Volume and connectivity differences in brain networks associated with cognitive constructs of binge eating

<https://doi.org/10.1523/ENEURO.0080-21.2021>

Cite as: eNeuro 2022; 10.1523/ENEURO.0080-21.2021

Received: 2 March 2021

Revised: 14 November 2021

Accepted: 29 November 2021

This Early Release article has been peer-reviewed and accepted, but has not been through the composition and copyediting processes. The final version may differ slightly in style or formatting and will contain links to any extended data.

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1 1. Volume and connectivity differences in brain networks associated with cognitive constructs
2 of binge eating

4 2. Brain network differences in binge eating

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24 6. Number of Figures: 5

25 7. Number of Tables: 2

26 8. Number of Multimedia: 0

27 9. Number of words for Abstract: 149

28 10. Number of words for Significance Statement: 119

29 11. Number of words for Introduction: 860

30 12. Number of words for Discussion: 934

31 13. Acknowledgements: N/A

32 14. Conflict of Interest: Authors report no conflict of interest

33 15. Funding sources: This work was supported by the Dutch Research Council (Nederlandse
34 Organisatie voor Wetenschappelijk Onderzoek, NWO) to T.S. [grant number 452-14-003] and
35 to C.Q. [grant number 446-15-003].
36

37 16. Due to the double-blind review process, we removed one sentence from Quality
38 Assessment, “(volumetric, functional-, and structural connectivity: BH and PvR; reward
39 sensitivity, cognitive control, and negative affect: BH and CWEMQ)”. This was originally
40 part of the following section:
41
42 “Quality assessment was performed independently by two researchers (volumetric,
43 functional-, and structural connectivity: BH and PvR; reward sensitivity, cognitive control,
44 and negative affect: BH and CWEMQ). There were no major discrepancies in overall quality
45 rating between the assessors (poor, fair, good).”.
46

Abstract

Bulimia nervosa (BN) and binge eating disorder (BED) are characterized by episodes of eating large amounts of food whilst experiencing a loss of control. Recent studies suggest that the underlying causes of BN/BED consist of a complex system of environmental cues, atypical processing of food stimuli, altered behavioral responding, and structural/functional brain differences compared with healthy controls (HC). In this narrative review, we provide an integrative account of the brain networks associated with the three cognitive constructs most integral to BN and BED, namely increased reward sensitivity, decreased cognitive control, and altered negative affect and stress responding. We show altered activity in BED/BN within several brain networks, specifically in the striatum, insula, prefrontal and orbitofrontal cortex, and cingulate gyrus. Numerous key nodes in these networks also differ in volume and connectivity compared with HC. We provide suggestions for how this integration may guide future research into these brain networks and cognitive constructs.

Significance statement

Binge eating disorder and bulimia nervosa are common eating disorders and remain a major problem due to the association with a variety of health risks. This review shows that three cognitive constructs that underlie these disorders, namely reward sensitivity, cognitive control, and negative affect, can be explained in terms of brain activity differences in key brain networks. These activity differences are interpreted in light of differences in brain volume and connectivity, observed in different studies. Furthermore, the role of these networks involving the striatum, insula, prefrontal and orbitofrontal cortex, and cingulate gyrus, are interpreted by means of the current understanding of their function and mechanisms. Finally, suggestions for further research integrating brain function and structure in binge eating are made.

71 1. Introduction

72 Despite widespread attention from the general public and the scientific community, bulimia
73 nervosa (BN) and binge eating disorder (BED) remain a major societal problem, with an estimated
74 prevalence of 2-3% (Stice et al., 2013). Due to unhealthy eating behavior and a strong association with
75 obesity, these disorders are associated with a number of diseases, such as type II diabetes, cancer,
76 cardiovascular diseases, and higher mortality rates (Guh et al., 2009; Hudson et al., 2007; Kessler et
77 al., 2013; Patel et al., 2018; Smink et al., 2012). Both BN and BED are characterized by binge eating
78 episodes, which have to meet two requirements (American Psychiatric Association, 2013). Firstly, a
79 certain amount of food has to be consumed within a 2-hour period that is definitely larger than what
80 most individuals would eat in a similar time period under similar circumstances. Secondly, the person
81 has to experience a feeling that they cannot stop eating or control what or how much they are eating
82 during the binge eating episode. Both BED and BN diagnosis require a frequency of these episodes of
83 once a week on average, lasting for at least 3 months. In addition, stress regarding bingeing is a
84 criterion for the diagnosis of both BN and BED (American Psychiatric Association, 2013). The
85 disorders are also associated with several changes in eating patterns, such as eating much more rapidly
86 than normal. However, only BN is accompanied by inappropriate compensatory behaviors to prevent
87 weight gain, such as fasting, laxative use, or excessive exercise (American Psychiatric Association,
88 2013).

89 Given the numerous health risks, research into the mechanics of BN and BED is essential to
90 improve our understanding of these disorders. Recent studies suggest that the underlying causes
91 consist of a complex system of environmental cues, altered processing of food stimuli and behavioral
92 responding, and brain differences. In particular, the literature indicates that three major cognitive
93 constructs play a large role in BN and BED, namely reward sensitivity, cognitive control, and negative
94 affect (for an overview see, for example, Appelhans, 2009; Vainik et al., 2019). Reward sensitivity
95 includes alterations in cue reactivity and hypo-responsiveness to food consumption (in which craving
96 toward food is heightened but food liking when consumed is reduced), and serves as a motivational
97 basis for impulsive behavior and engaging in binge eating (Giel et al., 2017). Cognitive control is

highly connected to instrumental behavior and goal-directed behavior in particular, and reduced cognitive control may form the basis of losing control over one's eating behavior (e.g. Kar et al., 2019; O'Doherty et al., 2017; Quaedflieg et al., 2019; Ridderinkhof et al., 2004; Voon et al., 2017). Negative affect, or increased sensitivity to negative emotions (Vainik et al., 2019), is shown to be important in the development of BN and BED (e.g. Allison et al., 2007; Grilo and Masheb, 2002; Rojo et al., 2006; Striegel-Moore et al., 2007) and the frequency of binge eating episodes (Haedt-Matt and Keel, 2012; Berner et al., 2017). Particularly, an increase in negative affect is shown to be strongly connected to and typically caused by stress (e.g. Wemm and Wulfert, 2017; Mendonça-de-Souza et al., 2007). Stress-induced changes in appetite related hormones and reward brain circuitry are an important factor in BN and BED (Wierenga et al., 2018; Gluck, 2009; for animal model see Hardaway et al., 2015). Specifically, in BN and BED several physical differences in the stress response can be observed, such as hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, elevated cortisol awakening response, and blunted responses to acute stressors compared with HC (Culbert et al., 2016; Naishe et al., 2018; Wierenga et al., 2018). We will demonstrate that functional imaging studies show differences in BN/BED specifically in brain areas associated with reward sensitivity, cognitive control, and negative affect as cognitive constructs underlying the disorders and that these overlap with gray matter (GM) volume and structural and functional connectivity differences.

To our knowledge no review has integrated the findings of the three major cognitive constructs underlying BN and BED with structural and task-based neuroimaging studies in these disorders. The current narrative review is intended to supply an integrative account to identify key brain networks that are affected to aid further research. To do so, we will discuss 1) the differences between BN/BED and HC in brain networks associated with the three aforementioned cognitive constructs, and 2) differences in brain organization in BN/BED, including differences in GM volume and connectivity. Specifically, we will first give an overview of prominent studies related to the three cognitive constructs in BN/BED (e.g. food tasting, instrumental learning tasks, acute stress exposure). We will explore behavioral differences, their relation to physical measurements (e.g. cortisol response), and the connection to task-based brain activation studies. Subsequently, we will give an overview of differences in GM and white matter (WM) volume compared with HC, structural

connectivity (diffusion weighted imaging studies) and functional connectivity (resting state studies). In the last section, we will integrate task-independent and task-dependent brain differences, discuss the potential function of these areas, and give suggestions for future research. As will be shown in this review, neuroimaging studies can help in understanding the neurobiological underpinnings of BN and BED, and so may aid in early detection or serve as a potential biomarker (Val-Laillet et al., 2015).

131

132 **2. Cognitive constructs associated with binge behavior**

Binge eating disorders are, as previously mentioned, associated with differences in three major cognitive constructs (e.g. Vainik et al., 2019): reward sensitivity (2.1), cognitive control (2.2), and negative affect (2.3.1 and 2.3.2). In the sections below these three cognitive constructs are discussed, first in the context of binge behavior and subsequently in a neural context.

137

138 **2.1 Reward sensitivity**

139 **2.1.1 Concepts and behavioral studies**

Reward sensitivity is the propensity to seek out rewards and encompasses both the anticipation of the reward and the actual affective experience during receiving the reward (Loxton and Tipman, 2017; Vainik et al., 2019). High reward-sensitive individuals are thought to more often seek out high palatable foods (e.g. Nansel et al., 2016), and thus reward sensitivity may have similar behavioral effects in BN/BED. The two aspects of reward anticipation and the affective experience are represented in the distinction between ‘wanting’ (i.e. anticipation) and ‘liking’ (i.e. during receiving the reward; Robinson and Berridge, 1993). Berridge (1996) proposed that this distinction could affect the processing of food rewards, represented in two separate brain networks, although others have argued that this distinction cannot be easily made (Rogers, 2017; Rogers and Hardman, 2015). BN/BED could be explained by an increase in initial reward anticipation (i.e. wanting or craving), and repeated ingestion of that food could diminish its rewarding effects (i.e. liking) (Berridge, 1996).

151 Changes in wanting and liking operates through Pavlovian conditioning, where food-related
152 environmental cues (e.g. seeing a bag of crisps), elicit a learned response (i.e. wanting/anticipation).
153 This response seems to be stronger in BN and BED compared with HC (Meule et al., 2018). Several
154 aspects of the learning process can be affected in BN/BED, such as enhanced learning of stimuli-
155 response associations, responses generalizing more easily to novel food stimuli, or an increased
156 difficulty to extinguish craving (wanting; for an overview see, for example, van den Akker et al.,
157 2018).

158 Not only Pavlovian conditioning but also instrumental conditioning is likely to play a large
159 role in BN/BED, operating mainly through behavioral responses (e.g. binge eating). In instrumental
160 conditioning, responses to stimuli that lead to positive outcomes are reinforced, thereby increasing the
161 probability of that response being repeated. In the literature this association between a stimulus,
162 response (e.g. pressing a button), and outcome (e.g. a food reward) is often abbreviated to S-R-O. If
163 this sequence is repeated several times, the outcome (O) is thought to lose its functional role and the
164 stimulus will thus automatically come to elicit the response (S-R). In the example, a food reward is no
165 longer necessary to elicit the response (R), the stimulus (S) is sufficient to generate a response, leading
166 to a S-R association (for a complete overview, see O'Doherty et al., 2017). These association-based
167 behaviors are also known as goal-directed (S-R-O) and habitual behavior (S-R), respectively, and are
168 related to differences in cognitive control in BN/BED, the second important cognitive construct
169 (Vainik et al., 2019). Patients with BED appear to rely more often on habitual behavior compared with
170 HC (Voon et al., 2015). Thus, the insensitivity to reward value (i.e. outcome) in habitual behavior may
171 explain the behavioral hypo-responsiveness for the reward value experienced during binge eating
172 episodes, even though large quantities of food are consumed (Berner et al., 2017). Most studies that
173 investigated reward sensitivity experimentally suggest higher reward sensitivity on a subjective level
174 and in food-related tasks (Loxton and Tipman, 2017; Schag et al., 2013; for a systemic review see
175 Harrison et al., 2010). However, this effect does not correspond well with studies using non-food-
176 related tasks where often no differences between BN/BED and HC are found (Appelhans, 2009;
177 Balodis et al., 2019; Giel et al., 2017; Hutson et al., 2018; Kessler et al., 2016; Rogers, 2017; Simon et
178 al., 2016; Wierenga et al., 2018). From the behavioral results it seems clear that reward sensitivity is

179 not consistently higher in BN/BED across all reward types and that it might be limited to food rewards
 180 alone (Appelhans, 2009)

181 **2.1.2 Functional imaging studies**

182 Using a variety of reward sensitivity tasks, several differences in brain activation are observed
 183 between BN and BED and HC (see Table 1 and Figure 1). Brain areas where differences in activation
 184 were found were the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), the ventral
 185 striatum, and the insula, all of which are involved in reward sensitivity (Oberndorfer et al., 2013;
 186 Schienle et al., 2009; Simon et al., 2016; Weygandt et al., 2012; Balodis et al., 2013a; Balodis et al.,
 187 2014). The ACC has been associated with reward learning and outcome prediction (Alexander &
 188 Brown, 2019), and the PCC with storing and retrieving reward values (Rolls, 2019). The ventral
 189 striatum is thought to compare these predicted reward values with the outcome (Wang et al., 2016).
 190 Finally, the insula is typically implicated in the actual somatosensory experiences such as taste and
 191 touch (Rolls, 2016).

192 In more detail, in the insula and ACC, food cue exposure increases brain activation in BN,
 193 BED, and HC (Schienle et al., 2009; Wang et al., 2011). Yet in BED and particularly in BN, this
 194 increase appears larger compared with HC (Oberndorfer et al., 2013; Schienle et al., 2009; Weygandt
 195 et al., 2012). In contrast, activation of the PCC in BN and BED was decreased in an anticipatory task
 196 compared with HC, while it was increased in a consummatory task (Simon et al., 2016). Using a
 197 monetary incentive delay task, obese BED showed lower activity in ventral striatum during
 198 anticipation of reward, and in the prefrontal cortex (PFC) and insula in the outcome phase compared
 199 with obese non-BED and HC (Balodis et al., 2013a). The regional specific responses again point to
 200 differences in anticipating and receiving rewards. While the role of the cingulate cortex and insula are
 201 not domain-specific, the ventral striatum has a specific role in the reward network.

202 All in all, research shows clear differences in food-specific reward sensitivity in BN and BED.
 203 This is supported by the results of a study demonstrating that subjects could be successfully identified
 204 as BED, BN, HC, and obese with an accuracy of 59-90% based on activity patterns of the insula,
 205 ventral striatum, ACC, and the orbitofrontal cortex (OFC) (Weygandt et al., 2012). In the future this

could add further specificity to diagnosis of BN or BED. This seems to be partially associated with post-treatment outcome. BED patients who continued to report binge eating after treatment, were shown to have lower activity of ventral striatum and inferior frontal gyrus (IFG) during anticipation phase, and lower medial PFC activation during the outcome phase versus recovered patients (Balodis et al., 2014).

----- Insert Figure 1 around here -----

2.2 Cognitive control

2.2.1 Concepts and behavioral studies

Cognitive control is multi-dimensional in that it covers various aspects of cognitions and behavior, such as planning, attention/distraction, motoric impulsivity, non-planning impulsivity or lack of concern for the future (Fineberg et al., 2014; Fischer et al., 2003; Kessler et al., 2013; Rosval, 2006). Not all of these cognitive components are unambiguously affected in BN/BED compared with HC. The most notable differences are found in impulsivity during food-related tasks (Fischer et al., 2003; Waxman, 2009; Wu et al., 2014). However, some authors (e.g. Neveu et al., 2018) have emphasized that BN/BED patients cannot be fully identified by their loss of control. Because binges can be planned in advance, BN subjects are able to postpone a binge if conditions such as food availability are not met, and subjects often choose food that is often consumed outside binges. Thus, in BN/BED loss of cognitive control is not a domain-general failure, but seems specific to the bingeing episodes (Neveu et al., 2018). However, in BED subjects planned binges are often longer and larger than initially intended by the subject (Curtis and Davis, 2014). This indicates that a deficit in cognitive control, resulting in a behavioral loss of control, was found to be primarily present during the binge itself (also see Adams et al., 2019). Crucial to both BN and BED is the specific, food-related loss of control during the binge eating episode itself, as illustrated by an increase in intake, even if the episode is planned beforehand (Curtis and Davis, 2014). This loss of control could be explained through a switch from goal-directed to habitual behavior, where direct S-R associations are able to drive

232 behavior (Watson et al., 2017; Cartoni et al., 2016; Watson et al., 2014). Of course, it is not necessary
233 that this loss of control always leads to an increase in intake, as seen in subjective binge eating (where
234 there is only an experience of loss of control).

235 Since cognitive control is multi-dimensional it is measured by a variety of tasks and self-
236 reported questionnaires (e.g. stop-signal task, Stroop, Go/noGo, memory paradigms, Simon tasks,
237 delay discounting; see for example Bartholdy et al., 2016; Lavagnino et al., 2016). Using self-reported
238 questionnaires, BED patients show increased impulsivity, elevated compulsivity, decreased self-
239 control, impaired set-shifting reflective of compulsive behavior, motoric impulsivity, attention
240 impulsivity, and a higher tendency to seek out novel experiences and stimuli (Claes et al., 2002;
241 Danner et al., 2012; Fahy and Eisler, 1993; Favaro et al., 2005; Galanti et al., 2007; Hege et al., 2015;
242 Kessler et al., 2016; Rosval, 2006). Self-reported cognitive control was positively associated with task
243 performance or amount of food eaten during the experiment (Galanti et al., 2007; Hege et al., 2015;
244 Kessler et al., 2016). Other studies, including two meta-analyses, confirm the important role of self-
245 reported cognitive control, but also report that not all components are consistently found (Fischer et
246 al., 2003; Waxman, 2009; Wu et al., 2014). In particular, while planning does not seem to be impaired,
247 acting rashly, general impulsivity, and impairments in set-shifting do seem present in both BED and
248 BN in these studies.

249 These diversely affected subcomponents of cognitive control further demonstrate that it is not
250 a solitary cognitive construct. Evidence of cognitive control impairments in BN and BED obtained
251 from experimental paradigms is equally inconsistent. Several systematic reviews and meta-analyses
252 (e.g. Kittel et al., 2015; Lavagnino et al., 2016) demonstrate that differences in inhibitory responding
253 in BN and BED are often task-dependent. Only around half of the studies included in these meta-
254 analyses showed impaired performance on relevant tasks by patients compared with HC matched on
255 BMI (body mass index) (e.g. stop-signal task, Stroop task; Bartholdy et al., 2016; Kittel et al., 2015;
256 Lavagnino et al., 2016). Results of the stop-signal task (SST) indicate that the observed impairments
257 are due to reduced inhibitory control and not to motor response deficits. Overall SST scores correlate
258 with eating pathology in BED but not in BN. Two other studies showed that the impairment in
259 inhibitory responding (using a Simon and go/no-go task) might be related to symptoms of BN (Bruce

et al., 2003; Marsh et al., 2009). Symptom severity (e.g. number of binge eating and vomiting episodes) was inversely correlated with task accuracy and activation of the frontostriatal network (Marsh et al., 2009). A systematic review showed that inhibition and delay gratification deficits might actually be limited to food related tasks (Kittel et al., 2015). Similarly, Svaldi and colleagues (2014) found that inhibition was more impaired for food stimuli (however, see Manasse et al., 2016).

265

266 **2.2.2 Functional imaging studies**

267 Compared to the inconsistent findings in self-reported and behavioral tasks assessing cognitive
268 control, imaging studies do show a consistent reduction in task-related brain activity in the associated
269 PFC network. As proposed by the schematic control theory (Badre & Nee, 2018), the frontal areas can
270 be divided into three subnetworks. This network consists of anterior PFC areas involved in schematic
271 control (organizing features and relations), rostral mid-lateral PFC areas involved in contextual control
272 (implementing behavioral strategies), and caudal frontal areas involved in sensory-motor control
273 (executing behavior and sensory feedback) (Badre & Nee, 2018). The reduced task-related brain
274 activity has been found in all three networks for both BN and BED compared with HC, using a variety
275 of paradigms (tasks are for example the SST, Simon, and Stroop; see Table 1 and Figure 2). A meta-
276 analysis (Lavagnino et al., 2016) reported two studies investigating BED subjects. In one, obese BED
277 subjects showed lower activation of the dorsolateral prefrontal cortex (dlPFC) and IFG compared with
278 obese non-BED in a food-specific Go/No-go task (Hege et al., 2015). Obese BED subjects also scored
279 higher on a self-reported impulsiveness measure, and in both obese BED and obese non-BED this
280 score was negatively correlated with response inhibition and activity in the prefrontal networks. BED
281 subjects showed reduced activity in OFC, IFG, superior temporal gyrus, ventromedial prefrontal
282 cortex (vmPFC), and insula compared with HC and obese subjects during a Stroop task (Balodis et al.,
283 2013b), whilst no differences were found in task performance. In addition, BED showed the highest
284 self-reported dietary restraint scores, and this was negatively correlated with activation in vmPFC,
285 OFC, IFG, and insula. In obese subjects, however, these scores were positively correlated with IFG
286 and insula activation in obese subjects (Balodis et al., 2013b). This shows that there is a strong relation

287 between measures of cognitive control and activation patterns during a task involving cognitive
288 control. During the Simon task, BN patients showed decreased activation compared with HC in the
289 bilateral IFG, lenticular and caudate nuclei, and ACC when responding correctly to incongruent
290 stimuli (Marsh et al., 2011). In short, these studies show an overall reduction in activity in cognitive
291 control networks, particularly several frontal areas.

292 As mentioned before, instrumental conditioning is highly related to cognitive control. Indeed,
293 some authors have proposed that instrumental conditioning is implicated in many of the tasks used to
294 measure cognitive control (e.g., Liefooghe, & de Houwer, 2016). It is indeed possible that a shift from
295 goal-directed to habitual control likely precedes or occurs during a binge eating episode. One fMRI
296 study directly assessed this possibility in obese BED and obese non-BED (Voon et al., 2015). Using a
297 two-step sequential learning task, Voon et al. (2015) showed that obese BED had a lower engagement
298 of a model-based strategy compared with obese non-BED and lean HC. This demonstrates a shift
299 away from goal-directed toward habitual responses. In BED, higher scores on a binge eating scale
300 were negatively associated with the amount of goal-directed responding during the task. In other
301 words, the more severe BED was, the more likely the person was to respond in a habitual fashion. A
302 subsample of the BED subjects in the Voon et al. (2015) study showed reduced volume in the left
303 ventral striatum, left lateral OFC, bilateral medial OFC, and bilateral caudate compared with non-BED
304 obese. When adding the goal-directed/habitual score as a covariate, Voon et al. (2015) found that the
305 differences in medial OFC, caudate, and ventral striatum disappeared, indicating that the structural
306 differences likely drive the differences in habitual and goal-directed responding between these groups.
307 This is likely to be associated with a reduction in activation of networks associated with goal-directed
308 responding, rather than a simple increased activation in networks associated with habitual responding.
309 Overall then, habit formation in BED could very well be mediated by the medial OFC-caudate-striatal
310 network. These findings are consistent with those in BN. A recent study by Neveu and colleagues
311 (2018) did demonstrate the involvement of vmPFC and dlPFC in a cognitive conflict task in BN,
312 where subjects had to choose between healthy and tasty food. The authors proposed that the results of
313 this study demonstrated increased goal-directed responding in BN. However, it is important to note

314 that vmPFC activity can also be illustrative of value estimation (Wunderlich et al., 2012), rather than
 315 goal-directed responding.

316 Taken together, whilst differences on a behavioral level are limited and inconsistent,
 317 information processing in the brain is consistently different in subjects with BN or BED. Both seem to
 318 be characterized by an overall hypoactivity in frontal regions (OFC, vmPFC, dlPFC, IFG), ventral
 319 striatum, and insula in a variety of tasks measuring cognitive control. Additionally, decreased
 320 activation in the caudate nucleus in the aforementioned Simon task (Marsh et al., 2011) corresponds
 321 well with the interpretation that behavior could be biased toward habitual and away from goal-directed
 322 control (Voon et al., 2015). This is particularly likely since the caudate nucleus is hypothesized to be
 323 part of the goal-directed network together with frontal areas such as OFC, and the insula (Watson et
 324 al., 2018). These fMRI paradigms indicate that whilst there may not always be a behavioral difference
 325 between BN, BED, obese, and HC, differences in activation are often present. This illustrates a
 326 difference in processing that together with increased reward sensitivity, plays a large role in eating
 327 behavior in BN and BED.

328

329 ----- Insert figure 2 around here -----

330

331 **2.3.1 Concepts and behavioral studies**

332 Negative affect refers to increased sensitivity to negative stimuli and increased likelihood to
 333 experience negative emotions (Vainik et al., 2019) and is also highly related to the balance between
 334 habitual and goal-directed behavior. Heightened negative affect is typically the result of stress (e.g.
 335 Wemm and Wulfert, 2017; Mendonça-de-Souza et al., 2007), alters this balance in instrumental
 336 learning tasks, rendering behavior more habitual (Schwabe et al., 2012; Schwabe and Wolf, 2010,
 337 2009; Wirz et al., 2018; Smeets et al., 2019; Hartogsveld et al., 2020; Quaedflieg et al., 2019).
 338 Negative affect and stress are also closely related to the concept of ‘comfort eating’, the idea that some
 339 people have an increased tendency to consume food when stressed, in order to relieve stress and
 340 improve affect (Gibson, 2012). Whilst support is inconsistent, several studies demonstrate that stressed

(HC) subjects show a clear preference for food high in sugar and fat (but see Bongers and Jansen, 2016). Some authors have therefore suggested that bulimic episodes could be a form of learned behavior through negative reinforcement (Berner et al., 2017; Wierenga et al., 2018; Racine and Martin, 2017). One proposed model to explain this further is the acquired preparedness model of binge eating (Racine and Martin, 2017). This model poses that certain high-risk personality traits, such as impulsivity, can alter learning through reward value and make it more likely that food is seen as a positive stimulus that can temporarily alleviate negative affect. Indeed, it has been shown that impulsivity under stress is associated with a greater risk for dysregulated eating in people with BN symptoms (Fischer et al., 2018). This association is contingent on the belief that food can alleviate negative affect, body dissatisfaction, and dietary restraint (Racine and Martin, 2017). It also might be connected to overall self-reported difficulties in emotion regulation in BN/BED compared with HC (Brockmeyer et al., 2014; Troop et al., 1998). Lastly, sensitivity to negative effect has also been associated with a higher frequency of binge eating episodes, greater severity of the disorder (Carrard et al., 2012), and playing a role in the development of BN/BED (Razzoli et al., 2016). For example, a meta-analysis revealed that negative affect increased before binge eating episodes compared with diurnal affect and affect before normal meals (Haedt-Matt and Keel, 2012). After this increase, negative affect decreases following the binge eating episode (Berner et al., 2017; Crosby et al., 2009; Johnson and Larson, 1982; Kaye et al., 1986).

Stress may also be considered a form of negative affect. In support of the role of stress in BN/BED are the multiple alterations in stress hormone levels that are observed in BN/BED. Stress exposure causes a rapid release of catecholamines (e.g. adrenalin and noradrenalin) and activates the slower-acting HPA axis that results in the release of glucocorticoids (e.g. cortisol) in the blood. Collectively, these fast and slow stress hormones alter the responding of numerous circuits in the brain and other aspects of homeostasis (Ulrich-Lai and Herman, 2009). BN and BED are associated with differences in these hormones and circuits, namely long term HPA axis hyperactivity, elevated cortisol awakening response, ultimately resulting in a blunted response to acute stressors (Culbert et al., 2016; Naish et al., 2018; Wierenga et al., 2018).

368 In a lab setting, several studies have experimentally investigated acute stress-induced changes
369 in eating behavior in BED, since acute stress is relatively easily and reliably inducible (Klatzkin et al.,
370 2018; Laessle and Schulz, 2009; Lyu and Jackson, 2016; Schulz and Laessle, 2012). Acute stress
371 mostly seems to affect eating rate, with a faster initial eating rate and smaller decrease in eating rate
372 over time in BED (Laessle and Schulz, 2009; Schulz and Laessle, 2012). Effects of acute stress on
373 overall food intake in BED are inconsistent, with some studies showing increased overall intake
374 compared with non-BED after acute stress (e.g. Lyu and Jackson, 2016) but with most studies finding
375 no differences (Klatzkin et al., 2018; Laessle and Schulz, 2009; Schulz and Laessle, 2012). A possible
376 explanation for the inconsistent results in food intake might be the lab setting and the stress tasks used.
377 Whilst it has not been investigated in BN/BED, overweight subjects eat less in social settings
378 compared with being alone, this could be more pronounced in BN/BED because of negative emotions
379 such as shame (Krantz, 1979; Salvy et al., 2007). The stress tasks also differed between studies.
380 Physical and psychological stressors activate the various stress systems to different degrees (McRae et
381 al., 2006). A physical stressor results in rapid activation of the autonomic nervous system via reflexive
382 mechanisms in brainstem and hypothalamus, while a psychological stressor requires processing in the
383 PFC and in turn activates the slower HPA-axis via connections with limbic structures. Related to this,
384 the timing of the food consumption after stress was also different between studies with some
385 measuring before and other during the cortisol peak (i.e. 20-40 minutes after stress onset; Dickerson &
386 Kennedy, 2004).

387 Many studies have also investigated heart-rate variability (HRV), blood pressure, salivary
388 alpha-amylase, and cortisol responses to acute stress (Carroll et al., 2017; Culbert et al., 2016; Naish et
389 al., 2018; Peschel et al., 2016; Wierenga et al., 2018). HRV responses in BN/BED are not affected by
390 acute stress and seem to not display the decrease during acute stress and increase post-stress normally
391 found in HC, even though baseline levels are higher in BN/BED (Het et al., 2015a; Hilbert et al.,
392 2011; Messerli-Bürge et al., 2010; Murialdo et al., 2007). Blood pressure increase in response to acute
393 stress was shown to be blunted in BN subjects compared to HC (Koo-Loeb et al., 1998; Ginty et al.,
394 2012). Similarly, the majority of studies report a blunted cortisol response in BN and BED following
395 acute stress (Carnell et al., 2018; Culbert et al., 2016; Ginty et al., 2012; Het et al., 2015b; Koo-Loeb

et al., 1998; Naish et al., 2018; Rosenberg et al., 2013; Vaz-Leal et al., 2018; Wierenga et al., 2018), but not all do (Coutinho et al., 2007; Vannucci et al., 2015). Interestingly, the blunted cortisol reactivity was positively associated with binge-eating severity in BED (Coutinho et al., 2007) and an increase in desire to eat after acute stress exposure (Rosenberg et al., 2013). Some have hypothesized that the blunted cortisol reactivity could be caused by long-term HPA axis activation (Culbert et al., 2016; Het et al., 2015b) due to high levels of chronic stress. Baseline HRV differences largely point to increased parasympathetic activity (Peschel et al., 2016), suggesting a blunted influence of the HPA axis. In addition, this idea is supported by the findings of increased baseline cortisol levels in BN (e.g. Monteleone et al., 2017; see Culbert et al., 2016 for an overview). Though, baseline cortisol results are rather inconclusive, with only some suggesting a decrease in baseline cortisol levels and cortisol awakening response (e.g. Rosenberg et al., 2013; Vaz-Leal et al., 2018).

To summarize, most studies suggest an overall blunted physiological effect of stress in BN and BED, both after acute stress induction and in resting baseline measurements. This largely seems to be related to higher chronic stress levels and negative affect in these disorders. Even though lab studies do not show a behavioral link between food intake and acute stress, they are related physiologically. Acute stress elicits an increase in salivary ghrelin, a peptide that promotes food intake in BN compared with non-BN (Gluck et al., 2014; Monteleone et al., 2012; Monteleone and Maj, 2013). Other studies confirm the importance of hormonal responses in eating behavior, including insulin, leptin, and extrahypothalamic corticotrophin releasing factor (CRF; for an overview, see Sinha, 2018; Schepers and Markus, 2015). Similar to the effects of acute stress, it is proposed that in healthy individuals CRF suppresses appetite during and directly after a stressful event. Subsequently, glucocorticoids stimulate feelings of hunger to offset the expended energy. Chronic stress on the other hand appears to be able to expose the individual to long-term heightened levels of glucocorticoids, thereby increasing ghrelin levels and stimulating eating behavior of high caloric foods through reward sensitivity (Sominsky and Spencer, 2014; Sinha, 2018; Schepers and Markus, 2015). These effects on reward sensitivity by metabolic state can also potentially drive individuals to make more risky (variable outcome) choices when hungry (see for example Symmonds et al., 2010).

424 2.3.2 Functional imaging studies

425 Acute stress and the processing of food stimuli appear to be associated, as reward sensitivity is
426 shown to be altered in BN and BED after acute stress exposure (see Table 1 and Figure 3; Collins et
427 al., 2017; Fischer et al., 2017; Lyu and Jackson, 2016; Wonderlich et al., 2018). Relevant brain areas
428 seem to largely overlap with the network involved in reward sensitivity when not under acute stress.
429 As mentioned previously, the cingulate cortex and insula are involved in processing reward values
430 (e.g. Alexander & Brown, 2019; Rolls, 2019) and have been observed to be affected by acute stress
431 (van Ruitenbeek et al., 2021). Other areas like the amygdala and hippocampus are commonly known
432 to regulate stress. Specifically, the hippocampus is associated with inhibition of the HPA-axis (Ulrich-
433 Lai and Herman, 2009) and the amygdala is well-known to respond during stress (e.g., Marle et al.,
434 2009; for an overview see Zhang et al., 2018). In addition, these areas project to several relevant areas
435 for reward sensitivity (Abivardi and Bach, 2017; Salzman and Fusi, 2010). In support of the overlap,
436 they have been implicated in reward sensitivity tasks without acute stress manipulation (e.g., Filbey et
437 al., 2012).

438 When comparing pre- with post-stress reward processing in BN compared with HC, a decrease
439 in activation is predominantly reported in the vmPFC, ACC, precuneus, and amygdala in BN patients
440 (Collins et al., 2017; Fischer et al., 2017; Smith et al., 2018). Furthermore, the decrease in activity pre-
441 to post-stress in the bilateral precuneus, ACC, and dlPFC during a reward sensitivity task was
442 associated with higher subjective stress prior to binge eating episodes in daily life (Fisher et al., 2017).
443 On the other hand, amygdala and the vmPFC activation did not moderate subjective stress levels prior
444 to binge eating episodes (Fischer et al., 2017). However, another study showed that activation in the
445 bilateral vmPFC and right amygdala moderated negative affect pre- and post-binge episode in BN
446 (Wonderlich et al., 2018). Larger decreases in activity in these areas were associated with larger
447 increases in negative affect before a binge eating episode. Conversely, positive affect pre- and post-
448 binge eating episode was moderated by activation in the right ACC and bilateral vmPFC, with larger
449 decreases in activity also being associated with larger increases in positive affect after a binge eating
450 episode. Combined, these results suggest that the vmPFC, ACC, amygdala, precuneus, and dlPFC play

a role in regulating negative and positive affect before and after a binge eating episode. Indeed, the role of the vmPFC in successfully regulating negative affect has also been demonstrated in healthy samples; with larger decreases in activation following acute stress being reflective of a reduced coping and a higher frequency of maladaptive coping behaviors, including emotional eating (Sinha et al., 2016). Two independent samples of BN showed reduced activity in the precuneus, paracingulate gyrus, and anterior vermis of the cerebellum, whilst healthy controls showed an increased activity from pre- to post-stress on reward sensitivity (Collins et al., 2017). Furthermore, decreased activation in the hippocampus in BED compared with non-BED was found for showing high-caloric and low-caloric foods compared with neutral images, and the decrease was largest in response to high-caloric food images (Lyu and Jackson, 2016). Interestingly, reduced hippocampal activation predicted larger amounts of chocolate intake after the fMRI scans in the entire sample (Lyu and Jackson, 2016).

Taken together, these results show that several networks are affected pre- to post-stress in BN/BED during reward processing. In BN, there is support for a decrease in activation post-stress in the vmPFC, amygdala, precuneus, and ACC. Decrease in these areas are also associated with increased negative affect pre-stress, and positive affect post-stress. So far, only one study has investigated reward sensitivity after acute stress exposure in BED (Lyu and Jackson, 2016), suggesting that the hippocampus may play an inhibitory role in reward sensitivity after acute stress. Overall then, the results from these studies suggest that the vmPFC and ACC are likely to be involved in regulating negative affect, in addition to their role in reward sensitivity and cognitive control. Crucially, the ventral striatum and OFC, which are involved in processing of reward values, do not seem to be affected in reward processing post-stress in BED/BD. A blunted stress response is confirmed by a number of different measures, including salivary cortisol, blood pressure and brain activity. The blunted stress response might disproportionately be associated with an increased drive for bingeing and is likely reflective of prolonged activation of the HPA axis and autonomic nervous system. Several studies (e.g. Fischer et al., 2018; Carrard et al., 2012; Haedt-Matt and Keel, 2012) suggest that the link between acute stress, negative affect, and eating behavior outside the lab is strong, even though lab studies could not find differences in food intake.

479 ----- Insert Figure 3 around here -----

480

481 ----- Insert Table 1 around here -----

482

483 **3. Brain differences in BN/BED**

484 **3.1 Volumetric differences in Gray Matter (GM)**

485 Neuroscientific studies investigating volumetric GM differences between BN subjects and HC
486 reveal specific volume reductions and increases in cortical and subcortical structures (please see
487 Figure 4 and Table 2 for an overview), which reflect those part of the networks associated with the
488 three cognitive constructs discussed in section 2. In both BN and BED, several structures associated
489 with reward processing were shown to be affected, such as the ventral and dorsal striatum (Amianto et
490 al., 2013a; Coutinho et al., 2015; Frank et al., 2013; Voon et al., 2015; Schäfer et al., 2010). Both the
491 ventral and dorsal striatum comprise multiple substructures that are associated with processing
492 different kinds of information. Therefore, identifying which structures are affected is important to
493 determine potential functional roles. The ventral striatum is comprised of the olfactory tubercle and
494 nucleus accumbens, the dorsal striatum is comprised of the putamen and caudate nucleus (Meredith et
495 al., 2008). For the dorsal striatum, GM volume in the bilateral caudate was shown to be reduced in BN
496 compared with HC, with a larger reduction in the right hemisphere (Amianto et al., 2013a; Coutinho et
497 al., 2015) and particularly in the dorsal caudate nucleus (Frank et al., 2013). Differences in GM of the
498 putamen seem even more lateralized, with BN showing increased volume in the left putamen
499 compared with HC (Amianto et al., 2013a) but reduced volume in the right dorsal putamen (Frank et
500 al., 2013). Slightly different patterns are observed in BED (Voon et al., 2015; Schäfer et al., 2010), but
501 the number of studies is limited. A reduction in GM volume was only observed in the bilateral caudate
502 nucleus, no differences between BED and HC were found in putamen volume (Coutinho et al., 2015;
503 Frank et al., 2013; Voon et al., 2015; Schäfer et al., 2010). A study directly comparing BED, BN, and
504 HC subjects showed that BN subjects had greater GM volume in the dorsal striatum than BED

505 subjects, suggesting that it might be more affected in BN (Schäfer et al., 2010). For the ventral
 506 striatum, specifically for the nucleus accumbens, differences in volume seem to be relatively
 507 inconsistent. Some studies indicate an increase in accumbal volume in BN compared with HC and
 508 BED (Schäfer et al., 2010; but see Coutinho et al., 2015), while one study indicated that GM volume
 509 was reduced in BED in the bilateral nucleus accumbens (Voon et al., 2015).

510 Differences in volume of cortical areas have also been reported (e.g. Frank et al., 2013; Berner
 511 et al., 2019; Wagner et al., 2006; Wallace et al., 2020), although findings are not always consistent
 512 with each other (e.g. Amianto et al., 2013a; Marsh et al., 2015). One of these areas is the insula, which
 513 is associated with a large number of functions (e.g. perception, self-reflection, cognitive functioning,
 514 emotion, homeostasis) and is shown to be involved in a wide variety of tasks (e.g. Uddin et al., 2017).
 515 Insula GM volume seems particularly affected in BN, with studies predominantly showing an increase
 516 in GM volume compared with HC (Amianto et al., 2013a; Frank et al., 2013). These differences seem
 517 to persist to some extent after recovery, with recovered BN subjects showing an increase in volume
 518 when age was controlled for (Wagner et al., 2006). However, larger insula volume might be limited to
 519 patients only, as a large subclinical group with limited BN symptoms showed a negative association
 520 between BN subscale scores (Eating Disorder Inventory, EDI-3) and GM thickness of the bilateral
 521 insula and the left inferior parietal cortex (Wallace et al., 2020). Indeed, parts of the parietal cortex are
 522 also affected in BN with most consistent findings in the inferior parietal cortex. Reduction in volume
 523 is observed of the right inferior parietal lobule (Marsh et al., 2015), but also in the right superior
 524 parietal cortex (Berner et al., 2018; Marsh et al., 2015), and both an increase and reduction in volume
 525 in the precuneus (Amianto et al., 2013a; Marsh et al., 2015). In addition, BN symptom severity (Eating
 526 Disorder Examination Questionnaire, EDE-Q) was shown to be negatively associated with cortical
 527 thickness in parts of the inferior parietal cortex and temporal cortex (Westwater et al., 2018). The ACC
 528 seems uniquely increased in GM volume in BED compared with HC (Schäfer et al., 2010), although
 529 the PCC was found to be reduced in GM volume in BN (Berner et al., 2019; Marsh et al., 2015).

530 Frontal areas, and in particular the OFC, are associated with reward processing and show GM
 531 differences between BN and HC, and BED and HC. Several studies show an increase in GM volume
 532 in BN compared with HC, in particular in the bilateral medial OFC (Frank et al., 2013; Schäfer et al.,

2010; Cyr et al., 2017). In contrast, OFC GM thickness was shown to be negatively associated with bulimia subscale scores (EDI-3) and BN symptoms (EDE-Q) in subclinical populations (Westwater et al., 2018; Wallace et al., 2020), and the number of vomiting episodes in BN subjects was negatively associated with lateral OFC GM volume (Cyr et al., 2017). Some studies showed that several other parts of the prefrontal cortex were also affected, such as the inferior frontal gyrus (Marsh et al., 2015; Cyr et al., 2017). Likewise, BN symptoms (EDE-Q) were found to be negatively associated with cortical thickness in caudal and rostral parts of the middle frontal gyrus and the superior frontal gyrus (Westwater et al., 2018). In addition, BED patients also showed reduced left lateral OFC volume compared with HC (Schäfer et al., 2010; Voon et al., 2015). Results concerning medial OFC volume are however inconsistent, with one study finding an increase in volume, and another finding a reduction in volume (Voon et al., 2015; Schäfer et al., 2010).

To summarize, GM volumetric differences between BED and HC and especially between BN and HC are consistently found in the OFC, striatum, and insula (see Figure 4). These are associated with a number of functions that are associated with BN and BED pathology (Uddin et al., 2017; Yan et al., 2016; Setogawa et al., 2019; Stalnaker et al., 2018). Specifically, these areas show considerable overlap with those presented in the previous section; areas associated with reward sensitivity, cognitive control, and negative affect (see section 2). We will intergrate these findings in section 4. Interestingly, some of the discussed studies (e.g., Frank et al., 2013; Marsh et al., 2015) indicate that GM volumetric differences in a number of cortical areas are related to the underlying WM connectivity, particularly in the parietal cortex. In further support, Westwater et al. (2018) observed that while BN symptoms were negatively associated with cortical thickness in a number of areas (e.g. OFC, frontal gyrus, superior parietal cortex), the areas also showed an increase in estimation of WM connectivity (Westwater et al., 2018). In general, brain areas and their connections are organized into networks, and this connectivity plays a crucial role in information processing in the brain. Volumetric differences in the WM that connects these areas likely affect the functioning of these connections. Subsequently, connectivity studies will be informative to determine whether these are also affected in BN and BED, and what role they might play in these pathologies.

561 ----- Insert Figure 4 around here -----

562 **3.2 Structural connectivity**

563 Brain regions are physically connected via white matter tracts, typically measured using
564 diffusion weighted imaging (e.g. Fields, 2008). Differences in this structural connectivity between BN
565 and HC reflect the GM volumetric differences, as the connectivity between these areas is particularly
566 affected (see Table 2; i.e. connections between parts of the ventral and dorsal striatum, insula,
567 (pre)frontal cortex, amygdala). For example, compared with HC, BN patients showed reduced
568 connectivity in the bilateral corona radiata extending in the posterior and anterior limb of the internal
569 capsule (Mettler et al., 2013; He et al., 2016), which lies between the caudate nucleus and putamen.
570 Connections of the ventral striatum with both cortical and subcortical areas are also affected. For
571 example, connectivity between the ventral striatum and the insula and the frontal cortex (inferior and
572 medial OFC) was shown to be increased in BN compared with HC (Frank et al., 2016; Wang et al.,
573 2019), while connectivity between the ventral striatum and the right basolateral amygdala was reduced
574 (Frank et al., 2016). Network analysis in BN compared with HC shows that mesocorticolimbic
575 pathways and other subcortical connections in the right hemisphere might be negatively affected in
576 global efficiency (Wang et al., 2019), a measure associated with parallel information processing
577 (Bullmore & Sporns, 2012). Pathways in the left hemisphere seem largely unaffected or even
578 increased (Wang et al., 2019). This fits with the volumetric differences discussed in section 3.1, which
579 show reductions in volume in the right hemisphere but some increases in the left hemisphere.

580 Connectivity of the insula also seems affected in BN. Overall the left insula shows increased
581 connectivity (Wang et al., 2019), corresponding with the increase in volume. However, depending on
582 the projection, some white matter tracts are increased in connectivity, and others decreased.
583 Particularly, white matter tracts between the anterior insula and cortical areas show increased
584 connectivity, whilst decreased connectivity is observed between the anterior insula and subcortical
585 areas (Frank et al., 2016). Specifically, connectivity was increased between the bilateral anterior insula
586 and the medial PFC and the middle OFC, but was reduced between the right anterior insula and the
587 basolateral amygdala, and the left anterior insula to the central nucleus of the amygdala and the

588 inferior OFC (Frank et al., 2016). Some other areas show differences in connectivity as well, such as
589 reduced connectivity from the left ACC, right precuneus, hypothalamus, but increased connectivity
590 from the temporal cortex, hippocampus, and thalamus (Wang et al., 2019; Frank et al., 2016). One
591 exception is the study by Canna et al. (2017) that found no differences in structural connectivity
592 between BN and HC.

593 In long-range white matter association fiber tracts that connect the frontal lobe with other
594 lobes and subcortical areas, a reduction in connectivity was found in BN compared with HC (Mettler
595 et al., 2013; He et al., 2016). Namely, connectivity differences were observed in the superior
596 longitudinal fasciculus (SLF) (Mettler et al., 2013; He et al., 2016), which predominantly connects the
597 frontal cortex to the parietal cortex, whilst passing through the insula and around the putamen.
598 Similarly, reduced connectivity was observed in BN in the bilateral inferior fronto-occipital fasciculus
599 that connects the (pre)frontal cortex to the occipital cortex, and the uncinate fasciculus that connects
600 the prefrontal cortex to the amygdala, parahippocampus, and anterior temporal cortex (Mettler et al.,
601 2013; He et al., 2016). This was also the case for numerous long range connections between the two
602 hemispheres, with connectivity being reduced in BN compared with HC in the major and minor
603 forceps, bilateral corpus callosum, and cingulate gyrus (Mettler et al., 2013; He et al., 2016). In
604 contrast, a recent paper (Estella et al., 2020) showed that connectivity in some of these white matter
605 tracts appears to be increased in BED compared to HC and obese controls. Compared to obese
606 controls, BED subjects showed increased connectivity in the minor forceps, corpus callosum, and
607 cingulate gyrus (connecting the two hemispheres) and the SLF (connecting the frontal to parietal
608 cortex). Some of the same results (forceps, SLF) were found when comparing BED and normal-weight
609 HC (see Table 2), and when comparing obese controls to normal-weight HC (Estella et al., 2020). This
610 suggests that some of these differences might be related to obesity, rather than BED per se.

611 To summarize, the observed WM tract differences echo those in GM volume and correspond
612 to the networks associated with the three cognitive constructs. Differences in volume of the OFC,
613 insula, and striatum fit well with the consistent differences in connection strength and/or
614 microstructure between these areas. Indeed, the nature of some of the parameters that are affected (see
615 Table 2) suggests that the differences might be relatively specific to myelin loss (although a loss of

axons and/or a reduced density of axons is also possible; Aung et al., 2013; Solowij et al., 2017). Myelin forms a protective sheath around the axons of neurons, and by speeding up axon potentials, ensures normal cognitive and sensory function, being involved in several other psychiatric disorders as well (Fields, 2008). Compared to BN, BED subjects show an increase in connectivity rather than a decrease (Estella et al., 2020). More research is needed to confirm these findings and to elucidate the functional consequences for BN and BED.

3.3 Functional connectivity

Functional connectivity is a measure of the functional association between brain areas operationalized by the temporal correlation or covariation of activity between those brain areas. Instead of structural images, functional connectivity uses functional magnetic resonance imaging (fMRI) i.e. blood oxygenation level dependent (BOLD) imaging to do so. Differences between BN/BED and HC in functional connectivity measures (see Table 2) largely overlap with those of structural connectivity, although not all do. Connectivity from the right dorsal caudate nucleus and putamen to other subcortical structures (putamen, globus pallidus, thalamus) was increased in BN compared with HC, compared to connectivity from the ventral striatum and putamen to cortical areas (central gyrus, occipital gyrus, superior frontal gyrus), which was shown to be reduced (Wang et al., 2020).

Connectivity of the parietal cortex seems to be largely reduced. For example, BN is shown to be characterized by a reduction in volume of GM and structural connectivity of the parietal cortex. Similarly, functional connectivity was reduced compared with HC within the inferior parietal cortex (Stopyra et al., 2019), within the temporo-parietal junction (TPJ; Spalatro et al., 2019), and between the parietal lobes and the cerebellum (Amianto et al., 2013b). In contrast, functional connectivity was shown to be increased in BN between the precuneus and cerebellum (Amianto et al., 2013b). BED subjects showed a similar pattern, with reduced connectivity strength compared with HC within the inferior parietal cortex (Stopyra et al., 2019) and less connectivity to the right superior parietal cortex

(Oliva et al., 2019). Reduced connectivity compared with BN in the angular gyrus (Stopyra et al., 2019), and a reduction in connectivity to the right insula was also reported (Oliva et al., 2019).

In general, functional connectivity within and between frontal regions was found to be reduced in BN and BED compared with HC (Stopyra et al., 2019; Spalatro et al., 2019; Canna et al., 2017). Namely, reduced connectivity within the IFG (Spalatro et al., 2019) was found in BN compared with HC. Similarly, BN showed reduced connectivity within and between a cluster extending from the OFC to the dlPFC (Canna et al., 2017). Connectivity between the two hemispheres for this cluster was reduced as well (e.g. between the left IFG and right IFG) (Canna et al., 2017). Interestingly, BN showed an increase in functional connectivity within the dorsomedial prefrontal cortex (dmPFC), while BED showed a reduction in the dmPFC connectivity compared with HC (Stopyra et al., 2019). Moreover, when comparing BN and BED directly, BED also showed a reduction in functional connectivity compared with BN within the middle frontal gyrus (MFG) (Stopyra et al., 2019), showing that areas in the frontal cortex are differently affected in BN and BED. Compared to HC, BED similarly showed less connectivity to the MFG and reduced connectivity strength from the right MFG to the right anterior insula and right IFG (Oliva et al., 2019). In the cingulate cortex, BED showed increased functional connectivity within the dorsal part of the PCC compared with BN (Stopyra et al., 2019). However, no differences for the PCC were found when comparing BED or BN with HC. For the ACC, BN and BED did show similar reductions in functional connectivity compared with HC (Stopyra et al., 2019). Connections between the ACC and left OFC, right precuneus, and cerebellum were only increased in BN (Lee et al., 2014; Amianto et al., 2013b). Connectivity between the ACC and parahippocampal gyrus was reduced compared with HC.

To summarize, numerous functional connectivity differences can be observed in BN and BED compared with HC. Most of these areas are also affected in terms of GM volume and structural connectivity, such as parietal areas, frontal areas (particularly the OFC), insula, and cingulate cortex. Only in BN an increase in functional connectivity between the insula and cerebellum was observed (Amianto et al., 2013b). It has to be mentioned that structural and functional connectivity are not always connected in a straightforward manner, even though they are often positively correlated (see for example Uddin, 2013). This was confirmed by an animal study where severing connections

670 between areas did not always lead to a change in functional connectivity (O'Reilly et al., 2013).
671 Nevertheless, the overall patterns reflect similar differences between BED/BN and HC in GM volume,
672 structural and functional connectivity.

673

674

675 ----- Insert Table 2 around here -----

676

677

678 **4. Concluding remarks**

679 In this review, we gave an overview of the brain networks associated with the three cognitive
680 constructs most integral to BN and BED. Subsequently, we showed how these networks show an
681 atypical brain organization, both in volume and connectivity compared with HC. We will now shortly
682 summarize the findings presented in these sections, and explain how these differences in volume and
683 connectivity may explain BED and BN symptomatology, and how this is likely involved in eliciting
684 and maintaining binge eating.

685

686 **4.1 Reward sensitivity**

687 Activation differences between BN/BED patients and HC evoked by tasks assessing reward
688 sensitivity are not uniform. A distinction has to be made between passive viewing (anticipatory) tasks
689 and actively receiving or consuming food (consummatory tasks). Both patient groups show a
690 difference in activity in passive viewing tasks in the cingulate cortex (ACC and PCC), the ventral
691 striatum, ventral tegmental area (VTA), and the insula (e.g., Filbey et al., 2012; Oberndorfer et al.,
692 2013; Balodis et al., 2013a; Balodis et al., 2014; Schienle et al., 2009; Simon et al., 2016). Generally,
693 activity in the PCC is lower compared with HC, whilst activation is shown to be higher in the other
694 areas (see Figure 1). Activity differences in the medial OFC, that connects to the ventral striatum
695 (nucleus accumbens), seem largely limited to BED in passive viewing tasks (Schienle et al., 2009). As
696 mentioned previously, the ventral striatum is thought to play a role in reward prediction error, by

697 comparing expected with received outcome values (e.g., Wang et al., 2016). The role of the medial
 698 OFC has been more controversial, especially when comparing it to the lateral OFC (e.g., Noonan et
 699 al., 2012). The medial OFC has been suggested to be involved value estimation (Sescousse et al.,
 700 2010; Setogawa et al., 2019; Stalnaker et al., 2018). However, it has been suggested that it is involved
 701 in a broader evaluation of value-guided decision making (Noonan et al., 2012), in particular in a
 702 working memory role when comparing previous to current choices (Wallis & Kennerley, 2011). The
 703 ACC in comparison has been implicated in action-outcome learning, choice predictions, prediction
 704 errors and surprise signals, more in line with ventral striatum function (Alexander & Brown, 2019;
 705 Wallis & Kennerley, 2011). The PCC on the other hand is associated with memory and
 706 encoding/retrieval of reward values (for an overview, see Rolls, 2019). Additionally, the insula has
 707 been more implicated in the somatosensory experience of rewards, such as taste and touch (Rolls,
 708 2016). This makes it likely that reward sensitivity is different in BED and BN in multiple aspects of
 709 reward processing, namely altered reward prediction error, perception of rewards, reward memory,
 710 value-guided decision making, and reward-based learning.

711 Some care must be taken when interpreting the function of areas, the roles of all
 712 aforementioned areas in reward prediction and estimation are still not completely clear. Some seem
 713 related to the reward value directly (i.e., ventral striatum), others (i.e., medial OFC, ACC, and insula)
 714 mostly to somewhat broader processes like attention elicited by reward (Uddin et al., 2017; Yan et al.,
 715 2016; Roefs et al., 2018). The cingulate cortex and insula in particular show activation patterns during
 716 presentation of both negative and positive outcomes (Liu et al., 2011). It is of course not necessary that
 717 each area has only one specific role. Rather, it is more likely that several loops in this network are
 718 involved in the same aspect, for example reward value estimation. Taken together, these results show
 719 that differences in this network associated with reward sensitivity in passive viewing tasks are more
 720 complex than an unequivocal increase in activity associated with increased processing of reward-
 721 related information. It is thus important to investigate the precise function of areas within this network
 722 further.

723 Activity differences in the medial OFC also show up in consummatory tasks (e.g., Simon et
 724 al., 2016) both in BED and BN, which is consistent with studies in HC (Liu et al., 2011). Activation

725 differences in the dorsal striatum, angular gyrus, and anterior medial PFC seem unique to
 726 consummatory tasks (Wang et al., 2011; Simon et al., 2016; Filbey et al., 2012). The dorsal striatum
 727 has been mostly associated with learning from rewards, including in instrumental conditioning (e.g.,
 728 O'Doherty et al., 2004; Tricomi & Lempert, 2015; Chen et al., 2015). It is important to note that
 729 differences in dorsal striatum activation were only found in a study comparing the effects of
 730 methylphenidate with placebo on reward sensitivity, and in a study without a matched control group
 731 (Wang et al., 2011; Filbey et al., 2012). The absence of a control group makes determining any
 732 differences with HC difficult. Similar to the dorsal striatum, parts of the medial PFC have been
 733 implicated in reward learning and implementing behavioral strategies (e.g., Alexander & Brown,
 734 2011; Badre & Nee, 2018). This strengthens the case for altered reward learning in BN and BED.
 735 Although the angular gyrus shows up in both BN and BED, it is unlikely that it is specific to reward
 736 sensitivity. The angular gyrus is a multimodal area that shows activation in a large variety of tasks,
 737 and integrates input from across the brain (e.g., from the cingulate cortex, precuneus, insula, prefrontal
 738 cortex; Seghier, 2013). Difference in activation in this area is thus more likely to be a result of
 739 difference in activation in other areas in the reward sensitivity network. Lastly, BN patients show in
 740 general an overall decrease in activity, while BED patients mostly show an increase in activity
 741 compared with HC. Differences in activity direction (negative/positive) in BN and BED could very
 742 well be related to a different way of processing received rewards, but not the anticipation of rewards.
 743 One possible difference between BN and BED is that the insular cortex has also been associated with
 744 body image distortion in BN (Mohr et al., 2011; Yan et al., 2016). Care must however be taken when
 745 making inferences, since brain activity does not map onto behavior or experiences directly.
 746 Nevertheless, a difference in overall activity in this network is promising in possibly explaining
 747 differences between the two disorders.

748 Regarding the findings of volumetric and connectivity studies, in the current review they show
 749 considerable overlap with the reward sensitivity networks. To summarize, in BN, GM in the left
 750 insula, left OFC, and ventral PCC is larger in volume, whilst right OFC, ventral striatum, and dorsal
 751 PCC show smaller volumes (e.g., Amianto et al., 2013a; Berner et al., 2018; Coutinho et al., 2015;
 752 Frank et al., 2013; Westwater et al., 2018). This suggests that reward processing in the OFC might be

753 somewhat lateralized and that the PCC has two separately implicated subregions. Functional
 754 connectivity similarly shows increased connectivity between the insula and PFC/OFC (Frank et al.,
 755 2016), the ACC and OFC (Lee et al., 2014), and between the caudate nucleus and putamen (Wang et
 756 al., 2020). In BED, left ventral striatum volume was also reduced, while ACC volume was found to be
 757 increased, and OFC volume seems ambiguously affected (Voon et al., 2015; Shafer et al., 2010). No
 758 related connectivity differences were found, although connectivity in the medial dorsal PCC was
 759 shown to be increased in BED compared with BN. Indeed, the dorsal PCC, but not ventral PCC, also
 760 showed a decrease in GM in BN (Berner et al., 2018). Together with a positive difference in PCC
 761 activity in BED during consummatory tasks, this indicates that the PCC could play a different role in
 762 reward encoding or attentional processes in BED. Further research into the specific contexts reward
 763 sensitivity might be altered in, will help in determining its exact role in BN/BED.

764

765 **4.2 Cognitive control**

766 In cognitive control tasks, both BN and BED patients show a reduction in activity in frontal
 767 areas compared with HC, including the IFG, OFC, dlPFC, superior frontal gyrus, and medial PFC
 768 (Marsh et al., 2011; Balodis et al., 2013b; Neveu et al., 2018; Hege et al., 2015; Voon et al., 2015).
 769 These are to be expected, as these areas play a large role in controlling our actions (for an overview
 770 see Badre & Nee, 2018). In BED and BN patients, activity differences can be observed throughout the
 771 anterior, rostral mid-lateral, and caudal frontal cortex during cognitive control paradigms, including
 772 during food-related tasks. Altered processing of food-based decisions is thus likely not limited to
 773 decision making, but perception and sensory feedback of food as well. This could also explain activity
 774 differences in the occipital gyrus in BED (Balodis et al., 2013b) through top-down processing.

775 The caudate nucleus and putamen show activity differences in BED and BN, respectively
 776 (Voon et al., 2015; Marsh et al., 2011). The caudate is thought to be crucial for goal-directed control
 777 (de Wit et al., 2012; Gasbarri et al., 2014; Watson et al., 2018), and decreased activity along with
 778 volumetric and connectivity differences within these areas could explain why a general increase in
 779 habitual responding in BED was found (Voon et al., 2015). This has been hypothesized to play a role

780 in the loss of control during binge eating episodes (Voon et al., 2015). The dorsal putamen is shown to
 781 be decreased in activity in BN (Marsh et al., 2011) and receives projections from the dorsal posterior
 782 insula (Postuma and Dagher, 2006). Activity in medium spiny neurons in the putamen appear to be
 783 critical for instrumental learning in primates (Laquitaine et al., 2013). Different parts of the putamen
 784 (the posterolateral in humans and caudo-ventral parts in rats) have been associated with habitual
 785 responding and habit learning (Balleine and O'Doherty, 2010; de Wit et al., 2012). Reductions in
 786 activity during cognitive control tasks could therefore indicate impaired instrumental learning and
 787 integration of reward value rather than diminished cognitive control per se. A larger volume of the left
 788 putamen in BN may suggest a potential increase in habitual control. Increased functional connectivity
 789 of the putamen to subcortical areas, but decreased connectivity with frontal areas (Wang et al., 2020),
 790 supports the hypothesis of impaired instrumental learning deficits in BN. However, more studies are
 791 needed to confirm whether differences are unique to BN and BED, not only for the striatum but for
 792 other areas as well.

793 Overall, cognitive control is impaired in both BN and BED. Particularly in BN this is
 794 illustrated by a reduction of activity in frontal areas such as the OFC, IFG, medial PFC, medial, and
 795 superior frontal gyri and is potentially associated with diminished GM volume in these brain areas.
 796 The impaired performance is possibly reflective of a decreased influence of the goal-directed network
 797 and increased influence of networks associated with habitual responding, potentially creating a bias
 798 toward seeking unhealthy eating behaviors.

799

800 **4.3 Negative affect**

801 Stress-related negative affect has been shown to influence reward sensitivity through
 802 activation differences in several areas (Lyu & Jackson, 2016; Collins et al., 2017; Fischer et al., 2017;
 803 Wonderlich et al., 2018). BED and BN differ in IFG activation while insula activity differences are
 804 unique to BED (Lyu & Jackson, 2016), and right ACC, paracingulate gyrus, precuneus, vmPFC and
 805 IFG activity differences are unique to BN (Balodis et al., 2014; Collins et al., 2017; Fischer et al.,
 806 2017; Wonderlich et al., 2018). However, since the results in BED are only based on a single study, it

807 is currently not warranted to conclude that BN and BED differ completely as more data is needed to
 808 assess the existence of potentially unique activation differences. Activity differences in the ACC,
 809 insula, precuneus, and vmPFC have been extensively implicated in similar reward sensitivity and
 810 cognitive control tasks outside of acute stress manipulation (e.g., Simon et al., 2016; Schienle et al.,
 811 2009; Neveu et al., 2018). It is likely that these are not unique to stress-related negative affect,
 812 although they could be a result of it.

813 Differences in activation of the hippocampus in BED and anterior vermis of the cerebellum in
 814 BN seem unique to these paradigms that measure reward sensitivity under acute stress. Differences in
 815 activation of the anterior vermis are somewhat difficult to evaluate since they have not been typically
 816 associated with acute stress or reward processing. As mentioned previously, differences in the
 817 amygdala and hippocampal projections to areas associated with reward sensitivity (Abivardi and Bach,
 818 2017; Salzman and Fusi, 2010) can also be observed through structural and functional connectivity
 819 studies in BN/BED. BN subjects showed reduced connectivity between the central nucleus of the
 820 amygdala (CeA) and the hypothalamus in the right hemisphere, and the ventral anterior insula in the
 821 left hemisphere (Frank et al., 2016). Connectivity between the CeA and insula has been associated
 822 with feeding behaviour in rats (Zhang-Molina et al., 2020), with activation of this pathway
 823 suppressing food intake. Projections of the CeA and insula also converge in the parasubthalamic
 824 nucleus, which together with the CeA and insula modulate feeding behaviour of palatable food
 825 (Barbier et al., 2020). Through these connections, the insula suppresses activity in the CeA associated
 826 with satiety and plays an important role in overfeeding behavior (Stern et al., 2021; for a
 827 comprehensive overview of the connections, see Barbier et al., 2020). Aside from the CeA, BN
 828 subjects also showed reduced connectivity in the right hemisphere between the basolateral amygdala
 829 (BLA) and the dorsal anterior insula (dAI), and ventral striatum. It has been shown that the BLA-dAI
 830 connections are crucial for reward learning through memory (Gil-Lievana et al., 2020). In particular,
 831 the BLA in rats is specifically involved in encoding changes in outcome value, but not the hedonic
 832 experience gained from rewards (e.g., Parkes et al., 2013; for an overview see Wassum & Izquierdo et
 833 al., 2015). Crucially, lesions in rat BLA disrupted R-O learning (Balleine et al., 2003), and primate
 834 BLA neurons show similar involvement by future-oriented activity to gain rewards (Hernádi et al.,

2015). Disrupted BLA-dAI structural connectivity could leave BN (and possibly BED) subjects more
reliant on S-R learning mechanisms. Indeed, a similar case can be made for the BLA-ventral striatum
connections. Connectivity between the BLA and core of the nucleus accumbens was also necessary for
R-O learning in rats (Shiflett & Balleine, 2010), although it is facilitated by a reduction of dopamine
release (Jones et al., 2010). Compared to the reward history function of BLA-dAI connectivity, BLA-
ventral striatum connectivity is thus more reliant on the current hedonic value of the reward (Wassum
& Izquierdo et al., 2015). Incidentally, BLA connectivity to the lateral and medial OFC have also been
shown to be necessary in reward encoding (Malvaez et al., 2019), however this has not yet been shown
to be affected in BN/BED.

It is important to mention that interpretations of these studies on stress and reward sensitivity
are complicated by not including or reporting cortisol values. One disadvantage of this is that it makes
responder classification (Miller et al., 2013) impossible, as this is shown to be a boundary condition in
a number of tasks, in particular for the shift from goal-directed to habitual control (e.g. Smeets et al.,
2019). Indeed, responder classification is also an important factor for food intake in healthy
participants. High cortisol reactivity after acute stress exposure was tied to greater food consumption
(Epel et al., 2001). It would be interesting to test whether there is an association between cortisol
reactivity in BN/BED, and the amount of food intake and the above-described hippocampus activation
and amygdala connectivity.

Taken together, these results show that the HPA axis and reward networks are closely
connected and differentially affected in BN/BED. Hippocampal activity, which has an inhibitory
function on the HPA-axis, is affected, and both the CeA and BLA likely play crucial roles in feeding
behavior and reward learning. Specifically, this is likely associated with disrupted R-O learning
habitual control, which has been shown in humans with BED directly (Voon et al., 2015). This fits
well with research showing that after acute stress, healthy participants show a shift from goal-directed
to habitual responding in instrumental learning tasks (e.g. Schwabe and Wolf, 2009; Wirz et al., 2018;
Smeets et al., 2019; Quaedflieg et al., 2019; Hartogsveld et al., 2020). Stress could therefore make
BN/BED subjects more likely to rely on S-R associations, whilst impairing reward values and
reducing cognitive control, connecting the three cognitive constructs.

863 4.4 Future directions

864 It is crucial to use a multimodal approach that will lead to a better understanding of BN/BED.
865 Such an approach could compromise assessing neural activation during the task itself and combine
866 volumetric and connectivity approaches, which could then establish associations between affected
867 brain areas/connectivity and cognitive processes and ultimately brain network functioning and
868 maladaptive behavioral output. Based on the present review, the three major cognitive constructs
869 affected in BN and BED provide key elements in this approach. There is a number of promising ways
870 that future research could pursue to more precisely delineate the association between brain function
871 and these cognitive constructs. To model mechanisms underlying binges more accurately, future
872 studies could integrate more than just a single of these three cognitive constructs in their paradigm to
873 examine the potential interactive influences they may have. Pavlovian-to-instrumental-transfer
874 (Cartoni et al., 2016; Mahlberg et al., 2019; Watson and de Wit, 2018) is a good example of a
875 paradigm that combines reward sensitivity and cognitive control. Indeed, this review shows that the
876 networks involved in Pavlovian conditioning show considerable overlap with those responsible for the
877 transfer to instrumental learning and reward sensitivity (Corbit and Balleine, 2016). Another
878 promising approach is to investigate how stress influences the balance between brain networks
879 involved in instrumental learning in BN/BED, as stress could make subjects more likely to rely on
880 stimulus-response associations (model-free) whilst also impairing reward value attribution to an
881 outcome. It is likely that the balance between goal-directed (model-based) and habitual (model-free)
882 behavior is affected in BN/BED and associated with structural brain differences, but unfortunately
883 there is only one study (Voon et al., 2015) investigating this in patients. However, Voon and co-
884 workers (2015) only investigated volumetric GM associations of a subsample of all the subjects
885 performing the instrumental learning task. To establish a more complete understanding of these
886 disorders, associations between GM volume, brain activation, structural and functional connectivity as
887 well as impaired cognitive functioning needs to be determined in larger samples. Advanced designs
888 and analyses such as multivariate pattern analysis for both activity and connectivity (Anzellotti et al.,

2018) and algorithmic network approaches (Bielczyk et al., 2019) show considerable promise and could be very effective in providing unambiguous results.

BN and BED seem to affect men and women equally (Guerdjikova et al., 2017; Hudson et al., 2007). Thus, future research also has to specifically address the lack of research on men with BN and BED, as most studies discussed in this review only involved women. This may be problematic, since there appears to be sexual dimorphism of the mesocorticolimbic system, particularly involving stress responses (Douma and de Kloet, 2020; Gillies et al., 2014). Moreover, sex hormones influence glucocorticoid secretion and functioning of ventro tegmental dopamine neurons. The ventro tegmental area is in turn connected to the ventral striatum and prefrontal cortex, which makes this network very likely to play a central role in reward sensitivity, particularly after acute stress exposure. This potentially could increase reward values for certain foods and the likelihood of binge eating. It has also been shown that the effects of acute stress are different for men and women, both when influencing decision making and the way it is involved in certain psychiatric disorders (Bale and Epperson, 2015; Bangasser and Valentino, 2014; Georgiou et al., 2017; Wellman et al., 2018). Therefore, stress may differentially affect decision making and binge eating in men and women with BN and BED. More refined research is needed to confirm these findings in male samples to identify their exact role in BN and BED.

Taken together, we show in this review that BN and BED are characterized by differences in three networks, involving the prefrontal and cingulate cortex, insula, striatum, amygdala and hippocampus. Each of these networks is associated with different cognitive constructs, namely reward sensitivity, cognitive control, and negative affect. Numerous key nodes in these networks are also different in volume and connectivity compared with HC. Moreover, some of the studies discussed indicate that alterations in volume are present in current, but not in recovered, patients, and that these alterations correlate positively with symptom severity (Cyr et al., 2017; Wagner et al., 2006). Nevertheless, the number of studies on BN and BED is still limited. Therefore, caution must be taken when drawing strong conclusions about these disorders based on the available evidence. A related issue is caused by the relatively small samples in the studies with BN/BED patients (even though studies investigating subclinical subjects have included larger samples). Especially in smaller samples,

917 smaller differences that may be present might not be substantial enough to be detected due to a lack of
918 statistical power. This leaves the possibility of smaller, but relevant structural or functional differences
919 in brain organization still undiscovered in BN and BED. There are some differences found in
920 volumetric and connectivity studies that do not map onto the three cognitive constructs proposed in
921 this review. These are the inferior parietal cortex (Marsh et al., 2015; Westwater et al., 2018; Wallace
922 et al., 2020), middle/inferior temporal gyrus (Westwater et al., 2018; Marsh et al., 2015), paracentral
923 lobule (Amianto et al., 2013a), lingual gyrus (Marsh et al., 2015; Stopyra et al., 2019), and the
924 fusiform gyrus (Marsh et al., 2015). These areas might be associated with other constructs not
925 discussed here (e.g., body image distortion, other psychiatric comorbidities such as depression or
926 anxiety disorder), or they might not map onto any construct at all. In addition, most of these
927 differences are only confirmed by a limited number of studies with relatively small sample sizes. It is
928 therefore essential that more high-powered multimodal studies are performed to improve our
929 understanding of the brain-behavior connection in BN/BED.

930 **Search strategy and selection criteria**

931 A literature search was performed for this narrative review in PubMed and Google Scholar. We used
 932 the following search terms: ((bulimia nervosa) OR (binge eating disorder)) AND ((volumetric) OR
 933 (cortical thickness) OR (diffusion) OR (resting state)) OR (((reward sensitivity) OR (cognitive control)
 934 OR (impulsivity) OR (decision making) OR (instrumental learning) OR (negative affect) OR (stress)
 935 OR (cortisol) OR (HPA axis) AND (fMRI)). The reference lists of the included articles were also
 936 searched for additional potentially relevant articles. The final search was conducted on the 10th of
 937 November 2020, yielding a total of 463 articles. Our exclusion criteria for this narrative research were:
 938 1) not including participants that are either BED or BN patients or experienced BED or BN symptoms,
 939 2) not including measures of brain structure, connectivity, or activity during relevant tasks, 3) the
 940 article scores poor on our quality assessment (see below) and/or includes extremely small samples, 4)
 941 review articles not reporting original data, 5) conference proceedings without full report publication.
 942 After removing excluded articles and duplicates, the final number of eligible studies was 45. Results
 943 were extracted from both the main paper and supplementary materials available online, and all tests
 944 are reported in Table 1 and 2.

945
 946 **Quality assessment**

947 Quality of the studies was evaluated based on the nine criteria described in Wolters et al. (2019): (1)
 948 description of participants; (2) description of imaging procedure and instructions; (3) description of
 949 psychological task; (4) description of spatial normalization procedure; (5) specification of regions of
 950 interest; (6) suitability of imaging pipeline for analyzing imaging data; (7) multiple testing problem;
 951 (8) support of all empirical claims by statistical tests; (9) quality of tables and figures. We added three
 952 criteria that were particularly relevant in evaluating the quality of studies using BN and BED samples:
 953 (10) quality of assessment of BN/BED status (e.g. formal diagnosis, questionnaire); (11) correct
 954 matching of control group to patient group; and (12) the size of sample within each subgroup. Each
 955 criterion could be scored with 1 point (+), 0.5 points (±) or 0 points (-). Total score was calculated and
 956 corrected for number of applicable criteria (total score/number of applicable criteria*10). A score of

957 7.5 or higher was considered as good quality, a score between 4 and 7.5 as fair quality, and a score of
958 4 or less as poor quality (Wolters et al., 2019). Quality of papers was considered while interpreting and
959 discussing the results of the data synthesis. Quality assessment was performed independently by two
960 researchers. There were no major discrepancies in overall quality rating between the assessors (poor,
961 fair, good). Differences between the assessors for individual criteria (e.g. 9. quality of tables and
962 figures) also did not exceed 0.5 points. The average score between the two researchers is reported in
963 the figure below.

964

965

----- Insert Figure 5 around here -----

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968

969 **References**

970

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1680 **Figure captions**

1681

1682 **Figure 1. Differences in activity in bulimia nervosa (BN) and binge eating disorder (BED) in**
 1683 **passive food viewing tasks and active food tasting tasks compared with matched controls.** For
 1684 each area, the bar graph indicates the number of studies that found a decrease in activity (= red), or an
 1685 increase in activity (= green), and the studies that found no difference in activity (= gray), during
 1686 passive food viewing tasks (i.e., studies using paradigms where participants had to merely view food
 1687 stimuli; shown in the two images on top) and active food tasting tasks (i.e., studies where participants
 1688 had to actively taste food in the scanner; represented in the two images at the bottom). All of the
 1689 included studies found at least one brain area that was significantly different in activation in BN and/or
 1690 BED compared with HC. **Abbreviations are as follows:** PCC = posterior cingulate cortex, ACC =
 1691 anterior cingulate cortex, ventr. striatum = ventral striatum, med. OFC = medial orbitofrontal cortex,
 1692 ant. med. PFC = anterior medial prefrontal cortex, ang. gyr. angular gyrus. If no indication of
 1693 lateralization is given (either left or right), differences are observed bilaterally.

1694

1695 **Figure 2. Differences in activity in bulimia nervosa (BN) and binge eating disorder (BED) in**
 1696 **cognitive control tasks compared with matched controls.** For each area, the bar graph indicates the
 1697 number of studies that found a decrease in activity (= red), or an increase in activity (= green), and the
 1698 studies that found no difference in activity (= gray), during cognitive control tasks. All of the included
 1699 studies found at least one brain area that was significantly different in activation in BN and/or BED
 1700 compared with HC. **Abbreviations are as follows:** med. front. gyr. = medial frontal gyrus, PCC =
 1701 posterior cingulate cortex, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus, sup. front.
 1702 gyr. = superior frontal gyrus, dlPFC = dorsolateral prefrontal cortex, med. PFC = medial prefrontal
 1703 cortex, temp. gyr. = temporal gyrus, lingual gyr. = lingual gyrus, occ. gyr. = occipital gyrus. If no
 1704 indication of lateralization is given (either left or right), differences are observed bilaterally.

1705

1706 **Figure 3. Differences in activity in bulimia nervosa (BN) and binge eating disorder (BED) under**
 1707 **acute stress / negative affect, using passive food viewing tasks, compared with matched controls.**

1708 For each area, the bar graph indicates the number of studies that found a decrease in activity (= red), or
 1709 an increase in activity (= green), and the studies that found no difference in activity (= gray), during
 1710 passive food viewing tasks under acute stress. All of the included studies found at least one brain area
 1711 that was significantly different in activation in BN and/or BED compared with HC. **Abbreviations**
 1712 **are as follows:** vmPFC = ventromedial prefrontal cortex, amygd. = amygdala, ant. vermis = anterior
 1713 vermis of cerebellum, ACC = anterior cingulate cortex, paracing. = paracingulate gyrus, IFG = inferior
 1714 frontal gyrus. If no indication of lateralization is given (either left or right), differences are observed
 1715 bilaterally.

1716
 1717 **Figure 4. Volumetric differences in bulimia nervosa (BN) and binge eating disorder (BED)**

1718 **compared with matched controls.** For each area, the bar graph indicates the number of studies that
 1719 found a reduction in volume (= red), or an increase in volume (= green), and the studies that found no
 1720 difference in activity (= gray). For BN, 10 of the 14 included studies found at least one brain area that
 1721 was significantly different compared with HC. Four studies did not find any significant differences
 1722 between BN and HC. **Abbreviations are as follows:** caudate = caudate nucleus, OFC = orbitofrontal
 1723 cortex, sup. par. = superior parietal cortex, IFG = inferior frontal gyrus, ventr. striatum = ventral
 1724 striatum, ACC = anterior cingulate cortex. If no indication of lateralization is given (either left or
 1725 right), differences are observed bilateral. For the left part (BN) of this figure only, areas with one study
 1726 indicating differences are not displayed, due to the large number of areas found in BN. For the right
 1727 part (BED) all studies are displayed. For a full overview for differences in BN, please see Table 2.

1728
 1729 **Figure 5. Summary of quality assessment performed for all included MR studies (related to the**
 1730 **three cognitive constructs, volumetric, or connectivity).** The studies were evaluated by two
 1731 independent raters, based on 12 criteria (see Quality assessment). Each criterion was scored with 1

1732 point (+), 0.5 point ($\pm$) or 0 points (-). The corrected average score ((total points/number of applicable
1733 criteria*10)/2) is presented in this figure, with yellow indicating a rating of 'fair' (<7.5) and green a
1734 rating of 'good' (≥ 7.5).

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Study	Subjects	Gender (♀/♂)	Age x̄ (SD)	BMI x̄ (SD)	Diagnosis	Task	Methods	Findings
REWARD SENSITIVITY								
BN								
Oberndorfer, Frank, Simmons et al. (2013) ^f	BN recovered (14)	14/0	26.6 (5.7)	22.9 (2.1)	SCID DSM-IV-TR	Taste of sucrose and sucralose	MRI, whole brain, ROI	Increased activation right AI during sucrose in BN compared with HC
	HC (14)	14/0	27.4 (5.5)	22.6 (1.5)				
BED								
Filbey, Myers, & DeWitt (2012) ^g	BED-spectrum (26)	14/12	32.88 (11.04)	32.72 (5.98)	BES > 8	Food cue exposure task	MRI, whole brain; PPI	Taste cues high-caloric food vs neutral mOFC, VTA, NAc, insula, caudate, putamen, precuneus, CG, thalamus, amygdala, hippocampus Positive correlation compulsive overeating scores with activity in: amygdala, putamen, insula, PCC, precuneus, hippocampus, thalamus, CG, VTA, MFG Functional connectivity during high-caloric cues vs. neutral NAc more positively correlated with mOFC and DS NAc connectivity with PCC/precuneus positively correlated with BES scores
Balodis, Kober, Worhunsky et al. (2013a) ^f	BED (19)	14/5	43.7 (12.7)	36.7 (4.05)	DSM-5	Monetary Incentive Delay task	MRI, whole-brain	HC,OB>BED, decreased activity VS (anticipation of reward) PFC and insula (outcome phase)
	OB (19)	10/9	38.3 (7.5)	34.6 (3.5)				
	HC (19)	10/9	34.8 (10.7)	23.3 (1.1)				
Balodis, Grilo, Kober et al. (2014) ^f	remain BED (10)	14/5, difference N.S.	43.7 (12.7) difference, N.S.	36.7 (4.05), difference N.S.	DSM-5, re-analysis of data Balodis et al. (2013)	Monetary Incentive Delay task	MRI, whole-brain	Remain BED group diminished VS and IFG in anticipation, reduced activity in medial PFC during outcome phase

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	recovered BED (9)	14/5, difference N.S.	43.7 (12.7), difference N.S.	36.7 (4.05), difference N.S.	Recovered is no binge eating last 28 days				
Wang, Geliebter, Volkow et al. (2011) [‡]	BED (10)	8/2	38.5 (13.3)	43.4 (13.5)	DSM-IV, EDE	Food cue and taste task (smell/view/taste); administered methylphenidate (MPH)	PET, [11C]raclopride	N.S., in placebo Food stimuli in MPH condition increased dopamine in caudate and putamen in BED, not in OB Dopamine increases caudate positively correlated binge eating scores, not BMI	
	OB (8)	5/3	41.8 (8.9)	36.5 (9.4)					
BN & BED									
Schienze, Schäfer, Hermann, & Vaitl (2009) [‡]	BED (17)	17/0	26.4 (6.4)	32.2 (4)	DSM-IV, EDI	Passive viewing, food/disgust/neutral pictures	food MRI, whole brain/ROI	Between-subject, Food>Neutral BED>OB, mOFC BED>HC, right mOFC BED>BN, right IOFC, right mOFC BN>OB, ACC, right insula BN>HC, right ACC, insula BN>BED, ACC, right insula	
	BN (14)	14/0	23.1 (3.8)	22.1 (2.5)				Within-subject, Food>Neutral Occipital cortex, OFC, ACC, insula	
	OB (17)	17/0	25 (4.7)	31.6 (4.7)				Reward sensitivity scores positively correlated with activity to Food>Neutral In BED: left ACC, right mOFC In BN: insula, ACC, mOFC	
	HC (19)	19/0	22.3 (2.6)	21.7 (1.4)				Arousal scores positively correlated with activity to Food>Neutral In BED: ACC, mOFC	
								EDI binge eating scores positively correlated with activity to Food>Neutral In BN: right insula	
Simon, Skunde, Walther et al. (2016) [‡]	BED (27)	N.R.	38.26 (13.75)	32.61 (4.55)	SCID DSM- 5	Monetary and Food Delay task	MRI, ROI	Anticipation of reward (high vs no-food reward) ROI: N.S. in striatum Whole-brain: decreased PCC, HC>BN and HC>BED	
	controls BED (28)	matched	38 (10.85)	34.02 (4.5)				Receipt of reward (high vs no-food reward) ROI: increased mOFC, BN>HC and BED>HC	

											Whole-brain: increased PCC, anterior medial PFC, AG, BN>HC and BED>HC N.S. In monetary delay task
		BN (29)	N.R.	27.45 (10.55)	21.33 (2.99)						
		controls BN (27)	matched	25.74 (5.25)	21.85 (1.85)						
		BN (14)	14/0	23.1 (3.8)	22.1 (2.5)						Activity predicts group for BED & HC: right insula, left IOFC BED & OB: right ACC, left insula, mOFC, right VS BN & HC: left ACC, right insula, left VS BN & OB: right IOFC BED & BN: right ACC, insula, left VS
		OB (17)	17/0	25.0 (4.7)	31.6 (4.7)						
		HC (19)	19/0	22.3 (2.6)	21.7 (1.4)						
COGNITIVE CONTROL											
BN											
Marsh, Wang (2011) *	Horga, et al.	BN & BN-spectrum (18)	18/0	18.4 (2.1)	22.03 (2)	N.R., subclinical	4	Simon task	MRI, brain	whole-	Greater deactivations in BN compared with HC in: left IFG, left SFG, right MFG, right PCC Greater activations in HC compared with BN in right: putamen, hippocampus, IFG, ACC, dlPFC
		HC (18)	18/0	17.3 (2.4)	21.98 (1.9)						Objective bulimic and vomiting episodes and preoccupation with weight scores correlated in BN with: Negatively: left IFG, precuneus, right putamen Positively: left SFG, left insula, right ACC Correlation between vmPFC activity and health rating was more negative in BN than HC In BN and HC, positive correlation between uncontrolled choices and activity dlPFC In BN and HC, positive correlation between uncontrolled choices and connectivity dlPFC-vmPFC
Neveu, Carrier (2018) *	Neveu, et al.	BN (31)	31/0	24 (3.87)	19.9 (2.5)	Patients, DSM-IV		Food evaluation choice task	MRI, brain	whole-	
		HC (23)	23/0	23 (2.7)	21.3 (2.36)						
BED											

Balodis, Molina, Kober et al. (2013b) ^g	BED (11)	9/2	47.6 (12.7)	37.1 (3.9)	SCID DSM-5, EDE-Q	Stroop task	MRI, brain	whole-	All groups showed consistent Stroop-related differences in incongruent>congruent e.g. insula, cingulate, striatum, thalamus, frontal gyri, cerebellum, cuneus
	OB (13)	5/8	35.4 (9.3)	34.6 (4.1)					Group differences on incongruent>congruent OB>BED, decreased activity IFG, MFG, SFG, OFG, MOG, IOG, LG, STG, insula, PreCG
	HC (11)	5/6	32.7 (11.3)	23.2 (1.1)					HC>BED, decreased activity SOG, MOG, STG, insula
Hege, Stingl, Kullmann, Schag, Giel, Zipfel, & Preissl (2015) ^f	BED (13)	13/0	41.15 (9.14)	33.45 (5.38)	SCID, DSM-IV-TR, EDE-Q	Food-related visual Go/noGo	MEG		Successful withholds during no-go trials associated with SFG and right SMG BIS-11 negatively correlated with right MFG activity. BED showed decreased activity on food stimuli on successful withholds in no-go trials
	OB (16)	16/0	40.19 (11.73)	36.38 (5.02)					
Voon, Derbyshire, Rück et al. (2015) ^g	BED (31)	19/12	42.79 (9.02)	34.97 (5.56)	DMS-IV-TR	Sequential instrumental learning task	MRI, VBM		In non-related HC group, bias toward goal-related responding positively correlated with volume in left mOFC, caudate, and lateral PFC. In subsample, adding HAB/GD as covariate, previously described differences (see Table 2) disappeared
	OB (31)	12/19	44.24 (9.39)	31.49 (3.6)					
NEGATIVE AFFECT									
BN									
Collins, et al. (2017) ^g	Sample 1								HC>BN, decreased activity: Precuneus, PaCG, anterior vermis
	BN (10)	10/0	21 (2.5)	21.75 (1.59)	DSM-5, SCID, EDE	Visual food cue processing task	Whole-brain		BN pre-stress> BN post-stress, decreased activity: Precuneus, PaCG, anterior vermis
	HC (10)	10/0	24 (5.5)	22.21 (1.28)		TSST (only mathematical part)			

Collins et al. (2017) *	Sample 2							Replicated findings study 1
	BN & OSFED-BN (17)	17/0	22.85 (5.42)	24.47 (3.25)	DSM-5, SCID, EDE	Visual food cue processing task TSST (only mathematical part)	ROI	
Fischer, Breithaupt, Wonderlich et al. (2017) *	BN & BN-spectrum (16)	16/0	22.85 (5.42)	24.47 (3.25)	DSM-5, BN, OSFED & BN symptoms, EDE	Visual palatable food cue processing, TSST	WS, ROI	BN pre-stress > BN post-stress, decreased activity: vmPFC, right ACC, left amygdala
Wonderlich, Breithaupt, Thompson, Crosby, Engel, Fischer (2018) *	BN & BN-spectrum (16)	16/0	22.85 (5.42)	24.47 (3.25)	DSM-5, BN, OSFED & BN symptoms, EDE, re-analysis of data Fischer et al. (2017).	Visual palatable food cue processing, TSST	EMA-fMRI integration, WS, ROI	Predictive of negative affect (high just before binge): right amygdala, vmPFC Predictive of positive affect (high before and after binge): Left amygdala, right ACC, vmPFC
Lyu & Jackson (2016) *	BED - stress (9)	9/0	19.22 (0.44)	20.8 (1.48)	DSM-IV	Visual food cue processing (high/low-caloric, neutral images)	BS, ROI	Stress condition - HC>BED, decreased activity <i>High-caloric vs. Neutral:</i> IFG, insula, hippocampus
	BED - no-stress (9)	9/0	19.89 (1.54)	20.72 (2.34)		CPT		<i>Low-caloric vs. Neutral:</i> hippocampus
	HC - stress (12)	12/0	20 (1.41)	19.19 (1.52)				<i>High-caloric vs. Low-caloric:</i> IFG, hippocampus, amygdala
	HC - no-stress (14)	14/0	19.43 (1.34)	19.22 (2.16)				Control condition - HC>BED, decreased activity <i>High-caloric vs. Neutral:</i> SFG, ACC <i>Low caloric vs. Neutral:</i> SFG, ACC, putamen <i>High-caloric vs. low-caloric:</i> PaCG

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1739 **Table 1. Overview of publications on reward sensitivity, cognitive control, and negative affect in BN and BED. Abbreviations general:** N.S. = not
1740 significant, N.R. = not reported. **Abbreviations subjects:** BN = bulimia nervosa, BED = binge eating disorder, HC = healthy control, OB = obese control,

1741 OSFED = Other Specified Feeding or Eating Disorders. **Abbreviations diagnosis:** SCID = Structured Clinical Interview for the DSM, DSM = Diagnostic and
 1742 Statistical Manual of Mental Disorders, DSM-IV-TR = DSM IV textual revision, EDE = Eating Disorder Examination Interview, EDE-Q = EDE
 1743 questionnaire, EDI = Eating Disorder Inventory, QWEP = Questionnaire on Eating and Weight Patterns, BES = Binge Eating Scale. **Abbreviations task:**
 1744 TSST = Trier Social Stress Task, CPT = Cold Pressor Test. **Abbreviations method:** VBM = voxel-based morphometry, ROI = region-of-interest analysis, PPI
 1745 = psychophysiological interaction, WS = within-subject, BS = between=subject, EMA = Ecological Momentary Assessment. **Abbreviations findings**
 1746 **general:** HAB/GD = habitual/goal-directed responding. **Abbreviations findings areas:** AI = anterior insula, VTA = ventral tegmental area, NAc = nucleus
 1747 accumbens, DS = dorsal striatum, VS = ventral striatum. **Abbreviations findings cortex:** mOFC = medial orbitofrontal cortex, IOFC = lateral OFC, vmPFC =
 1748 ventromedial prefrontal cortex, dlPFC = dorsolateral PFC. **Abbreviations findings gyri:** CG = cingulate gyrus, MFG = medial frontal gyrus, IFG = inferior
 1749 frontal gyrus, SFG = superior frontal gyrus, OFG = orbitofrontal gyrus, PreCG = precentral gyrus, AG = angular gyrus, LG = lingual gyrus, MOG = middle
 1750 occipital gyrus, IOG = inferior occipital gyrus, SOG = superior occipital gyrus, STG = superior temporal gyrus, SMG = superior medial gyrus, PaCG =
 1751 paracingulate gyrus.^{g, f} Refers to the quality assessment done by two independent raters (see 'Quality assessment' for more details). Represents a good (≥ 7.5)
 1752 or a fair (4-7.5; out of 10) rating respectively.

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Study	Subjects	Gender (♀/♂)	Age $\bar{x}$ (SD)	BMI $\bar{x}$ (SD)	Diagnosis	Method	Findings
VOLUMETRIC							
BN							
Amianto, Caroppo, D'Agata et al. (2013a) [#]	BN (13)	13/0	22 (3)	22 (2)	SCID DSM-IV-TR	VBM	BN>HC, increased volume
	HC (14)	14/0	24 (3)	21 (2)			GM: left PCL, precuneus, left putamen, left insula
Berner, Stefan, Lee et al. (2018) [#]	BN & BN-spectrum (60)	60/0	18.8 (4.1)	22.4 (2.4)	Patients, N.R.	Cortical thickness, ROI	HC>BN, reduced volume
	HC (54)	54/0	19.2 (5.5)	21.9 (2.1)			GM: caudate, right thalamus
							BN>HC, increased Cortical thickness: left ventral PCC
							HC>BN, reduced Cortical thickness: pars triangularis, right SPC, left dorsal PCC
Berner, Wang, Stefan et al. (2019) [#]	BN & BN-spectrum (62)	62/0	18.8 (4)	22.4 (2.5)	SCID DSM-IV-TR, EDE	VBM	HC>BN, inward deformations (vertex indices)
	HC (65)	65/0	19.3 (5.7)	22.6 (2.8)			right anterior lateral and medial pallidum; internal and external GP
Canna, Prinster, Monteleone et al. (2017) [#]	BN (13)	13/0	27.2 (2)	N.R.	Patients, DSM-5	SCID VBM	N.S.
	HC (16)	16/0	26.1 (3.5)	21.1 (1.6)			N.S.
Coutinho, Ramos, Maia et al. (2015) [#]	BN (21)	21/0	31.57 (8.27)	21.39 (2.36)	Patients, DSM-IV	Drawn ROIs	HC>BN, reduced volume
	HC (20)	20/0	30.9 (8.79)	22.11 (3.2)			GM: caudate nucleus
Cyr, Kopala-Sibley, Lee et al. (2017)* [†]	BN (33)	33/0	16.5 (1.5) - 18.1 (1.5) - 19.3 (1.5)	22.1 (2.8) - 23.2 (2.8) - 23.8 (2.7)	Patients, DSM-5, OSFED-BN	22 11 Cortical thickness, ROI, follow-up	HC>BN, reduced thickness
	HC (28)	28/0	16.2 (2.1) - 17.3 (2.1) - 18.8 (2.3)	21.4 (3.5) - 22.6 (3.5) - 23.9 (4.9)			Right inferior frontal gyrus pars opercularis and pars orbitalis (OFC), consistent over all time points
							IFG opercularis on baseline, 12 months, 24 months, but not 36 months follow-up (N.S.)
							Correlations
							Thickness frontal pole correlated negatively with objective binge eating episode frequency, baseline only
							Average thickness lateral OFC and IFC orbitalis correlated negatively with frequency vomiting, over all time points

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Frank, Shott, Hagman, & Mittal (2013) ^g	BN (19)	19/0	25.2 (5.3)	22.6 (5.7)	Patients, DSM-IV	SCID	VBM	BN>HC, increased volume GM: left OFC, left anterior ventral insula, GR
	HC (24)	24/0	27.4 (6.3)	21.6 (1.3)				HC>BN, reduced volume GM: dorsal caudate, right dorsal putamen WM: right MTL, right IFG
Joos, Klöppel, Hartmann et al. (2010) ^g	BN (17)	17/0	24.5 (4.8)	21.1 (2.5)	DSM-IV		VBM	N.S.
	HC (18)	18/0	26.9 (5.7)	21.2 (2)				
Marsh, Stefan, Bansal et al. (2015) ^g	BN (34)	34/0	21.6 (6)	22.1 (2)	SCID DSM-IV-TR		Cortical thickness	BN>HC, increased volume GM: MOG, IOG, LG, right IPL WM: reflective of these results
	HC (34)	34/0	22.08 (6.5)	22.13 (2.3)				HC>BN, reduced volume GM: MFG, PreCG, ITG, PCC, right PostCG, right SPG, right cuneus, left IFG, left LSG, left precuneus, left FG WM: reflective of these results
Mettler, Shott, Pryor, Yang, & Frank (2013) ^g	BN (20)	20/0	25.2 (5.3)	22.59 (5.69)	Patients, DSM-IV-TR		VBM	N.S.
	HC (21)	21/0	27.5 (6.6)	21.55 (1.19)				
Wagner, Greer, Bailer et al. (2006) ^f	BN, recovered (10)	10/0	24 (6.1)	23.1 (2.4)	Ex-patients, recovery (18.1) months.	29.8	VBM	N.S. When covarying for age, BN>HC GM insula
	HC (31)	31/0	26.8 (7.3)	21.9 (2)				
Wallace, Richard, Peng, Knodt, Hariri (2020) ^f	BN-spectrum (247)	169/78	19.43 (1.23)	N.R.	EDI-3 subtest, score >0	Bulimia	Cortical thickness	Negative correlation with bulimia scores in thickness GM: OFC, insula, left S1/S2, left IPC
Westwater, Seidlitz, Diederer, Fischer & Thompson (2018) ^g	BN & BN-spectrum (33)	33/0	22.6 (4.13)	23.9 (3.1)	N.R., EDE-Q	EDE,	Cortical thickness, & per vertex connectivity	Negative correlation EDE-Q BN symptoms with cortical thickness GM: rPostCG, right rostral MFG, rITG, rSFG, IOFC, IIPC, IMTG, left caudal MFG
								areas with reduced cortical thickness show increase in structural connectivity estimation (per vertex, T1 MPAGE)
BN+BED								
Voon, Derbyshire, Rück et al. (2015) ^g	BED (20)	12/8	43.95 (9.47)	34.12 (5.49)	DMS-IV-TR		VBM, ROI	HC>BED, reduced volume GM: medial OFC, caudate, left VS, left lateral OFC
	OB (20)	9/11	44.7 (10.12)	32.88 (3.53)				
Schafer, Vaitl, & Schienle (2010) ^g	BED (17)	17/0	26.4 (6.4)	32.2 (4)	DSM-IV-TR		VBM	BED>HC, increased volume GM: ACC, medial OFC

	BN (14)	14/0	23.1 (3.8)	22.1 (2.5)					BN>HC, increased volume GM: medial OFC, VS
	HC (19)	19/0	22.3 (2.6)	21.7 (1.4)					BN>BED, volume GM: VS, DS, left lateral OFC, left medial OFC
STRUCTURAL CONNECTIVITY**									
<i>BN</i>									
Canna, Prinster, Monteleone et al. (2017) *	BN (13)	13/0	27.2 (2)	N.R.	Patients, DSM-5	SCID	DTI		FA: N.S.
	HC (16)	16/0	26.1 (3.5)	21.1 (1.6)					
Frank, Shott, Riederer, Pryor (2016) *	BN (25)	25/0	24.64 (4.22)	23.56 (5.89)	Patients, DSM-IV	SCID	Diffusion, PFT		BN>HC, increased connectivity, left hemisphere pI an dAI to: medial PFC, middle OFC, VS vAI to: middle OFC, VS VS to: inferior OFC, GR
	HC (26)	26/0	24.39 (3.49)	21.61 (1.21)					BN>HC, increased connectivity, right hemisphere pI to: VS dAI to: medial PFC, middle OFC VS to: medial OFC
									HC>BN, reduced, left hemisphere vAI to: inferior OFC, CeA Hypothalamus to: middle OFC Medial PFC to: GR
									HC>BN, reduced, right hemisphere BLA to: dAI, VS CeA to: hypothalamus
He, Stefan, Terranova, Steinglass, Marsh (2016) *	BN (28)	28/0	21.32 (6.11)	21.95 (2.13)	SCID DSM-IV-TR		DTI, TBSS		HC>BN, reduced FA: FMajor, Fminor, SLF, IFOF, ATR, CST, UF, cingulate gyrus
	HC (28)	28/0	20.61 (6.12)	22.18 (2.14)					BN>HC, increased RD: FMajor, Fminor, IFOF, ATR, CST, cingulate gyrus, left SLF
Mettler, Shott, Pryor, Yang, & Frank (2013) *	BN (20)	20/0	25.2 (5.3)	22.59 (5.69)	Patients, DSM-IV-TR	DSM-IV-TR	DTI		BN>HC, increased ADC: CR into ALIC, corpus callosum, left IFOF, left UF, left EC
	HC (21)	21/0	27.5 (6.6)	21.55 (1.19)					HC>BN, reduced FA: CR into PLIC, corpus callosum
Wang, Bi, An, Li, Kong et al. (2019) *	BN (48)	48/0	22.0 (3.4)	21.0 (2.6)	Patients, IV, MINI	DSM-IV, MINI	DTI, nodal, NBS		BN>HC, increased nodal strength: left superior OFC, ITG, insula, hippocampus, PHG, thalamus local efficiency: left superior OFC, STG, ITG, superior temporal pole, thalamus, amygdala

	HC (44)	44/0	23.1 (1.7)	20.5 (1.4)					HC>BN, reduced nodal strength: left ACC, right precuneus global efficiency: left GR, right OFC, insula, putamen, pallidum, amygdala, PreCG, PostCG, SMG, precuneus, FG local efficiency: right PreCG, precuneus
BED									
Estella, Sanches, Maranhão et al. (2020) *	BED (17)	17/0	33.82 (7.2)	36.07 (0.8)	DSM-5, EDE		DTI, TBSS		BED>OB, increased FA: Fminor AD: left SLF, cingulum (ACC, PCC), corpus callosum
	OB (BED controls) (13)	13/0	38.03 (9.7)	33.64 (4.7)					BED>HC, increased AD: right Fminor, SLF left ILF, Fmajor, IFOF bilateral ATR
	HC (non-OB) (17)	17/0	34.70 (11.0)	22.50 (2.0)					
FUNCTIONAL CONNECTIVITY									
BN									
Amianto, D'Agata, Lavagnino et al. (2013b) *	BN (12)	12/0	23 (5)	21.57 (2.38)	Patients, DSM-IV		RS, ICA		BN>HC, increased connectivity Cerebellum (IX, X) to: left insula, TL Lateral cerebellum, ACC, precuneus
	HC (10)	10/0	24 (3)	21.35 (3.16)					HC>BN, reduced connectivity Cerebellum (IX, X) with PL Right IFG
Canna, Prinster, Monteleone et al. (2017) *	BN (13)	13/0	27.2 (2)	N.R.	Patients, DSM-5	SCID	RS, VMHC		HC>BN, reduced VMHC: FL, from OFC to dlPFC Coherence: Slow-4 and Slow-5 for OFC-dlPFC cluster
	HC (16)	16/0	26.1 (3.5)	21.1 (1.6)					
Lee, Kim, Ku, Lee, Namkoong, & Jung (2014) *	BN (20)	20/0	22.9 (3.9)	21.6 (2.3)	Patients, DSM-IV	SCID,	RS, ROI, seed-based		BN>HC, increased synchrony dACC to: left OFC, right precuneus, medial OFC
	HC (20)	20/0	23.3 (1.8)	19.9 (1.9)					HC>BN, reduced synchrony dACC to: left PHG
Spalatro, Amianto, Huang et al., (2019) †	BN (16)	16/0	21.56 (2.35)	21.84 (2.35)	Patients, DSM-IV-TR & DSM-5	SCID	RS, ROI		BN>HC, increased neural variability (SD) Slow-4: ventral attention network Slow-5: N.S.

	HC (17)	17/0	23.27 (2.19)	21.42 (1.85)					
Wang, Bi, Song, Zhang, Li, Kong et al., (2020) ^a	BN (51)	51/0	N.S.	20.8 (2.2)	Patients, DSM-IV, MINI		RS, ROI, seed-based	BN>HC, increased connectivity Right DC to bilateral putamen, GP, caudate, thalamus Putamen (DCP, DRP, VRP) to thalamus, GP, putamen	
	HC (53)	53/0	N.S.	20.4 (1.7)				HC>BN, reduced connectivity VS to PreCG, PostCG, OG Putamen (DCP, DRP, VRP) to right SFG/MFG	
BED									
Oliva, Morys, Horstmann et al., (2019) ^f	BED & BED-spectrum (19)	15/4	23.89 (3.4)	22.53 (2.04)	Eating attitude test (EAT-26), >1 episode per month		RS, ROI, seed-based	BED>HC, increased N.S. for seeds left putamen, ITG, SPL N.S. correlation with impulsivity scores	
	HC (20)	15/5	25.31 (3.2)	21.25 (2.07)				HC>BED, reduced Degree centrality: right MFG, left MTL/ITL, SPL, insula Connectivity: right MFG to right anterior insula, rMFG to rMFG/IFG	
BN+BED									
Stopyra, Simon, Skunde et al. (2019) ^g	BN (29)	29/0	27.45 (10.55)	21.33 (2.99)	Patients, DSM-IV	SCID	RS, ROI, seed-based	ICA, seed-based	BN>HC, increased connectivity ICA: right dorsal medial PFC
	HC (BN controls) (30)	30/0	26.86 (6.59)	21.85 (1.80)					OB>BED, reduced connectivity ICA: right medial dACC, right dorsal medial PFC
	BED (27)	23/4	38.39 (13.06)	32.64 (4.13)					BED>OB, increased connectivity seed-based with dACC: right cerebellum, right LG
	OB (BED controls) (28)	24/4	39.40 (10.48)	33.58 (4.54)					HC>BN, reduced connectivity ICA: left medial dACC, left ventral medial PFC
									BN>BED ICA: right dorsal medial PFC, left MFG, left AG seed-based with dACC: RSC
									BED>BN ICA: left medial dorsal PCC seed-based with dACC: left PreCG, right PostCG, left SMA

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Table 2. Overview of publications on volumetric, functional connectivity, and structural connectivity in bulimia nervosa (BN) and binge eating disorder (BED). Abbreviations general: N.S. = not significant, N.R. = not reported. **Abbreviations subjects:** BN = bulimia nervosa, BED = binge eating disorder, HC = healthy control, OB = obese control, EDIBul = bulimia symptoms on Eating Disorder Inventory. **Abbreviations diagnosis:** SCID = Structured Clinical Interview for the DSM, DSM = Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR = DSM IV textual revision, OSFED = Other Specified Feeding or Eating Disorders, EDE = Eating Disorder Examination Interview, EDI = Eating Disorder Inventory. **Abbreviations method:** VBM = voxel-based morphometry, ROI = region-of-interest analysis, ICA = independent component analysis, RS = resting state, VMHC = voxel-mirrored homotopic connectivity, DTI = diffusion tensor imaging, TBSS = tract-based spatial statistics, PFT = probabilistic fiber tractography, NBS = network-based statistic. **Abbreviations findings general:** GM = gray matter, WM = white matter, FA = fractional anisotropy, ADC = apparent diffusion coefficient, RD = radial diffusivity. **Abbreviations findings gyri:** MOG = middle occipital gyrus, IOG = inferior occipital gyrus, LG = lingual gyrus, AG = angular gyrus, MFG = middle frontal gyrus, IFG = inferior frontal gyrus, SFG = superior frontal gyrus, PreCG = precentral gyrus, PostCG = postcentral gyrus, ITG = inferior temporal gyrus, MTG = middle temporal gyrus, STG = superior temporal gyrus, SPG = superior parietal gyrus, LSG = lateral superior gyrus, FG = fusiform gyrus, PHG = parahippocampal gyrus, GR = gyrus rectus, SMG = supramarginal gyrus. **Abbreviations findings cortex:** PCC = posterior cingulate cortex, (d)ACC = (dorsal) anterior cingulate cortex, OFC = orbitofrontal cortex, PFC = prefrontal cortex, SPC = superior parietal cortex, RSC = retrosplenial cortex, S1/S2 = somatosensory cortex, IPC = inferior parietal cortex. **Abbreviations findings other areas:** SMA = supplementary motor area, PCL = paracentral lobule, TL = temporal lobe, PL = parietal lobe, FL = frontal lobe, MTL = medial temporal lobe, ITL = inferior temporal lobe, IPL = inferior parietal lobe, SPL = superior parietal lobe, VS = ventral striatum, DS = dorsal striatum, DC = dorsal caudate, GP = globus pallidus, DCP = dorsal caudal putamen, DRP = dorsal rostral put., VRP = ventral rostral put., CeA = central nucleus amygdala, BLA = basolateral amygdala, pI = posterior insula, dAI = dorsal anterior insula, vAI = ventral anterior insula, Cerebellum (IX,X) = vermis and paravermis of cerebellum, lobule IX/X. **Abbreviations findings WM:** SLF = superior longitudinal fasciculus, ILF = inferior longitudinal fasciculus, IFOF = inferior fronto-occipital fasciculus, UF = uncinate fasciculus, ATR = anterior thalamic radiation, CST = corticospinal tract, FMajor = major forceps, Fminor = minor forceps, CR = corona radiata, ALIC = anterior limb of internal capsule, PLIC = posterior limb of internal capsule, EC = external capsule. *Age and BMI are displayed as baseline, follow-up 1, and follow-up 2. ** Structural connectivity can be measured with a number of different techniques (e.g. diffusion tensor imaging, probability tracking, TBSS), and do not necessarily give perfectly comparable results. Values such as FA and MD are not specific (increase in FA and decrease in MD reflects reduction in white matter integrity), and differences could be attributed to myelin integrity, axonal diameter, axonal density, less coherent orientation of axons, etc. Higher RD is however more specific to myelin loss, and lower AD to axonal degradation (though there are exceptions; see Solowij et al., 2017; Aung et al., 2013). ^{g,f} Refers to the quality assessment done by two independent raters (see 'Quality assessment' for more details). Represents a good (≥ 7.5) or a fair (4-7.5; out of 10) rating respectively.

Reward sensitivity anticipation phase

Bulimia nervosa (BN)

Binge eating disorder (BED)

outcome phase

Bulimia nervosa (BN)

Binge eating disorder (BED)

Cognitive control

Stress

Bulimia nervosa (BN)

Binge eating disorder (BED)

Volumetric

Bulimia nervosa (BN)

Binge eating disorder (BED)

Quality Assessment