Aus der

Universitätsklinik für Psychiatrie und Psychotherapie Tübingen

Abteilung Allgemeine Psychiatrie und

Psychotherapie mit Poliklinik

Triglycerides and Food Reward Signaling in Binge Eating Disorder

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von

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2026

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Tag der Disputation: 12.03.2026

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List of abbreviations

BED	Binge Eating Disorder
BMI	Body Mass Index
BWL	Behavioral Weight Loss
BN	Bulimia Nervosa
BOLD	Blood Oxygenation Level Dependent
CBT	Cognitive Behavioral Therapy
CI	Confidence Interval
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DBT	Dialectical Behavior Therapy
DRD2	Dopamine Receptor Subtype 2
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
EAT	Effort Allocation Task
EDA-5	Eating Disorder Assessment for DSM-5
ED	Eating Disorder
EDE	Eating Disorder Examination
EDE-Q	Eating Disorder Examination Questionnaire
EPI	Echo-Planar Images
FAST	FMRIB’s Automated Segmentation Tool
FCR	Food Cue Reactivity
FDA	Food and Drug Administration (U.S.)
FEP	Fluoroethylene-Propylene
fMRI	Functional Magnetic Resonance Imaging
FTO	Fat Mass and Obesity-Associated
FUGUE	FMRIB's Utility for Geometrically Unwarping EPIs
FWHM	Full-Width at Half-Maximum

- GI Gastrointestinal
- GLP-1 Glucagon-Like Peptide-1
- GMT Guitar Masip Task
- GM Gray Matter
- GFD Grip Force Device
- HDL high-density lipoprotein
- ICD International Classification of Diseases
- IFG Inferior Frontal Gyrus
- IPT Interpersonal Therapy
- mPFC Medial Prefrontal Cortex
- MRI Magnetic Resonance Imaging
- NAcc Nucleus Accumbens
- No BE No Binge Eating
- PCC Posterior Cingulate Cortex
- SCID Structured Clinical Interview for DSM-IV Axis I
- SCOFF Sick, Control, One, Fate, and Food
- SD Standard Deviation
- SE Standard Error
- SSRI Selective Serotonin Reuptake Inhibitor
- subBED subsyndromal Binge Eating Disorder
- TE Echo Times
- TR Repetition Time
- UKT Universitätsklinikum Tübingen
- VAS Visual Analog Scale
- vmPFC Ventromedial Prefrontal Cortex
- WHO World Health Organization
- WHtR Weight to Height Ratio
- WM White Matter

1 Introduction

Our society is continuously expanding - not only in terms of population size, but also individuals' body mass indices (BMI) have risen dramatically in recent decades. ("Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants," 2016). The global obesity pandemic is considered a major public health issue according to the World Health Organization (WHO) ("Obesity: preventing and managing the global epidemic. Report of a WHO consultation," 2000). With the rising prevalence of obese individuals worldwide, further research is crucial to gain a better understanding of eating behaviors.

Binge Eating Disorder (BED) is the most common eating disorder (Aguera et al., 2020). It is characterized by recurrent binge episodes without compensatory behaviors, often leading to obesity and metabolic syndrome (Aguera et al., 2020; Brownley et al., 2016; Galmiche, Dechelotte, Lambert, & Tavolacci, 2019; R. C. Kessler et al., 2013; Udo & Grilo, 2018). Its development is linked to a dysregulation in food intake pathways, particularly dopamine signaling which influences motivation and reward (Giel et al., 2022; Jowik, Dutkiewicz, Slopien, & Tyszkiewicz-Nwafor, 2020). Neuroimaging studies indicate that individuals with BED exhibit altered neural responses to food cues and impaired inhibitory control (Schienle, Schäfer, Hermann, & Vaitl, 2009). Emerging research highlights the role of triglycerides in modulating dopamine signaling and reward processing, potentially contributing to overeating (Berland, Cansell, Hnasko, Magnan, & Luquet, 2016; Berland et al., 2020; Cansell et al., 2014; Cansell & Luquet, 2016).

This thesis explores the role of triglycerides in reward signaling and their impact on BED. Specifically, we examine the relationship between triglyceride levels, BMI, and insulin sensitivity in individuals with BED, subsyndromal BED, and a control group. Furthermore, we investigate how triglycerides influence brain responses to food cues

by analyzing functional magnetic resonance imaging (fMRI) responses during a food bidding task. 61 female participants were assessed through blood sampling, behavioral evaluations, and neuroimaging. This research aims to help advance the understanding of the role triglycerides play in food reward signaling and binge eating behavior, contributing to a deeper comprehension of BED and potential treatment approaches.

1.1 Binge Eating Disorder (BED)

1.1.1 Definition

BED was first recognized as a distinct diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (DSM-5;Association AP: Edition, 2013) and later included in the International Classification of Diseases, 11th Revision in 2019 (Organization, 2019/2021). Individuals with BED experience a loss of control over their eating behavior, leading to episodes of overeating in which a large amount of food is consumed within a short period (<2 hours) (Brownley et al., 2016). BED is characterized by binging episodes at least once per week for three consecutive months (Aguera et al., 2020). Binge eating episodes are typically accompanied by at least three of the following symptoms: eating faster than usual, eating despite not feeling hungry, eating until uncomfortably full, eating alone due to embarrassment, or experiencing guilt, disgust, or shame after overeating (DSM-5;Association AP: Edition, 2013).

1.1.2 Epidemiology and prevalence rates

BED is the most common eating disorder in both men and women (Galmiche et al., 2019; Hudson, Hiripi, Pope, & Kessler, 2007; R. C. Kessler et al., 2013; Udo & Grilo, 2018) and is associated with both high prevalence and significant psychological burden (Giel et al., 2022). However, data on BED outside North America, Australia,

and Europe remain limited and highly heterogeneous across different geographical regions (Giel et al., 2022; R. C. Kessler et al., 2013).

The lifetime prevalence for BED according to a meta-analysis from Qian et al. is 1,53% (95% CI, 1.00–2.17) which is ten times the lifetime prevalence of Anorexia nervosa (AN) (0,16%; (95% CI, 0.06–0.31)) and 2,5 times the lifetime prevalence of bulimia nervosa (BN) (0.63% (95% CI, 0.33–1.02)) (Qian et al., 2022). While BED is the most common eating disorder in both men and women, when comparing lifetime prevalence of BED between genders, women have a higher lifetime prevalence than men (Giel et al., 2022; Guerdjikova, Mori, Casuto, & McElroy, 2019; Keski-Rahkonen, 2021).

Researchers found that Adolescents exhibit the highest past-year prevalence of BED with a prevalence of 1,8-3,6% in girls, 1,5% in gender-diverse youths and 0,2-1,2% in boys, however, symptoms may be transient (Mitchison et al., 2020; Olsen, Koch, Skovgaard, & Strandberg-Larsen, 2021) and may also include fluent cross-over between BED and other eating disorders such as Bulimia nervosa (BN) or Anorexia nervosa (AN) (Ackard, Fulkerson, & Neumark-Sztainer, 2011; Allen, Byrne, Oddy, & Crosby, 2013; Stice, Marti, & Rohde, 2013). Long-term studies depict BED as a long-lasting medical condition with an average duration of 14-16 years (Giel et al., 2022; Udo & Grilo, 2018). This highlights the need for further research and attention to understand and address this complex eating disorder.

1.1.3 Etiology and Risk factors

While the exact pathogenesis of BED remains unclear and continues to be the focus of ongoing research, several studies have identified neural mechanisms such as altered pathways and receptors that affect reward signaling, hedonic eating behavior, and satiety as part of the multifactorial etiology of BED (Giel et al., 2022). This will be further discussed throughout this dissertation.

The risk factors that contribute to the development of an eating disorder such as BED must be thoroughly investigated in order to develop appropriate prevention strategies. Typically, a variety of factors contribute to the emergence of a diagnosis, including genetic and environmental factors such as socioeconomic status, education, experienced psychological distress, and access to health care. Solmi and colleagues reviewed several meta-analyses to examine risk factors leading to eating disorders, including BED. They describe an association between childhood abuse, both physical and sexual, and BED as well as between appearance-related teasing victimization and any eating disorder (Solmi et al., 2021). Moreover, severe childhood obesity, family overeating or binge-eating, parental neglect or death, bullying, behavioral problems, traumatic life events and substance abuse were found to be risk factors for the development of BED (Hilbert et al., 2014; Striegel-Moore et al., 2005). In addition to environmental risk factors, there are also individual risk factors that need to be considered. Eating disorders have a genetic component, with one of the most important known genes associated with an increased vulnerability to BED and other eating disorders being the fat mass and obesity-associated (FTO) gene (Castellini et al., 2017; Stabouli, Erdine, Suurorg, Jankauskienė, & Lurbe, 2021). This gene is associated with impairment in behavioral regulation and may aggravate binge eating (Cameron et al., 2019). Alterations in genes linked to the regulation of appetite and satiety may also be involved in the development of BED (Nicoletti, Delfino, Ferreira, Pinhel, & Nonino, 2019; Stabouli et al., 2021). Another important aspect is neural changes in both the neuroendocrine system and reward-related brain circuits, such as the striatum, midbrain, amygdala, and orbitofrontal cortex, which may lead to increased vulnerability to developing eating disorders. (Berridge, Ho, Richard, & DiFeliceantonio, 2010; Stabouli et al., 2021). Furthermore, personality traits such as low self-esteem and body dissatisfaction have been postulated to be contributors to the development of BED. Other risk factors that are increasingly being studied may include social isolation, dieting, and an altered gut microbiome (Carbone, D'Amato, Vicchio, De Fazio, & Segura-Garcia, 2020; Stabouli et al., 2021). Overall, understanding and identifying risk factors may help to further

increase knowledge about BED and apply this knowledge to promote prevention strategies and potentially develop more treatment concepts.

1.1.4 Diagnostic criteria and assessment tools

Despite being the most common eating disorder, BED is often underdiagnosed and individuals suffering from BED are left untreated for a lack of awareness in regards to recognizing and treating an eating disorder such as BED (Giel et al., 2022; Reas, 2017). Additionally, individuals suffering from BED face stigma and shame which negatively affects help-seeking behavior and partially accounts for a relatively low amount of only about 50% of affected patients seeking help (Giel et al., 2022; Kornstein, Kunovac, Herman, & Culpepper, 2016). It is therefore crucial to educate healthcare professionals and the public about screening, prevention and treatment tools for BED. For the diagnosis of BED, structured clinical expert interviews are the gold standard (Giel et al., 2022), there is however also a variety of screening tools available. The most commonly used screening tool is the five-item SCOFF questionnaire (Sick, Control, One, Fat, and Food). However, it is important to note that BED had not yet been formally defined when the SCOFF was developed (Giel et al., 2022). Other commonly used assessment tools include the Eating Disorder Examination (EDE) and its self-report version, the Eating Disorder Examination Questionnaire (EDE-Q) (Celio, Wilfley, Crow, Mitchell, & Walsh, 2004; Fairburn & Cooper, 1993). While the EDE is a structured expert interview that takes around 45-60 minutes, the EDE-Q is a shorter self-rating tool that can be used as a screening tool or for a follow-up and takes about 15 minutes (Herpertz, 2018; Kornstein et al., 2016). These screening instruments constitute an important approach to detecting and diagnosing BED in primary care as well as clinical settings (Kornstein et al., 2016).

As aforementioned, DSM-V and ICD-11 Criteria are used to diagnose and classify BED based on the following diagnostic criteria (DSM-5;Association AP: Edition, 2013; Berkman et al., 2015):

1. Recurring instances of excessive eating, characterized by both of the subsequent:
    a. Eating in a brief period of time (e.g., within a 2-hour period), eating an amount of food that is considered larger than other people would eat under similar circumstances or within the same amount of time
    b. A feeling of lack or loss of control during the binge eating episode
2. At least three of the following criteria are met:
    a. Eating faster than usual
    b. Eating until an uncomfortable feeling of fullness occurs
    c. Eating despite not being physically hungry
    d. Eating in isolation for a feeling of embarrassment about the consumed amount of food
    e. Feelings of guilt or disgust with oneself after binge eating
3. Individuals suffer from and feel burdened by episodes of overeating
4. Frequency and duration criteria: Binge-eating occurs at least once a week for 3 months
    a. Based on the frequency a severity grading can be distinguished:
        i. Mild: 1 to 3 binge eating episodes per week
        ii. Moderate: 4 to 7 binge eating episodes per week
        iii. Severe: 8 to 13 binge eating episodes per week
        iv. Extreme: 14 or more binge eating episodes per week
5. No utilization of compensatory mechanisms (e.g., purging, excessive amounts of exercise, fasting)

ICD-11 classification is mostly similar to the DSM-V, with one distinction being a more liberal definition of the duration and frequency of binge-eating episodes and no differentiation of different severity grades (Giel et al., 2022).

1.1.5 Clinical manifestations and associated comorbidities

Since BED is not associated with compensatory behaviors such as purging or excessive exercise, and individuals with BED typically binge on high-caloric foods (Bello & Hajnal, 2010), it is strongly linked to obesity (Aguera et al., 2020; Brownley et al., 2016; R. C. Kessler et al., 2013) and an increased risk of metabolic syndrome. Metabolic syndrome is characterized by abdominal obesity and at least two of the following four criteria: elevated triglycerides, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated fasting blood sugar or type 2 diabetes mellitus (Brownley et al., 2016). In fact, according to Ágh and colleagues, 30% of patients with obesity that want to undergo behavioral or surgical weight loss treatment also suffer from BED (Ágh et al., 2015). BED is also frequently associated with cardiovascular conditions, arthritis, and sleep disturbances (Giel et al., 2022). Additionally, individuals with BED often experience upper and lower gastrointestinal (GI) symptoms, including dysphagia, acid reflux, bloating, abdominal pain, diarrhea, constipation, and lower GI urgency (Cremonini et al., 2009) as well as respiratory and musculoskeletal problems (Thornton et al., 2017).

Furthermore, BED is comorbid with a wide range of mental disorders (Keski-Rahkonen, 2021) with mood and anxiety disorders being the most common (Aguera et al., 2020; C. Davis, 2015; Javaras et al., 2008). BED is also associated with increased suicide rates (Agh et al., 2016) (Udo, Bitley, & Grilo, 2019). Additionally, disorders characterized by impaired impulse control, such as alcohol use disorder, borderline personality disorder, and pathological gambling, are frequently observed in individuals with BED (Fernández-Aranda et al., 2008; Jiménez-Murcia et al., 2013; Udo & Grilo, 2019). As a result, BED significantly reduces quality of life and has a

profound negative impact on both psychological and physiological health with the standardized mortality ratio associated with BED estimated to be 1.50 (95% CI 0.87–2.40) to 1.77 (95% CI 0.60–5.27) (Ágh et al., 2015; Dawes et al., 2016; Giel et al., 2022; Keski-Rahkonen, 2021).

1.1.6 Current treatment approaches and limitations

Given the significant psychological and physiological burden of BED, treatment primarily aims to reduce binge-eating episodes while addressing psychiatric symptoms and metabolic comorbidities (Giel et al., 2022). A secondary, and often debated, treatment goal is weight loss. International guidelines recommend a combination of evidence-based psychological therapies and pharmacotherapy, namely antidepressants, central nervous system (CNS) stimulants, and anti-obesity medications (Giel et al., 2022; Hay et al., 2014; Hilbert, Hoek, & Schmidt, 2017). Therapy can be carried out either in an outpatient or an inpatient setting (Giel et al., 2022). The three main psychological therapies supported by randomized controlled trials are cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and dialectical behavior therapy (DBT), with the strongest evidence for CBT. Both guided and self-help CBT approaches have demonstrated effectiveness in BED treatment (Giel et al., 2022). In order to also address psychological comorbidities such as major depression and mood intolerance, emotion regulation skills may be incorporated into cognitive behavioral therapy (Giel et al., 2022). Notably, low weight concern has been identified as a positive predictor of CBT success, whereas a history of trauma is associated with poorer outcomes (Grilo, Thompson-Brenner, Shingleton, Thompson, & Franko, 2021; Hazzard et al., 2021). IPT has also shown promising results, particularly in achieving abstinence from binge eating (Giel et al., 2022; Linardon, 2018). All in all, studies show that after a time period of 12 months post psychological therapy only 51% of people with BED achieve complete remission (Hilbert et al., 2020; Linardon, 2018).

The second pillar of BED treatment is pharmacotherapy. As second line therapy this is not standard practice and should only be considered after failure or unavailability of psychotherapy. Further, drugs for the treatment of BED are not approved in every country and may have to be used off-label.

Notably, meta-analyses found pharmacological treatment to have a significant short-term impact on the reduction or cessation of binge eating episodes in patients with BED compared to placebo. However, there is a lack of long-term data, relapses may occur and the effects on mood and eating disorder psychopathology are inconsistent. The most commonly used pharmacological treatments for BED include second-generation antidepressants and lisdexamfetamine, a central nervous system (CNS) stimulant. Lisdexamfetamine, a prodrug of d-amphetamine, is FDA-approved in the U.S. for treating moderate to severe BED in adults. Research has shown that it significantly reduces weekly binge-eating episodes while also positively impacting body weight and BED-related psychopathology (Giel et al., 2022; Muratore & Attia, 2022). Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and citalopram, are the preferred antidepressants for treating BED. While they have a good safety profile and effectively reduce binge-eating frequency and increase remission rates, they have little impact on weight loss. Anticonvulsants like topiramate, however, have shown positive effects on both binge-eating frequency and weight, with sustained improvements observed after a 42-week follow-up (McElroy et al., 2004; Muratore & Attia, 2022).

A key consideration in BED treatment is the frequent coexistence of high body weight and its associated physical and mental health comorbidities. One approach to weight loss is behavioral weight loss treatment (BWL), which has been shown to be more effective than cognitive behavioral therapy (CBT) for weight reduction but less effective in reducing binge-eating frequency. However, evidence on the effectiveness of psychological treatments for weight loss in BED remains mixed. Additionally, weight-neutral treatment approaches are being explored to minimize relapse risk potentially linked to dietary restrictions (Giel et al., 2022). Diabetes

medication, namely glucagon-like peptide-1 (GLP-1) agonists may also be considered in aiding weight loss. With both a central and peripheral effect on appetite control, researchers observed promising effects on weight and binge eating behavior (Chao et al., 2019; Da Porto et al., 2020; Giel et al., 2022). Overall, pharmacological intervention constitutes a promising second line therapy and may be especially useful for patients with coinciding mood or anxiety disorders. As previously explained, there are several approaches to treating BED. The decision on which treatment option is most suitable for an individual with BED should be made on a case-by-case basis and may require the involvement of a multidisciplinary team.

If an individual with BED who has previously met full diagnostic DSM-V criteria manages to reduce the frequency of binge eating episodes to less than once a week for an extended period of time, they are considered to be in partial remission. If none of the criteria they previously fulfilled are applicable anymore, they are considered to be in full remission according to the DSM-V (DSM-5;Association AP: Edition, 2013; Giel et al., 2022).

Given that current treatment approaches only achieve long-term remission rates of around 50%, it is imperative to prioritize in-depth research on the treatment and prevention of BED. It is also essential to establish evidence-based treatments in clinical practice and ensure easy access for individuals with BED.

1.1.7 Prevention and impact on society

Prevention is a crucial step in reducing the prevalence of any disease, whether physical or mental. However, it remains largely unclear how BED prevention differs from obesity prevention and how they may influence each other, either positively or negatively (Giel et al., 2022). Individuals with BED are more likely to seek help for obesity and weight loss, often without realizing they have an eating disorder (Kornstein et al., 2016; Reas, 2017). Educating health care professionals and the

public about BED so they can recognize it and provide patients with the appropriate care is therefore crucial. Additionally, promoting nutrition education and ensuring easy access to healthy foods can aid in preventing both obesity and eating disorders like BED.

A multi-component strategy is likely necessary to achieve widespread prevention and early recognition of BED (Giel et al., 2022). Beyond individual health benefits, prevention efforts also impact socioeconomic factors, including healthcare costs and productivity losses due to eating disorders (Samnaliev, Noh, Sonneville, & Austin, 2015). Streatfeild and colleagues found that in 2018–2019, BED accounted for 30% of the total economic costs of eating disorders in the U.S (Streatfeild et al., 2021). Large-scale primary and secondary prevention initiatives could therefore yield broad societal benefits, such as reducing healthcare expenditures, improving employment rates, and increasing overall productivity.

1.2 Food Reward Signaling and Neurobiological Pathways in BED

The pathogenesis of BED may involve alterations in pathways that regulate food intake. Hunger and satiety are regulated by the integration of a variety of different signals from the digestive, endocrine, and nervous systems (Strubbe & Woods, 2004). A key structure in energy homeostasis is the hypothalamus, where hormones such as ghrelin and leptin play opposing roles - ghrelin stimulates hunger, while leptin promotes satiety (Berthoud & Morrison, 2008). In addition, neurotransmitters like dopamine, endogenous opioids, and endocannabinoids influence the food reward system, affecting the palatability and appeal of food. Dysregulation of these neuroendocrine pathways may contribute to binge-eating behavior (Giel et al., 2022).

When we consume palatable, energy-dense foods, our brains respond similarly to addictive substances by activating brain regions associated with reward (Burger &

Stice, 2011; Wang, Volkow, Thanos, & Fowler, 2004; Wise, 2004). Excessive consumption of such foods has been hypothesized to alter corticostriatal circuitry, thus affecting reward signaling (Voon, 2015). Notably, ultra-processed foods are particularly implicated in "addictive" eating patterns, such as the loss of control seen in binge eating behavior (Gearhardt & Schulte, 2021).

Motivation and reward have been closely linked to dopamine, a neurotransmitter that drives food cravings (Berland et al., 2020; Wang, Volkow, Thanos, & Fowler, 2009; Wise, 2004). This suggests that alterations in neural circuits related to motivation and impulse control may contribute to binge eating (Giel et al., 2022; Jowik et al., 2020).

In recent years, increasing attention has been given to dopamine's role in the mesocorticolimbic system, which mediates reward processing. This system connects the ventral striatum, midbrain, and ventral tegmental area with cortico-ventral basal ganglia structures, including the nucleus accumbens (NAcc), amygdala, hippocampus, and prefrontal cortex. Dysregulation in these pathways may play a key role in binge eating, as altered dopamine function could heighten reward sensitivity and drive the consumption of calorie-dense foods even in the absence of physiological hunger (Gomez, Tabernacki, Kobyra, Roberts, & Chiappinelli, 2020; Naef, Pitman, & Borgland, 2015; Palmiter, 2007; E. Stice & S. Yokum, 2016).

Over the past decades, competing theories have emerged to explain the link between dopamine neurotransmission and eating behavior. One theory, proposed by Wang et al. (2004), suggests that individuals prone to eating disorders exhibit hyposensitivity of Dopamine Receptor Subtype 2 (DRD2) to dopamine. This diminished sensitivity results in a reward deficit, leading individuals to overeat as a compensatory mechanism (Wang, Volkow, Thanos, & Fowler, 2004). On the other hand, the theory of hypersensitivity posits that a predisposing risk factor for the development of BED lies in a strong dopamine release upon food consumption,

reinforcing food consumption and promoting overeating (Burger & Stice, 2011; C. Davis, 2015; C. A. Davis et al., 2009). Supporting this theory, Filbey et al. found that binge eating severity was associated with increased blood-oxygen-level-dependent (BOLD) response to high caloric taste in reward-related brain regions (Filbey, Myers, & Dewitt, 2012).

A more integrative approach, proposed by Burger and Stice, suggests that individuals at risk for obesity initially exhibit a hyperresponsive striatum to food reward. However, chronic overeating - particularly of high-fat, high-sugar foods - leads to adaptations in dopamine receptors, including DRD2 downregulation and increased D1 activation. This shift creates a reward deficit, driving further overeating to compensate for the diminished striatal response (Burger & Stice, 2011). Nonetheless, Stice & Yokum (2016) later reviewed existing findings and argued that a reward deficit is also linked to lower caloric intake, thereby challenging the assumed relationship between reduced reward sensitivity and future weight gain (Eric Stice & Sonja Yokum, 2016).

To reconcile these conflicting perspectives, Neuser et al. (2020) proposed an alternative explanation, emphasizing intra-individual fluctuations in reward sensitivity over time rather than stable inter-individual differences. According to this model, increased variability in reward sensitivity may contribute to fluctuations in food intake, potentially promoting binge eating episodes (Neuser, Kuhnel, Svaldi, & Kroemer, 2020; van den Hoek Ostende, Neuser, Teckentrup, Svaldi, & Kroemer, 2021). These competing theories highlight the complexity of the relationship between dopamine and binge eating behavior, underscoring the need for further research to refine our understanding of these mechanisms.

Neuroimaging studies indicate that individuals with BED exhibit distinct neural responses during functional MRI tasks involving inhibitory control and reward processing. Reduced inhibitory control and impaired decision-making are associated with alterations in brain regions involved in emotional regulation and cognitive

control, including the ventromedial prefrontal cortex (vmPFC), the inferior frontal gyrus (IFG), and the insula (Jowik et al., 2020; R. M. Kessler, Hutson, Herman, & Potenza, 2016). These findings support the “emotion regulation model”, which suggests that negative affect may serve as a trigger for binge eating episodes. In a study conducted by Austrian researchers, they found that individuals with BED tend to respond more to food cues, regardless of calorie count, in the face of negative emotions, which further supports this model (Arend, Schnepper, Lutz, Eichin, & Blechert, 2022).

Moreover, individuals with BED tend to make riskier decisions and show a preference for immediate over delayed rewards compared to healthy controls. This may be due to reduced activation of the anterior insula (Aguera et al., 2020; Giel et al., 2022). Another model is the “behavioral model” and the concept of “food addiction”, which compare compulsive overeating to substance use disorders and other forms of addiction (di Giacomo et al., 2022; R. M. Kessler et al., 2016). With a variety of contributing factors and interactions influencing binge eating behavior, it remains imperative to focus research efforts on the complex etiogenesis of BED in hopes of improving long-term clinical outcomes for individuals with BED.

1.3 Altered Neural Response to Food Stimuli

Today's modern society is characterized by a pervasive excess. Excess of goods, excess of consumption, and excess of unhealthy foods. Combined with easy accessibility and extensive advertising, we are increasingly exposed to an abundance of food cues of high-calorie, high-fat foods. This constant availability promotes an energy surplus that leads to obesity and overeating, even in otherwise satiated individuals (Belfort-DeAguiar & Seo, 2018; Kanoski & Boutelle, 2022; Reichelt, Westbrook, & Morris, 2015). Current research suggests that individuals with BED exhibit altered neural responses to food cues. Kanoski and Boutelle found that an increased food cue responsivity was in fact associated with obesity and

overweight (Kanoski & Boutelle, 2022). Food cues can include visual, auditory, and olfactory stimuli. Response to food cues involves a triad of physiological responses, namely salivation and activation of endocrine pathways, psychological responses, such as craving, and neurocognitive responses, i.e., activation of specific brain regions (Kanoski & Boutelle, 2022). Food cues catch an individual's attention and may lead to craving. In BED attentional response to food cues and induced craving was found to be enhanced with a higher response to foods rich in fat and sugar as opposed to low calorie food items (Ferrer-Garcia et al., 2017; Kanoski & Boutelle, 2022; Meule et al., 2018; Reents & Pedersen, 2021). Further, individuals with BED demonstrated enhanced reward sensitivity and activation of the orbitofrontal cortex while being exposed to food cues (Schienle et al., 2009). This altered response to food cues, especially highly palatable foods, combined with reduced activation of cognitive control and inhibitory circuits, may contribute to the pathomechanism of disordered eating (Steward, Menchon, Jiménez-Murcia, Soriano-Mas, & Fernandez-Aranda, 2018). Food cue reactivity (FCR) can be assessed using MRI, which demonstrates that food-related cues activate specific brain regions associated with reward, motivation, inhibition, and learning. For instance, increased activity in the NAcc has been shown to predict cravings, eating behavior, and weight changes. Thus, neural FCR represents a crucial factor in understanding weight gain in humans (Kanoski & Boutelle, 2022).

1.4 Triglycerides, Metabolic Dysregulation and Food Reward Signaling in BED

Interestingly, one of the metabolic parameters associated with BED that has received little research attention is triglycerides (Mitchell et al., 2015). Triglycerides are important for the regulation of energy homeostasis (Magnan, Levin, & Luquet, 2015). While the cellular mechanisms remain unclear, it has been shown that chronically elevated plasma triglyceride levels damage energy homeostasis

(Berland et al., 2016; Berland et al., 2020; Cansell et al., 2014; Cansell & Luquet, 2016). Triglycerides serve as essential energy sources for the body. Stored in adipose tissue, they can be mobilized and broken down when needed to release energy. Structurally, triglycerides consist of one glycerol molecule esterified with three fatty acids. Their metabolism is tightly regulated by hormone-sensitive lipase in adipose tissue. Emerging data suggest that triglycerides may influence food reward signaling and contribute to disordered eating behaviors in individuals with BED.

Berland and colleagues have found that triglycerides can be metabolized in the mesocorticolimbic system and are able to influence dopamine signaling and thus food- and reward-seeking behavior (Berland et al., 2016; Berland et al., 2020; Cansell & Luquet, 2016). They achieve this by regulating the activity of neurons expressing DRD2 (Berland et al., 2020). Triglycerides are hydrolyzed by lipoproteinlipases in various brain regions, leading to decreased food and reward seeking, decreased preference for palatable food and lower locomotor activity (Berland et al., 2016; Berland et al., 2020; Cansell et al., 2014; Cansell & Luquet, 2016; Magnan et al., 2015). However, in the context of chronically elevated plasma triglyceride levels, desensitization may occur, altering the mesocorticolimbic system. This can lead to dysregulated reward control and responsiveness, promoting overeating while simultaneously reducing physical activity due to the sustained inhibition of locomotor behavior (Berland et al., 2016; Berland et al., 2020; Cansell et al., 2014; Cansell & Luquet, 2016). Consequently, by altering reward mechanisms, elevated plasma triglyceride levels predict weight gain (Berland et al., 2016; Berland et al., 2020; Berland, Small, Luquet, & Gangarossa, 2021; Cansell et al., 2014; Cansell & Luquet, 2016). These findings suggest that triglycerides may contribute to a self-perpetuating cycle of food cravings, compulsive eating, and obesity.

Consistent with these findings, studies show that lipoproteinlipase activity is associated with body weight control and that disruption of lipoproteinlipase leads to weight gain, increased food-seeking behavior (Berland et al., 2020), preference for

palatable foods, and decreased locomotor activity (Cansell & Luquet, 2016; Magnan et al., 2015). Lipoproteinlipase can be found in the mesocorticolimbic system, including the NAcc and hippocampus, as well as in the hypothalamus (Cansell et al., 2014; Cansell & Luquet, 2016; Magnan et al., 2015; Picard et al., 2014), supporting the hypothesis that triglycerides have a direct influence on reward and eating behavior (Cansell & Luquet, 2016) and that specialized neurons in reward-related brain regions may be able to sense circulating triglycerides (Magnan et al., 2015). In summary, triglycerides influence brain signaling pathways through lipoproteinlipase-dependent mechanisms.

Furthermore, triglycerides have been shown to stimulate orexigenic neurons in the hypothalamus, one of the main central regulators of energy balance (Cansell & Luquet, 2016; Karatayev, Gaysinskaya, Chang, & Leibowitz, 2009). Accordingly, a chronic high-fat diet leads to an increase in caloric intake compared to an equicaloric high-carbohydrate diet (Karatayev et al., 2009; Prentice, 1998; Rolls, 1995; Rolls & Hammer, 1995). High triglyceride responders tend to overeat more and postprandial triglyceride levels can predict weight gain in rodents (Cansell et al., 2014; Cansell & Luquet, 2016). Previous animal and human studies have examined the influence of carotid triglyceride infusion on the brain and found that triglycerides can alter the brain's response to food cues (Berland et al., 2020; Cansell et al., 2014) which is an attenuated BOLD response to palatable food (Berland et al., 2016). Because BED is also associated with a preference for high-caloric foods (Bello & Hajnal, 2010), it remains imperative to investigate the relationship between triglycerides, brain responses to high-caloric foods and eating disorders such as BED. Future research may then focus on interventions that target triglyceride levels, such as dietary changes or specific medications as an approach to managing binge eating in individuals with BED.

To date, only a few studies have investigated triglycerides in BED. As it is the most common eating disorder, there is an increasing need to investigate possible molecular mechanisms that influence the pathophysiology behind BED.

Here, we aim to better understand the role of triglycerides in reward signaling and BED by performing a FCR task with 61 female participants during functional MRI (fMRI). The aforementioned interaction was measured by looking at BOLD response amplitudes and functional connectivity during a food bidding task and comparing brain activity to triglyceride levels from previously collected blood samples. We hypothesized that elevated plasma triglyceride levels would be positively correlated with an attenuated response to palatable food in the FCR task. This study may shed light on the influence of metabolic factors on neuronal processes and the interplay between altered brain signaling and eating disorders such as BED.

2 Material and Methods

2.1 Participants

The sample consisted of 61 female participants between the ages of 21 and 64 years, divided into three age - and BMI-matched groups: 21 participants with BED (sample (2), BED), 20 participants with subsyndromal BED, characterized as patients who do not meet all the criteria for manifest BED but objectively experience binge eating at least once a week (sample (1), subBED), and 20 participants who had never experienced binge eating (sample (0), No BE). Eight participants had to be excluded due to MRI safety concerns or other issues. The participants had a mean age of 40,15 years and a mean BMI of 31,53 kg/m² and were recruited from the greater Tübingen area. To verify the inclusion and exclusion criteria we conducted a telephone screening interview with potential subjects. Inclusion criteria were age between 18 and 69 years, fluency in German, no acute or chronic diseases (especially no cardiovascular diseases and no epilepsy) and no contraindications to MRI. Exclusion criteria were any type of nonremovable metal or ferromagnetic material, large tattoos, permanent makeup, nonremovable medical devices (e.g., pacemakers), other eating disorders, lack of capacity to consent, co-occurring psychotic, bipolar disorders, alcohol or substance dependence within the past six months, claustrophobia, pregnancy, or lactation. Participants were excluded if they were taking medication or had a medical condition that affected their weight. Depression was not an exclusion criterion, as long as no suicidal tendencies had been reported in the previous three months and the dosage of antidepressants had been stable for at least two months.

BED was diagnosed using the EDE (Hilbert, Tuschen-Caffier, & Ohms, 2004); other diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis I (SCID) (Wittchen, Zaudig, & Fydrich, 1997). Symptom severity was determined using the EDE-Q (Hilbert, Tuschen-Caffier, Karwautz, Niederhofer, & Munsch, 2007). Subsyndromal binge-eating was defined as participants who had objective

bingeing episodes but did not meet the frequency criterion of one binge episode per week over three consecutive months.

Upon completion of the online assessment and telephone screening interview, participants received 20€ as a financial reward (or course credit if applicable) for their participation and around 70€ if they participated in the two laboratory sessions. The exact amount varied due to winnings on the game tasks performed during the sessions.

The study was approved by the local ethics committee of the Eberhard Karls University of Tübingen and was conducted in accordance with the ethical code of the World Medical Association (Declaration of Helsinki).

2.2 Experimental Procedure

All participants completed a multi-day online reinforcement learning assessment and were invited to two in-lab sessions. The first session included a diagnostic interview and behavioral assessments. The second session included fasting blood samples to determine glucose, insulin, and triglyceride levels, and repeated pre- and post-meal blood samples to monitor ghrelin and triglyceride levels. In addition, during this second session, participants performed reward-related tasks while brain activity was measured using MRI. The aim of our study was to explore associations between variability in brain response to reward, triglycerides and binge eating disorder.

To investigate reward sensitivity and reward-related learning participants conducted an online assessment named ‘Influenca’ (Neuser et al., 2021) that included self-report questionnaires about mood and eating behavior. After ten rounds of the browser-based online game, subjects were required to complete online trait questionnaires before proceeding to subsequent levels. Participants were required to complete at least 30 full rounds of the online assessment over a minimum of ten

days. Data from the online assessment and the telephone screening interview were stored on a local server.

Subjects were told to eat one hour before the first session began so that they would be neither hungry nor full. After giving informed consent, the first session started with questions about the last meal or drink they had, sleep quality, menstrual cycle, drugs and medications. In an audio-recorded diagnostic interview, we determined whether the participant could be assigned to BEDVAR_sample(0), BEDVAR_sample(1), or BEDVAR_sample(2) or had to be excluded, using the SCID (Wittchen, Zaudig, & Fydrich, 1997) and EDE-Q (Hilbert, Tuschen-Caffier, Karwautz, Niederhofer, & Munsch, 2007) screening interview. Audio recordings were stored using only a numerical ID, without any name reference. Physical measures such as body weight, height, and hip and waist circumferences were subsequently assessed. On a visual analog scale (VAS), participants were asked to indicate their current state of hunger, thirst, mood, and eating behavior on three occasions during the first session. After completing a training round of an effort allocation task (EAT), adapted from Meyniel, Sergent, Rigoux, Daunizeau, and Pessiglione (2013) and V. Teckentrup et al. (2019), participants performed a FCR task in which they were presented with images of high-calorie sweet, high-calorie savory, low-calorie sweet and low-calorie savory foods and asked to indicate how much they wanted and how much they liked the displayed reward. During the subsequent EAT, participants played for snacks and money by exerting force using a grip force device that had been previously calibrated to the subject's maximum force level. By holding a blue ball in a tube above a red line for a set period, participants could earn food and money tokens, which were later exchanged for snacks and money. The ratio of tokens to money was set at 100 to 17, while the ratio of tokens to food varied depending on a previous assessment of the participant's preference for food over money. After completing the EAT, participants underwent a taste test to assess their response to consummatory food cues. They were asked to rate the smell and taste of certain sweet and savory foods. Unbeknownst to the participants, the amount they consumed was weighed. A similar

FCR task was then administered, but instead of pictures of food, pictures of office supplies were shown. Subsequently, while answering state questions on a VAS, subjects were allowed to eat the remaining snacks ad libitum. The snack bowls were weighed beforehand and weighed again afterwards to indicate how much the subject had eaten. The first session was completed with a set of standardized online (IPAQ) (Craig, 2003) and paper (PSS10) (Sheldon Cohen, 1983) questionnaires.

For the second visit, participants were invited after a 12-hour fast to obtain fasting levels of ghrelin, glucose, and insulin. After informed consent and an MRI safety screening, the second session also began with questions about the last meal or drink, sleep quality, menstrual cycle, and medications. A peripheral venous catheter was placed in the participant's non-dominant arm to allow for five blood draws during the session. Fasting blood was drawn immediately after catheter placement (T1A), followed by the next blood draw fifteen minutes after puncture (T1B). On a VAS, subjects were asked to answer questions about current hunger, thirst, mood, and eating behavior. Subsequently, their physical measurements (weight, hip and waist circumference) were assessed. Fifteen minutes after T1B, another blood sample was taken (T2). Participants received a standardized breakfast consisting of a butter pretzel (~320kcal) and unsweetened tea or coffee and were asked to finish the whole meal in 20 minutes. After another set of state questions on a VAS, participants completed a reward learning task. Thirty minutes after breakfast, another blood sample (T3) was taken, after which the fMRI session began. The fMRI took approximately 100 minutes, including positioning of the patient, an anatomical scan, a resting state measurement, an effort allocation task, a FCR task, and short breaks between measurements. After the scan, the last blood sample (T4) was taken and the peripheral venous catheter was removed. After another set of state questions using a VAS, lunch was served. Lunch consisted of 800 g of cheese pasta with 200 g of cheese and 40 g of butter, served with 50 g of fried onions (~2500 kcal total). During a twenty-minute lunch break, participants were allowed to eat as much as they wanted, and unbeknownst to the subject, everything was weighed before and

after. Like the first session, this session ended with a series of standardized online (IPAQ) (Craig, 2003) and on paper (PSS10) (Sheldon Cohen, 1983) questionnaires, and participants received the money and snacks they earned during the tasks.

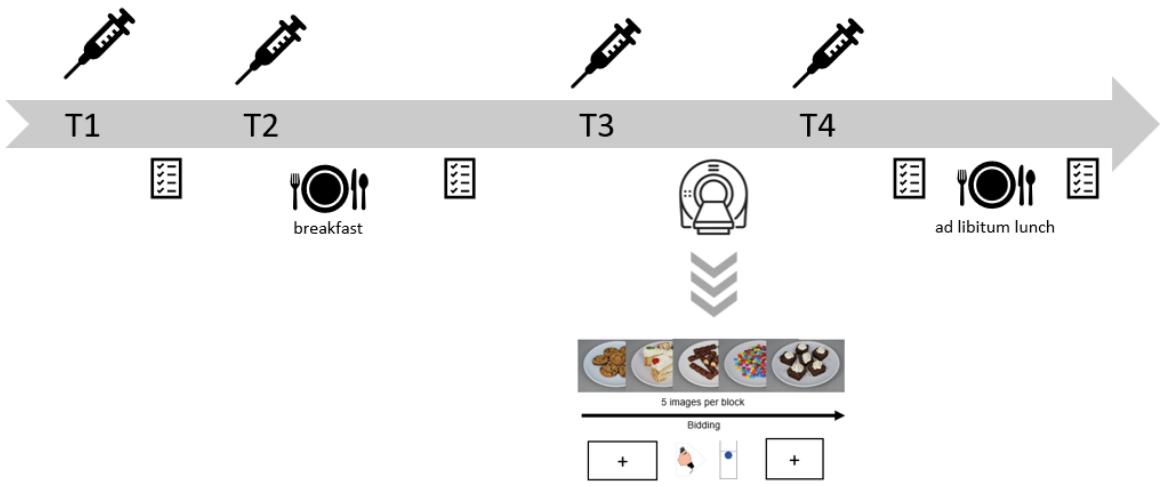

Figure 1: ***Schematic Study Design***

The study involved multiple timepoints for blood sampling (T1 – T4) and assessments using visual analog scales. Participants underwent fMRI neuroimaging while completing a food bidding task, where they viewed 24 blocks of images categorized as high-caloric food, low-caloric food, or non-food. Each block contained five images of the same category. After viewing each block, participants indicated their willingness to exert physical effort using a grip force device to gain access to a buffet featuring the previously shown food items.

2.3 Blood Protocol

At the beginning of the second visit a medical-technical assistant or a previously instructed advanced medical student placed a peripheral venous catheter using a Vasofix® Braunüle® 1.10 x 33 mm G 20 pink, fluorethylene-propylen (FEP) (BROWN) and immediately drew blood for fasting levels of glucose, insulin and triglycerides (T1A). The three samples were stored at 4°C and later transferred to the central laboratory of the Institute of Clinical Chemistry and Pathobiochemistry of the University Hospital Tübingen (UKT) about 100 minutes after blood draw. The S-Monovettes (Sarstedt) were connected using a multiadapter (Sarstedt). Glucose was

obtained in a yellow 2.7 ml fluoride-plasma monovette and measured with hexokinase and photometric endpoint measurement (reference: 70-99 mg/dl). Insulin was collected in a white serum monovette and was analyzed using CLIA (Centaur) (reference: <175 pmol/l). Triglycerides were sampled in a cooled (4°C) orange lithium-heparin monovette and were measured with the use of a glycerol kinase and an enzymatic color test (reference: <200 mg/dl). To prevent the blood in the venous access from coagulating between blood draws, it was subsequently rinsed with 5 ml of a physiological 0,9% saline solution and closed with a mandarin (Vasofix®, G 20 x 33 mm, pink (BROWN)). Before each blood draw the first few ml of blood were discarded to ensure that no remaining saline solution would falsify the blood values. In case of difficulties with placing the Braunüle®, a BD Vacutainer Safety-lok system was used instead for blood drawing. For T1B-T4 blood was obtained using two EDTA monovettes, one 2,6 ml and one 9 ml. The monovettes were gently inverted several times and centrifuged immediately at 4°C with 2000g for ten minutes. After centrifugation 500 µl of plasma were pipetted from the small 2,6 ml EDTA monovette into two yellow, cooled (-20°C) EPPi® cryo bottles each and 50 µl of cooled 1 M hydrochloric acid (HCL) were added to prevent ghrelin from deacetylating into its inactive form. The tube was immediately inverted several times and stored at -20°C. From the larger 9 ml EDTA monovette 500 µl were pipetted into four white, cooled (-20°C) EPPi® cryo bottles each and stored as well at -20°C. The pipettes and associated sterile tips were provided by Eppendorf (Eppendorf Research® plus (IVD) 10 – 100 µl and 100 – 1000 µl). At the end of the session blood samples were transferred into a -80°C fridge and the yellow EPPi® cryo bottles containing plasma and HCL were later send to Boehringer Ingelheim Pharma GmbH & Co. KG in 88397 Biberach for ghrelin analysis. After the last blood draw, the peripheral venous catheter was removed and the injection site was provided with a band aid.

2.3.1 Triglyceride Processing

Triglycerides from T2, T3 and T4 were analyzed by the central laboratory of the Institute of clinical Chemistry and Pathobiochemistry of the UKT using ADVIA® Chemistry Triglycerides_2 (TRIG_2) - Reagent (ADVIA® Chemistry XPT-System). A three step enzymatic reaction according to Fossati (Fossati & Prencipe, 1982) with a trinder-endpoint allowed the in vitro quantification of triglycerides from plasma samples (white EPPi® cryo bottles with 500 µl plasma of EDTA monovettes). Triglycerides are hydrolyzed to glycerol and free fatty acids by a lipase. The glycerol is then converted to glycerol-3-phosphate in the presence of ATP and glycerol kinase. The glycerol-3-phosphate is then oxidized by a glycerol-3-phosphatoxidase to hydrogen peroxide and dihydroxyacetonphosphate. The condensation of hydrogen peroxide with 4-aminophenazone and 4-chlorphenol in the presence of peroxidase produces a red colored chinonimine dye as an endpoint reaction, which absorbs at 505/694 nm. The intensity of the color of the sample is directly proportional to the triglyceride concentration.

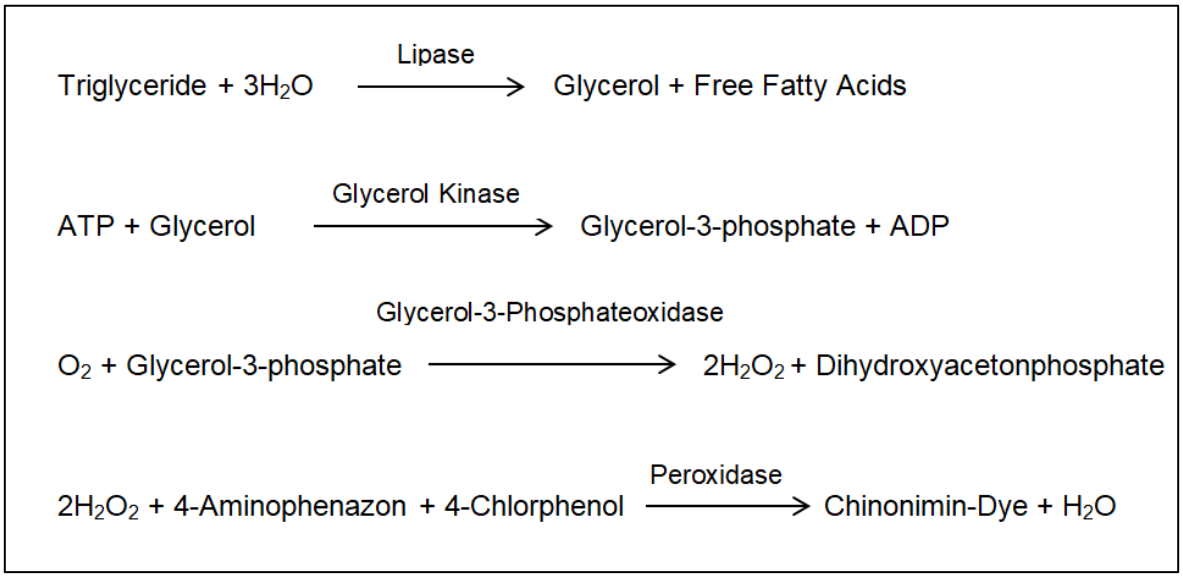

Figure 2: ***Enzymatic Reaction According to Fossati***

2.4 Food-cue Reactivity (FCR) task

During the in-lab sessions, an FCR task was administered on both visits. During the FCR, participants were presented with pictures of highly palatable foods divided into four categories: low-calorie sweet, low-calorie savory, high-calorie sweet, and high-calorie savory. Office supplies were shown as control pictures. To ensure standardized conditions, images of food and office supplies from Charbonnier et al. (2016) were used, that were all photographed on a white plate against a light grey background, with the camera lens angled at 45° and a fixed distance between camera and plate (L. Charbonnier, van Meer, van der Laan, Viergever, & Smeets, 2016). Participants were presented with twelve blocks of pictures, each block containing five images of the same category. Each picture was shown twice for 3.5 seconds, in a randomized order. Of the total of sixty pictures, forty were images of food, while twenty were images of office supplies. At the start of each trial and between blocks a black fixation cross appeared on the screen ((iming.min_ISI = 0.1 + jitter (mu = 2.5, max = 12)) (0.2s + jitter)). For the behavioral part of the FCR (session 1) participants were asked to indicate how much they *wanted* the item shown on a horizontal VAS reaching from “didn’t want at all” to “wanted very much” and state how much they *liked* the item shown on a vertical VAS reaching from “the worst possible experience” to “the best possible experience”. By moving a cursor, participants had two seconds per VAS to make their entry.

For the second session we measured brain-response correlates to highly palatable food cues in the fMRI by looking at BOLD signaling. After each FCR block participants were told to imagine a buffet with all the previously displayed items. They were then asked to demonstrate how much effort they were willing to exert in order to get access to the buffet by squeezing a grip force device (GFD). In this bidding phase the physical force applied to the GFD translated into the height of a blue ball inside of a tube. As described before, the GFD had previously been calibrated to the maximum force of the participant. The whole task took about 14 minutes.

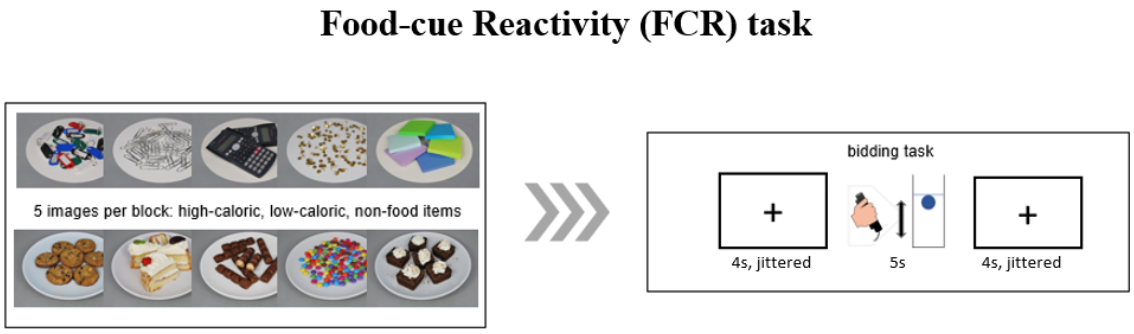

Figure 3: ***Procedure of the Food-Cue Reactivity (FCR) Task***

Participants performed the FCR task during fMRI, where they were shown images of food and non-food items in a randomized block design. The images were categorized based on prior research (L. Charbonnier, van Meer, F., van der Laan, L. N., Viergever, M. A., & Smeets, P. A. M., 2016). Each trial began with a fixation cross, followed by the presentation of each block twice, lasting approximately 17.5 seconds per block. Afterward, participants rated their wanting using a Grip Force Device during the bidding phase (5 seconds). The entire task lasted approximately 14 minutes.

2.5 fMRI Data Acquisition and Preprocessing

This section is based on a previously published paper of our scientific research group (Vanessa Teckentrup et al., 2021).

Images were acquired using a 3-Tesla PRISMA whole-body MR scanner (Siemens Medical Solutions, Erlangen, Germany) with a standard 64-channel head coil. Imaging sequences followed the COBIDAS consortium guidelines (Nichols et al., 2017). T1-weighted structural images were obtained using an MP-RAGE sequence with 176 sagittal slices covering the whole brain, a flip angle of 9°, a matrix size of 256 × 256, and a voxel size of 1 × 1 × 1 mm^3. Field maps were collected using a Siemens gradient echo field map sequence with short (5.19 ms) and long (7.65 ms) echo times (TE), resulting in a TE difference of 2.46 ms.

fMRI data consisted of a single 10-minute resting-state scan acquired using T2*-weighted gradient-echo echo-planar imaging (EPI) with a multiband factor of 4. Sixty-eight axial slices were acquired in an interleaved order, covering the whole brain,

including the brainstem. Imaging parameters were: repetition time (TR) = 1.4 s, echo time (TE) = 30 ms, flip angle = 65°, matrix size = 110 × 110, field of view = 220 × 220 mm², and voxel size = 2 × 2 × 2 mm³. During the scan, participants viewed the “Inscapes” stimulus and were instructed to remain still and relaxed.

Resting-state fMRI preprocessing followed the 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 (Abraham et al., 2014) [RRID:SCR_001362]. T1-weighted (T1w) volumes were corrected for intensity non-uniformity using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped with antsBrainExtraction.sh v2.1.0 (OASIS template). Brain surfaces were reconstructed using recon-all from FreeSurfer v6.0.1 (Dale, Fischl, & Sereno, 1999) [RRID:SCR_001847], and the estimated brain mask was refined through a custom variation of Mindboggle’s procedure (Klein et al., 2017) [RRID:SCR_002438] to reconcile ANTs-derived and FreeSurfer-derived segmentations of cortical gray matter. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov, Evans, McKinstry, Almli, & Collins, 2009) [RRID:SCR_008796] was performed via nonlinear registration using the antsRegistration tool of ANTs v2.1.0 (Avants, Epstein, Grossman, & Gee, 2008) [RRID:SCR_004757], utilizing brain-extracted versions of the T1w volume and template. White matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) segmentation was carried out on the brain-extracted T1w images using FMRIB’s Automated Segmentation Tool (FAST) (Zhang, Brady, & Smith, 2001) [FSL v5.0.9, RRID:SCR_002823].

Slice timing correction was applied using 3dTshift from AFNI v16.2.07 (Cox, 1996) [RRID:SCR_005927], and motion correction was performed with MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002) [FSL v5.0.9]. Field map-based distortion correction was conducted using FMRIB's Utility for Geometrically Unwarping EPIs (FUGUE) (Jenkinson, 2003) [FSL v5.0.9]. Co-registration to the

corresponding T1w image was completed using boundary-based registration (Greve & Fischl, 2009) through bbregister [FreeSurfer v6.0.1] with nine degrees of freedom. Transformations for BOLD-to-T1w, T1w-to-template (MNI) warping, motion correction, and field distortion correction were concatenated and applied in a single step using antsApplyTransforms [ANTs v2.1.0] with Lanczos interpolation. Physiological noise regressors were derived using Nilearn by averaging the signal within anatomically defined CSF and WM masks over time. Framewise displacement for each functional run was calculated using Nipype (Power et al., 2014). Participants were excluded if more than 50% of total volumes exceeded a framewise displacement threshold of 0.5 mm or if less than five minutes of usable data remained. Whole-brain voxel-based maps were smoothed with a 6 mm Full-Width at Half-Maximum (FWHM) Gaussian kernel, while unsmoothed data were retained to extract seed time series from the NTS. Respiratory recordings from the Siemens respiratory belt were processed using the PhysIO toolbox (Kasper et al., 2017). A nuisance regressor was generated by convolving the respiratory volume per time with the respiration response function (Birn, Smith, Jones, & Bandettini, 2008) to correct for noise in statistical models.

2.6 Data Analysis, Statistical Threshold and Software

Data of the FCR-task was collected and preprocessed in MATLAB R2018a. The descriptive and comparative statistics as well as analytical statistics of group characteristics were carried out with IBM® SPSS® Statistics (version 28.0.0.0), Matlab v2021a, and SPM12.

Standardized FMRIPREP pipeline (https://github.com/poldracklab/fmriprep) v20.1.1 (Esteban et al., 2019) was used for preprocessing of fMRI data based on (Gorgolewski et al., 2011) and Nilearn (Abraham et al., 2014). Level of significance was considered $\alpha < 0.05$, confidence interval was defined at 95%.

3 Results

The study contained diagnostic interviews, behavioral assessments, blood draws and reward-related tasks while brain activity was measured using MRI.

To our knowledge this was the first human study to investigate the connection between triglycerides and brain response to high vs low caloric food cues in BED patients through blood sampling and performing a FCR task in fMRI. One-way ANOVA was used to assess for group differences. There were no significant differences in age (p = 0,370), BMI (p = 0,184), WHtR (p = 0,099), insulin levels (p = 0,101) or glucose levels (p = 0,151) between the three groups of BED, subsyndromal BED and control group. Due to complications in blood drawing 21 triglyceride levels are missing. In total we have n = 255 of available triglyceride and n = 58 available fMRI measurements. Unless otherwise specified, reported metabolic parameters refer to fasting levels.

3.1 Study Sample

We recruited 61 female participants, divided into three groups, individuals with BED, subsyndromal BED and a control group, all of whom performed two in-lab sessions. The groups consisted of 21 individuals diagnosed with BED, 20 individuals with subsyndromal binge eating and a healthy control group of 20 individuals matched in age and weight. 8 women had to be excluded for not meeting MRI criteria but otherwise participated in blood draws and behavioral tests.

Table 1: ***Characteristics of Study Sample***

Abbreviations: SD - standard deviation, WHtR - Waist to Height Ratio

	Sample total (n = 69)	**BED** (n = 28)	**subBED** (n = 21)	**Control** (n = 20)
Age in years (mean [SD])	40.14 [13.38]	42.82 [13.31]	37.57 [12.34]	39.10 [14.47]
BMI (mean [SD])	31.53 [6.82]	32.89 [6.05]	29.32 [7.65]	31.96 [6.69]
WHtR (mean [SD])	0.57 [0.09]	0.59 [0.09]	0.54 [0.10]	0.57 [0.09]
Insulin levels (mean [SD])	70.75 [45.77]	85.19 [56.31]	57.62 [35.18]	65.75 [36.06]
Glucose levels (mean [SD])	88.33 [12.08]	91.92 [14.21]	87.05 [12.24]	85.20 [7.58]
Triglyceride levels (mean [SD])	104.00 [49.24]	122.92 [51.29]	79.05 [28.59]	105.60 [54.02]
Eaten cheese pasta (mean [SD])	395.93 [142.62]	396.04 [132.71]	391.48 [99.59]	400.45 [193.09]

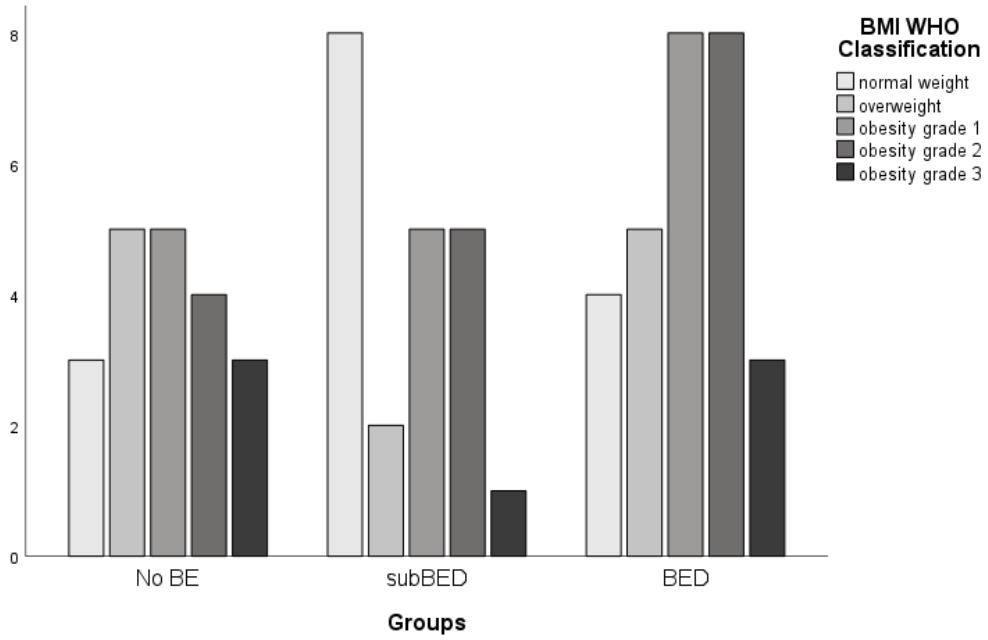

Figure 4: ***BMI WHO Classification Across Study Groups***

Bar graph displaying the distribution of BMI WHO classification categories (normal weight, overweight, obesity grades 1–3) across three groups: No Binge Eating (No BE), subsyndromal Binge Eating Disorder (subBED), and Binge Eating Disorder (BED).

One-way ANOVA was conducted to assess for group differences between BED study groups for BMI, categorized by WHO classification into five groups:

a) Normal weight (BMI < 25)
b) Overweight (BMI 25 – 29,9)
c) Obesity grade 1 (BMI 30 – 34,9)
d) Obesity grade 2 (BMI 35 – 39,9)
e) Obesity grade 3 (BMI ≥ 40)

No statistically significant difference was observed ($p = 0.303$). Similarly, a one-way ANOVA comparing BED study groups with Weight-to-Height Ratio as the dependent variable showed no statistically significant difference between groups ($p = 0.099$).

Additionally, a two-way ANOVA did not demonstrate a significant interaction between BED group and BMI WHO classification regarding Weight-to-Height Ratio ($p = 0.794$). However, BMI WHO classification had a significant impact on Weight-to-Height Ratio, as indicated by a p-value of <0.001, whereas the BED group variable was not significant ($p = 0.282$).

Post-hoc analysis (Sidak) confirmed a statistically significant difference between BMI WHO classification groups regarding Weight-to-Height Ratio, with p-values for different WHO classification groups all below 0.05. Furthermore, significant differences were observed between the control group and subsyndromal BED group ($p = 0.025$) as well as the subsyndromal BED and BED group ($p < 0.001$). However, no statistically significant difference was found between the control group and BED group ($p = 0.184$).

3.2 Metabolic Markers

3.2.1 Insulin

No statistically significant difference in fasting insulin levels was observed between study groups (p = 0.101). However, a one-way ANOVA revealed a significant effect of BMI WHO classification (p < 0.001). Post-hoc analysis (Tukey-HSD) showed significantly higher insulin levels in obesity grade 2 (+62.61, p < 0.001) and obesity grade 3 (+53.67, p = 0.029) compared to normal weight, as well as in obesity grade 2 vs. overweight (+60.86, p < 0.001) and obesity grade 3 vs. overweight (+51.92, p = 0.049). No significant differences were found for obesity grade 1 or between obesity grades 2 and 3.

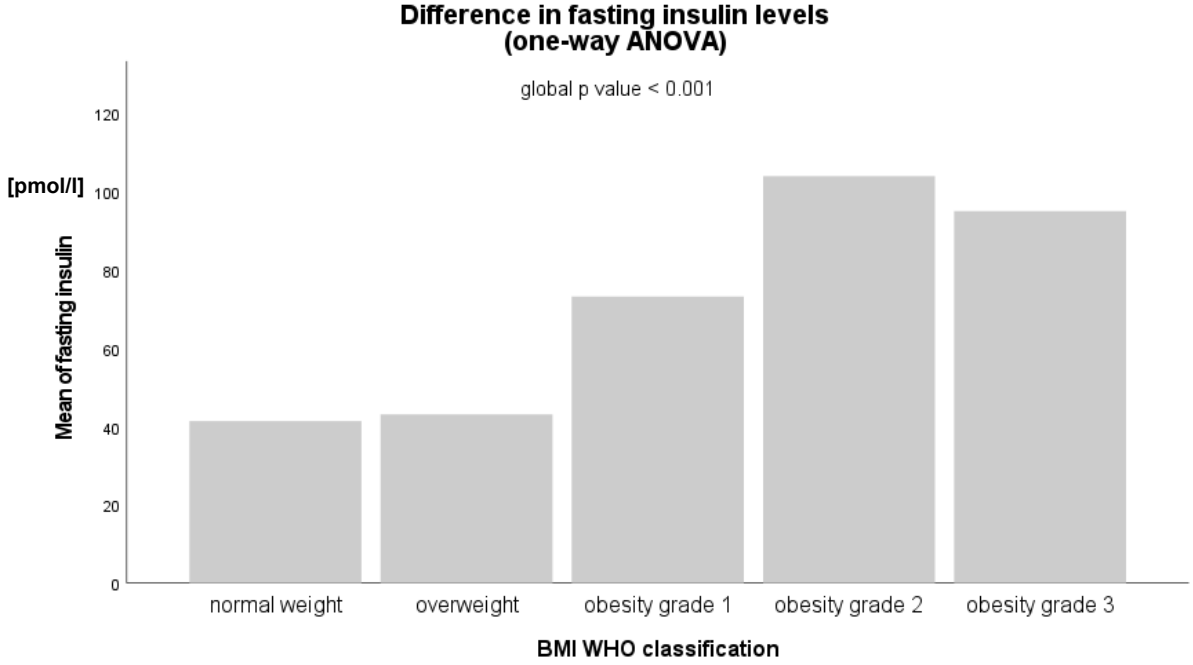

Figure 5: ***Mean Fasting Insulin Levels Across BMI Categories***

Bar graph showing the mean fasting insulin levels in pmol/l for different BMI categories (normal weight, overweight, and obesity grades 1–3). A one-way ANOVA test revealed a significant global difference (p < 0.001).

A two-way ANOVA found no significant interaction between BED group and BMI classification (p = 0.442), indicating that BMI independently influences insulin levels (p = 0.002), while BED status does not (p = 0.153). Post-hoc analysis (Sidak) confirmed the same significant BMI-related differences found in the one-way ANOVA, with no additional significant comparisons.

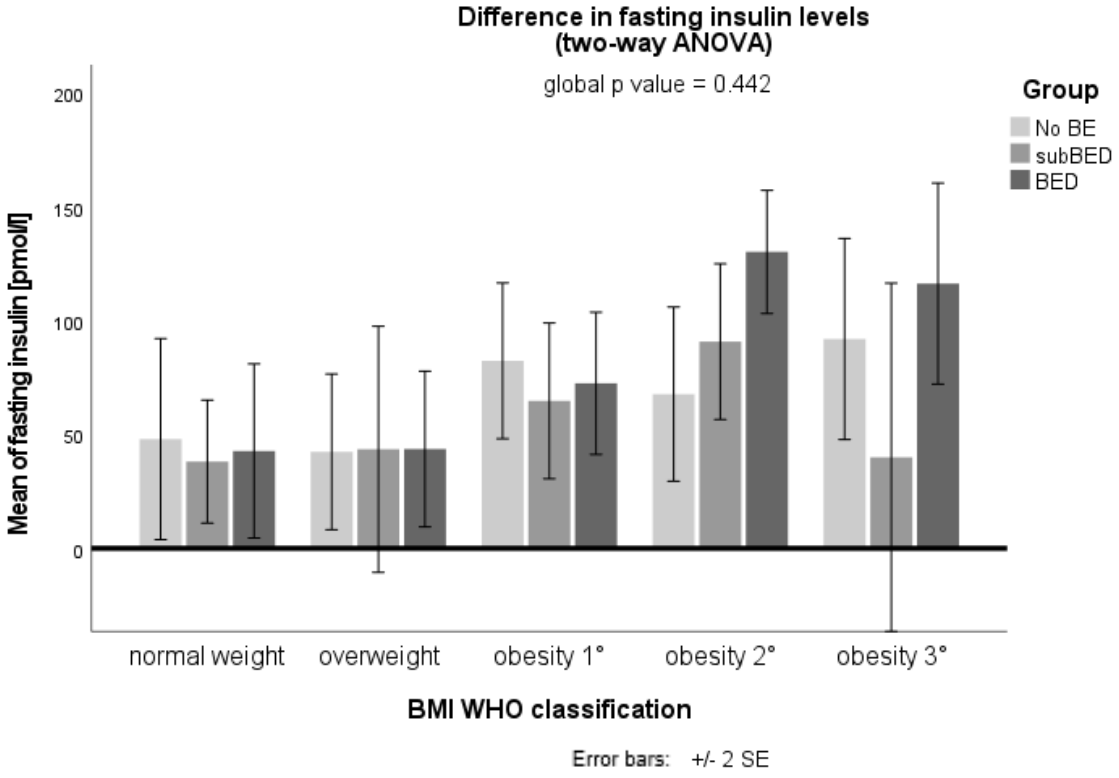

Figure 6: ***Mean Fasting Insulin Levels Across BMI Categories and Study Groups***

Mean fasting insulin levels in pmol/l across BMI categories, categorized by eating behavior groups (No Binge Eating, subsyndromal Binge Eating Disorder, and Binge Eating Disorder). Error bars represent ±2 standard errors (SE). The two-way ANOVA results indicate no significant differences (global p-value = 0.442).

3.2.2 Glucose

A one-way ANOVA showed no significant difference in fasting glucose levels across BED study groups (p = 0.151) but found a significant effect of BMI WHO classification (p = 0.005). Post-hoc analysis (Tukey-HSD) identified a significant difference between normal weight and obesity grade 2 (p = 0.002, +15.17 mg/dl). No other group differences were observed.

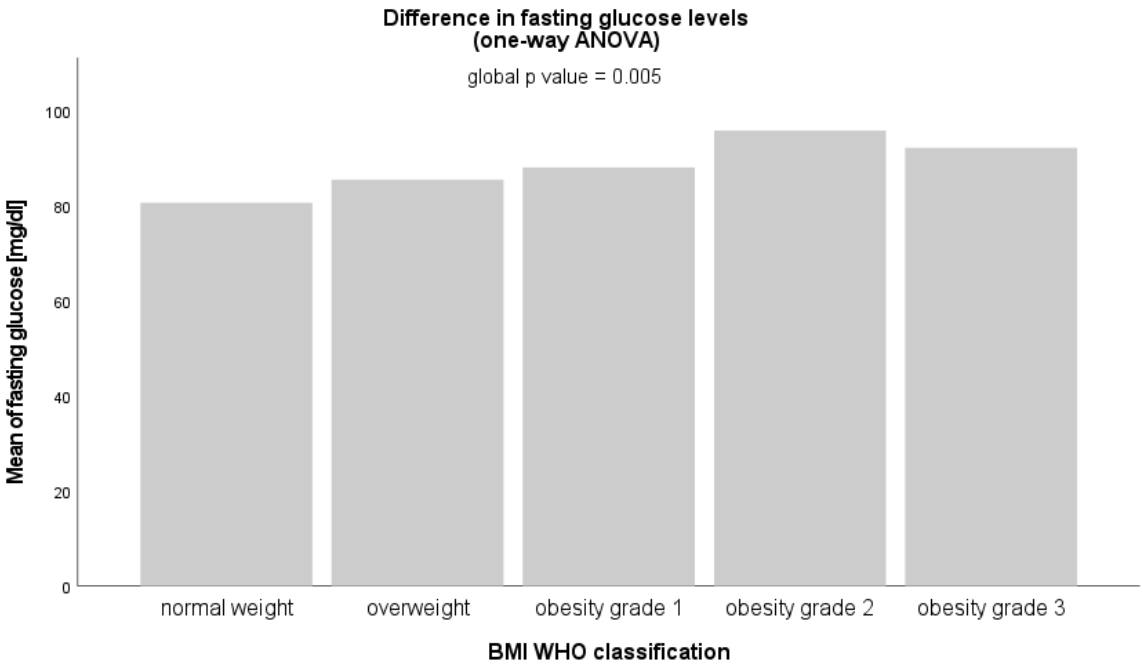

Figure 7: ***Mean Fasting Glucose Levels Across BMI Categories***

Mean fasting glucose levels (mg/dl) across BMI WHO classification categories. The one-way ANOVA results indicate a significant difference among BMI categories (global p-value = 0.005).

A two-way ANOVA found no significant interaction between BED and BMI classification (p = 0.833), confirming BMI's independent effect on glucose levels (p = 0.049), while BED status remained non-significant (p = 0.449). Post-hoc analysis (Sidak) again found a significant difference between normal weight and obesity grade 2 (p = 0.004, +15.17 mg/dl), with no other significant comparisons.

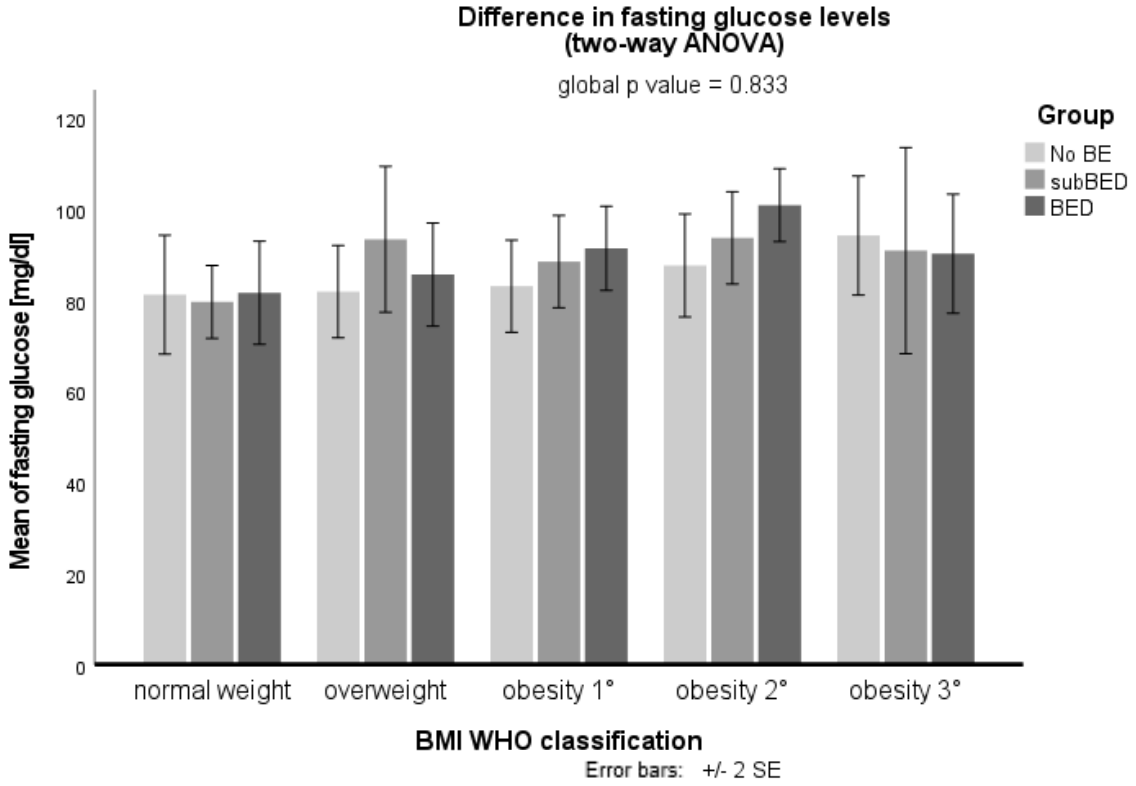

Figure 8: ***Mean Fasting Glucose Levels Across BMI Categories and Study Groups***

Mean fasting glucose levels (mg/dl) across BMI WHO classification groups, stratified by No BE, subBED, and BED. The two-way ANOVA results indicate no significant difference among groups (global p-value = 0.833). Error bars represent ±2 SE.

3.2.3 Triglycerides

Table 2: ***Triglyceride Levels Between Study Groups Across Different Timepoints (T2, T3, T4)***

Abbreviations: SD – standard deviation, SE – standard error, CI – confidence interval

T2	Mean	SD	SE	Lower 95% CI	Upper 95% CI	Minimum	Maximum
Total (n = 60)	99.41	45.35	5.85	87.69	111.12	42.45	222.36
BED (n = 24)	115.16	47.97	9.79	94.91	135.42	46.63	135.42
subBED (n = 18)	75.03	23.33	5.50	63.43	86.63	42.45	118.55
Control (n = 18)	102.78	49.87	11.76	77.98	127.58	43.13	217.81
T3							
Total (n = 60)	100.10	44.74	5.78	88.54	111.66	40.41	213.10
BED (n = 24)	111.27	46.18	9.43	91.77	130.76	48.53	213.10
subBED (n = 18)	80.84	32.34	7.62	64.75	96.92	42.18	167.38
Control (n = 18)	104.48	49.25	11.61	79.98	128.97	40.41	210.01
T4							
Total (n = 60)	123.42	53.11	6.86	109.69	137.14	51.72	271.42
BED (n = 24)	139.34	57.57	11.75	115.03	163.65	54.19	271.42
subBED (n = 18)	96.29	28.99	6.83	81.88	110.71	51.72	167.85
Control (n = 18)	129.31	57.37	13.52	100.78	157.84	51.89	255.57

Statistically Significant Group Differences in Triglyceride Levels at T2 and T4

A one-way ANOVA revealed significant differences in triglyceride levels between the subsyndromal BED and BED groups at T2 ($p = 0.015$) and T4 ($p = 0.023$).

a) T2: 30 minutes post punctuation (fasted)
b) T3: 30 minutes post breakfast
c) T4: immediately before lunch (⌀ 180 min after breakfast)

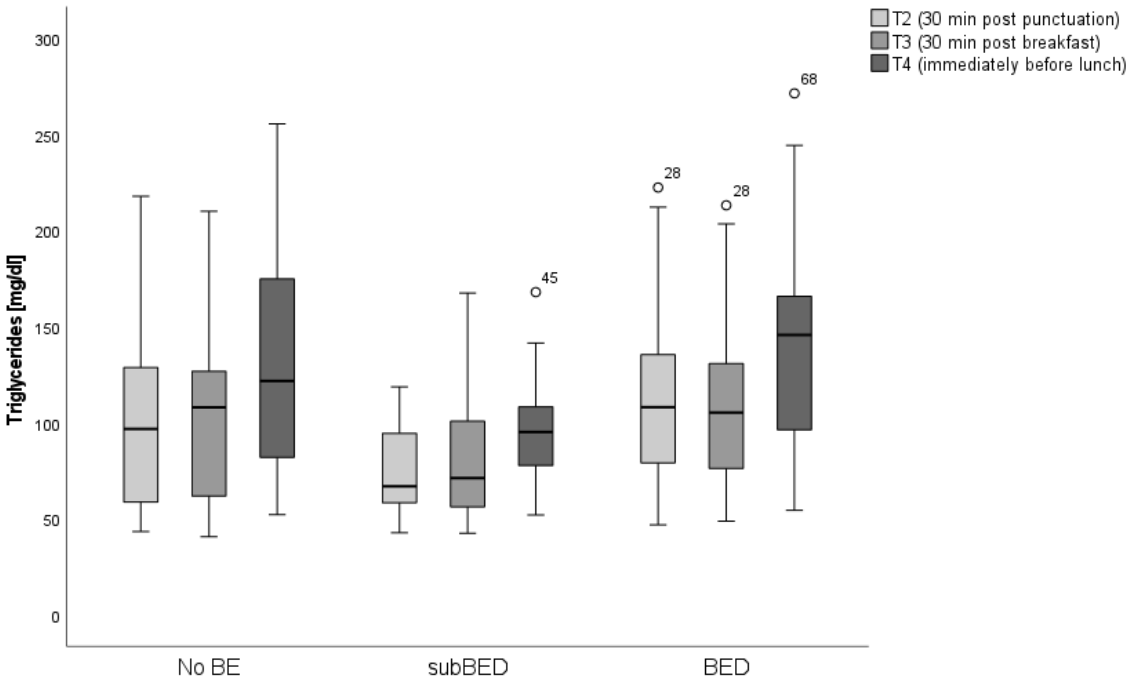

Figure 9: ***Triglyceride Levels Across Study Groups Over Multiple Timepoints***

This boxplot displays triglyceride levels at different time points (T2, T3, and T4) across the three study groups: No BE, subBED, and BED group.

T2 – Triglyceride Levels

A one-way ANOVA revealed a statistically significant difference in triglyceride levels at T2 between BED study groups (p = 0.021). Post-hoc analysis (Tukey-HSD) confirmed a significant difference between subsyndromal BED and BED (p = 0.015, +38.18 mg/dl in BED), while no significant differences were found between the control group and either BED group.

A separate one-way ANOVA for BMI WHO classification showed no significant effect on triglyceride levels at T2 (p = 0.057), though the relatively low p-value suggests a potential trend.

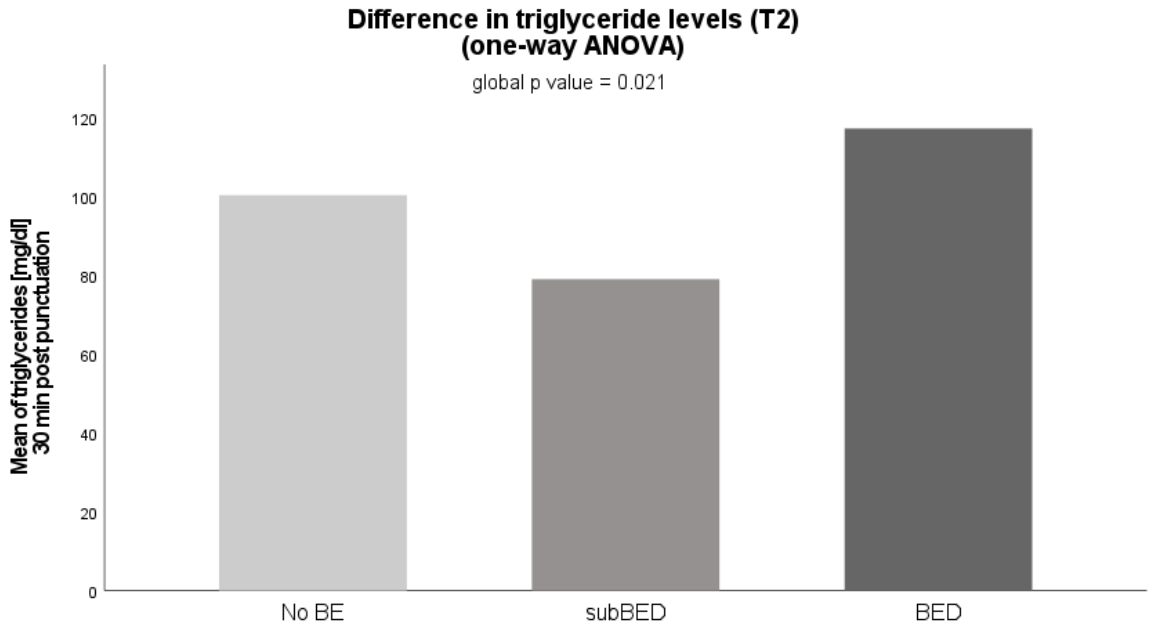

Figure 10: ***Mean Triglyceride Levels 30 Minutes After Punctuation (T2)***

This bar chart compares triglyceride levels 30 minutes post-punctuation across the three study groups: No BE, subBED, and BED group. A one-way ANOVA confirmed a significant difference (p = 0.021).

A two-way ANOVA found no significant interaction between BED group and BMI classification at T2 ($p = 0.229$), with neither factor showing a significant main effect (BED: $p = 0.064$; BMI: $p = 0.139$). However, post-hoc analysis (Sidak) again identified a significant difference between subsyndromal BED and BED ($p = 0.010$, +38.18 mg/dl in BED).

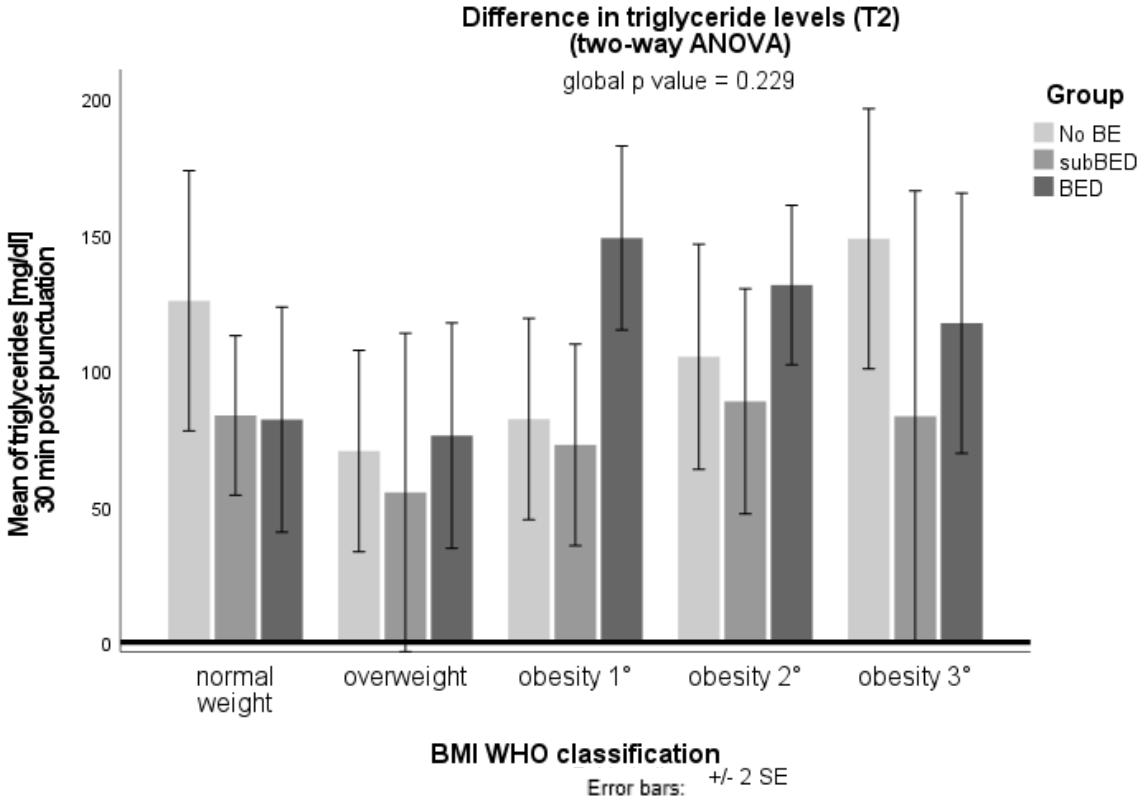

Figure 11: ***Mean Triglyceride Levels Across BMI Categories (T2)***

This bar chart presents triglyceride levels 30 minutes post-punctuation across different BMI categories and study groups. The two-way ANOVA shows no significant difference (p = 0.229).

T3 – Triglyceride Levels

A one-way ANOVA of BED study groups showed no statistically significant difference in triglyceride levels at T3 (p = 0.077).

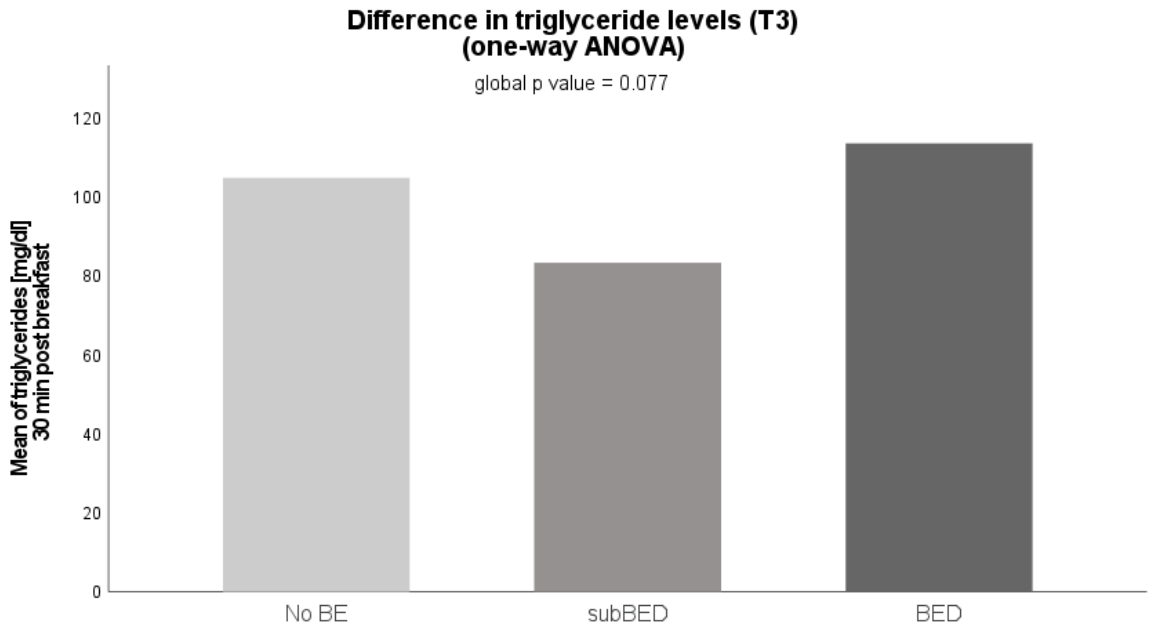

Figure 12: ***Mean Triglyceride Levels 30 Minutes After Breakfast (T3)***

This bar chart illustrates triglyceride levels 30 minutes post-breakfast across different study groups. The one-way ANOVA yields a p-value of 0.077 with BED participants showing the highest triglyceride levels.

A one-way ANOVA for BMI WHO classification groups revealed a statistically significant difference (p = 0.043). However, post-hoc analysis (Tukey-HSD) found no significant pairwise differences, suggesting that the variance stems from within-group variability rather than clear distinctions between groups.

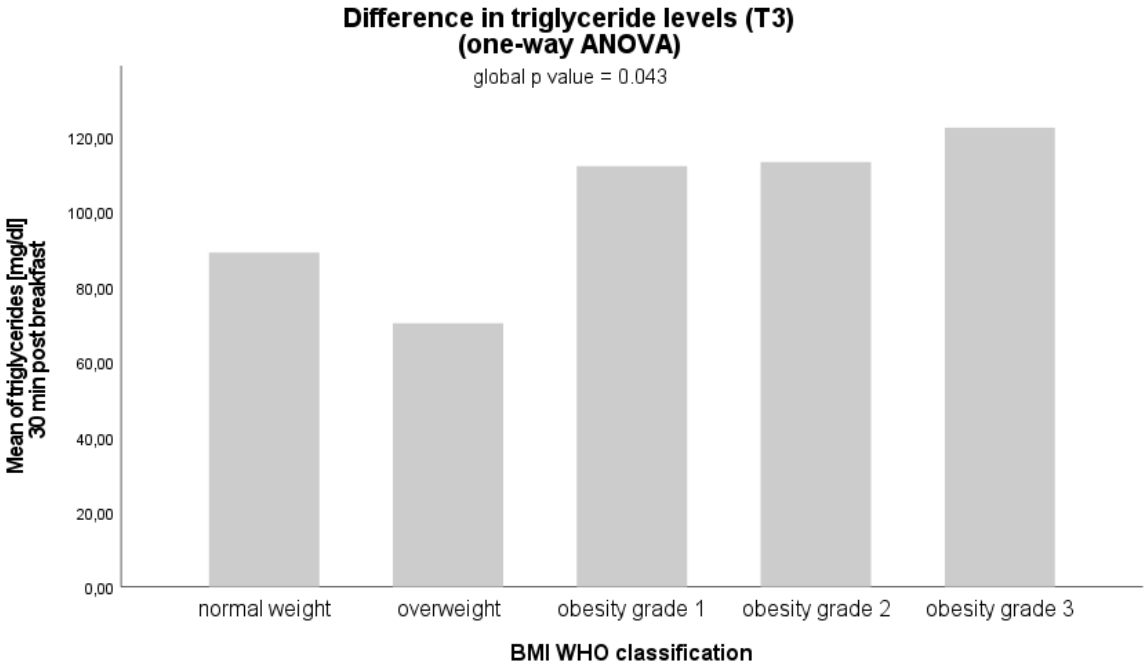

Figure 13: ***Mean Triglyceride Levels 30 Minutes After Breakfast Across BMI Categories (T3)***

This bar chart compares triglyceride levels 30 minutes post-breakfast across BMI categories. The one-way ANOVA results (p = 0.043) suggests an increasing trend with obesity severity.

A two-way ANOVA found no significant interaction between BED group and BMI classification (p = 0.255). Neither BED group (p = 0.089) nor BMI WHO classification (p = 0.121) had a statistically significant effect on triglyceride levels at T3.

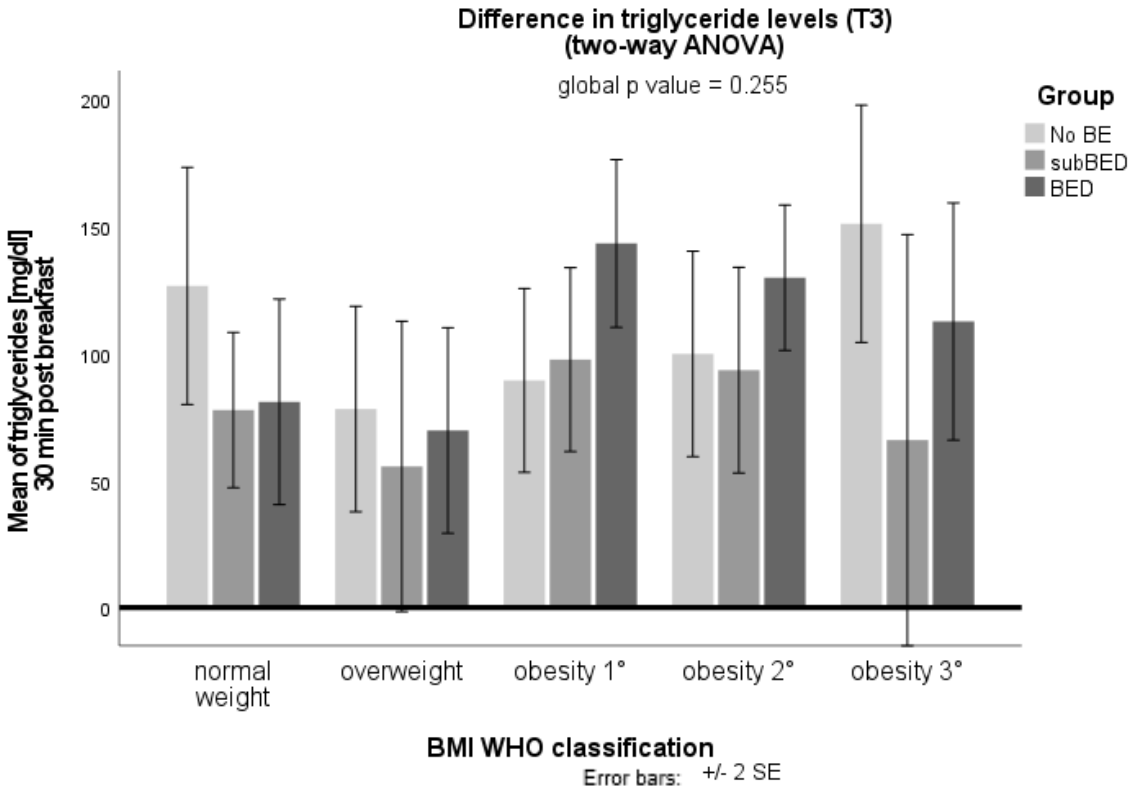

Figure 14: ***Mean Triglyceride Levels at T3 Across BMI Categories and Study Groups***

This bar chart presents triglyceride levels 30 minutes post-breakfast across different BMI categories, further subdivided by study groups (No BE, subBED, and BED). The two-way ANOVA results (p = 0.255) suggest no significant interaction between BMI classification and group status in influencing triglyceride levels.

T4 – Triglyceride Levels

A one-way ANOVA of BED study groups showed a statistically significant difference in triglyceride levels at T4 (p = 0.026). Post-hoc analysis (Tukey-HSD) identified a significant difference between the subsyndromal BED and BED groups (p = 0.023), with the BED group showing higher triglyceride levels (+43.05 mg/dl). No significant differences were found between the control and BED group or the control and subsyndromal BED group. Additionally, BMI WHO classification groups showed no significant differences (p = 0.069).

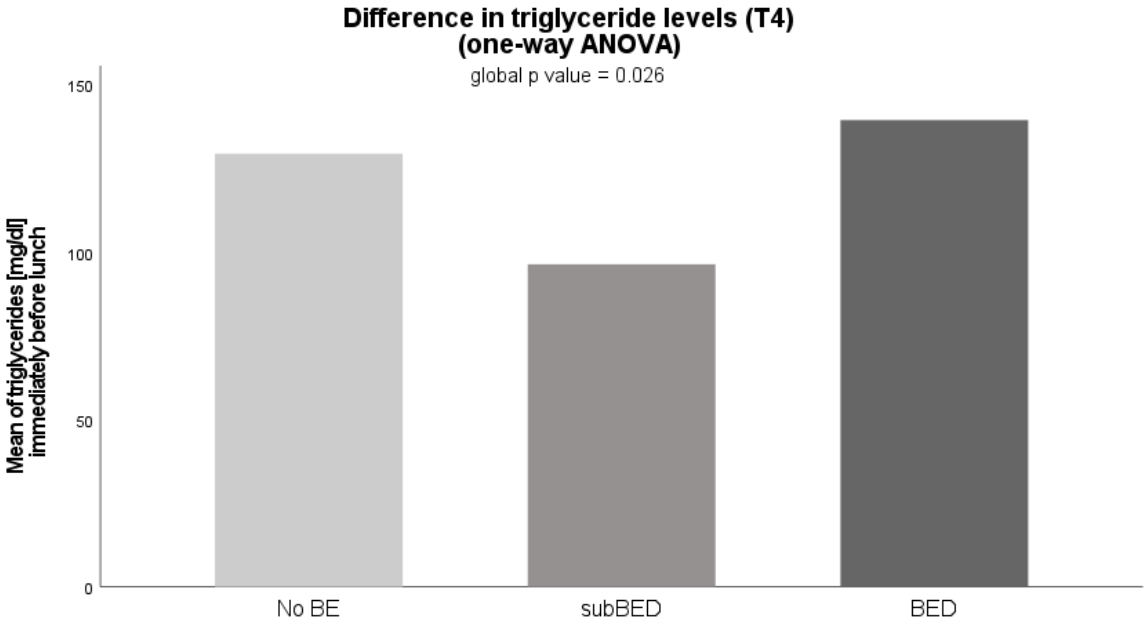

Figure 15: ***Mean Triglyceride Levels at T4 Across Study Groups***

This graph compares triglyceride levels immediately before lunch among different study groups (No BE, subBED, and BED). The global p-value of 0.026 suggests a statistically significant difference.

A two-way ANOVA found no significant interaction between BED group and BMI WHO classification (p = 0.068). However, BED group alone had a significant effect on triglyceride levels (p = 0.045), while BMI WHO classification did not (p = 0.195). Post-hoc analysis (Sidak) confirmed a significant difference between the subsyndromal BED and BED groups (p = 0.012), with the BED group displaying higher triglyceride levels (+43.05 mg/dl). No other significant group differences were observed.

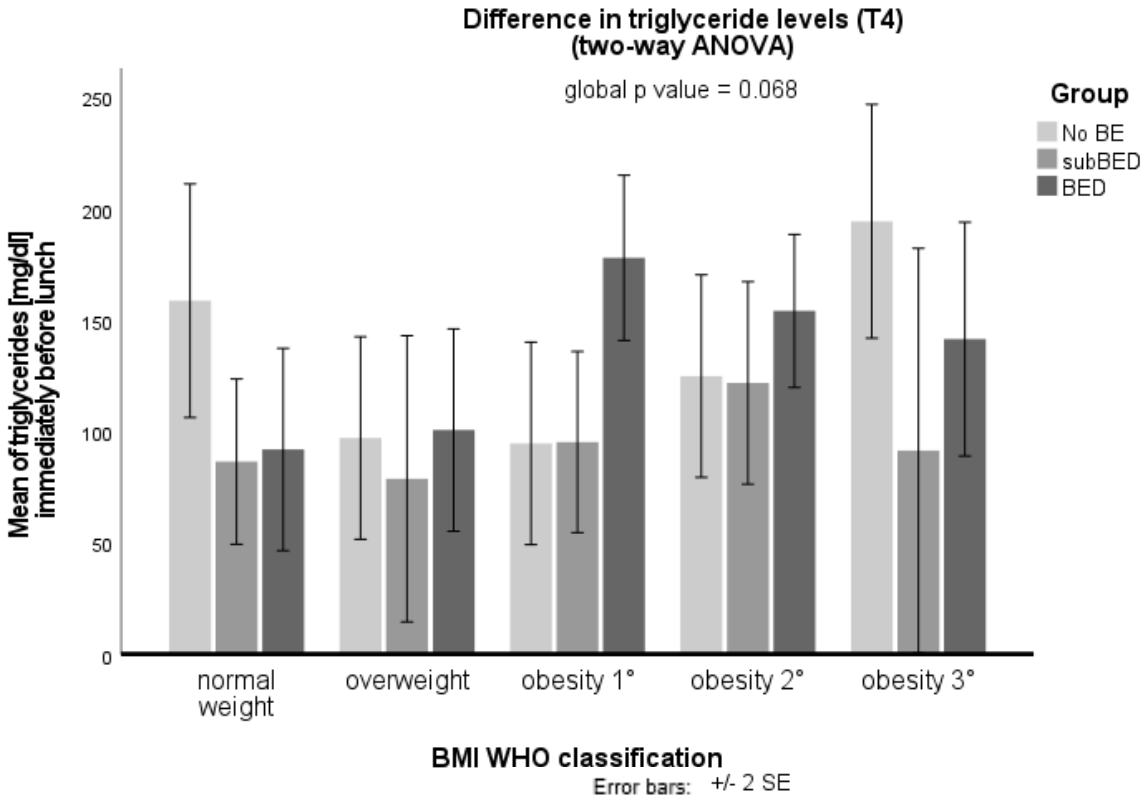

Figure 16: ***Mean Triglyceride Levels at T4 Across BMI Categories and Study Groups***

This graph shows triglyceride levels immediately before lunch across BMI categories and study groups (No BE, subBED, and BED). The global p-value of 0.068 suggests no statistically significant difference overall. Error bars represent ±2 SE.

Meal-Related Triglyceride Excursions

A one-way ANOVA comparing BED, subsyndromal BED, and control groups revealed no statistically significant difference in meal-related triglyceride excursions ($p = 0.701$).

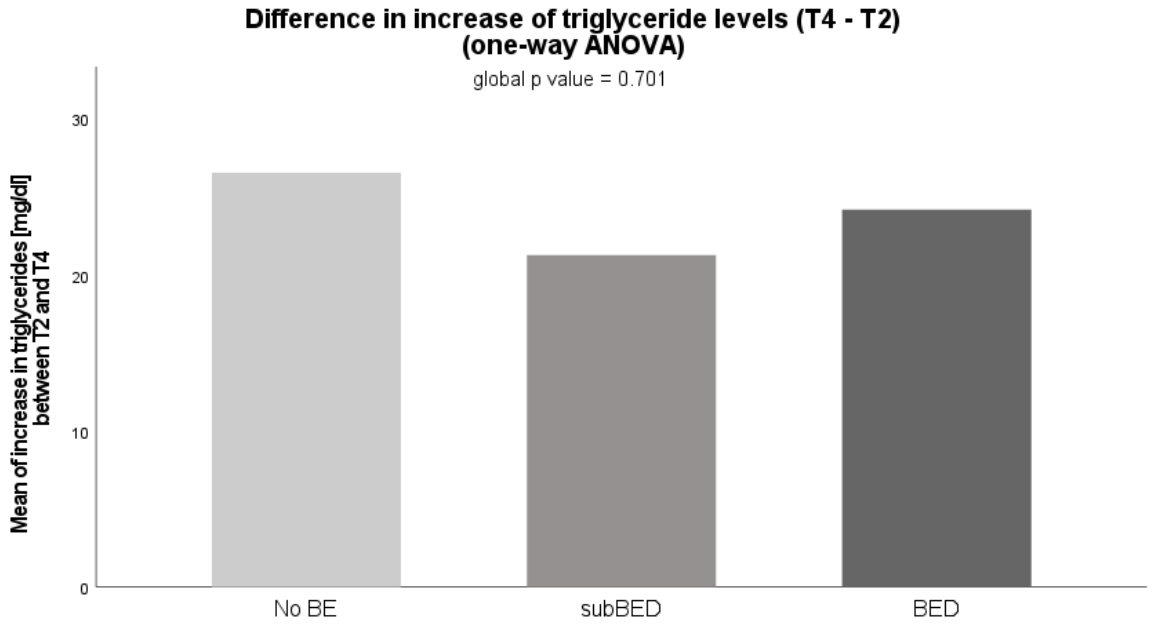

Figure 17: ***Mean Triglyceride Level Increase Between T2 and T4 Across Study Groups***

This graph shows the mean increase in triglyceride levels between T2 and T4 across study groups (No BE, subBED, and BED). The global p-value of 0.701 suggests no significant difference among the groups.

Similarly, a one-way ANOVA comparing BMI WHO classification groups on triglyceride differences between T4 and T2 showed no significant difference ($p = 0.492$). A two-way ANOVA also found no significant interaction between BED group and BMI WHO classification ($p = 0.438$), with neither BMI WHO classification ($p = 0.857$) nor BED group ($p = 0.547$) showing a significant effect. The same non-significant results were observed for T2-T3 and T3-T4.

To further evaluate triglyceride level differences across time points, paired t-tests were conducted. The comparison between T2 and T3 showed no statistically significant difference (two-sided $p = 0.943$). In contrast, triglyceride levels increased significantly between T3 and T4 (two-sided $p < 0.001$) with a mean difference of 23.32, although this increase was not significant when comparing different groups. Similarly, triglyceride levels between T2 and T4 showed a statistically significant increase (two-sided $p < 0.001$) with a mean difference of 24.01.

Correlation Between Triglycerides and BMI

A statistically significant but weak positive correlation was found between triglyceride levels and BMI for fasting triglycerides and at all three blood draw time points ($p < 0.05$, $R^2 = 0.110$). This suggests that BMI alone is not a strong predictor of triglyceride levels. Interestingly, no statistically significant correlation was observed between triglyceride levels and the amount of consumed cheese pasta.

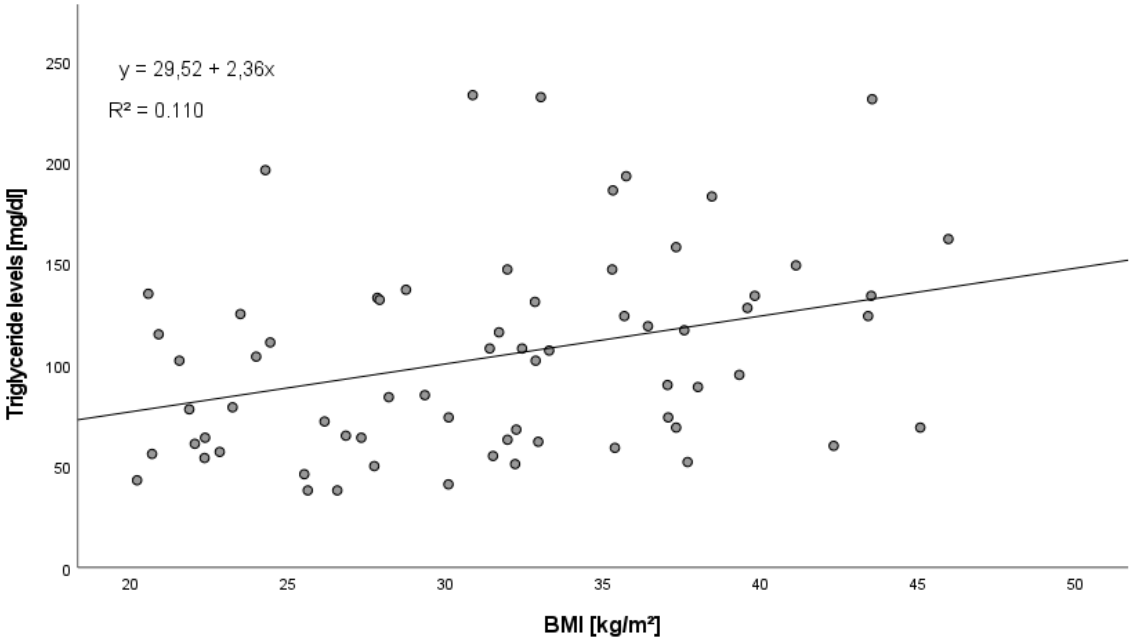

Figure 18: ***Correlation Between BMI and Triglyceride Levels***

This scatter plot illustrates the relationship between BMI and triglyceride levels. The regression equation suggests a slight positive association, but the R^2 value of 0.110 indicates a weak correlation.

3.3 Behavioral Outcome

3.3.1 Cheese Pasta Consumed

During the second lab visit, participants were instructed eat as much as they wanted of a bowl of cheese pasta (~2.500 kcal). Unbeknownst to the participants, the bowl was weighed before and after to measure the amount of eaten cheese pasta. A one-way ANOVA showed no significant difference in consumption across BED study groups (p = 0.98), with average intake of 400.45g (control), 391.48g (subsyndromal BED), and 396.04g (BED).

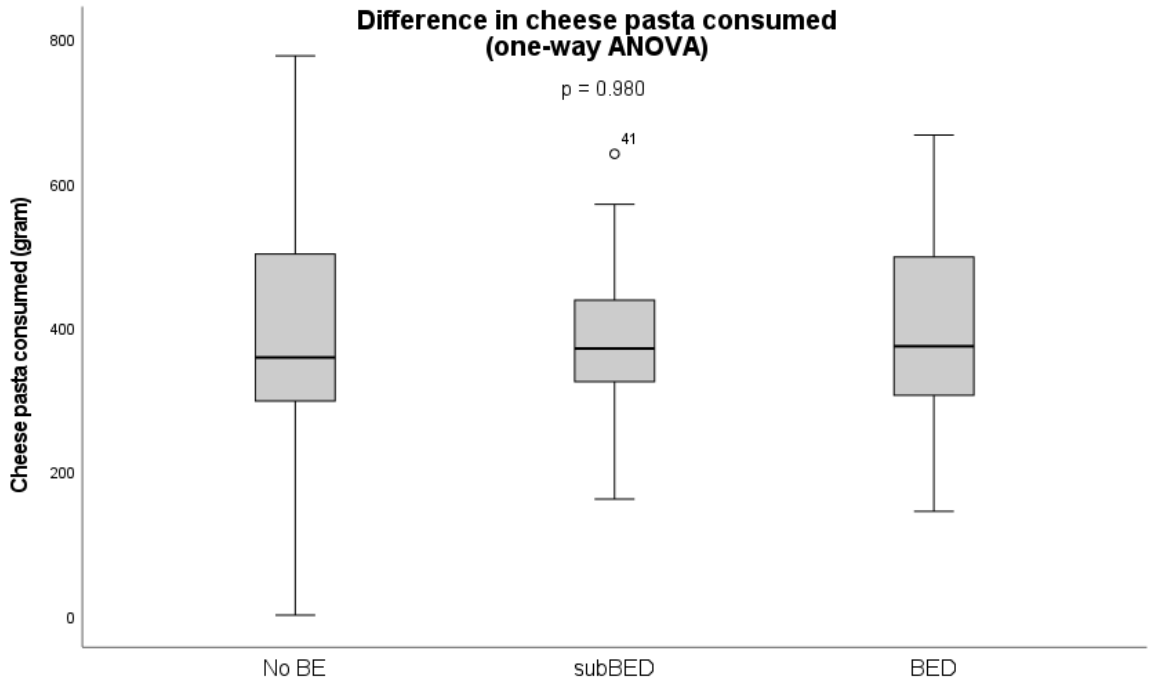

Figure 19: ***Cheese Pasta Consumed Across Study Groups***

The boxplot illustrates the differences in cheese pasta consumption among the three study groups (No BE, subBED, and BED). The p-value of 0.980 suggests no significant difference between the groups.

A one-way ANOVA for BMI WHO classification groups also found no significant difference ($p = 0.673$). Similarly, a two-way ANOVA revealed no significant interaction between BED group and BMI WHO classification ($p = 0.613$) or main effects (BED: $p = 0.908$; BMI WHO: $p = 0.765$), indicating no association between group classification and cheese pasta intake.

3.3.2 No Significant Link Between Binge Eating and Hunger and Fullness Ratings

Subjective ratings of hunger and satiety were compared between groups using VAS at four data collection times: fasting at the beginning of the session (R0), after breakfast (R1), after the MR task (R2), and immediately after lunch (R3). Lunch consisted of cheese pasta with approximately 2500 kcal. The trends in both hunger and fullness ratings follow a predictable pattern, with hunger decreasing sharply after food intake and then rising again, while fullness shows the opposite trend, increasing after food consumption and subsequently declining.

The three groups appear to follow very similar trajectories in their ratings, suggesting no major differences in subjective hunger and fullness perception. Although slight variations in absolute values between groups can be observed, their overall response patterns remain consistent, with overlapping confidence intervals. No statistically significant group differences were observed, suggesting a consistent pattern of hunger and fullness ratings across binge eating severity levels.

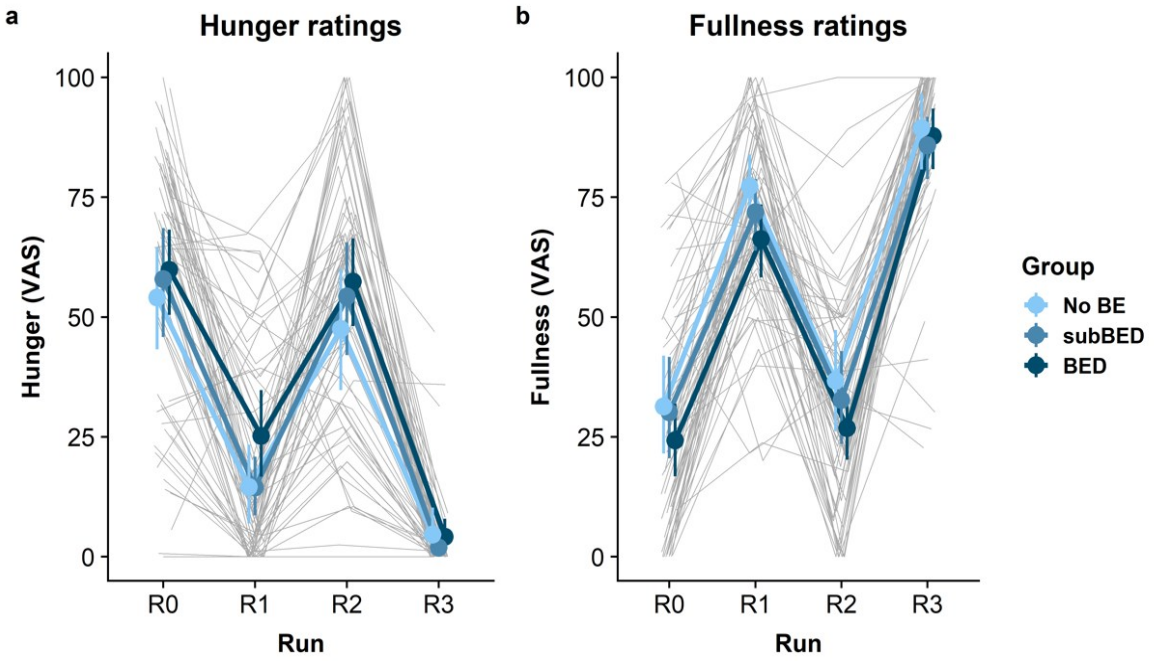

Figure 20: ***Subjective VAS ratings of Hunger and Fullness***

Line graph of hunger (a) and fullness (b) ratings measured by visual analog scale (VAS). Individuals were asked to rate their hunger and satiety at different timepoints during the in-lab session; before breakfast (R0), post breakfast (R1), after performing a task in the MR (R2) and post prandial after ad-libitum lunch (R3). Groups were divided into binge eating disorder group (BED), subsyndromal binge eating group (subBED) and no binge eating (No BE) group. Significant group differences in subjective ratings of hunger and fullness could not be observed. ($p > 0.05$)

3.4 Neuroimaging

3.4.1 High Caloric vs. Low Caloric Food Cues in fMRI

We then investigated the brain's response to food cues by looking at fMRI data. Therefore, individuals were presented with images of high-caloric as well as low-caloric food. Participants exhibited stronger BOLD responses to high-caloric than low-caloric food cues in the lingual gyrus, occipital gyrus, posterior cingulate cortex (PCC), NAcc, and medial prefrontal cortex. This effect was observed across all groups. However, individuals with BED showed significantly greater activation in the NAcc compared to the control group without BED. Extracted BOLD responses indicate that individuals with BED exhibit heightened neural responses to high-caloric food cues, with subBED participants showing intermediate activation levels between the BED and control groups.

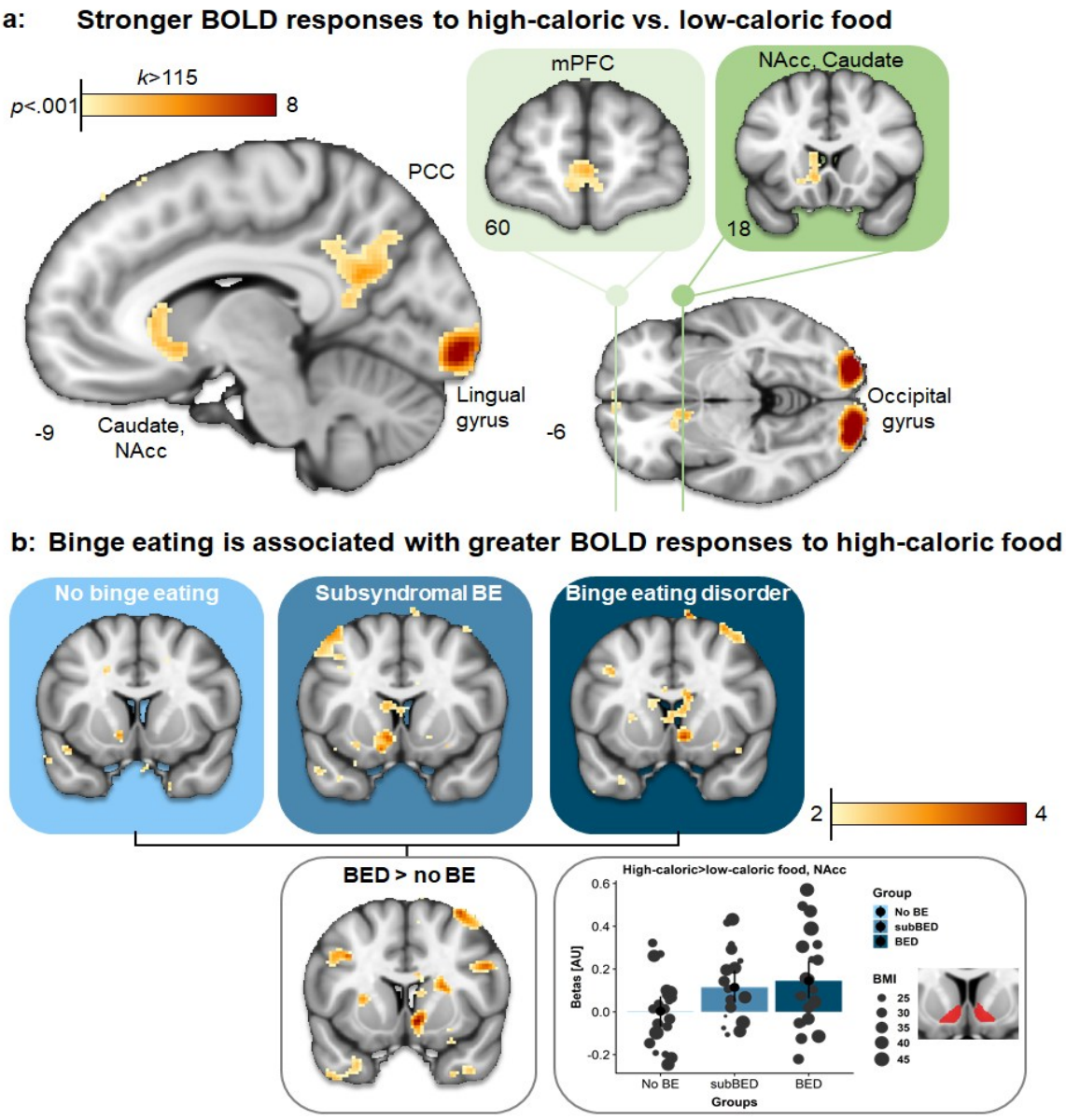

Figure 21: ***BOLD Responses to High-Caloric vs. Low-Caloric Food***

High-caloric food elicits a stronger BOLD response than low-caloric food (a) Differences in food-cue reactivity (FCR) are shown for participants without binge eating, with subsyndromal binge eating, and with binge eating disorder (b). Results are cluster-wise corrected at p < .001 (k > 115), with color bars indicating t-values.

3.4.2 Higher Fasting Triglyceride Levels are Associated with a Dampened Brain-Response to High-Caloric Food Cues

In addition to investigating food-cue reactivity in relation to binge eating, we examined how metabolic factors, specifically fasting triglyceride levels, influence neural responses to high-caloric food cues. Higher fasting triglyceride levels were associated with attenuated BOLD responses to high-caloric food cues in the ventral anterior and dorsal mid-insula, hippocampus, putamen and nucleus of the solitary tract. Significant negative correlations were found between triglyceride levels and activation in the insula ($r = -0.38$, $p < 0.01$) and hippocampus ($r = -0.43$, $p < 0.01$). Scatter plots illustrate these relationships, indicating that individuals with higher fasting triglyceride levels exhibited lower neural responses in these regions.

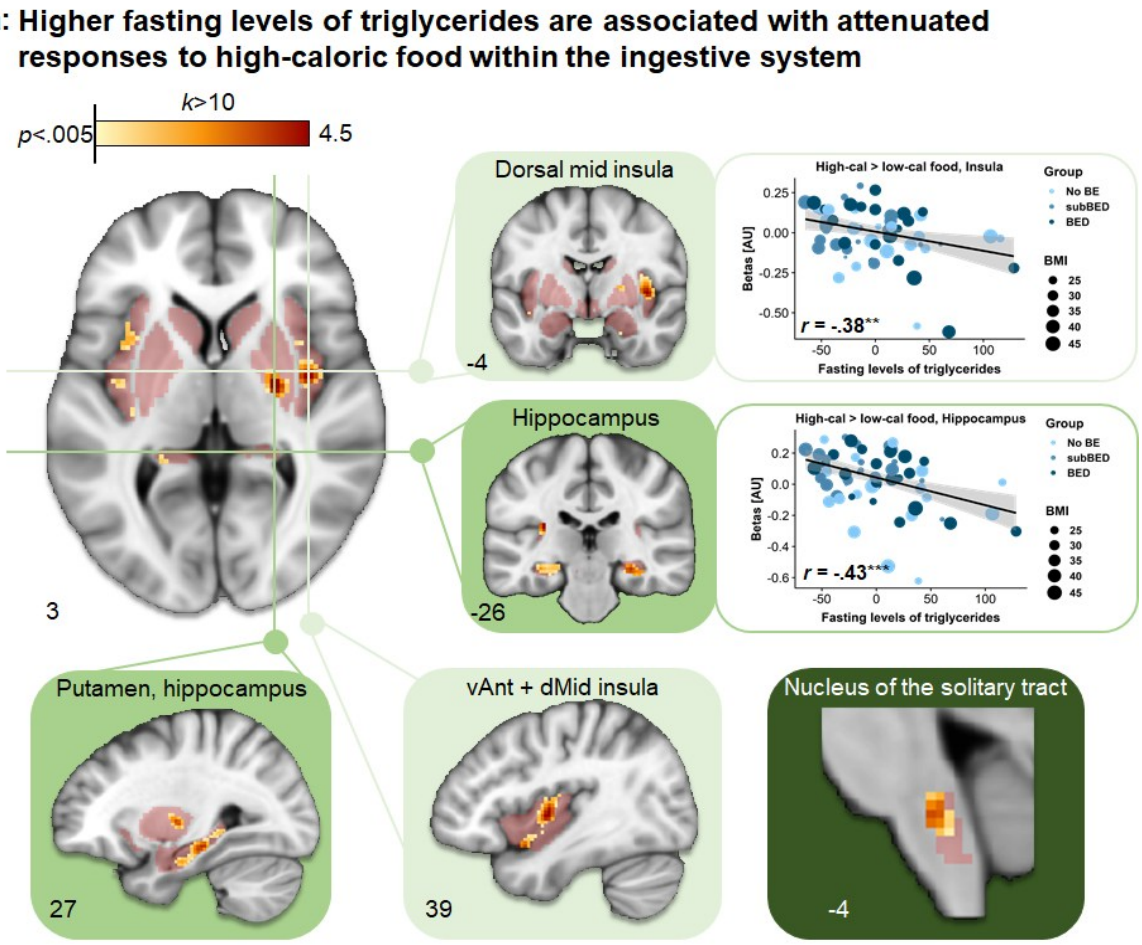

Figure 22: ***Relationship Between Fasting Triglycerides and Neural Responses to High-Caloric Food***

Higher fasting triglyceride levels are associated with attenuated BOLD responses to high-caloric food cues in key regions of the ingestive system, including the insula, hippocampus, putamen, and nucleus of the solitary tract. Scatter plots illustrate significant negative correlations between triglyceride levels and brain activity in the insula and hippocampus. All results are cluster-wise p < .005 corrected (cluster size k > 10), color bars represent t-values.

3.4.3 Meal-Related Excursions of Triglycerides are Associated with Attenuated Brain Response to High-Caloric Food Cues

Higher post-meal excursions of triglycerides were significantly associated with attenuated BOLD responses to high-caloric food cues in the substantia nigra and right globus pallidus. This effect was more pronounced in response to energy-dense food items compared to low-caloric food items.

As shown in Figure 23, brain activation maps highlight significant clusters in the substantia nigra and globus pallidus where triglyceride excursions negatively correlate with food-cue reactivity. Scatter plots illustrate significant negative correlations between triglyceride fluctuations and BOLD response in the substantia nigra ($r = -0.32$, $p < 0.005$) and the right globus pallidus ($r = -0.29$, $p < 0.005$).

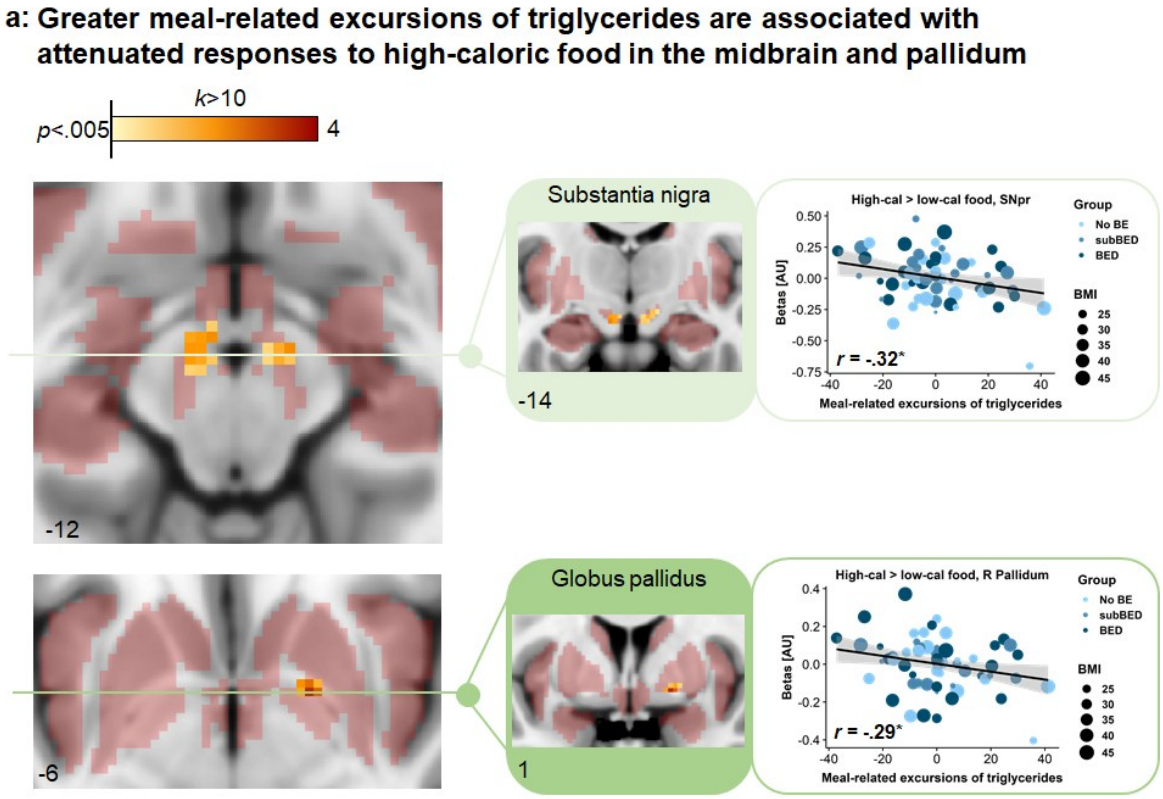

Figure 23: ***Reduced Brain Responses to High-Caloric Food Cues in Participants with Higher Triglyceride Excursions***

Brain regions with reduced responses to high-caloric food cues in participants with greater meal-related triglyceride excursions compared to those with lower excursions. (a) All results are cluster-wise corrected at p < .005 (cluster size k > 10); color bars represent t-values.

4 Discussion

To the best of our knowledge, this is the first study to examine morning serum levels triglycerides in a large sample of fasted symptomatic women with BED.

We investigated the relationship between triglyceride levels and brain responses to food images in 61 female participants, including women with BED, subsyndromal BED, and those without binge eating. Triglycerides, dietary fats metabolized by lipases in various brain regions, are known to influence neural responses to food stimuli (Berland et al., 2016; Berland et al., 2020; Cansell & Luquet, 2016).

Using fMRI, we analyzed brain activity in response to high- and low-calorie food cues. High-calorie images elicited stronger BOLD responses in regions such as the lingual gyrus, occipital gyrus, NAcc, and mPFC. Notably, individuals with a history of binge eating showed heightened activation in the NAcc compared to controls. Furthermore, higher fasting triglyceride levels and greater post-meal excursions were negatively correlated with activity in reward-related brain regions when presented with energy-dense food cues.

4.1 High-Caloric Food Elicits Stronger BOLD Response than Low-Caloric Food

fMRI analysis showed heightened BOLD responses in several brain regions when participants viewed high-caloric food compared to low-caloric food. Among the activated regions, the NAcc and caudate play a crucial role in reward processing and motivation, reinforcing the idea that high-caloric food is perceived as more rewarding (Aron et al., 2005; Chen et al., 2023). The mPFC, which plays a crucial role in decision-making and emotion regulation, was also engaged, likely reflecting the strong desirability of high-caloric foods (Xu, Chen, Li, Xing, & Lu, 2019). In addition, increased activation in the lingual and occipital gyri indicates the involvement of

visual processing which suggests, that visual processing of food cues plays a role in food perception, while the PCC may be functioning as a connection between motivation and visual processing, further contributing to food-related decision-making (Leech & Smallwood, 2019).

Interestingly, we also found that food cue reactivity (FCR) varied based on binge eating severity. Participants without binge eating showed minimal activation, while those with subsyndromal binge eating (subBED) exhibited greater responses—though still lower than individuals with full BED. The BED group displayed significantly stronger activation in reward-related brain areas, particularly in the NAcc, indicating heightened neural sensitivity to high-caloric food cues. This is consistent with Filbey et al. who found that greater binge eating severity correlated with heightened BOLD response to high-caloric taste stimuli in reward-related brain regions (Filbey et al., 2012) as well as other previously published studies that investigated altered response to food cues in individuals with BED (Ferrer-Garcia et al., 2017; Kanoski & Boutelle, 2022; Meule et al., 2018; Reents & Pedersen, 2021).

These findings suggest that high-caloric foods trigger stronger activation in brain regions involved in reward processing, decision-making, and visual perception, highlighting their heightened neural appeal. Research by Kanoski and Boutelle has linked increased food cue reactivity to obesity and overweight (Kanoski & Boutelle, 2022). Similarly, individuals with BED have been shown to exhibit exaggerated neural responses to food cues, particularly within the brain’s reward system, supporting theories that BED involves heightened reward sensitivity (Schienle et al., 2009). This increased sensitivity to high-calorie foods may, in turn, contribute to the challenge individuals with BED face in regulating their dietary habits.

4.2 Triglyceride Levels are Inversely Correlated with Brain Response to High-Caloric Food Cues

We then investigated the association between triglyceride levels and brain-response to high-caloric food. Elevated fasting triglyceride levels were found to reduce responses in the brain to high-calorie food images in areas linked to motivation and reward processing, including the dorsal mid insula and hippocampus. These results indicate that higher fasting triglyceride levels are associated with attenuated BOLD responses in brain regions involved in food-related reward processing, motivation, interoception, and memory (Stevenson & Francis, 2017; Wiebking et al., 2014) which suggests that metabolic state may modulate the way individuals perceive and process food stimuli. This aligns with previous studies that found that elevated triglyceride levels attenuate the brain's response to palatable food. (Berland et al., 2016; Berland et al., 2020; Cansell et al., 2014).

The main brain regions identified in our analysis include the anterior ventral and dorsal mid-insula, hippocampus, putamen, and the nucleus of the solitary tract. The insula is known for its role in interoceptive awareness, integrating homeostatic states with subjective experiences of hunger and satiety (Wiebking et al., 2014). The observed negative correlation between fasting triglyceride levels and insular activation suggests that individuals with elevated triglycerides may experience a blunted neural response to food cues, potentially reducing their sensitivity to internal hunger and satiety signals.

Similarly, the hippocampus, which is crucial for memory and learning, showed reduced activation in individuals with higher triglyceride levels. This aligns with prior research suggesting that metabolic dysregulation can impair hippocampal function, potentially affecting memory-related aspects of eating behavior, such as recalling previous meals or regulating future intake based on past experiences (Stevenson & Francis, 2017). The putamen, which is another key region involved in habit formation and reward-related behaviors, also exhibited reduced activation, which may indicate

a dampened motivational drive toward food in individuals with higher triglyceride levels (Ghandili & Munakomi, 2025; Krentzel & Meitzen, 2018). Another brain region that we found to be less activated with increased triglyceride levels is the nucleus of the solitary tract. It is located in the brainstem and plays a critical role in processing visceral sensory information and regulating ingestive behavior (Shi et al., 2021). Attenuated responses in this region suggest that metabolic alterations, such as elevated triglyceride levels, may influence the brainstem's ability to regulate appetite and food intake. Additionally, using scatter plots we were able to depict the relationship between triglyceride levels and neural activation in the insula and hippocampus. Significant negative correlations demonstrate that individuals with higher fasting triglyceride levels exhibit lower neural responses to high-caloric food, further supporting the hypothesis that metabolic state affects food-related brain activity.

Overall, these findings provide insight into how metabolic state can shape neural responses to food cues. Higher triglyceride levels appear to be associated with a reduced neural response in key regions responsible for reward processing, interoception, and memory. This blunted response may contribute to altered eating behaviors, potentially influencing food choices and overall energy balance. Understanding these mechanisms could help in developing targeted dietary or pharmacological interventions aimed at targeting the effects of metabolic dysregulation on brain function and eating behavior.

4.3 Greater Post-Meal Triglyceride Excursions are Associated with an Attenuated Brain Activation to High-Caloric Food Cues

Conducting further fMRI analysis, we examined how meal-related excursions of triglycerides influence brain responses to high-caloric food cues, particularly in the substantia nigra and globus pallidus, two key regions involved in reward processing and motor function (Azcorra et al., 2023; Imtiaz et al., 2024; Javed & Cascella, 2025).

The results indicate that greater increases in triglyceride levels after meals are associated with a reduced neural response to high-caloric food cues in these areas. With scatter plots, we were able to show a negative correlation between post-meal triglyceride fluctuations and BOLD responses in the substantia nigra ($r = -0.32$) and right globus pallidus ($r = -0.29$). This suggests that individuals experiencing greater triglyceride spikes after meals exhibit a weaker neural reaction to high-caloric food cues, potentially reflecting altered reward sensitivity.

At first, it may seem counterintuitive that increased triglyceride levels - linked to high BMI and weight gain - are associated with reduced brain activity in response to food cues, as this might suggest lower motivation to eat. However, this could reflect brain adaptation to chronic overconsumption, where prolonged exposure to high-caloric foods desensitizes the reward system. Despite this blunted neural response, individuals with BED or chronic overeating tendencies may continue excessive intake due to habit, emotional eating, or metabolic dysregulation (e.g., insulin resistance). A dampened reward response may even drive compulsive eating, as individuals seek to compensate for reduced food-related pleasure, reinforcing the cycle of overeating and weight gain. Increased triglyceride levels further complicate this by disrupting hunger and satiety regulation. Even as food cues elicit weaker neural responses, hunger signals may still drive excessive intake, creating a vicious cycle where overeating raises triglycerides, which in turn alter brain responses without curbing consumption.

Given the role of these beforementioned brain regions in dopaminergic signaling, our findings suggest that metabolic factors, such as triglycerides, modulate food-related reward processing. A blunted response to food cues could contribute to dysregulated eating behaviors, particularly in individuals with binge eating tendencies. While our study includes groups with and without BED, it remains unclear whether the observed effects significantly differ between them. Further research could explore how these metabolic and neural interactions influence eating behaviors over time.

4.4 BED is not Linked to Increased Hunger or Decreased Fullness Ratings

Subjective evaluations of feelings of hunger and fullness were compared between multiple groups through the use of VAS scales. Ratings of hunger decreased following a meal whereas ratings of fullness increased, however, no significant differences were discovered between the groups with regards to their ratings of hunger or fullness. Therefore, binge-eating is not believed to be linked to elevated ratings of hunger or reduced ratings of fullness. These findings align with the previously published results of Samuels and colleagues, who similarly observed no variations in subjective ratings of pre- and postprandial hunger and fullness between the binge eating, subsyndromal, and healthy control groups (Samuels, Zimmerli, Devlin, Kissileff, & Walsh, 2009). However, a different study found that people with BED consumed significantly more food and had less divergence between hunger and satiety during both binge and non-binge meals (Sysko, Devlin, Walsh, Zimmerli, & Kissileff, 2007). It is important to note that the investigation analyzed subjective perceptions of hunger and satiety during breakfast and lunch. Many individuals however, exhibit binge eating behaviors and food cravings at night, indicating that circadian rhythms may influence disordered eating patterns (Romo-Nava et al., 2022).

4.5 Data Reliability

Compared to prior fMRI studies on BED, our study included a substantially larger sample size, allowing for a more comprehensive investigation of the role of triglycerides in reward signaling. This enhances the generalizability and reliability of our findings. Additionally, our carefully designed methodology ensures optimal accuracy and reproducibility.

4.6 Limitations, Remaining Questions, and Future Directions

Our study had several limitations that warrant discussion. Firstly, we categorized participants into three groups: individuals with binge eating disorder (BED), individuals with subsyndromal binge eating (subBED), and a healthy control group. The subBED category, defined as meeting most of the diagnostic criteria for BED but not the required frequency, is not an officially recognized classification in the DSM-5. It therefore remains unclear whether categorizing individuals based solely on binge eating frequency accurately captures significant distinctions between groups. Future research may benefit from a more standardized classification system.

Secondly, to measure fasting triglyceride levels, participants were required to fast for 12 hours before arriving. Nevertheless, we had no control over the food that the participants consumed the day before, which could have impacted their triglyceride levels based on their food selections.

Furthermore, we chose to include only female participants in our sample because eating disorders are more prevalent among women than men. Nonetheless, BED is the most common eating disorder in both men and women (Galmiche et al., 2019; Hudson et al., 2007; R. C. Kessler et al., 2013; Udo & Grilo, 2018), so it remains imperative to include male participants in future studies. This is particularly relevant when considering the potential impact of differential metabolic profiles in men and women on binge eating behavior. A comprehensive study of type 1 diabetes patients carried out by Braffet et al. (2022) reveals that men exhibit higher triglyceride levels relative to women (Braffett et al., 2022). Additionally, emerging research highlights the gut microbiome as an important factor in the development of disordered eating, and again, there are notable differences in the gut microbiota between the sexes (Haro et al., 2016). Studies on brain activation in response to food cues have revealed distinct activation patterns between obese women and men. Specifically, brain regions associated with cognition and emotion tend to be more active in women, whereas areas linked to motor control and visual attention show greater

activation in men (Geliebter et al., 2013). These differences highlight the importance of considering sex-specific factors for a comprehensive understanding of disordered eating behaviors.

Another potential confounding factor for studies regarding energy homeostasis and food reward such as ours, is the menstrual cycle in women. Hormones such as estradiol and progesterone have been shown to influence food perception and cravings, with women more frequently craving sugar and fat during the premenstrual phase (Souza et al., 2018). Prior research has also demonstrated intra-individual differences in emotional eating and binge eating throughout the menstrual cycle (Hildebrandt et al., 2015; Klump et al., 2015). Given the association between binge eating behaviors and menstrual irregularities, as observed in polycystic ovary syndrome (Burnatowska et al., 2023; Krug, Giles, & Paganini, 2019), it is important to consider the menstrual phase of participants during the in-lab sessions as a potential factor impacting the food bidding tasks. Future research should address this potential effect.

Similarly, sleep regulates eating behavior. Insufficient sleep is associated with poor impulse control, which is linked to binge eating. Leptin, a hormone that reduces appetite, decreases during sleep deprivation, whereas ghrelin, a hormone that increases appetite, increases, potentially contributing to disordered eating. Additionally, sleep deprivation is linked to compromised executive function, which may result in erratic eating and heightened caloric intake (Cerolini, Ballesio, Ferlazzo, Lucidi, & Lombardo, 2020; Doan, Parker, Rosati, van Beers, & Ferro, 2022; Manasse et al., 2022). Thus, task performance may have been affected by the duration and quality of sleep experienced by participants. Participants were asked to report the amount and quality of sleep they had the night before, but this information should be further considered when comparing food bidding tasks between participants.

In addition, our study sample predominantly consisted of white women of Western European descent. However, Kuller et al have discussed racial disparities in triglyceride levels and various risk factors or diseases (Kuller, 2004). Therefore, it is recommended that future research endeavors include diverse ethnicities in their sample to better generalize conclusions to different racial groups.

Moreover, future studies with larger sample sizes would enhance statistical power and allow for a more comprehensive analysis of the relationship between triglycerides, brain responses, and BED. A larger sample could help detect subtle effects and identify potential subgroups, providing deeper insight into factors contributing to the development of BED. Additionally, incorporating longitudinal study designs would be beneficial in capturing the progression and underlying mechanisms of the disorder over time.

Despite these limitations, our study provides valuable insights into the relationship between triglycerides and brain responses to food cues in individuals with BED.

4.7 Conclusion

Our findings highlight that triglycerides are associated with neural alterations in reward signaling. High-caloric food cues elicited stronger activation in reward-related regions, particularly the NAcc and mPFC, emphasizing the heightened food cue reactivity in individuals with BED. However, elevated triglyceride levels as well as greater meal-related excursions were linked to attenuated activation in key reward-processing areas, such as the substantia nigra and globus pallidus, suggesting a potential desensitization of the reward system due to chronic overconsumption.

This paradox - heightened food cue reactivity in BED despite a blunted neural response in individuals with elevated triglycerides - reflects the complex interplay between metabolic dysregulation and reward processing. While BED is marked by

increased motivation toward high-caloric foods, prolonged overeating and metabolic changes may gradually dampen the brain’s response to these cues. Nevertheless, psychological and habitual factors likely sustain excessive food intake, overriding these neural adaptations.

Our study underscores the need for further research into the interaction between metabolic markers, neural responses, and eating behaviors to better understand the mechanisms underlying BED and its metabolic consequences.

5 Summary

Emerging research increasingly suggests that triglycerides influence dopamine pathways, impacting appetite regulation and reinforcing binge-eating behaviors. To investigate this, we recruited 61 female participants categorized into three groups: patients with BED, subsyndromal BED, and a control group. Each participant completed two in-lab sessions, including diagnostic interviews, behavioral assessments, blood draws, and reward-related tasks while undergoing MRI scans. During the study, participants performed a FCR task, measuring BOLD response amplitudes and functional connectivity during a food bidding task. Neural activity was then analyzed in relation to triglyceride levels obtained from blood samples. Our hypothesis was that elevated plasma triglyceride levels would be associated with a reduced neural response to palatable food cues.

Through our findings, we were able to confirm this hypothesis, showing that while individuals with BED exhibit heightened activation in reward-related brain regions, elevated triglyceride levels correlate with a blunted response in key reward-processing areas. Subsyndromal BED participants displayed intermediate activation, suggesting a continuum of reward sensitivity in binge eating behaviors.

Notably, higher fasting triglyceride levels were linked to reduced activation in brain regions involved in reward processing, interoception, and memory. Significant negative correlations between triglyceride levels and activation in the insula and hippocampus suggest that metabolic dysregulation may dampen neural responsiveness to food-related stimuli. Additionally, greater post-meal triglyceride fluctuations were associated with attenuated activation in regions critical for dopamine signaling and reward regulation. These findings suggest that chronic overconsumption and metabolic alterations may lead to a gradual desensitization of the brain’s reward system.

Overall, our findings highlight the critical role of metabolic factors in shaping neural responses to food. Understanding these mechanisms could enable targeted interventions aimed at restoring reward sensitivity and improving appetite regulation in individuals with BED. Future research should explore how metabolic modulation may serve as a potential therapeutic strategy for disordered eating behaviors.

6 Zusammenfassung

Neuere Forschungsergebnisse deuten zunehmend darauf hin, dass Triglyceride Dopamin-Signalwege beeinflussen, die die Appetitregulation steuern und dysreguliertes Essverhalten verstärken können. Um diesen Zusammenhang zu untersuchen, rekrutierten wir 61 Probandinnen, die in drei Gruppen eingeteilt wurden: Teilnehmerinnen mit BED, subsyndromaler BED und eine Kontrollgruppe. Alle Probandinnen nahmen an zwei Studienterminen teil, die diagnostische Interviews, Verhaltensbeurteilungen, Blutabnahmen und Belohnungsaufgaben umfassten, während ihre Gehirnaktivität mittels MRT aufgezeichnet wurde. Im Rahmen der Studie absolvierten sie eine FCR-Aufgabe, bei der BOLD-Reaktionsamplituden sowie funktionelle Konnektivität gemessen wurden. Die neuronale Aktivität wurde anschließend mit den Triglycerid Werten zu verschiedenen Messzeitpunkten korreliert. Unsere Hypothese lautete, dass höhere Triglycerid Spiegel mit einer reduzierten neuronalen Reaktion auf Nahrungsreize assoziiert sind.

Unsere Ergebnisse bestätigen diese Hypothese: Während Personen mit BED eine verstärkte Aktivierung in belohnungsassoziierten Hirnregionen aufwiesen, waren hohe Triglycerid Spiegel mit einer abgeschwächten neuronalen Reaktion verbunden. Probandinnen mit subsyndromaler BED zeigten eine Aktivierung, die zwischen jener der BED Gruppe und der Kontrollgruppe lag, was auf ein Kontinuum der Belohnungssensitivität innerhalb der BED Gruppen hindeutet.

Besonders auffällig war der Zusammenhang zwischen höheren Nüchtern-Triglycerid Werten und einer verminderten Aktivierung in Hirnregionen, die für Belohnungsverarbeitung, interozeptive Wahrnehmung und Gedächtnis relevant sind. Signifikante negative Korrelationen zwischen Triglycerid Werten und der Aktivierung der Insula sowie des Hippocampus legen nahe, dass eine gestörte Stoffwechselregulation die neuronale Reaktionsfähigkeit auf nahrungsbezogene Reize beeinträchtigen könnte. Darüber hinaus gingen stärkere postprandiale

Triglycerid Anstiege mit einer verminderten Aktivierung zentraler Regionen für die Dopaminregulation und Belohnungsverarbeitung einher. Dies könnte darauf hindeuten, dass chronische Überernährung und die daraus resultierenden metabolischen Veränderungen langfristig zu einer Desensibilisierung des Belohnungssystems beitragen.

Insgesamt unterstreichen unsere Ergebnisse die entscheidende Rolle metabolischer Faktoren bei der Modulation neuronaler Reaktionen auf Nahrung. Ein vertieftes Verständnis dieser Mechanismen könnte gezielte therapeutische Ansätze ermöglichen, die darauf ausgerichtet sind, die Belohnungssensitivität zu stabilisieren und die Appetitregulation bei Menschen mit BED zu verbessern. Künftige Forschung sollte untersuchen, inwiefern metabolische Interventionen - sei es durch Ernährungsumstellung oder pharmakologische Ansätze - dazu beitragen können, neuronale Belohnungsprozesse zu normalisieren und dysreguliertes Essverhalten zu reduzieren.

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8 Declaration of Contributions to the Dissertation

This study was conducted in the Department of General Psychiatry and Psychotherapy, University of Tübingen, Translational Psychiatry, under the supervision of Dr. rer. nat. Nils B. Kroemer. The study was designed in collaboration with Prof. Nils B. Kroemer and Monja Neuser, who also served as the study coordinator.

Following training by Jacob Schwab and Monja Neuser, I independently collected the data in collaboration with Franziska Müller, Jacob Schwab, and Dana Wentz. I processed the data and conducted the statistical analysis of group and blood parameters. Prof. Nils B. Kroemer performed the initial statistical preprocessing of fMRI data and provided the resulting figures for my independent analysis.

I declare that I have written this manuscript independently under the supervision of Nils B. Kroemer and that all sources used are properly cited.

Tübingen, 30.05.2025

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Lilith Sophie Irtel von Brenndorff

9 Acknowledgements

First and foremost, I would like to express my gratitude to my supervisor, Prof. Nils B. Kroemer, for his support and feedback throughout my dissertation.

I would also like to extend my heartfelt thanks to the entire NeuroMADLAB team, especially Dana Wentz, Jacob Schwab, Monja P. Neuser, and Mechteld M. van den Hoek Ostende, for their collaboration, assistance with data acquisition, shared experiences and continuous support.

A special thank you goes to my family, who have always been there to listen and whose constant encouragement and emotional support have been invaluable throughout this journey. I would not be where I am today without them.

Thank you all for your support and inspiration!