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SPINNING OUT OF CONTROL

HOW STRESS AND NEGATIVE AFFECT LEAD TO BINGE BEHAVIOR IN BULIMIA NERVOSA AND ALCOHOL USE DISORDER

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Abbreviations

ACC	Anterior cingulate cortex	JITAI	Just-in-time adaptive intervention
AN	Anorexia nervosa	MIST	Montreal Imaging Stress Task
AUC	Area under the curve	ML	Machine learning
AUD	Alcohol use disorder	MRI	Magnetic resonance imaging
AUDIT	Alcohol Use Disorder Identification Test	MRS	Magnetic resonance spectroscopy
APA	American Psychiatric Association	MSEM	Multilevel structural equation model
BE	Binge eating	NA	Negative affect
BED	Binge eating disorder	NAc	Nucleus accumbens
BD	Binge drinking	NU	Negative urgency
BMI	Body Mass Index	NIAAA	National Institute on Alcohol Abuse and Alcoholism
BN	Bulimia nervosa	NIMH	National Institute for Mental Health
BOLD	Blood-oxygen-level-dependent	NPV	Negative predictive value
CBF	Cerebral blood flow	OFC	Orbitofrontal cortex
CI	Confidence interval	PA	Positive affect
CN	Caudate nucleus	PCC	Posterior cingulate cortex
CT	Cortical thickness	PET	Positron emission tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders	RDoC	Research Domain Criteria
DA	Dopamine	ROI	Region of interest
DD	Delay discounting	PPV	Positive predictive value
DDT	Delay discounting task	SCID-5-S	Structured Clinical Interview for DSM-5
dlPFC	Dorsolateral prefrontal cortex	SD	Standard deviation
DS	Dorsal striatum	SE	Standard error
ESM	Experience sampling method	SOOC	Spinning-Out-Of-Control
EDE-Q	Eating Disorder Examination Questionnaire	SRD	stress-response dampening model
FC	Functional connectivity	TRT	Tension reduction theory
fMRI	Functional magnetic resonance imaging	vmPFC	Ventromedial prefrontal cortex
GMV	Grey matter volume	VS	Ventral striatum
HC	Healthy controls	WHO	World Health Organization
ICD	International Classification of Diseases		

Abstract

Alcohol use disorder (AUD) and bulimia nervosa (BN) are two psychiatric disorders that are characterized by binge behavior where large quantities of alcohol (i.e., binge drinking [BD]) or food (i.e., binge eating [BE]) are consumed within a short period of time. Furthermore, both disorders are highly prevalent, impactful, and challenging to treat. Therefore, new and improved treatments are needed for both disorders, but in order to develop them, a better understanding of what triggers binge behavior is required.

It is thought that stress and negative affect (NA) are important triggers for BD and BE. Indeed, studies in a laboratory context have shown that inducing stress and NA can lead to increased alcohol and food consumption in patients with AUD or an eating disorder respectively. Furthermore, studies conducted in daily life report that NA increases in the hours before a BE episode and that NA is higher before a BE episode than before a regular meal. However, these findings raise the question how stress and NA cause patients to experience a higher desire to binge drink or binge eat, as well as lose control, making them more likely to display binge behavior. Previous authors have hypothesized that there are several important factors such as craving, negative urgency (i.e., the tendency to act rashly under elevated stress or NA), and disturbances in reward processing including delay discounting (i.e., preferring more immediate rewards). Therefore, this thesis explores the role of these factors in how stress and NA lead to binge behavior.

First, an experience sampling method (ESM) study was performed where 76 controls, 53 patients with AUD, 51 patients with BN, and 19 patients with AUD and BN reported on their mood, behavior, and context in daily life. When it comes to BE, we found that NA was related to subsequent BE in patients with BN through rash action and craving, highlighting the importance of negative urgency and craving in the relation between NA and BE. Contrastingly, we also observed that NA was associated with subsequent not eating, indicating that NA can have competing effects on eating behaviors in patients with BN. When it comes to alcohol use, we saw that NA was non-linearly related to craving, alcohol use, and BD in patients with AUD, emphasizing that both lower and higher levels of NA can lead to alcohol consumption in patients. However, these findings raise the question whether factors such as NA, rash action, and craving can actually predict binge behavior in daily life.

Therefore, we used machine learning to build person-specific and pooled prediction models for BE, alcohol use, and BD in patients with AUD and/or BN. We found that pooled models performed better at predicting BE, alcohol use, and BD, but that predictors from person-specific models might be more useful clinically. Importantly, craving and time of day were the most important predictors for all behaviors, while there were differences in how affect and social context were related to BE, alcohol use, and BD.

Second, the role of the neurobiological reward system in BE was explored by conducting a systematic review of previously published studies. We found that individuals who binge eat display a lower striatal dopamine release in rest, a change in the volume of the striatum, frontal cortex and insula as well as a lower fronto-striatal connectivity. Furthermore, there was a higher activity of the brain reward system when anticipating or receiving food, and individuals who binge eat relied more on previous experiences when making decisions and displayed more habitual behavior. These results show that individuals who binge eat display structural and functional changes in the neurobiological reward system, which could play a vital role in the onset and maintenance of BE episodes.

Third, an MRI study was performed with 50 controls, 27 patients with AUD, and 25 patients with BN. In this study, the effect of stress on alcohol and food delay discounting was investigated to see whether stress makes patients with AUD or BN prefer more immediately available alcohol or food respectively. We found that stress increased delay discounting of alcohol in patients with AUD, but not in controls, and that this was related to a lower activity of the right supplementary area. In contrast, we observed that stress increased delay discounting of food in controls, but not in patients with BN, and that this was related to a lower activity of the anterior cingulate cortex. These results suggest that acute stress could indeed make patients with AUD prefer more immediately available alcohol, while this relation might not be as straightforward in patients with BN.

Fourth, a PET/MR study was conducted in 12 controls investigating the relation between stress-induced dopamine release in the ventromedial prefrontal cortex (vmPFC), fronto-striatal functional connectivity and negative urgency in daily life. Here, stress decreased functional connectivity between the vmPFC and dorsal striatum, but increased connectivity with the contralateral ventral stiatum. However, individuals with a higher connectivity between the vmPFC and dorsal striatum showed more negative urgency in daily life. Furthermore, individuals with a higher stress-induced DA release had a higher change in fronto-striatal connectivity and displayed more daily life negative urgency. These results

highlight how stress can impact dopamine signaling and fronto-striatal connectivity and how this can lead to rash action.

Taken together, this thesis shows that there is a complex relation between stress and NA on the one hand and binge behavior on the other hand. Specifically, the results indicate that stress and NA might have competing effects on eating behaviors in patients with BN, while both lower and higher levels of stress and NA might be related to alcohol use in patients with AUD. Furthermore, the findings of this thesis highlight the importance of craving, negative urgency, reward processing, and delay discounting in this relation, and demonstrate the key role of dopamine transmission and fronto-striatal connectivity. Future studies should explore how stress and NA lead to binge behavior in more depth with more diverse samples, longitudinal designs, and by combining multiple modalities.

CHAPTER 1

General Introduction

This chapter provides an overview of the subject matter of this thesis. To begin, it discusses the definitions of alcohol use disorder (AUD) and bulimia nervosa (BN), and presents information on their occurrence, treatment options, and impact. Second, it describes the literature on how stress and negative affect (NA) play a role in AUD and BN, and on important contributing factors. Third, it explains the experimental techniques employed in this thesis.

1.1. Alcohol use disorder and bulimia nervosa

1.1.1. Definition

AUD is characterized as a problematic pattern of alcohol use that leads to significant impairments or distress (American Psychiatric Association [APA], 2013). This pattern can involve different types of alcohol consumption, one of them being binge drinking (BD), which is defined as drinking a significant amount of alcohol (i.e., at least 4 units for a woman, 5 units for a man) within 2 hours (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2022). BN involves a recurrent pattern of binge eating (BE) accompanied by compensatory behaviors and an excessive influence of body shape and weight on self-evaluation (APA, 2013). In turn, BE is characterized as eating an amount of food that is definitively larger than what most individuals would eat in a similar period of time, combined with a feeling of loss of control (APA, 2013). These general definitions of AUD and BN have been expanded upon by various organizations to create specific criteria for diagnosis, treatment, and research. These criteria can be found in the Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the APA and in the International Classification of Diseases (ICD) produced by the World Health Organization (WHO). However, the criteria for both disorders have undergone significant changes over time.

For problematic alcohol use, the DSM-1 only mentions ‘alcoholism’ which it defines as a dependence on alcohol and places under the category of ‘addictions’ (APA, 1952). This has subsequently been altered in the DSM-II, which recognizes that individuals can engage in problematic drinking without being dependent, adding episodic and habitual excessive drinking as types of ‘alcoholism’ (APA, 1968). However, grouping these types of problematic alcohol use under the umbrella term ‘alcoholism’ has increasingly been regarded as problematic and stigmatizing (Schuckit et al., 1991). As a result, the DSM-III and DSM-IV redefine problematic alcohol use as ‘alcohol abuse’ and ’alcohol dependence’ (APA,

1980, 1994). Here, alcohol abuse refers to a pattern of pathological alcohol consumption that causes impairments in functioning, while alcohol dependence also involves the presence of withdrawal and/or tolerance symptoms. However, the distinction between alcohol abuse and alcohol dependence came under scrutiny as more recent research shows that problematic alcohol use may be better understood as a continuum rather than two distinct categories (Saha et al., 2006). This has led to combination of the alcohol abuse and alcohol dependence diagnoses into a single AUD category in the DSM-5 (APA, 2013). The DSM-5 criteria for AUD can be found in Table 1.

Table 1. DSM-5 criteria for alcohol use disorder and bulimia nervosa

Alcohol Use Disorder

At least 2 of the following 11 symptoms need to be present in the past 12 months:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following: a need for markedly increased amounts of alcohol to achieve intoxication or desired effect, or a markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following: the characteristic withdrawal syndrome for alcohol, or alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid alcohol withdrawal symptoms.

Bulimia Nervosa

The following criteria need to be met in the past 3 months:

1. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
    a. Eating, in a discrete period of time (e.g., within a two-hour period), an amount of food that is definitely larger than what most people would eat during a similar period of time and under similar circumstances.
    b. Lack of control over eating during the episode (e.g., a feeling that you cannot stop eating, or control what or how much you are eating).
2. Recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise.
3. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for three months.
4. Self-evaluation is unduly influenced by body shape and weight.
5. Binging or purging does not occur exclusively during episodes of behavior that would be common in those with anorexia nervosa.

BN is first introduced in the DSM-III-R, although a definition of "bulimia" is already included in the DSM-III (APA, 1980). The DSM-III describes “bulimia” as a repeated pattern of BE accompanied by compensatory behaviors, but does not mention a lack of control during the BE episode or the impact of weight and body shape on self-evaluation (APA, 1980). These criteria have been added in the DSM-III-R, which also specifies that the BE episodes and compensatory behaviors needed to occur at least twice a week for a period of three months (APA, 1987). However, more recent research finds that individuals who have a BE episode at least once a week do not differ significantly from those who binge eat more frequently (Wilson, 1992; Wilson & Walsh, 1991). This has led to a change in the DSM-5, which only requires BE episodes and compensatory behaviors to occur once a week (APA, 2013). The DSM-5 criteria for BN can be found in Table 1.

Though the DSM classification system has faced criticism, it has provided a common language for professionals to communicate about and understand AUD and BN, thereby enabling the study of the prevalence, impact, and treatment of these disorders.

1.1.2. Prevalence and impact

Though estimates vary, studies find that the lifetime prevalence of AUD ranges between 8.6 and 29.1%, while the lifetime prevalence for BN is lower and lays between 0.3 to 4.6% (Galmiche et al., 2019; Grant et al., 2015; Nagl et al., 2016). However, AUD and BN are often comorbid, with the life-time prevalence of AUD among individuals who binge eat being 19.9% (Bogusz et al., 2021). Young adults may be particularly vulnerable for binge behavior, with 7.0% of Flemish students reporting weekly BD episodes and 7.3% reporting to experience a BE episode at least every two weeks (Damme et al., 2022; Serra et al., 2020). Indeed, AUD and BN typically begin in early adulthood as the mean age of onset for AUD ranges between 18 and 30.1 years, while the mean age of onset for BN lays between 18.2 and 19.3 years (Favaro et al., 2009; Grant et al., 2015; Slade et al., 2021; Volpe et al., 2016). Interestingly, the age of onset for both disorders is higher in men than in women (Carlat & Camargo, 1991; Goh et al., 2022). Additionally, the lifetime prevalence of AUD appears to be 1.5 times higher in men than in women, while the lifetime prevalence of BN seems to be 3 times higher in women than in men (Galmiche et al., 2019; Grant et al., 2015; Nagl et al., 2016).

Importantly, these disorders can have a significant impact on the individuals afflicted, their friends and family, and society as a whole. When it comes to AUD, it is estimated that 3 million people die each year from problematic alcohol use worldwide, which represents 5.3%

of all deaths in a given year (Glantz et al., 2020). This can be due to the direct effects of AUD, such as gastritis, pancreatitis, liver disease, and cancer, as well as indirect effects such as injuries and sexually transmitted infections (de Doncker Jasmien et al., 2015). In addition to its individual impacts, AUD can also affect family members, who may experience emotional distress, legal problems, economic hardship, and even violence (Lander et al., 2013). The societal cost of AUD is also significant, with estimates suggesting that it amounts to at least 125 billion euros per year in the EU and 249 billion dollars per year in the US (Anderson & Baumberg, 2009; Sacks et al., 2015).

When it comes to BN, studies have shown that patients have an increased mortality rate of 1.7 per 1000 person-years (Arcelus et al., 2011). Medical complications, primarily metabolic alkalosis and hypokalemia, are the most frequent cause (57.1%) of this increased mortality rate, while death by suicide is the second most frequent reason (22.9%), with substance use as a third cause (11.4%), and traumatic injury as a fourth reason (8.6%) (Crow et al., 2009). However, besides the increased mortality rate, BN is associated with a higher health service use and an increased societal cost, and importantly, patients with BN experience one of the lowest qualities of life among patients with psychiatric disorders, (Ágh et al., 2016; Striegel-Moore et al., 2004).

Taken together, AUD and BN have a high prevalence and significant impact, which highlights the need for effective treatments.

1.1.3. Treatment

Several psychological and pharmacological therapies have been developed for AUD and BN. For the treatment of AUD, evidence-based psychotherapies include brief interventions, operant conditioning approaches, cognitive behavioral treatments, and acceptance- and mindfulness-based approaches (Witkiewitz et al., 2019; Witkiewitz & Alan Marlatt, 2011). Treatments often focus on motivational interviewing, increasing awareness of high-risk situations, coping skills training, and relapse prevention (Witkiewitz et al., 2019). Pharmacotherapies approved by the European Medicines Agency or Food and Drug Administration include acamprosate, disulfiram and naltrexone (Kranzler & Soyka, 2018). Acamprosate has been shown to sustain abstinence from alcohol and may work by acting as a partial co-agonist on the N-methyl-D-aspartic acid (NMDA) receptor, which is thought to reduce the impact of alcohol-related cues (Rösner et al., 2010). Disulfiram is an aldehyde dehydrogenase inhibitor that metabolizes the toxic metabolites of alcohol (Kranzler & Soyka, 2018). When combined with alcohol, disulfiram causes unpleasant symptoms such as nausea,

vomiting, and sweating, which is thought to extinguish alcohol use. Naltrexone is an opioid receptor antagonist that is believed to reduce the rewarding effects of alcohol and therefore decrease alcohol consumption (Kranzler & Soyka, 2018).

For the treatment of BN, cognitive behavioral therapy is the first-line approach, targeting the regulation of eating patterns and self-weighing behavior before addressing shape and weight concerns (Hagan & Walsh, 2021). If cognitive behavioral therapy is not effective, interpersonal therapy may be used as a second-line treatment (Hagan & Walsh, 2021). This approach proposes that interpersonal problems contribute to negative emotions and therefore BE, and focuses on addressing these issues to indirectly treat BN. In addition to these psychological treatments, high-dose fluoxetine can be prescribed, which is a selective serotonin reuptake inhibitor (Hagan & Walsh, 2021). While the exact mechanism of action of fluoxetine in the treatment of BN is not fully understood, it is thought to work by regulating appetite and reducing rash action (Hagan & Walsh, 2021).

Despite the availability of psychological and pharmacological therapies, the similar treatment outcomes for AUD and BN remain poor. Of all individuals who meet the criteria for AUD and BN in a given year, only 17.3% and 15.6% will receive treatment (Hudson et al., 2007; Mekonen et al., 2021). Among those who do receive treatment, up to 60% will not achieve remission (Fleury et al., 2016; Linardon & Wade, 2018). Therefore, new and improved therapies are needed to improve treatment outcomes, but to develop these therapies, it is important to better understand the triggers of BE and BD. To do so, previous studies have typically focused on either BE or BD. However, as mentioned before, these behaviors share a number of a number of similarities such as an early onset, high impact, and responsiveness to cognitive behavioral therapy, but also several contrasts when it comes biological targets for pharmacotherapy as well as differences between men and women. Therefore, it would be interesting to study BE and BD together and compare their triggers, as this could result in a more nuanced understanding of each behavior.

1.2. Stress and negative affect

It is thought that stress and NA are important factors in the onset and maintenance of both AUD and BN. The following paragraphs explain how stress and NA are conceptualized and why they are hypothesized to play a key role in these disorders.

1.2.1. Definition

Stress is a complex phenomenon that can be broadly defined as the body's non-specific response to a demand (Selye, 1956). More specifically, stress is the physiological and psychological response to a perceived internal or external threat, known as a stressor, which challenges an individual's steady state (Fink, 2010). Some authors separate this response into eustress (i.e., a positive response) and distress (i.e., a negative response), though this distinction has come under scrutiny (Bienertova-Vasku et al., 2020).

NA, on the other hand, subsumes several negative emotions such as sadness, anxiety, anger, loneliness, or guilt (Watson et al., 1988). Importantly, higher levels of NA can be a part of the psychological response to a stressor, although the presence of a stressor is not required for an individual to experience more NA (Lazarus & Folkman, 1984).

The distinction between stress and NA is not always clearly drawn in the literature and the terms are often used interchangeably. For example, feelings of 'distress, defined as emotional arousal and nervous tension, are typically included in assessments of NA (Watson et al., 1988). However, in this introduction, the term 'stress' will be used to refer to a stress response and 'NA' will be used to refer to negative emotions.

1.2.2. Stress, negative affect and alcohol use disorder

The importance of NA in the development and maintenance of AUD has been recognized for centuries, but was first formulated as a theory by Conger (Conger, 1956). According to his tension-reduction theory (TRT), individuals with 'alcoholism' drink alcohol as a means of reducing tension, which reinforces their drinking behavior and increases the likelihood of alcohol use when tension is high in the future. This theory was based on the drive-reduction theory of learning, which proposes that the buildup of a drive (e.g., tension) motivates individuals to engage in behaviors that reduce this drive (Hull, 1943). In the following decades, researchers attempted to test the TRT in animals and in humans, but found mixed results (Cappell & Herman, 1972). These inconsistent findings were thought to be the result of the overly broad concept of 'tension' as well as the use of invalid experimental paradigms (Levenson et al., 1980). This led to the formulation of the stress-response dampening model (SRD) by Levenson, Sher and colleagues, which proposes that alcohol specifically dampens the anticipation and receipt of stress, and emphasizes the use of valid stressors (Levenson et al., 1980). Indeed, studies find that administering alcohol can dampen stress at moderate doses (Mello, 1968; Tamerin & Mendelson, 1969). However, they also report that alcohol can increase excitation at low doses and increase anxiety at high doses (Mello, 1968; Tamerin

& Mendelson, 1969). Furthermore, significant inter-individual variability is seen in the response to alcohol, with a stress-dampening effect being particularly apparent in patients with AUD, individuals with a family history of AUD, and women (Conrod et al., 1995; Peltier et al., 2019; Stewart et al., 1992). Importantly, these findings raise the question whether stress then actually drives individuals to consume alcohol. A large number of studies have therefore explored this question in a laboratory setting, with a meta-analysis finding that experimentally inducing stress can indeed increase alcohol consumption across patients and controls, although there is a high variability between individuals (Bresin et al., 2018).

Though these findings indicate that people could drink alcohol to cope with stress and NA, it has also been suggested that people drink alcohol to regulate their positive affect (PA), which is the extent to which somebody experiences positive emotions such as feeling alert, excited, and satisfied (M. L. Cooper et al., 1995; Wills & Shiffman, 1986). On the one hand, it is thought that lower levels of PA (e.g., feeling bored) cause individuals to drink alcohol to enhance their PA (M. L. Cooper et al., 1995; Wills & Shiffman, 1986). On the other hand, it has been hypothesized that higher levels of PA lead to alcohol use by making individuals more attentive to rewards and more likely to approach them (Tamir & Robinson, 2007; Young & Nusslock, 2016). Indeed, studies report that experimentally inducing PA can increase the expectancy that alcohol is rewarding and lead to higher levels of craving for alcohol (Birch et al., 2004).

Importantly, the previously mentioned studies have all been performed in a laboratory setting, which raises the question whether stress, NA and PA are actually associated with alcohol consumption in daily life. This is due to the 'laboratory-field' problem, whereby findings from a laboratory context do not always translate to daily life (Turner et al., 1990). For example, studies report that changes in heart rate and blood pressure due to a laboratory stressor do not always correspond to changes due to a daily life stressor (Turner et al., 1990). Therefore, an increasing number of studies have investigated the relation between affect and alcohol use with ambulatory assessments. Interestingly, a recent meta-analysis on these studies finds that alcohol use is indeed predicted by higher levels of PA in daily life, but not by changes in NA (Dora et al., 2022). One reason why most studies in daily life have failed to find a relation between NA and alcohol use could be that they have typically been performed in non-problematic drinkers. Therefore, there is a need for daily life studies exploring the relation between affect and alcohol consumption in patients with AUD.

1.2.3. Stress, negative affect and bulimia nervosa

BN was first described by Gerald Russel in 1979, who noted that patients with BN often have 'depressive symptoms' and a 'marked irritability' (Russell, 1979). However, he did not consider these symptoms to be the most important trigger of BE, but rather thought that dietary restriction is the key driver behind BE (Russell, 1979). In the following years, several researchers expressed similar ideas and mentioned that 'the accompanying dysphoric mood states of bulimia nervosa are likely to be a secondary manifestation' (P. J. Cooper & Fairburn, 1986; Johnson-Sabine et al., 1984). Contrastingly, at the same time, studies also found that patients with BN experience higher levels of NA before a BE episode in daily life (Davis et al., 1988; Johnson & Larson, 1982). Additionally, studies showed that experimentally inducing stress caused restrained eaters to overeat (Herman & Polivy, 1975). Therefore, these findings gave rise to several theories positing that NA can indeed lead to BE in patients with BN, though different theories assume different mechanisms. The escape theory hypothesizes that BE provides an escape from NA by shifting the patient's focus on simpler actions and sensations (Heatherton & Baumeister, 1991). In the emotion regulation theory, BE is not thought to provide an escape from NA, but rather reduce it (Lacey et al., 1986). However, the trade-off theory posits that BE doesn't alleviate NA, but rather exchanges more aversive emotions (e.g., anger) for less aversive and therefore more tolerable emotions (e.g., guilt) (Kenardy et al., 1996).

In the following years, several studies have investigated the effect of inducing stress on food intake in a laboratory setting (Cardi et al., 2015; Westwater et al., 2021). A meta-analysis of these studies finds that experimentally inducing stress can indeed lead to overeating in patients with binge-eating disorder and healthy volunteers, though the only study in patients with BN does not report a significant effect (Cardi et al., 2015; Westwater et al., 2021). Additionally, a number of studies have explored the relation between NA and BE in daily life and show that NA is higher before a BE episode than before a regular eating episode and that NA increases in the hours before a patient binge eats (Haedt-Matt & Keel, 2011; Mikhail, 2021). Therefore, these findings provide evidence that stress and NA can indeed lead to BE in patients with BN, but they do not explain how.

Importantly, these results raise the question whether PA also plays a role in BN. In contrast to AUD, it is typically thought that higher levels of PA decrease the risk for a BE episode (Burton et al., 2007; Pearson et al., 2015). Indeed, studies find that PA decreases in the hours before a patient binge eats and increases afterwards (Smyth et al., 2007; Schaefer et al., 2020). Contrastingly, studies also report that inducing PA causes overeating across

patients with an eating disorder and controls, and that patients with BN who act rashly when PA is high tend to overeat during an ad libitum meal (Cardi et al., 2015; Davis et al., 2023). Therefore, it could be that the relation between PA and BE is more complex than previously thought, where in some cases, it could increase the probability that a patient with BN binge eats.

1.3. Variables of interest

A large number of variables are thought to influence how stress and NA are related to AUD or BN. However, four variables are of interest to this thesis: craving, negative urgency (NU), reward processing, and delay discounting (DD).

1.3.1. Craving

Craving is typically defined as 'an intense and conscious desire for a specific substance', with some authors adding 'while attempting to abstain' to this definition (van Lier et al., 2018). Researchers started to develop an interest in craving around the same time that the TRT for alcohol use was formulated. Initially, most researchers thought of craving as a physical phenomenon that resulted from withdrawal (Jellinek, 1955; Rankin et al., 1979). However, subsequent studies showed that craving is heavily influenced by social and psychological triggers, implying that it is also psychological in nature (Rankin et al., 1979). Stress and NA are important triggers, as studies find that inducing stress or NA in a laboratory context can increase craving for alcohol or a BE episode, especially when the stressor includes negative self-evaluation (Bresin et al., 2018; Gluck et al., 2004; Rosenberg et al., 2013). Additionally, experiencing more craving in response to NA also predicts relapse in patients with AUD (Cooney et al., 1997; Higley et al., 2011). However, as these studies were mostly performed in a laboratory context, they raise the question whether their findings are also valid in daily life. Indeed, studies on the relation between NA and craving for alcohol in daily life again report mixed results (Serre et al., 2018; Waddell et al., 2021). Furthermore, no studies have explored whether NA also predicts craving for a BE episode in patients with BN in daily life. Therefore, it remains unclear whether NA leads to increases in craving in patients with AUD and BN in daily life and whether this then leads to binge behavior.

1.3.2. Negative urgency

NU is a personality trait which stands for the tendency to act rashly when experiencing high levels of NA (Cyders & Smith, 2008). It is one of several traits that contribute to 'impulsive' behavior, which can be defined as 'actions that are poorly planned, prematurely expressed, unduly risky, or inappropriate to the situation, and often result in undesirable consequences' (Evenden, 1999; Sharma et al., 2014). Initially, 'impulsivity' was considered to be a unidimensional construct and measured using scales such as the Guilford-Zimmerman Temperament Survey's Restraint versus Impulsiveness scale (Guilford & Zimmerman, 1949; Sharma et al., 2014). Researchers later recognized that a unidimensional construct of impulsivity could not adequately explain the diversity of results obtained from the different measurement scales and therefore began to adopt a multidimensional approach (Sharma et al., 2014). The Barratt Impulsiveness Scale is an example of this approach as it separates 'impulsivity' into three factors: non-planning impulsiveness, attentional impulsiveness, and motor impulsiveness (Patton et al., 1995). However, many very different 'impulsivity' measures were created over the years which caused Whiteside and Lynam (2001) and Cyders et al. (2007) to develop the UPPS-P Impulsive Behavior Scale to consolidate them. This scale resulted in five personality traits: NU, positive urgency (i.e., acting rashly when experiencing high levels of PA), sensation seeking, lack of planning, and lack of perseverance (Whiteside & Lynam, 2001). However, these traits were poorly correlated with one another, prompting the authors to suggest that they are distinct from each other (Whiteside & Lynam, 2001). This view received support by later psychometric, neurobiological, and clinical evidence (Strickland & Johnson, 2021).

Importantly, the acquired preparedness model posits that individuals high in NU have different learning experiences that predispose them to acquire certain maladaptive behaviors (Combs et al., 2010). Namely, the general tendency to act rashly when experiencing NA could make them more likely to binge eat or binge drink when experiencing NA, which could cause them to acquire the expectancy that BE and BD alleviates NA. Indeed, studies show that NU is the impulsivity-like personality trait that is the most associated with BE and problematic alcohol use and that higher levels of NU predict the onset of BE (Fischer et al., 2013; Fischer & Smith, 2008). However, these studies raise several questions. First, as they examine NU at the trait level with retrospective questionnaires, they do not address whether high levels of NA lead to rash action in daily life and whether this, in turn, leads to BE, alcohol use, or BD. Second, they do not shed light on the neurobiological changes that may cause individuals to display impulsive behavior when experiencing high levels of NA.

Several authors suggest that NU may be the result of an insufficient control of the ventromedial prefrontal cortex (vmPFC) over the striatum, mediated by disturbances in dopamine release (Basar et al., 2010; B. S. Kim & Im, 2019; S. Kim & Lee, 2011; Ott & Nieder, 2019). However, no studies have yet examined whether stress-induced dopamine release changes the connectivity between the vmPFC and striatum and whether this is related to NU in daily life.

1.3.3. Reward processing

Reward processing is an umbrella term for the psychological processes that allow individuals to experience pleasure from rewards, learn the relationships between stimuli and consequences, and feel motivated to obtain rewards (Berridge & Robinson, 2003). Several theories posit that disturbances in reward processing play a key role in AUD and BN (Pearson et al., 2015; Robinson & Berridge, 1993). As mentioned previously, the acquired preparedness model hypothesizes that patients display high-risk personality traits that influence reward learning and predispose them to acquire maladaptive expectancies about food and alcohol (Combs et al., 2010). Furthermore, it is though that repeated alcohol use and BE sensitize the reward system, leading to an excessive incentive salience (i.e., motivational value) for food and alcohol and causing patients to experience craving (Robinson & Berridge, 1993). Because of the supposed importance of reward processing in AUD and BN, there has been an increasing number of studies on the neurobiological reward system in these disorders. However, these studies often report contrary and difficult to interpret results, which could be due to a lack of uniformity and specificity in the definition of reward processing in these studies (Zald & Treadway, 2017). This could be improved by using the Research Domain Criteria (RDoC), which were developed by the National Institute for Mental Health (NIMH) to have more uniform definitions in neuroscience (Insel et al., 2010). However, no studies have reviewed the literature on the neurobiological reward system in BE or BD with the RDoC as a framework.

1.3.4. Delay discounting

DD is the process by which rewards decrease in value the more delayed they are, making individuals prefer short-term rewards over long-term ones (Odum, 2011). DD is a construct rooted in behavioral economics where it has been used to understand economic decision-making in individuals but has later on been applied to study psychiatric disorders (Bickel et al., 2014; Chung & Herrnstein, 1967). From a behavioral standpoint, DD is thought to have

both a reward processing and an impulsive-like component. On the one hand, it is subsumed under the positive valence systems of the RDoC as a moderator of reward valuation (Insel et al., 2010). On the other hand, it is regarded as one of four behavioral measures of impulsivity, along with response inhibition, attention, and risk sensitivity (Strickland & Johnson, 2021). From a neurobiological standpoint, DD is the result of a complex interaction between several brain areas (Frost & McNaughton, 2017). It is thought that the comparison between the values of the immediate and delayed rewards is performed by a dual system, which consists of a beta (β) system that is focused on the immediate reward and a delta (δ) system considers both immediate and delayed rewards (Frost & McNaughton, 2017; Schüller et al., 2019).

Researchers have studied DD in patients with AUD or BN, to understand why the short-term benefits of coping with stress through alcohol or BE might outweigh the long-term benefits of remission (Amlung et al., 2019). Meta-analyses of studies on monetary DD indicate that patients with AUD or BN indeed show a preference for more immediately available monetary rewards (Amlung et al., 2019; MacKillop et al., 2011). However, it is unknown whether patients also prefer more immediately available alcohol and food, whether this preference is impacted by stress, and which neurobiological changes are associated with these differences in DD.

1.4. Experimental techniques

This thesis uses several experimental techniques to achieve its aims. They are briefly explained in the following paragraphs.

1.4.1. Experience sampling method

The experience sampling method (ESM), also known as ecological momentary assessment, is a collection of techniques that involve participants reporting on their mood, behavior, and context in daily life (Shiffman et al., 2008). One advantage of ESM is that data are collected in the moment, which can reduce recall bias (Bradburn et al., 1987; van den Brink et al., 2001). Additionally, data are collected in real-life settings, potentially resulting in a lower error variance and greater power (Mckenzie et al., 2004). ESM data are also collected repeatedly, allowing for the investigation of temporal sequences of events (Shiffman et al., 2008). While early ESM studies used written diaries, most recent studies use mobile phones, which can provide a large amount of data. These data can then be analyzed in a variety of

ways (Walls & Schafer, 2012). Namely, they can be used to investigate the temporal relations between individual variables, such as whether higher levels of NA at a previous assessment are related to higher levels of craving the current assessment. Additionally, machine learning techniques are increasingly being applied to ESM data, which can learn associations between a multitude of variables without any explicit instruction. However, ESM studies also have their limitations, including a potential reduced compliance and increased dropout due to the repeated assessment of participants, leading to missing data that can be challenging to handle (Shiffman et al., 2008).

1.4.2. Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a technique that uses the magnetic properties of the hydrogen nucleus to create detailed images of the body (Grover et al., 2015). Namely, these nuclei possess a 'spin', a property whereby they revolve around their own axis. In MRI, the hydrogen nuclei are subjected to a strong magnetic field, causing them to align with the external field. A second magnetic field is then applied perpendicular to the original field, disrupting the alignment of the hydrogen nuclei. This process is repeated in short pulses, and as the nuclei return to their original alignment, they emit radiofrequency energy that is measured and used to create an image (e.g., of the brain). MRI allows for high-resolution imaging without the use of radiation. It can be used to visualize the structure of the brain, but also to study brain function through functional MRI (fMRI) (Matthews, 2004). Specifically, fMRI measures the blood-oxygen-level-dependent (BOLD) signal, which is based on the difference in magnetic properties between deoxyhemoglobin and oxyhemoglobin. Deoxyhemoglobin is paramagnetic and distorts the magnetic field in its vicinity, while oxyhemoglobin is isomagnetic and causes little or no disruption of the magnetic field. When neural activity in a particular brain area increases, there is a corresponding rise in energy demand, which leads to an increase in local blood flow. This higher blood flow exceeds the actual energy demand, resulting in an increase in the relative amount of oxyhemoglobin to deoxyhemoglobin and a change in the BOLD signal. By measuring these changes in BOLD signal, fMRI can therefore provide insights into brain function. However, it is important to note that the variance in the BOLD signal is most often explained by changes in local field potentials (i.e., the post- and presynaptic activity of multiple neurons) and not by the spike rate of neurons (Grover et al., 2015; Logothetis, 2003).

1.4.3. Positron emission tomography

Positron emission tomography (PET) is a technique that allows researchers to investigate neurochemical processes in the body (Hooker & Carson, 2019). It involves the use of a radiotracer, which is a molecule that is labeled with a radioactive isotope and binds to a specific biological target. After being administered intravenously, this tracer spreads throughout the body. The short-lived radioactive isotope then decays and produces positrons, which collide with electrons and are annihilated, resulting in the production of two gamma rays emitted at an angle of 180 degrees. These gamma rays are detected by a ring of coincidence detectors, and this information is used to reconstruct a 3D image showing the distribution of radioactivity in the body. The type of neurochemical process that can be quantified depends on the nature of the radiotracer. In this thesis, the radiotracer [18F]Fallypride is used to visualize dopaminergic activity (Mukherjee et al., 1995). This radiotracer has a high affinity for the D2/D3 receptor and can be used to investigate dopaminergic activity in areas with a low number of receptors, such as outside of the striatum. It can also be used in dynamic PET imaging to characterize endogenous neurotransmitter release in response to pharmacological, behavioral, or cognitive interventions.

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CHAPTER 2

Objectives

Stress and NA are thought to play a key role in the onset and maintenance of AUD and BN and are a target for treatment in these disorders. However, there are clear gaps in the literature which limit our understanding of AUD and BN and hinder the development of new therapies. Therefore, the general aim of this thesis is to deepen our knowledge on how stress and NA lead to binge behavior in patients with AUD or BN, and to identify which neural mechanisms are implicated in this process. To achieve this aim, the following objectives have been set:

Objective 1: To investigate how NA leads to binge behavior in the daily lives of patients with AUD or BN.

Previous research indicates that NA is an important trigger of BE in the daily lives of patients with BN. It has been hypothesized that craving and negative urgency could play an important role in this relation, but this has not yet been investigated. Therefore, Chapter 3 explores the connections between NA, craving, rash action, and BE in daily life and whether craving and rash action mediate the relation between NA and BE. Furthermore, though studies show that NA is related to alcohol use in a laboratory setting, studies often fail to find a relation between NA and alcohol use in daily life. However, this could be due to studies not including a sample of problematic drinkers. Therefore, Chapter 4 investigates how NA and PA lead to subsequent craving, non-heavy alcohol use and BD in patients with AUD and controls.

Objective 2: To predict BE, alcohol use, and BD in the daily lives of patients with AUD or BN.

Traditionally, studies in daily life only investigate the relation between individual variables. More recently, researchers have been applying machine learning techniques where the information of a multitude of variables is used to predict behaviors in daily life. In line with these studies, Chapter 5 uses an elastic net regularized regression with nested cross-validation to predict BE, alcohol use, and BD in the daily lives of patients with AUD and BN. Doing so, it evaluates the predictive value of a large number of variables scoring mood, behavior, and contextual factors.

Objective 3: To review the literature on the role of the neurobiological in BE.

Disturbances in reward processing are thought to play a key role in the onset and maintenance of BE. Because of this, a large number of studies have investigated the neurobiological reward system in individuals who binge eat. Chapter 6 reviews these studies

using the RDoC frame work to identify structural and functional changes in the brain reward system and to formulate directions for future research.

Objective 4: To investigate how stress impacts food and alcohol DD in patients with AUD or BN.

Stress could increase DD in patients with AUD or BN, making the short-term benefits of coping through eating or drinking outweigh long-term negative consequences. However, there is a lack of studies investigating the DD of food and alcohol in patients, the impact of stress, and the associated changes in brain activity. Therefore, Chapter 7 compares different types of DD between patients with BN or AUD and controls, the impact of stress of food and alcohol DD, and the associated changes in brain activity.

Objective 5: To investigate the relation between stress-induced DA release, fronto-striatal connectivity, and negative urgency.

NU could be the result of an insufficient control of the vmPFC over the striatum and could be mediated by disturbances in DA transmission. However, studies have typically only investigated the effect of stress on DA release, or the effect of stress on fronto-striatal connectivity, but not how these two are related and whether they are also related to NU in daily life. Therefore, Chapter 8 investigates the relation between stress-induced DA release in the vmPFC, fronto-striatal connectivity and NU in daily life.

CHAPTER 3

Thesis Dataset

The data for this thesis come from the Spinning-Out-Of-Control (SOOC) study, which included patients with AUD and/or BN as well as controls. The study included an ESM, MRI and PET/MR component. An overview of the study can be seen in Figure 1, and the specific data used in each chapter is listed in Table 1.

3.1. Study population

A total of 199 participants (controls: 76, AUD:53, BN: 51, AUD and BN: 19) were included in the SOOC study. Participant inclusion ran from September 2019 to February 2022. The inclusion criteria were the following: (1) female; (2) understand Dutch; (3) age ≥ 18 years; (4) BMI ≥ 18.5 kg/m2. Additional inclusion criteria for patients were: (5) meet the criteria for AUD and/or BN of the DSM-5 (APA, 2013); (6) illness duration ≤ 5 years. This maximum illness duration was set as the role certain factors is thought to change over the course of AUD and BN (Boness et al., 2021; Pearson et al., 2015). Participants with AUD also needed to display a pattern of repetitive BD according to the criteria of the NIAAA (i.e., drinking 4 units of alcohol within 2 hours for women). Participants were excluded for the following reasons: (1) major medical pathology; (2) chronic use of sedatives; (3) pregnancy; (4) presence of psychiatric pathology for controls or major psychiatric pathology (i.e., schizophrenia, autism spectrum disorder, bipolar disorder, substance use disorder other than alcohol use disorder) for patients with AUD and/or BN.

3.2. Study procedure

Participants were initially screened via telephone or mail after which they attended an in-person assessment where a resident of psychiatry confirmed their eligibility to participate. Additionally, the participants had their weight and height measured with a calibrated scale and stadiometer and completed clinical interviews and questionnaires.

3.2.1 Experience sampling method study

All 199 participants (controls: 76, AUD:53, BN: 51, AUD and BN: 19) started with ESM on the first Thursday after the in-person assessment. The ESM study had a repeated measurement design where 7 bursts of data collection were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks.

During the bursts, data were only collected on Thursday, Friday, and Saturday to limit the protocol's impact on the participants. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis.

3.2.2. Magnetic resonance imaging study

A subset of 102 participants (controls: 50, AUD: 27, BN: 25) performed an MRI scan, which was planned in the first weeks after the in-person assessment. Additional exclusion criteria for the MRI scan were: (1) left-handed; (2) contraindication for magnetic resonance imaging (MRI); (3) known cerebral structural abnormalities; (4) use of psychoactive medication other than SSRI's. The scan itself was divided into four main parts. First, all participants performed a monetary DD task. Second, the participants performed a disorder-specific (e.g., food or alcohol) DD task. This meant that patients with BN completed a DD task with food while patients with AUD completed one with alcohol. The controls were randomly allocated to either the food or alcohol DD task as a comparison for the patients with BN and AUD respectively. Third, stress was induced with the Montreal Imaging Stress Task (MIST) (Dedovic et al., 2005). Fourth, the participants repeated the food or alcohol DD task post-MIST.

3.2.2. Positron emission tomography/Magnetic resonance imaging study

A subset of 12 controls performed a [^{18}F]fallypride PET/MR scan, which was planned in the first weeks after the in-person assessment. In addition to the exclusion criteria of the previously described MRI study, the participants also couldn't have been exposed to ionizing radiation (>1mS) in the past 12 months. The scan consisted of four 45-minute-long segments which were separated by 15-minute-long breaks during which the participants could leave the scanner. This resulted in a total scan time of 225 minutes. The first two segments represented a 'rest' condition during which the participants did not perform any task. The third segment was a 'control' condition where the participants performed the control version of the MIST. The fourth segment represented a 'stress' condition during which the participants performed the stress version of the MIST. PET data was acquired during all four scan segments, while fMRI data was collected during the control and stress versions of the MIST.

Figure 1. Study procedure

A total of 199 participants (controls: 76, AUD: 53, BN: 51, AUD and BN: 19) were included in the study. All participants enrolled in an ESM study where they received seven three-week-long bursts over the course of 12 months. A subsample of 102 participants (controls: 50, AUD: 27, BN: 25) took part in an MRI study investigating the effect of stress on food and alcohol delay discounting. A subset of 12 controls participated in a PET/MR study exploring the effect of stress on dopamine release and brain activity. Abbreviations: AUD, alcohol use disorder; BN, bulimia nervosa; DDT, delay discounting task; ESM, experience sampling method; HC, healthy controls; MRI, magnetic resonance imaging; PET, positron emission tomography; SOOC, spinning out of control.

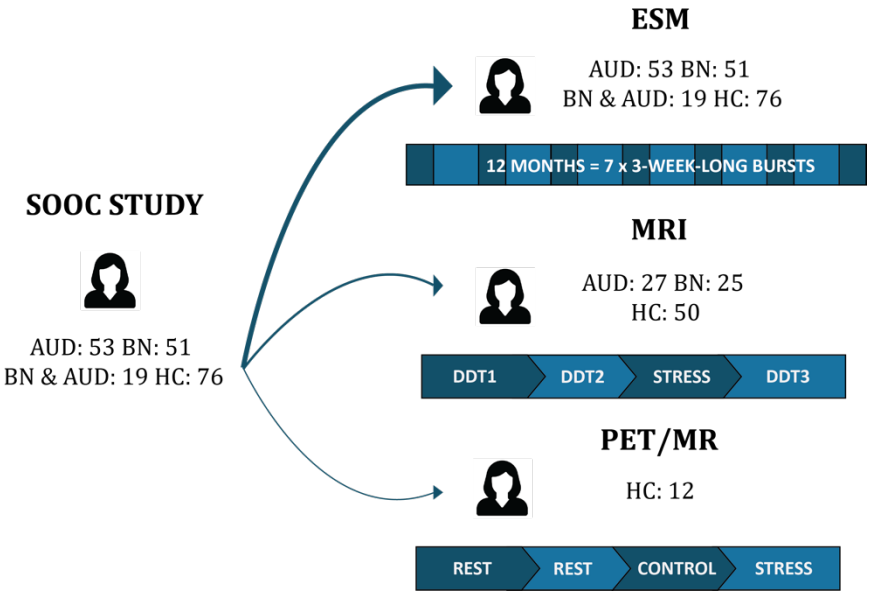

Table 1. Sample characteristics of the studies included in this thesis

Chapter	Study	Sample
4	How negative affect does and does not lead to binge eating - the importance of craving and negative urgency in bulimia nervosa	BN: 70 Controls: 76
5	The impact of negative and positive affect on craving, non-heavy alcohol use, and binge drinking in patients with alcohol use disorder and controls: An experience sampling method study.	AUD: 53 Controls: 75
6	Person-specific and Pooled Prediction Models for Binge eating, Alcohol Use and Binge Drinking in Bulimia Nervosa and Alcohol Use Disorder: An Experience Sampling Method Study.	AUD: 51 AUD/BN: 19 BN: 50
7	The neurobiological reward system and binge eating: A critical systematic review of neuroimaging studies	58 previously published studies
8	The effect of stress on delay discounting in bulimia nervosa and alcohol use disorder: a functional magnetic resonance imaging study.	AUD: 27 BN: 25 Controls: 50
9	The relation between stress-induced dopamine release in the ventromedial prefrontal cortex, fronto-striatal functional connectivity, and negative urgency: A multimodal investigation using [18F]Fallypride PET, MRI and experience sampling.	Controls: 12

Abbreviations: AUD, alcohol use disorder; BN: bulimia nervosa

3.3 References

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Dedovic, K., Renwick, R., Khalili Mahani, N., Engert, V., Lupien, S. J., Pruessner, J. C., Mahani, K., & -Douglas, P. (2005). The Montreal Imaging Stress Task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. *J Psychiatry Neurosci*, *30*(5).

Pearson, C. M., Wonderlich, S. A., & Smith, G. T. (2015). A risk and maintenance model for bulimia nervosa: From impulsive action to compulsive behavior. *Psychological Review*, *122*(3), 516–535. https://doi.org/10.1037/A0039268

CHAPTER 4

How negative affect does and does not lead to binge eating - the importance of craving and negative urgency in bulimia nervosa

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Abstract

Background: Studies suggest that negative affect (NA) can trigger binge eating (BE) in patients with bulimia nervosa (BN). Important factors in this relation between NA and BE could be craving (an intense desire for a BE episode) and negative urgency (the tendency to act rashly when NA is high). Therefore, this study wants to firstly explore the relations between NA, craving, rash action, and BE in daily life and secondly whether craving and rash action mediate the relation between NA and BE.

Methods: A sample of 70 female patients with BN and 76 female healthy controls (HC) took part in an experience sampling study where they reported on momentary NA, craving, rash action, and eating behaviors in daily life in a burst-measurement design over a period of 12 months. Assessments occurred eight times a day on Thursdays, Fridays, and Saturdays in seven bursts of three weeks, all separated by 5-week periods of no assessment.

Results: First, NA predicted subsequent rash action in the whole sample but this was more pronounced in patients with BN. Second, NA predicted subsequent craving in patients with BN, but not in HC. Third, rash action and craving predicted subsequent BE in patients with BN. Fourth, NA had competing effects on eating in patients with BN, predicting subsequent BE through rash action and craving, but also predicting subsequent not eating.

Conclusions: These results suggest that NA can lead to BE in daily life through rash action and craving, but that NA can also lead to dietary restriction.

4.1. Introduction

Bulimia nervosa (BN) is a psychiatric disorder that is characterized by recurrent binge eating (BE) episodes, compensatory behaviors, and an excessive influence of body shape and weight on self-evaluation (American Psychiatric Association [APA], 2013). BE is defined as eating an amount of food that is definitively larger than what most people would eat under similar circumstances, combined with a feeling of loss of control (APA, 2013). Despite the availability of treatments for BN, such as cognitive behavioral therapy and interpersonal therapy, up to 60% of patients may not be able to stop BE after undergoing therapy (Hagan & Walsh, 2021; Linardon & Wade, 2018). More effective therapies are therefore needed, but a better understanding of the causes of BE is required in order to develop them.

Most recent theoretical models hypothesize that BE can be triggered by negative affect (NA), which is often defined as a feeling of 'subjective distress and unpleasurable engagement' and subsumes several negative emotions such as sadness, anxiety, anger, loneliness, or guilt (Burton & Abbott, 2017; Watson et al., 1988). These models assume that patients binge eat to cope with NA, though different models propose different mechanisms. The escape theory suggests that BE provides an escape from NA by shifting the patient's focus on simpler actions and sensations (Heatherton & Baumeister, 1991). In the emotion regulation theory, BE is not thought to provide an escape from NA, but rather reduce it (Lacey et al., 1986). However, the trade-off theory posits that BE doesn't alleviate NA, but rather exchanges more aversive emotions (e.g., anger) for less aversive and therefore more tolerable emotions (e.g., guilt) (Kenardy et al., 1996).

Some studies have investigated this hypothesis in a laboratory setting and report that inducing NA can indeed cause patients to have a BE episode (Agras & Telch, 1998; Cardi et al., 2015). However, the controlled nature of these studies raises the question whether these results also apply to daily life. To explore this question, other studies have used the experience sampling method (ESM), also known as ecological momentary assessment, where a participant's emotions, behavior, and context are repeatedly assessed in daily life (Shiffman et al., 2008). These studies do find that NA is higher before a BE episode than before a regular eating episode and that NA increases in the hours before a patient has a BE episode (Haedt-Matt & Keel, 2011; Mikhail, 2021). These studies also show that stressors involving interpersonal relations or negative self-evaluation are an important cause of the NA experienced before a BE episode and that some negative emotions (e.g., anger and guilt) are

more closely linked to BE than others (Berg et al., 2013; Goldschmidt et al., 2014; Reichenberger et al., 2021). However, through which mechanisms NA then leads to BE is less clear.

Two factors that could be important in this relation are craving and negative urgency. First, craving is often defined as 'an intense and conscious desire for a specific substance', with some authors adding 'while attempting to abstain' to the definition (van Lier et al., 2018). This conceptualizes craving as a construct with both a motivational component (i.e., the desire for a substance) and an inhibitory component (i.e., the attempt to abstain) (van Lier et al., 2018). When it comes to food, craving is typically directed at particular kinds of food and can only be satisfied by the consumption of these items (Meule, 2020). Furthermore, patients can experience a distinct craving for a BE episode and plan these episodes well in advance (Ferriday & Brunstrom, 2011; Gluck et al., 2004; Manasse et al., 2019). Second, negative urgency is often described as a tendency to act rashly when NA is high (Sharma et al., 2014). It is one of several distinct personality traits that can give rise to impulsive-like behavior (Strickland & Johnson, 2021; Whiteside & Lynam, 2001). For example, a meta-analysis on self-report measures finds that three distinct traits can lead to impulsive-like behavior: positive emotionality (i.e., positive urgency, sensation seeking), disinhibition and negative emotionality (i.e., negative urgency) (Sharma et al., 2014).

Both craving and negative urgency are thought to be inherently associated with NA and BE.

When it comes to craving, the addictive appetite model posits that NA is an important trigger for craving in patients and that higher levels of craving can lead to BE (van Lier et al., 2018). Indeed, after inducing NA in a laboratory, studies find that NA is positively related to craving for a BE episode in individuals who binge eat, but not in healthy controls (HC) (Gluck et al., 2004). Also, studies using ESM report that average craving levels in daily life are associated with BE symptoms (Smith, Mason, Schaefer, et al., 2021).

When it comes to negative urgency, the acquired preparedness model posits that individuals high in negative urgency may have different learning experiences that involve BE and NA (Combs et al., 2010). Namely, the general tendency to act rashly when experiencing NA could also make them more likely to binge eat when experiencing NA, which could cause them to acquire the expectancy that BE alleviates NA. The risk and maintenance model for BN then proposes that subsequent elevations of NA could activate these expectancies, while also decreasing self-control due to the higher levels of negative urgency, making patients more likely to engage in BE (Pearson et al., 2015). Studies using self-report

measures do find that patients with BN report higher levels of negative urgency and that this is predictive of increases in BE over time (Anestis et al., 2007; Claes et al., 2015). ESM studies also show that patients who display more negative urgency need less of an increase in NA to trigger BE (Fischer et al., 2018, Smith et al., 2021).

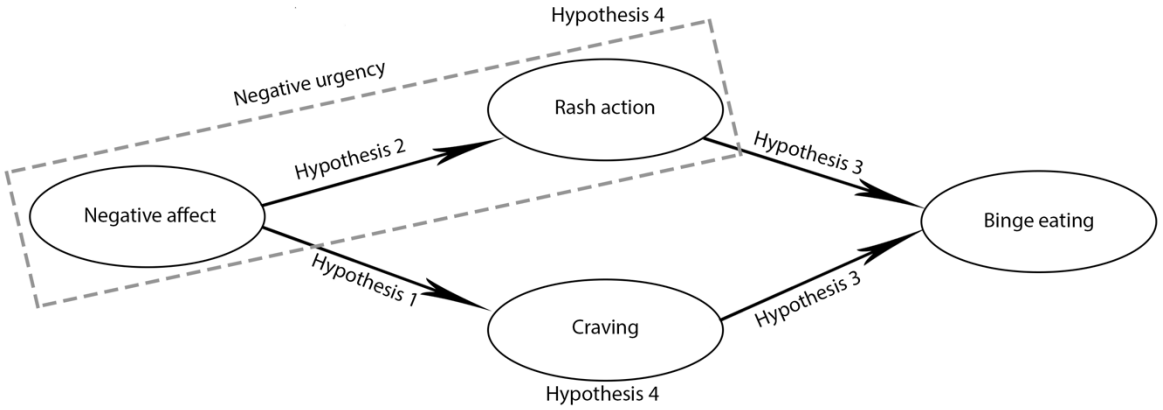
However, these studies have their limitations. First, they typically look at craving and negative urgency on a trait level and don't investigate the momentary changes in the underlying emotions and behaviors. Recent studies have shown that it is possible to deconstruct negative urgency in daily life and directly investigate the relation between NA and rash action, but this has not yet been done in the context of eating disorders (Sperry et al., 2018, 2021). Second, they often fail to explore the relation between NA, craving, rash action, and BE in its entirety. Most studies either investigate how craving or rash action are related to NA or how they are associated with BE. Furthermore, they usually focus on the role of either craving or rash action and do not study them together. However, studies on alcohol or substance use suggest that craving and rash action are not independent from each other. This is because they consistently report that individuals who display higher levels of negative urgency also experience more craving when NA is high (Chester et al., 2016; Li et al., 2021).

Because of these limitations, the precise role of craving and rash action in the relation between NA and BE remains unclear. This study explores their roles with ESM and repeatedly assesses NA, craving, rash action, and eating behaviors in patients with BN and HC in daily life. This makes it possible to investigate whether emotional and behavioral changes within a person at a previous assessment (t-1) predict emotions and behaviors at the current assessment (t0). This study then firstly explores the direct relations between the individual emotions and behaviors, and secondly investigates whether craving and rash action mediate the relation between NA and BE. More specifically, this study explores the following hypotheses (Figure 1):

1. Within-person NA predicts subsequent craving for a BE episode in patients with BN, but not in HC.
2. Within-person NA predicts subsequent rash action in patients with BN and HC, but more so in patients with BN. In other words, patients with BN display higher levels of negative urgency in daily life than HC.
3. Within-person craving for a BE episode and within-person rash action predict subsequent BE in patients with BN.
4. Within-person NA predicts subsequent BE in patients with BN and this is mediated by within-person rash action and within-person craving.

Figure 1. Study hypotheses

This study firstly explores the direct relations between negative affect (NA), craving, rash action and binge eating (BE), and secondly investigates whether craving and rash action mediate the relation between NA and BE. More specifically, this study explores the following hypotheses: (1) within-person NA predicts subsequent craving for a BE episode in patients with bulimia nervosa (BN), but not in healthy controls (HC). (2) within-person NA predicts subsequent rash action in patients with BN and HC, but more so in patients with BN. In other words, both patients with BN and HC display negative urgency in daily life, but this is more pronounced in patients with BN (3) within-person craving for a BE episode and within-person rash action predict subsequent BE in patients with BN. (4) within-person NA predicts subsequent BE in patients with BN and this is mediated by within-person rash action and within-person craving.



4.2. Methods

4.2.1 Study Sample

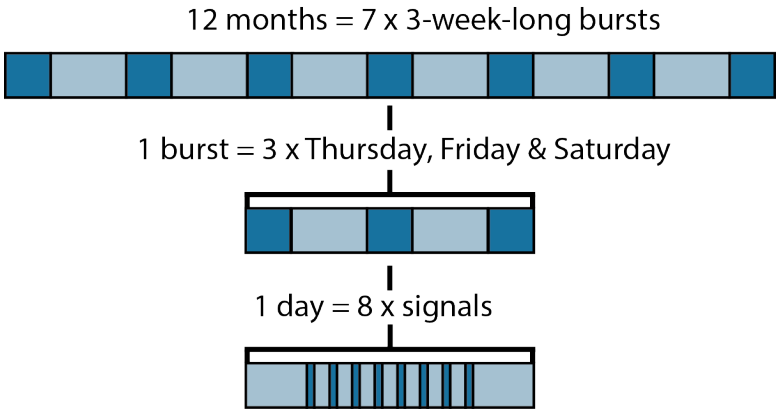
The participants were drawn from an ongoing ESM study. The study set out to include 70 HC and 70 patients with BN, which was based on recommendations for multilevel designs and previous drop-out rates (Burke et al., 2017; Maas & Hox, 2005). Participant inclusion ran from September 2019 to February 2022. The participants were recruited in Flanders, Belgium through residential and ambulatory care centers, patient groups, universities, social media, and by handing out flyers on the street. The inclusion criteria were the following: (1) female; (2) understand Dutch; (3) age ≥ 18 years; (4) BMI ≥ 18.5 kg/m2. Additional inclusion criteria for patients were: (5) meet the criteria for BN of the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; APA, 2013); (6) illness duration ≤ 5 years. This maximum illness duration was set as the role of negative urgency is thought to be largest in the first years after the onset of BN (Pearson et al., 2015). Participants were excluded for the following reasons: (1) major medical pathology; (2) chronic use of sedatives; (3) pregnancy; (4) presence of psychiatric pathology for HC or major psychiatric pathology (i.e., schizophrenia, autism spectrum disorder, bipolar disorder, substance use disorder other than alcohol use disorder) for patients with BN. All participants gave their written consent, and the study was approved by the ethical committee of the UZ/KU Leuven.

2.2 Study Design

After an initial screening via telephone or email, potential participants attended an in-person assessment. Here, a resident of psychiatry confirmed an individual's eligibility to participate based on the in- and exclusion criteria. Afterwards, the participants had their weight and height measured with a calibrated scale and stadiometer and completed clinical interviews and questionnaires. All participants underwent a briefing on the ESM questions and practiced the use of the mobile application. Then, participants entered the ESM protocol on the first Thursday after the in-person assessment. A visual representation of the protocol can be seen in Figure 2. It consisted of a repeated measurement design where 7 bursts of data collection were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday to limit the protocol's impact on the participants. These specific days were selected to consecutively gather data on both week and weekend days. This resulted in 9 days of data collection per burst and 63 days in total. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis. This meant that there were 72 signals scheduled per burst and 504 signals per participant. The number of days and signals per burst was similar to those in most cross-sectional ESM studies in patients with BN (Mikhail, 2021). The ESM data were initially collected with the app MobileQ (Meers et al., 2020). When the development of the app was discontinued in October 2020, data collection continued using m-Path (Mestdagh et al., 2022.). More information about the apps can be found in eMethods 1 and eTable 1 in the supplement.

Figure 2. Experience sampling method protocol.

The protocol consisted of 7 bursts of data collection which were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis.



4.2.3 Measures

4.2.3.1 Baseline measures

The Structured Clinical Interview for DSM-5 (SCID-5-S) was used to confirm the diagnosis of BN and to screen for other psychiatric disorders (APA, 2017). Eating disorder severity was assessed using the Eating Disorder Examination Questionnaire (EDE-Q) (Fairburn & Beglin, 1994). The EDE-Q had a good internal consistency with a Cronbach's alpha of 0.95.

4.2.3.2 ESM measures

Negative Affect: Participants were asked to rate how much they agreed with feeling 6 emotions in the moment (afraid, lonely, insecure, sad, distressed, guilty) on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). These scores were then averaged to get one score for NA at each assessment. The questions were based on previous ESM research investigating the role of NA in psychiatric disorders (Collip et al., 2011; Lataster et al., 2013; Rintala et al., 2020).

Rash action: Participants needed to answer how much they agreed to have displayed 5 behaviors since the last prompt (doing something risky, without thinking, they will regret, that will get them into trouble, wish they had not done) on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). The answers were then averaged to get one score for rash action. The questions were validated in previous ESM studies investigating rash action and were based on the UPPS-P impulsive behavior scale (Sperry et al., 2018). Furthermore, they were used to deconstruct negative urgency in daily life and directly investigate the relation between NA and rash action (Sperry et al., 2021).

Craving: Participants were asked to rate their desire for a BE episode in the moment on a 5-point Likert scale (1: "None", 5: "Overwhelming"). This was based on previous ESM studies investigating craving in eating disorders (Wonderlich et al., 2017).

Eating behaviors: Participants needed to indicate if they had eaten since the last prompt. If so, they had to identify the eating event as undereating, normal eating, or overeating. Then, participants were asked if they experienced a loss of control over their eating behavior. The participants were trained to interpret undereating and overeating as eating an amount of food that is definitely smaller or larger than what most people would eat under similar circumstances. Based on previous studies, BE was defined as an episode of overeating with loss of control (Ambwani et al., 2015). More information on the ESM questions and the internal consistency of the ESM scales is found in eMethods 2, eMethods 3 and eTable2 in the Supplement.

4.2.4 Statistical analysis

4.2.4.1 Sample characteristics

If normally distributed, continuous variables were described by the mean and standard deviation. Otherwise, they were described by the median, first quartile, and third quartile. Count data were described by the frequency and proportion. The 95% confidence intervals of the continuous, binomial, and multinomial variables were calculated with the CI, MedianCI, BinomCI, and MultinomCI functions in R, version 4.1.1.

4.2.4.2 Data characteristics

This study used the data collected up to July 2022. To measure the participants' compliance to the ESM protocol, per burst we calculated the percentage of answered signals out of the total number of signals received per burst by each participant who had not dropped-out of the study. The compliance during the first burst was compared between the participant groups with a Wilcoxon rank-sum test. The compliance over the entire ESM protocol was evaluated with a linear mixed-effects model. This model included compliance as the outcome while burst number and participant group were added as main and interaction effects. This made it possible to evaluate if there was a change in compliance over the bursts and if there was a difference between the groups. The model included random intercepts for the participants. The analyses were performed with PROC NPAR1WAY and PROC MIXED in SAS, version 9.4.

4.2.4.3 Hypothesis testing

For the first three hypotheses, three separate mixed models were fitted to the data to investigate the relations between NA, rash action, craving and BE. These included an outcome at the current assessment (t0) and a predictor at a previous assessment within the same day (t-1), which was split into within- and between-person effects through person-mean centering. This made it possible to explore whether within-person deviations from the mean at t-1 predicted the outcome at t0. All models included random intercepts for the participants as well as age, BMI, and the number of days since the participant started with the protocol as covariates. To test hypothesis 1, a generalized linear mixed model was fitted to the data of the HC and patients with BN with maximum likelihood estimation. The model included craving for a BE episode as an outcome and NA as a predictor. Additionally, to compare patients with BN and HC, group was added as a main and interaction effect with the within-person predictor at t-1. Due to the ordinal nature of the outcome, a multinomial distribution with a

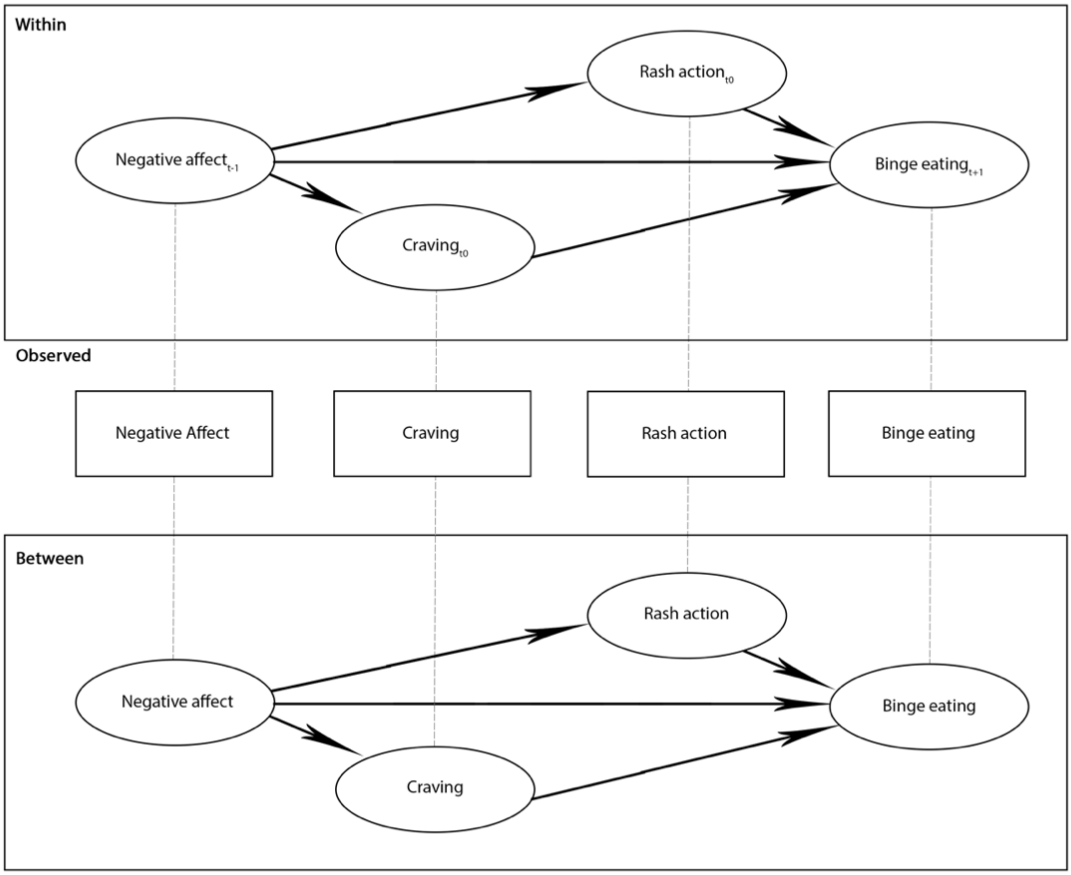
cumulative logit link was used. For hypothesis 2, a linear mixed model was fit to the data of the HC and patients with BN with restricted maximum likelihood estimation. This model included rash action as an outcome and NA as a predictor. Group was also added as a main and interaction effect with the within-person predictor at t-1. As mentioned previously, the relation between NA and rash action in this model can be seen as a measure of negative urgency (Sperry et al., 2021). To test hypothesis 3, a generalized linear mixed model was fitted to the data of the patients with BN with maximum likelihood estimation. The model included BE as an outcome and NA, rash action, and craving as predictors. Due to the binary nature of the outcome, a binomial distribution with a logit link was used. The models were fit using PROC MIXED and PROC GLIMMIX in SAS, version 9.4. The continuous variables in these models were standardized so that estimates can be interpreted as effect sizes. To deal with autocorrelation, an AR(1) covariance structure of the errors was assumed for the models of hypothesis 2 and 3 (Allison, 2015). This was not possible for hypothesis 1 as this was not implemented in SAS for ordinal outcomes. To test the robustness of the results, sensitivity analyses were performed that added compliance, treatment, app type, comorbidities, or medication use. P-values below 0.05 were considered significant. All models were valid under a missing at random assumption as they were fitted with different types of maximum likelihood estimation. The formulas for the models can be found in eMethods 4.

When it comes to hypothesis 4, a 1-1-1 multilevel structural equation model (MSEM) was fitted to the data of the patients with BN. As in previous studies, a Bayesian estimation technique was used with non-informative priors, which can more easily estimate parameters and can result in more accurate estimates than frequentist approaches (Depaoli & Clifton, 2015; Smith, Mason, Reilly, et al., 2021). The MSEM jointly modeled the effect of NA on BE on a within-person and between-person level, though the hypothesis was tested on the within-person level. Here, the MSEM investigated whether NA at a previous assessment (t-1) led to BE at the next assessment (t+1) (i.e., total effect), whether this was mediated by rash action or craving at the current assessment (t0) (i.e., indirect effect) and whether NA at t-1 still led to BE at t+1 when controlled for rash action and craving at t0 (i.e., direct effect). To deal with autocorrelation, a lagged outcome variable was included as a covariate in each of the separate regressions (Andersen & Mayerl, 2022). More information on how autocorrelation was handled in this study can be found in the supplement (eMethods 5). A path diagram of the MSEM can be seen in Figure 2. The model was fit using the TWOLEVEL RANDOM procedure in Mplus version 8.7. As a Bayesian approach was used, results were considered significant when the Bayesian credibility intervals did not include 0.

The model was valid under a missing at random assumption as it was fitted with a Bayesian estimation approach. The data and scripts that support the findings of this study are available at the Research Data Repository of the KU Leuven at https://rdr.kuleuven.be/dataset.xhtml?persistentId=doi:10.48804/QQNNHO.

Figure 3.

Path diagram of the 1-1-1 multilevel structural equation model to explore hypothesis 4 (within-person negative affect predicts binge eating in patients with bulimia nervosa and this is mediated by rash action and craving).



4.3. Results

4.3.1 Sample characteristics

There were 146 study participants at the time of the analyses. This included 70(47.9%) patients with BN and 76(52.0%) HC. Their characteristics can be found in Table 1. More information can be found in eResults 1. There were no between-group differences when it comes to age, education and ethnicity. However, the BMI of the patients with BN (mean=25.1; SD=5.30, CI=23.9,26.4) was higher than that of the HC (mean=22.3; SD=2.22; CI=21.8,22.8).

4.3.2 Data Characteristics

Data collection was completed for 115(78.8%) participants with another 31(21.2%) still needing to finish 2 bursts on average. A total of 28(19.2%) participants (18(25.7%) BN; 10(13.2%) HC) dropped out of the study before the follow-up ended. The median compliance per participant during the first burst was 90.3% for the HC and 83.3% for the patients with BN. This is similar to the compliance rates of previous cross-sectional ESM studies in patients with an eating disorder (Fischer et al., 2018; Schaefer et al., 2020). The compliance during the first burst did not differ significantly between patients and controls ($z=-1.56$, $p=0.119$). Compliance decreased over the course of the study in patients with BN ($\beta=-0.062$; $SE=0.005$; $CI=-0.072,-0.052$, $p<0.001$) and HC ($\beta=-0.034$; $SE=0.005$; $CI=-0.043,-0.025$, $p<0.001$), but this was more pronounced in patients with BN ($\beta=-0.028$; $SE=0.007$; $CI=-0.041,-0.015$, $p=<0.001$). In total, the HC answered 23168 (73.0%) of their scheduled beeps, while the patients with BN answered 16222 (58.5%). Though no ESM studies of a similar length were performed in patients with an eating disorder, the overall compliance of this study fell in the range of the lengthier ESM studies on substance use (Jones et al., 2019). More information on the drop-out and compliance rates as well as the average number of data points per burst can be found in eResults 1, eResults 2 and eTable 3 in the supplement.

4.3.3 Hypothesis testing

The results for hypotheses 1 to 3 can be found in Table 2 and Figure 3. The inclusion of compliance, medication use, therapy, app type or presence of comorbidities did not change the significance of these results. The results for hypothesis 4 can be seen in Table 2 and Figure 4. The full results of all the statistical models can be seen in eTable 4 in the supplement.

Table 1. Sample characteristics

	Healthy controls (n=76)		Patients with BN (n=70)	
	Mean (SD), median (Q1-Q3) or No (%)	95% CI	Mean (SD), median (Q1-Q3) or No (%)	95% CI
Age	21.7 (3.05)	21.0, 22.4	22.0 (3.87)	21.1, 23.0
BMI	22.3 (2.22)	21.8, 22.8	25.1 (5.30)	23.9, 26.4
Education (years)	15.0 (1.63)	14.6, 15.3	14.5 (2.14)	14.0, 15.0
Therapy (General)				
Past,	23 (30%)	20%, 41%	50 (71%)	61%, 82%
Present	3 (4%)	0%, 8%	16 (23%)	13%, 33%
Therapy (ED)				
Past	0 (0%)	0%, 0%	26 (37%)	26%, 49%
Present	0 (0%)	0%, 0%	14 (20%)	10%, 30%
Ethnicity				
Caucasian	74 (97%)	95%,100%	63 (90%)	84%, 96%
Asian	1 (1%)	0%, 4%	3 (4%)	0%, 11%
Middle-Eastern	0 (0%)	0%, 0%	4 (6%)	0%, 12%
Mixed	1 (1%)	0%, 4%	0 (0%)	0%, 0%
Illness Duration (years)	0 (0)	0, 0	2.55 (1.52)	2.18, 2.91
EDE-Q				
Restraint	0.54 (0.86)	0.35, 0.74	2.84 (1.50)	2.48, 3.20
Shape Concern	1.10 (1.09)	0.85, 1.34	4.23 (1.43)	3.89, 4.57
Weight Concern	0.87 (1.00)	0.64, 1.10	4.07 (1.60)	3.69, 4.46
Eating Concern	0.25 (0.36)	0.17, 0.33	2.87 (1.45)	2.52, 3.21
Total	0.74 (0.77)	0.57, 0.92	3.60 (1.26)	3.30, 3.90
Eating disorder symptoms (days/4 weeks)				
Binge eating	0 (0)	0, 0	8.13 (6.79)	6.51, 9.75
Fasting	0 (0)	0, 0	7.81 (8.10)	5.88, 9.74
Vomiting	0 (0)	0, 0	2.11 (5.51)	0.80, 3.43
Laxative use	0 (0)	0, 0	0.31 (1.95)	0, 0.78
Diuretic use	0 (0)	0, 0	0.77 (4.45)	0, 1.83
Compensatory exercise	0 (0)	0, 0	6.53 (7.21)	4.81, 8.25
Psychoactive medication use	0 (0%)	0%, 0%	11 (16%)	7%, 24%
Comorbidities[a]				
MDD	0 (0%)	0%, 0%	9 (17%)	6%, 32%
AUD	0 (0%)	0%, 0%	19 (36%)	25%, 51%
PD	0 (0%)	0%, 0%	5 (9%)	0%, 24%
AP	0 (0%)	0%, 0%	4 (8%)	0%, 22%
SAD	0 (0%)	0%, 0%	6 (11%)	0%, 26%
PTSD	0 (0%)	0%, 0%	10 (19%)	8%, 33%
ESM measures				
NA	2.07 (1.02)	2.06, 2.09	3.13 (1.37)	3.11, 3.15
Rash action	1.56 (0.82)	1.55, 1.57	2.09 (1.07)	2.07, 2.10
Craving	1.10 (0.35)	1.10,1.11	1.70 (1.04)	1.68, 1.71
BE[b]	0 (0-1)	0,0	22 (7-41)	14, 30

[a] Number and percentage of participants with a certain comorbidity. [b] Binge eating episodes per participant. Abbreviations: AP, agoraphobia, AUD, alcohol use disorder; BE, binge eating; BMI, body mass index; BN, bulimia nervosa; CI, confidence interval; ED, eating disorder; EDE-Q, Eating Disorder Examination Questionnaire, ESM, experience sampling method; Q1, 25% quartile; Q3, 75% quartile; MDD, major depressive disorder; n, number; NA, negative affect; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SD, standard deviation.

Hypothesis 1 (Within-person NA predicts subsequent craving for a BE episode in patients with BN, but not in HC): Higher levels of within-person NA at a previous assessment (t-1) were associated with higher levels of craving at the current assessment (t0) in patients with BN (β=0.128; SE=0.019; CI=0.091,0.165; p<0.001), but not in HC (β=0.027; SE=0.030; CI=-0.033,0.86; p=0.380).

Hypothesis 2 (Within-person NA predicts subsequent rash action in patients with BN and HC, but more so in patients with BN): Higher levels of within-person NA at t-1 were associated with higher levels of rash action at t0 in HC (β=0.036; SE=0.006; CI=0.025,0.048, p<0.001) and patients with BN (β=0.073; SE=0.006; CI=0.062,0.085, p<0.001). Furthermore, there was a significant interaction effect where this relation was more pronounced in patients with BN than in HC (β=0.036; SE=0.006; CI=0.019,0.52, p=0.001). These results indicate that both patients with BN and HC display negative urgency in daily life, but that patients with BN display higher levels of negative urgency than HC.

Hypothesis 3 (Within-person craving and within-person rash action predict subsequent BE in patients with BN): A higher probability of reporting a BE episode at t0 was associated with higher levels of within-person rash action at t-1 (β=0.105; SE=0.037; CI=0.033,0.177; p=0.004) and craving at t-1 (β=0.400; SE=0.027; CI=0.349,0.452; p<0.001), but not with within-person NA at t-1 (β=-0.026; SE=0.033; CI=-0.090,0.083; p=0.431).

Hypothesis 4 (*Within-person NA predicts subsequent BE in patients with BN and this is mediated by within-person rash action and within-person craving*):

At the within-person level, there was an indirect effect of NA at t_{-1} on BE at t_{+1} through rash action at t_0 (β=0.003; $SD_{posterior}$=0.002; CI=0.001,0.007) and craving at t_0 (β=0.006; $SD_{posterior}$=0.002; CI=0.003,0.011). There was no significant direct (β=-0.013; $SD_{posterior}$=0.022; CI=-0.055,0.032) or total effect (β=-0.003; $SD_{posterior}$=0.22; CI=-0.046,0.046) of NA at t_{-1} on BE at t_{+1}. The absence of a total effect of NA on BE does not invalidate the presence of indirect effects (Zhao et al., 2010). However, it could indicate that there are competing effects through which NA also lowers the probability of a BE episode.

Table 2. Model results

Hypothesis	Outcome	Variable	β	OR	SE/SDp	95% CI	p
1[a]	Craving t_0	Within-person NA t_{-1} *(HC)*	0.027	1.03	0.030	-0.033,0.086	0.380
		Within-person NA t_{-1} *(BN)*	0.128	1.14	0.019	0.091,0.165	<0.001
		Within-person NA t_{-1} *(BN vs HC)*	0.102	1.11	0.036	0,032 0.171	0.004
		Between-person NA	0.492	1.64	0.145	0.206,0.779	0.001
2[a]	Rash action t_0	Within-person NA t_{-1} *(HC)*	0.036	.	0.006	0.025,0.048	<0.001
		Within-person NA t_{-1} *(BN)*	0.073	.	0.006	0.062,0.085	<0.001
		Within-person NA t_{-1} *(BN vs HC)*	0.036	.	0.006	0.019,0.052	<0.001
		Between-person NA	0.429	.	0.059	0.312,0.546	<0.001
3[b]	Binge eating t_0	Within-person NA t_{-1}	-0.026	0.97	0.033	-0.090,0.083	0.431
		Between-person NA	-0.142	0.87	0.130	-0.404,0.119	0.279
		Within-person rash action t_{-1}	0.105	1.11	0.037	0.033,0.177	0.004
		Between-person rash action	0.458	1.58	0.168	0.123,0.794	0.008
		Within-person craving t_{-1}	0.400	1.49	0.027	0.349,0.452	<0.001
		Between-person craving	0.504	1.65	0.100	0.304,0.703	<0.001
4[b]	Binge eating t_{+1}	Direct effect *(within-person NA t_{-1})*	-0.013	.	0.022	-0.055,0.032	.
		Indirect effect *(within-person NA t_{-1} -> within-person rash* action *t_0)*	0.003	.	0.002	0.001,0.007	.
		Indirect effect *(within-person NA t_{-1} -> within-person craving t_0)*	0.006	.	0.002	0.003,0.011	.
		Total effect *(within-person NA t_{-1})*	-0.003	.	0.022	-0.046,0.046	.
Post-hoc 1[a]	Eating t_0	Within-person NA t_{-1} *(HC)*	-0.035	0.97	0.016	-0.067,-0.003	0.032
		Within-person NA t_{-1} *(BN)*	-0.043	0.96	0.018	-0.078,-0.008	0.015
		Between-person NA	0.053	1.06	0.039	-0.025,0.132	0.178
Post-hoc 2[b]	Binge eating t_0	Within-person NA t_{-1}	0.055	1.06	0.031	-0.006, 0.115	0.079
		Between-person NA	0.294	1.34	0.127	0.040, 0.548	0.024
Post-hoc 3[c]	Binge eating t_0	Within-person NA t_{-1}	0.104	1.11	0.035	0.035, 0.173	0.003
		Between-person NA	0.294	1.34	0.137	0.020, 0.568	0.036

[a] Based on the entire dataset. [b] Based on the data of the patients with BN. [c] Based on the data of the patients with BN when they indicated to have eaten. Abbreviations: β, standardized estimate; BN, bulimia nervosa; CI, confidence interval/credibility interval; HC, healthy controls; NA, negative affect; OR, odds ratio; p, p-value; SDp, standard deviation of the posterior; SE, standard error; t_{-1}, previous assessment; t_0, current assessment; t_{+1}, next assessment.

4.3.4 Post hoc analyses

To explore possible competing effects, 3 post hoc analyses were performed. Their results can be seen in Table 2. Post hoc analysis 1 investigated whether NA can also predict not eating. This was done with a mixed effects model that included eating (1: having eating since the last beep; 0: having not eaten) as the outcome and the lagged within-person effect of NA as a fixed effect. In this model, higher levels of within-person NA at t-1 were associated with a lower probability of eating at t0 in HC (β=-0.035; SE=0.016; CI=-0.673,-0.003; p=0.032) and patients with BN (β=-0.043; SE=0.018; CI=-0.078,-0.008; p=0.015). Post-hoc analysis 2 and 3 wanted to explore whether NA does predict BE if its effect on eating is taken into consideration. In both analyses, a mixed model was constructed with BE as the outcome and the lagged within-person effect of NA as a predictor of interest. However, post-hoc analysis 2 used all of the data of the patients with BN whereas post-hoc analysis 3 only used the data when patients with BN indicated to have eaten. Here, higher levels of within-person NA at t-1 were not related to a higher probability of BE at t0 in post-hoc analysis 2 (β=0.055; SE=0.031; CI=-0.006,0.115; p=0.079), but there was a relation in post-hoc analysis 3 (β=0.104; SE=0.035; CI=0.035,0.173; p=0.003). This suggests that NA does predict BE when its competing effect on eating is taken into account.

Figure 4.

Smoothed loess curves for the original data as well as the data predicted by the models for hypothesis 1, 2, and 3. Abbreviations: BN, bulimia nervosa; HC, healthy controls; t_{-1}: previous assessment; t_0, current assessment.

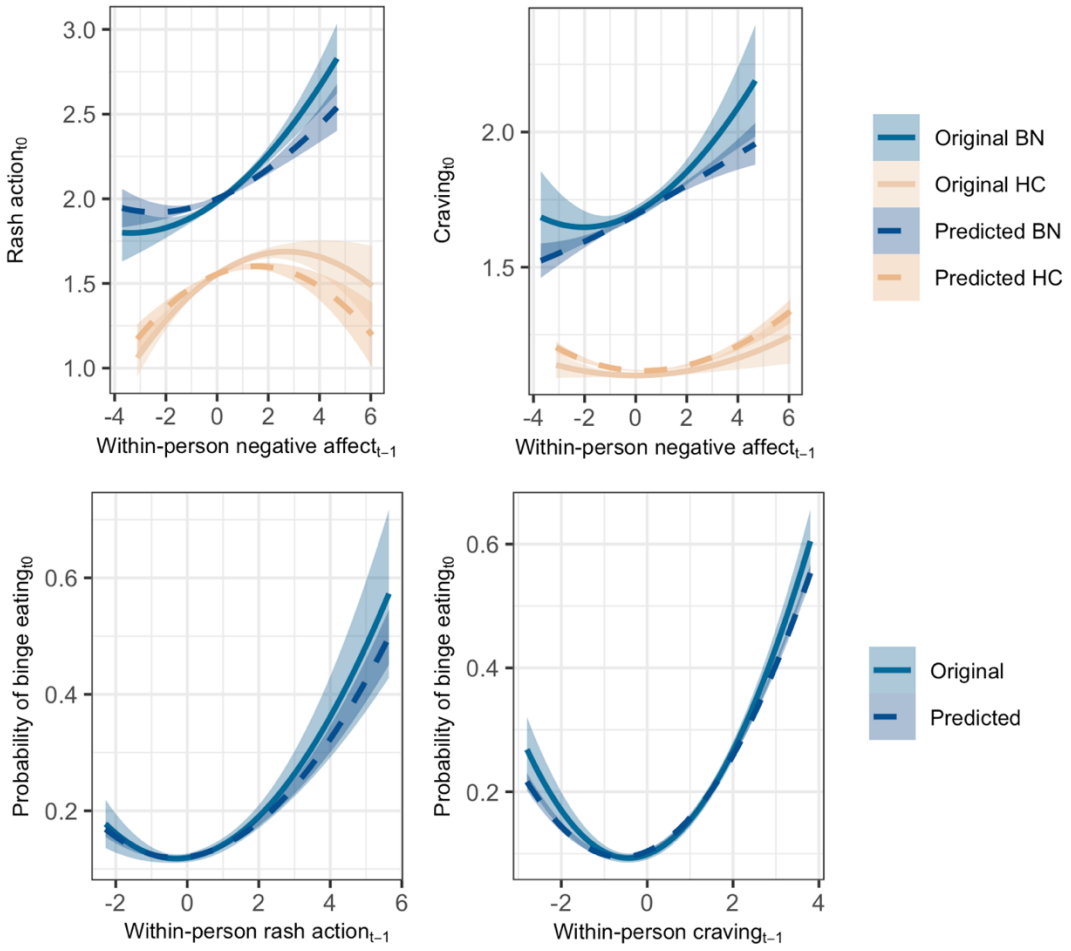
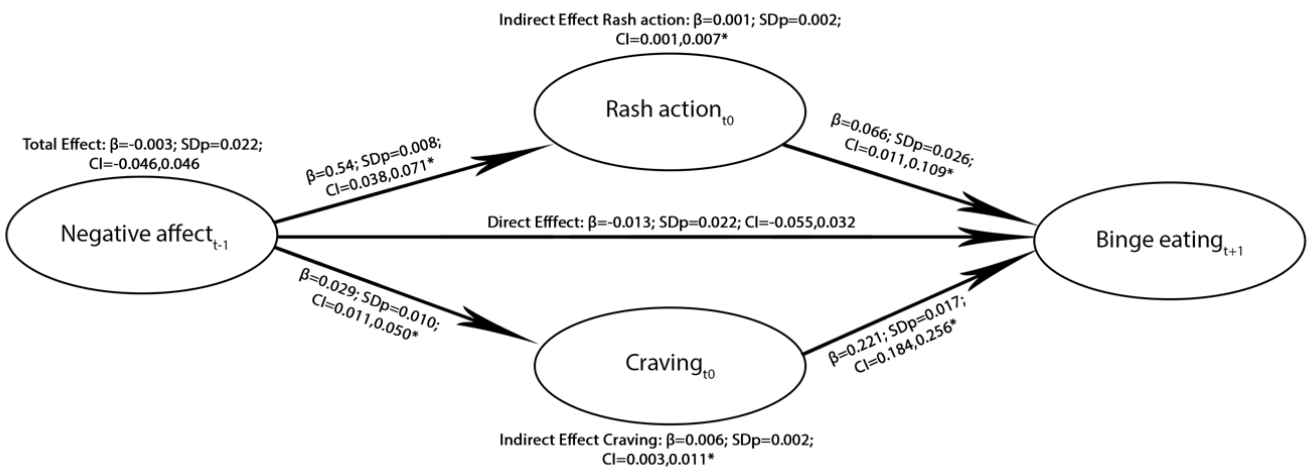


Figure 5.

Within-person effects of the 1-1-1 multilevel mediation model.

* Significant result. Abbreviations: β, estimate; CI, 95% Bayesian credibility interval; SDp, standard deviation of the posterior.



4.4. Discussion

This study is the first to explore the mediating role of craving and rash action in the relationship between NA and BE in daily life. First, its results show that NA predicts craving and rash action in patients with BN, more so than in HC. Second, they suggest that NA can lead to BE in patients with BN through craving and rash action but that NA can also lead to not eating.

Previous ESM studies report that NA is higher before a BE episode than before a regular eating episode and that NA increases in the hours before someone binge eats (Haedt-Matt & Keel, 2011; Mikhail, 2021). Based on these results, it is unexpected that the present study has not found that within-person NA at the previous assessment (t-1) predicts BE at the current assessment (t0). However, we could identify 9 other ESM studies that have performed the same analysis, and of these studies, only 2 have found a significant relationship (Ambwani et al., 2015; Fitzsimmons-Craft et al., 2016; Heron et al., 2014; Moskovich et al., 2019; Pearson et al., 2018; Smith et al., 2018, 2019; Smith, Mason, Juarascio, et al., 2020; Smith, Mason, Schaefer, et al., 2020). The findings of the current study suggest that this could be due to NA having competing effects on BE, meaning that NA could also lead to dietary restraint. Though most ESM research has focused on how NA leads to BE, this notion that NA can also result in dietary restraint has already been suggested by models such as the integrated cognitive model for eating disorders (Burton & Abbott, 2017).

This is supported by a previous ESM study which reports that NA has a positive indirect effect on BE through rumination, but after controlling for this effect, is associated with a lower probability of BE (Smith, Mason, Reilly, et al., 2021). Another study also finds that the induction of NA in individuals who binge eat can lead to both overeating and undereating (Russell et al., 2017). Furthermore, one study reports that patients with BN are less likely to choose high-fat food items, even when NA is high (Gianini et al., 2019). Likewise, studies in the general population show that NA is associated with both eating more and eating less (Torres & Nowson, 2007). Nevertheless, the number of studies investigating how NA leads to dietary restriction in patients with BN is limited. Therefore, to have a more complete understanding of how NA is related to disordered eating behaviors, future ESM studies should not only investigate how NA leads to BE, but also how it leads to dietary restriction.

On the one hand, NA could result in dietary restriction depending on its source and underlying emotions. Namely, some studies in healthy volunteers have shown that stressors causing strong physical responses (e.g., something threatening or frightening) are related to eating less (O'connor et al., 2008). Furthermore, delivering a strong acute stressor reduces food intake in rats while repeatedly administering a mild stressor increases the intake of energy-dense food (Torres & Nowson, 2007). Also, studies in individuals who binge eat find that negative emotions such as feeling nervous or afraid are less related to BE than others (Schaefer et al., 2020). Future studies should therefore explore which stressors (interpersonal versus physical, once versus repeated, or mild versus severe) and which emotions (e.g., down versus nervous) lead to BE or dietary restriction in daily life. On the other hand, NA could lead to BE through craving and a general tendency to act rashly, as proposed by the addictive appetite, acquired preparedness, and risk and maintenance models (Combs et al., 2010; Pearson et al., 2015; Treasure et al., 2018). In support of these models, this study is the first to show that patients with BN display a stronger relationship between NA and craving as well as between NA and rash action in daily life. It is also the first to show that NA has an indirect effect on BE through craving and rash action in daily life. However, these findings leave several questions unanswered.

First, although our findings indicate that craving and rash action are both independent mediators of the relationship between NA and BE, it could be possible that their roles also interact. Namely, previous research on alcohol and substance use reports that individuals who score high on negative urgency also display more craving when NA is elevated (Chester et al., 2016; Li et al., 2021). However, studies have also shown that not all BE episodes are the result of rash action; some are planned well in advance (Manasse et al., 2020) Furthermore, patients may consume a substance without experiencing any craving at all (van Lier et al., 2018). Future studies should therefore explore the interdependence of craving and rash action in relation to BE.

Second, the results of this study raise the question how NA leads to craving and rash action in patients with BN. For craving, it has been suggested that the repeated use of BE episodes to manage NA could reinforce positive expectancies about food (e.g., that eating relieves NA) (Schaefer et al., 2021). Subsequently, when patients experience NA, it could activate these positive expectancies and therefore increase the desire to binge eat (May et al., 2012). Indeed, ESM studies have found that stronger decreases of NA after a BE episode predict higher levels of eating expectancies and that NA is more strongly related to BE when eating expectancies are high (Schaefer et al., 2021; Smith, Mason, Juarascio, et al., 2020).

However, whether this relation between eating expectancies and BE is mediated by craving has not yet been explored. For rash action, studies have shown that individuals with an eating disorder have a lower distress tolerance, meaning that NA is less bearable for them, which could urge them to act rashly to relieve NA (Corstorphine et al., 2007). Though studies using questionnaires do suggest that distress tolerance could mediate the relationship between NA and negative urgency on a trait level, whether it also mediates the relation between momentary changes in NA and rash action remains unclear (Barrios et al., 2022).

The results of this study could have important clinical implications. Namely, if it would be possible to prevent NA from leading to higher levels of rash action and craving, then it might be possible to prevent a BE episode from happening. Current treatments for BN typically do not target this relationship, but a few interventions focusing on food-related rash action and craving have been developed (İnce et al., 2021; Rebello & Greenway, 2016). The IMPULS and ImpulsE trials have focused on reducing food-related response inhibition and report reductions in BE that lasted longer than in the treatment as usual group (Preuss et al., 2017; Schag et al., 2019). A virtual reality treatment for reducing food craving reports higher abstinence rates than additional cognitive behavioral therapy in patients who did not respond to an initial program (Ferrer-García et al., 2017). These results are encouraging, but other interventions focusing on rash action or craving have shown no effect on BE frequency(İnce et al., 2021). These mixed findings could be the result of insufficient knowledge on how NA leads to rash action and craving and how craving and rash action interact. Future studies could significantly expand our understanding by exploring these relations and whether they can be changed by interventions.

This study has several limitations. First, the sample of patients with BN mostly consists of female participants with a short illness duration who compensate through fasting and excessive exercise. The limited compensation through purging could be due to most participants having a short illness duration and being non-treatment-seeking. This limits the generalizability of the results to all patients with BN. Future studies should therefore investigate the relationship between NA, craving and rash action in other samples of patients with BN. Second, the use of some ESM measures could impact the measurement of behaviors and cognitions in this study. For example, this study has chosen to define craving as a desire for a BE episode, but craving can also be conceptualized as a desire for food in general (Smith, Mason, Schaefer, et al., 2021). The definition of the current study has several implications as the HC group does not engage in BE. Namely, it is a reason why we have hypothesized that the HC do not display a relation between NA and craving (Gluck et al.,

2004). Future studies should compare the relationship between NA and a more general concept of food craving in patients with BN and HC. Also, this study does not assess negative emotions such as anger, which have been linked to BE (Reichenberger et al., 2021). Additionally, this study does not include questions about dietary restriction, so it investigates the relationship between NA and not eating. This is not ideal, as undereating can also be a sign of dietary restriction, and there may be other reasons why patients do not eat. For example, an individual could be ill and therefore experience more NA and be less inclined to eat, but the NA might not be the reason why they are not eating. Third, the decreasing compliance over the duration of the study could impact the results due to the missing data. However, the techniques used in this study are valid under a missing at random assumption and a sensitivity analysis finds no impact of compliance on the results. Fourth, limiting the ESM measurements to Thursday, Friday and Saturday could have influenced the results if participants would experience a different relation between NA, craving, rash action, and BE on the other days of the week. This study also has several strengths. This ESM dataset is the largest in patients with BN when it comes to the number of signals and the second largest when it comes to the number of patients (Mikhail, 2021). Furthermore, it is the first to show that NA predicts rash action and craving in patients with BN in daily life and that this relation is stronger than in HC. It is also the first to show that rash action and craving mediate the relation between NA and BE in daily life. Importantly, they highlight that NA can lead to both BE and not eating in patients with BN. This could be an important reason why previous studies often do not find a relation between NA at the previous assessment (t_{-1}) and BE at the current assessment (t_0).

4.5. Conclusion

This study is the first to show that NA predicts subsequent craving and rash action in patients with BN, more so than in HC. It is also the first to show that NA predicts subsequent BE through craving and rash action, but that NA can also predict subsequent not eating. Future studies should explore how NA leads to rash action and craving, how craving and rash action interact and investigate when NA leads to BE and when NA leads to dietary restriction.

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CHAPTER 5

The impact of negative and positive affect on craving, non-heavy alcohol use, and binge drinking in patients with alcohol use disorder and controls: An experience sampling method study

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Abstract

Introduction: Studies find that higher levels of positive affect (PA) and lower levels of affect (NA) are related to craving and alcohol consumption in daily life. However, they have mostly been performed in non-problematic drinkers. Therefore, this study compares how NA and PA are related to craving, non-heavy alcohol use, and binge drinking (BD) in patients with alcohol use disorder (AUD) and controls.

Methods: A total of 53 female patients with AUD and 75 female controls were included in an experience sampling study where they reported on momentary NA, PA, craving, and alcohol use in daily life over a period of 12 months. Assessments occurred eight times a day on Thursdays, Fridays, and Saturdays in seven bursts of three weeks.

Results: Subsequent craving was predicted by NA and PA in a quadratic fashion in patients with AUD, but not in controls. Future non-heavy alcohol use was predicted by lower NA and higher PA in both samples, but also by lower PA in patients with AUD. Subsequent BD was predicted by PA in a quadratic manner in both samples, but only by NA in a quadratic fashion in patients with AUD. Non-heavy alcohol use, but not BD, predicted subsequent lower levels of NA and PA in both samples.

Conclusions: Affect and craving or alcohol are often non-linearly related in daily life. Furthermore, a worse mood can indeed predict subsequent alcohol use in patients with AUD. However, this could be more pronounced for BD than for non-heavy alcohol use.

5.1. Introduction

Alcohol use disorder (AUD) is defined as a maladaptive pattern of alcohol use that leads to significant impairments or distress (American Psychiatric Association [APA], 2013). This problematic pattern of alcohol use has a considerable impact on individuals, their surroundings, and society as a whole. It has been estimated that 3 million people die worldwide every year due to problematic alcohol use, and that its societal cost amounts to at least 125 billion euros in the EU and 249 billion euros in the US (Anderson & Baumberg, 2009; Sacks et al., 2015; World Health Organization, 2018). Additionally, treating AUD is challenging as only 17.3% of patients receive treatment within a given year, and as up to 60% of those who receive treatment do not achieve remission (Fleury et al., 2016; Mekonen et al., 2021). This high impact and poor treatment outcome highlight the need for new and improved therapies for AUD, but in order to develop them, a better understanding of the triggers for alcohol use is required.

It is believed that momentary changes in levels of both negative affect (NA) and positive affect (PA) can be triggers of alcohol use, and that craving is a mediator of this relation (Baker et al., 2004; Cooper et al., 1995; Cox & Klinger, 1988; van Lier et al., 2018). First, NA is characterized as a feeling of 'subjective distress and unpleasurable engagement' that includes several negative emotions such as anger, anxiety, guilt, loneliness, or sadness (Watson et al., 1988). Theories such as the tension reduction theory, the stress-response dampening model, and the affective processing model of addiction propose that higher levels of NA cause patients with AUD to consume alcohol, and that the subsequent reduction in NA has a reinforcing effect on future alcohol use (Baker et al., 2004; Conger, 1956; Levenson et al., 1980). Indeed, studies have found that experimentally inducing NA can lead to more alcohol use across patients and controls, and that alcohol consumption can lower NA (Bresin, 2019; Bresin et al., 2018). However, patients with AUD report more often that they drink to cope with NA than controls, and relapse in patients is predicted by higher levels of NA (Carpenter & Hasin, 2015; Witkiewitz & Villarroel, 2009). Additionally, a more pronounced relation between NA and alcohol use is also found in individuals with a family history of AUD and women (Miller et al., 1974; Peltier et al., 2019; Sayette, 1999).

Second, PA reflects the extent to which somebody experiences positive emotions such as feeling alert, excited, and satisfied (Watson et al., 1988). Theories such as the motivational model of alcohol use posit that patients not only drink alcohol to cope with NA, but also

drink alcohol to enhance PA, and that this behavior is influenced by factors such as social enhancement expectancies and sensation seeking (Cooper et al., 1995; Cox & Klinger, 1988). For example, an individual could experience lower levels of PA (i.e., feeling bored and inactive) and drink alcohol to feel more excitement (Cooper et al., 1995; Cox & Klinger, 1988). However, studies also suggest that higher levels of PA could lead to alcohol use by making individuals more attentive to rewards and more likely to approach them (Tamir & Robinson, 2007; Young & Nusslock, 2016). Indeed, studies find that experimentally inducing PA can lead to more alcohol use and that drinking alcohol can increase PA (Dinc & Cooper, 2015; Mason et al., 2008; Wilkie & Stewart, 2005). Importantly, it has been suggested that patients with AUD initially consume alcohol for its positive reinforcing effects (i.e., increasing PA), but that a shift occurs over time, after which alcohol is consumed for its negative reinforcing effects (i.e., decreasing NA) (Koob & le Moal, 1997; Koob & Volkow, 2016). In line with this hypothesis, individuals who experience more rewarding effects from alcohol use have a higher risk of developing AUD (King et al., 2014).

Third, craving can be defined as 'an intense and conscious desire for a specific substance', though the precise definition of craving has been the topic of discussion (Sayette et al., 2000; van Lier et al., 2018). Despite this debate, several conditioning-based, cognitive, psychobiological, and motivational models have been developed which propose that changes in NA and PA can increase craving and that higher levels of craving lead to alcohol use (van Lier et al., 2018). Across patients and controls, studies do report that experimentally inducing NA can lead to more craving for alcohol (Bresin et al., 2018). Importantly, experiencing more craving in response to NA is also predictive of relapse in patients with AUD (Cooney et al., 1997; Higley et al., 2011). Furthermore, though the number of studies on PA is limited, one study does find that experimentally inducing PA can increase craving in patients with AUD (Mason et al., 2008).

Taken together, numerous studies show that NA and PA play a significant role in alcohol use and that craving could mediate this relation. However, these studies have typically been performed in a laboratory setting or have used retrospective questionnaires, which can suffer from limitations such as a lack of ecological validity or recall bias (Shiffman et al., 2008). Therefore, there has been an increasing interest in studying the impact of momentary NA and PA on craving and alcohol use in real life using the experience sampling method (ESM), also known as ecological momentary assessment, whereby participants repeatedly report their mood, behavior, and context in real-time (Shiffman et al., 2008). Importantly, though studies using ESM consistently report that higher levels of PA are

associated with alcohol use in daily life, the majority of ESM studies does not find a similar relation between NA and alcohol use, raising the question whether changes in PA, and not NA are the key driver of alcohol use in daily life (for a review, see Dora et al., 2022). However, these ESM studies have several limitations. First, almost all studies have been performed in individuals who do not drink problematically. This could have influenced the findings as the relation between NA and alcohol use is hypothesized to be the strongest in patients with AUD (Carpenter & Hasin, 2015). Indeed, one of the few ESM studies in patients with AUD reports that higher levels of NA do predict relapse in daily life (Waters et al., 2020). Second, a large number of ESM studies on alcohol use primarily include men, even though studies show that women are more likely to drink alcohol to regulate NA and that this tendency plays a key role in the development of AUD of women (Peltier et al., 2019). Third, ESM studies typically do not differentiate between various types of alcohol use. However, studies suggest that NA especially predicts binge drinking (BD; i.e., the consumption of large amounts of alcohol within a short period of time) over non-heavy alcohol use (i.e., the consumption of a limited amount of alcohol) (Stene-Larsen et al., 2013). Additionally, studies find that individuals who BD are more likely to meet the criteria for AUD and that BD predicts the onset of AUD (Addolorato et al., 2018; Tavolacci et al., 2019). Fourth, the majority of ESM studies have investigated the relation between affect and alcohol use on a daily level, meaning that they aggregate several measurements within a day. This could be an issue if the relation between NA and alcohol use exists on a smaller timescale. If so, it might be better suited to investigate whether higher or lower than average levels of NA and PA within a person at one moment predict craving and alcohol use at the next moment.

This study aims to overcome these limitations by exploring the role of momentary affect in the daily lives of female patients with AUD and healthy volunteers, and investigate the temporal relations between NA and PA on the one hand and craving, non-heavy alcohol use, and BD on the other hand. More specifically, it aims to investigate the following hypotheses:

1. Within-person NA and PA predict subsequent craving in patients with AUD, but only within-person PA predicts subsequent craving in controls.
2. Within-person NA and PA predict subsequent non-heavy alcohol use and BD in patients with AUD, but only within-person PA predicts subsequent non-heavy alcohol use and BD in controls.
3. Non-heavy alcohol use and BD predict a subsequently lower NA and higher PA in patients with AUD and controls.

5.2. Methods

5.2.1. Study sample

The participants were drawn from a larger ESM study, which set out to include 70 controls and 70 patients with AUD, based on recommendations for multilevel studies and previously reported drop-out rates (Burke et al., 2017; Maas & Hox, 2005). Participants were recruited from September 2019 to February 2022 in Flanders, Belgium through residential and ambulatory care centers, patient groups, universities, social media, and by handing out flyers on the street. The inclusion criteria were: (1) female; (2) understand Dutch; (3) age ≥ 18 years; (4) BMI ≥ 18.5 kg/m2. Additional inclusion criteria for patients were: (5) meet the criteria for AUD of the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; APA, 2013); (6) display a pattern of repetitive BD according to the criteria of the National Institute of Alcohol Abuse and Alcoholism (NIAAA) (i.e., drinking 4 units of alcohol within 2 hours for women) (NIAAA, 2022); (7) illness duration ≤ 5 years. This maximum illness duration was set as the role of certain factors in AUD are thought to change over the course of the disorder (Boness et al., 2021). Participants were excluded for the following reasons: (1) major medical pathology; (2) chronic use of sedatives; (3) pregnancy; (4) presence of psychiatric pathology for controls or major psychiatric pathology for patients with AUD (i.e., schizophrenia, autism spectrum disorder, bipolar disorder, substance use disorder). All participants gave their written consent, and the study was approved by the ethical committee of the UZ/KU Leuven.

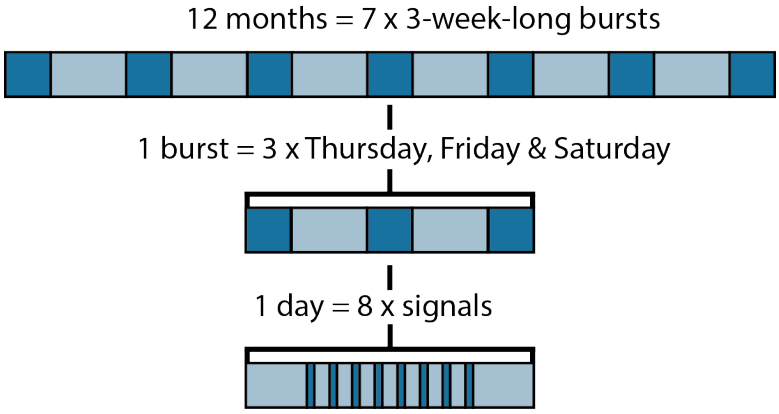
5.2.2. Study procedure

All potential participants were initially screened via telephone or email, after which they attended an in-person assessment. During this assessment, a resident of psychiatry confirmed whether an individual was eligible to participate based on the in- and exclusion criteria. Afterwards, the participants had their height and weight measured with a calibrated scale and stadiometer and completed clinical interviews and questionnaires. Next, the participants were briefed on the ESM questions and practiced the use of the mobile application. All participants started with the ESM protocol on the first Thursday following the in-person assessment. An overview of the protocol can be seen in Figure 1. The protocol consisted of a repeated measurement design where seven bursts of data collection were spread out over a 12-month period. The bursts had a duration of three weeks and were separated by intervals of five

weeks. During each burst, data were only collected on Thursday, Friday, and Saturday to limit the protocol's impact on the participants. These days were selected to consecutively gather data on week and weekend days. In addition, these are the days with the highest alcohol consumption among young adults in Flanders (Damme et al., 2022). This resulted in nine days of data collection in each burst and 63 days in total. On a given day of data collection, participants received eight assessments on a signal-contingent (i.e., semi-random) basis. This meant that there were 72 assessments per burst and 504 assessments per participant. The data were initially collected with the app MobileQ (Meers et al., 2020). When the app was no longer maintained in October 2020, data collection continued using m-Path (Mestdagh et al., 2022). More information on the apps can be found in the supplement (eMethods 1, eTable 1).

Figure 1. Experience sampling method protocol.

The protocol consisted of 7 bursts of data collection which were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis.



5.2.3. Measures

5.2.3.1. Baseline measures

The Structured Clinical Interview for DSM-5 (SCID-5-S) was used to confirm the diagnosis of AUD and to screen for other psychiatric disorders (APA, 2017). AUD severity was assessed with the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001).

5.2.3.2. ESM measures

Negative and positive affect: For NA, participants needed to rate how much they agreed with feeling six emotions in the moment (afraid, distressed, guilty, insecure, lonely, sad) on a seven-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). For PA, participants were required to rate how much they agreed with experiencing three emotions in the moment (cheerful, relaxed, satisfied) on a seven-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). These scores were then averaged to get one score for NA and PA at each assessment. The questions for NA and PA were based on previous ESM studies (Collip et al., 2011; Lataster et al., 2013; Rintala et al., 2020).

Craving: Participants needed to rate their urge to drink alcohol in the moment on a five-point Likert scale (1: "None", 5: "Overwhelming"). This is similar to other ESM studies on craving (Waddell et al., 2021).

Alcohol use: Participants were required to indicate whether they drank alcohol since the last assessment. If so, they needed to report how many units of alcohol they consumed (1, 2, 3, 4, 5, 6, >7). The participants were instructed about the definition of an alcohol unit (i.e., 250 ml beer, 100 ml wine, 35 ml liquor). For the analyses, based on the criteria of the NIAAA, non-heavy alcohol use was defined as having drunk less than four units of alcohol since the last assessment, while BD was defined as having drunk at least four units of alcohol since the last assessment with the mean (SD) time between assessment of 103 (44) minutes.

More information on the ESM questions and the internal consistency of the ESM scales is found in eMethods 2, eMethods 3 and eTable2 in the Supplement.

5.2.4. Statistical analysis

For the first two hypotheses, six separate mixed-effects models were fitted to the data to investigate whether NA and PA at a previous timepoint (t_{-1}) predict subsequent craving, non-heavy alcohol use and BD at the current timepoint (t_0) in patients with AUD and controls. Only the assessments answered within 90 minutes of the prompt were used in the analyses. Furthermore, the different models only used a subset of the entire dataset to limit the influence of alcohol consumption on the results. For craving, only the data before the first report of alcohol consumption of the day was used together with the data on days where participants drank no alcohol. For non-heavy alcohol use, only the data up to the first report of non-heavy alcohol consumption on days without BD was used, in addition to data from days where participants did not drink any alcohol. For BD, only the data up to the first report of a BD episode was used together with the data on days where participants drank no alcohol.

Additionally, the analyses for craving and non-heavy alcohol use were performed in patients with AUD and controls who reported to have drunk alcohol in the past year, while the analyses for BD were carried out on the data from patients with AUD and controls who reported to have experienced at least one BD episode in the past year. The latter was done to ensure that the analyses concerning BD were not influenced by the data of controls who do not binge drink.

The use of a generalized linear mixed-effects model with a multinomial distribution was explored for craving due to its ordinal nature. However, the models did not achieve an adequate fit of the data, which prompted a switch to a linear mixed model. Furthermore, a generalized linear mixed-effects model with a binomial distribution and a logit link was used for non-heavy alcohol use and BD due to their binary nature. The predictors were separated into within- and between-person effects through person-mean centering, which made it possible to investigate whether higher than average levels of NA or PA at t_{-1} predicted subsequent craving, non-heavy alcohol use or BD at t_0. However, it was clear from an inspection of the models and data that the relation between the predictors and outcomes was non-linear. Therefore, the inclusion of polynomial terms was explored using a forward selection procedure with Wald tests. These showed that including both linear and quadratic polynomials, but not cubic polynomials, would best fit the data. Furthermore, to compare patients with AUD and controls, group (i.e., AUD or control) was added as a main and interaction effect with the within-person polynomials at t_{-1}. For the random effects, a maximal random effects structure was first fit to the data and then simplified with a backward elimination procedure using likelihood-ratio tests. This showed that there was no single random effects structure that would best suit all models. Therefore, the backward elimination procedure was performed for each model separately, resulting in varying random-effects structures for the individual models. The different structures can be found in the supplement (eTable 3). Furthermore, all models included age, BMI and day since the start of the study as covariates. These covariates were included to control for previously reported relations between age, BMI, and alcohol use and to control for changes in alcohol use over time (Bray et al., 2019; Kleiner et al., 2008).

For the third hypothesis, four linear mixed models were fitted to the data to investigate whether non-heavy alcohol use and BD at the current assessment (t_0) predicted a subsequently lower NA and higher PA at the following assessment (t_{+1}) in patients with AUD and controls. These models used the same data from the analyses for non-heavy alcohol use and BD mentioned previously. The random-effects structure was determined in the

previously described backward elimination procedure and can be found in the supplement (eTable 3). Furthermore, all models included age, BMI and day since the start of the study as covariates.

All models were fit using the lmer and glmer packages in R, version 4.1.1. The continuous variables in the models were standardized so that estimates can be interpreted as effect sizes. To test the robustness of the results, sensitivity analyses were performed that added compliance, treatment, app type, comorbidities, or medication use to the model as covariates. Furthermore, AUDIT-scores and BD frequency were added as a moderator to investigate the impact of disease severity on the results. All models were fitted with maximum likelihood estimation or restricted maximum likelihood estimation and were therefore valid under a missing at random assumption. P-values below 0.05 were considered significant. The data and the scripts that support the methodological decisions and results can be found at https://rdr.kuleuven.be/privateurl.xhtml?token=9b7f1cd5-116f-47a2-bf3d-147c9b884417.

5.3. Results

5.3.1. Sample characteristics

The data of 128 study participants (AUD 53; controls: 75) were used in the analyses concerning craving and non-heavy alcohol use. One control participant who reported to not drink alcohol was excluded. Furthermore, the data of 92 study participants (AUD: 53, controls: 39) were used in the analyses on BD. The characteristics of the different study groups can be found in Table 1. There were no significant differences in age, BMI, education, and ethnicity between the patients with AUD and controls. Additional information on the sample characteristics can be found in the supplement (eResults 1).

5.3.2. Data characteristics

There were 33(25.8%) participants (21(39.6%) AUD; 12(16.0%) controls) who dropped out of the study before the follow-up ended. During the first burst, the median compliance per participant was 90.2% for the controls and 81.9% for the patients with AUD. This is similar to the compliance rates of previous cross-sectional ESM studies with a substance use disorder (Jones et al., 2019). Over the course of the entire study, the controls answered 24437 (72.2%) of their scheduled beeps, while the patients with AUD answered 12338 (62.5%). This is

similar to the compliance in lengthier ESM studies on substance use (Jones et al., 2019). More information on the drop-out and compliance rates as well as the average number of data points per burst can be found in the supplement (eResults 2 and eTable 4).

5.3.3. Hypotheses

The main results concerning hypothesis 1 to 3 can be found in Table 2 and are visualized in Figures 2 to 4. The full results of all the statistical models can be found in the supplement (eTable 5). The inclusion of compliance, medication use, therapy, app type or presence of comorbidities did not change the significance of these results.

Hypothesis 1 (*Within-person NA and PA predict subsequent craving in patients with AUD, but only within-person PA predicts subsequent craving in controls*). Within-person NA at a previous assessment (t_{-1}) predicted craving at the current assessment (t_0) in patients with AUD with a significant quadratic (β=0.040; SE=0.012; CI=0.017,0.064; p=0.001) relation. Stated differently, patients with AUD reported more craving after experiencing both lower and higher than average levels of NA. Importantly, higher AUDIT scores were associated with a stronger linear relation (β=0.022; SE=0.003; CI=0.015,0.029; p<0.001), while a higher BD frequency was related to a stronger linear (β=0.051; SE=0.017; CI=0.018,0.085; p=0.004) and quadratic relation (β=0.029; SE=0.011; CI=0.008,0.051; p=0.007). Within-person PA at t_{-1} predicted craving at t_0 in patients with AUD with a significant positive quadratic relation (β=0.044; SE=0.012; CI=0.020,0.068; p<0.001), indicating that patients reported more craving after experiencing both lower or higher levels of PA. Furthermore, higher AUDIT scores were related to a more negative linear (β=-0.018; SE=0.003; CI=-0.024,-0.012; p<0.001) and a stronger quadratic relation relation (β=0.006; SE=0.002; CI=0.001,0.011; p=0.011), while a higher BD frequency was related to a stronger quadratic relation relation (β=0.037; SE=0.001; CI=0.014,0.059; p=0.001). In contrast, within-person NA or PA at t_{-1} did not predict craving at t_0 in controls and this was not impacted by AUDIT scores or BD frequency. Additionally, patients with AUD displayed a stronger quadratic relation for NA (β=0.39; SE=0.014; CI=0.011,0.068; p=0.006) and PA (β=0.042; SE=0.014; CI=0.014,0.070; p=0.003) than controls.

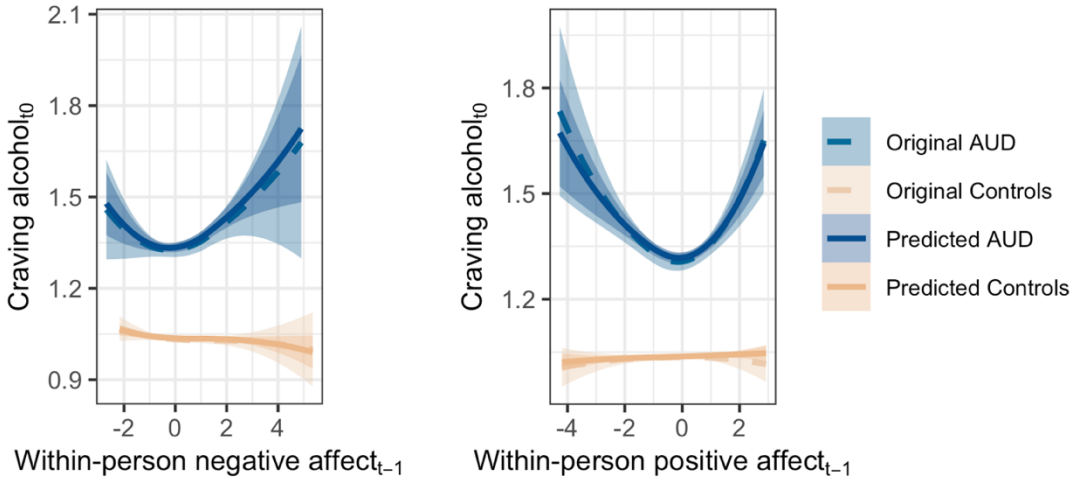
Table 1. Sample characteristics

	AUD (n=53)		HC			
			HC_{Total} (n=75)		HC_{Binge} (n=39)	
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
Age	21.4 (3.5)	20.5-22.4	21.7 (3.1)	21.0-22.4	21.2 (2.1)	20.4-22.4
BMI	22.7 (2.0)	22.1-23.3	22.3 (2.2)	21.8-22.8	22.2 (2.0)	21.6-22.9
Illness Duration AUD (years)	3.1 (1.3)	2.8-3.5	0 (0)	0-0	0 (0)	0-0
Education (years)	14.7 (1.6)	14.3-15.2	15.0 (1.6)	14.6-15.3	15.0 (1.6)	14.5-15.5
AUDIT	15.1 (5.3)	13.7-16.6	4.0 (2.5)	3.4-4.5	5.2 (2.3)	4.6-6.1
ESM measures						
NA	2.3 (1.1)	2.3-2.4	2.1 (1.0)	2.1-2.1	2.0 (0.9)	2.0-2.0
PA	4.9 (1.3)	4.8-4.9	5.1 (1.2)	5.1-5.1	5.1 (1.1)	5.1-5.1
Craving	1.4 (0.8)	1.4-1.4	1.1 (0.3)	1.1-1.1	1.1 (0.3)	1.1-1.1
Alcohol use	25 (26)	12-31	14 (15)	6-15	16 (15)	5-18
BD	7 (9)	2-7	1 (3)	0-1	2 (3)	0-2
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Binge drinking frequency						
Never	0 (0%)	0-0%	36 (48%)	37-60%	0 (0%)	0-0%
Annually	0 (0%)	0-0%	5 (7%)	0-18%	5 (13%)	0-31%
Semiannually	0 (0%)	0-0%	10 (13%)	3-25%	10 (26%)	13-43%
Three-monthly	5 (9%)	0-24%	15 (20%)	10-32%	15 (38%)	26-56%
Monthly	10 (19%)	8-34%	5 (7%)	0-18%	5 (13%)	0-31%
Biweekly	21 (40%)	28-55%	3 (4%)	0-16%	3 (8%)	0-25%
Weekly	10 (19%)	8-34%	1 (1%)	0-13%	1 (3%)	0-20%
>Weekly	7 (13%)	2-28%	0 (0%)	0-0%	0 (0%)	0-0%
Therapy (General)						
Past,	29 (55%)	41-68%	23 (31%)	20-41%	10 (26%)	11-40%
Present	5 (9%)	1-17%	3 (4%)	0-9%	1 (3%)	0-8%
Therapy (AUD)						
Past,	1 (2%)	0-6%	0 (0%)	0-0%	0 (0%)	0-0%
Present	1 (2%)	0-6%	0 (0%)	0-0%	0 (0%)	0-0%
Ethnicity						
Caucasian	50 (94%)	91-100%	73 (97%)	95-100%	39 (100%)	100-100%
Latino	1 (2%)	0-8%	0 (0%)	0-0%	0 (0%)	0-0%
Mixed	2 (4%)	0-10%	1 (0%)	0-4%	0 (0%)	0-0%
Asian	0 (0%)	0-0%	1 (0%)	0-4%	0 (0%)	0-0%
Psychoactive medication	6 (11%)	3-20%	0 (0%)	0-0%	0 (0%)	0-0%
Comorbidities						
MDD	3 (6%)	0-17%	0 (0%)	0-0%	0 (0%)	0-0%
PD	2 (4%)	0-17%	0 (0%)	0-0%	0 (0%)	0-0%
SAD	1 (2%)	0-13%	0 (0%)	0-0%	0 (0%)	0-0%
ADHD	3 (6%)	0-17%	0 (0%)	0-0%	0 (0%)	0-0%
PTSD	2 (0%)	0-15%	0 (0%)	0-0%	0 (0%)	0-0%

Abbreviations: ADHD, attention deficit hyperactivity disorder; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; CI, confidence interval; BD, binge drinking; ESM, experience sampling method; HC, healthy controls; HC_{Binge}, healthy controls who reported at least one binge drinking episode in the past year; MDD, major depressive disorder; N, number; NA, negative affect; PA, positive affect; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SD, standard deviation.

Figure 2.

Smoothed loess curves showing the relation between within-person negative and positive affect at the previous assessment (t_{-1}) and craving for alcohol at the current assessment (t_0) in the original data and the data predicted by the linear mixed models. Abbreviations: AUD, alcohol use disorder; t_{-1}: previous assessment; t_0, current assessment.



Hypothesis 2: (*Within-person NA and PA predict subsequent non-heavy alcohol use and BD in patients with AUD, but only within-person PA predicts subsequent alcohol use and BD in controls*).

Alcohol use: Within-person NA at t_{-1} negatively predicted non-heavy alcohol use at t_0 in a linear fashion in controls (β=-0.526; SE=0.089; CI=-0.702,-0.350; p<0.001) and patients with AUD (β=-0.275; SE=0.067; CI=-0.406,-0.145; p<0.001), but this negative linear term was less pronounced in patients with AUD (β=-0.251; SE=0.112; CI=0.032,0.470; p=0.025). These results show that higher than average levels of NA are associated with a lower probability of non-heavy alcohol use in patients with AUD and controls, but that this is lesser pronounced in patients. Furthermore, within-person PA at t_{-1} significantly predicted non-heavy alcohol use at t_0 in controls and patients with AUD with a positive linear term (HC: β=0.492; SE=0.069; CI=0.357,0.627; p<0.001; AUD: β=0.373; SE=0.064; CI=0.247,0.499; p<0.001). However, this was supplemented by a positive quadratic term in patients with AUD (β=0.198; SE=0.066; CI=0.069,0.326; p=0.003), but not in controls (β=0.070; SE=0.066; CI=-0.059,0.199; p=0.285). In other words, higher levels of PA predicted subsequent non-heavy alcohol use in patients with AUD and controls, but lower levels of PA also predicted subsequent non-heavy alcohol use in patients with AUD. Also, higher AUDIT scores were associated with a weaker linear term (β=-0.025; SE=0.011; CI=-0.047,-0.004; p=0.023)

Binge drinking: Within-person NA at t_{-1} predicted BD at t_0 in patients with AUD with a significant quadratic term (β=0.267; SE=0.088; CI=0.095,0.440; p=0.002). Furthermore, Within-person PA at t_{-1} also predicted BD at t_0 in patients with AUD with a significant quadratic term (β=0.385; SE=0.083; CI=0.223,0.547; p<0.001). However, in contrast to non-heavy alcohol use, the linear terms were not significant, resulting in a stronger association between higher levels of NA, lower levels of PA, and BD in patients with AUD. Importantly, higher AUDIT scores were related to a weaker quadratic relation (β=-0.030; SE=0.014; CI=-0.057,-0.002; p=0.033) between PA and subsequent BD. Contrastingly, changes in within-person NA did not predict subsequent BD in controls, but within-person PA at t_{-1} did predict BD at t_0 controls in a quadratic fashion (β=0.489; SE=0.258; CI=0.179,0.799; p=0.002).

Hypothesis 3: (*Non-heavy alcohol use and BD predict a subsequently lower NA and higher PA in patients with AUD and controls*).

Alcohol use: Non-heavy alcohol use at t_0 predicted lower levels of NA at t_{+1} in both patients with AUD (β=-0.161; SE=0.046; CI=-0.250,-0.071; p=0.001) and controls (β=-0.114; SE=0.043; CI=-0.198,-0.029; p=0.010). Similarly, non-heavy alcohol use at t_0 predicted higher levels of PA at t_{+1} in both patients with AUD (β=0.181; SE=0.049; CI=0.085,0.276; p<0.001) and controls (β=0.194; SE=0.046; CI=0.103,0.284; p<0.001). The effect of alcohol use on subsequent NA and PA did not differ between the groups.

Binge drinking: BD at t_0 did not predict subsequent changes in NA or PA at t_{+1} in patients with AUD or controls. However, a higher BD frequency in controls was related to subsequently lower levels of NA (β=-0.234; SE=0.094; CI=-0.418,-0.051; p=0.012).

Figure 3.

Smoothed loess curves showing the relation between within-person negative and positive affect at the previous assessment (t_{-1}) and alcohol use or binge drinking at the current assessment (t_0) in the original data and the data predicted by the generalized linear mixed models. Abbreviations: AUD, alcohol use disorder; t_{-1}: previous assessment; t_0, current assessment.

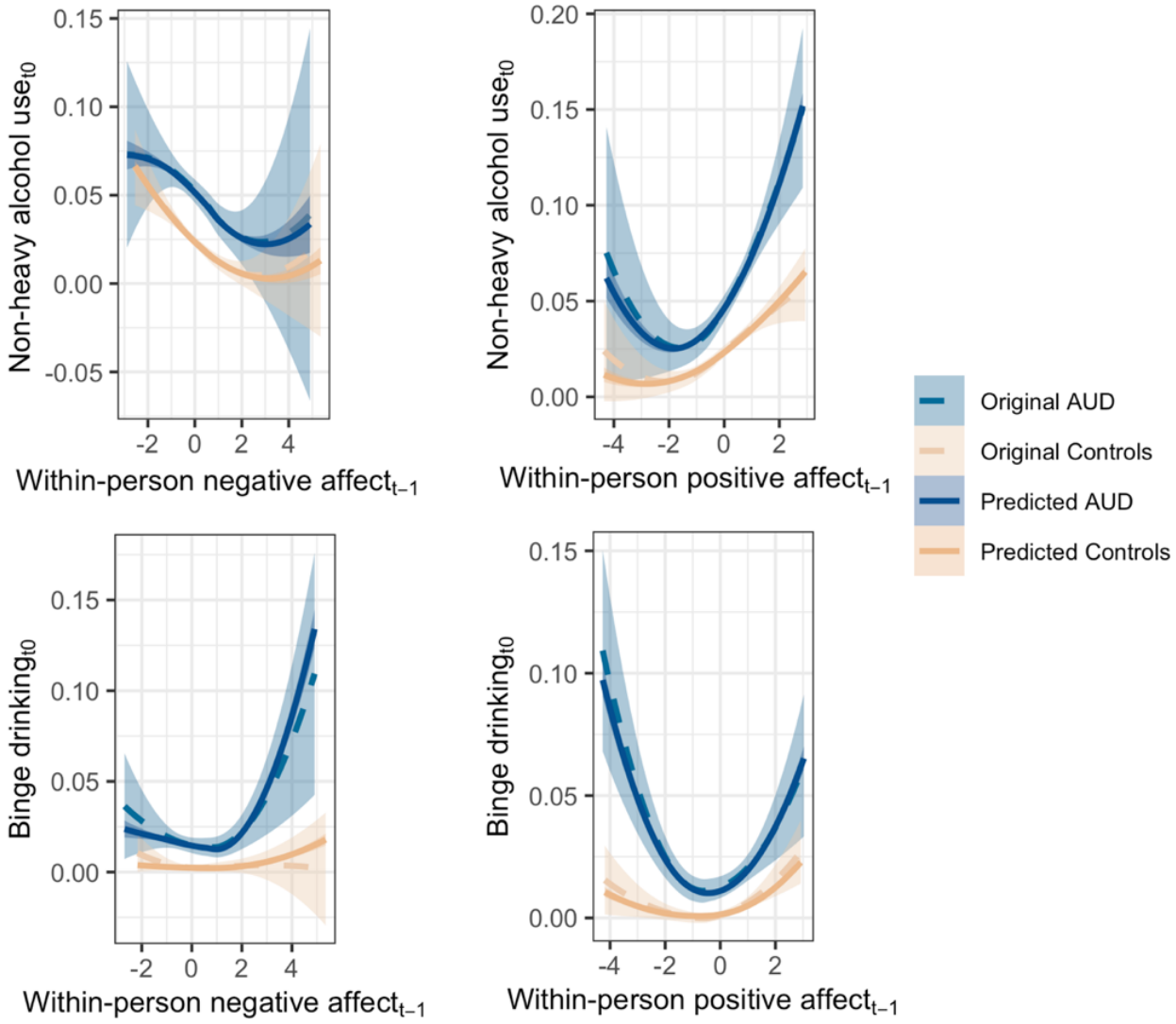


Figure 4.

Box plots showing the relation between alcohol use or binge drinking at the current assessment (t_0) and negative or positive affect at the next assessment (t_{+1}) in the original data. Abbreviations: AUD, alcohol use disorder; t_0, current assessment; t_{+1}: next assessment.

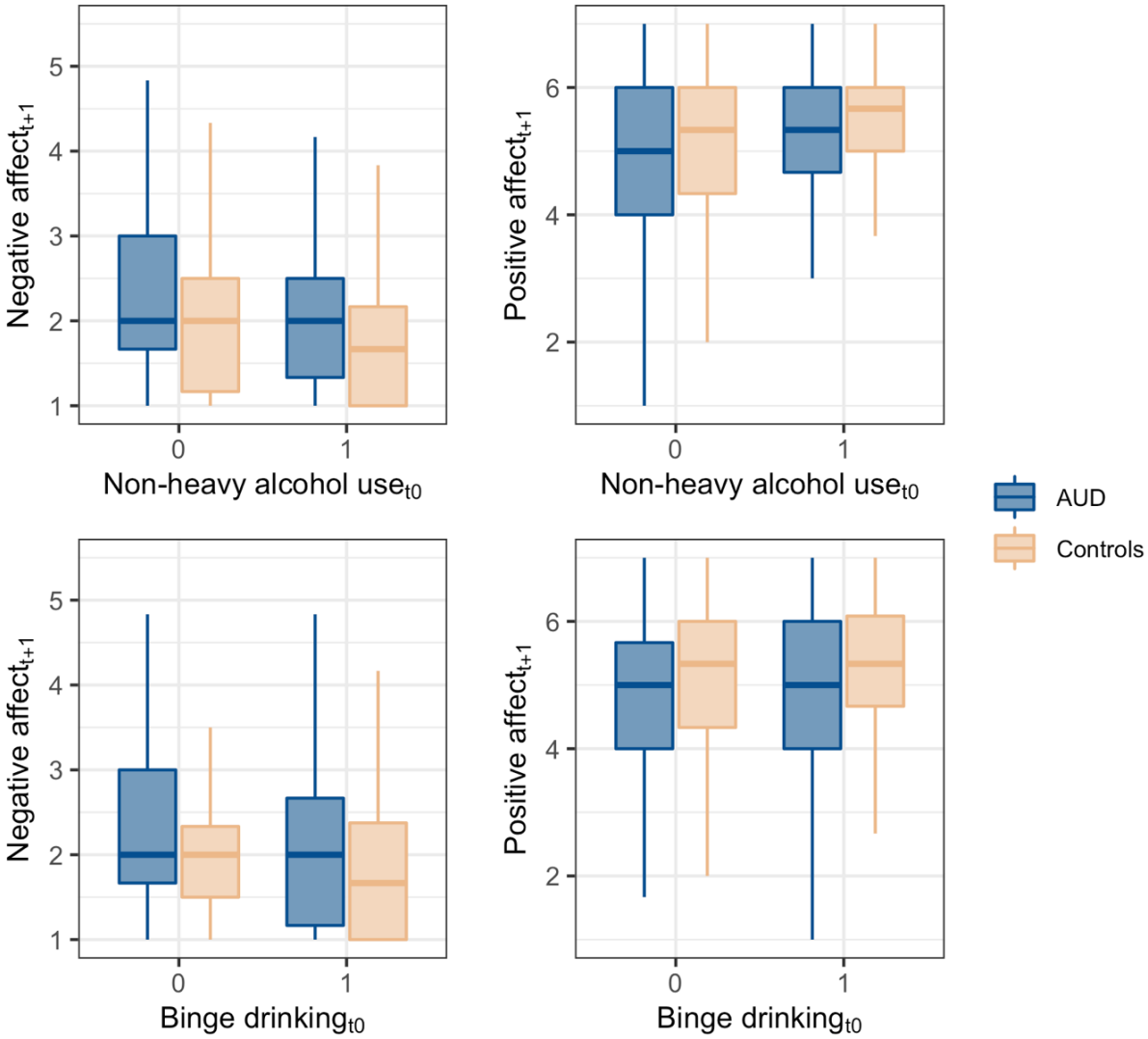


Table 2. Model results

Outcome	Variable	Group	Polynomial	β	OR	SE	95% CI	p
Craving t_0	NA t_{-1}	Controls	Linear	-0.009	.	0.017	-0.042, 0.024	0.593
			Quadratic	0.001	.	0.008	-0.015, 0.017	0.903
		AUD	Linear	0.041	.	0.021	0.000, 0.082	0.056
			Quadratic	0.040	.	0.012	0.017, 0.064	0.001*
		AUD vs Controls	Linear	0.050	.	0.027	-0.003, 0.103	0.068
			Quadratic	0.039	.	0.014	0.011, 0.068	0.006*
	PA t_{-1}	Controls	Linear	0.014	.	0.014	-0.015, 0.042	0.349
			Quadratic	0.002	.	0.007	-0.013, 0.016	0.820
		AUD	Linear	0.021	.	0.019	-0.016, 0.059	0.262
			Quadratic	0.044	.	0.012	0.020, 0.068	<0.001*
		AUD vs Controls	Linear	0.008	.	0.024	-0.039, 0.054	0.747
			Quadratic	0.042	.	0.014	0.014, 0.070	0.003*
Non-heavy alcohol use t_0	NA t_{-1}	Controls	Linear	-0.526	0.591	0.089	-0.702, -0.350	<0.001*
			Quadratic	0.007	1.007	0.090	-0.168, 0.183	0.934
		AUD	Linear	-0.275	0.759	0.067	-0.406, -0.145	<0.001*
			Quadratic	0.069	1.071	0.069	-0.065, 0.203	0.314
		AUD vs Controls	Linear	0.251	1.285	0.112	0.032,0.470	0.025*
			Quadratic	0.061	1.064	0112	-0.157, 0.280	0.581
	PA t_{-1}	Controls	Linear	0.492	1.636	0.069	0.357, 0.627	<0.001*
			Quadratic	0.070	1.072	0.066	-0.059, 0.199	0.285
		AUD	Linear	0.373	1.452	0.064	0.247, 0.499	<0.001*
			Quadratic	0.198	1.218	0.066	0.069, 0.326	0.003*
		AUD vs Controls	Linear	-0.119	0.887	0.094	-0.304, 0.065	0.206
			Quadratic	0.127	1.136	0.093	−0.054, 0.309	0.169

Outcome	Predictor	Group	Polynomial	β	OR	SE	95% CI	p
BD t_0	NA t_{-1}	Controls	Linear	-0.053	0.948	0.258	-0.558, 0.452	0.837
			Quadratic	0.237	1.267	0.172	-0.099, 0.573	0.167
		AUD	Linear	-0.070	0.932	0.099	-0.264, 0.124	0.480
			Quadratic	0.267	1.306	0.088	0.095, 0.440	0.002*
		AUD vs Controls	Linear	-0.017	0.983	0.276	-0.558, 0.524	0.951
			Quadratic	0.030	1.031	0192	-0.346, 0.407	0.875
	PA t_{-1}	Controls	Linear	0.337	1.401	0.197	-0.050, 0.724	0.087
			Quadratic	0.489	1.631	0.158	0.179, 0.799	0.002*
		AUD	Linear	0.045	1.470	0.086	-0.125, 0.214	0.605
			Quadratic	0.385	1.306	0.083	0.223, 0.547	<0.001*
		AUD vs Controls	Linear	-0.293	0.746	0.215	-0.715, 0.129	0.174
			Quadratic	-0.104	0.901	0.178	-0.453, 0.245	0.559
NA t_{+1}	Non-heavy alcohol use t_0	Controls	.	-0.114	.	0.043	-0.198, -0.029	0.010*
		AUD	.	-0.161	.	0.046	-0.250, -0.071	0.001*
		AUD vs Controls	.	-0.047	.	0.063	-0.170, 0.075	0.454
	BD t_0	Controls	.	-0.057	.	0.136	-0.324, 0.209	0.673
		AUD	.	-0.052	.	0.062	-0.174, 0.070	0.405
		AUD vs Controls	.	0.006	.	0.150	-0.287, 0.298	0.971
PA t_{+1}	Non-heavy alcohol use t_0	Controls	.	0.194	.	0.046	0.103, 0.284	<0.001*
		AUD	.	0.181	.	0.049	0.085, 0.276	<0.001*
		AUD vs Controls	.	-0.013	.	0.067	-0.145, 0.119	0.846
	BD t_0	Controls	.	0.020	.	0.193	-0.359, 0.399	0.918
		AUD	.	0.064	.	0.102	-0.135, 0.263	0.532
		AUD vs Controls	.	0.044	.	0.218	−0.384, 0.472	0.840

* Significant result. Abbreviations: AUD, alcohol use disorder; β, standardized estimate; CI, confidence interval; BD, binge drinking; NA, negative affect; OR, odds ratio; p, p-value; PA, positive affect; SE, standard error; t_{-1}, previous assessment; t_0, current assessment; t_{+1}, next assessment.

5.4. Discussion

The purpose of this study is to investigate the relation between NA and PA on the one hand, and craving, non-heavy alcohol use, and BD on the other hand. Importantly, the results show that the relation between affect and craving or alcohol use is often non-linear, with both lower and higher than average affect levels predicting increased craving and alcohol use. More specifically, changes in both NA and PA predict subsequent craving, non-heavy alcohol use and BD in patients with AUD. However, in controls, affect does not predict subsequent craving, while only lower NA and higher PA levels predict non-heavy alcohol use, and only changes in PA have predictive effects on subsequent BD. Furthermore, non-heavy alcohol use, but not BD, predicts subsequently lower levels of NA and higher levels of PA in both patients with AUD and controls.

The non-linear relation between affect and craving or alcohol use

As to our knowledge, only one previous study also reports that affect is related to craving and alcohol use in a non-linear manner (Bragard et al., 2022). Nevertheless, this is not unexpected as alcohol use is thought to be related to both NA and PA, which are negatively correlated with one another, and because both lower as well as higher levels of PA are hypothesized to lead to alcohol consumption (Cooper et al., 1995; Cox & Klinger, 1988; Schmukle et al., 2002). However, there could be several reasons why the current study is particularly well-suited to detect this non-linear relation. The study's burst measurement design, which has resulted in a large number of observations per participant, could have facilitated the modelling of complex within-subject relations. Additionally, this study includes patients with AUD who have a short illness duration, which could imply that they are still at a stage where both NA and PA play a role (Koob & le Moal, 1997; Koob & Volkow, 2016). Regardless, the finding that NA and PA can be non-linearly related to craving and alcohol use seems to be essential for the different theories on affect and alcohol consumption to converge. Future studies should therefore not simply assume a linear relation between affect and craving or alcohol use, but pay attention to potential non-linear effects.

Differences between patients with AUD and controls

The results of this study suggest that patients with AUD and controls differ in the way that NA and PA are related to craving and alcohol use in daily life.

First, the current study finds that both lower and higher levels of NA and PA are associated

with subsequent craving in patients with AUD, but not in controls. These results are in line with research showing that experimentally inducing NA or PA increases craving in patients with AUD, but contradict certain ESM studies which report that NA predicts craving in non-problematic drinkers (Bresin et al., 2018; Mason et al., 2008; Pedersen et al., 2022; Treloar Padovano et al., 2019; Waddell et al., 2021). One possible explanation for these conflicting results is that previous ESM studies typically examine the relationship between concurrent affect and craving levels, while the current study focuses on lagged relations. Specifically, if the impact of affect on craving in non-problematic drinkers would be limited in size and duration, then it would be more difficult to detect this effect with a lagged analysis where the average lag was 100 minutes. Nevertheless, the difference between patients and controls is in line with most theories on craving, which posit that certain predisposing and acquired factors strengthen the relation between affect and craving in patients with AUD (van Lier et al., 2018). For example, patients are thought to have more positive expectancies of alcohol consumption compared to controls, such as the belief that drinking alcohol will help to cope with NA or enhance PA (Marlatt, 1985). Indeed, individuals with higher drinking to cope expectancies display a stronger relation between NA and craving in daily life (Waddell et al., 2021). Future ESM studies should therefore further explore which predisposing and acquired factors contribute to the relation between affect and craving and how this differs between patients and controls.

Second, the current study shows that patients with AUD could be more likely to drink alcohol in daily life in response to a worse mood (i.e., low PA or high NA), and that this could be more pronounced than in non-problematic drinkers (Cooper et al., 1995; Cox & Klinger, 1988). Specifically, only lower levels of NA and higher levels of PA predict subsequent non-heavy alcohol use in controls, though lower levels of PA also predict subsequent non-heavy alcohol use in patients with AUD. Furthermore, though only changes in PA predict BD in controls, changes in NA also predict BD in patients with AUD. Additionally, patients with a more severe AUD seem to have a stronger relation between a worse mood and alcohol use as higher AUDIT scores and a higher BD frequency are related to experiencing more craving in response to high NA and low PA.

Importantly, this difference between patients and controls could be the reason why previous ESM studies report that there is no relation between high NA or low PA and alcohol use, as they have typically been performed in non-problematic drinkers (Dora et al., 2022). Future ESM studies that want to investigate the role of affect in problematic alcohol use should therefore aim include a sample of problematic drinkers.

Differences between non-heavy alcohol use or binge drinking

The findings of the current study suggest that the relation between affect and alcohol use depends on the amount of alcohol that is consumed.

First, it appears that higher levels of NA and lower levels of PA are more strongly associated with subsequent BD in daily life than with subsequent non-heavy alcohol use. This is due to NA and PA exhibiting a linear negative and positive association, respectively, with non-heavy alcohol use, though they are quadratically related to BD. Indeed, studies suggest that NA increases the risk for BD more so than for non-heavy alcohol use and that individuals who experience more NA are more likely to start BD (Cheng & Lo, 2015; Stene-Larsen et al., 2013).

Second, it seems that non-heavy alcohol use could play a larger role in affect regulation in daily life than BD. This is because non-heavy alcohol use predicts subsequently lower levels of NA and higher levels of PA in the current study, while this is not the case for BD. Indeed, there are studies who report that a small amount of alcohol can lead to feelings of euphoria, while larger amounts increase feelings of depression (Tamerin & Mendelson, 1969). However, there have also been studies in daily life who show that reductions in NA are higher on days with heavy drinking days than on moderate drinking days (Russell et al., 2020). More research is therefore needed on how NA and PA are related to different types of alcohol use in daily life.

Limitations

This study has several limitations. First, the sample of patients with AUD mostly consists of Caucasian non-treatment seeking female individuals with a short illness duration. This impacts the generalizability of the results to all patients with AUD. Second, the sample of controls consists of different types of drinkers (i.e., social drinkers and non-problematic heavy drinkers). However, there could be differences between these drinking patterns. Third, the decrease in compliance over the course of the study could impact the results due to the missing data. However, the analysis techniques used in this study are valid under a missing at random assumption and a sensitivity analysis finds no impact of compliance on the results. Fourth, limiting the ESM assessments to Thursday, Friday and Saturday could have influenced the results if participants would experience a different relation between affect, craving, and alcohol use on the other days of the week. Fifth, the signal-contingent

assessment schedule could have influenced the measurement of alcohol use, especially at night, and could have been improved with the addition of event-contingent assessments.

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CHAPTER 6

Person-specific and Pooled Prediction Models for Binge eating, Alcohol Use and Binge Drinking in Bulimia Nervosa and Alcohol Use Disorder: An Experience Sampling Method Study

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Abstract

Introduction: Machine learning could play a key role in the development of new interventions for bulimia nervosa (BN) and alcohol use disorder (AUD) as it can be used to predict and identify specific triggers of binge behavior in daily life. Therefore, this study has the following two aims. First, to evaluate person-specific and pooled prediction models for binge eating (BE), alcohol use and binge drinking (BD) in daily life. Second, to identify important predictors for these behaviors.

Methods: A total of 120 patients (BN: 50; AUD: 51; BN/AUD: 19) participated in an experience sampling study, where over a period of 12 months they reported on their eating and drinking behaviors as well as on several other emotional, behavioral and contextual factors in daily life. The study had a burst-measurement design, where assessments occurred 8 times a day on Thursdays, Fridays, and Saturdays in 7 bursts of 3 weeks. Afterwards, person-specific and pooled models were fit with elastic net regularized regression and evaluated with cross-validation. From these models, the variables with the 10% highest estimates were identified.

Results: The person-specific models had a median AUC of 0.61, 0.80, and 0.85 for BE, alcohol use and BD respectively, while the pooled models had a median AUC of 0.70, 0.90, and 0.93. The most important predictors across the different behaviors were craving, and time of day. However, predictors concerning social context and affect differed between BE, alcohol use and BD.

Conclusion: This study shows that BE, alcohol use and BD can be predicted in daily life, but that pooled models outperformed person-specific models and that models for alcohol use and BD outperformed those for BE. Future studies should investigate how model performance can be improved and how these models can be used to deliver interventions in daily life.

6.1. Introduction

Bulimia nervosa (BN) and alcohol use disorder (AUD) are two psychiatric disorders that share a number of similarities (American Psychiatric Association [APA], 2013). First, they can both be characterized by binge behavior where large amounts of food (i.e., binge eating [BE]) or alcohol (i.e., binge drinking [BD]) are consumed within a short period of time (APA, 2013). Second, they can both have a significant impact on health with BN having a high mortality of 1.7 per 1000 person-years and with AUD being the largest risk factor for disease and disability among 15- to 49-year-olds (Arcelus et al., 2011; Griswold et al., 2018). Third, both disorders can be difficult to treat, with up to 60% of patients who receive treatment not achieving remission (Fleury et al., 2016; Linardon & Wade, 2018). Taken together, the high impact and poor treatment outcomes highlight the need for more effective therapies for BN and AUD.

One promising new form of therapy is the just-in-time adaptive intervention (JITAI) (Nahum-Shani et al., 2018). In a JITAI, support is given 'just-in-time' or when a patient needs it the most. For example, a patient could report their emotions, behaviors, and context with a smartphone application, and an algorithm could evaluate the risk of BE or BD based on this information, after which an intervention could be sent out when this momentary risk is elevated. The support can also be adaptive, meaning that it can be tailored to a patient's in-the-moment needs. For instance, a patient could receive a text message alert when the estimated risk for BE or BD is moderate, but a phone call when the estimated risk is high. Because of its potential benefits, several researchers have developed and implemented JITAIs in recent years, but their results have been mixed (Carpenter et al., 2020; Hardeman et al., 2019; Wang & Miller, 2020). One reason for this could be the limited adaptive nature of these JITAIs. Namely, the research designs of these JITAIs were primarily based on previous literature (e.g., which information should be gathered from participants and how it should be evaluated), which means that the decision to send out an intervention was static and based on findings from previous studies. However, if such decisions were to be based on the actual data provided by participants, a JITAI would be more adaptive and perhaps more effective.

This goal could be realized with the help of machine learning (ML) where statistical models and algorithms learn from data without explicit instruction (Shatte et al., 2019). A ML model could learn when individuals are at risk of BE or BD in daily life and then subsequently predict this risk when presented with new data in a JITAI. A ML model could

also determine which of the many possibly assessed variables (e.g. momentary mood, location, social context, time) are predictive of BE or BD and which ones are not. Several ML algorithms can examine a large number of variables and select only those that are most predictive of an outcome (Cai et al., 2018) This kind of information could then provide targets for the interventions in a JITAI. However, researchers are confronted with specific challenges when using ML to predict daily life behavior. Namely, they need to decide whether they want to build person-specific or group-level (pooled) prediction models. On the one hand, person-specific models are trained with the data of an individual patient (Soyster et al., 2021). This type of model can be built more easily and can result in more person-specific information. On the other hand, pooled prediction models are trained with the data of multiple patients (Soyster et al., 2021). This model type is more difficult to build as more patients need to be included, but can result in a better model performance, particularly if the factors driving a momentary behavior are similar across the study participants.

In recent years, several studies have built person-specific and/or pooled models to predict BE, alcohol use, and BD in daily life (Arend et al., 2023; Bae et al., 2017; Levinson et al., 2022; Soyster et al., 2021; Walters et al., 2021) Their results are encouraging, but have their limitations. First, their generalizability to a broader clinical population could be limited. This is because only a few studies include a clinical sample and those that do, include a small number of participants for which they only have a limited number of observations. This can be problematic as a small sample size can have serious methodological implications in ML (Way et al., 2010). Indeed, several studies could not hold out data when training or tuning their ML models and therefore were not able to evaluate model performance on unseen data. This means their models could be overfit and not generalize well to new data. Second, the majority of variables in these studies assess emotions or behaviors and do not look at the social or situational context of a patient. However, previous studies show the importance of context in BE, alcohol use, and BD (Allison & Timmerman, 2007; Clapp et al., 2009). Third, to our knowledge only one study evaluated both person-specific and pooled prediction model and did so only for alcohol use, leaving the question unanswered which model type performs best for BE and BD.

Because of these limitations, it is still unclear to what extent BE, alcohol use and BD can be predicted in the daily lives of patients with BN and/or AUD and which variables are important predictors. This study aims to fill that gap. We followed patients with BN and/or AUD over a period of 12 months during which we used the experience sampling method (ESM) to repeatedly assess the patient's emotions, behaviors and contexts in daily life. We

then used this data to fulfill the following two objectives. First, to build and evaluate person-specific and pooled prediction models for BE, alcohol use and BD in daily life. Second, to identify the most important predictors of these behaviors.

6.2. Methods

6.2.1. Study sample

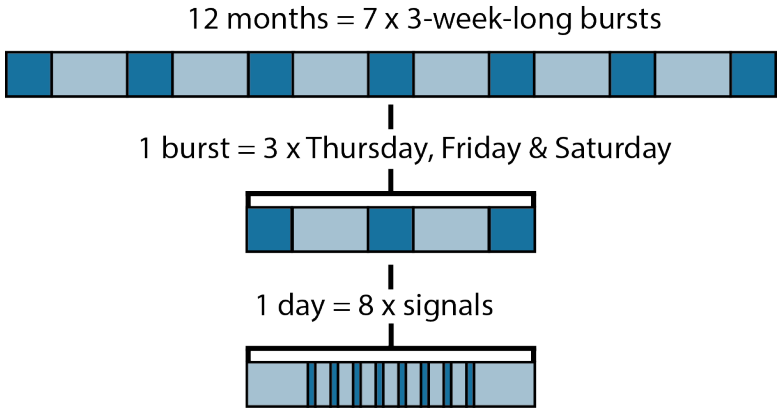
The participants were drawn from a larger ESM study that followed patients with BN and/or AUD as well as control volunteers without these diagnoses in daily life. In the current study, only the data of the patients with BN (n=50), with AUD (n=51) or with BN and AUD (n=19) were used, after the elimination of one patient with BN and two patients with AUD due to insufficient data. Recruitment happened in Flanders, Belgium through residential and ambulatory care centers, patient groups, universities, social media, and by handing out flyers on the street. Inclusion ran from September 2019 to February 2022. The inclusion criteria were: (1) being assigned female at birth; (2) understanding Dutch language; (3) being of age ≥ 18 years; and (4) being of BMI ≥ 18.5 kg/m2. It was decided to not include individuals assigned male at birth as the prevalence of BN in significantly lower in this population (Galmiche et al., 2019). Additional inclusion criteria for patients were: (5) meeting the criteria for BN or AUD of the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013); (6) meeting those diagnostic criteria for a duration of ≤ 5 years. This maximum was set as the role of certain factors in BN and AUD is thought to depend on illness duration (Boness et al., 2021; Pearson et al., 2015). Participants with AUD also needed to display a pattern of repetitive BD according to the criteria of the National Institute on Alcohol Abuse and Alcoholism (i.e., drinking 4 units of alcohol within 2 hours for women) (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2022). Participants were excluded for the following reasons: (1) major medical pathology (e.g., severe liver or kidney disease, uncontrolled diabetes, cancer or untreated hyper- or hypothyroidism); (2) chronic use of sedatives (i.e., more than three times in the past three month); (3) pregnancy; (4) presence of major psychiatric pathology (i.e., schizophrenia, autism spectrum disorder, bipolar disorder, substance use disorder). All participants gave their written consent, and the study was approved by the ethical committee of the UZ/KU Leuven.

6.2.2. Study design

Potential participants were initially screened via telephone or email, after which they attended an in-person assessment. Here, a resident of psychiatry confirmed an individual's eligibility to participate. The participants had their weight and height measured with a calibrated scale and stadiometer and completed clinical interviews and questionnaires. All participants underwent a briefing on the ESM questions and practiced the use of the mobile application. Then, the participants entered the ESM protocol on the first Thursday after the in-person assessment. An overview of the protocol can be seen in Figure 1. It consisted of a repeated measurement design where 7 bursts of data collection were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday to limit the protocol's impact on the participants. These specific days were selected to consecutively gather data on both week and weekend days. On a given day of data collection, participants received 8 signals which were sent out on a signal-contingent (i.e. semi-random) basis. The ESM data were initially collected with the app MobileQ (Meers et al., 2020). When the development of the app was discontinued in October 2020, data collection continued using m-Path (Mestdagh et al., 2022). More information about the apps can be found in eMethods 1 and eTable 1 in the supplement.

Figure 1. Experience sampling method protocol.

The protocol consisted of 7 bursts of data collection which were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis.



6.2.3. Measures

6.2.3.1. Baseline measures

The Structured Clinical Interview for DSM-5 (SCID-5-S) was used to confirm the diagnosis of BN or AUD and to screen for other psychiatric disorders (APA, 2017). BN and AUD severity were assessed using the Eating Disorder Examination Questionnaire (EDE-Q) and the Alcohol Use Disorders Identification Test (AUDIT) (Fairburn & Beglin, 1994; Saunders et al., 1993).

6.2.3.2. ESM measures

At each assessment, the participants received questions evaluating different emotions, behaviors and contexts. The exact number of items varied at each assessment as the presentation of some questions was conditional on a participant's response to a previous question. The full list of questions can be found in the supplement (eMethods 2). Importantly, participants needed to indicate if they had eaten since the previous assessment. If so, they had to identify the eating event as undereating, normal eating, or overeating. Then, participants were asked if they experienced a loss of control over their eating behavior. As in previous studies, **BE** was defined as an episode of overeating with loss of control (Ambwani et al., 2015). Similarly, participants needed to indicate whether they drank alcohol since the previous assessment and if so, how many units they drank and if they experienced a loss of control over their drinking behavior. Here, **BD** was defined as having consumed at least four units of alcohol since the previous assessment while **alcohol use** was conceptualized as having consumed at least one unit since the previous assessment. Other questions examined **negative affect** (e.g. feeling down, stressed, guilty), **positive affect** (e.g., feeling satisfied, cheerful), **rash action** (e.g., doing something risky), **lack of perseverance** (e.g., something I should be doing but am not), **craving** (e.g., a desire for a BE episode or alcohol), **motivation** (e.g., feeling interested in doing things), **activity-related stress** (e.g., what am I doing, can I handle the situation), **social-related stress** (e.g., who am I with, do I like this company), **event-related stress** (e.g., what happened to me, how stressful was it, how pleasant was it), **location** (e.g., home, at a friend's house) and **substance use** (e.g., caffeine, nicotine). These questions were chosen based on previous research (Gevonden et al., 2016; Kasanova et al., 2018; Myin-Germeys et al., 2003; Rintala et al., 2020; Sperry et al., 2018; Vaessen et al., 2017; Wonderlich et al., 2017).

6.2.4. Data analysis

6.2.4.1. Data preparation

Only the assessments answered within 240 minutes of the prompt were used in the analyses. This lengthier assessment window allowed promts to be included which were answered later in the evening/night when the likelihood of a BE, alcohol use or BD episode happening is higher. Though not all ESM studies report their assessment window, some report using lengthier windows (Walters et al., 2021).

First, the scoring of the conditional ESM variables was corrected. A conditional ESM variable depended on a previous ESM answer (e.g., how stressful an event was, was only asked on the condition that a participant answered "yes" on experiencing a stressful event). The conditional ESM variables therefore included missing values, when the condition was not met, which could be filled in with zeroes (i.e. indicating that past events were not stressful at all). Second, temporal variables were created that represented assessment number (i.e., 1 to 8), day (i.e., Thursday, Friday and Saturday), time since starting participation in the study (linear, quadratic, cubic) and cycles of 12 hr, 24 hr, and weekly frequency (Flury & Levri, 1999). These temporal variables have been used in previous studies predicting BE and alcohol use (Arend et al., 2023; Soyster et al., 2021). Third, to account for the varying levels of COVID-19 prevention measures throughout the study, a COVID-19 stringency variable was created based on the Oxford COVID-19 Government Response Tracker (Kira et al., 2022). This brought the total number of predictors to 110. Fourth, all ESM variables except for the outcome variables were lagged by one assessment, with time between assessments measuring 102 minutes on average. The variables could be lagged across days, but not across weeks. The temporal variables and the COVID-19 stringency variable were not lagged and therefore remained aligned in time with the outcome variables. Fifth, observations with missing values were removed from the data.

This resulted in a dataset which could be used to predict BE, BD and alcohol use at a certain point in time, based on the temporal variables and the COVID-19 stringency variable at that timepoint as well as the ESM variables at a previous timepoint. As lagging across days was permitted, BE, BD and alcohol use episodes which happened at night but were reported in the morning could also be predicted.

6.2.4.2. Model training and evaluation

Person-specific as well as pooled prediction models were built for BE, alcohol use, and BD. Based on the definitions outlined under ESM measures, the moments of BD were also

considered moments of alcohol use. This approach was taken because a JITAI would most likely focus on either alcohol use or BD, rather than non-heavy alcohol use. For BE, the data of the patients with BN and the patients with BN and AUD were used (n=69). Similarly, for alcohol use and BD, the data of the patients with AUD and the patients with BN and AUD were used (n=70). The models were trained and evaluated with the *ensr*, *glmnet*, *pROC* and *caret* packages in R, version 4.1.1 (Friedman et al., 2010; Max Kuhn, 2021; Peter DeWitt, 2019; Robin et al., 2011). The script and data for the analyses can be found at https://rdr.kuleuven.be/dataset.xhtml?persistentId=doi:10.48804/OBLDWE. More information on the elastic net wrappers which were developed for this paper can be found at https://github.com/mikojeske/MBR_ML.

Person-specific

The models were fitted and evaluated on the data of each participant with nested k-fold cross-validation. A visual representation of this method can be seen in Figure 2. More information on nested cross-validation can be found in the supplement (eMethods 3). For the outer loop, a stratified 5-fold cross-validation was used. Due to the stratification, the distribution of positive events was similar across folds. The allocation of observations to specific folds was random, meaning that the observations within each fold were not temporally contiguous. However, due to the lagging procedure described above, each instance of the dependent variables was only ever predicted by the independent variables for the immediately previous observation. The continuous variables of the training folds were standardized. This can increase performance of regression-based models and simplify comparisons between model estimates (Shahriyari, 2019). Additionally, the continuous variables from the test fold were also standardized, but with the mean and standard deviation from the training folds. This separated procedure transforms the testing data to the same scale as the training data, but prevents any information from leaking.

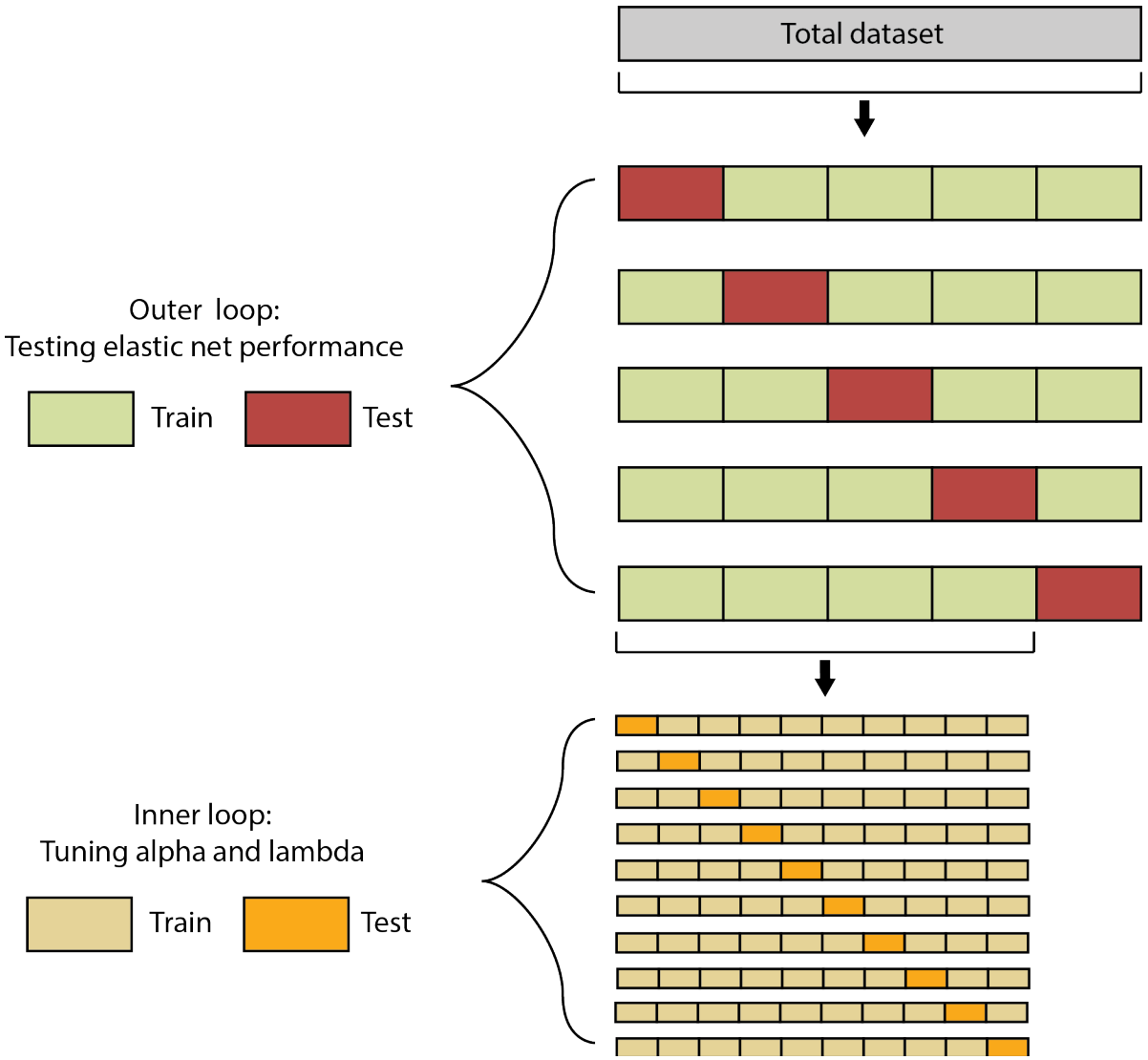
For the inner loop, an elastic net regularized regression model was fitted to the training folds of the outer loop (Zou & Hastie, 2005). Though other machine learning techniques exist, elastic net is especially suited for the objectives of the current manuscript. This is because it is a performant machine learning technique that reduces overfitting and can work with high-dimensional data, but also provides information on the strength and nature of the relation between a predictor and an outcome. It combines two regularization methods, ridge regression which shrinks model estimates and LASSO regression which removes variables that do not contribute to the model. The amount of ridge and lasso regression is

expressed by a variable alpha which varies from 0 (exclusively ridge regression) to 1 (exclusively LASSO). The strength of the regularization is defined by a variable lambda with higher values leading to more shrinkage of the coefficients. The most optimal alpha and lambda were selected with a grid search of 10 alphas and 100 lambdas (i.e., the default settings of *ensr*). For each possible combination, a cross-validation error was calculated with 10-fold cross-validation. The combination with the lowest cross-validation error was then used to fit the definitive elastic net model on the training folds of the outer loop. This elastic net model was then used to predict BE, BD or alcohol use in the data of the test fold of the outer loop. The predictions were then compared with the actual BE, BD and alcohol use events in the test fold to calculate the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV). Due to the nested cross-validation, a participant needed to have a sufficient number of BE, BD or alcohol use events (n>5) to be included in the analysis.

Pooled

The pooled models were also fitted and evaluated with nested k-fold cross-validation. However, they were trained on the pooled training data of all the participants and tested on the individual test data of each participant. More specifically, in the outer loop, the training folds were a combination of the standardized training folds of the participants. Due to the standardization at a participant-level, the values of the continuous variables represented a deviation from the within-person means. As no multilevel variant of elastic net regularized regression exists, this accounted in part for the within-person nesting of the data (Soyster et al., 2021). In the inner loop, the most optimal alpha and lambda were again determined with 10-fold cross-validation and used to fit the final elastic net model. This model was then applied to the test fold of every individual participant to evaluate the AUC, sensitivity, specificity, accuracy, PPV, and NPV of the pooled model for each participant. As the training folds were pooled, a participant only needed to have one BE, BD or alcohol use event in the test fold to be included in the analyses.

Figure 2. Nested cross-validation.
In the outer loop, the total dataset was divided into five folds which were processed in five rounds. During each round, one fold was used as a test set while the other four folds were used a training set. In the inner loop, the training folds were used to select the most optimal alpha and lambda and to fit the elastic net model. A grid search of 10 alphas and 100 lambdas was performed with a 10-fold cross-validation. The combination with the lowest cross-validation error was used to fit the definitive elastic net model. This model was then evaluated on the test fold of the outer loop.



6.2.3.3 Exploratory analyses

For each participant and each outcome, the difference between the AUC of the person-specific and pooled models was calculated. To explore reasons why some participants had a better performance with the person-specific or with the pooled model, this difference in AUC was compared between the different analyses groups and correlated to age, BMI, EDE-Q scores, AUDIT scores, BE frequency and BD frequency. Due to the non-normal distribution of the AUCs, non-parametric Mann–Whitney U tests and Spearman correlations were

performed. Furthermore, for each outcome and each model type, the 10% best predictors were identified. This was based on the raw estimates for the pooled model (as only one estimate per variable existed) and the mean estimates over all participants for the person-specific models.

6.3. Results

6.3.1. Sample characteristics

The characteristics of the different patient groups can be found in Table 1. Additionally, the characteristics of the different analysis groups (i.e., for BE or BD/alcohol use) can be found in the supplement (eTable 2). Notably, the age of the patients with BN/AUD (mean=20.4, SD=1.7, CI=19.6-21.2) was lower than that of the patients with BN (mean=22.4, SD=4.1, CI=21.3-23.6). Also, the BMI of the patients with BN (mean=25.6, SD=5.9, CI=23.9-273) was higher than that of the patients with AUD (mean=21.5, SD=3.5, CI=20.5-22.4).

6.3.2. Data characteristics

In total, 41 (34.2%) participants (16 (32.0%) BN, 19 (37.3%) AUD, 6 (31.6%) BN/AUD) dropped out of the study before the end of the ESM protocol. The mean compliance (percentage of signals answered) per participant during the first burst was 80.4% for the patients with BN, 75.2% for the patients with AUD and 73.6% for the patients with BN/AUD. This is similar to the compliance rates of previous cross-sectional ESM studies in patients with an eating disorder or AUD (Fischer et al., 2018; Jones et al., 2019; Schaefer et al., 2020). In total, the patients with BN answered 12,932 (61.5%) of their scheduled beeps, while the patients with AUD answered 12,328 (62.9%) and the patients with BN/AUD answered 3,947 (51.2%). The overall compliance of this study fell in the range of the lengthier ESM studies on substance use (Jones et al., 2019). More information on the reasons for dropout and the compliance per burst can be found in the supplement (eResults 1 and eTable 3).

Table 1. Sample characteristics

	AUD (n=51)		BN and AUD (n=19)		BN (n=50)	
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
Age	21.5 (3.5)	20.5-22.4	20.4 (1.7)	19.6-21.2	22.4 (4.1)	21.3-23.6
BMI	22.8 (2.0)	22.2-23.4	24.2 (3.0)	22.8-25.7	25.6 (5.9)	23.9-27.3
Illness Duration BN (years)	0 (0)	0-0	2.7 (1.4)	2.1-3.4	2.4 (1.6)	2.0-2.9
Illness Duration AUD (years)	3.1 (1.3)	2.7-3.5	2.2 (1.4)	1.5-2.9	0 (0)	0-0
Education (years)	14.7 (1.7)	14.3-15.2	13.9 (1.6)	13.2-14.7	14.7 (2.3)	14.0-15.3
AUDIT	15.2 (5.3)	13.7-16.7	16.6 (4.3)	14.6-18.7	4.5 (4.2)	3.3-5.7
EDE-Q						
Restraint	0.7 (0.8)	0.5-1.0	2.7 (1.6)	1.9-3.5	2.9 (1.5)	2.4-3.3
Shape Concern	1.9 (1.4)	1.5-2.3	4.0 (1.4)	3.3-4.7	4.3 (1.5)	3.9-4.7
Weight Concern	1.5 (1.3)	1.1-1.9	4.0 (2.0)	3.0-5.0	4.1 (1.5)	3.7-4.5
Eating Concern	0.5 (0.7)	0.3-0.7	2.9 (1.4)	2.2-3.5	2.8 (1.5)	2.4-3.2
Total	1.2 (1.0)	1.0-1.5	3.5 (1.3)	2.8-4.1	3.6 (1.3)	3.3-4.0
Eating disorder symptoms (days/4 weeks)						
Binge eating	0 (0)	0-0	6.5 (5.5)	3.8-9.1	8.7 (7.2)	6.7-10.8
Fasting	0 (0)	0-0	7.6 (7.5)	4.0-11.2	8.0 (8.4)	5.6-10.4
Vomiting	0 (0)	0-0	1.9 (3.8)	0.1-3.8	2.2 (6.1)	0.5-4.0
Laxative use	0 (0)	0-0	0.1 (0.5)	0-0.3	0.4 (2.3)	0-1.0
Diuretic use	0 (0)	0-0	0 (0)	0-0	1.1 (5.3)	0-2.6
Compensatory exercise	0 (0)	0-0	6.7 (7.1)	3.3-10.1	6.5 (7.4)	4.4-8.6
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
Binge drinking frequency						
Never	0 (0%)	0-0%	0 (0%)	0-0%	27 (54%)	42-68%
Annually	0 (0%)	0-0%	0 (0%)	0-0%	8 (16%)	4-30%
Semiannually	0 (0%)	0-0%	0 (0%)	0-0%	2 (4%)	0-18%
Three-monthly	5 (10%)	0-25%	1 (5%)	0-31%	6 (12%)	0-26%
Monthly	9 (18%)	6-33%	3 (16%)	0-42%	3 (6%)	0-20%
Biweekly	21 (41%)	29-56%	9 (47%)	32-74%	3(6%)	0-20%
Weekly	9 (18%)	6-33%	5 (26%)	11-53%	1 (2%)	0-16%
>Weekly	7 (14%)	2-29%	1 (6%)	0-31%	0 (0%)	0-0%
Therapy (BN or AUD)	1 (2%)	0-6%	6 (32%)	9-54%	8 (16%)	6-26%
Ethnicity						
Caucasian	48 (94%)	90-100%	19 (100%)	100-100%	43 (86%)	78-95%
Latino	1 (2%)	0-8%	0 (0%)	0-0%	0 (0%)	0-0%
Asian	0 (0%)	0-0%	0 (0%)	0-0%	3 (6%)	0-15%
Mixed	2 (4%)	0-10%	0 (0%)	0-0%	0 (0%)	0-0%
Middle-Eastern	0 (0%)	0-0%	0 (0%)	0-0%	4 (8%)	0-17%
Psychoactive medication	6(12%)	3-21%	3 (16%)	0-33%	8 (16%)	6-26%
Comorbidities						
MDD	3 (6%)	0-16%	4 (21%)	5-47%	5 (10%)	0-24%
PD	2 (4%)	0-14%	1 (4%)	0-31%	4 (8%)	0-22%
SAD	1 (2%)	0-13%	1 (4%)	0-31%	5 (8%)	0-24%
ADHD	3 (6%)	0-16%	0 (0%)	0-0%	0 (0%)	0-0%
PTSD	0 (0%)	0-0%	4 (21%)	5-47%	5 (10%)	0-24%
AP	0 (0%)	0-0%	0 (0%)	0-0%	4 (8%)	0-22%

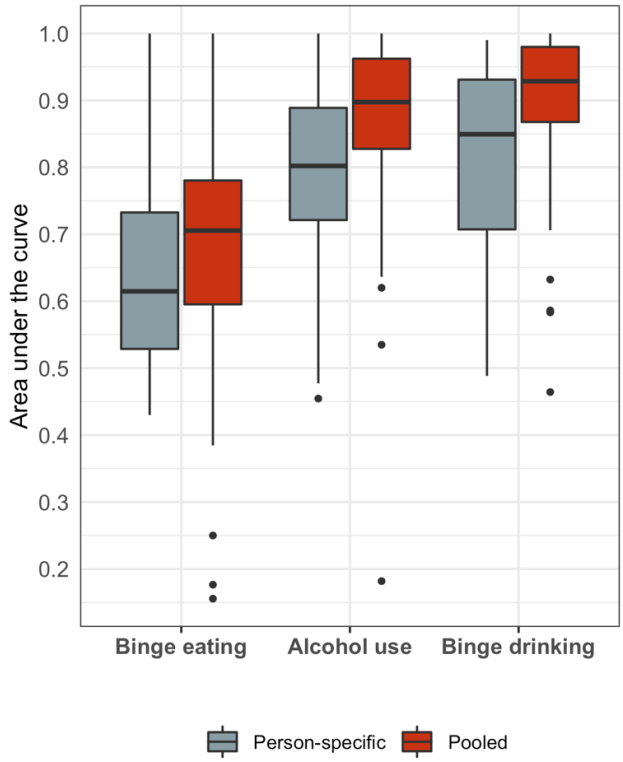
Abbreviations: ADHD, attention deficit hyperactivity disorder; AP, agoraphobia; AUD, alcohol use disorder; BMI, body mass index; BN, bulimia nervosa; CI, confidence interval; EDE-Q, Eating Disorder Examination Questionnaire; MDD, major depressive disorder; N, number; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SD, standard deviation.

6.3.3. Model performance

The performance metrics had a skewed distribution within and between participants. Therefore, the median across folds and across participants was used to describe them. An extended overview can be found in Table 2. A visual summary can be seen in Figure 3.

Figure 3. Model Performance.

Performance of the person-specific and pooled prediction models for binge eating, alcohol use and binge drinking. Due to a skewed distribution of the performance metrics within participants, the median across folds was taken for the area under the curve



Binge eating

A person-specific model could be fitted and evaluated for 48 (69.6%) participants. The performance of the person-specific models was poor with a median AUC of 0.61 (Q1:0.53; Q3:0.73), sensitivity of 0.83 (Q1:0.67; Q3:1.00) and specificity of 0.71 (Q1:0.56; Q3:0.78). The pooled model could be evaluated on 66 (95.7%) participants. Its performance was adequate with a median AUC of 0.71 (Q1:0.60; Q3:0.78), sensitivity of 01.00 (Q1:0.75; Q3: 1.00) and specificity of 0.75 (Q1:0.60; Q3:0.86).

Table 2. Model Performance

The performance metrics had a skewed distribution within and between participants. Therefore, they are best described by the median across folds and participants. To compare, the results after taking the mean across folds is also presented.

Outcome	Type	CV aggregation	N (%)	AUC	Sensitivity	Specificity	Accuracy	PPV	NPV
Binge eating	Person-specific	Mean	48 (69.6%)	0.64	0.82	0.67	0.68	0.34	0.95
		Median		0.61	0.83	0.71	0.71	0.31	0.97
	Pooled	Mean	66 (95.7%)	0.69	0.88	0.73	0.73	0.41	0.96
		Median		0.71	1.00	0.75	0.74	0.33	1.00
Alcohol use	Person-specific	Mean	43 (61.4%)	0.80	0.90	0.80	0.80	0.43	0.98
		Median		0.80	1.00	0.80	0.80	0.38	1.00
	Pooled	Mean	63 (90.0%)	0.87	0.96	0.86	0.87	0.56	0.99
		Median		0.90	1.00	0.88	0.87	0.50	1.00
Binge drinking	Person-specific	Mean	14 (18.6%)	0.81	0.90	0.90	0.85	0.35	0.99
		Median		0.85	1.00	0.90	0.86	0.28	1.00
	Pooled	Mean	49 (70.0%)	0.90	1.00	0.89	0.90	0.54	1.00
		Median		0.93	1.00	0.93	0.93	0.50	1.00

Abbreviations: AUC, area under the curve; CV, cross-validation; N, number of participants with a successful model; NPV, negative predictive value; PPV, positive predictive value.

Alcohol use

There were 43 (61.4%) participants with a person-specific model. The performance of these models was good with an AUC of 0.80 (Q1:0.72; Q3:0.89), sensitivity of 1.00 (Q1:0.79; Q3:1.00) and specificity of 0.80 (Q1:0.75; Q3:0.88). The pooled model could be evaluated on 63 (90.0%) participants. It had an outstanding performance with an AUC of 0.90 (Q1:0.83; Q3:0.96), sensitivity of 1.00 (Q1: 1.00; Q3: 1.00) and specificity of 0.88 (Q1:0.80; Q3:0.96).

Binge drinking

A person-specific model could be fitted and evaluated for 13 (18.6%) participants. The performance of the person-specific models was good with a median AUC of 0.85 (Q1: 0.71; Q3: 0.93), sensitivity of 1.00 (Q1:0.75; Q3:1.00) and specificity of 0.90 (Q1:0.78; Q3: 0.96). The performance of the pooled model could be evaluated on 49 (70.0%) participants. Its performance was outstanding with an AUC of 0.93 (Q1: 0.87; Q3: 0.98), sensitivity 1.00 (Q1: 1.00; Q3: 1.00) and a specificity of 0.93 (Q1: 0.84; Q3: 0.99).

6.3.4. Model comparison

The difference in AUC between the person-specific and pooled models did not differ significantly between the groups and did not correlate with age, BMI, EDE-Q scores, AUDIT scores, BE frequency and BD frequency.

6.3.5. Model predictors

A visual summary of the 10% best predictors for each outcome and each model type can be seen in Figure 4.

Binge eating

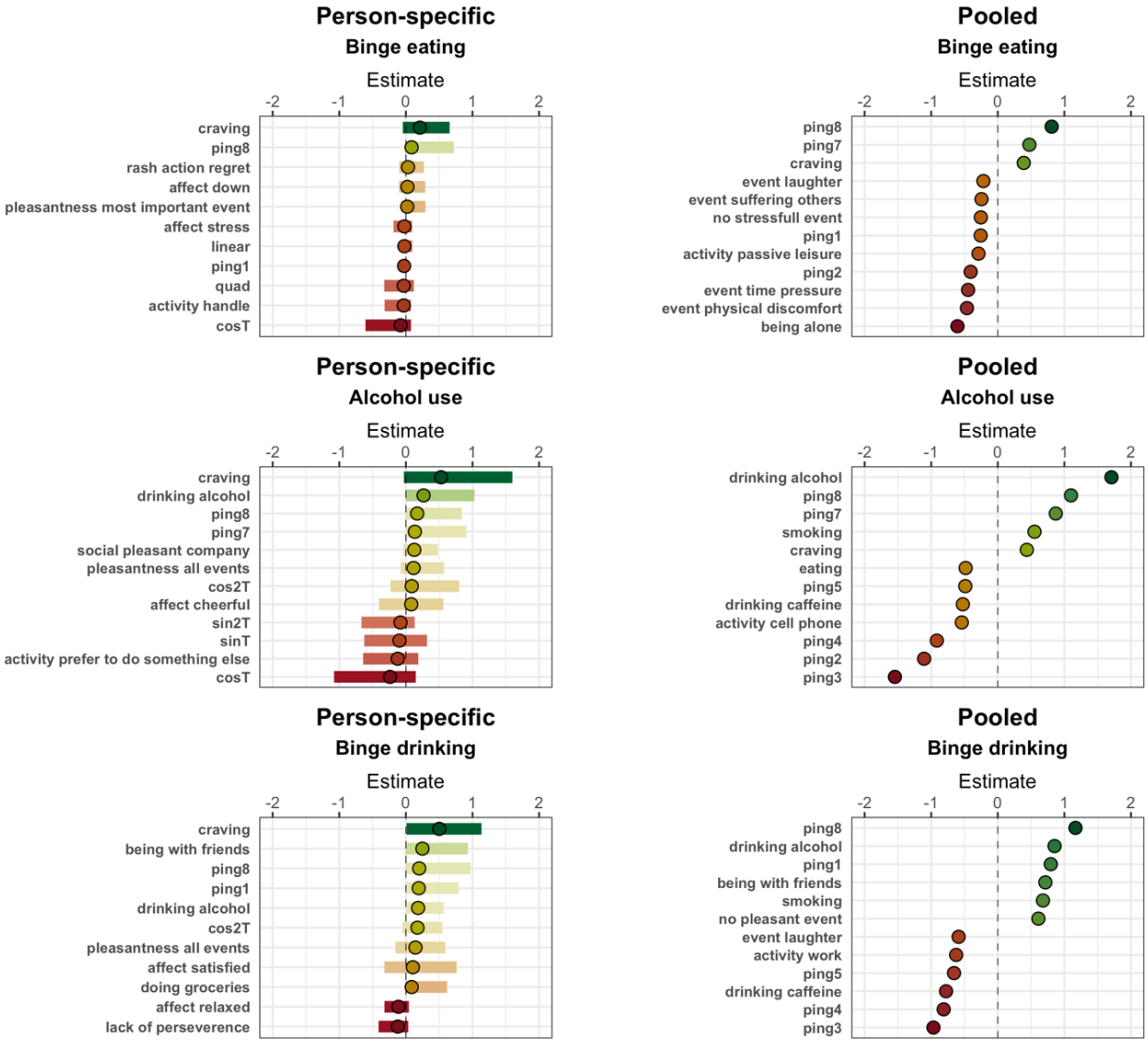
For the person-specific models, BE was positively predicted by craving, evening hours (i.e., ping 8), doing things that you regret, feeling down, and the pleasantness of the most important event. It was negatively predicted by feeling like you can handle the situation, feeling stressed, and night (i.e., ping 1). For the pooled model, the best positive predictors were evening (i.e., ping 7, ping 8) and craving. The best negative predictors were being alone, experiencing physical discomfort, being under pressure, morning (ping 2), night (ping 1), being in a calm environment (i.e., passive leisure activities, experiencing no stressors), experiencing the suffering of others, and having laughed.

Alcohol use

For the person-specific models, alcohol use was positively predicted by craving, having drunk alcohol, evening (i.e., ping 7 and ping 8), pleasant company, experiencing pleasant events, and feeling cheerful. It was negatively predicted by wanting to do something. The best positive predictors for the pooled model were having drunk alcohol, evening (i.e., ping 7 and 8), smoking, and craving. The best negative predictors for the pooled model were morning/noon (ping 2, 3, 4 and 5), drinking caffeine, having eaten and being on your cellphone.

Figure 4. Model predictors.

The predictors of the person-specific and pooled prediction models with the 10% highest estimates for binge eating, alcohol use and binge drinking. For the person-specific models, the mean estimate and 95% interval across all participants is shown. For the pooled predictions models, the single estimate is displayed.



<u>Binge drinking</u>

For the person-specific models, BD was positively predicted by craving, being with friends, drinking alcohol, evening (i.e., ping 8), night (i.e., ping 1), experiencing pleasant events, feeling satisfied, and doing groceries. However, BD was negatively predicted Zby a lack of perseverance, and feeling relaxed. For the pooled models, Important positive predictors were evening (i.e., ping 8), night (i.e., ping 1), drinking alcohol, being with friends, smoking and experiencing no positive events. Important negative predictors were noon (i.e., ping 3, 4, and 5), drinking coffee, studying/working, and having laughed.

6.4. Discussion

This study had two objectives. First, to build and evaluate person-specific and pooled prediction models for BE, alcohol use, and BD in patients with BN and/or AUD. Second, to identify the most important predictors of these behaviors.

Model performance

The performances of the prediction models ranged from poor to outstanding, but were similar or slightly better than those in studies predicting eating behaviors and alcohol use in healthy volunteers (Goldstein et al., 2018; Soyster et al., 2021). Nevertheless, this does not provide any information on whether these models performed well enough to be used in a clinical context. To our knowledge, only one study has implemented the use of ML in a JITAI (Forman et al., 2019). In this study, the authors found that dietary lapses could be predicted and prevented with a ML model whose performance was similar to that of the current study`s pooled model for BE (Forman et al., 2019). This suggests that the pooled prediction models of the current study as well as the person-specific models for alcohol use and BD could be used in a JITAI. However, there remains room for improvement. First, the study design could be adapted to the needs of the individual patients. Namely, the ESM questions of the current study are based on previous literature. However, if the questions would be based on the reported triggers of the individual patients, the performance of the ML models might improve (Arend et al., 2023). Second, other ML analysis techniques could be better at predicting certain behaviors. For example, it could be that elastic net regression is not well suited to predict BE and that other ML techniques would result in a better predictive performance.

The results also showed that the pooled prediction models outperformed the person-specific ones, which is in line with the majority of previous studies (Cheung et al., 2017; Goldstein et al., 2018; Ntekouli et al., 2022; Rozet et al., 2019; Soyster et al., 2021). This could be due to several reasons. On the one hand, the difference in performance could be the result of the larger number of observations that were used to train the pooled models. Indeed, studies show that ML performance is related to dataset size (Althnian et al., 2021). One study also found that the performance of person-specific models increases with a greater number of observations until it is similar to that of pooled models (Rozet et al., 2019). On the other hand, the better performance of the pooled models could be the result of the characteristics of the participants. Namely, previous studies show that group-level methods lend themselves

well to samples that are homogenous (i.e., with a low inter-individual variability), which is the case in the current study (Fisher et al., 2018; Molenaar, 2004).

Taken together, these findings raise the question whether pooled prediction models would translate well to a clinical setting, where it could be difficult to gather a large dataset and where more inter-individual variability is seen. However, though it would be easier to build a person-specific model, it might be difficult to observe enough events of interest, as evident from the current study's low percentage of person-specific models for BD. This suggests that it could be interesting to explore a combination of both person-specific and pooled approaches. Indeed, studies bridging this gap show encouraging results, but further research is needed (Ren et al., 2022).

Most important predictors

There were significant differences between the most important predictors of the person-specific and pooled prediction models. This is not unexpected as previous studies have shown that the agreement between person-level and group-level analyses is limited (Fischer et al., 2018). Furthermore, the differences between the types of predictors could have important implications for the development of JITAIs. Namely, it could be challenging to develop interventions that target the predictors of the pooled models as these mostly concern the time of day (e.g., evening or night) or recent events (e.g., experiencing something boring or being under pressure). It might be more valuable to focus on the predictors of the person-specific models as they deal with thoughts (e.g., craving), emotions (e.g., negative affect, positive affect) and behaviors (e.g., acting rash). This suggests that though pooled models might have a better performance, person-specific models could still be of value when it comes to tailoring daily life interventions.

The results also showed that there are both similarities and differences in the predictors for BE, alcohol use and BD. First, it can be seen that craving was the most important predictor across the person-specific models of all behaviors. Though the relation between craving and alcohol use has been investigated by a large number of studies, this is less the case for BE (Cavicchioli et al., 2020; Novelle & Diéguez, 2018; Seo & Sinha, 2014). Future studies should therefore investigate the relationship between craving and BE in more depth. Second, positive events (i.e., the pleasantness of all events) and affect (i.e., feeling cheerful and satisfied) were important predictors of alcohol use and BD. This showcases the hypothesized link between positive emotions and alcohol consumption (Cooper et al., 1995). However, the pleasantness of the most important event was also a predictor of BE. Though

studies have shown that positive affect often decreases before a BE episode, other studies indicate that patients who act more rashly when positive affect is high also have a higher BE frequency (Michael & Juarascio, 2021; Schaefer et al., 2020). Future studies should therefore explore whether positive emotions can also be a trigger for BE episodes in patients with BN. Third, BE was predicted by changes in negative emotions. More specifically, it was positively predicted by feeling down and negatively predicted by feeling stressed. Though studies show that negative emotions can indeed trigger BE, others also have found that negative emotions can also lead to dietary restriction and that some emotions could be more related to BE than others (Berg et al., 2013; Haedt-Matt & Keel, 2011; Leenaerts et al., 2023b; Mikhail, 2021). Future studies should therefore explore when negative emotions lead to BE and when they lead to dietary restriction. Contrastingly, negative emotions or events were not included in the most important predictors of alcohol use or BD. Though the induction of negative affect has been shown to lead to increases in alcohol consumption in a laboratory context, a recent meta-analysis reports that this is not the case in daily life (Bresin et al., 2018; Dora et al., 2022). This could be one reason why negative emotions were not an important predictor of alcohol use and BD in the current study. However, in our own recent work, we found that there was a relation between negative affect and alcohol use, but a non-linear one (Leenaerts et al., 2023a). This could another reason why the elastic net regression did not retain negative emotions as an important predictor as it assumes a linear relation between variables.

Limitations

This study has several limitations. Importantly, the sample mostly consists of female participants who were Caucasian and had a short illness duration. This could mean that the results of the current study would not generalize well to all patients with BN and AUD. Therefore, future studies should try to predict BE, alcohol use and BD in other samples. Also, there was a considerable amount of missing data due to the study's repeated measures design. However, this study also had the strength of having a large sample size. To our knowledge, it included the largest number of participants and observations of all studies trying to predict BE, alcohol use and BD in daily life. Though no adequate tools exist to calculate the sample size for elastic net regularized regression models, an approximate calculation based on formulas for regularized regression suggests that several thousands of observations are needed to adequately develop the prediction models in this study (eDiscussion 1) (Riley et al., 2020). This means that the pooled prediction models probably included a large enough

number of observations, but that the person-specific models might not have an adequate sample size for the high number of predictors. However, further research is needed on the required sample size for elastic net regression models with many predictors, especially in a person-specific context where datsets are typically smaller.

6.5. Conclusion

This study builds and evaluates person-specific and pooled prediction models for BE, alcohol use, and BD in patients with BN and/or AUD. The performances of the different models vary between poor and outstanding, but the pooled models outperform the person-specific ones and the models for alcohol use and BD outperform those for BE. This study also explores which variables are the most important predictors in the different models. Here, the predictors of the pooled models mostly concern the time of day and recent events, while those of the person-specific models mostly concern thoughts, emotions, and behaviors. Future studies should explore whether pooled and person-specific approaches could be combined and how BE, alcohol use, and BD can be impacted by interventions in daily life.

6.6. References

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CHAPTER 7

The Neurobiological Reward System and Binge Eating: A Critical Systematic Review of Neuroimaging Studies

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Abstract

Objective: Changes in reward processing are hypothesized to play a role in the onset and maintenance of binge eating (BE). However, despite an increasing number of studies investigating the neurobiological reward system in individuals who binge eat, no comprehensive systematic review exists on this topic. Therefore, this review has the following objectives: (1) identify structural and functional changes in the brain reward system, either in rest or while performing a task; (2) formulate directions for future research.
Methods: A search was conducted of papers published until March 31st 2022. Neuroimaging studies were eligible if they wanted to study the reward system and included a group of individuals who binge eat together with a comparator group. Their results were summarized in a narrative synthesis.
Results: A total of 58 articles were included. In rest, individuals who binge eat displayed a lower striatal dopamine release, a change in the volume of the striatum, frontal cortex and insula as well as a lower frontostriatal connectivity. While performing a task, there was a higher activity of the brain reward system when anticipating or receiving food, more model-free reinforcement learning and more habitual behavior. Most studies only included one patient group, used general reward-related measures and didn't evaluate the impact of comorbidities, illness duration, race or sex.
Discussion: Confirming previous hypotheses, this review finds structural and functional changes of the neurobiological reward system in BE. Future studies should compare disorders, use measures which are specific for BE and investigate the impact of confounding factors.

7.1. Introduction

Binge eating (BE) is defined as eating an amount of food, within any 2-hour period, that is definitively larger than what most individuals would eat in a similar time period under similar circumstances combined with a feeling that one cannot stop eating or control how much one is eating (American Psychiatric Association, 2013). It is a pivotal symptom of several psychiatric disorders such as binge eating disorder (BED), bulimia nervosa (BN) and anorexia nervosa binge/purge-type (AN-BP) (American Psychiatric Association, 2013). Changes in reward processing are thought to play an important role in the onset and maintenance of BE (Pearson et al., 2015). The acquired preparedness model hypothesizes that certain individuals acquire maladaptive expectancies about food because they display high-risk personality traits that influence reward learning (Combs et al., 2010). According to this model, Individuals who are more impulsive when negative affect is elevated could acquire the expectancy that impulsive actions such as BE alleviate negative affect. Separately, the incentive-sensitization theory suggests that repeated BE episodes are themselves a maintaining factor for BE (Robinson et al., 1993). This is because they are thought to sensitize the reward system to the anticipation of food, leading to a higher incentive salience (i.e., 'wanting') (Robinson et al., 1993). However, repeated BE episodes could also cause habituation of the reward system to receiving food, leading to a lower responsivity and necessitating the consumption of even larger amounts to elicit the same response (Berridge et al., 2016).

Indeed, several studies find differences in monetary and food reward processing between individuals who binge eat and controls. They find that individuals who binge eat display a higher incentive salience for food, a steeper discounting of monetary rewards and difficulties with reinforcement learning (Schaefer et al., 2021; Steinglass et al., 2019). These behavioral differences are thought to be the result of changes in the neurobiological reward system. Important brain regions for reward processing are the insula, the ventral striatum (VS) or nucleus accumbens (NAc), the dorsal striatum (DS) which consists of the caudate nucleus (CN) and putamen, the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), the ventromedial PFC (vmPFC) and the dorsolateral PFC (dlPFC) (Schultz, 2015). However, investigating the neurobiological reward system can be challenging with studies often reporting difficult to interpret or even contradictory results (Zald et al., 2017). One reason for these challenges could be the overall lack of uniformity and specificity in how reward processing is

defined in neuroimaging research (Zald et al., 2017). Therefore, to have more uniform definitions in neuroscience, the National Institute for Mental Health (NIMH) has developed the Research Domain Criteria (RDoC). In the RDoC framework, reward processing is subsumed under the Positive Valence Systems which consist of three constructs and nine subconstructs (Insel et al., 2010). For a detailed overview of the Positive Valence Systems, see Figure 1.

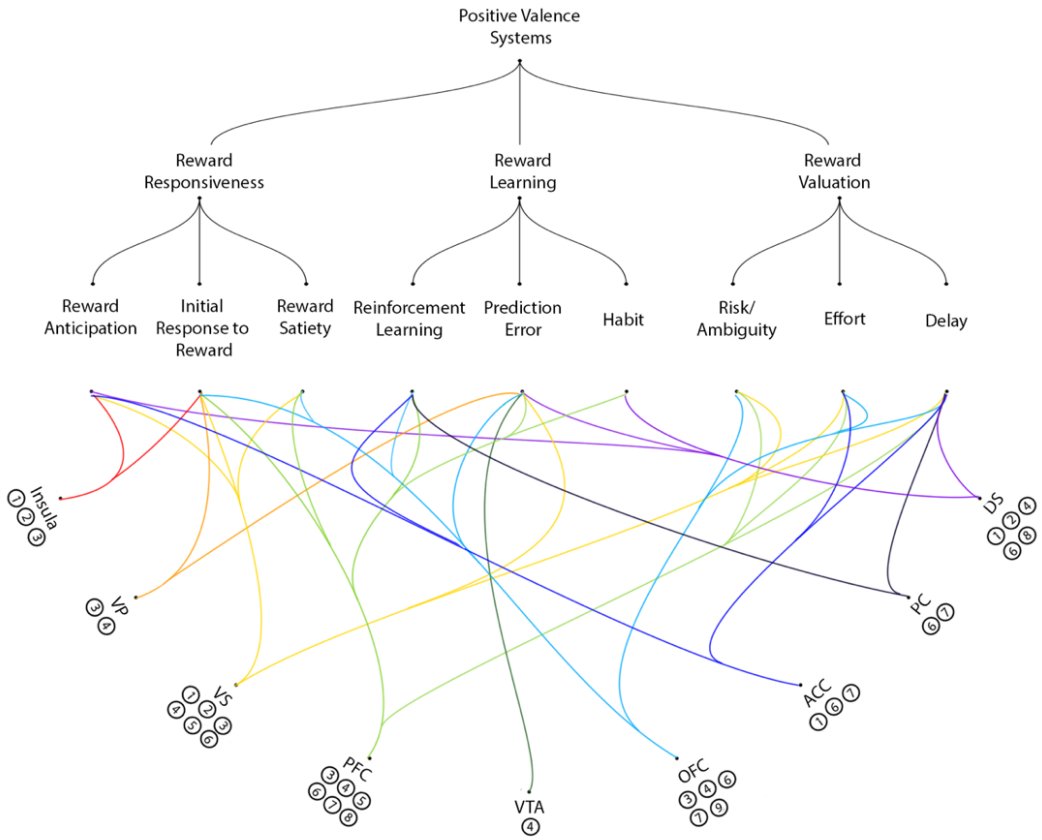
The first construct, reward responsiveness, is divided into reward anticipation, the initial response to a reward, and reward satiation. Reward anticipation is defined as the hedonic response in anticipation of a future reward while the initial response to a reward concerns the hedonic response to receiving a reward (National Institute of Mental Health, 2021). Reward satiation is the increase (sensitization) or decrease (habituation) of the motivational value of a reward after repeated exposure (Schmid et al., 2015). The second construct, reward learning contains the subconstructs reinforcement learning, prediction errors and habits. Reinforcement learning consists of model-free and model-based reinforcement learning. In model-free reinforcement learning, decisions are made reflexively and are formed by previous prediction errors which are the difference between the predicted value of a reward and the perceived value of the reward when it is acquired (Watabe-Uchida et al., 2017). In model-based reinforcement learning, an internal model of the current reward and the environment is constructed to make decisions (Lee et al., 2012; O'Doherty et al., 2017; O'Doherty et al., 2017). In turn, habits are defined as inflexible, unconscious and automatic behaviors which are acquired slowly and are insensitive to the devaluation of rewards (Seger et al., 2011). The third construct, reward valuation, refers to the attribution of subjective and motivational value (i.e., incentive salience) to a reward (Schultz, 2015). It is modulated by the effort needed to acquire the reward, the delay between the stimulus and the delivery of the reward and the uncertainty (risk/ambiguity) of the reward (Schultz, 2015).

Each subconstruct is linked to several brain regions within the reward circuit and each brain region can be associated with a number of subconstructs. A representation of these connections can be seen in Figure 1. The relationship between RDoC subconstructs and brain regions can be studied with several methods. On the one hand, the connections can be investigated in the absence of a task. This makes it possible to investigate the organization of the neurobiological reward system in rest. These results can then be linked to changes in reward processing by relating them to reward-related measures. On the other hand, these

connections can be explored with a task which makes it possible to directly link the neurobiological reward system to specific aspects of reward processing.

Figure 1. Figure displaying the RDoC positive valence systems with its constructs and subconstructs.

Based on previous literature, a non-exhaustive list of connections is illustrated between the subconstructs and several brain areas. Abbreviations: ACC, anterior cingulate cortex; DS, dorsal striatum; OFC, orbitofrontal cortex; PC, parietal cortex; PFC, prefrontal cortex; VP, ventral pallidum; VS, ventral striatum; VTA, ventral tegmental area. References: ① Wilson et al., 2018 ② Oldham et al. ③ Berridge et al., 2016 ④ Watabe-Uchida et al., 2017 ⑤ De Luca, 2014 ⑥ Schultz, 2015 ⑦ O'Doherty et al., 2017 ⑧ Seger et al., 2011 ⑨ Wallis, 2007.



The number of studies investigating the neurobiological reward system in BE has been steadily increasing. Some of these studies have also been the topic of reviews (Bello et al., 2010; Collantoni et al., 2021; Donnelly et al., 2018; Frank, 2013; Gianni et al., 2020; Hartogsveld et al., 2022b; Hiluy et al., 2021; Kessler et al., 2016; Mele et al., 2020; Steward et al., 2018; Wonderlich et al., 2021; Yu et al., 2022). However, these reviews have often

focused on specific brain reward pathways (e.g., dopamine transmission, brain activity, functional connectivity) and have frequently lacked a clear theoretical framework. This means that there is still a need for a systematic review that uses a well-defined theoretical framework to comprehensively review structural and functional findings on the neurobiological reward system in BE. This systematic review aims to fill that gap. It will use the RDoC as a framework to critically interpret study findings and will only include only studies that have stated to investigate the reward system. Both studies reporting on results in rest as well as results related to a task will be discussed. Studies using a task will be subdivided according to the RDoC criteria in papers probing reward responsiveness, reward learning and reward valuation. These results will then be used to formulate directions for future studies.

7.2. Methods

This systematic review was conducted according to the PRISMA guidelines and has been registered with the PROSPERO International Prospective Register of Systematic Reviews of the University of York (CRD42019133795 24) (Moher et al., 2015). A protocol was written based on the PRISMA-P statement and can be consulted with the following link: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=133795.
Deviations from the protocol can be consulted in the supplementary files.

7.2.1. Eligibility criteria

To establish the criteria for this systematic review, the PICOS-system was used (population, intervention/exposure, comparator, outcome, and study characteristics).

- **Population**: Studies were eligible if they were written in English, conducted with human participants, and investigated BE. For BE, the definition of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was used (American Psychiatric Association, 2013). No specific criteria concerning psychiatric disorder were implemented as BE can occur within a psychiatric disorder as well as on its own. Likewise, no specific criteria concerning age were used as BE is prevalent in all age groups (Goldschmidt et al., 2016, Micali et al., 2017, Mitchison et al., 2017, Smink et al., 2013).
- **Exposure**: No specific in- or exclusion criteria concerning participants were specified.

- **Comparator**: Studies needed to include either a group of healthy controls (HC) who did not meet the criteria for BE as comparator, or another group of individuals who binge eat (e.g., BN vs HC or BN vs BED).
- **Outcomes**: The primary outcomes were grey matter volume (GMV) or cortical thickness (CT) (regional and global) when using structural imaging modalities, activity or connectivity (regional or global, task-based or in rest) when using functional imaging modalities, brain neurochemistry (e.g., receptor, transporter or neurotransmitter availability) when using positron emission tomography, and diffusion metrics (e.g., fractional anisotropy, mean diffusivity) when using diffusion imaging.
- **Study characteristics:** Studies needed to be longitudinal or cross-sectional using neuroimaging techniques, with or without neuropsychological tasks, state that they want to study the reward system, and be published in peer-reviewed journals or be submitted as a preprint or dissertation. Only articles published or submitted before the 31st of March 2022 were included.

7.2.2. Search strategy

A literature search of all papers published up to the 31st of March 2022 was conducted through Medline, Embase, and Web of Science. A grey literature search was performed through PsyArXiv for preprints and ProQuest for dissertations. Three concepts were used in the search string: 'binge eating', 'reward', and 'neuroimaging'. These concepts were transformed into Medical Subject Headings (MeSH), Emtree and free-text terms. For the first concept 'binge eating', the MesH terms 'bulimia', 'bulimia nervosa', and 'binge-eating disorder' were used, as well as several free-text terms such as 'binge eating' and 'binge eating syndrome'. For the second concept 'reward', the MeSH terms 'Reward', 'Reinforcement', and 'Motivation' were supplemented with free-text terms such as 'instrumental learning' and 'decision making'. For the third concept 'neuroimaging', MeSH terms such as 'Positron-Emission Tomography' and 'Magnetic resonance imaging' were used together with free-text terms such as 'Functional MRI'. The full literature search strategy can be found in supplementary files.

7.2.3. Study selection

Relevant studies were selected by two researchers independently. A first researcher screened all titles and abstracts of the articles found using the search strategy. A second researcher screened a randomly selected 25% of the abstracts to test the accuracy of the selection process. Inter-rater agreement between the two researchers was calculated using Cohen's kappa (Sim,

2005). Afterwards, the same selection process was applied to the full articles and again, Cohen's kappa was calculated.

7.2.4. Data extraction

The following information was extracted from all included articles: general information (article title, author, year of publication), study characteristics (aim/objectives of the study, study design), study inclusion and exclusion criteria, participant characteristics (age, gender, race, ethnicity, socioeconomic status, disease characteristics, co-morbidities, number of participants in each characteristic category for intervention and control), intervention (task performed, imaging modality), and results (relevant results to the objective of this review).

7.2.5. Data analysis and risk of bias assessment

After data extraction, the risk of bias of each individual study was evaluated with an index based on the guidelines for neuroimaging research in patients with an eating disorder (Collantoni et al., 2021; Frank et al., 2018; Olivo et al., 2019). It includes 27 items which assess study design, participant characteristics, and analysis methods. Each item is given a score of 0, 0.5, or 1 which is then multiplied by the importance of the item (1: desirable, 2: strongly desirable, 3: essential). These scores are then added up to generate a total score for each article ranging between 0 and 68.5. The index and its items can be found in the supplementary files. A first researcher scored all the articles and a second researcher scored a randomly selected 25% of the articles to assess the accuracy of the quality assessment. Inter-rater agreement was evaluated by calculating the intraclass correlation coefficient. After quality assessment, a narrative synthesis of the articles was produced according to the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews (Popay et al., 2016). A meta-analysis was not performed due to the widely different designs of the studies included in this review.

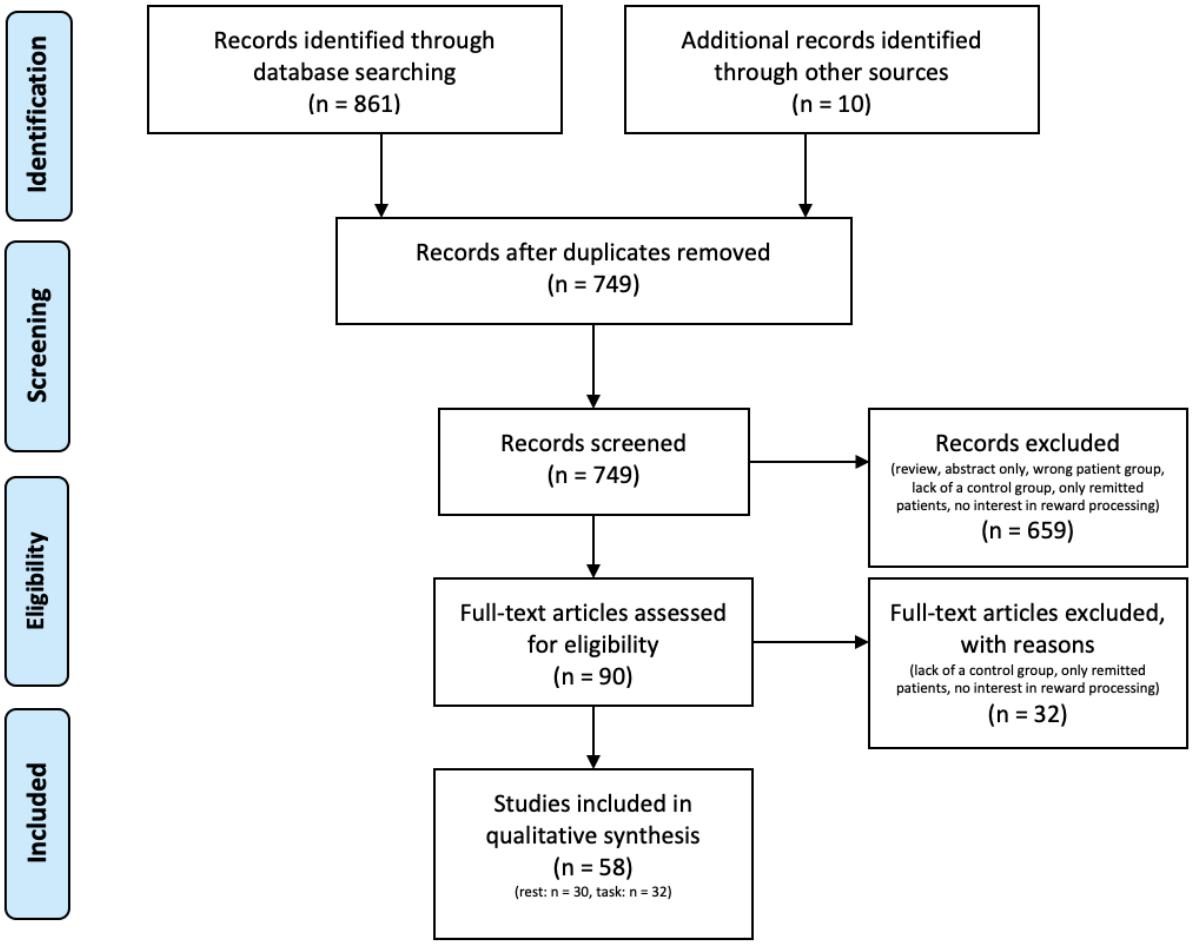
7.3. Results

7.3.1. Study selection

The search strategy yielded 58 articles which were included in this systematic review. The different phases of the review are represented in *Figure 2*. The inter-rater reliability for the screening of abstracts was 'good' with a Cohen's Kappa of 0.737. The inter-rater reliability for

the screening of the full-text articles was 'excellent' with a Cohen's Kappa of 0,948. Both researchers agreed on the inclusion of 89% of the articles.

Figure 2. PRISMA Flow Diagram



7.3.2. Study characteristics

Of the 58 articles in this review, 32(55%) included a sample of patients with BN, 20(34%) included a sample with BED, 2(3%) included a mixed sample with BN or BED, 2(3%) included a sample with AN-BP and 9(16%) included a sample of individuals who binge eat but do not meet the criteria for a specific disorder. Of the 20 studies that included patients with BED, 12(60%) had a HC group with overweight or obesity as comparator. Only 8(14%) studies included more than 1 sample with BE with only 3(5%) studies comparing them. The total sample sizes varied between 18 and 575 with a median of 52. The mean age of all patient groups ranged from 9.9 to 49.4 years with a median of 25.74, while the mean age of HC ranged from 10.0 to 47.0 years with a median of 25.2. Most studies (n=43, 74%) only included female participants. The majority of studies (n=49, 84%) used magnetic resonance

imaging (MRI), and the remaining studies (n=9, 16%) used Positron Emission Tomography imaging (PET). Of these, 30(52%) reported on results in rest and 32(55%) reported on task-based results. The quality scores for the articles ranged from 11.25 to 49 with a median score of 30. The inter-rater reliability for the quality assessment was 'excellent' with an intraclass correlation of 0.91. Less than 10% of all articles mentioned recent weight changes or controlled for contraceptive use. Less than 20% considered race in their analyses, quantified exercise, mentioned treatment length or controlled for cycle phase. A total of 25(43%) studies reported the socioeconomic status (education: n=24(41%), unemployment: n=1(2%); benefits: n=1(2%)) of their participants and only 11(19%) studies reported on race or ethnicity.

7.3.3. Summary of findings

An overview of the different modalities, tasks and outcomes can be found in *Table 1*. The findings concerning the neurobiological reward system in rest are summarized in *Table 2* and *Figure 3*. The results of the studies using a task are summarized in *Table 3* and *Figure 4*. A brief explanation of the methods and analysis techniques of the studies can be found in the supplementary materials. In order to respect the page limit of this thesis, Table 2 and Table 3 were added to the supplementary files on https://osf.io/k84zc/.

Table 1. Tasks (type and allocation to RDoC subconstructs), modalities and outcomes of the studies included in this systematic review.
Abbreviations: ASL, arterial spin labeling; CB1R, cannabinoid type 1 receptor; CBF, cerebral blood flow; CT, cortical thickness; D(A), dopamine; DWI, diffusion weighted imaging; fMRI, functional magnetic resonance imaging; GMV, grey matter volume; mGlu5, glutamate receptor 5; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; PET, positron emission tomography; SERT, serotonin transporter.

	Positive Valence Systems									
	Reward Responsivity			Reward Learning			Reward Valuation			
Task	Reward Anticipation	Initial Response to Reward	Reward Satiation	Reinforcement Learning	Prediction Errors	Habits	Risk/ Ambiguity	Effort	Delay	Modality/Neural Assessment Approach
Rest				●						PET (D2/D3-receptor, presynaptic DA, CB1R, μ-opioid receptor, SERT, mGlu5 availability)
										Structural MRI (GMV and CT)
										DWI (fiber bundle integrity, structural connectivity)
										fMRI (functional connectivity)
										ASL (CBF)
										MRS (myo-inositol, NAA and glutamate levels)
Food cue reactivity	●									fMRI (neural activity, functional and effective connectivity)
Food odor reactivity	●									fMRI (neural activity)
Monetary/Food incentive delay task	●	●								fMRI (neural activity)
Reward-guessing task	●	●								fMRI (neural activity)
Taste reactivity		●	●							fMRI (neural activity)
										PET (DA-release)
Spatial learning task		●		●	●					fMRI (neural activity)

Temporal difference model Task				●	●					fMRI (neural activity)
Weather prediction task				●						fMRI (neural activity)
Two-step task				●		●				PET (correlation with SERT availability)
Reward-guided decision-making task					●					fMRI (neural activity)
Instrumental learning task						●				fMRI (neural activity) MRS (correlation with myo-inositol, NAA and glutamate levels)
Reversal learning task						●				fMRI (correlation with resting-state functional connectivity)
Risky decision-making task							●			PET (correlation with μ-opioid receptor availability)
Delay discounting task									●	fMRI (neural activity)

7.3.3.1 Rest

7.3.3.1.1 Neurochemistry

A total of 6 PET studies investigated the neurochemistry of the reward system in rest. A sample of patients with BN was included in 4(67%) studies and a sample of patients with BED was included in 2(33%) studies. Of these, 2(33%) investigated the dopaminergic system, 2(33%) the endocannabinoid system, 1(17%) the serotoninergic system, 1(17%) the endogenous opioid system and 1(17%) the glutamatergic system. The studies that investigated the dopaminergic system found no difference in striatal $D_{2/3}$ receptor availability, but they did find that BE is related to a reduction in striatal dopamine transmission (Broft et al. 2012, Majuri et al., 2016). They reported that patients with BED had lower levels of presynaptic dopamine in the NAc, CN and putamen and that patients with BN displayed less dopamine release in the putamen (Broft et al. 2012, Majuri et al., 2016). Furthermore, patients with BN who displayed less dopamine release in the putamen had higher BE frequencies (Broft et al. 2012). For the endocannabinoid system, patients with BN had a higher cannabinoid type 1 receptor (CB1R) availability in the insular cortex (Gérard et al., 2011). However, this was also found in the AN group and was associated with a lower BMI and a higher drive for thinness (Gérard et al., 2011; Ceccarini et al. ,2016). This led the authors to suggest that the higher CB1R availability is not related to BE but to other factors such as restrictive eating. More specifically, they suggest that a lower endocannabinoid activity due to a restrictive eating pattern could lead to an upregulation of the CB1R. The studies that investigated the other neurotransmitter systems pointed to a disturbance in striatal and orbitofrontal neurotransmission with a lower μ-opioid receptor and serotonin transporter availability in patients with BED and a higher glutamate receptor 5 distribution volume ratio in patients with BN (Majuri et al., 2016, Majuri et al., 2017, Mihov et al., 2020). However, this was not associated with any clinical measures. Summarized, the studies using PET point to a link between BE and a lower striatal dopaminergic transmission in rest. Changes in other neurotransmitter systems have been found as well, but their relation to BE is less certain.

7.3.3.1.2 Volume

Overall, 14 articles assessed GMV or CT. A sample of patients with BN was included in 8(57%) studies, a sample with BED in 4(29%) studies, a mixed BN/BED sample in 1(7%) study and a sample of individuals who binge eat in 2(14%) studies. Most studies used voxel-based morphometry (VBM; n=11 studies, 79%) while others used surface-based morphometry

(SBM; n=2, 14%) or a manual segmentation technique (n=1, 7%). Across the samples, the studies found a lower volume of the CN (n=4 studies, 29%) as well as a higher volume of the medial/total OFC (n=4, 29%), right ventral striatum/NAc (n=2, 14%), left insula (n=2, 14%), left postcentral gyrus (n=2, 14%) and ACC (n=2, 14%) (Amianto et al., 2013; Coutinho et al, 2014; Frank, Shott et al, 2013; Murray, Duval et al., 2022; Schäfer et al, 2010; Turan et al, 2021; Voon et al., 2014). There were 2(14%) studies that followed participants longitudinally (Cyr et al., 2017; Zhang et al., 2021). One of these reported that a higher volume of the right putamen and globus pallidus at age 14 was predictive of developing BE in the next 2 to 5 years (Zhang et al., 2021). Only 2(14%) studies investigated the relation between volume and reward processing (Frank, Shott et al., 2013; Murray, Duval et al., 2022). Though both studies found a higher OFC volume, one study did so in adult patients with a higher reward sensitivity while another study in adolescents found an association with lower behavioral approach scores (i.e., the drive to approach rewards) (Murray, Duval et al., 2022). This could indicate that that the relation between volume and reward processing differs depending on the age or illness duration of the patient. In summary, the studies find that individuals who binge eat have a higher volume of the ACC, insula, and OFC as well as a lower volume of the CN. The relation between these findings and reward processing varied and could be dependent on the age and illness duration of the patient.

7.3.3.1.3 Connectivity

Several types of connectivity can be distinguished, namely structural, functional and effective connectivity (Fingelkurts et al., 2005). Structural connectivity investigates WM tracts connecting different areas of the brain, functional connectivity is based on statistical dependencies among remote neurophysiological events and effective connectivity looks at the causal influence that one neural system exerts over another.

Structural connectivity:

There were 6 studies that looked at structural connectivity of which 5 (83%) studies had a sample of patients with BN and 1(17%) had a sample of patients with BED. There were 4(67%) studies that used diffusion tensor imaging (DTI) to investigate the axonal integrity of fiber tracts. The results of these studies pointed to a lower integrity of the fiber bundles between the frontal cortex and other cortical (parietal, temporal and occipital) and subcortical (thalamus) areas in both patients with BN and BED (Estella et al., 2020; Hé et al., 2016; Mettler et al., 2013). This lower integrity was also associated with a higher BE frequency in patients with

BN (Hé et al., 2016). Another 2(33%) studies investigated the structural connectivity (i.e. the number of fibers) between brain regions through fiber tracking and found a higher connectivity between the OFC, insula and striatum in patients with BN (Frank, Shott, Riederer et al., 2016; Wang et al, 2019). Taken together, these results suggest that individuals who BE have more fibers connecting the OFC, insula and striatum, but that the integrity of these fibers is lower. Frank, Shott, Riederer et al. (2016) state that this is also seen in other populations and pose that the higher number of fibers could be a compensation for the lower fiber bundle integrity.

Functional connectivity:

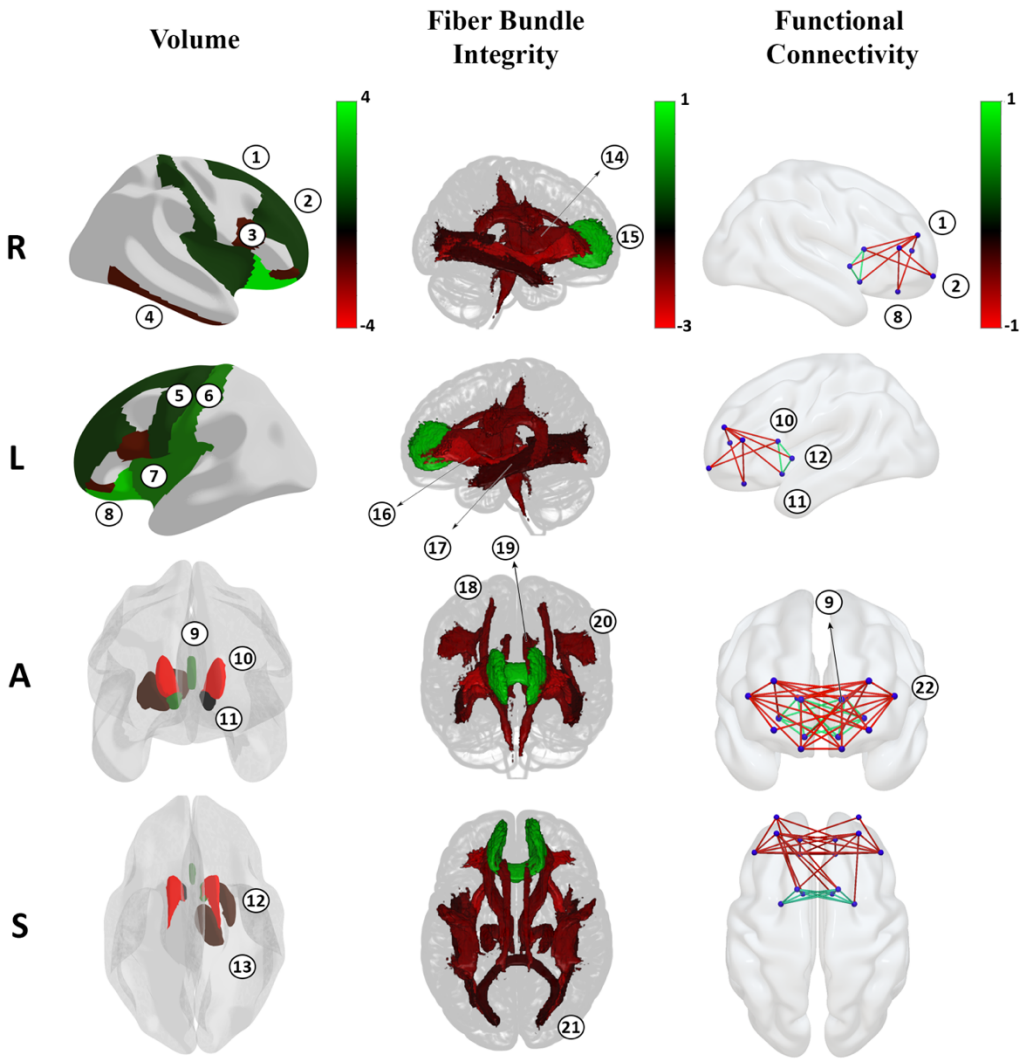
A total of 6 studies investigated resting-state functional connectivity. There were 4(75%) studies with a sample of patients with BN and 3(50%) with a sample of patients with BED. Of these studies, there were 5(83%) that used a seed-based approach and 1(17%) that used a graph theory-based approach. Their results showed a higher connectivity between the different regions of the striatum in patients with BN, a lower connectivity between the frontal cortex and striatum in patients with BN and BED as well as a lower connectivity between the different regions of the frontal cortex in patients with BN and BED (Canna et al., 2017, Haynos et al., 2021; Murray, Alba et al., 2022; Wang et al. 2017; Wang et al. 2019). A lower frontostriatal connectivity was also related to a higher BE frequency (Haynos et al., 2021). One (20%) of the studies also used an independent component analysis (ICA) in patients with BN and BED. It found a lower connectivity of the ACC within the salience network in both patients with BN and BED but this was more pronounced in patients with BN (Stopyra et al., 2019). The results also showed a lower connectivity of the mPFC within the default mode network in patients with BED but a higher connectivity in patients with BN (Stopyra et al., 2019). To summarize, studies find that individuals who binge eat display a common lower functional connectivity between the different frontal cortex regions as well as between the frontal cortex and striatum, but that there are also differences in the functional connectivity of specific networks between the different disorders.

7.3.3.1.4 Perfusion

There was one study that investigated perfusion with arterial spin labeling (ASL). Here, patients with BN or BED had a higher cerebral blood flow (CBF) in the medial PFC, OFC, inferior/middle temporal gyrus, insula and ACC (Martins et al., 2020). The relation of these results with reward processing was not investigated but a higher CBF in these regions was associated with a higher disease severity (Martins et al., 2020).

Figure 3. Representation of the results concerning volume, fiber bundle integrity and functional connectivity (in the frontal cortex and striatum).

The results are shown on a scale representing the number of studies that found a lower or higher volume, integrity or connectivity in individuals who binge eat. Numbers: 1, superior frontal gyrus; 2, middle frontal gyrus; 3, inferior frontal gyrus; 4, inferior temporal gyrus; 5, precentral gyrus; 6, postcentral gyrus; 7, insula; 8, orbitofrontal cortex; 9, anterior cingulate cortex; 10, caudate nucleus; 11, nucleus accumbens; 12, putamen; 13, thalamus; 14, anterior thalamic radiation; 15, forceps minor; 16, inferior longitudinal fasciculus; 17, inferior fronto-occipital fasciculus; 18, corticospinal tract; 19, cingulum; 20, superior longitudinal fasciculus; 21, forceps major; 22, dorsolateral prefrontal cortex. Abbreviations: A, anterior; L, left; R, right; S, Superior.



7.3.3.1.5 Metabolites

Only one study investigated metabolite concentrations in the brain with magnetic resonance spectroscopy (MRS). In this study, patients with AN-BP had lower levels of myo-inositol and N-acetylaspartate (NAA) in the inferior left PFC, but this was not the case in patient with BN. These lower levels of myo-inositol and NAA were associated with eating disorder and depressive symptoms in the BN group, but not in patients with AN-BP.

7.3.3.2 Task

The following findings concern differences of the neurobiological reward system reported by studies using a task. Of the 32 studies, there were 29(91%) that used MRI and 3(9%) that used PET. A univariate voxel-based or ROI-based analysis was performed in 27(84%) studies, a multivariate machine learning approach was used in 2(6%) and functional or effective connectivity was investigated in 7(22%).

7.3.3.2.1 Reward responsiveness

Reward anticipation:

Of the 13 studies looking at reward anticipation, there were 8(62%) that showed images of food, 1(8%) that presented food odors and 4(31%) that used a monetary or food reward task. There were 6(46%) studies with a sample of patients with BN, 3(23%) with a sample of patients with BED, 1(8%) with a mixed sample of patients with BN or BED, 3(23%) with a sample of individuals who binge eat and 1(8%) with a sample of patients with AN-BP. When showing images of high energy-density food, a higher activity of the ACC (n=2 studies, 25%), anterior insula (n=2, 25%) and mOFC (n=1, 13%) was found across the different samples, as well as a higher functional connectivity between the insula and mOFC (Geliebter et al., 2016, Kim et al., 2012; Schienle et al., 2009). Patients with BN displayed more activation of the ACC while patients with BED displayed more activation of the mOFC (Schienle et al., 2009). There was no difference in liking and wanting scores between patients and controls and the scores were not correlated to the findings. However, activation in the ACC and mOFC in patients with BN or BED was positively associated with behavioral approach system scores, suggesting that these results are related to the drive to acquire rewards (Schienle et al., 2009). Contrastingly, a lower activity of the anterior insula was found when patients with BN viewed images of food in general (Brooks et al., 2011). This suggests that different types of food are associated with different brain activity changes in individuals who binge eat. This was also found in the study

presenting food odors. Here, patients with BN had lower wanting scores and a lower activation of the anterior ventral pallidum and anterior insula when rating high energy-density food odors, but a lower activation in the CN when they were rating food odors in general (Jiang et al, 2019). Of the 4 studies using a monetary or food reward task, 3(75%) used a monetary incentive delay task (MID) or a food incentive delay task (FID) and 1 (25%) used a reward-guessing task. In the MID and FID, participants were shown a possible reward or loss and needed to press a button as quickly as possible in order to win the reward or prevent the loss. In the reward-guessing task, participants were asked to guess the value of a card before being shown a potential win or loss and then the outcome. Most studies (n=3, 75%) found no difference in brain activity during the anticipation of money (Bodell et al., 2018; Murao et al., 2017; Simon et al., 2016). The study looking at the anticipation of food found that patients with BED or BN had a lower activation of the PCC during the FID, but this was not related to food craving (Bodell et al., 2018; Murao et al., 2017; Simon et al., 2016). To summarize, individuals who binge eat show a higher activity of the ACC, insula and OFC when anticipating food rewards, but not monetary rewards, and this could be related to a higher drive to acquire food.

Initial response to reward:

There were 9 studies that investigated the initial response to reward. Of these studies, 5(55%) presented a taste stimulus and 4(45%) used a monetary or food reward task. A sample of patients with BN was included in 5(56%) studies, a sample of patients with BED in 2(22%), a mixed sample of patients with BN or BED in 1(11%), and a sample of individuals who binge eat in 1(11%). The studies giving a taste stimulus found that patients with BED, but not HC, had a significant dopamine release in the CN and putamen and that this was related to BE frequency (Wang et al., 2011). Their results also provide evidence for different taste stimuli being related to different changes in brain activity in patients with BN. Opposite to HC, they had a larger response to sucrose than to a bitter stimulus in the left dlPFC, brainstem, OFC and right postcentral gyrus (Monteleone et al., 2017). But after giving an umami stimulus, patients with BN reported lower liking scores and displayed more activity of the right middle insula and ACC (Setsu et al., 2017). Of the 4 studies that used a reward task, there were 2 (50%) that used a MID or FID, 1(25%) that used a reward-guessing task and 1(25%) that used a spatial learning task where participants needed to navigate a maze in order to find rewards. They found a lower responsivity to monetary rewards and a higher responsivity to food rewards in individuals who binge eat. During the spatial learning task, where visuospatial memory was important, patients with BN had a lower activation in the right anterior hippocampus and left

SFG (Cyr et al., 2016). In the MID, where the delivery of the reward depended on the performance of the participant, a lower activation of the insula, CN, NAc, ACC, STG, IFG and MFG was found in patients with BED (Balodis et al., 2013). In contrast, during the reward-guessing task, where the delivery of the reward was randomized, a higher activity of the CN was found in individuals who BE (Bodell et al., 2018). When it comes to the FID, patients with BN or BED had a higher activation of the mOFC, PCC, anterior medial PFC and angular gyrus (Simon et al., 2016). Taken together, the results point to a lower responsivity to monetary rewards and a higher responsivity to food rewards in individuals who binge eat. However, there is considerable variability in the brain regions involved which could be due to differences between the tasks and the populations of the studies.

Reward satiation:

As part of a sensitivity analysis, one study that presented a sucrose and bitter stimulus also looked at the effect of the repetition of the stimuli in patients with BN and HC and found no differences between the groups (Monteleone et al., 2017).

3.3.2.2 Reward learning

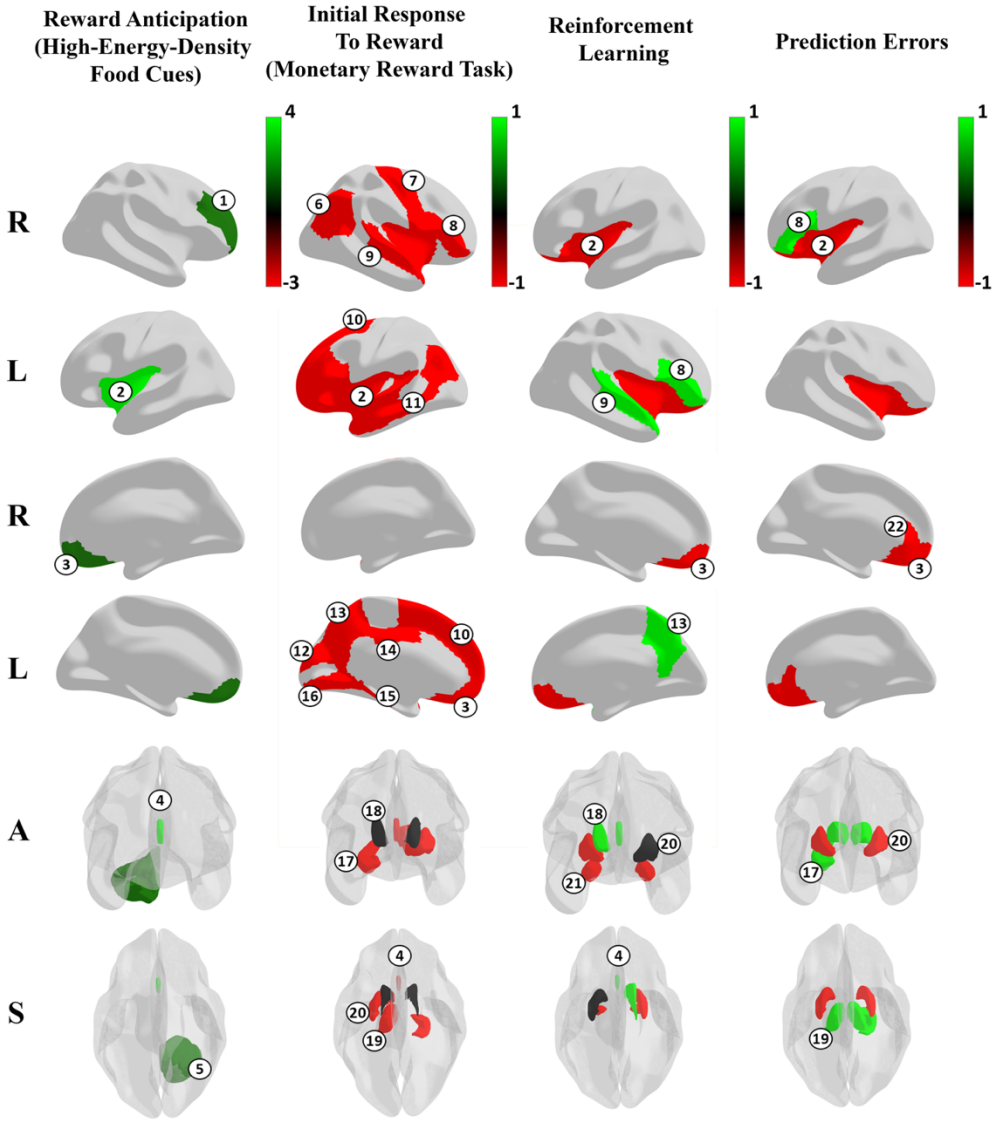
Reinforcement learning:

In total, 5 studies investigated reinforcement learning. Of these, 1(20%) used a spatial learning task, 1(20%) used a temporal difference model task where participants learned to associate a taste stimulus to a visual stimulus, 1(20%) used a weather prediction task (WPT) where participants needed to find out which cards predict a certain weather condition and 2(40%) used a two-step task where participants needed to learn which symbols were associated with the greatest reward. There were 2(40%) studies that included a sample of patients with BN, 2(40%) that included a sample of patients with BED and 1(20%) that included a sample of individuals who binge eat. Patients with BED displayed more model-free learning during the two-step task in 1(20%) study, but no behavioral differences were found in the other studies (Voon et al., 2014). There were differences in brain activity, but they varied greatly. During the temporal difference model task, patients with BN had a lower activity in the putamen, amygdala, insula and OFC (Frank et al., 2011). However, in the WPT, individuals who binge eat had a greater activity of the CN, ACC and DLPFC (Celone et al., 2011). During the spatial learning task, patients with BN had a higher activity of the right IFG (Cyr et al., 2016). Summarized, these studies find that individuals who binge eat display more model-free learning and that reward learning is encoded differently in the brain of individuals who binge eat.

However, the brain areas involved differed between the studies, which could be due to differences between the tasks and the populations of the studies.

Figure 4. Representation of the results concerning reward anticipation (high-energy-density food cues), initial response to reward (monetary reward task), reinforcement learning and prediction errors.

Only RDoC subconstructs with more than one study describing changes in brain activity have been included in this figure. The results are shown on a scale representing the number of studies that found a lower or higher task-based neural activity in individuals who binge eat. Numbers: 1, middle frontal gyrus; 2, insula; 3 orbitofrontal gyrus; 4, anterior cingulate cortex; 5, cerebellum; 6, precuneus; 7, precentral gyrus; 8, inferior frontal gyrus; 9, superior temporal gyrus; 10, middle frontal gyrus; 11, middle temporal gyrus; 12, cuneus; 13, precuneus; 14, posterior cingulate cortex; 15, parahippocampal gyrus; 16, lingual gyrus; 17, hippocampus; 18, caudate nucleus; 19, thalamus; 20, putamen; 21, amygdala; 22, ventromedial prefrontal cortex. Abbreviations: A, anterior; L, left; R, right; S, Superior.



Prediction errors:

In total, 5 studies looked at prediction errors. There were 3 (60%) studies that used a temporal difference model task where sometimes a sucrose solution was given when none was expected and vice versa, 1(20%) study used a spatial learning task and 1(20%) study used a 'reward-guided decision-making task'. In the 'reward-guided decision-making task', participants needed to choose between two cards where one card had a high probability of a reward and the other a high probability of a loss. After a certain number of trials, these probabilities switched. A sample of patients with BN was included in 4(80%) studies, a sample of patients with BED in 2(40%) and a sample of individuals who binge eat in 1(20%). During the temporal difference model task, 1(33%) study found that patients with BN had lower responses to prediction errors in the putamen, insula and OFC in but no differences were found in 2(67%) other studies with larger sample sizes (Frank et al., 2011; Frank et al., 2021; Olsavsky et al., 2019). In the spatial learning task, patients with BN had a higher activation of the right anterior hippocampus when receiving unexpected rewards and a higher activation of the bilateral thalamus, left SFG, and IFG when not receiving expected rewards (Cyr et al., 2016). In the study using the 'reward-guided decision-making task', patients with BED showed more switching behavior and a lower activity in the vmPFC (Reiter et al., 2017). In summary, the results of these studies are inconclusive with studies reporting a higher PE response, a lower PE response or no difference at all. This could be due to the studies using different rewards (i.e., food or money) in different contexts (i.e., a passive or active task).

Habits:

There were 4 studies that investigated habits. Of these, 2(50%) used an instrumental learning task where participants needed to learn which stimulus led to a reward. Afterwards, the reward was devalued (e.g., participants were required to eat when the reward was a food item) and the task was performed again. Another study (25%) used a reversal learning task where participants were presented with two patterns and needed to learn which pattern led to a reward. After every 10 correct choices, the strategy switched and participants needed to change their reactions and choose the formerly wrong stimulus. Another study (25%) used a two-step task where the probability of a stimulus leading to a certain reward varied over time. A sample of patients with BED was included in 3(75%) studies, a sample with AN-BP in 1(25%) study and a sample with BN in 1(25%) study. When it comes to behavior, patients with BED displayed more compulsive decision-making during the two-step task and patients with AN-BP and BN reported higher scores on the Creature Of Habit Scale (COHS) (Voon et al., 2014; Westwater

et al., 2022). Furthermore, there were behavioral differences which were linked to changes in brain connectivity and metabolites. The lower resting-state connectivity between the NAc and SFG in patients with BED was correlated to more habit-directed behavior in the reversal learning task (Haynos et al., 2021). The lower levels of NAA in the left inferior PFC in patients with AN-BP were associated with higher automaticity scores on the COHS (Westwater et al., 2022). Summarized, these studies suggest that individuals who binge eat display more habitual behavior and that this could be linked to a lower frontostriatal functional connectivity and lower levels of NAA in the frontal cortex.

7.3.3.2.3 Reward valuation

Two studies looked at reward valuation in patients with BN. One study looked at the expected value of trials during a temporal difference model task with food and found no difference in brain activity between patients and HC (Olsavsky et al., 2019). Another study let participants rate the healthiness and tastiness of food items and made them decide between them. Patients rated the food items as unhealthier and were more decisive about their choices (Neveu et al., 2018). Also, healthiness and tastiness both played a role in decision making in patients but only tastiness played a role in HC (Neveu et al., 2018). Overall, choice ratings were correlated with activity in the vmPFC, but the correlation with healthiness was more negative in patients (Neveu et al., 2018). Together, these results suggest that both healthiness and tastiness are important for the valuation of food items in patients with BN and that the vmPFC plays a key role in this process.

Risk/ambiguity:

One study investigated risk with a risky-decision-making task. Here, participants could choose to get a certain reward/loss or choose to gamble. Across all participant groups, risk-taking for rewards was positively correlated with μ-opioid receptor availability in the striatum, dorsal cingulate and insula (Skandali et al., 2021). No differences in risk taking for rewards were seen between patients with BED or HC. However, patients with BED had a lower striatal μ-opioid receptor availability and tended to display less risk-taking for rewards.

Effort:

No studies were identified that investigated effort.

Delay:

There were two studies that looked at the effect of delay during reward valuation. They did so in patients with BED and used a delay discounting task (DDT). During this task, participants were required to choose between a certain immediate amount of money versus another delayed amount of money. This made it possible to investigate delay discounting (i.e., the preference for more immediate rewards). However, no differences in delay discounting or brain response during the DDT were found (Haynos et al., 2021; Miranda-Olivos et al., 2021).

7.4. Discussion

This systematic review has the following two objectives: to interpret results from neuroimaging studies that investigate the reward system in BE and to formulate directions for future research.

Across samples, imaging studies in rest report three main findings in BE: First, a higher volume and CBF of cortical areas such as the ACC, insula, and OFC and a lower functional connectivity between these regions. Second, a higher volume of the NAc, a lower volume of the CN, a lower striatal dopamine transmission and a higher functional connectivity between the striatal subregions. Third, a lower functional connectivity, a lower fiber tract integrity and a higher structural connectivity between the frontal cortex and striatum.

The overlap between the cortical regions with a higher volume and a higher CBF is not surprising as previous studies report that these measures covary and that increases in CBF are mediated by increases in volume (Vaidya et al., 2007). However, the implication of these results for reward processing is unclear. The studies in this review find a relation between a higher OFC volume and a lower reward sensitivity in adolescence, but the opposite in adults (Frank, Shott et al., 2013; Murray, Duval et al., 2022). Furthermore, a higher volume of the putamen and globus pallidus is predictive of developing BE, but no difference in the volume of these regions is found in individuals who have BE episodes (Zhang et al., 2021). This could imply that changes in the volume of certain brain areas are associated with developing BE, but that BE itself can lead to changes in the volume of other brain areas. Indeed, studies in rodents have found that repeated ingestion of high-energy-density food can lead to morphological changes of the neurons in the OFC (Seabrook et al., 2020). However, whether

this is the reason behind the conflicting results remains uncertain. This is because most structural studies in BE have been cross-sectional or only followed participants over a short period of time. Future structural studies should therefore aim to follow individuals who binge eat for a longer time period, across different ages and illness stages.

The findings in this review suggest that individuals who binge eat show a structural and functional disconnect between the frontal cortex and striatum, that they display more habitual behavior and that there is a relation between the two. This is similar to findings in patients with an obsessive-compulsive disorder where a lower frontostriatal connectivity is also seen and where this is related to more habitual behavior (Vaghi et al., 2017). It also illustrates that reward processing is the result of a network of interactions and not always a simple hyper- or hypoactivity of a single brain region (Zald et al., 2017). Future studies should keep this in mind and consider exploring connectivity in their analyses.

Across imaging studies investigating BE with a task, two main findings are reported: First, a higher activity of the OFC, ACC and striatum during the anticipation and receipt of high-energy-density food, but a lower activity during the anticipation and receipt of money. Second, more model-free reinforcement learning and habitual behavior is seen together with an altered encoding of reward learning and reward valuation in the ACC, PFC and striatum.

The findings concerning the anticipation and receipt of high-energy-density food are in line with the incentive-sensitization theory of BE. This theory hypothesizes that repeated BE episodes sensitize the brain to food and that this leads to a higher incentive salience (i.e., wanting) for food (Robinson et al., 1993). This sensitization of the brain could be why a higher activity of the ACC, insula and mOFC is seen during the anticipation of high-energy-density food, but not money. These differences could also be related to a higher incentive salience as the studies find that a higher ACC and mOFC activity is associated with a higher drive to acquire rewards (Schienle et al., 2009). This is strengthened by findings in other populations were a higher activation of the ACC is linked to focusing on the edibility of food and where a higher activation of the insula is related to planning to eat until full (Roefs et al., 2018). Further evidence for the incentive-sensitization theory can be seen in the striatal dopamine response to food in patients with BN, but not in controls, similar to animal research (Robinson et al. 1993; Wang et al., 2011). This is combined with lower presynaptic dopamine levels and a lower dopamine release in rest, which has been found in substance use disorders

as well and could be a downregulation in response to repeated dopamine release (Trifilieff et al., 2017).

Of the studies investigating reinforcement learning, only one finds a difference in behavior. In this study, individuals who binge eat display more model-free learning, meaning that they rely more on previous prediction errors (i.e., previous rewards) to make decisions (Voon et al., 2014). This is in line with the acquired preparedness model which hypothesizes that individuals develop BE because they show a stronger response to learning events during which BE is rewarding (Smith et al., 2001). However, the other studies report no behavioral differences, but find changes in brain activity in the ACC, dlPFC and striatum. This contrast could imply that there are behavioral differences but that the tasks in the studies couldn't detect them. This could be the result of a lack of specificity for BE as the tasks focus on more general reinforcement learning processes with money as the reward. Future studies should therefore consider using tasks that are more adapted to BE. This could be done by using food as a reward and by investigating reward learning in more specific contexts such as during moments of stress. However, as the studies in this review suggest that different types of food are processed differently, special attention should be given to the food that is offered as a reward.

Only a small number of studies included more than one eating disorder subtype with BE and an even smaller number actually compared these different subtypes. These show that there are similarities such as a higher OFC volume, a lower functional connectivity of the ACC in the salience network and a higher activity of the ACC during the anticipation of high-energy-density food. They also show that there are differences, such as patients with BN having an even greater OFC volume and activation of the ACC during the anticipation of high-energy-density food compared to patients with BED. Future studies should consider comparing subgroups more, to further unravel the extent of their similarities and dissimilarities.

Limitations

This systematic review has several limitations. First, the studies in this review have used widely different designs which has made it unfeasible to perform a meta-analysis. Some designs have only been used by a small number of studies, making it difficult to make conclusions about certain aspects of reward processing (e.g., reward valuation or reward satiation). Researchers should consider focusing on these aspects in future studies. Second, only a minority of studies

have reported and evaluated the impact of factors such as comorbidities, race, ethnicity, socioeconomic status and sex on their results. Furthermore, most of the studies reporting race or ethnicity show a lack of diversity. As studies have shown these factors are important in disordered eating behaviors, future research should evaluate their impact on results (Rodgers et al., 2018). Third, only half of the studies that included patients with BED had a control group with overweight or obesity. Including no overweight control group makes it difficult to know whether differences in patients with BED are due to the presence of BE behavior or differences in weight. Future studies looking at patients with BED should therefore aim to include a weight-matched control group. Fourth, as this systematic review wants to discuss the role of the reward system in BE, only papers specifically investigating the reward system are included. However, during our search, we have found that 13 studies have used similar designs to the ones included in this review but without the reward system in mind. Of these, 3(23%) have investigated inhibitory or self-control, 3(23%) have focused on attention, 3(23%) have studied self-referential processing and 3(23%) haven't reported any behavioral constructs of interest. When it comes to PET, there are 3 studies that investigate serotonin transporter availability with 1 of them also looking at dopamine transporter availability (Galusca et al., 2014; Kuikka et al., 2001; Tauscher et al., 2001). There are 3 studies that look at GMV or the cerebral surface of patients with BN (Berner et al., 2018; Marsch et al., 2015; Oliva et al., 2021). There are another 4 studies looking at resting-state functional connectivity (Domakonda et al., 2019; Lavagnino et al., 2014; Lee et al., 2013; Spalatro et al, 2019). Another 3 studies have showed images of food (Joos et al., 2011; Uher et al., 2004; Van den Eynde et al., 2013). The fact that these studies use the same design to study different mental processes is problematic for the interpretation of their results and shows that studies need to use a design that is specific for reward processing in BE.

7.5. Conclusion

The studies in this review show that there are structural and functional differences in the neurobiological reward system in BE. In some cases, this could be linked to differences in reward processing such as a higher sensitivity to food rewards, more model-free learning and more habitual behavior. However, the implication of a number of results for reward processing needs to be explored further. Future studies should use reward-related measures

which are specific for BE, include more than one participant group with BE and investigate the impact of factors such as illness duration, race and sex.

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CHAPTER 8

The effect of stress on delay discounting in bulimia nervosa and alcohol use disorder: a functional magnetic resonance imaging study

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Abstract

Background: Stress could increase delay discounting (DD) in patients with bulimia nervosa (BN) and alcohol use disorder (AUD), making the short-term benefits of coping through eating or drinking outweigh long-term negative consequences. Therefore, this study explores differences in DD between patients and healthy controls (HC), the impact of stress on food and alcohol DD, and associated changes in brain activity.

Methods: A total of 102 female participants (AUD: 27, BN: 25, HC: 50) underwent repeated fMRI scanning. Initially, all participants performed a monetary DD task (DDT). Then, participants performed a food or alcohol DDT before and after stress induction. Specifically, patients with BN completed a food DDT, patients with AUD completed an alcohol DDT and HC were randomly allocated to either DDT.

Results: Stress increased the DD of alcohol in patients with AUD, but not in HC. Stress also increased the DD of food in HC, but not in patients with BN. Furthermore, stress caused patients with AUD to display a lower activity of the right supplementary motor area while discounting alcohol. Stress also caused HC to display a lower activity of the frontal cortex and a higher activity of the motor cortex while discounting food, but caused patients with BN to display a higher activity of the occipital cortex.

Conclusion: The results suggest that stress induces neurobiological changes in patients with AUD which cause them to prefer more immediately available alcohol. However, the results observed in patients with BN suggest a more complex relation between stress and food.

8.1. Introduction

Both bulimia nervosa (BN) and alcohol use disorder (AUD) are characterized by binge behavior (e.g., binge eating [BE] and binge drinking [BD]) where large amounts of a substance (e.g., food or alcohol respectively) are consumed within a short period of time (American Psychiatric Association, 2013). Though treatments for BN and AUD exist, large numbers of patients are not able to abstain from BE and BD after treatment (Fleury et al., 2016; Linardon & Wade, 2018). More effective interventions are therefore needed, but in order to develop them, a better understanding of what triggers binge behavior is required. To explore these triggers, most studies have investigated BN and AUD separately. However, as BN and AUD share a number of similarities, studying these disorders together could provide more information by identifying common as well as unique triggers for BE and BD.

One factor that is thought to play a role in both BN and AUD is stress. Most theoretical models hypothesize that BE and BD can be a way for patients to cope with stress (Boness et al., 2021; Burton & Abbott, 2017). Indeed, studies in a laboratory setting report that inducing stress causes individuals who binge eat or binge drink to consume more food or alcohol than they would without stress (Bresin et al., 2018; Cardi et al., 2015). However, it remains unclear why the short-term benefits of coping with stress would outweigh more long-term negative consequences and potential relapse. One possible explanation for this could be that stress causes a disturbance in delay discounting (DD). DD is the process whereby rewards decrease in value the more delayed they are, meaning that individuals usually prefer more immediately available rewards over delayed ones (Odum, 2011). It could therefore be hypothesized that stress induces neurobiological changes in patients that increase DD, making them see the short-term benefits of coping through eating or drinking alcohol as more valuable than the long-term benefits of remission. However, it is unclear whether stress causes these behavioral and neurobiological changes in DD.

From a behavioral standpoint, DD involves both a reward processing and an impulsive-like component (Insel et al., 2010; Strickland & Johnson, 2021). On the one hand, DD is subsumed under the positive valence systems of the Research Domain Criteria (RDoC), where it regarded as a moderator of reward valuation (9). On the other hand, DD is described as a distinct construct of impulsive-like behavior, because it reduces the significance of negative consequences in the distant future, making it more likely for individuals to engage in behaviors that provide immediate gratification (Strickland & Johnson, 2021). DD behavior

can be investigated with a DD task (DDT) (Odum, 2011). In the DDT, participants need to choose between a smaller sooner and a larger later reward. Based on the decisions a participant makes, a DD rate can be calculated where higher values represent a stronger preference for more immediate rewards (Odum, 2011). Previous studies show that patients with BN and AUD prefer more immediately available monetary rewards over delayed ones (Amlung et al., 2019; MacKillop et al., 2011). However, when it comes to disorder-specific food and alcohol DD, only a few studies have been published and their results have been mixed (Hagan et al., 2021; Petry, 2001). We could identify one study that investigates alcohol DD in AUD, which finds higher discounting rates compared to healthy controls (HC) (Petry, 2001). We could also identify one study that investigates food DD in BN, but this study finds lower discounting rates (Hagan et al., 2021). Even less is known when it comes to stress. Studies in healthy volunteers find that acute stress increases DD for money and makes individuals choose more based on subjective value, but no studies have explored the impact of stress on DD in patients with BN or AUD (Kimura et al., 2013; Maier et al., 2015; Simon et al., 2021; White et al., 2008). Therefore, it remains unclear whether patients with BN and AUD inherently prefer more immediately available food and alcohol and whether this preference increases under stress. It is a first aim of this study to fill this gap and explore the following behavioral hypotheses:

1. Patients with BN and AUD display higher DD rates than HC for money.
2. Patients with BN and AUD display higher DD rates than HC for food and alcohol respectively.
3. Patients with BN and AUD, but not HC, display higher DD rates for food and alcohol when stressed.

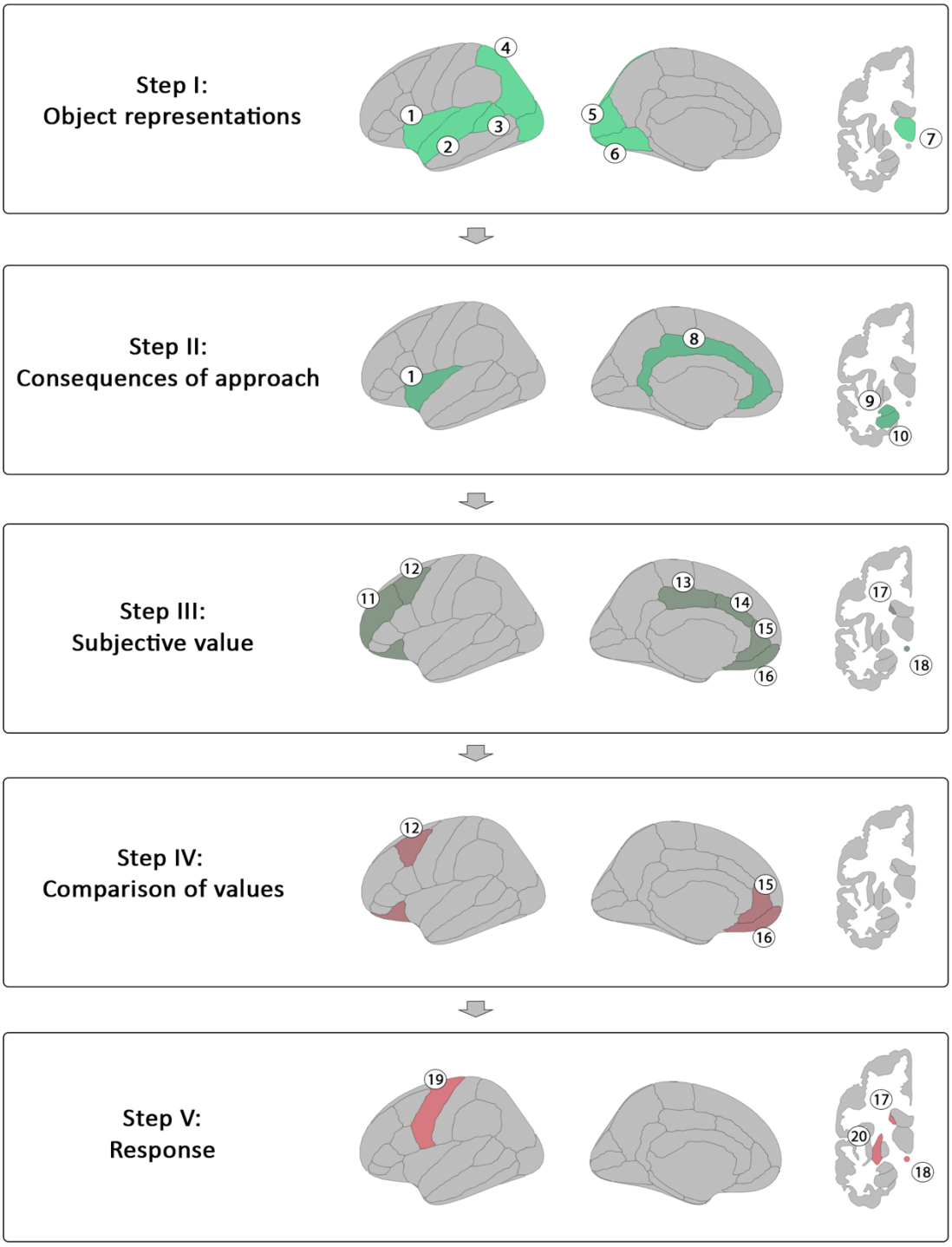
Moreover, from a neurobiological standpoint, one model suggests that DD is processed in five subsequent steps involving specific brain regions at each step (Frost & McNaughton, 2017). An overview of these steps can be seen in Figure 1. Important steps are step III and IV, corresponding to the attribution of subjective value to the sooner and delayed rewards and the comparison between them. The attribution of subjective value is thought to be performed by the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), middle frontal gyrus (MFG), orbitofrontal cortex (OFC), insula, nucleus accumbens (NAc) and caudate nucleus (CN) (Frost & McNaughton, 2017). The comparison between the subjective values is thought to be performed by a dual system, consisting of a beta (β) system that is impulsive,

reflexive, and focused on the immediate reward and a delta (δ) system which is controlled and considers immediate as well as delayed rewards (Frost & McNaughton, 2017; Schüller et al., 2019). The β system is thought to be represented in the ACC and OFC while the δ system is encoded in the dorsomedial prefrontal cortex (dmPFC) and dorsolateral prefrontal cortex (dlPFC) (Frost & McNaughton, 2017; Schüller et al., 2019). When it comes to the functioning of these brain regions during a DDT, no studies have compared current patients with BN and HC. However, a study in remitted patients with BN finds a lower activity of the CN during a monetary DDT after fasting, but a higher activity after eating (Bischoff-Grethe et al., 2021). More studies have been performed in patients with an AUD. Here, studies report that patients display a greater deactivation of the superior frontal gyrus (SFG) and PCC when making impulsive monetary choices, but a greater activation of the dlPFC, (pre)cuneus, insula and OFC when choosing the delayed option (Amlung et al., 2014; Boettiger et al., 2007; Claus et al., 2011). Nevertheless, though these studies indicate that DD for money could be processed differently in patients with BN and AUD, they have not explored whether this is also the case for food or alcohol and whether this is impacted by stress. It is a second aim of this study to fill this gap and explore the following neurobiological hypothesis:

4. Differences in DD between HC and patients with BN or AUD are associated with brain activity changes in regions involved in the attribution and comparison of subjective value (i.e., the ACC, PCC, MFG, OFC, insula, dmPFC, dlPFC, NAc, and CN).

Figure 2. Neural processing of delay discounting.

First, sensory information is transformed into object representations. Second, the object representations are used to establish the consequences of choosing the sooner or delayed reward. Third, the consequences are attributed a subjective value. Fourth, the subjective value between the sooner and delayed reward is compared by a dual system. Fifth, information on the decision is used to produce motor responses to acquire the reward. Regions: 1, insula; 2, superior temporal gyrus; 3, angular gyrus; 4, parietal cortex; 5, occipital cortex; 6 lingual gyrus; 7 thalamus; 8 cingulate cortex; 9 amygdala; 10, hippocampus; 11, middle frontal gyrus; 12, dorsolateral prefrontal cortex; 12, posterior cingulate gyrus; 13, anterior cingulate gyrus; 14, anterior cingulate gyrus; 15, ventromedial prefrontal cortex; 16, orbitofrontal cortex; 17, caudate nucleus; 18, nucleus accumbens; 19, precentral gyrus; 20, putamen.



8.2. Methods

8.2.1. Participants

A total of 102 female right-handed participants were included in the study (AUD: 27, BN:25, HC:50) after removing 4 participants (BN:3, HC:1) due to artefacts and incidental findings. Recruitment ran from September 2019 to February 2022 (eMethods 1). The full in- and exclusion criteria can be found in the supplement (eMethods 2). Importantly, patients needed to meet the criteria for BN or AUD of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) with a maximum illness duration of 5 years (American Psychiatric Association, 2013). This maximum illness duration was set as the role of impulsive-like behaviors is thought to be largest in the first years after the onset of BN and AUD (Boness et al., 2021; Pearson et al., 2015). Participants with AUD also needed to display a pattern of repetitive BD according to the criteria of the National Institute on Alcohol Abuse and Alcoholism (i.e., drinking 4 units of alcohol within 2 hours for women) (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2022). Patients could not meet the criteria for both AUD and BN. All participants gave their written consent, and the study was approved by the local ethical committee.

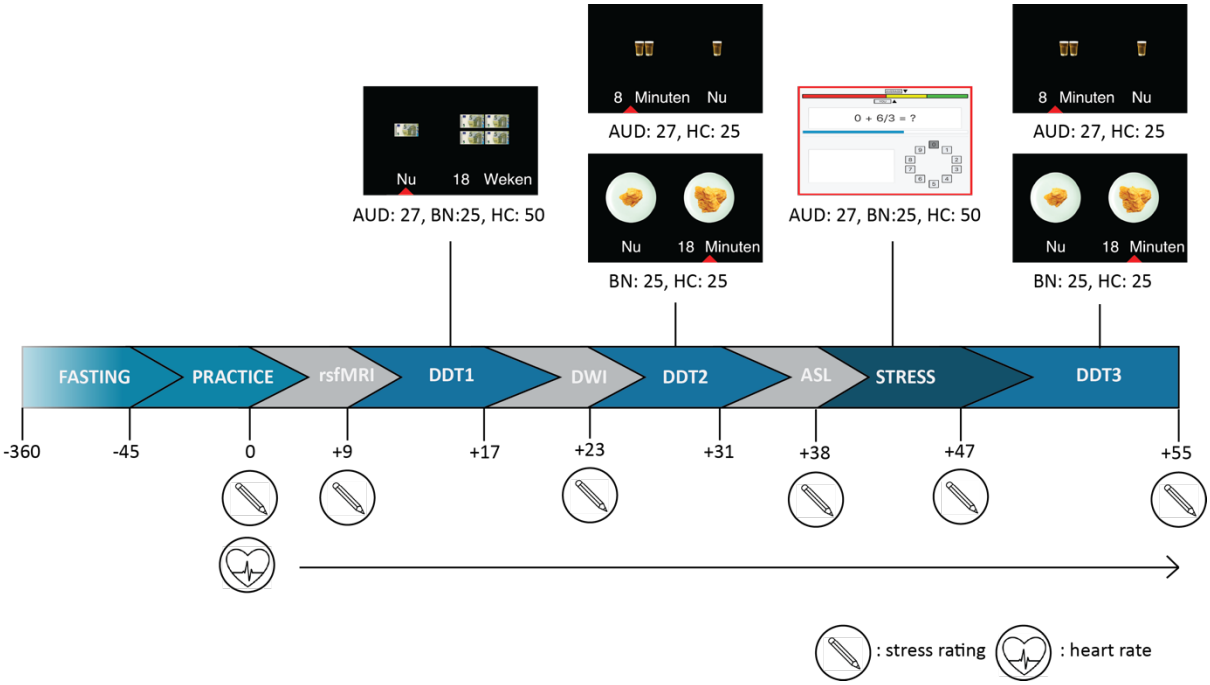
8.2.2. Procedure

The course of the magnetic resonance imaging (MRI) scan can be seen in Figure 2. Participants were instructed not to eat or drink anything in the six hours leading up to the scan and needed to refrain from using substances in the 24 hours before the scan. The participants were asked if they adhered to these instructions on the day of the scanning procedure, and if not, the scan was rescheduled. This was the case for one individual. The participants came in 45 minutes early to familiarize themselves with the tasks of the study in a practice session. Immediately before scanning, a photoplethysmography (PPG) sensor was placed on the left index finger to measure heart rate. The scan itself was divided into four main parts. First, all participants performed a monetary DDT (DDT1). Second, the participants performed a disorder-specific (e.g., food or alcohol) DDT (DDT2). This meant that patients with BN completed a DDT with food while patients with AUD completed one with alcohol. The HC were randomly allocated to either the food (HCfood) or alcohol (HCalcohol) DDT as a comparison for the patients with BN and AUD respectively. Third, stress was induced with the Montreal Imaging Stress Task (MIST) (Dedovic et al., 2005).

Fourth, the participants repeated the food or alcohol DDT post-MIST (DDT3). The DDT1, DDT2 and STRESS blocks were separated by other MRI sequences not analyzed in this manuscript (see Figure 1) Further information on the study procedure can be found in the supplement (eMethods 3).

Figure 2. Study design

Participants fasted in the six hours prior to the MRI scan. They came in 45 minutes early to practice the tasks. The scan was divided into four main parts. First, all participants performed a monetary delay discounting task (DDT1). Second, Patients with BN completed a DDT with food while patients with AUD completed one with alcohol. The HC were randomly allocated to either the food or alcohol DDT (DDT2 pre-stress). Third, stress was induced with the Montreal Imaging Stress Task (MIST; STRESS). Fourth, the participants repeated the food or alcohol DDT (DDT3 post-stress). During the scan, participants reported on their stress level. Their heart rate was measured with a photoplethysmography sensor. Abbreviations: AUD, alcohol use disorder; ASL, arterial spin labeling; BN, bulimia nervosa; DDT, delay discounting task; DWI, diffusion-weighted imaging; HC, healthy control, rsfMRI, resting-state functional magnetic resonance imaging.



8.2.3. Measures

8.2.3.1 Baseline measures

The Structured Clinical Interview for DSM-5 (SCID-5-S) was used to confirm the diagnosis of BN or AUD and to screen for other psychiatric disorders (American Psychiatric Association, 2017). BN and AUD severity were assessed with the Eating Disorder Examination Questionnaire (EDE-Q) and the Alcohol Use Disorders Identification Test (AUDIT) respectively (Fairburn & Beglin, 1994; Saunders et al., 1993). The EDE-Q had an excellent internal consistency with a Cronbach's alpha of 0.95 and the AUDIT had a good internal consistency with a Cronbach's alpha of 0.89. Of the patients with BN, 19 (76%) had an EDE-Q score over the clinical cut-off (i.e., 2.8) and out of the patients with AUD, 26

(96%) had an AUDIT score over the threshold of medium level problems (i.e., 8), and 13 (48%) had an AUDIT score over the threshold of high level problems (i.e., 15).

8.2.3.2. Delay Discounting Tasks

The DDTs were adapted from a food DDT that was used in a previous study (Weygandt et al., 2019). In each of DDTs, the participants chose between an amount of money, food or alcohol that was immediately available and a larger amount of the same reward that was available after a delay. The immediate rewards were 5 euro, around 250 kcal of food or 1 unit of alcohol, while the delayed rewards where multiples (2-5x) of the immediate reward. The rewards were hypothetical, which is a valid alternative for real rewards in studies on DD (Madden et al., 2003). The type of food and alcohol used in the DDT was picked by each participant from a list of possible food items and alcoholic beverages in the practice session (eMethods 4). Each of the multiples was paired with one out of 10 delays for each decision, resulting in 40 trials per DDT. These delays were the deciles of a maximally tolerated delay level plus ten percent that was determined in the practice session (eMethods 5). The delays for the DDT with money were expressed in weeks, while the delays for the DDTs with food and alcohol were expressed in minutes. Each trial started with an inter-stimulus interval (ISI) that varied between 3.5 and 5 seconds. Afterwards, the participants were shown the immediate and delayed options and had 6 seconds to make their choice with a button box. Then, a red arrowhead appeared beneath their chosen option for the remainder of the 6 seconds before the next trial started. The ISI as well as the magnitude, delay and position of the delayed reward were determined pseudorandomly for each trial. The total duration of every DDT was 6 minutes and 50 seconds.

8.2.3.3. Montreal Imaging Stress Task

The MIST is a task that uses mental arithmetic, failure and negative social evaluation to induce stress in participants (Dedovic et al., 2005). It typically consists of a rest condition (i.e., only the interface), a control condition (i.e., only mental arithmetic) and an experimental condition (i.e., mental arithmetic with the stress components). As the purpose of using the MIST in this study was to induce stress, the participants only completed the experimental condition in the scanner. During this condition, participants were given mathematical problems and needed to respond before a certain amount of time expired. The participants saw their own performance and a fictive average performance of all previously included subjects. The participants were instructed to beat this average, but the task adapted the

difficulty of the mathematical problems so that the participants performed poorly. In addition, negative feedback was given to the participants emphasizing their poor performance and urging them to perform better. The difficulty level for each participant in the scanner was established in the practice session (eMethods 6) (Wheelock et al., 2016). The total duration of MIST in the scanner was 6 minutes.

8.2.3.4. Subjective stress

The participants rated their stress levels at the beginning of the scan, before each task (DDT1, DDT2, STRESS, DDT3) and at the end of the scan with a visual analogue scale (VAS). The VAS had ten levels ranging from 0 (not stressed at all) to 10 (never experienced such stress before).

8.2.3.5. Heart rate

PPG data were gathered at 500 Hz with the wireless pulse oximeter of the MR system. These were then preprocessed with SCANPHYSLOG_Tools (Brian Welch, 2016). First, peaks were identified in the pulse waveforms. Second, the data were divided into 1-minute long epochs and the heart rate for each epoch was calculated. Third, implausible heart rates below 30 or above 200 were filtered out.

8.2.4. MR sequences

Scanning was performed on a 3T Achieva dStream Philips MRI scanner with a 32-channel receiver head coil. T2*-weighted echo-planar images were acquired during every DDT (275 volumes, 46 slices, TR=1.5s, TE=33ms, flip angle=80°, voxel size=2.14x2.14x3mm, MB=2). A high-resolution T1-weighted image was acquired during the MIST using a 3D turbo field echo sequence (208 slices, TR=5.9ms, TE=2.7ms, flip angle=8°, voxel size=0.8x0.8x0.8mm).

8.2.5. Data analysis

The data were analyzed and reported in accordance with the guidelines of Frank et al. (2018), which were specifically developed to help setup and analyze neuroimaging studies including patients with an eating disorder. A checklist can be found as an appendix to this manuscript.

8.2.5.1 Delay Discounting

For every DDT, a k-value (i.e., a DD rate) was estimated by fitting the choice data to a hyperbolic discounting model (eMethods 7) (Weygandt et al., 2019). These k-values were

logarithmically transformed due to their non-normal distribution. The log(k)-values at each DDT were compared between groups with robust linear regression models. These models included the log(k)-values as the outcome and included group as the main effect (BN, AUD, HC for the monetary DDT; BN, HC_{food} for the food DDT; AUD, $HC_{alcohol}$ for the alcohol DDT). The impact of stress was evaluated within groups with robust linear mixed models. These models included random intercepts for the participants, the log(k)-values of the disorder-specific DDT as the outcome as well as group (BN, HC_{food} for the food DDT; AUD, $HC_{alcohol}$ for the alcohol DDT) and time (before, after the MIST) as main and interaction effects. All models included age and BMI as covariates.

8.2.5.2 Subjective and physiological stress response

The impact of the MIST on subjective stress ratings and heart rate was evaluated with robust linear mixed models, similarly to the models described above but included the subjective stress ratings or heart rate as outcome. For subjective stress, only the data pre- and post-MIST were used. For heart rate, only the data from the six minutes pre-MIST (i.e., during a resting-state arterial spin labeling sequence) and six minutes during the MIST were used.

8.2.5.3 Functional MRI data

The fMRI data of each DDT were initially preprocessed with fmriprep, version 21.0.1., after which they were smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel in SPM12 (eMethods 8) (Esteban et al., 2019). These smoothed images were then used in a first-level analysis in SPM12 (eMethods 9). On the one hand, this analysis included boxcar regressors which separately modeled the decision and feedback stages. The decision stages started with the presentation of the rewards and ended when the participants submitted their choice through the response box. The feedback stages followed immediately after and ended 6 seconds after the initial presentation of the rewards. These boxcar regressors were convolved with the canonical hemodynamic response function. On the other hand, the first-level analysis included 3 rotation, 3 translation, 6 derivatives, 5 wCompCor, 5 cCompCor and 5 cosine variables as nuisance regressors (Behzadi et al., 2007; Muschelli et al., 2014; Parkes et al., 2018). More information on the nuisance regressors can be found in the supplement (eMethods 8). From the first-level analysis, contrast images were calculated for the decision stages.

These contrast images were used in a second-level analysis in SPM12. First, whole-brain analyses compared brain activity at each DDT between groups. This was done with an

ANOVA design (group: BN, AUD, HC) for the monetary DDT and a t-test design for the food (group: BN, HC_{food}) or alcohol (group: AUD, $HC_{alcohol}$) DDTs. Secondly, whole-brain analyses investigated the impact of stress on brain activity during the food or alcohol DDT within groups. This was done with a full factorial design which included group (BN, HC_{food} for the food DDT; AUD, $HC_{alcohol}$ for the alcohol DDT) and time (before, after the MIST) as main and interaction effects. All designs included age and BMI as covariates of no interest. The statistical contrasts were tested for significance using cluster-level inference with an uncorrected cluster-defining threshold of $p<0.001$ and a family-wise error (FWE) corrected cluster threshold of $p<0.05$. Third, underlying contrast values of the significant clusters were extracted with the MarsBaR toolbox and related to relevant participant characteristics. As advised by the guidelines of Frank et al. (2018), the contrast values were related to the log(k)-values, AUDIT and EDE-Q scores, BE and BD frequency, illness duration, age, BMI, presence of comorbidities and use of contraceptives (Frank et al., 2018). An exploration of the effect of ethnicity, menstrual cycle or history of anorexia nervosa was not possible due to a lack of observations. The analyses were performed with robust regression models which included the contrast values as the outcome and included a patient characteristic as predictor. As the whole-brain analysis included age and BMI as covariates, these variables were also entered as covariates in the robust regression models. Because of this reason, the relation between the contrast values and age or BMI were investigated with one model which included both age and BMI as predictors.

8.3. Results

8.3.1. Sample characteristics

The characteristics of the patients with BN (n=25) and AUD (n=27) and their respective controls (HC_{food}, n=25 and $HC_{alcohol}$, n=25) can be seen in Table 1. There were no significant differences in age, BMI or years of education between the patients and their control groups. The characteristics of the pooled HC group (n=50) can be found in the supplement (eTable 1). Here, there was a significant difference in BMI between the patients with BN (mean=25.5; SD=5.8; CI=23.2-28.0) and the pooled HC (mean=22.3; SD=2.2; CI=21.7-23.0).

Table 1. Sample characteristics

	AUD (n=27)		HC				BN (n=25)	
			$HC_{alcohol}$ (n=25)		HC_{food} (n=25)			
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI
Age	21.7 (4.6)	19.9-23.5	21.0 (1.9)	20.2-21.7	22.2 (3.0)	21.0-23.4	23.0 (4.5)	21.2-24.8
BMI	22.4 (2.1)	21.6-23.3	22.1 (1.6)	21.5-22.8	22.5 (2.7)	21.4-23.6	25.5 (5.8)	23.2-28.0
Illness Duration (years)	3.0 (1.2)	2.5-3.4	0 (0)	0-0	0 (0)	0-0	2.4 (1.5)	1.8-3.0
Education (years)	14.6 (1.8)	13.9-15.3	14.7 (1.2)	14.2-15.2	15.6 (1.9)	14.8-16.4	15.0 (2.0)	14.2-15.9
AUDIT	13.9 (4.4)	12.2-15.7	3.6 (2.1)	2.7-4.4	3.5 (2.1)	2.7-4.4	4.1 (3.6)	2.6-5.6
EDE-Q								
Restraint	0.8 (1.0)	0.4-1.2	0.3 (0.6)	0.1-0.6	0.5 (0.8)	0.2-0.9	3.0 (1.5)	2.3-3.6
Shape Concern	1.7 (1.5)	1.1-2.3	0.9 (0.8)	0.5-1.2	1.1 (1.1)	0.6-1.5	4.3 (1.4)	3.8-4.9
Weight Concern	1.3 (1.4)	0.7-1.8	0.8 (0.9)	0.4-1.2	0.7 (1.0)	0.3-1.2	4.1 (1.3)	3.6-4.7
Eating Concern	0.5 (0.9)	0.2-0.8	0.2 (0.2)	0.1-0.3	0.3 (0.5)	0.1-0.5	2.9 (1.6)	2.3-3.6
Total	1.2 (1.1)	0.7-1.6	0.6 (0.5)	0.4-0.8	0.7 (0.8)	0.4-1.1	3.7 (1.2)	3.2-4.2
Eating disorder symptoms (days/4 weeks)								
Binge eating	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	10.1 (8.5)	6.6-13.6
Fasting	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	6.6 (7.8)	3.3-9.8
Vomiting	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	4.3 (8.9)	0.6-8.0
Laxative use	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	0.6 (5.6)	0-2.0
Diuretic use	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	1.1 (5.6)	0-3.4
Compensatory exercise	0 (0)	0-0	0 (0)	0-0	0 (0)	0-0	6.1 (6.4)	3.4-8.7
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Binge drinking frequency								
Never	0 (0%)	0-0%	12 (48%)	32-69%	14 (56%)	40-76%	13 (52%)	36-73%
Annually	0 (0%)	0-0%	1 (4%)	0-25%	2 (8%)	0-28%	4 (16%)	0-37%
Semi-annually	0 (0%)	0-0%	3 (12%)	0-33%	3 (12%)	0-32%	1 (4%)	0-25%
Three-monthly	3 (11%)	0-32%	5 (20%)	4-41%	4 (16%)	0-36%	4 (16%)	0-37%
Monthly	6 (22%)	7-43%	3 (12%)	0-33%	2 (8%)	0-28%	2 (8%)	0-29%
Biweekly	12 (44%)	30-66%	1 (5%)	0-25%	0 (0%)	0-0%	0 (0%)	0-0%
Weekly	3 (11%)	0-32%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
>Weekly	3 (11%)	0-32%	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%
Therapy (BN/AUD)								
Past	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	10 (40%)	20-60%
Present[a]	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	4 (16%)	1-31%
Previous AN	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	6 (24%)	6-42%
Ethnicity								
Caucasian	26 (96%)	93-100%	25 (100%)	100-100%	23 (92%)	88-100%	24 (96%)	92-100%
Latino	1 (4%)	0-10%	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%
Asian	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-16%	0 (0%)	0-0%
Mixed	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-16%	0 (0%)	0-0%
Middle-Eastern	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-11%
Contraceptive use	21(78%)	61-94%	22 (88%)	75-100%	24 (96%)	88-100%	19 (76%)	58-94%
Amenorrhea	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-12%
SSRI	3 (11%)	0-24%	0 (0%)	0-0	0 (0%)	0-0%	4 (16%)	1-31%
Comorbidities								
MDD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
PD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
SAD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	1 (4%)	0-25%
PTSD	1 (4%)	0-18%	0 (0%)	0-0%	0 (0%)	0-0%	0 (0%)	0-0%

[a] Patients were in different treatment modalities (i.e., ambulatory psychologist, psychiatrist, dietician or outpatient treatment program). Abbreviations: AN, anorexia nervosa; AUD, alcohol use disorder; AUDIT, alcohol use disorders identification test; BMI, body mass index; BN, bulimia nervosa; CI, confidence interval; EDE-Q, Eating Disorder Examination Questionnaire; MDD, major depressive disorder; n, number; PD, panic disorder; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SD, standard deviation; SSRI, Selective serotonin reuptake inhibitors.

8.3.2. Behavioral and functional MRI data

The results for the statistical tests concerning the DDT's can be found in Table 2. A summary of the log(k)-values from the DDT's can be found in the supplement (eTable2). The results for the fMRI data can be seen in Figure 3 and Figure 4.

Table 2. Differences in delay discounting

Model	Effect	β	SE	p
DD money	Group (AUD vs HC)	0.134	0.122	0.271
	Group (BN vs HC)	0.137	0.135	0.311
DD alcohol before MIST	Group (AUD vs $HC_{alcohol}$)	-0.357	0.191	0.068
DD alcohol after MIST	Group (AUD vs $HC_{alcohol}$)	-0.253	0.184	0.174
DD alcohol after vs before MIST	Group (AUD)	0.073	0.019	<0.001*
	Group ($HC_{alcohol}$)	0.006	0.019	0.761
	Group (AUD vs $HC_{alcohol}$)	0.067	0.027	0.016*
DD food before MIST	Group (BN vs HC_{food})	-0.061	0.121	0.613
DD food after MIST	Group (BN vs HC_{food})	-0.098	0.132	0.416
DD food after vs before MIST	Group (BN)	0.020	0.028	0.478
	Group (HC_{food})	0.060	0.028	0.039*
	Group (BN vs HC_{food})	-0.039	0.040	0.324

*significant result. Abbreviations: AUD, alcohol use disorder; β, estimate; BN, bulimia nervosa; CI, confidence interval; DD, delay discounting; HC, healthy control; $HC_{alcohol}$, healthy controls who performed the alcohol delay discounting task; HC_{food}, healthy controls who performed the food delay discounting task; MIST, Montreal imaging stress task; SE, standard error.

8.3.2.1 Delay discounting of money

There were no significant differences between the log(k)-values of the different groups, nor were there any differences in brain activity.

8.3.2.2 Delay discounting of food and alcohol before stress

Food (pre-MIST): There were no significant differences between the log(k)-values of the patients with BN and HC_{food}. However, the patients with BN displayed a weaker deactivation of the left posterior insula (MNI: x=-47, y=-12, z=8; k=213, t_{46}=4.31; p_{FWE}=0.005) and right posterior insula (MNI: x=36, y=-21, z=2; k=131, t_{46}=4.27; p_{FWE}=0.039) than the HC_{food}. Furthermore, in patients with BN, BMI was negatively associated with brain activity in the left posterior insula (β=-0.046, SE=0.220, p=0.049) and right posterior insula (β=-0.040, SE=0.012, p=0.004). In other words, the weaker deactivation of the left and right posterior insula was more pronounced in patients with a lower BMI.

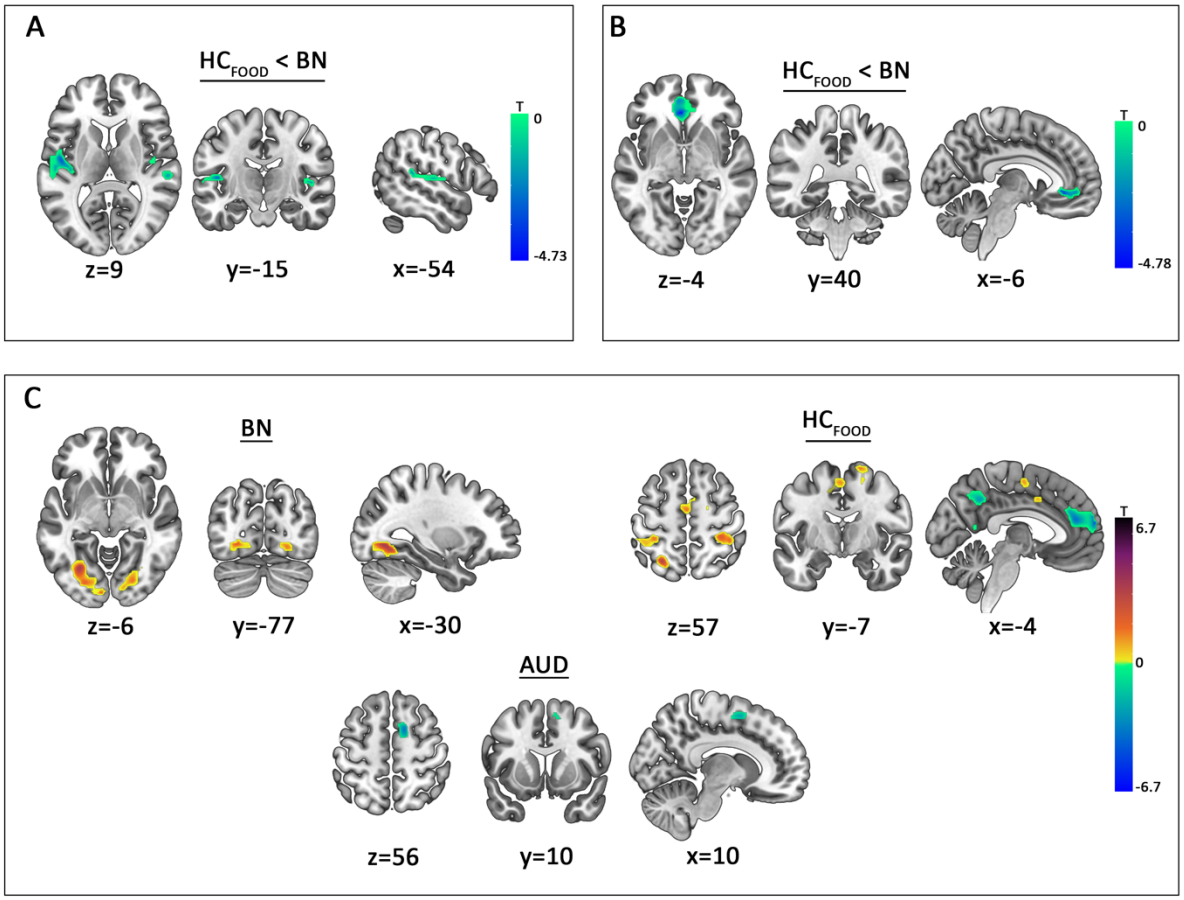
Alcohol (pre-MIST): There were no significant differences between the log(k)-values of the patients with AUD and the $HC_{alcohol}$, nor were there any differences in brain activity.

8.3.2.3. Subjective and physiological stress response

There was a significant increase in subjective stress ratings for all groups post-MIST compared to pre-MIST (HC: β=3.369, SE=0.270, p<0.001; BN: β=4.654, SE=0.381, p<0.001; AUD: β=4.335, SE=0.367, p<0.001), but this was more pronounced in patients (BN: β=1.30, SE=0.467, p=0.007; AUD: β=0.967, SE=0.456, p=0.036). There was also a significant increase in heart rate during the MIST compared to before the MIST in all groups (HC: β=10.084, SE=0.613, p<0.001; BN: β=10.416, SE=0.857, p<0.001; AUD: β=8.077, SE=0.872, p<0.001), but this did not differ significantly between the groups.

Figure 3. Whole-brain between-group and within-group differences during the delay discounting tasks.

A) During the food DDT before the MIST (pre-stress), the patients with BN showed a weaker deactivation of the left insula and right insula compared to HC_{FOOD} B) During the food DDT after the MIST (post-stress), the patients with BN displayed a weaker deactivation of the ACC compared to HC_{FOOD} C) After the MIST compared to before the MIST, patients with BN displayed a higher activity of the left occipital cortex and right occipital cortex. The HC_{FOOD} had a higher activity of the left and right postcentral gyrus, left and right supplementary motor area, but a lower activity of the middle and superior frontal gyrus and PCC. The patients with AUD displayed a lower activity of the right supplementary motor area. Abbreviations: AUD, alcohol use disorder; BN, bulimia nervosa; DDT, delay discounting task; HC_{FOOD}, healthy controls who performed the food delay discounting task; MIST, Montreal Imaging Stress Task.



8.3.2.4. Delay discounting of food and alcohol before compared to after stress

Food (within-group, pre- vs post-MIST): Compared to before the MIST, there were significantly higher log(k)-values after the MIST in HC_{food} (β=0.060, SE=0.028, p=0.039), but not in patients with BN (β=0.020, SE=0.028, p=0.478). This means that the HC_{food} chose the immediately available food options more often after the induction of stress. When it comes to brain activity, the HC_{food} group displayed a higher activity after the MIST in the left postcentral gyrus (MNI: x=-26, y=-60, z=60; t_{48}=5.07;p_{FWE}<0.001), right postcentral gyrus (MNI: x=0, y=36, z=54; t_{48}=4.49;p_{FWE}=0.009), left supplementary motor area (MNI: x=-11,

y=7, z=38; t_{48}=5.15,p_{FWE}=0.003) and right supplementary motor area (SMA) (MNI: x=17, y=-10, z=72; t_{48}=4.82;p_{FWE}=0.040), but a lower activity of the medial MFG/SFG (MNI: x=2, y=63, z=18; t_{48}=6.70;p_{FWE}<0.001) and PCC (MNI: x=4, y=-45, z=38; t_{48}=5.97;p_{FWE}<0.001). Furthermore, the patients with BN showed a higher activity after the MIST of the left inferior occipital, superior occipital, lingual and fusiform gyrus (MNI: x=-30, y=-66, z=-6; k=556; t_{48}=5.13;p_{FWE}=<0.001) and right lingual and fusiform gyrus (MNI: x=24, y=-79, z=-6; k=137, t_{48}=4.19;p_{FWE}=0.021).

Food (between-group, pre- vs post-MIST): There was no significant interaction effect between the MIST-task and group concerning the log(k)-values or brain activity.

Alcohol (within-group, pre- vs post-MIST): Compared to pre-MIST, there were significantly higher log(k)-values post-MIST in patients with AUD (β=0.073, SE=0.19, p=0.004), but not in $HC_{alcohol}$ (β=0.006, SE=0.019, p=0.761). In other words, the patients with AUD chose the immediately available alcohol more often after the induction of stress. When it comes to brain activity, the AUD group displayed a lower activity after the MIST of the right SMA (MNI: x=13, y=5, z=56; k=123, t_{48}=5.23; p_{FWE}=0.007). Furthermore, a lower activity of the right SMA was associated with higher log(k)-values after stress (β=-0.682, SE=0.190, p=0.003) in patients with AUD. This indicates that a lower activity of the right SMA was related to a higher preference for more immediately available alcohol in the patients with AUD.

Alcohol (between-group, pre- vs post-MIST): There was no significant interaction effect between the MIST-task and group concerning the brain activity, but patients with AUD did have a significantly higher increase in log(k)-values compared to the $HC_{alcohol}$ (β=0.067, SE=0.027, p=0.016).

8.3.2.5. Delay discounting of food and alcohol after stress

Food (between-group, post-MIST):Comparing brain activity between groups after the MIST, the patients with BN displayed a weaker deactivation of the ACC (MNI: x=-2, y=22, z=-4; k=203; T_{46}=4.78,p_{FWE}=0.008) than the HC_{food}. Furthermore, a lower activity of the ACC was associated with higher log(k)-values in HC_{food} (β=-0.733, SE=0.356, p=0.048) and with a higher BMI (β=-0.083, SE=0.029, p=0.009) in patients with BN. This means that a lower activity of the ACC was related to a higher preference for more immediately available food in the HC_{food}.

Alcohol (between-group, post-MIST): Comparing brain activity between groups after the MIST, no significant differences were found between patients with AUD and $HC_{alcohol}$.

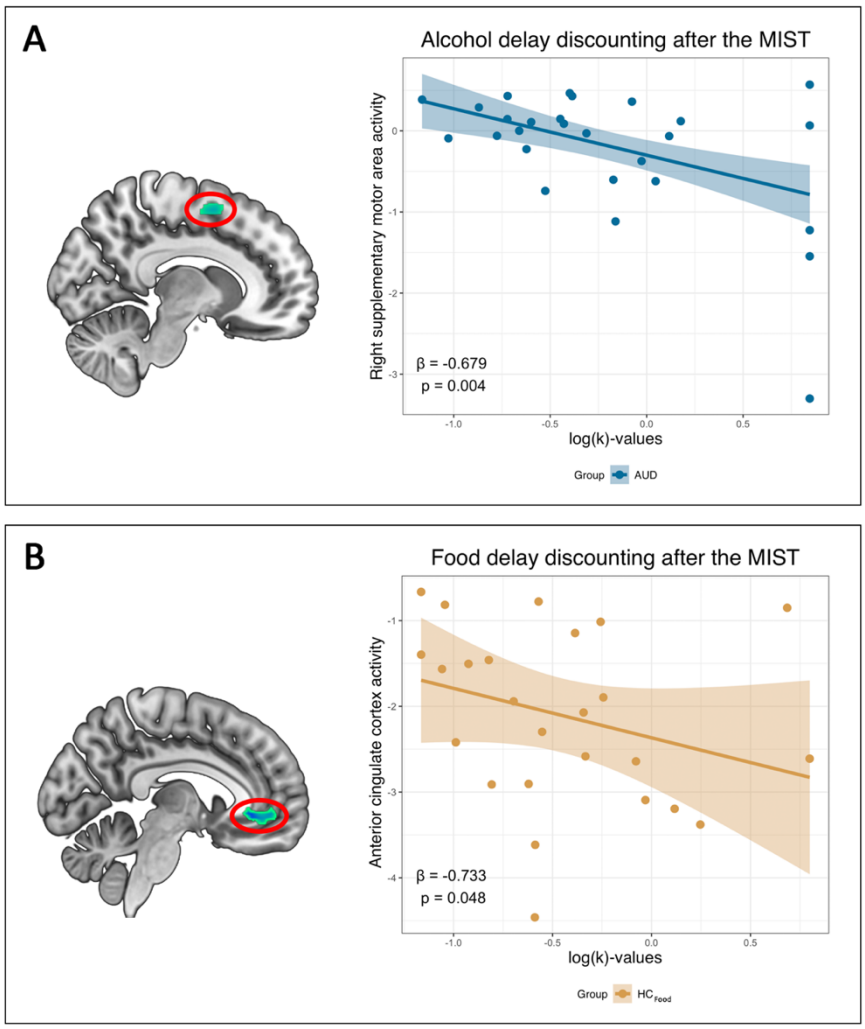


Figure 4. Associations between brain activity during the delay discounting tasks and the behavioral measures.

A) In patients with AUD, after stress, brain activity in the right supplementary motor area during the alcohol DDT was negatively associated with log(k)-values (β=-0.679, SE=0.201, p=0.004).

B) In HC_{FOOD}, after stress, brain activity in the ACC/vmPFC during the food DDT was negatively associated with log(k)-values (β=0.733, SE=0.356, p=0.048).

Abbreviations: AUD, alcohol use disorder; DDT, delay discounting task; β = estimate; HC_{FOOD}, healthy controls who performed the food DDT; MIST, Montreal Imaging Stress Task.

8.4. Discussion

This study investigates four hypotheses. First, that patients with BN or AUD have higher DD rates for money than HC. Second, that patients with BN or AUD have higher DD rates for food or alcohol than HC. Third, that patients with BN and AUD, but not HC, display higher DD rates for food or alcohol when stressed. Fourth, that these behavioral differences are related to brain activity changes in regions involved in the attribution and comparison of subjective value.

When it comes to behavior, this study could not find any differences in the DD of money, food or alcohol between HC and patients with BN or AUD. However, it does find that stress increases the preference for more immediately available food in HC, but not in patients with BN. It also finds that stress increases the preference for more immediately available alcohol in patients with AUD, but not in HC. When it comes to brain activity, the results show that patients with BN display a weaker deactivation of the left and right

posterior insula while DD food than HC. They also show that stress causes HC to display a lower activity of the frontal cortex and a higher activity of the motor cortex while DD food, but causes patients with BN to display a higher activity of the occipital cortex. Furthermore, the results show that stress causes patients with AUD to display a lower activity of the right SMA while DD alcohol.

The lack of a difference between patients and controls in the DD of money, food, and alcohol is unexpected as such a difference has been found in previous studies (Amlung et al., 2019; Hagan et al., 2021; MacKillop et al., 2011). These negative findings could be due to a relatively small sample size. Though this study meets the sample size requirements of guidelines and includes a similar number of participants as previous studies, the sample size is still limited (Amlung et al., 2019; Frank et al., 2018; MacKillop et al., 2011). Future studies should therefore explore behavioral differences in food or alcohol DD with a larger number of participants.

The finding that stress causes patients with AUD, but not HC, to prefer more immediately available alcohol is in accordance with our hypotheses. It expands our knowledge from previous studies which show that stress can increase the value of alcohol and make individuals prefer alcohol over other commodities such as money (Amlung & Mackillop, 2014; Rousseau et al., 2011). Together, these results suggest that stress causes patients to see immediately available alcohol as more valuable than any other type of reward. This is important as it could be the reason why stress causes patients to drink more alcohol and why stress is an important predictor of relapse (Bresin et al., 2018; Brown et al., 1990). Unexpectedly, this higher preference for more immediately available alcohol is related to a lower activity of the right SMA in the current study, which is involved in step V (response) of the neural processing of DD. Indeed, the SMA is known for its role in regulating goal-directed motor activity, but is also important for cognitive and inhibitory control (Matsumoto et al., 2003; Weafer et al., 2019). The lower activity of the SMA after stress could therefore reflect a loss of control over alcohol in the patients with AUD. Indeed, problematic drinkers have a higher tendency to lose control and act rashly when stress is high (Fischer et al., 2012). Future studies should explore whether this relation between stress and alcohol DD is predictive of treatment outcome and whether it can be impacted by interventions.

The absence of a difference in food DD between HC and patients with BN raises the question what the weaker deactivation of the posterior insula in patients with BN signifies. In general, the insula is important in step II (consequences of approach) of the neural processing of DD. Furthermore, previous studies show that the insula plays a role in the neural

processing of food rewards, especially in the encoding of the intensity and the aversity of food (Gehrlach et al., 2019; Huang et al., 2021; Rolls, 2019). For example, lesions to the posterior insula cause food to be perceived as less intense or unpleasant (Balleine & Dickinson, 2000; Mak et al., 2005). Taken together, the findings of the current study suggest that the patients with BN experienced choosing the food items as more intense or aversive. One reason why this study would find such a result is that the patients were asked to select an item of food with which they could have a BE episode. Indeed, previous studies report that food items consumed during a BE episode can be 'forbidden' outside of a BE episode (Guertin, 1999). This could make the patients in the current study more inclined to restrict their food intake. If so, this would be in line with a previous study reporting that patients with BN have lower DD rates for food than HC, meaning that they prefer the delayed food option over the immediately available one (Hagan et al., 2021).

This study does not find that stress causes patients with BN to prefer more immediately available food. Though previous studies have found that stress causes individuals who BE to eat more, most of these studies have been performed in patients with binge eating disorder who do not display compensatory behaviors such as fasting (Cardi et al., 2015). To our knowledge, there is only one study that investigates the impact of stress on food intake in patients with BN and it reports no effect (Westwater, Mancini, Shapleske, et al., 2021). This suggests that the acute kind of stress which is typically induced in a laboratory or neuroimaging setting does not make patients with BN lose control. Indeed, a previous study finds that such acute stress does not reduce inhibitory control in patients with BN (Westwater, Mancini, Gorka, et al., 2021). However, studies in daily life do find that negative emotions such as stress increase before a BE episode in patients with BN (Haedt-Matt & Keel, 2011; ME, 2021). They also find that some emotions are more related to BE than others (i.e., guilt versus nervousness) and that not acute stress, but the pileup of stress is predictive of BE (Berg et al., 2013; Smith et al., 2021). Together, these findings suggest that the relation between negative emotions and BE in patients with BN could be dependent on the underlying emotions and their dynamics. Future neuroimaging studies should explore this by investigating the effect of different negative emotions with different designs (e.g., longer or repeated stress induction).

Though this study finds no impact of stress on food DD in patients with BN, it does find that stress changes how food DD is processed in patients. Namely, patients display a higher activity of the occipital cortex after stress, which is involved in step I (object representations) of the neural processing of DD. This is in line with a study showing that

patients with BN display a higher activity of the occipital cortex when viewing images of food after stress (Collins et al., 2017). Indeed, previous studies report that stress can lead to a higher activity of the occipital cortex and that this could be a sign of hypervigilance or amplified sensory processing (Shackman et al., 2011; Waugh et al., 2012). Therefore, these results suggest that stress makes patients with BN process food differently, but the results do not explain how. Future studies should explore how stress changes the sensory processing of food in patients with BN and how this is related to certain cognitions about food.
In contrast to the patients with BN, this study does find that stress increases the preference for immediately available food in HC. In addition, the HC also displayed a lower activity of the PCC and medial MFG/SFG after stress. These regions play an important role in step III (subjective value) of the neural processing of DD. A decrease in their activity could indicate that the delayed food option has less value to the HC after stress. If so, this could be the reason why the HC were more likely to choose the immediately available food option and this would explain why a lower activity in the frontal cortex after stress was related to higher log(k)-values.

This study has several limitations. First, the relatively small sample size could have limited the power to detect differences between patients and HC. Second, the order of the different DDTs has not been randomized within a session or separated across sessions. The decision to place the monetary DDT before the food or alcohol DDT is based on previous studies reporting that exposure to cues can impact reward processing in patients (Kambouropoulos & Staiger, 2001). Also, the tasks have not been split across sessions to limit within-person variability. Third, as participant have not been randomized between a stress and control condition, it could be that some effects in this study are due to fatigue or the repeated use of the DDT. Fourth, most patients in this study are young Caucasian women with a short illness duration. This limits the generalizability of the results to all patients with BN or AUD. Future studies should aim to replicate the findings in other samples. Fifth, no multiple testing procedure was applied, but this was done as this study is the first to explore the impact of stress on DD in patients with AUD and BN. Sixth, like most studies investigating the neurobiological reward system in BE and BD, this study looks at voxel-wise brain activity (Leenaerts et al., 2022). However, reward processing is more than a simple hyper- and hypoactivation of brain areas (Leenaerts et al., 2022). Future studies should also explore connectivity or perform multi-variate analyses to examine neurobiological differences in DD. Seventh, the decision and feedback stages were modeled with boxcar

regressors, but they can also be modeled in other ways (e.g., with parametric regressors), and this could have influenced the results.

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CHAPTER 9

The relation between stress-induced dopamine release in the ventromedial prefrontal cortex, fronto-striatal functional connectivity, and negative urgency: A multimodal investigation using [18F]Fallypride PET, MRI and experience sampling

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Abstract

Background: Negative urgency (NU), or the tendency to act rashly when stressed, plays a key role in several psychiatric disorders. NU could be the result an insufficient control of the vmPFC over the striatum and could be mediated by disturbances in dopamine (DA) transmission. Therefore, this study investigates stress-induced DA release in the vmPFC and its relation with fronto-striatal functional connectivity (FC) as well as NU in daily life.
Methods: In total, 12 female participants performed a simultaneous [18F]fallypride PET and fMRI scan during which stress was induced. Regions displaying stress-induced DA release were identified and subsequently used in a ROI-to-ROI analysis to investigate stress-induced changes in fronto-striatal FC. Additionally, participants enrolled in an experience sampling study where they reported on daily life stress and rash actions over a 12-month-long period. Mixed models explored whether stress-induced DA release and functional connectivity moderated daily life NU (i.e., the relation between daily life stress and rash action).
Results: Stress led to a lower FC between the vmPFC and dorsal striatum, but a higher FC between the vmPFC and contralateral ventral striatum. Participants with a higher FC between the vmPFC and dorsal striatum displayed more NU in daily life. A higher stress-induced DA release in the vmPFC was related to a higher stress-induced change in FC between the vmPFC and striatum. Participants with a higher DA release in the vmPFC displayed more NU in daily life.
Conclusions: These results suggest that stress can differentially impact fronto-striatal FC whereby the connectivity with the dorsal striatum is especially important for daily life NU and which could be mediated by a higher, but not a lower, stress-induced DA release in the vmPFC.

9.1. Introduction

Negative urgency (NU) is a personality trait that plays a role in the onset and maintenance of several psychiatric disorders (Cyders & Smith, 2008; Zorrilla & Koob, 2019). It is defined as the tendency to act rashly when stress is high and is one of several personality traits that give rise to impulsive-like behavior (Cyders & Smith, 2008). Importantly, out of all these personality traits, NU is the most predictive of how often someone engages in binge eating, problematic drinking, and pathological gambling (Fischer & Smith, 2008). Additionally, higher levels of NU actually predict the onset of binge eating and non-suicidal self-injury (Fischer et al., 2013; Riley et al., 2015). This suggests that NU is an interesting target for interventions. Namely, if it would be possible to lower NU using psychopharmacological treatments, it might be easier for patients to stop binge eating, problematic drinking, or pathological gambling. However, in order to develop these interventions, a better understanding of the neurobiology of NU is required.

It is hypothesized that two brain regions are of special importance to NU (Basar et al., 2010; B. S. Kim & Im, 2019; S. Kim & Lee, 2011). On the one hand, there is the ventromedial prefrontal cortex (vmPFC) which is typically defined as the medial orbitofrontal cortex and the lower half of the medial prefrontal cortex (Mackey & Petrides, 2014). On the other hand, there is the striatum which consists of the ventral striatum (i.e., nucleus accumbens [NAc]) and dorsal striatum (i.e., caudate nucleus [CN] and putamen) (Basar et al., 2010; B. S. Kim & Im, 2019). It has been suggested that a disturbance in the functioning of these regions or their connectivity results in an insufficient control of the vmPFC over the striatum and make individuals more likely to display rash behavior (Fineberg et al., 2010). However, it is thought that an insufficient control over the ventral striatum makes individuals more rash in their desire to acquire awards, whereas an insufficient control over the dorsal striatum makes individuals more rash in their motoric activity (Fineberg et al., 2010). This is because the ventral and dorsal striatum are thought to have separate roles with the ventral striatum being more of a ‘critic’ and the dorsal striatum being more of an ‘actor’ (O’Doherty et al., 2004). In this model, the ventral striatum primarily assesses the valence, subjective value, and probability of outcomes whereas the dorsal striatum chooses the most favorable action based on this assessment (Basar et al., 2010; B. S. Kim & Im, 2019; O’Doherty et al., 2004).

Indeed, studies suggest that a higher activity of vmPFC is normally related to a lower activity of the striatum, and that when this relation is disturbed, individuals are more likely to display rash behavior. For example, studies report that a lower brain activity of the vmPFC is related to taking more risks and that a higher activity of the ventral and dorsal striatum is associated with choosing more immediately available rewards (Basar et al., 2010; B. S. Kim & Im, 2019; Schonberg et al., 2012; Steward et al., 2019). Studies also find that a higher functional connectivity (FC; i.e., a higher positive correlation in brain activity) between the vmPFC and striatum is related to choosing more short-term rewards (Achterberg et al., 2016; van den Bos et al., 2015). Furthermore, the FC between the vmPFC and CN/NAc decreases in puberty and this decrease is associated with a decrease in risk-taking (Ojha et al., 2022; Parr et al., 2021). A higher FC between the vmPFC and the different striatal subregions is also seen in several psychiatric disorders such as borderline personality disorder and substance use disorder, and it is reported that repeated transcranial magnetic stimulation of the vmPFC can reduce the desire for alcohol and cocaine through decreases in FC with the striatum (Harel et al., 2022; Kearney-Ramos et al., 2018; Sarkheil et al., 2020; Wilcox et al., 2011).

Importantly, it is thought that stress disturbs the FC between vmPFC and striatum, which could then cause rash behavior (Zorrilla & Koob, 2019). Namely, studies find that stress can lead to a lower activity of the vmPFC, a higher activity of the NAc, and a higher FC between these regions (Leenaerts et al., 2022, Maier et al., 2015). Furthermore, these changes are related to choosing more based on subjective value and preferring more immediately available rewards (Leenaerts et al., 2022, Maier et al., 2015). However, the number of studies remains limited and most studies have focused on the connectivity with the ventral and not the dorsal striatum. Additionally, studies mostly link their neurobiological findings to task performance or questionnaire scores, which suffer from a lack of ecological validity. This could be improved with the experience sampling method (ESM), also known as ecological momentary assessment, where participants repeatedly report their emotions, behavior and context in daily life (Shiffman et al., 2008). Specifically, the impact of stress on the FC between the vmPFC and striatum can be associated to NU in daily life, which can be directly modeled as the relation between stress and rash action (Leenaerts et al., 2023; Sperry et al., 2021). Therefore, it is a first aim of this study to explore the following two hypotheses:

1. Stress increases FC between the vmPFC and the different subregions of the striatum (NA, CN, putamen)

2. Individuals with a higher FC between the vmPFC and striatum during stress display more NU in daily life.

However, the previously discussed studies focus on brain activity, raising the question which neurochemical processes are involved in the FC between the vmPFC and striatum, and its relation with NU. One neurochemical that could of interest is dopamine (DA), which is a monoamine that binds to metabotropic receptors of the D1 family (D1 and D5 receptors) and D2 family (D2, D3, and D4 receptors) (Iversen & Iversen, 2007). Namely, studies suggest that a higher DA release in the vmPFC is related to a lower DA release in the striatum, and that a disturbance in the dopaminergic activity of these regions and their inverse relation is associated with rash action (Bosker et al., 2017). For example, studies show that DA-depleting lesions of the vmPFC lead to an increase in striatal DA release in non-human primates and that DA-depletion in the entire brain results in a decrease in FC between the vmPFC and CN (Caravaggio et al., 2022; Wilkinson, 1997). Furthermore, when it comes to the striatum, a lower D2/D3 receptor availability and a higher DA transporter availability are associated with preferring more short-term rewards and scoring higher on impulsivity-related questionnaires (Ballard et al., 2015; Costa et al., 2013). These findings are thought to be compensatory changes, suggesting that a higher dopaminergic activity in the striatum is related to rash action (Bosker et al., 2017). Indeed, a greater striatal DA release is seen in rodents who respond more prematurely and in individuals who score higher on impulsivity-related questionnaires. (Bellés et al., 2021; Buckholtz et al., 2010). When it comes to the vmPFC, a higher D2/D3 receptor availability is seen in patients with Parkinson's disease who suffer from impulse control disorders and a lower DA transporter availability is associated with a lower response inhibition in rodents, indicating that a lower dopaminergic activity in the vmPFC is related to displaying more rash action (Lee et al., 2014; Yates et al., 2016).

However, these results raise the question whether stress can induce similar changes in dopaminergic activity of the vmPFC and striatum. From the studies in healthy volunteers, it can be seen that stress reliably induces DA release in the vmPFC, but that it is unclear whether stress impacts DA release in the striatum (Vaessen et al., 2015). Nevertheless, some studies in patients with a psychiatric disorder do report that stress leads to DA striatal DA release (Saraf et al., 2021; Schifani et al., 2018; Soliman et al., 2008; Vaessen et al., 2015). Therefore, based on the findings in rest, it could be that stress only leads to DA release in the striatum when DA release in the vmPFC is impaired. Combined with the results concerning FC, it can be hypothesized that NU is the result of a lower stress-induced DA release in the

vmPFC, leading to a higher FC with the striatum and striatal DA release, making rash action more likely (Bosker et al., 2017). However, there are no studies investigating whether stress-induced DA release in the vmPFC changes its FC with the striatum, and whether this is related to NU. Therefore, it is the second aim of this study to explore the following two hypotheses:

3. Individuals with a lower stress-induced DA release in the vmPFC show a stronger stress-induced increase in FC between the vmPFC and striatum.
4. Individuals with a lower stress-induced DA release in the vmPFC display more NU in daily life.

First, this study performs a simultaneous [18F]Fallypride positron emission tomography (PET) and functional magnetic resonance imaging (MRI) scan in healthy volunteers. Doing so, it identifies regions of the vmPFC that release DA due to stress and investigates stress-induced changes in FC between these regions and the striatum. Furthermore, it evaluates whether the amount of DA release moderates the changes in FC. Second, it follows the same volunteers in daily life with ESM, and by combining the PET/MR and ESM data, explores whether stress-induced DA release in the vmPFC and fronto-striatal FC are related to NU in daily life.

9.2. Methods

9.2.1. Study sample

A total of 12 participants were included in the study between December 2019 and March 2022. They were recruited in Flanders, Belgium through universities, social media, and handing out flyers on the street. Inclusion criteria were: (1) female; (2) right-handed; (3) understand Dutch; (4) age ≥ 18 years; (5) BMI ≥ 18.5 kg/m2. Participants were excluded for the following reasons: (1) major medical pathology; (2) chronic use of sedatives; (3) pregnancy; (4) presence of psychiatric pathology; (5) contra-indications for MRI scanning; (6) known structural abnormalities of the brain; (7) exposure to ionizing radiation (>1mS) in the past 12 months. All participants gave their written consent, and the study was approved by the ethical committee of the UZ/KU Leuven.

9.2.2. Study procedure

9.2.2.1 General procedure

Participants were initially screened via telephone or mail after which they attended an in-person assessment where a resident of psychiatry confirmed their eligibility to participate. Additionally, the participants had their weight and height measured with a calibrated scale and stadiometer and completed clinical interviews and questionnaires (eMethods 1). All participants underwent a briefing on the ESM questions and practiced the use of the mobile application. Afterwards, the [^{18}F]fallypride PET/MR-scan was scheduled.

9.2.2.2 PET/MR procedure

Scanning protocol

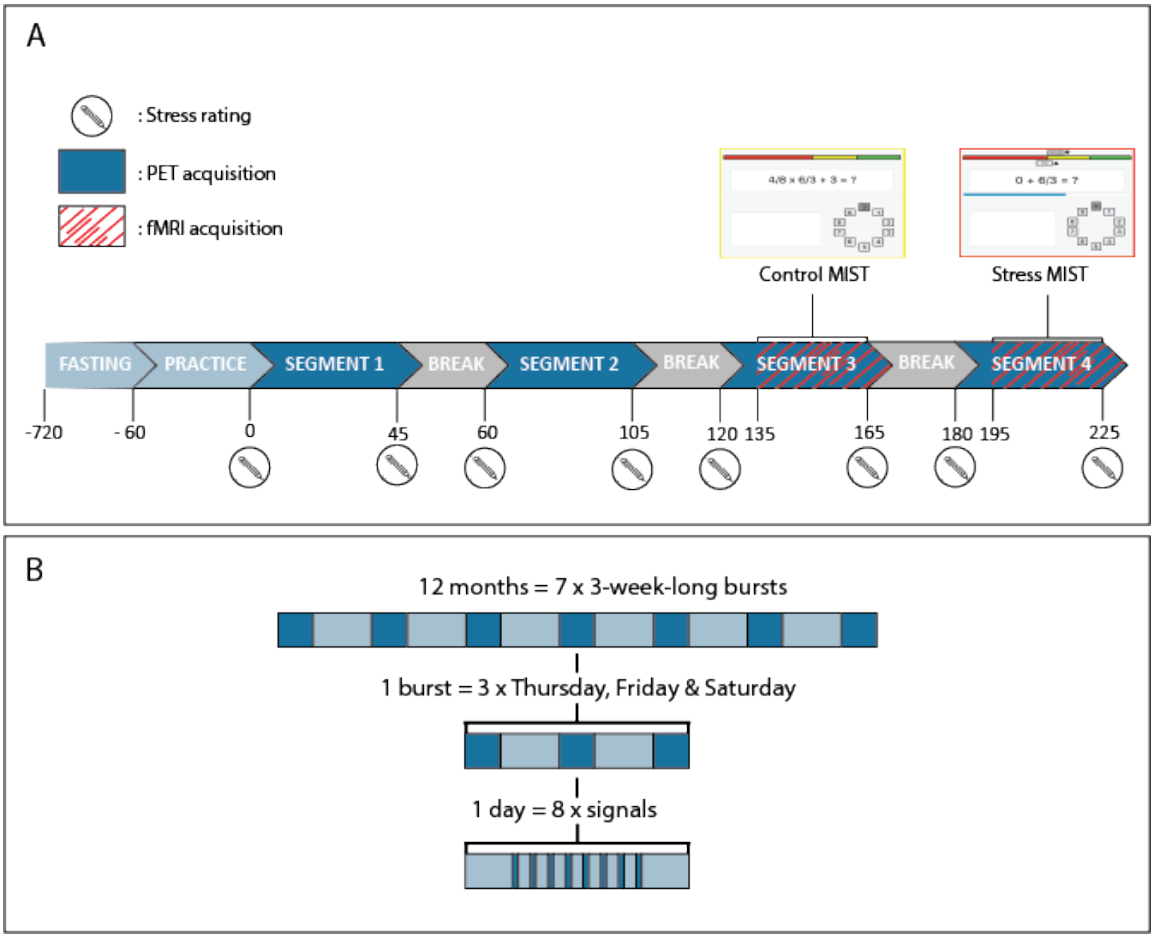
An overview of the simultaneous PET/MR session can be seen in Figure 1. In the 12 hours leading up to the scan, the participants needed to refrain from eating as well as drinking anything else than water. The participants came in 60 minutes early to familiarize themselves with the test setup and to practice the control version of the psychosocial stress task. Afterwards, a catheter was placed in their left median cubital vein and they were positioned in the scanner. Here, a response box was placed in the right hand of the participants and washcloths were used to fixate their head. After the injection of [^{18}F]fallypride, the simultaneous PET/MR scan started. The scan consisted of four 45-minute-long segments which were separated by 15-minute-long breaks during which the participants could leave the scanner. This resulted in a total scan time of 225 minutes. The first two segments represented a ‘rest’ condition during which the participants did not perform any task. The third segment was a ‘control’ condition where the participants performed the control version of the psychosocial stress task. The fourth segment represented a ‘stress’ condition during which the participants performed the stress version of the psychosocial stress task.

Figure 1. **Study procedure**

A) [^{18}F]fallypride PET/MR scanning procedure. The participants needed to refrain from eating and drinking anything else than water in the 12 hours leading up to the scan. They came in 60 minutes early to familiarize themselves with the scanning procedure. The scan consisted of four 45-minute-long segments which were separated by 15-minute-long break. The first two segments were a 'rest' condition. The third segment was a 'control' condition where the participants performed the control version of the MIST. The fourth segment was a 'stress' condition where the participants performed the stress version of the MIST.

B) ESM procedure. The protocol consisted of 7 bursts of data collection which were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis.

Abbreviations: fMRI, functional magnetic resonance imaging; MIST, Montreal imaging stress test; PET, positron emission tomography



Psychosocial Stress Task

The Montreal Imaging Stress Task (MIST) was used to induce stress in the participants (Dedovic et al., 2005). In the control version, participants needed to solve mathematical problems but could use as much time as they needed. However, in the stress version, participants needed to respond before a certain amount of time had expired. Additionally, they saw their own performance as well as a fictive average performance of all previous subjects. They were instructed to beat this average, but the task adapted the difficulty of the

mathematical problems so that the participants always performed poorly. Furthermore, negative feedback was given to the participants emphasizing their poor performance and urging them to perform better. The difficulty level for each participant in the scanner was established in the practice session (eMethods 2) (Wheelock et al., 2016). The duration of the control and stress versions in the scanner was 28 minutes and 30 seconds. The tasks started approximately 15 minutes after the beginning of a scan segment. This was done to ensure that [^{18}F]fallypride displacement was not the result of the participant taking a break or being repositioned (Lataster et al., 2011).

Subjective stress scale

Before and after each segment, the participants needed to indicate how much they agreed with 6 items ("I feel relaxed", "I'm in control", "I feel pressured", "I feel comfortable among these people", "I feel judged by these people", "I do not live up to expectations") on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). These items were based on previous research (Lataster et al., 2011). The items probing relaxation, control and comfort were reverse coded so that for all items, higher scores represented a higher stress level. Then, the answers for the different items were averaged to have a single stress scale. The internal consistency of this scale was good with a Cronbach's alpha of 0.82.

Image acquisition

Simultaneous PET and MRI scanning was performed on a 3T TOF GE Signa PET/MR system. After the administration of [18F]fallypride (mean injected dose ± sd = 176.65 ± 12.2MBq), the PET data were acquired in list mode during each of the four 45-minute-long segments. These were rebinned in 97 frames (89 slices, voxel size=1.56x1.56x2.78mm) and reconstructed with a three-dimensional ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm with four iterations and 28 subsets. This algorithm used time-of-flight information together with a decay, scatter, attenuation, deadtime, and random correction. The attenuation correction was performed with a validated zero echo time (ZTE) approach (Schramm et al., 2019). The MRI images were acquired with a 32-channel receiver head coil. T2*-weighted echo-planar images were obtained during the control and stress versions of the MIST (1035 volumes, 42 slices, TR=1.65s, TE=25ms, flip angle=80°, voxel size=2.29x2.29x3.6mm, MB=2). A high-resolution T1-weighted image was acquired during the first PET segment using a 3D Brain Volume Imaging (BRAVO) sequence (256 slices, TR=9.5ms, TE=3.7ms, flip angle=12°, voxel size=1x1x1mm)

9.2.2.3 ESM procedure

ESM design

The participants started with ESM on the first Thursday after the in-person assessment. An overview of the ESM design can be seen in Figure 1. It consisted of a repeated measurement design where 7 bursts of data collection were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday to limit the protocol's impact on the participants. These specific days were selected to consecutively gather data on both week and weekend days. This resulted in 9 days of data collection per burst and 63 days in total. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis. This meant that there were 72 signals scheduled per burst and 504 signals per participant. The ESM data were initially collected with the app MobileQ (Meers et al., 2020). When the development of the app was discontinued in October 2020, data collection continued using m-Path (Mestdagh et al., 2022.). More information about the apps can be found in eMethods 3 and eTable 1 in the supplement.

ESM measures

For stress, participants were asked to rate how much they agreed with feeling stressed in the moment on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). For rash action, participants needed to answer how much they agreed to have displayed 5 behaviors since the last prompt (doing something risky, without thinking, they will regret, that will get them into trouble, wish they hadn't done) on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). The scores for the different behaviors were then averaged to get one score for rash action at each assessment. The ESM measures were validated in previous studies (Collip et al., 2011; Rintala et al., 2020; Sperry et al., 2018).

9.2.3. Analysis

9.2.3.1. Subjective ratings: The effect of the psychosocial stress task on subjective stress

The stress ratings at the end of the control and stress versions of the MIST were compared with a paired t-test. A p-value below 0.05 was considered significant.

9.2.3.2. PET: Identifying regions of the vmPFC that release DA due to the psychosocial stress task

The [^{18}F]fallypride PET images were preprocessed in PMOD, version 4.1 (eMethods 4) (PMOD Inc., Zurich, Switzerland). Afterwards, two binary masks were created with the Hammers-N30R83 atlas (Hammers et al., 2003). A first mask included the regions for which DA release was to be estimated. This comprised the anterior cingulate gyrus, the frontal gyri (i.e., inferior, middle, and superior), the straight gyrus, and the orbitofrontal gyri (i.e., anterior, medial, lateral). A second mask included the cerebellum which was used as a reference region in the analysis. Then, DA release was estimated by modelling [^{18}F]fallypride displacement with the linearized simplified reference region model (LSRRM) (Alpert et al., 2003; Ceccarini et al., 2020). This model can account for changes in radiotracer binding by assuming that the dissociation rate of a radiotracer can differ over time (eMethods 5). Doing so, it can estimate a parameter γ, which represents the magnitude of radiotracer displacement due to a cognitive task. In the current study, the LSRRM was used to model the effect of the stress version of the MIST on [^{18}F]fallypride binding. As [^{18}F]fallypride is a D2/D3 receptor ligand, the γ parameter can be seen as a measure of DA release. More specifically, the LSRRM was used to estimate voxel-wise statistical parametric maps of the γ parameter within the first binary mask. The maps of the participants were then entered in a voxel-wise one-sample t-test in SPM 12 to detect clusters with a γ that differed significantly from zero. For this test, an uncorrected cluster-defining threshold of $p<0.001$ was applied together with a family-wise error (FWE) corrected cluster threshold of $p<0.05$ and a minimum voxel number of 100 voxels. This minimum number of voxels was set to have sufficiently large enough clusters as they were then used as regions of interest (ROIs) in the MRI and ESM analyses.

9.2.3.3. MRI: The effect of the psychosocial stress task on fronto-striatal FC and the moderating effects of dopamine release in the vmPFC

The fMRI data of the control and stress versions of the MIST were initially preprocessed with fmriprep, version 21.0.1 (eMethods 6) (Esteban et al., 2019). Afterwards, the average voxel timeseries data of the different ROIs were extracted and denoised with CONN (RRID:SCR_009550) version 19.c (eMethods 7) (Behzadi et al., 2007; Muschelli et al., 2014; Parkes et al., 2018; Whitfield-Gabrieli & Nieto-Castanon, 2012). This was done for the

vmPFC ROIs of the PET analysis as well as for ROIs of the left and right NAc, CN and putamen which were defined with the WFU PickAtlas (RRID:SCR_007378). These data were then used in a ROI-to-ROI connectivity analysis. Ideally, repeated measures data is analyzed with a multilevel or mixed-effects effects model, but this can be challenging in neuroimaging context due to the number of models that would have to be fit (Chen et al., 2013; Friston et al., 2005). Therefore, a two-stage approach is often applied whereby connectivity is summarized within a task, session or participant at a first stage (i.e., as a correlation coefficient) before being compared between tasks, sessions or groups at a second stage (Friston et al., 2005; Lindquist, 2008). This two-stage approach has several advantages such as computational efficiency. However, combining both analysis steps in one makes it possible to deal with within-person variability and can result in a higher power (Chen et al., 2013; Narayan & Allen, 2016). Because this study gathered a large amount of fMRI data (i.e., 2070 volumes) within a participant and only wanted to test a limited number of connections, it was decided to estimate FC with a mixed-effects model. These models were fit with the *lme4* package in R, version 4.1.1. First, stress-induced changes in fronto-striatal FC were investigated. This was done with a linear mixed-effects model where the timeseries of one of the striatal ROIs was included as the outcome and where the timeseries of one of the vmPFC ROIs was included as the predictor. Furthermore, the MIST version during which the data were gathered (i.e., control or stress) was included as a main and interaction effect with the timeseries of the vmPFC ROIs. All models included random intercepts for the participants. Second, the moderating effects of DA release on stress-induced changes in fronto-striatal activity were explored. To do so, the average γ value within each of the vmPFC ROIs was calculated for each participant. Then, these values were added as a moderator in the models that showed a significant effect of stress on fronto-striatal connectivity. As in the typical two-stage approach, a Benjamini-Hochberg correction was applied to correct for multiple testing. This was done separately for the results of the first and second model types. A p-value below 0.05 was considered significant.

9.2.3.4. ESM: The moderating effects of stress-induced dopamine release and fronto-striatal connectivity on NU in daily life

As in our previous research, NU was conceptualized as the relation between stress and subsequent rash action (Leenaerts et al., 2022). First, a linear mixed-effects model

investigated NU without any moderators. This model included rash action at the current assessment (t_0) as the outcome and stress at the previous assessment (t_{-1}) as a predictor, after it was split into within- and between-person effects through person-mean centering. This made it possible to explore whether higher than average stress levels within a person predicted subsequent rash action. The day since the start of the study was included as a covariate and the model included random intercepts for days, weeks, bursts and participants. Second, the moderating effects of stress-induced DA release were explored by entering the average γ value within each of the vmPFC ROIs as a main and interaction effect with within-person stress. Third, the moderating effects of fronto-striatal connectivity during stress were explored. To do so, the connectivity values between the vmPFC and striatal ROIs during stress were extracted from the significant mixed-effects models of the MRI analysis and entered as a main and interaction effect with within-person stress. The variables in the models were standardized so that the estimates can be interpreted as effect sizes. A p-value below 0.05 was considered significant.

9.3. Results

9.3.1. Sample characteristics

The sociodemographic characteristics of the 12 participants can be found in Table 1.

9.3.2. The effect of the psychosocial stress task on subjective stress

The subjective stress ratings were significantly higher after the stress version of the MIST than after the control version of the MIST ($Mean_{control}$=3.04(SD=1.08);$Mean_{stress}$=4.75(SD=.99); T_{11}=4.88; p<0.001).

Table 1. Sample Characteristics

	HV (n=12)
	Mean (SD), n (%)
Age (years)	20.8 (1.5)
BMI (kg/m^2)	21.7 (1.8)
Sex	
Female	12 (100%)
Education (years)	14.8 (1.6)
Smoking status	
Non-smoker	12 (100%)
Race	
Caucasian	12 (100%)
Contraceptive use	8 (75%)
DASS-21	
Anxiety	3.7 (5.1)
Depression	2.2 (2.1)
Stress	6.3 (4.8)
Total	8.8 (8.5)
BIS-11	
Attentional	15.1 (3.2)
Motor	21.1 (5.0)
Nonplanning	25.3 (3.1)
Total	61.5 (9.2)
ESM	
Stress	2.6 (1.5)
Rash behavior	1.6 (0.7)
Answered assessments	385 (101)
Compliance	0.76 (0.2)

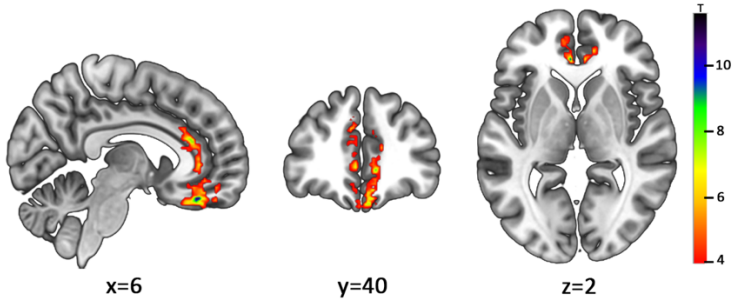
Abbreviations: BIS-11, Barratt Impulsiveness Scale - 11, BMI, body mass index; DASS-21, Depression Anxiety Stress Scales – 21; ESM, experience sampling method; HV, healthy volunteers; n, number; SD, standard deviation

9.3.3. Hypothesis 1 *(Stress increases FC between the vmPFC and the different subregions of the striatum)*

The stress version of the MIST led to significant [18F]fallypride displacement in two clusters (Figure 2). One was located in the left vmPFC (MNI: -4,38,2;k=504,T_{11}=10.57,p_{FWE}<0.001) and the other was located in the right vmPFC (MNI: 8,32,-24;k=480,T_{11}=11.88,p_{FWE}<0.001). Significant changes in FC between these regions and the striatum can be seen in Table 2. The results of all the models can be found in the supplement (eTable 2). There was a significantly

lower FC during stress between the left vmPFC and the left CN (β=-0.060, SE=0.014, p<0.001), right CN (β=-0.030, SE=0.013,p=0.034), and left NAc (-0.127, SE=0.058,p=0.042). There also was a significantly lower FC between the right vmPFC and the left CN (β=-0.047, SE=0.014, p=0.003), right CN (β=-0.028, SE=0.012, p=0.042), and left putamen (β=-0.053, SE=0.016,p=0.004). Contrastingly, there was a higher FC between the left vmPFC and right NAc (β=0.124,SE=0.051,p=0.034), and between the right vmPFC and left NAc (β=0.415,SE=0.058,p<0.001).

Figure 2. Regions showing significant [18F]fallypride displacement in response to the Monteal imaging stress task.



9.3.4. Hypothesis 2 *(Individuals with a higher FC between the vmPFC and striatum display more NU in daily life)*

The FC values during stress with a significant moderating effect on daily life NU can be seen in Table 3. The results of all the models can be found in eTable 3. A visual representation can be seen in Figure 3. Across all participants, there was a significant relation between within-person stress at the previous assessment (t_{-1}) and rash action at the current assessment (t_0) (β=0.028,SE=0.014,p=0.048). This relation was more pronounced in participants with a higher FC during stress between the left vmPFC and right CN (β=0.030,SE=0.013,p=0.023), the left vmPFC and left NAc (β=0.031,SE=0.016,p=0.046), the right vmPFC and right CN (β=0.039,SE=0.017,p=0.021), and between the right vmPFC and left putamen (β=0.027,SE=0.014,p=0.049).

Table 2. The effect of the psychosocial stress task on fronto-striatal functional connectivity and the moderating effects of dopamine release in the vmPFC

Results from the ROI-to-ROI functional connectivity analysis using the vmPFC ROIs of the PET analysis and the striatal ROIs defined with the WFU Pick Atlas. Regions with a significant change in functional connectivity were used in a second analysis exploring the moderating effects of DA release. The results were corrected for multiple testing using a Benjamini-Hochberg correction. Only significant results are displayed.

vmPFC	Striatum	Variable	β	SE	p
Left vmPFC	Left CN	MIST (stress vs control)	-0.060	0.014	<0.001
	Right CN		-0.030	0.013	0.034
	Left NAc		-0.127	0.058	0.042
	Right NAc		0.124	0.051	0.034
Right vmPFC	Left CN	MIST (stress vs control)	-0.047	0.014	0.003
	Right CN		-0.028	0.012	0.042
	Left putamen		-0.053	0.016	0.004
	Left NAc		0.415	0.058	<0.001
Left vmPFC	Left CN	MIST (stress vs control) *DA release left vmPFC	0.035	0.011	0.003
	Right CN		0.063	0.010	<0.001
	Right NAc		0.189	0.069	0.013
Right vmPFC	Left NAc	MIST (stress vs control)*DA release right vmPFC	0.191	0.040	<0.001

Abbreviations: β, estimate; CI, confidence interval; CN, caudate nucleus; DA, dopamine; MIST, Montreal Imaging Stress Task; NAc, nucleus accumbens; ROI, region of interest; SE, standard error; vmPFC, ventromedial prefrontal cortex.

Figure 3. Significant moderating effect of DA release in the ventromedial prefrontal cortex on NU (i.e., the relation between stress and rash action) in daily life.
Abbreviations: DA, dopamine; SD, standard deviation; vmPFC, ventromedial prefrontal cortex.

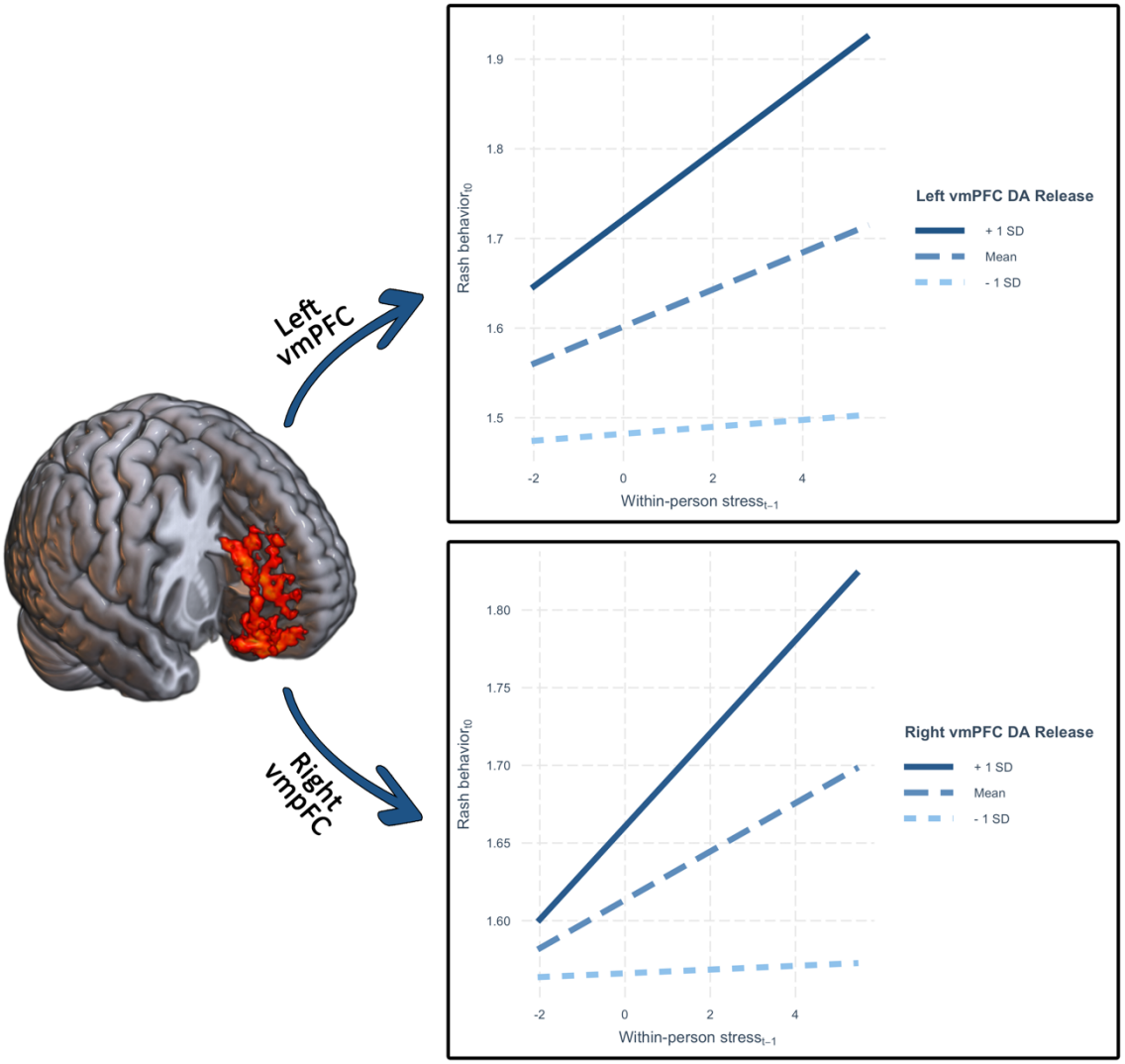


Table 3. The moderating effects of stress-induced dopamine release and changes in fronto-stratal connectivity on NU in daily life

Results of the different mixed-effects models that were fit on the ESM data. First, a general model was fit to explore whether higher than average stress levels within a person predicted subsequent rash behavior. Second, the moderating effects of stress-induced DA release were investigated. Third, the moderating effects of fronto-striatal connectivity during stress were explored. Only significant results are displayed.

Outcome	Variable	β	SE	95% CI	p
Rash behavior t_0	Within-person stress t_{-1}	0.028	0.014	0.001,0.055	0.048
	Within-person stress t_{-1} * DA release left vmPFC	0.036	0.013	0.010,0.062	0.007
	Within-person stress t_{-1} * DA release right vmPFC	0.030	0.014	0,002 0.058	0.030
	Within-person stress t_{-1} * FC left vmPFC right CN	0.030	0.013	0.004,0.057	0.023
	Within-person stress t_{-1} * FC left vmPFC left NAc	0.031	0.016	0.001, 0.062	0.046
	Within-person stress t_{-1} * FC right vmPFC right CN	0.039	0.017	0.006,0.072	0.021
	Within-person stress t_{-1} * FC right vmPFC left putamen	0.027	0.014	0.001,0.054	0.049

Abbreviations: β, estimate; CI, confidence interval; DA, dopamine; ESM, experience sampling method; FC, functional connectivity; NAc, nucleus accumbens; t_0, current assessment; t_{-1}, previous assessment; SE, standard error; vmPFC, ventromedial prefrontal cortex

9.3.4. Hypothesis 3 *(Individuals with a lower stress-induced DA release in the vmPFC show a stronger increase in FC between the vmPFC and striatum)*

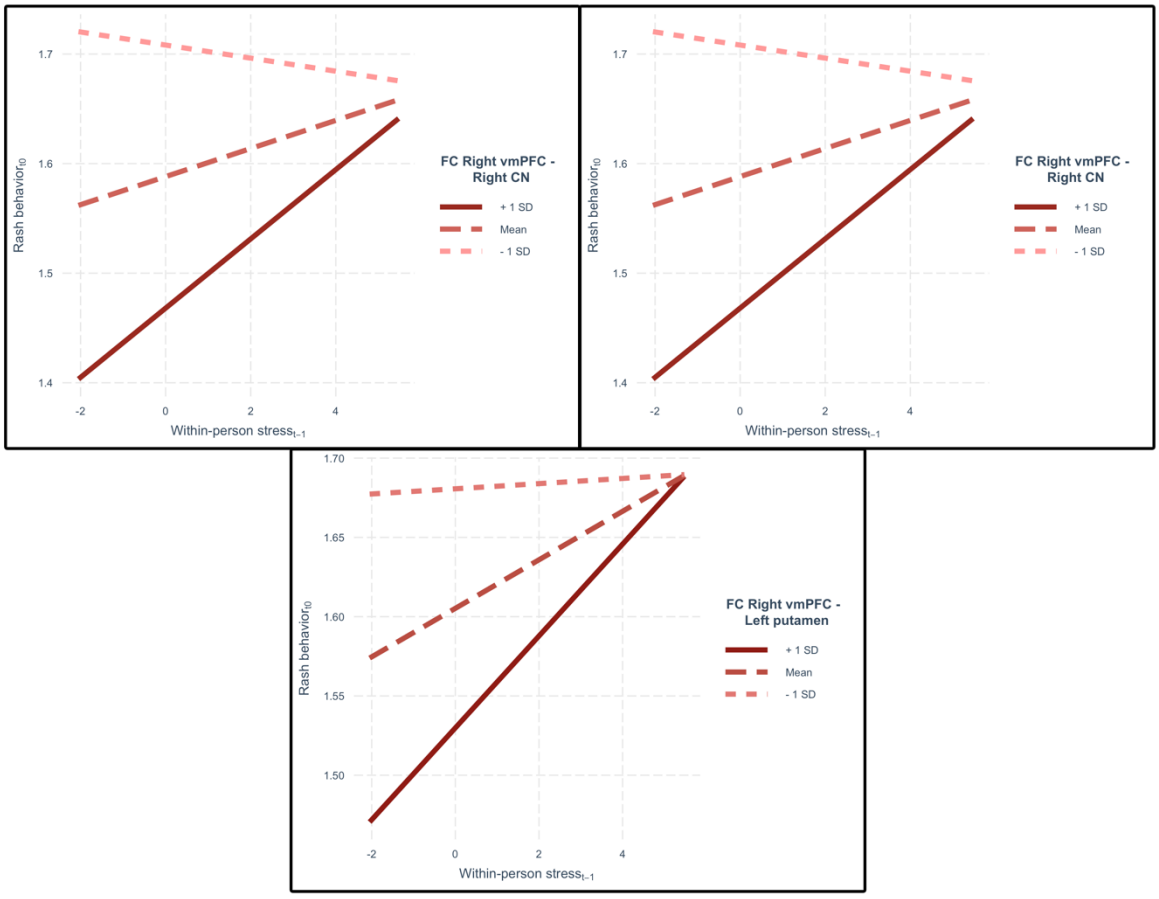
Models with a significant moderating effect of DA release can be seen in Table 2. The full results can be found in the supplement (eTable 2). The mean(sd) of the γ parameter was 0.034(0.006) in the left vmPFC and 0.040(0.008) in the right vmPFC. Individuals with a higher DA release in the left vmPFC had a more positive change in connectivity between the left vmPFC and left CN (β=0.035,se=0.011,p=0.003), right CN (β=0.063,SE=0.010,p<0.001), and right NAc (β=0.189,SE=0.069,p=0.013). Similarly, individuals with a higher DA release in the right vmPFC had a more positive change in connectivity between the left vmPFC and the left NAc (β=0.191,SE=0.040,p<0.001).

9.3.5. Hypothesis 4 *(Individuals with a lower stress-induced DA release in the vmPFC display more NU in daily life)*

The results of the models can be found in Table 3. The relation between stress and rash action was more pronounced in participants with a higher stress-induced DA release in the left vmPFC (β=0.036,SE=0.013,p=0.007) and right vmPFC (β=0.030,SE=0.014,p=0.030).

Figure 4. Significant moderating effect of frontro-striatal connectivity during stress on NU (i.e., the relation between stress and rash action) in daily life.

Abbreviations: CN, caudate nucleus; FC, functional connectivity; NAc, nucleus accumbens; SD, standard deviation; vmPFC, ventromedial prefrontal cortex.



9.4. Discussion

This study explores the relation between stress-induced DA release in the vmPFC, fronto-striatal FC, and NU in daily life. First, its results suggest that stress lowers FC between the vmPFC and CN, but increases the FC between the vmPFC and contralateral NAc. Second, participants with a higher FC between the vmPFC and dorsal striatum display more NU in daily live. Third, individuals with a higher stress-induced DA release in the vmPFC also have a higher stress-induced change in fronto-striatal FC. Fourth, participants with a higher stress-induced DA release in the vmPFC display more NU in daily life.

The findings concerning the impact of stress on fronto-striatal FC are not entirely in line with our hypotheses, which state that stress would increase fronto-striatal FC. Instead, they suggest that stress can differentially impact the FC between the vmPFC and striatum, which could be the result of the structural and functional dissimilarities between the subregions of the striatum (Basar et al., 2010; Grahn et al., 2008). As stated previously, the ventral striatum is thought to be more of a 'critic', connecting with the medial temporal cortex, amygdala and hippocampus, while the dorsal striatum is thought to be more of an 'actor', connecting with the motor cortex, insula and dorsolateral prefrontal cortex (Basar et al., 2010; B. S. Kim & Im, 2019; O'Doherty et al., 2004; Postuma & Dagher, 2006). If so, the higher FC between the vmPFC and contralateral NAc could reflect the appraisal of the emotional valence of the situation (i.e., stress in the current study). Additionally, the lower FC between the vmPFC and CN could be an adaptive response during the MIST whereby the vmPFC excerts greater control over the CN under stressful conditions, aiming to promote more deliberate decision-making when navigating the decision wheel and selecting the correct number. However, this is difficult to conclude based on the results of this study alone. Future studies should therefore evaluate the impact of other stress tasks on the FC between the vmPFC and the different subregions of the striatum.

The results on the relation between fronto-striatal FC following stress and NU in daily life are only partially in line with our hypotheses, as individuals with a higher FC between the vmPFC and dorsal striatum display more NU, while this is less the case for individuals with a higher FC between the vmPFC and ventral striatum. This could imply that disruptions in the control of the vmPFC over the dorsal striatum (i.e., the 'actor' choosing the best decision) are especially important in how stress leads to rash action in daily life, while this is less the case for disruptions in the control over the ventral striatum (i.e., the 'critic' assessing the

emotional valence of the situation). If so, this would be in line with studies showing that how much an individual can tolerate their distress is an important predictor for NU (Barrios et al., 2022). Nevertheless, these findings contradict previous research highlighting the important role of the ventral striatum in NU (Basar et al., 2010). Consequently, additional studies are necessary to further enhance our understanding of the relationship between post-stress fronto-striatal FC and NU in daily life.

The findings on how DA release is related to stress-induced changes in fronto-striatal FC and daily life NU are directly opposed to our hypotheses, which stated that a lower DA release in the vmPFC would be associated with a higher stress-induced change in fronto-striatal and more NU in daily life. At a first glance, this would contradict the idea that DA release in the vmPFC increases the vmPFC's control over the striatum and reduces rash behavior. However, though studies find that increasing cortical dopaminergic activity can lower fronto-striatal FC and lead to choosing more long-term rewards, there are also studies that report the opposite (Blum et al., 2015; Cole et al., 2013; Kayser et al., 2012). One possible explanation could be that the relation between DA release and fronto-striatal FC is dose dependent with a certain amount of stress-induced DA release in the vmPFC being adaptive and resulting in a lower fronto-striatal FC, but with an excessive amount of DA release being problematic and leading to a higher fronto-striatal connectivity. However, studies also find that a lower dopaminergic activity in the vmPFC in rest is related to displaying more rash behavior (Lee et al., 2014; Yates et al., 2016). This could imply that the relation between DA release and fronto-striatal FC is not only dose dependent, but also non-linear. Indeed, a number of studies find that the relation between dopaminergic activity and cognitive control is actually quadratic whereby both a lower and higher than dopaminergic activity is related to less control (Cools & D'Esposito, 2011; Weber et al., 2022). However, this then raises the question how a higher stress-induced DA release in the vmPFC would relate to DA release in the striatum. Though studies in rest indeed show an inverse relation between DA release in the vmPFC and striatum in rest, a more complex relation is seen during a task (Wilkinson, 1997). Therefore, to expand our knowledge, future studies should investigate how stress-induced DA release in the vmPFC and and stress-induced DA release in the striatum are related to each other.

This study has several limitations. First, the sample consists of young, female, Caucasian participants which limits the generalizability of the results to the general population. Future studies should therefore explore the relation between stress-induced DA release, fronto-striatal connectivity, and NU in other samples. Second, no a priori power calculation was

performed. Nevertheless, the number of participants is similar to other PET-studies and a substantial amount of fMRI and ESM data were collected per participant for the within-person analyses. However, having only 12 participants could have negatively impacted the power of the moderation analyses. Future studies should confirm the results of this study in a larger sample size. Third, due to the assumptions of the LSRRM, the control and stress versions of the MIST have been administered in a sequential order and not randomized across sessions. This could have impacted the results due to fatigue or carry over effects from the control condition. Fourth, the restriction of the ESM measurements to Thursday, Friday and Saturday could have influenced results if the participants would experience a different relation between stress and rash behavior on the other days of the week. This study also has several strengths. The current study uses an innovative design which uses simultaneous PET/MR data together with ESM data. It is the first to link stress-induced DA release to changes in fronto-striatal connectivity. It is also the first to explore how stress-induced DA release in the vmPFC or stress-related fronto-striatal connectivity is related to NU in daily life.

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CHAPTER 10

Discussion

10.1. Summary

This thesis aims to deepen our understanding of how stress and NA lead to binge behavior in patients with AUD or BN, and to identify the neural mechanisms that are implicated in this relation. To do so, this thesis has defined several objectives for which it now reports the following results.

Objective 1: To investigate how NA leads to binge behavior in the daily lives of patients with alcohol use disorder or bulimia nervosa.

Chapter 4 explores the relation between NA and BE as well as the mediating roles of craving and rash action. The results show that patients with BN report more craving and display more rash action after experiencing NA than controls. Furthermore, the results suggest that NA can lead to BE through increases in craving and rash action, but that NA can also lead to not eating. Chapter 5 investigates how NA and PA are linked to subsequent craving, non-heavy alcohol use and BD. It reveals that patients with AUD report more craving in response to higher or lower levels of both NA and PA, but that controls display no relation between craving and affect. The results also suggest that patients are more likely drink alcohol when they experience increases as well as decreases of both NA and PA. However, alcohol use in controls seems to be driven more by changes in PA than by changes in NA.

Objective 2: To predict BE, alcohol use, and BD in the daily lives of patients with alcohol use disorder or bulimia nervosa.

Chapter 6 constructs person-specific and pooled models to predict BE, alcohol use, and BD in patients with AUD and/or BN. Its findings show that person-specific models outperform pooled ones, and that alcohol use and BD could be more accurately predicted than BE. Also, craving and time of day (i.e., evening or night) are important predictors across the different behaviors, but affect and social context are varyingly predictive of BE, alcohol use, and BD. When it comes to affect, BE is positively predicted by feeling down, but negatively predicted by feeling distressed, while alcohol use and BD is predicted by experiencing positive events. When it comes to social context, alcohol use is predicted by being in pleasant company, while BD is predicted by being with friends.

Objective 3: To review the literature on the role of the neurobiological in binge eating.
Chapter 7 systematically reviews all studies that investigate the neurobiological reward system in BE and does so with the RDoC framework. In rest, studies find that individuals who binge eat display a lower striatal dopamine release, a change in the volume of the striatum, frontal cortex, and insula, as well as a lower fronto-striatal connectivity. While performing a task, studies report that individuals who binge eat show more activity of the neurobiological reward system while anticipating and receiving food, as well as more model-free reinforcement learning, and habitual behavior.

Objective 4: To investigate how stress impacts food and alcohol delay discounting in patients with AUD or BN.
Chapter 8 explores differences between patients and controls in the DD of money, food, and alcohol as well as the influence of stress on food and alcohol DD. It finds no difference between patients and controls when it comes to the DD of money, food, or alcohol before stress. However, the results do show that patients with BN display a weaker deactivation of the posterior insula than controls while DD food. Importantly, patients with AUD choose more immediately available alcohol after stress and this might be related to a change in activity of the right supplementary motor area. Furthermore, controls choose more immediately available food after stress and this could be related to a change in activity of the frontal cortex. However, no stress-induced change in food DD is seen in patients with BN, although a higher activity of the occipital cortex is found while DD food after stress.

Objective 5: To investigate the relation between stress-induced dopamine release, fronto-striatal connectivity, and negative urgency.
Chapter 9 examines the relation between stress-induced DA release in the vmPFC, fronto-striatal connectivity, and NU in daily life. Its results show that stress leads to DA release in the vmPFC as well as a lower functional connectivity between the vmPFC and dorsal striatum and a higher functional connectivity between the vmPFC and ventral striatum. Importantly, individuals with a higher stress-induced DA release also have a higher stress-induced change in fronto-striatal FC and display more NU in daily life.

10.2. Interpretation

10.2.1. Stress, negative affect and binge behavior

The results of this thesis highlight the complexity of the relation between stress, NA, and binge behavior.

When it comes to BE, the escape-theory, emotion regulation theory, and trade-off theory all posit that stress and NA are triggers of BE and that patients turn to BE as a means of coping with stress and NA (Heatherton & Baumeister, 1991; Kenardy et al., 1996; Lacey et al., 1986). In support of these theories, this thesis shows that NA is indeed related to subsequent BE through changes in craving and rash action, and that feeling down is a predictor of BE (Chapter 4; Chapter 6). In contrast, this thesis also finds that NA is related to subsequent not eating, that feeling distressed is a negative predictor of BE and that acute stress might not make patients with BN choose more immediately available food (Chapter 6; Chapter 8). These results could imply that stress and NA have competing effects on eating behaviors in patients with BN, leading to both BE and dietary restriction. Though this might seem surprising, it has already been suggested by theories such as the integrated cognitive and behavioral model of binge eating and is supported by several findings in the literature (Burton & Abbott, 2019). First, a previous study similarly reports that inducing NA in patients with BN can cause either overeating and undereating (S. L. Russell et al., 2017). Second, studies in animals and the general population also find that stress and NA can have competing effects on eating behaviors (O'connor et al., 2008; Torres & Nowson, 2007). For example, ESM studies show that mild stressors can make individuals eat more, while severe stressors can cause them to eat less, especially when the stressor is associated with a strong physical response (O'connor et al., 2008; Stone & Brownell, 2007). Third, stress and NA have been shown to lead to dietary restriction in other eating disorders such as anorexia nervosa, where higher levels of NA predict subsequent restrictive eating on the next day, and feelings of guilt increase in the hours before a restrictive eating episode (Engel et al., 2013; Haynos et al., 2017). Nevertheless, the majority of studies in BN only examine how stress and NA lead to BE, but not how stress and NA are related to dietary restriction. This could be problematic as dietary restriction is considered to be an important factor in BN, has been found to trigger BE, and is a target for therapeutic interventions (Hagan & Walsh, 2021; G. Russell, 1979; Zunker et al., 2011). Specifically, it could influence study results and be the reason why the vast majority of ESM studies does not find that higher levels of NA predict

subsequent BE (Ambwani et al., 2015; Fitzsimmons-Craft et al., 2016; Heron et al., 2014; Moskovich et al., 2019; Pearson et al., 2018; Smith et al., 2018, 2019; Smith, Mason, Juarascio, et al., 2020; Smith, Mason, Schaefer, et al., 2020).

When it comes to BD, theories such as the tension reduction theory, stress-response dampening model, and motivational model of alcohol use propose that patients with AUD drink alcohol to cope with stress and NA (Conger, 1956; Cooper et al., 1995; Cox & Klinger, 1988; Levenson et al., 1980). The findings of this thesis support these theories by showing that higher levels of NA are associated with subsequent BD in patients with AUD, and that stress makes patients prefer more immediately available alcohol (Chapter 5; Chapter 8). However, this thesis also shows that the relation between NA and alcohol use might be non-linear, whereby patients with AUD are more likely to drink alcohol when experiencing both higher and lower levels of NA (chapter 5). Furthermore, this thesis also finds that patients with AUD are more likely to drink alcohol after experiencing both higher and levels of PA (chapter 5). Therefore, the non-linear relation between affect and alcohol use could be the result of both NA and PA being related to subsequent alcohol use, as NA and PA are in part negatively correlated with one another (Schmukle et al., 2002). However, as to our knowledge, only one other study reports a similar non-linear relation whereby both higher and lower levels of loneliness predict alcohol use (Bragard et al., 2022). This could be due to several reasons. First, previous studies could have failed to detect a non-linear relation because of methodological reasons. Namely, studies in a laboratory context could be less likely to find such a relation as they only induce high levels of either NA or PA. Furthermore, some analysis techniques may fail to detect a non-linear relation due to their assumption of linearity. For example, negative or positive emotions are not included among the most important predictors of alcohol use in the elastic net regularized regression of Chapter 6, which could be due to its assumption that there is a linear relation between the predictors and the outcome. Second, studies might not find a non-linear relation between affect and alcohol use due to the characteristics of the sample being studied. Namely, over the course of AUD, the relation between alcohol use and PA decreases, while the relation with NA increases (Koob & le Moal, 1997; Koob & Volkow, 2016). This could be a reason why this thesis finds that both NA and PA are related to alcohol use in patients with AUD. However, this also implies that a study including a sample of patients with a more severe or longer-existing AUD might not find a relation between PA and alcohol use. In line with this hypothesis, a

study in hospitalized patients with AUD finds that NA is related to approaching alcohol while PA is associated with avoiding alcohol (Schlauch et al., 2013).

Taken together, the findings of this thesis illustrate that there is a complex relation between stress, NA, and binge behavior, which raises the question which variables are implicated in this relation.

10.2.2. Variables of interest

Craving

This thesis shows that craving plays a key role in AUD and BN. Specifically, the daily life results of this thesis show that craving mediates the relation between NA and BE in patients with BN, that changes in NA and PA are associated with subsequent craving in patients with AUD, and that craving is the most important predictor in the person-specific models for BE, alcohol use, and BD (Chapter 4; Chapter 5; Chapter 6).

Interestingly, the relation between affect and craving is specific to patients with AUD or BN in the current study and is not seen in controls (Chapter 4; Chapter 5). This might not be surprising for researchers studying AUD, as studies have already shown that craving distinguishes patients with AUD from controls, and which has led to the inclusion of craving as a criterion for AUD in the DSM-5 (American Psychiatric Association, 2013; Casey et al., 2012; Cherpitel et al., 2015). However, the findings of this thesis may be unexpected for researchers working with eating disorders. This is due to the concept of craving being traditionally associated with studies on alcohol and substance use disorders, and because the role of addiction in eating disorders has been the topic of debate (Corsica & Pelchat, 2010; Wilson, 2010). Nevertheless, this thesis highlights the importance of craving in AUD as well as BN, and the need for further research on the daily life and neurobiological aspects of craving in both disorders.

When it comes to daily life, several aspects concerning craving need to be investigated in more depth. First, the roles of expectancies and cue-reactivity in how craving mediates the relation between NA and binge behavior should be explored. Specifically, NA could activate the expectancy that eating food and drinking alcohol alleviates NA, causing individuals to experience more craving (May et al., 2012). Furthermore, exposure to cues when NA is high could increase craving. Research shows that the induction of NA and exposure to alcohol cues have additive effects on craving and that their combined effect is predictive of relapse in patients with AUD (Cooney et al., 1997). Second, most literature explores how craving is related to subsequent BE or BD, but not how recent binge behavior

could lead to craving itself. However, studies show that stronger acute alcohol withdrawal symptoms are related to higher scores on the obsessive subscale of the Obsessive Compulsive Drinking Scale, and studies on nicotine use indicate that heavy smokers experience stronger initial withdrawal symptoms and that this is accompanied by higher feelings of craving (Bujarski et al., 2015; Heinz et al., 2003). Third, research on craving in daily life is hindered by a lack of knowledge on how craving should be measured. For decades, there has been debate on how craving should be investigated with questionnaires, resulting several multidimensional rating scales for craving (Rosenberg, 2009; Sayette et al., 2000). In contrast, most ESM studies, including the ones of this thesis, measure craving with a single item that scores a general desire or urge for a substance (Serre et al., 2015). This ignores the fact that craving is typically defined as an intense desire, which is compulsive, and that craving is often combined with an attempt to abstain (Rosenberg, 2009; Sayette et al., 2000). Therefore, future ESM studies need to explore how craving is measured best in daily life.

When it comes to behavior and neurobiology, craving is thought to be caused by a disturbance in multiple cognitive constructs which are related to functional changes in several brain areas (Morris & Voon, 2016; Sinha, 2013). For example, craving is seen as the result of an attentional bias to cues (i.e., cues are detected more quickly), a higher incentive salience of substances (i.e., a higher motivational value), a lower response inhibition (i.e., craving is more difficult to control), and a shift from goal-directed to habitual behavior (i.e., whereby craving can be experienced in the absence of triggers) (Jones et al., 2013; Morris & Voon, 2016; Robinson & Berridge, 1993; Sinha, 2013). Interestingly, studies show that patients with AUD and BN display disturbances in these domains, and that they are linked to changes in the activity of the PFC and a lower fronto-striatal connectivity (Chapter 7; Ralph-Nearman et al., 2019; Westwater et al., 2021). However, these studies have yet to investigate whether these changes play a role in craving. In fact, most neuroimaging studies that focus on craving only use images of a substance (e.g., food or alcohol) (Chapter 7; Sinha, 2013). This method may be too general, and future studies should therefore investigate how craving is related to changes in brain functioning during tasks that explore more specific cognitive constructs.

Negative urgency

The daily life results of this thesis show that patients with BN exhibit more NU, that rash actions mediate the relationship between NA and BE, and that rash actions are an important predictor of BE (Chapter 4; Chapter 6). These findings align with the acquired preparedness model and the risk and maintenance model of BN, as well as other studies reporting that NU

is predictive of the onset and severity of BE and problematic alcohol use (Fischer et al., 2013; Fischer & Smith, 2008; Kaiser et al., 2016; Pearson et al., 2012; Riley et al., 2016; Settles et al., 2012). Additionally, this thesis identifies a potential neurobiological basis for NU, where individuals who release more DA when stressed also experience a weaker reduction in fronto-striatal connectivity and display more NU in daily life (Chapter 9). This finding could be interesting as studies show that patients with AUD and BN display changes in fronto-striatal connectivity, which based on the previously described findings, may contribute to the higher levels of NU observed in patients with AUD or BN (Chapter 7; Courtney et al., 2013; Galandra et al., 2019). However, the results need to be interpreted with caution, and more daily life and neurobiological research is needed in order to better understand why patients with BN display more NU in daily life.

For daily life, there are two main challenges. First, future ESM studies need to explore the role of NU in AUD. As to our knowledge, no studies have examined whether patients with AUD actually display a stronger relation between NA and rash action in daily life. Furthermore, it is not clear whether rash action mediates the relation between NA and alcohol use. For example, we could find one study in individuals with and without ADHD which reports that NU increases in the hours before alcohol use, but another study reports that rash action is not related to alcohol use (Dora et al., 2022; Wonderlich et al., 2022). Second, studies should explore mediating factors in the relation between NA and rash action. Previous research using questionnaires points to the importance of distress tolerance, but as to our knowledge, no ESM studies have explored whether distress tolerance plays a role in the relation between NA and rash action in daily life (Barrios et al., 2022).

For the neurobiology of NU, the results of this thesis highlight the need for further research on the impact of stress on DA transmission in patients with AUD and BN. Based on the previously mentioned findings in controls, it could be hypothesized that patients display more DA release in the vmPFC under stress, which in turn could then make them likely display more rash action. However, the literature shows that results concerning DA transmission in controls might not always translate well to patients (Bosker et al., 2017). This could be due to the lower baseline dopaminergic activity which is often found in patients with AUD and BN, and which could be the result of a repeated overconsumption of alcohol and food (Chapter 7; Söderpalm et al., 2011). Therefore, future studies should investigate whether patients with AUD and BN exhibit differences in stress-induced DA release in the vmPFC and how this relates to NU.

Reward processing and delay discounting

After a systematic review of the literature concerning the neurobiological reward system in BE, this thesis finds support for several theories on BE (Chapter 7). Specifically, the tendency to engage in more habitual behavior, which is associated with a lower fronto-striatal functional connectivity, agrees with the risk and maintenance model's hypothesis that BE becomes more compulsive over time (Haynos et al., 2021; Pearson et al., 2015). The finding that patients base their decisions more on previous choices also aligns with the proposed reward learning difficulties from the acquired preparedness model (Combs et al., 2010; Voon et al., 2015). Additionally, the increased activity of the OFC, ACC, and insula when viewing images of food is consistent with the incentive-sensitization theory, which posits that repeated BE episodes sensitize the brain to be more responsive to food cues (Chapter 7; Robinson & Berridge, 1993). However, there remain large gaps in the literature and several methodological challenges must be addressed in order to fill them. Namely, there is a need for research examining specific subcomponents of reward processing with designs tailored to the patient population (e.g. using food rather than money).

This thesis wanted to meet this need and has therefore investigated the impact of stress on the DD of alcohol and food in patients with AUD and BN (Chapter 8). Its results indicate that stress makes patients with AUD prefer more immediately available alcohol, but that stress might not have the same effect on food DD in patients with BN (Chapter 8). These results align with the findings of the ESM studies conducted in this thesis, which show that higher levels of NA are associated with subsequent BD in patients with AUD, but that NA in general is not related to subsequent BE in patients with BN (Chapter 4, Chapter 5). However, as the ESM studies in this thesis show that NU and craving play a vital role in the relation between NA and binge behavior, the question remains how DD is actually related to these variables.

When it comes to NU, a meta-analysis reports that there is no relation between DD rates and self-report scores for NU (Cyders & Coskunpinar, 2011). One explanation for this finding could be that DD by itself is not representative for NU as it does not include a negative emotionality component, suggesting that the change in DD due to stress might be a better behavioral correlate for NU. When it comes to craving, the number of studies is smaller, but there is evidence that higher DD rates are correlated with alcohol craving and AUD severity, and that individuals with lower DD rates are more susceptible for the effects of transcranial magnetic stimulation on food craving (Kekic et al., 2014; MacKillop et al., 2010). This is not unexpected as DD is seen as a moderator of incentive salience and because

incentive salience is thought to be important in craving (Insel et al., 2010; Robinson & Berridge, 1993). In contrast, there is also one study that finds no relation between DD rates and craving in patients with AUD (Joos et al., 2013). These mixed findings could be the result of the focus on monetary DD, and not food or alcohol DD, which could be more relevant for craving in patients with AUD and BN.

Taken together, it can be questioned to what extent the relationship between monetary DD and craving and NU exists, whereby stress-induced changes in food and alcohol DD may serve as more accurate correlates. However, since this thesis does not find that stress increases food DD in patients with BN, though it does show that NA predicts subsequent craving and rash action in these patients, it could be that the role of DD is limited whereby previously mentioned changes in attentional bias, incentive salience, response inhibition, habitual behavior, and distress tolerance might play a larger role in craving and NU.

10.2.3. Differences and similarities between alcohol use disorder and bulimia nervosa

The findings of this thesis indicate that there are both differences and similarities in the factors that contribute to binge behavior among patients with AUD and BN.

One difference that stands out is the contrast in the relationship between NA and binge behavior between the two disorders. Specifically, the finding that both higher and lower levels of NA are associated with BD in patients with AUD, while NA has competing effects on eating behaviors in patients with BN (Chapter 4, Chapter 5). This contrast raises the question which characteristics set food apart from alcohol in a way that NA can lead to dietary restriction. On the one hand, a reduction in food intake in response to acute stress and NA could be normal as it could be helpful during a 'fight-or-flight'-response (Torres & Nowson, 2007). Indeed, both patients with BN and controls display a relation between NA and not eating in this thesis, which could imply that the relation between these variables is a general response across individuals (Chapter 4). On the other hand, it is thought that patients with an eating disorder can also restrict their dietary intake in order to cope with stress and NA (Burton & Abbott, 2017; Fairburn et al., 1999; Haynos et al., 2022). Namely, though dietary restriction might initially be cumbersome and not rewarding at all, the resulting outcomes (e.g., weight loss, social praise) might be rewarding for patients (Fairburn et al., 1999; Haynos et al., 2022). The effect of the outcomes could then generalize, causing dietary restriction to become rewarding as well, which could then make patients restrict their dietary intake as a response to stress and NA (Fairburn et al., 1999; Haynos et al., 2022). If so, this could explain why this thesis finds that controls prefer more immediately available food after

acute stress, but not patients with BN, who might find delaying food intake more rewarding (Chapter 8).

Furthermore, the results of this thesis and previous research show that both patients with AUD and BN display more craving and NU in daily life, but this raises the question why some individuals are more prone to develop AUD while others develop BN. Several reasons have been suggested in the literature such as a genetic vulnerability to experience more positive effects of food or alcohol, or familial factors such as teasing about weight, parental drinking behavior, and lack of cohesion (Ellis et al., 1997; Laghi et al., 2020; MacBrayer et al., 2001; Munn-Chernoff & Baker, 2016). However, though there have been longitudinal studies linking these factors to BE and BD using questionnaires, no longitudinal ESM studies have been performed to investigate the importance of these factors in developing AUD and BN.

10.3. Limitations

Though the individual studies in this thesis suffer from several specific limitations, some limitations are shared by all studies.

To begin, this thesis uses the criteria set out by the NIAAA to define BD, namely a pattern of drinking that raises the blood alcohol concentration to 0.08 percent, which corresponds to drinking four drinks under two hours for a woman (NIAAA, 2022). However, the definition of a standard drink differs between countries, with the NIAAA stating that a standard drink contains 14 grams of alcohol, while the AUDIT and Vlaams Expertisecentrum Alcohol en andere Drugs (VAD) state that a standard drink includes 10 grams of alcohol (Damme et al., 2022; De Doncker et al., 2016; NIAAA, 2023; Saunders et al., 1993). This thesis uses the criteria of the AUDIT and VAD for a standard drink as this more accurately represents the drinking patterns of the participants (e.g., a glass of beer typically measures 250ml in Belgium, in contrast to 330ml in other countries). This resulted in a definition of BD that might not entirely represent that of the NIAAA, but is closer to that of the VAD, which defines BD as drinking four drinks under two hours for women (Damme et al., 2022).

Furthermore, an important limitation of this thesis is the patient sample. First, all participants in this thesis are female. This often the case in the eating disorders field as the prevalence of eating disorders is lower is men (Galmiche et al., 2019). However, previous studies have shown that there are important differences between men and women in what

triggers BE and BD. When it comes to BE, men report less emotional eating, image dissatisfaction, and drive for thinness than women, but are more likely to binge eat in social contexts (Bhadra et al., 2002; Phillips et al., 2016; Tanofsky et al., 1997). When it comes to BD, men binge drink more often and from a younger age than women, but may be less susceptible to its negative psychical and mental health consequences (Wilsnack et al., 2018).

Second, most participants are Caucasian. The underrepresentation of minority groups in studies is a known issue and has multiple causes such as socio-cultural barriers, stereotypes, and poorly adapted recruitment strategies (Hussain-Gambles et al., 2004). Though the number of studies is limited, there is evidence that there are racial differences in the factors involved in BE and BD. Specifically, studies have found that eating, weight, and shape concerns might be more pronounced in Hispanic women than in Caucasian women, while they might be less pronounced in African-American women (Franko et al., 2012; Ivezaj et al., 2010; Pike et al., 2001). Additionally, studies show that the highest frequency of BD is found among Caucasian individuals, and that BD happens less often in African-Americans and those of Asian descent (Banta et al., 2014; Bryant & Kim, 2012). Importantly, racial discrimination itself is associated with BE and negative drinking consequences (Brown et al., 2022; Desalu et al., 2017).

Third, all participants have a short illness duration. Although the majority of studies do not exclude patients based on illness duration, this thesis only includes patients with an illness duration less than five years as the role of certain factors is thought to change over the course of AUD and BN (Koob & le Moal, 1997; Pearson et al., 2015). Namely, it has been hypothesized that the role of PA decreases over the course of AUD, while the role of NA increases (Koob & le Moal, 1997). Furthermore, binge behavior might become habitual or compulsive over time, making the original triggers of the behavior no longer required for a BE or BD episode to occur (Pearson et al., 2015). Interestingly, in our previous work, we describe the case of a patient with BN who suffers from a COVID-19-related loss of smell and taste, and who reports to no longer enjoy eating in the way she did previously (Leenaerts et al., 2022). In addition, NA is no longer a trigger for BE episodes, but the patient still frequently binge eats and the episodes are now preceded by strong feelings of craving (Leenaerts et al., 2022).

Taken together, the characteristics of the patient sample in this thesis limit the generalizability of the results. Future research should therefore aim to include samples which consist of both men and women, are multiracial and include patients that are at different

stages of AUD and BN.

10.4. Clinical implications

The results of this thesis could have several clinical implications. First, though many psychotherapeutic approaches focus on the role of NA in BN and AUD, the findings of this thesis show that clinicians should recognize the complexity of the relationship between affect and binge behavior. When it comes to BN, the findings of chapter 4 and chapter 6 emphasize that clinicians should pay attention to how NA not only leads to BE, but how it can also lead to dietary restriction. Furthermore, the results from chapter 6 highlight that clinicians should differentiate between negative emotions and explore which ones are more likely cause BE (i.e., feeling down) and which ones are less likely to make patients binge eat (i.e., feeling distressed, feeling under pressure). When it comes to AUD, the findings from chapter 5 show that clinicians should not only focus on how higher levels of NA lead to alcohol use in patients, but also how lower levels of NA and changes in PA are triggers of alcohol consumption.

Second, the results of this thesis highlight the importance of rash action, craving, reward processing, and DD, and show the need for novel therapeutic approaches focusing on these factors. Indeed, several studies have explored how they can be impacted and report interesting results. For rash action, the IMPULS and ImpulsE trials have targeted food-related response inhibition and report report reductions in BE that lasted longer than in the treatment as usual group (Preuss et al., 2017; Schag et al., 2019). Additionally, studies show that treatments based on mindfulness or motivational enhancement might be less effective for patients with AUD who also display high levels of NU (Kozak et al., 2019). For craving, a study with a virtual reality treatment for food craving reports higher abstinence rates for BE than cognitive behavioral therapy (Ferrer-García et al., 2017). Furthermore, a meta-analysis finds that repeated transcranial magnetic stimulation of the left dlPFC could be effective at reducing craving in patients with AUD (Zhang et al., 2019). For reward processing, neurofeedback treatments aimed at reducing cue-reactivity (i.e., reward anticipation) report reductions in craving for food and alcohol, as well as binge eating episodes. For DD, studies using episodic future thinking, where patients are required to focus on desired long-term rewards, show decreases in DD as well as alcohol consumption in patients with AUD (Schacter et al., 2017; Snider et al., 2016).

Combined, this thesis shows that clinicians have to be aware of the full scope of the relation between affect and binge behavior, and emphasizes the need for more comprehensive treatments aimed at targeting this relation.

10.5. Future directions

This thesis has already proposed specific recommendations for future studies on AUD and BN in the individual chapters. However, the literature on these disorders as a whole needs to take the following directions to meaningfully advance our knowledge.

To begin, there is a need for more longitudinal studies to identify the factors involved in the onset and maintenance of AUD and BN. Though there have been longitudinal studies using questionnaires, most ESM and neuroimaging studies in AUD and BN have been cross-sectional (Fischer et al., 2013; Kaiser et al., 2016; Riley et al., 2016). However, only longitudinal studies will be able shed light on whether individuals who display more NU in daily life or a disturbance in fronto-striatal functional connectivity are more likely to begin BE and BD, and what the impact is of starting with BE and BD on daily life behavior and the brain.

Then, this thesis uses a categorical framework to define psychiatric disorders as it investigates binge behavior in patients with BN and/or AUD. However, this framework has come under scrutity, with multiple authors calling for a more dimensional approach to study eating disorders and AUD (Luo et al., 2016; Saha et al., 2006). This thesis partially incorporates such a dimensional framework by exploring the impact of disease severity with AUDIT or EDE-Q scores and with BE or BD severity. However, more research is needed which investigates binge behavior across the entire spectrum (eg., non-clinical, subclinical, clinical) and across different psychiatric disorders (eg., BN, BED, AN-bp).

Also, although several studies have tried to predict behavior in daily life using machine learning, the field remains in its infancy with several important questions that need to be answered before daily life interventions such as the just-in-time adaptive intervention can be developed and implemented. For example, there are multiple methodological issues in several published papers, highlighting the need for more methodological rigor and expertise when applying machine learning models to daily life data (Chapter 6). Also, it remains unclear whether person-specific or pooled prediction models are preferred in the prediction of daily life behavior or whether they can be combined in a meaningful way (Chapter 6).

Therefore, the eating and alcohol use disorder field needs to put more emphasis on the development of proper prediction models for BE, alcohol use, and BD in daily life.

Finally, though the studies in this thesis show that ESM and neuroimaging are informative by themselves, this thesis also shows that the combination of these modalities can help with the interpretability of neuroimaging results and can provide information on how neurobiological changes are related to differences in daily life behavior (Chapter 9). However, only a limited number of studies have actually combined ESM and neuroimaging to investigate BE and BD (Fischer et al., 2017; Goldfarb et al., 2022; Wonderlich et al., 2017, 2018). Future neuroimaging studies should therefore consider including an ESM component in their study design.

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EDUCATION

2018-ongoing	**Master after Master in Specialized Medicine** Faculty of Medicine, KU Leuven, Belgium
2019-2023	**Doctor of Philosophy in Biomedical Sciences** Cognitive and Molecular Neurosciences, Faculty of Medicine, KU Leuven, Belgium
2014-2018	**Master of Science in Medicine (Magna Cum Laude)** Faculty of Medicine, KU Leuven, Belgium
2011-2014	**Bachelor of Science in Medicine (Summa Cum Laude)** Faculty of Medicine, KU Leuven, Belgium

ADDITIONAL TRAINING

2022	**Writing Course** Nature Publishing (Online)
2021	**Eastern European Machine Learning Summer School** EEML (Online)
2021	**4th Modelling Symposium: Introducing Deep Neural Networks** NeuroWissenschaftiche Gesellschaft (Online)
2021	**Multivariate Statistics** KU Leuven, Belgium
2021	**Longitudinal Data Analysis** KU Leuven, Belgium
2021	**Introduction to Clustering Analysis** KU Leuven, Belgium
2021	**Introduction to Social Network Analysis** FLAMES
2020	**Summer School on Affective Neuroscience** University of Maastricht

2020	**Data Transformations** FLAMES
2020	**Missing Data Methodology** FLAMES
2020	**Concepts of Multilevel, Longitudinal and Mixed Models** KU Leuven, Belgium
2019	**Statistical Parametric Mapping for fMRI and PET** University College London
2019	**Python for Everybody** University of Michigan (Online)

ACADEMIC APPOINTMENTS

2019-2023	**PhD Candidate (Belgium)** Faculty of Medicine, KU Leuven Responsible Faculty: Prof. Dr. Elske Vrieze, Dr. Ir. Jenny Ceccarini, Prof. Dr. Stefan Sunaert
2022	**Visiting Student Researcher (USA)** Idiographic Dynamics Lab, Department of Psychology, University of California, Berkeley Responsible Faculty: Prof. Dr. Aaron Fisher

CLINICAL APPOINTMENTS

2023-ongoing	**Psychiatry Resident (Belgium)** OPZ Geel: Opname-eenheid 1 Netwerp GGZ Kempen: CKB-team
2018-2023	**Psychiatry Resident (Belgium)** UPC KU Leuven: Angst & Depressie, ADHD/Atmosfeer, Perinatale psychiatrie, Eetstoornissen

OTHER APPOINTMENTS

Ad Hoc Reviewer	Appetite Clinical Psychological Science European Eating Disorders Review Frontiers in Psychology Journal of Eating Disorder Psychology of Addictive Behaviors Psychological Medicine

HONORS, AWARDS, AND SUPPORT

2023	**Grant for participating in a conference abroad** Fonds Wetenschappelijk Onderzoek
2022	**Grant for participating in a conference abroad** Fonds Wetenschappelijk Onderzoek
2022	**Grant for a long stay abroad** Fonds Wetenschappelijk Onderzoek
2022	**Omkadering Jonge Onderzoekers** The Flemish Government
2021	**Omkadering Jonge Onderzoekers** The Flemish Government
2021	**Poster Prize** European College Of Neuropsychopharmacology

PUBLICATIONS

1. Schroyen, G., Sleurs, C., Ottenbourghs, T., **Leenaerts, N.**, Nevelsteen, I., Melis, M., Smeets, A., Deprez, S., & Sunaert, S. (2023). Changes in leukoencephalopathy and serum neurofilament after (neo)adjuvant chemotherapy for breast cancer. Translational Oncology, 37, 101769. https://doi.org/10.1016/J.TRANON.2023.101769

2. Melis, M., Schroyen, G., Blommaert, J., **Leenaerts, N.**, Smeets, A., Van Der Gucht, K., Sunaert, S., & Deprez, S. (2023). The Impact of Mindfulness on Functional Brain Connectivity and Peripheral Inflammation in Breast Cancer Survivors with Cognitive Complaints. Cancers, 15(14), 3632. https://doi.org/10.3390/cancers15143632

3. Melis, M., Schroyen, G., **Leenaerts, N.**, Smeets, A., Sunaert, S., Van der Gucht, K., Deprez, S. with Melis, M. (2023). The impact of mindfulness on cancer-related cognitive impairment in breast cancer survivors with cognitive complaints. Cancer, 129 (7), 1105-1116. doi: 10.1002/cncr.34640

4. **Leenaerts, N.**, Vaessen, T., Sunaert, S., Ceccarini, J., Vrieze, E. with Leenaerts, N. (2023). How Negative Affect Does and Does Not Lead to Binge Eating-The Importance of Craving and Negative Urgency in Bulimia Nervosa. Journal Of Psychopathology And Clinical Science. doi: 10.1037/abn0000830

5. Schroyen G, Schramm G, Van Weehaeghe D, **Leenaerts N**, Vande Casteele T, Blommaert J, Koole M, Smeets A, Van Laere K, Sunaert S and Deprez S (2022) Cerebral glucose changes after chemotherapy and their relation to long-term cognitive complaints and fatigue. Front. Oncol. 12:1021615. doi:10.3389/fonc.2022.1021615

6. Radwan, A., Decraene, L., Dupont, P., **Leenaerts, N.**, Simon-Martinez, C., Klingels, K., Ortibus, E., Feys, H., Sunaert, S., Blommaert, J., Mailleux, L. with Blommaert, J. (joint last author), Mailleux, L. (joint last author), Blommaert, J. (2023). Exploring structural connectomes in children with unilateral cerebral palsy using graph theory. Human Brain Mapping. doi: 10.1002/hbm.26241

7. **Leenaerts, N.**, Jongen, D., Ceccarini, J., Van Oudenhove, L., & Vrieze, E. (2022). The neurobiological reward system and binge eating: A critical systematic review of neuroimaging studies. International Journal Of Eating Disorders, 38 pages. doi:10.1002/eat.23776

8. **Leenaerts, N.**, Ceccarini, J., Sunaert, S., & Vrieze, E. (2022). The impact of COVID-19-related smell and taste disorders on a patient with bulimia nervosa: a case report. Neurocase, 28(1), 72-76. doi:10.1080/13554794.2021.2024859

9. Demyttenaere, K., **Leenaerts, N.**, Acsai, K., Sebe, B., Laszlovszky, I., Barabassy, A., . . . Correll, C. U. (2021). Disentangling the symptoms of schizophrenia: Network analysis in acute phase patients and in patients with predominant negative symptoms. European Psychiatry, 65(1), 10 pages. doi:10.1192/j.eurpsy.2021.2241

10. **Leenaerts, N.**, Vaessen, T., Ceccarini, J., & Vrieze, E. (2021). How COVID-19 lockdown measures could impact patients with bulimia nervosa: Exploratory results from an ongoing experience sampling method study. Eating Behaviors, 41, 1-6. doi:10.1016/j.eatbeh.2021.101505

PREPRINTS

1. **Leenaerts, N.**, Ceccarini, J., Weygandt, M., Sunaert, S., Vrieze, E. (2022). The effect of stress on delay discounting in bulimia nervosa and alcohol use disorder: a functional magnetic resonance imaging study.. PsyArXiv. doi: 10.31234/osf.io/cvqpk

2. **Leenaerts, N.**, Soyster, P. D., Ceccarini, J., Sunaert, S., Fisher, A. J., & Vrieze, E. (2023). Person-specific and Pooled Prediction Models for Binge eating, Alcohol Use and Binge Drinking in Bulimia Nervosa and Alcohol Use Disorder: An Experience Sampling Method Study. https://doi.org/10.31234/osf.io/9utrv

3. **Leenaerts, N.**, Vaessen, T., Sunaert, S., Ceccarini, J., & Vrieze, E. (2023). The impact of negative and positive affect on craving, non-heavy alcohol use, and binge drinking in patients with alcohol use disorder and controls: An experience sampling method study. https://doi.org/10.31234/osf.io/pr2sv

ABSTRACTS, PRESENTATIONS, AND POSTERS

1. Melis, M., Schroyen, G., **Leenaerts, N.**, Smeets, A., Sunaert, S., Van der Gucht, K., Deprez, S. (2023). The impact of mindfulness on peripheral inflammation in breast cancer survivors with cognitive complaints. Presented at the International Cancer and Cognition Task Force (ICCTF), San Diego, US.

2. **Leenaerts, N.**, Vaessen, T., Sunaert, S., Ceccarini, J., & Vrieze, E. (2022). HOW NEGATIVE AFFECT LEADS TO BINGE EATING: THE IMPORTANCE OF IMPULSIVITY AND CRAVING IN BULIMIA NERVOSA. In Eating Disorders Research Society. Philadelphia, United States of America.

3. Mailleux, L., Radwan, A., Decraene, L., Dupont, P., **Leenaerts, N.**, Simon-Martinez, C., . . . Blommaert, J. (2022). Exploring structural brain connectomes and its impact on sensorimotor function in children with unilateral cerebral palsy. In Developmental Medicine And Child Neurology (Vol. 64, Iss. S3). Barcelona: Wiley. doi:10.1111/dmcn.15214

4. Decraene, L., Radwan, A., Dupont, P., **Leenaerts, N.**, Simon-Martinez, C., Klingels, K., . . . Blommaert, J. (2021). Exploring the cerebral palsy structural connectome and its impact on clinical outcomes. In LBI scientific meeting. Online.

5. **Leenaerts, N.**, Ceccarini, J., Sunaert, S., & Vrieze, E. (2021). Temporal dynamics of impulsivity and craving before and after a binge drinking episode: results from an ongoing experience sampling study. In ESBRA 2021. Timisoara, Romania.

6. **Leenaerts, N.**, Ceccarini, J., Sunaert, S., & Vrieze, E. (2021). Striatal cerebral blood flow changes in patients with recent-onset bulimia nervosa and alcohol use disorder. In ECNP 2021. Lisbon, Portugal.

7. **Leenaerts, N.**, Ceccarini, J., Sunaert, S., & Vrieze, E. (2021). Temporal dynamics of impulsivity and craving before and after a binge eating episode: results from an ongoing experience sampling study. In EDRS 2021. Online.

8. **Leenaerts, N.**, Vaessen, T., Ceccarini, J., & Vrieze, E. (2021). How COVID-19 lockdown measures could impact patients with bulimia nervosa: Exploratory results from an ongoing experience sampling method study. In European Psychiatric Association. Online.

9. **Leenaerts, N.**, Vaessen, T., Ceccarini, J., & Vrieze, E. (2020). Beloningsgevoeligheid bij patiënten met bulimia nervosa: voorlopige resultaten van een experience sampling method studie. In Nationale Academie Eetstoornissen. Beesd.

10. **Leenaerts, N.**, Vaessen, T., Ceccarini, J., & Vrieze, E. (2020). How COVID-19 lockdown measures could impact patients with bulimia nervosa: exploratory results from an ongoing experience sampling method study.. In VAE Congres 2020 'Andere Perspectieven'. Online.

11. **Leenaerts, N.**, Vaessen, T., Ceccarini, J., & Vrieze, E. (2020). Linking stress to impulsivity in recent-onset bulimia nervosa and alcohol use disorder: preliminary results from an ecological momentary assessments study. In European College of Neuropsychopharmacology. Vienna.

12. **Leenaerts, N.**, Vrieze, E., Sunaert, S., Van Laere, K., & Ceccarini, J. (2020). Effects of lifetime alcohol consumption on surface morphometry in alcohol-dependent patients. In Organization for Human Brain Mapping. Montreal.

MENTORING

2022-2023 **Ellen Boon** (Role: Daily Supervisor)
Master of Science in Biomedical Sciences, KU Leuven
Thesis: The effect of stress on interoception in patients with Anorexia Nervosa.

2021-2022	**Lotte Buyle** (Role: Daily Supervisor) Master of Science in Biomedical Sciences, KU Leuven Thesis: Reward functioning in patients with Bulimia Nervosa or an Alcohol Use Disorder: Looking at daily life.
2020-2021	**Maxime Voet** (Role: Daily Supervisor) Master of Science in Biomedical Sciences, KU Leuven Thesis: Stress reactivity is related to higher dopamine release in the prefrontal and cingulate cortex.
2020-2021	**Danny Majid** (Role: Daily Supervisor) Master of Science in Medicine, Linköping university, Sweden Thesis: Stress and delay discounting in patients with bulimia nervosa: a functional magnetic resonance study

OTHER ACTIVITIES

2022	**Psychiatry 2.0: Towards a new way of thinking** Inter-universitary seminar (Role: Organizer)
2021	**Machine Learning in Psychiatry for Dummies** Inter-universitary seminar (Role: Organizer)
2021-Ongoing	**Current Topics in Psychiatry** Journal Club (Role: Co-founder)
2015	**Summer School of Psychiatry** Summer school (Role: Organizer)

Dankwoord

Wat blijft je het meeste bij van een doctoraat? Zijn het die late uurtjes wanneer je alleen achter een laptop zat in het donker? Is het die software update waardoor al je scripts niet meer werkten? Nee, het zijn die koffiemomentjes waarop je met collega's lachte en elkaar moed insprak. Het is die brainstormsessie waar je samen ballonnetjes opliet en doorprikte totdat eindelijk een topidee bovenkwam. Het zijn die keren dat je elkaar hielp wanneer de muis van de MRI-scanner weer bleef steken. Daarom wil ik de volgende personen bedanken.

Om te beginnen wil ik mijn promotor, **prof. Dr. Elske Vrieze** bedanken. Voor de start van dit doctoraat mocht ik al samenwerken met jou in de kliniek, eerst als co-assistent op de afdeling eetstoornissen en later als assistent op de raadpleging. Al snel viel het mij op hoe goed jij problemen kan doorgronden en aanpakken. Wanneer je de financiering binnenhaalde voor het 'Spinning Out Of Control'-project en een doctoraatsstudent zocht, heb ik niet lang moeten twijfelen om te solliciteren, want ik wist dat ik in goede handen zou zijn mocht ik aangenomen worden. Inderdaad, de voorbije jaren wist je perfect wanneer je mij kon loslaten en wanneer je mij moest bijsturen. Het is omwille van die begeleiding dat ik obstakels zoals de coronapandemie heb kunnen overkomen en dit doctoraat heb kunnen voltooien.

Natuurlijk zijn er ook mijn co-promotoren, **Dr. Ir. Jenny Ceccarini** en **prof. Dr. Stefan Sunaert**. Jenny, I was always impressed by the drive that you displayed when working on projects as well as by your knowledge about PET. Your passion influenced me and truly motivated me to make the 'Spinning Out Of Control' project a success. I cannot understate the importance of your help with the PET analyses. I don't think I could have survived PMOD without you. Stefan, je hebt me leren werken met een MRI-scanner, getoond hoe je neuro imaging data kan analyseren, en geïntroduceerd bij de collega's van het MIRC. Indien je me niet onder je vleugels zou hebben genomen, dan zou dit doctoraat er niet zijn geweest.

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Enkele maanden na de start van mijn doctoraat heb ik een plekje gekregen in het MIRC waar ik enkele geweldige collega's leerde kennen. We hebben samen analysemethoden geleerd, spectaculaire onderzoeksresultaten begeerd, ons met het tegendeel gefrustreerd, een congresje geprobeerd, van elkaar afgezonderd de coronapandemie getrotseerd, en ons erna gehergroepeerd. **Gwen**, wat een geluk dat je na een maandje toch dag bent komen zeggen! Keer op keer was ik onder de indruk van jouw talent om georganiseerd te werken. Maar nog belangrijker was ik onder de indruk van wat voor een geweldig persoon je bent, want je stond altijd klaar om me te steunen bij tegenslagen, maar je was er ook om te feesten bij meevallers. **Michelle,** Je doorzettingsvermogen is bewonderenswaardig. De manier waarop je volhield om een marathon te kunnen lopen of om je doctoraat tot een goed einde te brengen, was een voorbeeld dat ik probeerde te volgen. Daarnaast was je gevoel voor stijl ook altijd een voorbeeld, maar dit was voor mij minder haalbaar. **Jeroen**, wat voor een belangrijke rol heb je gespeeld in het begin van mijn doctoraat. Hoewel je het misschien niet altijd besefte, waren je passionele praatjes tijdens de koffie een perfecte manier om veel theoretische en praktische kennis over neuro imaging te vergaren. Een groot deel van de programma's die ik gebruikte tijdens mijn doctoraat, heb ik tijdens een van die praatjes voor de eerste keer gehoord. **Joke**, hoe vaak heb ik op je moeten wachten omdat je weer wat later was? Dat weet ik niet meer, maar het was wel elke keer de moeite waard. We konden over alles praten en je was steeds was het luisterend oor dat ik nodig had. Ik heb altijd opgekeken naar hoe je de kliniek en onderzoek succesvol combineert. **Ahmed,** we had such interesting conversations whenever our day-night-cycles eventually aligned. You were such a help in the beginning

when I was struggeling with neuro imaging data. **Charlotte,** ik heb niets dan lof voor jouw gedrevenheid op het gebied van werk, maar ook als het gaat om je Maine Coon. Toen je me vertelde dat je kon beginnen als Assistant Professor aan Tilburg University, was ik niet verbaasd, want net als je kat kom jij altijd op je pootjes terecht. Ten slotte zou ik **Ron, Kwinten, en Jef** willen bedanken voor het goed in banen leiden van de MR- en PET/MR-scans.

Naast mijn plekje in het MIRC, had ik mijn eigenlijke thuis in de Onderzoeksgroep Psychiatrie, meerbepaald in de eenheid Mind-body Research (MBR). Over de jaren heen heb ik de MBR zien veranderen, niet alleen maar van locatie waarbij het oude St. Rafael eindelijk werd ingeruild voor ON5bis, maar ook op het vlak van onderzoek waar grote stappen vooruit werden gezet. **Prof. Dr. Stephan Claes,** hartelijk dank voor de warme ontvangst in je onderzoeksgroep. Ik zal me altijd herinneren hoe je ons als een vis in het water rondleidde in Firenze, hoe je met je Italiaanse boek over de Piazza della Signoria liep, en hoe je moeiteloos babbeltjes maakte met de lokale bevolking. **Thomas,** dank voor het geduld dat je had telkens wanneer ik met een nieuwe analyse naar je toe kwam. Hopelijk zijn mijn statistische vaardigheden in de loop der jaren net zo gegroeid als je haren. **Hilde,** je kennis over de steeds veranderende procedures van de ethische commissie was van onschatbare waarde tijdens mijn doctoraat. **Kris,** onze leuke gesprekken zijn het bewijs dat volwassenpsychiaters en kinder- en jeugdpsychiaters wel degelijk met elkaar overeen kunnen komen. Hoe je gezicht oplichtte wanneer je sprak over Harry Potter zal me altijd bijblijven. **Jozefien,** ik heb vaak opgekeken naar hoe grondig jij zaken doorspit en zie dit nog steeds als een voorbeeld. **Laura,** wat was ik blij dat er iemand naast me kwam zitten die ook een passie had voor machine learning. Ik kijk uit naar de vernieuwingen die je op dit gebied zult brengen. **Robin,** omdat we allebei psychiater-in-opleiding en onderzoeker in de eetstoornissen zijn, hadden we onmiddellijk veel raakvlakken wanneer je in de onderzoeksgroep kwam. Het was een plezier om samen met jou Philadelphia en Wenen te ontdekken. **Roland,** wat een oog voor detail heb je. Hoe jij je vastgebeten hebt in de wearables, hopelijk wel niet letterlijk, was indrukwekkend. **Aleksandra,** dziękuję za wiele rozmów o Polsce. To zawsze rozgrzewało moje serce.

Buiten mijn collega's van de MBR, kon ik ook terecht bij de andere onderzoekseenheden binnen de onderzoeksgroep psychiatrie, en dan vooral bij de collega's van neuropsychiatrie die ook in het MIRC waren neergedaald. **Thomas**, wat was het tof om te praten over

interessante gevallen uit de kliniek of om samen een wandeling te maken. Ik zal me altijd herinneren hoe kleine dingen je aan het schaterlachen brachten, zoals het overduidelijke toupetje van een gearresteerde crimineel, of hoe prachtig het trouwfeest van jou en je vrouw was. **Maarten**, jouw oprechte interesse in onderzoek en je blijdschap wanneer je vooruitgang boekte zullen me bijblijven. Hoe leuk was het om samen door Wenen te trekken, een schnitzel te eten en een goede pint te drinken. **Margot,** wat voor een bommetje energie ben jij. De passie die je hebt voor je werk en voor je dochtertje kan ik enkel bewonderen. **Simon,** waar is de tijd dat jij assistent was op het crisisinterventiecentrum en dat ik daar stage liep? Wat was ik blij om je later terug te zien als doctoraatsstudent. Bedankt voor de leuke tijd op congres in Lissabon. **Laura en Anne-Marie,** bedankt voor de leuke momentjes tijdens de lunch, of wanneer we iets gingen drinken na het werk. Natuurlijk zijn er ook de collega's van Clinical Psychiatry. **Victor,** we hebben elkaar leren kennen in de studentenvereniging. Wie had toen gedacht dat wij later allebei psychiaters-in-opleiding en ook doctoraatsstudenten zouden zijn. Je was altijd een baken van rust en onze gesprekken over filosofie en de discussie over hoe lang een psychiatrische opvolging moet duren zal ik nooit vergeten. **Lise,** het was altijd leuk om met je samen te werken en om aan de After Works deel te nemen. Verder ook bedankt aan de doctoraatsstudenten van Developmental Psychiatry, **Tiffany, Lisa, Laura, Rowena, Xena**. Het was altijd leuk om met jullie van gedachten te wisselen tijdens de journal clubs. Uiteraard kunnen de collega's van Contextual Psychiatry en Public Health, zoals **Rafaël en Franco** niet ontbreken, bedankt voor de leuke gesprekken en uitstapjes.

I would also like to thank **Peter Soyster** and **prof. Dr. Aaron Fisher** and the whole Idiographic Dynamics Lab at University of California, Berkeley. You all welcomed me with open arms and it was amazing to work together and experience academic life in the United States.

Tijdens mijn doctoraat heb ik hulp kunnen krijgen van enkele geweldige thesisstudenten. **Danny, Maxime, Lotte en Ellen,** jullie waren een onmisbare hulp tijdens het recruteren en includeren van nieuwe deelnemers, en het was een plezier om jullie te begeleiden bij jullie thesis.

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