

Bachelor Degree Project



Binge Eating Disorder: Neural correlates and treatments

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Abstract

Binge eating disorder (BED) is the most prevalent of all eating disorders and is characterized by recurrent episodes of eating a large amount of food in the absence of control. There have been various kinds of research of BED, but the phenomenon remains poorly understood. This thesis reviews the results of research on BED to provide a synthetic view of the current general understanding on BED, as well as the neural correlates of the disorder and treatments. Research has so far identified several risk factors that may underlie the onset and maintenance of the disorder, such as emotion regulation deficits and body shape and weight concerns. However, neuroscientific research suggests that BED may characterize as an impulsive/compulsive disorder, with altered reward sensitivity and increased attentional biases towards food cues, as well as cognitive dysfunctions due to alterations in prefrontal, insular, and orbitofrontal cortices and the striatum. The same alterations as in addictive disorders. Genetic and animal studies have found changes in dopaminergic and opioidergic systems, which may contribute to the severities of the disorder. Research investigating neuroimaging and neuromodulation approaches as neural treatment, suggests that these are innovative tools that may modulate food-related reward processes and thereby suppress the binges. In order to predict treatment outcomes of BED, future studies need to further examine emotion regulation and the genetics of BED, the altered neurocircuitry of the disorder, as well as the role of neurotransmission networks relatedness to binge eating behavior.

Keywords: binge eating disorder, impulsivity, reward systems, dopamine, neuromodulation

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Introduction

"I feel incapable of controlling urges to eat. I have a fear of not being able to stop eating voluntarily" (Binge Eating Scale [BES], Gormally, Black, Daston, & Rardin, 1982, pp. 54). Some people have an urge to eat a large amount of food despite satiety. The actions seem to be beyond their control, even if it will have significant negative consequences. Why is that?

Binge-eating disorder (BED) is the most prevalent of all eating disorders (Kessler, Hutson, Herman, & Potenza, 2016) and associated with obesity, and medical and psychiatric comorbidities (Davis, 2015; Pearl, White, & Grilo, 2014). According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association [APA], 2013), the core characteristics of BED include recurrent episodes of eating a large amount of food in the absence of control (Balodis, Grilo, & Potenza, 2015; de Zwaan, 2001). There have been various kinds of research on BED, but the phenomenon remains poorly understood (Kessler et al., 2016). However, research suggests that the binge eating behavior in BED may be caused by psychopathological factors such as body shape and weight concerns (Grilo et al., 2008), disturbed eating patterns (Svaldi, Brand, & Tuschen-Caffier, 2010), and emotion regulation deficits (Leehr et al., 2015). Thus, the notion of that palatable food seems to have an impact on the reward systems (Berridge, 2009), and the fact that BED includes loss of control over eating and urges for palatable foods, has generated interest in investigating the underlying neural aspects involved in the binge eating behavior (Bello, & Hajnal, 2010). There are particularly three models regarding reward systems and rewarding eating: The reward deficiency model holds that individuals with reduced dopamine D2 receptor availability are more prone to be engaged in hedonic activities to compensate for the deficiency (Blum et al., 1996); the reward surfeit model holds that individuals with decreased D2 receptor availability and increased reward region responsivity to food cues are at elevated risk to overeat (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; Val-Laillet et al., 2015); while the incentive sensitization model holds that repeated consumption of palatable food may, in susceptible individuals, change the reward systems that usually regulate the incentive salience to food and provokes hypersensitive responses towards food which leads to compulsive binge eating behavior (Robinson, & Berridge, 1993). The altered brain activity and functions in BED seem to be similar as in substance abuse and impulsive/compulsive disorders, whereby researchers widely speculate whether BED is a "food addiction" disorder (Kessler et al., 2016; Schulte, Grilo, & Gearhardt, 2016). However, whether "food addiction"

includes similar components as traditional addictions such as alcoholism has not yet been established and is an ongoing area of research (Gearhardt, White, Masheb, & Grilo, 2013; Schulte et al., 2016; Ziauddeen, Farooqi, & Fletcher, 2012). Increased knowledge of the phenomenon BED and its underlying neural aspects, including reward systems and brain functions, has paved the way to search for new treatment interventions. Research suggests that neuromodulation approaches, together with neuroimaging methods, may alter food-related reward processes and thereby suppress binge eating. However, neuromodulation for treating food reward behavior is in its infancy, and further research is needed (Val-Laillet et al., 2015).

The aim of this thesis is to review the results of research on BED to provide a synthetic view of the current general understanding of BED, as well as the neural correlates of the disorder and neural treatments. The hypothesis is that the loss of control in BED is related to neuronal alterations. This thesis will highlight current gaps in research, as well as provide directions for further research. To achieve the aim of the thesis, a keyword search will be entered on Google Scholar and Scopus to identify relevant literature published in English concerning the pathology of BED, and relevant neuroscientist literature concerning the neural correlates of the disorder and neural treatments. The first part of the thesis will begin by presenting the psychopathology of BED, including diagnostic, prevalence, and comorbidity, followed by psychological aspects of the disorder, such as weight and body shape concerns, disturbed eating patterns, and emotional deficits. A presentation of treatments, including psychological and pharmacological treatments, will finish the first part. The second part of the thesis will address the neuroscientific findings of the neural correlates of BED, including constructs associated with impulsivity, cognitive functions, brain structure and functions, genetics, and neurotransmitter systems. The third part of the thesis will present an overview of findings from some neural treatments aimed at altered food-related reward processes. Lastly, in the discussion part of the thesis, the findings of the phenomenon BED, the neural correlates of the disorder and neural treatments will be summarized and discussed. Following this, the limitations for the current thesis is discussed, the strengths and limitations of the literature will be highlighted, as well as future challenges and directions for the research on BED. Finally, the thesis will end with a conclusion of the central findings.

Background

Diagnostics

BED was recognized in the DSM-5 (APA, 2013) in 2013 (Kessler et al., 2016). However, the symptom of the disorder was already identified in the 1950s (Ely, & Cusack, 2015). BED is characterized by distress and loss of control over eating. It is the loss of control that distinguishes a binge from overeating (Ely, & Cusack, 2015; de Zwaan, 2001; Kessler et al., 2016). According to DSM-5 (APA, 2013), the criteria for BED is associated with three or more of the following: (1) Eating much more rapidly than average, (2) eating until feeling uncomfortably full, (3) eating large amounts of food when not physically hungry, (4) eating alone because of being embarrassed by how much one is eating, (5) feeling disgust with oneself, depressed, or very guilty after the binge eating. Further, the binge eating must occur at least once a week for three months without a compensatory behavior (e. g., purging or excessive exercise). Assessments are used to measure the range and severity of BED. The BES (Gormally et al., 1982) is a self-administered questionnaire based on eating behaviors (e. g., *I have a problem stopping eating once I start, and usually I feel uncomfortably stuffed after I eat a meal*), and emotional and cognitive responses (e. g., *Almost all the time I experience strong guilt or self-hate after I overeat*). BES is reported very good internal consistency, with an alpha of 0.89 and test-retest reliability, with a correlation of .87 across a two-week time period (Celio, Wilfley, Crow, Mitchell, & Walsh, 2004; Gormally et al., 1982; Grupski, Hood, Hall, Azarbad, & Corsica, 2013). The Eating Disorders Examination - Questionnaire (EDE-Q; Fairburn & Beglin, 1994) is a self-report instrument, often used for measuring the change in eating disorders symptoms during treatment, including four parts (restraint, eating concerns, shape concerns, and weight concerns). EDE-Q reported perfect internal consistency, with an alpha of 0.85 and test-retest reliability, with a correlation of .89 across two weeks (Celio et al., 2004; Saules, Carey, Carr, & Sienko, 2015; Luce & Crowther, 1999).

Prevalence rates and comorbid conditions

BED is the most prevalent of all eating disorders. Studies examining the population prevalence of BED are based mostly on U. S. data, and they are rather few (Kessler et al., 2013; Davis, 2015). Based on interview assessments, the lifetime prevalence of BED is about

3% (Kessler et al., 2016; Mustelin, Bulik, Kaprio, & Keski-Rahkonen, 2016). Thus, according to self-administered questionnaires, the prevalence is estimated to 6,6% (Davis, 2015). The prevalence of BED may be higher than shown due to the great hidden statistic in obese individuals, and it seems that physicians often fail to recognize eating disorders (Kessler et al., 2013). For example, obese individuals often search treatment for comorbid problems or treatment for overweight, obesity, and bariatric surgery, when they instead meet the diagnostic criteria of BED (Brownley et al., 2016; Davis, 2015). When BED was included in the main section of DSM-5, there was speculation whether the prevalence of BED would increase, because of the symptom criteria of BED changed from a 6 month of duration and binge eating at least once a week, to a 3-months of duration and binge eating at least twice a week (Davis, 2015; de Zwaan, 2011). However, the new diagnostic criteria of BED meant a minor increase of 0,2% (Davis, 2015). BED is typically arising in later adolescence and young adult years and remains for approximately 1-12 years (Donnelly et al., 2018; Kessler et al., 2013). The ratio between the sexes in BED is not as large as in other eating disorders, such as anorexia nervosa (AN) and bulimia nervosa (BN), disorders that are common among mostly females (Davis, 2015). The main difference between men and women with BED seems to be that men have a lifetime diagnosis of substance dependence, while women are more likely to binge eat when having negative emotions, particularly anxiety, anger, and depression (Tanofsky, Wilfley, Spurrell, Welch, & Brownell, 1997).

BED is considered to be a public health problem because of its impact on psychiatric, physical, and social functioning. The physical comorbidities of BED are strongly related to the overweight or the obesity, such as diabetes, metabolic syndrome, chronic pain conditions, sleep problems, and heart diseases (Davis, 2015; Kessler et al., 2013; Olguin et al., 2017). BED also links with co-occurring psychiatric comorbidity, and almost half of the BED individuals have at least three other disorders, such as anxiety disorders and reductions in mood (Citrome, 2015; Davis, 2015; Welch et al., 2016). Other frequent co-occurring disorders include other eating disorders, bipolar disorders, and a higher risk of suicide attempts (Citrome, 2015; Kessler et al., 2016; Welch et al., 2016). Research suggesting the comorbidity of BED seems to be greater when the onset of the disorder starts in childhood or adolescence compared with onset in adulthood - even without more frequent binge eating or higher BMI. Other common comorbidities related to BED are different addiction disorders, including substance abuse, alcoholism, gambling, compulsive shopping, and impulsive/compulsive disorders (Davis, 2015). For instance, high school students who report

frequent binge eating seem to be much more likely to start using drugs, alcohol, or tobacco compared with those who do not binge eat (Ross, & Ivis, 1999).

Weight and body concerns and disturbed eating patterns

Weight and body shape concerns may be a risk factor of BED and seem to be one of the factors that predict the onset and maintenance of the disorder (Schulte et al., 2016).

Individuals with BED who report overvaluation of weight and body shape, that is, having self-worth based much on weight/body shape, seems to have more severe eating-disorder psychopathology, psychological distress, and functional impairments than those who do not report overvaluation (Grilo et al., 2008; Wang, Lydecker, & Grilo, 2017). Overvaluation of weight and body shape seems to appear regardless of BMI, and even healthy weight individuals with BED seem to report overvaluation (Goldschmidt et al., 2011; Hrabosky, Masheb, White, & Grilo, 2007). Rumination, which refers to a constant focus on oneself in a critical and pessimistic manner, seems to be associated with the psychopathology of BED. Moreover, rumination decreases cognitive flexibility and the ability to solve problems (Wang et al., 2017). Further, it is common that individuals with obesity feel discriminated due to their weight (i.e., weight bias internalization), which may lead to negative affect and trigger binge eating, which in turn leads to greater body dissatisfaction and thereby social isolation (Puhl, & Suh, 2015).

The eating behavior in BED individuals may be categorized into two subtypes: The pure dietary subtype (i.e., dieting) and the dietary-negative affect subtype (i.e., dietary-restraint). Research has found higher impulsivity scores for the dietary-negative affect subtype (Carrard, Crépin, Ceschi, Golay, & Van der Linden, 2011). Dietary-restraint and dieting are both associated with eating disorders but include two separate concepts with different ways to relate to food and weight. Dietary-restraint, which is more common among women, refers to a cognitive action, that is, the conscious effort to control food intake, such as form rigid dietary-rules, avoiding foods that are unhealthy, or eating at home because of weight and body shape concerns (Goldschmidt et al., 2011). For instance, those with BED seem to rate pictures of high-caloric food as more forbidden than low-caloric food compared with healthy controls (Svaldi et al., 2010). Further, dietary-restraint is often associated with negative thoughts and actions, such as higher concerns regarding eating, shape, and weight, as well as weaker response to treatment (Carrard et al., 2011). Healthy weight individuals with BED seem to

have even more restraint eating compared to obese individuals with BED. Findings suggest that those of healthy weight with BED eat fewer meals per day, exercising more, and avoid certain food for weight control (Goldschmidt et al., 2011). Dietary-restraint may be a reflection of hedonic hunger (i.e., the drive to eat to obtain pleasure in the absence of an energy deficit), which is related to increased food cravings of palatable food (Schulte et al., 2016; Stice, Burger, & Yokum, 2013). In contrast, dieting refers to cut down calories below a biological "set point" by decreasing caloric intake to lose weight (Goldschmidt et al., 2011). Dieting appears to generate binge eating in half of those who develop BED. Self-reports demonstrate that those with BED have backgrounds of frequent dieting attempts and fluctuations in weight (Schulte et al., 2016). For instance, eating in the absence of hunger at age 7 predicted binge eating at age 15. Furthermore, the girls at age 15, reported elevated BMI, more negative affect, and maladaptive thoughts and feelings about eating and weight. These findings suggest that eating in the absence of hunger in childhood may predict future risk of binge eating behavior and eating disorders (Balantekin, Birch, & Savage, 2016).

Emotional deficits

A common and well-known explanation for the onset and maintenance of BED is deficits in emotion regulation processes. Research has found that BED individuals compared with obese individuals without BED, have more severe emotional dysfunctions (Dingemans, Danner, & Parks, 2017; Leehr et al., 2015; Schulte et al., 2016). However, few experimental studies have investigated the causal relationship between negative affect and BED, and the results are mixed. Recent findings suggest that mood and anxiety disorders are the most prevalent comorbid psychiatric disorders in BED. Negative emotions, particularly stress, anger, sadness, and negative emotions related to interpersonal experiences, such as disappointment and loneliness, seem to be associated with BED. These negative emotions often lead to binge eating behavior because binge eating seems to serve as a coping strategy to find relief and temporarily improve mood. Moreover, in order to temporarily improve mood, self-harm, and substance abuse in BED are prevalent (Harrison, Mitchison, Rieger, Rodgers, & Mond, 2015; Leehr et al., 2015). Furthermore, the impulsivity characteristic in BED may have consequences on the relationship between negative affect and binge eating. Negative urgency (i.e., rashly behavior when having negative affect) seems to be more prevalent in BED than among obese individuals (Dingemans et al., 2017).

Research suggests that BED individuals have an emotional vulnerability, and they often suppress and ruminate on their negative emotions, which leads to greater psychopathological thoughts and symptoms. One study that was showing a sad film-clip was the participants should either suppress or process the emotion that arose showed that suppression of negative emotions, in contrast to processing, led to an increased desire to binge eat in for women with BED compared with healthy control women. Studies investigating positive affect and eating behavior in BED is sparse. However, a study found that on weeks with low negative affect and high positive affect, BED individuals reported fewer binge eating occasions, although the effect size was relatively small (Dingermans et al., 2017).

Psychological and pharmacological treatments

Psychological and pharmacological treatments are so far suggested to be the most efficient way to treat BED (Kessler et al., 2016; Peat et al., 2017). Research has found that a combination of specific pharmaceutical with psychotherapy produces superior outcomes (Grilo et al., 2016). A combination may generate in rapid response, which is a crucial outcome predictor across treatments of BED (Hilbert et al., 2019). Research has found that responding quickly to the treatment entails a 65 % greater reduction in binge eating behavior (Grilo, Masheb, & Wilson, 2006). However, the majority of individuals with BED do not seek treatment for their eating disorder, but instead for weight loss treatment. The severity of the disorder is therefore often far gone and intractable (Donnelly et al., 2018; Grilo, Reas, & Mitchell, 2016).

Most research investigating psychological treatments has involved cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), and behavioral weight loss (BWL). CBT aims to target the eating behaviors in BED through self-monitoring, normalizing eating patterns (e.g., healthy portion sizes, to regain hunger and satiety, and to eat all kinds of foods), and building behavioral and cognitive coping strategies (Ely, & Cusack, 2016). CBT and cognitive behavioral therapy for eating disorders (CBT-E) (Fairburn et al., 2015) seems to reduce binge eating abstinence and binge eating frequency but are not effective in long-term weight loss and depressive symptoms (Grilo, 2017; Peat et al., 2017). Studies suggest that only half of the BED patient who completes CBT treatment have lasting improvement, and one-third of these still meet the criteria for BED five years after starting the CBT (Ely, & Cusack, 2015). IPT, which focuses on the social and interpersonal deficits in BED, has shown

to reduce the binge eating frequency. However, whether it is sufficient for other BED-related symptoms, such as negative emotions, is unclear (Wilfey et al., 2002). BWL seems to produce modest short-term weight loss in BED individuals (Butryn, Webb, & Wadden, 2011; Grilo, 2017). Other treatments of BED are mindfulness-based interventions (MBIs) and dialectical behavioral therapy (DBT). These treatments are focusing on the emotion dysfunctions of BED. DBT is a mindfulness inspired method focusing on awareness and obtaining skills in order to improve emotion regulation and acceptance. Both MBIs and DBT seems to help BED individuals regulate negative emotions leading to binge eating (Alberts, Mulken, Smeets, & Thewissen, 2010; Telch, Agras, & Linehan, 2001).

Pharmacological treatments target brain chemistry directly has shown mixed results, and each of them has advantages and limitations (Peat et al., 2017). Antidepressants (e.g., fluoxetine) may regulate mood and seems to reduce the frequency of binge eating because they suppress appetite (Peat et al., 2017). Anticonvulsants (e.g., topiramate) seems to reduce binge eating and lead to weight loss. Thus, anticonvulsants have several negative consequences on cognition, such as memory and speech problem, dizziness, and nervousness (McElroy et al., 2016). Lisdexamphetamine (LDX) (e.g., Vyvanse), an amphetamine medication initially for treating ADHD, seems to be the most efficient of existing pharmaceuticals. LDX seems to suppress appetite and thereby weight loss, as well as reduce the food-reward seeking behavior. A clinical trial of 259 individuals with BED, suggests that LDX leads to a reduction of binge-eating behavior in up to 50 % of treated subjects. Moreover, it decreases the associated obsessive and compulsive features typical of BED (Brownley et al., 2016; Ely, & Cusack, 2016; McElroy et al., 2016; Peat et al., 2017). However, the negative consequences of LDX are widespread, including sleep problems, mood swings, and a significant risk of abuse and dependence (Ely, & Cusack, 2016).

Neural correlates

Impulsivity, compulsivity, and reward sensitivity

BED is associated with increased impulsivity and compulsivity and altered reward sensitivity, particularly towards food-related cues (Kessler et al., 2016; Schag, Schönleber, Teufel, Zipfel, & Giel, 2013). Impulsivity is a multidimensional construct related to both trait and state

variables and refers to having reward-related drives, rash-spontaneous behavior, and disadvantageous decision-making. In contrast, compulsivity refers to the tendency to act repetitively and persistently without goal or reward, and it occurs regardless of unfavorable outcomes (Kessler et al., 2016; Schienle, Schäfer, Hermann, & Vaitl, 2009). Increased impulsivity and reward sensitivity have also been reported in other eating disorders such as BN and the bingeing-purging subtype of AN, as well as in obesity, but to a lesser degree than BED (Giel, Teufel, Junne, Zipfel, & Schag, 2017; Fernández-Aranda et al., 2006). For instance, obese individuals seem to show impulsive responding to palatable food, but do not have the general tendency to react impulsively (Houben, Nederkoorn, & Jansen, 2014). BED individuals appear to score higher on questionnaires measuring trait impulsiveness such as the Barratt Impulsiveness Scale-11 (BIS-11) compared with obese individuals without BED and healthy weight individuals (Dawe, & Loxton, 2004; Mole et al., 2015). BED individuals also seem to report higher reward sensitivity on the Behavioral Inhibition/Activation Scales (BIS/BAS) when viewing pictures of food high in calories compared with normal weight and obese individuals without BED (Schienle et al., 2009). Further, impulsivity seems to have an impact on the loss of control that BED individuals experience during binge eating, as the higher score on the BIS-11 is suggested to correlate with larger test meal intake after 8-hour fasting (Galanti, Gluck, & Geliebter, 2007). The reward and punishment sensitivity in BED seem to differ in gender. Women with BED report greater punishment sensitivity compared with men with BED. On the other hand, men with BED had higher tendencies to seek out experiences that are novel and pleasurable (Eneva et al., 2017). The reward sensitivity in BED individuals is suggested to persist even after recovery. Because of this, some researchers propose that the reward sensitivity exists before the onset of the disorder (Bardone-Cone, Butler, Balk, & Koller, 2016). Further, greater impulsivity and sensitivity to punishment in BED seem to be associated with low self-esteem, depression, anxiety, and greater vulnerability to negative emotions leading to a reduced ability to use coping strategies other than binge eating (Carrard et al., 2011). The compulsive behavior in BED individuals seems to lead to decreased self-control and difficulties to adapt to changes in new situations (i.e., set-shifting) (Kessler et al., 2016). Findings suggest that men with BED score higher on scales measuring compulsivity compared with women with BED (Galanti et al., 2007). Altogether, these findings indicate that BED is an impulsive/compulsive disorder.

Shared mechanism with impulsive/compulsive disorders

Overall, eating disorders are considered to include varying degrees of impulsive and obsessive-compulsive traits. Obsessive individuals seem to avoid harm and reduce anxiety or discomfort. In contrast, impulsive individuals are novelty seekers who want and needs pleasure and arousal (Claes, Nederkoorn, Vandereycken, Guerrieri, & Vertommen, 2006). Studies investigating attention-deficit hyperactivity disorder (ADHD) have found that the prevalence of binge eating behaviors in individuals with ADHD is higher than expected (Corese, Bernardina, & Mouren, 2007). Several studies have found correlations between abnormal eating behaviors during childhood and ADHD. However, few studies have investigated ADHD and eating disorders (Fernández-Aranda et al., 2013). One hypothesis suggests that inattention and impulsivity traits could lead to binge eating behaviors. Another hypothesis suggests that ADHD and binge eating share some neural aspects, such as alterations in dopaminergic pathways (Corese et al., 2007). Research investigating the symptom level of ADHD in females with different eating disorders, suggesting that particularly obsessiveness and hostility were positively associated with ADHD symptoms (Fernández-Aranda et al., 2013). Researchers imply that obese women with binge eating behavior should be routinely evaluated for ADHD and vice versa because of the high association between ADHD and eating disorders (Nazar et al., 2014). When BED individuals are treated with LDX, the medication does reduce not only binge eating behavior but also decreases the associated obsessive and compulsive features of the disorder (McElroy et al., 2016).

Shared mechanism with addictive disorders

Impulsivity may be a critical risk factor for substance abuse due to altered dopamine neurotransmission in the reward system (Kessler et al., 2016). Individuals diagnosed with BED and Yale Food Addiction Scale (YFAS) are suggested to have more increased impulsivity traits compared with those BED individuals that not meet the criteria for YFAS. YFAS is a validated self-report questionnaire used to identify and diagnosticate eating patterns similar to behaviors seen in addiction, such as drugs and alcohol abuse. The increased impulsivity is suggested to provide much more severe and frequent episodes of 'addictive-like' binge eating and depression symptoms (Davis, 2015; Schulte et al., 2016). Approximately 50% of obese individuals diagnosed with BED seems to meet the criteria for YFAS, which suggests that "food addiction" might not be a general feature of BED, but

instead include a more severe type of BED linked to obesity (Davis, 2015). On the other side, "food addiction" has also been reported in BED individuals that are normal weight (Schulte et al., 2016). Neuroimaging studies suggest that BED individuals have similar dysfunction in the brain as more traditional addictive disorders. For instance, individuals with more than three YFAS "food addiction" symptoms show greater neural activity in reward systems when drinking chocolate milkshake compared with those with just one YFAS symptom. Moreover, both BED individuals and those with addictive disorders show faster response time toward the substance (e.g., food or drugs) (Schulte et al., 2016; Robbins, 2004). Further, substance use disorders seem to include features similar to BED, such as loss of control despite adverse consequences, consuming more than needed, emotion dysregulation, withdrawal symptoms, and tolerance. For instance, individuals with high YFAS symptoms report that they are more likely to consume palatable foods as a way to regulate negative emotional states (Schulte et al., 2016). However, the idea of that highly palatable food may have the same addictive consequences as drugs, such as alcohol, and that binge eating may represent an addictive-like binge eating behavior has long been discussed and is a controversial and ongoing research subject (Davis et al., 2017; Hebebrand et al., 2014; Schulte et al., 2016; Ziauddeen et al., 2012).

Cognitive functions

Neurocognitive research suggests that BED is associated with cognitive dysfunctions, including attentional and executive deficits and biases, which seem to contribute to the severity of BED. These cognitive dysfunctions have an impact on processes such as selective attention, inhibition control, cognitive flexibility (Mobbs, Iglesias, Golay, & Van der Linden, 2011), and decision-making (Svaldi, Brand, & Tuschen-Caffier, 2010). Research suggests that the cognitive impairments may not exclusively be related to BED but to obesity itself (Batterink, Yokum, & Stice, 2010; Houben et al., 2014; Lavagnino, Arnone, Cao, Soares, & Selvaraj, 2016; Wu et al., 2013). In some cognitive tasks, particular tasks measuring inhibitory control and attention, obese individuals with BED did not differ from BMI-matched individuals without BED. However, both groups performed worse than normal-weight individuals (Kessler et al., 2016; Wu et al., 2013). A small study investigating normal-weight individuals with BED did not report any significant prefrontal impairments compared with healthy controls (Balidos, Grilo, Potenza, 2015).

Increased attentional biases towards food-related cues

BED individuals seem to show increased attentional and memory biases for environmental cues, particularly food-related cues, and to some extent body-related cues (Kessler et al., 2016). When BED individuals and obese individuals without BED were completed a clarification task with obscured words, both groups detected food-related words faster than overweight individuals. However, the result was more pronounced for those with BED (Schmitz, Naumann, Trentowska, & Svaldi, 2014). BED individuals also show faster fixation on spatial cues that are located in the same area as food-related images and identifies food-related pictures and words faster compared with obese individuals without BED (Schag et al., 2013). Compared with BMI matched individuals, overweight individuals with BED showed elevated cognitive interference (i.e., unwanted thoughts) when performing a working memory task, both with and without food-related cues (Svaldi et al., 2014).

Impaired decision-making

BED is suggested to be associated with impaired decision-making (Kessler et al., 2016). Decision-making involves the cognitive evaluation of risks by weighing probabilities of outcomes with concern about gains and losses. Clinical observations of BED individuals suggesting that the binge eating sometimes seem to be "planned" hours or days ahead, which indicates that BED individuals often make disadvantageous decisions (Svaldi et al., 2010). Impaired decision-making may also be associated with impatience and aversion to taking risks. For instance, in a game of dice task (GDT) with clear rules for gains and losses, obese individuals with BED made significantly more risky decisions than obese individuals without BED (Svaldi et al., 2010). However, another study found that in GDT and a stop signal task (SST), obese individuals with BED and obese individuals without BED did not differ (Wu et al., 2013). The obese individual with BED also showed a reduced preference for delayed and probabilistic rewards, that is, they prefer smaller but immediate rewards instead of waiting for more substantial or more lasting rewards. The decision-making patterns seen in BED individuals, unlike obese individuals without BED, are similar to those of substance-use disorders (Voon et al., 2015).

Cortical and striatal alterations

Neuroscientific and neuroimaging research has found evidence suggesting that BED individuals seem to have alterations in cortico-striatal circuitry, including insular, prefrontal, and orbitofrontal cortical and striatum. Similar alterations have been found in addictive and impulsive/compulsive disorders (Kessler et al., 2016). The cortico-striatal circuit involves three neural pathways involved in eating behavior. The first codes for the perceived salience of food stimulus (i.e., insula), another codes for the rewarding sensations of the eating (i.e., the ventral striatum), and the third helps control the long term consequences of consuming the food, and determine eating behavior (i.e., the dorsal striatum and frontal cortex) (Ely, & Busack, 2015). A translational lesion study including individuals with frontotemporal dementia (FTD), a disorder associated with poor impulse control and executive functions, compulsive behavior, and frequent binge eating despite reported satiety, may gain further understanding of the neural aspects of BED. Findings revealed that binge eating FTD patients had significantly greater atrophy in the right ventral insula, striatum, and orbitofrontal cortex (OFC), which suggest that damages to the orbitofrontal-insular-striatal circuit may be associated with overeating behavior in humans (Woolley et al., 2007).

Existing neuroimaging studies have identified alterations in BED that is suggested to underlie impulsivity and rewarding processes (Kessler et al., 2016). When BED individuals were exposed to pictures of palatable food, they reported greater reward sensitivity and higher activity in the ventral striatum compared with obese individuals without BED and normal weight individuals (Kessler et al., 2016). When BED individuals, obese individuals, healthy and overweight controls, and BN patients were exposed to high caloric food pictures after an overnight fast, the food stimuli provoked increased activation in OFC, anterior cingulate cortex (ACC), insula, as well as the amygdala in all groups. However, BED individuals were reported elevated reward sensitivity and showed stronger medial OFC activity compared with the other groups (Schienle et al., 2009). Moreover, in a magnetic resonance imaging (MRI) study individuals with BED seem to have greater grey matter volumes of the medial OFC compared with healthy controls (Schäfer, Vaitl, & Schienle, 2010). In a non-food rewarding study using functional magnetic resonance imaging (fMRI) and monetary reward/loss task, BED individuals showed decreased activation in areas such as bilateral ventral striatal and insular cortex (Balodis et al., 2013a). In an fMRI study investigating decision-making, obese individuals with BED were more likely to use habit-based learning and showed lower left and

bilateral OFC, and lower bilateral caudate volumes than obese individuals without BED (Voon et al., 2015).

BED individuals appear to have abnormally low activity in impulse control related to the prefrontal cortex (PFC), a brain region involved in executive functions (Kessler et al., 2016). During a task measuring anticipatory reward and loss processing, BED individuals showed decreased activity in several brain prefrontal regions, including ventral lateral PFC and inferior frontal cortex, compared with obese adults without BED and healthy controls (Balodis et al., 2013a). Moreover, compared with obese individuals without BED and healthy controls, BED individuals appear to have reduced activation in ventral lateral PFC and inferior frontal gyrus in a Stroop task measuring inhibitory control (Balidos et al., 2013b). Further, compared with obese women without BED and normal weight women, BED individuals show increased blood flow in the left frontal and prefrontal cortices when exposed to food stimuli in contrast to neutral pictures (Karhunen et al., 2000).

Genetics

So far, few genetic studies have focused exclusively on BED (Bulik, Kleiman, & Yilmaz, 2016; Cacciatore et al., 2018). Twin studies and population studies have revealed both genetic and environmental heritable factors in BED and evidence suggest that BED is very likely a familial disorder (Bulik et al., 2016; Hudson et al., 2006; Trace, Baker, Peñas-Lledó, & Bulik, 2013). A U.S. study of overweight and obese adults with and without BED estimated that the heritability of BED was 57%. Thus, a Swedish study investigating twins with BED, showed a heritability of 41% (Bulik et al., 2016). A large family study, which has examined overweight and obese individuals with individuals with BED and without BED and their first-degree relatives, confirmed that obesity does not run within families, instead other familiar factors are involved, particular loss of control over eating and distress (Hudson et al., 2006; Kessler et al., 2016). Other genetic factors related to BED may be the parent's history of psychiatric illnesses such as bipolar disorder, personality disorders, or depression. Further, a Swedish population study revealed that the risk of suicide attempts was higher for those individuals (regardless of an eating disorder) who had a relative with an eating disorder (Bulik et al., 2016).

Dopaminergic and opioidergic polymorphisms

The sensitivity of dopamine reward pathways is associated with several psychiatric disorders, such as addiction abuse, alcoholism, ADHD, depression, as well as compulsive overeating. However, the evidence is divided about the direction of a causal association. Some research suggests that the rewarding behavior is due to a reward deficiency syndrome (Blum et al., 1996), while others argue that those with hypersensitivity to reward are at elevated risk of overeating (Robinson, & Berridge, 1993; Stice et al., 2008). In order to understand the mechanisms of rewarding behavior, both psychological and neurobiological mechanisms, must be considered (Davis et al., 2008). Genetic studies of BED have assessed important information about dopaminergic and opioidergic polymorphisms that might contribute to the neural alterations of the disorder, as well as distinguish the rewarding behavior between obese individuals without BED and individuals with BED (Val-Laillat et al., 2015).

Davis et al. (2007) suggest that those BED individuals carrying the 9-repeat *DAT1* allele, which is associated with decreased dopamine transporter binding and increased synaptic dopamine release, seem to have an increased reward sensitivity for palatable food. Lower dopamine transporter binding in the striatum seem to be correlated with higher BMI, as well as depression and ADHD. When BED individuals were administered with methylphenidate, which increases dopamine levels in the brain, they reported reduced appetite compared with healthy controls. These findings suggest that methylphenidate may be used for the treatment of overeating or overweight (Davis et al., 2007). Further, genetic studies suggest that the A1 allele of the *Tag1A* polymorphism on the *ANKK1* gene is linked to a deficient ability to experience natural rewards due to decreased dopamine levels in the striatum and may be a risk factor for obesity and various addiction disorders such as alcoholism (Davis et al., 2008). However, the A2 allele of the *Tag1A* polymorphism is associated with a hypersensitivity to reward due to increased dopamine signaling in the striatum (Davis et al., 2009). Studies have found that the *Tag1A+* allele, which includes one A1 allele and one A2 allele, is frequent in both obese individuals and individuals with BED and associated with increased reward sensitivity to hedonic activities, such as eating (Davis et al., 2008; Davis et al., 2012). Thus, the G+ allele of the A118G polymorphism on the *OPRM1* gene is related to an exaggerated response to the opioid system. The genetic combination *Tag1A+* A2/A118 G+, which appears to be significantly more common in obese individuals with BED compared with obese individuals without BED, is associated with a hyper-reactivity to reward and hedonic properties of palatable food (Davis, 2015; Davis et al., 2009).

Other neurotransmission systems, such as serotonergic, endocannabinoid, and *Circadian Locomotor Output Cycles Kaput (CLOCK)*, are also suggested to contribute to rewarding binge eating behavior (Kessler et al., 2016). For instance, one study found that obese binge eating women had significantly decreased serotonin transporter binding in the midbrain compared with obese controls (Kuikka et al., 2001).

Neurotransmitter systems

Interacted and dissociated neurotransmission: Reward sensitivity

BED is associated with excessive and uncontrolled consumption of palatable food, which seems to be driven by hedonic reward mechanisms, as well as the anticipatory phase towards the reward, which is influenced by environmental food-related cues that may enhance the urge to eat regardless of psychological hunger, and thereby cause obesity (Davis et al., 2009). An animal study using food-related cues together with Pavlovian and instrumental conditioning showed that after repeated presentation of cue stimulus with the delivery of palatable food, the learned cue itself eventually became salient and triggered an urge to obtain the reward, even in the absence of the reward (Giuliano, & Cottone, 2015). Human and animal studies have suggested that both dopaminergic and opioidergic neurotransmission is involved in rewarding eating behavior (Kessler et al., 2016), and underlie the psychological process of ‘wanting’ and ‘liking’ (Berridge, 2009). Dopaminergic neurotransmission in the ventral striatal/nucleus accumbens (NAc) mediates motivational salience which is associated with motivation and learned predictions about the rewarding outcome of the stimuli (i.e., ‘wanting’), while opioidergic neurotransmission in the ventral pallidum is strongly associated with the pleasurable and anticipatory phase that precedes the reward influenced by environmental food-related cues (i.e., ‘liking’). Dopaminergic and opioidergic neurotransmission typically interact (i.e., ‘wanting’ and ‘liking’) and trigger the motivation to eat (Berridge et al., 2009). An animal study showed that after rats were fed with palatable foods and became obese, they showed decreased levels of striatal dopamine D2 receptor binding and increased reward sensitivity compared with lean rats (Johnson, & Kenny, 2010). However, the process of ‘wanting’ and ‘liking’ can become dissociated, which leads to a dysregulation of the motivational salience and the ‘wanting’ and ‘liking’ process turns to incentive salience or ‘wanting’ without ‘liking,’ and the reward is no longer associated with pleasure and the action becomes less conscious (Berridge, 2009; Castro, & Berridge, 2014).

Animal models suggest that when rats have constant access to sugar solutions, they drink it in an ‘addictive-like’ way, and show significantly increased dopamine D1 receptor binding in the NAc, decreased dopamine D2 receptor binding in the dorsal striatum, and significantly increased μ -opioid-1 receptor binding in brain regions such as ACC, hippocampus, amygdala, and NAc, brain regions underlie such as attention, memory, and reward (Colantuoni et al., 2001). Palatable food seems to lead to obesity, increased reward sensitivity and decreased dopamine release. However, the development of compulsive behavior, which eventually seems to lead to addiction, is associated with reduced dopamine D2-like receptor levels in the dorsolateral striatum (Kessler et al., 2016).

While opioid receptor agonist is involved in the increasing of food consumption, opioid receptor antagonists seem to decrease it (Giuliano, & Cottone, 2015). Animal and human studies of binge eating behaviors suggest that some opioid receptor antagonist seem to suppress the hedonic aspect of eating, which in turn reduces the motivational aspect of eating (Nathan, & Bullmore, 2009; Ziauddeen et al., 2013). However, the implication of μ -opioid receptor antagonists for reducing binge eating symptoms in BED individuals has shown mixed results (Kessler et al., 2016). For instance, one fMRI study showed that when obese men and women with moderate-severe binge eating behaviors were exposed to pictures of food high in calories, the drug significantly reduced responses in the pallidum/putamen and thereby reduced the process of ‘wanting.’ Thus, the μ -opioid receptor antagonist instead increased the subjective ‘liking’ response (Cambridge et al., 2013). Serotonin transporter binding (i.e., fluoxetine) in the raphe nucleus in brainstem significantly reduced binge eating behavior in obese individuals with BED compared with healthy controls (Tammela et al., 2003). However, the μ -opioid receptor antagonists, ALKS-33, which has shown to suppress binge eating behavior in animals, was not superior compared with placebo in reducing binge eating episodes, binge eating frequency, or body weight in BED individuals (McElroy et al., 2013).

Other neurotransmitters systems, such as GABAergic, noradrenergic, and glutamatergic systems, seem also be involved in rewarding behavior, but to a lesser degree than dopaminergic and opioidergic neurotransmitter systems (Bello, Yeh, Verpeut, & Walters, 2014; Guardia, Rolland, Karila, & Cottencin, 2011; Kessler et al., 2016). For instance, a study investigating rats in a five-choice serial-reaction time task (5-CSRTT) found a relationship

between high trait impulsivity behavior and alterations in the GABAergic system and structural abnormalities in the NAc (Caprioli et al., 2014).

Altered dopaminergic neurotransmission: Impulsivity and compulsivity

Increased impulsivity seems to be related to alterations in dopaminergic neurotransmission in the ventral midbrain and NAc (Kessler et al., 2016). When healthy women were administered with either placebo or amphetamine, those with high impulsivity traits seemed to have decreased ventral striatal and ventral midbrain dopamine D2-like autoreceptor binding and elevated amphetamine-induced dopamine release in the anterior caudate and NAc, which was related with stimulant cravings (Buckholtz et al., 2010). Further, an animal study found that cocaine self-administration monkeys have been linked to decreased NAc/striatal dopamine D2-like receptor levels. These findings suggest that impulsivity may be a risk factor for substance abuse, which may be associated with altered D2-autoreceptor regulation of dopamine neurons in the ventral-midbrain, which in turn leads to increased dopamine neurotransmission in the NAc (Kessler et al., 2016).

Increased compulsivity seems to be associated with an altered balance of decreased dopamine D2 receptor levels in the dorsolateral striatum. When investigating rodents, studies have shown that the development of compulsive drug abuse or 'addictive-like' binge eating behavior is associated with progressive alterations in dopaminergic control of drug and food consumption. First, the consumption of food is rewarding, which involves the ventral-striatal reward pathway. Then, the food becomes goal-directed, which involve the posterior dorsomedial striatal pathway. Lastly, the food becomes chronic habitual/compulsive, which involve the anterior dorsolateral striatal reward pathway (Kessler et al., 2016). A small single study investigating the dopaminergic neurotransmission in BED using PET scans and stimulant medication in terms of methylphenidate showed that BED individuals reported greater hunger and desire for food stimuli and had enhanced striatal dopamine release, particularly in the caudate (which underlie compulsive behavior), compared to obese individuals without BED. The results associated higher caudate dopamine levels to binge eating severity rather than to BMI (Wang et al., 2011).

Neural treatments

Despite the severity associated with BED, there are limited treatment options. Psychological and pharmacological treatments are so far suggested to be the most efficient way to treat BED (Ely & Cusack, 2015; Kessler et al., 2016; Peat et al., 2017), but relapse is high and negative consequences from pharmaceuticals are common (Ely & Cusack, 2015; Dalton, Campbell, & Schmidt, 2017). The understanding of the mechanisms underlying human eating behavior and eating disorders, such as BED, has in recent decades slowly making progress. For instance, several neuroimaging studies have reported a link between reward and cognition in the regulation of eating behavior (Dunlop, Woodside, & Downar, 2016; Georgii, Goldhofer, Meule, Richard, & Blechert, 2017; Val-Laillet et al., 2015). Neuroimaging and neuromodulation approaches are advanced medical techniques that may modulate food-related reward processes and thereby suppress binge eating (Dalton et al., 2017; Val-Laillet et al., 2015). As noted by Schmidt and Campbell (2013), treatments of eating disorders cannot remain 'brainless' (Val-Laillet et al., 2015).

Neurofeedback with cognitive reappraisal

Neurofeedback is a non-invasive training method aimed to change the neural plasticity and learned behavior by informing individuals with real-time status about their brain activity in order to provide learned self-regulation of the neural activity that arises (Val-Laillet et al., 2015). Neurofeedback is provided via fMRI, called real-time fMRI (rtfMRI), or via electroencephalography (EEG). Combining rtfMRI neurofeedback and EEG neurofeedback with cognitive reappraisal strategies (i.e., explicit emotion regulation strategies aimed to change cognitive processes) may increase learning, neuroplasticity, and clinical outcomes (Dalton et al., 2017; Val-Laillet et al., 2015). Disorders of ingestive behaviors, such as BED, are suggested to have dysfunctions in two brain systems involved in cognitive reappraisal: One brain system codes for the hypersensitivity to rewarding cues (e.g., ventral striatum, amygdala, insula, ventromedial PFC, including OFC), and the other brain system codes for the impaired cognitive control towards food (e.g., ACC and lateral PFC, including dorsolateral PFC). Cognitive reappraisal strategies are suggested to regulate appetite responses and inhibitory control to palatable food (Val-Laillet et al., 2015).

Few studies have examined neurofeedback with cognitive reappraisal for food regulation and food intake behavior in BED. However, studies examined obese individuals have demonstrated that neurofeedback with cognitive reappraisal may reduce the reward sensitivity to food-related cues by activating brain regions involved in inhibitory control and emotions (Val-Laillet et al., 2015). For instance, when obese individuals were instructed to think of the long-term benefits of not eating the rewarding food, fMRI showed increased activation in inhibitory regions such as ventrolateral PFC, and reduced activation in attention-related regions such as posterior cingulate cortex (Yokum, & Stice, 2013). Studies examining obese individuals may provide further insight into BED. However, more research focuses exclusively on BED is needed, since BED individuals seem to have unique structural and functional mechanisms compared with obese individuals and other eating disorders (Balodis et al., 2015; Kessler et al., 2016). Although neurofeedback with cognitive reappraisal for food regulation and food consumption may lead to improved cognitive control, it does not seem to enhance the results of cognitive regulation strategies on reward systems. Therefore, researchers suggest that neurofeedback with cognitive reappraisal could be more effective if it intensifies with neuromodulation such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) (Val-Laillet et al., 2015).

Transcranial magnetic stimulation and transcranial direct current stimulation

TMS and DCS are non-invasive neuromodulation techniques used for treating psychiatric disorders, such as depression, by correcting dysfunctional cortical regions (Val-Laillet et al., 2015). TMS uses magnetic fields to stimulate nerve cells in a target area of cortex, which is delivered with a coil placed over the scalp of the subject. Treatment sessions often occur daily, for a total of 20-30 sessions. Higher frequency stimulation (5-20 Hz) is suggested to be anodal or excitatory stimulation (i.e., the postsynaptic neuron is more likely to generate action potential), while low frequency (> 1 Hz) is suggested to be cathodal or inhibitory stimulation (i.e., the postsynaptic neuron is less likely to generate action potential) (Dunlop et al., 2016). Repetitive TMS (rTMS) is a variant of TMS involving repetitive sequences of pulses in order to induce more lasting changes in cortical activity (30-60 minutes after stimulation) (Lowe, Vincent, & Hall, 2017). In the case of tDCS, a weaker electrical stimulus is applied directly over the head of the subject, delivered by scalp electrodes to alter cortical activity in underlying regions. Similar to rTMS, treatment sessions occur daily, for a total of 10-30 sessions. "Sham" is used in all the mentioned non-invasive neuromodulation techniques, in

order to control the placebo effect, in which the individuals are hooked up to the device but not receive stimulation (Dunlop et al., 2016). When comparing TMS and tDCS, they both have pros and cons. For instance, TMS has a better spatial resolution, temporal resolution, and regulatory status (such as depression and migraine) compared with tDCS. In contrast, tDCS has better tolerability, safety, and portability (Val-Laillet et al., 2015).

The first study investigating the results of TMS and tDCS in eating behavior was applied for about ten years ago (Val-Laillet et al., 2015). Most non-invasive neuromodulation studies have focused on targeting the dorsolateral PFC, a complex brain region mediating executive functions involved in food consumption, such as working memory, inhibition, decision-making, and cognitive flexibility. The dorsolateral PFC has connections with brain regions such as the OFC, as well as medial OFC. Dysfunctions in dorsolateral PFC are associated with depression, stress, and substance abuse (Hoshi, 2015). Under-activation of the right dorsolateral PFC in BED individuals seems to have an impact on binge eating behavior. Research suggests that an increase of the activity of dorsolateral PFC may alter the reward-cognition balance and perhaps suppress reward-related mechanisms, such as cognitive inhibition and the ability to regulate emotions (Dunlop et al., 2016; Val-Laillet et al., 2015). Most tDCS and rTMS studies have investigated the efficiency of food cravings, subjective appetite, and food consumption on overweight and obese individuals with frequent binge eating. So far, few studies have focused exclusively on BED individuals. However, one study examining food craving, food consumption, binge eating desire, and binge eating frequency in 30 individuals with BED by targeting the dorsolateral PFC with tDCS and sham sessions, found that tDCS compared with sham decreased cravings for food such as sweets (Burgess et al., 2016). Studies evaluated the effectiveness of single-session and multi-sessions of rTMS and tDCS to the dorsolateral PFC for modulating food cravings and consumption in a laboratory and therapeutic settings have consistently found, via self-reported food cravings and appetite measures, that neuromodulators have an acute impression on food suppression (Val-Laillet et al., 2015). However, when the results of tDCS and rTMS studies were estimated separately, studies investigating rTMS single-sessions reported more consistent results than tDCS concerning food cravings. The result of food consumption with single sessions of rTMS or tDCS laboratory settings are not reliable across studies and several studies have reported limitations, such as methodological variability in the way the modulation was delivered, placebo effect, and assessment of eating behavior (Hall, Vincent, & Burhan, 2018; Lowe et al., 2017; Val-Laillet et al., 2015).

Deep brain stimulation

Deep brain stimulation (DBS) is an invasive neuromodulation technique aimed to deliver electrical pulses to specific brain regions. Case studies suggest that targeting the subgenual cingulate, NAc, or ventral striatal have provided promising results in treating disorders such as Parkinson's disease (PD), obsessive-compulsive disorder (OCD), epilepsy, and major depression (Dalton et al., 2017; Val-Laillet et al., 2015). DBS is often utilized for those patients whose symptoms have not responded well to medications or for those whose medications no longer control the symptoms (Val-Laillet et al., 2015). Although, DBS may be useful to some people, severe complications and negative implications are frequent, such as the risks of major surgery, cognitive dysfunction, and hypersexuality (Kringelbach et al., 2007).

With gained knowledge of dysfunctional reward and dopaminergic circuits in individuals with distorted eating behavior, the primary target of DBS is the hedonic regulations for food intake control (Val-Laillet et al., 2015). Several animal studies suggest that targeting certain brain areas with DBS may have acute results on food consumption. For instance, acute DBS in the medial shell of the nucleus accumbens (NAcc), a part of the reward circuitry involved in the regulation of food intake, significantly reduced the binge eating episodes of high-fat diet intake in mice with BED behavior (Prinz, & Stengel, 2018). Further, the DBS modulation of amygdala showed that rats stopped working for food rewards and rejected available rewards. Moreover, the rats showed an aversive response to normally liked sucrose tastes. These findings suggest that DBS not only may decrease motivational 'wanting' of food rewards but also blocking the 'liking' of rewards (Ross et al., 2016). Studies investigating the therapeutic implications on DBS and food consumption in BED individuals are sparse, and most researchers have so far examined the implications of DBS in obese individuals and AN patient (Prinz, & Stengel, 2018). However, those case studies examining DBS in BED suggest that DBS may reduce the severity and the tendency to binge eat by targeting areas involved in metabolic processes and satiety, such as the lateral hypothalamus (LH) and ventrolateral nucleus of the hypothalamus (VMN). For instance, one BED patient receiving DBS of the VMN reported reduced cravings, decreased the tendency to binge eat, as well as weight loss. However, when DBS was switched off, the patient reported increased binge eating and regained the body weight. These results suggest that VMH is a potential and promising target in the treatment of BED (Prinz, & Stengel, 2018). Further, one study examining the

effectiveness of DBS on the lateral hypothalamic area (LHA) in three patients with BED, of which one patient had severe BED and the other two modest BED, found that after 35 months follow-up, the BED patient with severe symptoms showed reduced binge eating. The other two patients with moderate BED showed no differences in binge eating symptoms (Whiting et al., 2013). Research speculates whether there is a relationship between the degree on the severity in BED and the effectiveness of DBS (Prinz, & Stengel, 2018). The application of DBS in BED should only be considered in patients who failed drugs and psychological treatment, and ethical aspects must be considered. Although current animal studies and human case studies of DBS have revealed promising results in decreasing binge eating symptoms, the application of DBS in the treatment of BED is in its infancy and far from being standardized (Prinz, & Stengel, 2018).

Vagus nerve stimulation

The vagus nerve and its relations to the neurocircuitry of the reward system seem to play an essential role in the regulation of food consumption. Research suggests that palatable food or dietary restraint reduces satiety signals and increase the orexigenic peptide ghrelin, which might lead to overconsumption of food and weight gain (Kentish et al., 2012). The vagus nerve, consisting of the right and the left vagus nerve, is the tenth cranial nerve and emerge from the medulla and conveying sensory information about the state of bodily organs, such as the heart, lungs, and digestive tracts to the central nervous system (Val-Laillet et al., 2015). Vagus nerve stimulation (VNS) is an invasive neuromodulation technique and it was delivered on the left cervical vagus nerve to patients for the first time for about 25 years ago in order to treat epilepsy and treatment-resistant major depressive disorder. VNS delivers electrical impulses to the vagus nerve, via a device that is implanted under the skin on the chest. The device sends electrical signals along the left vagus nerve to the brainstem, which then sends the signals further to specific brain regions. Common consequences after using VNS are headache, dizziness, and nausea (Grigolon, Cordeiro, & Trevizol, 2017). A non-invasive VNS has recently been developed, called transcutaneous vagal nerve stimulation (tVNS), in which the device is not implanted, but electrical impulses are targeted at the ear (Van Leusden, Sellaro, & Colzoto, 2015).

VNS therapy is suggested to induce multiple physiologic functions related to food consumption, energy metabolism, as well as glycemic control, which may result in weight

loss. When treating epilepsy with VNS, researchers observed different implications, including significant weight loss. Moreover, when patients with treatment-resistant major depressive disorders were receiving VNS, they reported decreased craving rates for sweet food compared with patients not receiving VNS (Grigolon et al., 2017). These reports have generated further animal research in order to evaluate the outcome of VNS on food consumption and related weight loss. The first study to investigate the implications of VNS on food consumption was on rats, and it appeared that chronic VNS reduced food consumption and body weight. Moreover, the study showed that bilateral VNS seems to be more effective than unilateral VNS (Laskiewicz et al., 2003; Val-Laillet et al., 2015). Another animal study proposed that chronic VNS seems to reduce weight gain, food intake, and cravings for sweets in obese minipigs (Val-Laillet et al., 2015). However, even though positive results have been reported in almost all animal models, the same results have not been observed in humans. Due to regulatory restraints, human studies have targeted the left cervical vagus nerve, and stimulation settings have been similar to those used for epilepsy and depression. After long-term stimulation in humans, only half of the subjects reported weight loss. No clear explanation exists for these results. Thus, some researchers suggest that obese individuals are less responsive to VNS compared with normal weight individuals. Another suggestion includes the fact that a bilateral VNS is needed to receive the same results as in animal models. Alternatively, the explanation of the limited success of VNS in humans may be the poor understanding of the action of VNS on the brain systems in relation to food consumption (Val-Laillet et al., 2015).

Discussion

The goal of this thesis has been to review the results of research on BED to provide a synthetic view of the current general understanding of BED, as well as the neural correlates of the disorder and neural treatments. The hypothesis was that the loss of control in BED is related to neuronal alterations. Since BED is a complex phenomenon caused by several risk factors, it has been difficult to draw general conclusions and connections between the evidence. However, the studies that have been used in this thesis have shown some unitary patterns: The loss of control characterized in BED appears to include changes in reward systems as well as alterations in cortico-striatal circuitry, leading to increased impulsivity, compulsivity, and reward sensitivity (Kessler et al., 2016; Schag et al., 2013), along with

elevated attentional biases to food-cues (Schmitz et al., 2014), and cognitive dysfunctions (Mobbs et al., 2011).

Food is necessary for humans. From an evolutionary perspective, humans had preferred food high in fat, sugar, and calories when it was available because that strategy had the best survival benefits. However, in most Western societies today, there is plenty of processed, fatty, and sugaring food, and the survival strategy is no longer needed. Despite this, in developed countries, the majority of adults are nowadays more overweight than underweight (Davis, 2015). Since evidence has shown that chronic consumption of palatable foods may change brain function in those with increased vulnerability (Berridge, 2009), there are speculations whether the symptoms of BED are caused by the food itself, similar as addictive drugs (Schulte et al., 2016). However, whether BED is an addiction disorder is not yet established (Gearhardt et al., 2013; Schulte et al., 2016; Ziauddeen et al., 2012). The prevalence of BED is the highest among all eating disorders, but research suggests it may be higher due to hidden statistic among obese individuals (Brownley et al., 2016; Davis, 2015). Genetic studies of dopaminergic and opioidergic polymorphisms have found a correlation between genotypes and rewarding food consumption that may provide evidence in why some people develop obesity, while others are developing BED (Val-Lailliat et al., 2015). Those obese individuals carrying the A1 allele appears to be more prone to be involved in hedonic activities because of reduced dopamine D2 receptor availability (Davis et al., 2012). This result may provide support from the reward deficiency model (Blum et al., 1996). However, those individuals with the *Tag1A+* allele appears to be represented in both obese individuals and individuals with BED and seems to have hyperresponsiveness to rewarding food stimuli (Davis et al., 2012). This result may provide support from the reward surfeit model holding that individuals with elevated reward region responsivity to food are at elevated risk to overeating (Stice et al., 2008, Val-Laillet et al., 2015). However, according to Davis and colleagues (2009), most obese individuals with BED are suggested to carry the *OPRM1* gene, which is associated with an impulsive and compulsive food consumption without pleasure and subsequent consequences. The *OPRM1* gene includes one A2 allele which increases dopamine release in NAc and one G allele which has an exaggerated response to the opioid systems. This combination seems to reflect the ‘wanting’ without ‘liking’ process (Berridge, 2009; Davis et al., 2007). These findings may strengthen by the incentive sensitization model holding that repeated food intake of palatable food may change the reward systems that usually regulate the incentive salience to food and provokes hypersensitive responses leading

to a compulsive binge eating behavior (Robinson, & Berridge, 1993). These genetic findings may to some extent, explain why some individuals become obese, while others develop BED. However, even though BED appears to be a phenotype of obesity (Davis et al., 2009), not all individuals with BED are obese (Goldschmidt et al., 2011). An interpretation to this may be that normal weight individual with BED have the *Tag1A+* allele, which make them less prone to develop compulsive binge eating, or that normal weight individuals with BED appears to be more engaged in restraint eating (Goldschmidt et al., 2011). A further interpretation may be that normal weight individuals have a less degree of reward sensitivity leading to fewer binges including a smaller amount of food compared with obese individuals with BED. Studies examining normal weight individuals with BED are few. Therefore, it is proposed that this group need further investigation.

Even though few neuroimaging studies have been conducted on BED individuals, some unitary evidence has been revealed that provide evidence for that brain regions alterations underlies rewarding behavior (Kessler et al., 2016; Schienle et al., 2009). When BED individuals are exposed to pictures of palatable food they report increased activation in ventral striatum, which underlies goal-seeking behaviors, motivation, and reward sensitivity; insular cortex, which underlies such as decision-making, taste perception, and feeding regulation; ACC, which underlies attention, reward anticipation, decision-making, and impulse control; OFC, which underlies decision-making; medial OFC, which underlies the subjective evaluation of the rewarding stimuli; and amygdala, which underlies such as emotions, learning, attention, and perception (Balodis et al., 2013a; Kessler et al., 2016; Schienle et al., 2009). When BED individuals are exposed to non-rewarding stimuli, they show decreased activation in bilateral ventral striatal and insular cortex (Balodis et al., 2013a). BED individuals appear to show lower left and bilateral OFC volumes, and lower bilateral caudate volumes in decision-making tasks, which comprises habitual and compulsive behavior (Voon et al., 2015). Studies have also found decreased activation in prefrontal areas involved in executive functions (Balodis et al., 2013a; Balidos et al., 2013b). These results provide support for that BED is linked with cognitive dysfunctions (Kessler et al., 2016; Schag et al., 2013). However, in some tasks measuring attention and inhibitory control both obese individuals without BED and individuals with BED seem to perform worse than normal-weight individuals (Schmitz et al., 2014; Wu et al., 2013). This result may be correlated to obesity (Giel et al., 2017), due to reduced dopamine availability (Berridge, 2009; Davis et al., 2007), as well as they seem to show increased impulse responding to food-cues

(Houben et al., 2014). An interpretation to these findings may be that some obese individuals have the A1/A2 genotype (Davis et al., 2009), which increase their responsiveness to rewarding food stimuli (Davis et al., 2012).

Impulsivity, compulsivity, and reward sensitivity toward palatable food appears to be highly associated with BED and linked to alterations in reward systems (Galanti et al., 2007; Schag et al., 2013; Schienle et al., 2009). These traits and states seem to be associated with different addiction disorders (Davis, 2015), as well as impulsive/compulsive disorders (Fernández-Aranda et al., 2013). The relationship with impulsive/compulsive disorders appears to be linked to the *DAT1* due to its association with reduced dopamine transporter and increased synaptic dopamine (Davis et al., 2007). These results may be strengthening by the notion of that BED individuals report reduced food-seeking behavior and appetite, as well as a reduction of compulsive behavior when they are treated with amphetamine medication (Brownley et al., 2016; McElroy et al., 2016; Peat et al., 2017). The risk of developing substance abuse may be linked to the A1 allele, which is associated with hedonic pleasures (Davis et al., 2009). Studies investigating similarities between addiction abuse and BED have found several shared mechanisms (Kessler et al., 2016; Schulte et al., 2016). Typically, BED individuals have an intense urge for certain (palatable) food, which seems to trigger relapses when they are trying to restrain from the bingeing behavior. Restraint behavior appears even in addiction, such as repeatedly trying to cut back the consumption of drugs or addictive behavior (Schulte et al., 2016). However, some researchers argue that "food addiction" may be referred to those BED individuals with YFAS "food addiction" (Davis, 2015; Schulte et al., 2016). This may be interpreted as those BED individuals with YFAS "food addiction" carrying the *OPRM1* gene has over time developed tolerance to food, which makes their symptoms similar to more traditional addictive abuse. Others argue that "food addiction" is the process of 'wanting' without 'liking' (Berridge, 2009) since the degree of reward sensitivity seems to have a critical role in rewarding behavior. Impulsivity and reward sensitivity has also been reported in obese individuals but to a lesser degree compared with BED (Giel et al., 2017). Studies have found that those obese individuals with drug addiction seem to have lower reward sensitivity leading to compensatory drug intake (Blum et al., 1996; Ziauddeen et al., 2013). This may be interpreted as the A1 allele may underlie addiction abuse, while the polymorphisms *OPRM1* and *Tag1A* allele may underlie the loss of control over eating in BED and support the notion of dissociation of the dopaminergic and opioidergic reward systems. However, *if* palatable food is similar to addictive drugs and

thereby alter the connections in reward systems, interventions might consider to take the incentive sensitization model (Robinson, & Berridge, 1993) into account and limiting such foods, particularly for children, whose reward system is still developing, as well for those with a genetic predisposition for eating disorder or obesity (Balidos et al., 2015). Current treatments such as CBT argues that patients with eating disorders should not avoid certain food, but instead be trained to eat all kinds of foods, including palatable food. In contrast, Overeaters Anonymous (OA), similar to Alcoholics Anonymous (AA), has adopted the "food addiction" model, suggesting palatable food may be equal to addictive drugs and encourages their members to renounce that kind of food. However, the empirically support on OA's influence on "food addiction" is limited (Schulte et al., 2016).

Neural treatments, including neuroimaging and neuromodulation approaches, appears to be emergent and promising tools in order to understand the neural aspects of BED and provide innovative treatment strategies (Val-Laillet et al., 2015). However, few studies of neuroimaging and neuromodulation approaches have exclusively examined BED (Burgess et al., 2016). Thus, studies of obese individuals (Yokum & Stice, 2013), lesion studies (Dalton et al., 2017; Grigolon et al., 2017), and animal studies (Laskiewicz et al., 2003; Val-Laillet et al., 2015) have so far provided useful knowledge of reward systems, metabolic processes, cognitive and emotional processes, as well as brain functions, which could be translated to BED (Val-Laillet et al., 2015). For instance, studies have shown that neurofeedback with cognitive reappraisal may reduce the reward sensitivity to food-related cues by activating brain regions involved in inhibitory control and emotions (Val-Laillet et al., 2015). A crucial outcome predictor across treatments of BED appears to be a rapid response (Grilo et al., 2006; Hilbert et al., 2019). Studies of rTMS and tDCS targeting the dorsolateral PFC have consistently found that neuromodulators have an acute outcome on food suppression (Val-Laillet et al., 2015). Interesting findings have been made in an animal study suggesting that targeting amygdala with DBS may decrease motivational 'wanting' of food rewards, as well as blocking the 'liking' of rewards (Ross et al., 2016), since amygdala seems to mediate both arousal and sensory aspects of reward linked to emotions (Murray, 2007). This result may be promising since some μ -opioid receptor antagonist in studies on BED seems to increase the hedonic 'liking' response (Cambridge et al., 2013).

Animal studies investigating the result of VNS suggest that intervention reduces appetite as well as decreases the cravings for sugaring foods (Val-Laillet et al., 2015). Considering the

different target areas in neuromodulation approaches, they could in the future be utilized based on each's individual's severities. For instance, those BED individuals with modest BED may be applied neurofeedback with cognitive reappraisal, while those BED individuals with YFAS "food addiction" may need DBS or VNS. In fact, it may be so that DBS is more effective in those with worse symptoms (Prinz, & Stengel, 2018). Although neuromodulation approaches have presented some promising results, further research is needed in order to confirm its effectiveness. What is then required for neuromodulation techniques to be included in the medical treatment of BED? According to Val-Laillet et al. (2015), research needs to identify new biological markers of brain functions in BED. Furthermore, the treatment needs to be personalized; that is, each patient's genetic, anatomical, and physiological characteristics must be taken into account. Since BED is a complex phenomenon, including both psychological and physiological factors, treatments on BED entails several ethical dilemmas. For instance, individuals with BED often experience a lack of control in their lives, whereas it is of importance to developing and restore a sense of autonomy in the treatment. Furthermore, since neuromodulation techniques may modify conscious and unconscious functions, self-control, and decision-making processes, it is necessary that the decision to include in a particular therapy belongs to the patient. It is essential to be aware that societal views and pressure likely influence individual decisions. Therefore, medical authorities need to be aware of the rapid development of new technologies and approve and monitor all therapies. Research on BED and future treatments must carefully consider the ethical principles of justice, beneficence, and nonmaleficence. Research should bear in mind the wise words from Hippocrates: "First, do not harm."

Limitations, strengths, and future directions

This thesis has several limitations. In the search for the general understanding of BED and its neural correlates, this thesis has not taken the neuroendocrine system into account, as well as the deeper understanding of the role of emotions. Inadequate knowledge of the reward systems and its correlates have resulted in that some important aspects have been omitted. Further, this thesis has provided results from studies with methodological problems, such as Davis et al. (2009), which was based mostly on white female participants, and had a small sample, as well as low replicability. Overall, neuroimaging, neurocognitive, genetics, and animal studies have so far contributed with strong evidence on the neurobiology of BED, but research is still in its infancy, and further research is needed (Kessler et al., 2016). Genetic

and heritability studies have revealed important evidence related to obesity and BED that may provide support for the understanding of the neuronal as well as underlying behavioral mechanisms of the disorder (e.g., Davis et al., 2012). However, further genetic studies need to focus exclusively on BED to find effective treatments (Bulik et al., 2016). Studies examining the role of the reward system in BED have shown unitary results, but further research is needed to confirm its consistency (Kessler et al., 2016; Ziauddeen et al., 2012). Therefore, further studies need to investigate other neurotransmitters such as endogenous dopamine, serotonin, opiate involved in the striatum and cortex in obese individuals with BED versus obese individuals without BED (Kessler et al., 2016). The majority of existing neuroimaging studies have investigated females. However, since BED is common even among men, future studies should also examine this group, in order to discover potential gender differences (Balidos et al., 2015). Even though BED is mostly represented by obese individuals, several BED individuals are of normal weight. Thus, few studies have investigated this group and further research is warranted (Goldschmidt et al., 2011). Studies examining the population prevalence of BED are rather few and based mostly on U. S. data (Kessler et al., 2013; Davis, 2015). In order to gain further understanding of BED and if certain food is related to the rewarding eating behavior, it would be of interest to examining other ethnicities with other food preferences, such as Asians with BED. Research has not yet established whether BED is an addiction disorder or not, and further studies in this field are highly needed. Until then, future research needs to understand the concept of disordered eating, such as the concept of binge eating and “food addiction” (Schulte et al., 2015). Future research should also examine the reward surfeit and the incentive sensitization models further and investigate individual differences in neural responses to palatable food, such as what tastes cause the neural vulnerability leading to obesity and BED (Val-Laillet et al., 2015)

Conclusion

BED is characterized by loss of control over eating. The frequent binge eating episodes appears to be associated with altered impulsivity, compulsivity, and reward sensitivity, and cognitive dysfunctions. This may be due to altered functions of insular, orbitofrontal, and prefrontal cortices and striatum. A similar alteration as in those of substance and addiction abuse disorders. Evidence suggests that dissociation of dopaminergic and opioidergic neurotransmission functions is an essential contributor to the severity of the disorder.

Increased knowledge of the neurobiological mechanisms underlying BED has paved the way for research investigating neuromodulation techniques targeting brain regions involved in reward processes of food intake. However, although neuromodulation approaches have presented some promising results, further research is needed in order to confirm its effectiveness on BED.

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