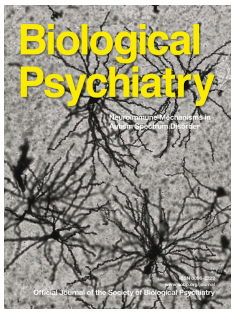
Journal Pre-proof



Multimodal investigations of structural and functional brain alterations in anorexia and bulimia nervosa and their relationships to psychopathology

Xinyang Yu, Lauren Robinson, Marina Bobou, Zuo Zhang, Tobias Banaschewski, Gareth J. Barker, Arun L.W. Bokde, Herta Flor, Antoine Grigis, Hugh Garavan, Penny Gowland, Andreas Heinz, Rüdiger Brühl, Jean-Luc Martinot, Marie-Laure Paillère Martinot, Eric Artiges, Frauke Nees, Dimitri Papadopoulos Orfanos, Hervé Lemaître, Luise Poustka, Sarah Hohmann, Nathalie Holz, Christian Bäuchl, Michael N. Smolka, Argyris Stringaris, Henrik Walter, Robert Whelan, Julia Sinclair, Gunter Schumann, Ulrike Schmidt, Sylvane Desrivières, on behalf of the IMAGEN, STRATIFY and ESTRA Consortia

PII: S0006-3223(24)01759-1

DOI: https://doi.org/10.1016/j.biopsych.2024.11.008

Reference: BPS 15651

To appear in: *Biological Psychiatry*

Received Date: 14 November 2023

Revised Date: 10 October 2024

Accepted Date: 10 November 2024

Please cite this article as: Yu X., Robinson L., Bobou M., Zhang Z., Banaschewski T., Barker G.J., Bokde A.L.W., Flor H., Grigis A., Garavan H., Gowland P., Heinz A., Brühl R., Martinot J.-L., Paillère Martinot M.-L., Artiges E., Nees F., Orfanos D.P., Lemaître H., Poustka L., Hohmann S., Holz N., Bäuchl C., Smolka M.N., Stringaris A., Walter H., Whelan R., Sinclair J., Schumann G., Schmidt U., Desrivières S. & on behalf of the IMAGEN, STRATIFY and ESTRA Consortia, Multimodal investigations of structural and functional brain alterations in anorexia and bulimia nervosa and their relationships to psychopathology, *Biological Psychiatry* (2024), doi: https://doi.org/10.1016/j.biopsych.2024.11.008.

during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Multimodal investigations of structural and functional brain alterations in anorexia and bulimia nervosa and their relationships to psychopathology

Authors

Xinyang Yu[1], Lauren Robinson[2,3,4], Marina Bobou[1,5], Zuo Zhang[1], Tobias Banaschewski[6], Gareth J. Barker[7], Arun L.W. Bokde[8], Herta Flor[9,10], Antoine Grigis[11], Hugh Garavan[12], Penny Gowland[13], Andreas Heinz[14], Rüdiger Brühl[15], Jean-Luc Martinot[16], Marie-Laure Paillère Martinot[16,17], Eric Artiges[16,18], Frauke Nees[6,9,19], Dimitri Papadopoulos Orfanos[11], Hervé Lemaître[11,20], Luise Poustka[21], Sarah Hohmann[22], Nathalie Holz[6], Christian Bäuchl[23,24], Michael N. Smolka[25], Argyris Stringaris[5], Henrik Walter[14], Robert Whelan[26], Julia Sinclair[27], Gunter Schumann[28,29], Ulrike Schmidt[2,3], Sylvane Desrivières[1], on behalf of the IMAGEN, STRATIFY, and ESTRA Consortia

[1]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [2]Department of Psychological Medicine, Centre for Research in Eating and Weight Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [3]South London and Maudsley NHS Foundation Trust, London, UK; [4]Oxford Institute of Clinical Psychology Training and Research, Oxford University, Oxford, UK; [5]Division of Psychiatry and Department of Clinical, Educational & Health Psychology, University College London, London, UK; [6]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [7]Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [8]Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin,

Ireland; [9]Institute of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [10]Department of Psychology, School of Social Sciences, University of Mannheim, Mannheim, Germany; [11]NeuroSpin, CEA, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France; [12]Departments of Psychiatry and Psychology, University of Vermont, Burlington, VT, USA; [13]Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, Nottingham, UK; [14]Department of Psychiatry and Psychotherapy CCM, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [15]Physikalisch-Technische Bundesanstalt (PTB), Braunschweig and Berlin, Germany; [16]Institut National de la Santé et de la Recherche Médicale, INSERM U1299 "Developmental trajectories & psychiatry"; Université Paris-Saclay, Université Paris Cité, Ecole Normale supérieure Paris-Saclay, CNRS; Centre Borelli UMR9010; Gif-sur-Yvette, France; [17]AP-HP. Sorbonne Université, Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Paris, France; [18]Psychiatry Department, EPS Barthélémy Durand, Etampes, France; [19]Institute of Medical Psychology and Medical Sociology, University Medical Center Schleswig Holstein, Kiel University, Kiel, Germany; [20]Institut des Maladies Neurodégénératives, UMR 5293, CNRS, CEA, Université de Bordeaux, 33076 Bordeaux, France; [21]Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, von-Siebold-Str. 5, 37075, Göttingen, Germany; [22]Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [23]Faculty of Psychology, Technische Universität Dresden, Dresden, Germany; [24]Department of Psychiatry, Technische Universität Dresden, Dresden, Germany; [25]Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany; [26]School of Psychology and Global Brain Health Institute,

Trinity College Dublin, Ireland; [27]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; [28]Centre for Population Neuroscience and Stratified Medicine (PONS), Department of Psychiatry and Neuroscience, Charité Universitätsmedizin Berlin, Germany; [29]Centre for Population Neuroscience and Precision Medicine (PONS), Institute for Science and Technology of Brain-inspired Intelligence (ISTBI), Fudan University, Shanghai, China

***Corresponding author:** Sylvane Desrivières (sylvane.desrivieres@kcl.ac.uk)

Running Title: sMRI- and fMRI-related alterations in AN and BN

Keywords: Eating disorder; anorexia nervosa; bulimia nervosa; magnetic resonance imaging; cognitive restraint; reward processing

Abstract

Background: Neurobiological understanding of eating disorders (EDs) is limited. This study presents the first comparative multi-modal magnetic resonance imaging (MRI) assessments of anorexia nervosa (AN) and bulimia nervosa (BN), uncovering neurobiological differences associated with these disorders.

Methods: This female case-control study included 57 healthy controls (HC) and 130 participants with EDs (BN and AN subtypes). Structural and functional MRI assessed gray matter volume (GMV), cortical thickness (CT), and task-based activities related to reward processing, social-emotional functioning, and response inhibition. Whole-brain group differences were correlated to ED psychopathology.

Results: Significant structural differences were observed in the ED group compared to HCs, including reduced GMV in the left lateral orbitofrontal cortex and lower CT in the left rostral middle frontal gyrus and precuneus, after adjusting for BMI. Specific structural alterations were only evident in AN subgroups. GMV reductions in the orbitofrontal cortex were linked to impulsivity, while lower CT in the frontal gyrus correlated with cognitive restraint in eating, suggesting these regions may play key roles in ED psychopathology. Functional MRI also revealed notable differences. During reward anticipation, participants with EDs exhibited deactivations in the cerebellum and right superior frontal gyrus, alongside reduced activation in the left lingual gyrus. These functional changes were associated with heightened neuroticism. Mediation analyses suggested that starvation-related GMV reductions in EDs disrupt reward-related brain function, increase neuroticism, and reinforce cognitive restraint, likely contributing to the persistence of ED symptoms.

Conclusions: These findings illuminate key neurobehavioral mechanisms underlying EDs, pointing to potential brain-based targets for developing specialized treatment.

Introduction

Eating disorders (EDs) are serious and hard-to-treat psychiatric disorders with high mortality and significant disability (1). The two main diagnostic subtypes are anorexia nervosa (AN) – characterized by an intense fear of weight gain or disturbed body image – and bulimia nervosa (BN) – characterized by recurrent episodes of binge eating and compensatory behaviors to prevent weight gain (2,3). Common psychological comorbidities, such as mood and anxiety disorders, contribute to adverse outcomes of EDs (4,5). Research into the neurobiological underpinnings of EDs has expanded in recent years (6,7), holding promise for developing more effective treatments (6,8). Structural (sMRI) and functional (fMRI) magnetic resonance imaging have yielded important insights into the neurobiology of EDs, although most studies have focused on AN, limiting our understanding.

Meta-analyses of sMRI have demonstrated globally reduced gray matter volumes (GMV) in AN compared with healthy controls (HCs; 8–10), with the largest effects observed in the thalamus (11). Similarly, reduced cortical thickness (CT) in AN, predominantly in the parietal and occipital lobes (11–13), with fewer affected regions in the frontal lobes (11,14). Findings in BN are conflicting. Some studies reported lower GMVs in the inferior frontal gyrus (IFG) (15) or caudate (16), while others found higher GMVs in the medial orbitofrontal cortex (mOFC) and ventral striatum (17). This inconsistency about the anatomical location and extent of differences may reflect the paucity of studies investigating BN and the fact that, besides one recent study that focused on AN (11), the current literature is based on studies with small sample sizes, assessing either GMV or CT (18).

Task-based fMRI studies suggest that alterations in brain mechanisms of reward, emotional processing, and response inhibition underlie ED behaviors and symptoms (19,20). Particularly,

dysregulations within and/or between limbic and executive frontostriatal circuits has been hypothesized to contribute to extreme eating behaviors in AN and BN, alongside shared comorbid traits, such as personality and anxiety (21), but limited data support this hypothesis. Despite a few studies on reward processing in EDs (22), an imbalance between reward and inhibition has been suggested to characterize these disorders (20). Compared to HCs, AN shows an enhanced ability to delay rewards (23) and low reward reactivity (24), which may contribute to the maintenance of persistent food restriction (25,26). Conversely, BN involves deficits in frontostriatal control circuits, which may lead to diminished inhibitory control (21,27,28), and affect reward-based learning (29). Yet, most studies have focused on AN, rather than BN or the comparisons between AN and BN, and almost none used multi-modal data combining sMRI and fMRI in relation to EDs. In addition, the focus on predefined regions of interest (ROIs) also narrows our knowledge of ED neurobiology.

To address these limitations, we provide here comprehensive, whole-brain characterizations of structural and functional brain alterations in EDs. Our MRI measures include GMV, CT, and blood oxygen level-dependent (BOLD) responses during reward, social-emotional processes, and response inhibition tasks. We performed between-group analyses to distinguish brain signatures that characterize ED and its subtypes, exploring how these brain differences correlate with ED psychopathology.

Methods and materials

Participants

Data were acquired from a female case-control cohort, comprising 57 HCs and participants meeting the diagnostic criteria for AN or BN (N=65/group), according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (2) and the Eating Disorder Diagnostic Scale (30). The clinical sample was recruited through the Eating Disorders Unit at the South London and Maudsley NHS Foundation Trust or via social media for the ESTRA or STRATIFY studies. HCs were recruited during the third follow-up of the IMAGEN study (31). All participants, aged 18-25 and of European ancestry, were recruited in London (**Supplementary Methods**). The ESTRA, STRATIFY, and IMAGEN studies employed identical study procedures to ensure group comparability. Written informed consent was obtained from all participants before their participation.

Psychopathological assessments

Personality traits were assessed using the revised NEO Personality Inventory (32) and Substance Use Risk Profile Scale (33); ED behaviors were measured using the short version of the Three-Factor Eating Questionnaire (34,35), focusing on cognitive restraint (CR), emotional eating (EE) and uncontrolled eating (UE). Comorbid symptoms, including depressive, anxiety symptoms, and harmful drinking were examined using the Patient Health Questionnaire-9 (36), the anxiety section from the Development and Well-Being Assessment (37), and the Alcohol Use Disorders Identification Test (38), respectively (**Supplementary Methods**).

MRI acquisition and preprocessing

The acquisition and preprocessing of sMRI and fMRI data are detailed in **Supplementary Methods**.

sMRI

Our analysis primarily targeted GMV and CT alterations, as GMV reductions are significant and replicable abnormalities in AN (39), and CT is considered biologically informative, and particularly sensitive to structural changes in AN (11,40). To ensure a comprehensive comparison between clinical samples and HCs, we also examined group differences in other surface-based measures (**Supplementary Methods** and **Results**).

fMRI

The analysis incorporated three fMRI paradigms relevant to reinforcement-related behaviors (41), crucial in understanding EDs: the monetary incentive delay (MID) task, emotional face task (EFT), and stop-signal task (SST; **Supplementary Methods**). In the MID task, we contrasted brain activation during the anticipation of a large win vs. anticipation of no win (i.e., reward anticipation), and between feedback of a large and no win (i.e., reward feedback). For the EFT, we contrasted brain activation during viewing of angry faces vs. control stimuli. In the SST, contrasts were chosen between brain activation during a successful stop and a successful go (i.e., successful inhibition) and between a failed stop and a successful go (i.e., unsuccessful inhibition).

Statistical analyses

To analyze differences in demographics, body mass index (BMI), personality traits, ED behaviors, and comorbid symptoms between EDs (AN or BN) and HC, we conducted a one-way analysis of covariance, adjusting for age. The analysis was performed using R version 4.1.0, with *p*-values corrected for multiple comparisons using the Holm-Bonferroni method.

Whole-brain analyses: Whole-brain analyses used generalized linear models (GLMs) in SPM12 to explore differences in sMRI and fMRI across groups, adjusting for age and scanners. In sMRI, whole-brain vertex-wise morphometry analyses examined anatomical differences in voxel- or surface-based measures, including total intracranial volume as an additional covariate for volumetric comparisons. BMI was considered as a covariate to account for its potential influence on structural changes when indicated in the results. In fMRI, whole-brain analyses assessed neural response variations between groups. To address multiple comparisons, cluster-wise family-wise error (FWE) correction was applied at $p < 0.05$, with a height cluster-forming threshold of $p < 0.001$ across the whole brain. Significant clusters identified in the statistical difference maps were neuroanatomically located using the automated anatomical labeling 3 atlas (AAL3; for GMV) or the Desikan-Killiany atlas (for CT). Sensitivity analyses were performed to assess the effects of BMI and comorbid symptoms on brain structural alterations (**Supplementary Methods**).

Regions of interest (ROI)-based analyses: Brain regions demonstrating significant group differences in the whole-brain analyses were selected as ROIs to further investigate their associations with ED-related psychopathology. *P*-values were adjusted for multiple comparisons using the false discovery rate (FDR) method.

Mediation analyses: Reasoning that behavior and personality constructs emerge in response to biological processes occurring in the brain, mediation models were performed to investigate whether ED-related psychopathology mediated the relationships between brain measures and ED diagnoses (AN or BN status). Continuous variables were standardized to z scores. Confidence intervals (CIs) for the mediation effect were estimated using the PROCESS macro

for R (version 4.1.0) and based on 5000 bootstrap samples. PROCESS model 4 was used for simple mediation models, and model 6 for the serial mediation model.

Results

Sample characteristics

Our analysis included 187 participants (65 AN, including 23 restrictive subtype (AN-R) and 42 binge-eating/purging subtype (AN-BP), 65 BN, and 57 HC), excluding some with incomplete neuroimaging data from specific MRI analyses (**Table 1**). As expected, AN had a significantly lower BMI compared to BN and HC. They were also slightly younger than HC (AN = 21.70 ± 2.08 years, HC = 22.63 ± 0.62 years, $p = 0.01$), with no age differences between AN and BN or BN and HC. BN scored higher on emotional eating (EE) and uncontrolled eating (UE) than HC and AN; AN and BN had higher cognitive restraint (CR) than HC. There were also differences in personality traits and comorbid symptoms; neuroticism, hopelessness, depression, and anxiety symptoms were significantly higher in AN and BN than in HC. BN had higher impulsivity and more harmful drinking than the other groups (ps < 0.001).

Neuroanatomical correlates of ED

Whole-brain voxel-wise analyses were run to identify GMV and CT differences across ED groups.

GMV: Compared to HCs, EDs exhibited significantly lower GMVs in 4 clusters with peaks in the bilateral supplementary motor area (SMA), right middle frontal gyrus (MFG, extending to the inferior frontal gyrus, pars orbitalis (IFGorb), left thalamus, and left IFGorb/posterior orbital gyrus (**Fig. 1A; Table S1**). After controlling for BMI, only the cluster in the left IFGorb/lateral orbitofrontal cortex (OFC) remained significant (**Fig. 1B**), suggesting that GMV differences in this region were unlikely due to BMI effects. Analyses of the AN and BN groups separately indicated that most GMV differences in the ED group were driven by AN (**Fig. 1C; Table S1**). In AN, GMV differences in the SMA and thalamus remained

significant after controlling for BMI (**Fig. 1D**). Additionally, smaller GMVs in the left inferior parietal lobule (IPL)/supramarginal gyrus (SMG) and right medial superior frontal gyrus (SFGmedial) were significant.

CT: EDs exhibited smaller thickness in several left-lateralized regions when compared to HCs, including the left rostral MFG, paracentral lobule, lingual gyrus/precuneus, and left middle temporal gyrus (**Table S2**). When controlling for BMI (**Fig. 2A**), CT differences in the left rostral MFG and left precuneus remained significant. Here again, CT differences were largely driven by the AN group, with lower CT in 10 clusters identified in AN (when compared to HCs), including in the left rostral MFG (**Fig. 2B**).

Further analyses of AN subgroups characterized by restrictive (AN-R), or binge-purge (AN-BP) behaviors are reported in **Supplementary Results** and **Tables S1 and S2**. Sensitivity analyses indicated that the observed neuroanatomical correlates were not driven by age, BMI, or other outliers (**Supplementary Results; Table S3)**.

Structural alterations in ED and their relations to eating behaviors and personality

We next investigated if the neuroanatomical differences identified above correlated with eating behaviors (cognitive restraint, CR; emotional eating, EE; uncontrolled eating, UE), personality, and comorbid symptoms in the whole sample. Using brain clusters distinguishing ED or AN from HCs in whole brain analyses as regions of interest (ROIs) and adjusted for BMI (**Table S4**), we found that GMV in the left lateral OFC/IFGorb (differentiating EDs from HCs) were not correlated with eating behaviors but with impulsivity (r = -0.24). GMV in ROIs differentiating AN from HCs associated with CR, notably in the SMA (r = -0.26) and thalamus (r = -0.26). Thickness of the left rostral MFG (differentiating ED and AN from HCs) also negatively associated with CR (r = -0.26, all $p_{Bonferroni} < .05$). CR negatively correlated with

BMI in the ED group (**Fig. 3A**), and BMI partially mediated the relationship between GMV differences in the SMA and thalamus (i.e., AN-related regions) and CR (36.47% mediation; **Fig. 3B)**. Direct relationship (c'= -0.23, p = 5.8×10^{-3}) between GMV in these regions and cognitive restraint still remained, independently of BMI. In contrast, BMI did not mediate the relationship between thickness in the left rostral MFG and CR. These results suggest a role for the left rostral MFG, SMA, and left thalamus in the etiology of EDs, via their effect on cognitive restraint.

Functional alterations in ED

Whole-brain fMRI analyses were conducted to investigate group differences in brain activation patterns related to reward (MID task), social-emotional (EFT) processing, and response inhibition (SST; **Fig. 4**; **Tables S5** and **S6**).

MID task: During reward anticipation (**Fig. 4A; Table S5**), EDs showed deactivations in the bilateral cerebellum (Crus II) and right SFG when compared to HCs, and lower activations in the visual cortex (left lingual gyrus/right calcarine fissure). Comparing AN and BN groups to HCs revealed that differences in cerebellar activations were driven by BN, while lower activations in the left lingual gyrus/right calcarine fissure were driven by AN. In addition, deactivations in the right middle temporal gyrus and triangular part of the left IFG (IFGtriang) were also observed in BN and in AN, lower activations or deactivation in other visual areas (right fusiform gyrus and left middle occipital gyrus (MOG). Lower activation in the left MOG, along with areas in the right frontal cortex, were also found associated with AN-R (**Supplementary Results; Table S6**). During reward feedback, no differences were found when comparing EDs to HCs, although BN had significantly lower activations in the right calcarine fissure/superior occipital gyrus when compared to HCs (**Fig. 4B**; **Table S5**).

EFT: No differences in brain activations were observed between EDs and HCs when they viewed angry faces vs control stimuli. The only significant differences in this task were observed when comparing AN to BN (**Table S5**). When viewing angry faces, participants with AN tended to activate the left insula, while those with BN showed deactivation in this region **(Fig. 4C)**.

SST: No significant group differences were found between ED, AN, or BN groups and HCs. Analyses of AN subgroups revealed differences in AN-R, and AN-BP, when compared to HCs (**Supplementary Results; Table S6**).

The observed alterations were not driven by age, BMI, or other outliers (**Supplementary Results and Table S7)**.

Relationships between task-based brain activation patterns in ED, eating behaviors, and personality

Analyses in the whole sample were conducted to explore relationships between altered brain activations in EDs, eating behaviors, personality, and comorbid symptoms, using brain clusters differentiating ED groups in the fMRI tasks as ROIs. The only brain activations significantly associated with these traits were those identified in the MID task (**Table S8**). During reward anticipation, activations in ED-related ROIs specifically associated with CR, not EE or UE, most significantly in the left lingual/right calcarine fissure (r = -0.29). As for associations with personality, activations during reward anticipation in all ROIs distinguishing EDs from HCs (i.e., cerebellum, left lingual gyrus/right calcarine fissure and right SFG) negatively correlated with neuroticism, not with impulsivity. They were also nominally associated with depression.

In contrast, activations in the left IFGtriang (i.e., ROI deactivated during reward anticipation in BN) negatively correlated with impulsivity (r = -0.30, all $p_{Bonferroni} < .05$).

Mediation analyses revealed that neuroticism fully mediated the relationship between brain activations during reward anticipation in ED-related ROIs (i.e., the bilateral cerebellum, left lingual gyrus, and right SFG) and CR. This mediation was significant when controlling for BMI (**Fig. 5A**).

Relationships between structural alterations, brain activations during reward anticipation, neuroticism, and cognitive restraint

Finally, we investigated whether the relationships between brain responses during reward anticipation, neuroticism, and CR may be related to structural brain alterations associated with ED. For this, we first summed up the GMVs or CTs within ROIs defined by brain regions that differed between groups (i.e., ED vs. HC or AN vs. HC) and investigated their associations with brain activation patterns within ROIs differentiating between groups, in the whole sample. Nominally significant findings were found for GMV, not CT (**Table S9**). These correlations were only observed for ROIs derived from voxel-wise whole-brain analyses that were not corrected for BMI. GMV in regions distinguishing EDs from HCs (i.e., SMA, right MFG, left thalamus, left IFGorb) correlated with brain activations in the left lingual gyrus/right calcarine fissure and right SFG (both ROIs, r = 0.17, $p < 0.05$). GMVs in regions distinguishing AN from HCs (SMA, left thalamus, left SFGmedial, left IFGorb, left olfactory, and right MFG) correlated with brain activations in the left MOG (r = 0.28, p = 0.006).

We next investigated whether lower GMV in these ED- or AN-related brain regions may relate to brain responses during reward anticipation, neuroticism, and CR in two serial mediation

models, whereby brain activations during reward anticipation and neuroticism mediated the relationship between GMV and CR. The model using ED-related ROIs (**Fig. 5B**) was significant: brain activations in the left lingual gyrus/right calcarine fissure and right SFG, along with neuroticism, partially mediated (8.5% mediation) the relationship between GMV in ED-related ROIs and CR. The model using AN-related ROIs (**Fig. 5C**) was also significant, indicating that activity of the left MOG partially and neuroticism mediated (7.1% mediation) the relationship between GMV in AN-related ROIs and CR. In both models, the relationships between GMV and anticipatory brain activations in the MID were dependent on BMI, as the mediating effects were lost after controlling for BMI. This suggests that in ED, lower GMV induced by starvation/low weight influences anticipatory brain responses to rewards and thereby neuroticism and cognitive restraint.

Discussion

This study represents the first multimodal, whole-brain MRI investigation comparing ED participants – including AN subtypes (AN-R and AN-BP) and BN – to healthy controls, highlighting structural and functional brain alterations associated with EDs and their relationships to psychopathological traits. After controlling for BMI, EDs exhibited reduced GMV in the left lateral OFC/IFGorb, which was linked to increased impulsivity, and reduced cortical thickness in the left rostral MFG, associated with cognitive restraint in eating. When analyzed separately, specific structural differences were observed only in the AN subgroups. Functional MRI analyses revealed disrupted anticipatory brain responses to rewards in EDs characterized by deactivations in the cerebellum (driven by BN) and right SFG, as well as decreased activation in the left lingual gyrus (driven by AN). These functional alterations correlated with heightened neuroticism, which fully mediated the relationship between altered reward responses in these regions and cognitive restraint. Serial mediation analyses further demonstrated that BMI-related GMV differences influenced reward anticipation, contributing to elevated neuroticism and cognitive restraint in EDs. These findings elucidate key neurobehavioral mechanisms underlying EDs, offering a promising foundation for the development of targeted, brain-based interventions aimed at addressing specific neurocognitive impairments associated with impulsivity, cognitive restraint, and reward anticipation.

Our analyses comparing participants with ED to controls while controlling for the impact of BMI on brain structure (42), suggest that the lateral OFC/IFGorb and rostral MFG play roles in the pathophysiology of EDs, rather than being the consequence of low weight or starvation. That lower GMV in the OFC correlates with impulsivity aligns with studies showing that patients with damage to this region are more impulsive (43). The lateral OFC, functionally connected with the IFG (44), is involved in flexible decision-making by associating sensory

stimuli with predicted outcomes (45,46). In relation to eating behaviors, studies suggest that the OFC assigns reward values to food, thereby guiding behavioral choices (47). For example, in rodent studies, activation of feeding-responsive neurons in the OFC causes increased feeding behavior (48), which may contribute to weight gain and obesity by biasing consumption toward highly palatable and rewarding foods.

Regarding the left rostral MFG, reduced thickness in this region negatively correlated with cognitive restraint, independently of BMI. This region is associated with craving regulation for food or substances like nicotine (49,50). Interestingly, food cravings are more closely associated with mood and emotional eating than food deprivation and cognitive restraint (51). The lower thickness in the left rostral MFG in EDs, notably in the AN-BP subtype, may thus underlie difficulties in regulating craving, potentially leading to the need for greater cognitive restraint, the conscious restriction of food intake to control body weight and shape.

Our study also expands existing knowledge by identifying structural alterations in fronto-temporo-occipital areas distinguishing AN subtypes from HCs. Notably, in addition to the alterations in the left rostral MFG noted above, lower volumes in the thalamus – a hub for brain function and connectivity in BN (52) and parietal regions (parietal lobule and left supramarginal gyrus) were specific to AN-BP. In contrast, lower volumetric alterations in frontal regions (SMA and SFG), which integrate sensory and reward information (53,54), and fusiform and lingual gyri, involved in visual information processing and abnormal body image perception (55,56), were specific to AN-R. The volumes of the SMA and left thalamus, lower in AN, were associated with cognitive restraint, even after controlling for BMI effects, suggesting a role for these brain regions in the etiology of EDs. In line with our expectations (57), as cognitive restraint increased, BMI decreased. Accordingly, cognitive restraint was

particularly pronounced in AN, possibly due to pronounced avoidance of food driven by intense fears of weight gain and a preoccupation with body shape, leading to low BMI. However, given the two dimensions of dietary restraint (58), cognitive restraint may also create food cravings that may lead to binge or overeating in some individuals (e.g., AN-BP). Thus, the identified links between SMA volume and AN-R and thalamus volume and AN-R raise the interesting possibility that these two brain regions may relate to distinct aspects of cognitive restraint.

Functionally, the disrupted anticipatory brain responses to rewards in the cerebellum observed in EDs, notably BN, support a prominent role for this region in feeding behavior. Lack of cerebellar activation in anticipatory responses to food has been associated with hyperphagia, and disruption of a cerebellum-driven satiety network controlling striatal dopamine release is proposed as an underlying mechanism (59). Our finding of lower cerebellar activation in ED/BN supports the cerebellum's role in reducing the reward value of food intake upon satiety and contributing to overeating. Alternatively, the bilateral Crus I/II deactivations seen during reward anticipation in BN may reflect deficits in working memory (60). In contrast, disrupted anticipatory brain responses in the lingual gyrus were driven by AN, characterized by disrupted activation patterns in occipitotemporal visual areas. These regions are activated by visual craving-inducing cues such as drugs (61), and activation of the lingual gyrus has been inversely related to food craving in individuals with obesity, possibly reflecting increased attentional or visual processing efforts to reduce craving (62).

Our findings suggest that alterations in GMVs in brain regions structurally affected by EDs influence cognitive restraint, partly through their impact on anticipatory brain activations and neuroticism. This relationship is both novel and intriguing. Notably, neuroticism fully mediated

the relationship between anticipatory brain activations in ED-related regions and cognitive restraint, independently of BMI. However, the influence of GMV differences on cognitive restraint, through brain activation and neuroticism, was related to BMI. This suggests that in EDs, GMV alterations caused by starvation or low weight disrupt reward-related brain function and heighten neuroticism, reinforcing cognitive restraint. This mechanism likely contributes to the maintenance of ED symptoms. These findings support a cognitive-behavioral theory of AN, which posits that once the disorder begins, a feedback loop is triggered wherein starvation reinforces further dietary restriction, making the disorder self-perpetuating (63).

While our multimodal investigation into EDs offers valuable insights, several limitations should be acknowledged. First, our study included only female participants of white ethnicity, limiting the generalizability of the findings to more diverse gender and ethnic populations. Second, the age range of participants was relatively narrow, which confines the applicability of our results to the earlier stages of EDs, despite these disorders often having a prolonged course. Although we controlled for age in our analyses, significant age differences between the controls and ED participants were noted. Future studies should aim for closer age matching to reduce potential confounding effects. Third, the lack of randomization in the task order may have influenced our results, as negative affective processes could have impaired subsequent cognitive performance (64). Fourth, while mediation analyses were used to explore relationships between brain structure, personality traits, and ED behaviors, the cross-sectional nature of our data means these findings should be interpreted with caution, without inferring causality. Finally, our study did not account for potential confounding variables such as illness duration, medication or treatment status, and socioeconomic factors, all of which should be considered when interpreting our results.

Conclusion

Our study identified critical neurobehavioral mechanisms underlying EDs, shedding light on both shared and distinct features across different ED subtypes. Specific structural and functional alterations observed in ED subgroups provide a more nuanced understanding of the complexity of these disorders. Key brain regions, such as the left orbitofrontal cortex, rostral middle frontal gyrus, cerebellum, and left lingual gyrus, were found to play significant roles in ED pathology. These findings highlight potential novel brain-based targets for developing specialized and effective interventions for EDs.

Acknowledgments

This work received support from the following sources: the Medical Research Council and Medical Research Foundation ('ESTRA'- Neurobiological underpinning of eating disorders: integrative biopsychosocial longitudinal analyses in adolescents: grant MR/R00465X/; 'ESTRA' - Establishing causal relationships between biopsychosocial predictors and correlates of eating disorders and their mediation by neural pathways: grants MR/S020306/1), the European Union-funded FP6 Integrated Project IMAGEN (LSHM-CT- 2007-037286), the Horizon 2020 funded ERC Advanced Grant 'STRATIFY' (Brain network based stratification of reinforcement-related disorders) (695313), the Medical Research Council (grant MR/W002418/1: 'Eating Disorders: Delineating illness and recovery trajectories to inform personalized prevention and early intervention in young people (EDIFY)', the National Institute for Health and Care Research (NIHR) Maudsley Biomedical Research Centre (BRC) and the National Institutes of Health (NIH) (Consortium grant 5U54EB020403-05-'ENIGMA') and National Institute on Aging (NIA) 1R56AG058854-02-'ENIGMA World Aging Center'). This work was co-funded by UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee (10041392 and 10038599) as part of the Horizon Europe HORIZON-HLTH-2021-STAYHLTH-01 under European Union grant agreement number 101057429 (environMENTAL). Xinyang Yu thanks the financial support from the China Scholarship Council (CSC No.202104910099). Zuo Zhang is supported by a fellowship from the Medical Research Foundation (MRF-058-0014-F-ZHAN-C0866).

Further support was provided by grants from: the Human Brain Project (HBP SGA 2, 785907, and HBP SGA 3, 945539), the Medical Research Council Grant 'c-VEDA' (Consortium on Vulnerability to Externalizing Disorders and Addictions) (MR/N000390/1), the NIH (R01DA049238, A decentralized macro and micro gene-by-environment interaction analysis of substance use behavior and its brain biomarkers), the Bundesministeriumfür Bildung und

Forschung (BMBF grants 01GS08152; 01EV0711; Forschungsnetz AERIAL 01EE1406A, 01EE1406B; Forschungsnetz IMAC-Mind 01GL1745B), the Deutsche Forschungsgemeinschaft (DFG grants SM 80/7-2, SFB 940, TRR 265, NE 1383/14-1), NSFC grant 82150710554, the ANR (ANR-12-SAMA-0004, AAPG2019 - GeBra), the Eranet Neuron (AF12-NEUR0008-01 - WM2NA; and ANR-18-NEUR00002-01 - ADORe), the Fondation de France (00081242), the Fondation pour la Recherche Médicale (DPA20140629802), the Mission Interministérielle de Lutte-contre-les-Drogues-et-les-Conduites-Addictives (MILDECA), the Assistance-Publique-Hôpitaux-de-Paris and INSERM (interface grant), Paris Sud University IDEX 2012, the Fondation de l'Avenir (grant AP-RM-17-013), the Fédération pour la Recherche sur le Cerveau; the National Institutes of Health, Science Foundation Ireland (16/ERCD/3797), U.S.A. (Axon, Testosterone and Mental Health during Adolescence; RO1 MH085772-01A1).

ESTRA Consortium

Lauren Robinson, Marina Bobou, Zuo Zhang, Gareth J. Barker, Gunter Schumann,
Ulrike Schmidt, Sylvane Desrivières

IMAGEN Consortium

Tobias Banaschewski, Gareth J. Barker, Arun L. W. Bokde, Christian Büchel, Herta Flor, Antoine Grigis, Hugh Garavan, Penny Gowland, Andreas Heinz, Jean-Luc Martinot, Marie-Laure Paillère Martinot, Frauke Nees, Dimitri Papadopoulos Orfanos, Luise Poustka, Michael N. Smolka, Henrik Walter, Robert Whelan, Sylvane Desrivières, Gunter Schumann

STRATIFY Consortium

Marina Bobou, Zuo Zhang, Lauren Robinson, Gareth J. Barker, Arun L. W. Bokde, Hervé Lemaître, Frauke Nees, Dimitri Papadopoulos Orfanos, Ulrike Schmidt, Julia Sinclair, Argyris Stringaris, Henrik Walter, Robert Whelan, Sylvane Desrivières, Gunter Schumann

Disclosures

Tobias Banaschewski served in an advisory or consultancy role for eye level, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Janssen, Medice and Takeda, and royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships. Dr. Barker received honoraria from General Electric Healthcare for teaching on scanner programming courses. Dr. Poustka served in an advisory or consultancy role for Roche and Viforpharm and received speaker's fee by Shire. She received royalties from Hogrefe, Kohlhammer and Schattauer. The present work is unrelated to the above grants and relationships. The other authors report no biomedical financial interests or potential conflicts of interest.

Supplement Description:
Supplemental Methods, Results, Figs S1-S3, Tables S1-S10

References

1. van Hoeken D, Hoek HW (2020): Review of the burden of eating disorders: mortality, disability, costs, quality of life, and family burden. *Curr Opin Psychiatry* 33: 521–527.

2. American Psychiatric Association (2013): *Diagnostic and Statistical Manual of Mental Disorders*. Arlington, VA: American Psychiatric Publishing.

3. Treasure J, Duarte TA, Schmidt U (2020): Eating disorders. *The Lancet* 395: 899–911.

4. Robinson L, Zhang Z, Jia T, Bobou M, Roach A, Campbell I, *et al.* (2020): Association of genetic and phenotypic assessments with onset of disordered eating behaviors and comorbid mental health problems among adolescents. *JAMA Netw Open* 3: e2026874.

5. Van Alsten SC, Duncan AE (2020): Lifetime patterns of comorbidity in eating disorders: An approach using sequence analysis. *Eur Eat Disord Rev* 28: 709–723.

6. Frank GKW, Shott ME, DeGuzman MC (2019): The neurobiology of eating disorders. *Child Adolesc Psychiatr Clin N Am* 28: 629–640.

7. Zhang Z, Robinson L, Jia T, Quinlan EB, Tay N, Chu C, *et al.* (2020): Development of disordered eating behaviors and comorbid depressive symptoms in adolescence: Neural and psychopathological predictors. *Biol Psychiatry* 90: 853–862.

8. Frank GKW, Favaro A, Marsh R, Ehrlich S, Lawson EA (2018): Toward valid and reliable brain imaging results in eating disorders. *Int J Eat Disord* 51: 250–261.

9. Fonville L, Giampietro V, Williams SCR, Simmons A, Tchanturia K (2014): Alterations in brain structure in adults with anorexia nervosa and the impact of illness duration. *Psychol Med* 44: 1965–1975.

10. Van den Eynde F, Suda M, Broadbent H, Guillaume S, Van den Eynde M, Steiger H, *et al.* (2012): Structural magnetic resonance imaging in eating disorders: A systematic review of voxel-based morphometry studies. *Eur Eat Disord Rev* 20: 94–105.

11. Walton E, Bernardoni F, Batury V-L, Bahnsen K, Larivière S, Abbate-Daga G, *et al.* (2022): Brain structure in acutely underweight and partially weight-restored Individuals with anorexia nervosa: A coordinated analysis by the ENIGMA eating disorders working group. *Biol Psychiatry* 92: 730–738.

12. Castro-Fornieles J, de la Serna E, Calvo A, Pariente J, Andrés-Perpiña S, Plana MT, *et al.* (2021): Cortical thickness 20 years after diagnosis of anorexia nervosa during adolescence. *Eur Arch Psychiatry Clin Neurosci* 271: 1133–1139.

13. Fuglset TS, Endestad T, Hilland E, Bang L, Tamnes CK, Landrø NI, Rø Ø (2016): Brain volumes and regional cortical thickness in young females with anorexia nervosa. *BMC Psychiatry* 16: 404.

14. Bär K-J, de la Cruz F, Berger S, Schultz CC, Wagner G (2015): Structural and functional differences in the cingulate cortex relate to disease severity in anorexia nervosa. *J Psychiatry Neurosci* 40: 269–279.

15. Hoffman GW, Ellinwood EH, Rockwell WJ, Herfkens RJ, Nishita JK, Guthrie LF (1990): Brain T1 measured by magnetic resonance imaging in bulimia. *Biol Psychiatry* 27: 116–119.

16. Coutinho J, Ramos AF, Maia L, Castro L, Conceição E, Geliebter A, *et al.* (2015): Volumetric alterations in the nucleus accumbens and caudate nucleus in bulimia nervosa: a structural magnetic resonance imaging study. *Int J Eat Disord* 48: 206–214.

17. Schäfer A, Vaitl D, Schienle A (2010): Regional grey matter volume abnormalities in bulimia nervosa and binge-eating disorder. *NeuroImage* 50: 639–643.

18. Donnelly B, Touyz S, Hay P, Burton A, Russell J, Caterson I (2018): Neuroimaging in bulimia nervosa and binge eating disorder: a systematic review. *J Eat Disord* 6. https://doi.org/10.1186/s40337-018-0187-1

19. Friederich H-C, Wu M, Simon JJ, Herzog W (2013): Neurocircuit function in eating disorders. *Int J Eat Disord* 46: 425–432.

20. Wierenga CE, Ely A, Bischoff-Grethe A, Bailer UF, Simmons AN, Kaye WH (2014): Are extremes of consumption in eating disorders related to an altered balance between reward and inhibition? *Front Behav Neurosci* 8: 410.

21. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Wagner A, Bischoff-Grethe A (2013): Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? *Biol Psychiatry* 73: 836–842.

22. Yu X, Desrivières S (2023): Altered anticipatory brain responses in eating disorders: A neuroimaging meta-analysis. *Eur Eat Disord Rev* 31: 363–376.

23. Steinglass J, Albano AM, Simpson HB, Carpenter K, Schebendach J, Attia E (2012): Fear of food as a treatment target: exposure and response prevention for anorexia nervosa in an open series. *Int J Eat Disord* 45: 615–621.

24. Harrison A, O'Brien N, Lopez C, Treasure J (2010): Sensitivity to reward and punishment in eating disorders. *Psychiatry Res* 177: 1–11.

25. Keating C, Tilbrook AJ, Rossell SL, Enticott PG, Fitzgerald PB (2012): Reward processing in anorexia nervosa. *Neuropsychologia* 50: 567–575.

26. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A (2013): Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends Neurosci* 36: 110–120.

27. Marsh R, Steinglass JE, Gerber AJ, Graziano O'Leary K, Wang Z, Murphy D, *et al.* (2009): Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. *Arch Gen Psychiatry* 66: 51–63.

28. Marsh R, Horga G, Wang Z, Wang P, Klahr KW, Berner LA, *et al.* (2011): An fMRI Study of Self-Regulatory Control and Conflict Resolution in Adolescents With Bulimia Nervosa. *Am J Psychiatry* 168: 1210–1220.

29. Berner LA, Marsh R (2014): Frontostriatal circuits and the development of bulimia nervosa. *Front Behav Neurosci* 8: 395.

30. Stice E, Telch CF, Rizvi SL (2000): Development and validation of the Eating Disorder Diagnostic Scale: a brief self-report measure of anorexia, bulimia, and binge-eating disorder. *Psychol Assess* 12: 123–131.

31. Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Büchel C, *et al.* (2010): The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. *Mol Psychiatry* 15: 1128–1139.

32. Costa Jr. PT, McCrae RR (2008): The Revised NEO Personality Inventory (NEO-PI-R). *The SAGE Handbook of Personality Theory and Assessment, Vol 2: Personality Measurement and Testing*. Thousand Oaks, CA, US: Sage Publications, Inc, pp 179–198.

33. Woicik PA, Stewart SH, Pihl RO, Conrod PJ (2009): The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles. *Addict Behav* 34: 1042–1055.

34. Anglé S, Engblom J, Eriksson T, Kautiainen S, Saha M-T, Lindfors P, *et al.* (2009): Three factor eating questionnaire-R18 as a measure of cognitive restraint, uncontrolled eating and emotional eating in a sample of young Finnish females. *Int J Behav Nutr Phys Act* 6: 41.

35. Karlsson J, Persson L-O, Sjöström L, Sullivan M (2000): Psychometric properties and factor structure of the Three-Factor Eating Questionnaire (TFEQ) in obese men and

women. Results from the Swedish Obese Subjects (SOS) study. *Int J Obes* 24: 1715–1725.

36. Kroenke K, Spitzer RL, Williams JB (2001): The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 16: 606–613.

37. Goodman R, Ford T, Richards H, Gatward R, Meltzer H (2000): The development and well-being assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* 41: 645–655.

38. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M (1993): Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addict Abingdon Engl* 88: 791–804.

39. Zhang S, Wang W, Su X, Kemp GJ, Yang X, Su J, *et al.* (2018): Psychoradiological investigations of gray matter alterations in patients with anorexia nervosa. *Transl Psychiatry* 8: 1–11.

40. King JA, Geisler D, Ritschel F, Boehm I, Seidel M, Roschinski B, *et al.* (2015): Global cortical thinning in acute anorexia nervosa normalizes following long-term weight restoration. *Biol Psychiatry* 77: 624–632.

41. Jia T, Ing A, Quinlan EB, Tay N, Luo Q, Francesca B, *et al.* (2020): Neurobehavioural characterisation and stratification of reinforcement-related behaviour. *Nat Hum Behav* 4: 544–558.

42. Gómez-Apo E, Mondragón-Maya A, Ferrari-Díaz M, Silva-Pereyra J (2021): Structural Brain Changes Associated with Overweight and Obesity. *J Obes* 2021: 6613385.

43. Berlin HA, Rolls ET, Kischka U (2004): Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain J Neurol* 127: 1108–1126.

44. Kahnt T, Chang LJ, Park SQ, Heinzle J, Haynes J-D (2012): Connectivity-based parcellation of the human orbitofrontal cortex. *J Neurosci Off J Soc Neurosci* 32: 6240–6250.

45. Banerjee A, Parente G, Teutsch J, Lewis C, Voigt FF, Helmchen F (2020): Value-guided remapping of sensory cortex by lateral orbitofrontal cortex. *Nature* 585: 245–250.

46. Wang BA, Veismann M, Banerjee A, Pleger B (2023): Human orbitofrontal cortex signals decision outcomes to sensory cortex during behavioral adaptations. *Nat Commun* 14: 3552.

47. Azevedo EP, Ivan VJ, Friedman JM, Stern SA (2022): Higher-Order Inputs Involved in Appetite Control. *Biol Psychiatry* 91: 869–878.

48. Jennings JH, Kim CK, Marshel JH, Raffiee M, Ye L, Quirin S, *et al.* (2019): Interacting neural ensembles in orbitofrontal cortex for social and feeding behaviour. *Nature* 565: 645–649.

49. Chase HW, Eickhoff SB, Laird AR, Hogarth L (2011): The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis. *Biol Psychiatry* 70: 785–793.

50. Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN (2010): Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci U S A* 107: 14811–14816.

51. Rodin J, Mancuso J, Granger J, Nelbach E (1991): Food cravings in relation to body mass index, restraint and estradiol levels: A repeated measures study in healthy women. *Appetite* 17: 177–185.

52. Wang J, Wu G, Wang M, Li W, Wang Y, Ren X, *et al.* (2023): Exploring the thalamus: a crucial hub for brain function and communication in patients with bulimia nervosa. *J Eat Disord* 11: 207.

53. Wallis JD (2007): Orbitofrontal cortex and its contribution to decision-making. *Annu Rev Neurosci* 30: 31–56.

54. Kahnt T, Heinzle J, Park SQ, Haynes J-D (2010): The neural code of reward anticipation in human orbitofrontal cortex. *Proc Natl Acad Sci U S A* 107: 6010–6015.

55. Tose K, Takamura T, Isobe M, Hirano Y, Sato Y, Kodama N, *et al.* (2024): Systematic reduction of gray matter volume in anorexia nervosa, but relative enlargement with clinical symptoms in the prefrontal and posterior insular cortices: a multicenter neuroimaging study. *Mol Psychiatry* 1–11.

56. Suchan B, Busch M, Schulte D, Grönermeyer D, Herpertz S, Vocks S (2010): Reduction of gray matter density in the extrastriate body area in women with anorexia nervosa. *Behav Brain Res* 206: 63–67.

57. Bryant EJ, Rehman J, Pepper LB, Walters ER (2019): Obesity and Eating Disturbance: the Role of TFEQ Restraint and Disinhibition. *Curr Obes Rep* 8: 363–372.

58. Westenhoefer J, Stunkard AJ, Pudel V (1999): Validation of the flexible and rigid control dimensions of dietary restraint. *Int J Eat Disord* 26: 53–64.

59. Low AYT, Goldstein N, Gaunt JR, Huang K-P, Zainolabidin N, Yip AKK, *et al.* (2021): Reverse-translational identification of a cerebellar satiation network. *Nature* 600: 269–273.

60. Schmahmann JD (2019): The cerebellum and cognition. *Neurosci Lett* 688: 62–75.

61. Hanlon CA, Dowdle LT, Naselaris T, Canterberry M, Cortese BM (2014): Visual cortex activation to drug cues: a meta-analysis of functional neuroimaging papers in addiction and substance abuse literature. *Drug Alcohol Depend* 143: 206–212.

62. Stopyra MA, Friederich H-C, Lavandier N, Mönning E, Bendszus M, Herzog W, Simon JJ (2021): Homeostasis and food craving in obesity: a functional MRI study. *Int J Obes 2005* 45: 2464–2470.

63. Fairburn CG, Shafran R, Cooper Z (1999): A cognitive behavioural theory of anorexia nervosa. *Behav Res Ther* 37: 1–13.

64. Baumeister RF, Bratslavsky E, Muraven M, Tice DM (1998): Ego depletion: is the active self a limited resource? *J Pers Soc Psychol* 74: 1252–1265.

Figure Legends

Fig. 1. Regional differences in gray matter volume (GMV) between ED (AN and BN) and HC. **A.** Brain regions showing significant differences in whole-brain analyses when comparing ED with HC. **B.** GMV differences between ED and HC, adjusted for BMI. **C.** GMV differences between AN and HC. **D.** GMV differences between AN and HC, adjusted for BMI. No volumetric differences were found between AN and BN when controlled for BMI, and no differences were found between BN and HC. The images illustrate views from the left and right brain hemispheres, the top rows being lateral, the middle medial, the bottom, anterior and posterior. The middle column displays superior and inferior views of the brain. The color bar indicates T values. All analyses were adjusted for age, scanning sites and total intracranial volume. Cluster-level $p_{FWE} < 0.05$ was used as significance threshold for all comparisons.

Fig. 2. Regional differences in cortical thickness (CT) between ED (AN and BN) and HC, when controlled for BMI. **A.** Brain regions with significant differences in whole brain analyses when comparing ED with HC. **B.** CT differences between AN and HC. The color bar indicates T values. All analyses were adjusted for age and scanning sites. Cluster-level $p_{FWE} < 0.05$ was used as significance threshold for all comparisons.

Fig. 3. A. Correlation between cognitive restraint (CR) and BMI. The analysis was adjusted for age and recruitment sites. **B.** Mediation analyses examining relationships between lower GMVs in the bilateral supplementary motor area and bilateral thalamus (the regions differentiated AN from HC), BMI and CR. These analyses indicated that BMI partially mediated the relationships between GMV changes and CR.

Fig. 4. Group differences in brain activity between ED (AN and BN) and HC groups in three functional MRI tasks. Cluster-level $p_{FWE} < 0.05$ was used as significance threshold for all comparisons. **A.** Differences in brain activation during the reward anticipation phase (anticipation of a large reward vs. anticipation of no reward) in the monetary incentive delay (MID) task when comparing ED to HC (top panel), AN to HC (middle panel), and BN to HC (bottom panel). No differences were found between AN and BN groups. **B.** Group differences between BN and HC during the reward feedback phase (feedback of large reward vs no reward) in the MID task. No other differences between groups were found in this contrast. **C.** Group differences between AN and BN in the left insula when viewing angry faces vs control stimuli in the emotional face task (EFT). No other group differences were found in this task. No group differences were found among these groups in the stop-signal task. All analyses were adjusted for age and scanning sites. The error bars indicate standard error. **, $p < 0.01$; ***, $p < 0.001$.

Fig. 5. A. Neuroticism as mediator for the relationship between brain deactivations during reward anticipation, in ROIs differentiating ED from HC, and CR. **B.** Serial mediation analyses in which brain activation patterns distinguishing ED from HCs (i.e., in the left lingual gyrus and right superior frontal gyrus) and neuroticism are tested as mediators for the relationship between GMV in ROIs differentiating ED from HC, and CR. **C.** Serial mediation analyses investigating brain activation patterns distinguishing AN from HCs (i.e., in the left middle occipital gyrus) and neuroticism as mediators for the relationship between GMV in ROIs differentiating AN from HCs, and CR. Analyses were conducted in the whole sample. Model in **a** was controlled for age, scanning sites, and BMI. Models in **B** and **C** were adjusted for age, scanning sites, and TIV, and were no longer significant when considering the effect of BMI.

Table legends

Table 1. Participants' characteristics stratified by analyses.

Table 1. Participants' characteristics stratified by analyses.

	HC	AN	BN	*F*	*p*	Post hoc analyses					
	Mean (SD)	Mean (SD)	Mean (SD)			AN vs HC		BN vs HC		AN vs BN	
Whole sample											
Sample size (N)	57	65	65			*p*	95% CI	*p*	95% CI	*p*	95% CI
Age: mean (SD); range	22.63 (0.62); 21.98-24.79	21.70 (2.08); 18.11-26.19	22.21 (2.01); 18.74-28.00	4.42	0.01	0.01	-1.69 – -0.17	0.54	-1.18 – 0.33	0.27	-1.23 – 0.21
BMI: mean (SD); range	25.24 (5.46); 18.35-45.96	16.92 (2.83); 13.06-21.92	24.06 (3.87); 18.79-36.06	70.17	2.40×10^{-13}	1.04×10^{-20}	-10.14 – -6.41	0.37	-2.99 – 0.66	1.11×10^{-17}	-8.88 – -5.34
Eating behaviors (TFEQ)											
Cognitive restraint	14.58 (4.23)	22.43 (3.56)	18.75 (4.47)	52.78	7.98×10^{-19}	2.31×10^{-19}	6.00 – 9.70	2.59×10^{-7}	2.37 – 5.98	3.00×10^{-6}	1.92 – 5.44
Emotional eating	6.79 (2.58)	5.98 (2.66)	9.94 (2.13)	48.60	1.18×10^{-17}	0.08	-2.11 – 0.09	2.24×10^{-10}	2.00 – 4.15	5.41×10^{-17}	-5.13 – -3.04
Uncontrolled eating	19.93 (5.85)	19.72 (6.26)	27.08 (5.41)	33.63	3.64×10^{-13}	1.00	-3.22 – 2.01	1.23×10^{-9}	4.44 – 9.56	1.68×10^{-11}	-10.10 – -5.11
Personality: NEO-PI-R											
Neuroticism	1.84 (0.58)	2.99 (0.62)	2.85 (0.65)	55.97	1.08×10^{-19}	1.68×10^{-17}	0.82 – 1.37	1.87×10^{-15}	0.72 – 1.26	1.00	-0.16 – 0.37
Extraversion	2.46 (0.57)	1.98 (0.66)	2.29 (0.61)	9.07	1.76×10^{-4}	1.49×10^{-4}	-0.75 – -0.20	0.45	-0.43 – 0.11	0.013	-0.58 – 0.05
Openness	2.45 (0.57)	2.51 (0.54)	2.80 (0.56)	7.54	7.11×10^{-4}	1.00	-0.25 – 0.25	3.78×10^{-3}	0.08 – 0.57	2.74×10^{-3}	-0.56 – -0.09
Agreeableness	2.87 (0.44)	2.48 (0.50)	2.56 (0.51)	8.71	2.44×10^{-4}	3.82×10^{-4}	-0.57 – -0.14	3.28×10^{-3}	-0.51 – -0.08	1.00	-0.27 – 0.15
Conscientiousness	2.70 (0.52)	2.48 (0.69)	2.25 (0.63)	7.78	5.70×10^{-4}	0.51	-0.43 – 0.12	4.73×10^{-4}	-0.70 – -0.16	0.04	0.01 – 0.53
Personality: SURPS											
Hopelessness	1.79 (0.38)	2.91 (0.63)	2.45 (0.63)	53.74	4.36×10^{-19}	1.61×10^{-19}	0.83 – 1.34	7.23×10^{-9}	0.40 – 0.90	5.90×10^{-5}	0.20 – 0.68
Anxiety sensitivity	2.37 (0.42)	2.62 (0.45)	2.70 (0.56)	7.27	9.20×10^{-4}	0.03	0.02 – 0.45	7.10×10^{-4}	0.12 – 0.54	0.77	-0.3 – 0.11
Impulsivity	1.90 (0.39)	2.14 (0.53)	2.48 (0.54)	20.69	7.59×10^{-9}	0.08	-0.02 – 0.43	6.74×10^{-9}	0.35 – 0.78	1.81×10^{-4}	-0.57 – -0.15
Sensation seeking	2.64 (0.54)	2.67 (0.65)	2.87 (0.60)	3.20	0.04	1.00	-0.30 – 0.23	0.02	-0.05 – 0.47	0.06	-0.50 – 0.01
Comorbid symptoms											
Depression	3.43 (3.58)	15.22 (5.90)	14.19 (6.48)	75.78	2.14×10^{-24}	2.57×10^{-21}	8.92 – 13.93	1.55×10^{-19}	8.18 – 13.14	1.00	-1.68 – 3.21
Anxiety (DAWBA)	1.27 (0.56)	2.68 (1.23)	2.63 (1.26)	30.51	4.28×10^{-12}	2.97×10^{-10}	0.91 – 1.90	7.14×10^{-10}	0.87 – 1.84	1.00	-0.43 – 0.53
Harmful drinking	5.40 (3.07)	5.74 (5.68)	9.40 (7.57)	8.27	3.67×10^{-4}	1.00	-2.84 – 2.65	4.13×10^{-3}	0.95 – 6.46	9.89×10^{-4}	-6.31 – -1.29
Sample for sMRI analyses (including GMV and CT)											
Sample size (N)	56	64	57								
Age	22.72 (0.62)	21.78 (2.10)	22.53 (2.09)	4.76	0.01						
BMI (kg/m2)	24.91 (4.72)	16.62 (1.80)	24.06 (4.00)	96.32	1.11×10^{-28}						
TIV (mm3)	1397.96 (94.17)	1416.80 (105.01)	1415.61 (113.76)	0.59	0.558						
Sample for fMRI analyses: MID task											
Sample size (N)	49	48	53								
Age	22.67 (0.59)	21.75 (2.09)	22.51 (2.07)	3.92	0.02						
BMI (kg/m2)	24.90 (4.60)	16.58 (1.62)	24.27 (3.95)	79.05	4.91×10^{-24}						
Sample for fMRI analyses: EFT											
Sample size (N)	54	62	61								
Age	22.72 (0.63)	21.79 (2.10)	22.48 (2.10)	4.30	0.02						
BMI (kg/m2)	24.78 (4.68)	16.71 (1.76)	24.17 (3.97)	91.88	5.81×10^{-28}						

Sample for fMRI analyses: SST					
Sample size (N)	50	61	61		
Age	22.73 (0.64)	21.92 (2.06)	22.49 (2.09)	3.07	0.05
BMI (kg/m2)	24.94 (4.77)	16.56 (1.79)	24.09 (3.94)	93.82	3.92×10^{-28}

BMI, body mass index. MID, monetary incentive delay; EFT, emotional face task; SST, stop-signal task. GMV, grey matter volume; CT, cortical thickness. AN, anorexia nervosa; BN, bulimia nervosa; HC, healthy control. TIV, total intracranial volume. NEO-PI-R, the Revised NEO Personality Inventory. SURPS, Substance use risk profile scale. The comparisons of age were controlled for sites. BMI, eating behaviours, personality and comorbid symptoms were controlled for age and site.

Fig. 1.

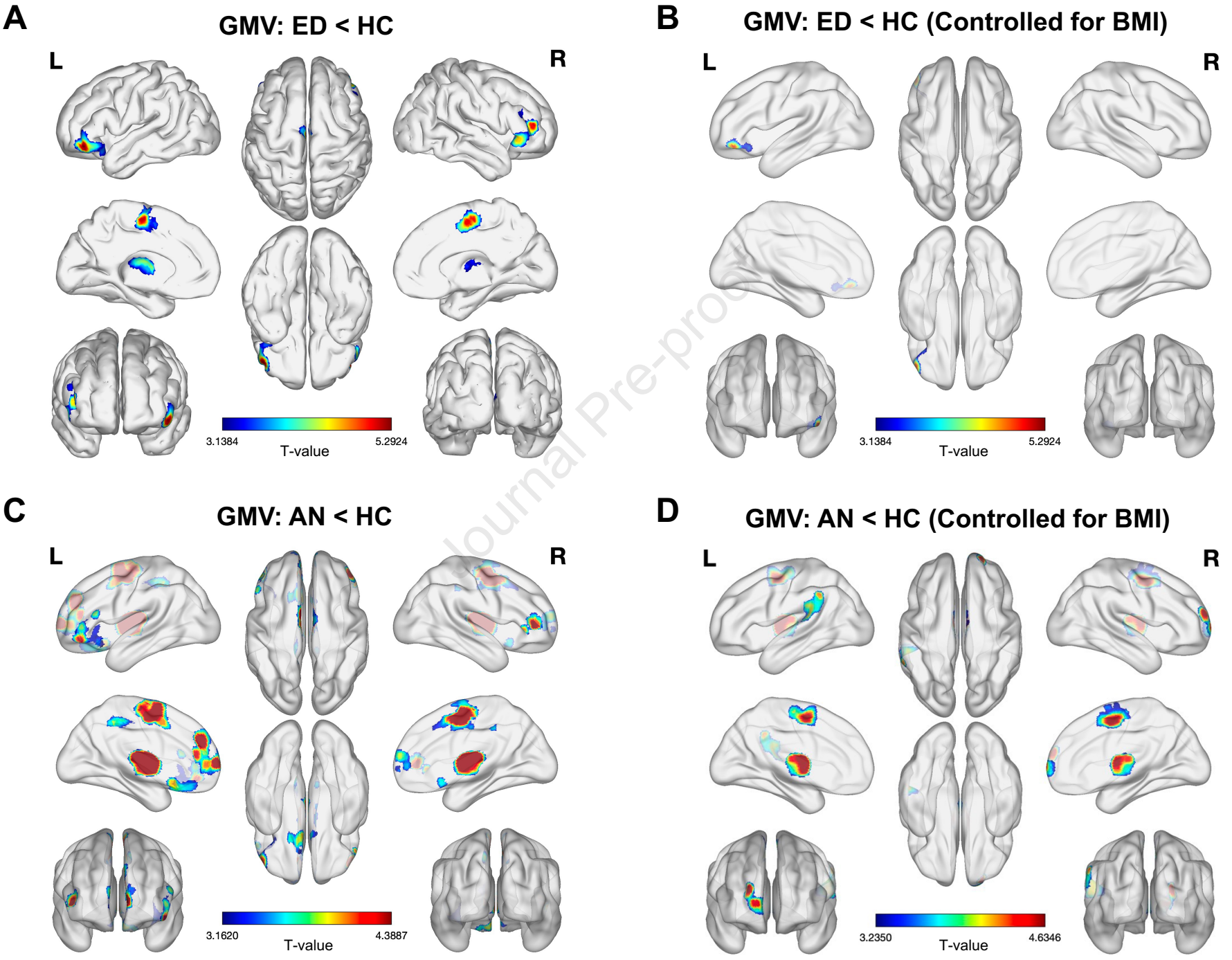
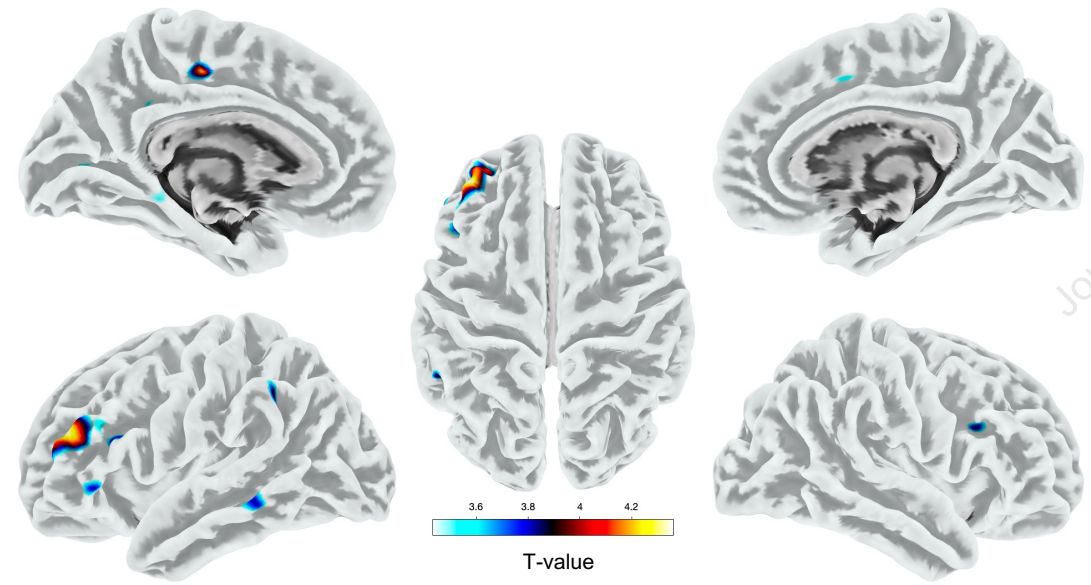


Fig. 2.

A

CT: ED < HC (Controlled for BMI)



B

CT: AN < HC (Controlled for BMI)

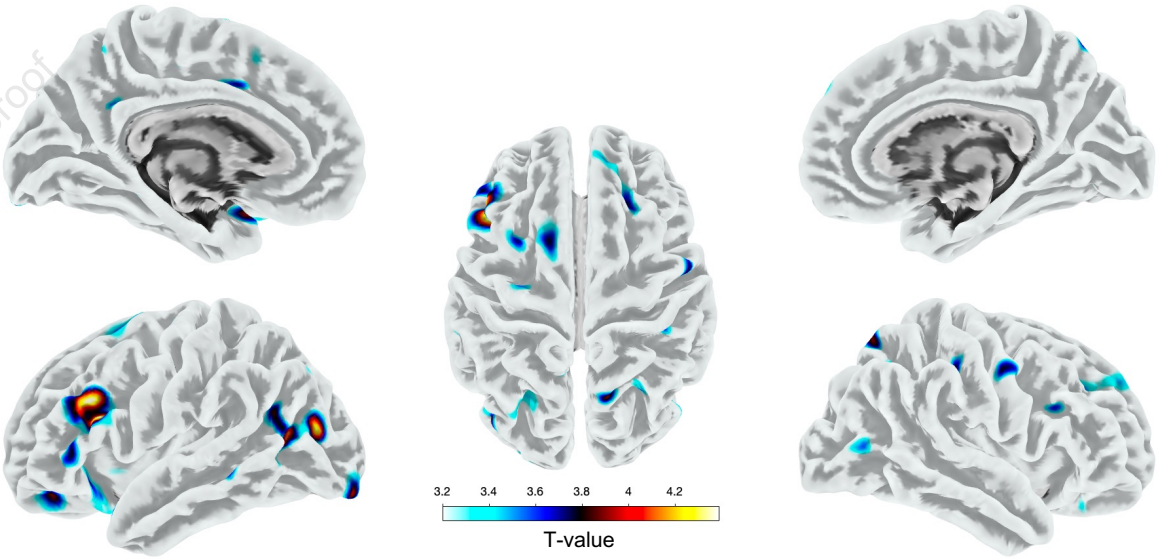


Fig. 3

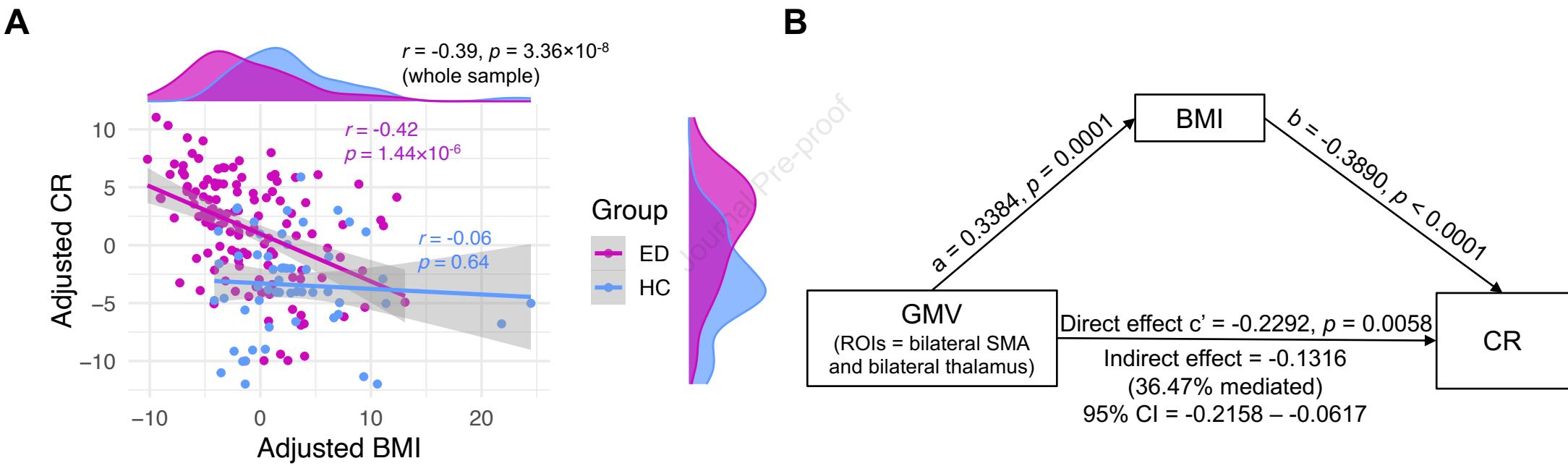
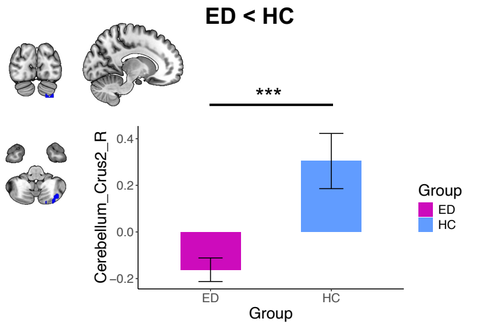
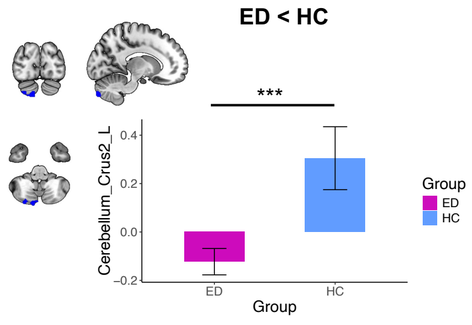
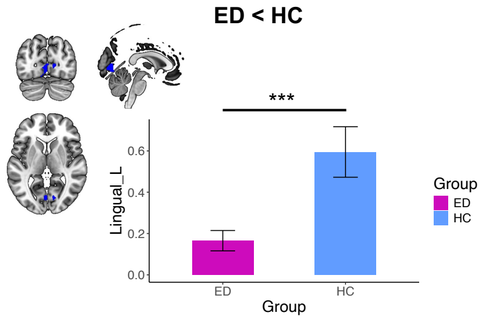


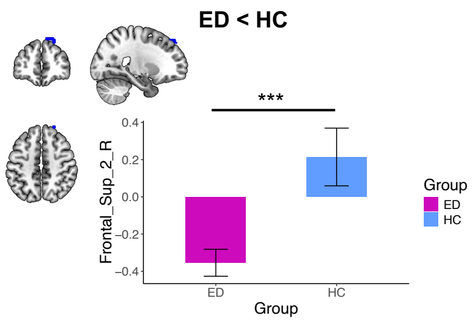
Fig. 4.

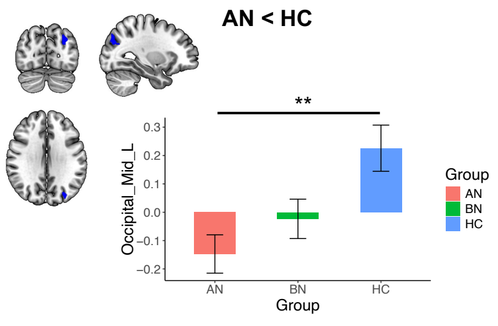
A Contrast: anticipation of large reward vs no reward in the

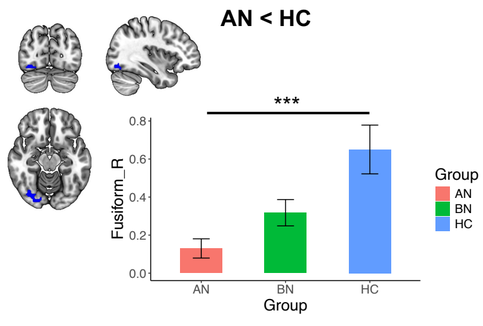


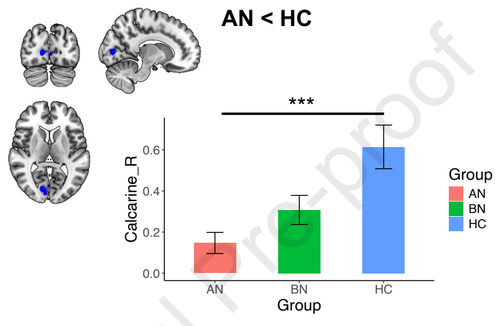


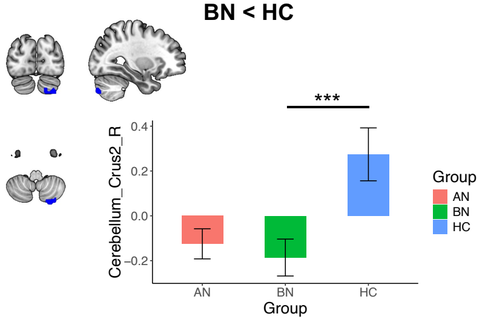


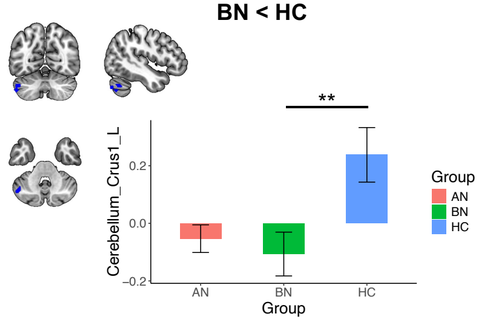


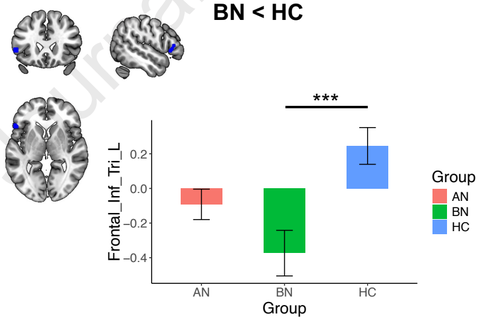


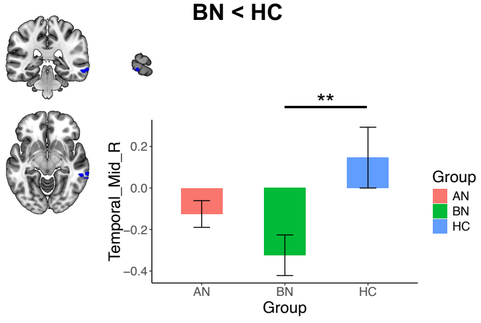




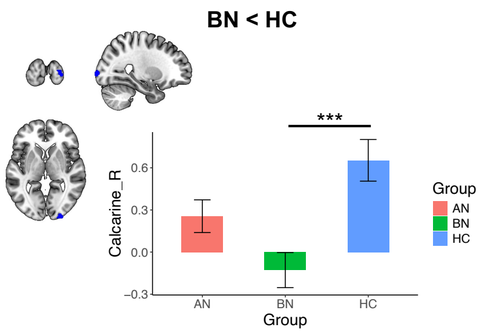








B Contrast: feedback of large reward vs no reward in the MID task



C Contrast: viewing angry faces vs control stimuli in the EFT task

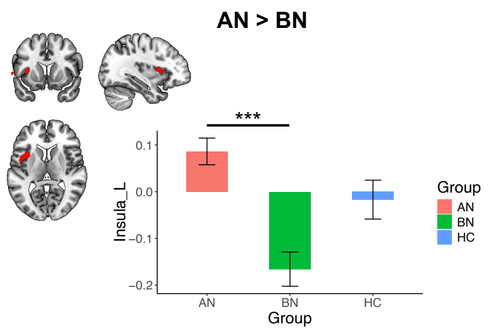


Fig. 5.