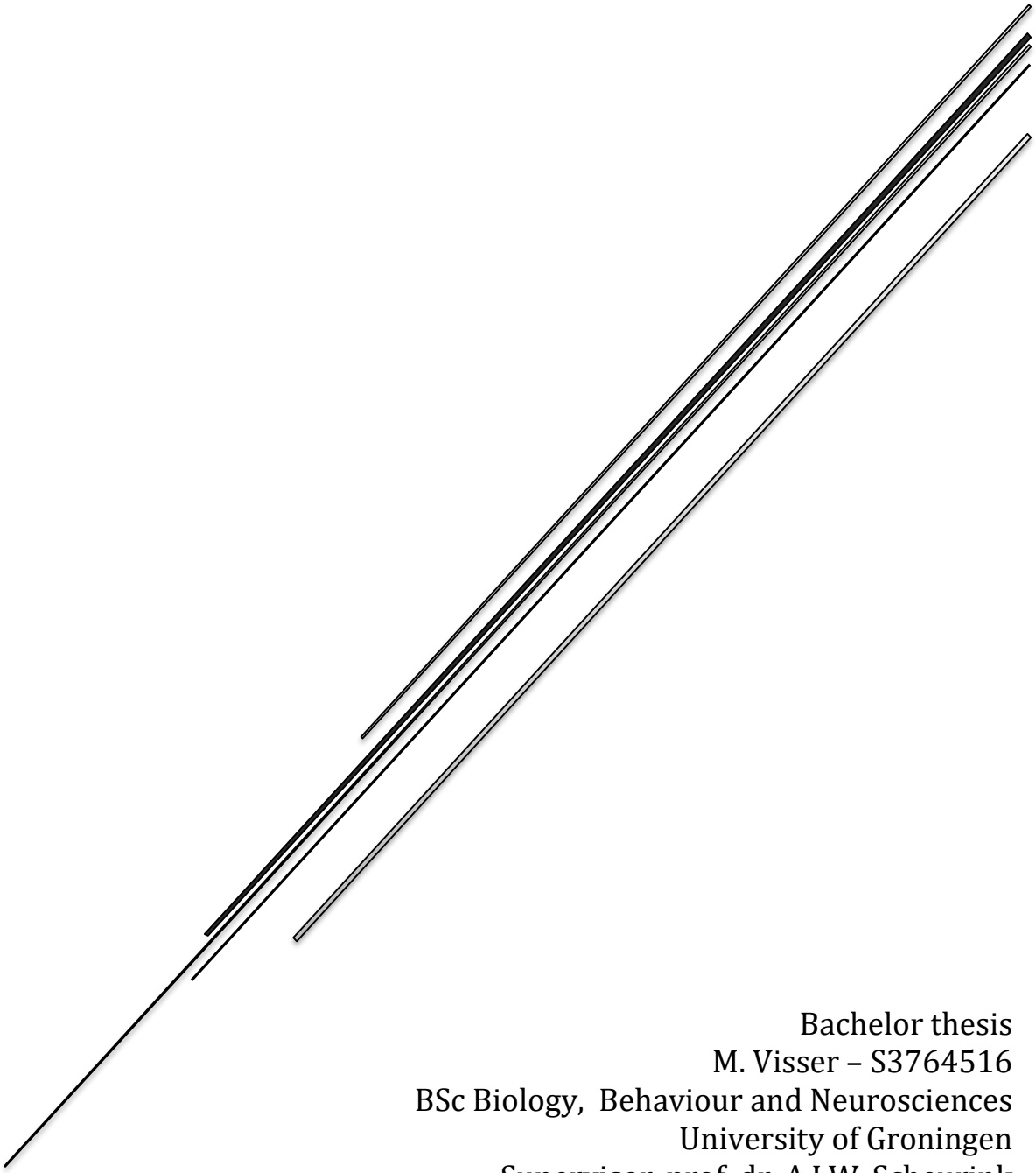
HYPERACTIVITY IN ANOREXIA NERVOSA

A proposed linkage to the reward system



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Abstract

Anorexia Nervosa (AN) is a severe eating disorder characterized by significant weight loss and restricted food intake. With a mortality rate of 5.9%, the disease is the leading cause of mental disorder related deaths. AN patients are observed to be hyperactive, meaning that they exercise excessively and are overall restless. In this thesis, the following question is answered: "Is AN accompanied by hyperactivity and, if so, which mechanisms are behind this hyperactivity?". Over the years, hyperactivity rates in AN patients have been observed ranging from 38 to 80%. Hyperactivity is most prevalent in the restricted subtype of AN patients. From a perspective that involves the energy homeostasis, it seems counterintuitive that AN patients are hyperactive. Yet, becoming active in times of food shortage was favoured by evolution. This activity has therefore evolved to be rewarding. In AN patients, the rewarding aspect of hyperactivity has become addictive. Hence, the hyperactivity in AN patients can be deemed as an addiction to them. The addictive aspect of being active should thus be taken into consideration when treating patients of AN.

TABLE OF CONTENTS

Introduction

Anorexia nervosa (AN) is a severe eating disorder characterized by a restricted food intake and significantly low body weight, and can even result in death. Other symptoms observed in patients include a distorted body image, intense fear of gaining weight, absence of menstruation, and hyperactivity, which entails increased physical activity and exercise (National Institute of Mental Health, 2021; Psycom.net, 2020). When researching the disease, it is unclear whether such observations are the consequences of AN or whether they are the cause of it. For instance, is AN caused by a distorted body image or has AN a different cause? If the latter would be the case, then the distorted body image would be a consequence of the disease.

In this thesis, however, the focus lies upon the hyperactivity of the AN patients. From a biological point of view, the observed hyperactivity seems counterintuitive at first glance. When food intake, and therefore energy intake, is restricted it would be logical that physical activity decreases, in order to save energy. Yet, AN patients seem to have increased activity levels. Two questions are the focus points of this thesis. The first question that will be answered is whether AN is truly accompanied by hyperactivity or not. If this indeed is the case, then the second question arises: Through which mechanism is the hyperactivity caused?

Chapter 1: Anorexia Nervosa

Anorexia nervosa (AN) is a disease, which is, according to the DSM V, characterized by the following symptoms: The patients restrict their energy intake relative to their requirements, leading to a significantly low body weight. Furthermore, AN patients have an intense fear of gaining weight or becoming fat regardless of the fact that they have a significantly low weight (American Psychiatric Association & Association, 2013). In addition to the aforementioned characteristics of the disease, AN patients also have disturbances in the way their body weight or shape is experienced and contribute a disproportionate influence of their body weight or shape on their self-evaluation. Lastly, they are unable to recognize the seriousness of their current low body weight (Psycom.net, 2020).

The prevalence of AN in society is 0.9% amongst young women and 0.3% amongst young men (CDC, 2008). From this it can be inferred that approximately 92% of the patients are female (Mitchell & Peterson, 2020). The average age of onset of the disease is 16-17 years old (Anorexia & Bulimia Care, n.d.).

AN is the leading cause of mental health related deaths; the mortality risk of the disease is around 5.9% (Chesney, Goodwin, & Fazel, 2014). Suicide is one of the causes of death that contributes significantly to this high percentage; AN patients are 18 times more likely to lose their lives due to suicide (Keshaviah et al., 2014). Of those that do survive AN, 50% recovers, 30% improves and 20% remains chronically ill (Anorexia & Bulimia Care, n.d.). When discussing AN, one should specify whether the patients are of the restricting type or of the binge-eating/purging type. The latter type has during the last three months engaged in recurrent episodes of binge eating or purging behaviour, whilst the former type has not (American Psychiatric Association & Association, 2013).

Risk Factors

Women are more at risk for developing AN than men. Psychological factors that contribute to developing a high risk for AN, are a.o. behavioural inflexibility and perfectionism (Peterson & Fuller, 2019). AN also has a genetic basis. People who have relatives diagnosed with AN are 11

times more likely to develop the disease themselves (Strober, 2000). From twin studies, family studies and population based studies, it is estimated that the heritability of AN ranges from 28% to 78% (Mayhew et al., 2017; Thornton et al., 2010). Moreover, multiple studies have found loci that seem to be involved with the disease (Duncan et al., 2017; Watson et al., 2019).
Besides these genetic and psychological risk factors, culture is also a major factor in the development of AN. Nowadays, sociocultural messages proclaim the perception that thin bodies are attractive. Mass media strengthens the notion that one is only socially approvable and attractive if they are thin even more. This results in women being more dissatisfied with their appearance and they may therefore be more likely to pursue this image of perfect thinness (Izydorczyk & Sitnik-Warchulska, 2018). When this pursuit escalates, it can result in AN.

Symptoms

Next to the most obvious symptoms of the disease, such as extreme weight loss and distorted body image, other symptoms of AN include: Fainting, dizziness, absence of menstruation, low blood pressure and thinning or brittle hair (Psycom.net, 2020). Over time, when the disease prolongs in the patient, other symptoms may arise as well, including but not limited to damage to the structure and function of the heart, brain damage, infertility and thinning of the bones (National Institute of Mental Health, 2021).
Furthermore, individuals diagnosed with AN often have another psychiatric condition, such as unipolar depression, anxiety disorders and substance abuse disorders (Hughes, 2012; Salbach-Andrae et al., 2007).
In addition to these symptoms, many patients with AN, although not all, are observed to be hyperactive. Hyperactivity can take multiple forms, ranging from restlessness observable as fidgeting to excessive exercising. From a psychological point of view, this hyperactivity is just a means in order to accomplish the goal of weight loss (Kohl et al., 2004). Yet, this traditional view may not be the right explanation for the observed hyperactivity. In the next couple of chapters, it will be discussed whether hyperactivity truly is a symptom of AN or whether these aforementioned observations are just individual incidents.

Chapter 2: Hyperactivity in Anorexia Nervosa

Over the years, research with the focus on hyperactivity in AN has become abundant. Even back in 1868, the physician William Gull observed his patients to be restless and active (Gull, 1997). Yet, nowadays uncertainty regarding hyperactivity still remains. Research has not led to an unanimous answer to the question whether hyperactivity should be associated with AN. Much of the uncertainty stems from the different definitions of hyperactivity and the diverging measuring methods of hyperactivity. Observing hyperactivity could entail looking at only the strenuous exercise of a patient (such as long distance running and cycling). Additionally, one could include the physical activity incorporated in daily activity, such as taking the stairs and fidgeting in the definition of hyperactivity (Gümmer et al., 2015) . Furthermore, studies differ in their distinction between normal activity levels and hyperactivity. Important to note as well, is that some studies record hyperactivity using questionnaires or interviews, whilst other studies assess hyperactivity using accelerometers or other equipment (Gümmer et al., 2015; Sauchelli et al., 2015).

In this chapter, certain findings in favour and opposed to hyperactivity in AN will briefly be highlighted, after which a stance will be taken. In addition to this, a brief intermezzo (Box 1) is

Box 1: Anorexia athletica
One of the subtypes of Anorexia is Anorexia athletica (AA), also called sports anorexia. As the name indicates, the eating disorder is present in athletes. In certain sports, low body weight gives athletes an advantage over their competitors, as their performance partly depends on body weight. Additionally, in certain sports low body weight is promoted due to aesthetics, for example in ballet. From this point of view, athletes often restrict their calorie intake and/or overexercise in order to reach low body weight (Sudi et al., 2004). It has been shown that for both males and females, the prevalence of eating disorders is higher in athletes compared to the general public (Park & Im, 2021). A Norwegian study found that prevalence of eating disorders for males is highest in antigravitation sports (22%). For females, prevalence of eating disorders is highest in aesthetic sports (42%) (Sundgot-Borgen & Torstveit, 2004). The high prevalence in females is accompanied by a higher drive for thinness compared with healthy controls (Silverii et al., 2021). Additionally, menstrual arrhythmia is present in high level rhythmic gymnastics, a symptom shared with AN (Maïmoun et al., 2013). Risk factors of procuring AA include the levels of commitment of an athlete to their sport, the amount of pressure that is put on an athlete for getting the ideal body shape, and the levels of an athlete's competitiveness and perfectionism (Park & Im, 2021).
As AA has its origins in excessive exercise, it indicates great importance of exercise, and thereby hyperactivity in AN as well. It would be interesting for future research to investigate the link between hyperactivity in AN and hyperactivity in AA.

provided regarding Anorexia athletica, a subtype of Anorexia in which excessive exercise is a central factor as well.

Research Supporting Hyperactivity in AN

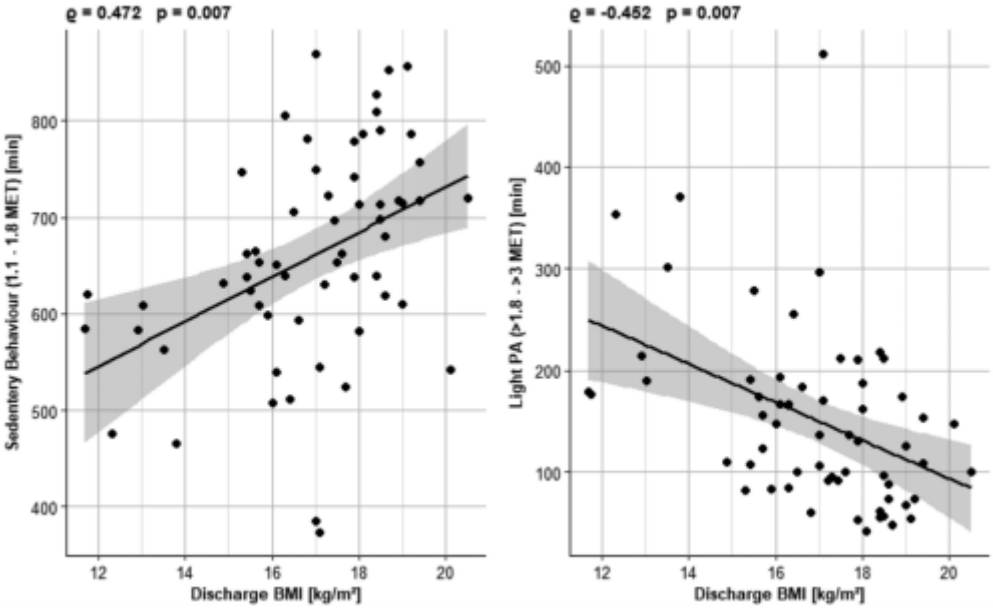
Ever since Gull described the hyperactivity in AN patients, hyperactivity has been observed in many studies. Hyperactivity rates of 38% to 80% in AN patients have been documented. The primary reason for this difference can be attributed to the aforementioned diverging definitions of what activity is and when it classifies as hyperactivity (Davis et al., 1997). Studies that support these above-mentioned rates include that of Casper et al., 2020; Dalle Grave et al., 2008; Davis et al., 1994; Kron et al., 1978; Sternheim et al., 2014.
Excessive strenuous exercise has been found to increase in AN patients, as well as light to moderate activity. One study that justifies the former, is that of Davis et al. (1997), in which 167 patients with eating disorders were inquired about their physical activity. Activity was deemed excessive, when the activity exceeded 1 hour per day for at least 6 days per week for a period not less than 1 month. One hour per day may not seem that much, but since the patients are emaciated, this bar was considered reasonable. 81% of the AN patients in this study were found to be hyperactive (Davis et al., 1997). These results are depicted in table 1. Evidence that light to moderate exercise increases in AN patients as well, is given by Grosser et al. (2020) 60 patients who received inpatient treatment were monitored with a portable accelerometer, the

Table 1 2x2 Contingency Table: *Prevalence of Excessive Exercise in AN and Bulimia Nervosa*

Frequency, Row Percent and Column Percent	Nonexcessive	Excessive	Total
AN	15	63	78
	19.2%	80.8%	61.4%
	41.7%	69.2%	
BN	21	28	49
	42.9%	57.1%	38.6%
	58.3%	30.8%	
Total	36	91	127

Note. Of 78 AN patients, 63 were deemed excessive exercisers. Adapted from Davis et al. (1997)

Figure 1 *Sedentary Behaviour and Light PA of AN Patients*



Note. BMI was measured on the day of patient's discharge. Adapted from Grosser et al. (2020)

SenseWearArmband. Their main findings can be seen in figure 1. It becomes clear from the graphs that patients with a lower BMI participate in less sedentary behaviour and have increased light physical activity. These data suggest that AN patients also incorporate more activity during their daily activities. Research not only implies that AN patients are more active during the daytime, they also have been found to have a higher motility during the night (Crisp, 1980). Hyperactivity is found to be more prevalent in the restricted anorexics (approximately 80%) than in the binge/purge subtype (43%) (Dalle Grave et al., 2008).

If anorexia really is accompanied by hyperactivity, then hyperactivity should decrease when patients are treated for the disease. This is indeed the case, as has been shown by Kostrzewa et al. (2013). In their research, they found that the high levels of physical activity of their 37 patients decreased with their treatment.
Overall, all the aforementioned findings suggest the obvious presence of hyperactivity in the clinical picture of anorexia nervosa.

Research Opposing Hyperactivity in AN

Regardless of the previous evidence given, it is crucial to remain critical. Several studies have found that, compared with healthy controls, AN patients do not seem to have a higher physical activity (PA) (Bouten, van Marken Lichtenbelt, & Westerterp, 1996; Keyes et al., 2014). This is in stark contrast with what has been discussed in the previous section. Bouten et al. (1996) monitored 11 AN patients and 13 healthy controls during a 7 day period under free-living circumstances. This was being done using a Tracmotor motion sensor. Their main finding was that AN patients with a BMI lower than 17 were equally or less active as healthy control individuals. In line with these findings is the study of Hechler et al. (2008). In this study, 10 AN patients and 15 healthy controls were monitored with a Tracmotor as well. The two groups did

not differ in physical activity, although there did seem to be a negative correlation in AN between the percentage of body fat and low to moderate activity. A limitation of these studies that simply cannot be overlooked, is the small sample size. This makes it more likely that a type II error has occurred: Namely that the null hypothesis where there is no difference in PA between AN and control people, is falsely accepted.

The study of Sauchelli et al. (2015) had a larger sample size; 88 AN patients and 116 healthy control individuals. They were monitored for 6 days by wearing an Actiwatch. The study found that the daytime PA did not differ between the two groups, and neither did the moderate-to-vigorous PA. Yet, the AN patients were more dispersed regarding their PA; the group consisted of individuals with low activity and with high activity. One thing that should be taken into account is the fact that these studies consisted of AN patients of both the restricted, as well as the purge/binge eating type. As the restricted subtype shows more hyperactive behaviour than the purge/binge eating subtype (Dalle Grave et al., 2008), the findings that some patients have increased PA, and others do not, are therefore still in line with the hypothesis that AN is accompanied by hyperactivity.

Interim Conclusion

Now evidence from both points of view have been discussed, it is argued here that hyperactivity does belong to anorexia nervosa. As the research of Sauchelli et al. is not in complete disagreement with this stance, and since the other two researches opposed to this stance consist of a small sample size, their findings can be disregarded. In addition to this, the studies in favour of hyperactivity in AN are much more numerous. Critics could mention the fact that some of these findings are the results of questionnaires, which are subjective and can therefore not fully be trusted. Yet, since the same conclusions have been found time on time again, they are therefore consistent and these studies thus have high external validities.

After having taken evidence both pro and contra hyperactivity in AN into consideration, the first main question can be answered. It can be concluded that AN is indeed accompanied by hyperactivity.

Chapter 3: Energy Homeostasis and Activity

Now that it has been established that AN patients are hyperactive, the focus will be put upon the mechanisms underlying this phenomenon. As briefly touched upon in the introduction, hyperactivity seems counterintuitive: Why would someone who is emaciated, and therefore has low energy levels, spend excessive amounts of their energy on exercising? In this chapter, this conflict will be the central focus; it will be discussed with regard to the energy homeostasis of the body and with regard to evolutionary pressure.

Energy Homeostasis

The body carefully balances energy intake (food intake) and energy expenditure. If the energy intake is higher than the energy expenditure, weight gain is the result. If the energy intake is lower, then weight loss is the result. When in equilibrium with each other, body weight is maintained (National Research Committee on Diet and Health, 1989). To maintain a balance between the energy intake and expenditure, and thus maintaining the energy homeostasis, there are regulatory mechanisms of both food intake and energy expenditure.

One hormone involved in the long term regulation of the energy homeostasis is the hormone leptin. Leptin is secreted by white adipose tissue and signals satiety as well as information about

fat storage to the brain. The hormone is positively correlated with increasing fat tissue mass (Kelesidis, 2010). Leptin performs its function by binding to receptors of neurons in the arcuate nucleus (ARC) of the hypothalamus. These neurons include neurons secreting the peptides POMC (proopiomelanocortin) and CART (cocaine- and amphetamine-regulated transcript). From POMC, alpha MSH (alpha-melanocyte-stimulating hormone) is made, which, together with CART, suppresses appetite. In addition to this, a reduction of leptin levels in the arcuate nucleus stimulates neurons that secrete the peptides NPY (neuropeptide Y) and AgRP (agouti related peptide). These peptides stimulate appetite (Bear, Connors & Paradiso, 2015; Feher, 2017). Not only does leptin regulate food intake via these mechanisms, it also regulates energy expenditure. It increases and decreases metabolism via POMC/CART (which stimulate sympathetic division of the autonomous neural system (ANS)) and NPY/AgRP respectively (which stimulate parasympathetic division of ANS) (Bear et al., 2015).
A different hormone involved in the regulation of energy intake and expenditure, is the hormone ghrelin, which is secreted by the gut before mealtimes. Ghrelin influences these same processes, but in a shorter time span than leptin. Additionally, whilst leptin inhibits appetite, ghrelin stimulates it. Ghrelin inhibits POMC neurons and stimulates the neurons that secrete NPY and AgRP (Ibrahim Abdalla, 2015).
Naturally, these processes are much more complex than described here. Nevertheless, it becomes clear that via stimulating and suppressing appetite and via stimulating different divisions of the ANS, energy intake and expenditure are regulated so as they are in balance with one another.

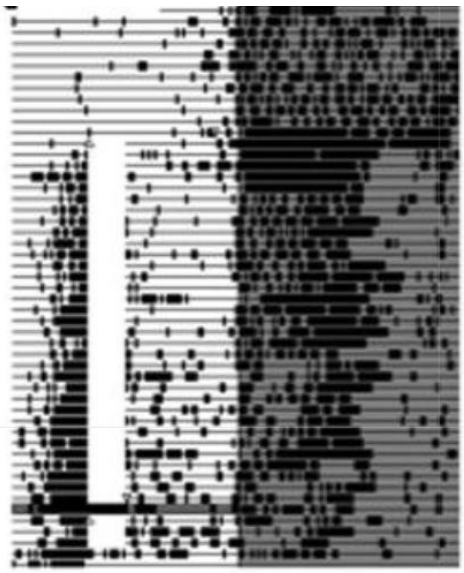
Evolutionary Pressure

However, imbalances of the energy homeostasis may have been favoured by evolutionary pressure. During the course of human evolution, humans were constantly subjected to periods of feast and famine (Genné-Bacon, 2014). Evolution selected for genes that enabled humans to adapt to these periods. In times when food was abundant, one should store energy efficiently in adipose tissue as a reserve for when times of famine would come. Additionally, in times of feast, it was important to rest, so as to not spend the stored energy excessively (Stöger, 2008). In the present, times of famine no longer occur (in the Western world). Yet, humans still possess the genes that enable efficient energy storage. This adaptive mechanism has now become maladaptive; people are stimulated to eat too much, with obesity as a possible result. The theory that has coined this mechanism, is the thrifty gene hypothesis of James Neel (Genné-Bacon, 2014).

The same mechanism also holds true for the opposite. In times of starvation, it is important to search for food. Evolution therefore favours mechanisms that stimulate activity. It is hypothesized that the mechanism for this is preserved in humans as well, only it has now become maladaptive. Anorexia patients are emaciated and their body stimulates them to search for food, resulting in higher physical activity (Epling, Pierce, & Stefan, 1983; Södersten et al., 2019). The behaviour of becoming active in order to search for food, is called food anticipatory activity (FAA). FAA has been found under experimental settings in rats and mice (Degroot & Rusak, 2004; Flôres et al., 2016; Patton et al., 2014). The usual protocol for showing FAA in these rodents is letting the animals get used to a 12 hour light, 12 hour dark schedule first, with ad libitum food. After this, a restricted feeding protocol is started. This does differ between studies. In general, it means that the rodents are allowed to eat for only a few hours per day at a fixed time. One study in which such a protocol has been executed is that of Patton et al. (2014). In this experiment, 36 rats received food 2 hours/day after the light was 4 hours on, when the rodents are usually asleep. In

figure 2, the resulting actogram is depicted. The black beams represent bouts of activity of the animals. The grey area is the dark phase, the phase in which rats are mostly active. The vertical white beam is the time during which rats had access to food. As is visible, many bouts of activity are present just before the onset of food availability (Patton et al., 2014). The time before food restriction can serve as control as well. During this entertainment period, the rats were not active around the same time. Overall, this implies that the FAA is present in rats when food availability is restricted.

Figure 2 *Actogram showing FAA*



Note. The vertical white bar represents the time food is available. The black bars represent bouts of activity. Adapted from Patton et al. (2014)

The observations of FAA are not only limited to rats and mice. FAA has been found to be present in many organisms, such as hamsters, rabbits, bees, fish and even in primates (Mistlberger, 1994). AN patients have been shown to display FAA as well (Scheurink et al., 2010; Tappe et al.,1998). They have for instance, compared to healthy controls, more non-ingestive behaviours during mealtime (Tappe et al.,1998).
FAA can be translated into a model: The Activity Based Anorexia model (ABA). In the ABA model, the conditions under which FAA occurs remain present for too long, resulting in a.o. mice and rats running themselves to death (Scheurink et al., 2010). In the next chapter, this model will be elaborated upon.

For now, it can be concluded that hyperactivity is inevitably intertwined with AN and that this likely is due to evolutionary pressure, as activity was adaptive in times of famine.

Chapter 4: Hyperactivity and Reward

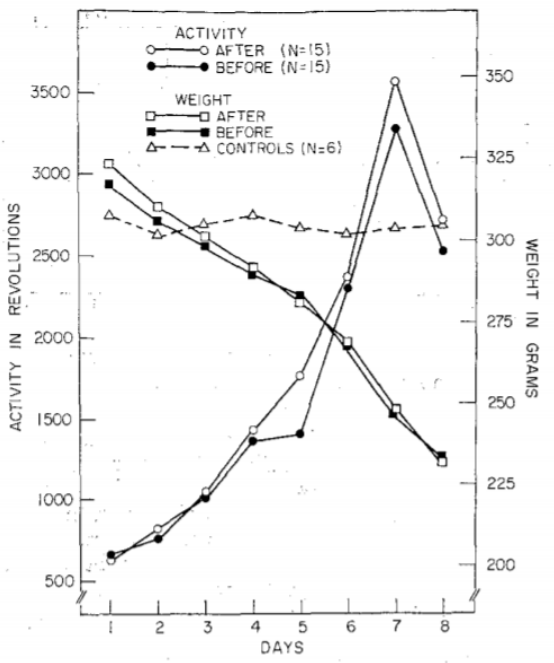
As is mentioned in the previous chapter, there is a model that represents FAA and therefore the hyperactivity in AN patients. This model is called the Activity Based Anorexia model (ABA). In this chapter, the model will be explained first. It is then proposed that the mesolimbic pathway may be involved in the development of ABA behaviour. There will be a closer look taken to this pathway and relate it to ABA.

Anorexia Based Activity Model

The protocol for ABA starts with an acclimatization period to the wheel, when food is still given ad libitum. Following the acclimatization period, starvation is induced by limiting food access to less than 2 hours per day. During these 2 hours, the food is still provided ad libitum. Would the food access not be restricted in time, but with a fixed amount, no semi starvation induced hyperactivity will be observed. In addition to a period of food restriction, running wheel access is given 22-24 hours per day. After losing body weight due to the food restriction, the animals increase their running wheel activity, resulting in decreased food intake, severe weight loss and even more increased physical activity (Humana Press, 2021; Schalla & Stengel, 2019). The ABA cycle is therefore self-maintaining (Epling & Pierce, 1988). This pattern does not arise when no

running wheel is present. One of the early studies with the focus on ABA is that of Routtenberg et al. (1967), in which this protocol for ABA has been established for a great part. In this research, 30 rats were subjected to food restriction. 15 of those were restricted 1 hour before food access to a running wheel, and 15 rats had this same restriction after food access. Additionally, they had voluntary running wheel access during the rest of the day. 6 rats functioned as a control. The results are visible in figure 3. As can be inferred from the graph, all food restricted animals had a decrease in body weight and an increase in activity. The controls were able to retain their body weight. Ultimately, all food restricted animals ran and starved themselves to death (Routtenberg & Kuznesof, 1967).

Figure 3 *Running Wheel Activity and Body Weight in the ABA model*



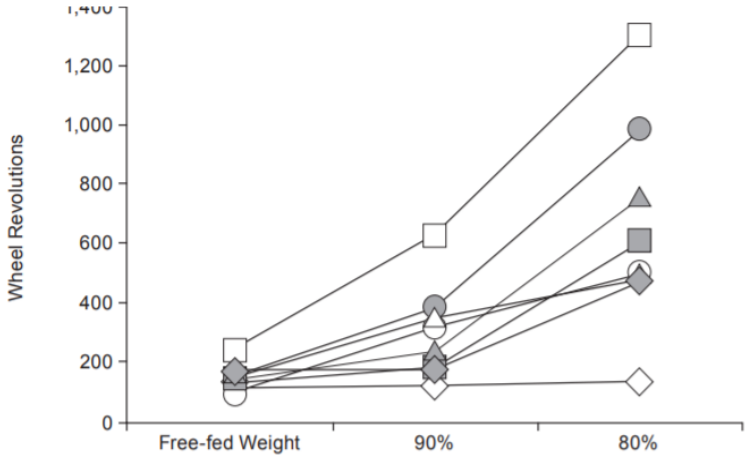
Note. Adapted from Routtenberg et al. (1967)

A different study that reinforces these findings is that of Brinegar et al. (2011). Specifically, it shows that running wheel activity especially increases once the animals are at 80% of their body weight (Figure 4). This suggests that ABA develops after 20% loss of the original body weight.

The ABA model shows overlap with AN. This overlap includes the fact that younger individuals are more vulnerable to ABA, which accounts for AN as well. ABA rats display hypothermia and anhedonia, which are some symptoms of AN (Lamanna et al., 2019). Furthermore, ABA captures the most important clinical features of AN: Voluntary food restriction, severe weight loss and excessive exercise (Humana Press, 2021).

In the previous chapter, it has been established that hyperactivity used to be favoured in times of famine by evolution, as it was adaptive to become active in the search for food. Since evolutionary adaptive behaviour is rewarding (such as ingesting food (Bear et al., 2015)) it is suggested that hyperactivity is rewarding as well.

Figure 4 *Running Wheel Activity in Relation to Body Weight %*



Note. Each line represents running wheel activity of one animal. As visible, not all animals were susceptible to ABA. Adapted from Brinegar et al. (2011)

Reward and Addiction

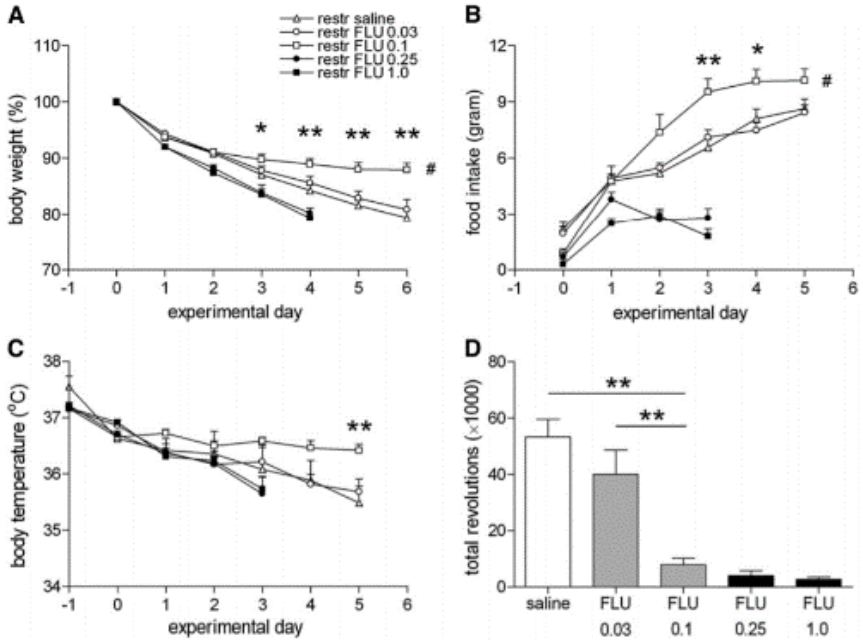
Certain behaviours (eating, shopping etc.) or drugs stimulate a pathway in the brain resulting in a pleasurable feeling of reward. This pathway involved with reward, is the mesolimbic dopamine pathway. The primary reward pathway involves the projection of dopaminergic neurons from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) located in the ventral striatum. In response to these reward related stimuli, the NAc releases dopamine. Moreover, the VTA also innervates other areas such as the amygdala, prefrontal cortex, hippocampus and the thalamus. All these areas involved are interconnected with each other. The exact connections are too complex to go into further detail here (Cooper, Robison, & Mazei-Robison, 2017; Russo & Nestler, 2013). Over time, as the pleasurable factors keep on stimulating the reward system, the liking of these factors can shift to wanting them. When this shift occurs, one speaks of addiction. The development of addiction is associated with a transition from activity in the ventral striatum to activity in the dorsal striatum, which is involved with habitual behaviour (Lipton et al., 2019; Volkow & Morales, 2015). The reinforced addictive behaviour becomes a habit and will be performed by the addict despite negative consequences (Pickard, 2016).

The Anorexia Based Activity model and Reward

Firstly, it should be noted that normal exercise is already rewarding (Greenwood et al., 2011). It has been shown, for instance, that exercise increases the activity of dopaminergic neurons in the VTA (Herrera et al., 2016). Additionally, exercise increases endocannabinoid levels in the brain. Simply put, endocannabinoids stimulate dopaminergic release from VTA neurons, thereby stimulating a feeling of reward (Wenzel & Cheer, 2017).

From this, it seems logical that the reward system is involved in the ABA model as well. After all, exercise is an important factor in this model. As mentioned, dopamine plays a big role in the brain reward mechanisms. It thus can be hypothesized that altered dopamine signalling has an effect on ABA. This has indeed been found. Mice that were genetically modified to be hyperdopaminergic, were more vulnerable to ABA (Beeler & Burghardt, 2021). On the other hand, the infusion of dopamine antagonists, which block dopamine signalling, rescues both mice and rats from ABA (Klenotich et al., 2015; Verhagen et al., 2009). Klenotich et al. have shown this with antagonists for D2 and D3 receptors, whilst Verhagen et al. have shown this with a nonselective D1/D2 receptor antagonist (flupenthixol). The results of the latter study are shown in figure 5 (depicted on the next page). Each of the treatment groups consisted of 8 food restricted female rats. Those who received an antagonist concentration of 0.1 mg/day showed the best recovery from ABA: They had, respectively to the other experimental groups, an increased body weight, an increased food intake, an increased body temperature and reduced running wheel activity. Despite finding reduced running wheel activity, FAA was not found to be significantly reduced (Verhagen et al., 2009). The latter finding suggests that other factors are also involved in the regulation of FAA. One of these factors could be leptin. In addition to its functions described in chapter 3, leptin seems also to be involved in the regulation of hyperactivity. Leptin is able to bind to a certain type of receptor, STAT3, in dopaminergic neurons of the VTA. Knockout mice for this receptor show greater voluntary running (Fernandes et al., 2015). Furthermore, leptin treatment has been found to decrease FAA (Verhagen et al., 2009). From this it can be inferred that in times of famine, when leptin levels are low, running is stimulated by the reward system.

Figure 5 *Sedentary Behaviour and Light PA of AN Patients*



*Note. p < 0.05 *, p < 0.01 **. Adapted from Verhagen et al. (2009)*

As with all rewarding behaviour, liking can turn into wanting and the rewarding behaviour can become an addiction. This is also the case for ABA. Whereas ABA is initially pleasurable, it becomes an addiction. Withdrawal symptoms such as body shakes, escape attempts and teeth chattering were observed in rats with ABA, when they became unable to run (Kanarek et al., 2009). Further evidence suggesting the addictive component is the involvement of the SIRT1 (silent mating-type information regulation 2 homolog 1) in ABA development. The enzyme is linked to addiction. SIRT1 activation is found to stimulate ABA, which contributes to the hypothesis that ABA is an addiction (Robinette et al., 2020).

The findings discussed here translate to AN patients. Initially, dieting and weight loss behaviours are positively reinforced by feelings of reward (Barbarich-Marsteller et al., 2011; Hsu & Blandford, 2014; Park et al., 2014). Over time, when weight loss has become significant, the feeling of reward due to exercise changes from liking to wanting. This is when AN patients start to become hyperactive and the activity is reinforced in a manner that is pathological (Keating, 2010). AN patients keep being highly active despite negative impact on their physical and emotional health, as well as on their social life (Barbarich-Marsteller et al., 2011). It has been reported that AN patients feel distressed when missing their exercise, that their exercise interferes with daily routines, and that it is continued despite illness or physical injuries (Dittmer, Jacobi, & Voderholzer, 2018). These are all observations in line with a classical addiction such as substance abuse. Hyperactivity thus has become an addiction for AN patients.

In previous chapters it has been established that hyperactivity accompanies AN. After having discussed ABA and the reward system in this chapter, it can be concluded that the hyperactivity arises in these patients because it is initially rewarding to be active (due to activity being evolutionary adaptive). After a certain period of time however, being active becomes addictive.

Discussion

In the antecedent chapter, ABA has been introduced as an animal model for AN. Yet, the ABA model has several limitations. As with all animal models, it is questioned how well ABA translates to humans. ABA fails to be representative for all AN patients, as not everyone has a hyperactive phenotype (Schalla & Stengel, 2019). Yet, not all animals subjected to the ABA protocol develop ABA. Indeed, more research regarding the susceptibility to ABA should be done. Furthermore, whilst AN patients voluntarily limit their food intake, reduced food intake is initially forced upon animals in the ABA model (Dwyer & Boakes, 1997). This aspect of ABA enables us to uncouple the neurobiological aspect of the disease from the sociocultural aspect (Chowdhury, Chen, & Aoki, 2015). When looking only at the former, this is an advantage of the ABA model, instead of a limit. Additionally, animals subjected to ABA restrict their food intake further than animals that are food restricted, but have no access to a running wheel. This indicates a certain level of voluntary food restriction as well.

Other criticism regarding the ABA model comes from Wu et al., who found that postprandial activity (PPA, activity after eating a meal) contributes more to loss of body weight than FAA (Wu et al., 2014). Nevertheless, these data do not invalidate the effect of FAA completely. Rather, it indicates that it is important to study PPA as well, since this likely is rewarding for the individual as well.

Despite the limitations that accompany an animal model, ABA is useful when studying AN as it captures the most important clinical features of AN: Voluntary food restriction, severe weight loss and excessive exercise (Humana Press, 2021).

This literature review has several limitations involving the complexity of the disease. The involved factors in AN and their interplay is much too complex to be completely investigated here. What is discussed in this thesis, is just a small part in the bigger whole. When looking at the reward system, for example, the focus should be broadened to other mechanisms besides dopamine, the VTA and the nAC. For instance to the serotonergic system, as it has been suggested that there is a serotonergic mediation as well (Kranz et al., 2010). Additionally, there is evidence that implies that ghrelin is involved in the mediation of ABA regarding the reward system as well (Mifune et al., 2020). The aforementioned observations are just a few of the many factors involved in the AN pathology that should be looked into. Nevertheless, the limitations of this literature research do not nullify the importance of the findings discussed in this thesis.

Conclusion

In this thesis, the following two questions have been discussed: Is AN accompanied by hyperactivity? And if so, what are the mechanisms behind this hyperactivity?

Since the first observations of hyperactivity in AN patients, research repeatedly has reported this hyperactivity, with rates of 38 - 80%. An increase in excessive exercise, as well as an increase in restlessness in AN patients has been observed by Davis et al. and Grosser et al. respectively. In addition to this, treatment of AN has been found to reduce hyperactivity. From this, it can be concluded that AN indeed is accompanied by hyperactivity.

The mechanisms that result in this hyperactivity stem from evolutionary advantages in times of famine. It used to be adaptive to become active in search for food. As evolutionary adaptive behaviour has evolved to be rewarding, the hyperactivity in AN is rewarding to the patients. The animal model ABA has served as evidence for this; blocking for instance dopamine release in the VTA diminishes the typical ABA. Over time, when significant weight loss is induced (80% of the

original body weight remaining), hyperactivity becomes addictive in AN patients. This has been shown both with the ABA model, as well as in clinical settings.

Thus it can be concluded that AN often is accompanied by hyperactivity. Due to evolutionary pressure, hyperactivity has become linked with reward mechanisms in the brain. Consequently, many AN patients become addicted to this hyperactivity.

Future Prospects

Unquestionably, more research should be done regarding AN. Many factors involving the disease remain unknown. Additionally, current treatment options such as cognitive behavioural therapy and family interventions are far from optimal, as relapse rates are still substantial nowadays (Berends et al., 2018). However, the idea that AN is an hyperactivity addiction, may improve treatment. If it is acknowledged that AN is for a great part an addiction to hyperactivity, AN patients should be treated in a manner suitable for addicts, which is not an easy task. Suggested here is that since habits are a major factor involved in addictions, AN patients should be taken out of the usual environment in which they perform their habitual hyperactivity. This should be done in order to minimize cues that stimulate habit performance, which is similar to how substance abusers should be taken out of the environment in which they usually take the substance. In addition to this, long term psychological help should be given in order to prevent relapse. Yet, since not all patients show this hyperactivity and since AN in general is different in each patient, the exact treatment should be adapted to each individual.

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