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REWARD-RELATED BEHAVIORAL AND BIOLOGICAL RESPONSES ASSOCIATED WITH EATING – INSIGHTS FROM ANOREXIA NERVOSA AND OBESITY RESEARCH

RÉPONSES BIO-COMPORTEMENTALES LIÉES À LA RÉCOMPENSE – APERÇUS DE LA RECHERCHE EN ANOREXIE MENTALE ET EN OBÉSITÉ

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"In every victory, let it be said of me: 'my source of strength, my source of hope is Christ alone'".

I was given so much! And I'm so thankful for that, for I'm sure it's God's grace that's brought me this far.

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ABSTRACT

Research on clinical populations with eating disturbances has shown the involvement of reward processing in the maintenance of disease-associated symptoms. Investigation on food as a reward indicates the metabolic or feeding state (i.e. fasted or fed state) as a modulator of food as a reward, but little is known about how these states influence other types of reward. This is important because responses to rewards other than food are also altered in several disorders, including those involving eating disturbances. Therefore, the aim of this dissertation was to investigate behavioral and biological responses to monetary reward during fasting and fed states in healthy women, women with anorexia nervosa and women with obesity. For the behavioral responses, we used an experimental gambling task, the wheel of fortune, to evaluate responses to winning or losing a monetary reward involving different probabilities. The patients with anorexia nervosa (AN) repeated the same procedures after weight-restoration treatment. This procedure resulted in empirical studies 1 and 2. The biological responses consisted of circulating levels of endoncannabinoids (eCB) in the participants, and investigation of the correlation between eCB and the responses to reward were reported in empirical study 3. In summary, our results show higher positive mood to winning monetary rewards during fasting for normal-weight women, but not women with anorexia nervosa and more negative mood to not winning during the fed state in normal-weight women and women with AN. No difference regarding mood between feeding states was observed for women with obesity. Regarding affect before and after the task, independently of the feeding state, women with AN and women with obesity reported more negative affect than normal-weight women, with positive affect improving in normal-weight women and women

with AN after the task, but not in women with obesity. Patients with AN's mood reactivity to losing monetary rewards was blunted in comparison to normal-weight controls. Patients with obesity also showed blunted activity to losing low-risk monetary rewards, but also showed less mood reactivity to winning high-risk rewards than controls. Reaction times to categories that involved equal chance (50% of chance of either option) in AN were longer than controls and other categories. With regards to the biological responses, no significant correlations were found between eCB and behavioral responses to monetary rewards. Anandamide, and eCB, was found to be significantly lower during fasting in comparison to the fed state. In patients with AN, levels of anandamide were significantly lower than in healthy controls and remained unchanged following weight-restoration treatment. These results indicate that some types of responses to monetary rewards can be modulated by the feeding state. The applicability of the results is discussed.

INTRODUCTION

Eating is perhaps one of the most common behaviors across species (Rozin & Todd, 2015), and it has developed as an important behavior to guarantee the survival of humans and animals, as a way to generate energy (Zucoloto, 2011). One of the mechanisms responsible for maintaining eating behaviors is the rewarding potential found in food (Enax & Weber, 2016; Lutter & Nestler, 2009; Saper, Chou, & Elmquist, 2002). One of the reasons humans and animals go back to food is because of the rewarding effects it produces (Berridge, 2009). And finding pleasure in food has become easier with the development of processing techniques and of the food industry. This complex relationship between humans and food has led to the development of several disorders associated with eating (Zucoloto, 2011). In that vein, the general aim of this dissertation is to investigate reward-related behavioral and biological responses associated with eating, bringing insights from research on anorexia nervosa and obesity.

The processing of reward is one of the dimensions involved in the new framework developed for investigating the pathophysiology of mental disorders (Insel et al., 2010). Anything people and animals put effort into acquiring may be considered a reward (Schultz, 2010), and, many times, reward comes associated with sensorial pleasure (Berridge & Kringelbach, 2008). For instance, primary needs in humans and animals (e.g. food, sex) are considered *primary* rewards, due to their direct association with the survival of the species (Schultz, 2010). Other *non-primary* rewards (e.g. gambling, money), are not directly related to the survival of the species, but, in the long-term, they work to strengthen primary rewards (Schultz, 2010).

Research has shown similar brain structures involved in the processing of primary and non-primary rewards. Regions like the orbitofrontal cortex, ventromedial

prefrontal cortex, nucleus accumbens (NAcc), ventral pallidum, and even the brainstem are involved in processing rewards (Berridge, 2009). Many of these areas have been associated with behavioral measures such as valuation of food as pleasant or not (Zald, 2009), and stimulation of these areas can increase or decrease food intake depending on the type of stimulation (Bakshi & Kelley, 1993; Tuulari et al., 2017).

The metabolic state (i.e. fasted or fed states) also plays an important role in modulating the rewarding potential of food (Kringelbach, 2004). Besides the reward system, the homeostatic system is also involved in controlling food intake by maintaining a stability related to body fat and eating (Enax & Weber, 2016). It involves several hormones and ligands that circulate peripheral regions and communicate with brain structures, which are then responsible for suppressing or increasing food intake (Lutter & Nestler, 2009) and modulating, through hunger, reward processing (Briers, Pandelaere, Dewitte, & Warlop, 2006). One of the systems working in the intersection food x reward is the endocannabinoid (A. M. Monteleone et al., 2015; P. Monteleone et al., 2005; B. A. Watkins & Kim, 2014). Greater concentrations of these endocannabinoids have been associated with food initiation, also modulating the rewarding effect of food (Cooper, 2004; Jarrett, Limebeer, & Parker, 2005; Kirkham & Williams, 2001). The aspects of food as a reward, reward processing, homeostatic signaling, and the impact of the metabolic state on food as a reward will be introduced in chapter 1.

In the same sense, research has shown that alterations in these regions in relation to reward are implicated in the development and maintenance of several disorders, both at behavioral and neural levels (Blum et al., 2006), from mental (Barbato, Fichele, Senatore, Casiello, & Muscettola, 2006; Bergen et al., 2005; Davis &

Woodside, 2002; Ehrlich et al., 2014; Piazza et al., 1993; Wagner et al., 2007) to metabolic disorders (Ho, Kennedy, & Dimitropoulos, 2012; Kenny, 2011; Rothemund et al., 2007). Anorexia nervosa (Wagner et al., 2008) and obesity (Kenny, 2011), for instance, have been associated with several dysfunctions related to reward processing of primary and non-primary rewards, at neural, behavioral, and self-reported levels. The second chapter will focus on the relationship of these disorders and the processing of reward, and more focus will be given to the processing of money as a non-primary reward. More specifically, Chapter 2 will examine how monetary reward is processed in anorexia nervosa and obesity.

Since the value of food as a reward is modulated by the metabolic state of the individual (Cassidy & Tong, 2017; Kringelbach, 2004), and research has shown similarities between the processing of primary and non-primary rewards, it may be important to evaluate how the metabolic state influence other types of reward, which have also shown to be processed differently across disorders involving eating. In that sense, the following section of this dissertation will focus on empirical research developed to evaluate behavioral (including mood and affect) and biological responses to monetary rewards in healthy women, women with anorexia nervosa, and women with obesity, during a fasted and a fed condition. We used a computerized task, the *wheel of fortune* (Ernst et al., 2004), designed to measure mood and affect to winning vs losing monetary rewards in different decision categories. Chapter 3 shows the study in individuals with anorexia nervosa (Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019), and chapter 4 reports the same procedure done with individuals with obesity without the presence of any mental disorder (Piccolo, Milos, et al., 2020). The fifth and last chapter aimed at evaluating how fasting modulated

circulating endocannabinoid levels in patients with anorexia nervosa during the underweight phase, and following weight-restoration treatment (Piccolo, Claussen, et al., 2020), and how that was associated with processing of monetary reward.

THEORETICAL BACKGROUND

CHAPTER 1

THE REGULATION OF EATING BEHAVIORS

"Let food be thy medicine and medicine be thy food"

Hippocrates

1. EATING AS A COMPLEX BEHAVIOR

Eating, or food intake, is a common behavior across species. It has been suggested that knowledge related to eating is part of the most important information one can obtain about humans (Rozin & Todd, 2015). In most species, eating starts with a physiological stress in response to deprivation, followed by a search phase, involving the questions of what and where to search, mostly depending on availability and nutritional potential (Kearney, 2010). Then, a stage of capture of food precedes its preparation and, finally, consumption happens, mostly with the purpose of generating energy (Rozin & Todd, 2015). In humans, however, due to different phylogenetic and cultural aspects, this process may not be exactly as it once was, and eating has evolved to be something more than a simple source of energy intake, influenced by several aspects, such as religion, familiarity, and sociopolitics, for instance (Zucoloto, 2011).

Although humans and animals have very similar nutritional needs, eating patterns vary not only from humans to animals, but also among humans, with a great range of variability (Zucoloto, 2011). Animals obtain their food mostly from nature. In contrast, due to the advance of technology and culture, humans can also obtain food from secondary sources, being even able to fabricate different types of food (via processing) whenever needed (Tomaselo, 2003), taking eating habits from a baseline

which exclusively depended on availability – since food could become scarce due to climatic conditions, for instance – to one that involves abundance of choices.

Besides processing, a social meaning was added to food with the development of language. According to some evolutionists, early human ancestors would gather around fire (once fire control had been obtained) to better make use of food by eliminating possible toxins. Moreover, since operant control of the vocal cords had also been acquired, meaning they could then talk, it is very likely that this context also consisted of a social gathering for early humans (Zucoloto, 2011). One can hypothesize that the environment changed, but humans continue to gather around food, and this could also be due to the rewarding properties that eating socially has acquired. A recent study investigated the connection between social eating and happiness in 2000 participants (Dunbar, 2017). The results showed that those who frequently eat socially feel more emotionally supported and also better about themselves than those who eat socially less often. In ancient times, social gatherings around food also warded off predators (Zucoloto, 2011), and social gatherings around food were, and still remain, especially rewarding.

The positive effects of food and social gatherings may exist even in the absence of a crowd. One can understand the reminiscence of these reinforcing

properties by looking at the paradigm of classical conditioning. Pavlov (1897/1902) realized that after a number of associations of an unconditional stimulus (US) to a neutral one, the latter became a conditioned stimulus (CS) that would, in turn, elicit similar reflexive responses (conditioned responses) to those that before only the UC produced, even the absence of it. In his experiments, he observed that when food was presented for a dog, the dog salivated. Following that, he introduced a bell, which, at first, was considered a neutral stimulus to the response of salivation. After some conditioning associations (bell + food → salivation), only the bell, which then would be considered a CS, could produce salivation in the dog, even in the absence of the food. Because of the rewarding effects of social eating, food alone could evoke similar feelings experienced when in the presence of people, even in the absence of the social crowd. This classically-conditioned response to food-related cues can be considered one aspect of *emotional eating* (Cardi, Leppanen, & Treasure, 2015), but there are a number of other aspects of emotional eating since human's relationship to food is much more complex.

Specifically, Macht (2008) proposes a model that involves five different ways that emotion can influence eating behaviors. The first type of relationship involves food-related cues leading to eating, mainly through classic conditioning. The second

is that intense emotions may suppress eating to some extent, mainly among normal-weight people. Finally, the author suggests that moderate emotions affect eating depending on the motivation in three different ways. For example, *restrained eaters* (i.e. those who intentionally restrict food intake motivated by weight gain or loss) mostly increase food intake in reaction to negative and positive emotions. According to Mach's theory, for *emotional eaters* (i.e. those who increase food intake in response to negative emotions, leading to a high risk of overweight), there is a tendency to increased intake of caloric and sweet foods in response to negative emotions. Besides the conception that emotional eating can also refer to increased food intake in response to positive emotions (Cardi et al., 2015), a recent review showed that, although there is some evidence supporting that theory, most studies show contrasting or unclear results (Bongers & Jansen, 2016). And, lastly, among *normal eaters* (i.e. those within the considered normal weight, with emotional and restrained eating scores falling in the average), amount of food intake is related to the type of emotion it follows. Happiness, for instance, would be associated with a maximized ability to perceive stimuli, thus, enhancing food intake, while sadness would cause the opposite. In summary, according to Mach's theory, eating seems to be influenced by psychological and

emotional states. It is important to note that weight (high or not) does not necessarily define disturbances in eating behaviors.

2. ORGANIC SYSTEMS REGULATING EATING

The emotional system controlling food intake is supported by biological systems (Fig. 1). Research suggests that food intake in humans is regulated by at least two systems: the *homeostatic* and the *reward* systems (Enax & Weber, 2016; Lutter & Nestler, 2009; Saper et al., 2002).

2.1. THE HOMEOSTATIC SYSTEM

The homeostatic system works in a way to maintain a stable balance between food intake and exergy expenditure, which enables a stability between body fat and weight (Enax & Weber, 2016). This involves peripheral hormones that work to communicate with the central nervous system in order to inform available energy stores which will, in turn, regulate food intake, mostly by modulating the motivation to eat (Lutter & Nestler, 2009). One important region in this process is the hypothalamus. In early studies, Hetherington and Ranson (1940) reported that rats with hypothalamic lesions presented altered feeding patterns, leading to accumulated fat. More recently, Bagnasco, Dube, Kalra, and Kalra (2002) clarified this relationship by establishing that the ventromedial hypothalamus (VMH) and the arcuate nucleus

(ARC) were responsible for the inhibition of food intake. On the other hand, lesions in the lateral hypothalamus (LH) would be responsible for promoting food intake (Anand & Brobeck, 1951). These early studies showed that the hypothalamus was associated with hunger and satiety. However, recent studies have brought new interpretation to such findings. The hypothalamus is believed to serve to functions, among others, related to the energetic metabolism, and, thus, alterations such as lesions and/or electrical stimulations in its lateral and/or ventromedial parts may lead to weight increase or loss (Pinel, 2011). This occurs mostly in response to two different hormones: *leptin* and *ghrelin* (Lutter & Nestler, 2009). Research has shown that leptin is mainly responsible for suppressing food intake (Enax & Weber, 2016), whereas ghrelin promotes eating (Kojima et al., 1999).

Leptin, an adipocyte hormone, sends signals to the brain about available energy, and sends a negative feedback to regulate energy intake and expenditure (Zigman & Elmquist, 2003). Leptin-deficient mice, for instance, were shown to develop obesity, while the administration of leptin was efficient in reducing its severity (Y. Zhang et al., 1994).

Levels of leptin increase in proportion to the amount of fat (Lutter & Nestler, 2009), and, although people with obesity present high amounts of fat, which,

intuitively, would be thought to reduce food intake, these individuals seem to be less sensitive to its signaling than normal-weight controls (Lustig, Sen, Soberman, & Velasquez-Mieyer, 2004). It has been reported, for instance, that obesity would promote a sort of leptin resistance, leading to increased weight gain, in spite of the great levels of leptin (Myers, Leibel, Seeley, & Schwartz, 2010).

If, on the one hand, leptin is involved in suppressing food intake to maintain homeostasis, ghrelin has been reported to increase in animals in response to food deprivation (Kojima et al., 1999) and to have its peak before meals in humans (Cummings et al., 2002), thus favoring food intake. For instance, the administration of ghrelin led to increased eating in healthy humans, and ghrelin's levels were correlated with self-reported hunger, regardless of time- and food-related cues (Cummings, Frayo, Marmonier, Aubert, & Chapelot, 2004).

Leptin and ghrelin modulation also plays an important role regarding motivation to obtain food related to the reward system and dopamine processing (Lutter & Nestler, 2009). Animal research showed that leptin reduced basal and food-stimulated dopamine release (Krugel, Schraft, Kittner, Kiess, & Illes, 2003). Ghrelin administration, instead, stimulated the release of dopamine into the striatum (Abizaid

et al., 2006). The role of dopamine and the reward system in the food intake will be discussed in detail in the next section of this chapter.

2.2. THE REWARD SYSTEM

Besides the homeostatic system, research suggests the involvement of the reward system in modulating food intake (Enax & Weber, 2016; Lutter & Nestler, 2009; Saper et al., 2002), and its malfunctioning has been implicated in the studies of various disorders (Blum et al., 2006).

Rewards have been defined as "objects or events that generate approach and consummatory behavior, produce learning of such behavior, represent positive outcomes of economic decisions and engage positive emotions as hedonic feelings" (Schultz, 2010), being most of the time related to pleasure (Berridge & Kringelbach, 2008). Primitive and primary needs (e.g., food, sex) as well as more complex behaviors (e.g., gambling) are related to the reward system (Schultz, 2010). According to Berridge and Kringelbach (2008), reward involves three major components. The first is *liking*, which is directly related to pleasure, whether or not in a conscious way. The second component involves *wanting*, and that is related to the motivation for obtaining something. As *liking*, *wanting* can also be done consciously or not. Finally, the last component of reward includes *learning*, which involves "associations, representations,

and predictions about future rewards based on past experiences" (p. 458). Learning would therefore include explicit and cognitive predictions as well as implicit knowledge related to associative conditioning.

The processing of reward has evolved to maximize the survival of the species. Schultz (2015) categorizes the functions of rewards as follows: 1) learning; 2) approach behavior; 3) decision-making), and; 4) pleasure or positive emotions. Rewards produce learning through different mechanisms to ensure that individuals will return to the choices made that contribute to fitness. In consequence, approach and decision-making will involve those rewards offering potential benefits to the organism, which will, in turn, evoke positive emotions, establishing its value as rewarding.

In that sense, research has shown the existence of a neural circuitry involved in the processing of reward (Schultz, 2000). Reward-related neurons are spread through different brain structures, including the striatum (caudate nucleus, putamen and the nucleus accumbens; NAcc), amygdala, ventromedial prefontal cortex (vmPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), hippocampus, hypothalamus, and midbrain dopamine (DA) neurons (McGinty, Lardeux, Taha, Kim, & Nicola, 2013; Schultz, 2015).

Rewards can be categorized in different types: *primary* and *nonprimary* rewards. Primary rewards (e.g. homeostatic and reproductive) are those that evolved to guarantee the survival of the species (Schultz, 2015). Food, for instance, is considered a primary reward, since its consumption is essential for the survival of the species, as is mating and reproduction. All other rewards are considered nonprimary (e.g. monetary, social), and they serve to strengthen primary rewards in the long-term, thus also increasing evolutionary fitness.

2.2.1. FOOD AS A REWARD

Food is considered a primary reward, and as a reward, it is processed by different brain structures, and understanding the systems involved may yield important knowledge regarding normal and aberrant eating behaviors. (Berridge, 2009). Frontal cortical regions with increased activation to pleasant foods are similarly involved in emotion regulation (e.g. OFC, ACC, and the insular cortex), and analogous patterns of activation can also be found in subcortical limbic structures, such as the ventral pallidum and the mesolimbic dopaminergic system and even the brainstem (Berridge, 2009).

The OFC, for instance, is involved in coding the pleasure of food stimuli through opioid transmission. In specific subregions (e.g. medial edge and mid-anterior

site), it tracks changes in food pleasure in relation to hunger and satiety (Berridge, 2009), and is involved in valuation of available food as rewarding or not (Zald, 2009). Early studies in rats show that lesions in OFC led to aphagia (i.e. inability or refusal to swallow), firstly showing the involvement of this region in food-intake control (Kolb & Nonneman, 1975). Since then, studies have pointed OFC as responsible for receiving sensory input about food, and, then, evaluating among options available, taking pleasantness (or the unpleasantness) as reference (Zald, 2009).

The vmPFC is also involved in processing food as a reward. When presented with pictures of high-calorie food, fasted women showed increased activation in the vmPFC (Stoeckel et al., 2007). Also, higher activation was shown in vmPFC when food odors were presented, and that was correlated to how much external cues lead to eating (Eiler, Dzemidzic, Case, Considine, & Kareken, 2012), suggesting the involvement of the vmPFC in encoding value of food as a reward. Furthermore, DA neurons' activity in vmPFC is increased with food intake, and DA blocking in the same area decreases eating (Land et al., 2014), possibly modulating wanting for food.

Hedonic hotspots in the NAcc are also involved in processing food as a reward, mostly through opioid signaling. Showing a bidirectional relationship, increased opioid release in NAcc was seen following a diet high in glucose (Colantuoni

et al., 2001; Dum, Gramsch, & Herz, 1983), with opioid injections also leading to hyperphagia in rats (Bakshi & Kelley, 1993). Moreover, infusions of opioids in the NAcc, leading to an increase in the firing of NAcc neurons, triggered rats to overeat in spite of not being food deprived (Bakshi & Kelley, 1993). Likewise, an opioid release has been reported in response to eating, regardless of food palatability (Bakshi & Kelley, 1993; Tuulari et al., 2017). Finally, opioid blockers (e.g. naltrexone) reduced self-reported food palatability ratings in humans and decreased consumption of palatable foods in rats (Na, Morris, & Johnson, 2012).

Signals leaving from NAcc go mainly in direction to the ventral pallidum. Berridge (2009) suggests that the ventral pallidum may have a key role in modulating eating behaviors through reward processing. This is supported by research showing, for instance, that lesions in the ventral pallidum may shift pleasantness to unpleasantness (Cromwell & Berridge, 1993). It is possible that the early studies focusing on the LH (Anand & Brobeck, 1951) may have also lesioned the ventral pallidum (due to its proximal location to LH), confusing the functions of these regions. Also, by stimulation of the opioid hotspot in the ventral pallidum, pleasure in relation to food is enhanced (Smith & Berridge, 2005). Smith and collaborators (2005) showed that an opioid injection to the ventral pallidum led to an increase in positive reactions

(e.g. "liking" facial expressions) in animals, and increased food intake. Finally, greater activation to food rewards in the ventral pallidum were shown to code taste in a way that is sensitive to the physiological need of the individual (Tindell, Smith, Pecina, Berridge, & Aldridge, 2006). For instance, humans and animals mostly show aversion to saline solutions. However, after inducing through hormones a state where salt was needed, the ventral pallidum activation increase was correlated to the increase of a saline solution intake in comparison to baseline condition (Tindell et al., 2006). Further research is needed to clarify the involvement of the ventral pallidum and its relationship with the LH in food control.

Finally, food seems to be processed as a reward already at brainstem level both in humans (Steiner, 1973), and animals (Grill & Norgren, 1978). Anencephalic human babies (those born without cortex) show positive facial expressions in reaction to sweet tastes and negative facial expressions in response to sour tastes (Steiner, 1973). Similar results were found in animal research with decerebrated rats (Grill & Norgren, 1978), suggesting the early involvement of the brainstem in food reward processing. Also, benzodiazepine injections in the parabrachial nucleus of the pons showed an increase in sweet-taste reactions (Higgs & Cooper, 1994).

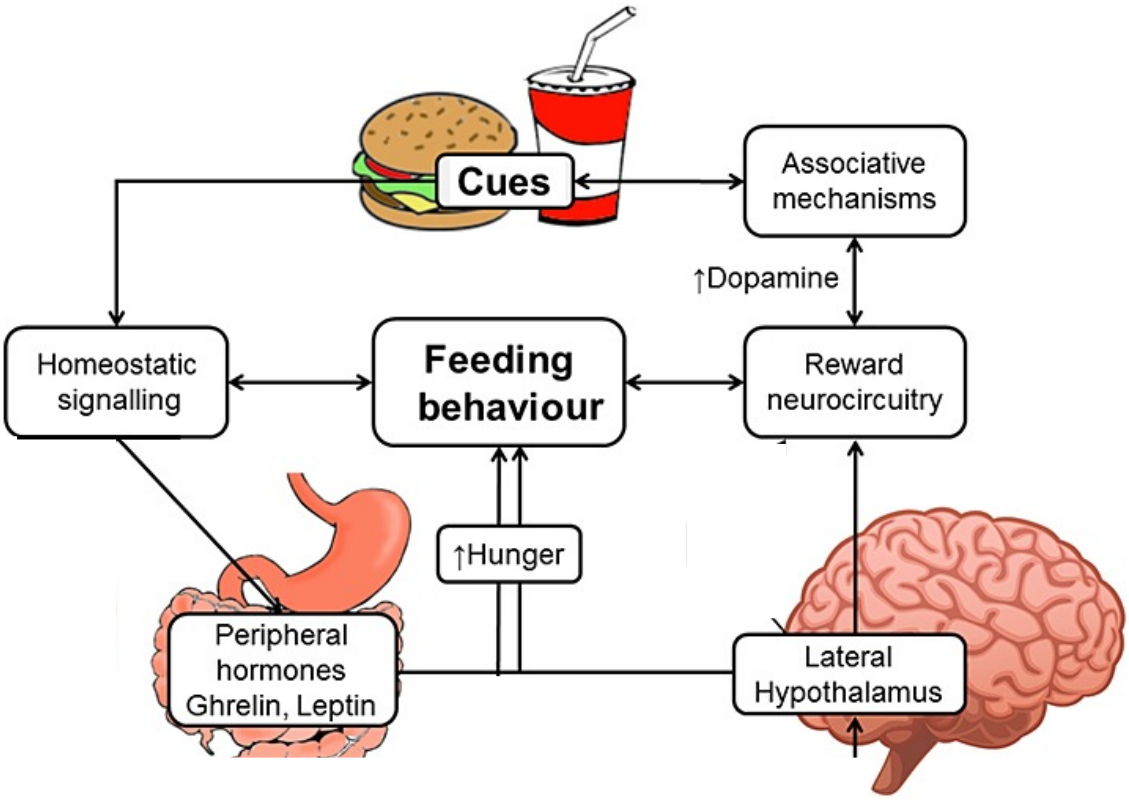

Figure 1. Reward and homeostatic integration in eating behaviors.

Food intake may be controlled by homeostatic signals for energy balance (modulated by hormones such as Ghrelin and Leptin), and also by the appetitive cues of foods, activating reward processing mechanisms (including the dopamine circuit). Eating may be evoked by the rewarding properties of foods as learned through associative mechanisms in the individual's history. *Adapted from* Reichelt, A. C., Westbrook, R. F., & Morris, M. J. (2015). Integration of reward signaling and appetite regulating peptide systems in the control of food-cue responses. *British Journal of Pharmacology, 172(22)*, p. 5225-5238.

2.2.2. DOPAMINE AND EATING

Dopamine (DA) neurons are mostly contained within the ventral tegmental area (VTA) and the substantia nigra (SNc) (Arias-Carrion, Stamelou, Murillo-Rodriguez, Menendez-Gonzalez, & Poppel, 2010). From there, DA is projected to the

striatum, the dorsal and prefrontal cortex, and is involved in many goal-seeking behaviors (Schultz, 2015), including foraging and eating. Long associated with the pleasure component of reward (*liking*), DA has recently been proposed as mostly involved in motivation (*wanting*) (Berridge, 2009). Besides that, DA has been appointed as a fundamental mediator in learning (Arias-Carrion et al., 2010), which is also an intrinsic part of reward.

Specifically, in relation to eating, DA has been reported to greatly influence food intake, and, similar to addictive drugs, palatable foods are related to a DA increase in the reward system (Alonso-Alonso et al., 2015). Several results shared by Wise (2006) lead to the conclusion that, when DA-suppressing methods were applied in animal models, the reinforcing[1] properties of food ceased to be observed.

Even if the role of DA is still not completely clarified, it seems well established that is it involved in eating behaviors. For instance, increased DA release in the dorsal striatum has been shown in response to palatable foods. Small, Jones-Gotman, and Dagher (2003) used positron emission tomography (PET) to test the relation between dopamine release and self-reported food pleasantness in humans.

[1] It is important to differentiate reinforcement from reward. Reinforcement mostly refers to a process that increases the occurrence of a specific behavior in a given context (Skinner, 1938).

Their results not only showed increased dopaminergic activity in the striatum, but also a direct correlation between the amount of dopamine released and the perceived food palatability in healthy subjects. To extend that, Volkow et al. (2003) correlated the type of eating (i.e. restraint, emotional) with DA brain levels in a PET study. They found that higher DA concentrations were correlated with higher levels of restraint, while lower DA responsivity represented higher emotionally while eating. Again, these changes were observed in the dorsal striatum, once again indicating the involvement of this region in modulating eating behaviors.

2.2.3. Fasting and Food as a Reward

The metabolic state of the individual (fasted or fed) was shown to influence the value of food as a reward (Cassidy & Tong, 2017; Kringelbach, 2004). A classic study showed, for instance, that subjective ratings of pleasantness of a sweet solution were higher during fasting compared to fed states (Cabanac, 1971). Further research has pointed to the same direction, with the addition of different methodologies to support their findings. For instance, while having participants picture their favorite food in an MRI scanner, Hinton et al. (2004) reported higher activation in the striatum, a putative region for reward processing, in fasted compared to fed state. In that vein, Goldstone et al. (2009) also reported increased activation in the ventral striatum,

amygdala, anterior insula and OFC in response to high-caloric food vs low-caloric food pictures during fasting. Besides that, self-reported pleasantness ratings of high caloric food were increased after a fasting period. It is interesting to note that the difference in ratings between high- and low-caloric food pictures were correlated with activation in the OFC, which is believed to encode the value of food as a reward (Small et al., 2007). Similarly, Führer, Zysset, and Stumvoll (2008) reported stronger activation in the OFC during fasting in response to food pictures in comparison to non-food pictures.

Recent studies using self-reported measures have also found similar results. Pursey, Contreras-Rodriguez, Collins, Stanwell, and Burrows (2019) assessed subjective ratings of "appeal to food", "desire to eat food" and "effect of food in increasing appetite" during fasted and fed states and reported significant differences between states, with fasting yielding higher scores. Similarly, Cameron, Goldfield, Finlayson, Blundell, and Doucet (2014) reported higher self-report of food pleasantness during fasting.

Taken together, these results suggest that the nutritional state modulates how food is perceived as a reward, both at neuronal and behavioral levels, with fasting increasing the rewarding potential of food. However, the effect of fasting on other

types of reward, including monetary reward, has been little investigated. Understanding how other types of reward are modulated by the nutritional state may bring insights to disorders that involve eating, since other types of reward, such as social and monetary, may be also altered in such cases.

2.3. THE ENDOCANNABINOID SYSTEM: HOMEOSTASIS AND REWARD PROCESSING

The endocannabinoid system (eCB) has also been identified as a potential regulator of eating behaviors (A. M. Monteleone et al., 2015; P. Monteleone et al., 2005; B. A. Watkins & Kim, 2014) and also seems to be influenced by the metabolic state (Kirkham, Williams, Fezza, & Di Marzo, 2002). Cannabinoid receptors are widely found in the brain and many organs and tissues besides the nervous system. It includes both synaptic and peripheral signaling functions (B. A. Watkins & Kim, 2014). The main endocannabinoids studied in relation to eating behaviors are the endogenous ligands *anandamide* (arachidonoylethanolamide, AEA) and *2-arachidonoylglycerol* (2-AG), as well as the receptors CB_1 and CB_2 (Cota et al., 2003). AEA and 2-AG were found in greater concentration in brain regions in response to fasting in rats (Kirkham et al., 2002). Furthermore, fasting also increased AEA levels in peripheral regions (small intestine), and peripheral administration (intraperitoneal in rats) of AEA increased food intake (Gomez et al., 2002). These studies point to a role of eCB in food-intake

control, and has suggested AEA's role as a meal initiator (Marco, Romero-Zerbo, Viveros, & Bermudez-Silva, 2012), promoting eating and feeding behaviors.

The role of the eCB in meal initiation may be connected to the rewarding effects it attributes to food (A. M. Monteleone et al., 2015; P. Monteleone et al., 2005; B. A. Watkins & Kim, 2014). For instance, research has shown that endocannabinoid administration enhances perceived food palatability (Kirkham & Williams, 2001). Similar results have been found in animal research as well (Cooper, 2004; Jarrett et al., 2005), and the NAcc seems to have a special hotspot for anandemide (Mahler, Smith, & Berridge, 2007). Mahler and colleagues (2007) showed that microinjections of anandemide to NAcc increased positive reactions to pleasant tastes in rats, besides increasing eating.

Eating, as any other complex behavior, is multidetermined and controlled by several different systems. The objective was to understand the involvement of the systems that will be further discussed in this work. The previous mechanisms and systems were mostly investigated in healthy controls, as general functioning and controlling of eating behaviors. Following, the same systems will be approached in anorexia nervosa and obesity, since the main objective of this work is to bring insights

from research on these conditions to the comprehension of reward processing affected by eating behaviors.

CHAPTER 2

FROM EATING BEHAVIORS TO EATING DISTURBANCES

"Thou shouldst eat to live; not live to eat".

Socrates

The ethologically atypical relationship between humans and food may have led to some consequences in terms of mental and general health. Changes in eating and feeding habits may have influenced the development of diseases in humans (Zucoloto, 2011). In that sense, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) devotes an entire section to mental disorders related to eating and feeding behaviors. Eating and feeding disorders are characterized as "a persistent disturbance of eating or eating-related behavior that results in the altered consumption or absorption of food and that significantly impairs physical health or psychosocial functioning" (p. 329).

As previously seen, the reward system is one aspect involved in controlling food-intake, and the malfunctioning of reward processing has been implicated in the studies of various disorders as well, both at behavioral and neural levels (Blum et al., 2006), from mental (Barbato et al., 2006; Bergen et al., 2005; Davis & Woodside, 2002; Ehrlich et al., 2014; Piazza et al., 1993; Wagner et al., 2007) to metabolic disorders (Ho et al., 2012; Kenny, 2011; Rothemund et al., 2007). Taking that into consideration, the aim of this chapter is to investigate reward processing in two clinical conditions involving eating: anorexia nervosa (AN) and obesity.

1. ANOREXIA NERVOSA

Anorexia Nervosa (AN) is the eating disorder with highest mortality rate (Fichter & Quadflieg, 2016). First reported scientifically in the late 1800s, AN received Dr. Gull (1873) attention due to the characteristic emaciation (i.e. the state of being atypically thin) in some of his patients. Some of his young female patients showed similar symptoms that could not be fit into other disease categories. Those patients were extremely underweight, presented long-lasting amenorrhea (i.e. the absence of menstruation), and had weak vital functioning. All of that could be explained by an anorexia (i.e. lack of appetite) that led to starvation and, consequently, the weakening of all vital functions (Gull, 1873). Since that first scientific report of AN, although considerable effort has been made towards a better understanding of the disorder, much is still to be learned (Strober, 2005).

1.1. DIAGNOSTIC CRITERIA OF ANOREXIA NERVOSA

One of the main measures used in the diagnosis of AN is body mass index (BMI), defined as someone's weight in kilograms divided by the square of their height in meters (kg/m^2) and used to indicate nutritional status in adults (World Health Organization, 2016). The core features of AN involve "behavioral disturbances related to eating or weight control practices that leads to a significantly low body weight,

disturbance in the experience of body shape and/or weight, disturbance results in substantial impairment in physical, social and/or mental functioning, disturbances is not secondary to any other medical or psychiatric disorder" (Treasure et al., 2015).

A normal-weight BMI ranges between 18.5 to 24.9 kg/m^2 (WHO, 1995). In AN, a BMI above 17 kg/m^2 is considered of mild severity. A moderate AN is diagnosed when the patient's BMI lies between 16-16.99 kg/m^2; a severe AN, 15-15.99 kg/m^2; and an extreme AN, when the BMI is under or equal 14.99 kg/m^2. AN's prevalence is mostly among young females (0.4% -12-month prevalence); although AN also occurs in men, it is much less common.

1.2. COMORBIDITIES IN ANOREXIA NERVOSA

The condition has been associated with several psychosocial features, such as depression, social withdrawal, irritability and reduced interest in sex (American Psychiatric Association, 2013). Moreover, individuals with AN tend to present increased interpersonal problems (Carter, Kelly, & Norwood, 2012), which also reflect on their social contexts, included but not limited to family dysfunctionality (Espindola & Blay, 2009). Carter and colleagues (2012) investigated how interpersonal issues relate to AN and its treatment. They reported an association between AN and interpersonal problems (mainly related to submissiveness, non-assertiveness, and

social inhibition), which tended to decrease after an interdisciplinary treatment. Furthermore, AN has been reported to normally co-occur with affective and anxiety disorders (Halmi et al., 1991), with symptoms of the latter emerging prior to the onset of AN (APA, 2013). In addition, general medical comorbidities have also been reported in AN, involving skin and hair development, cardiovascular and gastrointestinal system, among others (Rikani et al., 2013).

1.3. Anorexia nervosa and Reward processing

Research has pointed to dysfunctional reward processing as one of the factors responsible for the peculiar eating behaviors in AN (Barbato et al., 2006; Bergen et al., 2005; Davis & Woodside, 2002; Ehrlich et al., 2014; Wagner et al., 2007). For instance, by using eye blink rate, a potential peripheral measure of central dopaminergic activity, Barbato et al. (2006) showed altered DA processing in patients with AN. Furthermore, it has been hypothesized that a DA malfunctioning might lie behind the maintenance of food deprivation behaviors in AN (Bergh & Södersten, 1996). The constant absence of food, leading to a state of starvation, would provoke a physiological stress response by activating the hypothalamic-pituitary-adrenal axis, which, in turn, would activate DA neurons, thus, reinforcing non-eating behaviors due to a dopaminergic misprocessing (Bergh & Södersten, 1996). In that sense, Piazza et al.

(1993) showed that physiological levels of stress can indeed have reinforcing properties, and that has been speculated to be the case in AN. For instance, research with animals showed that rats would self-administer corticosterone, which is connected to stress and potentiates pleasure properties of drugs of abuse, even though that meant undergoing the stress of intravenous injections (Piazza et al., 1993).

Baseline neural processing across reward-related areas in AN is also altered (Haynos et al., 2019). By investigating resting state functional connectivity (RSFC), Haynos et al. (2019) have recently shown weaker connection between areas implicated in reward processing (NAcc and ventral regions of the caudate) in patients with AN when compared to healthy controls. Besides that, Cha et al. (2016) also reported abnormalities associated with RSFC of the ventral frontostriatal network in AN.

Davis and Woodside (2002) compared the degree to which patients with AN report pleasure related to physical sensations. Their findings showed that, in comparison to healthy controls and individuals with bulimia nervosa, the participants with AN were much more anhedonic, suggesting an altered activation pattern in reward-related regions. Altered activation was also observed in response to food stimuli (Wagner et al., 2008), strengthening the idea of a diminished ability to

experience pleasure among these patients in comparison to the general population. Besides food, response to non-primary rewards have also been investigated in AN.

Finally, it is important to note that the differences between cases and controls previously stated may be a correlate or a consequence of the disorder. In other words, it is not possible to establish whether alterations in neural mechanisms cause the disorder or whether these alterations arise as a result of the disease state. The latter is a particular concern in research on AN, since differences observed in individuals with the disorder may be attributable to confounds such as starvation (Steinglass et al., 2019). For example, it is not clear whether changes in structural and/or functional connectivity are a result of the nutritional status. In this vein, Santos and collaborators (2018) have recently shown that brain structure in AN is strongly correlated with body mass index (BMI), suggesting that nutritional status is a confounding factor when researching eating disorders.

1.3.1. ANOREXIA NERVOSA AND MONETARY REWARDS

Responses to monetary rewards, as *non-primary* rewards, have also been evaluated by using several different methods and instruments, including fMRI, behavioral and self-report data, and alterations to monetary reward processing have

also been observed in patients with AN (Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019).

To be as accurate as possible with the current state of the literature on studies involving anorexia nervosa and monetary rewards, a quasi-systematic literature review was done following the PRISMA framework (Moher, Liberati, Tetzlaff, & Altman, 2009). The search was done in one database (*PubMed*) with the terms *"Anorexia Nervosa", and "Money or Monetary Reward"*, but no inter-rater reliability was performed. Empirical studies with individuals with anorexia nervosa that involved monetary rewards, published until May 2019 were included. Nineteen papers were identified through database searching (Fig. 2). After screening, 4 papers were excluded for 1) not involving patients with anorexia nervosa; 2) not involving monetary rewards; and 3) not reporting empirical research (Table 1).

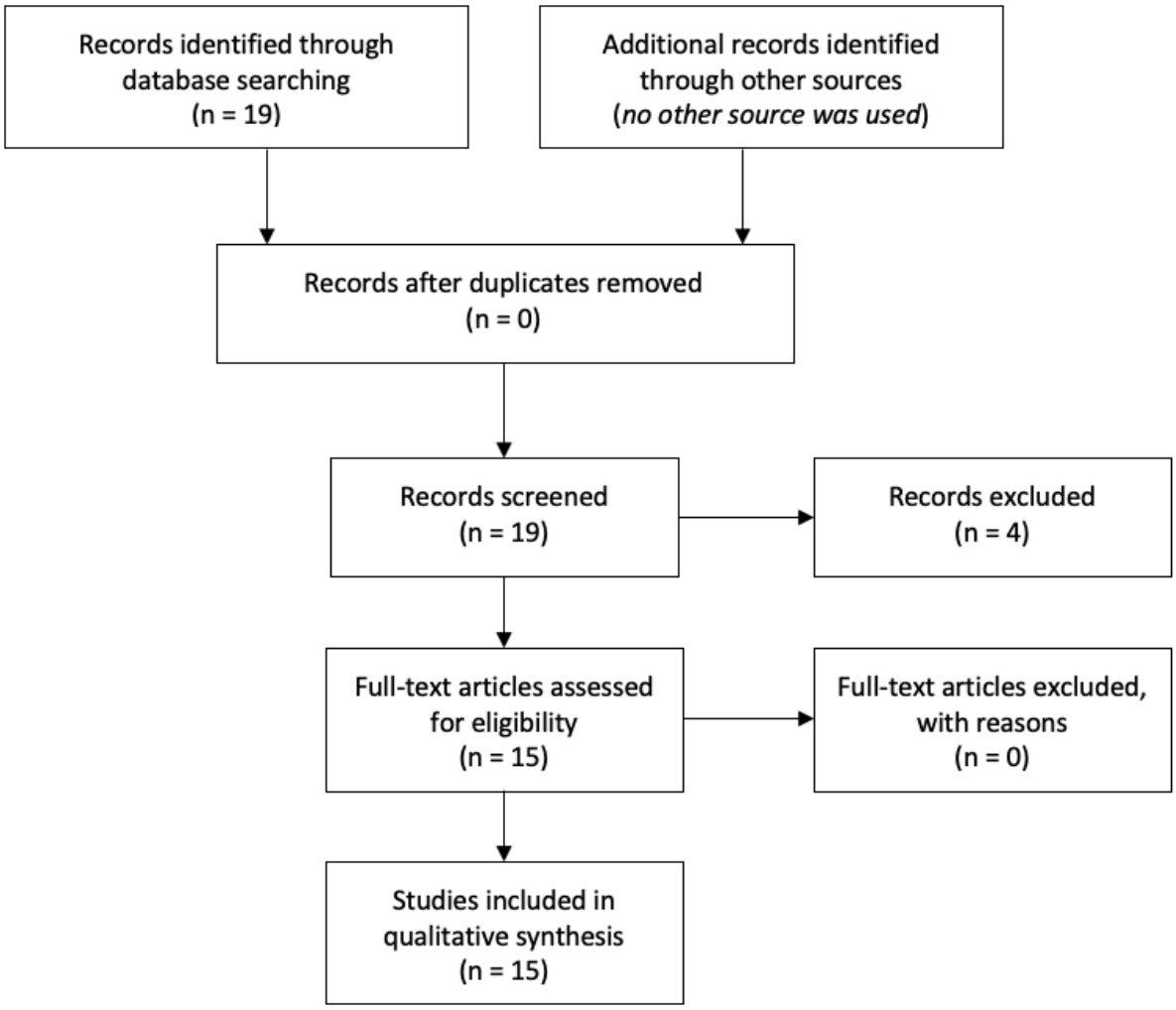

Figure 2. PRISMA flow diagram of studies involving "anorexia nervosa" and "money OR monetary reward".

The 14 remaining papers included (Table 2) reported behavioral, self-report and neural responses to monetary reward in patients with AN, and the results will be discussed below.

1.3.1.1. Behavioral responses to monetary rewards in AN

Behavioral data have been obtained by the same tasks used for fMRI research and others (Bischoff-Grethe et al., 2013; Decker, Figner, & Steinglass, 2015; King et al.,

2016; Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019; Ritschel et al., 2015; Steinglass et al., 2012; Steinglass et al., 2017; Steward et al., 2017). In general, research shows that patients with AN prefer larger/later rewards than smaller/sooner rewards (Decker et al., 2015; Steinglass et al., 2012; Steinglass et al., 2017; Steward et al., 2017), again, showing greater cognitive control than normal-weight participants. However, one study found no difference between AN and HC (Ritschel et al., 2015). The later study also evaluated delay discounting responses to monetary rewards in recovered patients, and no difference was found.

1.3.1.2. Self-reported responses to monetary rewards in AN

Self-report measures to reward have been assessed by the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) (Carver & White, 1994). BIS consists of two scales measuring the concern about negative future events, and the sensitivity to negative past events. BAS measures how rewarding experiences are found and responses towards goal pursuing.

One study has evaluated how AN responds to reward using BIS/BAS (DeGuzman, Shott, Yang, Riederer, & Frank, 2017). While AN did not differ from controls in reward sensitivity, both before and following weight-restoration, patients

with AN showed higher sensitivity to punishment than HC, both before and after weight-treatment(de Zwaan, 2001).

1.3.1.3 Neural responses to monetary rewards in AN

Regarding neural responses, six studies used fMRI measures in combination with a monetary discounting delay task – choosing larger later over smaller sooner rewards (Bailer et al., 2017; Decker et al., 2015; Ehrlich et al., 2014; King et al., 2016; Murao et al., 2017; Wierenga et al., 2015). Other tasks, such as card guessing games, where participants were asked to guess whether a hidden card was higher or smaller than the number shown, have also been used to measure neural responses to monetary rewards in AN (Bischoff-Grethe et al., 2013; DeGuzman et al., 2017; Wagner et al., 2007).

Two studies have shown no difference in striatal activation during monetary reward anticipation (i.e. when the prospect of a reward is initiated) between patients with AN and healthy controls (Ehrlich et al., 2014; Murao et al., 2017). For instance, increasing activation in the striatum, mOFC, and DLPFC were found to increase in relation to the reward magnitude in both AN and controls (Ehrlich et al., 2014). On the other hand, Ehrlich et al. (2014) showed stronger activation in the DLPFC in AN compared to controls during anticipation.

Regarding reward delivery (i.e. when the outcome is received), differences between AN and controls can be found. For instance, Wagner et al. (2007) reported that, while HC show different activation patterns to winning vs losing in the striatum (i.e. increased activation to winning vs decreased activation to losing), no difference between outcomes was seen in AN. Contrarily, Bischoff-Grethe et al. (2013) have shown stronger activation to winning and decreased activation to losing in NAcc and ACC in both AN and HC.

Table 1. Studies excluded from review after screening and reason for exclusion in anorexia nervosa.

Study	Reason for exclusion
Haynos et al. (2019)	Did not involve response to monetary rewards
Kekic et al. (2016)	Did not involve patients with anorexia nervosa
Wierenga et al. (2014)	Did not report empirical research
Wagner et al. (2010)	Did not involve patients with anorexia nervosa

Table 2. Studies identified through search on PubMed investigating monetary reward processing in anorexia nervosa.

Study	Sample Size	Measures	Instruments	Relevant findings
Isobe et al. (2018)	AN = 24 HC = 22	Behavioral	Ultimatum game (splitting of money between players)	• AN required more money from the other player than HC to accept an offer.
Steward et al. (2017)	AN = 56 (AN-R = 37; AN-BP = 19) HC = 80	Delay discounting	Intertemporal choice task	• AN-BP had greater discounting than HC; • AN-R showed more preference for delayed reward than AN-BP.
Murao et al. (2017)	AN = 23 (AN-R = 11; AN-BP = 12) HC = 20	fMRI	Monetary delay task	• AN striatum activation during anticipation was similar to controls; • AN-BP rostral ACC and right posterior insula activation was greater during loss anticipation than AN-R and HC; • AN-R ACC and posterior insula activation was similar to HC.

DeGuzman et al. (2017)	AN = 21 HC = 21 (adolescents before and after weight treatment)	fMRI Self-report	Monetary reward task BIS/BAS	• AN showed greater activation in the caudate body, right caudate head, NAcc, and insula associated with prediction error than HC before treatment; • AN showed greater activation in the left caudate body during unexpected reward omission before treatment; • AN showed higher activation than HC in the right dorsal anterior insula during unexpected reward receipt before and after treatment; • AN showed higher activation than HC in the left dorsal anterior insula and the right ventral anterior insula during unexpected reward receipt only after treatment: • AN showed higher activation than HC in the right posterior insula during unexpected reward receipt; • AN did not differ from controls in sensitivity to reward in the acute phase and after treatment; • AN showed higher sensitivity to punishment than HC at both timepoints;

				• Sensitivity to punishment correlated to activation in NAcc.
Steinglass et al. (2017)	AN = 27 HC = 50	Delay discounting	Monetary incentive delay task	• AN show higher preference for delayed reward than HC.
Bailer et al. (2017)	ANRec = 12	Correlation between fMRI and PET data obtained in previous studies (Bailer et al., 2013; Wagner et al., 2007)	Monetary choice task	• ANRec with greater activation in the dorsal caudate in response to winning and losing money had higher middle caudate D2/D3 binding.
King et al. (2016)	AN = 31 HC = 31 (predominately adolescents)	fMRI	Intertemporal choice task	• AN delayed discounting did not differ from HC; • AN reaction times were faster than HC; • AN showed decreased activation in comparison to HC in the dorsal ACC.
Decker et al. (2015)	Delay discounting task AN = 59	Delay discounting fMRI	Monetary delay task	• AN showed higher preference for delayed reward than HC only before treatment, with no difference between groups after treatment;

	HC = 39 fMRI + task AN = 30 HC = 22 (before and after treatment)			• Before treatment, AN showed less activity in the striatum and dorsal ACC in response to the larger/later compared to the shorter/sooner reward, while HC did not show different between types of reward. This was reversed after treatment.
Ritschel et al. (2015)	AN = 34 ANRec = 33 HC = 54 (reevaluation of AN after weight-recovery *n* = 21)	Delay discounting	Intertemporal choice task	• No group differences were found.
Wierenga et al. (2015)	ANRec = 23 HC = 17	Delay discounting fMRI	Delay discounting task	• ANRec striatal, dorsal caudate and ACC activation, different than HC, did not differ between hunger and satiety

				conditions. HC activation in these areas was increased during hunger.
Ehrlich et al. (2014)	ANRec = 30 HC = 30	fMRI Feedback about the magnitude of the reward received Instrumental responding (motivation assessment)	Instrumental motivation task (monetary incentive delay paradigm, while lying in the MRI scanner)	• ANRec, similarly to HC, showed increasing activation in the ventral striatum, mOFC and bilateral DLPFC as levels of monetary reward increased during reward anticipation; • ANR had higher activation than HC in DLPFC during reward anticipation; • During reward feedback, increasing levels of monetary reward were associated with decreasing activation in the striatum, mOFC and bilateral DLPFC in both AN and HC; • Decreases in activation in the aforementioned regions were steeper in HC in function of reward level; • ANRec did not differ from HC in reaction times nor instrumental responding (number of button presses).
Bischoff-Grethe et al. (2013)	AN-R = 10 HC = 12 (adolescents)	fMRI	Monetary guessing task	• AN-R strategies did not differ from HC in terms of responses to winning or losing; • AN and HC showed stronger activation to winning and a decreased response to losing in the NAcc and rostral ACC.

Steinglass et al. (2012)	AN = 36 HC = 28 AN-R = ? AN-BP = ?	Delay discounting	Intertemporal choice task	• Greater mean discount factor for AN-R compared to HC.
Wagner et al. (2007)	ANRec = 13 HC = 13	fMRI	Monetary guessing task	• Striatal activation in AN did not differ between winning and losing, while they were different in HC (stronger activation to winning).

Note. AN = anorexia nervosa, HC = healthy controls, AN-BP = anorexia nervosa binge-purge subtype, AN-R = anorexia nervosa restrictive type, fMRI = functional magnetic resonance imaging, ACC = anterior cingulate cortex, NAcc = nucleus accumbens, ANRec = recovered anorexia nervosa, DLPFC = dorsolateral prefrontal cortex, mOFC = medial orbitofrontal cortex.

Taken together, these results suggest blunted responses to reward processing in AN that is not only related to food, but also to monetary rewards. Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al. (2019) will be presented entirely as Chapter 3 and this will be further discussed.

2. OBESITY

If, on one hand, the complex relationship between humans and food may have led to the development of conditions of not enough food intake, leading to very low body weight in proportion to height, on the other hand, it may be have also led to the other extreme – overfeeding and above average weight for a given height. Although not considered an eating disorder, obesity, an important metabolic condition defined based on excess adiposity, is mainly attributed to an increased intake of food, relative to nutritional needs (Wright & Aronne, 2012).

Obesity has become a very serious problem. In the United States, for instance, two in three adults have been considered overweight, and one in three, obese (National Institute of Diabetes and Digestive and Kidney Diseases, 2017). Worldwide, 1.9 billion adults were overweight in 2016, with 650 million of these being obese (WHO, 2020). A person is considered overweight or obese when his/her weight is higher than what is considered as a historically normal weight, taking the height into

consideration, presenting abnormal or excessive fat accumulation that may impair health (World Health Organization, 2016). Still, it has been associated with high mortality rates all around the world, and its prevalence has more than doubled since 1980 (World Health Organization, 2016), leading to the thought that, if progression continues as in the last years, it might be too late to avoid an obesity epidemic (NCD Risk Factor Collaboration, 2016).

2.1. OBESITY AND COMORBIDITIES

Unlike AN, obesity is not considered a psychiatric disorder. Obesity is defined as excessive accumulation of fat (BMI equal to or greater than 30 kg/m^2) that may significantly impact the individual's health (World Health Organization, 2020). Individuals with obesity have also presented various comorbidities, including psychiatric comorbidities (Muller, 2013). They are considered to be at an increased risk for many other medical problems, including diabetes, hypertension and other cardiovascular diseases, cancer, among others, and, possibly due to social stigmatization and discrimination, depression and other psychological issues are more common among this population when compared to health controls (Khaodhiar, McCowen, & Blackburn, 1999). Dixon, Dixon, and O'Brien (2003) have reported that the risk of depression, for instance, is higher among women with obesity who also

report poor body image representation. These ratings tend to improve with weight loss, strengthening the relation between weight and these psychological factors. Besides that, obesity has also been linked to the development of anxiety disorders, and the characteristic eating pattern could represent strategies to cope with such negative emotions (Muller, 2013).

2.2. Obesity and Food Reward

Obesity has also been related to disturbances in reward processing (Kenny, 2011). Enhanced activation patterns in cerebral areas related to reward processing were seen in response to palatable food in patients with obesity relative to normal-weight controls (Rothemund et al., 2007) during both fasting and after food intake (Ho et al., 2012). In contrast, normal-weight individuals exhibited higher striatal activation in response to high-caloric food only during fasting, suggesting that food may remain rewarding to people with obesity and not normal-weight controls after feeding (Goldstone et al., 2009). Furthermore, resting state functional connectivity was higher leaving from reward-related cerebral regions in individuals with obesity in comparison to normal-weight controls (Hogenkamp et al., 2016). Following weight loss due to bariatric surgery, activation in the putamen, for instance, was decreased (Wiemerslage et al., 2017). Further, research suggests that alterations in reward

processing play a role in the persistence of obesity: in a weight loss intervention, individuals with higher levels of anhedonia (i.e. a diminished ability to experience pleasure overall) were more likely to experience pathological overeating and had poorer weight loss outcomes (Keranen, Rasinaho, Hakko, Savolainen, & Lindeman, 2010).

Hypofunctioning to food reward receipt has been proposed to underlie the increased food consumption leading to excessive weight gain in obesity (Kenny, 2011; E. Stice, Spoor, Bohon, & Small, 2008). However, it remains unclear how other types of reward are processed in obesity. This question is important because overeating, one of the main causes of obesity (Wright & Aronne, 2012), might serve as a compensatory behavior for a diminished response to other types of reward (Kenny, 2011). Research has been conducted using monetary reward, but the results were inconsistent (Tang, Chrzanowski-Smith, Hutchinson, Kee, & Hunter, 2018).

Besides food, responses to non-primary rewards, such as money, have also been evaluated in people with obesity. Responses to monetary rewards in obesity will be discussed in the following session.

2.3. Obesity and Monetary Reward

Similar to research in AN, neural, behavioral and self-reported measures have been used to study responses to monetary rewards in individuals with obesity. A quasi-systematic literature review was done following the PRISMA framework (Moher et al., 2009). The search was done in one database (*PubMed*) with the terms "*Obese or Obesity*", *and* "*Money or Monetary Reward*", but no inter-rater reliability was performed. Empirical studies with individuals with obesity that involved monetary rewards, published until May 2019 were included. Out of 84 papers retrieved, 43 were included (Figure 3). The reasons for exclusion can be found in Table 3. All other studies were included, and neural, behavioral, and self-reported data were also found (Table 4).

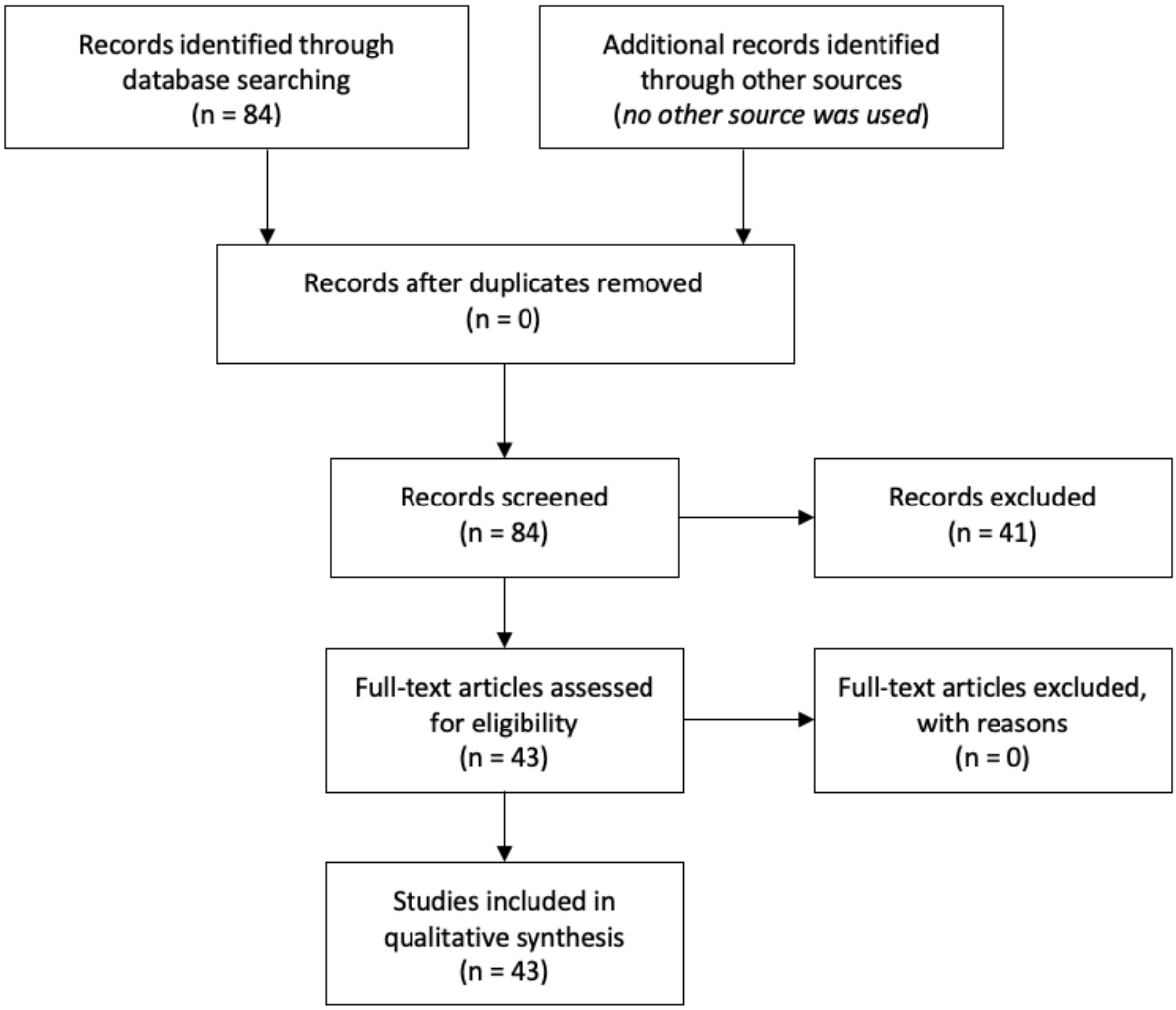

Figure 3. PRISMA flow diagram of studies involving "obese OR obesity" and "money OR monetary reward".

Table 3. Studies excluded from review after screening and reason for exclusion in obesity.

Study	**Reason for exclusion**
Appelhans, Tangney, French, Crane, and Wang (2019)	Did not include people with obesity or overweight
Barker et al. (2019)	Did not include people with obesity or overweight
Castrellon et al. (2019)	Review paper
Rihm et al. (2019)	Did not include people with obesity or overweight
Weafer, Crane, Gorka, Phan, and de Wit (2019)	Did not include people with obesity or overweight
Berg Schmidt et al. (2018)	Did not include people with obesity or overweight
Lancaster, Ihssen, Brindley, and Linden (2018)	Did not include people with obesity or overweight
Lesser, Thompson, and Luft (2018)	No BMI measures
Navas et al. (2018)	No BMI measures

Spetter et al. (2018)	Did not include people with obesity or overweight
Tang et al. (2018)	Review paper
Simon et al. (2017)	Did not include people with obesity or overweight
E. Stice, Yokum, Veling, Kemps, and Lawrence (2017)	Did not involve monetary rewards
Amlung, Petker, Jackson, Balodis, and MacKillop (2016)	Review paper
Barlow, Reeves, McKee, Galea, and Stuckler (2016)	Review paper
Eisenstein et al. (2016)	Erratum
Melrose et al. (2016)	Did not include people with obesity or overweight
Eric Stice and Yokum (2016)	
Cawley (2015)	Review paper
Dolan, Galizzi, and Navarro-Martinez (2015)	Did not include people with obesity or overweight
S.-L. Lim and A. S. Bruce (2015)	Did not include people with obesity or overweight
S. L. Lim and A. S. Bruce (2015)	Did not include people with obesity or overweight
Luo, Monterosso, Sarpelleh, and Page (2015)	Did not include people with obesity or overweight
Sykes-Muskett, Prestwich, Lawton, and Armitage (2015)	Review paper
Davidson and Martin (2014)	Theoretical paper
Wierenga et al. (2014)	Review paper
Yantis, Anderson, Wampler, and Laurent (2012)	Did not include people with obesity or overweight
"Money talks: financial incentives for health" 2011)	Theoretical paper
Anderson, Laurent, and Yantis (2011)	Did not include people with obesity or overweight
Bardugo, Moses, Shemmer, and Dubman (2010)	Did not involve monetary rewards; Disabled patients with obesity
Rollins, Dearing, and Epstein (2010)	Did not include people with obesity or overweight
Epstein, Dearing, Temple, and Cavanaugh (2008)	Results are reported in relation to children's parents
Collier et al. (2002)	Review paper
Adkins, Mathewson, Ayllon, and Jones (1999)	Did not include people with obesity or overweight
Kramer, Jeffery, and Snell (1986)	Did not include people with obesity or overweight
Colvin, Zopf, and Myers (1983)	No clear description of participants. They are described as "willing to lose weight".
Stachnik and Stoffelmayr (1981)	Theoretical paper

Table 4. Studies identified through search on PubMed investigating monetary reward processing in obesity.

Study	Sample Size	Measures	Instruments	Relevant findings
Verdejo-Roman, Vilar-Lopez, Navas, Soriano-Mas, and Verdejo-Garcia (2017)	OB = 21 OW = 21 HC = 39	fMRI Behavioral Self-report	Willing to Pay; Money Incentive Delay; BIS/BAS	• Higher bilateral activation in the dorsal caudate, NAcc, ventral putamen, VTA, intraparietal, vmPFC, ACC, anterior insula extending to the lateral orbitofrontal gyrus to high-palatable vs plain food for all participants; • OB had increased activations bilaterally in the dorsal caudate and NAcc in comparison to OW and HC; • OB had higher ACC activation compared to HC; • Linear and positive correlation between BMI and bilaterally activation in the dorsal caudate, NAcc, and the dorsal anterior cingulate gyrus; • OW had higher activation in ACC in comparison to OW and HC; • OW had VTA, ventral putamen, lateral OFC, and hippocampus-amygdala complex activation in comparison to HC; • OB had higher rostral-ventral pons than HC when winning vs losing money; • OB had higher NAcc activation than OW to winning vs losing;

				• OB and OW paid more money for palatable food than for plain food, while for HC there was no difference between food types; • OB paid less money for plain food than did HC; • All participants were faster when the higher reward was presented; • OB had slower reaction times than HC in response to neutral and low reward; • No differences between groups in reward or punishment sensitivity (BIS/BAS).
Eisenstein et al. (2015)	OB = 27 Non-obese = 20 (including 2 OW participants)	PET fMRI Behavioral	Money Incentive Delay; Probabilistic Reward Discounting	• OB did not differ from Non-obese in striatal dopamine (DR2) binding; • Only OB (and not non-obese) with higher D2R BPnd discounted delayed rewards to a higher degree than those with lower striatal D2R; • No difference is discounting between groups.
VanderBroek-Stice, Stojek, Beach, vanDellen, and MacKillop (2017)	Total Sample = 181 (32% obese)	Behavioral	Money Incentive Delay	• Delayed discounting did not predict obesity.

Verdejo-Roman, Fornito, Soriano-Mas, Vilar-Lopez, and Verdejo-Garcia (2017)	OW = 39 HC = 37	fMRI Behavioral	Willing to Pay Money Incentive Delay	• OW was associated with decreased connectivity during food reward processing in frontal and striatal areas, with increased functional connectivity in frontal and parietal areas during monetary reward processing; • OW did not differ from HC in valuating high palatable foods; • OW were less willing to pay for plain food than HC; • OW paid more money for palatable food than for plain food, while no difference was found for HC; • OW showed greater responsivity to reward.
Balodis et al. (2013)	OB with BED = 19 OB = 19 HC = 19	fMRI Behavioral	Monetary Incentive Delay Task	• OB without BED showed increased activation in the ventral striatum and vmPFC during monetary reward anticipation in comparison to HC; • OB with BED showed decreased bilateral ventral striatum activation during anticipation in comparison to OB without BED; • OB with BED did not differ from HC in ventral striatum activation.

Z. Zhang, Manson, Schiller, and Levy (2014)	OB = 68 (34 women) HC = 67		Appetitive Reversal Learning Task (learn and modify cue-reward associations)	• OB did not differ from HC when money was used as an outcome associated with learning; • OB women showed impaired learning when food was used as an outcome associated with learning.
Sze, Slaven, Bickel, and Epstein (2017)	OB = 84 (Weight loss preference = 61; money preference = 23).	Behavioral	Monetary Choice Questionnaire Monetary and Weight Choices Questionnaire (modeled after the monetary choice questionnaire and the weight loss questionnaire)	• OB preferred weight loss more than money; • Those who initially showed a preference for money over weight-loss discounted more weight loss than those who initially said to prefer weight loss.
Coppin, Nolan-Poupart, Jones-Gotman, and Small (2014)	OB = 15 HC = 15	Behavioral	Conditioning cue preference test Probabilistic learning task	• OB showed higher preference than HC for patterns implicitly associated with losing money.

Schiff et al. (2016)	OB = 23 HC = 23	Behavioral	Temporal discounting task (food, money, and discount vouchers as rewards)	• OB chose more small-immediate rewards than HC; • OB discounted more food choices compared to HC and compared to the other types of reward; • OB did not differ from HC for the other types of reward.
Kube et al. (2016)	OB = 14 HC = 14 (women)	ECG Behavioral	Social incentive delay task Monetary incentive delay task	• OB's RTs were slower in the social compared to the monetary reward tasks; • OB did not differ in heart rate during monetary reward anticipation and outcome;
Simon et al. (2018)	OB 6 months after a diet protocol = 33 (17 maintained weight-loss; 16 regained weight)	fMRI Behavioral	Incentive delay task (food and monetary reward)	• No group differences were found regarding monetary reward.
Opel et al. (2015)	OB = 29 HC = 29	fMRI Behavioral	Card guessing paradigm	• OB showed increased activation in OFC, insula and putamen than HC in response to monetary reward; • OB showed increased activation in ACC to reward vs control condition, while no difference was seen for HC.

Meemken, Kube, Wickner, and Horstmann (2018)	OB = 30 OW = 28 HC = 29	Behavioral	Willing to Pay Reversal learning task	• OB did not differ from HC in willingness to pay for food items; • OB showed better learning than HC, especially when food was used as an outcome associated with learning; • OB did not differ from HC when monetary outcomes were used.
Losina et al. (2017)	OB = 112 OW = 88 HC = 92	Behavioral	Physical activity track associated with monetary compensation	• Non-obese (HC and OW) were more successful in meeting activity requirements with the compensation than did OB (mostly African Americans with lower impulsivity scores).
Kube et al. (2017)	OB = 19 HC = 23	fMRI Behavioral	Probabilistic learning task	• OB and HC showed higher activation to winning monetary rewards in the striatum, insula, ACC, middle frontal gyrus, and midcingulate cortex; • While there was an increase in activation in mPFC for OB in response to monetary losses, there was a decrease in HC; • Only HC showed higher activation to winning money vs neutral stimulus in the right middle OFC, cerebellum, and occipital cortex; • OB did not differ from HC in neural responses to winning money or a • Avoiding money loss increased activation in the insula, middle frontal gyrus, cerebellum, and inferior parietal lobule;

				• OB had lower learning rates than HC; • OB made less advantageous choices in the task than HC; • OB won less money than HC in the task.
Kulendran et al. (2014)	OB = 53 (adolescents)	Behavioral	Money incentive delay task	• OB decreased in preference for immediate smaller rewards after a camp intervention designed to lose weight.
Verdejo-Garcia et al. (2015)	OW = 36 HC = 44	fMRI Self-report	Sensitivity to Punishment and Sensitivity to Reward Questionnaire	• OW showed lower sensitivity to reward; • Reward sensitivity was negatively correlated with anterior insula / frontal operculum activation only for OW.
E. Stice, Yokum, and Burger (2013)	Total sample = 162	fMRI (1-year follow-up)	Money reward paradigm	• Higher activation in the caudate and putamen to monetary rewards did not predict weight gain.
Hendrickson and Rasmussen (2013)	OB = 102	Behavioral	Money incentive delay task	• OB showed a preference for immediate small rewards over larger delayed monetary rewards; • OB did not differ from HC in money discounting after a mindful eating intervention.
Jarmolowicz et al. (2014)	Total sample = 100	Self-report	Money Choice Questionnaire	• Higher temporal discounting rates in OB, which decreased according to the magnitude of the monetary reward in

	(OB = 23; OW = 26; HC = 49; Underweight = 2)			comparison to the other participants (HC + Underweight); • Higher BMI was associated with choosing more immediate monetary rewards.
Kakoschke, Hawker, Castine, de Courten, and Verdejo-Garcia (2018)	OB = 29 OW = 31	Behavioral (intervention study)	Money incentive delay task	• OB did not differ in delay discounting after the proposed interventions.
Kullgren et al. (2016)	OB = 32	Behavioral	Monetary contingency contract	• OB weight loss was not motivated by monetary deposit contracts.
Paloyo, Reichert, Reuss-Borst, and Tauchmann (2015)	OB = 700	Behavioral	Financial incentives to promote weight loss	• OB weight loss was significantly motivated by monetary incentives.
Simmank, Murawski, Bode, and Horstmann (2015)	Total sample = 52 (no difference between groups n is presented)	Behavioral	Money incentive delay task	• OB showed more discounting of future rewards than HC; • OB did not differ from HC in sensitivity related to changes in reward magnitude.
Balodis et al. (2014)	OB with BED = 19	fMRI Behavioral	Money incentive delay task	• OB with BE after treatment showed diminished activation of the ventral striatum and the inferior frontal gyrus

	(OB with BE after treatment = 10; OB without BE after treatment = 9)	(intervention study)		compared to OB without BE during monetary reward anticipation; • OB with BE showed decreased activation in the mPFC monetary compared to OB without BE during reward outcome.
Adise, Geier, Roberts, White, and Keller (2019)	OB = 30 HC = 31 (children)	fMRI Behavioral	Card guessing paradigm	• Across groups, stronger striatal activation was seen in response to food and winning money during anticipation.
E. Stice, Burger, and Yokum (2015)	Total sample = 153 (adolescents) OB & OW = 130	fMRI Behavioral Self-report	Food and monetary reinforcement	• Responses to monetary reward did not predict weight gain.
McGill et al. (2018)	(mid-older adults)	(intervention study)	Online survey	• Participants report that monetary incentives may motivate weight loss.
Sykes-Muskett, Prestwich, Lawton, Meads, and Armitage (2017)	OB and OW = 56	Self-report	Survey	• OW and OB participants reported they would be willing to participate in monetary contingency contracts

Adise, Geier, Roberts, White, and Keller (2018)	OW = 28 HC = 31 (children)	fMRI Behavioral	Card guessing paradigm	• Across groups, participants showed increased activation in mPFC for food in comparison to money anticipation; • OW did not differ from HC in activation to monetary rewards.
Voon et al. (2014)	OB with BED = 30 OB without BED = 30 Abstinent alcohol-dependent = 30 Methamphetamine-dependent =23 HC = 30	Behavioral	Premature responding task	• OB with or without BED did not differ from HC in impulsivity responding to monetary rewards.
Simon et al. (2014)	Total sample = 24	fMRI Behavioral	Money incentive delay task	• No correlation between BMI as monetary reward processing was found.
Appelhans et al. (2012)	OB & OW = 78	Behavioral	Money incentive delay task	• Delay discounting was not associated with weight and/or BMI.
Weller, Cook, Avsar, and Cox (2008)	OB = 48 HC = 47 (women OB = 29; HC = 26)	Behavioral	Money incentive delay task	• OB women (and not men) had greater delay discounting than HC women.

	OB = 24			
Kishinevsky et al. (2012)	(fMRI n = 19)	fMRI Behavioral	Money incentive delay task	• Increased activation in the mPFC to difficult vs easy delay discounting trials.
	(women)			
Kastner, Kube, Villringer, and Neumann (2017)	Total sample = 48 (OB = 24)	ECG Behavioral	Probabilistic learning task	• OB showed slower learning than HC associated with punishment; • OB did not differ from HC in other measures.
Jeffery, Gerber, Rosenthal, and Lindquist (1983)	OB = 89	Behavioral (intervention study)	Money contingency contract	• OB lost more weight when participating in group rather individual contracts; • OB maintained weight loss after 1-year follow-up; • Deposit value was positively correlated to weight loss in short-term.
Leahey et al. (2016)	OB = 75	Behavioral (intervention study)	Monetary and social reinforcement contingent to weight loss	• OB who received monetary and social reinforcement contingent to weight loss lost more weight that a group following the traditional treatment.
Jeffery, Wing, Thorson, and Burton (1998)	OB = 193	Behavioral	Monetary reinforcement contingent to weight loss Presence of a personal trainer	• Use of monetary incentives doubled attendance at exercise sessions; • Combination of monetary incentives and the presence of a personal trainer showed

		(intervention study)		three times more efficacy in attendance than baseline.
Jeffery et al. (1993)	OB & OW = 202	Behavioral (intervention study)	Behavioral therapy Food provision (participants were given 5-day food provisions) Monetary reinforcement contingent to weight loss	• Food provision yielded more weight loss than, including after an 18-month follow-up, other incentive and behavioral therapy alone.
John et al. (2011)	OB = 66	Behavioral (intervention study)	Money contingency contract	• OB in the money contingency group lost more weight than the control group; • The difference between weight disappeared after an 18-month follow-up.
Manwaring, Green, Myerson, Strube, and Wilfley (2011)	OB with BED = 30 OB without BED = 30 HC = 30	Behavioral	Money incentive delay task	• OB with BED showed more delayed discounting than OB and HC for money; • OB without BED did not differ from HC.
Best et al. (2012)	OB = 241 (children)	Behavioral	Money incentive delay task	• Monetary discounting predicted weight loss in OB children.

OB = individuals with obesity, OW = overweight, HC = healthy controls, NAcc = nucleus accumbens, VTA = ventral tegmental area, ACC = anterior cingulate cortex, fMRI = functional magnetic resonance imaging, BIS/BAS = reward reactivity/behavioral inhibition system, OFC = orbitofrontal cortex, PET = positron emission tomography, ECG = electrocardiogram, BED = binge eating disorder, RT = reaction times, mPFC = medial prefrontal cortex, BMI = body mass index, BE = binge eating.

The findings will be discussed based on the outcomes evaluated, neural, behavioral and self-reported. Most studies made use of tasks to evaluate responses to monetary reward. The tasks used for delay discounting are the same used in anorexia nervosa and previously mentioned (Appelhans et al., 2019; Appelhans et al., 2012; Balodis et al., 2014; Best et al., 2012; Eisenstein et al., 2015; Hendrickson & Rasmussen, 2013; Kakoschke et al., 2018; Kishinevsky et al., 2012; Kube et al., 2016; Kulendran et al., 2014; Manwaring et al., 2011; Schiff et al., 2016; Simmank et al., 2015; Simon et al., 2018; Simon et al., 2014; Verdejo-Roman, Fornito, et al., 2017; Verdejo-Roman, Vilar-Lopez, et al., 2017; Weller et al., 2008), as are the card/money guessing tasks (Adise et al., 2018, 2019; Opel et al., 2015).

Other tasks have been used as well (e.g. willingness to pay, and conditioning learning tasks). In the willingness to pay task, participants are given some fictitious amount of money and are asked to determine how much money they are willing to pay for different types of food, involving palatable and plain foods (Meemken et al., 2018; Verdejo-Roman, Fornito, et al., 2017; Verdejo-Roman, Vilar-Lopez, et al., 2017). Conditioning tasks have used money and food as positive reinforcers for learning procedures (Coppin et al., 2014; Kastner et al., 2017; Sze et al., 2017; Z. Zhang et al., 2014), and also to promote weight loss and adherence to weight-loss programs (Jeffery

et al., 1983; Jeffery et al., 1998; Jeffery et al., 1993; John et al., 2011; Kullgren et al., 2016; Leahey et al., 2016; Losina et al., 2017; Paloyo et al., 2015; E. Stice et al., 2015).

2.3.1. BEHAVIORAL RESPONSES TO MONETARY REWARDS IN OBESITY

Behavioral data have yielded mixed results (de Zwaan, 2001). Verdejo-Roman, Fornito, et al. (2017) and Verdejo-Roman, Vilar-Lopez, et al. (2017), for instance, have reported that OB and OW were willing to pay more money for palatable food in comparison to plain food, while no difference between food type was found in controls. Meemken et al. (2018), on the other hand, reported no difference between OB and controls in the same task.

Reward learning tasks have provided knowledge associated with learning in people with obesity and monetary rewards. Z. Zhang et al. (2014) showed that, when money was used as positive reinforcer for learning, individuals with obesity did not differ from controls in learning. Only when food was used as consequence for learning, did women, and not men, with obesity show impaired learning. Meemken et al. (2018) replicated Z. Zhang and collaborators' (2014) results on monetary rewards. However, in this study, OB learned better than controls when food was used as an outcome. Further research is necessary to clarify these differences; however, money seems to be an important variable in the study of obesity.

Responses to monetary reward in obesity have also been studied in terms of delay discounting (Appelhans et al., 2019; Appelhans et al., 2012; Balodis et al., 2014; Best et al., 2012; Eisenstein et al., 2015; Hendrickson & Rasmussen, 2013; Kakoschke et al., 2018; Kishinevsky et al., 2012; Kube et al., 2016; Kulendran et al., 2014; Kullgren et al., 2016; Manwaring et al., 2011; Schiff et al., 2016; Simmank et al., 2015; Simon et al., 2018; Simon et al., 2014; Verdejo-Roman, Fornito, et al., 2017; Verdejo-Roman, Vilar-Lopez, et al., 2017; Weller et al., 2008), with most studies showing that, in comparison to controls, OB prefers smaller but sooner monetary rewards to larger but longer ones (Coppin et al., 2014; Hendrickson & Rasmussen, 2013; Simmank et al., 2015). Weller et al. (2008), however, found that this effect was exclusively in women, and not men, with obesity. In contrast, Eisenstein et al. (2015) reported no differences in discounting between OB and controls.

Simon et al. (2018) assessed delay discounting in people with obesity six months after participants had been submitted to a diet protocol. They then compared the responses between those who had maintained the weight-loss vs those who had gained weight and found no difference between groups. Kakoschke et al. (2018) also reported no differences in discounting after a weight-loss intervention. Best et al.

(2012), on the other hand, showed that, in children, money discounting predicted weight loss across time.

Research in monetary delay is inconclusive in relation to obesity, with 29 studies showing a group effect, and 29 reporting no differences. Tang et al. (2018) have recently carried out a systematic review on delay discounting in people with obesity and concluded that the absence of a factual conclusion might be due to the different methodologies used. Another reason, again, might be associated with the high prevalence of BED in obesity. It has been shown that discounting immediate rewards is stronger in people with obesity with BED in comparison to those without BED (Manwaring et al., 2011).

Finally, another form of measuring behavioral responses to money in obesity is the use of money contingence contracts, having money as an outcome contingent to weight-loss (Jeffery et al., 1983; Jeffery et al., 1998; Jeffery et al., 1993; John et al., 2011; Kramer et al., 1986; Kullgren et al., 2016; Leahey et al., 2016; Paloyo et al., 2015). And, although Kullgren et al. (2016) did not find an effect of money as an incentive for weight-loss, other authors have shown positive results (Jeffery et al., 1983; Jeffery et al., 1998; Jeffery et al., 1993; John et al., 2011; Kramer et al., 1986; Leahey et al., 2016; Paloyo et al., 2015).

2.3.2. *Self-reported responses to monetary rewards in obesity*

Two studies have also used a self-report version of the monetary incentive delay task (Jarmolowicz et al., 2014; Sze et al., 2017). One of these versions, include questions regarding weight-loss besides money (Sze et al., 2017). In the later, they separated two groups between those who would rather lose weight, and those who would prefer money over weight loss. Questionnaire responses showed that for both groups, losing weight was preferred over monetary incentives, even for those who initially stated to prefer money over weight-loss. Jarmolowicz et al. (2014) reported that BMI was positively correlated to choosing more immediate rewards.

2.3.3. *Neural responses to monetary rewards in obesity*

Research on neural responses to monetary reward in people with obesity has shown differences between people with obesity and normal-weight controls (Kenny, 2011). For instance, increased activation mostly to anticipation of monetary rewards in putative reward regions such as NAcc, ACC, ventral tegmental area, putamen, vmPFC and, OFC have been observed in OB in comparison to HC (Balodis et al., 2013; Opel et al., 2015; Verdejo-Garcia et al., 2015; Verdejo-Roman, Fornito, et al., 2017). Contrarily, Simon et al. (2018) and Adise et al. (2018) reported no difference in activation to

monetary, but only to food rewards in people with obesity. When looking more closely at differences between individuals with overweight (OW) and obesity, Verdejo-Roman, Vilar-Lopez, et al. (2017) observed that the stronger activation was in relation to food rewards in OB, while in OW, it was stronger to monetary rewards.

One possible explanation for the difference in the results could be that participants with obesity are not very often screened for the presence of binge eating disorder (BED), for instance. It is important to screen for BED in people with obesity because of the high prevalence of the disease among OB (de Zwaan, 2001). Besides that, neuroimaging data have shown different patterns of activation in OB with BED vs OB without BED (Balodis et al., 2013).

Taken together, although some studies indicate differences between participants with obesity and healthy controls, others report no differences. As mentioned, one possibility could be the absence of screening for mental disorders, thus increasing the heterogeneity within the groups, and biasing the results. However, part of the results suggests an altered reactivity to monetary rewards in obesity.

3. Anorexia Nervosa, Obesity and Monetary Rewards

Obesity and AN present with completely different symptomatology. However, both have shown to include altered responses to rewards, both primary,

such as food, and non-primary, as money. Besides that, both conditions may be associated with eating disturbances, with participants with AN by definition presenting with hypophagic behaviors, whereas participants with obesity are more likely to experience hyperphagia. Investigating how responses to monetary rewards in general and in these population may help inform treatment of conditions involving eating disturbances.

Because eating is a distinctive behavior involving these conditions, and the metabolic state modulates responses to reward (most focus has been given to food as a reward), it may be interesting to investigate how reactivity to monetary rewards differ across feeding conditions. This will be further discussed in the next chapters.

EMPIRICAL RESEARCH

Given that the encoding of food as a reward is altered in participants with obesity and anorexia nervosa, that the metabolic state (i.e. fasted vs fed) modulates the value of food as a reward, and that the mechanisms involved in processing food as reward are also involved in other types of reward, including non-primary rewards, the objectives of the empirical part of this dissertation are as follows.

General aim: Investigate mood in response to winning/losing in each trial, general affect before and after the task, behavioral and biological responses to monetary reward during fasting and following a standard meal in healthy individuals, individuals with anorexia nervosa and individuals with obesity.

Aim Study 1: Investigate the effect of fasting on mood, affect and behavioral reactivity to monetary reward in healthy controls and participants with anorexia nervosa.

Hypotheses Study 1: we hypothesized more negative affect and less mood reactivity to winning or losing monetary rewards in anorexia nervosa compared to healthy controls. We expected less mood reactivity to losing higher rewards compared to controls, which would be stronger during fasting.

Aim Study 2: Investigate the effect of fasting on mood, affect and behavioral reactivity to monetary reward in participants with obesity without the presence of a mental disorder.

Hypotheses Study 2: We hypothesized higher negative affect in people with obesity in general, which would be stronger during fasting. We also expected money to improve affect in controls in both sessions (fasted and fed), and in individuals with obesity only following the standard meal. Because we measured responses following reward receipt, and because responses to increased food intake might be due to a

diminished reward sensitivity to other types of reward, we hypothesized diminished mood responsivity to monetary rewards in participants with obesity, independent of the session.

Aim Study 3: explore the association of mood, affect and behavioral reactivity to monetary reward with circulating levels of endocannabinoids in individuals with anorexia nervosa during the underweight phase and following weight-restoration treatment, both during fasting and following a standard meal.

Hypotheses Study 3: we expected higher levels of endocannabinoids during fasting in comparison to the fed conditions, which would be significantly higher in healthy controls than in individuals with anorexia nervosa. We hypothesized this difference would diminish following successful weight-restoration treatment. We also expected correlations between the levels of endocannabinoids and some form of response to monetary reward.

Methods

These studies were included within the framework of a study on gastrointestinal function following eating in participants with anorexia nervosa and obesity before and after weight-change treatment (Bluemel, et al., 2017), funded by the Swiss National Science Foundation (grant 320030/125333).

Ethical approval. All studies followed the Good Clinical Practice and the Declaration of Helsinki principles. The protocol was approved by the University of Zurich Ethics Commission (KEK-2009-0115/1) and registered on ClinicalTrials.gov (NCT00946816). All participants provided written informed consent.

Participants. Each of the following study describes the population with more details (exclusion and inclusion criteria as well), since it varied according to the study.

All recruitment was performed at the University Hospital Zurich. The individuals with anorexia nervosa were inpatients of the Eating Disorders Centre of the Clinic of Psychiatry and Psychotherapy. Individuals with obesity were recruited via the outpatient clinic of the Department of Endocrinology of the University Hospital Zurich. Healthy controls were recruited via public announcements. A more detailed description of the samples can be found in Tables 5, 8 and 11.

Procedure. Figure 4 indicates the procedure. Data collection started following an 8-hour fasting period. When participants arrived, blood was drawn and they performed the questionnaires and the Wheel of Fortune (Fig. 7), a computerized task developed to measure responses to reward (Ernst, et al., 2004). We ran exploratory analyses on the mood reactivity to different probabilities of winning/losing, since the task offered that possibility. Immediately after that, they were taken to the scanner room (related to Bluemel, et al., 2017), where they ate a standardized meal. Blood was drawn 120 and 240 minutes following to that. After 240 minutes, the participants had another standardized meal and performed the task one more time.

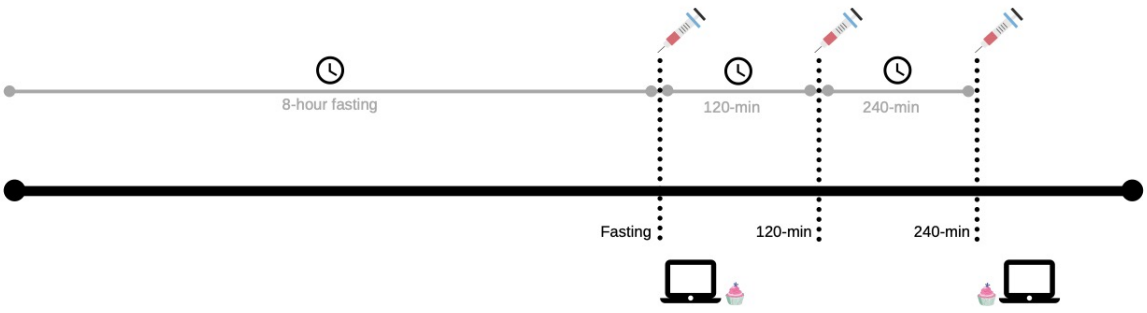

Figure 4. General procedure.

The next three chapters discuss the methodology applicable to each of the study in further details, including data analysis.

CHAPTER 3

FOOD VS MONEY? EFFECTS OF HUNGER ON MOOD AND BEHAVIORAL REACTIVITY TO REWARD IN ANOREXIA NERVOSA

This chapter is the accepted version of

Piccolo, M., Milos, G., Bluemel, S., Schumacher, S., Mueller-Pfeiffer, C., Fried, M., Ernst, M., & Martin-Soelch, C. (2019). Food vs money? Effects of hunger on mood and behavioral reactivity to reward in anorexia nervosa. *Appetite, 134*, 26-33. doi:10.1016/j.appet.2018.12.017

Abstract

Background: Previous studies using neuroimaging and behavioral measures reported altered reward processing in anorexia nervosa (AN). In addition, anhedonia states are frequently reported in AN, potentially due to the physiological stress produced by the permanent starvation. We investigated the effect of fasting and satiety on mood and time reactions to monetary rewards in AN patients and healthy controls. Methods: Twenty-four participants with acute AN (BMI 14.4 (11.9-15.5) Kg/m^2) and 17 age and gender matched healthy, normal weight subjects (HW) (BMI 21.8 (18.9-24.9) Kg/m^2) performed a reward task (the wheel of fortune) involving uncertain (50/50 probability of winning high and low rewards), safe and risky (30/70 and 10/90 probabilities) categories in fasted (after an 8-hour fasting period) and fed (after intake of a standardized meal) states. Data analysis was done with linear mixed models. Results: AN reacted slower than HW when maximum uncertainty (50/50) was involved. Positive mood in response to winning was higher when fasting especially for HW, while negative mood in response to not winning was higher in the fed state for both groups. Still, HW were more reactive than AN to not winning a highly predictable monetary reward (10/90 safe). Conclusion: The data on the reaction times indicate an impaired motor response to uncertainty in AN. Mood reactivity to winning a

monetary reward does not seem to be impaired in AN, however, our results suggest that negative mood in response to not winning is less adaptive in AN. Implications to clinical psychotherapy are discussed.

Keywords: Anorexia Nervosa; Reward; Fasting; Anhedonia; Mood; Affect.

1. INTRODUCTION

Anorexia Nervosa (AN) is an eating disorder, mainly affecting women, with a prevalence of approximately 1% (Mohler-Kuo, Schnyder, Dermota, Wei, & Milos, 2016). AN is the eating disorder with the highest mortality rate (Fichter & Quadflieg, 2016), and its pathophysiology remains mostly unclear. It is important to elucidate the mechanisms involved in the acquisition and maintenance of the disorder, especially those related to what is responsible for triggering disease-maintained behaviors.

Previous studies reported altered reward processing in AN at neural level, showing reduced striatal activation to natural and monetary rewards as well as reduced dopamine (DA) function (Barbato et al., 2006 Casiello, & Muscettola, 2006; Bergen et al., 2005; Davis & Woodside, 2002; Ehrlich et al., 2014; Piazza et al., 1993; Wagner et al., 2007). As it is well established that DA is involved in the processing of reward, a DA deficiency has been hypothesized in the etiology of AN (Berridge & Robinson, 2016; Martin-Soelch et al., 2011; Schultz, 2000). Furthermore, animal studies showed that DA-deficient rats ingest less food than the least necessary for survival (also one of the characteristic behaviors for AN) (Szczypka et al., 1999). Anhedonia, a lessened ability to experience pleasure from rewards, also greater among patients with

AN (Davis & Woodside, 2002), has also been connected to poor DA functioning (Willner, Daquila, Coventry, & Brain, 1995).

Tapper (2005) suggests the importance of controlling hunger for research involving feeding and eating behaviors. With regard to that, a recent study showed that fasting increases the reinforcing potential of food rewards, in particular for highly caloric ones in normal weight controls (Goldstone et al., 2009). This effect has not been tested in participants with current AN. However, several studies indicated that food reward processing is different in AN patients. For instance, Stoner, Fedoroff, Andersen, and Rolls (1996) reported that preferences for high-fat food is stronger in controls than in AN, both in the acute phase and after weight gain. Nonetheless, hunger was not controlled in their study. Many studies with AN are performed with women remitted from AN in order to avoid the confounding effects of malnutrition (Wagner et al., 2007; Wierenga et al., 2015), since research with food rewards showed similarities between acute and remitted patients (Stoner et al., 1996). However, that might not be completely true when monetary rewards are used. One recent study, for instance, has shown that responses to monetary reward were normalized after weight gain in patients remitted from the disorder (Steinglass, Decker, Figner, Casey, &

Walsh, 2014), therefore, studying patients in the acute phase may be essential for understanding specific responses to non-food rewards in the disorder.

Investigating monetary reward in AN patients is particularly relevant, because, on one hand, several studies indicated changes in the neural processing of monetary reward in AN patients; and, on the other hand, fasting resp. hunger was evidenced to influence responses to monetary reward (Briers et al., 2006). For instance, behavioral results of a functional Magnetic Resonance Imaging (fMRI) study showed a diminished sensibility to the feedback associated with monetary reward in recovered AN patients that could be associated with increased cognitive control when dealing with monetary rewards (Wagner et al., 2007). A study using a gambling task revealed that individuals with AN showed poorer decision-making performances to reward compared to controls, but not remitted AN (Tchanturia et al., 2007). More specifically, patients with AN insisted on choosing cards from decks which allowed them to win larger amounts of money (but more often losing them too), and did not shift, different than did controls and remitted patients, to decks that represented safer conditions, lower rewards, but the possibility of actually winning money (Tchanturia et al., 2007). Taken together, the findings suggest an impairment in the processing of reward, which might also lead to altered perceptions of hedonic mood in severe AN. Regarding the

effect of hunger on responses to money, one previous study reported that hunger increased the rewarding value of money in students, who were less willing to give it up while fasting (Briers et al., 2006). Yet, a recent study in women remitted from AN showed that hunger does not modulate responses to monetary reward in this group compared to healthy women (Wierenga et al., 2015), but, up to this date, no study has investigated its effect in acutely ill AN patients.

In summary, altered responses to monetary rewards were observed in patients with AN. Considering the occurrence of fasting in AN and its influence on responses to reward, it is relevant to investigate the effect of the feeding state on these responses in participants with AN. Therefore, the aim of this study was to investigate the effect of fasted and fed states on mood and behavioral reactivity to monetary rewards in acutely ill patients with AN. We hypothesized that AN would show more negative affect and less mood reactivity to winning and losing a monetary reward than healthy controls during fasting, and this group difference would be less strong during the fed state. Also, according to the results obtained by Tchanturia and colleagues (2007), we expected patients with AN to show less mood reactivity than controls to losing higher amounts of reward, as well as the group difference to be stronger during fasting.

2. METHODS

2.1. ETHICS

The study was carried out according to Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the University of Zurich Ethics Commission (KEK-ZH-No 2009-0115/1) and registered on ClinicalTrials.gov (NCT00946816). All participants provided written informed consent.

2.2. PARTICIPANTS

We recruited 24 women who met the DSM-IV (American Psychiatric Association, 2000) unit criteria for AN and had a BMI <17.5 kg/m2 from an inpatient psychotherapy unit for patients with severe eating disorders of the Psychiatric Department of the University Hospital to participate in this study. Concomitant collected data on gastric emptying and postprandial symptoms from these subjects was recently published (Bluemel et al., 2017). In brief, recruitment and data collection occurred within the first 2-4 weeks after admission to the rehabilitation, within the so called "orientation phase", a period to make patients familiar with the inpatient clinic setting, after stabilizing somatic and psychiatric symptoms following to admission, and before patients started to gain weight. They should try to eat regularly, although not with the intention of gaining weight. Normal weight age-matched healthy women

(HW), with BMI between 18.9 and 24.9 kg/m^2 (n=17) were recruited via public announcements. Detailed excluding criteria can be found in Bluemel et al. (2017).

2.3. PROCEDURE

All participants completed the Beck Depression Inventory (BDI), a 21-item self-report inventory used to assess levels of depression (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961 Mock, & Erbaugh, 1961; Hautzinger, Bailer, Worall, & Keller, 1994 & Keller, 1994), and the State-Trait-Anxiety Inventory (STAI), a self-assessment inventory of the presence and severity of symptoms and generalized propensity to anxiety (Laux, Glanzmann, Schaffner, & Spielberger, 1981 & Spielberger, 1981; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983 Vagg, & Jacobs, 1983). On the study day, all participants fasted for at least an 8-hour period. Details can be found in Bluemel et al. (Bluemel et al., 2017). They were not allowed to have any food or drink other than those made available for them during the study. During fasting, the participants were asked to complete the Positive and Negative Affect Schedule (PANAS, T1) (Watson, Clark, & Tellegen, 1988 1988), a 20-item self-reported measure of positive and negative affect, followed by the Wheel of Fortune (WoF) to measure reward-related responses (Ernst et al., 2004), and a second completion of the PANAS (T2). Four hours later, participants ingested a standardized muffin (430 kcal, 21% fat,

63% carbohydrate, 16% protein) (Bluemel et al., 2017), and this was followed by a second completion of PANAS – WoF – PANAS. The timing for the muffin ingestion was related to MRI measures of the digestive function. At each time point, hunger was measured using a well-validated procedure by asking the patients to score, in a scale ranging from 0 ("not full", "not hungry") their hunger (Bluemel et al., 2017).

2.4. *The Wheel of Fortune Task (WoF)*

The WoF (Ernst et al., 2004) consists of a two-choice, computerized task, involving monetary gratification. Participants were shown probability circles with two potential monetary rewards, in three different possibility settings (10/90; 30/70; and 50/50). Participants were instructed to win as much money as possible. In each setting, there was a circle showing the probability of winning the amount of money indicated in relation to the given probability. For example, under the 10/90 condition, the circle would show a 10% chance of winning an amount opposed to a 90% chance of winning another. The computer randomly selected the winning option. If the participant selected the same option, she won the chosen amount of money. Otherwise, no money was awarded. After each choice, a Visual Analogue Scale (VAS), ranging from 1 (not sure) to 5 (completely sure) measured how sure the participant had been of her answer. In addition, participants were asked to rate their mood according to their previous

performance (loss x win) also using an emoji VAS, ranging from 1 (the saddest x neutral) to 5 (neutral x the happiest). After a familiarization practice (50/50 wheels), participants performed a total of 62 trials during two runs of 31 trials (11 10/90 wheels; 8 30/70 wheels; and 12 50/50 wheels) each. Selecting the low-probability/high-reward option (the 10 and 30 parts of the 10/90 and 30/70 respectively) was considered a "risky" choice, while selecting the other parts (90 and 70) was considered a "safe" choice. The 50/50 wheels were included because they reflect decision-making during maximum uncertainty.

2.5. Data analysis and statistics

We used linear mixed model analyses and applied restricted maximum likelihood estimation to compare conditions. The following models were fitted for the cross-sectional comparison of AN patients and HW. For affect and hunger ratings before and after the task, full factorial models were fitted including group (AN; HW), session (fasted; fed), and time (before (T1) and after (T2) the task) as fixed factors. In all models, subjects were treated as a random effect. To best account for correlations between repeated measurements, all models were optimized by the covariance type for the repeated observations which produced the lowest Akaike's Information Criterion (AIC; (West, Welch, & Galech, 2007). Reaction times during positive mood

(after winning trials) and negative mood after (non-winning trials), full factorial models were fitted including: group (AN; HW), session (fasted; fed), and decision category (50/50 high reward, 50/50 low reward, 30/70 risky decision, 30/70 safe decision, 10/90 risky decision, 10/90 safe decision) as fixed factors, and subjects as random effects. A diagonal covariance structure was accommodated for the repeated observations of reaction time. For mood after trials, a first-order autoregressive moving average covariance structure was accommodated for the repeated observations. We further explored significant interactions by investigating post-hoc contrasts and pairwise comparisons by using Bonferroni corrections. Statistical analyses were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1. DEMOGRAPHICS AND DESCRIPTIVE STATISTICS

Demographic data and descriptions of the investigated study population are summarized in Table 5.

3.2. SELF-REPORTED HUNGER

We found significant main effects of group ($F_{(1, 31.6)} = 8.09$, $p < 0.01$), session ($F_{(1, 93.5)} = 97.53$, $p < 0.001$), and an interaction of group x session ($F_{(1, 93.5)} = 9.78$, $p < 0.01$)

for hunger. HW generally reported more hunger (M = 34.3, SE = 4.2) than AN (M = 18.8, SE = 3.5). Across groups, more hunger was reported in the fasted session (M = 42.0, SE = 3.6) than in the fed session (M = 11.1, SE = 2.6). The interaction 'group x session' showed that HW only reported more hunger than AN in the fasted session (HW: M = 54.6, SE = 5.6; AN: M = 29.3, SE = 4.7, $p < 0.001$). In the fed session, the group difference for hunger levels was not significant (HW: M = 13.9, SE = 3.9; AN: M = 8.2, SE = 3.3, $p > 0.5$). Results for hunger are shown in Figure 5A.

Table 5. Demographic and descriptive data of study population. Descriptive data are given as mean ± standard errors.

	HW	AN
# Participants	17	24
Age [years, mean]	23 (18-37)	23 (17-41)
BMI [kg/m2, mean][a]	21.8 (18.9-24.9)	14.4 (11.9-16.0)
BDI [a]	3.5 ± 2.0	26.0 ± 9.6
STAI (state) [a]	45.1 ± 7.6	62.6 ± 8.6
STAI (trait) [a]	45.0 ± 7.2	66.4 ± 10.1

Demographic data are given as mean (range); descriptive data are given as mean ± standard error.

[a] indicates a significant different distribution between groups (Kruskal-Wallis, all p values < 0.05).

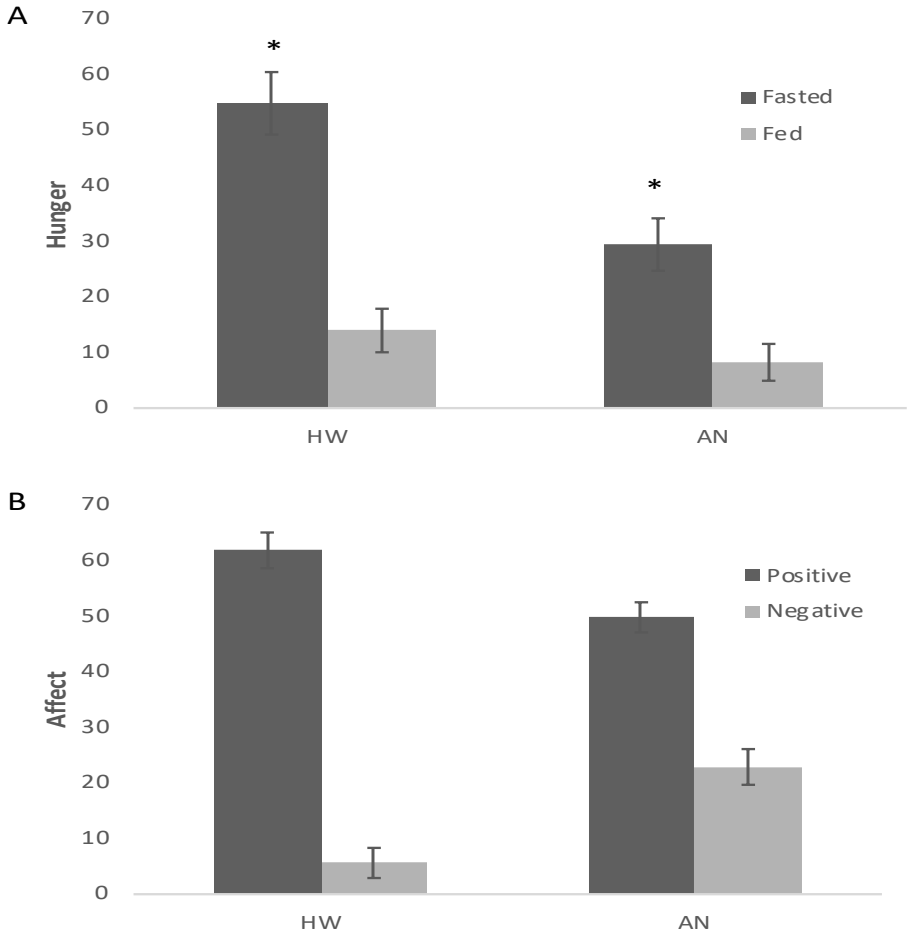

Figure 5. Means and standard error for self-reported hunger under fasted and fed (A) and self-reported affect across time (B) in healthy women (HW) and anorexia nervosa (AN). Both HW and AN reported stronger hunger mood under fasted compared to fed, while HW reported by AN.

3.3. *Self-reported Affect (PANAS)*

We found significant main effects of group ($F_{(1, 39.0)}$ = 8.05, p < 0.01) and time ($F_{(1, 57.4)}$ = 21.75, p < 0.001) on positive affect. With regard to the group effect, HW reported more positive emotions (M = 61.6, SE = 3.2) than AN (M = 49.6, SE = 2.7). For

time, participants reported more positive emotions after the task (M = 58.9, SE = 2.3) than before the task (M = 52.2, SE = 2.1) across groups. There was a significant main effect of group on negative emotions ($F_{(1, 40.6)} = 16.74$, $p < 0.001$), i.e., AN reported more negative affect (M = 22.8, SE = 2.7) than HW (M = 5.6, SE = 3.2). Means and standard errors for affect are shown in Figure 5B.

3.4. Responses to Reward

The results of the Wheel of Fortune will be presented regarding reaction time and mood following to winning and non-winning trials. Detailed means and standard errors are reported in Table 6 for reaction times and Table 7 for mood.

Reaction times. Significant main effects of session ($F_{(1, 2828.3)} = 190.81$, $p < 0.001$), decision category ($F_{(5, 2789.8)} = 6.16$, $p < 0.001$), and an interaction of group x decision category ($F_{(5, 2789.8)} = 5.29$, $p < 0.001$) were found. Across groups, decisions were faster in the fed than during the fasted state. HW reacted faster in 50/50 trials than AN patients, and no group differences were significant in the remaining decision categories.

Mood after winning trials. A main significant effect of decision category ($F_{(5, 2311.5)} = 109.01$, $p < 0.001$) as well as interactions of group x session ($F_{(1, 142.9)} = 4.73$, $p < 0.05$), group x decision category ($F_{(5, 2311.5)} = 9.25$, $p < 0.001$), and session x decision

category ($F_{(5, 2329.3)} = 3.41$, $p < 0.01$) was found for positive mood after winning trials. . All participants reported higher positive mood after winning trials with 50/50 high reward and winning trials with 10/90 risky compared to the remaining four decision categories. Less positive mood was reported after trials with low and safe rewards. Across decision categories, HW reported higher positive mood after winning trials in the fasted than in the fed session, while the difference between sessions was not significant for AN (Fig. 6A). The 'group x decision category' interaction (Fig. 7A) revealed that for HW positive mood was significantly higher after winning trials involving high (50/50) and risky rewards. For AN, higher positive mood after winning was also seen after the higher and riskier reward. After winning trials with 30/70 safe decisions as well as winning trials with 10/90 risky decisions, positive mood was stronger in the fasted state.

Mood after non-winning trials. Significant main effects of session ($F_{(1, 176.2)} = 7.02$, $p < 0.01$), decision category ($F_{(5, 2188.2)} = 14.95$, $p < 0.001$), and an interaction of group x decision category ($F_{(5, 2188.2)} = 2.90$, $p < 0.05$) were found for negative mood after non-winning trials. Across sessions, participants reported more negative mood after non-winning trials in the fed state. Also, higher negative mood was reported after non-winning trials with high and safe rewards (50/50 high reward; 10/90 safe

decisions). The 'group x decision category' revealed that in both groups, participants reported more negative mood after non-winning trials with 50/50 high reward compared to low as well as after non-winning trials with 30/70 risky decisions. For AN, these were the only significant comparisons between decision categories. HW additionally reported more negative mood after non-winning trials with that involved

high and safe rewards. Means and standard errors for negative mood after non-winning trials are presented in Figure 7B.

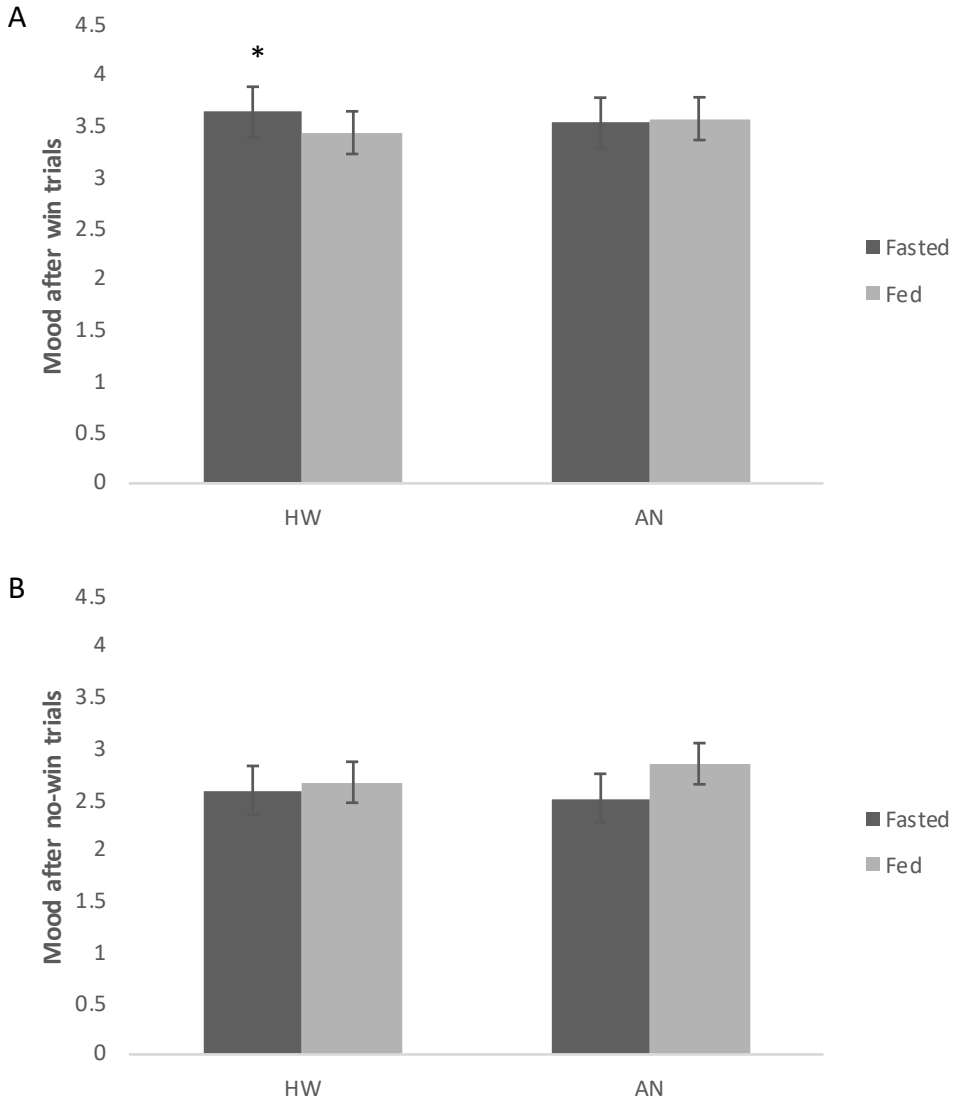

Figure 6. Positive mood after winning trials (A) and negative mood after non-winning trials (B) across sessions.

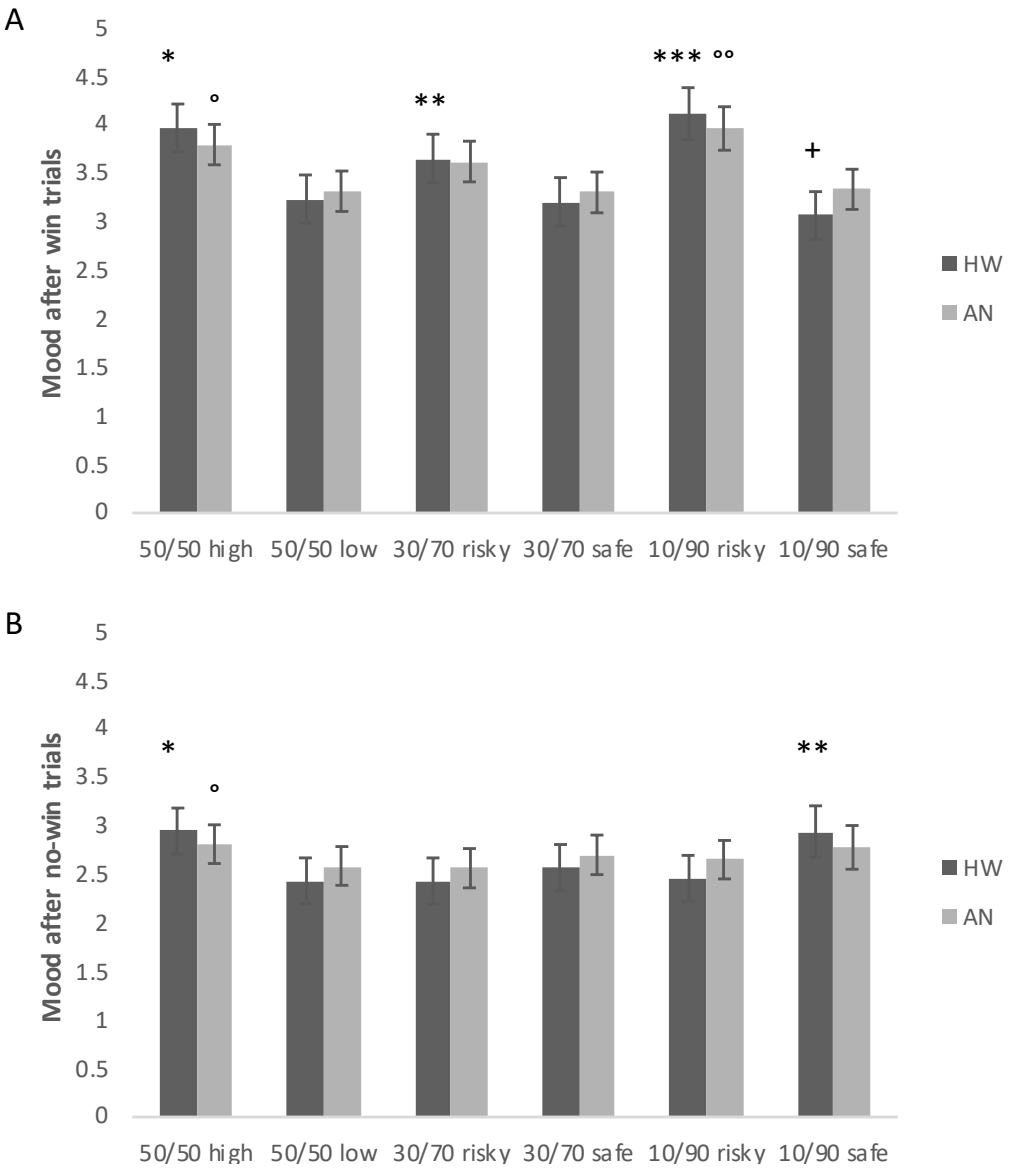

Figure 7. Positive mood after winning trials (A) and negative mood after non-winning trials (B) across groups and decision categories.

Table 6. Reaction time in response to reward in the Wheel of Fortune in Anorexia Nervosa (AN) and healthy women (HW) means and standard error (SE) during Fasting and Fed States.

	Session	Decision Category	AN (n=24), mean	±	SE	HW (n=19), mean	±	SE	Fixed Effects	F	P value
Reaction Time	Fasting	50/50 high	2970.30	±	182.23	2358.56	±	182.23	Group	1.395	0.245
		50/50 low	2709.07	±	187.07	2167.58	±	187.07	Session	190.810	0.000
		30/70 risky	2657.96	±	207.90	2466.20	±	207.90	Decision Category	6.163	0.000
		30/70 safe	2410.36	±	196.63	2449.77	±	196.63	Group * Session	1.754	0.186
		10/90 risky	2799.29	±	194.73	2566.44	±	194.73	Group * Decision Category	5.287	0.000
		10/90 safe	2503.03	±	182.92	2321.65	±	182.92	Session * Decision Category	1.518	0.181
	Fed	50/50 high	2295.35	±	167.75	2025.95	±	167.75	Group * Session * Decision Category	1.748	0.120
		50/50 low	2213.60	±	168.45	1658.71	±	168.45			
		30/70 risky	1933.53	±	176.60	2133.37	±	176.60			
		30/70 safe	2123.37	±	175.64	1973.28	±	175.64			
		10/90 risky	1943.25	±	175.93	1973.21	±	175.93			
		10/90 safe	1930.05	±	167.46	1586.61	±	167.46			
	Fasting	50/50 high	2632.83	±	138.01	2192.25	±	162.36			
	+ Fed	50/50 low	2461.34	±	137.34	1913.15	±	163.91			
		30/70 risky	2295.75	±	141.91	2299.79	±	172.41			
		30/70 safe	2266.86	±	145.27	2211.52	±	168.77			
		10/90 risky	2371.27	±	140.09	2269.82	±	168.72			
		10/90 safe	2216.54	±	138.71	1954.13	±	162.92			

Table 7. Mod ratings in response to reward in the Wheel of Fortune in Anorexia Nervosa (AN) and healthy women (HW) means and standard error (SE) during Fasting and Fed states.

	Session	Decision Category	AN (n=24), mean ± SE	HW (n=19), mean ± SE	Fixed Effects	F	P value
Positive Mood (to winning)	Fasting	50/50 high	3.68 ± 0.21	3.96 ± 0.25	Group	0.002	0.963
		50/50 low	3.25 ± 0.21	3.27 ± 0.25	Session	1.999	0.160
		30/70 risky	3.61 ± 0.21	3.76 ± 0.26	Decision Category	109.007	0.000
		30/70 safe	3.37 ± 0.22	3.30 ± 0.26	Group * Session	4.733	0.031
		10/90 risky	3.95 ± 0.24	4.42 ± 0.29	Group * Decision Category	9.248	0.000
		10/90 safe	3.33 ± 0.21	3.12 ± 0.25	Session * Decision Category	3.406	0.005
	Fed	50/50 high	3.91 ± 0.21	3.96 ± 0.25	Group * Session * Decision Category	0.816	0.538
		50/50 low	3.37 ± 0.21	3.20 ± 0.25			
		30/70 risky	3.63 ± 0.22	3.54 ± 0.26			
		30/70 safe	3.24 ± 0.22	3.10 ± 0.26			
		10/90 risky	3.97 ± 0.24	3.81 ± 0.29			
		10/90 safe	3.33 ± 0.21	3.01 ± 0.25			
	Fasting + Fed	50/50 high	3.79 ± 0.21	3.96 ± 0.25			
		50/50 low	3.31 ± 0.21	3.23 ± 0.25			
		30/70 risky	3.62 ± 0.21	3.65 ± 0.25			
		30/70 safe	3.30 ± 0.21	3.20 ± 0.25			
		10/90 risky	3.96 ± 0.22	4.11 ± 0.27			
		10/90 safe	3.33 ± 0.21	3.06 ± 0.25			
Negative Mood (to losing)	Fasting	50/50 high	2.61 ± 0.21	2.93 ± 0.25	Group	0.029	0.865
		50/50 low	2.43 ± 0.21	2.50 ± 0.25	Session	7.017	0.009
		30/70 risky	2.39 ± 0.21	2.35 ± 0.26	Decision Category	14.946	0.000
		30/70 safe	2.57 ± 0.22	2.59 ± 0.25	Group * Session	2.709	0.102
		10/90 risky	2.41 ± 0.21	2.45 ± 0.25	Group * Decision Category	2.897	0.013
		10/90 safe	2.67 ± 0.25	2.71 ± 0.30	Session * Decision Category	0.895	0.484
	Fed	50/50 high	3.01 ± 0.21	2.96 ± 0.25	Group * Session * Decision Category	1.067	0.377
		50/50 low	2.75 ± 0.21	2.36 ± 0.25			
		30/70 risky	2.73 ± 0.22	2.51 ± 0.25			
		30/70 safe	2.83 ± 0.22	2.55 ± 0.25			
		10/90 risky	2.89 ± 0.21	2.46 ± 0.25			
		10/90 safe	2.88 ± 0.26	3.17 ± 0.30			
	Fasting + Fed	50/50 high	2.81 ± 0.20	2.95 ± 0.24			
		50/50 low	2.59 ± 0.20	2.43 ± 0.24			
		30/70 risky	2.56 ± 0.20	2.43 ± 0.24			
		30/70 safe	2.70 ± 0.20	2.57 ± 0.24			
		10/90 risky	2.65 ± 0.20	2.46 ± 0.24			
		10/90 safe	2.78 ± 0.23	2.94 ± 0.26			

4. DISCUSSION

The aim of this study was to investigate behavioral and affective reactions to monetary reward in AN and healthy women during fed and fasted states. HW reported higher positive and lower negative affect than AN throughout the study. HW's reaction time was faster than AN's when maximum uncertainty was involved, regardless the session. HW reported higher significant positive mood in response to winning during fasting compared to a fed state, while the same difference was not observed in AN. Higher negative mood to not winning a highly predictable reward was only reported among HW, while no significant distinction was seen in AN.

Confirming our hypothesis, reward had a more significant effect on positive mood after winning in the *fasted* state, especially in healthy participants. This is in line with a recent questionnaire study that investigated the effect of hunger in healthy women and stated that their self-reported sense of reward increased proportionally to the fasting time (E. Watkins & Serpell, 2016). The lack of mood differences between the sessions in reward-related mood in participants with AN could be explained by a general blunted reactivity to reward that could be linked to anhedonia (Davis & Woodside, 2002). This is partly supported by our findings showing more negative and less positive affect in AN as measured by the PANAS, even though AN participants

also show an increase of positive affects measured after the WoF. One explanation for that could be related to a diminished self-awareness of hunger among in AN compared to controls, which may have led to a smaller effect of the session. Davis and Woodside (2002) suggest that the anhedonic state in AN could be connected to hunger and to the physiological stress caused by starvation. Interestingly, a model integrating reward, stress and hunger was proposed in the pathophysiology of AN. Eating less food would be initially rewarding and, therefore, maintained through conditioning learning (Bergh & Södersten, 1996; Södersten, Nergärdh, Bergh, Zandian, & Scheurink, 2008), which could indicate that participants with AN were more under control of the anhedonia than the sensation of hunger, diminishing the positive mood reactivity to winning a monetary reward. Moreover, food deprivation is said to increase the reinforcing effectiveness of food reward in healthy participants (Tapper, 2005). Our findings alongside those from Watkins and Serpell (2016) indicate the same is true regarding monetary reward for healthy women. The effect is not the same in AN, perhaps because anhedonia levels are usually high in the condition, independently of comorbidities like depression (Davis & Woodside, 2002).

We also found interactions of mood and winning/not-winning according to groups and decision categories. For both HW and AN, conditions involving the

highest and riskiest rewards evoked stronger increases of positive mood after winning. A reward dysfunction has been reported in AN mostly in relation to aspects proper to the disorder, such as food and body image, and might not be generalized to monetary reward (Keating, Tilbrook, Rossell, Enticott, & Fitzgerald, 2012), but this could be especially when only winning is investigated. In non-winning conditions, AN significantly showed diminished negative mood reactivity in response to more decision categories in comparison to HW, especially those involving the safest condition, i.e. the most predictable reward. Indeed, the most adaptive response to not winning a highly predictable reward would be negative mood (Dollard et al., 1939), as seen in HW, but this is not the case in AN. In line with that are the results obtained by Tchanturia and collaborators (2007), that showed participants with AN kept choosing cards that yielded higher amounts of money (they were sensitive to winning money), even though that also meant losing higher amounts of money. The latest did not control AN's responses, even though it did for recovered patients and healthy controls. Although this aspect has not yet been investigated, and our study specially aimed at behavioral and mood responses, it could be hypothesized that the DA dysfunction may lie behind the lower reactivity to not winning a predictable monetary reward in AN. Increased DA release was seen in animal models in response to unpredictable

rewards (Schultz, Dayan, & Montague, 1997), and DA is known to play an important role in motivational behaviors (Berridge & Kringelbach, 2008). Further investigation is necessary to clarify this hypothesis.

Regarding reaction times, shorter time was observed in HW under certain decision categories. Specifically, participants with AN had slower reaction times than HW when a maximum uncertainty decision-making attempt (50/50 conditions) was presented. This leads to the comprehension of an existing impairment connecting uncertainty and motor response in AN. In fact, research has shown motor impairments in patients with eating disorders, and specifically in AN (Green, Elliman, Wakeling, & Rogers, 1996; Hamsher, Halmi, & Benton, 1981), with patients reacting slower than controls in some neuropsychological tests. Our results add to the field suggesting this impairment is stronger in response to trials involving uncertainty. Furthermore, a wide range of research has shown intolerance of uncertainty (IU) among patients with eating disorders (Brown et al., 2017), stating, for instance, that uncertainty is strongly avoided (Sternheim, Konstantellou, Startup, & Schmidt, 2011) in AN. Intolerance to uncertainty (IU), as any broad concept, may have different definitions, depending on the context in which the term is used. Here, in the context of decision-making, IU refers to the propensity to prefer sure outcomes to probabilistic (uncertain) ones. Related to

this, research has established two different factors defining IU: 1) desire for predictability and 2) uncertainty paralysis (Berenbaum, Bredemeier, & Thompson, 2008). Accordingly, IU influences affective, cognitive and behavioral responses to uncertain situations (Heimberg, Turk, & Mennin, 2004). IU in anorexia nervosa and other eating disorders has been evidenced mostly by means of self-reported questionnaires (Brown et al., 2017), and not more directly via behavioral measures (Sternheim, Startup, & Schmidt, 2011). Still, compared to healthy controls, AN cared more about being successful in choices with uncertainty (Sternheim, Startup, et al., 2011). Recently, Shihata, McEvoy, Mullan, and Carleton (2016) suggested the use of probability-based decision-making tasks for evaluating this pattern in clinical populations. And, although we have not used the most commonly IU questionnaires, AN's slower reaction time to uncertain conditions could support this hypothesis. Nevertheless, these conditions did not evoke more negative mood in the patients than controls, maybe because the mood rating followed the outcome and was strictly connected to it (winning or losing). Another interpretation could be that IU, in the context of the task, might modulate more closely cognitive than affective responses.

This study is not without limitations. First, it is important to note that these results may not generalize to other types of reward. Second, our hunger scale assessed

only one dimension, on a Likert scale. Although it included a measure used in other studies (Marciani et al., 2010; Marciani et al., 2012), a more comprehensive psychological evaluation should be done, perhaps using a multidimensional scale. Also, a longer fasting time could also be considered. However, we used a standardized way to manipulate fasting (Bluemel et al., 2017; E. Watkins & Serpell, 2016), which ensured the avoidance of ethical concerns. Finally, one last point of attention would be the number of participants, which, although very well characterized, was not large. Larger samples could provide further knowledge regarding the intersection between decision-making, illness severity and intolerance to uncertainty.

Future research should focus on elaborating different forms of evaluating hunger in this population and also in larger groups. Something more objective, rather than based on the patients' self-description, especially for AN. That because when it comes to factors related to the disorder, patients' perception may be deceived (Milos et al., 2013). Also, hunger should be an aspect controlled in other trials within AN population, especially those considering food reward. Concerning monetary rewards, other validated tasks should be used in order to further analyze the effect of hunger on mood and affect and on reward itself, both behavioral and by means of functional neuroimaging, since Wagner and colleagues (2007) report reward-related cerebral

activation in AN in response to monetary reward, again, having hunger as an independent variable. Besides that, investigating how DA modulates reward predictability in AN may also bring considerable advances. Finally, the connection between IU and AN by using the WoF to evaluate behavioral responses and their correlation to the IU questionnaire scores should also be explored.

One of the most remarkable findings of this study was that mood reactivity to winning a monetary reward is higher under fasted compared to fed states, leading to the understanding that fasting alters the reinforcing potential of money in healthy women, but not in acutely ill AN patients. Mood reactivity to winning a monetary reward does not seem to be impaired in AN, however, negative mood in response to not winning is less adaptive in the disorder. Finally, behavioral responses to the WoF strengthen the hypothesis of IU in AN.

These findings could be important for therapeutic treatment targets in AN. For instance, interventions should include coping strategies, with the aim to enhance the patients' decision-making ability. In regard with the positive mood produced by monetary reward, the development and testing of an incentive program could be used to address eating, linking proper eating to winning points (avoiding the use of point loss as punishers, since there seems to be a weaker reactivity to losing money in AN).

Using behaviors that are more likely (such as winning points that could be exchanged for some form of reward) as potential reinforcers to those less likely (such as eating) to happen have proved efficient in enhancing clinical population's repertoire (Mitchell & Stoffelmayr, 1973; Winkler, 1970).

CHAPTER 4

EFFECTS OF HUNGER ON MOOD AND BEHAVIORAL REACTIVITY TO REWARD IN WOMEN WITH OBESITY – A PILOT STUDY

This chapter is the accepted version of

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Abstract

Worldwide, nearly 3 million people die every year because of being overweight or obese. Although obesity is a metabolic disease, behavioral aspects are important in its etiology. Hunger changes the rewarding potential of food in normal-weight controls. In obesity, impairments related to reward processing are present, but it is not clear whether these are due to mental disorders more common among this population. Therefore, in this pilot study, we aimed at investigating whether fasting influence mood reactivity to reward in people with obesity. Women with obesity (n=11, all mentally healthy) and normal weight controls (n=17) were compared on a computerized monetary reward task (the wheel of fortune), using self-reports of mood and affect (e.g., PANAS and mood evaluation during the task) as dependent variables. This task was done in 2 satiety conditions, during fasting and after eating. Partially, in line with our expectation of a reduced affect and mood reactivity to monetary reward in participants with obesity accentuated by fasting, our results indicated a significant within-group difference across time (before and after the task), with monetary gains significantly improving positive affect in healthy controls ($p>0.001$), but not in individuals with obesity ($p=0.32$). There were no significant between-group differences in positive affect before ($p = 0.328$) and after ($p = 0.70$) the task. In addition,

women with obesity, compared to controls, reported more negative affect in general ($p < 0.05$) and less mood reactivity during the task in response to risky gains ($p < 0.001$) than healthy controls. The latter was independent of the level of satiety. These preliminary results suggest an impairment in mood reactivity to monetary reward in women with obesity which is not connected to the fasting state. Increasing the reinforcing potential of rewards other than food in obesity may be one target of intervention in order to verify if that could reduce overeating.

Keywords: Obesity; Reward; Fasting; Mood; Affect.

1. INTRODUCTION

Obesity represents an increasing public health concern (World Health Organization, 2020). Worldwide, nearly 3 million people die every year from being overweight or obese. Its prevalence has nearly doubled in the past 30 years (World Health Organization, 2020) leading to what has been described as a global obesity epidemic (NCD Risk Factor Collaboration, 2016). Individuals with obesity often suffer from somatic comorbidities, including diabetes, cardiovascular diseases and cancer, among others (WHO, 2020). Due to possible social stigmatization and discrimination, depression and other psychological issues are more common among this population in comparison to healthy controls (Khaodhiar et al., 1999; Pattullo, Alkazaz, Sockalingam, & Heathcote, 2011). Although obesity is a metabolic disease, insights from behavioral research could provide new knowledge to the field.

Obesity has been related to perturbations in reward processing (Kenny, 2011). Enhanced activation patterns in cerebral areas related to reward processing were seen in response to palatable food in patients with obesity (OB) relative to normal-weight controls (HC) during both fasting and after food intake (Ho, Kennedy, & Dimitropoulos, 2012). In contrast, normal-weight individuals exhibited striatal activation in response to high-caloric food only during fasting (Goldstone et al., 2009).

Consistent with these findings, a recent questionnaire study reported that 'feelings of reward and achievement' (measured daily as women were fasting by a visual analogue scales) increased progressively with greater fasting time in normal-weight women (E. Watkins & Serpell, 2016). This suggests that food is rewarding for OB independently of the satiety state, while in HC, reward to highly palatable food is mostly present when fasting.

Hypersensitivity to food rewards has been proposed to underlie the increased food consumption, leading to excessive weight gain in obesity (Kenny, 2011). However, it remains unclear how other types of reward are processed in obesity. This question is important because overeating, one of the main causes for obesity (Wright & Aronne, 2012), might serve as a compensatory behavior for a diminished response to non-food rewards (Kenny, 2011). According to this model, individuals with obesity would evidence blunted responses to food and non-food rewards.

In that context, studies investigating reactions to non-food rewards in participants with obesity – most research works were conducted using monetary reward – showed inconsistent results (Tang, Chrzanowski-Smith, Hutchinson, Kee, & Hunter, 2018), and behavioral studies which compared behavioral responses to monetary reward in individuals with obesity compared to a control group have

yielded mixed results. For instance, Verdejo-Roman, Fornito, Soriano-Mas, Vilar-Lopez, & Verdejo-Garcia (2017) and Verdejo-Roman, Vilar-Lopez, Navas, Soriano-Mas, & Verdejo-Garcia (2017) reported that participants with obesity were willing to pay less money for plain food than controls. Meemken, Kube, Wickner, & Horstmann (2018), on the other hand, reported no significant difference between participants with obesity and controls using the same task in a different sample. In a study investigating reward-learning using monetary reward as positive reinforcer in a conditioning task, individuals with obesity did not differ from controls in learning. However, when food was used as positive reinforcer, women, and not men, with obesity showed impaired learning (Z. Zhang et al., 2014). In a replication study, Meemken et al. (2018) found however that individuals with obesity learned better than controls when food was used as an outcome. These studies suggest that different responses to monetary rewards can be found between healthy controls and individuals with obesity (Verdejo-Roman, Fornito, Soriano-Mas, Vilar-Lopez, & Verdejo-Garcia, 2017), but that these differences are dependent on the methodology and the samples used.

Studies investigating delay discounting in obesity participants compared to health controls also yield partially contradictory results. On one hand, Amlung et al. (2016) found significant results, with people with obesity tending to prefer smaller

short-term rewards to larger long-term ones. On the other hand, a recent review of the literature failed to evidence clear changes in delay discounting in obesity (Tang et al., 2018), showing that results on decision-making in relation to monetary reward is unconclusive in this population. These negative findings might be related to the different methodologies used and uneven study populations (Tang et al., 2018). Moreover, these inconsistent results might reflect the presence of psychiatric comorbidities, tested in some studies, but not others. Screening for binge eating disorder (BED) is important because it is a mental disorder with a prevalence of 30% among people with overweight problems and of 2-5% in the general population (de Zwaan, 2001), and research has shown differences in monetary reward processing between people with obesity with and without BED (Balodis et al., 2013).

Little has been investigated in terms of affect and mood reactivity to monetary rewards in obesity. Pasco, Williams, Jacka, Brennan, and Berk (2013) investigated positive (happiness, joy, interest, excitement, contentment, enthusiasm and alertness) and negative (distress, anger, disgust, fear and shame) affect in people with obesity, who showed increased negative affect in comparison with controls, but no difference in positive affect. Stoeckel et al. (2007), on the other hand, reported no differences in negative affect between groups. These differences could be related to the

fact that, while one study controlled for hunger (Stoeckel, et al., 2008), the other did not (Pasco, et al., 2013), and fasting states have shown to alter reward reactivity (Goldstone et al., 2009). It is however unclear whether different feeding states would affect mood responses to reward in participants with obesity; and in general, it is not clear whether mood in individuals with obesity is differentially altered in response to monetary reward. This is important as overeating could be explained as a compensatory mechanism for blunted responses to non-food rewards (Kenny, 2011). We focus here on affect associated to winning or not winning money on a computerized gamble task, and mood responses immediately following win and non-win trials, during fasting and after food intake in mental-disorder-free females with obesity in this pilot study.

It still remains unclear whether money is as rewarding in individuals with OB as in controls. In addition, fasting has been shown to influence mood reactions to rewards (Dimitropoulos, Tkach, Ho, & Kennedy, 2012; E. Watkins & Serpell, 2016), but it is not clear whether individuals with OB without associated mental disorders would show distinct responses to reward under fasting and satiety states. To extend the knowledge on monetary reward among this population, we used a computerized task to investigate the rewarding value of money in obesity by measuring affect and mood

reactivity to monetary rewards during fasting and after food intake in mental-disorder-free females with obesity in this pilot study. The main aim of this study was therefore to test whether there was a reduced mood resp. affect reactivity to monetary reward in participants with obesity (OB) compared to healthy controls (HC) and how this change in affect would be influenced by starving. Our first hypothesis postulated that winning money would improve positive affect and decrease negative affect, both measured with the Positive and Negative Affect Schedule (PANAS) Watson, Clark, & Tellegen, 1988 (Watson et al., 1988) in HC more than in OB participants during fasting, with no difference between groups after eating (H1). Secondly, we hypothesized that OB participants would show higher negative affect compared to healthy controls (HC) across all timepoints independently of the satiety state (H2). And thirdly, we expected higher negative affect during fasting compared to fed state in both groups, but stronger in OB participants (H3). Because our reward task used different probability conditions and because a previous study by our group indicated that reward-related mood changes can be influenced by probability conditions in participants with an eating disorder, i.e. anorexia (Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019; Piccolo, Milos, Bluemel, Schumacher, Mueller-Pfeiffer, et al., 2019), we performed exploratory analyses to test how self-reports of mood evaluation during

the task would be influenced by winning probabilities in OB compared to HC participants and whether the satiety states would affect the interaction between group and winning probabilities.

2. METHODS

2.1. ETHICS

The study was carried out according to Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the University of Zurich Ethics Commission (KEK-ZH-No 2009-0115/1). Written informed consent were provided by every participant.

2.2. PARTICIPANTS

Twenty-eight women participated in this study (17 healthy controls and 11 participants with OB). The including criteria for the group with obesity was a body mass index (BMI) higher than 30 kg/m2. For the control group, the BMI had to range between 18.5 and 24.9 kg/m2 (see Table 8). Excluding criteria were age <18 years and >60 years, and the presence of mental disorders. The Mini International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998), and the German version of the Structured Interview for Anorexic and Bulimic Disorders (Fichter, Herpertz, Quadflieg, & Herpertz-Dahlmann, 1998) were used to exclude patients with a history or presence of mental disorders from the obesity and control groups. The participants with obesity were recruited from the outpatient clinic of the Division of Endocrinology

of the University Hospital Zurich and via public announcements. Normal-weight healthy controls were recruited via public announcements. The results for the control group have been published elsewhere in comparison to a group of patients with anorexia nervosa (Piccolo et al., 2019). Data were simultaneously collected with this associated study. Since the recruitment for both studies was done at the same time, the same variables were controlled for both studies.

Table 8. Description of the study population.

	HC	OB	t	Sig.
Participants	17	11		
Age [years, mean]	23 ± 5.1	28 ± 8.4	-2.087	0.177
BMI [kg/m2, mean]	21.8 ± 1.7	34.8 ± 4.7	-10.369 [a]	0.000
Money won [Swiss Francs, CHF] [b]	79.65 ± 13.38	82.72 ± 16.26	-.547	.575

Descriptive data are given as mean ± standard deviation.

a indicates a significant different distribution between groups (Independent Samples T Test, p value < 0.001);

b CHF 1 is approximately equivalent to USD 1.

2.3. The Wheel of Fortune Task (WoF)

The WOF (Ernst et al., 2004) consists of a computerized task involving different winning probabilities. Each trial displays a wheel of fortune. The task comprises three different wheels, based on the probabilities and amounts of win/lose: two 50/50 wheels, one with high and the other with low monetary rewards; two 30/70 wheels, one safe and the other risky; and two 10/90 wheels, one safe and the other risky (Fig 1). Choosing the smallest probability (30 or 10) associated with the higher

amount was considered a risky choice, whilst choosing the bigger probability (70 or 90) in association with the higher amount, a safe one. When the option chosen by the participant was the same as the one that had been randomly chosen by the computer, the participants won the chosen amount of money. Otherwise, they did not win any money. After each win/lose feedback, participants were asked to rate their mood in accordance to the previous performance (loss, win) using an emoji visual analogue scale, ranging from 1 (neutral) to 5 (the saddest in the case of loss, or happiest in the case of winning) in response to the question: "how happy/sad do you feel at the moment?". After a 3-trial familiarization practice (50/50 wheels), participants performed a total of 62 trials during two runs of 31 trials (11 10/90 wheels; 8 30/70 wheels; and 12 50/50 wheels) each. The 50/50 wheels were included because they reflect decision-making during maximum uncertainty (Ernst et al., 2004; Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019; Piccolo, Milos, Bluemel, Schumacher, Mueller-Pfeiffer, et al., 2019). Prizes were as follows: for the 10/90 risky wheels, 10 represented a chance of winning CHF 4, and 90 a chance of winning CHF 1. For the 10/90 safe wheels, 10 represented a chance of winning CHF 1, while 90, CHF 4. For the 30/70 risky wheels, 30 represented the chance of getting CHF 1, while 70, CHF 0.50. For the 30/70 safe wheels, 30 represented the chance of winning CHF 0.50,

and 70, CHF 1. The 50/50 wheels included either a high reward (CHF 4), or a low reward (CHF 1) for both wheels. The experiment took between 20- and 30-min, and at the end of the experiment, the participants were given the amount of money won and were compensated for their transportation costs.

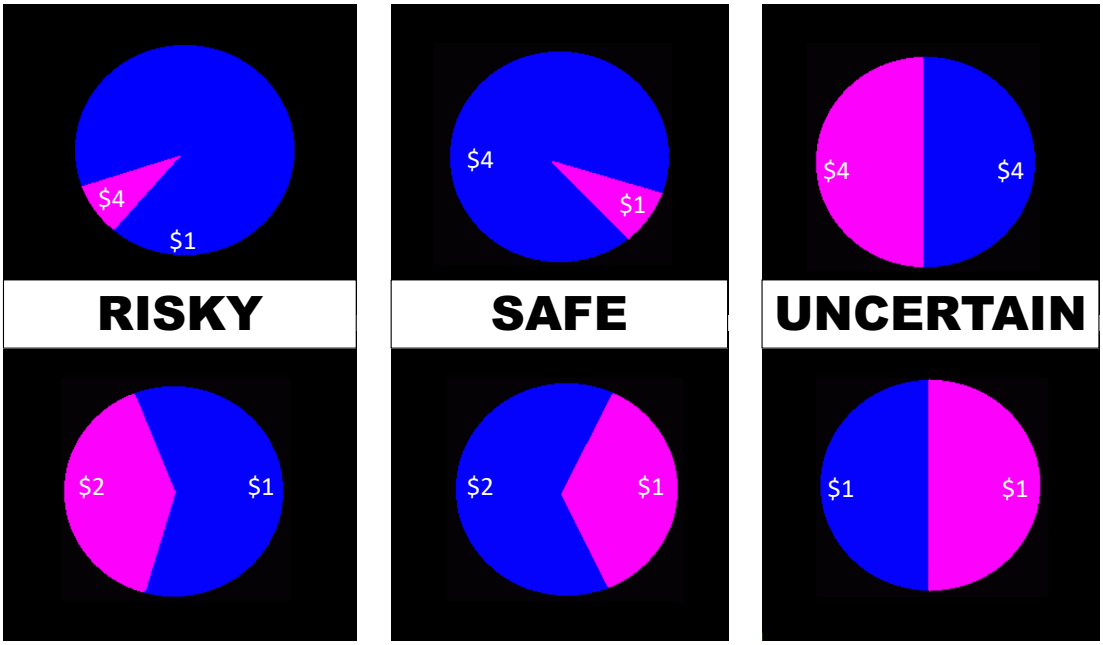

Figure 8. The wheel of fortune, a computerized task used to measure responses to monetary rewards under risky, safe and uncertain conditions.

2.4. Procedure

The data were collected during a gastric motility study published recently, where further details of the study procedures can be found (Bluemel et al., 2017). In brief, participants fasted for 8 hours prior to the experimentation. After that period, participants were asked to complete the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988), a 20-item self-reported measure of

positive (enthusiastic, interested, determined, excited, inspired, alert, active, strong, proud, and attentive) and negative affect (scared, afraid, upset, distressed, jittery, nervous, ashamed, guilty, irritable, and hostile) (T1); the WoF, to measure reward-related responses; followed by a second round of the PANAS (T2), i.e., affect was evaluated at two different timepoints: before (T1) and after (T2) the task. T1, WoF and T2 was considered a test round. Participants then ate a standardized meal (430 kcal, 21% fat, 63% carbohydrate, 16% protein) (Bluemel et al., 2017). After 4 hours (fed state), a second muffin was ingested, and a second test round was performed. The intervals were also related to Bluemel and collaborators' (2017) testing. At each state (fasting and fed), hunger was also measured by a previously used procedure (Farooqi et al., 2007). At each time point, participants were asked to rate their perceived hunger using visual analogue scale from *zero* (not hungry) to *one hundred* (very hungry).

2.5. DATA ANALYSIS AND STATISTICS

To increase statistical power, the general linear model, a type of multilevel analyses, was used to perform our data analyses. This type of analyses allows for the use of each trial rather than the use of general means and was used in previous publications of our group with the wheel of fortune task and with similar experimental settings (Milos et al., 2013; Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al.,

2019; Piccolo, Milos, Bluemel, Schumacher, Mueller-Pfeiffer, et al., 2019). All analyses were performed using IBM SPSS Statistics 25 (IBM Corp. Armonk, NY, USA).

We ran a total of 5 models. The first two models used the PANAS (Watson, Clark, & Tellegen, 1988) scores as dependent variable (one with positive affects and one with negative affects as dependent variables) and group (OB versus HC participants), time (before and after the task, i.e. T1 versus T2) and satiety state (fasting versus fed state) as independent variables (fixed factors) to test hypotheses H1 to H3. More specifically, we expected a significant threefold interaction between group x time x satiety state for both positive and negative affects to test H1. To test H2, we expected a significant main effect of group for the negative affects. And finally, to test H3, we expected a twofold interaction group x satiety state for negative affects. The third and fourth models used self-reported mood evaluations during the task as dependent variables and group, satiety state, and decision category (50/50 high, 50/50 low, 30/70 risky, 30/70 safe, 10/90 risky, and 10/90 safe) as independent variables (fixed factors). Model 3 was performed using only winning trials, and model 4 used only not winning trials. For these exploratory analyses, we were interested in the threefold interaction between group x satiety state x probability conditions. The last model (model 5) used self-report of hunger as dependent variable and satiety states as independent variable

(independent factor) to control whether the experimental induction of starving resp. satiety had worked. For all models, a heterogeneous first-order autoregressive covariance structure was used for the repeated observations (sessions and trial blocks). In all models, subjects were treated as a random effect. To best account for correlations between repeated measurements, all models were optimized by the covariance type for the repeated observations which produced the lowest Akaike's Information Criterion (West et al., 2007). Bonferroni corrections were applied to all comparisons, and the reported p values are those that survived to the corrections at a significance level of $p<0.05$ after Bonferroni corrections.

3. RESULTS

3.1. HYPOTHESIS 1

Positive and negative affect was measured by using the PANAS. There was a significant main effect of time (T1, T2) ($F(1, 35.2) = 14.69$, $p < 0.001$) and of an interaction between group x time ($F(1, 35.2) = 5.06$, $p < 0.05$) for positive affect (means (M) and standard errors (SE) in Fig 9). In general, more positive affect was reported after the task ($M = 60.4$, $SE = 2.8$) than before it ($M = 54.9$, $SE = 2.2$) by all participants. Partially confirming H1, the group x time interaction (Fig 9) revealed that HC's positive affect improved after winning money in the task (T1: $M = 57.2$, $SE = 2.7$; T2:

M = 65.9, SE = 3.5), while no improvement was seen for OB (T1: M = 52.7, SE = 3.5; T2: M = 55.0, SE = 4.4). No difference was seen between groups before ($p = 0.328$) or after ($p = 0.70$) the task. No difference between groups or state (fasting vs fed) was observed for positive affect (group $p = 0.133$; state $p = 0.741$).

3.2. Hypothesis 2

For negative affect, a main effect was seen for group ($F(1, 26.1) = 6.46$, $p < 0.05$). Confirming hypothesis 2, OB reported more negative affect (M = 12.7, SE = 2.2) than HC (M = 5.6, SE = 1.7) overall. There was no effect of group x time for negative affect ($F(1, 38.922) = 0.331$, $p = 0.568$).

3.3. Hypothesis 3

A main effect was also seen for state ($F(1, 28.2) = 6.64$, $p < 0.05$) in negative affect. Partially confirming hypothesis 3, more negative affect was reported during fasting (M = 10.1, SE = 1.4) compared to fed (M = 8.2, E = 1.5) across groups, The interaction group x state revealed a trend ($p = 0.072$), with HC but not OB showing a trend to diminished negative affect after eating (fasting: HC, M = 7.25, SE = 1.799; OB, M = 13.027, SE = 2.237; fed: HC, M = 3.997, SE = 1.829; OB, M = 12.511, SE = 2.299).

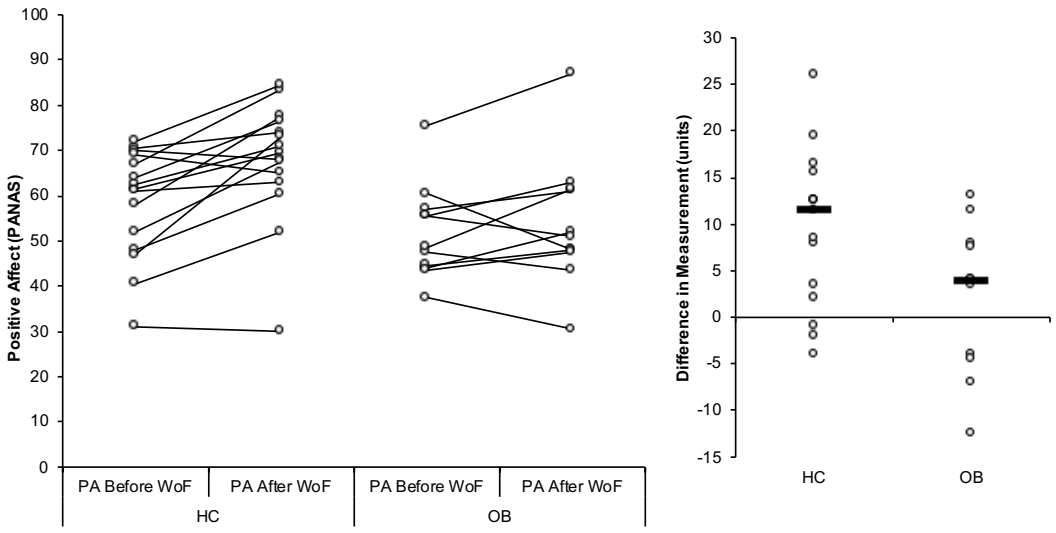

Figure 9. Affect ratings measured by the PANAS across groups and timepoints.

3.4. HYPOTHESIS 4

Responses to reward were measured on the Wheel of Fortune task (Piccolo et al., 2018). Exploratory analyses were run on mood in response to after win and no-win trials. Groups did not differ in amount of money won (Table 8).

3.4.1. MOOD AFTER WIN TRIALS.

Significant main effects of decision category ($F_{(5, 1532.9)} = 74.24$, $p < 0.001$) as well as interactions of group x decision category ($F_{(5, 1532.9)} = 4.19$, $p < 0.001$) and satiety state x decision category ($F_{(5, 1551.6)} = 2.28$, $p < 0.05$) were found for positive mood after win trials. Regardless of the satiety state, subjects reported higher positive mood after winning in the conditions that involved higher and riskier rewards in comparison to those involving lower and safer rewards. The analysis of group x decision category

interaction showed that when the highest and riskiest category was involved, HC reported more positive mood than OB after winning (Fig 3). Satiety state x decision category interaction analysis revealed that across groups, more positive mood was reported during fasting after 10/90 risky. Means and standard errors for positive mood after winning are shown in Table 9.

3.4.2. MOOD AFTER NO-WIN TRIALS

Significant main effects of decision category ($F(5, 1444.6) = 10.41$, $p < 0.001$) and group x decision category interaction ($F(5, 1444.6) = 2.34$, $p < 0.05$) were found for negative mood after no-win trials. Regardless of the satiety state, more negative mood was reported after not winning in the categories that involved high rewards of equal possibility and those involving the safest decisions in comparison to most categories. Group x decision category interaction analysis revealed that these differences were mostly among HC, with no significant difference found for OB. Means and standard deviation of responses to mood can be found in Table 9.

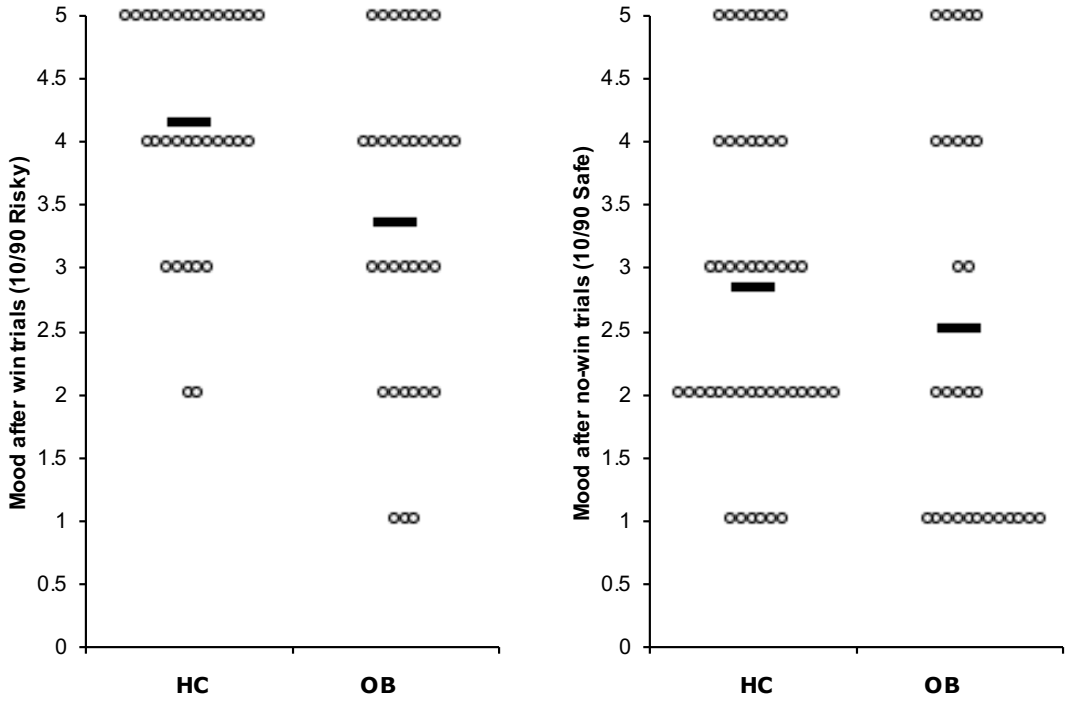

Figure 10. Mood ratings. Mood reactivity to winning and not winning in the 10/90 conditions.

3.5. SELF-REPORTED HUNGER

Hunger was assessed using a specific scale (Farooqi et al., 2007). Significant effects of state ($F(1, 68.8) = 37.62$, $p < 0.001$) as well as an interaction of group x state ($F(1, 68.8) = 7.03$, $p < 0.01$) were observed for hunger. Across groups, subjects reported more hunger in the fasted state (M = 48.3, SE = 5.0) than in the fed state (M = 19.9, SE = 4.2). The analysis of the interaction of group x state showed that both groups reported higher levels of hunger in the fasted state (HC: M = 54.6, SE = 6.3; OB: M = 42.0, SE = 7.8) compared to fed (HC: M = 13.9, SE = 5.2; OB: M = 25.8, SE = 6.7, p values

< 0.05). The difference between feeding states was significantly higher for HC (Δ = -40 points) in comparison to OB (Δ = -16 points).

4. DISCUSSION

Here we present preliminary data of the effect of feeding states on mood reactivity to monetary reward in individuals with obesity in comparison to normal-weight controls. According to our hypotheses, women with obesity showed higher negative affect than normal weight controls, and this was regardless of the satiety state. Although positive affect was improved after the task in general, this effect was stronger in healthy controls, suggesting a poorer value of monetary reward to improve affect among women with obesity. Further exploratory analysis on mood revealed less mood reactivity in obesity in response to the different winning/losing possibilities regardless of the satiety state. Finally, women with obesity showed less positive mood after winning the highest and riskiest reward, and, accordingly, less negative mood after losing the highest and safest reward than normal weight controls.

With regard to the changes in affect, reward had a significant effect of increasing positive affect mostly in healthy controls, independently of the satiety state. On the other hand, the task did not decrease negative affect. Recently, it has been reported that winning money at a monetary task increased positive affect in healthy

women (Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019). Our results add to the literature suggesting money is not as rewarding for people with obesity as it is for health controls. In line with that, neuroimaging data involving a monetary reward task revealed decreased brain response in reward anticipation among people with obesity (Balodis et al., 2013). Also, reaction times to low monetary rewards were slower in mental-disorder-free individuals with obesity, suggesting reduced reward sensitivity to money (Verdejo-Roman, Vilar-Lopez, et al., 2017). These findings are in accordance to what would be expected in relation to dopamine availability and striatal activation (Burgdorf & Panksepp, 2006) in the study population (Blum et al., 2006; Blum, Thanos, & Gold, 2014). Dopamine availability has been linked to positive affect (Burgdorf & Panksepp, 2006; Young & Nusslock, 2016), and is reported to be altered in individuals with obesity (Michaelides, Thanos, Volkow, & Wang, 2012). In line with blunted neural responses to reward, negative emotions and other psychological issues are more common among obese individuals relative to healthy controls (Khaodhiar et al., 1999). Dixon et al. (2003) reported that the risk of depression, for instance, is higher among obese women. Another interesting fact reported in their research was that this risk decreased with weight loss, strengthening the relation between weight and psychological factors.

Our exploratory analysis revealed that mood reactivity to winning/not winning monetary rewards was not as strong in women with obesity compared to lean women. In healthy women, positive mood was higher when winning a risky than predictable reward, while negative mood was stronger when incurring a predictable than risky loss, which is consistent with previous work (Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019). Healthy women showed stronger mood reactivity to winning unpredictable and losing predictable rewards (10/90 conditions), but this pattern was not seen in obesity. To the best of our knowledge, mood reactivity to winning or losing expected vs unexpected monetary rewards has not been previously examined in individuals with obesity. Our results suggest that individuals with obesity would show a diminished capacity for experiencing monetary rewards as positive. Accordingly, Kube et al. (2017) showed that, neural responses to a monetary task did not differentiate between loss or gain in individuals with obesity, suggesting that reward-related dysfunction also pertains to money and not only to food in this population.

This pilot study showed preliminary data demonstrating that food does not influence the perception of monetary reward in women with obesity, and that winning money does not improve affect in obesity while it does in normal-weight controls.

Although the sample size was small, and generalizability of these results might be limited, mixed-model analyses were used, which made it possible to maximize the degrees of freedom by using every trial performed by every subject, and not simply the means of all participants in a group, therefore increasing statistical power. However, small sample sizes may overestimate effects, therefore, future studies should replicate this procedure in larger samples, especially for the affect responses, which represent more an exploratory analysis. Another important issue is that visits were not counterbalanced, with fasting always preceding the fed states. Future studies should counterbalance visits, besides testing other types of reward (e.g. social) in the same population. Finally, these findings cannot be generalized to males, since exclusively women were tested.

To the best of our knowledge, this is the first investigation of mood reactivity in obesity after risky vs safe monetary reward winning, before and after food intake. Our results suggest that eating may not modulate mood reactivity to monetary rewards. Furthermore, our preliminary data suggests blunted mood reactivity to monetary reward in women with obesity, independently of satiety state. This might be linked to impaired DA reactivity. However, this remains to be elucidated. It is important to consider refining interventions/diet counseling and self-education of

patients with obesity in a way to increase the rewarding potential of types of reward other than food (e.g. social, monetary). If overeating may be a compensation for a diminished response to non-food rewards, increasing the reinforcing potential of other types of reward may help reduce this behavior in obesity.

Table 9. Mood ratings in response to reward in the Wheel of Fortune in women with obesity (OB) and healthy controls (3) during Fasting and Fed States.

	Session	Decision Category	OB (*n*=11), mean	±	SE	HC (*n*=17), mean	±	SE	Fixed Effects	F	p value
Positive Mood	Fasting	50/50 high	3.61	±	0.28	3.93	±	0.23	Group	0.935	0.342
(to winning)		50/50 low	3.05	±	0.28	3.24	±	0.23	Session	0.465	0.497
		30/70 risky	3.32	±	0.29	3.73	±	0.23	Decision Category	74.239	0.000
		30/70 safe	2.70	±	0.29	3.27	±	0.23	Group * Session	1.728	0.191
		10/90 risky	3.48	±	0.33	4.37	±	0.28	Group * Decision Category	4.187	0.001
		10/90 safe	2.95	±	0.28	3.09	±	0.22	Session * Decision Category	2.281	0.044
	Fed	50/50 high	3.72	±	0.28	4.00	±	0.23	Group * Session * Decision Category	1.527	0.178
		50/50 low	3.02	±	0.28	3.23	±	0.23			
		30/70 risky	3.56	±	0.29	3.58	±	0.23			
		30/70 safe	3.08	±	0.29	3.15	±	0.23			
		10/90 risky	2.94	±	0.35	3.85	±	0.28			

		10/90 safe	3.03	±	0.28	3.05	±	0.22			
	Fasting	50/50 high	3.66	±	0.27	3.96	±	0.22			
	+ Fed	50/50 low	3.03	±	0.27	3.24	±	0.22			
		30/70 risky	3.44	±	0.28	3.66	±	0.22			
		30/70 safe	2.89	±	0.28	3.21	±	0.22			
		10/90 risky	3.21	±	0.31	4.11	±	0.25			
		10/90 safe	2.99	±	0.27	3.07	±	0.22			
Negative Mood	Fasting	50/50 high	2.39	±	0.31	2.94	±	0.25	Group	0.418	0.524
(to losing)		50/50 low	2.24	±	0.31	2.53	±	0.25	Session	0.3624	0.548
		30/70 risky	2.24	±	0.32	2.36	±	0.26	Decision Category	10.414	0.000
		30/70 safe	2.22	±	0.32	2.60	±	0.26	Group * Session	0.052	0.820
		10/90 risky	2.27	±	0.31	2.46	±	0.25	Group * Decision Category	2.341	0.040
		10/90 safe	2.66	±	0.38	2.73	±	0.30	Session * Decision Category	0.648	0.663

								Group * Session * Decision		
Fed	50/50 high	2.56	±	0.32	2.93	±	0.25	Category	1.241	0.288
	50/50 low	2.29	±	0.32	2.34	±	0.25			
	30/70 risky	2.40	±	0.33	2.49	±	0.26			
	30/70 safe	2.52	±	0.33	2.52	±	0.26			
	10/90 risky	2.38	±	0.31	2.44	±	0.25			
	10/90 safe	2.37	±	0.38	3.13	±	0.30			
Fasting	50/50 high	2.48	±	0.30	2.93	±	0.24			
+ Fed	50/50 low	2.26	±	0.30	2.44	±	0.24			
	30/70 risky	2.32	±	0.30	2.43	±	0.24			
	30/70 safe	2.37	±	0.31	2.56	±	0.24			
	10/90 risky	2.32	±	0.30	2.45	±	0.24			
	10/90 safe	2.51	±	0.34	2.93	±	0.26			

CHAPTER 5

ALTERED CIRCULATING ENDOCANNABINOIDS IN ANOREXIA NERVOSA DURING ACUTE AND WEIGHT-RESTORED PHASES – A PILOT STUDY

This chapter is the last accepted version of

Piccolo, M., Claussen, M. C., Bluemel, S., Schumacher, S., Cronin, A., Fried, M., Goetze, O., Martin-Soelch, C., & , Milos, G. (2020). Altered circulating endocannabinoids in anorexia nervosa during acute and weight-restored phases: A pilot study. *European Eating Disorders Review, 28*, 46-54. doi: 10.1002/erv.2709

Abstract

Anorexia nervosa (AN) is an eating disorder characterized by a low food-intake and often exceeding exercise, leading to a particularly low body x weight proportion. Patients with AN usually report less hunger than healthy controls. Endogenous endocannabinoids (eCB), specifically the anandamide, have been associated with hunger, as a meal initiator, but research regarding AN and eCB and inconclusive. In this pilot study, we investigated plasma levels of eCB in inpatients with anorexia nervosa during fasting and after eating, both during the acute AN phase and after weight-recovery. After an 8-hour fasting period, blood sample was collected from all participants. After that, participants were given a muffin test meal. Blood samples for the investigation of endogenous endocannabinoids anandamide (N-arachidonoylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG) were then collected after 120-min and 240-min. Participants were only allowed to eat and drink what was offered them during the research. AN reported less hunger than controls during fasting and at the end of the experiment. Also, plasma levels of AEA were significantly smaller in AN in comparison to controls in all time points. No significant difference was found for 2-AG plasma levels. After recovery, no significant difference was found for eCB levels. These findings could be interpreted as an AEA deregulation in AN before and after food intake, which persists after weight recovery. These findings may have implications to the pharmacological treatment of AN and to relapse occurring in the disorder.

Keywords: Anorexia Nervosa; Fasting; Endocannabinoids; Appetite.

1. INTRODUCTION

Anorexia nervosa (AN) is an eating disorder characterized by a low food-intake leading to emaciation, an extremely low body x weight proportion (American Psychiatric Association, 2013), with considerable mortality (Keshaviah et al., 2014). Although the latest version of the Diagnostic Manual of Mental Disorders (DSM-5) does not include over-exercising as a criterium for the diagnostic of AN (American Psychiatric Association, 2013), it has been reported in up to 80% of participants in studies evaluating its prevalence, and contributes the low body-weight maintenance (Rizk et al., 2015).

Eating is controlled by many systems in humans (Enax & Weber, 2016; Lutter & Nestler, 2009; Saper et al., 2002), and several of these systems have been reported to be impaired in AN, like the reward system, homeostatic system (Keating et al., 2012; P. Monteleone et al., 2006; P. Monteleone et al., 2005), including the endocannabinoid (eCB) system (A. M. Monteleone et al., 2015; P. Monteleone et al., 2005; B. A. Watkins & Kim, 2014). In turn, the eCB system is involved in homeostatic control of several physiological functions, including food-intake and exergy expenditure, besides fat storage and body mass through mechanisms spread centrally and peripherally located (Marco et al., 2012). More specifically, two endocannabinoids are mostly involved in food-intake: the endogenous ligands anandamide (arachidonoylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG), as well as the receptors CB_1 and CB_2 (Cota et al., 2003).

Greater concentrations of eCB in the blood and in the brain were evidenced in several disorders, ranging from reproductive, metabolic and gastrointestinal to neurological and psychiatric disorders (Di Marzo, Bifulco, & De Petrocellis, 2004),

including eating disorders (P. Monteleone et al., 2005) and obesity (Gatta-Cherifi et al., 2012).

AEA and 2-AG were also found in greater concentration in brain regions in response to fasting in rats (Kirkham et al., 2002). Furthermore, fasting also increased AEA levels in peripheral regions (small intestine), and peripheral administration (intraperitoneal in rats) of AEA increased food intake (Gomez et al., 2002). These studies point to a consistent role of eCB in food-intake control. Taking that into consideration, a previous study assessed eCB plasma levels in outpatients with AN during fasting (P. Monteleone et al., 2005), and, unexpectedly found higher plasma AEA levels in AN in comparison to healthy controls. These contradictory results might be associated with a lack of control of diet type, as the study included outpatients. Besides that, intense exercising also promotes an increase in circulating levels of AEA (Heyman et al., 2012), and exercise-induced eCB levels were not possible to be controlled during this study.

A better understanding of the eCB mechanisms related to anorexia nervosa may yield important knowledge for the pathophysiology of the disorder, and might help establish whether alterations in the eCB system are consistent with the state or trait of the disease (A. M. Monteleone et al., 2015; P. Monteleone et al., 2005). For such, longitudinal studies must be carried out in order to verify if changes observed during the acute phase remain after recovery. In that sense, we investigated plasma levels of endogenous endocannabinoids (AEA and 2-AG) in inpatients with anorexia nervosa during fasting and after eating, both during the acute AN phase and after weight-restoration phase. In line with the general literature on AEA and fasting, we expected to find higher levels of AEA during fasting in both groups, with a decreased amount

in AN in comparison to HC both before and after eating. Furthermore, we expected to find no significant changes in 2-AG levels, in line with previous findings.

2. METHODS

2.1. ETHICS

The study was carried out according to Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University of Zurich (KEK-ZH-No 2009-0115/1) and registered at ClinicalTrials.gov (trial number NCT00946816). All participants were thoroughly informed on the procedures and provided written informed consent.

2.2. PARTICIPANTS

Participants in the AN (n = 15) group met the DMS-V criteria (American Psychiatric Association, 2013) for inclusion. They were recruited from an inpatient weight multimodal interdisciplinary therapeutic program of the Department of Consultation-Liaison-Psychiatry and Psychosomatic Medicine, at the University Hospital Zurich. The experiment consisted of two visits. V**isit 1** occurred between the second and fourth week after admission, during the first phase (orientation) of the therapy. This is the time when patients get used to the clinic setting and also have somatic and psychiatric symptoms stabilized. During the first phase, patients are not supposed to eat to gain weight, but are oriented to eat regularly. Goals of the therapeutic program are to reach a normalization of weight and eating behaviors. V**isit**

2 occurred after AN patients attained BMI >17.5 kg/m², when they are also close to a minimal normal weight (ANR, n = 10, since some of the patients did not gain weight after treatment), following a three-month-long multimodal treatment, which aimed at reducing pathological eating behaviors, improving body weight, and treating somatic as well as psychiatric comorbidities. The therapeutic goal of the unit is to reach BMI > 18.5 kg/m², but in the last phase of the treatment, inpatients are often under pressure to organize their life outside the unit. To reduce dropout, we chose a BMI close to the goal, but in a therapeutic phase in which is still enough time for the research visit. Furthermore, a 17.5 kg/m² BMI represents the threshold for diagnosing AN (American Psychiatric Association, 2013).

Normal-weight age-matched healthy controls (HC, *n* = 9) were recruited via public announcements. Detailed information on participants can be found on Table 10. Exclusion criteria included a history of drug or alcohol abuse, a history of gastrointestinal disorders (since it has been reported they can increase AEA concentrations (Di Marzo et al., 2004)), and the presence of mental disorders (other than AN for the AN group). Participants also underwent a gastro-interstinal Magnetic Resonance Imaging, and further exclusion criteria in relation to that can be found in Bluemel et al. (2017).

2.3. PROCEDURE

All procedures were done in the acute and then the weight-restored phase with AN patients. Participants completed the Beck Depression Inventory (BDI), an inventory used for assessing depression levels (Beck et al., 1961). Self-report of hunger was assessed every 15 minutes during the first two hours, and every 30 minutes during

the last two hours using a specific scale previously used (Marciani et al., 2010; Marciani et al., 2012).

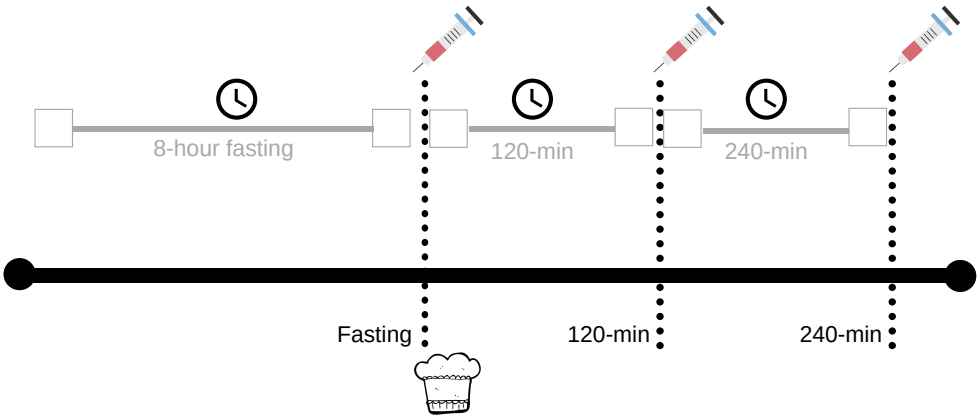

Figure 11. Study procedure.

2.4. *ENDOCANNABINOID MEASUREMENTS*

After an 8-hour fasting period, blood sample was collected from all participants. After that, participants were given a muffin test meal (430 kcal, 21% fat, 63% carbohydrate, 16% protein). Blood samples were then collected after 120-min and 240-min (Fig. 11). Participants were only allowed to eat and drink what was offered them during the research. Blood for the investigation of endogenous endocannabinoids anandamide (N-arachidonoylethanolamide, AEA) and 2-arachidonoylglycerol (2-AG) was drawn into pre-cooled 2 ml K-EDTA tubes (Greiner Bio-One VACUETTE®, St. Gallen, Switzerland). Immediately after the tube was filled, phenylmethanesulfonylfluoride (PMSF) solved in methanol was added to a final

concentration of 0.5 mM to avoid degradation of endocannabinoids. Tubes were centrifuged at 4°C with 1750 G for 10 minutes. Supernatants were collected into 2 ml tubes (Rotilabo®, Carl Roth AG, Arlesheim, Switzerland) and stored at -80°C until measurement. Plasma samples were thawed on ice and 500 µl of the samples were extracted with 2.5 volumes of toluene after adding internal standards (AEA-d8, 2-AG-d8 and 1AG-d5). Samples were mixed thoroughly and phases were separated by centrifugation for 5 min at 4 °C and 10.000 rpm. The organic layer was transferred to a new tube and the extraction was repeated. The combined organic phases were dried under a stream of nitrogen after addition of 10 µl of trapping solution (30% glycerol in methanol). The residues were reconstituted in 100 ul of 50% acetonitrile, pelleted for 10 min at 10.000 g, and transferred to glass vials for LC-MS/MS analysis. Because of the endogenous levels of endocannabinoids in biological matrices, calibration curves (concentrations ranging from 0.1 to 50 pmol/ml) were prepared in a substitute matrix (phosphate buffered saline containing 0.5 mg/ml bovine serum albumin, pH 7.4) to test for linearity and extraction efficiencies.

LC-MS/MS analyses. The sample separation was performed on a Phenomenex Gemini-NX-C18 reverse phase column (2.3 x 150 mm, 5 µm pore size) with a corresponding opti-gard pre-column on an Agilent 1100 liquid chromatography

system. The mobile phase consisted of (A) 4 mM ammonium acetate and (B) 95% methanol, 5% acetonitrile containing 4 mM ammonium acetate at a flow rate of 300 µl/min using an injection volume of 60 µl. An isocratic flow of 87% B was held for 11 min. The HPLC system was coupled to a 4000 QTRAP hybrid triple quadrupole linear ion trap mass spectrometer (Applied Biosystems) equipped with a TurboV source and electrospray (ESI) interface. Analytes were recorded using multiple reaction monitoring (-MRM) in negative mode using the following source specific parameters: IS -4500V, TEM 450°C, curtain gas (CUR = 30), nebulizer gas (GS1 = 50), heater gas (GS2 = 70) and collision gas (CAD = 10). The compound specific parameters for the different substrates were determined by direct infusion of standard solutions (100-300 nmol/ml) in acetonitril at a flow rate of 10 µl/min using the quantitative optimization function of Analyst software 1.5.2. LOQ for AEA and 2-AG in plasma were estimated to 0.2 and 0.1 pmol/ml, respectively. Extraction efficiencies for AEA and 2-AG were on average 60%.

Acyl migration. In contrast to AEA, 2-AG undergoes acyl migration to its regioisomer 1-AG under acidic conditions. Certain organic solvents used for the extraction from biological matrices further facilitate this process. While 2-AG is almost completely converted to 1-AG in ethanol, a conversion to 1-AG in toluene is negligible

(2011, Zoerner et.al). 2-AG and 1-AG (eluting approximately 0.5 min after 2-AG) were separated under chromatographic conditions, and samples contained on average 5% 1-AG.

2.5. DATA ANALYSES AND STATISTICS

Statistical analyses were performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA). Full factorial models were fitted for 2AG and AEA including group (AN; HC) and time (fasting; 120 min after meal; 240 min after meal) as fixed factors. A first-order ante-dependence covariance structure was accommodated for the repeated observations. For the longitudinal analyses, full factorial models were fitted including the disorder phase (acute and weight restored) and time (fasting, 120-min after meal, 240-min after meal) as fixed factors. A first-order factor analytic covariance structure was accommodated for the repeated observations. In all models, subject was specified as a random factor. Bonferroni-corrected pairwise comparisons of the estimated marginal means were used as post-hoc tests. Finally, the psychological measures were correlated with the eCB measures during fasting.

3. RESULTS

3.1. SELF-REPORT OF HUNGER

We found significant effect of group x time interaction ($F_{(1, 383.0)}$ = 2.254, p < 0.05). HC reported more hunger than AN during fasting and 240-min after eating. There was no significant difference for other time points (Fig.12).

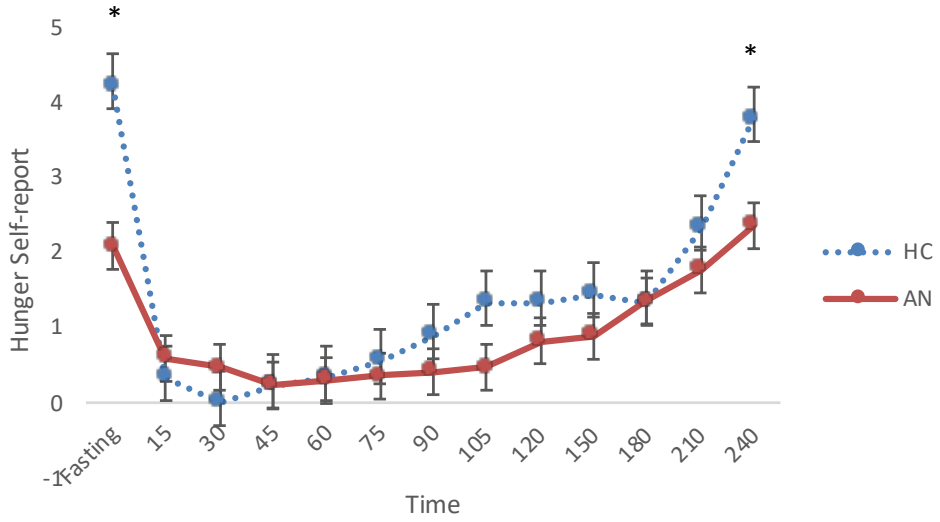

Figure 12. Self-report of hunger in healthy controls (HC) and patients with anorexia nervosa (AN).
Endocannabinoid measurements

3.1.1.1. Acute phase of AN

Anandamide (AEA). There were main effects of group ($F_{(1, 22.1)}$ = 29.11, p < 0.001), time ($F_{(2, 22.3)}$ = 47.81, p < 0.001) as well as an interaction of group x time ($F_{(2, 22.3)}$ = 5.46, p = 0.012). HC showed higher concentrations of AEA (M = 5.830, SE = 0.436) than AN (M = 2.854, SE = 0.338) (Fig. 14a). Across groups, concentrations of AEA

were higher in the fasting condition (M = 7.281, SE = 0.593) than 120 min (M = 3.071, SE = 0.178, $p < 0.001$) and 240 min (M = 2.674, SE = 0.213, $p < 0.001$) after the meal. The group x time interaction revealed that, although HC showed higher concentrations of AEA at all time points (HC: fasting M = 9.9, SE = 0.9, 120-min M = 4.0, 0.3, 240-min M = 3.6, SE = 0.3; AN: fasting M = 4.7, SE = 0.7, 120-min M = 2.2, SE 0.2, 240-min M = 1.7, SE = 0.3), the difference between groups was significantly stronger in the fasting condition ($\Delta = 5.180$, $p < 0.001$) than 120 min ($\Delta = 1.801$, $p < 0.001$) or 240 min after meal ($\Delta = 1.948$, $p < 0.001$) (Fig. 13a).

2-arachidonoylglycerol (2-AG). No main or interactive effects of group and time were found for 2AG. Means and standard errors can be seen in Figure 13b, 13d.

Depression and eCB. Depression scores at BDI were negatively correlated to plasma levels of AEA ($r = -.62$, $p < 0.001$) and positively correlated to 2-AG ($r = .639$, $p < 0.001$) during fasting.

3.1.1.2. Comparison of eCB between the acute and weight-restored phases

Anandamide (AEA). We found a significant main effect of time ($F_{(2, 8.9)} = 43.67$, $p < 0.001$), but no main effect of disorder phase was found ($p = 0.75$) Figure 13c. Across disorder phases, concentrations of AEA were higher in the fasting condition (M =

4.604, SE = 0.452) than 120 min (M = 2.194, SE = 0.218, $p < 0.001$) and 240 min (M = 1.555, SE = 0.160, $p = 0.002$) after meal.

2-arachidonoylglycerol (2-AG). No significant main effects or interactions were found for 2-AG (Fig. 13d, Table 11).

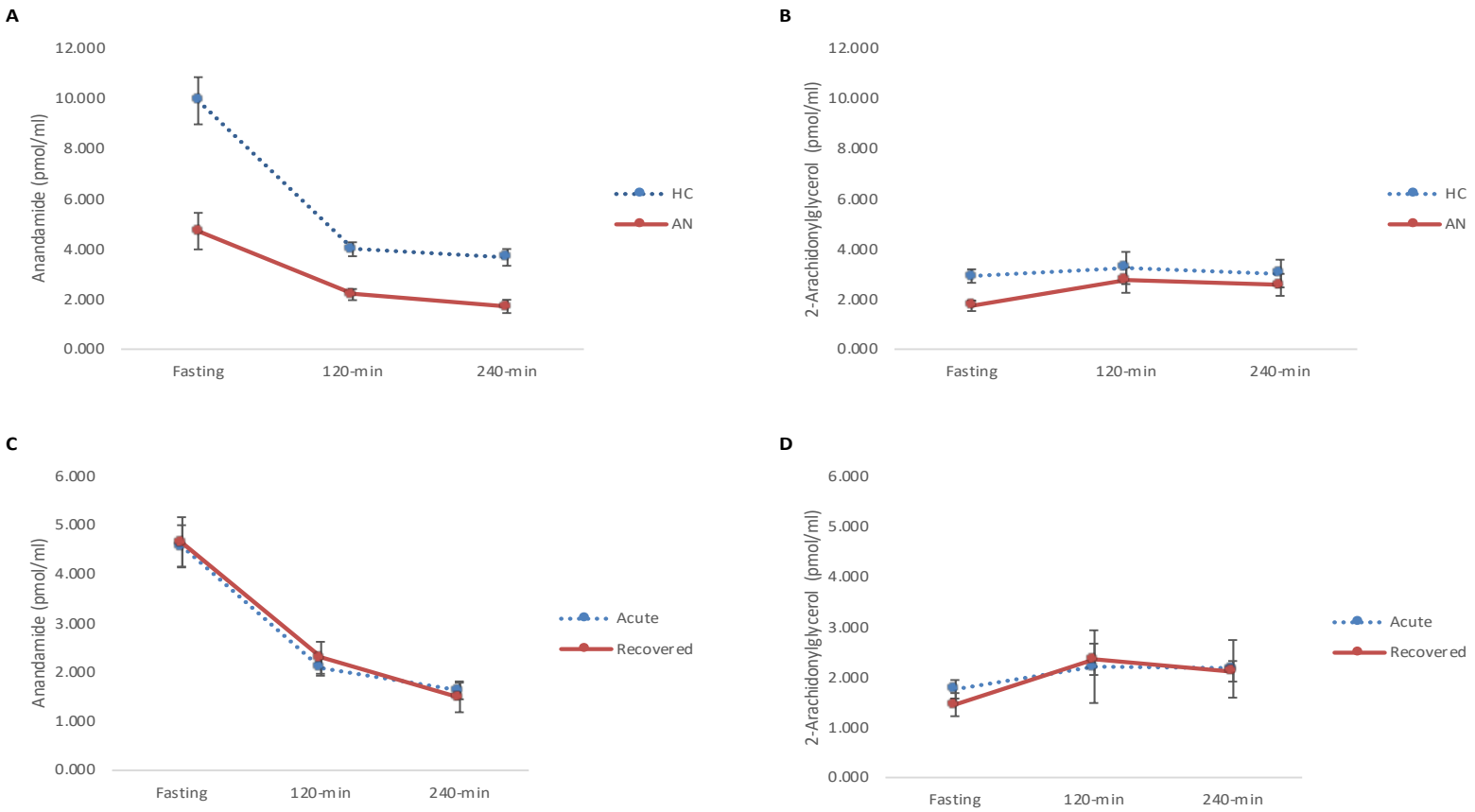

Figure 13. Circulating endocannabinoids across time points (Fasting, 120-min and 240-min after eating a standard meal).

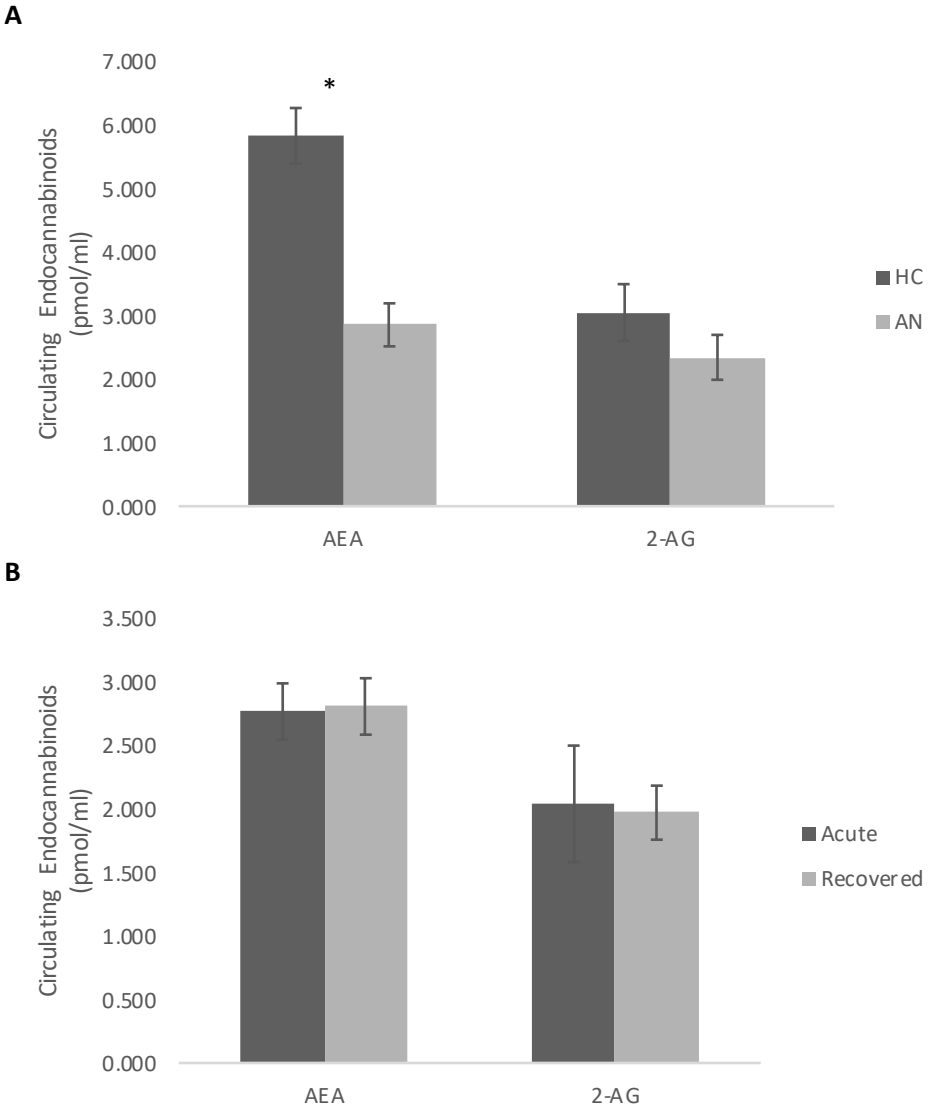

Figure 14. Total circulating levels of endocannabinoids across groups and anorexia nervosa phase.

4. DISCUSSION

We investigated plasma levels of endogenous endocannabinoids in patients with anorexia nervosa during fasting and after eating, in acute and weight-restored phases. To our best knowledge, this is the first study carried out with inpatients with

acute AN and weight-restored patients. Higher plasma levels of anandamide were found in healthy controls in comparison to patients with anorexia nervosa. Also, higher concentrations were found during fasting in comparison to after 120 and 240 minutes following a standard meal in both groups, with stronger effect during fasting. These results were specific for AEA, as we did find significant results for 2-AG. Finally, we found no significant difference in eCB levels between the acute and weight-restored phases.

Lower plasma levels of AEA in AN in comparison to HC are in line with our hypothesis and compatible to the hunger self-report. This is in line with previous studies that have reported AEA as a physiological meal initiator (Gatta-Cherifi et al., 2012). In their study, Gatta-Cherifi et al. (2012) showed increased plasma levels of AEA during fasting in healthy controls and people with obesity, with only healthy controls' AEA decreasing after eating. They also did not find significant change in 2-AG levels. Given the fact that hunger levels are decreased in AN in comparison to controls (Bluemel et al., 2017; Piccolo, Milos, Bluemel, Schumacher, Muller-Pfeiffer, et al., 2019) and also here, and AEA increases food-intake (Gomez et al., 2002), it is possible to infer that low food intake in AN may be due to a deregulation in the eCB system, more specifically, the AEA. Furthermore, cannabis-based treatments have shown to increase

food-intake of highly palatable food (Foltin, Fischman, & Byrne, 1988), and patients with AN show lower palatability rating in comparison to controls (Keating et al., 2012).

When examining eCB changes across phases of the disorder, our results showed no significant changes in circulating eCB levels across conditions (acute vs weight-restored). For AN patients, the failure of food intake is rewarding, this symptoms are often present during all in-patients therapy, and frequently still present at the end of the treatment (Zink & Weinberger, 2010).

Interesting AEA do not reach with the normalization of weight the values of the control group. This could indicate that an eCB deregulation may consist of a trait, and not simply a state of AN. One possible explanation could be related to exaggerate exercising in the disorder. Over-exercising could represent a compensatory behavior in an attempt to regulate AEA levels, since exercising increases circulating AEA levels, as previously mentioned (Heyman et al., 2012). A recent clinical case report showed a significant reduction in the urge to engage in physical activity in a male patient with AN treated with an eCB agonist, without major side effects (Graap, Erim, & Paslakis, 2018), pointing to the direction that overexercising could be a compensatory response to a diminished availability of eCB. In that sense, Kron, Katz, Gorzynski, and Weiner (1978) show, for instance, that intense exercising remains present even after recovery

in people with a history of AN. These findings could also be related to eating regulation processes and might explain the high relapse rates (Carter, Mercer-Lynn, et al., 2012). Since no change occurs in eCB circulating levels, these patients would continue with a decreased appetite in comparison to healthy controls, leading to a reduced food intake, which would contribute to the below-average body weight (Mayer, Schebendach, Bodell, Shingleton, & Walsh, 2012).

Depression levels were negatively correlated to AEA. In line with that, a recent study on rats showed that low doses of AEA were successful in reversing depression-like behaviors (de Morais et al., 2016). In line with that is the positive correlation found between 2-AG levels and the BDI scores. La Porta et al. (2015) reported a positive correlation between 2-AG and depression scores in pain patients. The altered levels of AEA could explain the high rates of comorbidity between AN and depressive disorders. It has been reported that up to 75% of the individuals with an eating disorder may experience depression (2006).

This study is not without limitations. First, our sample sizes were small. Larger studies should be carried out in order to further strengthen these findings. Second, we did not measure other forms of eCB concentrations (such as in brain regions involved in the motivation to eat). These data could provide better

understanding between the relationship of AEA and appetite control. Also, future research should focus on establishing the relationship between AEA levels and intensity of exercise. Moreover, it would be interesting to see AEA levels in longitudinal studies evaluating larger periods after the recovery to establish how far these traits can go, and measure to what extent relapse and the eCB system are related.

In conclusion, our findings show an AEA deregulation in AN before and after food intake, which persists after weight restoration. These findings may have implications to the pharmacological treatment of AN and to relapse occurring in the disorder. Cannabinoid treatments have significantly improved appetite in several disorders (Beal et al., 1995; Nelson, Walsh, Deeter, & Sheehan, 1994), including AN (Badowski & Yanful, 2018). A recent review on the use of Dronabinol, a synthetic form of Δ-9-tetrahydrocannabinol, an exocannabinoid, concluded that this treatment could be beneficial for patients with AN and other conditions involving low food-intake. Taken together, these findings should foment the development and larger clinical trials involving eCB agonists for the treatment of AN and other appetite-related disorders.

Table 10. Description of study population. Body mass index, the Beck Depression Inventory (BDI) scores, and the State-Trait Anxiety Inventory (STAI) scores for healthy controls (HC) patients with anorexia nervosa during the acute phase (AN), and weight-restored patients at the end of treatment (ANR).

	HC (*n* = 9)	**AN** (*n* = 15)	**ANR** (*n* = 10)
Age [years, mean]	20	22	22
BMI [kg/m2, mean][a]	21.8	14.4	17.9
BDI [a]	4.4 ± 0.89	27.0 ± 2.32	13.2 ± 8.5
STAI (state) [a]	32.8 ±2.1	50.5 ± 2.6	-
STAI (trait) [a]	31.5 ± 2.3	54.2 ± 3.3	46.0 ± 15.8

Demographic data are given as mean; descriptive data are given as mean ± standard error.
[a] indicates a significant different distribution between groups (ANOVA, all p values < 0.05).

Table 11. Means and standard errors for plasma levels of endocannabinoids (pmol/ml) in healthy controls (Pattullo et al.), patients with anorexia nervosa during the acute phase (AN), and weight-restored patients at the end of treatment (ANR).

Endocannabinoids (eCB)	AN (n=15), mean	±	SE	ANR (n=10), mean	±	SE	HW (n=9), mean	±	SE
Anandemide	2.85	±	0.34	2.81	±	0.22	5.83	±	0.44
(AEA) *pmol/ml*		±			±			±	
Fasting	4.69	±	0.73	4.64	±	0.51	9.87	±	0.94
120-min	2.17	±	0.22	2.29	±	0.33	3.97	±	0.28
240-min	1.70	±	0.26	1.48	±	0.30	3.65	±	0.33
2-Arachidonoylglycerol	2.34	±	0.35	1.97	±	0.21	3.05	±	0.45
(2-AG) *pmol/ml*		±			±			±	
Fasting	1.72	±	0.21	1.45	±	0.23	2.91	±	0.27
120-min	2.75	±	0.51	2.35	±	0.31	3.23	±	0.64

240-min	2.56	±	0.44	2.11	±	0.20	3.01	±	0.55

5. ADDITIONAL ANALYSES

5.1. WHEEL OF FORTUNE AND CIRCULATING ECB CORRELATION

To evaluate whether circulating levels of endocannabinoids are linked to the mood responses to monetary reward, we performed a correlation between the performance on the wheel of fortune (see Chapter 3 for description) and eCB, in healthy controls and AN before and after treatment. No correlation was found between the responses to the task and the circulating levels of eCB. The results can be found in Table 12.

Table 12. Correlation between mood ratings to winning and not winning under different categories of the wheel of fortune for patients with anorexia nervosa and healthy controls.

		Win 50/50	Win Risky	Win Safe	No Win 50/50	No Win Risky	No Win Safe
Anorexia Nervosa							
2-AG	*Pearson Correlation*	-0.22	-0.187	-0.292	-0.16	-0.179	-0.241
	Sig.	0.302	0.418	0.166	0.456	0.415	0.256
	N	24	21	24	24	23	24
AEA	*Pearson Correlation*	-0.21	-0.058	-0.251	-0.338	-0.261	-0.349
	Sig.	0.325	0.802	0.236	0.106	0.229	0.094
	N	24	21	24	24	23	24
Healthy Controls							
2-AG	*Pearson Correlation*	-0.318	-0.355	-0.613	0.234	0.149	0.115
	Sig.	0.404	0.489	0.079	0.545	0.725	0.768
	N	9	6	9	9	8	9
AEA	*Pearson Correlation*	-0.216	0.439	-0.189	-0.225	-0.078	-0.227
	Sig.	0.577	0.384	0.626	0.561	0.854	0.556
	N	9	6	9	9	8	9

CONCLUSION

This work investigated behavioral, affect, mood and biological responses to monetary reward in relation to fasted and fed states in healthy controls, individuals with anorexia nervosa and individuals with obesity. Our results suggest that some responses to monetary reward are modulated by the metabolic state of the individuals, while others not.

Our results suggest that negative affect (measured with PANAS; Watson, Clark, & Tellegen, 1988) in general is higher while fasting in healthy women and women with obesity. There is a trend among normal-weight women but not women with obesity toward reduced negative affect following to eating, but further investigation is necessary. We did not find effects of the feeding state on affective responses measured by PANAS. In general, more negative affect was reported by women with anorexia nervosa and women with obesity in comparison to healthy women. Regarding positive affect, winning money at the Wheel of Fortune increased positive affect in all of our participants, independent of the feeding state. However, a stronger effect of winning was seen in women without obesity compared to women with obesity.

In terms of mood, our results suggest that fasting increases reactivity to winning risky high monetary rewards in healthy women, but not in women with

anorexia nervosa. Independent of the feeding state, winning monetary rewards seems to evoke similar mood reactivity in healthy women and women with anorexia nervosa, while losing safe high monetary rewards produces stronger mood reactivity in healthy women compared to women with anorexia nervosa. Similar results were found in women with obesity with regards to losing, with the addition that winning risky high rewards arouses less mood reactivity in this population in comparison to healthy women.

Reaction times, as behavioral measures, were slower during fasting for all participants. Interestingly, not associated with a particular feeding state, individuals with anorexia nervosa had slower reaction times to the decision categories involving equal chances of winning equal rewards (50/50). As suggested in Chapter 3, this could represent a behavioral marker of a construct often seen in eating disorder as well as mood disorders known as *intolerance of uncertainty*. Following weight-restoration treatment, those participants who successfully gained weight underwent the same procedure described in Chapter 3. We did not observe any difference in terms of affect and mood responses, but reaction times to the 50/50 categories improved significantly. More detailed description of the analysis and results were not included

in this dissertation but can be found in (Piccolo, Milos, Bluemel, Schumacher, Mueller-Pfeiffer, et al., 2019).

Finally, we did not observe any association between behavioral and mood reactivity to monetary rewards and circulating levels of endocannabinoids. However, anandamide levels were higher during fasting for all groups, confirming recent research in the field. When comparing across groups, our results revealed diminished circulating anandamide in individuals with anorexia nervosa in comparison to health controls. Anandamide levels were negatively correlated with depression scores.

Our results indicate that the feeding state of the individuals may modulate some types of response to monetary rewards, suggesting the need to control for that also in research involving non-primary rewards. As previously reported in each chapter, these studies come with limitations, and larger samples are required to confirm these results, especially those stated in Chapters 4 and 5, which consisted of pilot studies. Another important limitation to be addressed in future studies is counterbalancing in feeding states, with the fed condition always being carried out following the fasted condition. Including fMRI measures to the procedures described here may yield interesting results and extend the knowledge of how fasted versus fed states modulate non-primary rewards. Finally, extending investigation to other types

of non-primary rewards, such as social, may advance the knowledge on reward-related disorders.

Reward processing is considered one of the priorities in the Research Domain Criteria (RDoC) in mental disorders and other related problems (Insel et al., 2010), and research suggests dysregulations in this system may reflect a vulnerability factor common to different disorders. Therefore, it is crucial to understand what differentiates this dysfunction across disorders, its relation to the symptoms and specificities in each disorder so that preventive as well as treatment strategies may be developed.

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Research fellow, September 2017 to August 2019

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- Experimental lab coordinator

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FELLOWSHIPS AND AWARDS

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PUBLICATIONS

Piccolo, M., Milos, G., Bluemel, S., Schumacher, S., Müller-Pfeiffer, C., Ernst, M., Martin-Soelch, C. (2019). Food vs money? Effects of hunger on mood and behavioral reactivity to reward in anorexia nervosa. *Appetite, 139C,* 26-33. https://doi.org/10.1016/j.appet.2018.12.017

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WORKS IN PROGRESS

Piccolo, M., Javaras, K., Nickerson, L.,Martin-Soelch, C., & Pizzagalli, D. (manuscript under preparation). Resting state functional connectivity in depressed patients with hyperphagia vs hypophagia.

Piccolo, M., Milos, G., Bluemel, S., Schumacher, S., Müller-Pfeiffer, C., Ernst, M., Martin-Soelch, C. (under review) Effect of fasting on behavioral reactivity to monetary reward in women with obesity. *PLOS One*

Piccolo, M., Milos, G., Bluemel, S., Schumacher, S., Müller-Pfeiffer, C., Ernst, M., Martin-Soelch, C. (manuscript under preparation) Risk taking predicts treatment outcome in anorexia nervosa.

Piccolo, M., Estanislau, C., Haymoz, S., Milos, G. & Martin-Soelch, C. (manuscript under preparation). Altered perception patterns in obesity.

Piccolo, M., Martin-Soelch, C., Javaras, K., Milos, G., & Haymoz, S. (manuscript under preparation). Food portion estimation in people with obesity and overweight.

PRESENTATIONS

Piccolo, M., Lenza, L. G. R., Cinel, K. C., Juliani, J., & Garcia, M. R. (2020, February). *Teaching intraverbal to children with autism spectrum disorder*. Poster presented at the 14th Annual Autism Conference –, Miami, United States of America. doi 10.13140/RG.2.2.15076.53126

Piccolo, M., Milos, G., Bluemel, S., Schumacher, S., Müller-Pfeiffer, C., Ernst, M., Martin-Soelch, C. (2018, October). *Food vs money: reactivity to monetary rewards in anorexia nervosa*. Paper presented at the Cognition Day –, Fribourg, Switzerland.

Piccolo, M., Milos, G., Bluemel, S., Schumacher, S., Müller-Pfeiffer, C., Ernst, M., Martin-Soelch, C. (2018, September). *Interactions between hunger and reward: mood reactions to reward in anorexia nervosa under starvation and satiety states*. Paper presented at the 48th Annual Congress of the European Association of Behavioral and Cognitive Therapies – EABCT, EABCT, Sofia, Bulgaria.

Piccolo, M. (2014, May). *A Duração do 'Efeito Advertência' no Contexto Escolar*. Paper presented at the III Congresso de Psicologia e Análise do Comportamento (CPAC), Universidade Estadual de Londrina – UEL, Londrina, Brazil.

Piccolo, M.; Potoski, D.; Assuncao, I. S.; Moryiama, F. M.; Reis, L. (2014, May). *Agressividade no Contexto Escolar - Uma Revisão de Literatura*. Paper presented at the VII Congresso de Psicologia e IV Congresso Nacional de Psicologia, Universidade Filadélfia – UniFil, Londrina, Brazil.

Suzuki, E. H.; Zancopelli, B.; Moryiama, F. M.; **Piccolo, M.**; Reis, L. A. (2014, November). *NAP - Núcleo de Apoio Psicopedagógico*. Paper presented at the Fórum Científico da Faculdade de Apucarana, Faculdade de Apucarana, FAP, Apucarana, Brazil.

Piccolo, M. (2018, June). Anorexia nervosa and the reward system. In Filgueiras, G. B. (Chair). *The reward system and research on clinical neuroscience*. Symposium conducted at the V Congresso de Psicologia e Análise do Comportamento (CPAC), Londrina, Brazil.

Piccolo, M., Zatorre, L. D., Cinel, K. C. & David, L. (2018, June). Cause vs Function: behavior analysis and evolutive biology revisited, In Muchon, C. (Chair). *A dialog between radical behaviorism and evolutive biology*. Symposium conducted at the IV Congresso de Psicologia e Análise do Comportamento (CPAC), Londrina, Brazil.

Piccolo, M. (2016, June). O tratamento do TDAH : medicar é um exagero? In Filgueiras, G. B. (Chair). *Caracterização, Diagnóstico e Tratamento do TDAH. O que o psicólogo precisa saber*. Symposium conducted at the IV Congresso de Psicologia e Análise do Comportamento (CPAC), Londrina, Brazil.

Cinel, K. C.; **Piccolo, M.**; Zatorre, L. D.; David, L. (2016, June). Aplicação e considerações sobre o programa de desenvolvimento do comportamento "emitir sons vocálicos" em crianças. In Kienen, N. (Chair). *Aplicacoes da programacao de ensino em diferentes contextos*. Symposium conducted at the III Congresso de Psicologia e Análise do Comportamento (CPAC), Londrina, Brazil.

Piccolo, M., Martin-Soelch, C. (2018, September). *Altered patterns of perception in obesity*. Poster session presented at the 48th Annual Congress of the European Association of Behavioral and Cognitive Therapies – EABCT, EABCT, Sofia, Bulgaria.

Piccolo, M. (2016, May). Orientações para o desenvolvimento de intervenções em grupo com filhos do divórcio. Poster session presented at the *IV Jornada de Terapias Cognitivo-Comportamentais*, Universidade de Sao Paulo, Ribeirao Preto, Brazil.

David, L.; **Piccolo, M.** (2016, June). Noção de causalidade: um diálogo entre a análise do comportamento e a biologia evolutiva. Poster session presented at *the IV Congresso de Psicologia e Análise do Comportamento*, Universidade Estadual de Londrina, Londrina, Brazil.

TEACHING AND ADVISING EXPERIENCE

Head Teaching Fellow, University of Fribourg, Switzerland
Intercultural Workshop on Psychopathology, Spring Term 2019
Personality Disorders, Fall Term 2018
Competences in Diagnostic of Feeding and Eating & Depressive Disorders, Spring Term 2018

Assistant Thesis Advisor, University of Fribourg, Switzerland
Master's in Clinical Psychology (Prof. Dr. Chantal Martin-Soelch), 2017-19

Head Teaching Fellow, Universidade Norte do Paraná, Brazil
Organizational Behavior, Spring 2017
Communication Psychology, Fall 2016
Development & Learning, Spring 2016

Head Teaching Fellow, Faculdade Tecnológica do Vale do Ivai, Brazil
Psychology: Science and Practice, Spring 2017

Head Teaching Fellow, Instituto Rhema de Educação, Brazil
Scientific Methodology, Spring 2017
Theories of Personality, Fall 2016

Head Teaching Fellow, University of Fribourg, Switzerland
Intercultural Workshop on Psychopathology, Spring Term 2019
Personality Disorders, Fall Term 2018
Competences in Diagnostic of Feeding and Eating & Depressive Disorders, Spring Term 2018

CLINICAL PRACTICE

Psychotherapist, Athletica, Brazil
Cognitive-behavioral group therapy for weight management, 2016-17

Cognitive-behavioral group therapy for children of divorce, 2016-17
Private practice, Spring 2017

ACADEMIC SERVICE

Scientific Correspondent at the inaugural meeting of the Swiss special research interest group on Cognitive and Affective Neuroscience of Pain – Pain Research Forum
Representative of the PhD Students of the University of Fribourg at CUSO
Organization of conferences

LANGUAGES

Fluent in English, Portuguese, Spanish and French.

« Je déclare sur mon honneur que ma thèse est une œuvre personnelle, composée sans concours extérieur non autorisé, et qu'elle n'a pas été présentée devant une autre Faculté »

Mayron Pereira Picolo Ribeiro

Cambridge, United States of America, April 20, 2020