure depending on the type and location of a neuron (Gazzaniga, et al., 2016). The extended axon, on the other hand, transmits electrical signals, so-called action potentials, from the neuron to other cells. The action potential is an all-or-nothing signal, meaning that the signal either will occur or it will not, it is never a fluctuating process. The signal is triggered by a sufficient stimulus and is regenerated at regular intervals as it travels along the axon terminal. Longer axons are covered with a sheath of myelin, that is a fatty substance that insulates and thereby promotes the speed of action potentials. The presynaptic terminals are located at the end of the axon, and transmit the signal to the postsynaptic cells, i.e. the dendrites of neighbouring neurons (Kandel, et al., 2013). Most neurons are therefore both presynaptic and postsynaptic cells (Gazzaniga, et al., 2016).

Neurons are connected to each other by synapses. The spaces between neurons are referred as the synaptic cleft (Kandel, et al., 2013). Within the neurons, the transmission of information involves electrical changes and in the synaptic cleft information typically transfers with chemicals (Gazzaniga, et al., 2016).

2.2 Glia Cells

Glia cells are another type of cells in the CNS. In contrast to other cells in the CNS, glia cells are able to expand, i.e. both increase in number and alter in strength of connections. This developmental process, called gliogenesis, occurs not only during brain maturation, but also in adults. There are about 2 to 10 times more glia cells than neurons in the human brain. Glia cells differ from neurons both structurally and functionally. First, they do
not have the electrical properties that neurons do. Neurons are rather surrounded by glia cells (Kandel, et al., 2013), i.e. they work as structural support for the nervous system, but also e.g. help to form the blood-brain-barrier and constitute the myelin sheaths that are wrapped around the neuronal axons (Gazzaniga, et al., 2016). The CNS has three types of glia cells, namely astrocytes, microglia and oligodendrocytes, all of which will be described below.

According to Kandel, et al., (2013) astrocytes are generally thought to not be essential for information processing in the brain. They modulate neuronal activity by accumulating and releasing several ions and water both locally and at a distance, but also regulate the concentration of neurotransmitters by control the extracellular ion balance (Kandel, et al., 2013). However, this type of glia also constitutes the blood-brain-barrier, which separates the CNS from the vascular system in order to absorb molecules such as oxygen, carbon dioxide and important hormones. At the same time, astrocytes prevent bacteria and other microscopic substances, such as drugs and neuroactive chemicals, from entering the CNS. Furthermore, astrocytes are known for their synaptic formation and cell supporting properties (Kandel, et al., 2013). Relatively new findings (Schummers, Yu, & Sur, 2008) show that activation of astrocyte is able to modulate neural activity, and could therefore be hypothesized to directly or indirectly affect the reuptake of substances in the CNS (Gazzaniga, et al., 2016).

Microglia cells are first used when tissue is damaged or during any disturbances of the blood-brain-barrier. They remove damaged cells in the CNS (Gazzaniga, et al., 2016). It has been shown that microglia not only aim to responding to inflammation in the CNS (Parkhurst et al., 2013), they also play a crucial role when it comes to remodelling neuronal and synaptic functions in the healthy brain. During CNS development, microglia seem to be a key regulator in the refinement of immature synapses. Furthermore, microglia are involved in changes in strength of neuronal connections as well as plasticity processes throughout life (Parkhurst et al., 2013).

Oligodendrocytes are a highly specialised type of glia cells that create a myelinated sheath that covers the axon terminal, and are in this way promote insulation and thereby rapid signal transmission (Gazzaniga, et al., 2016). The number of layers of myelin depends on the size of the axon; larger axons receive thicker sheaths and generate stronger signals (Kandel, et al., 2013).

2.3 Synaptic Transmission

Synaptic transmission is the process by which neurons communicates with each other. About \(10^{14}\) to \(10^{15}\) synaptic connections are found in the human brain (Kandel, et al., 2013). The neuronal connections are highly specialized, although their synapses can be either
electrical or chemical. These two types of synapses are very different from each other. In electrical synapses, no synaptic gap separates the neurons. They contain gap junctions, which include physically connected pores formed by cytoplasm of the pre-and postsynaptic neurons. Electrical synapses are beneficial when signals have to be transmitted rapidly, and are mostly found in muscles with reflexive functions (Kandel, et al., 2013).

However, most of the synapses in the brain are chemical, relying on neurotransmitters for their function. Chemical synapses require an action potential from the presynaptic neuron in order to transmit the signal to the postsynaptic neuron. The arrival of the action potential at the presynaptic axon terminal leads to depolarization in the terminal membrane, which causes certain channels located in the neuronal membrane to open. The opening of these channels leads to a difference in voltage inside and outside the neuron which triggers vesicles to unify with the presynaptic membrane, thereby releasing the neurotransmitters stored within them (Kandel, et al., 2013). The vesicles protect the neurotransmitters from being damaged by enzymes (Julien, Advokat, & Comaty, 2014). Vesicles are highly concentrated in the axonal nerve endings. About 100 to 200 vesicles packed with thousands of neurotransmitters are transported though the presynaptic terminal and clustered at active zones of the presynaptic membrane. Active zones refer to the specific region of the presynaptic membrane that mediates neurotransmitter release. An action potential causes the vesicles to fuse with the membrane and release the neurotransmitters into the synaptic cleft, in order to interact with the receptors of the postsynaptic neuron (Kandel, et al., 2013). After discharging, the vesicles are generally recycled for new neurotransmitter uptake. In turn, this interaction triggers electrical changes in the membrane potential of the presynaptic neuron, which is crucial for the signal to carry further. The synaptic cleft is about 20 nanometres, which means that the chemical transmission occurs at a small distance. The neuronal signalling is therefore both fast and precisely directed. The active zones work as specialized release sites and are responsible for the focused and direct release (Kandel, et al., 2013).

The action of a neurotransmitter is not dependent on the properties of the neurotransmitters itself, but on the properties of the receptors located at the target neuron (Kandel, et al., 2013). Nevertheless, the effect of a neurotransmitter also depends on the connections of the neurons involved (Gazzaniga, et al., 2016). This means that the same neurotransmitter can have different effects due to the way it is released and received in the synaptic cleft (Kandel, et al., 2013). The ability to recognize specific neurotransmitters is what characterizes receptors (Julien, et al., 2014).
After the release has occurred, there are two ways to remove the neurotransmitters that are left in the synaptic cleft. They are either broken down by enzymes in the synaptic cleft or transmitted back into the presynaptic neuron to get repackaged for additional synaptic release (Julien, et al., 2014).

2.4 Neurotransmitters

This section will describe neurotransmitters in general, with a particular focus on dopamine. Kandel et al. (2013) highlight the complexity of how to comprehensively and precisely define neurotransmitters, since they are expressed different depending on how they are influenced of each other and other factors. Also, the definition has to be modified continually to meet new neurobiological information.

Neurotransmitters could be described as chemical substances which are released by a neuron and act on a specific target, which could be another neuron or an effector organ. A substance has too meet several criteria in order to be classified as a neurotransmitter (Kandel, et al., 2013):

1. It is produced in the presynaptic neuron.
2. It must be found within the presynaptic terminal and released in a sufficient amount to have a biological effect on the presynaptic neuron or effector organ.
3. When it is applied exogenously, it should have the same effect as when it is released by a neuron.
4. A specific mechanism generally exists to remove the neurotransmitter from the synaptic cleft (Kandel, et al., 2013).

More than 100 neurotransmitters have been identified, and classified into groups based on their different properties, that is biochemically and the typical effect they induce in the postsynaptic neuron (Gazzaniga, et al., 2016).

As mentioned earlier, the effect of a neurotransmitter depends on the postsynaptic receptors that receive the signal, but also on the connections of the neurons involved in the transmission. Neurotransmitters are classified into two groups based on their functional properties. Neurotransmitters that generally have an excitatory effect, i.e. increase the firing of neurons, include acetylcholine, catecholamine, glutamate, serotonin, histamine and some of the neuropeptides. Inhibitory neurotransmitters, i.e. those that decrease neuronal firing, usually include gamma-aminobutyric acid (GABA), glycine and some of the peptides. Most transmitters act in an either excitatory or inhibitory manner (Kandel, et al., 2013).

Drugs affect the neurotransmitters in different ways, and can behave as an agonists or antagonists. Agonistic drugs have a similar structure to a neurotransmitter and
mimic its action. Antagonistic drugs, on the other hand, binds to receptors to by block or dampen the neurotransmission. There are drugs that are similar to normal neurotransmitters that can act as false neurotransmitters by being packaged into vesicles and released in the synaptic cleft as if they were real neurotransmitters (Kandel, et al., 2013).

2.4.1 Dopamine and its Receptors

Understanding the effects of dopamine in the CNS is of great interest to neuroscientists (Gazzaniga, et al., 2016), since the dopaminergic neurons are the most prominent in the brain (Snyder et al., 1970). Abusive drugs that modify the levels of dopamine act as agonists and mimicking dopamine signalling which leads to very fast increase of dopamine and activity in the mechanisms responsible for reward, including NAc. The large and fast dopamine increase are sufficient in order to activate dopamine receptors in this area, and furthermore, to obtain reinforcing effects from the drug (Volkow & Morales, 2015; Kalivas & Volkow, 2005).

Catecholamine refers to a subgroup of neurotransmitters in the CNS including dopamine and norepinephrine. Dopamine is combined from an amino acid called tyrosine, which is converted into L-dihydroxyphenylalanine (L-DOPA). Norepinephrine is produced by the oxidation of dopamine. Many psychoactive drugs are affect the CNS by altering the neuronal action of dopamine and norepinephrine (Julien, et al., 2014).

Thus, dopamine is crucial for normal brain function and is involved in several important physiological processes and functions (Enyedy, Sakamuri, Zaman, Johnson, & Wang, 2003; Snyder, Taylor, Cotle, & Meyerhoff, 1970). Dopamine was recognized in the 1960s (Julien, et al., 2014). The circuits and functions of dopamine are usually investigated by different brain imaging methods, such as electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI), extracellular recording of dopaminergic firing activity as well as extracellular concentrations of dopamine (Dichiara & Bassareo, 2007).

Dopamine release sites are located closely outside the synaptic cleft (Dichiara & Bassareo, 2007). After release from the presynaptic terminals, dopamine diffuses in the extracellular fluid, connect to the pre-and postsynaptic neuron and introduces responses in the receiving neuron. Inactivation of dopamine appears primarily by reuptake into the presynaptic terminal where enzymes, such as monoamine oxidase, clears the neurotransmitter (Julien, et al., 2014).

Activation of dopamine receptors involves G proteins, which describes why all dopamine receptors belong to a large family of receptors called G protein-coupled receptors (Luttrell et al., 1999; Dichiara & Bassareo, 2007). Dopamine affects the postsynaptic neuron
trough six types of receptors, which are divided into two groups, D<sub>1</sub> type and D<sub>2</sub> type. D<sub>1</sub> receptors include two subtypes, namely D<sub>1</sub> and D<sub>5</sub>. D<sub>2</sub> receptors consist of four subtypes, namely D<sub>2A</sub>, D<sub>2B</sub>, D<sub>3</sub> and D<sub>4</sub> (Julien, et al., 2014). The classification of dopamine receptors is based on their biochemical, pharmacological and structural properties. Generally, the different subtypes of dopamine receptors vary when it comes to how sensitive they are to agonists and antagonists (Missale, Nash, Robinson, Jaber, & Caron, 1998).

The D<sub>2</sub> receptor seems to be a dominant dopamine receptor involved in the presynaptic regulation of firing rate, as well as synthesis and release of dopamine. However, Missale et al. (1998) claims that D<sub>3</sub> receptors play a complementary role in these presynaptic regulation processes. Effects of longer-lasting stimulation of D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> caused by drugs has been less investigated (Volkow & Morales, 2015). However, functions generated by activation of D<sub>4</sub> and D<sub>5</sub> receptors seems to be relatively limited (Missale et al., 1998).

As mentioned earlier, dopamine and its receptors are highly involved in reward circuitries and reinforcement processes in the brain, particularly activation of D<sub>1</sub>, D<sub>2</sub>, but also D<sub>3</sub> receptors. Alterations in dopamine receptor function result in significant changes in responses to natural rewards and addictive drugs (Missale et al., 1998; Kalivas & Volkow, 2005). Drugs act reinforcing by triggering dopaminergic neurons in NAc. D<sub>1</sub> stimulation in NAc is necessary to generate reward, whereas D<sub>2</sub> is not. However, both D<sub>1</sub> and D<sub>2</sub> stimulation produce maximal drug reward, which seems to occur when drugs reach fast peak concentrations, such as when cocaine is administered by smoking or intravenous injection (Volkow & Morales, 2015). Thus, dopamine receptors are of a direct interest for drug addiction research (Missale et al., 1998). However, Volkow, Wang, Fowler, Tomasi and Telang (2011) states that different molecular targets interact and are responsible for increased dopamine activity. The dopamine hypothesis refers to the fact that many opiates have receptors in dopaminergic pathways, either in parallel or along with dopamine synapses (Kandel, et al., 2013). For example, serotonin is shown to be important for temporal discounting of reward (Tanaka et al., 2007). As stated earlier, neurotransmitters can act differently due to the involved neurons, as well as the properties of the specific synapses and their receiving receptors (Kandel, et al., 2013; Gazzaniga, et al., 2016). Bur insofar as dopamine is the main neurotransmitter in rewarding circuitries and processes, this will be described in more detail in the following chapter.
3. Reward Systems

This chapter will explain the neurobiology of reward, that is the principal structures and pathways. Moreover, the three phases of rewarding processes and how reward is associated to dopamine will clarified.

3.1 What is reward?

Berridge and Kringelbach (2008) argue that pleasure is essential for a normal extent of wellbeing. Pleasant stimuli usually refer to rewarding stimuli or just rewards. Food, sex and social interactions are basic sources that generates pleasure, also called natural rewards (Berridge & Kringelbach, 2008). Animals tend to engage in several voluntary behaviours because they are rewarding, which means that those behaviours activate neural circuits that have as function to motivate the animal to maintain the contact with certain environmental stimuli (Kolb, Whishaw, & Teskey, 2016; Volkow & Morales, 2015), both in the present as well as in the future. Very likely, the animal experiences this neural activation as pleasant. In contrast to abusive drugs, repeated exposure of natural rewards in a healthy brain entails the dopaminergic neurons decrease to respond. When dopamine activity decreases, the motivation to continued intake reduces (Volkow & Morales, 2015).

The brain systems underlying reward were first discovered in 1954, in an electrical self-stimulation experiment on rats. The rats pressed a button, which generated stimulation to specific sites in the brain, thousands of times per hour until they were exhausted. When animals receive stimulation generated by natural rewards, dopamine release rapidly increases in areas where dopamine receptors are critically located, such as in NAc (Olds & Milner, 1954). The rat experiment showed that animals engaged in behaviour that did not generated any survival value, i.e. without any natural reward. This indicates that reward and pleasurable stimulation can help maintain nonadaptive behaviour, such as drug addiction. In the same way as natural rewards increase the levels of dopamine in NAc, addictive substances, such as cocaine, produce similar but more intense dopamine (Olds & Milner, 1954; also reviewed in Kolb, et al., 2016). Although reward processing involves an interplay of many neurotransmitters, much of the research on reward has focused on dopamine. Gazzaniga, et al. (2016) suggest dopamine to be the neural correlate of reward. Dopamine selectively increases the motivational process of reward, which is the experience of wanting, but does not directly affect the liking reaction. In addictive drugs, such as cocaine, dopamine generates intense levels of wanting. Still, dopamine-related drugs are reported to be pleasant (Berridge & Kringelbach, 2013).
3.2 Areas and Pathways

There are several structures and circuitries in the brain involved in reward processing, however, they are broadly distributed (Kandel, et al., 2013). Lateral hypothalamus and medial forebrain are two essential regions that stimulate the dopaminergic neurons that form the pathways of reward (Kolb, et al., 2016). These neuronal dopamine pathways are highly involved in various CNS functions, such as reward, affect, learning, impulse control, attention, working memory and voluntary movement (Snyder et al., 1970). There are four major dopamine pathways identified, including the mesolimbic pathway. The central mechanisms of the mesolimbic pathway of reward are dopaminergic neurons in the ventral tegmental area (VTA), NAc, medial prefrontal cortex and other forebrain structures (Kandel, et al., 2013; Lammel et al., 2008). VTA neurons are regulated by neurons from the brainstem (Kandel, et al., 2013). Dopamine neurons in VTA primarily projects the NAc (Volkow & Morales, 2015). Inhibitory GABA-ergic neurons activate in the NAc and ventral pallidum, and excitatory glutamatergic neurons stimulate the prefrontal cortex areas involved in the reward circuitry (Kandel, et al., 2013). Also, amygdala is highly interacted to dopaminergic structures within the mesolimbic pathway (Kalivas & Volkow, 2005).

3.3 Phases of Reward

Reward is not a unitary process, rather it includes multiple processes and neuropsychological subcomponents, which are all activated during several every day life activities. Primarily, there seem to be two aspects of reward, namely hedonic impact and incentive salience. Hedonic impact refers to the liking or pleasure of reward. Incentive salience refers to the wanting or desire process of reward and include both motivational and perceptual features, such as reward-associated predictions and cues (Berridge, 1996). Additionally, Berridge and Robinson (2003) argue for the existence of a further learning component of reward. Hence, liking is the actual pleasure, wanting is the motivation, and learning combines representations, associations and predictions of future experiences based on previous pleasurable experiences (Berridge & Kringelbach, 2008). These three processes of reward will now be explained in more detail.

3.3.1 Wanting

Contradictory to the liking component of reward, the process of wanting is mainly influenced by dopamine (Berridge & Robinson, 2003). Investigating the wanting component of reward is highly important in order to better understand the mesolimbic pathway of reward. The wanting component is the motivational process, since manipulation of dopamine systems changes the motivational behaviour. Berridge and Robinson (2003) argue that cognitive
wanting refers to an experienced subjective desire, based on sensory information about the wanted source of reward. Motivation is the force to get to a reward and maintain the contact with reinforcing stimuli (Berridge & Robinson, 2003).

### 3.3.2 Liking

Dopamine, which has often been correlated to pleasurable experiences, seems to be insufficient for generating a liking reaction after all. Changes in dopaminergic regions, such as NAc and striatum, do not affect the expression of liking (Berridge & Robinson, 2003). Dopamine activation in NAc fails to increase the reported liking reaction, but rather seems to improve the motivational process of reward. In other words, dopamine does not generate immediate pleasure, and is therefore not perceived as a pleasure neurotransmitter (Berridge & Robinson, 2003; Berridge, 2006). In fact, the mesolimbic dopamine pathway seems to be unable to change hedonic reactions to liking experiences directly (Berridge, 2006). This is consistent with results from a study on Parkinson’s disease patients using electrogustometer and subjective rates of intensity and pleasantness. Thus, dopaminergic dysfunctions in Parkinson’s patients, the subjects reported having normal ratings of pleasure from rewarding stimuli (sweet food), and did not differ from the control group (Sienkiewicz-Jarosz, 2005). Accordingly, dopamine mesolimbic neurotransmission is related to wanting processing, but not necessarily liking processing, in rewarding stimuli such as drugs (L-dopa) (Evans et al., 2006; for similar findings, see Leyton, Casey, Delaney, Kolivakis, & Benkelfat, 2005).

However, rewarding stimuli that is liked is often also wanted. Liking and wanting are generally connected and often neurally activated together, but dissociable in the way that they have different neural substrates (Berridge & Robinson, 2003). There seems to be a network of hedonic hotspots in subregions of the brain, more specifically located in NAc, ventral pallidum, in some forebrain and limbic cortical regions, but also in deep brainstem areas. These hotspots are activated by opioids, which have the special capacity to increase liking, if the activation occurs within the hotspots (Berridge & Kringelbach, 2013).

### 3.3.3 Learning

Many different systems in the brain are responsible for learning processing, including hippocampus, PFC and amygdala (Volkow & Morales, 2015). Alterations in some of these systems might lead to changes in responses to rewarding stimulation. Learned responses involve some knowledge about the relationship between stimuli and actions, in order to make reward predictions, anticipatory responses, as well as guidance for goal-directed actions. Learned knowledge can be either conscious memories or more habitual activities. The features of learning can involve just stimuli or both stimuli and responses (Berridge & Robinson, 2003).
Early in the process of learning, dopamine plays a crucial role (Saddoris, Sugam, & Carelli, 2016). Dopaminergic neurons are found to respond to reward-predictive stimuli and associated cues (Dichiara & Bassareo, 2007). When dopamine signalling is sufficiently great to activate D₁ in NAc, it can induce associative learning, also called *conditioning*. Environmental and contextual stimuli can be associated, and thereby conditioned, with rewards such as drugs. Repeated exposure of certain stimuli will trigger dopamine neurons in the VTA and lead to increased dopamine activity in NAc. Increased dopamine activity triggered by conditioned stimuli are suggested to reflect expectations of received reward. Dopamine stimulation of D₁ receptors produces the expectation of rewarding stimuli, whereas dopamine stimulation of D₂ receptors more likely maintains the motivation required to obtain and consume the reinforcing effect. Interestingly, when the dopamine concentration starts to decrease after stimulation, D₂ are predominantly stimulated. Slowly uptake of dopamine trough D₂, is not reported to be as rewarding as stimulation of D₁ and D₂ at the same time, which occurs during fast peaks of dopamine concentrations (Volkow & Morales, 2015).

The three components of reward could also be described in a “cycle of pleasure”. The cycle of pleasure involves three phases that are associated with appetitive, consummatory and satiety phases. The process of wanting seems to take place in the appetitive phase, liking dominates during the consummatory phase and learning processing can occur throughout the cycle (Rømer, Whybrow, & Kringelbach, 2015). Although researchers often separate these components, interconnected and distributed circuits in the brain allow the different components of reward to constantly interact with each other within the process of reward (Berridge & Robinson, 2003).

### 3.4 Conscious vs. Unconscious Reward

One fundamental distinction concerning the different phases of reward is between the liking and motivational consequences. This implicates that the processes of reward are not necessarily experienced subjectively, which means that the brain is able to react to rewarding stimuli without subjective awareness of either the stimuli or the actual pleasurable reaction (Berridge & Robinson, 2003). Some of our brain activity does not have access to conscious introspection, and some unconscious activity is connected to hedonic regions and may lead to pleasurable reactions. Nevertheless, unconscious activity is shown to be important for controlling our behaviour (Berridge & Kringelbach, 2008). Winkielman, Berridge and Wilbarger (2005) investigated properties of unconsciously triggered affective reactions and how they influence behaviour, interact with conscious pleasurable feelings, as well as motivational processes. They investigated the effects of happy versus angry face expressions...
on pouring and consumption of beverage, but also the perception on beverage value and reported conscious feelings. First, the participants were instructed to rate their motivational state (thirst and hunger), then they were exposed to series of happy, angry and neutral faces. Lastly, they received a sweet drink (hedonic stimulus). They discovered that reactions to affective stimuli are always unconscious, but alterations in subjective experience are not always needed for affective reactions to take place and influence the evaluation of following events. I.e. they found that changes in behaviour, altered desire, and rating values for stimuli, without the participants reporting any subjective awareness of emotional changes (Winkielman, et al., 2005). Similarly, people suffering from drug addiction could work to self-administer drugs even in low doses where no subjective effect or autonomic reaction are reached (Berridge & Kringelbach, 2008). Hence, objective measures of affective reactions are as useful as subjective measures for analysing the circuitries of reward (Berridge & Kringelbach, 2013). Neurobiological studies and analyses of reward in general are highly important since they provide understanding in a variety of psychopathologies, such as drug addiction, which is the topic of the next chapter (Berridge & Robinson, 2003).

4. Cocaine Addiction

This section will provide an overview of the science of addiction, as a neural and physical disorder. In addition, cocaine, which influence the levels of dopamine in the brain, will be explained in more detail. To date, there is no effective treatments for cocaine addiction (Siciliano, et al., 2016). Initially, dysregulation of reward homeostasis in relation to chronic drug use will be described.

4.1 Homeostasis

*Homeostasis* refers to when an organism maintains balance within all of its physiological, cognitive and emotional systems, including the mesolimbic reward system (Koob & Moal, 1997; Koob, 2001). Homeostasis can be described as the body’s autonomic self-regulating process for maintaining parameters within a range critical for survival (Koob, 2001). Environmental aspects that challenge homeostasis are managed with counter-actions, such as stress and drugs. Parameters such as body temperature are held more or less constant, whereas parameters such as stress hormones vary. *Allostasis*, on the contrary, refers to the complex process of physiological attempts to alter the internal parameters outside the normal range of homeostasis in order to handle with the environmental stressors, and thereby maintain stability (Koob, 2001). For example, to maintain apparent reward stability by altering the rewarding mechanisms in the brain. If the system remains challenged, the process of allostatic
state will cost enormous amounts of energy to maintain stability at the pathological state, where the system is highly vulnerable to further external and internal stressors (Koob & Moal, 1997). This is the beginning of the cycle of addiction (Koob & Moal, 1997; Koob, 2001).

When the organism has reached a point of dysregulation where it cannot recover by its own organismic resources and CNS mechanisms, it is usually considered as spiralling distress that causes illness (Koob & Moal, 1997). Dysregulation of the mesolimbic reward system may lead to loss of control, compulsive drug intake, and, eventually, drug addiction. The reward system is regulated by numerous interacting brain-body signals, such as hormones and neurotransmitters. When drug intake become chronic, the systems adapt and alter their set point of homeostasis, where drug withdrawal could create a state of distress and unpleasantness, i.e. a new stabilized level of activity far outside the range of homeostasis – an allostatic state of chronic arousal. Chronic drug use would, in other words, lead to changes in drug reward set points and a failure for dopamine to maintain reward activity within the homeostatic range (Koob & Moal, 1997; Koob, 2001)

4.2 Expression and Symptoms

Substance addiction refers to the use of drugs in which the individual relies on the drug chronically and excessively, and allows it to take a central role in one’s life (Parekh, 2017; Kolb, et al., 2016). A substance of abuse is not consumed for a medical purpose, it could be illegal and is very likely harmful for the abuser. The reinforcing and euphoric qualities of addictive drugs are thought to underlie their abusiveness potential, and these rewarding qualities seems to be partly due to the increase of dopamine release in structures responsible for reward (Jentsch & Taylor, 1999). Dopamine is considered to be crucial for the rewarding effects generated by addictive drugs, and that is why such drugs are consumed by humans (Gazzaniga, et al., 2016; Volkow, et al., 2011).

The correlation between dopamine and addictive drugs was discovered in the 1970s (Dichiara & Bassareo, 2007). Substances that increase synaptic dopamine, do so by different pharmacological mechanisms. Psychostimulants, including cocaine and amphetamine, act on presynaptic dopaminergic neurons in different ways. Amphetamine enters the presynaptic terminals in order to affect the storage vesicles of dopamine (Kandel, et al., 2013). Cocaine, on the other hand, binds to and blocks the presynaptic dopamine transporters. Dopamine transporters, placed on the presynaptic neuron, reuptake dopamine in the synaptic cleft for further synaptic release. Blockage of dopamine transporters means that the dopamine cannot re-enter the presynaptic neuron. This causing abnormally high levels of dopamine to be left in the synaptic cleft, and leads to an hyperactivation of dopamine in the postsynaptic neuron
Chen et al. (2006) investigated the role of dopamine transporters in cocaine reward by using a mouse, whose dopamine transporters are functional but insensitive to cocaine. This mouse model is unique and designed to separate the role of dopamine transporter from the roles of norepinephrine transporter and serotonin transporter in biochemical and behavioural effects of cocaine abuse. The results from this study support that inhibition of dopamine transporter in the mesolimbic dopaminergic system plays a critical role in rewarding and addictive features of cocaine and other abusive drugs, since mice with functional but cocaine-insensitive dopamine transporter did not generate rewarding effects as response to cocaine stimulation (Chen et al., 2006; Kandel, et al., 2013).

As mentioned earlier, addictive drugs, including cocaine, generate reward activation in the brain, which leads to willing and repetitive consumption. In contrast to natural rewards, drugs are much more likely to produce a loss of control and compulsive patterns of self-administration. Repeated use of addictive drugs continue to increase dopamine stimulation during consumption, which sustains the motivation and progressively increases the desire and craving for the drug. There is no satiety phase (Koob & Moal, 1997; Volkow & Morales, 2015). Due to drug’s pharmacological properties, they introduce molecular and cellular changes that promote motivational behaviour for continued drug use. Hyman, Malenka and Nestler (2006) state that abnormal plasticity of the mechanisms of reward are associated with drug abuse, which indicates that dopamine plays an important role in drug related disorders, such as addiction.

Drug abuse is a behaviour that seems to emerge gradually and become more and more difficult to control (Kandel, et al., 2013; Volkow & Morales, 2015). Initially, drug experimentation is usually a voluntary behaviour, while continued consumption disturbs the brain’s function of self-control over drug-taking (Volkow & Morales, 2015), but it also becomes threatening toward one’s health and ability to function in general. Individuals who abuse drugs may develop addiction (Kandel, et al., 2013), which is described as the core behaviour of people who misuse substances. In addiction, the individual has developed a tolerance, and must increase the dose in order to obtain a desired effect, i.e. become physically dependent on the drug (Kolb, et al., 2016). Addiction includes maladaptive patterns of substance misuse, i.e. repetitive use of the substance, causing distress and several other problems for the individual suffering from the addictive disorder (Morrison, 2014).

Many addictive drugs, including cocaine, produce psychomotor activation in some part throughout their dose range. This means that the abuser feels energetic and experiences control after certain levels of consumption. This common effect of different
substances has led to the hypothesis that all addictive drugs act on the mesolimbic dopamine pathway by increasing activation in this system. Other drugs that do not seem to be as addictive rather decrease mesolimbic activity (Kolb, et al., 2016).

As stated earlier, reward circuitries are responsible for activity generated from pleasurable stimuli, such as eating, having sex and socially interacting with other people. Since such neural activity involves the recreational use of addictive substances, mesolimbic reward circuitry is considered to be the substrate for addiction as well as for natural sources of pleasure (Julien, et al., 2014; Koob & Moal, 1997). Furthermore, lesions in the mesolimbic dopamine neurons reduce the rewarding effect of psychostimulants, such as cocaine (Jentsch & Taylor, 1999).

Understanding why some people are more vulnerable to addictive disorders is very challenging (Volkow, et al., 2011). The fact is that, most people who use drugs do not become abusers or addicted. There are individual differences in one’s response to a particular substance, due to factors like genetics, history of drug use, body size, age, brain development, metabolism, stress and sensitivity to different drugs (Koob & Moal, 1997; Volkow, et al., 2011; Kolb, et al., 2016). Larger people are usually less sensitive to substances than smaller individuals due to their greater volume of body fluid. Older individuals seem to be twice as sensitive than younger people because of their less effective barriers to absorption and metabolism (Kolb, et al., 2016), as well as processes for eliminating substances from their body. Women may be about twice as sensitive as men due to average body size and hormonal dissimilarities. However, the same individual can respond to the same drug in different ways at different times (Kolb, et al., 2016). Volkow and Morales (2015) state that individuals with genetic vulnerabilities affected by chronic stress or other psychiatric conditions, but also those who misused drugs during early youth, run a greater risk to develop compulsive behaviours typical for addiction. There seems to be critical periods for addiction onset. More specifically, the neurodevelopment of regions involved in motivation, self-control and impulsivity occur in adolescence, and are shown to be vulnerable for chemical impacts (Chambers, Taylor, & Potenza, 2003).

4.3 Neural Basis of Addiction

There seems to be multiple brain systems underlying the neurobiology of addiction. When individuals first consume a drug, it activates corticical structures in prefrontal areas of the brain, more specifically regions responsible for cognitive choice, evaluation and decision making, also called executive functions (Kolb, et al., 2016). Changes in executive areas are shown when giving drugs that affect dopaminergic transmission (Jentsch & Taylor, 1999).
When such a drug is consumed, it activates opioid systems in the brainstem, responsible for liking and pleasure experiences. Cues associated with drug-taking activate dopaminergic systems in the mesolimbic pathway, which are the neural correlates for motivation and wanting processes (Kolb, et al., 2016), and seems to be crucial for reward generated by drugs. Dopamine also underlies the conditioned activation that triggers craving, which is similar to wanting and usually very intense in addicted individuals (Volkow, et al., 2011).

The development from controlled to compulsive drug intake are associated with changes to the striatal subregions, such as NAc, involved in reward processing (Volkow & Morales, 2015). Within the mesolimbic pathway, midbrain neurons signal basal ganglia structures, further on to the frontal cortex and the limbic system neurons. Dorsal striatum is a region in basal ganglia that is believed to be responsible for conditioning of drug-related cues. Repeated drug-taking and activation of this region forms a habit (Kolb, et al., 2016; Volkow & Morales, 2015), which entails a lack of voluntary control. Dopamine-triggered conditioned drug responses and habits may underlie the compulsive drug consumption (Volkow, et al., 2011). Loss of conscious control and decision making gives way to the craving aspects of addiction. Habitual users continue to abuse drugs even when it does not generate any pleasurable experiences anymore (Kolb, et al., 2016).

In a review article, Robinson and Berridge (2008) describes the wanting-and-liking theory, since the processes of wanting and liking occur in different brain systems. This theory suggests that the initial experience of a drug, when it affects the brain areas associated with pleasure, is the proposed road to drug addiction (Robinson & Berridge, 2008). This theory is applicable to many everyday life situations, not least to cues of human basic sources of pleasure, namely food, sex and social interactions. We tend to eat when we are in situations where others eat, and do not necessarily experience that much pleasure from eating every time (Kolb, et al., 2016).

4.4 Neural Changes

In the long run, drugs change the brain in both complex and persistent ways. These molecular and cellular changes alter various psychological functions, and result in numerous negative symptoms of addiction (Robinson & Berridge, 2008). When a drug is exposed in the CNS over a longer period of time, it creates long-term alterations in the properties of the neurons and their receptors, as well as in the function of neural circuits (Julien, et al., 2014). These alterations occur gradually and could lead to complex behaviours characterized as addictive symptoms, such as increased tolerance, dependence and craving. Thus, neuronal changes as a result of chronic drug exposure are related to addictive behavioural
changes (Nestler & Aghajanian, 1997). The pharmacological mechanisms of the actions of different drugs affect the neuronal changes caused by repeated drug use. Drugs, such as cocaine, that act on dopamine trigger several forms of neuroplasticity, which may result in weakening or strengthening of connectivity within dopaminergic reward systems, such as VTA, NAc, prefrontal cortex and amygdala (Volkow & Morales, 2015; Siciliano, Fordahl, & Jones, 2016). Amygdala share anatomical similarities with the NAc (Dichiara & Bassareo, 2007). The interaction between amygdala, VTA, NAc and prefrontal cortex have been demonstrated by neuroimaging studies reviewed in Kalivas & Volkow (2005) when healthy subjects been exposed to natural rewarding stimuli. Amygdala consists of several basal forebrain structures and have showed selective activation of dopamine as response to most of the addictive drugs (Koob & Moal, 1997).

4.5 The Cycle of Addiction

As mentioned earlier, addictive drugs such as cocaine initially generate reward and positive feelings that generally merge to anxious, illness and other negative feelings. To cope with the negative symptoms, abusers consume the drug again to alleviate these symptoms and the destructive circle goes on (Volkow, et al., 2011). At first, the user may experience pleasure from the drug’s effect, but also like to take it within a given social context. After repeated use, the expression of liking decreases as the tolerance increases. At this stage, a higher dose is needed to reach the same liking levels as reached initially. This theory also states that addiction primarily leads to hypersensitivity to the motivational effects of drugs and drug-associated stimuli, i.e. compulsive seeking and desire of abused drug (Robinson & Berridge, 2008). This could explain why addicts tend to be particularly motivated to consume drugs when they are in associated contexts, such as the environment and the people within the context, i.e. the availability of the entire drug-taking experience. These associated cues can come to induce incentive salience and work as triggers for dopaminergic systems and, thereby, drug-taking behaviour. A stimulus that is linked to a reinforcer is able to itself increase dopamine in striatum (NAc) (Robinson & Berridge, 2008; Jentsch & Taylor, 1999; Volkow, et al., 2011; Siciliano, et al., 2016).

Volkow et al., (2006) presents results that support the hypothesis that cocaine-associated cues increase dopamine in the dorsal striatum when exposed for addicted subjects. They tested 18 cocaine-addicted subjects by using position emission tomography (PET) and a dopamine D2 receptor radioligand that is sensitive to competition of endogenous dopamine. The participants were tested two days, one day during presentation of neutral video and one day during presentation of cocaine-associated video. Cocaine Craving Questionnaire (CCQ)
was obtained before and at the end of videos to evaluate the cocaine craving. The PET scans were started as soon as the ligand was injected and obtained 20 scans at 54 minutes. The videos were started ten minutes before injection and continued for thirty minutes after. The results showed a relation between cocaine craving and increased dopamine activation in dorsal striatum, involved in selection and initiation of actions, but also habit learning. The dopamine activity correlated with rated subjective experience of desire and craving. The more the dopamine increased, the greater the desire for cocaine (Volkow et al., 2006; Volkow, et al., 2011). Motivational and desirable aspects of addiction are powerful forces. It makes addicts do what they have to do, as well as go where they have to go, to get the drug, even if it requires actions and engagements that never have been performed before (Robinson & Berridge, 2008).

Cocaine abusers are shown to have reductions in dopamine release and D₂ in striatum (Volkow & Morales, 2015). Reductions in striatal D₂ receptors are correlated with decreased metabolism in several subcortical and frontal areas, including orbitofrontal cortex and prefrontal cortex. These areas are involved in incentive salience, inhibitory control, emotional processing and decision making, also called executive functions. Low levels of D₂ and abnormal regulation of dopamine in these regions could underlie an addict’s compulsive drug administration and reduced emotional regulation (Volkow, Fowler, Wang, Baler, & Telang, 2009; Volkow & Morales, 2015; Kalivas & Volkow, 2005). Moreover, impairments in the orbitofrontal cortex and cingulate gyrus are associated with obsessive and compulsive behaviours (Volkow, et al., 2009), which characterizes addiction. Additionally, higher levels of D₂ receptors in the striatum are correlated with subjective ratings of lower pleasantness (Volkow, et al., 2009). This suggests that higher levels of D₂ receptors lead to higher metabolism in involved areas and may protect against addictive symptoms such as inhibitory voluntary control and self-administration (Volkow, et al., 2009). However, cocaine activates D₂ receptors which inhibit the dopamine activation. This could explain why the intensity of cocaine rush is reduced after frequent administrations, whereas the motivation for continued cocaine-intake stays the same (Volkow & Morales, 2015).

Reduction of dopamine signalling after repeated drug use could also help to explain the decreased sensitivity to natural reinforces in addicted individuals. However, drugs are much more powerful at affecting dopamine-regulated reward systems than natural rewards are, and are therefore still able to activate inhibited reward circuits. This may lead to decreased interest and value for natural rewards (Garavan et al., 2000; Kalivas & Volkow, 2005) and increased seeking for drug stimulation in order to temporarily activate these reward circuits, not necessarily to get high but rather to feel normal, i.e. obtain a normal extent of reward and
pleasure within its modified homeostatic range (Volkow, et al., 2009; Volkow & Morales, 2015).

In an EEG study by Parvaz et al. (2012) 35 subjects, who met DMS-IV criteria for current cocaine use disorder, were tested in reward-related information processing. Urine test divided this sample into two subgroups, namely those who tested positive (CUD+, n=21) and those who tested negative (CUD-, n=14) to cocaine. The CUD+ group reported higher frequency and more recent cocaine use as well as higher craving symptoms than CUD-. The study also included 23 healthy controls. All the subjects completed a reward processing task in a laboratory which included six blocks of “Go” and No-go” trails. Subjects were instructed to response on stimulus by press a button and received money (rewarding stimulus) for correct responses. They could obtain up to $50 in their performance. EEG electrodes received signals showing that CUD- had the lowest amplitudes, but also task accuracy. This indicates that chronic drug use is associated with lower sensitivity to rewarding stimuli, in this case money. Moreover, these results support the hypothesis that cocaine may be administered in order to cope with cognitive and emotional disruptions in reward circuitries, including decreased sensitivity to non-drug rewarding stimuli which is a consequence of long-term cocaine use. However, these results should be compared to longitudinal studies in order to allow generalization to longer abstinence periods generated by cocaine addiction (Parvaz et al., 2012).

4.6 Drug Relapse

Addicted individuals usually find it hard to reduce drug abuse, even if they desire to do so (Robinson & Berridge, 2008). Reduction of drug abuse often includes abstinence symptoms of negative affect, such as dysphoria, anxiety, irritability and depression, which are considered to be motivational behaviours in nature (Koob & Moal, 1997).

Reduced dopamine activation in the mesolimbic reward system has been reported after removal of addictive drugs, which could support theories arguing for the development of anhedonia (lack of pleasure) after drug withdrawal (Dichiara & Bassareo, 2007). Furthermore, a desire to avoid a state of anhedonia might contribute to the motivation to resume a drug-seeking behaviour and relapse to drug-taking (Jentsch & Taylor, 1999; Koob & Moal, 1997). Addicts are usually very vulnerable to relapse, even after abstinence (when the drug is no longer self-administered) symptoms have disappeared (Robinson & Berridge, 2008). Addiction is influenced by unconscious cues conditioned by the drug and its context, but also several neural changes in the brain. Nevertheless, non-habitual individuals are highly vulnerable to relapse (Kolb, et al., 2016). Volkow, et al., (2009) notes that exposure to conditioned cues is the key reason for drug relapse. It increases dopamine in NAc and dorsal striatum, and is correlated
with drug-seeking behaviour. Moreover, even when addicts avoid contextually associated drug cues, motivation could have a spill-over effect on other rewards, such as food and sex (Robinson & Berridge, 2008; Koob & Moal, 1997). Although dopamine activation in the mesolimbic pathway is not related to pure distinction between reward and hedonia, this circuitry is highly important to better understand different motivational stimuli and our behavioural responses (Jentsch & Taylor, 1999).

4.7 Cocaine

Cocaine is one of the most prominent illegal drugs of abuse (Nestler & Aghajanian, 1997). According to DSM-5 (Morrison, 2014), cocaine might be the strongest pharmacological reinforcer ever discovered. Repeated cocaine use is associated with both structural and metabolic abnormalities in several regions in the brain, particularly frontal areas responsible for executive functions (Hester, 2004). In animal studies, the animals prefer cocaine over food, water and sex, and will to use it again and again until death. People consume cocaine by snorting, injecting or smoking it (Morrison, 2014). The speed that the drug enters the brain underlies its reinforcing effects. When cocaine is entering the brain rapidly (smoked), it generates a more intense rush than when it is entering the brain more slowly (snorted) (Volkow, et al., 2011). Cocaine are metabolized very slow in the brain. It can be detected in the urine up to two weeks and in the hair for up to three to four months after initial use in chronic abusers (Julien, et al., 2014).

Cocaine induce abnormal high levels of dopamine in the synapses of the CNS. Since dopamine signalling is important for reward encoding, chronic use of cocaine may disrupt normal rewarding processes (Saddoris, et al., 2016). The fact is, even a single cocaine dose has the capacity to trigger an upregulation of the dopamine transporter on the presynaptic neuron, which can last for a month. This indicates that not only repetitive cocaine use can cause modulations in dopaminergic neurons, but even after one dose there is a decrease in dopamine in the synapse. Thus, even acute cocaine use may lead to craving and drug-seeking behaviour (Julien, et al., 2014; Kalivas & Volkow, 2005).

About 60-77 percent of all dopamine transporters are blocked by doses of cocaine commonly abused. Blockade of the dopamine transporter increases the extracellular levels of dopamine and, thereby, prolong the action of it within the synaptic cleft. Increased stimulation of dopamine in NAc and other dopaminergic reward structures seem to be responsible for the initial euphoric symptoms of cocaine (Julien, et al., 2014; Siciliano, et al., 2016). Studies using PET have shown that cocaine conditioned cues, in this case videos of subjects consuming cocaine, significantly increase dopamine in dorsal striatum. Activity in dorsal striatum are
associated with craving and drug-seeking behaviour (Volkow et al., 2006). This region is also involved in habit learning and are most likely effect the strengthening habitual cocaine-addictive behaviour (Volkow, et al., 2011).

The symptoms of cocaine consumption typically include increased alertness, self-confidence and sexual desire (Morrison, 2014), but it also generate more physical symptoms such as increased blood flow, body temperature and blood glucose. Pupils dilate, appetite is reduced and sleep is prevented (Julien, et al., 2014). These symptoms usually least for some minutes before it develops to dysphoria and usually intense craving for more of the substance. Motivation becomes directed toward one goal; getting more cocaine (Morrison, 2014). However, the desire is usually greatest when the addicted person is maximally high (Kolb, et al., 2016). Other symptoms of addiction that could be increased are willingness to take risks, violence, aggression, delusions and haptic hallucinations as well as increased sensory awareness and anxiety (Morrison, 2014; Julien, et al., 2014). After long-term use, the positive feelings normally reduce and the negative completely takes over (Morrison, 2014).

The tolerance for the euphoric effects develops very quickly and may lead to a continuous cocaine rush lasting for hours. The abuser may go from intranasal to injection or inhalation methods, in order to receive a more intense euphoric rush as the tolerance develops (Julien, et al., 2014). Other long-term complications from cocaine consumption could be loss of grey matter in several brain regions. Ersche et al. (2011) used magnetic resonance imaging (MRI) to scan the brains of 60 healthy individuals and 60 chronic cocaine abusers. They found that the longer one had been abusing cocaine, the greater was the loss of grey matter in cingulate and frontal cortex, motor areas, temporal regions, insula and cerebellum (P=>0.001). The volume of grey matter loss was also related to greater compulsive and impulsive cocaine-taking behaviour (Ersche et al., 2011).

Most cocaine-related studies are based on animal models, where subjective self-reports are not possible. Another study on the human brain by Risinger et al. (2005) presents a naturalistic human model of self administration where they use neural activation from fMRI combined with real-time subjective self-reports in order to better understand cocaine-induced neural activity in relation to subjective effects of cocaine use.

Six males meeting DSM-IV criteria for cocaine use disorder, all exclusively and non-treatment seeking cocaine users, participated in this study. The subjects were informed of the danger of cocaine use, offered full description of the study and provided written informed consent. The subjects were self-administered cocaine intravenously by press a button during fMRI. For subject’s safety reasons, cocaine was limited to one dose per five minutes and up
to six injections per hour. Also, electrocardiogram (EKG), heart rate (HR) and blood pressure (BP) were measured continuously. During cocaine administration session, the subjects were instructed to rate their current level of high, rush, craving and anxious once every minute throughout the experiment (Risinger et al., 2005).

The participants self-administered an average of 4.5 cocaine injections per one-hour scanning session. Three of six subjects took all six doses within the first 35 minutes. Changes of cardiovascular parameters were greatest following the first cocaine injection. Rated high correlated with neural activity in limbic and mesocortical areas, and was decreased before and increased after the first four cocaine injections. Craving correlated with activity in NAc, anterior cingulate (AC) and other forebrain areas, and increased before and decreased after administration. Activation of these areas correlated negatively with high. Also, pre-injection craving tended to decrease after each injection (Risinger et al., 2005).

Results from this study support drug-seeking and self-administration behaviour in cocaine addicted individuals. It shows that the experience of high rapidly decreases after repeated doses. In contrast, craving reported increase up to the point of injection and decrease immediately after administration. However, as mentioned earlier in this thesis, the different components of reward, including wanting (craving) and liking (high), are not completely separate from each other and are impossible for subjects to disentangle during intense stimulation of cocaine (Risinger et al., 2005).

4.7.1 Eventual Treatments

Cocaine addicts are highly prone to relapse. Abstinence often lasts for a long time, even years, after cessation of cocaine use (Kalivas & Volkow, 2005). Cocaine addiction has been shown to be very difficult to treat (Siciliano, et al., 2016) and the need for effective treatment and cures is self-evident. To date, there is no effective pharmacological or psychological treatments for cocaine addiction (Siciliano, et al., 2016).

Chronic cocaine abuse causes reductions in dopamine receptor’s capacity to get activated within a normal range. Therefore, functional “boosting” of signalling in dopaminergic neurons through neurostimulation techniques could have beneficial effects in moderating neuronal excitability through modulation of neurotransmitters, including dopamine, in regions involved in symptoms of addictive disorders. In a recent review article from this year (Rachid, 2018), the authors analysed neurostimulation techniques, which could work as therapeutic alternatives when treating cocaine addiction. Two of these techniques are transcranial magnetic stimulation (TMS) and deep TMS. They are able to modify neuronal voltage by using focused electromagnetic pulses through the scalp into the cortex. Deep TMS, though, reaches deeper
cortical and subcortical structures. The magnetic pulses from TMS and deep TMS generate an electrical current which is able to induce depolarization of target neurons and interconnected regions. Transcranial direct current stimulation (tDCS) is another neurostimulation technique, which instead passes an electrical current between two electrodes located on the scalp. TMS, deep TMS and tDCS are relatively safe techniques. Deep brain stimulation (DBS), on the other hand, involves implantation of electrodes in deep brain regions. DBS allows stimulation of specific brain areas in order to regulate abnormal impulses, and has been shown to work on several neuropsychiatric disorders, such as Parkinson’s disease and depression (Rachid, 2018).

Results from the studies used in this review article were relatively heterogeneous, which makes it complex to establish the most effective neurostimulation technique to treat cocaine addiction. Nevertheless, clinical evidence supports repetitive TMS, deep TMS and tDCS to have some positive influence on cocaine craving. Additionally, DBS has shown successful results in decreasing the severity of cocaine dependence. However, there have been few studies, and with small sample sizes, hence, no conclusions can be drawn from them. No long-term effects of neurostimulation techniques have been examined, which is needed considering the prolonged abstinence symptoms of cocaine withdrawal. Concerning this, no conclusions can be drawn from the neurostimulation studies analysed in this review. Before applying neurostimulation techniques in daily clinical practice, there is a requirement for more research to support and improve recent findings (Rachid, 2018).

World Drug Report (2017) highlights the requirement for more effective and evidence-based treatments for drug addiction disorders overall. No one should be left behind for drug prevention and treatment interventions. In order to find effective treatments, more understanding and research of the neural basis of cocaine dependence and relapse are needed.

5. Discussion

The aim of this thesis is to present an overview of the neuronal impact of cocaine on dopaminergic reward systems in the brain. The main focuses have been on reward and addiction in relation to cocaine, from a dopaminergic perspective. Cocaine acts on the dopaminergic neurons mainly located within the mesolimbic reward circuitries, and cause abnormally high levels of dopamine in these areas. Overstimulation of dopamine often results in addiction, including neuronal and behavioural changes that is threatening for one’s health and life in general.

Initially, neural communication, synaptic transmission and neurotransmitters were explained in order to provide a foundational understanding of the CNS and the basic
function of neural processes. It is important to highlight the complexity of neural communication and processes, such as reward, and how different substances affect the brain, to better understand disorders, such as cocaine addiction. Thousands of molecular and cellular elements are interacted in order to provide chemical and electrical signals which creates connected networks and eventually complex behaviours. Neurons carry physiological properties specialized for rapid processing that is required for the transmission of neural information. More than 100 neurotransmitters have been found in the brain. One of them is dopamine, which is known for its relation to motivational factors and shown to be the neural correlate of reward (Gazzaniga, et al., 2016). Motivation is highly related to human engagement in rewarding activities, but also in addictive disorders.

Further on, the neurobiology of the mesolimbic reward system and cocaine addiction was described and correlated to dopamine. Humans are certainly driven by rewards and motivated to maintain contact with rewarding stimuli that give us pleasurable experiences. Pleasure is essential for a normal extent of human wellbeing. Food, sex and social interactions are examples of natural sources that generates both pleasure and reward. The wanting-and-liking theory suggests that the processes of wanting and liking often are activated together, but in different neural substrates (Robinson & Berridge, 2008). However, rewarding stimuli that are liked, are also often wanted. Cocaine is not an exception. Dopaminergic neurons are mainly located in NAc and activation of this region is associated with craving (wanting) aspects, and furthermore correlated negatively with high (liking) experience of cocaine consumption (Risinger et al., 2005). This means that dopamine increases the motivational process of reward, in structures such as NAc, but does not directly affect the liking reaction or generate immediate pleasure. Drugs acting on dopaminergic neurons also activates opioid system, responsible for liking and pleasure experiences (Kolb, et al., 2016) Liking could be perceived as a phase of reward, which occurs when opioids activated hedonic hotspots in the brain. However, dopamine is necessary and dominant during the first phase of reward (motivation) in order to get to the rewarding stimulus and maintain contact with it.

Initially, cocaine typically generates reward and euphoria. Unlike natural rewards, cocaine tends to change the brain both structurally and functionally. It penetrates the CNS and reconstructing its homeostatic levels of dopamine in the mesolimbic reward system (Koob & Moal, 1997; Koob, 2001), but also inhibit the receptor’s capacity to receive dopamine signals. It triggers several forms of neuroplasticity, which may result in weakening or strengthening of connectivity within dopaminergic neurons (Volkow & Morales, 2015; Siciliano, et al., 2016).
However, even one single dose is able to alter the reuptake capacity in dopamine neurons (Julien, et al., 2014).

The positive experiences of cocaine generally emerge to negative symptoms. As the drug’s negative effects increase, it creates a downward spiral leading to continued drug consumption. A study showed that the subjective experience of high (liking) increased only the first four of six injections of cocaine (Risinger et al., 2005), which supports the notion of gradually decreased liking reaction after repeated cocaine consumption. Another great cost of long-term cocaine consumption is the gradually loss of voluntary control (Kandel, et al., 2013; Volkow & Morales, 2015). Studies have shown loss of grey matter in areas responsible for compulsive behaviour (Ersche et al., 2011), such as NAc (Volkow & Morales, 2015). Repeated activation in dorsal striatum from cocaine forms a habitual drug-intake pattern, which not entails voluntary control (Kolb, et al., 2016; Volkow & Morales, 2015). Moreover, loss of control seems to promote the experience of craving and cocaine seeking behaviour in addicted individuals. Craving is correlated with neural activation in NAc, AC and other forebrain areas (Risinger et al., 2005). Volkow et al. (2006) states that the more the dopamine level increases, the greater the desire for cocaine become. Enhanced craving and motivation makes one do whatever and go wherever one have to in order to retain contact with the rewarding stimuli, in this case; cocaine.

Additionally, the tolerance of the euphoric effects develops very fast. This resulting in a need of higher doses to reach the same liking levels as obtained initially. After long-term cocaine use, dopaminergic reward system generally gets problem to reach natural levels of dopamine. This might lead to decreased interest and value of natural rewards, and increased seeking for drug-related reward stimulation. Not necessarily to get high but rather to feel normal, i.e. obtain a normal extent of reward and pleasure within its modified allostatic state (Garavan et al., 2000; Kalivas & Volkow, 2005; Volkow, et al., 2009; Volkow & Morales, 2015).

As we have seen in this essay, the side effects of cocaine abuse emerge progressively, and the experiences develops from positive to highly negative. Cocaine is suggested to be a complex drug with extremely risky long-term consequences. It enters the brain rapidly, but is only metabolized slowly (Julien, et al., 2014), which indicates the powerful effects of cocaine on the brain.

Furthermore, drug relapse after cocaine withdrawal is highly common; addicts are usually very vulnerable to relapse, even years after abstinence symptoms are gone (Robinson & Berridge, 2008; Kalivas & Volkow, 2005). This is due to activation of dopamine in NAc and
dorsal striatum when addicts are exposed to drug-conditioned cues. Activation of these areas stimulates drug-seeking behaviour, even when expressed to non-drug rewarding cues such as food, sex and social contexts, which is not possible avoid.

Despite the widespread use of cocaine, there is no effective medical or therapeutic treatment for cocaine addiction (Siciliano, et al., 2016; Rachid, 2018). Even though the dopaminergic mesolimbic system has been well studied, its molecular and functional features are less well defined (Lammel et al., 2008). Anyway, there are some limitations when studying the dopamine and its relation to rewarding circuitries in the brain. That is the fact that many neurotransmitters work in parallel or along with dopamine synapses. For example, opiates are involved in the pleasure aspects of reward and interact with dopaminergic neurons in these processes (Kandel, et al., 2013; Gazzaniga, et al., 2016). Therefore, it is important to remember that dopamine does not present the whole picture of the neurobiology of addiction, even if it plays a central role in the brain circuitries involved in reward and addictive disorders. Additionally, this field of research is limited when it comes to individual differences of dopamine levels, receptors and their sensitivity to cocaine and other substances.

Chen et al. (2006) notes that more knowledge about the roles of related genes and proteins involved in cocaine action is important to better understand the role of cocaine addiction and will contribute to the development of effective therapeutic interventions and pharmacological treatments for drug abuse (Chen et al., 2006; Lammel et al., 2008). The World Drug Report (2017) state that treatment for addiction is limited; less than one in six individuals with drug abuse disorders is provided with treatment each year. Several behavioural therapy methods, in combination with pharmacotherapy, have been shown to be helpful in treating addiction. These forms of therapy could act on the dysregulated cycle of reward in order to return and maintain it within its homeostatic boundaries (Koob & Moal, 1997). Volkow, et al., (2009) indicate it would be effective to involve areas that are responsible for subjective perception of desires and needs in a therapeutic treatment for addicted individuals. A review article from this year (Rachid, 2018), the authors suggest different neurostimulation techniques to be beneficial when moderating neuronal excitability in dopaminergic circuitries involved in addictive disorders. These techniques could work as therapeutic alternatives when treating cocaine abuse. Neurostimulation techniques have shown positive results in decreasing cocaine dependence and craving symptoms. Although, these results are very limited due to the small sample sizes and number of studies, which makes it difficult to draw any conclusions from such studies. Koob (2001) notes that multiple levels of analysis, namely molecular, cellular and
system, have to be done. Only an interaction of these dimensions of analysis will derive a complete understanding of the neural basis of addictive disorders.

It would be important to investigate more in the dopaminergic reward systems on a molecular level, in order to better understand these circuits when they are disturbed and deconstructed by addictive drugs, such as cocaine. To see if there is some effective way to prevent the disconnection between the consummatory and satiety phase of reward, when individuals lose the ability to control their drug-intake. Also, decreased capacity in reaching natural levels of dopamine is another common consequence of cocaine addiction. If individuals suffer from anhedonia or seek for more reward, how could they stimulate the dopaminergic mesolimbic system without addictive substances? Despite drug’s (but also other rewards’) relatively short sequences of pleasure and reinforcement, individuals are apparently willing to take the risks involved in addictive drugs. Does this indicate lack of pleasure before initial drug intake or the evolutionary strength of reward-seeking behaviour of ours? It would be of an interest for neuroscience research to investigate in methods to achieve and maintain long-lasting reward and satisfaction, if there are any.

Thus, cocaine addiction is a clinical disorder, without any evidence-based and effective treatment. It is important to spread the knowledge of the additive drug’s actual effects on our mental and physical health. The National Institute on Drug Abuse (NIDA, 2014) believe that a deeper understanding of the basic molecular science of the brain in relation to addiction and its consequences will identify new revolutionary treatment methods. It will also empower individuals with science-based guidelines when making life choices, which would result in reduced drug abuse rates, and further on; enhanced individual and public wellbeing. To sum up, individuals worldwide should be conscious of the neural and cognitive processes, in order to be aware of the eventual consequences of cocaine on the brain, but also that you are able to chronically influence the neurochemistry yourself. You only get one brain, so take care of it.
References


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