Addiction treatment for the fight against Anorexia Nervosa

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A neurobiological perspective on the application of addiction treatments in the field of Anorexia Nervosa

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Abstract

Anorexia Nervosa (AN) is a complex eating disorder that shows extreme starvation and excessive exercise as characteristic behaviour. Consequences of this can include a range of health issues and even death. Similarities in neuronal mechanisms have caused AN to be linked with addiction, as described in the auto-addiction opioid model. This review takes a neurobiological approach to find out how the overlap between AN and addiction can be useful for treating AN. The overlapping mechanism between the two diseases has been found to be a dependency on either an exogenous or endogenous rewarding substance. Such dependency results in increased dopamine thresholds and a state of anhedonia during abstinence. Those things associated with the addictive behaviour become conditioned stimuli that trigger craving. Current knowledge about the mechanisms and treatments for both diseases is examined to find opportunities in AN treatment. Pharmacological and behavioural therapies have been found to be potential candidates for new approaches in the fight against AN.

Keywords
Addiction, Anorexia Nervosa, auto-addiction opioid model, behavioural therapy, conditioned stimuli, craving, dependency, dopaminergic system, eating disorder, neurobiology, pharmacotherapy, reward.

Table of Contents

Chapter 1: Introduction

Anorexia Nervosa is an eating disorder that consists of restrictive food intake and often goes together with compulsive exercise. Together, these symptoms result in a sustained calory deficit and thus low weight. AN tends to initiate during adolescence and is primarily prevalent in females with a desire to lose weight. 1% to 4% of women in Europe report suffering from AN (Keski-Rahkonen & Mustelin, 2016). Effects of AN are intense, ranging from amenorrhea and infertility to death. Therefore, several therapies and treatments have been developed to fight this (Yager & Andersen, 2005). Yet, the mortality rate of AN remains the highest of all eating disorders, with a weighted mortality rate of 5.1 deaths per 1000 person-years (Arcelus et al., 2011).

Though the comorbidity of AN with substance abuse was already apparent, a relatively new perspective hypothesizes that AN is actually a form of addiction. This hypothesis is based on the idea that endogenous peptides cause pleasure or relieve discomfort during starvation. This mechanism is supposed to be similar to that of addiction (Davis & Clardige, 1998). Addiction itself is a widespread disease, still rising globally. As with AN, effects can be severe on the physical as well as the emotional level. Nutrition is compromised as well (Saini et al., 2013). There is extensive research about the corresponding neuronal pathways, medications and therapies for addiction. What if all of this knowledge can be used for a different purpose as well? The aim here is to find out if this research can be applied to the aspects that AN has in common with addiction. This leads to the central question of this research, formulated as follows:

How can treatments against addiction play a role in the treatment of Anorexia Nervosa?

This report will go through the available information on addiction and AN, the mechanisms behind these disorders and how they are similar. Then, an analysis of current treatments of both disorders forms the basis for a discussion of opportunities in addiction treatments for AN. It is hypothesized that some similarities in mechanisms of AN and addiction are found. Furthermore, research about treatment on these mechanisms in addiction is expected to be available. This research is used to formulate suggestions for treatments in AN. Eventually, the new ideas are discussed, and possible complications are taken into consideration.

Chapter 2: Addiction

Before it is clear how AN can be considered as an addiction, it is necessary to explain what addiction is.
"*Addiction designates a process whereby a behavior, that can function both to produce pleasure and to provide escape from internal discomfort, is employed in a pattern characterized by (1) recurrent failure to control the behavior (powerlessness) and (2) continuation of the behavior despite significant negative consequences (unmanageability*)."
This is the way that Aviel Goodman described the disorder of addiction in 1990. Before addiction is fully developed, several steps have preceded that together cause a certain drug or behaviour to become addictive. Addiction is likely to occur for some drugs due to the addictiveness of the substance. Still, many people can try out a range of addictive and non-addictive drugs without becoming an addict (Robinson & Berridge, 2000). Though evidence for genetic influence on the vulnerability to addiction is strong, no consistent susceptibility genes have been identified (O'Brien, 2011). The difference that causes some people to become addicted is a shift from sole drug use towards drug dependency. The road from use to dependency is formulated in a cycle of three major components, namely preoccupation-anticipation, binge-intoxication and withdrawal-negative effects. As shown in Figure 1, this cycle eventually causes failure to self-regulate behaviour (Koob & Moal, 1997).

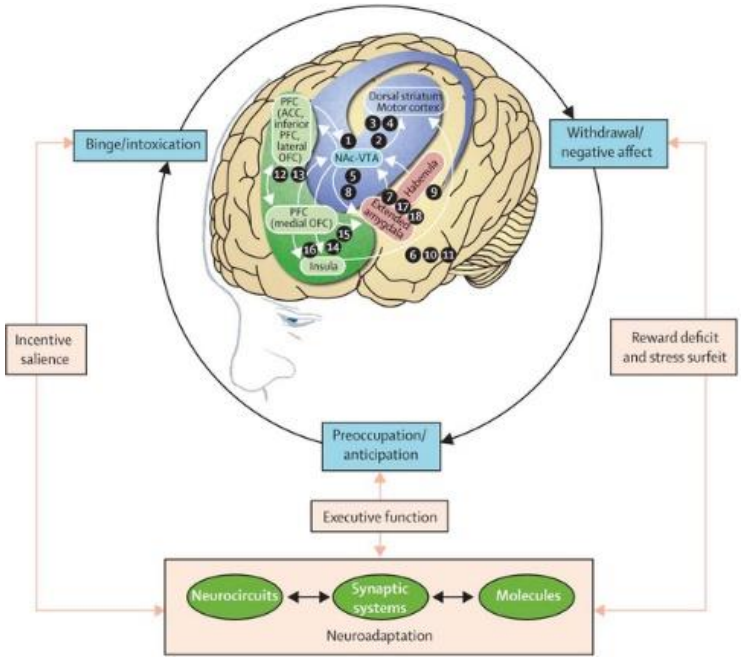

Figure 1 Three stages of addiction: blue is binge and intoxication (reward, incentive salience), red is withdrawal and negative affect (reward deficit and stress surfeit), and green is preoccupation and anticipation (craving, executive function). PFC = prefrontal cortex, ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, NAc-VTA = Nucleus Accumbens-Ventral Tegmental Area (Koob & Volkow, 2018).

In Figure 2, the complicity of addiction prediction is shown. Whether one becomes addicted is dependent on the agent, which can be a drug as well as a behaviour, on the host and on the environment. All three can have either a positive or negative influence. For example, low drug price, genetic susceptibility and low availability of pleasure in life could increase the risk of addiction (O'Brien, 2011).

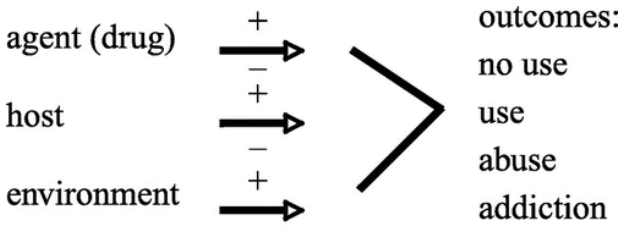

Figure 2 The variable effects of agent, host and environment on the development of addiction (O'Brien, 2011).

The reward system of the brain is the dopaminergic mesolimbic system, connected to the ventral tegmental area (VTA), the nucleus accumbens (NAcc) and the prefrontal cortex (PFC). The VTA is the region in the midbrain that releases dopamine and sends projection neurons into its connection with the NAcc. This is an important pathway for motivation (Sinnott-Armstrong & Pickard, 2013). Both the VTA and the NAcc project to the PFC and stimulate the amygdala. This is part of the circuitry of emotion. One of its functions is to make associations with reward, thus recognizing the source of pleasure, and functions in negative reinforcement (Ndasauka & Kayange, 2019). Additionally, it projects to the hippocampus and the PFC. Together, they function in memory processing and learning reinforcement. The fact that some drugs are significantly more addictive than others explains why this process happens more quickly for some than for others. That is why many countries illegalize highly addictive drugs, such as cocaine and heroin (Sinnott-Armstrong & Pickard, 2013). Cocaine works directly on the NAcc, while heroin works on the dopaminergic neurons of the VTA. The VTA projects to the NAcc, so the effects are similar (Bear et al., 2016). Other drugs are more often socially accepted and not directly associated with addiction, like alcohol and caffeine (Sinnott-Armstrong & Pickard, 2013). The production of dopamine functions as an incentive for the brain to continue performing this act to get more dopamine. Hereby, it influences human behaviour (Ndasauka & Kayange, 2019).

Brain stimulation reward thresholds always decrease after acute administration of any drug of abuse, which causes increased feelings of reward. Simultaneously, chronic administration causes *increased* reward thresholds, resulting in decreased feelings of reward. The most sensitive regions, having the lowest thresholds for reward stimulation, are the trajectory of the medial forebrain bundle, connecting the ventral tegmental area to the basal forebrain. The ascending monoamine systems in the medial forebrain bundle play a role in this. This is executed through norepinephrine and dopamine as well as the nondopaminergic systems. Thus, activating this midbrain dopamine system is a crucial factor for giving incentive salience to stimuli (Koob & Volkow, 2009).

The dopaminergic system is affected by stimuli that can be either natural, like food and sex, or artificial, like psychoactive drugs. The system stimulates the repetition of exposure to pleasurable stimuli. Thus, exposure to pleasure stimulates more exposure to pleasure. This cycle is known as positive reinforcement. Since drugs have a very direct effect, this reinforcement is higher than for natural stimuli. After discovering the source of pleasure, positive reinforcement causes a person to increase exposure to this stimulus. Such behaviour is part of the stage of binging and intoxication, where regular exposure to a stimulus causes a "dopamine high." However, this stage causes an increase in dopamine by elevated stimulation of the reward system. When there is an excess of dopamine, it causes desensitization. This phenomenon is the need for higher dopamine levels to get the same perception of pleasure as before. Individuals can compensate for this by increasing exposure to the stimulus that caused pleasure before. In the case of drug addiction, one can increase drug dosage to reach higher levels of stimulation. This, in turn, increases the down-regulation of dopamine receptors, thereby reducing the effects of stimulation and lower activity in the reward pathway. This is the next step in addiction, where withdrawal symptoms and negative effects arise. As long as the addictive behaviour is continued and increased, dopamine levels stay constant. The individual feels 'normal.' Once the behaviour stops, stimulation reduces, and dopamine receptors remain at a high threshold. Thus, natural pleasurable behaviours reach this threshold less often than before. Negative symptoms can be anxiety and depression, social withdrawal, irritability and anhedonia, which is the difficulty to experience pleasure. This induces a craving for the stimulus because it is an easy way to increase reward stimulation and stop negative symptoms (Ndasauka & Kayange, 2019; Koob & Volkow, 2009).

When addictive behaviour continues, it causes long-term neuroadaptive changes. The three stages of addiction all have separate discrete circuits. First, the binge and intoxication stage has its key elements in the ventral tegmental area and ventral striatum. The extended amygdala influences the withdrawal and negative effect stage. The third stage is preoccupation and anticipation. This consists of craving based on a wide network consisting of the orbitofrontal cortex-dorsal striatum, prefrontal cortex, basolateral amygdala, hippocampus, and insula. The disrupted inhibitory control has its focal point in the cingulate gyrus, dorsolateral prefrontal and inferior frontal cortices. Severe addiction develops through the alteration of the neuroplasticity of these structures. This may start in the mesolimbic dopamine system. Then, a cascade of neuroadaptations follows, from the ventral to the dorsal striatum and the orbitofrontal cortex. It may end in the dysregulation of the prefrontal cortex, cingulate gyrus and extended amygdala. This progression causes such changes in reward neurocircuitry that relapse becomes increasingly hard to avoid (Koob & Volkow, 2009).

Addiction can also occur without the consumption of a substance. Amongst others, this can include Internet addiction, gambling and compulsive sexual behaviour (Grant et al., 2010).

"*Behavioural addiction is defined as an intense desire to repeat some action that is pleasurable, or perceived to improve the well-being or alleviating some personal distress, despite the awareness that such an action may have negative consequences*" (Ndasauka & Kayange, 2019).

The Diagnostic and Statistical Manual of Mental Disorders-5 only has a specific description for the diagnosis of one behavioural addiction, gambling, which is shown in Appendix I. Similarly to psychoactive drugs, addictive behaviours influence the corresponding brain regions for reward. Behaviours like gambling have proven to stimulate the NAcc (Ndasauka & Kayange, 2019). As with drug abuse, behavioural addictions consist of a loss of control, with continued repetition of unwanted behaviour through the urges that arise. Another similarity is the high prevalence in adolescents and young adults and the mechanism of negative reinforcement (Leeman & Potenza, 2013).

Environmental stimuli trigger cravings in addicts by reminding them of their drug of abuse and the corresponding positive experience (Stelten et al., 2008). This attentional bias is an increased level of consciousness towards those stimuli that are associated with addictive behaviour. For example, alcohol attentional bias is found in alcohol-dependent adults. Drug-associated cues cause an enhanced physiological response in people with a history of drugs and result in craving feelings. This cue reactivity predicts relapse in addicts. Additionally, contiguous presentation of a cue during drug delivery can enhance drug intake. This can eventually cause a cue to trigger reward effects by itself. However, not accepting these feelings of craving that arise through drug-associated stimuli does not help. Suppressing these feelings has an opposite effect by causing stress and reducing mental stability. Thus, acceptance is necessary for healthy abstinence (Garland et al., 2010).

Based on the above-explained mechanisms of addiction, it is possible to elaborate on current treatments and how they work.

Chapter 3: Treatment for Addiction

In order to find useful treatments for AN within the field of addiction, current approaches for addiction need to be decribed. It is important to keep in mind that the search for treatment does not result in one answer that can treat anyone with an addiction. Genetics, personality and mental health all differ in patients, and the cause and course of the disease are variable (Ward et al., 2003; Halmi, 2005). Therefore, a range of suitable treatments is necessary and may need to be combined to reach high levels of effectiveness. Analysis of treatment is currently shifting. Until now, the focus was mainly on whether a treatment can prove to be effective. Currently, research also aims to find out how treatments work and, especially, for whom. No treatment has been proposed to selectively remove the addiction memory that makes abstinence so difficult. Therefore, more recent treatments tend to aim at helping to cope with cravings and reducing them (O'Brien, 2011). The main available groups of treatment will be discussed, starting with detoxification and pharmacotherapy and followed by rehabilitation programs and therapies.

A significant part of addiction treatment has focused on the reduction of substance use: detoxification. Several drugs and techniques are developed for this in order to keep withdrawal symptoms minimal (O'Brien, 2011). For this, techniques, pharmacotherapies, rehabilitation centres and therapies are available. An example of a technique is to start drug cessation immediately, which regularly occurs without the assistance of others. This is called stopping "cold turkey." It proved to be more effective than the use of products such as nicotine patches or gum for smoking. It showed to be the most frequently chosen method, even with wide availability of therapies like telephone quitlines or smartphone applications (Khariwala et al., 2018).

Unfortunately, the method of detoxification overlooks the fact that addiction fundamentally changes neuronal circuits. It is not true that stopping the behaviour solves the problem because the addict is still left with the alterations that addiction induced, such as reduced dopamine transmission in the nucleus accumbens during drug withdrawal (Tcheremissine & Krupitsky, 2004). This chronic character of addiction is why long-term treatment is recommended to avoid recurrence after cessation of therapy (O'Brien, 2011). In chapter 2, the different states of addiction are described. The last state shows feelings of anhedonia. The corresponding inability to derive pleasure from typically pleasurable stimuli results in strong cravings to feel better again. What remains is the knowledge that the drug can exactly do what other stimuli cannot: activate this reward pathway. Thus, the craving to restart drug use remains. This is the reason why relapses still occur long after drug abstinence. Though the exact characteristics of withdrawal differ throughout types of addictions, anhedonia remains common for any kind. This feeling of misery is what makes addiction so hard to treat. The addictive behaviour is the only thing that can make a person feel "good" again in the short term. This is why Tcheremissine and Krupitsky researched the stage of craving with symptoms of anhedonia in 2004. NMDA receptor antagonists counteract somatic and behavioural symptoms of opioid withdrawal. This blockade also reduces drug-conditioned behaviour. Memantine, one of several NMDA receptor antagonists, has proven to reduce craving and anhedonia scores. It also reduced relapse compared to placebo treatment in alcohol. Similarly, dopamine receptor antagonists have proven to block drug self-administration in animal studies (Koob, 2000). Antidepressants, such as bupropion, have proven positive effects against drug dependence. Mechanisms remain unclear but seem to help against cravings by relieving the state of anhedonia (O'Brien, 2011).

The above-described methods are part of pharmacotherapy, which is the use of drugs to reduce craving or take away the reward of the addictive agent. Addiction to opiates results in a more calming, satisfied state as opposed to an addiction to stimulants. For this, methadone has shown to reduce cravings and to allow patients to participate in constructive activities. The mechanism behind it is that methadone is an opiate receptor agonist and thus prevents the feeling of euphoria when patients relapse by taking an opiate dose. Methadone does not impair cognition or alertness, which makes it a stable pharmacotherapy for coping with addiction. The partial agonist buprenorphine has similar effects. Though both of these build physiological dependency, withdrawal symptoms are mild (O'Brien, 2011).

Another, more common, approach in the fight against addiction is the establishment of rehabilitation centres. Such addiction recovery clinics aim to tackle substance use disorders by using pharmacological and behavioural treatments. One of the approaches of rehabilitation programs is the avoidance of drug-related external cues. This is because such cues affect relapse by triggering craving. Respondent extinction is used to eliminate such conditioned responses. For example, avoidance of drug-using friends helps in recovery (Litt et al., 1990). However, further research also showed that induced mood states such as depression and anxiety can trigger cravings and conditioned behavioural responses related to drugs. These internal cues cannot be avoided physically, so this conditioning needs to be altered in alternative ways (Childress et al., 1994). A wide range of psychotherapies has been developed to reduce addictive behaviour. One of the categories within this field is that of Cognitive-Behavioural Therapy (CBT). This consists of training addicts in treatment. For example, incentives for abstinence are provided, and coping skills for stress and craving are enhanced (Markus & Hornsveld, 2017). As described in chapter 2, the environmental reminders of drugs called substance-associated stimuli can be responsible for relapse. Therefore, Cue Management is developed, where high levels of exposure to drug-related cues eventually reduce patients' subjective emotional response to these cues. It is a form of training to combat craving (Van horn & Frank, 1998). This way, the effectiveness of CBT lies in the improvement of prefrontal cortex functioning (Markus & Hornsveld, 2017). As explained in chapter 2, this is part of the rewards and memory processing, which is compromised in addiction. Unfortunately, the effectiveness of psychotherapy against addiction remains a point of debate, with little evidence for significant functionality (Epstein, 2019).

Besides therapy within a rehabilitation centre, a range of other methods is available. For example, one therapy is the participation in Alan Carr seminars, which consists of a single session of intensive group counselling. This cessation training has primarily been in practice and been proven to be effective for the fight against smoking addiction (Moshammer & Neuberger, 2007). Similar, but much more elaborate, is the 12-step Minnesota approach, consisting of group and family therapy, individual counselling and assignments. This has been proven to be effective in the reduction of adolescent drug abuse (Winters et al., 2000). Mindfulness is also a growing area of research for treatment. People suffering from addiction tend to suppress feelings of craving, while research has proven that thought suppression decreases heart rate variability (HRV). High HRV helps in emotion regulation and thus in better mental and physical health. The brain areas associated with cravings, as described in chapter 2, are also affected by mindfulness training. Mindfulness-based relapse prevention (MBRP) is a treatment developed to accept uncomfortable states, thus decreasing craving (Witkiewitz & Bowen, 2013). A study on alcohol dependency showed that mindfulness reduces stress from thought suppression and improves the alcohol attentional bias (Garland et al., 2010). Later on, mindfulness also proved to be effective for behavioural addictions. The mechanisms that make this treatment effective remain to be elucidated, but several hypotheses with a neurobiological basis have been made. For one, it may help to objectify cognitive processes. That may permit individuals to apprehend that stimulus-induced craving is a passing phenomenon. This also reduces the suppression of feelings that decrease HRV (Shoning et al., 2014).

Eye Movement Desensitization and Reprocessing (EMDR) is a treatment used for reprocessing addiction memory (AM), such as drug effects. It is guided by the theory that dysfunctional memories are the driving force of psychopathology: the Adaptive Information Processing (AIP) model. AM is accompanied by increased levels of arousal during activation. This memory partly drives the conscious and unconscious cravings, environmental response and feelings of satisfaction. During recall of a memory, it can be reconsolidated making use of neuroplasticity. This can weaken or strengthen the original learning. “Eye movements lead to weakening or desensitizing of the original memory” (Markus & Hornsveld, 2017). Precisely this is how EMDR can reduce cravings as well as drug-seeking behaviour. Effectiveness in alcohol dependency has been proven (Hase et al., 2008). Its effect on sexual addiction has been reviewed. More specifically, the role of trauma in addiction maintenance is reviewed in a case study by R. Cox and M. Howard (2007). As EMDR has become a leading method of trauma intervention, they theorize that it is especially useful for those addictive diseases that come with and maybe fuelled by trauma. Though there is some neurobiological research available on the mechanisms of EMDR (e.g. Bergmann, 2008), the main focus of this has been on stress and trauma circuitry as opposed to reward.

Difficulties within the field of addiction treatments lie in the mechanisms behind effectiveness. Besides those treatments discussed above, a wide range of research is available about different drugs, therapies and their effect on different addictions. Though effectiveness can regularly be proven for the separate treatments, comparing them does not show superiority of one above the other. No full explanation for this is available yet (Longabaugh & Magill, 2011).

Thus, a range of approaches allow addicts to reach abstinence. The next step in this study is to find out where these approaches may be applied in the field of AN. The mechanisms of AN will be clarified in the following chapter to find similarities with addiction.

Chapter 4: Anorexia Nervosa

AN is a disease that mainly consists of a daily calory intake deficit by food restrictions, high levels of activity and restlessness. This determined dieting results in the sustenance of low weight. Adolescents are most likely to develop this eating disorder, though diagnosis proves to be complicated. This is because AN has a range of subclinical features making patients seem healthy when they are not. Thus, physical examinations do not immediately show signs of sickness. Common symptoms are that patients desire to lose more weight, have a fear of fatness and stay in denial. An attentional bias towards food and food-related stimuli is typically seen, as well as a disturbed body image, called Body Dysmorphic Disorder (BDD) (Yager & Andersen, 2005).

The causation of AN is multifactorial and most likely a combination of personality, genetics, culture and neurobiology (Støving et al., 1999). It comes with altered appetite regulation and several endocrine abnormalities, but it is unknown whether this is secondary or aetiologic. At first, the risk of AN mainly seems to be influenced by psychosocial factors, such as stress or anxiety. However, once the disease sustains and worsens, biological abnormalities start to play a role as well. Some are induced by the calory restriction that is part of AN. It seems that these alterations actually counteract recovery and some even exacerbate the behaviour of AN. The consequence is that an unstable feedback system develops (Troscianko & Leon, 2020). It is a vicious cycle making the disease increasingly intractable. The diagnostic criteria for AN are shown in Appendix II. A wide range of altered functioning and structuring in the brain is reported, ranging from weakened white matter integrity in the bilateral fimbria-fornix to decreased homovanillic acid (HVA) in the cerebrospinal fluid (CSF). Which parts of these alterations are cause and which are consequence remain unclear (Phillipou et al., 2013). In order to remain specified, this study keeps its focus on those aspects of AN that have been found to show similarities with addiction.

Feeding activities are regulated through many different factors. Norepinephrine, dopamine and serotonin show a clear contribution to this. These neurotransmitters play a role in the theory that neurological changes can occur and form a loop towards an eating disorder. This influence of the neurobiological processes on behaviour might be engendering, sustaining or even amplifying systems within the disorder. Besides this physiological reinforcement, psychological reinforcement occurs through the development of security. Patients realize that they are in control when they are good at losing weight and maintaining a diet. This feeling is aided by the physiological effects of dopamine, serotonin and opioids (Morley & Blundell, 1988). The dopamine theory states that dopaminergic activity is elevated, and the receptors are downregulated. High doses of amphetamine can even induce anorectic behaviour through action on catecholamines. In this, DA plays a significant role. However, anti-dopaminergic agents have not proven to give convincing effects for treatment (Støving et al., 1999).

To indicate how AN is similar to addiction, two sentences from above are repeated here. A quote from chapter 3:

"Addiction designates a process whereby a behavior, that can function both to produce pleasure and to provide escape from internal discomfort, is employed in a pattern characterized by (1) recurrent failure to control the behavior (powerlessness) and (2) continuation of the behavior despite significant negative consequences (unmanageability)" (Goodman, 1990).

This quote mentions both the compulsivity of the behaviour and the fact that patients know that their behaviour is unhealthy but that this is not enough to stop them from it. Both are true for AN. The other quote makes a specification to behavioural addictions:

"Behavioural addiction is defined as an intense desire to repeat some action that is pleasurable, or perceived to improve the well-being or alleviating some personal distress, despite the awareness that such an action may have negative consequences" (Ndasauka & Kayange, 2019).

In this article, food and eating disorders are already included in the category of behavioural addiction. For AN, the intense desire is to lose weight. In this case, the disorder does not originate from something generally regarded as a risk for addiction, unlike, for example, heroin. Naturally, AN does not originate from consumption of any sort. On the contrary, it grows out of the lack of consumption. Research has proven that individuals with AN, like with addiction, show a structural change in the brains that does not reverse after recovery. A long-term healthy relationship with food and daily life may reverse part

of the effects of AN, such as a return of menses, but some changes appear to be chronic. The latter means that former AN patients have to learn how to deal with these chronic alterations and what they mean for daily life. This is similar to addicts, who sometimes show relapse after years of soberness. The altered brain structure causes the cravings to always remain (Phillipou et al., 2013).

For neurobiology, it is straightforward to only look at the level of hormones and neurons in the brain. However, this disease consists of several dynamic systems that all interact. To understand neurobiology, also cognitive and emotional patterns need to be taken into consideration (Troscianko & Leon, 2020). People diagnosed with addiction regularly get cravings from substance-associated stimuli (Stelten et al., 2008). As reported by J. Powell (1995), these conditioned stimuli cause a response that reduces withdrawal symptoms. Similarly, conditioned stimuli associated with a state of abstinence can induce withdrawal symptoms, thereby increasing the risk of relapse. Thus, a stimulus is associated with an addiction at the emotional level, which translates into a physiological response. Considering AN as an addiction means that AN related stimuli can have the same effect on AN patients as drug-associated stimuli do for addicts. Patients with AN have a craving for the security they find in starvation. When they cannot continue this behaviour, the state of anhedonia arises. This reduced capacity for feeling pleasure and reward causes a disturbed relationship with food and social impairments. One of the results is that up to 80% of AN patients show excessive exercise as a symptom because they aim to compensate for their dysphoric mood state (Keating & Rossell, 2014). Research suggests that anhedonia is a trait-characteristic for AN and thus not necessarily caused by starvation on its own. This means that an increase in body weight only partly reduces anhedonia (Boehm et al., 2017).

Two main theories explain the relationship of AN with substance abuse disorders. On the one hand, comorbidity is recognized between the two. Explanations could be the underlying predisposition of some people based on genetic vulnerability or addictive personality style. Others favour the hypothesis that both disorders create a "coping" pattern, thereby making the individual more likely to develop another addiction for coping. Another theory considers self-starvation to be a chemical dependency in itself, as formulated in the auto-addiction opioid model. This model explains how a chronic eating disorder like AN forms an addiction to the endogenous opioids of the body, the beta-endorphins. This occurs because the starvation and strenuous exercise behaviours of AN enhance endorphin activity. Thus, higher levels of endorphin are reached, and a stronger drive for starvation and exercise follows. For that matter, AN is like any kind of substance abuse. The endogenous opioids have reward properties by themselves, which supposedly makes them as addictive as exogenous opiates. An anorectic dieter is more powerfully influenced by the opioid changes that are induced during dieting and exercise than healthy people, similar to a drug addict that is influenced by exogenous addictive substances (Davis & Clardige, 1998).

Chapter 5: Treatment for Anorexia Nervosa

Similar to what is described in chapter 3 about the treatment for addiction, there is no one answer to the question of how someone heals from AN. Multiple theories and thus multiple therapies are available. The most prominent treatments are medical management and behavioural, cognitive and family therapy. Sometimes, pharmacotherapy is added to one of these treatments. The first crucial steps are to reach nutritional rehabilitation as well as weight restoration.

Behavioural therapy is used for the development of a healthy eating pattern (Halmi, 2005). It remains largely unclear which therapies are significantly effective and to what extent. Dropouts from therapy and withdrawal due to relapse or medical complications make research trials complex. Cognitive therapy is focused on mental health by reducing the feelings of fatness and basing self-worth on body image. For example, cognitive structuring is a thorough analysis of negative thoughts to form a conclusion about a patients behaviour. Similarly, such therapy is used to improve problem-solving skills to find solutions rationally. Monitoring is used to record the total food behaviour, environment, exercise and mood (Halmi, 2005). For cognitive-behavioural therapy (CBT), there is empirical evidence that it is more effective than nutritional counselling in reducing rates of relapse and increasing "good" outcomes of therapy (Pike et al., 2003). CBT for AN aims to reduce the behavioural symptoms such as dieting and purging and to restore the disturbed body image. As described in the previous chapter, patients with AN initially feel reward through food restriction because it increases DA levels. In therapy, this conditioning is attempted to be reversed, meaning that eating should be considered "good" instead of "bad," which might also alter the way reward is generated in neurocircuitry. Mainly for those underage, family therapy is used (Halmi, 2005).

As well as in addiction, EMDR is used to fight AN. Where CBT aims at improving current behaviour, EMDR focuses on previous events that may be drivers for the onset of this eating disorder. Similar to addiction, the possible traumatic basis for this disease increases the likelihood of effectiveness for EMDR. Mainly emotional abuse is associated with a trauma that causes more severe problems in emotion regulation and eating disorder symptoms (Zaccagnino et al., 2017). Besides reconsolidating behaviour memory, the traumatic memory can also be altered into a less intense memory.

One of the pharmacological solutions to reduce the chance of relapse is fluoxetine (Halmi, 2005). Fluoxetine is a serotonin reuptake inhibitor (Kaye et al., 2001). This inhibition alters the symptoms that come with the disturbed serotonin pathway of AN. Another pharmacotherapy is the use of antipsychotics for those who suffer from severe anxiety and have difficulties gaining weight. Furthermore, cyproheptadine functions as an antidepressant and chlorpromazine or olanzapine might reduce the obsessional and compulsive behaviour as seen in AN. Both help in weight gain as well. Citalopram possibly reduces depressive feelings and anxiety during weight gain. Unfortunately, patients do not show high motivation levels for such treatments and dropout rates are high (Halmi, 2005).

Chapter 6: Synthesis

Now that treatments have been discussed, the goal is to answer the central question of this thesis.

How can treatments against addiction play a role in the treatment of Anorexia Nervosa?

This chapter discusses how the current use of treatment for addiction may be integrated for AN. To start, some differences that do not seem to be worth sifting through. Detoxification, such as the 'cold turkey approach, is suitable for the cessation of substance abuse but cannot directly be adapted to AN. The only way to abruptly stop the toxic behaviour is to start eating a healthy diet, but that is exactly what AN patients have difficulty with. Force-feeding keeps patients alive, but it comes with a range of ethical issues for the patients and high levels of distress for their caregivers (Dresser, 1984). This chapter will focus on those aspects that indicate opportunities from addiction for AN.

One way in which the knowledge of addiction is starting to be integrated into the treatment for AN is using a Mandometer. A Mandometer is a device that can be embedded into a table to record eating rate based on the weight loss on the plate. The patient records his/her satiety with this device as well. The Mandometer is used to let patients follow an established eating rate. The hypothesized mechanism through which this is effective is that conditioned stimuli are taken away (Bergh et al., 2002). As described, substance-associated stimuli are reduced in addiction by taking an addict out of its ordinary environment. This way, those stimuli that usually trigger feelings of craving are taken away. The theory of addiction has been adapted to AN by developing this new way of eating. Since eating with the Mandometer is largely different from their former way of eating, stimulus triggering is reduced, which is hypothesized to simplify eating for patients. The large effect size of altering eating behaviour is shown in Figure 3. By tackling the difficulty patients have with eating, the Mandometer treatment not only influences food intake and body weight but also a range of cognitive aspects.

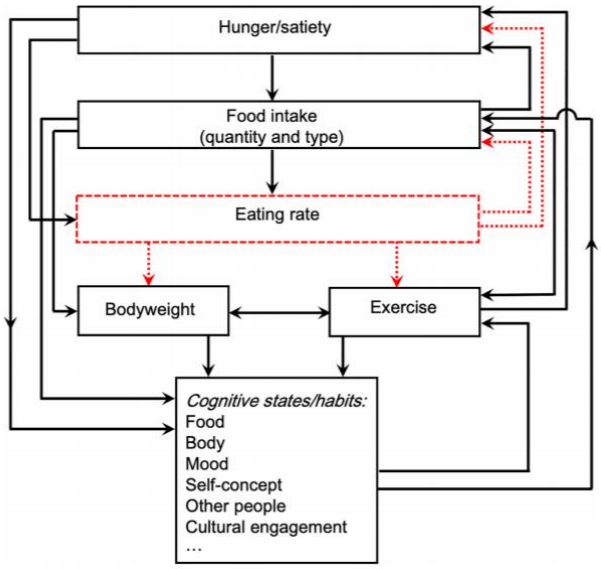

Figure 3 Interactions between cognitive, physiological and behavioural components of eating. The red colour signifies the basal function eating rate has in these systems (Troscianko & Leon, 2020).

The chemical dependency in AN that is hypothesized in the auto-addiction opioid model suggests that available treatments against addiction could be as valuable for AN. A 12-step Minnesota approach should improve conditions of mental health through improving cognition and behaviour that concerns eating. Cue Management can be used to combat cravings for abstinence. Patients can be exposed to those stimuli that trigger them to reduce food intake and increase physical activity. Similarly, CBT is already used to improve cognition concerning eating. CBT includes incentives for abstinence and coping skills for stress and craving in addiction. In AN, incentives for eating and these same coping skills should be developed. This may reduce emotional response and improve prefrontal cortex functioning. Reducing attentional bias through MBRP should improve AN as well. This approach has already been explored in eating disorders as a co-concurrence for patients with substance use disorders

(Elmquist, 2017). This indicates that it may also be suitable for reducing AN symptoms when this disease occurs on its own.

In chapter 4, research about memantine as a pharmacologic agent to optimize treatment was discussed. Animal research has shown that after the termination of chronic drug abuse, ICSS thresholds remain elevated. ICSS, intracranial self-stimulation, is used in animals to quantify reward. It suggests that reward is commonly reduced after any kind of drug administration (Tcheremissine & Krupitsky, 2004). For this reason, memantine could also be effective in the reduction of anhedonia symptoms in AN. Other NMDA receptor antagonists could be used as well. An obstacle for this is that AN patients do not feel bad when they are not using a substance, but when they are. It might be most effective to administer memantine during meals. This way, the reduced feelings of anhedonia are not related to food abstinence but food consumption.

Remarkable is that there are already quite some treatments simultaneously used for addiction and AN. Cognitive behavioural therapy, group therapy and rehabilitation already exist for both diseases. At some locations, the available treatments are even aimed specifically at these two diseases (ChangesGGZ, 2020, September 14). Little research is available about the development of such treatments and what they are based on. To a large extent, psychologists have developed therapies based on psychological research instead of neurobiological research. In order to reach optimal results, neurobiological research should be integrated into clinical practice for a full understanding of this disease. Vice versa, clinical expertise can be used for the research to specify what problems still occur and require a solution.

One of the limitations of this study is that research on the neurobiological aspects of AN is focused on the food regulatory pathways, such as the neural control of appetite and genetics (Litwack, 2013). This is a logical first step for a disease that has its main focus on eating behaviour. However, those factors that play a role in addiction should also be examined now that AN is considered an addiction. Reasons why research can still be lacking is, for example, the limiting effect of technological possibilities. Characterizing brain circuits is only recently available, and only gross systems have yet been identified. The technologies are mostly focused on one molecule every time, thus not being able to show complex interactions or functioning (Kaye, 2008).

A big gap of knowledge is the one between current treatments for addiction and the neurological basis for this process. A reasonable base of research is available about neurological aspects of addiction and its pathways. At the same time, a range of addiction treatments exists that have proven some significant positive effects. However, these two groups have limited overlap. On the one hand, neurobiological research does not show to be translated regularly into actual treatment. On the other hand, current therapies are often based on experience in the field. Research about their effectiveness is available. Nevertheless, the underlying mechanisms that should show why therapies work are only scarcely elucidated. An integrative approach is required to reach optimal results for treatment.

For the next steps, it might be interesting to look into prevention. Research about the prevention of addiction is available (e.g. Gerstein & Green, 1993), and analysis about using this research for AN could give interesting new insights. Similarly, instead of adapting addiction research on AN, a reversed analysis may open up new opportunities for addiction treatment. Furthermore, these suggestions might not only apply for AN but also for similar disorders like Bulimia nervosa, binge eating and Orthorexia Nervosa. These disorders all have a commonality of compulsive behaviour that continues against better judgement (Milos et al., 2018; Zwaan, 2001; Dell'Osso et al., 2017). A more general field of study for any such diseases might be the most efficient path towards reducing addictive behaviour.

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Appendix

I. Gambling

Diagnostic Criteria **312.31 (F63.0)**

A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period:

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

B. The gambling behavior is not better explained by a manic episode.

Specify if:

Episodic: Meeting diagnostic criteria at more than one time point, with symptoms subsiding between periods of gambling disorder for at least several months.

Persistent: Experiencing continuous symptoms, to meet diagnostic criteria for multiple years.

Specify if:

In early remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met for at least 3 months but for less than 12 months.

In sustained remission: After full criteria for gambling disorder were previously met, none of the criteria for gambling disorder have been met during a period of 12 months or longer.

Specify current severity:

Mild: 4–5 criteria met.

Moderate: 6–7 criteria met.

Severe: 8–9 criteria met.

Figure 4 DSM-5 diagnostic criteria for gambling (American Psychiatric Association, 2021)

II. Anorexia Nervosa

Diagnostic Criteria

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. *Significantly low weight* is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.

B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.

C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Coding note: The ICD-9-CM code for anorexia nervosa is **307.1**, which is assigned regardless of the subtype. The ICD-10-CM code depends on the subtype (see below).

Specify whether:

(F50.01) Restricting type: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

(F50.02) Binge-eating/purging type: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

In partial remission: After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.

In full remission: After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

Mild: BMI ≥ 17 kg/m²

Moderate: BMI 16–16.99 kg/m²

Severe: BMI 15–15.99 kg/m²

Extreme: BMI < 15 kg/m²

Figure 5 DSM-5 diagnostic criteria for Anorexia Nervosa (American Psychiatric Association, 2021)