NEUROBIOLOGY OF OPIOID ADDICTION

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Abstract

Since the use of opioids started to emerge for analgesic reasons in the 19th century with the synthetization of morphine, opioids have been studied rigorously to better understand its effects on the brain. This thesis shows that both the analgesic effects and the reinforcing effects of opioids are mediated by the same receptor, the mu opioid receptor (MOR). MOR activity has been correlated to both primary and secondary reinforcers and should be considered to cause positive reinforcement together with increases in dopamine transmission for all drugs of abuse, and not only in relation to opioids. Opioid tolerance, dependence and even addiction are to some extent thought to relate to opioids' acute effect of cyclic adenosine monophosphate (cAMP) superactivation. Based upon these findings, the allostasis theory of addiction is considered to be the most suitable in defining opioid addiction. The theory claims that the mesolimbic dopamine system becomes sensitized, increasing the attractiveness of opioids. This while counteradaptation increases the pleasurable tolerance of opioids, encouraging the user to increase its intake for the same initial reward. Furthermore the theory claims that cAMP superactivation is causing an unfolding effect of neurobiological and neurochemical expressions which leads to the disorder of addiction. cAMP superactivation is mediating the negatively reinforcing aspects of opioid addiction together with changes to corticotropin-releasing factor (CRF) in the brain stress system, such as the hypothalamic-pituitary-adrenal (HPA) axis and the extended amygdala.

Keywords: opioids, reinforcement, mu opioid receptor, addiction, allostasis, cAMP
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Introduction

Opioid addiction has been named as one of the most pressing public health issues in the United States (Compton & Volkow, 2006; Zacny et al., 2003). During the past 10 years opioids have been the drug with the highest treatment demands (ranging from 40 to 50%) in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2017). These percentages of opioid addiction treatment demands are very similar to those of the United States (United Nations Office on Drugs and Crime, 2018), which tells us that this is a global public health problem. According to Ballantyne and LaForge (2007) the widespread misuse of opioids can be traced back to the discovery of low rates of addiction when treating acute pain. These observations led to extending opioid treatment for patients with chronic pain, hoping for equivalent results. However, it soon became obvious that there was a difference in addiction rates relating to short-term contra long-term opioid treatments (Ballantyne & LaForge, 2007).

Even though opioids have been researched for many years, and their effects by now are well-established, the rates of addiction are seemingly not decreasing and maintained somewhat stable (European Monitoring Centre for Drugs and Drug Addiction, 2017; United Nations Office on Drugs and Crime, 2018). This tells us that while we understand the main reasons as of how and why use of opioids can lead to the disorder of addiction, we yet seem to be lacking treatments fit to counteract the widespread epidemic. The fact that the endogenous opioid receptor systems extensive involvement in many functions ranging beyond analgesia (Kieffer, 1999; Kieffer & Gavériaux-Ruff, 2002; Koob & Le Moal, 2005; Waldhoer, Bartlett, & Whistler, 2004) suggests that extended administration of opioids may lead to consequences that are not only hard to predict but also demanding to adapt into a standardized treatment model. Of course, this is not an issue separate for opioids, but for all drugs of abuse. However, as opioid receptor function has been implicated not only in the
reinforcing effects of opioids, but that of other drugs of abuse too (Bryant, Zaki, Carroll, & Evans, 2005; Contet, Kieffer, & Befort, 2004), opioids may be a specifically suitable candidate in understanding addiction over all.

In exploring these claims, this review will be introduced with an overview of the endogenous opioid receptor system. Said overview will be followed by a description of both the acute effects, such as analgesia and reinforcement, as well as the chronic effects, such as tolerance and dependence, of exogenous administration of opioids. After understanding these effects, their relation to the behavioral changes taking place during the development of an addiction will be considered based on neurobiological adaptations resulting from extended opioid use. Taken together these findings will aid in exploring different models of addiction as well as evaluate as per which model of addiction opioid addiction should be defined.

**Opioid receptor system**

Most opioids, whether used for analgesia or hedonistic purposes, mimics the effects of endogenous endorphins found in the brain by acting as agonists on the endorphin receptors, from here on referred to as opioid receptors (Somogyi, Barratt, & Coller, 2007). Out of the three main opioid receptors – mu, delta and kappa - mu opioid receptors (MOR) are the ones to which both natural and pharmaceutical opioids bind most selectively (Kolb, Whishaw, & Campbell Teskey, 2016). However, there is some disagreement regarding receptor selectivity of opioids, for example Bryant et al. (2005) claim that definitive receptor selectivity is rare amongst the most common opioids. Initially, the sigma receptor was incorrectly classified as an opioid receptor but was excluded once it became clear it was targeted by other drugs of abuse, such as phencyclidine (PCP) (Waldhoer et al., 2004). More recently, the nociceptin opioid receptor (NOP) was discovered but contrary to other opioid
agonists NOP agonists seemingly does not mediate analgesia to the same extent (Toll, Bruchas, Cox, & Zaveri, 2016). Lambert (2008) states that currently NOP is regarded a non-opioid member of the opioid receptor family. This is mainly due to that its activity is not suppressed by the administration of naloxone (an opioid antagonist), which is a main characteristic of the other opioid receptors (Lambert, 2008).

MOR, together with NOP, delta opioid receptors (DOR) and kappa opioid receptors (KOR) make up the opioid receptor family, consisting of seven transmembrane G protein-coupled receptors (Fields & Margolis, 2015; Toll et al., 2016; Waldhoer et al., 2004). The neurotransmitters which bind to opioid receptors are part of the neuropeptide family. The opioid peptides include endorphins, enkephalins (Gazzaniga, Ivry, & Mangun, 2013), dynorphins (Kolb et al., 2016) and nociceptin (Lambert, 2008). Neuropeptides synthetize in a different way compared to that of faster acting small-molecule transmitters, such as for example serotonin and acetylcholine (Kolb et al., 2016). Neuropeptides are a much larger transmitter consisting of amino acids acting as neurotransmitters directly on synaptic receptors influencing cell structure and function by translating mRNA from a neurons DNA (Kolb et al., 2016).

Koob and Le Moal (2005) suggest that while opioids are very efficient in treating the secondary pain, defined as the extended ache which is experienced after a harmful stimulus inducing acute pain, as well as proving effective in treating emotional pain, they are less effective at treating the initial and often sharply experienced pain. Apart from aiding in analgesia, the receptors to which opioids bind are endogenously involved in key mechanisms of the body such as respiratory and gastrointestinal functions, as well as behavioral aspects such as reinforcement, stress response and nociception (Kieffer, 1999; Kieffer & Gavériaux-Ruff, 2002; Koob & Le Moal, 2005; Waldhoer et al., 2004).
Nociception is defined as the perception of pain, which is caused by a noxious stimulus at a nociceptor.

The endogenous opioids’ widespread involvement in mood regulation and general well-being suggests the opioid system does not only relate to opioid addiction, but other substances of abuse as well. In researching these claims, studies have shown that the reinforcing effects of delta-9-tetrahydrocannabinol (THC), the active component in cannabis, nicotine and alcohol can all be diminished if an opioid antagonist is administered (Bryant et al., 2005; Contet et al., 2004). The administration of a NOP agonist in animal models reduces reward expression of not only morphine, a MOR agonist, but alcohol and stimulants, too (Lambert, 2008). Furthermore, reinforcement from many drugs of abuse, not limited to opioids, have been observed to be completely depleted in MOR deficient strains of knockout mice (Bryant et al., 2005; Contet et al., 2004). This means that the rewarding effects of opioids, and drugs of abuse in general, seem to be at least partially dependent on opioid receptor function, contrary to the previous belief that drug reward mostly is mediated by dopamine. Furthermore, the activation of opioid receptors by both endogenous opioid peptides and exogenous administration of opioid drugs seemingly induce similar effects, both in terms of analgesia and reinforcement. One example of this is Stein, Hassan, Lehrberger, Giefing, & Yassouridis (1993) study in which the administration of naloxone, an opioid antagonist, to human subjects undergoing a knee surgery significantly increased the pain experienced (n = 9), which do suggest that even a reduction in endogenous opioid peptide activity lead to an increased experienced pain.

**Opioid receptors: analgesia and reinforcement**

While analgesia seemingly is mediated by all three main opioid receptors, some receptor variability between various kinds of pain has been observed. Kieffer and Gavériaux-
Ruff (2002) review of knockout mice found that MOR deficient mice expressed a decreased threshold for thermal pain, but neither DOR or KOR deficient mice showed any notable changes to heat induced pain. However, KOR deficient mice showed an increase of chemical pain experienced, while MOR deficient mice expressed an increased threshold for chemical pain, and DOR mutants exhibited no significant changes (Kieffer & Gavériaux-Ruff, 2002).

Even though most literature concerning the reinforcing effects of opioids relate to MOR activity, there are other views too. For example, Waldhoer et al. (2004) suggest that both MOR and DOR agonists mediate rewarding effects, while KOR agonists mainly elicit dysphoria. In discussing possible alternatives to morphine, Coop and MacKerell Jr (2002) mention DOR agonists as a possible candidate. According to them, DOR agonists seem to have few unwanted side-effects - they do not lead to the same rewarding effects as MOR agonists nor the dysphoria related to KOR agonists. However, the reason as of why DOR agonists are not used for analgesia is that compared to MOR and KOR agonists they lack in analgesic potential (Coop & MacKerell Jr, 2002). This is a good example which illustrates the complicated issue of understanding opioid reward and analgesia - although numerous studies have been investigating these matters, certain aspects remain unclear to the extent that alternatives to morphine are hard to find.

That said, the correlation of MOR activity to both analgesia and reward is the most established. Perhaps one of the strongest findings correlating MOR agonists to analgesia is that both DOR and KOR deficient mice with intact MOR still get full analgesic effect from morphine (Kieffer & Gavériaux-Ruff, 2002). Taken together with previous statements regarding analgesia and reinforcement, this will stand as an introducing argument for this thesis’ MOR specification, which the next section will discuss in detail.

Mu opioid receptor
MOR receptor activity’s relation to reinforcement and analgesia can be traced back to Matthes et al. (1996) groundbreaking study. By administering morphine to knockout mice, they noticed no changes to behavior if DOR and KOR were excluded. But when excluding the MOR, both the analgesic effects and behavioral changes related to addiction were eliminated. This is in line with Kieffer (1999) review which suggests MOR relate to the highest analgesic effects and positive reinforcement out of the three main opioid receptors. Acting as confirmation to these results, Fields and Margolis (2015) review found that the analgesic effects and the effects recreational users pursue are related to the same receptor activity, namely the MOR. According to Fields and Margolis (2015) MOR are most commonly found within the ventral tegmental area (VTA) in the midbrain, an area known to be involved in reward mechanisms highly featured in addiction development (Fields & Margolis, 2015; Koob & Le Moal, 2001).

However, the statement that one region is denser than another in terms of MOR expression is widely debated. For example, Kieffer (1999) suggests the highest density of MOR is found in the thalamic nuclei. Further adding to the ambiguity, Waldhoer et al. (2004) suggest the highest density of MOR are in locus coerules, an area that has been correlated to the negative reinforcing aspects of opioid addiction (Nestler, 2001). The most balanced view is presented by Contet et al. (2004) as well as Le Merer et al. (2009), stating that MOR are found in all regions in the brain relating to addiction, including the mesolimbic dopaminergic neurons projecting from the VTA to the nucleus accumbens (NAc).

Before turning to specifics correlating MOR activity with reinforcement, first an understanding of what a reinforcer is, is warranted. Commonly, two distinct types of reinforcers are considered. Primary reinforcers, or natural reinforcers, are defined as something which has a direct benefit for survival (e.g. food and sex), whereas a secondary reinforcer is something with no direct value for our survival but have been conditioned to be
desired through repeated experiences or culture, such as a drug or the concept of money (Gazzaniga et al., 2013).

But what brain regions are involved in the expression of rewarding behavior? The most commonly cited areas concerning reinforcement is the VTA and NAc. The mesolimbic dopamine system originates in the VTA with neurons projecting to the NAc in the basal ganglia before leading all the way to the prefrontal cortex (Kolb et al., 2016). Together, VTA and the NAc make up what is most commonly referred to as the dopamine reward system (Gazzaniga et al., 2013). The reward system, acting through the mesolimbic dopamine pathway, is believed to be involved in the expression of feelings such as wanting, liking and other kind of motivational and goal-oriented behavior related to both primary and secondary reinforcers (Gazzaniga et al., 2013; Kolb et al., 2016).

Furthermore, the amygdala plays a vital role for emotional processing in the brain. Not only does it mediate the expression of different emotions, but it plays an integrative role of emotions in a series of behaviors such as decision making and learning (Gazzaniga et al., 2013), which we will come to learn are all key components in the development and maintenance of addiction. Finally, the hypothalamus is the mediating brain region between the nervous system and the hormone system of the body. It plays a regulatory role between different hormonal expressions and their effects on behavior, including but not limited to the experience of hunger, control of body temperature as well as circadian rhythm (Gazzaniga et al., 2013). All these behavioral effects are mediated by the autonomous nervous system which is under the control of hypothalamic input. Furthermore, behavior such as hunger and sleep control are vital for the maintenance of homeostasis, which is defined as the normal state of the body (Gazzaniga et al., 2013; Kolb et al., 2016). Homeostasis relation to addiction will be discussed more in-depth in a later section, as the focus now will shift to investigate the correlation of MOR activity and reinforcement.
**MOR activity and natural reinforcers.** Le Merrer et al. (2009)

review of reward processing relating to the opioid system in rodent-based models suggest that MOR activity in the NAc and VTA relate to natural reinforcers. While the NAc and the VTA seemingly both mediate the experienced reward from food, the VTA seems to be a sole mediator of sexual reinforcement (Le Merrer et al., 2009). However, other areas of the brain which receive projections from the NAc or VTA play a role too. For example, administering a MOR agonist to the posterior regions of the ventral pallidum has been proven to relate to an increased food reinforcement. Different subareas of the hypothalamus and amygdala seem to have a primary role in both food and sexual reinforcement (Le Merrer et al., 2009). For instance, injecting a MOR agonist to the paraventricular hypothalamus (PVN) elicits a response of increased food intake. Similar results have been observed with the administration of a MOR agonist to the central nucleus of the amygdala (CeA) (Le Merrer et al., 2009). The relation between MOR agonists and sexual reinforcement is more sparsely discussed compared to its relation to food reinforcement according to Le Merrer et al. (2009). That said, the sexual dimorphic medial preoptic area (MPOA) in the anterior region of the hypothalamus is known to relate to sexual control, in which the administration of opioid agonists has shown to relate not only to increased conditioned place preference (CPP), but also increased sexual activity (Le Merrer et al., 2009). CPP, or its counterpart conditioned place aversion (CPA), is a common method used in animal studies to determine the effects of certain reinforcers. First, the amount of time spent in various parts of the test environment are recorded. After conditioning a certain part of the test environment with a drug and another part with a placebo, the researchers compared the amount of time spent after the conditioning session to the pre-test. By doing so, one can tell if the substance has motivational or aversive effects (Bruijnzeel, 2009). Taken together, this discussion highlights the role of the
endogenous opioid system, and MOR activity specifically, in key behavioral features related to brain regions which mediate control and reward of both primary and secondary reinforcers.

**MOR activity and drug reinforcement.** Together with changes to dopamine transmission, Le Merrer et al. (2009) suggest the opioid receptor system to be key to not only opioid reinforcement, but to that of other drugs of abuse too, mainly mediated through MOR. In accordance with the research on natural reinforcement, the VTA and NAc has received much attention in addiction research, with the strongest evidence concerning the VTA based on studies of CPP and self-administration of MOR agonists. While Le Merrer et al. (2009) suggest the evidence concerning opioid reinforcement and NAc is debatable, they mention studies which correlate opioid receptors in the NAc to be involved in in the expression of reinforcement in opioid dependent but not non-dependent animals. Even though evidence correlating the ventral pallidum to opioid reward is sparse, Le Merrer et al. (2009) suggest it contributes to opioid reinforcement based on studies of morphine producing CPP, while a MOR antagonist induced CPA if administered to the ventral pallidum. Furthermore, Johnson, Stellar and Paul (1993) study of DAMGO (a MOR agonist) injections to caudal ventral pallidum found significant increases of reward directed behavior (n = 21), while injections into the rostral ventral pallidum significantly reduced reward behavior. In conclusion, the role of the amygdala in opioid reinforcement is discussed but the results are varying and inconsistent (Le Merrer et al., 2009). More recently however, Wassum, Cely, Balleine, & Maidment (2011) found that MOR activity in the basolateral amygdala significantly relates to changes of incentivizing stimuli. Even though their sample sizes are limited (n = 7 administered with CTOP, a MOR antagonist; n = 12 administered with DAMGO) these findings suggest a possible role for the amygdala and MOR in drug reinforcement. As discussed earlier, the amygdala is a critical component of emotional processing, but what about the ventral pallidum? The ventral pallidum receives neuronal
inputs as well as project to the NAc, VTA and prefrontal cortical structures. This suggests that the ventral pallidum plays an integrative role in reward and motivational behavior contrary to previous beliefs that it only mediated motor actions (Smith, Tindell, Aldridge, & Berridge, 2009). Furthermore, the ventral pallidum contains a high density of MOR, whose activity is a central component in CPP as well as self-administration of drugs (Smith et al., 2009).

**Neurobiology of MOR mediated reinforcement.** In relation to the dopamine and its connection to reward, Johnson and North (1992) found MOR agonists to inhibit GABAergic neurons in the VTA, leading to excitation of dopaminergic neurons indirectly. This may be one of the reasons as to why MOR agonists exhibit reinforcing effects. Zhu and Reith (2008) review investigating the effects of dopamine transporter (DAT) in drugs of abuse found that in relation to opioids, MOR facilitate dopamine release via GABAergic neurons in the VTA and substantia nigra. Moreover, morphine specifically increases dopamine release in the mesolimbic dopaminergic neurons, a system known to relate to addiction (Koob & Le Moal, 2001; Zhu & Reith, 2008). However, Langlois and Nugent (2017) question whether the addictive properties of opioids can be explained by the sole involvement of dopamine, based on limited evidence in human studies compared to that of other drugs of abuse. This is confirmed by Nutt, Lingford-Hughes, Erritzoe, and Stokes (2015), who claim that drugs which do not increase dopamine levels in a similar fashion to stimulants such as for example amphetamine and cocaine may need to be explained with a theory of addiction more encompassing than the dopamine theory of reward, pointing to for example the endogenous opioid and GABA receptors. Further questions arise from observations where dopamine depleted mice still developed CPP after morphine administration, suggesting opioid reward may not be dependent on the involvement of dopamine (Fields & Margolis, 2015). Opioid reward is seemingly not mediated by one single
neurotransmitter or region of the brain, rather it appears to include an integration of mechanisms such as motivation, attention, executive control and memory where dopamine certainly may have a place, although not as the sole mediator (Fields & Margolis, 2015). The in-depth review of MOR activity presented in this thesis so far suggest that MOR endogenously are involved in mediating the reward values of natural reinforcers such as food and sex, as well as giving rise to the reinforcing effects of drugs of abuse in general, including but not limited to opioids.

**Neurobiological effects of opioids**

**Acute effects**

The main reason why opioids have been the go-to drug for clinicians in aiding physical pain is their superior analgesic properties compared to that of the alternatives. Opioid analgesia is related to inhibitory effects of nociception ascending from the dorsal horn of the spinal cord, which receives nociceptive input from the rest of the body, and activation of pain modulating systems descending from the midbrain through the rostral ventromedial medulla to the dorsal horn of the spinal cord (Koob & Le Moal, 2005). In terms of their addictive properties from a behavioral perspective, Koob & Le Moal (2005) define the acute hedonic effects of opioid administration which addicts seek consisting of four phases. The initial phase, termed the rush, consists of an overwhelming euphoria, often described in sexual terms. It is the only effect of opioids which is resistant to tolerance development. After the initial and short-lived rush, the second phase termed the high follows. It is defined as a state of general well-being and is experienced during a much longer time than the rush, sometimes up to hours after administration (Koob & Le Moal, 2005). Following the high is the nod phase, in which the person is distanced from reality as if they were sleeping, or even...
unconscious. The last phase is termed being straight, in which neither of the previous states are experienced, but the withdrawal is yet to occur, and this state can last up to 8 hours after administration (Koob & Le Moal, 2005). All of these phases and their timespans vary depending on route of administration (Koob & Le Moal, 2005). These hedonic effects can be closely related to the previous discussion of opioid reinforcement.

As with any drug, the administration of opioids also come with a variation of undesirable effects and complications. The most common acute side-effects of opioids are nausea and constipation (Benyamin et al., 2008), which both can make treatment difficult. White and Irvine (1999) claim that the most lethal side-effect of opioids is respiratory depression, which is mediated by MOR and DOR. According to them, MOR could be divided into MOR1 and MOR2 subtypes, of which both differ in analgesic properties whereas respiratory depression is mostly mediated by MOR2. This opens for the possibility for some pain to be treated with a safer opioid, developed without the respiratory depressing effects (White & Irvine, 1999).

**Long-term effects**

**Tolerance.** Tolerance is defined either as the loss of drug effects after extended exposure to the drug, as a result of pharmacokinetic, pharmacodynamic or learned effects, or as an innate tolerance to the drug, likely due to genetic differences (Benyamin et al., 2008). Both Kadiev et al. (2008) and Somogyi et al. (2007) confirm that genetic differences do play a part in opioid efficiency and propose that pharmacogenetics could be useful in treatment plan design to avoid giving patients too much medicine. This is based upon significant findings that doses of opioids can vary up to 40-fold in clinical settings (Somogyi et al., 2007).
There are various theories as to why tolerance to opioids develop. Waldhoer et al. (2004) discuss some of them in their review on opioid receptors. The idea that MOR density is downregulated during chronic exposure to opioids has yielded confirmation in vitro, but in vivo studies found evidence for both downregulation and upregulation, as well as no difference at all (Waldhoer et al., 2004). Based on these uncertainties, the idea that MOR might become desensitized gained attention. Yet, as with downregulation, the results vary between in vitro and in vivo studies (Waldhoer et al., 2004). Bryant et al. (2005) confirm these results while arguing that neither desensitization nor downregulation could be responsible for the receptor adaptations relating to tolerance. However, MOR desensitization studies in rat-based animal models show a discrepancy between different brain regions. The most desensitized MOR function was noted in areas relating to nociception, while areas linked to reinforcing effects of opioids displayed little to no desensitization, which could be one of the reasons why analgesic tolerance develops as the reinforcing effects remain untouched (Waldhoer et al., 2004).

Another phenomenon termed cyclic adenosine monophosphate (cAMP) superactivation, known to be related to chronic opioid exposure, might be key to understanding tolerance better from a cellular level (Waldhoer et al., 2004). cAMP superactivation occurs as a response to opioids acute effects of lowering adenylyl cyclase levels, which in chronic use leads to an overcompensation of cAMP activity (Bryant et al., 2005; Nestler, 2001). This has been observed in regions involved in reward, such as the VTA, and regions relating to withdrawal, such as the locus coeruleus (Nestler, 2001; Waldhoer et al., 2004).

Furthermore, tolerance to opioids can vary depending on the environment of administration, i.e. taking an opioid in a different setting than what a user is accustomed to may be associated with a lower tolerance and hence increased risk of overdosing (Benyamin
et al., 2008; Koob & Le Moal, 2005; White & Irvine, 1999). According to Koob & Le Moal (2005) stimuli which have been paired with morphine injections in human studies have been shown to decrease symptoms of withdrawal when presented alone, and similar results have been observed with stimuli paired with opioid withdrawal. Additionally, certain side-effects can emerge depending on setting through associative learning, for instance hyperalgesia (Bryant et al., 2005), defined as an increased sensitivity for pain even when dosage is increased (Benyamin et al., 2008).

Moreover, White and Irvine (1999) mention that tolerance to respiratory depression seems to develop slower than for the rewarding effects, which may be yet another reason of opioids’ lethality. Tolerance to respiratory depression is also observed to decrease after discontinuation, which is an issue for users after detoxification in the case they should relapse (White & Irvine, 1999). Coop and MacKerell Jr (2002) discuss weather tolerance buildup to morphine, a MOR agonist, and its side-effects could be reduced by administering it together with a DOR antagonist. Though, for metabolic reasons a solution as such is yet to be found more successful than the administering of a MOR agonist alone.

**Dependence and withdrawal.** When an opioid tolerance has emerged, some patients develop a physiological dependency of continuous administration of opioids to combat the effects of withdrawal. Opioid dependence can be categorized into two sub-categories, one including the physiological side-effects observed during the withdrawal state, and the other consisting of the psychological effects which can cause a user to relapse despite the discontinuation of the physiological effects (Waldhoer et al., 2004). Koob & Le Moal (2005) define the psychological effects of withdrawal as a state of negative affect, often experienced as dysphoria and anxiety relating to changes in reward thresholds. While the anxiety and depressive states related to opioid withdrawal generally do not qualify as a major psychological disorder, such as depressive or anxiety disorder, the negative affect state is
unpleasant enough to drive the addict back to obtaining more drugs to relieve it, which is why it sometimes is referred to as motivational withdrawal (Koob & Le Moal, 2005). The psychological effects are often experienced together with physiological effects during the withdrawal. These effects include but are not limited to nausea, diarrhea, insomnia, tremors, temperature and blood pressure elevations, dehydration and changes in heart rate (Koob & Le Moal, 2005). Recalling the previous discussion about opioids reinforcing effects it becomes clear that the effects observed during withdrawal, of both psychological and physiological kinds, relate to the same brain areas which are correlated to opioids’ reinforcing effects.

As the effects of opioid dependence are many and varied, Waldhoer et al. (2004) suggest the involvement of multiple regions of the brain in opioid dependence. Waldhoer et al. (2004) state that cAMP superactivation could be a potential hot-topic for future studies relating to both dependence and tolerance, as means of connecting the fields of research. Ballantyne and LaForge (2007) also suggest a role for cAMP in physiological dependence related to opioid use, specifically related to cAMP upregulation in the locus coeruleus. Furthermore, knockout studies with mice found that MOR deficient strains exhibited no signs of morphine withdrawal (Kieffer, 1999), strengthening the indication that changes to MOR activity is responsible for the unpleasant affect states experienced during drug discontinuation. Although, KOR upregulation is likely to be involved in some of the adaptive changes relating to withdrawal (Kieffer, 1999), due to the anxiety-like effects KOR agonists produce (Bruijnzeel, 2009). Koob and Le Moal (2005) relate physical signs of dependence to the periaqueductal gray (PAG), dorsal thalamus and locus coeruleus, while the NAc and amygdala are more likely to be mediating the effects of psychological or motivational dependence. Le Merrer et al. (2009) also suggest that the PAG is likely to be involved in mediating the effects of physical dependence from opioids. In relation to the NAc and amygdala, Le Merrer et al. (2009) suggest that based on our current understanding
neither area is likely playing a key role in dependence. Koob and Le Moal (2005) refer to studies in which decreased extracellular levels of dopamine in the NAc and increased extracellular levels of dopamine in the medial prefrontal cortex as a possible neurobiological cause of the effects observed during opioid withdrawal. Furthermore, Koob and Le Moal (2005) discuss the possible role of corticotropin-releasing factor (CRF) in withdrawal, as well as the role of the extended amygdala, which will be explored in detail in a later section.

Motivational withdrawal aspects of opioids aside, what functions can be correlated to the areas believed to mediate the physical aspects of opioid withdrawal? The PAG is located in the midbrain (Behbehani, 1995) and receives neuronal projections from the limbic system of emotion, including the amygdala (Gazzangia et al., 2013). Its functions range from being involved in analgesia and pain perception to the expression of emotions such as fear and anxiety (Behbehani, 1995). The thalamus has been referred to as the gateway of the cortex (Crick, 1984), and it is providing information from all sensory input apart from olfactory to the cortex (Crick, 1984; Gazzaniga et al., 2013). The locus coeruleus is part of the pons located in the brainstem, for example it is believed to be involved in pain alterations, cardiovascular control and arousal (Gazzaniga et al., 2013). Sara (2009) states that most of the brains’ noradrenaline originates from the locus coeruleus. Noradrenaline is a neuromodulator which is involved in many higher cognitive functions of the forebrain and hence the locus coeruleus could be key to identifying further roles in attention and reinforcing behavior (Sara, 2009). In exploring these brain regions’ effects on the body and behavior, we can see that they all modulate some features relating to the physical aspects commonly related to opioid withdrawal, whether it is the emotional aspects relating to negative affect states or increased experienced pain.
Neurotoxicity

Cunha-Oliveira, Rego and Oliveira (2008) argue that while opioids result in neurotoxicity to a certain extent, compared to other drugs of abuse, such as stimulants, there is much less evidence relating opioid use to neurotoxicity. More recently, different drugs relation to inhibition of neurogenesis has been researched, for which there is a clearer relation to opioid use compared to that of neurotoxicity (Cunha-Oliveira et al., 2008). Furthermore, it has been suggested that during opioid use, KOR are playing a protective role by inhibiting dopamine release in the striatum. The upregulation of KOR activity is a neuroadaptation which remains if chronic opioid use is discontinued. This could pose as a possible answer to the unpleasant effects of opioid withdrawal as well as possibly explain the lower neurotoxicity of opioids compared to stimulants (Bruijnzeel, 2009; Cunha-Oliveira et al., 2008).

Addiction

Based on the previous discussion of MOR activity’s relation to reinforcement, opioids and dopamine activation as well as the current understanding of tolerance and dependence, the following sections will turn to exploring opioid addiction. According to American Psychiatric Association (2013) addiction, or substance use disorder, is defined by a combination of cognitive, behavioral and physiological changes which makes an individual continue to use drugs even though obvious negative side-effects of said drug use are present. Furthermore, typical of addiction is that drugs induce changes to the brain which often persist even after a prolonged period of drug abstinence (American Psychiatric Association, 2013). The American Psychiatric Association (2013) has a specific definition of opioid use disorders, which touches on the complex phenomena of addiction. In their definition, to
mention a few examples, the inability to show up for work due to opioid use or the avoidance of social activities to use opioids could be defined as having an opioid use disorder. Furthermore, more obvious requirements such as developing a tolerance to opioids, experiencing withdrawal or craving opioids are listed as possible diagnostic criteria for an opioid use disorder. This definition leads us to other considerations of addiction, such as that of Koob and Volkow (2010). According to them, addiction is to be defined as a transition from the impulsive act of recreational drug use eventually leading to the compulsivity of addiction. In their opinion, vulnerability for such a transition to occur may be due to a combination of genetic, environmental and social factors that varies between individuals. This is very much in line with how the American Psychiatric Association (2013) currently defines addiction and its possible triggers, which is why this thesis has chosen to adapt this definition over one of the countless other definitions available.

However, Koob and Volkow (2010) definition of addiction further develops on American Psychiatric Association (2013) definition by stating that most addictions can be understood in terms of a cycle consisting of three stages – anticipation (relating to attention and motivation), binge (relating to a failure of executive control) and withdrawal or negative affect (expressed as an increased experienced stress leading to further drug use). Notably, this is not contradictory to American Psychiatric Association (2013) definition, but rather a neurobiological extension of their diagnostics criteria put into a comprehensive model of how an addiction develops and is maintained. There are numerous theories relating to why drug use in some individuals develop into addiction, and while some focus more on one process of the cycle there are more all-encompassing views as well. This is confirmed by human imaging studies which have found the disorder of addiction to involve functional changes to areas of the brain which process: (1) reward and motivation, (2) memory, conditioning and habituation, (3) executive function and inhibitory control, (4) interoception (defined as the
perception of internal state and sensations of the body) as well as self-awareness, and (5) stress reactivity (Koob & Volkow, 2010).

**Neurocircuitry of addiction**

Koob & Volkow (2010) discuss the evidence connecting neuroadaptations and plasticity of brain regions relating to beforementioned processes thought to be involved in addiction. To begin with, the mesolimbic dopamine system has been related to features such as salience attribution (Koob & Volkow, 2010), which means it is involved in attributing stimuli with a subjective feeling of wanting, making the stimuli correlating to its increased activity attractive (Berridge, 2007). While the model of addiction specifically focused on incentivizing stimuli will be discussed in more depth later, it should be noted that the largest base of evidence for such a view is related to stimulants and not opioids (Everitt & Robbins, 2005; Koob & Volkow, 2010). However, it is hypothesized that all drugs of abuse in some respect alter dopamine release leading to plastic transformations on the dopamine system and its receiving neuronal regions (Koob & Volkow, 2010), something which we know opioids do but indirectly so (Johnson & North, 1992). Initial drug use is thought to activate the mesolimbic dopamine system, which projects from the VTA to NAc. Long-term potentiation (LTP) of dopamine neurons in these areas have been observed in relation to morphine administration, mediated through a change of glutamate activity (Koob & Volkow, 2010). Taken together, the integrated dopamine activation in these areas, with extended projections from the orbitofrontal cortex to the dorsal striatum, are thought to relate to incentivizing stimuli. This dopaminergic activation is believed to condition drug taking with pleasantness and reward, masking the initial negative effects of chronic use with salience attribution (Berridge, 2007; Koob & Volkow, 2010). However, as previously noted MOR activity has
been related to increased attractiveness of both primary and secondary reinforcers (Le Merrer et al., 2009) as well as relates to the reinforcing effects of more drugs of abuse not limited to opioids (Bryant et al., 2005; Contet et al., 2004). This suggests that our current understanding of reward and reinforcement may need to include opioid receptor activation in addition to dopamine.

Furthermore, impairments in cognitive control and memory have been shown to be an issue in addicted individuals (Koob & Volkow, 2010). Loss of cognitive control and memory are hypothesized to relate to neuroanatomical changes in frontal structures of the brain such as the orbitofrontal cortex and the anterior cingulate gyrus (Goldstein & Volkow, 2002). In Liu, Matochik, Cadet and London (1998) study of prefrontal cortex volume of polysubstance addicts, i.e. addicts with multiple substance use, they noted that the addicts (n = 25) volume of the prefrontal lobe was significantly lower compared to the control group (n = 14). One direct example of effects relating to such changes is that addicts tend to favor the immediate rewards in studies of delayed gratification, where the ability to resist a small immediate reward for a larger delayed reward (Koob & Volkow, 2010). Impaired performance in delayed gratification tasks has been significantly correlated with decreased gray matter in the inferolateral and dorsolateral frontal cortex (Bjork, Momenan, & Hommer, 2009). As earlier suggested, opioids can disrupt neurogenesis in the hippocampus (Cunha-Oliveira et al., 2008). This could be a vital part of the addiction disorder, as the hippocampus has been proven to assist in conditioning of memories (Koob & Volkow, 2010).

Even though much of the recent models of addiction do not account for negative reinforcement as the sole mediator of addiction, it certainly still plays a part in the integrative decline of cognition seen during addiction. The CeA has been observed with increased CRF activity in the withdrawal process of all drugs of abuse. This function is hypothesized to relate to the compulsivity seen in addiction, as means of alleviating negative
affect states (Koob & Volkow, 2010). In a later section, a model of addiction based upon the dysregulation of these circuits will be discussed more in depth.

**Molecular changes of addiction**

All the beforementioned changes in neural plasticity come with molecular changes that contribute to the maintenance and regulation of said changes to neural systems. While most of the molecular changes are beyond the scope of this review, this section will briefly mention some of the most established ones.

Koob and Volkow (2010) as well as Nestler (2001) discuss cAMP response-element-binding protein (CREB) and its significant role in cAMP upregulation. cAMP upregulation has been proven to relate to all drugs of abuse, but its role in opioid addiction is specifically clear. cAMP upregulation has been observed as an immediate effect of chronic opioid use and it is evidently involved in mediating the effects seen in opioid addiction, particularly in withdrawal (Nestler, 2001). As acute opioid administration leads to lowered levels of adenylyl cyclase, the bodily response is to upregulate cAMP levels in order to compensate during chronic opioid use (Nestler, 2001). While the role of chronically opioid induced cAMP modulations in the rat locus coeruleus has been previously established (Nestler & Tallman, 1988), Terwilliger, Beitner-Johnson, Sevarino, Crain and Nestler (1991) looked for similar alterations in other areas of the brain known to relate to addiction and dependence. Terwilliger et al. (1991) found that apart from the locus coeruleus, significant increases of adenylyl cyclase correlating to chronic morphine administration was observed in the NAc, and less so but still significant increases in the amygdala. Additionally, Nestler (2001) state that cAMP upregulation in the NAc and VTA mediate an increased dysphoria
during early withdrawal stages, while in the dorsal horn of the spinal cord it is related to analgesic tolerance.

cAMP and CREB upregulation in the NAc, thought to relate to opioid effects of dependency as well as withdrawal, seems to be partially mediated by dynorphin, which through a negative feedback loop inhibits dopamine receptors by dynorphinergic actions on KOR (Koob & Volkow, 2010; Nestler, 2001; Nestler, 2005). The modulated effects of dynorphin, CREB and cAMP have all been found to be brief and return to their normal state within a period of days to a week, which does suggest that their role is mostly central to the understanding of the early effects of withdrawal (Nestler, 2001).

Another transcription factor involved in changes to protein expression is Delta FBJ murine osteosarcoma viral oncogene homolog B (Delta FosB) (Koob & Volkow, 2010). Delta FosB has been observed to increase in its availability through extended periods of drug exposure in correlation to many drugs of abuse in the NAc and dorsal striatum (Nestler, 2001). This is of importance because transcription factors alter the speed at which DNA is transmitted into RNA, which leads to changes in cell expression, and could be one of the reasons behind changes to neural functions of these systems after chronic drug intake (Nestler, 2001). Based on animal models of Delta FosB expression in the NAc and dorsal striatum, Nestler (2001) expands its role to not only relate to features of dysphoria, as noted with cAMP upregulation, but to include for the mediation of sensitization of reward and relapse. Animal models of Delta FosB effects has found that it changes the expression of glutamate receptor coding genes in the NAc, reducing the excitability of neurons. Reduced excitability of neurons in the NAc has been observed to correlate with chronic drug administration, suggesting a possible role for Delta FosB in the reduction of drug reward seen in chronic drug use (Nestler, 2001).
The Incentive-Sensitization Theory of Addiction

The most prominent theory of reward and motivation, with clear links to memory, conditioning and habituation is Robinson and Berridge (1993) incentive-sensitization theory of addiction, which resolves around the understanding of why addicts crave drugs. As hypothesized by Robinson & Berridge (1993), neither the urge to get rid of negative effects of persistent drug use, termed negative reinforcement, nor the desire for the subjective pleasurable effects of drugs, termed positive reinforcement, sufficiently explains why addiction develops (Berridge, 2007; Robinson & Berridge, 1993).

The incentive-sensitization theory begins with the proposition that drugs of abuse share a common underlying neuronal activity responsible for their addictive features. Robinson and Berridge (1993) claim that the mesolimbic dopaminergic neurotransmission, known to be involved in incentivizing stimuli, or to make them attractive, is where we should focus our attention. Their central claim is that repeated use of drugs sensitizes the mesolimbic dopamine system, allowing for locomotor, behavioral and motivational effects of drugs to be elicited by a lower dose than normally considered while the set-point for reward is increased (Robinson & Berridge, 1993). While Robinson and Berridge (1993) mostly focus on stimulants in the evidence they present for psychomotor sensitization (i.e. an increased psychomotor activity that correlates with repeated drug exposure), there are studies with similar findings concerning opioids. For example, Joyce and Iversen (1979) found that a direct infusion of morphine into the VTA of rats enhanced locomotor activity, which increased with repeated infusions but was blocked with the addition of an opioid antagonist such as naloxone.
As for the sensitization of incentivizing and motivational effects, Robinson and Berridge (1993) confirm the best evidence to come from studies using CPP. Gaiardi et al. (1991) found that morphine experienced rats, but not morphine naïve rats, significantly correlated with an increased time spent on the previously least preferred side of the cage as well as an increased saccharin intake. Koob, Wall and Bloom (1989) study of opioid antagonist administration in opioid dependent rats found a significantly increased sensitivity to aversive effects of withdrawal relating to opioid receptor activity in the NAc. Their findings suggest that neurobiological adaptations to the NAc may not only relate to changes of reward expression, but also the effects seen during withdrawal such as food aversion. This sensitization is also argued to be persistent and long-lasting, which could explain why relapse is so common in treating addiction even though there has been a long pause in their habit.

Another claim of Robinson and Berridge (1993) theory is that said sensitization can be conditioned to be triggered from environments in which the drug has previously been taken. In Lu et al. (2002) study opioid dependent rats with an established CPP were put under a 21-day morphine free period until the rats stopped showing signs of a CPP. After this period, a single administration of morphine significantly induced CPP yet again and the administration of an opioid antagonist stopped this expression (Lu et al., 2002).

Contrary to previous theories of dopamine and its relation to pleasure, Robinson and Berridge (1993) model of incentive motivation claims that dopamine neurotransmission within the mesolimbic system does not only mediate pleasure or positive reinforcement, as per other models’ suggestions. Pleasure and salience attribution is considered to be of different neural substrates (Robinson & Berridge, 1993), which through interactions between pleasure, learning and incentive salience produce what they refer to as incentive motivation (Berridge, 2007). In addiction incentive motivation is defined as a process starting with generated pleasure from an event, or positive reinforcement, which is associated with an
object or environment through learning to which salience is attributed for future reference. Importantly though, a distinction between pleasure and salience is required – as Robinson and Berridge (1993) argue that pleasure in itself is not what drives addicts’ cravings for drugs, it is the salience attributed which through time is increased by sensitization. Within their report, multiple suggestions as to why this is the case is presented, of which the most compelling could be that repeated drug exposure rarely leads to more subjective pleasurable effects, but less, while the cravings persist and is more challenging to resist.

The neurological basis for these effects are suggested to relate to dopamine, however not exclusively so. Berridge (2007) mentions that the dopamine mediated reward likely is assisted with integration of glutamate, GABA and opioid peptides. Specific focus has been directed to the ventral pallidum, posterior to the NAc with direct projections from the ventral tegmentum. Animal models of neuronal recordings within the ventral pallidum seem to strengthen the relationship between the ventral pallidum and salience attribution to stimuli, after findings that it is involved in the process of conditioning stimuli with aspects of subjective wanting (Berridge, 2007; Smith et al., 2009).

The Allostasis Theory of Addiction

The allostasis theory of addiction could be viewed as an attempt to expand theories of addiction to include a broader scope of understanding, contrary to simply focusing on either reward or motivation (Koob & Le Moal, 1997). It attempts to present a view of addiction based on the understanding of functions relating to all the components of the addiction cycle. In its essence, the effects of the sensitization theory of reward is considered together with the theory of counteradaptation, which states that changes to pleasurable tolerance is due to so called opponent processes. An opponent-process is divided into two
parts. The initial part consists of the positive reinforcing effects of a drug closely related to its administration with a steep tolerance development. The second part relates to the negative reinforcing effects of a drug which tends to exhibit after the initial, pleasurable effects has ended. The secondary effects are slower to decline and get increased exhibition with chronic use (Koob & Le Moal, 2001).

In short, the theory of allostasis resolves around the concept of homeostasis – defined as the maintenance of balance between different physiological systems vital for our survival, in which the reward system is certainly included. When homeostasis is presented with sudden changes to its physiological environment, e.g. intense stressors such as drug exposure, allostasis is the process activated to correct for errors outside of the normal homeostatic range and to ensure that stability is maintained through change (Koob & Le Moal, 2001).

Vital to understanding the allostasis theory is its formulation of how addiction develops and is maintained, which is based upon the addiction cycle briefly mentioned before. Koob & Le Moal (2001) posit that the following three components contribute to the cycle of addiction, also termed spiraling distress: preoccupation-anticipation, binge-intoxication, and withdrawal-negative affect.

The beginning of addiction is thought to relate to cases in which allostasis need to use most of the system’s capacity to correct for noxious alterations, after which a minor set off can trigger the effect of spiraling distress (Koob & Le Moal, 1997). Through counteradaptation and sensitization after continued use, the balance is changed far outside of the normal homeostatic range, leading to further negative affect and compulsory use of drugs as an attempt to reach the previous endogenous balance (Koob & Le Moal, 2001). Koob and Le Moal (2001) review hypothesize that it is mainly changes in activity of the mesolimbic
dopamine system and opioid peptides within it which mediates for reward variations. After an extended exposure to drugs of abuse, the reward system starts to struggle to facilitate not only for the reinforcing effects of drugs, but natural reinforcers too. This altered expression is possibly partly mediated by recruitment of the hypothalamic-pituitary-adrenal (HPA) axis (Koob & Le Moal, 2001), commonly related to mediating components of the fight-or-flight system. The neuroadaptational changes to the HPA axis amongst other brain stress systems is thought to be responsible for the negative affect states, such as abstinence and withdrawal, which further encourages drug use to alleviate the dysphoria. It is a combination of changes to reward set-points in the reward system and a different expression within the brains stress systems which leads a person down the spiral of the addiction cycle after chronic use, specifically if the drug becomes unavailable to the addict (Koob & Le Moal, 2001).

Hence, the allostasis theory of addiction offers a broader scope of the addiction disorder by accounting for more parts of the brain than simply considering the positive reinforcing aspects of drugs of abuse (Koob & Le Moal, 2001; Koob & Volkow, 2010). However, similarly to the incentive sensitization theory of Robinson and Berridge (1993), the allostasis theory claim that the same system which is activated by acute administration of opioids undergo neuroadaptational changes given that the use of drugs is prolonged. As the brain regions which mediate the negative affect states of addiction such as withdrawal becomes sensitized, more neurotransmitters and brain areas are recruited in the process of allostasis to compensate for changes to the original balance (Koob & Le Moal, 2001).

As the mesolimbic dopamine system has been discussed in detail in earlier sections of this review, the coming sections will mainly elaborate on opioids effects on other parts of the brain. CRF systems has been observed to mediate features of withdrawal in animal models (Koob & Le Moal, 2001; Koob & Volkow, 2010). CRF expression in the HPA axis is described to occur through an interaction between CRF, adrenocorticotropic
hormone (ACTH) and glucocorticoids. A stressor such as drug exposure or withdrawal will first increase CRF release, stimulating ACTH release in the pituitary resulting in increased levels of glucocorticoids. Increased levels of glucocorticoids decrease CRF in the PVN but increases CRF levels in the CeA (Koob & Le Moal, 2001). This neurochemical interaction in the HPA axis is thought to relate not only to an increased risk of relapse when presented with a stressful stimulus, but to symptoms experienced during opioid withdrawal (Koob & Le Moal, 2001). CRF activation in the CeA has been observed during opioid withdrawal (Koob & Le Moal, 2001), and administering a CRF receptor antagonist have shown to decrease behaviors linked to opioid withdrawal in animal models (Heinrichs, Menzaghi, Schulteis, Koob, & Stinus, 1995; Koob & Volkow, 2010). Furthermore, while Koob & Le Moal (2001) mostly discuss neuropeptide Y (NPY) role in alcohol addiction and withdrawal, Woldbye, Klomp and Madsen (1998) suggest a role for increases of NPY in opioid withdrawal. They mention a high frequency of NPY neurons and binding sites in brain areas relating to opioid withdrawal, such as the locus coeruleus. Woldbye et al. (1998) found that administering an NPY agonist significantly induced withdrawal in morphine dependent rats, an effect which was dose dependent.

In conclusion, evidence for the extended amygdala involvement in positive and negative drug reinforcement is discussed. The extended amygdala is consisting of basal forebrain structures such as the bed nucleus of the stria terminalis (BNST), the central medial amygdala and the medial posterior part of the NAc (Koob & Le Moal, 2001). The subsystems of the extended amygdala projects to many of the regions previously discussed in relation to both positive and negative reinforcement, such as for example the ventral pallidum and the VTA. Koob & Le Moal (2001) hypothesize that because of this mediating and central role, the extended amygdala may be key to understanding both issues of reinforcement, such as cravings and relapse, as well as negative affect states and compulsivity. While most of the
research correlating the extended amygdala to addiction relates to how MOR and KOR mediates effects of alcohol addiction, Delfs, Zhu, Druhan and Aston-Jones (2000) argue for a significant role of noradrenaline in the BNST for opioid withdrawal. Specifically, afferent projections of noradrenaline from the caudal medulla to the BNST increased in activity during opioid withdrawal, and the increase in cell activity was significantly higher in dependent compared to non-dependent rats (Delfs et al., 2000). Using CPA, Delfs et al. (2000) showed that noradrenaline afferent neurons to the BNST are involved in some of the somatic signs of opioid withdrawal. Furthermore, they suggest that increased noradrenaline during opioid withdrawal has been related to decreased dopamine levels in the NAc, commonly observed in withdrawal from opioids (Delfs et al., 2000).

Evans and Cahill (2016) also favor an allostatic position on addiction, but with the further extension of including associative learning as means of relating opioids effects to alleviating dysphoria or other withdrawal induced negative affect states. Evans and Cahill (2016) propose this thesis’ strongest position on negative reinforcements role in driving addiction, as they state the fear of withdrawal may be a key component in an addict’s urge to continue drug use. In this light, the authors suggest that we consider opioid addiction as a disorder of associative learning, similarly to for example post-traumatic stress disorder (PTSD). This may be fruitful not only for understanding how delayed drug cravings years after drug cessation occur, but for individual susceptibility differences to addiction, too (Evans & Cahill, 2016). Evans and Cahill (2016) suggest that opioids produce a learned relationship for the user between opioids and their effects, which may be remembered in the light of a stressful life event triggering the memory that opioids alleviate emotional pain even years after drug use ceased (Evans & Cahill, 2016). Specifically, opioids with a fast onset and short-half life, such as heroin or fentanyl, are suggested to increase the process of associative learning as it leaves the user often experiencing the reinforcing effects as well as the early
withdrawal (Evans & Cahill, 2016). Furthermore, opioid addiction is not only a cause of the learned associations to the effects experienced during withdrawal, but often occur as a result of an already established mental disorder (e.g. anxiety or depression).

Evans and Cahill (2016) claim the PVN, which projects to both the NAc and the extended amygdala, as well as the BNST to be potential candidates involved in the recall that opioids alleviate emotional pain when presented with a stressor. Regarding which brain areas are involved in triggering cravings during withdrawal Evans and Cahill (2016) argue for the most prominent evidence pointing to the basolateral amygdala and the CeA. In conclusion, Evans and Cahill (2016) argue that due to opioid receptors’ high density throughout the brain together with opioids’ acute effects of inducing cAMP superactivation an allostatic domino effect is created, which can reach far beyond the original site of action.

**Interoception and the Insulas’ Role in Addiction**

Based on neuroimaging studies of the insula as the main location of interoceptive processing (Verdejo-Garcia, Clark, & Dunn, 2012) as well as the observation that lesions to the insular cortex could lead smoking cessation (Naqvi & Bechara, 2009) has lead researchers to investigate its role in addiction. The interoceptive processing of subjective feelings relating to the sensory experience of drug taking (i.e. the feeling of smoking, snorting or injecting opioids), which are mediated by the insula, has been argued to relate to the conscious urges of drug use onset and maintenance (Naqvi & Bechara, 2009). The amygdala and ventromedial prefrontal cortex (VMPFC) have been suggested to mediate the reward value of interoceptive stimuli together with the insula, and for opioids specifically the agranular insula, the anterior regions of the insula, is of interest due to a high density of MOR (Naqvi & Bechara, 2009). Naqvi and Bechara (2009) hypothesize that associative learning
changes the subjective value of certain interoceptive effects relating to drug use, i.e. the unpleasant feeling of smoking becomes pleasant, through dopaminergic neuroadaptations in the insula, amygdala and VMPFC. Additionally, they claim that said changes are habituated to be environmentally conditioned.

Goldstein et al. (2009) review of impaired self-awareness as a basis of addiction involves the insula, the anterior cingulate cortex and the dorsal striatum. Comparing addiction to other disorders of cognition the authors argue that drugs of abuse might modulate the beforementioned brain areas in ways leading to a similar subjective lack of awareness of their disease such as a person with for example unilateral neglect. While most evidence of impaired insula activity relates to a reduction in nicotine addiction, there are studies establishing a role for impaired insula activity relating to other drugs of abuse as well (Goldstein et al., 2009). The anterior cingulate cortex, believed to modulate for decision making, has been observed with reduced activity amongst drug users of numerous drugs, including opioids (Goldstein et al., 2009). Goldstein et al. (2009) also hypothesize that the change from recreational use of drugs to a more compulsive use is characterized by a shift from prefrontal control mechanisms to striatal control, something which Everitt and Robbins (2005) review confirm. Said shift is thought to relate to a reduction of dopamine receptor activity, resulting in a strengthened stimulus-response relationship of conditioned drug signals (Everitt & Robbins, 2005; Goldstein et al., 2009).

However, Verdejo-Garcia et al. (2012) claim that there is little to no clinical evidence speaking for the models that attempt to give the insula a role in our understanding of addiction while its role in mediating subjective feelings such as cravings is well-established (Craig, 2009). Furthermore, the models connecting the insula and addiction are suggested to lack in their ability to account for individual differences of the interoceptive system as well as how this could possibly relate to the separate stages of the addiction cycle. Verdejo-Garcia et
al. (2012) attempt to counteract the lack of previous models’ ability to account for individual differences by suggesting that interoception regulates the relationship between physical responses and processes such as emotional arousal, craving and decision making. This suggestion is an extension to that of other models of interoception and the insula, as Verdejo-Garcia et al. (2012) model considers the strength and accuracy of bodily signals and how they are appraised. Changes in these modulations are what they propose may be the basis of some of the behavioral transitions seen in addicts.

**Loss of Executive Control and Addiction**

With a focus on individual differences in vulnerability to the development of an addiction, George and Koob (2010) discuss how changes to specific modules within the prefrontal cortex, commonly related to functions of executive control, can lower the threshold of control affecting to the correlating part of the addiction cycle of anticipation, intoxication and withdrawal. They suggest that by incorporating a view of the mind as modular, made up of separate and distinct modules independent from one another in their expression, we might be able to understand how some individuals fall victims to addiction while others may not even use recreationally (George & Koob, 2010). While George and Koob (2010) state that there may be a collective component relating to addiction susceptibility, a contrasting view of modularity combined with the concept of loss of control may explain for the individual differences commonly observed with addiction which the collective component theories may fail to encapsulate. With the caveat that no region in the brain is truly modular (i.e. that it exists completely separately from other regions), George and Koob (2010) point toward clear individual differences observed in the mesolimbic dopamine system, stress system of the HPA axis, the extended amygdala, systems of pain processing, modules of habit formation
and decision making. Evidence relating individual differences in all these systems and how they are expressed in correlation with drug related cues and test paradigms are well-established (George & Koob, 2010). In a fully functional brain, the prefrontal cortex and its subareas are in top-down control of modules such as pain and stress. But if said subareas are damaged, their underlying modules of behavior is loosened from the top-down control generally keeping them in balance (George & Koob, 2010). Perhaps most connected to opioid addiction and not yet extensively discussed is how differences in pain perception can aid in the development and maintenance of addiction. Changes to the activity of subareas of the prefrontal cortex, such as the anterior cingulate cortex and the insula, have been correlated with various aspects of decreased control of pain, which certainly contributes to opioid addiction (George & Koob, 2010).

Discussion

The aim of this review has been to present an overview on the thoroughly studied effects of opioids on the central nervous system, accounting for the acute analgesic and reinforcing effects as well as long-term effects such as tolerance and dependence. Building on this framework the second part of the review considers how opioid addiction develops and is maintained from a neurobiological and neurochemical standpoint while referring to common theories of addiction.

Before this discussion turns to its specific findings, two issues regarding the terminology of addiction research will be addressed to clarify the decision making of this thesis. First, the term substance dependence was implemented two decades ago to replace substance addiction as an attempt to de-stigmatize the disorder. However, according to Ballantyne and LaForge (2007), this change of terminology surfaced other issues, especially
in patients with pain where dependence (of physiological and psychological kinds) can develop independently of an addiction. Perhaps due to this ambiguity, there are still many articles being published using the older terminology of addiction. In 2013 DSM-V was published and once again the terminology was changed, this time to substance use disorder, to avoid the possible confusion that substance dependence created (American Psychiatric Association, 2013). In the light of this debate, this review has chosen to use the terminology most frequently used in the published literature, which in certain aspects may reflect the older definitions of addiction which are still frequently being used by researchers. Furthermore, defining addiction is not an easy task as there are countless of definitions available from multiple fields of research ranging from psychology, social sciences, various aspects of health care and neuroscience. For a thesis resolving around cognitive neuroscience, the definition of Koob and Volkow (2010) seemed to be the most suitable definition available. Their definition expands on the neuroscientific findings correlated to the multiple cognitive functions involved in addiction as it is currently defined by American Psychiatric Association (2013). Notably, considering how many times the definition and terminology of addiction have changed during the past two decades it can expected to change soon again, hence the definition used in this thesis may not be accurate to reflect what we consider addiction in the future. The last caveat which needs to be expressed is that if addiction was to be considered from the perspective of another field of research, say psychology, the definition applied in this thesis may not be accurate to the same extent as it is in this context.

Secondly, another issue of terminology is that of opiates contra opioids. Literature, as well as treatment options for opioid addiction, still wrongfully differentiate between opiates and opioids (Monwell & Gerdner, 2017). However there is little to no subjective and pharmacological difference between the classical opiates, such as morphine, and recent pharmaceutical derivates, such as Oxycodone (Kolb et al., 2016; Koob & Le Moal,
2005; Somogyi et al., 2007). Therefore, this review has exclusively used the more including and modern terminology of opioids – which includes the classic opiates as a subgroup, as well as the more recent pharmaceutical opioids.

The recent rise of attention directed toward opioid addiction, specifically in the United States, has so far not been represented in a statistical increase of opioid addiction treatment demands compared to that of previous years even though opioids in many regions is the drug with the highest treatment demands (European Monitoring Centre for Drugs and Drug Addiction, 2017; United Nations Office on Drugs and Crime, 2018). However, the recent report of Brinkley-Rubinstein et al. (2018) state that there is a lack of treatment options available. Furthermore, they state that there is no proper screening procedure for addiction disorders given that someone is caught with an illicit substance in the United States. Therefore, instead of being processed through diversion programs for treatments, addicts may, if caught by the police, be sent to jail and not offered treatment. This suggests that there may be better variables to consider to properly represent the rise of opioid addiction, such as for example overdoses. Rudd, Aleshire, Zibbell and Matthew Gladden (2016) state that from 2000 there was an increase of 200% in deaths from opioid overdoses in the United States, and between 2013 and 2014 there was a 14% increase. This suggests that while problematic use of opioids increase, the ability to systematically treat and counteract this behavior is not working as intended. Moreover, another variable behind the increased overdoses may be that the quality and potency of drugs has increased in the past years while the use of internet has increased its availability (Compton & Volkow, 2006). For example, Compton & Volkow (2006) claim that between 1994 and 2002 emergency care mentions involving the high potency opioid fentanyl increased 50-fold while the prescription of fentanyl only increased 7.2-fold.
The effects of opioid drugs can be traced to the key functions of the opioid receptors to which they bind, such as nociception and stress responses. The opioid receptors extensive involvement in mood regulation has led researchers to investigate their role in not only opioid reward, but also in how opioid receptor activation significantly increases salience attribution to natural reinforcers (Le Merrer et al., 2009) as well as other drugs of abuse (Bryant et al., 2005; Contet et al., 2004). This justifies an increased understanding of how the opioid receptor system mediates reward in general. This review shows that out of the three main opioid receptors, the rewarding effects are mostly mediated through interactions with the MOR (Fields & Margolis, 2015). The MOR’s extensive availability in brain areas commonly related to reinforcing behavior, such as the VTA and the NAc of the mesolimbic dopamine system (Contet et al., 2004; Le Merrer et al., 2009), establish some of the initial links to opioids’ rewarding effects. MOR agonists have been shown to inhibit GABAergic receptors in the VTA, which leads to excitatory effects on dopamine neurons (Johnson & North, 1992). However, recently authors have questioned opioid addiction to be reliant on dopamine’s involvement to the same extent as for example stimulants (Langlois & Nugent, 2017; Nutt et al., 2015).

Apart from the analgesic and pleasurable effects of opioid administration, the use of opioids come with a series of unwanted effects and complications, some of which contribute to opioids lethality. For example, constipation and respiratory depression are an issue both in medicinal and addictively defined use. While the effects of constipation can be treated together with a laxative during prolonged opioid use and supposedly poses the biggest risk in undeveloped countries, the respiratory depressive effects are not as easily avoided through treatment. Additionally, there are numerous drugs which interact with opioids, further increasing the likelihood of respiratory depression to occur, for example alcohol, benzodiazepines and other sedatives. A specifically vulnerable population is for example
individuals undergoing treatment for anxiety disorders with sedatives as well as many polysubstance addicts (due to the high frequency of alcoholism in polysubstance abuse). As per White and Irvine (1999) proposal that a MOR2 agonist could possibly mediate analgesia without the same respiratory depressive effects as the normal MOR agonists such as morphine, so far, the claim seems impossible. The best candidate representing these qualities may be the MOR2 agonist TRIMU-5, but according to Pick, Roques, Gacel, and Pasternak (1992) TRIMU-5 is a mixed MOR2 agonist and a MOR1 antagonist. Their study shows that TRIMU-5 results in little to no analgesic effects when administered alone but can potentiate the effects of spinal analgesia from morphine administration (Pick et al., 1992). This suggests that a mixed dose of TRIMU-5 and morphine could decrease the dosage needed of morphine while the analgesic effect could be kept the same. Lambert (2008) touches on the topic of developing an opioid effective for analgesia with less tolerance development and suggests that administering an MOR agonist together with a NOP antagonist may be the solution.

Furthermore, as with the prolonged use of any drug, the user develops tolerance to the effects of opioids. While most authors agree to that there are genetic and individual differences in the innate tolerance to opioids (Koob & Volkow, 2010; Somogyi et al., 2007) the theories around why tolerance develops after chronic use is less clear, and the results differ between in vivo and in vitro studies correlating to downregulation as well as desensitization of MOR density (Waldhoer et al., 2004). The best candidate to mediate the neuroadaptational changes during chronic opioid use is cAMP superactivation (Waldhoer et al., 2004). cAMP superactivation is not only a direct result of opioid use but it is also observed in many areas of the brain known to be related to opioids’ positive and negative reinforcing effects (Nestler, 2001). For example, cAMP superactivation is believed to cause some of the effects of early withdrawal in the VTA and NAc, as well as causing tolerance to analgesia in the dorsal horn of the spinal cord (Nestler, 2001).
Another major component of chronic opioid use is the dependency which develops, both of physiological and psychological kinds which are often experienced together during cessation of use. Many authors agree that cAMP superactivation is likely to be involved in the effects observed during withdrawal (Ballantyne & LaForge, 2007; Koob & Le Moal, 2005; Nestler, 2001; Waldhoer et al., 2004). However, there seem to be some discrepancy of which brain areas contribute to what effects of withdrawal. For example, Koob & Le Moal (2005) state that the NAc and amygdala are likely mediating the effects of psychological withdrawal, and Le Merrer et al. (2009) argue that neither the NAc or amygdala are thought to be involved in dependence.

The statement that all drugs of abuse alter dopamine release (Koob & Volkow, 2010) is certainly a matter of definition. Looking at the drugs currently scheduled as the ones with highest abuse potential and no medicinal use in the United States, drugs such as lysergic acid diethylamide (LSD) and psilocybin are found (United States Department of Justice Drug Enforcement Administration, 2017). Both LSD and psilocybin are agonists at the 5-HT2A receptor (Egan, Herrick-Davis, Miller, Glennon, & Teitler, 1998; Vollenweider, Vontobel, Hell, & Leenders, 1999), hence neither of these drugs’ main mechanisms is by actions on dopamine receptors. However, there are studies correlating LSD administration to increased dopamine activity in the mesolimbic dopamine system (Kelly & Iversen, 1975). And Vollenweider et al. (1999) study suggest that psilocybin through 5-HT2 interactions modulate dopamine release in the dorsal, but not the ventral striatum. Furthermore, current research state that classic psychedelics such as LSD and psilocybin possibly could treat addiction and other mental disorders such as anxiety and depression, rather than being the cause of them (Bogenschutz & Johnson, 2016; Carhart-Harris et al., 2016), which begs the question if Koob & Volkow (2010) even consider these drugs to have abuse potential.
Based on human imaging studies, addictive drugs have been observed to induce changes to brain systems of reward, memory, executive function and control, interoception and stress response (Koob & Volkow, 2010). In relation to reward and dopamine, morphine results in LTP of dopamine neurons in the mesolimbic dopamine system (Koob & Volkow, 2010), which could pose as an answer to how morphine and other opioids lead to a sensitized incentivization. Furthermore, MOR activity has been directly correlated to influence the attractiveness of both primary and secondary reinforcers. Exploring executive control and memory, in relation to addiction, the volume of the prefrontal cortex has been observed to be smaller in addicts compared to controls (Liu et al., 1998) which has been shown to be a direct cause of impairments in gratification studies (Bjork et al., 2009). However, Cunha-Oliveira et al. (2008) state that opioids are severely less neurotoxic than other drugs of abuse such as alcohol and stimulants, and correlate opioids’ memory impairments more to their ability to hinder neurogenesis in the hippocampus. Notably in Liu et al. (1998) study the addicts, which according to their surveys stated to use heroin, only took what amounts to one small dose of heroin per week, a dosage which probably would not yield any effects in an opioid addict, taking tolerance into consideration. The highest frequencies and dosages were for alcohol and stimulants such as cocaine (Liu et al., 1998). In terms of negative reinforcement, increased CRF activity in the CeA is thought to be the cause for not only opioid withdrawal, but withdrawal from all drugs of abuse (Koob & Le Moal, 2001).

Neurobiological changes aside, opioids and drugs of abuse also induce molecular changes to cell expression by altering not only cAMP levels, but to that of transcription factors too. This means that drugs’ functional changes could be partly due to mutagenic influences (Nestler, 2001).

When discussing theories of addiction, it becomes clear that the theory of incentive-sensitization presents less evidence concerning opioids addictive properties compared to that
of the theory of allostasis. This is in line with the suggestions of Nutt et al. (2015) that opioid addiction is probably a cause of more neuroadaptational and neurochemical changes than those elicited by dopaminergic interactions of opioids. However, even though the focus of the incentive-sensitization theory of addiction is drugs’ ability to induce changes to dopaminergic receptor function, Berridge (2007) remains clear that these effects are not dopamine exclusive. Furthermore, this review shows that the perception that the incentive-sensitization theory relates solely to positive reinforcement, and that the theory of allostasis is based on negative reinforcement only, is rather incorrect. While there is some truth to these definitive statements, they do not capture the full picture. If we are to consider the following statement of the incentive-sensitization theory, that it is not the pleasure derived from drug administration that has the addict coming back for more, it is the urge to get relief from a sensitized state of which the only cure seemingly is to administer more drugs (Robinson & Berridge, 1993), it becomes clear it does not solely resolve around positive reinforcement. The theory of allostasis certainly focuses more on the negative affect states resulting from long-term use of drugs than the initial brief and positive effects. However, if the positively reinforcing states were not as powerful, the addict would perhaps not come back for more, meaning there would be no allostatic changes to the brain. Additionally, a vital part of the allostasis theory is the sensitization of the mesolimbic reward system, which not only confirms the findings of the incentive-sensitization theory but expands it to include the negative reinforcing aspects which are disregarded by the beforementioned theory.

Hence, the inclusion of the brain’s stress systems of the allostasis theory of addiction makes it a more viable candidate to describe opioid addiction compared to that of the incentive-sensitization. The withdrawal characterized by chronic opioid use is thought to be mediated by changes to CRF expression in the CeA and the HPA. The extended amygdala and its sub-regions are also believed to be involved in the effects of both positive and
negative reinforcement, with the best amount of evidence for a role in withdrawal (Delfs et al., 2000; Koob & Le Moal, 2001).

Evans and Cahill (2016) further add the variable of associative learning to the allostasis theory of addiction which makes an interesting point for opioid addiction specifically. For example, tolerance to opioids can also be developed to be environmentally dependent (Koob & Le Moal, 2005; White & Irvine, 1999). This does not only relate to the acute effects of pain alleviation and reinforcement, but environmentally dependent tolerance can be observed with side-effects such as hyperalgesia (Benyamin et al., 2008). This suggest that learned associations might not only be important for the understanding of relapse, but for our understanding of non-pharmacological tolerance too. Again, a role for the extended amygdala and the CeA is suggested in the recall process of opioids’ ability to alleviate negative affect. Most striking is perhaps the argument that cAMP superactivation is causing an allostatic domino effect due to the high frequency of opioid receptors in the brain (Evans & Cahill, 2016) which could pose as an answer to opioids’ widespread effects.

The relation of interoception to addiction is seemingly motivated mostly by research on nicotine addiction. However, in the case of opioids, Naqvi and Bechara (2009) suggest that the anterior region of the insula, the agranular insula, might be involved in mediating interoceptive changes due to the high density of MOR. The shift in interoceptive changes, i.e. the unpleasantness of injecting heroin turning into an activity to look forward to, is explained by changes of dopamine expression in the insula, amygdala and VMPFC (Naqvi & Bechara, 2009). Furthermore, Goldstein et al. (2009) state that the anterior cingulate cortex is of importance in the impaired decision making often seen in addicts. Finally, George and Koob (2010) discuss how the loss of executive control observed in addicts could be due to a shift from top-down control of pain and stress towards a bottom-up model of control, possibly in
the same way Goldstein et al. (2009) as well as Everitt and Robbins (2005) state a shift to occur toward striatal control from prefrontal control.

The largest constraint of this review is that it is very reliant on animal-based models of addiction operationalized to human conditions. Yet, the conditions in which the animals in these studies live generally do not reflect the conditions in which a human addict tend to live. Furthermore, amongst many of the cited articles speaking in favor for claims of a theory of addiction, the sample sizes are very small. Additionally, most of the studies performed on animals are with the use of knockout mice or rats, in which an entire category of receptors has been depleted from their nervous systems. While most of the studies using animal-based models have asserted that knocking out certain receptors doesn’t affect the animal in a way that would hinder the research to be significant, it begs the question whether all the subjective and psychological effects of well-being can be discovered using CPP or CPA, and other locomotive measurements. Even if this is the case, that knockout strains of rodents can posit significant results, the question how well such results translate to a human with an intact and unmodified nervous system is an important one. Yet, ethically there are no better choices to be made than to use knockout mice for these kinds of pharmacological studies to assert human safety.

That said, human subjects do come with challenges to the experimental design too. In the event in which human subjects have been involved in studies of addiction, the designs tend to rely on the addicts’ ability to reliantly reflect upon their drug use and report correct dosage and frequency of use, something which addicts tend to have an issue with. For example, in the study of the volume of the prefrontal cortex in polysubstance addicts most of the ones noting themselves as users of heroin reported a weekly dosage for one single low-threshold dose, which does not accurately reflect a dose someone dependent on heroin would take (Liu et al., 1998). Therefore, it begs the question how much of a change to the volume of
the prefrontal cortex is from the alcohol and cocaine use, which had the highest dosages and frequencies, rather than from heroin use.

Conclusions

Opioids have many and widespread effects on the brain, consciousness and body. The focus has been to describe the positives (such as analgesia) and the negatives (such as reinforcement) of opioids’ pharmacological effects, which is of high value to understanding both for analgesic care and combating the rise in addiction. By considering how opioids lead to the long-term effects of tolerance and dependence, as well as understanding how the transition from sporadic to compulsive use of addiction is mediated by the effects of opioids this thesis ends in a debate about which of the many theories of addiction seem to be most suitable to define opioid addiction. The conclusion is that the allostatic theory of addiction is providing most evidence in favor of describing the many variables of opioid addiction, which resolves around a combination of effects derived from both positive and negative reinforcement. This thesis suggest that the future of opioid addiction research should be focused on finding better ways of treating chronic pain with a substance less damaging than opioids. Perhaps, we need to find or develop a substance which increase the potency of opioids by acting as agonists to the MOR but with less damaging side-effects compared to those of opioids, thereby reducing the dosage needed of opioids.
References


