THE MECHANISMS OF ADDICTION AND IMPAIRMENTS RELATED TO DRUG USE

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Abstract

This thesis contains an overview of the mechanisms of addiction as well as a description of the impairments related to drug abuse. The general view of addiction is that it depends on three characteristics that have separate neural mechanisms, called “wanting”, liking and learning. “Wanting” is described as a desire evoked by reward cues, liking refers to the pleasure of getting a reward and learning is described in terms of classical conditioning. “Wanting” and liking are usually in agreement but in addiction they are dissociable, that is, wanting a drug but getting no pleasure from it. Reward cues, acquired through learning, awakes the motivation to obtain the drug again. This can be problematic when trying to cease drug taking. The dopamine system in the brain is much discussed in relation to addiction and its neural correlates. The prefrontal cortex (PFC) is suggested to be altered in addiction, and this may underlie some of the impairments discussed. Addiction is also strongly related to cognitive impairments such as working memory problems, impulsivity, attentional problems and decision-making impairments. Affective impairments, such as empathy problems, may also to have some connection to addiction, although this is less clear.

*Keywords:* Addiction, drug abuse, mesocorticolimbic system, cognitive impairments, affective impairments
Table of Contents

Introduction ........................................................................................................................................... 5
Reward, Addiction and Dependence ........................................................................................................... 6
Development of Addiction and Addiction Theories .................................................................................... 9
Mesocorticolimbic Pathway ....................................................................................................................... 12
Dopamine and Other Neurotransmitters in Addiction ................................................................................. 14
“Wanting”, Liking and Learning in The Brain............................................................................................. 16
Vulnerability and Impairments ................................................................................................................... 17
Affective Impairments ............................................................................................................................... 18
Cognitive Impairments .............................................................................................................................. 20
  Working Memory ................................................................................................................................... 20
  Impulsivity ............................................................................................................................................. 21
  Attention ............................................................................................................................................... 23
  Decision-Making ................................................................................................................................... 24
Discussion .................................................................................................................................................. 28
Conclusion ............................................................................................................................................... 31
References ................................................................................................................................................. 32
**Introduction**

Drugs have been used in human history for a very long time in different settings and for different purposes: for example, by priests in religious settings, for medical purposes (opium) and in everyday life in socially approved settings (alcohol, caffeine and nicotine). Drugs such as cocaine and nicotine are relatively new drugs of abuse, but drugs such as opium and cannabis have been cultivated for a long time. The issue of addiction has been discussed for hundreds of years (Crocq, 2007).

Today, substance use is a big problem in many parts of the world. It is estimated that five percent of the world population that is a quarter of a billion people have used illicit drugs, at least once in 2015; and 0.6 percent of the world’s population that is, 29.5 million people have substance use problems, such as dependence or addiction, and may require treatment. Around 28 million years of healthy lives were lost in the year 2015 as a result of disability and premature death caused by drug use. There is limited availability of treatment, less than one in six substance users being provided with treatment, which may explain drug use often continues. Cannabis is the most common illicit drug with 183 million people having used it in the past year, followed by amphetamines and opioids with roughly 35 million users each and next is ecstasy with 21 million users and then cocaine with 17 million users. Opioid use is arguably the most harmful drug problem today accounting for 70 percent of lost healthy years in 2015. Opioid use is associated with some health risks: overdoses and transmission of infectious diseases (e.g. HIV) through unsafe injection techniques and development of mental health issues (all data from United Nations Office on Drugs and Crime, 2017).

Drug addiction can be seen as a compulsive behavior with negative consequences because one loses control over the drugs. The negative consequences may be criminal activity and failure to fulfil life roles. A recent meta-analysis connecting studies of cannabis users in adolescents and young adults showed a small but significant reduced cognitive functioning in cannabis users compared to controls. However, studies that tested on cannabis users that were abstinent for at least 72 hours showed no significant effect, suggesting that its use is not associated with severe cognitive problems (Scott et al., 2018).

Other studies have suggested that many types of drugs, such as stimulants, depressants and opiates, is associated with several affective and cognitive impairments, such as attentional problems, impulsive behavior, working memory deficits and problems in decision-making (Bayrakçı et al., 2015; Fridberg et al., 2010; Lopes et al., 2017; Monterosso et al., 2007; Rapeli et al., 2006; Simon, Dean, Cordova, Monterosso, & London, 2010). It has also been
suggested that drug use is associated with impairments in several parts of the brain, for example the prefrontal cortex (PFC) and ventral striatum (e.g. Liu et al., 2009).

Given ongoing discussion about the effects of drug misuse, the aim of this thesis is to examine impairments related to substance abuse. There are two main sections of this thesis. First there will be a description of addiction, involving a description of reward, how an addiction might develop, some addiction theories and models and a discussion of why some people might be more vulnerable to drug abuse compared to others. There will also be a description of the neural correlates of addiction, containing a detailed explanation of the reward pathway (a pathway much involved in addiction), a short description of some different neurotransmitters involved (e.g. dopamine) and some other brain areas involved in addiction. This is done to provide an understanding of the basics of addiction and better understand how impairments appear. This will be followed by a presentation of the research on impairments related to substance abuse. A discussion of both affective impairments, such as motivation, empathy and emotional facial recognition, and cognitive impairments, such as working memory, impulsivity, attention and decision-making related to different kind of drugs is provided. There will also be a discussion of this evidence, some conclusions and indicators for a possible future focus.

**Reward, Addiction and Dependence**

Addiction can appear not just with drugs, but other kinds of rewarding aspects that may appear in life, such as for food and sex. However, I will focus on addiction of drugs in this thesis. Addiction can be distinguished from dependence. Addiction, also referred to as abuse, is generally described as compulsive behavior, whereas dependence usually refers to symptoms of physical dependence. Dependence involves tolerance and withdrawal symptoms that occur because of repetitive drug taking. In tolerance there is a decreased effect of the amount used which gives the feeling of having to increase the dose to get the desired effect (Gruber, Silveri, & Yurgelun-Todd, 2007). This can lead to overdose and death. There might be a desire to stop drug taking but one continues despite negative physical or psychological consequences. Addiction is more focused on the behavior that occurs because of drug use, such as failure to fulfil obligations in life domains (e.g. work, home or school), social problems, legal problems, engaging in criminal activity and use in dangerous settings (e.g. driving). Substance use disorder can be described as use of a substance leading to negative consequences and a changed behavior because of the frequent intake. These concepts can
overlap on some points and in this field of research they have often been used interchangeably.

In addiction, drugs become the most important goal, and other life goals are often forgotten. Therefore the lives of addicted people can become very narrow because the focus is primarily one of obtaining drugs (Hyman, Malenka, & Nestler, 2006). For example, during taking of cocaine in a high frequency, sleep, nurturance, loved ones, responsibility and survival do not matter as much anymore (Loewenstein, 1996). This pathology often involves relapse. There is evidence of brain changes related to repeated drug taking and this provides a big problem for recovery (Castilla-Ortega et al., 2016).

Although addiction is seen generally as a disease, Lewis (2017) argues that it is not, and instead should be seen as a developmental process and habit. A development means that it matures with time due to learning and the brain changing. The change in the brain during initiation of drug use should be seen as initially normal, not a pathology, as the same things happens during pursuit of other goals not seen as disorders, such as falling in love or engaging in fights during sport events.

To explain addiction, reward should first be examined. According to Delgado (2007) rewards can be defined as desirable outcomes that influence behavior. One is motivated to achieve rewards or avoid punishment. According to Schultz (2015) rewards are crucial for survival, their purpose is to make us eat, mate and drink. The better rewards our brains want, the better for our survival. The brain has neuronal reward signals to process all important aspects of reward, such as control of movement and sensory discrimination (e.g. seeing and hearing) (Schultz, 2015).

Learning, approach behavior, decision-making and positive emotions are closely related and important functions of reward (Schultz, 2015). Learning is described through classical conditioning and associative learning, where links are formed between stimuli and behavioral event (Berridge & Kringelbach, 2008). A song playing can become a cue for wanting a drug, and after a while only the song is needed to activate the reward-related parts in the brain. Humans quickly learn how available the reward is and these cues motivate the human (or animal) to find more (Hyman et al., 2006). The cues and memories between stimuli and rewards are generally good for survival, however in disorders such as post-traumatic stress disorder and anxiety disorders the associations of the trauma can cause pathological responses for many years (VanElzakker et al., 2014). Approach behavior means that rewards get us ready to make an effort to obtain the reward one needs to approach the reward to get it. Decision-making means that sometimes there must be choice made between rewards, to get
the best possible reward. Identification of the value associated with the different rewards must be made and weigh them against each other (Schultz, 2015). Positive emotions are evoked by a reward. How rewarding a reward is is based on the pleasure it induces. For example, thirst provides the want to drink (Schultz, 2015). When visceral factors get more intense, they draw more attention and motivation towards the wanted substance. Hunger draws attention and motivation toward associations of food and things not associated with food lose their value and can be sacrificed to get the wanted good (Loewenstein, 1996). Desires provides purpose and gets one ready to strive towards a goal (Schultz, 2015). Liking refers to the pleasurable feelings of reward and “wanting” a desire to obtain a reward. Usually these two aspects of reward are in agreement, but it might not always be the case. Dissociation of “wanting” and liking is usually the case in addiction (Berridge & Robinson, 2016). This will be further discussed later.

Some things are valuable for survival, such as food and mating. These things are rewarding and reinforcing. Some drugs, such as cocaine, opiates, alcohol, nicotine and cannabis, are also rewarding. The more one takes the drug, the more motivated one gets to find more (Hyman et al., 2006). The process of addiction shares similar neural plasticity with natural reward learning and memory (Kelley, 2004).

A drug can be defined as something that alters the normal state of consciousness. Drugs can have different effects such as proving alertness, positive emotions, calming effects, hallucinations or relieving pain. Because of the rewarding effects of drugs, one may become addicted. Stimulants is a division containing different drugs such as amphetamine (which is also contains methamphetamine), cocaine and ecstasy among others (Hyman et al., 2006). Depressants is a division containing cannabis or marijuana and alcohol among others. Opium, or opiate, refers to drugs derived from the poppy plant. Opioid refers to all substances, natural and synthetic, that bind to opioid receptors. That includes codeine, morphine, heroin, fentanyl, oxycodone, hydrocodone and thebaine (Hemmings & Egan, 2013). Endorphins are the body’s own pain reliever, similar to morphine, which binds to opioid receptors and has agonist effects, meaning that they provide action in the neurons (Gruber et al., 2007). Opiates relieve pain and give a feeling of euphoria and are therefore extremely addictive (Langlois & Nugent, 2017). Opioid addiction can start through prescription medicine of pain relievers and then evolve to an addiction of e.g. heroin. Approximately eighty percent of heroin users report earlier use of opioid pain relievers (Jones, 2013). In addition to creating tolerance and addiction, opioid treatment may create opioid-induced hyperalgesia, meaning that it makes the person more sensitive to pain. Initially, opioids alleviate the acute pain, but in chronic use it
may instead create hypersensitivity because the body is trying to compensate with more pain through upregulation of pain pathways (Angst & Clark, 2006). Although there are many more drugs, stimulants, depressants and opiates are the main types which have been focused on in this thesis.

**Development of Addiction and Addiction Theories**

Addiction is complex and results from interactions of social, cultural, economic, biological and psychological variables. Development of addiction is usually gradual and progressive (Robinson & Berridge, 1993), typically starting with voluntary intoxication. After a while, there can be an experienced loss of control at which point the drug taking becomes compulsive and a habit, meaning that the actions are not controlled by the person. The change from voluntary to compulsive habitual drug taking may depend on habit formation and classical conditioning (Everitt & Robbins, 2005). Castilla-Ortega et al. (2016) states that in cocaine use, habits and memories are important to get an understanding about why addiction often involves relapse. Hippocampus, which is involved in memory, is an important part in cocaine addiction. After first use the user will learn cues to predict availability. The person will remember and associate internal and external events that occur during intake to the drug, for example a song playing (Castilla-Ortega et al., 2016).

According to Ahmed (2017) there are two types of decision involved in drug taking. First there is an important, opening decision to take drugs for the first time. This kind of decision is based on previous knowledge, expected effects and knowledge about oneself, such as one’s vulnerability. After first use of the drug, there is a subsequent decision to use again. That decision is based on the same mechanisms active in the initial intoxication, except that the initial use has changed the brain in such a way that it could bias the brain to make decisions to continue drug taking (Ahmed, 2017).

Chronic stress also seems to be an important feature involved in the continuous use of drugs (Koob & LeMoal., 1997). Acute stress compared to chronic stress have different effects on the reward system. Acute stress leads to active coping and motivation but chronic stress instead leads to helplessness and anhedonia (Ironside, Kumar, Kang, & Pizzagalli, 2018), which is lack of pleasure or lack of reaction to pleasurable stimuli (American Psychiatric Association, 2013). Animal studies have suggested that early life stress is associated with reduced motivation to pursue rewards in adulthood. Studies about early life stress and adverse events have shown long-lasting effects on the reward system (Pizzagalli, 2014). Other studies have suggested that a person might eat either more or less than usual during stressful times,
which suggests that the reward system is not functioning normally (e.g. Stone & Brownell, 1994). Failure in self-regulation may lead a person to taking more drugs and therefore feeling more distressed and taking more drugs, leading to a spiraling cycle of distress (Koob & LeMoal., 1997). Some people may very easily become addicted to a drug, and some people can use drugs for a long time and never develop an addiction (Egervari, Ciccocioppo, Jentsch, & Hurd, 2018).

“Wanting” and incentive salience both refers to desire. “Wanting” is triggered by cues or imagery of the drug (Berridge & Robinson, 2016). Some have suggested that this is different from the ordinary sense of wanting because ordinary wanting refers to a cognitive desire that is linked to a cognitive goal. The “wanting” we are talking about, which will be put into quotation marks to better differentiate between them, is not very linked to a cognitive goal but instead linked to the reward cues. “Wanting” is similar to craving (Hickey & Peelen, 2015; Berridge & Robinson, 2016). These two kinds of wanting are usually in agreement but for addicted people they are dissociated. For example, a person can have a cognitive goal of wanting to quit the addiction but the reward-related cues of “wanting” makes her want the opposite at the same time. The “wanting” is sensitive for “unseen” or subliminal cues, suggesting that “wanting” may be unconscious (Childress et al., 2008; Winkielman, Berridge, & Wilbarger, 2005). Addiction is much about “wanting” and not much about pleasure or satisfaction. The liking part of reward is more associated with pleasure and the hedonic aspect of reward (Berridge & Robinson, 2016). Learning refers to associations and predictions about future rewards based on past experiences. By conditioning or Pavlovian association, one is forming links and cues between stimuli and the behavioral event (Berridge & Kringelbach, 2008). For example, as noted earlier, a song playing can become a cue for wanting a drug, and after a while only the song is needed to activate the reward-related areas in the brain. According to Berridge (2007) learning guides “wanting” to specific and appropriate targets. The reward-related cues (learning) activates a state of “wanting”. All of the three components are needed in order for reward to exist. To get a clearer view of these concepts, they are further summarized in Table 1.
### Table 1

**Clarification of Concepts**

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Wanting”, incentive salience</td>
<td>Connected to reward cues</td>
</tr>
<tr>
<td>Wanting</td>
<td>Connected to a cognitive goal</td>
</tr>
<tr>
<td>Liking</td>
<td>Pleasure and positive affect</td>
</tr>
<tr>
<td>Learning</td>
<td>Classical conditioning and memory</td>
</tr>
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</table>

One theory to describe addiction is through the incentive-sensitization theory of addiction. The discovery that “wanting” and liking trigger different brain systems is a start of explaining the theory (Berridge & Robinson, 2016). Liking and “wanting” usually go together for the same reward but for addicts, this is dissociative, by manipulation of especially dopamine (Berridge, 2013), which will be described in detail later. Sensitization refers to an increased effect of a drug (Robinson & Berridge, 1993), sensitization of the dopamine system appears when the drug is taken repeatedly and in high doses (Kalivas & Stewart, 1991). This sensitization means that the ”wanting” part of reward become hyper-reactive (very sensitive) to reward cues, this leads to release of dopamine and motivation to get the drug, therefore it leads to compulsive drug taking. When the sensitization has started, it is long-lasting and possibly permanent (Berridge & Robinson, 2016). The liking part is not affected by this or it can even decrease. For example, a person may not get much pleasure from the drug but still “want” it, this feeling can last for many years (Berridge & Robinson, 2016). There has been a discussion of what activates tolerance and what activates sensitization, which is roughly opposite responses. Tolerance which refers to a downregulation of the dopamine system because of excessive stimulation of the reward system in the brain, leading to the brain adapting and one needing to take more e.g. drugs to get the same desired effect as in the initiation of drug use. Tolerance usually occur when the drug take is regular and taken in the same amount and sensitization occurs when the drug take is irregular and taken in different amounts (Hinson & Poulos, 1981; Hyman et al., 2006).

Other models describing addiction are divided into two classes called negative reinforcement models and positive reinforcement models (Robinson & Berridge, 1993). Positive reinforcement models state that addiction maintenance occurs because of the state that the drugs bring, that they induce euphoria and positive affect. Especially in the beginning of drug use, the drug taking is voluntary because it brings positive feelings and therefore have
positive reinforcing effects, this leads to animals and humans making an effort to get the drug. The drugs that have high positive reinforcing effects are also the ones that are the most addictive. This kind of reinforcement seems to be most important in the initiation of drug use to develop a drug taking behavior. But as stated above, continued use of drugs leads to tolerance or sensitization which do not involve as much positive affects. For maintenance of drug use negative reinforcement seems to more important (Koob, 2000).

Negative reinforcement models states that in addiction drugs are taken to avoid the negative emotions associated with withdrawal symptoms or one can also take drugs to escape from pain, anxiety and depression that occur in life that is not associated with the drugs (Robinson & Berridge, 1993). Withdrawal symptoms from all kind of drugs includes negative affects, such as anxiety, sadness or irritability. There might be some differences in withdrawal symptoms depending on the drug used, but some withdrawal symptoms may also include hallucinations, tremor and convulsions (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004).

Early studies states that dependence for morphine develops after a very small number of times used (Wikler, 1948) and therefore suggesting that this negative reinforcement starts relatively early in the drug addiction phase. However, this may have different results depending on the drug used.

Another negative reinforcement theory, called the Solomon opponent process model suggest that in the early stages of drug taking, there are positive effects, but after a while, there is a downregulation of this system in the brain (Solomon, 1980). Today studies have made clear that withdrawal symptoms, important as they are to addiction, are not the most important factor to develop and maintain an addiction. Research have also suggested that positive affect is not necessary or sufficient to explain addiction. Many of the existing models of addiction have problems (Robinson & Berridge, 1993).

**Mesocorticolimbic Pathway**

The mesocorticolimbic pathway is often mentioned in the research field of reward and addiction. This system is involved in processing of rewards and because drugs of abuse is a kind of reward, the system is also involved in addiction. In addiction the system becomes overstimulated and hypersensitive to drug cues. The system handles the activation of dopamine. As a result of overstimulation, depending on amount and how often the drug is taken, the brain might try to compensate, such as trying the diminish the dopamine release. This pathway involves many brain regions and is located in many parts of the brain, such as frontal areas and limbic areas (Hyman et al., 2006).
The reward pathway, often also referred to as the mesocorticolimbic system, is related to the striatum (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000) which is a large part of the basal ganglia. Basal ganglia are a group of structures that are mostly involved in learning and motor aspects of behavior. Striatum is the main input to basal ganglia, it receives input from motor cortex and dopaminergic projections from substantia nigra and ventral tegmental area. Striatum can be divided into dorsal and ventral striatum. The dorsal striatum consists of caudate nucleus and putamen and the ventral striatum consists mostly of nucleus accumbens (NA) (Delgado, 2007). Especially the ventral striatum receives input from the amygdala, which is associated with emotion, and the hippocampus, primarily associated with memory (Delgado et al., 2000). The striatum is associated with learning (such as habit learning and reward related learning) and visual aspects (Delgado, 2007) and has been proposed to be involved in integrating these reward related cues, leading to fast recognition of changes in reward (Delgado et al., 2000).

This mesocorticolimbic system is associated with drug reinforcement and addiction and can be seen as involving three parts: the mesolimbic dopamine circuit, the mesocortical dopamine circuit and the nigrostriatal, also referred to the mesostriatal pathway. The mesolimbic dopamine circuit handles motivational processes and involves NA (Goldstein & Volkow, 2002), amygdala, which is involved in emotional processing and memories that contain emotionally arousing experiences (McGaugh, Cahill, & Roozendaal, 1996), hippocampus, which have been linked to craving and are likely involved in the emotional and motivational changes during withdrawal for drug abusers (Goldstein & Volkow, 2002) and the ventral pallidum (Smith, Tindell, Aldridge, & Berridge, 2009). The mesolimbic pathway also contains the ventral tegmental area (VTA). The dopamine cells in VTA project information to the NA (Volkow, Wang, Fowler, Tomasi, & Telang, 2011).

The mesocortical dopamine circuit, which involves PFC, orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), is likely to be involved with the conscious experience of drug use and addiction, such as drug expectation and compulsive drug administration (Goldstein & Volkow, 2002). PFC, OFC and ACC are involved in complex aspects of organizing, planning and executive behavior, which is tasks that require integration of behavior over time. People with problems in these areas often have problems in reaching goals and problems with motivation to initiate, modulate or stop an action once it is happening. OFC is also involved with the feelings of anger and regret (Gazzaniga, Ivry, & Mangun, 2009). Research shows that the feeling of regret leads to more risky decisions over time (Coricelli et al., 2005). ACC may also be important for generalized emotional processing.
Dopamine cells in VTA projects information to the frontal cortex (Volkow et al., 2011). The dopamine cells in VTA are crucial for acquiring new motor skills through repeated training (Gazzaniga et al., 2009).

In the mesostriatal dopamine pathway dopamine cells in substantia nigra project to the dorsal striatum (Volkow et al., 2011). NA receives input from both substantia nigra and VTA. VTA dopamine neurons mostly come to the shell of NA and substantia nigra mostly targets the core of NA (Haber, Fudge, & McFarland, 2000; Corrigall, Franklin, Coen, & Clarke, 1992). These circuits interact with each other and some behaviors involve them both, and this interaction may be responsible for the vicious cycle of drug taking and addiction (Goldstein & Volkow, 2002).

Earlier, there has been a division between the substantia nigra and VTA into two different pathways, called the nigrostriatal system and the mesocortical system. The nigrostriatal system has mostly been connected to the study of Parkinson’s disease, where the dopaminergic neurons in the substantia nigra decreases, and has not been connected to the research of addiction and reward. The mesocortical and mesolimbic systems that originates in the VTA has been more connected to the study of addiction and motivation (Wise, 2009). Now, the nigrostriatal system has also been connected more to the study of addiction, because findings have shown that these systems overlap. There is found that the substantia nigra projects to different systems, it has been found to project to the PFC (mesocortical), dorsal striatum and other limbic areas, such as amygdala (Wise, 2009).

**Dopamine and Other Neurotransmitters in Addiction**

According to Lewis (2017) dopamine is crucial for motivating, directing and rewarding goal-directed behavior and for memory and attention. Dopamine is a neurotransmitter in the brain and there are several different kinds of dopamine receptors. Dopaminergic neurons are located throughout the brain (Gazzaniga et al., 2009) and may be most prominent in the VTA, substantia nigra and the midbrain (Kelley, 2004).

There has been a debate over what role dopamine has in reward and why the release of dopamine in the brain is rewarding (Berridge, 2007). Some have stated that dopamine was mostly connected to liking and pleasure, proposing that dopamine has positive reinforcement effects in reward (Volkow et al., 2006). Dopamine has been connected to hedonic pleasure also because many rewards that activate the mesocorticolimbic pathway provide pleasurable feelings, such as food and sex (Becker, Rudick, & Jenkins, 2001; Roitman, 2004). However,
liking has later been found to have most connections to so called hedonic hotspots in the brain and not the dopamine pathway (e.g. Small et al., 2001).

There are some arguments stating that dopamine is mostly connected to learning (Berridge, 2007), that dopamine is connected to reward-related learning and reinforcement (Montague, Hyman, & Cohen, 2004). Reinforcement is not just linked to the hedonic factors, but also learning. One explanation may be through conditioning. Some drug cues or conditioned stimuli increases the dopamine level when the drug is expected. After a while the dopamine stops responding the drug itself (Volkow et al., 2011), suggesting that dopamine activates anticipation of reward, through conditioned stimuli (De la Fuente-Fernández et al., 2002). Habit learning and prediction error is also a part of this learning. An important distinction is that the correlation has only been seen in the connection of dopamine and learning, not if dopamine really causes learning. Also, dopamine cannot alone explain reward-related learning, it is just one mechanism involved (Berridge, 2007). Reward learning may be indirectly connected to learning, through “wanting” as they are connected. Learning may also be connected to dopamine through for example motivation, attention, rehearsal, cognition and consolidation (Phillips, Setzu, & Hitchcott, 2003; Dalley et al., 2005) but is not necessary for direct learning mechanisms (Cannon & Palmiter, 2003).

There seems to be most evidence for that the dopamine is most strongly connected to “wanting”, which is about motivation for a reward (Berridge, 2007). “Wanting” has most evidence for the causal association, that dopamine activates “wanting”. For example in a study of mice, a mouse that is hyper activated on dopamine in the striatum show higher “wanting” behavior for sweet rewards, but not increased learning or liking (Pecina, Cagniard, Berridge, Aldridge, & Zhuang, 2003; Cagniard, Balsam, Brunner, & Zhuang, 2006). In rodents, dopamine transmission in the amygdala, ACC and ventral striatum affects the motivation to approach a reward in short- and long term goals (Floresco & Ghods-Sharifi, 2007; Howe, Tierney, Sandberg, Phillips, & Graybiel, 2013) and dopamine transmission in the OFC influences attention and impulsivity; it regulates the will to wait in order to get a bigger reward (Winstanley et al., 2010).

The reward system also activates other neurotransmitters, such as glutamate, GABA and opioid (Berridge, 2007). Glutamate encodes specific sensory, motor and mnemonic information while dopamine responds to a more global sense of unpredicted, rewarding or outstanding events in the environment (Mirenowicz & Schultz, 1994; Rebec, 1998; Kelley, 2004). The integration of glutamate and dopamine may play an important role in motivation, learning and memory. They appear in many regions of the brain, such as cortex, limbic areas
and basal ganglia. Their coordinated signaling is thought to be crucial in what leads to perhaps permanent changes in the brain and therefore behavior that appears in reward related learning and addiction (Baldwin, Sadeghian, Holahan, & Kelley, 2002; Smith-Roe & Kelley, 2000). The sensitization of the reward system alters not only the dopamine neurotransmitters but the glutamate neurons as well (Wolf, 2010).

Opioids increase release of dopamine in the VTA (Johnson & North, 1992). Opiates makes GABAergic neurons in the VTA, that normally inhibits dopaminergic release, switch from inhibitory to excitatory signaling mode (Laviolette, Gallegos, Henriksen, & Van Der Kooy, 2004). This brings the pleasurable feelings and is thought to mediate positive reinforcing effect of the drug and motivation to get more (Dacher & Nugent, 2011).

“Wanting”, Liking and Learning in The Brain

“Wanting” is primarily connected to the mesocorticolimbic systems in the brain, which handles dopamine, as described above (Anselme, 2016; Berridge & Kringelbach, 2015). As mentioned earlier, so-called, “hedonic hotspots” have been found in the brain related to the liking part. They are activated in several different types of pleasures, such as food, drugs and social pleasures (Berridge & Kringelbach, 2015). These hotspots are tiny and easily disrupted which can explain why “wanting” is more usual than liking. The hotspots appear in parts of limbic areas, such as the ventral pallidum and NA, as well as parts of the cortex, such as the OFC (Castro & Berridge, 2017; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Castro & Berridge, 2014; Mahler, Smith, & Berridge, 2007; Peciña & Berridge, 2005). The hotspot located in ventral pallidum seems to be especially important. A lesion to this part can eliminate normal pleasure and reverse the influence of sweet sensation, from liking to disgusting (Ho & Berridge, 2014). In mice, a coldspot has also been found in the brain, possibly there to suppress the hedonic impacts. It has been found posterior to the OFC hotspot, and it covers most of the insula (Castro & Berridge, 2017). Another coldspot has been found in the NA (Castro & Berridge, 2014). Learning is mostly related to hippocampus, which plays a crucial role in associative learning, encoding and consolidation of environmental information and learning the relationship between different environmental stimuli (Kelley, 2004).

There is also evidence that the insula plays an important role in urges to take drugs and executive functions (Naqvi & Bechara, 2009). The insula is typically correlated with the perception of internal bodily states; it is activated in sensual touch, thirst, itch, expansion of the intestinal tract and bladder, exercise and heartbeat. The insula is also important for
emotional awareness; feelings such as love, anger, fear, disgust, sadness, happiness and trust activate the insula. This suggests that the insula is important for integration of emotional and cognitive information (Gazzaniga et al., 2009). Some evidence also points to the conclusion that a dysfunctional insula can explain some of the strange decisions made to continue to take drugs (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004; Ernst & Paulus, 2005). Evidence suggests that the more risky a decision is, the more activated the insula (Xue, Lu, Levin, & Bechara, 2010). Cocaine users have reduced grey and white matter in the insula, pointing to the idea that the insula underlies some problems in drug addiction (Franklin et al., 2002). The hypothalamus is an area controlling circadian rhythm and maintaining a normal state of the body. It gives signals to behave toward alleviating feelings of thirst, hunger and fatigue. It also controls body temperature (Gazzaniga et al., 2009). Hypothalamus, as well as insula, are thought to be involved in regulating autonomic and physical responses to emotional and rewarding stimuli (Menon & Levitin, 2005).

**Vulnerability and Impairments**

As stated above, some people can use drugs for a long time but never develop an addiction and some people are more vulnerable to developing an addiction (Egervari et al., 2018). What might be the reason that some people are more vulnerable? There has been found to be a correlation between substance use and impulsivity, novelty seeking (Belin, Mar, Dalley, Robbins, & Everitt, 2008; Jentsch et al., 2014; Belin, Berson, Balado, Piazza, & Deroche-Gamonet, 2011), deficits in executive functions and response regulation (Ersche et al., 2012). People that have neurological diseases that lead to poor impulse control and decision-making deficits might also have more vulnerability to develop substance use disorder, such as attention deficit hyperactivity disorder (ADHD) (Gordon, Tulak, & Troncale, 2004; Wilens, Biederman, Mick, Faraone, & Spencer, 1997). Low dopamine receptor availability of a certain type (as explained earlier that there are several types of dopamine receptors in the brain) in striatum have been found to be correlated with impulsivity and this might explain why some substance abusers might keep on using the drug despite negative consequences (Ballard et al., 2015).

Drug use often lasts over time, this may lead to impairment of the neural processes that serve cognitive and affective processes. These impairments involve e.g. executive function, decision-making, impaired memory function, motivational changes and impulsivity (Lopes et al., 2017; Fattore & Diana, 2016; Rogers & Robbins, 2001; Bechara, 2005). Roughly stated, the limbic structures such as NA handles affective components and prefrontal areas handles
cognitive components (Fattore & Diana, 2016). These structures are all involved in the mesocorticolimbic dopamine system, described above.

**Affective Impairments**

Affective impairments connected to drug abuse involves motivational, empathic changes and emotional processing. Drugs influence emotional and motivational information and may lead to maladaptive outcomes. Motivation refers to the ability to respond to stimuli with the ultimate goal of survival, in relation to needs (Fattore & Diana, 2016). As stated, drug craving demands attention towards drug cues and takes away attention from other cues not related to the drug (Sayette, Schooler, & Reichle, 2010), and this is also connected to motivational changes. Motivation is much connected to dopamine. As stated above, dopamine is activated in “wanting” states: that is, when motivation towards for example a drug occurs. Therefore the mesocorticolimbic system is involved with motivation and reward (Berridge, 2007; Lewis, 2017). One area especially connected to motivational processes is NA, suggesting that the NA shell is associated with activating aspects of motivation and the core is connected to goal driven (directional) aspects of motivation and habit forming (Corbit, Muir, & Balleine, 2001; Di Chiara, 2002).

Empathy can be described simply as having sympathy and compassion for others. This characteristic includes both cognitive and affective components. The cognitive component refers to the ability to understand others through an accurate perception of affective and social cues. The affective components refer to the ability to feel the feelings of others and to care about their well-being. Empathic behavior requires emotional regulation, regulation of one’s own emotions allows one to respond with empathic concern instead of in a self-oriented fashion. Empathy is considered as a spectrum, instead of having empathy or not having empathy, where it can range from very low levels to high levels of empathy. Empathy is related to theory of mind (Massey, Newmark, & Wakschlag, 2017). People that have difficulty in theory of mind often have difficulties in explaining one's own behavior and in understanding emotions, perspectives and intentions of others. This has been found to be impaired in alcohol-dependent people and methamphetamine users. Mixed results were found in cocaine dependent and no result was found in recreational cannabis and cocaine users (Sanvicente-Vieira et al., 2017; Kim, Kwon, & Chang, 2011). Motivation to care for others is connected with positive feelings and activation of reward related areas and release of dopamine (Insel, 2003; Moll & Schulkin, 2009). The relevant areas related to empathy includes the insula, PFC and ventral striatum (Eres, Decety, Louis, & Molenberghs, 2015;
Shaun Ho, Konrath, Brown, & Swain, 2014), which are parts related to the reward system providing evidence for that empathy disruption is a deficit related to drug abuse.

Individuals that have low empathy level may be at risk for substance abuse (Massey et al., 2017). Also individuals with disorders where low empathy is usual, such as schizophrenia (Dørnt et al., 2009), bipolar disorder (Shamay-Tsoory, Harari, Szepsenwol, & Leikovitz, 2009; Swendsen et al., 2010), borderline personality disorder (Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010) and psychopathy (Harvey, Stokes, Lord, & Pogge, 1996), may be at risk for substance abuse. Individuals that have low empathy may also be more prone to continue drug use compared to abusers that are high in empathy, because they do not feel bad about the harm caused for others (Massey et al., 2017) and may not even notice other people expressing cues of fear (White et al., 2016). Also, they may be more prone to relapse and less prone to recovery (Massey et al., 2017). Developing empathy problems may be a complex pathway involving many different aspects. For example, early impulsivity connected with low emotional traits, psychopathy and depression could influence the ability to develop empathy, and therefore increasing the risk of addiction (Neumann, Vitacco, Robertson, & Sewell, 2003).

Overall, there have been varying results in investigating the relationship between empathy and substance abuse. An early study using a survey on self-identified substance using adolescents showed no relationship between substance use and empathy (Jurkovic, 1979). In a study examining alcohol abusers, it was found that empathy levels were significantly lower than in controls (Martinotti, Nicola, Tedeschi, Cundari, & Janiri, 2009). Beyond empathy, alcohol abusers also showed among others lower scores on responsibility, self-esteem, emotional consciousness, optimism, autonomy and general emotional intelligence compared to controls (Mohagheghi, Amiri, Mousavi Rizi, & Safikhanslou, 2015). A study examining adolescents found that empathy was positively correlated to drug refusal and this suggests that empathy may be indirectly protective from drug taking behavior (Nguyen, Clark, & Belgrave, 2011). The causal relationship between empathy and drug abuse is not entirely clear.

Facial emotion recognition is an important capacity in order to have efficient social communication and emotional functioning. There are six basic emotions usually seen facial expressions, including fear, disgust, anger, happiness, sadness, surprise (Castellano et al., 2015). Recognition of these facial expressions has been found to be impaired in abusers of alcohol, opiates (Kornreich et al., 2003), ecstasy (Yip & Lee, 2006), cocaine (Fernández-Serrano, Moreno-López, Pérez-García, & Verdejo-García, 2012), methamphetamine (Kim et
al., 2011) and cannabis (Bayrakçι et al., 2015). Now we will go on to discuss cognitive impairments, here also referred to as executive impairments, in detail.

**Cognitive Impairments**

Executive function can be viewed as a connection of several different cognitive functions that are linked and influence each other. Executive functions are important to have a goal-directed behavior and includes mental processes that makes one able to plan, organize, multitask, prioritize and solve problems. Executive function includes components such as working memory, attention, response inhibition, problem solving, decision making, set shifting and so on. The most important functions are response inhibition, sustained attention, working memory and decision-making (Sofuoglu, Devito, Waters, & Carroll, 2013), which will be viewed in more detail below. PFC is an important part for executive function. For example, a study examining different types of executive function in early onset cocaine users and late onset cocaine users, showed that people that have used drugs for a long time have severe problems in neuropsychological functioning. People with early onset use of cocaine show worse performance in working memory, attention span, declarative memory, sustained attention and general executive functioning compared to controls, and people with late onset use of cocaine show worse performance in divided attention and general executive functioning. Early onset users also showed a greater frequency of poly drug use compared to late onset users. Problems for the early onset users may be because the drug use is interfering with normal neurodevelopment (Lopes et al., 2017). Studies of monkeys have shown that, cocaine use impairs cognitive performance, which is related to PFC and OFC function (Porter et al., 2011; Liu, Heitz, Sampson, Zhang, & Bradberry, 2008).

**Working Memory**

Working memory refers to a temporary storage containing information that is vital to perform other complex tasks. This short-term memory is rapidly erased because of the small capacity (Fattore & Diana, 2016). Dopamine in the PFC is involved in cognitive processes, such as the working memory. When tested on primates performing a working memory task, an increase of dopamine in the dorsolateral PFC was seen (Watanabe, Kodama, & Hikosaka, 1997). Another study tested elderly monkeys, as dopamine function is known to decrease with age. Higher dopamine levels showed an increase in working memory in the aged monkeys but produced impairment or no change in young adult monkeys (Castner & Goldman-Rakic, 2004). Drugs of abuse strongly affects working memory. A study with primates showed that drugs, such as morphine, can both impair and improve working memory (Wang et al., 2013).
In a rat study it has been shown that working memory is impaired in cocaine use (George, Mandyam, Wee, & Koob, 2008). Another study that tested on monkeys showed that sensitization of amphetamine impairs cognition and reduces dopamine transmission in PFC and striatum (Castner, Vosler, & Goldman-Rakic, 2005). In humans, cocaine abusers have shown lower activation of brain regions involved in the dopamine reward system, such as ACC, putamen, amygdala and parahippocampal gyrus as well as a decrease of working memory function compared to controls (Tomasi et al., 2007). Other findings have also shown that dopamine dysfunction in the cortex is crucial for dysfunction of working memory (Kienast & Heinz, 2006; Fattore & Diana, 2016).

Problems with working memory have been shown in users of depressants, stimulants and opiates. In a study that was testing on heroin- and amphetamine abusers found that both kinds of abuse showed impairments in cognitive function, such as working memory and memory function (Ornstein et al., 2000). Working memory deficits were shown in long-term cannabis users (Fletcher et al., 1996), long-term cocaine users and poly drug users, where it also was found that memory was negatively correlated with frequency and time of drug use (Rosselli & Ardila, 1996). Early studies have suggested that opiate abusers and controls do not differ in frontal lobe function (Rounsaville, Jones, Novelly, & Kleber, 1982), but more recent studies show results to the contrary, showing that opiate users have significant impairments in cognitive functions, such as working memory (Rapeli et al., 2006). Some evidence suggests that, for opioid abusers, improvements in memory function, such as verbal learning and memory, working memory and visuospatial memory, occurs after two months in treatment compared to before treatment (Gruber et al., 2006). A study of cocaine abusers performing the Iowa gambling task (which is a decision-making task) using positron emission tomography (PET) to measure cerebral blood flow show lower activation of dorsolateral PFC which is an area believed to be related to planning and working memory. These functions are required to perform the Iowa gambling task properly and working memory is therefore related to decision-making (Bolla et al., 2003). The Iowa gambling task involves a person choosing from four decks of cards which have different potential payoffs. When choosing a deck, one reviews feedback showing how much money one won or lost. This feedback enables normal decision-makers to learn to avoid the decks that provide high immediate gains but future losses (Bechara, 2005).

**Impulsivity**

Impulsivity and poor inhibitory control are associated with substance abuse. Impulsivity is the tendency to act prematurely without foresight and appears in many forms of substance use.
Although that is usually the case, impulsivity may not always be maladaptive. There are some situations where it might be positive to handle quickly. But the classic definition of impulsivity are actions which are poorly thought through, risky or inappropriate for the situation, prematurely expressed and usually resulting in unwanted consequences (Dalley, Everitt, & Robbins, 2011).

Increased impulsivity has been linked to use of stimulants, opiates and alcohol. In a study, measuring the ability of heroin and cocaine abusers to delay instant rewards in order to get higher rewards in the future, showed that they have poor abilities of doing so (Kirby & Petry, 2004). This has also been shown in alcoholics (Petry, 2001) and methamphetamine abusers (Monterosso et al., 2007). The neural correlates of this kind of impulsivity choice have been found to be the NA, where lesions in this area produce shifts for small immediate rewards (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001). The same results have been shown in the basolateral amygdala, in a study that tested on rats. Here, the opposite effect was found when examining lesions in the OFC, that lesions to this area produces preference for larger and delayed rewards (Winstanley, Theobald, Cardinal, & Robbins, 2004). However, another study has found the opposite result, that lesions in OFC is related to preference of smaller and immediate rewards (Mobini et al., 2002). There have also been suggested that the medial OFC and the lateral OFC have different effects on impulsive choice. That lesions to medial OFC has increased preference for larger and delayed rewards and lesions to lateral OFC show decreased preference for larger and delayed rewards, when tested on rats (Mar, Walker, Theobald, Eagle, & Robbins, 2011).

Other type of studies measuring impulsivity has measured the ability of inhibitory control, that is the ability to stop behavior. These studies have shown that substance abusers have poor inhibitory control. This has been shown in cocaine abusers (Fillmore & Rush, 2002) and methamphetamine abusers (Monterosso, Aron, Cordova, Xu, & London, 2005). Here a stop brain circuit have been suggested, that is supposed to stop or inhibit an action, involving the right inferior frontal gyrus, damage to this area leads to delays in response inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003), the medial PFC involving ACC, supplementary motor area and the presupplementary motor area (Picton et al., 2007), which is involved in motor planning and updating of motor plans (Chambers, Garavan, & Bellgrove, 2009) and the basal ganglia, which seems to be involved in motor suppression. Damage to this area brings slower stop reaction time (Rieger, Gauggel, & Burmeister, 2003). Although it is clear that impulsivity is correlated with drug abuse, the causal relationship is not as clear. A study examined impulsivity of substance abusers, their sibling who were not
substance abusers and matched controls. This showed that siblings had higher impulsivity compared to the controls. The study also showed that the substance abusers showed the highest impulsivity. This suggests that impulsivity in substance abusers may depend on a combination of heredity and drug induced effects (Ersche, Turton, Pradhan, Bullmore, & Robbins, 2010).

A relationship has also been found between impulsivity and working memory, showing that in cocaine abusers when demands are high for working memory, which have been found to increase during drug craving induced by cues, abusers find it difficult to inhibit their actions (Hester, 2004).

**Attention**

According to Petersen & Posner (2012) the attention system involves three components, alerting, orienting and executive networks. Alerting is about producing and maintaining alertness and performance during tasks. This has been studied through using a warning signal prior to a target event to produce a major change in alertness, this warning signal making one more prepared for detecting a target. It has also been studied over a longer course of time to measure sustained attention. These kinds of attention are associated with mechanisms in the right cerebral cortex (Petersen & Posner, 2012). The alerting network has also been strongly connected with the neurotransmitter norepinephrine, which has traditionally been connected with arousal and the fight-or-flight response (Aston-Jones & Cohen, 2005). For example, in tasks with sustained attention, using drugs that reduce norepinephrine response can impair sustained attention (Coull, Middleton, Robbins, & Sahakian, 1995). The norepinephrine pathway includes prefrontal areas and parietal areas that are related to dorsal visual pathways (Morrison & Foote, 1986). The orienting network refers to the ability to prioritize one sensory input by selecting a location. Frontal and posterior regions are involved in this kind of attention (Petersen & Posner, 2012), involving the frontal eye field (Thompson, 2005). Also, it has been found that the neurotransmitter acetylcholine, which has traditionally been linked to muscle movement, seems to be important for orienting (Voytko et al., 1994). The executive network is involved in target detection. Target detection is when a target comes into the conscious awareness. This captures attention in a very specific way, which slows down detection for another target, showing the limited capacity of attention. This kind of attention is further divided into two functionally distinct systems, called the fronto-parietal and the cingulo-opercular systems. The fronto-parietal system that includes lateral frontal areas and parietal areas (such as dorsal frontal cortex) is involved with task onset initiated by cues. The cingulo-opercular system that includes the midline areas and anterior insular regions (such as
the dorsal ACC) is involved with sustained attention. Executive attention also requires self-regulation (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Petersen & Posner, 2012). Attention is controlled by both bottom-up, exogenous (such as visual cues) and top-down, endogenous (executive attention) processes. Sustained attention is often measured through continuous performance tasks: for example, measuring how rapidly people attend to specific stimuli which is presented intermittently (Sofuoglu et al., 2013).

Impairments in sustained attention have been shown in abusers of depressants, stimulants and opioids (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Jovanovski, Erb, & Zakzanis, 2005; Simon, Dean, Cordova, Monterosso, & London, 2010; Lundqvist, 2005). This impairment is mediated by the drug craving, craving for a drug demands attention towards drug cues and therefore takes away attention from cues not related to the drug (Sayette et al., 2010). Attention failure in early abstinence may be related to behavioral impulsivity, often leading to relapse. These deficits leads to a takeover of brain by the drug cues (de Wit, 2009). This has been shown in heroin abusers. When testing on male abstinent heroin abusers and controls, showing pictures of heroin cues and neutral pictures, it showed that the previous abusers had larger attentional bias towards heroin cues, compared to control which showed no difference between the neutral and heroin cued pictures (Franken, Stam, Hendriks, & Van den Brink, 2003).

A study examining the relationship of cognitive deficits in young female drug abusers found that they had problems with a line of cognitive functions including sustained attention (Tarter, Mezzich, Hsieh, & Parks, 1995). Attentional difficulties among young drug abusers have also been found in a study measuring over a period of eight years (Tapert, Granholm, Leedy, & Brown, 2002). Some other studies also support the idea that use of cannabis seems to have both acute and long-term effect on attention (O’Leary et al., 2002; Solowij, Michie, & Fox, 1995).

**Decision-Making**

Functioning decision-making refers to the ability to choose the most advantageous alternative when choosing from a range of options, considering both the long-term and short-term consequences (Bechara, 2005). Impaired decision-making is an important component of substance abuse because substance abuse contains a choice of short-term positive outcomes but long-term negative outcomes. This suggests dysfunction in the neural mechanisms responsible for decision-making. This dysfunction contains three stages, called *preference formation, choice implementation and feedback processing*. **Preference formation** refers to when confronted with a choice, one develops a preference for one alternative over the other.
by analyzing the value of each alternative (Verdejo-Garcia, Chong, Stout, Yücel, & London, 2016). Studies have shown that abusers of cocaine, amphetamine and opioids utilize less information about the alternatives to make a choice compared to controls (Clark, Robbins, Ersche, & Sahakian, 2006; Stevens, Roeyers, Dom, Joos, & Vanderplasschen, 2015), suggesting that substance abusers are more prone to take risky decisions and tolerate uncertainty during preference formation (which is much related to impulsivity) (Verdejo-Garcia et al., 2016). For example this is shown in opiate users choosing riskier alternatives instead of smaller but more likely rewards (Brand, Roth-Bauer, Driessen, & Markowitsch, 2008). It has been shown that dopamine transmission in the basal ganglia decreases the ability to make distinctions between low- and high- value rewards, which might lead to risk taking (Simioni, Dagher, & Fellows, 2012). Studies have also shown that higher risks are taken when higher gains are at stake, which suggests that reward sensitivity plays a role in preference formation. Also, working memory has a role in preference formation, because of the importance of the ability to hold on to the information relating to the alternatives before making a decision. This ability, as described above decreases in drug abuse (Brand, Roth-Bauer, Driessen, & Markowitsch, 2008; Brevers et al., 2014).

Choice implementation refers to the processes involved in making a response to an option, that is action selection. This stage includes response initiation, self-regulation and cognitive inhibition. Response initiation refers to the amount of motivation towards the selected choices (Verdejo-Garcia et al., 2016). In substance abuse, these resources might be compromised as it has been argued that abusers have high levels of apathy. This have been shown in abusers of cocaine, opiates, methamphetamine, alcohol and poly substance users (Albein-Urios, Martínez-González, Lozano, & Verdejo-Garcia, 2013; Pluck et al., 2012; Verdejo-García, Bechara, Recknor, & Pérez-García, 2006). They are often motivated to use drugs but have low motivation to pursue other types of goals. Self-regulation refers to the ability to restrain from temptation (Verdejo-Garcia et al., 2016). As described in the section on impulsivity, abusers have a poor ability to choose a larger delayed reward before a small immediate reward (e.g. Kirby & Petry, 2004), and this means that substance abusers are less likely to restrain from immediate rewards, such as drugs. Opiate users usually select small short-term gains over larger long-term gains. This behavior results in long-term losses (Lemenager et al., 2011). The last part involved in this stage, called cognitive inhibition refers to the ability to inhibit competitive actions and alignment of action and intentions. As also explained in the section on impulsivity, abusers have difficulties in inhibiting actions (e.g. Fillmore & Rush, 2002). So although abusers usually can pick a strategy relevant to align
intentions and action they may have a poor ability to actually implement this behavior (Valls-Serrano, Verdejo-García, & Caracuel, 2016). This suggests that substance abusers’ impulsivity deficits may lead to difficulty in transforming goals to actions.

*Feedback processing*, the last stage, refers to how one’s behavior is shaped by the outcomes of previous experiences (Verdejo-García et al., 2016). In depressant and stimulant users, it has been shown that they show more efficient learning from rewarding outcomes and less efficient learning from punishing outcomes. They also usually rely more on recent compared to past outcomes and their choices are usually less aligned with outcomes. This contributes to poorer decision-making (Fridberg et al., 2010; Stout, Busemeyer, Lin, Grant, & Bonson, 2004). In opiate abusers, it has also been shown that they have less attention towards losses which may explain the reduced ability in decision-making (Ahn et al., 2014). Reward prediction error has been shown to be impaired in cocaine users: that is, how a person predicts an outcome to be, such as winning or losing. Impairments in mechanisms affecting negative reward prediction error in addiction may explain continuous use of drugs despite negative consequences (Parvaz et al., 2015). When tested on people with Parkinson’s disease, increased dopamine transmission in the basal ganglia makes people learn more from positive outcomes than from negative (Frank, Seeberger, & O’Reilly, 2004). Furthermore, in rat studies it has been found that impairments in decision-making can be induced by administrating opiates (Kieres et al., 2004).

As stated above, decision-making deficits often involve the impairment in learning from repeated mistakes. This is usually measured by the Iowa gambling task (Bechara, 2005). Drug abusers continue to make disadvantageous choices, despite losing more and more money (Grant, Contoreggi, & London, 2000). Similar problems have been seen with patients with impairments in the ventromedial PFC, also containing the OFC (Bechara, 2001). According to Bechara (2005) some addicts match patients with ventromedial PFC damage in physiological response, and some do not. The addicts matching with ventromedial PFC patients are only guided by immediate consequences and are oblivious to long-term consequences. One group of addicts who partially match with ventromedial PFC patients may be hypersensitive to drug cues, which then outweighs the aspects of future consequences.

Bechara (2005) further suggests that addiction depends on an imbalance between two separate neural systems controlling decision-making, a reflective system mediated by prefrontal systems for signaling pain for future aspects, and an impulsive system that is mediated by amygdala for signaling pain for immediate aspects. It has been shown that amygdala activation is rapid and stimuli are quickly conditioned: that is, specific responses
are quickly developed for the stimuli (Büchel, Morris, Dolan, & Friston, 1998). In normal decision-making, the reflective system overrules the impulsive system. However, in addiction the opposite happens, meaning that the impulsive system becomes hypersensitive and overrides the reflective system. This impulsive system can hijack the cognitive resources needed for reaching cognitive goals and to occupy the willpower needed to resist drugs. Willpower refers to a combination of self-discipline and determination needed in order to do something despite difficulties that are involved (Bechara, 2005). This switch from prefrontal areas to more striatal areas has also been discussed by Everitt et al. (2008) suggesting that that is the difference between voluntary decision of drug taking to compulsive drug taking. They also suggest that it involves a switch from ventral to more dorsal parts of the striatum.

Dysfunction in PFC has also been shown in opiate users. Opiate use is associated with reduced grey matter density and damage to the white matter in several parts of the PFC, such as OFC and dorsolateral PFC (Qiu et al., 2013; Yuan et al., 2010). Also abnormal functional connectivity has been seen in PFC areas, as well as other areas involved in the mesocorticolimbic pathways, such as ACC, ventral striatum, amygdala and hippocampus (Liu et al., 2009). Alterations in PFC areas, such as the OFC, have been linked to poorer decision-making performance (Qiu et al., 2011). In a study examining rats, opioid administration show reduced function in the OFC (Sun et al., 2006), an area that is known to be important for decision-making (Wallis, 2007).

On one hand, there seems to be evidence for a relationship between length of opiate use and more severe impairments in decision-making, suggesting that the longer one uses opiates the more severe the damage will be in the brain (Yuan et al., 2010; Yuan et al., 2009). However, this result was not found in a recent meta-analysis (Biernacki, McLennan, Terrett, Labuschagne, & Rendell, 2016). However, in this meta-analysis, only relatively long-term users of opiates were measured and brain changes may happen relatively early in the onset of drug use. This meta-analysis also showed that abstinence for an average of just under one year of opiate use was not associated with improvement in decision-making. More long-term studies are needed in order to further examine this question, but it is clear that at least 1.5 years after abstinence, decision-making improvements may be very small (Biernacki et al., 2016).

The kind of drug used may also affect the decision-making abilities. Some studies have suggested that there are differences between the different opiates in decision-making (Ersche
Discussion
The aim of this thesis is to examine the impairments related to substance abuse. Various aspects of addiction have been examined and a description of impairments related to substance use has been provided. The neural aspects of reward and addiction have also been examined identifying that reward generally consists of three parts: “wanting”, liking and learning. “Wanting” and liking may be in accordance but in addiction, that is usually not the case (Berridge & Robinson, 2016), which may be argued for as they have separate neural circuits.

A description of the evidence for and against impairments in cognitive and affective aspects was provided. Some research of working memory showed that substance use can both increase and impair working memory function (Wang et al., 2013). Some early studies suggested that there were not much support for impairments in relation to drug addiction (e.g. Rounsaville et al., 1982), however most recent evidence shows that there are several types of impairments connected drug addiction (e.g. Lopes et al., 2017). There was much support for that there are many impairments related to drug addiction, and in many types of drug addiction, such as in use of stimulants, depressants and opioids. This suggests that there are some similar mechanisms involved in different types of drugs resulting in similar impairments. The mesocorticolimbic system which involves many limbic and prefrontal areas, which handles dopamine, a neurotransmitter much involved in addiction, are compromised. Areas that have been shown to be connected with some impairments seen in addiction, are similar to areas involved in the mesocorticolimbic system. Such as areas of PFC which is involved in both the mesocorticolimbic system as well as many cognitive functions which is seen to be impaired in addiction, for example working memory and decision-making (Bolla et al., 2003). This connection may provide further evidence for impairments in drug use. The hedonic hotspots may with drug use over time become compromised as well, this may also be connected to some impairments related to drug use.

Many of the impairments have been connected to each other: for example, impulsivity and decision-making have a clear connection. As impulsivity often leads to one choosing short-term gains that have bad long-term consequences. Also, working memory is needed to make good decisions. There is also a relationship between impulsivity and working memory (Hester, 2004). This suggests that they go together in drug use, arguing that one may not be...
able to just have one impairment, which suggests that the impairments are extensive affecting many parts of functioning in everyday life. These impairments may also be an answer to the question why drug addiction often involves relapse. The combination of impairments, such as working memory impairments, impulsivity, problems with sustained attention and decision-making, as well as some affective impairments, as empathy deficits, may leave the person helpless to resist the drug. As stated above, when taking drugs the brain changes, and may change in order to make one more prone to take drugs again (Ahmed, 2017), with time the brain may be as changed that it may be almost impossible to recover from drug abuse.

Another reason why relapse is usual may be because of learning. Once we have learned to be motivated by cues related to drugs, it may be hard to break, and the more this is learned, the stronger this sensation gets, making it even harder to get well. In connection with the impairments showed in drug use, it may be hard to relearn, and get the brain motivated towards other things in life. Also, if a person has some of these problems, such as impulsivity, even before drug use, making one more vulnerable for drug addiction, in addition to the problems getting worse once they have started drug use, it might be even harder to resist the drug.

However, once abstinent from the drug, there is different evidence for how long-lasting these impairments may be. Although not comprehensively evaluated in this review, the few articles that were included that examined this had very different results. One study, suggested that improvements in opiate abusers memory function occurs two months after treatment has started (Gruber et al., 2006). A meta-analysis instead suggested that there were no or very small decision-making improvements at least 1,5 years after abstinence in opioid abuse, suggesting that there are long-term cognitive impairments associated with drug use (Biernacki et al., 2016). Another meta-analysis showed that cannabis use impairments were gone after 72 hours of abstinence (Scott et al., 2018) and one study suggesting that use of cannabis seems to have long-term effects on attention (Solowij, Michie, & Fox, 1995). How long-lasting a drugs effects are may not be entirely clear and require further testing, different results on different drugs may be the case.

There seems to be more research done, and therefore more evidence, for cognitive impairments compared to affective impairments in drug addiction. The evidence for affective impairments in this review was mostly based on empathy, however, the causal direction of that research was not entirely clear, suggesting that low empathy levels may be a pre-existing problem that makes a person more vulnerable to an addiction instead of something that is caused by the addiction. But it can also be both ways, that a person vulnerable to a drug
addiction because of low levels of empathy, when the person starts taking drugs, there might be another decrease in empathy. This may need further testing as well as more evidence for a correlation between empathy and drug use. However, there seems to be some affective component that is impaired in addiction, for example seen in problems with emotional facial recognition in drug abusers (Bayrakçi et al., 2015; Fernández-Serrano et al., 2012; Kornreich et al., 2003), although it may not be entirely clear the exact mechanisms mediating it. More focus towards affective impairments related to drug addiction may be required for future research.

In my opinion, as popular as drug taking is, probably because of its often-hedonic effects, they usually have negative long-term effects, because of the usually experienced loss of control over it. This appears in connection with habit forming and memories of the drug. In connection with this the downregulation or sensitization of the mesocorticolimbic pathway, the disease might have long-lasting, possibly permanent effects on the brain. It is hard to unlearn something that has once been learned, so when it has been learned that taking of a drug is rewarding, along with memories of pleasurable experiences with the drug, it might be hard to stay away from it. This is possibly why drug use often involves relapse.

In this modern society however, where demands are high in many domains in life, such as having a great career, at the same time as having a happy family, at the same time as having a healthy lifestyle and so on. It might be hard to live up to all sorts of expectations that society may put on a person. Failure to live up to expectations might lead one to feeling depressed or similar. In connection with having a stressful childhood or having some of the vulnerabilities discussed (e.g. impulsivity) one might be likely to start drug taking to suppress the negative emotions and replace them with short-term positive emotions. This may explain why drug taking is usual in the parts of the world which is not under threat for war or other negative events. However, in those countries, there might be even harder to stay away from drugs.

Some limitations with this thesis might be that it was too broad, the content could have been kept narrower and focused more on the impairments as that was the aim. Then a deeper discussion of the impairments and its neural correlates could have been provided. Important as the other parts describing addiction was, such as the addiction theories and neural parts, it could have been kept shorter. Another weakness might be that some studies could have been looked at in more detail and some could have been left out, which again would have provided a deeper discussion of especially the impairments.
For the future, there may be some parts of the current research field that is not entirely clear as discussed above. There may be more research needed to determine if there are some differences between different kinds of drugs when related to deficits. Although all drugs of abuse seem to be connected to some extent of impairments in the brain leading to behavioral difficulties, there might be differences in the degree of damage between different drugs. For example, as shown in opioid addiction, studies have suggested that there are differences between the different opiates in decision-making (Ersche et al., 2005; Pirastu et al., 2006) and some studies have suggested that is does not matter what kind of opiate is used (Darke et al., 2012; Soyka et al., 2008). This requires further testing as well as testing between different types of drugs. Also, how long impairments lasts after abstinence may require further testing and more testing on emotional/affective impairments related to drug use, as much research today seems to be focusing on cognitive impairments.

**Conclusion**

In conclusion, all the cognitive functions discussed seems to have some relationship with each other, and therefore the impairments may affect each other, for example poor impulse control might lead to poor decision-making. This suggests once cognitive impairments appear, which may appear after a short amount of time in drug use, this affects several parts of normal functioning in everyday life.

There was most research made on cognitive impairments, such as working memory, impulsivity, attention and decision-making. Showing that in substance users working memory usually gets poor, one has problems with delaying instant rewards for bigger future rewards, problems with stopping impulses, problems in sustained attention because that the attention is often drawn to drug cues (and away from other goals). Substance users often make risky decisions with short-term gains and long-term losses.

There also seems to be some affective components affected in drug abuse: for example, research showed that facial emotion recognition, which is important for functioning emotional processing is impaired in drug use. However, the affective impairments relationship with drug use is less clear. This may be a focus for future research.
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MECHANISMS OF ADDICTION


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