

THE NEUROBIOLOGY OF KETAMINE AND ADDICTION

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Abstract

Ketamine is a dissociative anesthetic prescription drug and has been used for general anesthesia. The research surrounding this chemical compound has revealed conflicting evidence of its potential use in health care and addiction treatment. On one side, ketamine is a widespread drug of abuse associated with neurocognitive deficits and neurotoxicity, on the other side ketamine has recently been found to have a variety of potential uses, including but not limited to; antidepressant effects, reconsolidation of drug-related memories and disrupting maladaptive rumination. Ketamine's ability to induce psychedelic and mystic experiences, reconsolidation of memories, antidepressant effects, and its ability to reduce cue-induced drug craving makes it a potentially useful tool in drug abuse therapy. Most of the negative side-effects of ketamine seem to be apparent at high doses and in frequent use but low doses and non-frequent use has a low risk of harm, therefore, careful consideration and extensive research are required before ketamine can be widely used in the public and in health care for treatment strategies. This thesis aims to explore the role of ketamine and its neurobiological effects in the treatment of addiction and depression.

Keywords: ketamine, addiction, antidepressants, depression, drug abuse

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Ketamine is a derivative from the compound phencyclidine hydrochloride (PCP) and affects various structures of the brain including N-methyl-d-aspartate receptors (NMDA) which are important for controlling synaptic plasticity and memory function, the dopaminergic system and serotonin receptors and a number of opioid receptors, which can explain ketamine's pain-relieving effects as well. As of the time, ketamine's full mechanism of action is not well-understood. A theorized mechanism of action is that ketamine blocks NMDA receptors on gamma-aminobutyric acidergic (GABA) interneurons, disinhibiting glutamate neurons and projecting to dopamine neurons in the midbrain. This increases glutamate release and subsequently increases dopamine neuron firing and thus increases dopamine levels in projection targets such as the striatum and frontal cortex (Moghaddam, Adams, Verma, & Daly, 1997). Ketamine was first discovered in 1962 by Calvin L. Stevens, an American professor of chemistry at Wayne State University and consultant at Parke Davis where he conducted research on alpha-hydroxyimine rearrangements. Ketamine was tested on human prisoners in 1964 and was approved for clinical use in 1970 in the United States by the Food and Drug Administration and subsequently used as a surgical anesthetic by US soldiers in the Vietnam war and has been used by U.S forces in Afghanistan. Ketamine was preferable over morphine in combat conditions because of ketamine's rapid pain-relieving effect and can be used without life-supporting equipment (Shackelford et al., 2015).

Since the year 2000, when the first placebo-controlled trial investigating the anti-depressant effects of ketamine took place, a number of studies have demonstrated a significant and fast anti-depressant effect of ketamine (Berman, Cappiello, Anand, Oren, Heninger, Charney, & Krystal, 2000; Costi, Van Dam, & Murrrough, 2015). Ketamine has been shown to have a reinforcing effect that induces self-administration and place preference in rats, which suggests that it has a high potential of drug abuse (Botanas et al., 2015; De Luca, & Badiani, 2011; Venniro, Mutti, & Chiamulera, 2015; Winger, Hursh, Casey, &

Woods, 2002). Due to ketamine's reinforcing properties, its use as a recreational drug became popular in the 1980s, and its illicit use has spread worldwide but has recently seen a decline (Bokor, & Anderson, 2014). Over the past decades, ketamine abuse has spread rapidly in cities in Asia, with Hong Kong being one of the major places for ketamine abuse. There was over 2000 reported cases of ketamine abuse in 2013 and 2014 in Hong-Kong alone (Liu, Lin, Wu, & Zhou, 2016).

Ketamine has a plasma half-life of 2-4h (Copeland, & Dillon, 2005). Plasma half-life is the time period required for the amount of the drug in the body to be reduced by one-half. The common administration routes include intravenous, intramuscular, intranasal, and smoking and the typical recreational dosages range from 50-100mg. Ketamine, when used clinically, is most often administered intravenously and rapidly induces sedation, dissociation, and analgesia. For anesthetic purposes, it lacks the major negative effects on the respiratory and circulatory system that many other anesthetics have and can be administered without oxygen and electricity. In this light, the World Health Organization have determined it as an essential medicine (Morgan, Muetzfeldt, & Curran, 2009; Ivan Ezquerra-Romano, Lawn, Krupitsky, & Morgan, 2018).

When ketamine is used in lower doses than those used for anesthetizing (sub-anesthetic doses) humans, it produces effects such as dissociation (including out-of-body experiences), euphoria, closed- and open-eyed visual hallucinations, spiritual experiences, antidepressant effects and pain relief (Muetzfeldt et al., 2008). Ketamine's abuse potential and antidepressant effects have been linked to ketamine's effects on the dopaminergic system, which is implemented in most theories of addiction which will be discussed further in this thesis.

The aim of this thesis is to explore the potential use of ketamine in the treatment of addiction and depression, and to review the positive and negative effects of ketamine

administration. The reason that addiction and depression is the most widely discussed subject in this thesis is because the body of research on ketamine to this date has mainly revolved around these topics.

The Evolving Role of Dopamine in Addiction

In 1954, our modern understanding of reward mechanisms of the brain was initiated by Olds and Milner. Rodents were given the opportunity to self-administer electrical stimulation to various brain regions. Septal areas, mammillothalamic tract and cingulate cortex were found to elicit persistent self-stimulation, often to the point where other behaviors were neglected. In subsequent research, it was later demonstrated that humans would similarly self-administer electrical stimuli obsessively to specific “pleasure areas” of the brain (Olds & Milner, 1954). Over the course of subsequent decades, the pathways, areas, and neurotransmitters implicated in the experience of reward were further discovered. The mesolimbic pathway was in particular identified as the key component in reward assessment. The mesolimbic pathway connects dopaminergic cell bodies in the Ventral tegmental area (VTA) mainly with the Nucleus accumbens (NAc) and the amygdala but also to some extent with bed nucleus of stria terminalis, lateral septal area, and lateral hypothalamus (Trigo, Martin-García, Berrendero, Robledo, & Maldonado, 2010; Volkow, Wang, Fowler, Tomasi, & Telang, 2011).

The experience of reward is accompanied by activation of this mesolimbic dopaminergic pathway. So-called ‘natural rewards’ such as food and sex and most recreational drugs respectively increase the extracellular concentration of mesolimbic dopamine (DA). Stimulants such as cocaine and amphetamines are considered as prototypic drugs of reward due to their direct effect on dopaminergic activity (Adinoff, 2004). This is why cocaine addiction is one of the most common dependencies to be scientifically studied. A famous study by Bozarth and Wise (1984) made clear that there is an anatomical distinction between drug reward and drug withdrawal and further confirmed the importance of the

mesolimbic pathway in drug self-administration. In this 1984 study, morphine was administered into the VTA or the periventricular gray (PVG) of rats' brains for a duration of 72 hours, and after the morphine administration, the substance naloxone which is an opioid antagonist was administered. The results showed that the PVG morphine-infused rats went through withdrawal, and the VTA morphine-infused rats did not go through withdrawal. The rats were also trained to self-administer morphine, but this only worked for the rats in which morphine was administered into the VTA but not for the rats in which morphine was administered into the PVG (Bozarth, & Wise, 1984). This study demonstrated a separation between the processes involved in withdrawal and reward and supports the role of the VTA in reward processes.

With the use of Functional magnetic resonance imaging (fMRI) Breiter et al. (1997), managed to distinguish the neural correlates of the “rush” experience from the “craving” experience in cocaine administration. During the rush but not craving for cocaine, increased activation in the VTA consistent with activation of the mesolimbic pathway was observed (Breiter et al., 1997).

A general assumption guiding addiction research for much of the past two decades has been that the addictive effects of the primary substances of abuse were dependent on dopaminergic activation of the mesolimbic pathway.

The association found between the mesolimbic activation and the high or rush suggested that DA was in itself responsible for the hedonic (pleasure) feelings associated with rewards. The addictive behaviors were thought of as a consequence of a continued need for heightened DA concentrations and the resulting pleasure in the mesolimbic pathway and associated regions (Adinoff, 2004). The binge use of dopaminergic substances would then result in a state of DA deficit, which would lead to a “crash” and a biologic demand (craving) for more substances to replenish the depleted DA stores (Adinoff, 2004). This drug-induced

DA-depletion has been referred to as the “dopamine depletion hypothesis” or the “general anhedonia model”. Further PET studies gave support to this theory of dysregulation of the dopaminergic system (Adinoff, 2004). There was shown to be an increase of striatal DAT (presynaptic dopamine transporters) and a decrease of DA D2 receptors by PET studies which further supported a dysregulation of the dopaminergic system. The attenuation of the D2 striatal concentrations was hypothesized to weaken the reinforcing salience of natural rewards and to strengthen the need for substance-induced DA elevations. An example of this was a study conducted by Thanos et al., (2001), who showed that an increase in D2 receptors decreases alcohol self-administration in rodents, but primates with a lower number of D2 receptors demonstrate higher rates of cocaine self-administration (Thanos et al., 2001).

However, attempts to treat cocaine addiction by activation of dopaminergic receptors have not been successful. Another puzzling discovery was made by Rocha et al. (1998) who studied genetically altered mice in which the DAT receptor was not expressed. Without DAT receptors, the administration of cocaine did not induce an increase in DA. The mice, however, still self-administered similar amounts of cocaine as mice with intact DAT receptors. This revealed that neither DAT nor increase of synaptic DA concentrations were essential for self-administration of cocaine (Rocha et al., 1998). Additional studies by Rocha and colleagues suggests that the reinforcing abilities of cocaine may be mediated by serotonergic reuptake transporters (Adinoff, 2004).

These findings have forced the research on dopamine’s relationship to addiction and withdrawal to change its course. It would seem that the relationship between dopamine and addiction is a much more complex one than first expected. It was later realized that dopamine function in reward is more often linked to anticipatory, preparatory, appetitive, or approach stages of motivated behavior. This realization led to the proposal of alternative

hypotheses regarding the psychological functions of mesolimbic dopamine systems in reward and addiction.

The Incentive-Saliency Hypothesis

The incentive-saliency hypothesis proposed by Berridge and Robinson, (1998, 2001, 2003, 2016) suggests that addictive behavior is due largely to progressive and persistent neuroadaptations caused by repeated drug use. To explain this, the authors claim that process of reward can be separated into two distinct components of ‘wanting’ and ‘liking’ and that these processes are mediated by different separable neural systems. It further suggests that dopamine mediates the ‘wanting’ but not the ‘liking’ component of rewards. Incentive-saliency transforms neural representations of conditioned stimuli from a neutral representation into an ‘attractive’ and ‘wanted’ incentive that can grab attention. This incentive-saliency is also motivational, it transforms the neural representation of a stimulus into an object of attraction that animals will put in an effort to acquire. In this hypothesis, the dopamine-related neural systems that mediate this ‘wanting’ also interact with but are separable from hedonic and associative learning components in order to produce the larger whole process of reward which cannot be reduced to one specific function or process.

By neural and pharmacological manipulations, incentive-saliency can be triggered independently from associative learning and hedonic activation. This separation was shown by a study by Lamb et al. (1991) who showed that drug liking was not a prerequisite for drug-seeking and drug-taking behavior, in which subjects would maintain self-administration of drugs without the subjective pleasure of the behavior. Another study discussed by Schultz in a review from 2010 showed that DA neurons fire only in response to novel rewards, regardless of the hedonic value of the reward, and the activation was dependent on the predictability of the reward. With each repeated presentation of the stimulus, the DA discharge lessens until the stimulus no longer produces a neuronal response (Schultz,

2010). This shows that the “liking” of a drug needs not increase with sensitization, the “liking” may even decrease. This would then be in line with the incentive salience hypothesis, meaning that individuals that are addicted to drugs experience less pleasurable feelings from the drug than non-addicted individuals.

Traditional methods of measuring reward value usually rely on measuring the degree to which the reward is ‘wanted’ such as consumption tests, choice tests, place preference etc. These behavioral measures require an animal to seek a reinforcer and infer ‘liking’ indirectly from ‘wanting’ on an assumption that if something is ‘wanted’ it is automatically ‘liked’. If the incentive-salience hypothesis is true, and there is a distinct separation between wanting and liking, then we cannot infer ‘liking’ on ‘wanting’, rendering these kinds of behavioral measures useless if we want to measure degrees of ‘liking’. Berridge and Robinson (1998) instead suggest that the use of measures based on affective reaction to access ‘liking’ for a stimulus independently of ‘wanting’ it is more reliant. Using these affective reaction measures Berridge and Robinson (1998, 2001, 2003) provided various lines of evidence against the anhedonia hypothesis. Berridge and Robinson suggested that if the anhedonia hypothesis were correct, then DA depletion should reduce hedonic reactions to sucrose because a DA deficit is suggested to weaken the salience of rewards and/or increase aversive reaction patterns to quinine (a bitter-tasting substance) because DA depletion was thought to increase aversive affective reactions.

This was not the case. Suppression of dopamine function by lesions did not alter the ability of rats to make hedonic evaluations, despite removing the incentive value of food, water, and other rewards. Nor did the dopamine depletion suppress the learning of new hedonic relationships between conditioned and unconditioned stimuli. Lacking incentive salience attribution, dopamine-depleted rats cannot use their hedonic and associative competence to transform the perception or representation of a reward into a target incentive

that is attractive and ‘wanted’. Dopamine-depleted rats still ‘like’ rewards, and still know the rewards they ‘like’. They simply fail to ‘want’ rewards they ‘like’.

There seems to be an increasing dissociation between the incentive properties of drugs and their subjective pleasurable effects during the span of repeated drug use. In the light of this, the seemingly irrational behavior of human adult addicts becomes more sensible. At a conscious level, the addict may know all the negative consequences of his or her drug use and even despise his or her situation, but still, experience a deep craving for the drug. If the process of salience attribution can be activated, independent of subjective pleasure, incentive salience can be strong even without any pleasurable effects of the drug. Gradually, ‘wanting’ is transformed into craving, and drug-associated stimuli elicit this craving independent of any pleasure they produce (Berridge, & Robinson, 1998, 2016).

Priming and Relapse Explained by Incentive-Salience Hypothesis

There is considerable evidence that re-exposure to drugs can reinstate compulsive drug-seeking and drug-taking behavior, a phenomenon known as ‘priming’. The ability of drugs to produce incentive salience by repeated drug administration is progressively increased by sensitizing the mesotelencephalic dopamine systems (Adinoff, 2004). Thus, in highly sensitized individuals such as drug-addicts, not relapsing to the drug is almost impossible after priming, because it acts on a hypersensitive neural system that elicits a very strong ‘wanting’ (craving) and therefore they relapse (Adinoff, 2004). One can say that the reinstating of drugs in the body of an addict produces strong ‘wanting’ instead of subjective pleasure.

Drugs can even prime responding for other drugs because the same dopamine systems are activated by different drugs and dopamine mediates the incentive-salience attributed to many different drugs (Berridge & Robinson, 1998). It’s not only direct re-exposure to drugs that can stimulate priming and relapse, exposure to environmental stimuli

that are associated with drugs are known to induce craving and relapse in humans, and prime drug responding in animals. The incentive-salience hypothesis can explain this as well. The sensitization of a neural system that is responsible for incentive-salience becomes expressed as addictive behavior mainly by increasing the incentive properties of stimuli associated with drugs. The heightened incentive-salience then focuses on these stimuli and their mental representations by processes of associative learning and they become the evokers and objects of craving. The drug-related stimuli stay potent conditioned incentives able to excite the attribution of incentive-salience even long after signs of withdrawal have faded (Berridge & Robinson, 1998). Stress is also something that is generally considered to potentially elicit relapse to drug use. The traditional explanation is thought to be that it triggers a need for escape from the unpleasant situation via drug use. The incentive-salience hypothesis instead suggests that both addictive drugs and stress activate and sensitize the dopamine systems. Drug-associated cues would be especially potent as a consequence of stress. If this hypothesis were true, then it could mean that prior exposure to regularly occurrent stress may predispose susceptible individuals to drug addiction by the same process of sensitization of neural systems that mediates the incentive motivational effects of drugs. In these individuals, the initial drug experience may have an increased effect on the incentive motivational processes because of previously sensitized neural systems (Berridge & Robinson, 1998).

Dopamine and Ketamine: The Relationship

In 2018 Kokkinou, Ashok and Howes published a meta-analysis of ketamine's effects on the dopaminergic system including primate, rodent and human studies. Acute ketamine administration leads to increased dopamine levels in the frontal cortex, striatum and nucleus accumbens in rodents. Kokkinou et al. (2018) suggest that these findings point to that the dopaminergic effects potentially contribute to the acute antidepressant and psychotomimetic (Schizophrenia-like) effects accompanied with ketamine use.

Three human studies on ketamine's effects on neurons in VTA (Ventral tegmental area) included in the meta-analysis showed an increase in neuronal firing. The findings that ketamine increases dopamine levels suggests that ketamine has similar dopaminergic effects as stimulants and other recreational drugs (Kokkinou et al., 2018). This implies that the dopaminergic effects may contribute to ketamine's abuse potential and the development of dependence (Kokkinou et al., 2018).

Subanesthetic doses of ketamine rapidly increase DA release in the medial prefrontal cortex (mPFC) of rats and repeated administration increases the basal dopamine levels (Lindfors, Barati, & O'Connor, 1997; Tan, Lam, Wai, Yu, & Yew, 2012). Dopamine transmission in the PFC is of importance for working memory, and an excess of dopaminergic transmission in the PFC interferes with cognitive functions such as working memory (Lindfors et al., 1997).

All studies of dopamine levels following anesthetic doses of ketamine included in the meta-analysis showed no change in dopamine levels. The dopaminergic and stimulatory effects of ketamine then only seem to be apparent at low dosages and disappear at higher anesthetic doses (Kokkinou et al., 2018).

Following long-term ketamine administration (3 months), results showed increased total DA levels correlated with an up-regulation of DA synthesis related enzymes in the brain. These findings suggest that long-term ketamine abuse leads to DA dysregulation in the central nervous system (Tan et al., 2012).

Findings from a study conducted by Masuzawa et al., (2003) demonstrated that ketamine significantly increased dopamine release in the NAC in a dose-dependent relationship. Drawing from their own research and earlier research, they hypothesize that this effect on the dopamine release in the NAC is the cause of both the psychotomimetic activity and the addictive potential of ketamine (Masuzawa et al., 2003).

The antidepressant effects of ketamine could be attributed to ketamine's ability to increase dopamine neuron firing, and consequently, dopamine release to enable the appropriate association between social interactions and reward (Kokkinou et al., 2018).

Ketamine Beyond Addiction: Treatment of Substance Abuse and Depression

The positive reinforcing properties of ketamine include a dissociative and euphoric effect. The most common negative effects of ketamine abstinence are fatigue, appetite loss, craving, anxiety, drowsiness and dysphoria (Liu et al., 2016).

People with substance abuse disorders show notably higher rates of depression than the average of the rest of the general population. High levels of anxiety and depression may also predispose relapse to various drugs of abuse. Hence, a treatment option that can rapidly and reliably treat depression and anxiety symptoms should be effective in treating substance abuse disorders (Ivan Ezquerra-Romano et al., 2018). There is a great deal of evidence that shows that ketamine is a useful and efficient tool for treating depression and furthermore addiction.

Drug-Related Memories

Research that explored the effects of ketamine on the expression of drug-related memories has been conducted. After memories have been consolidated, they are thought to be stored in a stabilized state after the initial acquisition. Shortly after reactivation of these consolidated memories, they are rendered unstable and labile for a short while before they re-stabilize, this process is called reconsolidation. After reconsolidation of memories, the memories can have been altered or updated in various ways, and each time they are reactivated, they are susceptible to change. This phenomenon was first demonstrated in animals using fear conditioning, where rats were trained to associate a neutral stimulus with an electrical shock to the extent that the neutral stimulus alone elicited a fear response. The researchers then continued to eliminate this fear response by pharmacologically disrupting the reconsolidation

process (Ivan Ezquerra-Romano et al., 2018). Based on this research, it might be possible to treat addiction by pharmacologically disrupting the reconsolidation of drug-related memories, and in that way changing the way those memories affect the addicted subject.

In one preclinical study, the effects of ketamine administration on memory reconsolidation of morphine-induced conditioned place preference in rats were examined. After the morphine conditioned place preference was induced, ketamine was administered at a dose of 60mg/kg after the rats were re-exposed to the conditioned context or as they were in their home cage. After the ketamine administration, the preference for morphine was decreased significantly in the first retest. This was interpreted that ketamine disrupts reconsolidation of the environmental-drug memory (Ivan Ezquerra-Romano et al., 2018). Furthermore, in line with these findings, a review from 2017 by Fattore, Piva, Zanda, Fumagalli, and Chiamulera suggested that ketamine and other psychedelic substances may be able to disrupt maladaptive appetite memories.

Ketamine Psychedelic Therapy (KPT)

In 1997, Krupitsky and Grinenko reported the successful use of ketamine to reduce the relapse in recently detoxified alcoholics. The procedure investigated was ketamine Psychedelic Therapy (KPT) which had been used in the former Soviet Union until ketamine was banned in Russia since 1998. Krupitsky and Grinenko reported that KPT was used in over 1000 alcoholics with no complications. Later on, in a further study by Krupitsky, Burakov, Romanova, Dunaevsky, Strassman, & Grinenko (2002), 70 detoxified heroin-dependent patients were randomized into two KPT groups. Each group was administered different dosages of ketamine, where one group received 0.2 mg/kg intramuscular ketamine, which was considered to be an active placebo and the other experimental group received 2.0mg/kg intramuscular ketamine. After a two-year follow-up control, the experimental group which received a higher dose of ketamine resulted in a significantly greater rate of abstinence than

the lower dose group (17% vs 2%). This was taken to be evidence that the effectiveness of ketamine was dose-dependent, and that ketamine has an ability to treat heroin-dependence (Krupitsky et al., 2002). Krupitsky, Burakov, Dunaevsky, Romanova, Slavina, & Grinenko, (2007) conducted further research where they compared the effectiveness of a single versus three KPT sessions in 59 detoxified heroin-dependent patients. After one year 50% of the group that underwent three KPT sessions remained abstinent and only 22% of the group that underwent a single KPT session remained abstinent. This would then demonstrate that KPT sessions are beneficial and that repeated doses of ketamine have a greater impact than a single dose.

Anecdotal and qualitative reports from these studies have suggested that the subjective psychedelic experiences seemed to help patients (Krupitsky et al., 2007). Mystical experiences and psychedelic effects have been shown to be beneficial for psychological health in long-term studies (Griffiths, Richards, Johnson, McCann, & Jesse, 2006, 2008). Patients reported that the degree of mystical experience was linked to the insight and impact of KPT (Ivan Ezquerra-Romano et al., 2018). Improvements after the ketamine experience reported were increased spirituality, self-concept, emotional attitudes to other people and positive life changes and purpose (Ivan Ezquerra-Romano et al., 2018). These changes in the psychological domain were considered as favorable and to promote abstinence (Ivan Ezquerra-Romano et al., 2018). In the majority of the literature, psychedelic and mystical experiences have been considered as adverse side-effects and this has limited the worldwide medical use of this substance (Ivan Ezquerra-Romano et al., 2018). The studies presented here suggest that these subjective psychological effects have an important impact on the ketamine treatments. Therefore, according to (Ivan Ezquerra-Romano et al., 2018) there needs to be a re-framing of these psychological effects as therapeutic and more research should be conducted on the subject.

Ketamine was shown to have promising effects on motivation to quit cocaine and reduce cue-induced cocaine craving, 24 hours after administration. This was shown in a study by Dakwar, Levin, Foltin, Nunes, and Hart from 2014, where 8 volunteers with an active cocaine dependence participated in a crossover, double-blind trial. The effects of a single ketamine infusion of either 0.41 mg/kg or 0.71 mg/kg over 42 minutes and the effects of two ketamine doses of 0.41 mg/kg and 0.71 mg/kg in randomized order were compared with an active control of lorazepam on assessments of motivation to quit cocaine and cue-induced craving. The motivation to quit cocaine was assessed using the University of Rhode Island change assessment, which is a 32-item questionnaire made to ascertain readiness for change in cocaine users. The cue-induced craving was assessed using the visual analog scale for cocaine craving. Both assessments were made at baseline and 24 hours post-infusion. The results showed that a single dose of 0.41 mg/kg increased the motivation to quit cocaine and lessened the cue-induced craving. A second dose of 0.71 mg/kg further lessened the cue-induced craving (Dakwar et al., 2014). However, this study is limited in its validity due to the small sample size.

Ketamine, Depression and Functional Connectivity

Studies using fMRI have found that there are certain brain regions that consistently show higher levels of activity during resting states (when doing nothing) than during cognitive tasks. The areas found to have this greater level of activity are the posterior cingulate cortex (PCC), ventral anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), left inferior parietal cortex (IPC) and together they are called the default mode network (Raichle et al., 2001). The default mode network is hypothesized to be active when the mind wanders, usually involving thinking about others, one's self, remembering the past, thinking about the future and assessing what is personally significant. The default mode network gives individuals the ability to disengage from the external world and turn their thought inwards

(Andrews-Hanna, 2012). Patients suffering from major depressive disorder (MDD), show a failure to down-regulate activity within the default mode network in the presence of external stimulation, with higher levels of default mode network activity being correlated with increased levels of maladaptive and depressive rumination and with lower levels of adaptive, reflective rumination (Scheidegger et al., 2012).

A study from 2010 conducted by Sheline, Price, Yan, and Mintun with the aim to better understand the intrinsic connections between brain areas in major depression, conducted a fMRI investigation of three major brain networks in 18 patients diagnosed with major depression the cognitive control network, default mode network and the affective network. They found that compared to controls, in depressed patients these three networks had increased connectivity to the same brain regions, located in the bilateral dorsal medial prefrontal cortex, which the researchers then termed as the dorsal nexus (DN) ($p < 0.001$). They suggest that this discovery could provide a possible mechanism to explain the symptoms of major depression – lessened ability to focus in cognitive tasks, copious self-focus, escalated alertness, and dysregulation of emotional, visceral, and autonomic functions- can occur simultaneously and synergistically. The theorized mechanism of action is that the depressed brain has somehow fused together these networks by the dorsal nexus, giving rise to the symptomatology of major depression. Hence, reducing this connectivity of the dorsal nexus could hypothetically improve the symptoms of major depression (Sheline et al., 2010).

Scheidegger et al., (2012) published a study using fMRI and Blood-oxygen-level dependent imaging (BOLD) and reported a reduction of resting-state functional connectivity between areas of the default mode network via the DN, pregenual anterior cingulate (PACC), and the MPFC, in 17 healthy volunteers after 24 hours of ketamine administration (0.25mg/kg intravenously over 45min) ($p < 0.05$). This finding of decreased functional connectivity via the DN after ketamine administration is suggested to have implications for ketamine's therapeutic

action in MDD patients recently observed in other studies. The authors suggest that the changes observed 24-hours after ketamine administration might be due to adaptive changes in neuroglial glutamatergic throughput, neuroplasticity and information processing of specific neurocircuits. This is in support of the theory that glutamatergic modulation is the cause of the antidepressant effects of drugs such as ketamine via reconfiguration of resting-state functional connectivity (Scheidegger et al., 2012).

In line with previous studies described, ketamine has further been shown to decrease connectivity between and within resting-state consciousness networks. Reduction in connectivity between the mPFC and the rest of the default mode network along with the activity of salience and visual network has been shown in studies with subjects suffering from depression (Ivan Ezquerra-Romano et al., 2018). Studies which incorporate subjects affected by depression have shown that the connectivity with the mPFC is elevated, and ketamine's ability to reduce this connectivity could be a useful tool to treat depressive states which are highly correlated with addiction and a common predictor of relapse. However, Vollenweider and Komater (2010) have proposed a common mechanism of psychedelics in depression treatment, which is an increase in neuronal activity in the PFC, anterior cingulate cortex, and insula. This increase in activity is hypothesized to help normalize corticolimbic system connectivity which is suggested to be disrupted in addiction, by elevating extracellular glutamate levels (Ivan Ezquerra-Romano et al., 2018). This disruption of the default mode network may be interpreted as a reduction in rumination and maladaptive repetitive thoughts.

Ketamine, Neurogenesis, and BDNF

Animal models of depression, addiction, and other psychiatric disorders have been linked to a reduction in adult neurogenesis (Chambers, 2013). Brain-derived neurotrophic factor (BDNF) which is a protein that acts on certain neurons in the brain helps support the survival of existing neurons and encourage the growth of new neurons and synapses. Studies

investigating BDNF levels have observed decreased BDNF in cortical and hippocampal regions of postmortem brains of depressed subjects compared to controls (Ota, & Duman, 2013).

A study from 2005 by Karege, Bondolfi, Gervasoni, Schwald, Aubry, and Bertschy assessed the blood and serum BDNF levels of 43 drug-free patients diagnosed with major depression and 35 healthy control subjects. The BDNF serum levels of the participants with diagnosed major depression were significantly lower than those of the control group ($p < 0.05$) but not the whole blood BDNF levels. A decrease in serum BDNF was correlated with the severity of depression (Karege et al., 2005).

The apparent reduction of neurogenesis in addiction is attributed to the reduction of BDNF in the brain. Studies of alcohol, cocaine, and heroin-dependence have shown significant reductions in BDNF levels compared to healthy individuals and these levels seem to recover during withdrawal (Ivan Ezquerra-Romano et al., 2018). There seems to be evidence suggesting that increasing or stabilizing BDNF could be an important part of treating addiction (Ivan Ezquerra-Romano et al., 2018). Studies investigating ketamine's effects on BDNF have established that one of the critical components of ketamine's mechanism of action seems to be a rapid and transient up-regulation of BDNF. Findings from recent research showing that ketamine increases BDNF in depressed people who respond to treatment but not in treatment non-responders or patients receiving an active placebo further confirms this hypothesis (Ivan Ezquerra-Romano et al., 2018). However, one recent study in humans with depression have failed to show an increase in BDNF, suggesting that the mechanisms may be much more complex (Machado-Vieira, Salvadore, Diazgranados, & Jr, 2009).

Antidepressant Effects of Ketamine

In 2000, Berman et al conducted a study on eight patients with treatment-resistant depression (TRD), examining the effects of sub-anesthetic ketamine dose (0.5 mg/kg) administered intravenously over 40min. They observed that half of their subjects experienced an antidepressant response (reduction in depression rating scores on the Hamilton Depression Ratings Scale by $<50\%$, $p = <0.05$) within four days, and some even responded within 24 hours. In 2006, Zarate et al. replicated the study with a larger sample ($n=18$) and reported even more positive outcomes. Seventy-one percent responded to ketamine at 24 h and 30% showed scores low enough to be considered in remission. The reduction of depression rating was rapid and lasted longer than the subjective effects of ketamine, lasting for three days after administration.

A systematic review and meta-analysis assessing the results of seven well-controlled studies of ketamine's efficacy to treat major depressive disorder (MDD) was published in 2015 by McGirr et al. A total of 183 subjects with a major depressive episode were utilized in these seven studies that were included in the meta-analysis (34 with bipolar disorder and 149 with major depressive disorder). They found that ketamine administration (six of the studies administered 0.5 mg/kg ketamine intravenously over 40min and one study administered 50 mg intranasally) was associated with higher rates of clinical remission and clinical response at one, three and seven days compared to an active placebo. After 24 hours, depression scores were significantly lower ($p = <0.05$) for patients treated with ketamine compared to placebo-treated patients (McGirr et al., 2015).

Another study from 2013 by Sos, Klirova, Novak, Kohutova, Horacek, and Palenicek studied the effects of 0.54 mg/kg ketamine administered intravenously over 30 minutes on 27 hospitalized depressed patients between the ages of 18 and 65 years old. This was a double-blind, placebo-controlled study. The patient's depressive symptoms were

assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline, one, four, and seven days after each ketamine/placebo session. The outcome was measured by comparing the MADRS score. They found a significant effect of the treatment ($p < 0.03$) and a correlation between the intensity of psychotomimetic symptoms (measured using the Brief Psychiatric Rating Scale) and the lessening of depression scores in the MADRS on day 7 ($p < 0.04$) (Sos et al., 2013). This sheds light on the relationship between ketamine's antidepressant effects and its subjective psychological effects. Based on these findings, it could be that the subjective experience of an altered state of consciousness is needed for the antidepressant effect of ketamine and that the intensity of that experience can predict the outcome of the treatment.

Ketamine has shown a 65-70% response rate in treating depression within one day, compared to conventional antidepressants (monoaminergic) with only 47% response rates after weeks or months. This indicates that ketamine is significantly more efficient for treating depression than conventional antidepressants. Ketamine's antidepressant effects are nearly immediate and last as long as a week, whereas the monoaminergic antidepressants take weeks to show effects and need to be administered daily, and most of them fail to produce long-lasting effects (Ivan Ezquerra-Romano et al., 2018).

Several psychological addiction treatment strategies aim to change the patients outlook on life, and ketamine is hypothesized to expedite this process -by disrupting the default mode network, producing mystical experiences which can be perceived as spiritual by the patient, up-regulating BDNF levels and its apparent efficacy in treating depression, and therefore it could be useful in the treatment of addiction (Ivan Ezquerra-Romano et al., 2018). Based on these findings ketamine seems to be a promising treatment tool for addiction.

Adverse Effects of Ketamine Use

Some of the adverse effects experienced by ketamine administration include delirium, increased intracranial pressure and cerebral blood flow, hyperthermia, impaired motor functions, increased heart rate and cardiac output, increased muscle tone, and hypertension (Bokor & Anderson, 2014). Although deaths from ketamine ingestion alone are rare, adverse drug interactions and accidents are known to happen with fatal outcomes. Therefore, I will review the reported adverse effects of ketamine administration and evaluate whether the possible benefits outweigh the possible risks.

Ketamine-Induced Cognitive Impairments

The mechanism underlying the ketamine-induced cognitive impairments are not well understood yet. Neuroimaging studies have revealed that acute administration of ketamine in healthy individuals resulted in impaired verbal working and episodic memory, in conjunction with altered activities in the cingulate cortex, striatum and frontal cortex (Liu et al., 2016). Chronic ketamine users also present disrupted frontal and medial temporal functioning, although the disruption is specific to verbal information processing (Liu et al., 2016). Chronic use has also been suggested to produce schizophrenia-like symptoms such as hallucinations, detachment, delusions, amotivation, and auditory verbal hallucinations. Some users report these as positive symptoms while others report them as negative (Liu et al., 2016).

A large-scale longitudinal study by Morgan et al., (2009) investigating the effects of ketamine use on cognition and psychological well-being compared 30 frequent users (using the drug more than 4 times/week), 30 infrequent users (using the drug less than 4 times/week but at least 1 time/month), 30 abstinent users (abstinent for a minimum of 1 month), 30 polydrug users (matched with the current ketamine using groups for use of other drugs) and 30 non-drug users in a series of neurocognitive and psychological well-being assessment tests over the course of one year. They found that the cognitive deficits that emerged were mainly

confined to the frequent ketamine users. In assessments of pattern recognition memory (PRM), the results reflected significant group differences where frequent users recognized fewer patterns than the other groups.

The assessment of Spatial working memory (SWM), reflected significant group differences where the frequent users showed a greater number of errors and overall poorer strategy.

To assess spatial planning and frontal lobe functioning they used a test called Stockings of Cambridge (SOC). They found that frequent users solved significantly fewer problems in the minimum number of moves compared to all other groups.

To assess the performance of episodic memory (awareness of when and where a stimulus was encoded), the researchers used a source memory task and the results reflected a significant difference in discriminability where the frequent users had lower scores than all other groups.

The findings suggest persistent deficits in spatial working memory, pattern recognition memory and poorer performance in verbal recognition memory that could be associated with prolonged ketamine use. In the measures of psychological well-being, there was evidence of a dose-response effect on delusional symptoms, where frequent users are often those that scored highest. Increases in ketamine use over the year correlated with a reduction in scores on the pattern recognition task and the spatial working memory task. Healthy volunteers receiving a dose (0.4 mg/kg) of ketamine did not show any impairment in these tasks, therefore the authors suggest that the impairments seen in frequent users appear to be a chronic effect, similar to the impairments of chronic alcohol use. There was also no evidence of improvements in cognitive function in abstinent users, however, the abstinent users showed no cognitive deficits compared to non-drug users or polydrug-users. Schizotypal scores showed a decline in all participants following repeated measures, with an exception for

the frequent users whose score remained constantly high. This supports the idea that repeated heavy ketamine use may induce some psychotic-like symptoms (Morgan et al., 2009).

White Matter and Disconnections of Brain Areas

In 2014 Edward Roberts, Curran, Friston and Morgan investigated differences in white matter structure between healthy volunteers and recreational ketamine users. They found alterations to indices of white matter microstructure with widespread reductions in axial diffusivity in the right hemisphere of the PFC, and differences in connectivity between the caudate and PFC in the recreational users compared to healthy controls. The authors suggest that the differences in connectivity between the PFC and caudate are related to the dissociative symptoms in ketamine users. Sustained excess glutamate as a consequence of repeated NMDA-receptor antagonism may be responsible for these abnormalities in the frontal areas through an excitotoxic mechanism. These white matter abnormalities have also been observed in a variety of drug abusers in the population and therefore this may reflect a more general consequence or vulnerability to drug addiction (Edward Roberts et al., 2014). Recent research into structural brain differences associated with addiction demonstrated that siblings to addicts show similar patterns of white and gray matter structural alterations when compared to non-related controls. Therefore, it is possible that the differences observed in this study do not necessarily correlate with a lifetime of ketamine consumption, these differences may be related to the cause rather than the effect of the drug use (Edward Roberts et al., 2014).

There are numerous studies that suggest that there are functional disconnections between the PFC and striatum in schizophrenia (Edward Roberts et al., 2014). Both dopaminergic and glutamatergic abnormalities have also been proposed in schizophrenia and non-competitive NMDA antagonists, such as ketamine, cause psychotic states in normal subjects and worsen the symptoms in individuals with schizophrenia (Edward Roberts et al., 2014). DA release in the Nac in adult rats after ketamine administration was greater in

animals where the PFC was disconnected by the use of a microinjected toxin than in control animals. This suggests that the PFC disconnections could induce a sensitization to ketamine-induced DA responses and supports the theory that disconnection is a potential contributor to ketamine addiction (Edward Roberts et al., 2014).

A study from Liao et al. (2016) investigated the resting-state functional connectivity of the thalamus in chronic ketamine users compared to drug-free healthy controls. The study also focused on individual ketamine craving scores as a variable to distinguish between-group differences in the ketamine users accordingly. The score was assessed using The Visual Analogue Scale for Craving (VASc) which ranges from 0–10, a score of 0 represents no craving and a score of 10 the most extreme craving. They found that chronic ketamine users have an abnormal thalamocortical connectivity of resting-state brain activity compared to healthy controls. Chronic ketamine users had significantly less connectivity between the thalamus and other important brain regions, including the PFC. They also found that the functional connectivity between the posterior parietal area and the right laterodorsal nucleus was correlated in a significant manner to individual scores in ketamine craving, where lower scores were significantly associated to higher connectivity ($p < 0.05$) (Liao et al., 2016).

Cell Death

Another potential adverse effect of ketamine use is the increased risk of cell death. A study using forebrain cell cultures showed that ketamine induces cell death in concentrations of 10 μm or 20 μm and that lower dose concentrations did not induce cell death (Wang et al., 2005).

A study investigating the neurotoxicity of ketamine compared a single 10 and 20 mg/kg dose and repeated 10/20 mg/kg doses in seven rat pups. The single dosages of either 10 or 20 mg/kg did not produce any neurodegeneration, but the repeated administration of 20mg/kg increased the number of degenerating neurons in the dorsolateral thalamus ($p <$

0.01). The blood levels of ketamine that produced neurotoxicity were about 14 µg/ml, which is extremely high. The anesthetic ketamine blood level in humans is about 2 µg/ml (Scallet et al., 2004).

Ketamine is thought to activate mitochondria apoptotic pathway and induce cell death through the activation of NMDA receptors that leads to cell swelling and death. Increased activation of NMDA receptors is considered to induce cell membrane damage, which is the hallmark of necrosis (cell death) (Tan et al., 2012).

Synaptic-Depression

Ketamine, at subanesthetic doses (30 mg/kg) by intraperitoneal injection, seems to induce synaptic depression in the hippocampus-nucleus accumbens pathway or the hippocampus-PFC pathway. The evidence presented indicates that ketamine may increase the release of glutamate by disinhibiting GABAergic or other inhibitory inputs to glutamatergic neurons. This increased glutamate may, in turn, trigger long-term depression (LTD) that impairs hippocampal functions (Ting-Ting Duan et al., 2013).

Dopamine receptors can be categorized into two subfamilies, the D1-like dopamine receptors (D1 and D5) and the D2-like dopamine receptors (D2, D3, and D4) based on their neurochemical and pharmacological properties (Ting-Ting Duan et al., 2013). There is considerable evidence for a significant role of D1/D5 receptors in the regulation of hippocampus-dependent synaptic plasticity and memory. Either excessive or inadequate dopamine D1/D5 receptor activation is damaging for learning and memory (Ting-Ting Duan et al., 2013). In line with this converging evidence, Ting-Ting Duan et al., (2013) found that dopamine D1/D5 receptor agonists prevented synaptic depression and restored memory deficits induced by ketamine in rats. This indicates that the D1/D5 receptors play an important role in the neurological changes induced by ketamine. These changes are, however, transient: the synaptic depression lasted no more than 24 hours after ketamine administration ($p < 0.01$).

These synaptic changes may, however, activate intracellular processes such as gene expression and protein synthesis. Therefore, although the ketamine-induced synaptic depression was normalized in 24h, its impairing effects on memory may last for days or even weeks (Ting-Ting Duan et al., 2013).

Cognitive Tasks and Ketamine

Ketamine also induces a significant increase in errors on delayed response tasks which could suggest that it may affect more than the maintenance of information in working memory but also earlier processes related to attention (Roberts, Seymour, Schmidt, Williams, & Castner, 2010). This was observed during a study of the dose-dependent effects of ketamine on behavior and spatial working memory of 10 adult rhesus monkeys. All of the monkeys were trained on a spatial delayed response task for 1 year prior to the testing. They tested three doses of ketamine (0.1, 0.3, and 1.0 mg/kg intramuscularly) administered 15 minutes prior to testing. The negative effects on cognition were dose-dependent where the 0.1 and 0.3 mg/kg had no apparent main effect on the spatial delayed response task performance, but in doses ranging between 0.7-1.7 mg/kg, they found profound impairment of the spatial working memory (Roberts et al., 2010).

A study from 2004 by Morgan, Mofeez, Brandner, Bromley, and Curran investigated the acute and residual effects of two doses (0.4, 0.8 mg/kg) of ketamine intravenously in healthy human volunteers (N=54). They utilized response inhibition tests to investigate the cognitive effects of acute ketamine administration and residual effects three days after ketamine administration, along with measures of subjective effects of liking and wanting for ketamine. There were two main novel findings of this study, the first was that an acute dose of ketamine decreases response inhibition and increases subjective reinforcement ($p < 0.005$), and the second was that there were no residual cognitive impairments or schizotypal/dissociative effects three days after administration ($p < 0.005$). The authors suggest

that the subjective measures used in this study reflect to some degree the extent to which ketamine has become a reinforcing, positive stimulus (Liking) and the extent to which this reinforcement is salient (Wanting).

The finding of a lack of residual cognitive effects observed in this study could indicate that the residual effects found in recreational users (Curran, & Morgan, 2000; Curran, & Monaghan, 2001) are not related to transient neurological changes, but rather chronic effects or pre-existing differences in abusers and non-abusers (Morgan, Mofeez, Brandner, Bromley, & Curran, 2003). Preservation of fluency was also observed which suggests selective sparing of some frontal functions and that the response inhibition deficits observed were not a result of a global impairment in executive functioning (Morgan et al., 2003).

Acute ketamine administration also impaired memory for information learned under the influence but not for information learned prior to administration, suggesting that ketamine's effect on memory are a result of encoding deficits and not due to retrieval deficits (Morgan et al., 2003).

Non-Neurological Adverse Effects

This review is focused on neuroscience but there are some adverse effects that are not neurological that need to be mentioned. The main non-neurological adverse effect of ketamine is that it can cause damage to the urinary tract, bladder, and kidneys. Ketamine has a direct toxic effect on the interstitial cells of the bladder and renal papillae which causes a chronic inflammatory response. In the bladder, this can result in dysuria (painful urination), contracted bladder (resulting in involuntary urination) and a decrease in bladder size. Ketamine acts similarly in the kidneys as well, it can cause interstitial fibrosis and structural damage, leading to chronic kidney disease (Yek, Sundaram, Aydin, Kuo, & Ng, 2015). A study from 2012 estimated that the prevalence of urinary tract symptoms of ketamine abusers was 26.6%, with

a dose and frequency correlation, where more frequent and higher dosages increase the risk of urinary tract symptoms (Winstock, Mitcheson, Gillatt, & Cottrell, 2012).

Discussion

Drawing on the data gathered from the studies described in this thesis, ketamine seems to have a wide range of potential uses, pharmacologically, cognitively and psychologically. Ketamine's ability to induce reconsolidation of memories, antidepressant effects, and its ability to reduce cue-induced drug craving makes it a potentially useful tool in drug abuse therapy. However, extensive research into the adverse effects of ketamine use is needed to ensure the safety of ketamine administration. Most of the negative side-effects of ketamine seem to be apparent at high doses (blood levels of 14 µg/ml) and frequent use (4 days a week to daily use) but low doses and non-frequent use has a low probability of harm, with the negative side effects being transient and passing. The adverse side-effects of chronic ketamine use include but are not limited to; cell death (blood levels of 14 µg/ml), reduced connectivity between the thalamus and PFC, motor cortex, supplementary motor area, and the posterior parietal cortex, LTD of hippocampal functions, and ketamine addiction.

Ketamine administration leads to increased DA levels in the frontal cortex, striatum, and the NAC, and increases firing of neurons in the VTA (Kokkinou et al., 2018). Since ketamine has similar dopaminergic effects as other stimulants and addictive drugs, there is a strong reason to believe that ketamine is potentially addictive (Kokkinou et al., 2018). This is counterintuitive because there is also strong evidence pointing to that ketamine has the potential to treat substance addiction using KPT (Ivan Ezquerra-Romano et al., 2018; Krupitsky et al., 2002). There is also a potential risk for ketamine to increase the severity of schizophrenic-like and dissociative symptoms. There has to be a great deal of harm-benefit calculations and further research including utilizing larger sample sizes for using KPT, therefore, further research on the topic is needed.

There is conflicting evidence of ketamine's ability to increase BDNF which is suggested to be one of the main effects of ketamine as an antidepressant. One study found that the antidepressant effects were not mediated by changes in BDNF levels, however, the study did confirm that ketamine is efficient as a fast-acting antidepressant (Machado-Vieira et al., 2009). They suggest that the neuroplastic changes observed in ketamine administration rather is caused by activating early neuroplastic changes and synaptic potentiation through an α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), but not BDNF effects (Machado-Vieira et al., 2009).

There are research findings that suggest that AMPA receptors play a significant role in ketamine's antidepressant effects. Administration of low doses of ketamine has been found to stimulate the AMPA/kinase receptor by blocking the NMDA receptors and increasing the extracellular glutamate levels (Moghaddam et al., 1997). The antidepressant effects of ketamine can be blocked by an AMPA receptor antagonist, which is a clear indicator of AMPA receptors' critical role in ketamine's antidepressant effects (Koike, Iijima, & Chaki, 2011). Chronic low-dosage (0.5–2.5 mg/kg daily for 10 days) ketamine treatment leads to an increased AMPA/NMDA receptor density ratio in the hippocampus in female rats (Tizabi, Bhatti, Manaye, Das, & Akinfiresoye, 2012). The hippocampus has a critical role in mood regulation and the hippocampus has a postulated role in the effectiveness of many antidepressants (Tizabi et al., 2012). This could mean that some of the antidepressant effects of ketamine may be due to these effects on the AMPA/NMDA receptor density in the hippocampus.

There also seem to be conflicting evidence regarding ketamine's effect on memory. On one hand, there are findings that suggest that ketamine disrupts memory formation, spatial working memory, pattern recognition memory and results in poorer performance in verbal recognition memory (Morgan, Riccelli, Maitland, & Curran, 2004). But

on the other hand, there are studies that have found evidence for a beneficial role of ketamine on memory processes. The first line of evidence comes from looking at studies of AMPA-dependent emotional learning. Studies of stress have indicated that acute stress can weaken memory by the removal or translocation of synaptic AMPARs (Hu et al., 2007). Endogenous stress hormones are released shortly after emotional arousal and negatively affect memory formation by phosphorylation of specific AMPA receptors. This indicates that stress hormones underlie irregularities in AMPA receptor plasticity, giving rise to dysfunctions after traumatic events causing disorders such as major depression, post-traumatic stress disorder, general anxiety disorders and drug-relapse.

Studies using knockout mice and normal mice found that AMPAR trafficking is essential in amygdala-dependent learning (Rumpel, LeDoux, Zador, & Malinow, 2007; Humeau et al., 2007). As discussed in the previous section, ketamine seems to stimulate AMPA receptors and even increase AMPA receptor density in the hippocampus, which makes it probable that a learning facilitation effect would occur (Walter, Li, & Demenescu, 2014). Low doses of ketamine activate the mammalian target of rapamycin (mTOR) pathway which triggers synaptic protein synthesis and is crucial for long-term memory and co-occurs with an increase in the number of mature synapses. In 6-24 hours after ketamine administration, the activation of the mTOR signal pathways was occasioned with an up-regulation of protein synthesis and synaptogenesis. This makes it likely that ketamine could enhance learning and memory processes (Walter et al., 2014).

This stimulation of the AMPA receptors is also suggested to induce increased BDNF and upregulate the local protein synthesis, facilitate long-term potentiation and increase synaptic transmission which in turn facilitate improved memory formation (Walter et al., 2014). These findings point to the possibility that ketamine can be viewed as a cognitive enhancer.

A study from 2013 by Corlett et al., investigated ketamine's effect on memory reconsolidation in humans and found that ketamine enhanced reactivated memories and that this enhancing effect correlated with the profundity of the ketamine-induced perceptual disruptions (Corlett et al., 2013). This indicates a prolonged effect of ketamine that facilitates memory processes. However, generalization to the population is heavily restricted due to the small number of subjects in this study (N = 18). This study needs to be replicated on a larger scale to draw generalizations to the larger population.

Discussed earlier in this thesis, ketamine seems to have a potential to disrupt the reconsolidation of maladaptive and harmful memories (Ivan Ezquerra-Romano et al., 2018). The ability to enhance reactivated memories along with the disruption of harmful memories might be an interesting and potentially beneficial line of further research of the treatment of post-traumatic stress disorder (PTSD). Perhaps with the use of KPT, it is possible to transform traumatic memories into memories without major affective abilities. This has to be investigated with much caution, there could be a potential risk of making matters worse than before if these maladaptive and harmful memories are enhanced the PTSD could worsen. There is a need for further research to explain these conflicting lines of evidence concerning ketamine's effects on the human brain and psyche. There is a strong need for research into ketamine with more validity than those that have been conducted to this date. There are issues with validity when conducting studies using animals-models to predict human responses to drugs and other chemicals. Medical practice does not tolerate the risks that are acceptable in some experiments in a laboratory setting. Getting the answer wrong in medical practice can have severe consequences, subjects can die or get seriously harmed. There are well known qualitative and quantitative differences between species regarding gene regulation and expression, epigenetics and complexity to name a few. A study that investigated the predictability of animal models on human toxicity (HT) showed a true positive HT

concordance rate of 71% for rodent and nonrodent species, with nonrodents alone being predictive for 63% of HTs and rodents alone for 43% (Olson et al., 2000). For the purposes of basic research, this can be acceptable, but the societal standards for medicinal practice are very high. However, there is an extensive list of sedative and antidepressant medications with reported negative side-effects such as suicidal thoughts, insomnia, muscle spasm, cognitive and psychomotor impairments being prescribed to this date. Benzodiazepines (BZD) is a common prescription drug that is prescribed to reduce anxiety and insomnia, the adverse effects such as long-term cognitive and psychomotor impairment, increased mortality hazards, dependence, and withdrawal (Lader, 2014). Selective serotonin reuptake inhibitors (SSRI) have various known side effects e.g. sexual dysfunctions, drowsiness, insomnia, nausea, tremors, gastrointestinal disturbances and psychiatric side effects such as aggression, anxiety, and mania (Ferguson, 2001). Ketamine seems to have potential to replace these medications, even though ketamine has some side-effects in long-term use the treatment with ketamine may be much more effective. The main advantage of ketamine treatment compared to other antidepressants is that it only need to be administered on infrequent occasions and in low doses, which minimalizes the risks of adverse side-effects.

Conclusion

The issue of drug addiction and depression are major problems in our society. Conflicting theories about their causes and methodological treatment strategies complicate the situation further. Several key components of reward and addiction have been discovered, such as the mesolimbic pathway and the neurotransmitter dopamine that has been heavily implemented in most theories of addiction. Perhaps one of the most important findings is the discovery that drug “liking” is not a prerequisite for drug-seeking and drug-taking behavior, which means that subjects maintain self-administration of drugs without the subjective pleasure of the behavior. This would mean that individuals that are addicted to drugs, experience less

pleasurable feelings from the drug than non-addicted individuals. This can and hopefully will change the way that we think about addiction, instead of placing guilt and shaming addicts, we now have a neurological explanation of the pathological and illogical behavior of addicts. Such factors as prior exposure to regularly occurrent stress may predispose susceptible individuals to drug addiction by the same process of sensitization of neural systems that mediate the incentive motivational effects of drugs. Realizing that addiction is a pathological mental health problem and that it is more than often accompanied with other depressive symptoms is a great step in the much-needed process of shaping addiction treatment into something better.

Ketamine certainly can be abused, and uncontrolled and uninformed use can lead to severe adverse effects. The steadily growing body of research into the use of ketamine has revealed that it can also be very beneficial, in the right circumstances and in controlled settings. The effectiveness of KPT in the treatment of addiction has shown great promise, as well as administration of ketamine in clinical settings for treating depressive disorders. Some of the main promising findings can be summarized in that:

- Ketamine was shown to have promising effects on motivation to quit cocaine and reduce cue-induced cocaine craving, 24 hours after administration.
- Ketamine and other psychedelic substances may be able to disrupt maladaptive appetitive memories, such as environmental drug-cues.
- Reports of successful use of ketamine to reduce the relapse in recently detoxified alcoholics.
- Ketamine has been shown to act as an antidepressant via reconfiguration of resting-state functional connectivity.
- One of ketamine's mechanisms of action seems to be a rapid and transient up-regulation of BDNF, which potentially can stimulate neurogenesis.

- Ketamine administration is associated with higher rates of clinical remission and clinical response compared to an active placebo in patients with bipolar- and major depressive disorder.
- Ketamine's antidepressant effects are nearly immediate and last as long as weeks.

The cause of the effectiveness of ketamine treatment is however still up for debate, the research to this date has produced many varying hypotheses. It could be that there is one single mechanism of action of ketamine that could explain these findings, but more probably it is a mix of many different mechanisms. There are however no miracle substances, as the research into addictions and depressive disorders have shown, the treatment is often something that needs to be done during a long time-span. This is evident from the results that multiple ketamine sessions had a significantly better effect than a single one. There is also a need for careful consideration and extensive replication of the research to increase the validity of the findings to this day before utilizing ketamine as a generalized tool for addiction treatment.

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