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THE ADDICTION OF AGGRESSION

WHY AGGRESSIVE BEHAVIOR CAN BE SEEN AS ADDICTIVE BEHAVIOR

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Foreword

The thesis in front of you is 'The addiction of aggression'. The research of this thesis is about whether aggressive behavior can be an addiction. This thesis is written in the context of my bachelor's degree Biology at the University of Groningen. During my study, I have chosen to follow the major focused on behavior and neuroscience. The combination of the brain network and how this affects human behavior is a subject that continues to fascinate me. Especially since addiction as well as aggression are components related to daily life, but not related to each other, I found it interesting to dive into this. I want to express my gratitude to Anton Scheurink for making it possible for me to write a thesis about this. I want to thank him for being my supervisor during my writing process. He assisted me in finding a topic that caught my interest. I also want to thank him for his support, thinking along and enthusiasm.

I hope you enjoy reading.

Marit Kuik
Groningen, 13th of July 2022

Summary

In today's society, we almost all have experienced or witnessed senseless violence. People might have an innate tendency to become aggressive. When the goal of this senseless aggression is the kick, there might be feeling of reward involved. Just as in addictive behavior, those feelings are important in continuing the addiction. In this research, the comparison is made between requirements for aggressive behavior and requirements for addiction. Based on this, it is possible to respond to the research question of whether senseless aggressive behavior can be addictive. Due to the planned and goal-directed behavior that is not primarily motivated by anger, proactive aggression can be most closely compared to senseless aggression. What stands out when comparing the requirements is that the animal models used to study aggressive and addictive behavior are similar. Especially self-administration models are used to look at the motivation of reinforcement for both types of behavior. Besides the animal models, the most important brain regions involved are similar as well. These regions include the PFC, the amygdala and the NAc. Serotonin and DA are the main neurotransmitters involved in both behaviors. Due to its control over reward, DA is primarily linked to addictive behavior, whereas serotonin is crucial for aggression due to its role in mood regulation. These findings of cognitive and behavioral similarities imply that aggression may be addictive. It is important to keep in mind that the majority of these findings apply to aggressive behavior in general rather than proactive aggression in particular. Therefore, more research can be done to determine in what extent proactive aggression and addiction are related.

Key words: senseless violence, aggression, addiction, substance abuse, DA, serotonin

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Chapter 1 – Introduction

"The wives of football players from the teams Vitesse and Willem-II had gathered in a parking lot near the highway" is a pun from a Dutch newspaper's cartoon. This joke, however, is based on news that football hooligans are banding together more frequently to riot.

Nowadays, we are facing more and more of senseless violence around us. Every day, hundreds of people around the world are victims of senseless violence or have witnessed aggressive behavior up close. Despite the fact that few of these incidents make the news, the social problem is far more serious than it appears. Consider the case of a 27-year-old Dutch boy who was kicked to death while out on the town in Mallorca by a gang of Dutch teenagers looking for trouble (Nesselaar, 2021). Or Amber (22), who was beaten up by a group of boys after defending a friend (Hensbergen, 2021). However, we encounter more aggression on a daily basis than these extreme forms. Think about verbally abusing railway employees, as well as football fans who look forward to being able to go wild on match-day. The real societal issue is that we no longer hold this in high regard, and senseless violence appears to have become the norm.

People might have an innate tendency, or even instinct, to be aggressive, since there is violence. Aggression is defined as behavior intended to harm another individual who is motivated to avoid that harm (DeWall et al., 2012). The ability to be aggressive under certain circumstances is consistent with the principles of evolution and natural selection (Stangor et al., 2014). Aggression is advantageous to evolution, necessary for survival, and well-preserved across species (Golden et al., 2017). However, aggression seeking against own species and finding this experience rewarding has been described as a distortion of the hunting instinct in the general population. This appetitive aggression has a phenomenology that is similar to other rewarding experiences, such as sexual pleasure and drug intake. As a result, aggression is sometimes pursued despite immediate or long-term negative consequences (Golden et al., 2017). Furthermore, we always look for a reason to commit violence, whether it's social, economic, or personal. Violence is frequently viewed as a means of achieving a specific goal, but it can also be viewed as a means of simply experiencing it; it gives a kick. Violence for the sake of violence is how autotelic violence describes itself (Kitzen, 2006). As a result, there is not always a declaration. Football supporters' violence and aggression is one type of violence in which the kick plays a key role. While fighting is only a small part of the violence, constantly thinking about it takes a long time. The kick and the euphoria the fighting produces are reasons for hooligans to become aggressive and organize violence (Kitzen, 2006). When the goal of this senseless aggressive behavior is most likely to be a kick, this may be experienced as rewarding. This rewarding experience of behavior is also seen in substance abuse and addiction behavior. This similarity arises the question whether senseless aggressive behavior can be rewarding and even addictive?

There are some requirements that must be taken into account in order to respond to this research question. The DSM-V criteria for addiction will be compared to aggressive behavior in order to determine whether subjects can develop an addiction to aggression. Additionally, the reward of both aggressive and addictive animal models is contrasted. Finally, aggression must be motivating and trigger the reward system in order to produce rewarding experiences.

Chapter 2 - Aggression

One of the most commonly used theories for understanding human aggression is the General Aggression Model (GAM) (figure 1). It considers the role of cognitive, social, developmental and biological factors on aggression (Allen et al., 2018). The processes described in the GAM are divided into three stages: inputs, routes and outcomes. How person and situation factors influence the likelihood of aggressive behavior is outlined by the first stage 'inputs'. These factors can influence a person's internal state variables, like cognition, affect and arousal, in stage two. The input variables that increase the likelihood of aggression are considered risk factors, whereas those that decrease the likelihood of aggression are considered protective factors (Allen et al., 2018). In the third stage, the person appraises the situation and decides how to respond, which can be an aggressive or nonaggressive outcome. The final action has an influence on the encounter, which then has an impact on the person and situation factors, restarting the episodic cycle (Allen et al., 2018). The input factors in the GAM can rely on genetic and environmental factors that can produce and interact with aggressive behavior. Studies in twins have found that genetic substrate underly the development of aggressive, antisocial and violent behavior (Mendes et al., 2009). Moreover, cognitive deficits and environmental elements like poverty, family history and attention deficit during childhood and adolescence are key social predictors of violent and aggressive behavior.

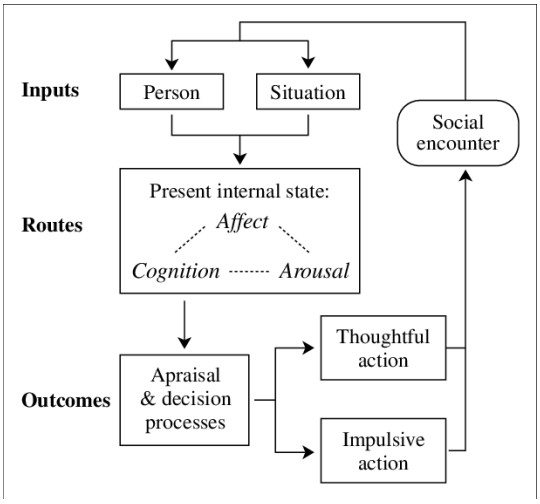

Figure 1: The General Aggression Model. The process of aggression is divided into three stages: inputs, routes and outcomes. The input variables can increase or decrease the likelihood of aggressive behavior (Anderson and Bushman, 2001).

Besides this basis of the GAM for aggressive behavior, different types of aggression can be defined. Aggression can be classified into two categories based on the type or level of intent that motivates aggressive behavior: reactive and proactive aggression (Lui, 2004; DeWall et al., 2012). Aggression that occurs with little forethought or intent and is primarily determined by impulsive emotions is referred to as reactive aggression (also known as hostile, affective, angry, impulsive, or retaliatory aggression) (table 1) (Stangor et al., 2014; Lui, 2004). This type of aggression is impulsive and tends to happen in the heat of the moment. The purpose of this aggression is to cause pain or injury to the victim and there is little to no advantage to the aggressor (Lui, 2004). Aggression that is intentional, planned, and used to achieve a desired goal is known as proactive aggression (also known as instrumental aggression) (table 1) (DeWall et al., 2012). Despite the victim's discomfort, proactive aggression results in a positive reward or other advantage for the aggressor (Lui, 2004). However, distinguishing between reactive and proactive aggression is difficult because motives are frequently mixed (DeWall et al., 2012) and few aggressive acts are purely reactive or proactive (Lui, 2004).

Table 1: Characteristics of reactive and proactive aggression.

Hostile (reactive) aggression	Instrumental (proactive) aggression
Impulsive	Planned
Proximal motive: to inflict harm	Goal-directed (material benefit, status etc.)
Driven by anger	Not primarily driven by anger

Although it is not very common, certain aggressive behavior can be seen as a disorder. Intermittent explosive disorder (IED) is a personality disorder which was first introduced in DSM-III (Cocarro, 2012). IED is characterized by recurrent and problematic aggressive behavior (Fanning et al., 2019), which begins in adolescence or early adulthood and has a prevalence of five percent (Cocarro, 2012). It consist of either high-intensity outbursts of aggression occurring several times yearly or less intensive outbursts several times monthly (Cocarro, 2012). The aggressive outbursts in IED have a rapid onset, are impulsive and thus not premediated (table 2) (Coccaro, 2012). Therefore, this disorder is more connected to reactive aggression. The aggression of football hooligans and thus this type of senseless aggression, on the other hand, can be seen as proactive aggression rather than reactive aggression because the emphasis is on planned aggression, which is not primarily motivated by anger and goal-directed for the satisfied feeling.

Table 2: The DSM-V criteria and research criteria for IED (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (2013), p. 466).

DSM-V criteria Intermittent Explosive Disorder	**Research criteria Intermittent Explosive Disorder**
A. Several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property.	A. Recurrent incidents of aggression manifest as either: 1. verbal or physical aggression towards other people, animals, or property occurring twice weekly on average for one month OR 2. three episodes involving physical assault against other people or destruction of property over a one year period.
B. The degree of aggressiveness expressed during the episodes is grossly out of proportion to any precipitating psychosocial stressors.	B. The degree of aggressiveness expressed is grossly out of proportion to the provocation or any precipitating psychosocial stressors.
C. The aggressive episodes are not better accounted for by another mental disorder (e.g., antisocial personality disorder, borderline personality disorder, a psychotic disorder, a manic episode, conduct disorder, or attention deficit hyperactivity disorder) and are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., head trauma, Alzheimer's disease).	C. The aggressive behavior is not premeditated (i.e., is impulsive) and is not committed to achieve some tangible objective (e.g., money, power, intimidation, etc.). D. The aggressive behavior causes either marked distress in the individual or impairment in occupational or interpersonal functioning. E. The aggressive behavior is not better accounted for by another mental disorder (e.g., major depressive disorder, a manic episode, a psychotic disorder), a general medical condition (e.g., head trauma, Alzheimer's disease), or the direct physiological effects of a substance (e.g., a drug of abuse, a medication).

Chapter 3 - Animal models for aggression

Different behavioral procedures can be used to study motivated aggression seeking behavior in mouse models against conspecifics. The animal models used for studying this behavior can be divided into two types: non-contingent models and contingent models. Non-contingent models are simple and quick to set up (Kuhn et al., 2019). Non-contingent reinforcement is independent on behavior and happens on a set schedule. Furthermore, contingent models rely on operant learning during repeated exposure to the stimuli of interest (Kuhn et al., 2019). Here, an animal performs an action, like lever pressing or nose poking, in order to receive a the stimuli. A common contingent model for studying behavior is self-administration.

Non-contingent models

During earlier studies, most research on aggression was done by using variations of resident-intruder procedures. These procedures can consist of the T-maze test, partition test and conditioned place preference (CPP) test (appendix A, figure A.1). In these cases, a submissive intruder mouse is placed within the home-cage of the resident mouse and encounters are recorded. Physical aggression was

sufficient to condition mice to prefer aggressive behavior against the intruder in the absence of external stimuli (Golden et al., 2019). However, determining whether these observed behaviors reflect defensive, reactive, proactive, or appetitive (rewarding) aggression is difficult using these resident-intruder procedures (Golden et al., 2019).

Contingent models

In addition to these non-contingent models, self-administration models are set up to investigate aggression seeking more specifically. These self-administration models are set up based on active lever presses or nose poking by a fixed ratio (FR) or progressive ratio (PR), both schedules of reinforcement (appendix A, figure A.2). During FR, reinforcement is delivered after the completion of a number of responses, which remains constant. During PR, an increase in response is required to deliver the reinforcer over successive sessions (May and Kennedy, 2009). In both schedules, motivation for reinforcement plays a major role and so motivation for aggression seeking can be determined by applying these models, which is done in the study of May and Kennedy (2009). Here, the resident mice learned that nose poking led to delivery of an intruder mouse. This self-administration model showed the willingness of the mice to work for the reinforcement as the PR goes up after each successful session. Furthermore, aggression seeking after forced abstinence of reinforcement was studied in the research of Golden (2017). Resident mice were first trained for self-administration by lever pressing. Active lever presses led to delivery of a submissive younger intruder mouse in the operant chamber. The mice increased their aggression self-administration over days as successful trials of attacking the intruder increased. After this training phase, relapse behavior to reinforced aggression seeking was tested after forced abstinence. The results show high rates of active lever presses after forced abstinence (appendix B, figure B.1), indicating that persistent aggression seeking is independent of the duration of forced abstinence (Golden et al., 2017). These outcomes of the self-administration models indicate that reinforcement of motivation for aggression seeking plays a major role. Additionally, the behavior observed in the resident-intruder models, especially when self-administration was induced, provide planned aggressive behavior, indicating that these mice models represent proactive aggressive behavior. As mentioned previously, this proactive aggression is goal-directed behavior causing an advantage for the aggressor. The desired goal of this behavior seems to be the positive reward feeling after winning the attack.

Chapter 4 - Brain compartments involved in aggressive behavior

Brain regions

The amygdala is a brain structure primarily involved in processing emotions and memories associated with fear (Rosell and Siever, 2015). Due to its importance in processing emotions, the amygdala has been associated with aggressive behavior (figure 2). Studies in brain imaging found that the left and right amygdala volumes were reduced in individuals with above average aggressive behavior (Rosell and Siever, 2015). Furthermore, in pathological aggression, such as IED, amygdala activity increased in response to provocation, whereas in non-pathological aggression, like proactive aggression, amygdala activity decreased. Besides the amygdala, the critical role of the prefrontal cortex (PFC) in aggression was found after PFC lesions resulted in disinhibited aggressive behavior (figure 2) (Larry and Siever, 2008). The PFC controls executive function and thereby modulates decision making and impulse inhibition, making it an important

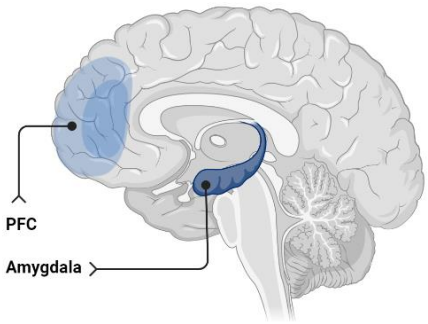

Figure 2: The PFC and amygdala depicted as the brain regions involved in aggressive behavior. (Made with Biorender.com)

brain region in controlling aggressive behavior. The limbic parts of the PFC that are mainly involved in aggression include the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC). The lack of prefrontal regulation combined with decreased amygdala reactivity increases the likelihood of aggressive behavior (Larry and Siever, 2008).

Neurotransmitters

In addition to the most important brain regions involved in aggressive behavior, several neurotransmitters play a role in regulating this behavior. One of the best studied neurotransmitters related to aggression is serotonin (Rosell and Siever, 2015), since it is mainly involved in mood regulation. The serotonergic system seems to be the main component in aggressive behavior. Serotonergic neurons originate in the raphe nuclei and can reach almost every structure in the brain (figure 3) (Narvaes and Almeida, 2014). Serotonin can modulate the emergence of aggressive behavior by acting on the serotonin receptors in the OFC and ACC (Larry and Siever, 2008). In these prefrontal regions, serotonin facilitates inhibition and therefore insufficient serotonergic activity can result in disinhibited aggression upon provocation (Larry and Siever, 2008). In addition, studies have shown that selective serotonin reuptake inhibitors (SSRI's) can reduce aggression due to enhanced levels of serotonin. Besides the well-studied serotonergic system, the role of dopamine (DA) in the dopaminergic system has much less been described in regard to aggression. Despite, it plays an important role due to its involvement in movement control, decision making, reward processing, motivated behavior and persistence of long-term memory (Rosell and Siever, 2015; Narvaes and Almeida, 2014; Seo et al., 2008). The dopaminergic system consist of four pathways, of which the mesolimbic dopaminergic pathway, the connection from the ventral tegmental area (VTA) towards the nucleus accumbens (NAc), is the most important (figure 3). This pathway specifically plays a role in regulating aggressive behavior and the rewarding effect of aggression (Yamaguchi and Lin, 2019). Activation of the dopamine system can be caused by both pleasant and stressful events (Narvaes and Almeida, 2014) like aggression. On the other hand, elevation of DA levels due to activation of the dopamine system can also result in an increase of aggressive behavior (Yamaguchi and Lin, 2019). The third main neurotransmitter involved is gamma-aminobutyric acid (GABA). GABA is the main inhibitory neurotransmitter in the mammalian brain (Narvaes and Almeida, 2008) and it can regulate several brain mechanisms. Gabaminergic activity on GABA receptors can reduce subcortical activity. Therefore, when gabaminergic activity is reduced, aggressive behavior will increase (Larry and Siever, 2008). So the involvement of GABA in aggressive behavior is mostly associated with its inhibitory action (Narvaes and Almeida, 2008).

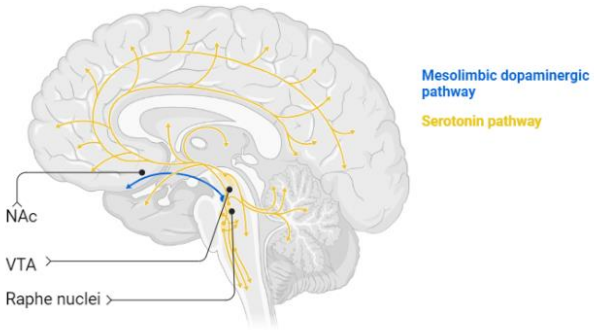

Figure 3: The two major pathways involved in aggressive behavior are visualized together with the important brain areas for the neurotransmitters. The blue line represents the mesolimbic dopaminergic pathway and the yellow line represents the serotonin pathway. (Made with Biorender.com)

Steroid hormones

Next to the neurotransmitters, there is a growing evidence that steroid hormones, like testosterone, may contribute to aggression and violent behavior (Rosell and Siever, 2015). These testosterone levels are regulated via the hypothalamic-pituitary-gonadal (HPG) axis. High levels of testosterone can decrease the activity of the medial region of the OFC and therefore aggressive behavior is stimulated (Narvaes and Almeida, 2008). A potential mechanism by which testosterone is able to reduce the activity of the OFC is by regulating serotonin. Previous findings showed that testosterone can downregulate serotonin receptors and serotonin turnover in the medial PFC (Narvaes and Almeida, 2008), which can be related to increased aggressive behavior. In addition, the dual-hormone hypothesis suggests that high testosterone levels lead to higher levels of aggression and low testosterone levels lead to evasion of the fight response (Narvaes and Almeida, 2008).

Chapter 5 - Addiction

Besides the societal issue of aggression, addiction and substance abuse represent a serious threat to human health (Mennis et al., 2016). Addiction is estimated to affect 10-15% of the adult population (MacNicol, 2016). It is defined as a neuropsychiatric disorder characterized by a recurring desire to continue the action despite the harmful consequences (Zou et al., 2017). This disorder acts on the brain circuitry that is responsible for memory, reward and motivation (MacNicol, 2016). Because it activates the reward circuitry of the brain, substance abuse leads to intensely positive feelings and can therefore be addictive.

The term addiction can apply to substance abuse or non-substance abuse. Where substance addiction is characterized by the persistent desire of taking a drug, non-substance abuse covers behavioral addiction as gambling, food addiction or internet addiction (Zou et al., 2017). The specific diagnostic criteria for substance addiction is set in the DSM-V criteria (table 3). Although society is familiar with substance addiction, non-substance addiction has become a new rising problem in modern society (Zou et al., 2017). Though there is no drug taking in non-substance addiction, the brain mechanisms and symptoms are similar to drug addiction (Zou et al., 2017). However, the diagnosis of various non-substance addictions is frequently challenging because they differ from one another even though they are all addictions. Consequently, researchers frequently define and diagnose them using the substance addiction model. The only non-substance addiction recognized by the DSM-V is gambling disorder, which shows that the understanding about this type of addiction remains sparse (Zou et al., 2017).

Table 3: DSM-V criteria for substance use disorder (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (2013), p. 481-484).

DSM-V criteria Substance Use Disorder

A. Impaired control over substance use.
   1. The individual may take the substance in larger amounts or over a longer period than was originally intended.
   2. The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use.
   3. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects.
   4. Craving

B. Social impairment
   5. Recurrent substance use may result in a failure to fulfill major role obligations at work, school, or home.
   6. The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
   7. Important social, occupational, or recreational activities may be given up or reduced because of substance use.

C. Risky use of the substance
   8. Recurrent substance use in situations in which it is physically hazardous.
   9. The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

D. Pharmacological
   10. Tolerance
   11. Withdrawal

Note: substance use disorder occur in a range of severity, with severity based on the number of symptom criteria endorsed.

- Mild: 2-3 symptoms
- Moderate: 4-5 symptoms
- Severe: 6 or more symptoms.

Multiple biological and environmental factors play an important role in an individual's susceptibility to addiction. Examples are genetic predisposition, environmental risk factors and cognitive characteristics (Mennis et al., 2016). It is presumed that genetic factors account for between 40 and 70 percent of individual differences in risk for addiction. Moreover, experiences during childhood and adolescence can influence future substance abuse and addiction. These experiences can be emotional and sexual abuse, poverty and household instability. These social stressors can be seen as risk factors due to the effect on the same stress circuits in the brain as addictive substances (US Department of Health and Human Services, 2016, p. 2-21). Additionally, it is known that substance abuse is a coping mechanism for challenging social or economic circumstances.

The process of addiction can be described as a repeating addictive cycle with three stages (US Department of Health and Human Services, 2016, p. 2-6), going from 'liking to wanting'. At first, an

individual consumes an intoxicating substance that provides a pleasurable sensation and gives the feeling of reward. Consequently, the tolerance for the substance increases, indicating that more substance is required to produce the reward feeling and the natural reward of the substance is diminished. This is followed by the stage of withdrawal in which the individual experiences negative emotions in absence of the substance. After a period of abstinence, the preoccupation and anticipation stage causes the individual to seek substances again (US Department of Health and Human Services, 2016, p. 2-6). A strong dependence on the substance has developed, which is now only used to relieve stress. The trigger to seek substances is related to lack of impulse control in addiction (Kirby et al., 2011). For many people, initial substance use involves an element of impulsivity, or acting without foresight or regard for the consequences (US Department of Health and Human Services, 2016, p. 2-7). Therefore, elevated levels of impulsivity are considered to be a risk factor for developing substance use disorder.

Chapter 6 - Animal models for addiction

Various non-contingent and contingent models can be used for studying addiction related behaviors in animals. For understanding addictive behavior mostly drug addiction is studied.

Non-contingent models

CPP is a model that allows to test the rewarding properties of an addictive experience or stimulus. It relies on Pavlovian learning, memory and motivated behaviors (McKendrick and Graziane, 2020). During CPP the goal is that the animals learn to associate an experience, such as non-contingent drug delivery, to a recognizable (paired) context (figure 4) (Kuhn et al., 2019). In addition, the animals are also exposed to a different neutral (unpaired) context which is not associated to a stimuli. Following a first phase of habituation to both contexts, the drug is paired with the recognizable context in an acquisition phase. During the test day, the animal is free to explore both environments. The stimulus is considered rewarding when the time spent in the paired context is longer than the time spent in the unpaired context (Kuhn et al., 2019). This CPP for addictive behavior is done with mice in a study of Itzhak (2002). They injected a group of mice with saline and a group of mice with cocaine in the drug-paired compartment. The results (appendix C, figure C.1) show that before injection, the time spent in both paired and unpaired compartments is the same. However, the amount of time spent in the drug-paired compartment increases after cocaine injection, indicating that mice have a preference for the cocaine compartment. The amount of time spent in the paired compartment for the mice receiving saline injections did not differ significantly from the time prior to injection (Itzhak, 2002). This suggests that the cocaine injection is associated with a rewarding feeling. As the CPP test, the runway model can also be used to evaluate the rewarding component of addictive substances like drugs. The runway model was developed to be able to study goal-directed behavior with rewarding aspects (Kuhn et al., 2019). The animals learn to cross a 6-foot long straight corridor (the runway) to reach the goal compartment, which contains the rewarding substance. The time it takes the animals to reach the goal compartment is used as a measure of their motivation to obtain

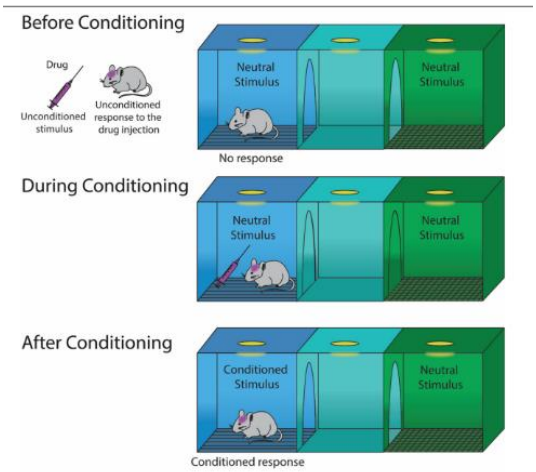

Figure 4: Conditioned place preference. The animal learns to associate an unconditioned stimuli (here drugs) to a paired context (McKendrick and Graziane, 2020).

reward. This 'run time' can be associated with how rewarding and therefore addictive a particular stimuli or experience is.

Contingent models

Moreover, the runway model (appendix D, figure D.1) is also used to study goal-seeking motivated behavior in rats and mice by self-administration of addictive drugs. In the study of Pandy and Khan (2016) mice were injected with saline, ethanol, heroin or nicotine. During preconditioning, there was no significant difference in the run time between the mice. However, after the conditioning phase there was a decrease in run time of mice injected with either ethanol or heroin. This indicated that these components give a pleasurable feeling. Additionally, there is a significant difference between the run times of the four groups (appendix D, figure D.2). The results show that an injection with saline or nicotine does not affect the run time and thus not affect the reward system. A more common self-administration model used to study addictive behavior are models based on active lever presses. In the study of Tsibulsky and Norman (2021), rats were trained to self-administer cocaine under a FR-1 schedule and afterwards under the PR schedule of drug delivery. The results show an increase in active lever presses, indicating that the rats are willing to work for the drug delivery. Even during the unloaded (extinction) phase of lever presses and cocaine self-administration the motivation for reinforcement increased under PR schedule (Tsibulsky and Norman, 2021). Moreover, voluntary abstinence of drug self-administration by making a choice model between drug use and non-drug social rewards for rats prevents drug seeking behavior (Venniro and haham, 2020). The choice of rats for the social interaction instead of drug use causes voluntary abstinence from the drug (Vanniro and Shaham, 2020). However, a period of forced abstinence from rewarding drugs shows a dramatic increase in drug craving (appendix E, figure E.1). This suggest that drug-seeking behavior is independent of forced abstinence.

Chapter 7 – Brain compartments involved in addiction

Brain regions

The brain consist of many regions interconnecting with each other. Three of these regions are key components involved in development and persistence of substance use disorder: the PFC, the extended amygdala and the basal ganglia (US Department of Health and Human Services, 2016, p. 2-5). The PFC is involved in executive function and decision making and so involved in the exerting control over substance taking. Furthermore, the basal ganglia consist of several subcortical structures of which the NAc and the dorsal striatum are specifically important in substance use disorders. The NAc is mainly involved in motivation and the experience of reward and the dorsal striatum plays a role in routine behavior and forming habits. The extended amygdala is important for emotions and the brain's reaction to stress-including behavioral responses like 'fight-or-flight' response. The negative emotions that rely on the extended amygdala, like anxiety, irritability and unease, are accompanied with substance withdrawal (US Department of Health and Human Services, 2016, p. 2-5).

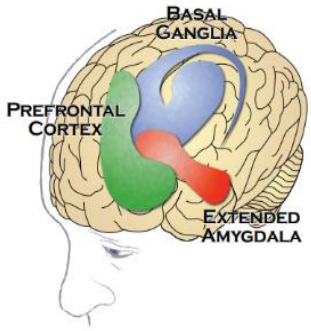

Figure 5: The three most important brain areas involved in addiction are depicted in this figure. The blue area represents the basal ganglia, the red area the extended amygdala and the green area the PFC (US Department of Health and Human Services, 2016, p. 2-5).

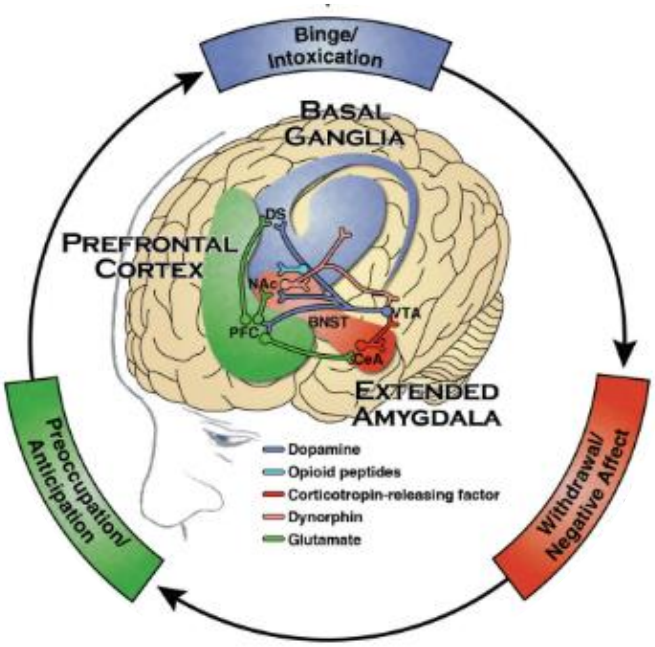

Figure 6: The neurotransmitters and the pathways involved in substance abuse and addiction are represented in the brain regions they act on. DA is represented by the blue pathway. CRF is the red pathway and dynorphin is represented as the pink pathway. The pathway of glutamate is green. (US Department of Health and Human Services, 2016, p. 2-19)

Neurotransmitters

The neurotransmitters involved play a role in the different phases of the addictive cycle. The main neurotransmitter involved in reward and therefore in addiction is DA. Due to its pleasurable effect, DA is associated with the binge and intoxication phase in which the basal ganglia is heavily involved. When taking a drug, DA is released via the mesolimbic dopaminergic pathway and will go from the VTA towards the ventral striatum (VS) via the NAc (figure 6) (Ikemoto, 2010). The extracellular levels of DA in the striatum will increase due to an increase of DA release or blocking of the DA transporters by the drug (Volkow et al., 2007). The loss of control and compulsive drug taking cannot be explained by short-term drug-induced DA level increase. For developing the characterizations of addiction, long-term drug administration is required (Volkow et al., 2007). Brain imaging studies show that subjects with a wide variety of addiction have reduced DA receptor availability in the striatum and a decrease in DA release in the striatum (Volkow et al., 2007), leading to decreased sensitivity of reward circuits. In addition to DA, various drug of abuse have an impact on serotonin activity and its receptor functions. Besides this, research suggests that the amount of serotonin in the brain can be a factor in developing addiction. As serotonin plays a key role in modulating certain aspects of impulse regulation (Kirby et al., 2011), it contributes to the vulnerability to development and maintenance of addiction. A lack of serotonin or serotonin receptors in the brain can stimulate this impulsivity (Kirby et al., 2011). Furthermore, the withdrawal phase in addiction is related to the extended amygdala. In this phase, stress neurotransmitters like corticotropin releasing factor (CRF), norepinephrine (NE) and dynorphin are activated (figure 6). This provides a negative emotional state in which compulsive substance taking is reinforced to alleviate the negative feelings (US Department of Health and Human Services, 2016, p. 2-15). After a period of abstinence, substance-seeking behavior is triggered. Then the NAc is stimulated to release glutamate, the main excitatory neurotransmitter of the brain. Release of glutamate can create the urge for substance use. Thus, it acts on control behavior and executive function of the PFC (figure 6) (US Department of Health and Human Services, 2016, p. 2-16).

Chapter 8 - Discussion

Biological and environmental risk factors play a role in an individual's susceptibility to become aggressive or to develop an addiction. Especially early life experiences and social factors during childhood and adolescence can have a major influence. These negative experiences can contribute to development of a few or multiple DSM-V criteria for IED or substance use disorder. Because there are no criteria for proactive aggression, the criteria of the only aggressive disorder acknowledged, IED, are discussed. The most important criteria are that IED behavior happens frequently, it is impulsive and not committed to achieve some tangible objective. Furthermore, the behavior is caused by distress in

the individual or impairment in interpersonal functioning. However, the majority of these requirements are unique to IED and not requirements for substance use disorder. The most important symptoms for substance abuse are social impairment, withdrawal effects and impaired control over substance abuse. This impulsivity is in common with the impulsivity seen in IED. However, comparing IED with substance use does not imply findings for proactive aggression. Different standards must be established for this, which can be considered in the future. Furthermore, when comparing the animal models discussed, more similarities appear. For studying both aggressive and addictive behavior, the same non-contingent and contingent animal models are used. The CPP test for aggression shows via the resident-intruder procedure that this behavior can be rewarding since the paired context is preferred. Additionally, the same results became visible in the CPP test for drug delivery. However, contingent self-administration models with rodents are better for understanding both types of behavior due to the more specific measurements and results. The self-administration model for attack behavior provides planned aggressive behavior, indicating that this can be compared to proactive aggressive behavior. The results provided that motivation of reinforcement plays a major role in both types of behavior as the PR increased after each successful session. Furthermore, aggression seeking and drug seeking behavior is determined. In both models, this seeking behavior seems to be independent on the duration of forced abstinence. Thus, the type of animal models used and the results show that proactive aggression and substance use have a lot in common. However, it is important to keep in mind that the animals model studied rely on substance addiction, whereas addiction can also take the form of non-substance addiction. This type of addiction may be more comparable to aggressive behavior than addiction to substances. The limited knowledge on non-substance abuse, however, suggests that more research is necessary to understand the link between aggressive behavior and non-substance addiction. Moreover, there is a clear overlap when comparing the most important brain regions involved. The PFC and the amygdala play a key role in both aggressive and addictive behavior. Additionally, the NAc is a crucial component of addiction as well as aggression because it is the most important structure for experiencing reward. Although the brain regions involved are similar, there is a difference in the key neurotransmitters that play a role. In aggressive behavior, serotonin is the best studied neurotransmitter due to its involvement in mood regulation. An insufficient amount of serotonin or serotonergic activity can result in disinhibited aggression. Next to this, serotonin can also contribute to the development of addiction. Lack of serotonin can increase impulsivity because it affects impulse control, making an individual more susceptible to addiction development and drug seeking behavior. DA, which controls behavior and the rewarding effects of behavior, is the second significant neurotransmitter involved in aggression. However, DA is the main neurotransmitter in the onset and maintenance of addiction. Namely, substance and non-substance abuse raises DA levels, which causes individuals to experience the feeling of reward. Besides DA, multiple neurotransmitters are involved in the different stages of the addictive cycle like glutamate and dynorphin, which are not mainly involved in aggressive behavior. It is important to keep in mind that these specific brain compartments are based on addiction and on aggression in general. More specific brain research is required to determine whether various forms of aggression affect various brain regions differently and how neurotransmitters play a role in this.

With these results, it is possible to draw a conclusion about the research question whether senseless aggressive behavior can be rewarding and even addictive. It is important to keep in mind that multiple findings are not based specifically on senseless and proactive aggression, but on aggression in general. The neurotransmitters related to aggressive behavior activate the mesolimbic dopaminergic pathway that is important in reward. Thus, this finding suggest that aggressive behavior can be rewarding. Moreover, the overlap in environmental and social cues that can trigger onset of substance use and aggression also indicate the similarity in brain compartments that are involved. Besides acting on the same brain regions, the similarity of animal behavior implies that aggression and addiction may be related. These results overall suggest that aggressive behavior can be addictive. The ambiguous findings suggest that additional research on the various forms of aggressive behavior, such as reactive and proactive aggression, is necessary to determine which form of aggression is most likely to develop

into addiction or whether there is no distinction between the various forms of aggression. This could ultimately result in the innovation that aggression can be classified under the DSM criteria for non-substance addiction.

Afterword

It was an exciting and educational experience for me to write this thesis. I'm pleased with the outcome and I'm delighted I was able to get this done. For me, Information search and subject division were successful aspects of the process. However, I have also encountered difficulties during the writing process. Due to the large amount of information, I struggled to structure it and include only the most relevant information. Writing this thesis had made me aware to set high standards in terms of the data required and deadlines.

Marit Kuik

Groningen, 13th July 2022

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APPENDIX - Table of Content

APPENDIX A – Non-contingent and contingent models

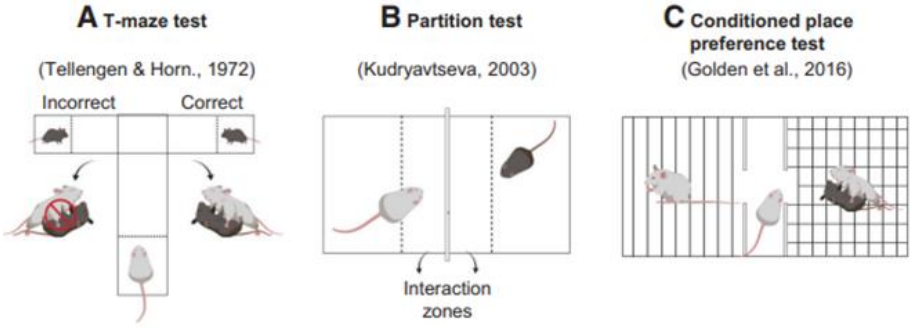

Figure A.1: The non-contingent mice models for aggression seeking behavior. "**A**, In the T-maze test, dominant mice undergo preliminary aggressive experiences with a subordinate in their home cage. On test day, they are placed at the end of the long arm of the T-maze in a start box. At the ends of the short arms are "correct" or "incorrect" goal boxes. A subordinate mouse is placed at each end of the goal boxes and separated by a partition. Upon choosing the "correct" goal box, the partition separating the subordinate mouse is raised and the dominant mouse can engage in attack. Upon choosing the "incorrect" goal box, the subordinate mouse is removed before the partition is raised, eliminating the possibility of attack. **B**, In the partition test, the behavior of a dominant mouse is assessed when a subordinate mouse is placed at the opposite end of a box separated by a partition. The partition allows for all forms of sensory contact with the subordinate mouse, except for tactile contact. Approach behaviors and time spent in the "interaction zone" are recorded. **C**, In the CPP test, dominant mice are conditioned to two different contextual chambers, with one chamber paired to the presence of a subordinate mouse and the other chamber serving as an unpaired control. On test day, dominant mice are placed in a middle chamber connecting both contextual chambers. Time spent in the paired chamber compared with the unpaired chamber is measured" (Golden et al., 2019).

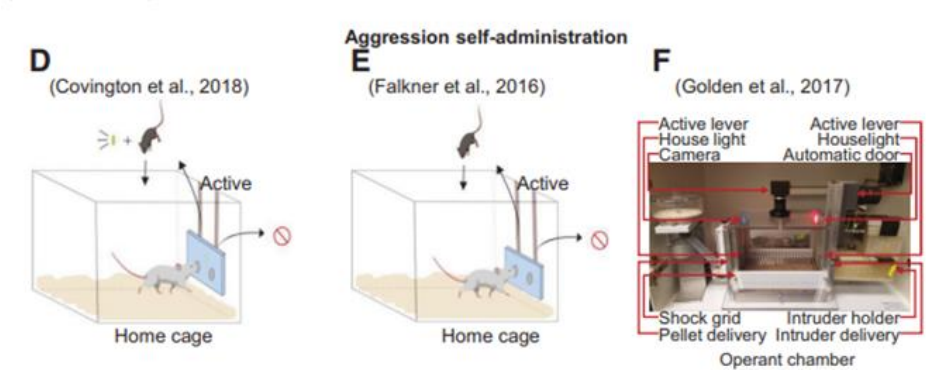

Figure A.2: The contingent mice models for aggression seeking behavior. "**D**, Operant approach. A nose-poke apparatus is inserted into the dominant mouse's home cage. Nose-pokes in the active port are reinforced on a fixed-interval schedule (FI) with presentation of an intruder mouse into the home cage. An aggression-paired house light illuminates upon insertion of an intruder. The other port serves as an inactive control. **E**, Operant approach. As in D, a nose port panel containing two ports with infrared detectors is inserted into the dominant mouse's home cage. However, nose-pokes in the active port are reinforced on a fixed ratio-1 (FR-1) reinforcement schedule. **F**, Operant approach. Behavior is assessed in an operant chamber with an active and inactive lever. Active lever presses are reinforced on an FR-1 reinforcement schedule. A successful lever press results in sounding of a discriminative tone and opening of an automated guillotine door housing an intruder on the opposite side. An intruder is then guided into the operant chamber" (Golden et al., 2019).

APPENDIX B – Aggression self-administration

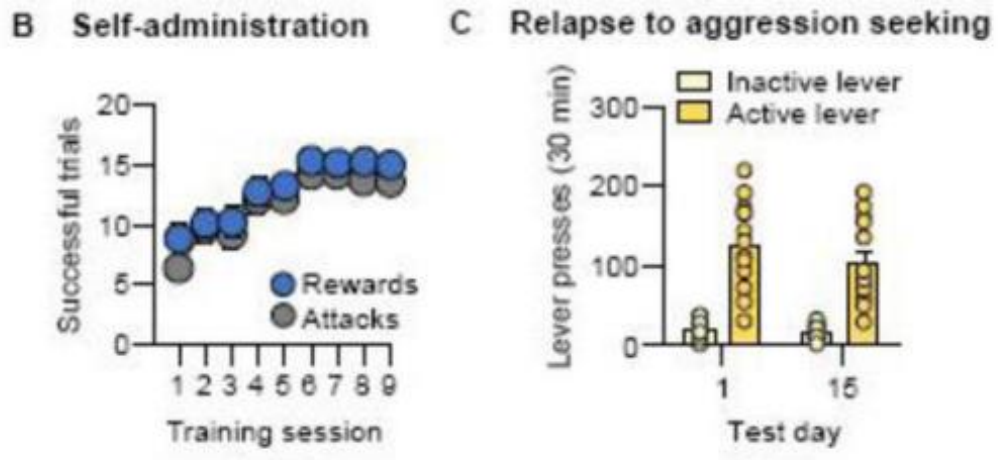

Figure B.1: Relapse to aggression seeking after forced abstinence. "**B**, Number of rewarded and attack trials over 9 days of aggression self-administration under a trial-design fixed-ratio-1 (FR1) reinforcement schedule. These mice increased aggression self-administration over days as measured by the daily number of rewarded trials and attacks towards the intruder. **C**, Number of nonreinforced active-lever and inactive-lever presses to aggression seeking test on day 1 or day 15 of forced abstinence. The high rates of active lever pressing indicate persistent aggression seeking that was independent of the duration of forced abstinence" (Golden et al., 2017).

APPENDIX C – CPP test for drug preference

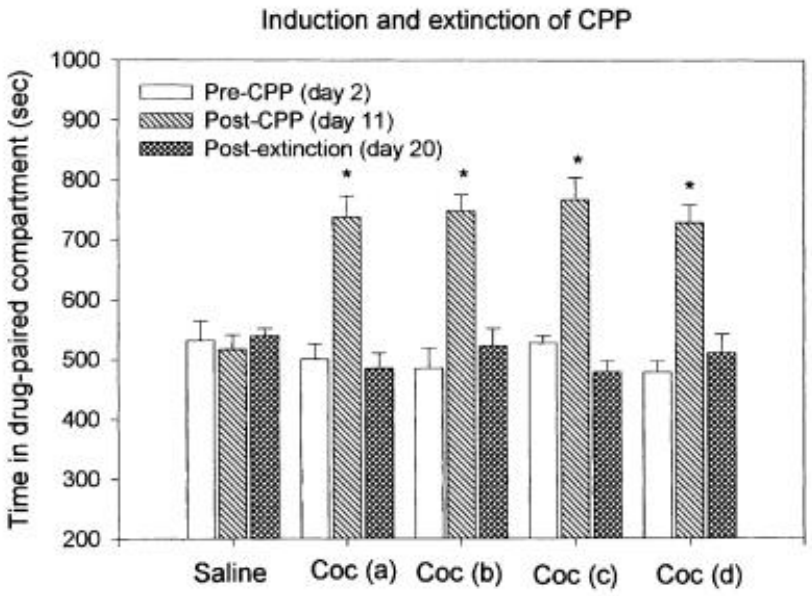

Figure C.1: results of the CPP. The results are presented as the mean time that mice had spent in the drug-paired compartment (in seconds) before and after induction of CPP. It shows that there is a significant preference for cocaine compartment compared with the time spent in the same compartment before drug administration. Saline injections did not produce a significant change in compartment preference (Itzhak, 2002).

APPENDIX D – The runway model for drug preference

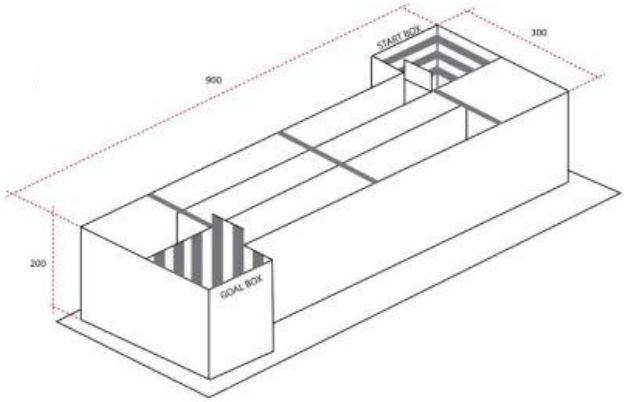

Figure D.1: The schematic diagram of the straight alley runway apparatus used in the research of Pandy and Kahn (2016). The measurements are shown in mm (Pandy and Kahn, 2016).

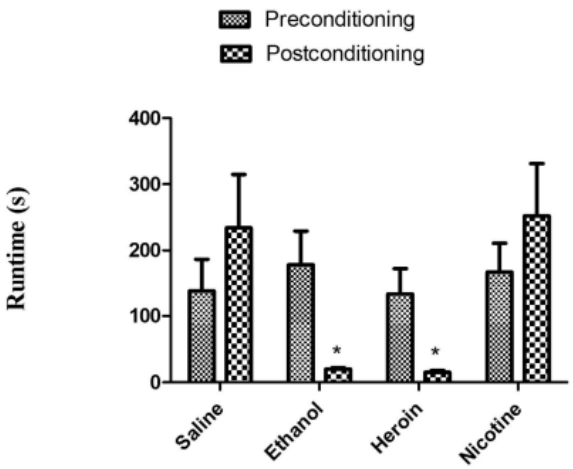

Figure D.2: The runtime in the runway model before and after injections. The results show that there is no significant different in runtime in preconditioning. In postconditioning, there is a significant decrease in runtime after injection of ethanol and heroin (Pandy and Kahn, 2016).

APPENDIX E – Voluntary abstinence versus forced abstinence of drugs

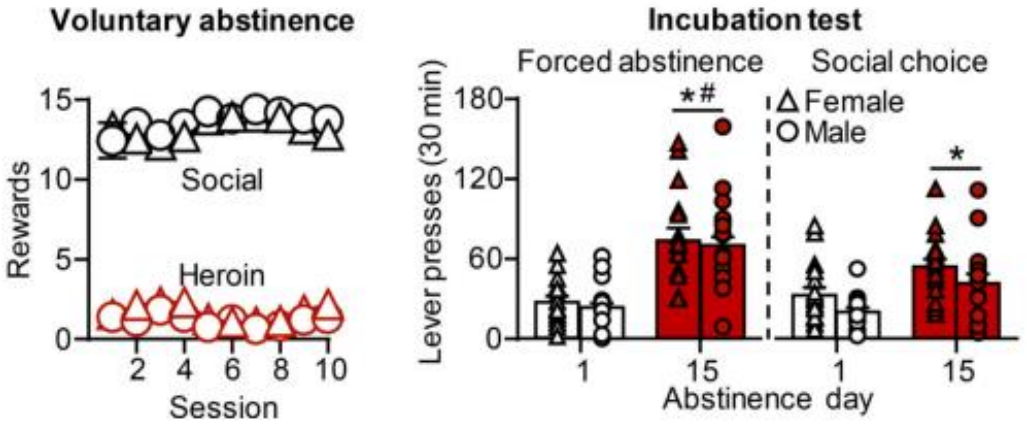

Figure E.1: The effect of social choice-induced voluntary abstinence on incubation of heroin craving. "Voluntary abstinence: number of social rewards and heroin infusions earned during the 10 discrete-choice sessions. Relapse or Incubation tests: active-lever presses during the 30-min test sessions; left: forced abstinence, right: social choice abstinence" (Venniro and Shamam, 2020). Drug seeking behavior increased after forced abstinence compared to voluntary abstinence and is time independent (Venniro and Shamam, 2020).