

BMJ Open Brain functional changes in individuals with bulimia nervosa: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Bulimia nervosa (BN) is a disorder with high health and socioeconomic burdens that typically arises in late adolescence and early adulthood. Previous neuroimaging studies have found functional brain changes in patients with BN. This study aims to review the latest neurobiological evidence from studies of individuals with BN, examine the consistency of these findings and evaluate the food addiction hypothesis of the disease.

Methods and analysis A systematic search will be performed using the Cochrane Library, PubMed, Embase and Web of Science databases, covering the period from database inception to 30 November 2021. Two researchers will be responsible for study selection, quality assessment and data extraction. The anisotropic effect size version of the signed differential mapping method will be used to conduct a coordinate-based meta-analysis. Publication bias will be examined with the Egger test. The quality of studies will be evaluated using the Newcastle-Ottawa Scale.

Ethics and dissemination No ethics approval is required for this is a systematic review protocol and does not require the collection of primary data. Findings will be disseminated through peer-reviewed journal or related conferences.

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INTRODUCTION

Background

Bulimia nervosa (BN) is a psychiatric and psychological disorder that often occurs in late adolescence and early adulthood; recurrent binge eating is a core diagnostic criterion for BN.¹ People with BN have recurrent episodes of binge eating followed by inappropriate compensatory behaviours (purging) to avoid weight gain, such as self-induced vomiting, use of laxatives, fasting and excessive exercise.^{2–4} Psychiatric comorbidity, including depression and anxiety, is very common in patients with BN,^{5 6} and more than one-fifth of patients with BN have attempted suicide.⁶ Studies have shown that patients with BN have attention deficits,^{7–10} which are associated with an increase in the incidence of attention deficit hyperactivity disorder.^{8 11 12}

Strengths and limitations of this study

- This systematic review protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.
- Two or more reviewers will independently perform the study selection, data extraction and assessment of the risk of bias.
- High heterogeneity is expected in the reporting of functional MRI findings from different tasks.

Recent neuroscience studies have shown that the function of the prefrontal lobe, insular cortex, orbitofrontal cortex (OFC) and striatum differ in patients with BN from those in healthy controls, and that alterations in the corticostriatal circuits are similar to those observed in individuals with substance abuse.¹³ It has been suggested that the OFC and anterior cingulate cortex (ACC) are overactive in this patient group, and that impaired inhibitory control of the lateral prefrontal circuit mediates the urges to binge eat.¹⁴ Compared with healthy controls, patients with BN manifest hyperactivity of the parieto-occipital regions and hypoactivation of the executive control network¹⁵ and show insula and ACC activation that is greater in response to pictures of food than that in response to pictures of household items.¹⁶ The role of inhibitory control disruption is increasingly recognised in BN studies. Faced with stimuli related to eating, patients with BN have impaired response inhibition and inhibitory control.¹⁷ The frontostriatal area plays a central role in controlling goal-directed thoughts and behaviours, including response inhibition and reward processing.¹⁸

The evidence from research examining the food addiction hypothesis has changed the explanatory models of eating disorders. Eating behaviour is central in models of eating disorders.¹⁹ Changes in the food environment that interact with individual vulnerability may be key risk factors for BN, and



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neuroadaptive changes in reward circuits are likely to maintain these disorders.¹⁹ Recent small sample studies have examined the neurobiology of individuals with BN,^{20–22} showing a strong association between the frontostriatal area function and BN.¹⁸ In fact, the diminished activation of the frontostriatal area in patients with BN has been shown to contribute to the severity of symptoms.²³ However, small sample sizes and heterogenous protocols of the previous studies preclude any meaningful conclusions on the neurocognitive profile of individuals with BN or binge eating disorder.²⁴

Neurobiological research on BN is expanding rapidly. Given the high psychiatric comorbidity and suicide rates in patients with BN, a rigorous review of the evidence on the neurological underpinnings of BN is required.^{6 25} Therefore, this systematic review aims to comprehensively examine the evidence on functional brain changes in patients with BN to evaluate the food addiction hypothesis and support disease management. This meta-analysis, which synthesises the latest neuroimaging evidence, will be performed using the anisotropic effect-size version of seed-based d mapping (AES-SDM). This software's main features include:

1. Accounting for both increases and decreases of the outcome of interest (eg, activation and deactivation) so that contradictory findings cancel each other.²⁶
2. Use of effect size estimates with random-effect modelling, which increases reliability and performance.²⁷
3. Potential simultaneous inclusion of available 3D statistical images (ie, maps of t-test values).
4. Use of threshold-free cluster enhancement (TFCE) statistics.²⁸

Objective

The purpose of this systematic review is to fully understand the functional changes that occur in the brains of patients with BN and to provide evidence for the food addiction hypothesis.

METHODS AND ANALYSIS

Study design

This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.²⁹ The results of this systematic review and meta-analysis will be published in a specialist journal or presented at a conference. A preliminary search was performed using the Cochrane Library, PubMed, Embase and Web of Science, including records from database inception to 30 November 2021. The search strategy for the PubMed database is presented in [table 1](#).

Criteria of selection for study

The present study will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols guidelines.²⁹ Following the population, interventions, comparators, and outcomes framework, inclusion and exclusion criteria will be based on the type of patients,

Table 1 Search strategy for PubMed

Search strategy for PubMed	
#1	Bulimia [MeSH]
#2	"Bulimia Nervosa" [MeSH]
#3	Bulimi* [Title/Abstract]
#4	Bing* [Title/Abstract]
#5	Overeat* [Title/Abstract]
#6	"Compulsive eat*" [Title/Abstract]
#7	"Eating disorder*" [Title/Abstract]
#8	EDNOS [Title/Abstract]
#9	1–8/or
#10	fMRI [Title/Abstract]
#11	functional MRI [Title/Abstract]
#12	functional MRI [Title/Abstract]
#13	BOLD [Title/Abstract]
#14	10–13/or
#15	nine and 14

interventions, comparisons and outcomes reported ([table 2](#)). Only studies published in the English language will be included, and we will exclude data from non-human and duplicate studies.

Outcomes

The primary outcomes are functional changes (activation and deactivation) in individuals with BN.

Selection of studies

Search results will be exported to an Endnote database. Two reviewers will independently screen study titles and abstracts and exclude those studies that do not meet the eligibility criteria. Studies whose eligibility is not clear from title and abstract screening will undergo full-text reading. In case of between-reviewer discrepancies on study eligibility, a third reviewer will arbitrate. Study flow is presented in [figure 1](#)

Data extraction and management

Two reviewers will extract data on the following variables: publication characteristics (first author name, year of publication, reference ID), study characteristics (study design, control group, method of analysis), participant characteristics (age, sex, and country of origin), task paradigm (task details, specific contrasts of interest, cognitive processes interrogated), imaging parameters (peak coordinates, magnetic field strength, smoothing kernel, stereotactic template space, analysis software), and statistical thresholds. Disagreements between the two reviewers will be resolved by consensus. Data sheets will be created in Microsoft Excel. Data quality control will be performed by the third reviewer.

The units from each study dataset will be converted to the International System of Units before statistical analysis. The P-statistics and T-statistics will be converted

Table 2 Inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
P—Population	Individuals with bulimia nervosa, with fMRI	Diagnosed by unofficial diagnostic criteria
I—Intervention	None	None
C—Comparator	Bulimia nervosa patients versus healthy controls	No comparisons
O—Outcome	<ul style="list-style-type: none"> ▶ Whole-brain results in three-dimensional coordinates (x, y, z) of changes in standard stereotactic space (Talairach or MNI) ▶ Thresholds for significance corrected for multiple comparisons (cluster level corrected, $p < 0.05$ FWE/FDR). 	<ul style="list-style-type: none"> ▶ Studies only reporting region of interests (ROIs) findings ▶ Studies using coordinates relative to analyse employing small volume corrections in preselected ROIs.

FDR, False Discovery Rate; FWE, Family Wise Error.

into Z-statistics using the SDM online converter (<http://www.sdmproject.com/utilities/?show=Statistics>). The peak data (coordinates, significance level and direction of change) will be extracted and combined to recreate an effect-size map. Peak coordinates not in the Montreal Neurological Institute space will be converted using coordinate mapping software. Aggregate data on participants' demographic characteristics will be reported as means with SD. Data processing will be performed according to the manufacturer's instructions.

Risk of bias and quality assessment

Qualitative risk of bias assessment will be performed for each study. The *Cochrane Handbook for Systematic Reviews of Interventions* will be used in this study. Two authors will evaluate six areas of selection bias: selection, performance, detection, attrition, reporting and other sources. Trials will be rated as 'low', 'high', or 'unclear' risk.³⁰ Any discrepancies in assessment will be resolved by consensus or third-author arbitration.

Study quality will be assessed using the Newcastle-Ottawa Scale, which accounts for study participants, comparability of groups, and measurement of exposure factors. The quality of evidence in each study will be defined as high (≥ 8 points), medium (6–7 points), or low (≤ 5 points). Any discrepancies in quality assessments between the two authors will be resolved by third-author arbitration.

Meta-analysis

The meta-analysis of eligible studies will involve a variance-weighted standard random effects model. An uncorrected p value of < 0.005 will be set as the main threshold, with an additional peak height Z-value of > 1 and a cluster extent of ≥ 10 voxels to optimally balance sensitivity and specificity.²⁶ Study maps will be calculated voxel-wise to estimate the random-effects mean, which considers the sample size, intrastudy variability and between-study heterogeneity. AES-SDM (<https://www.sdmproject.com/software/>) will be used to quantitatively synthesise findings of functional brain alterations. SDM is a statistical technique for meta-analysis that examines differences in brain activity detected by neuroimaging techniques, including functional MRI.^{28,31}

SDM includes five primary steps:

1. Coordinates of cluster peaks (significant BNs-vs-HCs voxels of activation) are selected.
2. The lower and upper bounds of possible effect size images are estimated.
3. MetaNSUE is used to estimate the most likely effect size and its SE. Several imputations are generated premised on adding noise to these estimations within the bounds.
4. Each imputed dataset is meta-analysed. Rubin's rules are implemented to combine imputed meta-analysed datasets.
5. A standard permutation test is ran by the recreated of subject images. The process is repeated with each set of permuted images. The maximum statistic of the final image is saved. The distribution of these maxima is used to familywise error correct for multiple comparisons.

The minimum number of studies required for synthesis is three per analysis. When more than 10 studies are

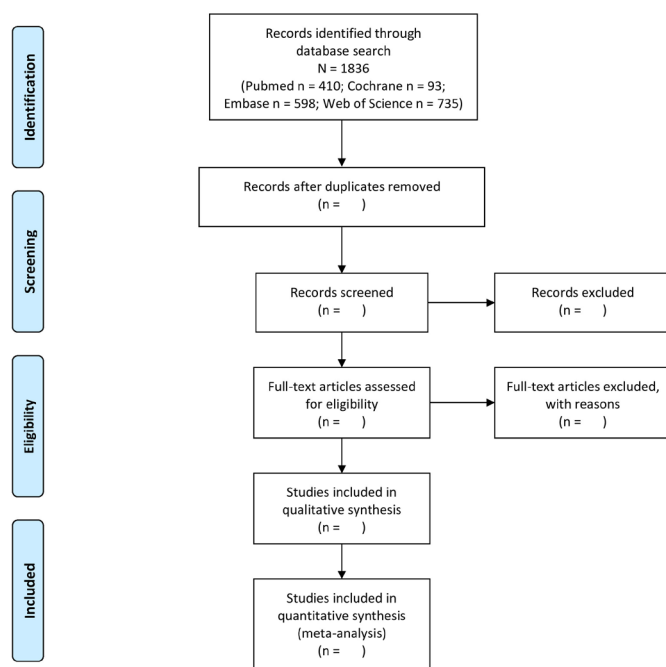


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

included, it was sufficient to detect publication bias in the meta-analytical procedures.^{32,33} The probability threshold will be decreased to 0.005 to minimise the detection of false correlations.

Sensitivity analysis

Leave-one-out jackknife sensitivity analysis will be used to test the stability of estimates derived from the functional MRI studies; this technique involves repeating the main analysis and systematically removing one study at a time before repeating the analysis.

Metaregression or subgroup analysis

If enough studies are included, the following potential sources of among-study heterogeneity will be explored using subgroup analyses or metaregression²⁶: task paradigm; FEW or FDR; participants' mean age, mean BN duration and mean frequency of binge eating, among others.

Patient and public involvement

Neither time nor funding has been allocated to public engagement pertaining to this study. The review findings will provide a summary of evidence on neuroimaging characteristics in BN, which may be relevant to clinicians and researchers focused on the physiopathology of BN.

Ethics and dissemination

This review does not require an ethics board approval, as the data used are anonymised and do not infringe on individuals' rights. The results will be reported and discussed, as required by the Meta-analysis of Observational Studies in Epidemiology guidelines.³³ The present findings will be published in a peer-reviewed journal or presented at relevant conferences.

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Contributors YS and YD conceived the review topic. RS drafted the search strategy after background exploratory searches. YS and QY cowrote the initial protocol. YD and RS provided critical appraisal and senior oversight of the protocol. For the systematic review, QW and XRL will perform the searches, data extraction and analysis. RS will provide oversight of the searches, data analysis and extraction. QW will provide statistical input for data analysis. RS and YD will provide critical appraisal and senior oversight of the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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