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# Functional connectivity and treatment response in obesity and eating disorders: Current evidence and empirical data

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## Abstract

Alterations in large-scale brain networks have been reported in obesity (OB) and eating disorders (ED), but their relevance to treatment outcomes remains unclear. We reviewed evidence on neurobiological predictors of treatment outcome in ED and OB and present preliminary empirical analyses exploring baseline rsFC differences between individuals with anorexia nervosa (AN), obesity with comorbid ED (OB + ED), and obesity without ED (OB − ED) and healthy controls (HC), and examining whether these connectivity differences are associated with treatment outcome in the clinical groups. A total of 98 women (AN = 27, OB + ED = 25, OB − ED = 21, HC = 25) underwent resting-state functional magnetic resonance imaging (rs-fMRI). rsFC networks were subsequently identified using probabilistic independent component analysis (ICA), and their associations with treatment outcomes were examined within each clinical group. Both OB groups showed reduced rsFC relative to HC within a thalamic–basal ganglia network, specifically in a cluster located in the left inferior occipital cortex encompassing extrastriate visual regions. Baseline connectivity in this occipital cluster showed a positive, although non-significant, association with treatment outcome in the OB − ED group, whereas no significant associations were observed in AN or OB + ED. Given the non-significant nature of this exploratory association, the observed relationship should be considered hypothesis-generating and requires confirmation in adequately powered samples. Further work is needed to clarify the role of sensory–integrative networks in treatment response across extreme weight conditions.

**Keywords** Obesity · Eating disorders · Anorexia nervosa · Resting-state functional connectivity · Treatment outcome · Thalamic network

**Abbreviations**

| | |
|---|---|
| %TWL | Percentage of total weight loss |
| ACC | Anterior cingulate cortex |
| AN | Anorexia nervosa |
| BED | Binge eating disorder |
| BN | Bulimia nervosa |
| BOLD | Blood oxygen level-dependent |
| BS | Bariatric Surgery |
| CBT | Cognitive behavioral therapy |
| DBT | Dialectical behavior therapy |
| DLPFC | Dorsolateral prefrontal cortex |
| DMN | Default mode network |
| DS | Duodenal switch |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| ECN | Executive control network |
| ED | Eating disorder |
| EWC | Extreme weight conditions |
| FBT | Family-based therapy |
| FPN | Frontoparietal network |
| FWE | Family-wise error rate |
| GIP | Glucose-dependent insulinotropic polypeptide |
| GLM | General linear model |

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| | |
|---|---|
| GLP-1 | Glucagon-like peptide-1 |
| HC | Healthy controls |
| ICA | Independent component analysis |
| MELODIC | Multivariate Exploratory Linear Optimized Decomposition into Independent Components |
| MRI | Magnetic resonance imaging |
| NAcc | Nucleus accumbens |
| OAGB | One-anastomosis gastric bypass |
| OB | Obesity |
| OB+ED | Obesity with eating disorder |
| OB-ED | Obesity without eating disorder |
| OFC | Orbitofrontal cortex |
| rsFC | Resting-state functional connectivity |
| rs-fMRI | Resting-state functional magnetic resonance imaging |
| RSNs | Resting-state networks |
| RYGB | Roux-en-Y gastric bypass |
| SADI-S | Single anastomosis duodenal-ileal bypass with sleeve gastrectomy |
| ScN | Subcortical network |
| SN | Salience network |
| TFCE | Threshold-free cluster enhancement |

## 1 Introduction

The concept of Extreme Weight Conditions (EWC) has been proposed to capture a clinical continuum characterized by maladaptive eating behaviors and shared alterations across the weight spectrum [1–6]. At opposite ends of this continuum lie anorexia nervosa (AN), defined by severe weight loss and restrictive eating patterns, and obesity (OB), characterized by excess adiposity and frequently accompanied by metabolic, endocrine, and cardiometabolic complications.

Although OB is not classified as an eating disorder (ED), in contrast to AN, a substantial proportion of individuals with OB present comorbid ED, such as binge eating disorder (BED) or bulimia nervosa (BN) [7–9]. This overlap in prevalence underscores the frequent coexistence of excessive adiposity and maladaptive eating behaviors, emphasizing the necessity to distinguish between OB accompanied by and without ED symptoms to ensure appropriate treatment [7, 10, 11]. OB with comorbid ED (OB + ED) constitutes a clinically distinct phenotype compared to OB without ED (OB-ED), primarily due to the presence of psychopathology and behavioral dysregulation, despite sharing a common excess-weight profile [10]. This distinction is also clinically relevant because it may influence treatment selection, adherence, and therapeutic outcome.

In the case of AN and OB, although they show opposite physical traits in body weight, research has reported disturbances in brain systems that control energy regulation and eating behavior in both conditions [1, 3, 12, 13]. Accordingly, rather than reflecting entirely independent pathophysiological entities, these extremes may partially converge in domains related to the integration of internal physiological states and external environmental cues [12, 14]. From this perspective, transdiagnostic models have emerged suggesting that maladaptive eating behaviors arise from neurobiological alterations in distributed systems that integrate homeostatic, interoceptive, cognitive, and sensory information [1, 3, 12, 15, 16].

### 1.1 Transdiagnostic neurobiology of EWC: From regional alterations to brain network-level dysfunction

For instance, alterations in hypothalamic function have been hypothesized to contribute to a decoupling of the homeostatic signals that regulate hunger and satiety [3]. In OB, the persistence of food intake beyond physiological satiety signals has been linked to metabolic dysregulation, including impairments in glucose homeostasis and in peptide signaling pathways such as leptin signaling [13]. Conversely, in AN, sustained food restriction despite physiological hunger is likewise associated with functional alterations in hypothalamic circuits [17]. Under this framework, metabolic state may further modulate the activity of broader networks involved in interoceptive integration and sensory processing. For example, fasting has been associated with increased activation in visual cortical regions in response to food-related versus neutral stimuli [18], suggesting that hunger biases attentional resources toward food cues. Consistently, studies in OB have reported enhanced visual cortex responses to food stimuli [19], whereas such effects appear attenuated or absent in AN [20].

The increased salience attributed to food-related stimuli in OB may also reflect alterations in reward processing and inhibitory control mechanisms. Some authors have proposed that AN and OB represent opposing ends of a spectrum in reward-related neural responsivity, particularly within orbitofrontal circuits involved in reward valuation [3, 12]. For instance, heightened orbitofrontal cortex (OFC) activation in AN has been associated with increased cognitive control during the evaluation of rewarding stimuli, whereas OB has been linked to reduced orbitofrontal cortex (OFC) engagement and diminished regulatory capacity during reward processing [12]. Similarly, while ventral striatal regions may show increased responsivity to food-related cues in OB with and without ED [21, 22], in AN these regions may instead be preferentially engaged by disorder-relevant stimuli (e.g., thin-body images) [23], suggesting a shift in the motivational salience of stimuli across conditions.

## 1.2 Resting-state functional connectivity as a framework to study EWC

A growing body of evidence from resting-state studies highlights functional connectivity as a system-level framework to characterize the organization and interaction of human brain networks [24]. Resting-state fMRI (rs-fMRI) enables the examination of intrinsic connectivity patterns that may reflect the functional integrity of these circuits in the absence of external stimuli or task demands [25]. These patterns have been investigated using complementary methodological approaches. Hypothesis-driven analyses, such as seed-based functional connectivity, assess temporal correlations between a priori regions of interest, based on consistent task-based studies, and whole-brain [26, 27]. Data-driven whole-brain approaches identify patterns of coherent activity without predefined regions, allowing the characterization of large-scale functional networks [26]. ICA is widely used to decompose the resting-state signal into spatially independent components, each corresponding to a functionally connected network. From these approaches, canonical resting-state networks, including the Default Mode Network (DMN), Salience Network (SN), Executive Control Network (ECN), and subcortical networks (ScN), have been consistently reported [28].

### 1.2.1 Default mode network (DMN)

The Default Mode Network (DMN) is a large-scale network implicated in self-referential processing, autobiographical memory, and the integration of internal states with external information. Alterations in DMN connectivity may reflect disruptions in the balance between internally oriented cognition and the processing of salient environmental cues, both of which are critical for regulating eating behavior [29–33].

In both AN and OB, alterations in the intrinsic functional organization of the DMN may reflect disruptions in the integration of internal states and external environmental cues, processes that are critical for the regulation of food intake and goal-directed behavior [34, 35]. A recent study showed that patients with OB without ED exhibited aberrant DMN activity in regions overlapping with the ECN (i.e., dorsolateral prefrontal cortex; DLPFC) and the SN (i.e., insula), compared with healthy controls (HC) [36]. Moreover, studies directly comparing individuals with OB with and without ED have reported significantly greater connectivity in the dorsomedial prefrontal cortex—a core DMN component—in OB without ED relative to those with comorbid BED, suggesting that the presence of ED in OB may be associated with reduced internal coherence of the DMN [37]. This pattern may reflect the intrusion of food- and body-related cognitions in individuals with OB and comorbid ED.

In AN, DMN connectivity alterations have also been reported, although findings remain heterogeneous [31, 38]. For instance, reduced functional connectivity within core DMN regions, including the medial prefrontal cortex and posterior cingulate cortex, has been described in AN compared with controls [31], whereas other studies have reported increased connectivity between the DMN and SN regions, particularly the anterior insula, in acute patients [38]. These alterations have been interpreted as reflecting disturbances in self-referential processing and impaired integration of interoceptive and external information.

### 1.2.2 Salience network (SN)

The salience network (SN), functionally implicated in the detection of behaviorally relevant stimuli—including both interoceptive and external cues—and in the reorientation of attentional focus, has been consistently implicated in the pathophysiology of OB and ED.

In OB, the SN has been consistently reported to exhibit altered functional connectivity in individuals with OB, with and without comorbid ED, compared to HC [32, 39]. For instance, García-García et al. [40] observed increased functional connectivity of the putamen within the SN in individuals with OB, suggesting an imbalance between interoceptive processing and reward-related responses to food cues. Similarly, Wijngaarden et al. [41] found a stronger baseline connectivity between the hypothalamus and the left insula, alongside reduced connectivity between the hypothalamus and the anterior cingulate cortex (ACC) following prolonged fasting, indicating altered integration of homeostatic and salience-related signals in OB. In individuals with OB and a comorbid ED, reduced ACC connectivity relative to HC has also been reported [37]. Overall, SN alterations may contribute to core behavioral features of OB. Specifically, regions such as the anterior insula and putamen may predominantly support interoceptive awareness and reward-related aspects of eating, whereas the dACC appears more closely involved in the cognitive control of appetite and goal-directed regulation of food intake.

In AN, findings regarding salience network (SN) connectivity remain mixed, and it may depend on illness stage or recovery status [42]. Studies in acute AN have reported reduced functional connectivity within the SN, particularly in the ACC [31, 43]. Such reductions in SN connectivity in AN may contribute to altered emotional processing and impaired perception of internal states [43]. However, alterations do not appear to consistently normalize following recovery. Other studies have reported no differences in SN connectivity compared to healthy controls (HC), as well as increased functional connectivity in individuals recovered from AN [42], suggesting heterogeneity in illness stages.

#### 1.2.3 Executive control network (ECN)

The executive control network (ECN), encompassing the dorsolateral prefrontal cortex and parietal regions, is involved in cognitive control, decision-making, and goal-directed behavior. Although evidence remains limited, both OB and AN have been associated with alterations in ECN connectivity [30, 32, 44], suggesting potential deficits in top-down regulatory processes.

A recent study found reduced connectivity between DLPFC and the hypothalamus during fasting in individuals with OB compared to HC [45], suggesting a disruption between the ECN and homeostatic systems in OB. Similarly, Wang et al. [36] reported increased DLPFC connectivity with the precuneus (DMN) and insula (SN), alongside decreased connectivity between the DLPFC and sensorimotor areas, including the precentral and postcentral gyri and the paracentral lobule. This dissociative connectivity pattern, characterized by enhanced coupling with higher-order associative networks and reduced interaction with sensorimotor systems, may indicate an imbalance in the integration of cognitive, interoceptive, and motor-related processing.

In individuals with OB and comorbid ED, reduced functional connectivity between striatal regions (e.g., nucleus accumbens) and frontal areas implicated in executive functioning has been reported in BED [46], suggesting impaired integration between reward-related and cognitive control systems. Similar patterns of fronto-striatal hypoconnectivity have also been observed in studies of OB samples, including a proportion of individuals with BED [47].

Regarding AN, alterations in frontoparietal regions associated with the ECN have also been reported, although findings remain heterogeneous. For example, reduced functional connectivity between the DLPFC and the Fronto Parietal Network (FPN) in AN [48] has been interpreted as reflecting excessive top-down control and cognitive rigidity. Complementary evidence further suggests altered fronto-thalamic organization, with increased functional connectivity between the thalamus and the DLPFC alongside reduced connectivity between the thalamus and anterior prefrontal regions, which has been associated with poorer cognitive control and working memory performance [49]. This pattern may reflect an imbalance within the ECN, characterized by enhanced engagement of control processes but reduced efficiency in higher-order executive functions.

#### 1.2.4 Subcortical Networks (ScN)

Subcortical networks include key structures such as the hypothalamus, thalamus, and striatum, which play a central role in integrating homeostatic, reward-related, and sensory information relevant to eating behavior [49, 50]. Rather than constituting a single large-scale network, these regions form dynamically interconnected systems that interact with cortical networks, including the DMN, SN, and ECN, to support the regulation of energy balance and motivated behavior [33, 46, 50, 51].

In OB, altered subcortical connectivity has been consistently reported in the hypothalamus. A systematic review by Syan et al. [33] showed increased functional connectivity between the hypothalamus and reward, limbic, and SN, but decreased connectivity with regions implicated in cognitive control. This pattern supports the notion of an imbalance between brain systems involved in reward valuation and interoceptive salience, which may contribute to a bias toward hedonic and cue-driven eating, with diminished cognitive control over food intake. Similarly, in individuals with OB and comorbid ED, reduced frontostriatal functional connectivity was associated with increased binge-eating frequency [21].

In the case of AN, alterations in subcortical connectivity have primarily involved the thalamus as a central hub within fronto-subcortical circuits [46, 49, 52]. Specifically, increased functional connectivity between the central-medial thalamus and the DLPFC, but reduced connectivity between the anterior thalamus and anterior prefrontal cortex, has been reported in AN compared to HC [49]. Converging evidence from graph-based approaches further indicates reduced functional connectivity in both the thalamus and the insula [52], pointing to impaired integration of homeostatic and interoceptive signals. Together with reports of reduced frontostriatal connectivity in individuals with OB and comorbid ED, these findings point to a transdiagnostic disruption of circuits linking subcortical reward and homeostatic regions with prefrontal control systems.

Despite the growing evidence supporting alterations in fronto-subcortical and large-scale network connectivity across EWC, the predominantly cross-sectional nature of this literature limits causal inference, restricting conclusions to descriptive associations rather than establishing directional or mechanistic relationships. Longitudinal and intervention-based studies are particularly relevant, as they provide a framework for examining whether these neural alterations are modifiable and the extent to which they may underlie treatment-related changes.

### 1.3 Resting-state network alterations and treatment outcomes in EWC

From a clinical perspective, the management of EWC involves heterogeneous, multidisciplinary approaches that address different aspects of the disorder across phenotypes. Treatments are primarily centered on psychological

interventions, often combined with nutritional rehabilitation and medical management [53–55]. In contrast, the treatment of OB without ED typically focuses on lifestyle modification, pharmacological approaches, and, in some cases, bariatric surgery (BS) [56].

#### 1.3.1 Treatments in OB without ED and brain functional connectivity

Management of OB has traditionally followed a stepped approach, beginning with lifestyle modification and psychological interventions such as cognitive-behavioral therapy (CBT), and progressing to pharmacological treatments, including incretin-based therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonists. In more severe or refractory cases, BS [e.g., sleeve gastrectomy, Roux-en-Y gastric bypass, One-Anastomosis Gastric Bypass (OAGB), and Duodenal Switch (DS)/Single Anastomosis Duodenal-Ileal Bypass with Sleeve Gastrectomy (SADI-S)], which remains the most effective intervention for achieving substantial and sustained weight loss, as well as meaningful metabolic improvement, in appropriately selected patients [57].

Rs- fMRI evidence has primarily characterized connectivity changes in the context of BS [58, 59]. In a Roux-en-Y gastric bypass (RYGB) intervention, individuals with OB exhibited increased functional connectivity at baseline within reward and salience-related regions, including the nucleus accumbens (NAcc), ventral striatum, insula, and hypothalamus. At one-year follow-up, this hyperconnectivity was reduced, approaching patterns observed in HC [60]. Baseline resting state functional connectivity (rsFC) of nucleus accumbens–insula and hypothalamus–precentral circuits predicts 12-month weight loss following sleeve gastrectomy, while rsFC within hippocampal, frontoparietal, and DMN predicts improvement in cognitive control of eating behavior after BS [58]. Evidence on rsFC changes following non-surgical interventions (e.g., lifestyle or pharmacological treatments) remains limited and less consistent and has not been as systematically characterized as in bariatric cohorts. Studies examining treatment outcome of dietary interventions have shown that baseline rsFC within hypothalamic–corticostriatal and cerebellar circuits predicts subsequent weight loss at a 3-month follow-up diet [61]. Likewise, preoperative rsFC between NAcc and insula, as well as between the hypothalamus and sensorimotor regions (e.g., precentral cortex) were predictors of a greater postoperative weight loss, indicating that these circuits may index individual variability in treatment response [58].

#### 1.3.2 Treatments in OB with ED and brain functional connectivity

The presence of a comorbid ED in OB prioritizes early psychological intervention. For instance, CBT and psychoeducational programs target dysfunctional eating patterns, emotion regulation, and binge-related behaviors, improving adherence and long-term outcomes [62, 63]. Pharmacological approaches are typically used as adjunctive treatments targeting associated features such as psychiatric comorbidity, impulsivity, or weight regulation, rather than the core eating psychopathology [8, 54, 55]. To date, Lisdexamfetamine is the only medication approved by the FDA for moderate-to-severe BED in adults, with proposed effects on dopaminergic signaling that may contribute to reductions in binge eating episodes [64, 65]. BS in this population requires careful case-by-case evaluation, as the presence of clinically significant binge-eating symptoms may adversely affect postoperative adherence and outcome, underscoring the need for structured pre and post-surgical psychological assessment and follow-up [66, 67].

In individuals with OB and an ED, available resting-state studies related to treatments are limited. Nonetheless, reduced connectivity between striatal regions and prefrontal areas at baseline has been associated with greater binge frequency and impaired cognitive flexibility [21]. These patterns suggest that, in OB + ED, treatment effects may be more specifically linked to the restoration of control over reward circuits, rather than the broader normalization observed in OB without ED. In this vein, fronto-striatal functional connectivity may represent a mechanistically relevant target for both behavioral and pharmacological interventions.

#### 1.3.3 Treatments in AN and brain functional connectivity

The management of AN requires a comprehensive, multidisciplinary approach due to the severity of malnutrition and associated medical risks. In acute phases, hospitalization may be necessary to ensure medical stabilization and supervised refeeding, with particular attention to endocrine dysfunction, cardiovascular monitoring, and prevention of refeeding syndrome. Nutritional rehabilitation constitutes the first step of treatment. Concurrently, psychological interventions are central. CBT is the first-line treatment in adults, while family-based therapy (FBT) is the standard for adolescents. Additional approaches, including dialectical behavior therapy (DBT), focal psychodynamic therapy, and third-wave CBT interventions (e.g., cognitive remediation therapy, emotional skills training), aim to address cognitive rigidity, emotional dysregulation, and treatment adherence.

Pharmacological options remain limited and are primarily used to target comorbid symptoms.

Longitudinal rs-fMRI studies indicate that treatment in AN is associated with partial and non-uniform changes in rsFC. Weight restoration has been linked to reductions in hyperconnectivity within limbic fronto-striatal circuits, such as NAcc–OFC, suggesting normalization of reward-related processing. However, these changes are not paralleled by full recovery at the network level [44, 68]. For instance, reduced connectivity between the SN and ECN has been reported to persist following treatment, indicating limited normalization of circuits supporting emotional–cognitive integration [44].

Evidence directly linking baseline connectivity to treatment outcome in AN remains scarce. Available findings suggest that persistent alterations in the SN and DMN may be associated with poorer clinical trajectories, including incomplete weight restoration or a higher risk of relapse [68]. Clinically, these findings support the notion that weight restoration alone may be insufficient to normalize intrinsic brain function. Therefore, effective treatment in AN likely requires multimodal interventions targeting both metabolic and neurocognitive processes, particularly those related to emotional regulation and cognitive control.

### 1.4 Literature search and study selection

A literature search was conducted in PubMed and Scopus, without restrictions on publication date, using the following search terms: "resting-state functional connectivity AND anorexia", "resting-state functional connectivity AND obesity", and "resting-state functional connectivity AND eating disorder". The search identified studies published from 2012 onwards. Only studies conducted in adult populations were considered. Studies that did not investigate resting-state functional connectivity, including electroencephalography, magnetoencephalography or animal studies, were excluded. Following screening for relevance, 59 studies were considered relevant to the broader literature on resting-state functional connectivity in AN, obesity, and eating disorders. However, given the specific focus of this narrative review on treatment-related evidence, studies were subsequently considered in detail when they included either (i) pre–post treatment or intervention assessments of resting-state functional connectivity or (ii) baseline resting-state functional connectivity measures examined as predictors of subsequent treatment response or treatment-related clinical or behavioural outcomes. 24 studies met these criteria (20 = OB and 4 = AN).

A summary of the main resting-state functional connectivity findings related to treatment response, treatment-induced connectivity changes, and baseline predictors of treatment outcome across AN, OB + ED, and OB − ED is provided in Fig. 1 and detailed in Table 1.

## 2 Empirical data

### 2.1 Goals

The present study aimed to explore whether baseline resting-state functional connectivity differentiates individuals with AN, OB with ED (OB + ED), and OB without ED (OB-ED) from HC, and whether connectivity patterns in clinical groups (i.e., AN, OB + ED, and OB-ED) are prospectively associated with treatment outcome. We hypothesized that baseline resting-state functional connectivity would differentiate AN, OB + ED, and OB-ED from HC, reflecting disorder-specific alterations including DMN, SN, ECN, and ScN. We expected that baseline differences in functional connectivity patterns would be significantly associated with treatment outcome across clinical groups, within reward–interoceptive circuits in OB and fronto-striatal control networks in OB + ED, whereas, in AN, persistent inter-network dysconnectivity (e.g., SN–ECN) would be associated with poorer clinical response.

### 2.2 Methods

#### 2.2.1 Participants

A total of 98 participants were included in this study. Of these, 27 comprised the group of patients diagnosed with AN of whom one participant met criteria for AN-OSFED (BMI = 18.01); 25 comprised the group of patients with OB and a comorbid ED (either BN or BED; OB + ED); 21 comprised the group of patients with OB without any ED (OB-ED); and 25 comprised the HC group.

During the assessment, sociodemographic and clinical data were collected through a semi-structured, face-to-face interview. The presence of psychiatric disorders was evaluated using the Mini-International Neuropsychiatric Interview (M.I.N.I.), administered by experienced clinical psychologists and psychiatrists. For participants with AN and OB + ED, only depressive and anxiety symptomatology was not considered an exclusion criterion given its high prevalence in eating-disorder populations [69]. For participants with OB-ED and HC, exclusion criteria included a lifetime or current history of ED or other psychiatric disorders, according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

Exclusion criteria applied to all participants encompassed being male, having an organic mental disorder or intellectual disability, the presence of neurological conditions such

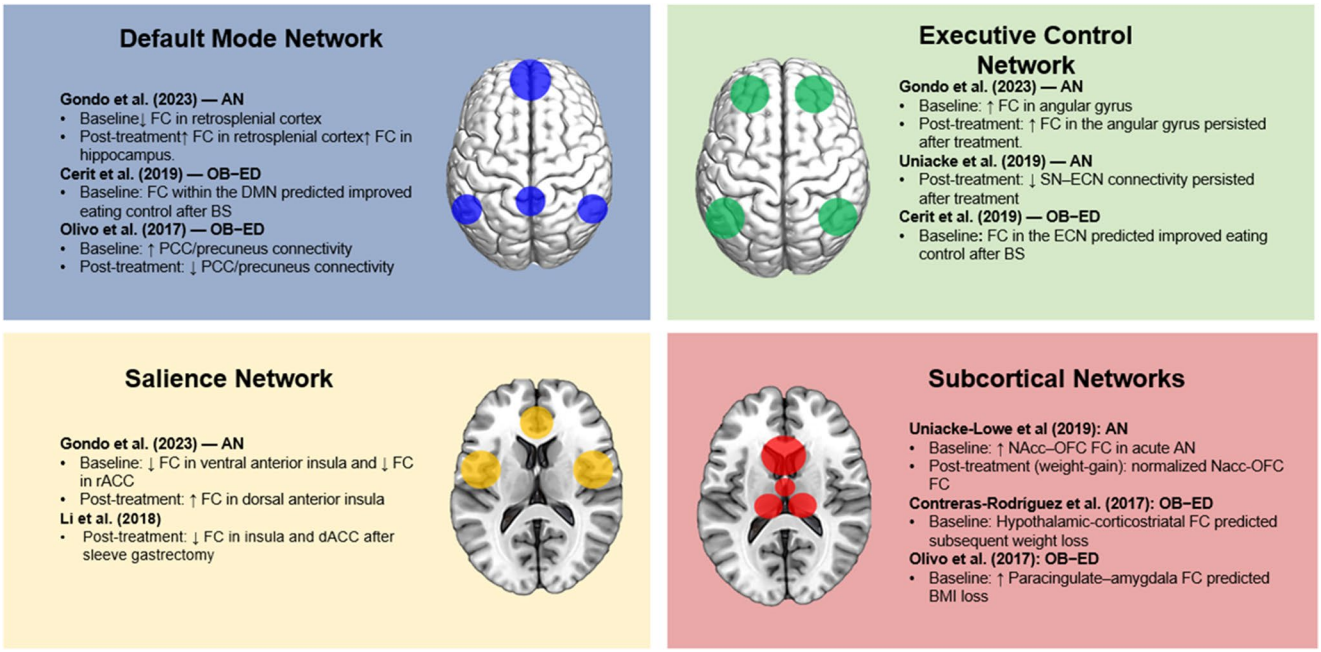



**Fig. 1** Resting-state functional connectivity findings associated with treatment outcomes in extreme weight conditions. Summary of resting-state functional connectivity (rsFC) associated with treatment response in anorexia nervosa (AN), obesity without eating disorders (OB − ED), and obesity with eating disorders (OB + ED). **Note**: AN, anorexia nervosa; BS, bariatric surgery; DMN, default mode network; ECN, executive control network; FC, functional connectivity; HC, healthy controls; NAcc, nucleus accumbens; OB − ED, obesity without eating disorder; OB + ED, obesity with eating disorder; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex; RYGB, Roux-en-Y gastric bypass; SN, salience network

as epilepsy or multiple sclerosis, a history of brain injury, and any contraindication to MRI scanning, such as metallic implants or severe claustrophobia.

All participants were thoroughly informed of the procedures and provided written informed consent. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and approved by the Ethics Committee of the Bellvitge University Hospital (PR146/14).

### 2.2.2 Treatment outcomes categories

**Obesity (OB-ED) treatment** Patients with OB underwent one of three BS procedures: sleeve gastrectomy (SG), RYGB, or DS/SADI-S. SG consisted of longitudinal resection of the stomach over a 36 French catheter. RYGB involved the creation of a small gastric pouch with a 60 cm biliopancreatic limb and a 150 cm alimentary limb. DS/SADI-S combined SG with duodenal-ileal anastomosis, with a common channel of 200–300 cm depending on the specific procedure.

The treatment outcome in patients with OB was quantified as the percentage of total weight loss (%TWL) at one year following bariatric surgery, in accordance with current recommendations for reporting weight-loss outcomes [70]. Although bariatric outcomes are commonly described using established weight-loss metrics, for the purposes of the present study, %TWL was additionally dichotomized at a $\geq$ 33% threshold to classify participants as good or bad responders (i.e., higher vs. lower weight-loss response). This cutoff should be interpreted as an operational study-specific definition, selected to ensure sufficient distribution across outcome categories and to facilitate comparability with the binary outcome definitions used in the ED groups. Accordingly, treatment outcome in OB-ED should be interpreted as a surgery-related weight-loss outcome rather than as a multidimensional clinical remission construct.

**Eating disorder (ED) treatment** Patients with OB + ED participated in a structured outpatient program consisting of sixteen weekly 90-minute group sessions delivered by experienced clinical psychologists. Patients with AN who did not require inpatient treatment attended a day hospital program including ten weekly group cognitive-behavioral therapy (CBT) sessions over approximately three months. Therapeutic groups were organized by diagnosis; however, all interventions followed a CBT framework. In addition to group therapy, patients received individualized sessions tailored to their clinical profiles.

At discharge, treatment outcome was classified according to DSM-5 criteria into full remission, partial remission,

**Table 1** Summary of studies on functional connectivity and treatment response in OB and AN

| First author, year | Sample size (*n* groups) | Intervention / treatment | rsFC | Time points | rsFC finding /treatment outcome |
|---|---|---|---|---|---|
| Dunlop et al., 2015 | 11 AN-BP+17 BN | dmPFC-rTMS | Seed-based resting-state FC from dmPFC and dACC | 1w before and after rTMS | Reduced dmPFC–OFC/insula and dACC–insula/hippocampus rsFC predicted better outcome; dACC–striatal/insula rsFC increased after treatment in responders. |
| Cha et al., 2016 | 22 AN / 18 HC | CBT | NAcc-OFC functional connectivity | 0 - ~1.5mo | Increased NAcc–OFC FC AN vs. HC, but no change after weight restoration |
| Contreras-Rodriguez et al., 2017 | 42 OB / 39 HC | Dietary counseling | Seed-based whole-brain FC (hypothalamus) | 0–3mo | Decreased MH–posterior BNST and LH–cerebellar connectivity predicted greater weight loss |
| García-Casares et al., 2017 | 16 OB | Mediterranean diet+PA | DMN, SN, and SMN | 0-6mo | Decreased connectivity within the DMN (inferior parietal–PCC), within the SN (temporo-insular regions), and between temporal-SMN FC |
| Olivo et al., 2017 | 16 OB / 12 HC | RYGB | Whole-brain ROI-to-ROI resting-state FC (132 ROIs) | 0 -1mo-1 y post-surgery | Decreased DMN–temporal and DMN–limbic FC at 1 month, persisting at 1 year, with further decreases in DMN–temporal/parietal FC |
| Li et al., 2018 | 22 OB-LSG / 19 OB-noLSG | LSG | Seed-to-voxel whole-brain FC; VMPFC and PCC/precuneus seeds derived from significant FCD clusters | 0–1 mo post-surgery | Increased vmPFC–dlPFC and PCC/precuneus–caudate/left dlPFC FC, and decreased vmPFC–HIPP FC post LSG; reductions in vmPFC and PCC/precuneus FCD were associated with BMI reduction. |
| Wang et al., 2018 | 16 OB-Naltrex / 20 OB-placebo | Pharmacological | Whole-brain FCD (local/global) + seed-based FC from right superior parietal cortex | 0–1mo | OB-Naltrex showed decreased FCD in the parietal cortex and middle frontal gyrus and increased anterior insula–parietal rsFC |
| Cerit et al., 2019 | 14 OB-SG | LSG | Seed-to-voxel | 0-12mo post-surgery | NAcc–insula and hypothalamus–precentral FC predicted weight loss; hippocampal, FPN and DMN FC predicted improved cognitive control of eating; decreased FC within/between DMN, SN and FPN post-SG |
| Kim et al., 2019 | 20 OB-rTMS / 16 OB-sham | dlPFC-rTMS | ICA-based network FC | 0–1mo post-rTMS | Increased FPN FC after rTMS and weight loss and reduced food intake. |
| Uniacke et al., 2019 | 25 AN / 24 HC | Weight restoration | Seed-based whole-brain FC (Nacc) and ICA (DMN, SN, and ECN) | 0 - ~2mo | NAcc–OFC FC was higher in AN vs. HC at baseline, with no differences after weight restoration; no changes in ICA networks. |
| Zhang et al., 2019 | 30 OB-LSG / 26 OB-noLSG | LSG | Seed-to-voxel FC; HIPP and PCC seeds | 0–1mo post LSG | HIPP–insula and PCC–DLPFC FC post-LSG |
| Dong et al., 2020 | 14 OB-LSG | LSG | ROI-to-ROI pairwise | 0–6mo post LSG | Decreased precuneus–putamen FC post LSG and positively associated with FA |
| Wang et al., 2020 | 30 OB-LSG | LSG | Seed-based FC from INS and PCC | 0–1mo −3mo | Increased INS–PCC FC and decreased PCC–DMPFC FC at 1 and 3 months post-LSG. No changes between 1 and 3 months |
| Heinrichs et al., 2021 | 33 OB-BS / 15 OB-WL | BS | NAcc–reward network and PCC/precuneus–DMN seed-based whole-brain rsFC | 0–6mo − 12mo | No changes pre–post; increased NAcc–posterior medial frontal FC associated with BMI reduction. |
| Salem et al., 2021 | 16 OB-RYGB / 19 OB-VLCD | RYGB vs. VLCD | Seed-to-voxel whole-brain FC (hypothalamus) | 0–1mo post intervention | RYGB: increased hypothalamus–dlPFC, putamen, globus pallidus and cingulate gyrus FC; VLCD: no significant increase in hypothalamic FC. |
| Zhang et al., 2021 | 19 OB-OWL / 18 SOWL | LSG | Whole-brain ROI-to-ROI RSFC | 0–6mo post LSG | Baseline frontal–parietal FC predicted weight loss at 6 months post-LSG |
| He et al., 2022 | 20 OB-EA / 15 OB-sham | EA | Seed-to-voxel RSFC from DC, Nacc, and DP | 0 - ~2mo | Increased DC–precuneus FC were associated with reductions in BMI and leptin levels in OB-EA group |
| Li et al., 2022 | 25 OB-LSG | LSG | ROI-to-ROI FC (INS, ACC, putamen, caudate, and PCC/precuneus) | 0–12mo | Decreased INS–caudate FC post-LSG |
| Gondo et al., 2023 | 18 AN / 18 HC | CBT and nutritional rehabilitation | ICA-based RSN FC (DMN, SN, and FPN) | 0–4mo | Increased DMN FC in the hippocampus and retrosplenial cortex, and increased SN FC in the dorsal anterior insula after treatment |

**Table 1** (continued)

| First author, year | Sample size (*n* groups) | Intervention / treatment | rsFC | Time points | rsFC finding /treatment outcome |
|---|---|---|---|---|---|
| Langer et al., 2023 | 34 OB-BS | RYGB or LSG | ICA-based RSN FC (CON, FPCN, DMN, DAN, and limbic network) | 0–3mo | Increased within-ScN (limbic network) post-surgery |
| Merege-Filho et al., 2023 | 12 OB-BS / 12 OB-BS + PA | BS vs. BS + PA | Seed-to-voxel hypothalamic FC | 0–3mo − 9mo | OB BS + PA showed increased hypothalamus–sensory/visual FC, decreased DMN-SN FC, and increased ScN–frontal FC; OB-BS decreased within SN |
| Mallio et al., 2023 | 42 OB-LSG / 20 OB-noLSG | LSG | ICA-based network FC | 24 mo post LSG | Good LSG outcome showed lower within-DMN FC and within-FPN FC vs. OB and bad LSG outcome, and greater ECN–SN anti-correlation, positively associated with %EWL<br>Bad LSG outcome showed higher within-VN FC vs. OB. |
| Ester-Nacke et al., 2024 | 10 OB | tDCS | Seed-based whole-brain FC from hypothalamus | baseline | Higher baseline hypothalamic RSFC predicted greater improvement in inhibitory control after anodal vs. sham net-tDCS |
| Li et al., 2025 | 18 OB-LSG | LSG | Seed-based whole-brain RSFC from OFC | 0–12mo post-LSG | Increased mOFC–SMA, ACC, precuneus and left STG FC post-LSG; changes in OFC–SMA, OFC–precuneus and OFC–cingulate FC were associated with weight loss/adiposity changes |

Note: ACC, anterior cingulate cortex; AN, anorexia nervosa; AN-BP, anorexia nervosa, binge/purge subtype; BN, bulimia nervosa; BMI, body mass index; BNST, bed nucleus of the stria terminalis; BS, bariatric surgery; CBT, cognitive behavioral therapy; CON, cognitive control network; DACC, dorsal anterior cingulate cortex; DAN, dorsal attention network; DC, dorsal caudate; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; DP, dorsal putamen; EA, electroacupuncture; ECN, executive control network; EWL, excess weight loss; FC, functional connectivity; FCD, functional connectivity density; FPCN, frontoparietal control network; FPN, frontoparietal network; HC, healthy controls; HIPP, hippocampus; INS, insula; ICA, independent component analysis; LH, lateral hypothalamus; LSG, laparoscopic sleeve gastrectomy; MH, medial hypothalamus; mOFC, medial orbitofrontal cortex; NAcc, nucleus accumbens; OB, obesity; OFC, orbitofrontal cortex; OWL, obesity with weight loss; PA, physical activity; PCC, posterior cingulate cortex; RYGB, Roux-en-Y gastric bypass; RSFC, resting-state functional connectivity; ScN, salience network; SG, sleeve gastrectomy; SMN, sensorimotor network; SN, salience network; SOWL, severe obesity with weight loss; SMA, supplementary motor area; STG, superior temporal gyrus; tDCS, transcranial direct current stimulation; VN, visual network; VLCD, very-low-calorie diet; WC; WL, weight loss

and non-remission. Full remission was defined as the complete absence of ED symptoms for at least four consecutive weeks. Partial remission was defined as substantial symptom improvement with residual symptoms, while non-remission indicated a poor clinical response. Dropout was defined as absence from at least three consecutive therapy sessions; in some cases, this category included individuals who discontinued treatment shortly after initiation, resulting in minimal exposure to the intervention. For analysis, treatment outcome was re-coded into a binary variable: good outcome (full or partial remission) and poor outcome (non-remission or dropout), consistent with previous studies [71, 72].

#### 2.2.3 Procedures

Participants completed assessments across two separate sessions. The first session included a clinical interview, self-report questionnaires, and measurements of height and weight for BMI calculation. The second session involved magnetic resonance imaging (MRI) acquisition, performed in afternoon scanning slots between 15:00 and 18:00. However, the exact time of the last meal before scanning was not systematically recorded. Participants with ED (AN and OB + ED) were recruited through the Eating Disorders Unit during the first week of treatment. Participants with OB-ED were recruited from the Endocrinology Department immediately before bariatric surgery. HC were recruited from the community.

#### 2.2.4 Clinical assessments

**The eating disorders inventory-2 (EDI-2)** Spanish version, is a 91-item self-report questionnaire assessing 11 ED–related domains. The total score was used as an index of overall ED symptom severity.

**The symptom checklist-90-Revised (SCL-90-R)** Spanish version, assesses general psychopathology across nine dimensions. The Global Severity Index (GSI) was used as a measure of overall psychological distress.

**Body mass index (BMI)** was calculated using height measured with a stadiometer and weight obtained with a Tanita Multi-Frequency Body Composition Analyzer BC-420MA (Tanita Corp., Tokyo, Japan).

#### 2.2.5 Imaging data acquisition

Whole-brain rs-fMRI data were acquired using a 3.0 Tesla MRI scanner equipped with a 32-channel phased-array head coil (Philips Achieva). During an 8-minute acquisition, participants were instructed to remain still, stay awake, and fixate on a cross with their eyes open. A total of 240 volumes were obtained using T2*-weighted echo-planar imaging (EPI) (TR = 2000 ms, TE = 25 ms, flip angle = 90°, FOV = 24 cm, matrix = 80 × 80), yielding isotropic voxel sizes of 3 × 3 × 3 mm. A high-resolution T1-weighted anatomical scan was also acquired to enable normalization to MNI space and anatomical localization (voxel size = 0.75 mm isotropic; 233 slices; TR = 10.43 ms; TE = 4.8 ms; flip angle = 8°).

#### 2.2.6 Resting-state fMRI data preprocessing

Functional data were preprocessed using fMRIPrep (version 23.0.11), including slice-timing correction, motion correction, co-registration to T1-weighted images using boundary-based registration, and normalization to Montreal Neurological Institute (MNI) space. Structural images were processed with FreeSurfer (recon-all) as implemented in fMRIPrep. Denoising included regression of cerebrospinal fluid and white matter signals, DVARS, mean framewise displacement (FD), and the first six principal components derived from aCompCor (fsl_regfilt). Data were spatially smoothed with a 6 mm FWHM Gaussian kernel and band-pass filtered (0.01–0.08 Hz) using fslmaths. Quality assessment was conducted through visual inspection of fMRIPrep reports to identify motion outliers (mean FD > 0.3 mm) and evaluate co-registration accuracy.

### 2.3 Statistical analysis

Sociodemographic and clinical variables were analyzed using IBM SPSS Statistics (version 27; IBM Corp., Armonk, NY, USA) with parametric tests, as appropriate. Statistical significance was set at $p < 0.05$ (two-tailed).

#### 2.3.1 Resting-state fMRI analysis

Resting-state networks (RSNs) were identified using a group probabilistic independent component analysis (ICA) approach performed jointly across all 98 participants included in this study and implemented in the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) toolbox of FSL. This approach decomposes resting-state fMRI data into spatially independent components based on temporal correlations in Blood Oxygen Level-Dependent (BOLD) signal fluctuations across brain regions, while maximizing the spatial independence between components [73]. Thirty-five independent components were estimated from the rs-fMRI data. RSNs were identified by experienced researchers (RMO and VDA) through visual inspection of the spatial distribution

of the resulting components. Components associated with motion or predominantly localized to non-neuronal regions (e.g., ventricles, white matter, or extracerebral areas) were excluded from further analyses. To further refine component selection, spatial maps were cross-correlated with canonical RSN templates provided by the Stanford Greicius Lab using the FSL command fslcc.

A total of 12 RSNs of interest were finally selected for further analyses, comprising the left and right executive control networks, dorsal attention network, somatosensory network, thalamic–basal ganglia network, primary and high visual networks, precuneus network, language network, ventral and dorsal default mode networks, and anterior salience network (See Figure S1).

Subsequently, dual-regression analyses were performed to estimate subject-specific spatial-temporal maps corresponding to the group-wise RSNs. Specifically, after a spatial regression, the degree of regional contribution of each specific voxel value to the overall temporal pattern of the independent component was computed (i.e., temporal regression).

Group-level analyses were conducted to identify differences in functional connectivity across RSNs. Individual voxel-wise connectivity maps were entered into a general linear model (GLM), and 5 predefined contrasts were specified to compare the AN, OB + ED, OB − ED groups with the HC group. Age was included as a re confounding in the group-level GLM all analyses. Statistical significance was assessed using the nonparametric permutation testing procedure implemented in FSL's randomize tool [74]. Threshold-free cluster enhancement (TFCE) was used to identify significant effects while controlling the family-wise error rate (FWE). Statistical significance was set at $p < 0.05$ for each RSN and contrast, based on 5,000 permutations. were performed. No additional correction for multiplicity across the 12 RSNs or the prespecified contrasts was applied.

Significant clusters identified in the group-level analyses were used to extract subject-specific functional connectivity measures. For each cluster, mean connectivity values were summarized as eigenvariates representing the principal component of the signal within the cluster. The rsFC–outcome analysis was subsequently restricted to clusters showing significant between-group differences in the preceding group-level analysis.

#### 2.3.2 Association with treatment outcome

Treatment outcome was operationalized as a binary variable (good vs. bad) across all groups, as defined above. Point-biserial correlation coefficients (r_pb) were computed separately within each clinical group (AN, OB+ED, and OB−ED) to assess the association between cluster-derived connectivity eigenvariates and treatment outcome. Positive coefficients indicate that higher baseline rsFC values were associated with the good-outcome group, whereas negative coefficients indicate higher rsFC values in the bad-outcome group. Given the sample size, these analyses were considered exploratory. Because statistical significance is strongly influenced by sample size, the magnitude and direction of the point-biserial correlation coefficients were considered informative indicators of the strength and direction of the observed associations.

## 3 Results

### 3.1 Sample characteristics

Demographic and clinical characteristics of the sample are summarized in Table 2. Significant group differences were observed in BMI, with both OB groups (OB-ED and OB+ED) showing higher BMI than HC and AN, and AN having the lowest BMI. Group differences were also found in clinical variables. Both the AN and OB+ED groups showed higher scores on the EDI-2 and SCL-90R than the HC and OB-ED groups.

### 3.2 Outcome-based characteristics

Participant characteristics stratified by treatment outcome (good vs. bad) are presented in Table 3. No significant differences were observed between good- and bad-outcome

**Table 2** Description of the sample

| | HC; $n=25$ | | AN; $n=27$ | | OB+ED; $n=25$ | | OB-ED; $n=21$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | $p$ |
| Age | 38.32 | 9.03 | 23.15 | 6.53 | 37.48 | 7.95 | 42.95 | 10.42 | **<0.001*** |
| Age range | 22–56 | - | 18–48 | - | 24–56 | - | 18–56 | - | |
| BMI | 21.72 | 1.97 | 16.48 | 1.23 | 37.81 | 6.17 | 44.64 | 4.97 | **<0.001*** |
| Onset | - | - | 17.39 | 4.09 | 21.22 | 8.82 | - | - | |
| EDI-2: Total | 22.28 | 14.84 | 82.81 | 37.08 | 109.92 | 36.09 | 70.24 | 36.75 | **<0.001*** |
| SCL-90R | 0.58 | 0.43 | 1.82 | 0.68 | 1.88 | 0.66 | 1.22 | 0.64 | **<0.001*** |

Note. HC: healthy controls; AN: anorexia nervosa; OB+ED: obesity with eating disorder. OB-ED: obesity without eating disorder. BMI: Body mass index (kg/m2). SCL-90-R GSI Total: Symptom Checklist-90-Revised, general psychopathological severity index. EDI-2: Eating Disorders Inventory-2 total score. SD: standard deviation. *Bold: significant comparison (0.05 level)

**Table 3** Outcome-based characteristics in clinical samples

| | Group | GOOD OUTCOME | | BAD OUTCOME | | | |
|---|---|---|---|---|---|---|---|
| | | *Mean* | *SD* | *Mean* | *SD* | T | *p* |
| Age | **AN** | 21.65 | 4.5 | 27.43 | 9.57 | -2.15 | **0.041** |
| | **OB+ED** | 37.82 | 7.91 | 36.75 | 8.53 | 0.31 | 0.76 |
| | **OB-ED** | 43.01 | 11.45 | 42.9 | 9.79 | 0.02 | 0.983 |
| BMI | **AN** | 16.36 | 1.32 | 16.81 | 0.91 | -0.84 | 0.411 |
| | **OB+ED** | 39.25 | 6.4 | 35.9 | 4.46 | 1.33 | 0.196 |
| | **OB-ED** | 44.65 | 4.24 | 44.63 | 5.91 | 0.01 | 0.993 |
| EDI-2: Total | **AN** | 83.90 | 40.43 | 79.57 | 23.21 | 0.27 | 0.792 |
| | **OB+ED** | 105.18 | 35.1 | 119.99 | 35.96 | -0.98 | 0.339 |
| | **OB-ED** | 72.91 | 44.97 | 67.3 | 27.14 | 0.34 | 0.736 |
| SCL-90R: GSI | **AN** | 1.77 | 0.74 | 1.97 | 0.33 | -0.67 | 0.507 |
| | **OB+ED** | 1.76 | 0.61 | 2.13 | 0.61 | -1.41 | 0.171 |
| | **OB-ED** | 1.31 | 0.59 | 1.13 | 0.61 | 0.68 | 0.506 |

Note. HC: healthy controls; AN: anorexia nervosa; OB+ED: obesity with eating disorder. OB-ED: obesity without eating disorder. BMI: Body mass index (kg/m2). SCL-90-R GSI Total: Symptom Checklist-90-Revised, general psychopathological severity index. EDI-2: Eating Disorders Inventory-2 total score. SD: standard deviation. *Bold: significant comparison (0.05 level)

**Table 4** Group differences in resting-state functional connectivity

| Functional connectivity | Region | MNI Coordinates (x, y, z) | | | ke[a] | t |
|---|---|---|---|---|---|---|
| HC > (OB+ED and OB-ED) | Left inferior occipital cortex (extrastriate visual cortex) | -36 | -90 | -6 | 3 | 3.88 |

Note: HC: healthy control. OB+ED: obesity with eating disorder. OB-ED: obesity without eating disorder. Results are reported at pTFCE < 0.05, family-wise error (FWE) corrected using permutation testing. Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) atlas space. a Cluster extent in voxels

participants, except for age in the AN group, where participants with a good outcome were younger than those with a bad outcome ($p=0.041$). The distribution of good and bad outcomes in the AN, OB+ED, and OB-ED groups is summarized in Table S1.

### 3.3 Group differences in resting-state functional connectivity

Reduced rsFC was observed in the OB groups (OB+ED and OB-ED) compared to HC within the thalamic-striatal intrinsic connectivity network (Table 4; Fig. 2). This effect was localized to a cluster in the left extrastriate visual cortex ($t=3.88$; $p_{TFCE} = 0.045$). No additional significant clusters were observed for contrasts involving AN vs. HC or between clinical groups. No further adjustment for multiple testing across the 12 RSNs and the 5 contrasts was applied.

### 3.4 Association with treatment outcome

A positive association trend was observed in the OB−ED group (r_pb=0.425, $p=0.055$), indicating that individuals with a good outcome in this group tended to show higher baseline rsFC in the left extrastriate visual cortex than those with a poor outcome. The corresponding associations were small and negative in the OB+ED group (r_pb=−0.143) and small and positive in the AN group (r_pb=0.076), with neither reaching statistical significance (Table 5). To formally assess whether the connectivity–outcome association differed across groups, an additional logistic regression model including group, connectivity, and their interaction was fitted. The overall group × connectivity interaction was not statistically significant (Wald=3.743, df=2, $p=0.154$). Examination of the individual interaction terms showed that one group comparison approached conventional statistical significance ($p=0.063$), whereas the other was not significant ($p=0.320$). Thus, although the estimated associations differed in magnitude and direction across groups, the interaction analysis did not provide statistically significant evidence that the connectivity–outcome association differed between groups.

## 4 Discussion

### 4.1 Summary of main findings

A subcortical ICA-derived network encompassing the thalamic–basal ganglia network showed reduced rsFC in individuals with OB (both OB-ED and OB + ED) compared to

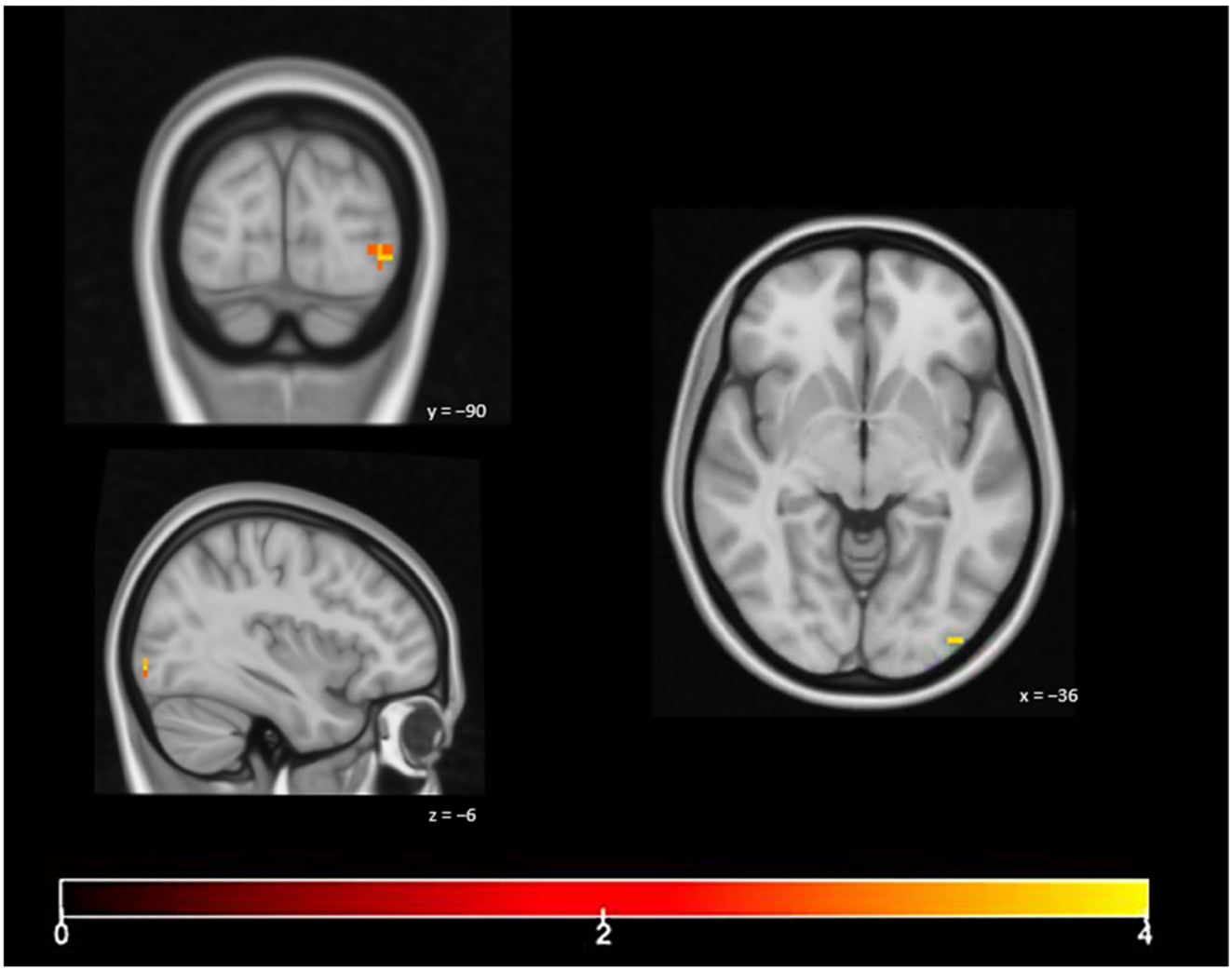



**Fig. 2** Reduced resting-state functional connectivity (rsFC) in the OB groups (OB + ED and OB − ED) compared with healthy controls (HC) within the thalamic–striatal intrinsic connectivity network, localized to the left extrastriate visual cortex. The color bar represents t-values. Results are displayed at family-wise error (FWE) probability ($p_{FWE} < 0.05$)

**Table 5** Point-biserial correlations (non-parametric estimation) between baseline functional connectivity and treatment outcome within each clinical group

| Network | Region | AN | OB + ED | OB-ED |
|---|---|---|---|---|
| Thalamic-basal ganglia | Left inferior occipital cortex (extrastriate visual cortex) | 0.076 | -0.143 | **0.425** |

Note: AN: anorexia nervosa; OB + ED: obesity with eating disorder. OB-ED: obesity without eating disorder. Bold: effect size within the moderate/medium range

HC. These differences were localized to a cluster in the left extrastriate visual cortex, similar to previous findings [75, 76]. No additional between-group functional connectivity differences were observed. Furthermore, higher baseline functional connectivity within the thalamic–basal ganglia network in the left extrastriate visual cluster showed a positive, although non-significant, association with treatment outcome in the OB − ED group. No comparable associations were observed in AN or OB + ED.

## 4.2 Functional interpretation of visual cortical alterations within the thalamic–basal ganglia network in obesity

From a functional perspective, the inferior occipital cortex, encompassing extrastriate visual regions, is involved in the processing of visually salient stimuli. It integrates visual input relayed via the lateral geniculate nucleus with top-down modulatory influences from prefrontal, limbic,

and attentional control regions. These processes have been consistently implicated in the processing of food-related cues [77]. Within this framework, reduced functional connectivity involving an extrastriate visual region within the thalamic–basal ganglia network may reflect alterations in the integration of sensory input with motivational and regulatory systems in OB [75].

Previous resting-state studies have reported altered rsFC between thalamic–striatal and visual associative networks in both ED [12, 51] and OB [12, 40, 75, 76]. Frank et al. [12] reported reduced responses in OB in several key nodes of the sensory-reward circuitry, including the thalamus, insula, ventral striatum, and prefrontal cortex, during the processing of visual or taste stimuli. In the context of resting-state functional connectivity, reduced connectivity in the extrastriate visual cortex within the thalamic–basal ganglia network may reflect diminished integration between visual associative regions and subcortical systems involved in eating-related processes in OB with or without ED [75].

### 4.3 Absence of group differences in AN

No significant differences in baseline functional connectivity were observed between the AN group and HC in the present study. Previous neuroimaging studies in AN have consistently reported alterations in reward-related and fronto-striatal circuits compared to HC. However, these alterations have frequently been identified using approaches targeting specific regions, circuits, or task-related processes. As such, they may reflect neural abnormalities at a more localized or context-dependent level than those captured by large-scale ICA-derived resting-state networks.

Within this framework, the absence of group differences in the present study should be interpreted cautiously. Although alterations in rsFC networks have been reported in AN [38, 42, 48], evidence from ICA-based resting-state studies remains relatively limited. Further research using larger samples is needed to clarify the extent to which RSN alterations in AN are reflected in large-scale resting-state networks.

### 4.4 Association with treatment outcome and EWC phenotype-specific effects

In OB-ED group, higher baseline rsFC in this visual region showed a positive, although non-significant, association with treatment outcome whereas no such association was found in OB+ED.

Previous neuroimaging studies have shown that baseline neural activity and connectivity within circuits involved in reward processing, salience attribution, and cognitive control are associated with treatment response in both OB and ED [21, 22, 58]. Variability across regions involved in processing food-related cues may influence intervention success by modulating how such stimuli are processed. Given the exploratory nature of these analyses, this observation should be considered hypothesis-generating and requires confirmation in adequately powered samples.

However, the present findings suggest that the relationship between baseline RSNs organization and treatment response may differ across OB phenotypes. One plausible explanation concerns the nature of the outcome measures used across clinical groups. In this exploratory study, treatment outcome was modeled as a categorical variable and examined retrospectively in relation to baseline connectivity measures, without incorporating domain-specific pre–post changes. In OB-ED, treatment response was assessed using a single quantitative measure (%TWL), whereas in patients with ED (i.e., AN and OB+ED), outcome was determined using a broader set of behavioral, cognitive, and physiological criteria. Consequently, treatment outcome may capture partially distinct clinical constructs across groups. This heterogeneity may reduce the sensitivity to detect associations with baseline rsFC, particularly in studies with modest sample sizes and in clinical populations where recovery is inherently multidimensional. Future studies may benefit from examining specific domains of treatment response separately to better characterize their relationship with intrinsic functional connectivity.

### 4.5 Limitations and strengths

Several limitations should be considered. First, the sample consisted exclusively of treatment-seeking women, which may limit generalizability. Second, the sample size within each group constrained the use of multivariate models to examine the joint contribution of multiple clinical variables to treatment outcome. Third, treatment response was operationalized as a categorical variable and examined retrospectively in relation to baseline connectivity, without incorporating domain-specific longitudinal changes. Fourth, several clinical and treatment-related factors that may influence resting-state functional connectivity were not incorporated into the present analyses. These included pharmacological treatment at the time of scanning, psychiatric comorbidities in the ED groups, and hormonal factors such as amenorrhea, contraceptive use, and menstrual-cycle-related factors. In the OB groups, type 2 diabetes and glucose-lowering medication were also not accounted for. These factors may contribute to variability in brain connectivity and represent potential sources of residual confounding. Fifth, metabolic state at the time of MRI acquisition was not systematically characterized or standardized across participants. Fasting status and the exact interval since the last meal were not recorded, which may be relevant when

interpreting resting-state connectivity in networks involved in the integration of homeostatic and sensory signals. Future studies with larger samples, more comprehensive pharmacological, psychiatric, reproductive, and metabolic characterization, and more detailed clinical measures to define treatment outcome will be necessary to further clarify the relationship between intrinsic functional connectivity and treatment response across eating-related conditions.

Although limitations, study presents several strengths, including its transdiagnostic design encompassing AN, OB-ED, and OB + ED, the use of a data-driven ICA approach to characterize large-scale networks, and the integration of resting-state functional connectivity with treatment outcomes. Importantly, the identification of a differential association between baseline connectivity and treatment response within OB phenotypes highlights neurobiological heterogeneity across clinical presentations. Additionally, the focus on thalamic–visual connectivity extends current models beyond canonical reward and control circuits, emphasizing the role of sensory processing systems in eating-related conditions.

### 4.6 Conclusions

This study provides evidence that OB, regardless of the presence of ED, is characterized by reduced rsFC within a thalamic–basal ganglia network, specifically in occipital regions involved in visual processing. Baseline connectivity within this thalamic–occipital circuitry showed a positive, although non-significant, association with treatment outcome in individuals with OB without ED. Further investigation is needed to determine whether thalamic–occipital connectivity is relevant to treatment outcome across different obesity and eating-disorder phenotypes. These findings suggest that sensory–integrative networks, beyond canonical reward and control systems, may play a relevant role in eating-related conditions. Further research should explore the longitudinal and multidimensional aspects of treatment response, as well as the potential of resting-state connectivity to inform personalized interventions.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s11154-026-10097-8.

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**Author contributions** RM-O: Conceptualization, Investigation, Methodology, Data curation, Writing-original draft. CSM: Conceptualization, Investigation, Methodology, Writing-original draft. VDA: Methodology, Data curation. IB: Conceptualization, Investigation. IL: Investigation, Data curation. LCB: Conceptualization, Investigation. IS: Investigation, Data curation. RG: Methodology, Data curation. AGP: Conceptualization, Investigation. JS: Conceptualization, Investigation. JFF: Data collection, Data curation. FG-P: Data collection, Data curation. RLU: Data collection, Data curation. NV: Data collection, Data curation. SJM: Project administration; Funding acquisition. FF-A: Conceptualization, Investigation, Project administration; Funding acquisition, Writing-original draft, Supervision and review.

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**Data availability** The datasets generated and/or analysed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request and subject to approval by the relevant ethics committee. All inquiries regarding availability of the data should be referred to the corresponding author (FFA), as there are ongoing studies using the data and to preserve patient confidentiality. Requests will be considered on a case-by-case basis.

## Declarations

**Ethics approval** The study was approved by the Ethics Committee of Bellvitge University Hospital (PR146/14) and was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

**Consent to participate** Written informed consent was obtained from all participants included in the study.

**Clinical trial number** Not applicable.

**Competing interests** Fernando Fernández-Aranda received consultancy and speaking honoraria from Novo Nordisk. The remaining authors declare no competing interests.

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