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Neuroendocrine modulation of food reward in binge eating: Insulin sensitivity has dissociable effects on insular food-reward signals in binge eating

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List of abbreviations

Abbreviation	Designation
ACC	Anterior Cingulate Cortex
AN	Anorexia Nervosa
BED	Binge Eating Disorder
BES	Binge Eating Störung
BMI	Body-Mass-Index
BN	Bulimia Nervosa
BOLD	Blood-Oxygenation-Level-Dependent
CBT	Cognitive Behavioral Therapy
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DA	Dopamine
dlPFC	Dorsolateral Prefrontal Cortex
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDE	Eating Disorder Examination
EDE-Q	Eating Disorder Examination-Questionnaire
EEfRT	Effort Expenditure for Reward Task
EKF	Else Kröner-Fresenius-Stiftung
EMA	Ecological Momentary Assessment
EPIs	Echo-Planar Images
FCR	Food-Cue Reactivity
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
GM	Grey Matter
GLP-1	Glucagon-like peptide-1
HOMA-IR	Homeostasis Model Assesment for Insulin Resistance

ICD	International statistical Classification of Diseases and related health problems
IOFC	Inferior Orbitofrontal Cortex
INI	Intranasal Insulin
IPT	Interpersonal Therapy
NAc	Nucleus accumbens
noBE	No Binge Eating
OFC	Orbitofrontal Cortex
PCOS	Polycystic ovary syndrome
ROI	Regions Of Interest
SSRI	Selective Serotonin Reuptake Inhibitors
subBED	Subsyndromal Binge Eating Disorder
T1w	T1-Weighted
T2D	Type 2 Diabetes
TE	Echo Time
TR	Repetition Time
UKT	University Hospital Tübingen
VAS	Visual Analog Scale
VS	Ventral Striatum
VTA	Ventral Tegmental Area
WM	White Matter

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1 Introduction

Binge eating disorder (BED) is the most common typical eating disorder with the highest prevalence rate in the population (Galmiche, Dechelotte, Lambert, & Tavolacci, 2019; Udo & Grilo, 2018) and is described by recurring episodes of overeating without compensatory countermeasures such as vomiting or excessive exercise. This clearly distinguishes the disease from other eating disorders such as bulimia nervosa (BN) and anorexia nervosa (AN). Patients are often overweight or obese (BMI > 30 kg/m^2) and increasingly suffer from physical comorbidities such as arterial hypertension, type 2 diabetes mellitus (T2D) and pain disorders (Bhaskaran, Dos-Santos-Silva, Leon, Douglas, & Smeeth, 2018), as well as from psychological comorbidities such as depression, substance abuse and anxiety disorders (R. C. Kessler et al., 2013). Therefore, BED patients are assigned an increased mortality. In addition, BED is associated with a significantly lower quality of life compared to healthy participants (Gudmundsdóttir et al., 2023). So far, there are no effective treatment options, as it has been shown that only about half of all patients respond to their therapy and live without binge eating afterwards (Linardon, 2018).

Among established mechanisms, food craving and overeating play a crucial role in BED (Ferrer-Garcia et al., 2017; Leslie, Turton, Burgess, Nazar, & Treasure, 2018) and the occurrence of a binge eating episode results from a complex interplay of external and internal signaling (Hartogsveld, Quaedflieg, van Ruitenbeek, & Smeets, 2022). In the search for the pathomechanism, it has already been investigated whether people with BED react more sensitively to food stimuli as a reward and whether excessive food intake is controlled in a dopaminergic manner. Visual food-cues, (e.g., pictures of palatable food) activate specific neuronal brain regions and can trigger appetite (Reichelt, Westbrook, & Morris, 2015) and food craving (Boswell & Kober, 2016). Since food-cues work as a learned conditioned stimuli, pictures of food not only signal the availability of food but also an upcoming reward. Previous research already found higher food-cue reactivity in people who suffer from BED, especially in areas related to reward and motivation (Aviram-Friedman, Astbury, Ochner, Contento, & Geliebter, 2018; J. E. Lee, Namkoong, & Jung, 2017; Schienle, Schafer, Hermann, & Vaitl, 2009). Another brain region that has been underestimated to date, the insula, also seems to be significantly involved in eating behavior. The insula forms the primary gustatory center and is also part of the paralimbic system. The insula is integrated into the vegetative nervous system through interoceptive afferents of the gastrointestinal tract. There it regulates the energy homeostasis by processing food-related information (e.g. visual food-cues) and by comparing peripheral markers, such as circulating insulin or energy stores (Kroemer et al., 2013). The insula contributes to a hedonic drive in food intake since external information is processed through reward-related areas (Frank, Kullmann, & Veit, 2013). Previous research found higher functional activity in insular cortex in obese versus lean participants in response to food-cues (Avery et al., 2017). In addition, a higher activity was observed in food craving (Pelchat, Johnson, Chan, Valdez, & Ragland, 2004) and in BED (Aviram-Friedman et al., 2018).

So, we know that food intake is controlled by interactions of the central nervous system (CNS) with metabolic signals that mediate the nutrient state of organism. Here, insulin act as a negative feedback signal in reward-related food intake because it signals satiety. We in fact have numerous insulin receptors in reward centers and in the cortex (Kullmann et al., 2020). By intranasally applied insulin it has already been shown that ‘brain insulin resistance’ could lead to several pathologies, including overeating (Hallschmid, 2021). Patients with binge eating are more at risk of developing a metabolic syndrome that is associated with insulin resistance (J. E. Mitchell, 2016). Previous research already observed altered communication between insula and coupled regions in T2D (Farr & Mantzoros, 2018). Taken together, there must be connections between insula activity and insulin resistance in BED. And so far, it remains unclear how neuroendocrine modulation through insulin sensitivity effects neuronal response to food reward especially in BED. Therefore, we hypothesize that altered insulin sensitivity in BED affect neuronal activation in the insula. Here we wanted to gain new insights into the interplay of metabolic and neuronal processes though investigating peripheral insulin resistance (HOMA-IR) and through performing a food-cue reactivity task in fMRI.

1.1 Binge eating disorder (BED)

1.1.1 Definition and DSM-V criteria/ICD 11

BED was first included as a research diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) by the American Psychiatric Association in 1994 and has emerged as the most common typical eating disorder in recent years (Galmiche et al., 2019; Udo & Grilo, 2018). Since the symptoms of BED can be clearly distinguished from other eating disorders, it was recognized as a stand-alone clinical diagnosis in the DSM-V in 2013 (American Psychiatric Association, 2013) including the following definition:

BED is described by recurring episodes of overeating, in which an above-average amount of food is consumed within a limited period of time. Those affected by BED experience a loss of control and overeating occurs at least once a week for the past 3 months. In comparison to other eating disorders - such as BN - no inappropriate, compensatory behavior (purging) such as vomiting or taking laxatives, excessive sport or fasting is applied (American Psychiatric Association, 2013).

BED is classified using the DSM-V including following diagnostic criteria:

(A): Recurring episodes of binge eating with two main characteristics

1. A greater amount of food is consumed in a definable period of time (~2h) than would be the case in similar circumstances in a similar period of time in persons without BED.
2. During binge eating, those affected feel a loss of control because they cannot limit or stop their consumption.

(B): At least 3 of the following 5 general behavioral characteristics occur during binging:

1. Eating until uncomfortable feeling of fullness

2. Consumption of larger quantities despite lack of hunger pangs and hasty eating
3. Eating faster than normal
4. Eating alone because of the embarrassment of overeating
5. Feelings of disgust, shame, or dejection after a binge

(C): Suffering or having stress from binge eating episodes
(D): A binge eating episode occurs at least once a week for the last 3 months
(E): No regularly inappropriate compensatory behaviors to prevent weight gain and binge eating does not occur exclusively in the context of an AN or a BN

The current degree of severity can be classified as follows:

- Mild: 1-3 binge episodes per week
- Moderate: 4-7 binge episodes per week
- Severe: 8-13 binge episodes per week
- Extreme: 14 or more binge episodes per week

According to International Statistical Classification of Diseases and Related Health Problems (ICD-10), BED was referred to as atypical BN or as an unspecified eating disorder (ICD-10: F50.9). With the entry into force of ICD-11 in January 2022 BED is classified as a separate diagnosis (ICD-11: 6B82).

1.1.2 Epidemiology

BED is the most common eating disorder compared to BN and AN with the highest lifetime prevalence rates worldwide, as it was estimated with 1.53 % and is nearly 10 times higher than AN (Qian et al., 2022). Yu and Muehleman (2023) found that Covid-19 also contributed to higher development and worsening of BED in western countries (USA & Italy) due to increasing anxiety and stress levels. As well as snacking with boredom and less attending to therapy sessions.

Women are more likely to show harmful eating behavior in the form of restriction or binge eating than men (Stephan Herpertz, Fichter, Herpertz-Dahlmann, & Hilbert, 2018), which results in a form of a gender-specific distribution in BED. But it is noticeable that BED is the most common eating disorder in men (Marzilli, Cerniglia, & Cimino, 2018; Striegel, Bedrosian, Wang, & Schwartz, 2012). The female to male ratio in the lifetime prevalence of BED is more balanced than in BN and AN (Qian et al., 2022) with 6:4 compared to 9:1 (Guerdjikova, Mori, Casuto, & McElroy, 2019).

As with AN and BN, the prevalence of BED increases with age and occurs more frequently in middle age (Brewerton, Rance, Dansky, O'Neil, & Kilpatrick, 2014). Interestingly, there are not any significant differences in prevalence in high-, middle- and low-income countries, which Erskine and Whiteford (2018) attributed to the increasing numbers of obesity worldwide.

Although there is limited data available on the incidence (S. Herpertz, Fichter, M., Herpertz-Dahlmann, B., Hilbert, A., Tuschen-Caffier, B., Vocks, S., Zeeck, A., 2018), it appears that late adolescents are most at risk of an initial manifestation (Bohon, 2019). Hudson, Hiripi, Pope, and Kessler (2007) found that the median age of onset of BED is 21 years. But there are also studies indicating that BED can occur long before late adolescence (Kjeldbjerg & Clausen, 2021). Prevalence of BED (1.32 %) and subclinical BED (3 %) were observed in childhood and adolescence (Kjeldbjerg & Clausen, 2023) indicating that BED not only occurs in adults and further studies should also include younger study samples.

1.1.3 Etiology

The pathogenesis is the subject of current research, and the exact mechanism is still relatively unknown, as BED was only recognized as a stand-alone clinical diagnosis in 2013. The multifactorial etiology of BED, including altered structural & functional mesocorticolimbic pathways with changes in neurotransmitter receptor density, expression and secretions, mediating decision-making and hedonic eating behavior, as well as deviated cognitive functions, motivation, reward and emotions through reinforcement-learning and interoceptive signaling (Bulik et al., 2022) is subject of this work and we highlight the metabolic-neuronal component in detail in the next chapters.

1.1.4 Diagnostic

Note: The dissertation refers to the german S3 guideline ‘Diagnostik und Behandlungen der Essstörungen’ which was published in 2018 and is currently being revised. In the meantime, the new ICD-11 classification has been implemented.

If an eating disorder such as BED is suspected and the DSM-V or the ICD-10 criteria apply, a diagnosis should be initiated (S. Herpertz, Fichter, M., Herpertz-Dahlmann, B., Hilbert, A., Tuschen-Caffier, B., Vocks, S., Zeeck, A., 2018). There are various questionnaires to choose from, which ask about eating behavior and possible comorbidities in a structured way. A diagnostic tool that is frequently used in research and clinical practice is the Eating Disorder Examination (EDE) (C. G. Fairburn & Cooper, 1993), it also exists in a german language version (Hilbert, Tuschen-Caffier, & Ohms, 2004) and contains 4 scales (restraint, eating concern, shape concern and weight concern subscale). In addition, 14 diagnostic items allow a differential diagnostic classification of AN, BN and BED, including DSM-IV and ICD-10 criteria. The expert interview using EDE takes about 45 min. The Eating Disorder Examination-Questionnaire (EDE-Q) by Fairburn and Beglin (1994) (german: Hilbert, Tuschen-Caffier, Karwautz, Niederhofer, and Munsch (2007)) is a further development that summarizes the obligatory questions of EDE and reduces the diagnostic time to 15 min. EDE-Q can be used as a screening tool and for follow-up, but does not replace the more detailed EDE (S. Herpertz, Fichter, M., Herpertz-Dahlmann, B., Hilbert, A., Tuschen-Caffier, B., Vocks, S., Zeeck, A., 2018).

1.1.5 Risk factors

To date, an interplay of biological, psychological, and social risk factors has been identified that appear to contribute to the development of BED. Eating disorders are hereditary and the genetic association of binge eating has been shown in family/twin studies (hereditary 0.39 to 0.45 (Yilmaz, Hardaway, & Bulik, 2015)) and is topic of genome-wide associated data (Bulik, Blake, & Austin, 2019; Bulik et al., 2022).

Previous studies have focused on polymorphic dopamine (C. Davis et al., 2008; C. Davis et al., 2012; C. A. Davis et al., 2009) and mu-opioid receptor genes (C. A. Davis et al., 2009), as these are associated with the hedonic reward system.
Physical and emotional abuse in childhood was associated with BED (Solmi et al., 2021) and a higher prevalence was observed in persons who suffered traumatic life experiences (e.g., war veterans) hence overeating might be used as coping mechanism (Keski-Rahkonen, 2021; Wooldridge, Herbert, Dochat, & Afari, 2021). In addition, BED shows a high co-morbidity with post-traumatic stress disorder (Mason et al., 2017). Stice, Gau, Rohde, and Shaw (2017) identified risk factors in female adolescents that predicted future onset of BED including overeating, dieting, thinness expectations, thin-ideal internalization, negative affect, and functional impairment.

1.1.6 Therapy and outcome

Due to the multifactorial etiology and the various symptoms that can have a negative impact on the social, psychological, and physical spheres, various treatment goals are considered in the individual treatment plan. In addition to the treating of binge eating and the associated problems of shame or self-esteem as well as obesity, concomitant psychological disorders such as depression or anxiety are also treated. According to the german '*S3 guideline for the diagnosis and treatment of eating disorders S. Herpertz, Fichter, M., Herpertz-Dahlmann, B., Hilbert, A., Tuschen-Caffier, B., Vocks, S., Zeeck, A. (2018)*', psychotherapy is considered the therapy of first choice for BED, since cognitive behavioral therapy (CBT) showed extensive evidence of efficacy in adults and should be offered to patients. This recommendation remains constant with new meta-analyses supporting the long-term effectiveness of psychotherapy (performed mainly with CBT), regarding a significant decreased frequency of binge-eating episodes and depression in more than 12 months posttreatment, with weight loss (1.9 - 6.1 kg) and a abstinence rate between 46 and 52 % (Hilbert et al., 2020). Interpersonal therapy can be recommended as an alternative psychotherapy, as it showed the best results for abstinence rate (Linardon, 2018). However, according to the S3 guidelines for psychotherapy, interpersonal therapy is not a recognized psychotherapy method that is covered by health insurances in Germany. There is limited evidence for depth psychology-based psychotherapy. It can be offered as an alternative to CBT. Linardon (2018) found that only 51 % of patients that underwent any kind of BED therapy (not pharmacological/surgical) showed complete remission posttreatment and in ≥ 12-month follow-ups, which suggests that a large proportion of those affected do not respond to psychological therapy.

Another therapy option for BED contains drugs. Psychotropic drugs are currently not approved for the treatment of BED in Germany. Therefore, patients must be informed about off-labe use, as there are no long-term studies on long-term effects of taking psychotropic drug. Second-generation antidepressants, anticonvulsants, and centrally acting stimulants such as lisdexamfetamine are therefore only considered when psychotherapy is refused or unsuccessful. The positive effects of lisdexamfetamine on binge eating behavior compared to placebo convinced the Food and Drug Administration (FDA) for approval in the therapy of BED in 2015. In a randomized clinical trial Hudson, McElroy, Ferreira-Cornwell, Radewonuk, and Gasior (2017) showed that lisdexamfetamine treatment led to a significantly lower relapse risk than placebo within 6 months (3.7 vs. 32.1 %).

Muratore and Attia (2022) found several positive pharmacological effects in a meta-analysis. Especially SSRIs (e.g. Flouxetin, Citalopram) are associated with significant reductions in binge eating episodes, a higher rates of remission and abstinence of binge eating. Unfortunately no weight reduction could be achieved with the use of SSRIs. Topiramat, a anticonvulsant, achieved not only a reduction in binge eating episodes but also led to weight loss.

Dossat et al. (2023) found GLP-1 receptor expression in insular gustatory cortex in mice and observed that receptor activation affected food intake. Consequently, in patients with BED and T2D, antidiabetic drugs (e.g., Dulaglutide and Gliclazide) reduced binge eating episodes, appetite, BMI, and fat mass (Da Porto et al., 2020) and Exenatide (i.e., a GLP-1 receptor agonist) reduced anticipatory brain responses to food in the insula, which might be mediated by improved insulin sensitivity (van Bloemendaal et al., 2015). Radkhah et al. (2025) conducted a systematic review and meta-analysis for glucagon-like peptide 1 (GLP-1) agonist studies and found greater weight loss/reduced BMI as well as a significantly improved Binge eating scale. Anti-obesity drugs as might improve body weight as well as severity and frequence of BED (Riboldi & Carrà, 2024).

Combination therapies with psychotherapy, psychotropic/anti-obesity drugs, and conservative weight loss therapy should be discussed on a individual basis when monotherapy is not successful. Inpatient treatment should be based on strict indications. For example, in the case of pronounced somatic or psychological comobidities, a high degree of disease severity, social or familial influencing factors that would strongly hinder or complicate a therapeutic or recovery effect, or the need for treatment by a multiprofessional team is seen.

Aylward, Konsor, and Cox (2022) conducted a meta-analysis and found that bariatric therapy (e.g., gastric banding/gastric bypass surgery/sleeve stomach) as obesity therapy in BED showed fluctuating results recording binge eating post-surgery. Since restricted gastric volume hinders consuming a higher amount of food, the prevalence of binge eating episodes are typically lower after surgery but tend to increase over time. Due to the recurring symptoms of binge eating, anxiety and depression post-surgery Ribeiro, Giapietro, Belarmino, and Salgado-Junior (2018) pointed out the importance of ongoing psychological assessment and interventions after bariatric surgery. And there is still controversy as to whether untreated BED counts as a contraindication to surgical therapy or not, as it could worsen the outcome (Sarwer et al., 2019).

Javaras et al. (2024) investigated the natural course of BED in a longitudinal follow-up study with interviews and questionnaires at baseline, at 2.5 and at 5 years after. Over the time full BED decreased, as subBED and no BED increased. But full remission of BED with higher BMI takes many years and often relapse.

1.1.7 Comorbidities, mortality, and implications on society

Those affected by BED show a high co-occurrence of other mental health issues (Keski-Rahkonen, 2021) and 22.9 % of people suffering from BED stated a suicide attempt (Udo, Bitley, & Grilo, 2019). There is a significant occurrence of lifetime mood disorders (69.9 %), with major depressive disorder as the most prevalent (65.5 %), substance (alcohol/drugs) use disorders (67.7 %), any anxiety disorder (59 %), with generally anxiety disorder as the most prevalent (33 %), any personality or conduct disorder, (e.g., borderline or schizotypal) with 56 %, and post-traumatic stress disorder (31.6 %) (Udo & Grilo, 2019). BED is also associated with chronic somatic conditions such as hypertension (31.2 %), high cholesterol (27.2 %), arthritis (24 %), sleep problems (21.3 %), heart conditions (17.2 %), T2D (13.6 %) and fibromyalgia (5.3 %) (Udo & Grilo, 2019). Since patients with BED are more prone to physical and psychological comorbidities (Iqbal & Rehman, 2020; Yu & Muehleman, 2023) they are assigned an increased mortality. The standardized mortality ratio is 1.50 to 1.77 (Keski-Rahkonen, 2021).

In addition to the personal disadvantages caused by BED, there is also a high monetary burden on society, which must bear the costs for therapy and comorbidities. For example, Streatfeild et al. (2021) researched that BED caused almost a third of the economic costs associated with eating disorders. In the fiscal year 2018-2019 BED accounted for 30 % of overall $64.7 billion (95 % CI: $63.5–$66.0 billion). Since the mechanisms for the development and maintenance of BED are largely unclear, the pathophysiological processes must be further investigated in order to be able to develop more successful therapies (Aguera et al., 2020; Jowik, Dutkiewicz, Slopien, & Tyszkiewicz-Nwafor, 2020). In addition, there is a political and social interest in primary prevention and in the implementation of early detection examinations as part of secondary prevention to be able to offer evidence-based therapy as quickly as possible (Streatfeild et al., 2021).

1.2 Binge Eating and the reward system

There are several hypotheses about the development of BED. At the neuropsychological level, the similarity of obesity and BED to substance abuse or drug addiction is discussed (Schreiber, Odlaug, & Grant, 2013; Volkow, Wise, & Baler, 2017; G. J. Wang, Volkow, Thanos, & Fowler, 2009). Mechanisms of reward-associated learning play a role in the development and maintenance of an addiction disease. Substances such as drugs or alcohol trigger learning processes in the dopaminergic mesolimbic amplifier system, which increases the likelihood of behavior that is aimed at rewards (Bilke-Hentsch & et, 2014). A short-term significantly increased dopamine (DA) concentration in nucleus accumbens (NAc) can be detected when consuming psychoactive substances (Baik, 2013; Volkow & Wise, 2005), but also in people who receive food reward (Wise, 2006).

In the context of BED research the mesocorticolimbic system is of particular interest, as it includes the reward system which comprises ventral striatum (VS) and midbrain with the ventral tegmental area (VTA), which sends dopaminergic projections into the cortico-ventral basal ganglia, including the NAc, amygdala, hippocampus and pre-frontal cortex (Palmiter, 2007). The NAc is also under the control of the viscerosensory cortex of insula (Cho et al., 2013). Food intake can also be triggered by peripheral appetite-stimulating peptides, such as ghrelin (Howick, Griffin, Cryan, & Schellekens, 2017; Young & Jialal, 2022), which positively correlates with activation in corticolimbic system (e.g., insula and amygdala) (Zanchi et al., 2017).

Previous neuroimaging studies have primarily investigated brain areas involved in reward-related and motivational processes in BED (Donnelly et al., 2018; Mele, Alfano, Cotugno, & Longarzo, 2020; Steward, Menchon, Jimenez-Murcia, Soriano-Mas, & Fernandez-Aranda, 2018). Aberrations in dopaminergic mesocorticolimbic pathways seem to play a crucial role in overeating (Naef, Pitman, & Borgland, 2015). Gomez, Shnitko, Caref, Nicola, and Robinson (2022) found that DA might drive high calorie food seeking behavior even in the absence of homeostatic needs. Slightly overweight and obese people also tend to have lower striatal DA synthesis capacity and a faster DA washout rate (Y. Lee et al., 2018). The low DA tone and the associated rapid volatilization of the reward sensitivity, coupled with a short-term, excessively high secretion during eating, could be the main risk factors for the binge eating attacks and thus weight gain (Yohn, Galbraith, Calipari, & Conn, 2019).

1.3 Binge Eating and altered neural responses to food stimuli

The ‘Incentive Salience Theory’ describes three neurobiological components in relation to reward and reinforcement learning in the mesolimbic dopamine system, consisting of ‘liking’, ‘wanting’ and ‘learning’ (Berridge & Robinson, 1998). ‘Liking’ is the hedonic need and describes the immediate experience or the anticipation of a pleasure. For example, through the orosensory or visual presentation of foods. The reward-seeking component, which leads to increased motivation around food procurement, is called ‘wanting’ and triggers the consumption of the target object (Berridge & Kringelbach, 2015). In patients suffering from addiction, these mesolimbic circuits react over-sensitively to cues that lead to a strong, triggered ‘desire’ to take the substance and make patients relapse (Berridge & Robinson, 2016). The Incentive Salience Theory was introduced in 1998 and has expanded beyond drug addiction to include other diseases and psychopathologies over the past 10 years.

Accordingly, visual food-cues are understood as conditioned stimuli and active specific neuronal brain patterns (Boswell & Kober, 2016). They signal the availability of food and their detection triggers the body to adapt for upcoming food intake (Kanoski & Boutelle, 2022). A meta-analysis of Yang, Wu, and Morys (2021) observed activation of medial orbitofrontal cortex (OFC), insula and amygdala, among other regions, when viewing high-calorie food-cues in fMRI in healthy participants. In today´s environment we are constantly confronted by food-cues that signal the availability of food, increase the motivation for food intake, and prepare the body for eating (Belfort-DeAguiar & Seo, 2018). Hedonic hunger, palatability and constant availability of food in our society promote the development of obesity through a constant excess of energy (Yeomans, Blundell, & Leshem, 2004). Food-cue reward learning influences eating behavior and implies obesity and overeating (Kanoski & Boutelle, 2022). Here, food intake is observed not only to satisfy the homeostatic energy requirement, but also during the lack of feeling of hunger, especially with tasty, rewarding foods with a high fat and sugar content (Reichelt et al., 2015). Therefore, food-cues trigger craving, which is in fact higher presented in BED compared to healthy individuals (Ferrer-Garcia et al., 2017; Meule et al., 2018). When being presented with pictures of e.g., high palatable food, the neuronal response in food addiction (Schulte, Yokum, Jahn, & Gearhardt, 2019) and in BED has been observed to show alterations in neuroimaging (Leenaerts, Jongen, Ceccarini, Van Oudenhove, & Vrieze, 2022). Meule et al. (2018) demonstrated higher cue-induced craving in participants with binge eating compared to healthy eating. Likewise, elevated food-cue reactivity (FCR) has been repeatedly reported in BED (Aviram-Friedman et al., 2018; J. E. Lee et al., 2017; Schienle et al., 2009), and a higher FCR has been associated with a risk of weight gain (Boswell & Kober, 2016; Boutelle, Manzano, & Eichen, 2020; Demos, Heatherton, & Kelley, 2012; Yokum, Ng, & Stice, 2011). The theorized heightened FCR as a pathomechanism in BED is reflected in successful interventional strategies showing that inhibitory cue learning reduces binge eating, snack intake, and body weight (Schyns, van den Akker, Roefs, Houben, & Jansen, 2020). Brain activation patterns during FCR may also differentiate between BED, BN, and healthy control participants (Weygandt, Schaefer, Schienle, and Haynes (2012). Therefore, studying FCR may provide an opportunity to evaluate mechanistic links between food reward signals and potential risk factors for aberrant eating such as insulin resistance.

1.4 Binge Eating, insula, and the metabolic-neuronal component

Food reward signals are regulated by integrating external reward-related information with feedback provided by internal metabolic signals (e.g., glucose and insulin) (Kroemer & Small, 2016; Kroemer, Sun, et al., 2016; Neary, Goldstone, & Bloom, 2004; Stouffer et al., 2015; Woods et al., 2016). These metabolic signals help convey information on the metabolic state of the organism to the brain and tune brain responses according to energetic demands (C. S. Mitchell & Begg, 2021). To support adaptive brain responses to food, the insula plays a crucial role in orchestrating energy homeostasis. The insula seems to be significantly involved in eating behavior since it forms the primary gustatory cortex and is integrated into the vegetative nervous system through interoceptive afferents of the gastrointestinal tract (Uddin, Nomi, Hebert-Seropian, Ghaziri, & Boucher, 2017). Energy homeostasis is mediated by insula processing food-related information (e.g., visual food-cues, see chapter 1.3) and by comparing peripheral markers, such as glucose or insulin concentration, and thus controls food intake (Kroemer et al., 2013). A systematic review by Schulz, Vezzani, and Kroemer (2023) provides evidence for the neuromodulatory effect of gut hormones (e.g., ghrelin and GLP-1) on altered reward responses. Insular hedonic hotspots that increase ‘liking’ to palatable food and influence food reward were also found previously in rodents (Morales & Berridge, 2020; Price, Stutz, Hommel, Anastasio, & Cunningham, 2019). There are first indications that altered insula functional connectivity (FC) to limbic areas in obesity lead to reward-seeking food consumption (Avery et al., 2017) and altered FC between the NAc and the insula/operculum is associated with changes in appetite and weight in patients with major depressive disorder (Kroemer et al., 2022). Collectively, these findings support the hypothesis that food consumption is controlled by metabolic signaling in an extended reward circuit including the insular ingestive cortex.

1.5 Peripheral insulin affects energy homeostasis and hunger

Food intake is thus controlled by interactions of CNS with metabolic signals that mediate the nutrient state of organism. Appetite can be triggered through food-cues (Reichelt et al., 2015) and is mediated by peripheral circulating orexigenic and anorexigenic acting hormones, such as insulin which signals saturation postprandial and can cross the blood-brain barrier in the CNS through receptor-mediated transport (Neary et al., 2004). Insulin is a peptide hormone that is produced in the ß-cells of the endocrine pancreas. Insulin secretion lowers the blood sugar level by supplying the cells with glucose and generating energy stores through glycogen and lipid biosynthesis. Thus, insulin has an anabolic mode of action and plays a major role in signal transduction. Insulin sensitivity describes how sensitive the body's cells react to insulin. For example, it is reduced in T2D and can be calculated using the Homeostasis Model Assessment (HOMA-IR) (Matthews et al., 1985).

Early rodent models demonstrated the expression of insulin receptors throughout the CNS (Havrankova, Roth, & Brownstein, 1978). In humans, the highest proportion of expressed receptors was found in the cerebellum, followed by hypothalamus, cortex, and reward-related centers as the VTA which sends mesolimbic dopamine projection into NAc, the striatum and amygdala (Kullmann et al., 2020). Several animal models (Mebel, Wong, Dong, & Borgland, 2012) and lately fMRI studies on healthy humans showed that administration of intranasal insulin (INI) alters dopaminergic midbrain projections (Edwin Thanarajah et al., 2019). Tiedemann et al. (2017) administered INI to healthy participants with normal fasting insulin levels and observed reduced DA activity in VTA and, through the forward projections, also in NAc which in turn was associated with decreased ratings of palatability food stimuli. INI also influences gustatory areas and increases activation in insular cortex (Schilling et al., 2014) and enhances differences in BOLD response in the prefrontal cortex, reward and taste systems between people with obesity vs. healthy weight (Wingrove et al., 2022). Hallschmid, Higgs, Thienel, Ott, and Lehnert (2012) demonstrated that postprandially administered INI promotes saturation after meal intake and decreases palatable snack intake afterwards. Hence central insulin might not only act as a negative feedback signal in reward-related food intake (Kullmann et al., 2020) and may play a role as strong moderator in reward processing (Kroemer, Burrasch, & Hellrung, 2016) but also might regulate short-term satiety (Hallschmid et al., 2012). Tiedemann et al. (2017) also showed that insulin resistance led to a lower rating of appetizing stimuli in the first place which remained stable afterwards INI administration. This could be traced back to the fact that insulin resistance lead to permanent high concentration of circulating insulin which could lead to adapted chronically decreased modulation in mesolimbic pathways. E.g. the appearance of less endogenous dopamine in the VS at the DA2/3 receptors (Caravaggio et al., 2015) or altered DA2/DA3 receptor density associated with obesity (Horstmann, Fenske, & Hankir, 2015). Overeating might occur due to insulin resistance through those reduced activations in dopaminergic reward circuits in BED, because insulin is missing as a satiating factor. In addition, in obese rats a reduced expression of superficial insulin receptors and a loss of insulin receptors mediated excitatory transmission was seen as well. Which support an upcoming thesis talking about ‘brain insulin resistance’ playing a role in pathogenesis of metabolic and cognitive disorders (Anthony et al., 2006; Hallschmid, 2021).

1.6 How does insulin resistance affect insular food-cue reactivity in binge eating disorder?

Likewise, alterations in peripheral insulin influence the mesocorticolimbic circuit and lead to less reaction to food-cues (Kroemer et al., 2013). There are currently few studies that have examined altered insulin sensitivity in BED (Ilyas et al., 2019) and it is unclear whether there is a general connection with an increased BMI in eating disorders. And so far, it remains unclear how neuroendocrine modulation through insulin sensitivity effects neuronal response to food reward especially in BED. Here we will gain new insights into the interplay of metabolic and neuronal processes through performing a FCR task in fMRI on 61 female participants who were divided into BED, subBED and healthy eating habits to show a smooth transition within the groups. During the measurement, we recorded individual liking/wanting ratings and investigated the neuronal and behavioral response in dependence of insulin resistance.

The hypotheses examined in this work are:

- BED and subBED are associated with higher insulin resistance (HOMA-IR) vs. noBE after controlling for BMI.

- BED and subBED show alterations in behavioral tasks (increased liking rates for high palatable foods and greater willingness to work for reward) in comparison to healthy participants.
- BED and subBED are positively related with higher food vs. non-food FCR in our ROIs (insula, VTA, NAc).
- Insulin resistance is linked to alterations in neuronal areas (insula, VTA) especially in BED.

The aim of this study is to give new insights in understanding the neural pathomechanism of BED and support new therapeutic approaches.

2 Material and methods

2.1 The study ‘BEDVAR‘

The ‘BEDVAR’ study (Binging and Neuronal Variability) was conducted at the University hospital of General Psychiatry and Psychotherapy in Tübingen, Department of Translational Psychiatry, under the direction of Prof. Dr. rer. Nat. Nils B. Kroemer. ‘BEDVAR’ is third-party funded project by the Else Kröner-Fresenius-Stiftung (EKF). A part of the detailed study is covered in this doctoral thesis. Official project start was 01.03.2018. Data collection started in December 2019 and ended in May 2021. The study took place on the premises of the Institute for Clinical Psychology in Tübingen, the Centre for Integrative Neuroscience Tübingen and in the research MR scanner of the University hospital Tübingen.

2.2 Participants

The approved age range for participation was between 18 and 69 years. All subjects were given a written informed consent before both lab assessments. The sample consisted of women who were divided into 3 groups. One group of individuals diagnosed with binge eating, a group of individuals with subsyndromal binge eating and a control group of healthy control persons, without any lifetime history of binge eating or other eating disorders. All subsamples were matched regarding age and BMI. The BED sample was assessed using the Eating Disorder Examination (EDE: Hilbert et al. (2004)). All other diagnoses were assessed using The Structured Clinical Interview for DSM IV (SCID: Wittchen, Zaudig, and Fydrich (1997) (S. Herpertz et al., 2011). The Eating Disorder Examination Questionnaire (EDE-Q: Hilbert et al. (2007)) helped to determine the severity of the symptoms. Subsyndromal binge-eating was classified as not meeting the frequency criteria (an average of 1 binge per week over the last 3 months) and as meeting only two instead of three of the criteria for an objective binge or not having no obvious suffering. The diagnostic interviews were conducted by a psychologist and the audio was recorded for a second diagnostic assessment by an independent rater.

Participants who met exclusion criteria such as other eating disorders, objective binge-eating, taking medication or suffered from illnesses that influenced weight, had severe comorbidity, were pregnant or breast feeding, had bipolar disease or substance addictions in the past 6 months or standard exclusion criteria for MRI scanning were screened out. MR exclusion criteria include non-removable piercings and metallic implants such as pacemakers. Other ferromagnetic material that was introduced into the body through accidents or operations, large tattoos, especially in the head and neck area and claustrophobia. Participants with T2D and major depression disorder were also included, if they were not acutely suicidal, since those affected by BED often suffer from accompanying mental illnesses, such as depression (R. C. Kessler et al., 2013). In case of pharmacological treatment, a stable dose of antidepressants for at least two months was required.

The study has been approved by the local ethics committee and was conducted in accordance with the ethical code of the World Medical Association (Declaration of Helsinki). Participation was rewarded financially or in form of course credits. For completing the online assessment, they received 20 € in addition to ~90 € for the two laboratory appointments. The exact amount of expense allowance varied based on winnings on gaming tasks where participants could earn money and snacks.

The participants were recruited via online advertisements (social media, e.g., Facebook, Instagram), posters in public places and magazine articles (e.g., health insurances). The BED sample was also recruited in cooperation with the Institute for Clinical Psychology in Tübingen, which has a focus on eating disorders.

2.3 Experimental procedure

The whole study BEDVAR consisted of an online assessment and two sessions of lab-based assessment (behavioral and fMRI-assessment) on different days. The online assessment comprised of the browser-based online game ‘Influenca’, which involves repeated runs of a reward learning task combined with ecological momentary assessment (EMA) of mood and homeostatic states, and of a set of trait questionnaires measuring different facets of general eating behavior and mental disorders (Neuser et al., 2023). All participants completed at least 30 runs á 5 min of ‘Influenca’ and participants of the sub samples were contacted and screened by phone (⌀ 25 min) if they met the inclusion criteria and matched one of the BED sample.

For the first lab-based session, including the behavioral part, participants were told to appear neither hungry nor full during any time on a day. The participants were informed about of the procedures before they gave consent. Their last meal was queried and should have taken place 2 h in advance of study begin. The use of alcohol, drugs, and medication in the period before the study day was also recorded. All participants were female and were asked about the last date and average duration of their menstrual cycle.

A standardized diagnostic interview (⌀ 1.5 h), consisting of SCID (Wittchen et al., 1997) and EDE-Q (Hilbert et al., 2007) was accomplished by a psychologist on the first study day to identify the group membership of the participants (BED, subBED or noBE). After that, physical values such as body height and weight, waist and hip circumference were captured. Subsequently participants completed an effort allocation task (van den Hoek Ostende, Neuser, Teckentrup, Svaldi, & Kroemer, 2021), a FCR task and a taste-test. Current hunger, thirst, fullness, and mood was assessed occasionally three times using a visual analog scale (VAS) during the study day. The first visit of the study was terminated after answering a block of standardized questionnaires including IPAQ (Craig, 2003) and PSS-10 (Sheldon Cohen, 1983) and took about 4 h in total.

On the second study day the session started at 9 AM. Participants were required to appear after fasting 12 h over night because fasting levels of glucose, insulin, triglycerides, and ghrelin were measured. Participants were allowed to drink water or unsweetened beverages including coffee or tea, if they usually drink that in the morning. A peripheral venous catheter was placed at the beginning of the session and blood was drawn over it several times (see ‘2.4 Blood protocol’). Body values (weight, waist, and hip circumference) were measured again, and participants completed a go / no-go reinforcement learning task (Kuhnel et al., 2020). Thereafter the fMRI session started and took approximately 100 min including an anatomical scan, a resting-state measurement, a slot machine, and effort allocation task. Participants also completed a FCR task with a grip force device in the scanner. After fMRI and the last blood drawing the peripheral venous catheter was removed and participants finished the study day with standardized questionnaires (IPAQ & PSS-10). At the end of each day of the experiment, participants received the earned money and snacks from the effort allocation task. The second study day lasted ⌀ 4.5 h (endpoint ~1:30 PM) and participants received breakfast and lunch (see ‘2.6 Breakfast and lunch’).

The content of the second study day including blood sampling, VAS and FCR task in the scanner is particularly relevant for this doctoral thesis (see Figure 1).

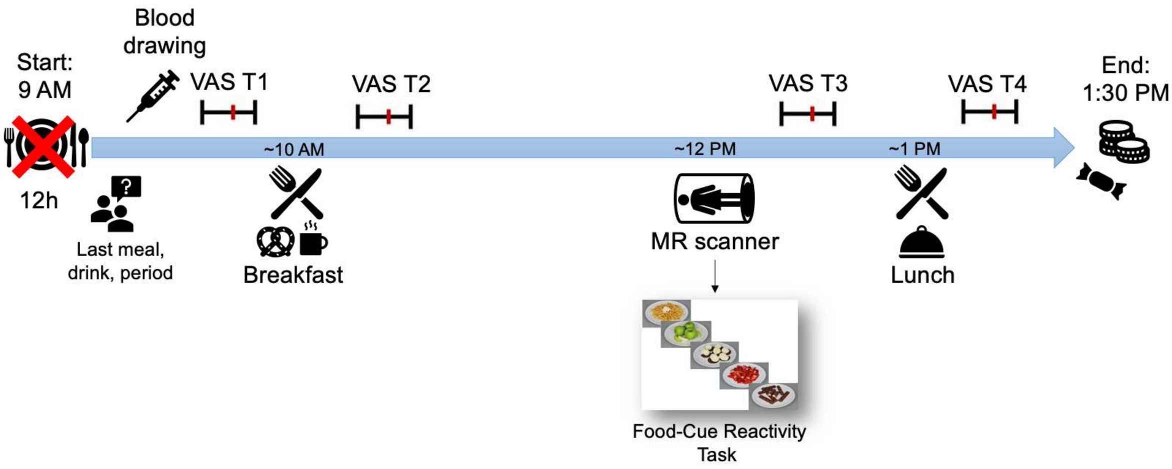

Figure 1: **Schedule study day 2**
The study day started at 9 AM, participants had to fast for at least 12 hours. After a brief interview, fasting blood was taken. Participants completed a visual analogue scale task four times over the session. They received breakfast at ~10 AM and lunch at ~1 PM. In the meantime, the MR task with FCR took place. The study day ended around 1:30 PM and participants received the money and snacks they had earned.

2.4 Blood protocol

Blood samples for fasting glucose, insulin and triglycerides were taken at the beginning of the second study day after a 12 h overnight fast. A peripheral venous catheter (Vasofix® Braunüle® 1.10 x 33 mm G 20 pink, FEP (BROWN)) was placed at the beginning of the session and blood was drawn over it several times for further blood values (ghrelin) which are not discussed further here. Blood collection time was session start, 10 and 25 min after placing the catheter, 30 min and ⌀ 180 min after breakfast. The venous catheter was removed after the last blood taking and the injection site was provided with a compress bandage. The procedure was carried out by a medical-technical assistant or by advanced medical students who were previously instructed by a study doctor.

Samples for fasting blood levels were taken using compatible S-Monovettes and stored in the refrigerator at 4 °C. For fasting venous glucose, a yellow uncooled 2.6 ml S-Monovette (sodium fluoride plasma), a white uncooled S-Monovette (serum) for insulin and an orange cooled (4 °C) 2.6 ml S-Monovette (lithium heparin plasma) for triglycerides were taken.

For routine analyses they were transferred to the central laboratory of the Institute for Clinical Chemistry and Pathobiochemistry of the University Hospital Tübingen (UKT) about 2 h after the blood draw. Venous glucose was measured through hexokinase and photometric endpoint measurement (reference: 70 – 99 mg/dl). Serum insulin underwent CLIA (Centaur) (reference: < 175 pmol/l) and triglycerides were measured with enzymatic color test and glycerol kinase (reference: < 200 mg/dl).

2.5 Insulin resistance (HOMA-IR)

Insulin resistance was calculated in a 12 h fasted state using the Homeostasis Model Assessment (HOMA-IR) that included fasting glucose and insulin (Matthews et al., 1985). This type of measurement is readily available as it only requires a blood draw and is widely used as it has been used in numerous studies (Tahapary et al., 2022). The formula is:

$$HOMA-IR = \frac{\text{Insulin } \left(\frac{\text{mU}}{\text{l}}\right) * \text{Glucose } \left(\frac{\text{mg}}{\text{dl}}\right)}{405}$$

The cut-off value for the HOMA-IR must be adjusted for the respective population, gender, age and disease (Tang, Li, Song, & Xu, 2015). For Germany Matli et al. (2021) found a median (IQR) HOMA-IR of 1.09 (0.85 / 1.42) with no significant sex difference. The higher the HOMA-IR value, the more likely insulin resistance is. Since HOMA-IR values are rarely normally distributed they should be transferred logarithmically (Wallace, Levy, & Matthews, 2004), therefore we used log_HOMA-IR for calculation.

2.6 Breakfast and lunch

Breakfast was a standardized meal consisting of ~370 kcal. Participants had to eat a butter prezel and a drink of their choice (tea or unsweetened black coffee) within a maximum of 10 min. Participants arrived in the morning on an empty stomach and received breakfast (~10 AM). The FCR in the scanner task took place about 2 h later. Lunch started around 13 o'clock and consisted of a bowl with cheese pasta (Käsespätzle, ~2.500 kcal) and a drink of choice (apple, multivitamin or orange juice). Participants were instructed to eat as much as they want (ad libitum) within 20 min.

2.7 Visual Analog Scale (VAS)

Participants had to rate their physical (e.g., hunger, fullness) and affective (e.g., shame, enthusiasm) state several times during the sessions on a computer task using a mouse. VAS contained a vertical scale rating scale from 0 to 100. Hunger and fullness were recorded 4 times in total at the second study day, before and after breakfast and lunch.

2.8 Food-Cue Reactivity (FCR) task

In a quantitative meta-analysis, Boswell and Kober (2016) found that the reactivity to visual food-cues is strongly related to the results to real food presented. This paradigm is often used to measure predictive ‘reward response’ to food. In order to assess the incentive effect of food stimuli, pictures of very tasty foods and control images are shown, while corresponding evaluations of preferences and wishes are collected. During the fMRI measurement, correlates of the brain response, in detail dopaminergic transmission, can be quantified using blood-oxygen-level dependent (BOLD) signaling (Bruinsma et al., 2018).

In the FCR task (see Figure 2) participants were presented with pictures with highly palatable food and control objects (non-food) on a screen in the scanner, while correlates of brain responses were measured using fMRI. The standardized images were provided by Charbonnier (2016) and consisted of food-cues and office materials (Blechert, Lender, Polk, Busch, & Ohla, 2019). The consistent representation was ensured by recording them in a photo studio on a white, homogeneous plate with a light gray background, with a fixed angle and distance between the camera and the object. The food items were divided into four categories: high-calorie salty, high-calorie sweet, low-calorie salty and low-calorie sweet products. The pictures were standardized and randomly selected for the participants.

The entire task consisted of 12 different blocks, which were randomly shown twice. This repetition accounted for individual variance and inconsistency in ratings. Each trial started with a fixation cross (iming.min_ISI = 0.1 + jitter (mu = 2.5, max = 12)) and showed a block consisting of 5 images of the same category on a screen. Each picture was shown for 3.5 sec, making one block 17.5 sec long. After a block of pictures, the participants were asked to state how much physical effort they were willing to put in to gain access to a buffet consisting of the pictures just seen, measuring wanting ratings. For the evaluation phase, they were shown a vertical vessel that contained a blue ball. The ball could be lifted by hand by pressing a grip force device. The height of the ball was proportional to the maximum force that the test subjects could apply, which had previously been recorded in a training phase of a effort allocation task (van den Hoek Ostende et al., 2021). The subjects should hold the ball at the respective height for about 5 sec during the subsequent bidding phase. The whole task took 14 min to finish.

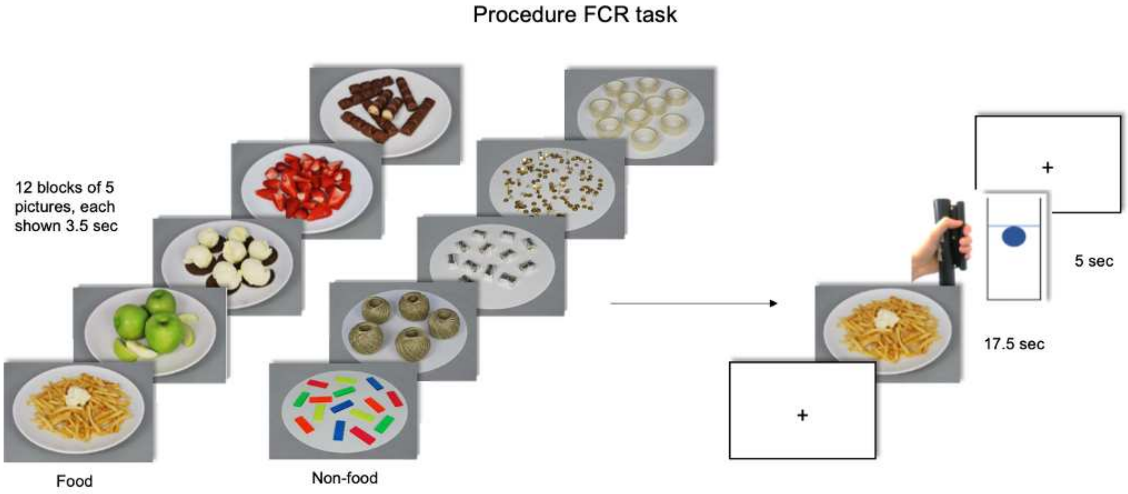

Figure 2: **Food-cue reactivity task**
Participants completed a Food-cue reactivity task during fMRI with pictures of food and non-food in a randomized block design. The pictures were divided standardize and provided by Charbonnier (2016). The trial started with a fixation cross. Every block was shown twice and lasted about 17.5 sec. Participants rated their wanting scales afterwards in the bidding phase with a grip force device (5 sec), making the whole task 14 min long.

2.9 Grip Force Device

Participants had to rate their ‘wanting’ values during the FCR task in the scanner. We measured physical effort through squeezing a pressure sensitive device with the dominant hand (see Figure 3). Grip force devices have already been used in numerous studies and is suitable for recording effort-based decision making (Meyniel, Sergent, Rigoux, Daunizeau, & Pessiglione, 2013; Pessiglione et al., 2007; Schmidt, Lebreton, Clery-Melin, Daunizeau, & Pessiglione, 2012). We used a nonmagnetic and non-electronic Force Fiber Optic Response Pad (SKU#: HHSC-1x1-GRFC-V2) by Current Designs.

Figure 3: **Grip force device**
The grip force device was placed in the dominant hand to record bidding ratings of exerted force in an effort-based reward task.

2.10 fMRI data acquisition and preprocessing

Images were collected using a 3-Tesla PRISMA whole-body MR scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard 64-channel head coil. Details of the imaging sequences were collected following the COBIDAS consortium guidelines (Nichols et al., 2017; Teckentrup et al., 2021). T1 weighted structural images were measured using an MP-RAGE sequence with 176 sagittal slices covering the whole brain, flip angle = 9°, matrix size = 256 × 256 and voxel size = 1 × 1 × 1 mm^3. Field maps were acquired by a Siemens gradient echo field map sequence with short (= 5.19 ms) and long (= 7.65 ms) echo time (TE), which resulted in a TE difference of 2.46 ms. fMRI data consisting of 10 min pre-stimulation baseline a 10 min concurrent simulation was acquired as T2*-weighted gradient echo echo-planar images (EPIs) using a multiband factor of 4, 68 axial slices with an interleaved slice order covering the whole brain including brainstem, repetition time (TR) = 1.4 s, TE = 30 ms, flip angle = 65°, 110 × 110 matrix, field of view = 220 × 220 mm^2 and voxel size = 2 × 2 × 2 mm^3. We also recorded the breathing rate with the Siemens respiratory belt during the measurement.

Preprocessing of resting-state fMRI data was carried out with the latest version of standardized FMRIPREP pipeline (https://github.com/poldracklab/fmriprep) (Esteban et al., 2019) [RRID:SCR_016216] based on Nipype (Gorgolewski et al., 2011) [RRID:SCR_002502] and Nilearn (A. Abraham et al., 2014) [RRID:SCR_001362]. T1-weighted (T1w) volumes was corrected using this pipeline for intensity non-uniformity using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped using antsBrainExtraction.sh v2.1.0 (OASIS template). Brain surfaces were reconstructed by using recon-all from FreeSurfer v6.0.1 (Dale, Fischl, & Sereno, 1999) [RRID:SCR_001847] and the previously estimated brain mask is refined with a custom variation of the procedure to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (Klein et al., 2017) [RRID:SCR_002438]. The spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov, Evans, McKinstry, Almli, & Collins, 2009) [RRID:SCR_008796] took place through nonlinear registration with the antsRegistration tool of ANTs v2.1.0 (Avants, Epstein, Grossman, & Gee, 2008) [RRID:SCR_004757], by using brain-extracted versions of T1w volume and template. Brain tissue segmentation of white- (WM) and gray matter (GM), as well as cerebrospinal fluid (CSF) was performed on the brain-extracted T1w using FAST (Zhang, Brady, & Smith, 2001) [FSL v5.0.9, RRID:SCR_002823].

Using 3dTshift from AFNI v16.2.07 (Cox, 1996) [RRID:SCR_005927] and motion corrected using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002) [FSL v5.0.9] functional data was slice time corrected. Correction of distortion was performed using field maps processed with FUGUE (Jenkinson, 2003) [FSL v5.0.9] with the following program of co-registration to the corresponding T1w using boundary-based registration (Greve & Fischl, 2009) by bbregister [FreeSurfer v6.0.1] (9 degrees of freedom). BOLD-to-T1w transformation, T1w-to-template (MNI) wrap, field distortion correcting warp and motion correcting transformations was concatenated and applied in a single step using antsApplyTransforms [ANTs v2.1.0] based on Lanczos interpolation. Physiological noise regressors were extracted using Nilearn by calculating the average signal inside anatomically derived CSF and WM masks across time. Framewise displacement of each functional run was calculated using Nipype (Power et al., 2014). The number of volumes per run was calculated with exceed a framewise displacement threshold of 0.5 mm. Respective subjects were excluded from further analyses if > 50 % of the total number of volumes exceeded this threshold or if < 5 min of data below this threshold remained. In addition, whole brain voxel-based maps were smooth with a 6 mm FWHM kernel. Unsmoothed data was held in parallel to extract unsmoothed seed time series from the NTS.

Respiratory recordings from the Siemens respiratory belt were preprocessed using PhysIO toolbox (Kasper et al., 2017). By convolution of respiratory volume per time with respiration response function (Birn, Smith, Jones, & Bandettini, 2008), toolbox generated a nuisance regressor which corrected noise into statistical models (Teckentrup et al., 2021).

2.11 Statistical threshold, software and data analysis

The descriptive and comparative statistics of group characteristics, as well as t-tests and ANOVA/ANCOVA were carried out with the software program IBM® SPSS® Statistics (version 26.0.0.0). Levene's test was used to check for equality of variance. Data of the FCR-task was collected and preprocessed in MATLAB_R_2018a.

Figures were created with SPSS. A p value ≤ 0.05 was considered as statistically significant and confidence interval was given as 95 %.

3 Results

To our knowledge this was the first human study to investigate the connection between insulin sensitivity and neuronal reward activity through blood sampling and a FCR task in BED, subBED and healthy overweight controls (no BE).

3.1 Study sample

After the diagnostic interview, we excluded 12 participants because they were diagnosed with BN instead (N=6), reported only subjective binge eating (N=4), or had MR contraindications (N=2). Moreover, participants with BED who had to be excluded for MRI scanning were invited for an equivalent session with blood draws and tasks, but without concurrent neuroimaging (N=8). For the neuroimaging part reported here, the sample consisted of 61 participants who were divided into 3 groups (BED, subBED, no BE). One group of individuals diagnosed with binge eating (N_{BED}=21), a group of individuals with subsyndromal binge eating (N_{subBED}=20) and a control group of healthy control persons (N_{noBE}=20), without any lifetime history of binge eating or other eating disorders. The characteristics of the study sample is illustrated in Table 1 (61 women; M_{age} = 39.7 years ± 13.2; M_{BMI} = 31.5 kg/m^2 ± 7.1 [20.2, 46]; M_{WtHR} = 0.57 ± 0.1 [0.4, 0.7]; $M_{HOMA\text{-}IR}$ = 2.7 ± 2.2; $M_{log\_HOMA\text{-}IR}$ = 0.33 ± 0.29).

Table 1: **Characteristics of the study sample**

Characteristics of the study sample, stratified by group membership				
	Sample	**Groups**		
Characteristic	total (N=61)	BED (N=21)	subBED (N=20)	no BE (N=20)
Age, years (mean [SD])	40 (13.21)	42 (12.65)	38 (12.65)	39 (14.47)
BMI (mean [SD])	32 (7.11)	33 (6.46)	29 (7.82)	32 (6.70)
WHtR* (mean [SD])	0.57 (0.09)	0.60 (0.09)	0.54 (0.1)	0.57 (0.09)
Number of binge episodes during last 28 days (mean [SD])		11.2 (8.4)	5.5 (5.8)	0 (0)
Number of binge episodes during last 3 months (mean [SD])		10.9 (8.3)	5 (4.7)	0 (0)
	Available blood data			
	total N=58	BED N=18	subBED N=20	no BE N=20
Glucose in mg/dl (mean [SD])	87.7 (11.87)	91.6 (14.49)	86,7 (12.45)	85.2 (7.58)
Insulin in mU/l (mean [SD])	11.8 (7.79)	14.94 (10.06)	9.56 (6.04)	11.18 (6.13)
Homa-IR (mean [SD])	2.7 (2.16)	3.7 (3.13)	2.1 (1.38)	2.4 (1.36)
Abbreviation: SD = standard deviation, WHtR = Waist-to-Height Ratio (Waist Circumference / Height)				

Due to difficulties in blood drawing (poor venous status or dislocation of venous catheter) log HOMA-IR of 3 participants with BED is missing, resulting in a total of N=58 with available blood and fMRI data.

3.2 BED is not associated with higher insulin resistance

We investigated insulin resistance in participants with available blood data (N=58) using log_HOMA-IR. The mean log_HOMA-IR in total was 0.33 (BED 0.45, subBED 0.23, no BE 0.32, see Table 2).

Table 2: **log_HOMA-IR between the groups**

				95% CI for mean difference			
Groups	*Mean*	*SD*	*SE*	*Lower limit*	*Upper limit*	*Minimum*	*Maximum*
BED (N=18)	0.45	0.32	0.08	0.29	0.61	-0.05	1.06
subBED (N=20)	0.23	0.27	0.06	0.11	0.37	-0.32	0.82
noBE (N=20)	0.32	0.24	0.05	0.20	0.43	-0.19	0.81
Total (N=58)	0.33	0.29	0.38	0.26	0.41	-0.32	1.06
Abbreviation: SD = standard deviation; SE = standard error; CI =confidence interval							

To assess potential differences in insulin sensitivity (as indexed by In-transformed HOMA-IR, corrected for BMI and age) between the groups, we first used an one-way ANOVA. The data was normally distributed for each group (Shapiro-Wilk test, p > .05) and the variance was homogeneous (Levene´s test, *p* > .05). There was one outlier in the subsyndromal group, according to inspection with a boxplot (see Figure 4). Using the neuroimaging sample, we found no group difference in log_HOMA-IR, F(2,55) = 2.73, p = .074.

In order to investigate further group differences in insulin sensitivity we invited 8 participants with BED that were excluded due to MR safety reasons and executed blood collection sessions without fMRI. To re-examine the insulin sensitivity, we also included them in the insulin sensitivity analysis, but we still did not find any statistically relevant group differences F(2,63) = 2.47, p = .093.

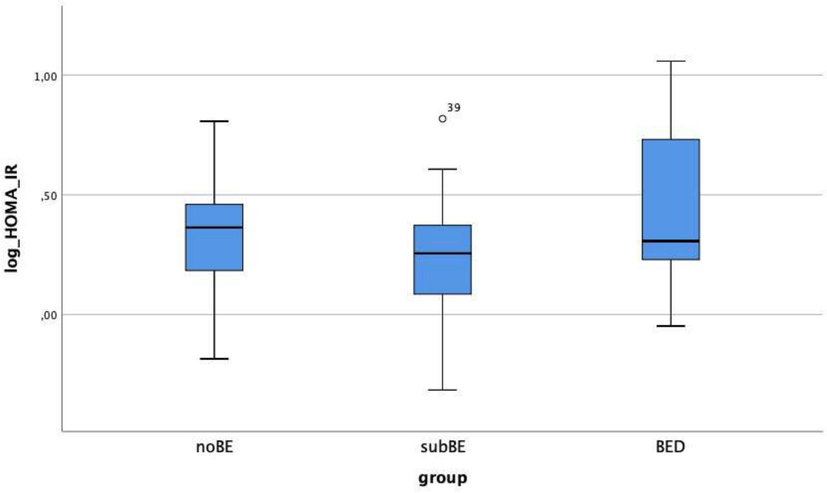

Figure 4: **Box plot - log_HOMA-IR**
Box plot analysis für insulin resistance (log_HOMA-IR) between the 3 groups (noBE = healthy participants, subBE = subsyndromal binge eating, BED = binge eating disease). The x-axis display the 3 groups and the y-axis shows the insulin resistance as log_HOMA_IR. Binge eating disease is not significantly associated with higher insulin resistance compared to subsyndromal binge-eating and healthy participants.

Table 3: **One-way ANOVA (log_HOMA-IR)**

	One-way ANOVA (log_HOMA-IR)				
	Sum of squares	df	Mean of the squares	F	significance
Between the groups	0.43	2	0.21	2.73	0.07
Within the groups	4.29	55	0.08		
total	4.72	57			
Abbreviation: df = degrees of freedom					

In analysis of covariance for BMI and age using ANCOVA, we found homogeneous of covariance (p_{BMI} = .061, p_{age} = .497) and regression slopes (p_{BMI} = .441, p_{age} = .878). log_HOMA-IR over the groups with no covariates showed partial eta squared (η^2p = .090). BMI influenced partial eta squared (η^2p_{BMI} = .037) for insulin resistance stronger than age (η^2p_{age} = .085). To assess differences in insulin resistance depending on weight (using WHO classification of BMI), we conducted a ANOVA and found statistically significant differences, F(4,53) = 9.991, p = .000). To summarize, we found significantly increased insulin resistance with higher BMI but not with BED.

3.3 Binge eating is not associated with subjective hunger and fullness

Hunger and fullness ratings were recorded via VAS on a computer at baseline in a fasting state (R0) at the beginning of the session, after breakfast (R1), after the fMRI-FCR task at noon (R2), and at the end of the session after consuming the ad libitum lunch (R3, see Figure 5). As expected, hunger ratings increased, whereas fullness ratings declined after time between meals, resulting in a mirror-inverted pattern. Participants had to appear with an empty stomach to our study session, which shows in the initial hunger-ratings before breakfast. After breakfast, participants were moderately saturated in comparison to lunch. Here participants voted higher fullness. Although patients with BED gave slightly higher hunger and lower fullness ratings compares to the other groups, these differences were not significant (p > .05). Hence, binge eating was not associated with altered subjective ratings of metabolic state throughout the session.

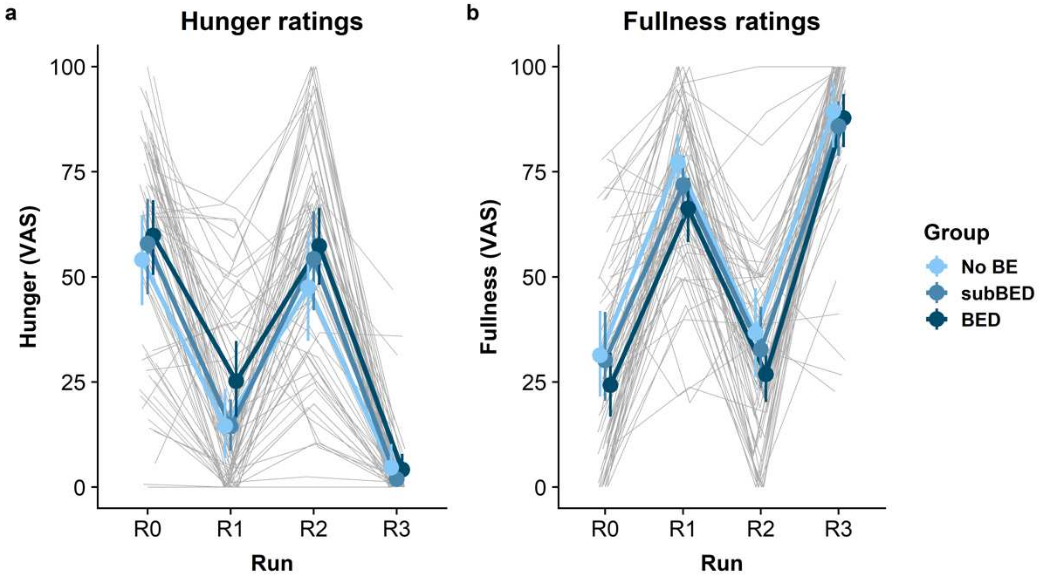

Figure 5: **Visual analog scale ratings of hunger and fullness across different time points**
Hunger and fullness ratings distributed across the groups (No BE = healthy participants, subBED = subsyndromal binge eating, BED = Binge eating disease) through the study session between meals (breakfast and lunch). The x-axis show different time points (R0-R3). In (a) the y-axis shows hunger ratings on a visual analog scale (0-100) where higher values indicate stronger hunger. In (b) the y-axis displays fullness ratings (0-100) where higher ratings are associated with stronger satiety.

3.4 *Neither BED nor HOMA-IR is associated with higher relative effort in a MR based food vs. non-food bidding task*

Participants were shown pictures of food vs. non-food items in a MR scanner and they were instructed to use a grip force device to make a bid on how much they wanted the presented item. The wanting ratings were examined according to group membership and insulin resistance (low or high HOMA-IR). Effort initially rapidly increases within the first seconds and then stabilizes. Distributed across all groups, it can be seen that higher bids were placed for food items than for non-food items. Healthy participants showed the highest bids for non-food items, followed by BED and finally subBED. Although it can be observed that the BED group rated food higher than non-food (see Figure 6a), the results are not significant. BED, subBED and noBE showed equally high wanting ratings for food-items.

Wanting ratings were not influenced by insulin resistance (see Figure 6b). Participants with low and with high HOMA-IR voted equally for food vs. non-food items.

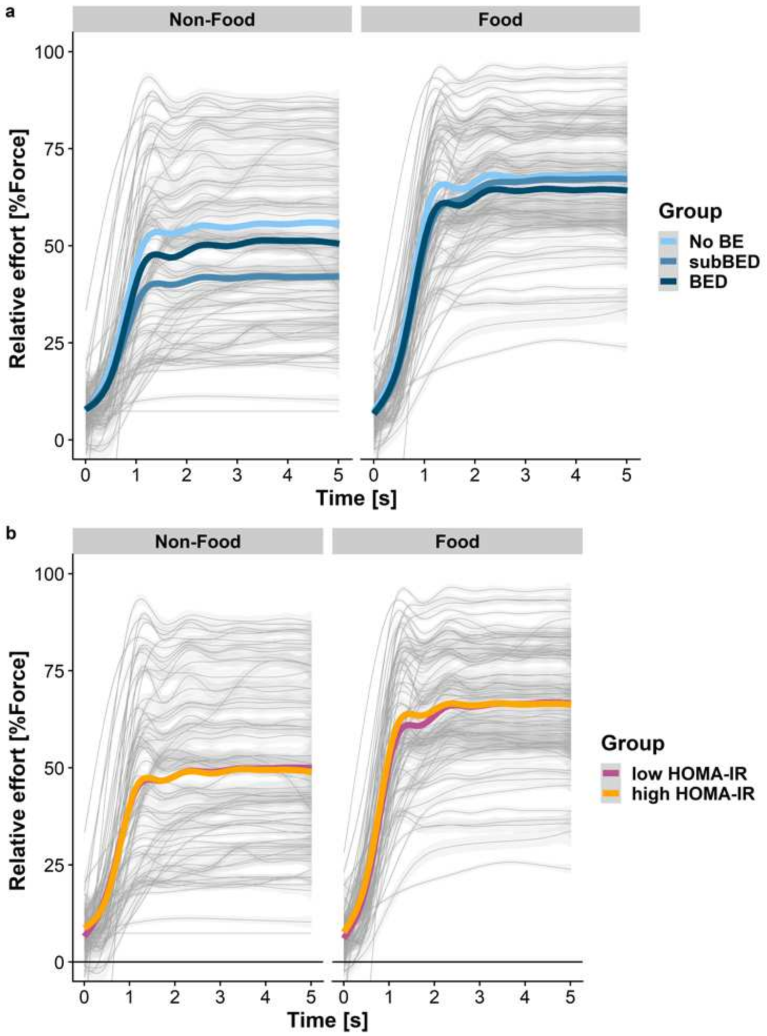

Figure 6: **MR bidding phase food vs. non-food**
Relative effort measured by a grip force device in the dominant hand in a MR bidding phase. 'Wanting'-rates of food vs. non-food objects were investigated separated by groups (a) and insulin resistance (HOMA-IR) (b). The x-axis displays the time (seconds) and the y-axis shows the relative effort (% force) the participants were willing to deliver. Participants had to hold their bid for at least 5 seconds for it to log-in.

3.5 Lower insulin sensitivity is associated with reduced hedonic scaling of effort

Hedonic scaling reflects how much a person is willing to work for a reward based on how much they like it (rated during the baseline session). To evaluate associations with BED and insulin sensitivity, a mixed-effects model was created predicting the effort bids (% of force exerted via an MR-compatible grip force device) based on individual preferences (‘liking‘ rating) for the depicted food or non-food cues in the preceding block. There is a general trend that as rated liking increases, the relative effort also increases. Steep lines show a stronger connection between liking and effort. The tendency to put a lot of effort into things that one enjoys. Both groups (low HOMA-IR and high HOMA-IR) show this positive trend, although the slopes differ slightly (see Figure 7a).

In Figure 7b higher HOMA-IR show decreasing hedonic scaling of effort for food in the food bidding task. The black regression line shows a slightly negative correlation, i.e., higher HOMA-IR values (on the x-axis) tend to be associated with lower unbiased EB slopes. This may indicate that increasing insulin resistance leads to a reduced correlation between liking an bidding behavior.

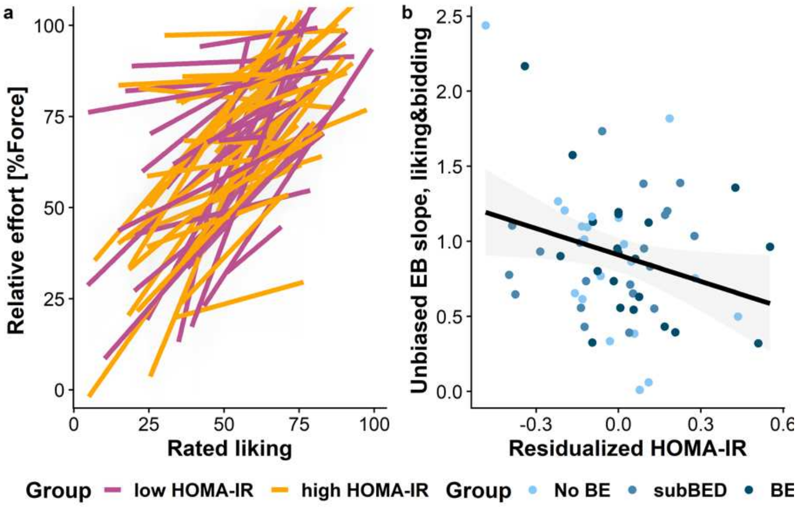

Figure 7: **Relationship between liking ratings, effort and HOMA-IR**
Association between liking rates and relative effort through grip force device separated by low and high HOMA-IR (a). The x-axis represents ‘liking’ from 0-100, the y-axis shows the relative effort (% force) that participants provide to obtain the presented food- or non-food cue. Each slope represents multiple trials by one participant. Group distribution of unbiased EB slope, liking and bidding with residualized HOMA-IR (b). The x-axis displays insulin resistance (residualized HOMA-IR) and the y-axis (unbiased EB slope) shows the strength of the association between liking and bidding behavior.

3.6 Food images generate stronger BOLD responses than non-food images

To verify that the food bidding paradigm induced food reward signals, we first analyzed the contrast between blocks of food and non-food items. Stronger BOLD responses to food were observed in an extended ingestive network including the dorsal mid insula (primary ingestive cortex), ventral tegmental area (VTA)/substantia nigra, striatum, thalamus, inferior orbitofrontal cortex (IOFC), dorsolateral prefrontal cortex (dlPFC) as well as the lingual and fusiform gyrus as part of a visual network. Independent of the group, all participants showed a greater FCR to food-cues in contrast to non-food (see Figure 8a).

3.7 Binge eating is associated with greater insular response to food-cues

Compared to participants without binge eating, we observed significant alterations in insular food processing and reward centers. BED was associated with greater bilateral FCR in the insula, especially in dorsal mid & ventral anterior insula (see Figure 8b). BED shows significant greater response to food-cues compared to noBE.

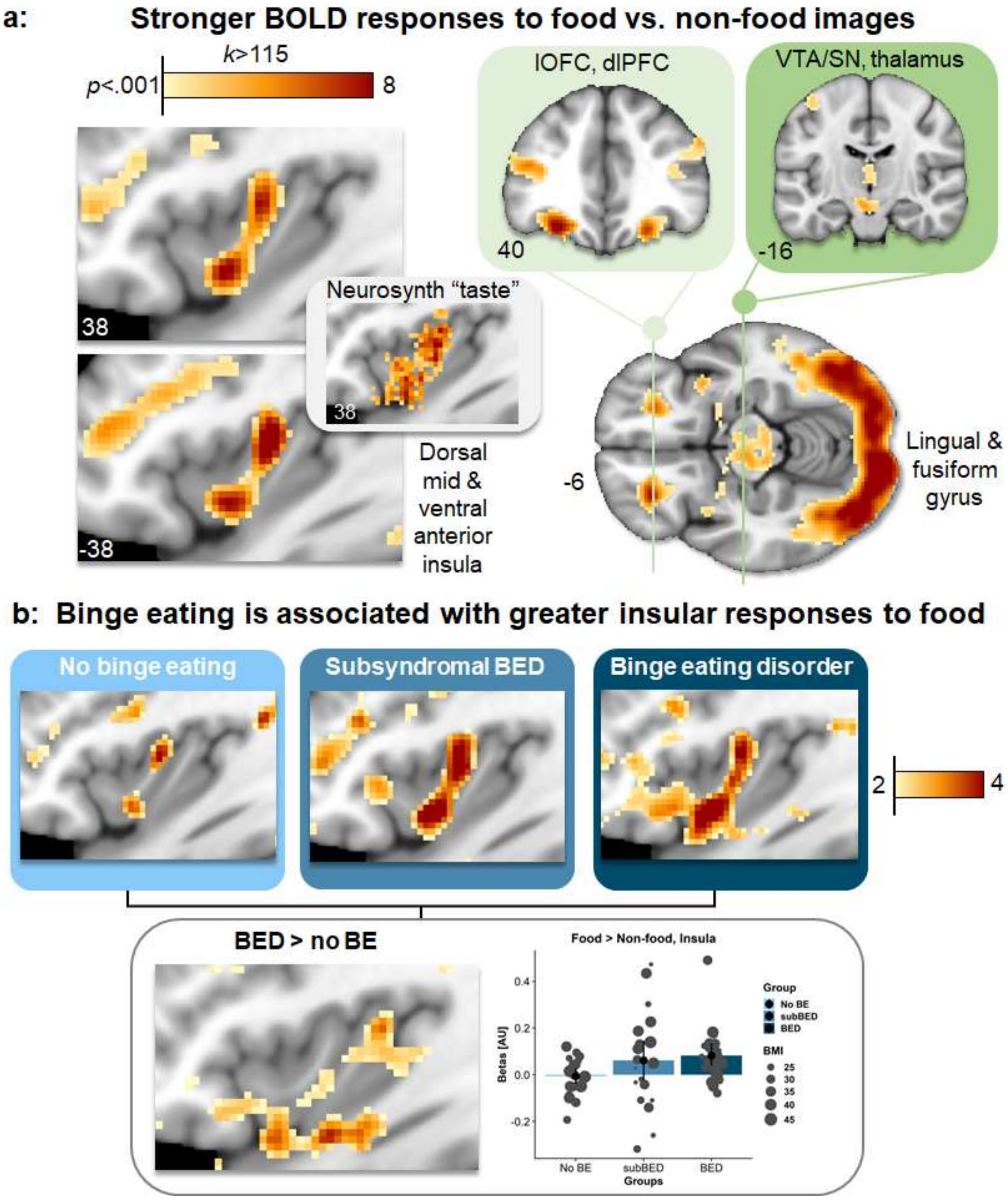

Figure 8: **BOLD responses to food vs. non-food images**
Brain regions including reward related centers showing significant responses to food vs. non-food images in all groups (a) and significant differences in food-cue reactivity (FCR) between binge eating disease (BED), subsyndromal binge eating (subBED) and healthy eating behavior (no BE) (b). BED is associated with significant higher FCR in insula, compared to no BE. All results are cluster-wise p < .001 corrected (cluster size k > 115), color bars represents t-values.

3.8 Insulin resistance is linked with attenuated insular responses to food

To evaluate the association of insulin resistance (as indexed by log HOMA-IR, corrected for BMI and age) with FCR (as indexed by the contrast between food and non-food picture blocks), we estimated the correlation in a second-level analysis. We discovered one cluster in the dorsal insula (t_{max} = 3.80, k = 41, $p_{SVC\_cluster} < .05$; 34/6/10) that showed a negative association that survived correction for multiple comparisons in our a priori ROIs ($k_{perm} > 28$). No cluster exceeded a whole brain corrected threshold. Hence, insulin resistance is associated with dampened neural activity to food-cues in insula ($p < .005$) and shows altered bilateral expression of insulin receptors (see Figure 9). Insular insulin receptor expression is more pronounced on the left than on the right insula.

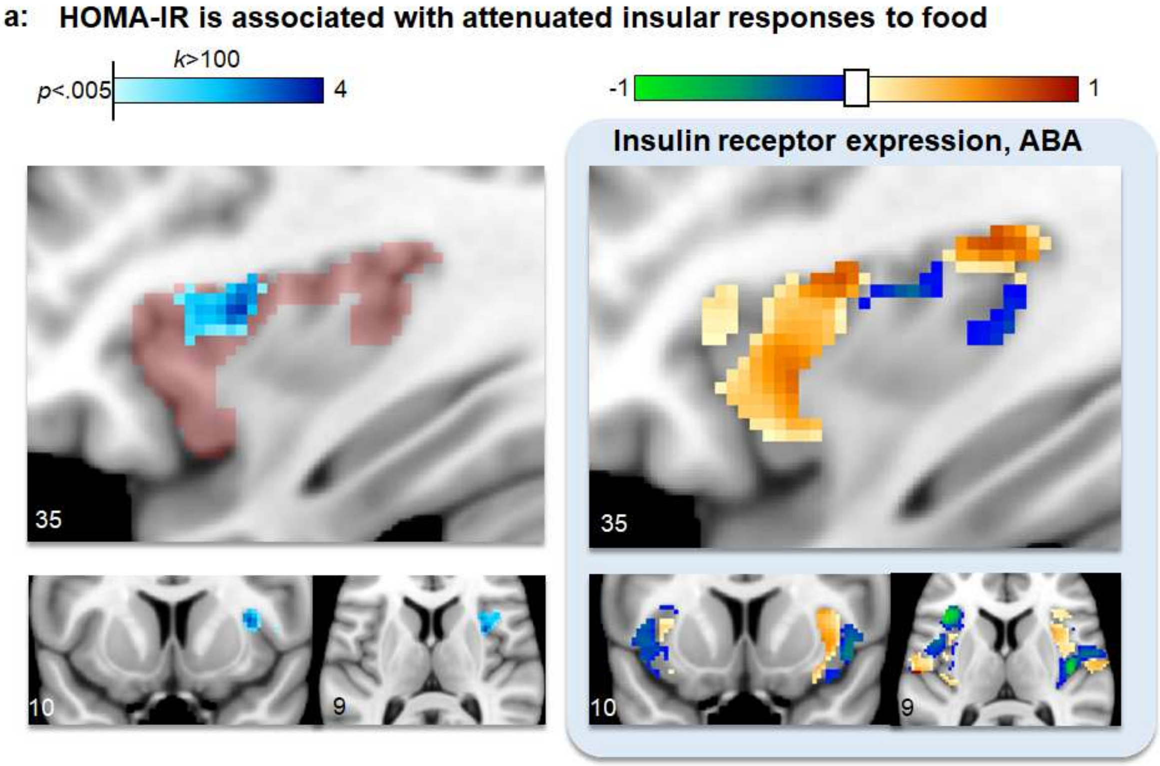

Figure 9: **Associations between insulin resistance and insular FCR**
The activation map (left) shows regions in insula where increased insulin resistance correlates with dampened FCR. With the insulin receptor expression map in insula (right) overlapping regions can be identified where FCR was attenuated. Receptor-rich areas are particularly affected. We observed altered bilateral insular insulin

receptor expression in participants with higher HOMA-IR. Results are cluster-wise p < .005 corrected (cluster size k > 100), color bars represents t-values

To verify this association by incorporating gene expression data provided by the Allen Brain Atlas (Allen Institute for Brain Science (2004). To this end, we estimated the co-localization with insulin receptors by extracting t-estimates of each voxel from the insula and the operculum (i.e., brain regions known to track ingestive information) and correlated the map with a smoothed map of the gene expression of the insulin receptor (see Figure 10). We observed, that a higher expression of insulin receptor is associated with stronger effects of HOMA-IR on FCR, especially in insula and left parietal operculum.

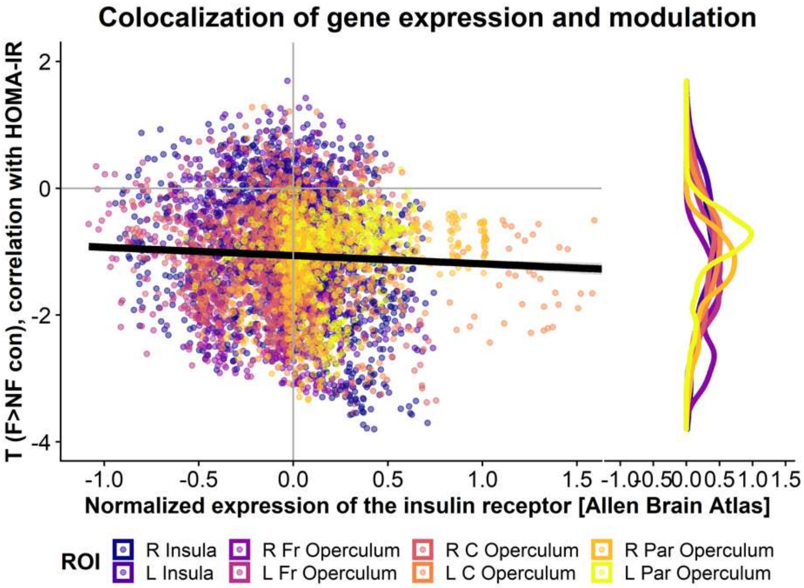

Figure 10: **Colocalization of insulin receptor expression and modulation through HOMA-IR**
Scatter plot visualizing the colocalization of insulin receptor expression in insula/operculum and modulation through food-cue reactivity (FCR) and peripheral insulin resistance (HOMA-IR). The x-axis displays standardized expression of insulin receptor from the Allen Brain Atlas data. The y-axis shows t-values which express the correlation of neural reaction (food vs. non-food) and HOMA-IR. The black regression line shows a slight negative correlation, which indicates that higher expression of insulin receptors is associated with stronger effects of HOMA-IR on FCR. The density curves highlight the distribution of insulin receptors for the ROI. ROI = regions of interests, R = right, L = left, FR = frontal , C = central, Par = parietal.

3.9 Insulin resistance is associated with steeper hedonically-scaled responses to food

To test whether insulin resistance has an impact on hedonic brain evaluation of food cues, we recorded FCR during food-cue anticipation in the MR and measured BOLD activation. Here, we found that increased HOMA-IR is associated with a stronger relationship between hedonic ‘liking‘ and FCR in insula ($p < .005$, see Figure 11a). Primarily sensori-motor areas (supplementary motor area (SMA), pre-SMA, sensorimotor regions) and gyrus related regions (precentral & postcentral gyrus) also are involved ($p < .001$).

3.10 Insulin resistance influence functional connectivity between the insular subregion and the sensorimotor network

Since altered functional connectivity (FC) of insula to limbic areas influence eating behavior, we investigated the effect of HOMA-IR on insular FC (see Figure 11b). Here, we found that HOMA-IR has modulatory effects on FC between bilateral subregions of insula and sensorimotor areas.

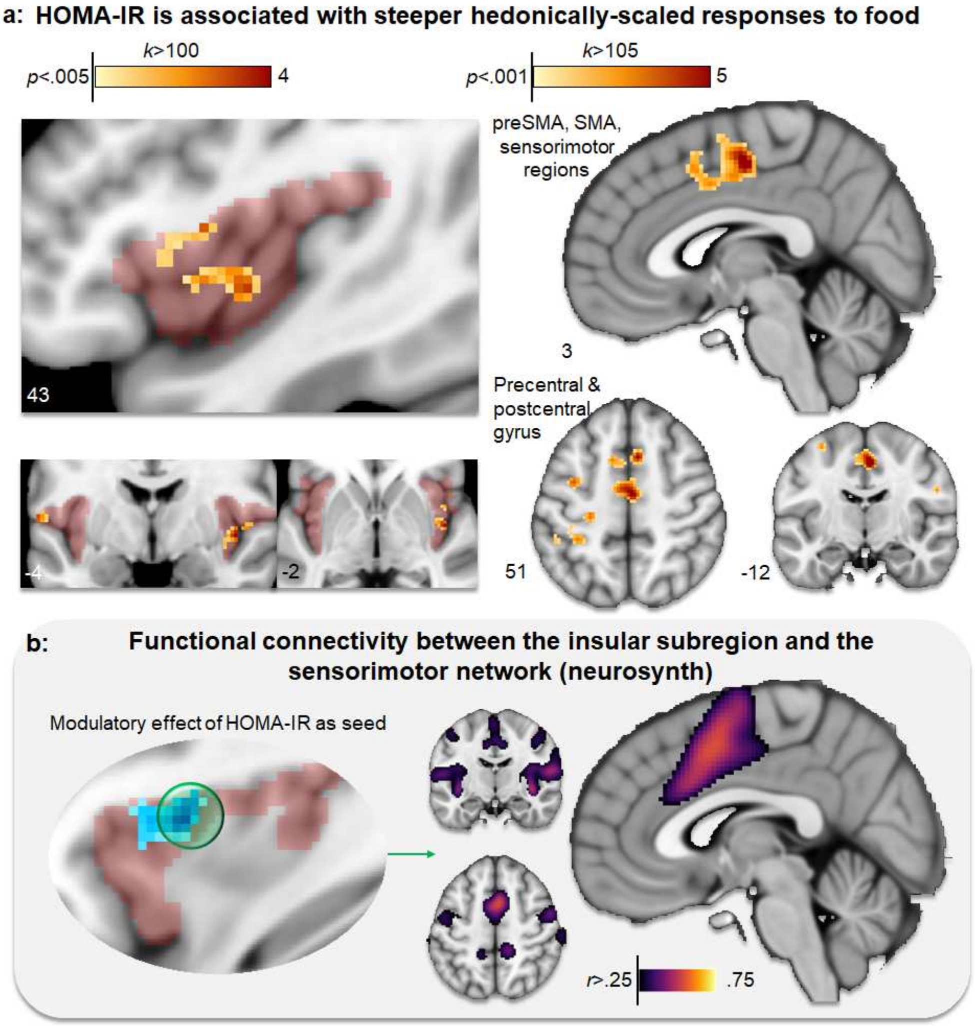

Figure 11: **HOMA-IR and steeper hedonically-scaled responses to food and insular functional connectivity**

Association of insulin resistance (HOMA-IR) and hedonically-scaled responses to food (a) and correlation of functional connectivity (FC) between the insular subregion as a seed region and the sensorimotor network in participants with higher HOMA-IR (b). Higher HOMA-IR was associated with stronger BOLD activation in insula and sensorimotor regions (supplementary moto area (SMA), pre-SMA, pre- & postcentral gyrus) and influences FC between insula and the sensorimotor network. Results are cluster-wise p < .0005 corrected (cluster size k > 100) (left) and p < .001 (k > 105) (right). In (b) the highlighted insular subregion served as seed region for functional connectivity analyses. Brain regions that are more functionally connected to insula (HOMA-IR as modulator) are displayed color scaled. Regions with stronger correlation (r) are highlighted purple than those with weaker correlation (yellow). FC between insula and sensorimotor network is influenced by insulin resistance.

4 Discussion

Contrary to our expectations we found no significant association between BED and increased insulin resistance (HOMA-IR). Ilyas et al. (2019) conducted a meta-analysis and found that there are generally few studies with inconsistent results, investigating the link between insulin sensitivity and BED. Succurro et al. (2015) found significant higher insulin resistance in BED ($p < .01$). In contrast to our study, participants with T2D were excluded and they had to have a BMI > 30 kg/m^2. (Zhou, Rifas-Shiman, Haines, Jones, & Oken, 2022) also found higher HOMA-IR in adolescents with binge eating behavior. The effect was attenuated after adjusting for BMI. Abraham, Massaro, Hoffmann, Yanovski, and Fox (2014) used a large BED sample (N=172) from the Framingham Heart Study. Here, log_HOMA-IR was significant higher in BED (0.4 vs. 0.2 in healthy participants, $p < .0001$), but not after adjusting for BMI. However, they did not conduct a diagnostic interview for BED diagnostic but draw questions from the Questionnaire on Eating and Weight Patterns-Revised, based on DSM-IV, which differs from frequency and duration criteria. The authors also state that they did not explicitly ask about the criteria for BN. The BED sample can therefore also contain other eating disorders. Geliebter, Gluck, and Hashim (2005) also found no significant differences in HOMA-IR but used a small BED sample (N=11). Here we contributed results to a general lack of studies assessing alterations in peripheral insulin in participants with BED (Ilyas et al., 2019) and provided a basis for further investigations and discussion.

In line with previous results (Samuels, Zimmerli, Devlin, Kissileff, & Walsh, 2009; Sysko, Devlin, Walsh, Zimmerli, & Kissileff, 2007), we found no alterations in subjective pre- and post-meal hunger ratings between binge-, subsyndromal- and healthy eating. Carnell et al. (2018) observed lower fullness-ratings in participants with BED compared to healthy people after dinner, which can make this time of day more prone to binge attacks (Harvey, Rosselli, Wilson, Debar, & Striegel-Moore, 2011; Raymond, Neumeyer, Warren, Lee, & Peterson, 2003). In our study, we only recorded VAS ratings of fullness/hunger between morning and at lunchtime. Not to be neglected is that lunch was served in such a size and presentation that even those with healthy eating habits tend to overeat, resulting in similarly high saturation values.

In the food bidding task we investigated effort-based decision-making in BED, subsyndromal BED and healthy participants. We measured wanting ratings for food vs. non-food cues and expected that BED is associated with higher ratings for food-cues. In fact, however, we could not identify any significant group differences and ratings were also not influenced by insulin resistance. Only a few studies have examined effort-based task in eating disorders. In a review from Brassard and Balodis (2021) only two studies were found and showed divergent findings: participants with binge-eating like symptoms tend to work harder for desirable food (Racine, Horvath, Brassard, & Benning, 2018), whereas obese participants showed a lower effort for obtaining monetary rewards (Mata et al., 2017). Both used Effort Expenditure for Reward Task (EEfRT), an alternative method to assess effort-based decision-making. In Racine et al. (2018) the sample consisted of non-clinical BED and Mata et al. (2017) excluded participants with diseases listed in DSM-V. Therefore, more work highlighting the connectivity between effort-base decision-making and BED is necessary to compare our results.

The hedonic scale reflects how much effort a person is willing to put into obtaining a reward based on how much they like it. It is to be expected that people are more willing to work for particularly attractive rewards in the form of food. But we found, that insulin resistance was associated with a reduced correlation between liking and bidding behavior. Here, we found that insulin resistance reduces the willingness to work for preferred foods, across groups unrelated to BED. In context of a meal, less effort could mean that people with higher insulin resistance are more likely to prefer quickly available food (e.g., fast food) to a amore elaborate but freshly cooked meal. Existing data on these results is limited and further research is needed to understand the mechanisms behind this correlation.

In line with previous fMRI studies, we observed an increased FCR in BED compared to age- and BMI-matched participants without symptoms of binge eating. We found that BED was associated with greater bilateral FCR in the insula, especially in dorsal mid (primary ingestive cortex) & ventral anterior insula. Previous fMRI studies showed increased activity in VS (J. E. Lee et al., 2017) and anterior cingulate cortex (ACC) (Aviram-Friedman et al., 2018; Schienle et al., 2009) in a food vs. non-food reactivity task in BED participants, indicating that altered FCR in BED may contribute to pathological eating behavior. The assumption that FCR has an influence on the pathomechanism of BED can be seen in first successful interventions in which binge eating attacks, snack intake and body weight were reduced through inhibitory learning cue exposure (Schyns et al., 2020). However, there are still no large-scaled fMRI studies that allow conclusions to be draw about general neurobiological characteristics in BED and further research needs to be carried out (Donnelly et al., 2018).

We observed altered insular responses to food in participants with elevated HOMA-IR. This reinforces the notion that peripheral insulin resistance affects neuronal food signaling and that diseases with altered receptor expression are at risk for pathological eating behavior. We found that higher insulin resistance dampened FCR in insular apex (anterior short, middle short & posterior short insula gyri) and was also associated with altered bilateral expression of insulin receptors. In contrast, previous T2D studies investigating alterations in food reward processing due to insulin resistance found a positive link between FCR and HOMA-IR during food reward anticipation in insula. Drummen et al. (2019) found higher FCR in increased insulin resistance in left and right insula in 39 overweight/obese individuals, with similar BMI to our sample (32 ± 7.11 vs. 32.3 ± 3.7). The sample differed in the average age of participants (~+10 years) and in including men (N_{women}=22, N_{men}=19). Jastreboff et al. (2013) also found a positive relation between HOMA-IR levels and brain activation in obese but not lean participants in insula. Their sample consisted of only 38 % female. Compared to our sample, both studies contain a relatively high proportion of men. Central effect of insulin on food response and the resulting impact on eating behavior was observed differently in women and men (Gabay, London, Yates, & Convit, 2022; Wagner et al., 2022). Novelle and Diéguez (2019) found that hedonically food intake is sex-dependent and estrogens act as a modulator to control energy homeostatis. What also stands out is that the mean HOMA-IR in the obese groups was comparable to our sample (3.9 ± 1.9 & 3.8 ± 1.4 vs. 3.7 ± 3.13) without binge eating disorder, and still yielded different results. These opposing findings highlight the need for further studies. Additional factors that play a role in the altered insular response to food, such as age (Jacobson, Green, Haase, Szajer, & Murphy, 2017; Morys, Garcia-Garcia, & Dagher, 2020) and differences in insular subregions should be considered.

HOMA-IR was associated with stronger hedonic responses to food-cues in insula but also in sensorimotor cortex. This indicates that insulin resistance is associated with an increased evaluation of food as rewarding and that strength of motivation (e.g., searching for food or ingestion) could be driven by the steeper hedonically scaled responses to food. Insulin resistance was associated with a stronger connectivity in reward related centers after a meal intake, suggesting that insulin fails as a suppressor of reward (Isganaitis & Lustig, 2005; Ryan, Karim, Aizenstein, Helbling, & Toledo, 2018). Hence, suppressed cognitive control could promote overeating in persons with insulin resistance.

We noticed that insular FC to sensorimotor centers is influenced by insulin resistance as a modulator. Xia et al. (2015) found altered interhemispheric connectivity in T2D which may contribute to cognitive dysfunction. Sensori-motor dysfunction has been linked to various neuropsychiatric disorders (Hirjak, Meyer-Lindenberg, Sambataro, & Christian Wolf, 2021), such as schizophrenia spectrum disorders (Hirjak, Meyer-Lindenberg, Sambataro, Fritze, et al., 2021) and bipolar disorder (Zhu et al., 2021). The influence of HOMA-IR on FC to sensori-motor areas may drive eating behavior and may contribute to altered eating behavior. However, since the modulatory effect occurs across groups, detached from binge eating, it is questionable whether this might play a role in the pathomechanism of BED. There is also a lack of fMRT studies to compare our results and more investigations should pay attention to HOMA-IR as modulator in insular FC.

BED is characterized by altered food reward signals, but it was not known whether altered insulin sensitivity contributes mechanistically to binge eating symptoms. Here, we investigated the association between HOMA-IR and brain responses to food images in participants with and without binge eating. In line with previous findings, we observed elevated food reward responses in patients with BED as well as modulatory effects of HOMA-IR in the insular cortex. Moreover, individual differences in HOMA-IR were associated with hedonic scaling of food reward responses in an extended somato-motor network that is functionally connected with insulin-sensitive regions of the insular cortex. However, modulatory effects of HOMA-IR were co-localized with insulin receptors and largely independent of individual differences related to binge eating. Hence, our results suggest that differences in insulin sensitivity do not explain altered food reward signaling in the insular cortex of patients with BED.

4.1 Data reliability

To ensure data quality, standardized protocols and established methods (fMRI, HOMA-IR) were used for all collected data. We adhered to strict inclusion criteria and adjusted the sample according to BMI and age to achieve heterogeneity and to avoid potential bias. Measurements were taken under the same conditions for all participants. Fasting blood data samples were collected from medically qualified personnel under standardized specifications and delivered to the laboratory at the earliest possible time. fMRI data was collected using a calibrated scanner and preprocessing minimized artefacts and noise.

4.2 Limitations and remaining questions

Despite the notable strengths such as the range of binge eating symptoms and BMI, as well as a high number of participants of BED compared to similar complex fMRI studies, there are limitations that should be addressed in future work.

Data collection took place during the Covid-19 pandemic. Acquisition of participants was difficult and the studies hat to be conducted under strict hygiene guidelines. Due to spatial and temporal circumstances the survey period was extended. It was subsequently observed that anxiety, stress, as well as prevalence and severity of BED increased significantly during the pandemic (Yu & Muehleman, 2023). It should be taken into account that emotional und motivational results could be influenced by the health politic situation during that time. Hence, a longitudinal study design would be more advantageous to identify confounding factors and take into account snapshots (X. Wang & Cheng, 2020). Even though we were able to show initial relationships between variables with our cross-sectional study design, these should be confirmed in further measurements over time to determine causalities.

Since women are more often diagnosed with BED, we decided to include only women to avoid that we have too few men per cell to estimate sex-dependent differences (Hallschmid, 2021). Still, the 12-month prevalence of BED in men is higher compared to other eating disorders (Stephan Herpertz et al., 2018; Marzilli et al., 2018), so future studies should include men with BED as well (Striegel et al., 2012).

Before collecting data, we recorded time and duration of the last period, but did not match the study date to the menstrual cycle of the participants. Ovarian hormones affect eating behavior and consistent with this, polycystic ovary syndrome (PCOS) is characterized with irregular menstruation (oligomenorrhea, amenorrhea) and insulin resistance. Therefore patients with PCOS are at high risk for BED (Lalonde-Bester et al., 2024). For instance, Hollinrake, Abreu, Maifeld, Van Voorhis, and Dokras (2007) found higher prevalence of BED in patients with PCOS compared to healthy (12.6 % vs. 1.9 %) (Hollinrake et al., 2007). Klump et al. (2014) found post-ovulatory peaks in food intake and binge eating. Since variations in appetite and satiety were recorded across the menstrual cycle (Guerdjikova et al., 2019) and menstrual dysfunction is associated with binge eating behavior, further studies should consider evaluating of menstrual status carefully (Algars et al., 2014) and adjust the examination periods.

Although the HOMA-IR is often used as an index of insulin resistance, post-load measurement of insulin and glucose provide a better sensitivity to diagnose metabolic syndrome (Carnevale Schianca et al., 2006). In addition, the cut-off point of HOMA-IR defining insulin resistance varies to demographic characteristics (sex, race, and age) (Tahapary et al., 2022). Therefore, more extensive characterizations of insulin sensitivity combined with larger samples might be necessary to detect smaller associations between binge eating and altered glucose metabolism.

4.3 Future directions

Since insulin resistance is unlikely to mechanistically explain the observed differences in insular food reward signals in BED, alternative pathomechanisms must be considered. Other theories include the influence of other hormones, e.g. ghrelin, an appetite hormone, that also appears to regulate energy homeostatis and glucose regulation, possibly via the vagus nerve (Sovetkina, Nadir, Fung, Nadjarpour, & Beddoe, 2020) or dysregulation of stress and emotions (R. M. Kessler, Hutson, Herman, & Potenza, 2016).

Furthermore, decreased impulse control and difficulties in regulating emotions are discussed (Leehr et al., 2018). Compared to healthy test subjects, overweight subjects show less inhibitory control and less activity in the dorsolateral prefrontal cortex when performing inhibitory control tasks. However, a meta-study showed that this phenomenon occurs independently of eating disorders (Lavagnino, Arnone, Cao, Soares, & Selvaraj, 2016).

Recent studies suggest the influence of dysbiosis in gut microbiome on the gut-brain-axis in BED (Guo & Xiong, 2024). Intestinal microbiota produce neurotransmitter (e.g., GABA) (Auteri, Zizzo, & Serio, 2015) and dysbiosis can lead to alterations in neural pathways between gut and brain. Further investigations may implicit the therapeutic approach for balancing gut microbiome for instance through antibiotics, pre-/probiotics or fecal microbiota transplantation. However, relatively little is known about the pathomechanism of BED and research is still in its early stages. Most neuroendocrinological studies are based on a cross-sectional design and causalities are difficult to determine (Baenas, Miranda-Olivos, Solé-Morata, Jiménez-Murcia, & Fernández-Aranda, 2023).

4.4 Broader conclusions

In sum, our data provided strong evidence that insulin resistance (HOMA-IR) is not likely to mechanistically explain the pathological eating behavior in BED. However, we found interesting modulatory effects on the insula. HOMA-IR dampened FCR in insula and higher HOMA-IR was associated with altered bilateral insulin receptor expression in insula. HOMA-IR was also associated with greater hedonic scaling of food reward responses in an extended network including somato-motor regions that are functionally connected with insulin-sensitive regions of the insula.

Collectively, our results show that changes in insulin sensitivity contribute independently to altered food reward signals and argue against a mechanistic role in BED. Our findings highlight that insulin sensitivity affects food reward signaling and may promote pathological eating behavior. Further studies are needed to investigate the gut-brain-axis to provide new insights and therapeutic approaches for metabolic syndrome which may help reduce negative sequelae of BED.

5 Summary

Our society faces ever-increasing rates of obesity and type 2 diabetes mellitus, associated with increased healthcare costs and mortality rates, and eating disorders are a major contributor. This also includes binge eating disorder (BED), which, after being recognized as a single clinical diagnosis in 2013, turned out to be the most common eating disorder. Research on the mechanisms of genesis and maintenance is correspondingly young and mainly deals with the processing of food stimuli in dopaminergic reward centers. Previously, it was assumed that decreased peripheral insulin sensitivity contributes to altered signaling in neuronal centers, as it has been shown that many insulin receptors are expressed in areas affecting motivation, food anticipation and reward. This has not yet been studied in people with BED.

Here, we investigated associations between symptoms of binge eating, peripheral insulin sensitivity, and neural FCR in 61 participants (M_{age} = 39.7 years ± 13.2; M_{BMI} = 31.5 kg/m^2 ± 7.1 [20.2, 46]; M_{WtHR} = 0.57 ± 0.1 [0.4, 0.7]) who were divided into 3 groups (N_{BED}=21, N_{subBED}=20, N_{noBE}=20). In line with previous results, we found that binge eating is associated with a greater FCR in mesocorticolimbic regions that have been linked to food reward and insulin sensitivity (i.e., insula, striatum, VTA, amygdala, OFC). Contrary to expectation, BED was not associated with higher peripheral insulin resistance or subjective hunger/fullness. Interestingly, increased HOMA-IR was associated with multiple neuronal alterations affecting the insula: HOMA-IR dampened FCR in insular, showed altered expression of insular insulin receptors, changed modulatory effects on functional connectivity between insula and sensori-motor areas, and we found a stronger relationship between hedonic liking ratings in FCR and primary sensori-motor areas.

To summary, we found that both individual differences in binge eating and insulin sensitivity were associated with altered brain responses to food in the insular cortex. However, modulatory effects of HOMA-IR were co-localized with insulin receptors and largely independent of individual differences related to binge eating. Hence, our results suggest that differences in insulin sensitivity do not explain altered food

reward signaling in the insular cortex of patients with BED. Our findings highlight that alterations in insulin sensitivity are unlikely to mechanistically explain the observed differences in insular food reward signals in patients with BED. Nevertheless, an improved understanding of the modulatory effects of insulin sensitivity on food reward signaling including participants with marked symptoms of binge eating may provide new avenues for the treatment of the metabolic syndrome which may help reduce negative sequelae of BED.

6 Zusammenfassung

Unsere Gesellschaft sieht sich mit stetig steigenden Zahlen an Adipositas und Diabetes mellitus Typ 2 konfrontiert, die mit erhöhten Gesundheitskosten und Mortalitätsraten einhergehen. Essstörungen tragen dabei einen nicht zu vernachlässigenden Anteil bei. Dazu zählt auch die Binge-Eating-Störung (BES), die erst seit 2013 als alleinstehende Diagnose in das DSM-V aufgenommen wurde und sich in den letzten Jahren als häufigste Essstörung herauskristallisiert hat. Die Forschung über Entstehungs- und Aufrechterhaltungsmechanismen ist dementsprechend jung und beschäftigt sich überwiegend mit der neuronalen Verarbeitung von Lebensmittelhinweisen in dopaminergen Belohnungszentren (Food-cue reactivity (FCR)). Bisher wurde angenommen, dass eine erniedrigte periphere Insulinsensitivität Signalübertragungen in neuronalen Zentren beeinflussen könnte, da dort nachweislich viele Insulinrezeptoren exprimiert werden. Dies wurde bisher in klinischen Studien in Personen mit BES unzureichend erforscht.

In der vorliegenden Doktorarbeit wurden die Zusammenhänge zwischen Symptomen von Binge-Eating, peripherer Insulinresistenz (HOMA-IR) und neuronaler FCR bei 61 Probandinnen (M_{age} = 39,7 Jahre ± 13,2; M_{BMI} = 31,5 kg/m^2 ± 7,1 [20,2; 46]; M_{WtHR} = 0,57 ± 0,1 [0,4; 0,7]) untersucht, die in drei Gruppen eingeteilt wurden (N_{BED}=21, N_{subBED}=20, N_{noBE}=20). In Übereinstimmung mit früheren Ergebnissen fanden wir heraus, dass BES mit einer signifikant stärkeren FCR in mesocorticolimbischen Regionen, die mit Nahrungsbelohnung und Insulinsensitivität in Verbindung gebracht wurden (z.B. Insula, Striatum, VTA, Amygdala, OFC), assoziiert ist. Entgegen unserer Annahme fanden wir keine signifikanten Gruppenunterschiede in der peripheren Insulinresistenz. BES ist außerdem nicht mit abweichenden subjektiven Hunger- oder Völlegefühlen assoziiert. Interessanterweise ist ein höherer HOMA-IR mit mehreren neuronalen Veränderungen verbunden, die die Insula betreffen: der HOMA-IR dämpft die FCR und zeigt eine veränderte bilaterale Expression von Insulinrezeptoren in der Insula.

Der HOMA-IR zeigt außerdem veränderte modulierende Wirkungen auf die funktionale Aktivität zwischen Insula Regionen und somatomotorischen Bereichen und es wurde eine stärkere Beziehung in hedonischen ‘liking‘-ratings der FCR in primären sensomotorischen Bereichen gefunden.

Zusammenfassend stellten wir fest, dass sowohl individuelle Unterschiede bei Binge-Eating, als auch bei der Insulinsensitivität, mit veränderten Reaktionen des Gehirns auf Nahrung im Inselkortex einhergehen. Die modulatorischen Wirkungen vom HOMA-IR scheinen jedoch mit Insulinrezeptoren kolokalisiert und weitgehend unabhängig von individuellen Unterschieden im Zusammenhang mit Binge-Eating aufzutreten. Daher deuten unsere Ergebnisse darauf hin, dass Abweichungen in der Insulinsensitivität die veränderten Nahrungsbelohnungsverarbeitungen im Inselkortex von Patienten mit BES wahrscheinlich nicht mechanistisch erklären können. Nichtsdestotrotz kann ein verbessertes Verständnis der modulierenden Wirkungen der Insulinsensitivität auf das Belohnungssystem von Nahrungsmitteln, einschließlich Probandinnen mit ausgeprägten Symptomen von Binge-Eating, neue Wege für die Behandlung eines metabolischen Syndroms eröffnen, um negative Folgen von BES zu reduzieren.

7 References

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8 Erklärung zum Eigenanteil der Dissertationsschrift

Die Arbeit „Neuroendocrine Modulation of food reward in binge eating: Insulin sensitivity has dissociable effects on insular food-reward signals in binge eating” wurde an der Universitätsklinik für Psychiatrie und Psychotherapie Tübingen, Bereich Translationale Psychiatrie, unter der Betreuung von Herrn Prof. Dr. rer. nat. Nils B. Kroemer durchgeführt.

Teile dieser Dissertation decken sich mit noch unveröffentlichten Manuskripten, in denen ich als Autorin mitgewirkt habe: Wentz, DJ., Neuser, MP., Kullmann, S., Small, DM., Hallschmid, M., Svaldi, J., Kroemer, NB. ‘Insulin sensitivity has dissociable effects on insular food-reward signals in binge eating disorder‘ und

Schulz, C., Schwab, J., Wentz, DJ., Neuser, MP., Hallschmid, M., Svaldi, J., Kroemer NB. ‘Ghrelin is associated with hedonic drive and food reward signaling in binge eating disorder‘.

Die Konzeption der Studie erfolgte durch Herr Prof. Dr. rer. nat. Nils B. Kroemer als Studienleiter in Zusammenarbeit mit Frau Monja P. Neuser als Studienkoordinatorin. Die Probandenrekrutierung wurde durch mich und Monja P. Neuser ausgeführt. Die telefonischen Probandenscreenings erfolgten durch mich und durch weitere Studierende der Arbeitsgruppe neuroMADLAB.

Die Versuche und Blutentnahmen (Blutprotokoll), wurden nach Einarbeitung durch einen Studienarzt (Dr. med. Johannes Klaus) und Astrid Wither (Study nurse) von mir durchgeführt. Jacob Schwab, Franziska Müller und Lilith Irtel v. Brenndorff, allesamt zum damaligen Zeitpunkt Studierende der Humanmedizin, führten nach Einarbeitung durch mich, die weitere Datenerhebung nach meinem wissenschaftlichen Freisemester (Sommersemester 2020) durch. Die fMRT-Untersuchungen wurden von Monja P. Neuser und Vanessa Teckentrup als MR Supervisor und durch mich, Jacob Schwab, Franziska Müller und Lilith Irtel v. Brenndorff als MR Basic User durchgeführt.

Die Abbildungen und Fotografien im Methodenteil wurden durch mich eigenständig erstellt. Die deskriptive Auswertung des Probandenkollektives, inklusive der

Blutdaten, sowie die weitere statistische Auswertung und Erstellung der Grafiken im Ergebnisteil erfolgte durch mich eigenständig.
Die Analyse der Verhaltens- und fMRT-Daten wurde durch Herrn Prof. Dr. rer. nat. Nils B. Kroemer durchgeführt. Die dabei entstandenen Abbildungen wurden mir zur weiteren Auswertung zur Verfügung gestellt.

Ich versichere, das Manuskript selbstständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Tübingen, 15.03.2025
Dana Julischka Wentz