

ORIGINAL ARTICLE

History of early life adversity is associated with increased food addiction and sex-specific alterations in reward network connectivity in obesity

V. Osadchiv^{1,2} , E. A. Mayer^{1,2,3,4}, R. Bhatt^{1,5}, J. S. Labus^{1,2,3}, L. Gao¹, L. A. Kilpatrick^{1,2,3}, C. Liu^{1,2,3}, K. Tillisch^{1,2,3,5}, B. Naliboff^{1,2,3}, L. Chang^{1,2,3} and A. Gupta^{1,2,3} 

¹G. Oppenheimer Family Center for Neurobiology of Stress and Resilience, Ingestive Behavior and Obesity Program, University of California, Los Angeles (UCLA), Los Angeles, CA, USA; ²David Geffen School of Medicine, University of California, Los Angeles (UCLA), Los Angeles, CA, USA; ³Vatche and Tamar Manoukin Division of Digestive Diseases, University of California, Los Angeles (UCLA), Los Angeles, CA, USA; ⁴Ahmanson-Lovelace Brain Mapping Center, University of California, Los Angeles (UCLA), Los Angeles, CA, USA; ⁵Pediatric Pain and Palliative Care Program, University of California, Los Angeles (UCLA), Los Angeles, CA, USA;

Received 4 May 2019; revised 17 July 2019; accepted 18 July 2019

Address for correspondence: A Gupta, G. Oppenheimer Family Center for Neurobiology of Stress and Resilience, Ingestive Behavior and Obesity Program, University of California, Los Angeles (UCLA), CHS 42-210 MC737818, 10833 Le Conte Avenue, Los Angeles, CA, USA.
E-mail: agupta@mednet.ucla.edu

Summary

Background

Neuroimaging studies have identified obesity-related differences in the brain's resting state activity. An imbalance between homeostatic and reward aspects of ingestive behaviour may contribute to obesity and food addiction. The interactions between early life adversity (ELA), the reward network and food addiction were investigated to identify obesity and sex-related differences, which may drive obesity and food addiction.

Methods

Functional resting state magnetic resonance imaging was acquired in 186 participants (high body mass index [BMI]: ≥ 25 : 53 women and 54 men; normal BMI: 18.50–24.99: 49 women and 30 men). Participants completed questionnaires to assess ELA (Early Traumatic Inventory) and food addiction (Yale Food Addiction Scale). A tripartite network analysis based on graph theory was used to investigate the interaction between ELA, brain connectivity and food addiction. Interactions were determined by computing Spearman rank correlations, thresholded at $q < 0.05$ corrected for multiple comparisons.

Results

Participants with high BMI demonstrate an association between ELA and food addiction, with reward regions playing a role in this interaction. Among women with high BMI, increased ELA was associated with increased centrality of reward and emotion regulation regions. Men with high BMI showed associations between ELA and food addiction with somatosensory regions playing a role in this interaction.

Conclusions

The findings suggest that ELA may alter brain networks, leading to increased vulnerability for food addiction and obesity later in life. These alterations are sex specific and involve brain regions influenced by dopaminergic or serotonergic signalling.

Keywords: Early life adversity, food addiction, obesity, sex difference.

Introduction

Despite countless advances in the field, the pathophysiology of obesity remains complex and poorly understood – with multiple factors, including environmental factors such as a toxic food environment, playing a key role (1,2). For some individuals, a history of early life adversity

(ELA), including physical and emotional abuse, trauma, neglect and family discord, can increase the risk of developing obesity in adulthood through mechanisms associated with stress, inflammation, emotional perturbations, maladaptive coping, metabolic disturbances and food addiction (3,4). As highlighted by a recent meta-analysis, a history of childhood abuse (physical, emotional, sexual

or general) is significantly associated with greater odds of adulthood obesity, and the odds of obesity increased depending on the severity and number of types of abuse (5). Another study found that severely obese adults undergoing gastric bypass surgery had prevalence rates of childhood abuse as high as 76% even after accounting for factors such as stigma, shame and guilt associated with underreporting (6). An additional study found that all but two of 63 participants who underwent bariatric surgery reported a history of adverse childhood experience (7).

Early life adversity experiences can become biologically embedded and lead to cognitive, emotional, somatic and behavioural problems in adulthood (8). Evidence from neuroimaging studies suggests that a history of ELA can have a sustained impact on the integrity and function of the brain (9–12), with brain regions associated with emotional regulation, cognitive modulation and feeding behaviours frequently implicated (12–16). Furthermore, salience and emotion regulation brain networks are especially susceptible to topological restructuring associated with ELAs (11).

Although the relationship between ELA and adult obesity is incompletely understood, some possible explanations for the reported associations have been offered. One main factor has been the link with a compulsive eating behaviour termed *food addiction* (17,18). Although not a *Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnosis, the concept of food addiction is based on the substance dependence criteria found in the DSM-IV and DSM-V, describing excessive food intake primarily for pleasure, beyond the homeostatic needs of the organism; this behaviour often involves loss of control over eating, excessive time or focus on food, neglect of other activities and continuation of the behaviour despite known negative consequences (19,20). A background of ELA may potentiate food addiction behaviours in some individuals, especially within the context of an environment rich in highly processed, calorie dense and extremely palatable food (4,21,22).

Food addiction is driven by the interactions of dopaminergic pathways with other central nervous system (CNS) networks, such as those involving the hypothalamus. Overindulgence of foods rich in fat and sugar has been shown to reduce CNS reward thresholds, resulting in a drive for higher intake of such palatable foods to achieve similar levels of satisfaction (22). A history of ELA contributes to an imbalance in these CNS networks (4). One theory posits that adversity during childhood, a key neurodevelopmental period, may disrupt neuronal growth by making stress-sensitive brain circuits vulnerable to the effects of glucocorticoids, inflammatory cytokines and excitatory microbial metabolites (15,23). There is also evidence to suggest a role for changes in the brain's

serotonergic signalling by ELA and that these alterations may contribute to obesity and food addiction (15). For example, a study of 55 women showed that lowering of CNS serotonin by acute tryptophan depletion resulted in increased sweet calorie intake and a heightened preference for sweet foods in overweight but not normal weight individuals (24). Disruptions to these brain networks may override homeostatic needs and drive the overconsumption of highly palatable foods (25,26).

The other factors to consider within a systems biological model of obesity are sex differences – an important basic variable that influences the quality and generalizability of biomedical research (27). Although studies in the USA suggest similar rates of obesity in men and women (28), international studies show a greater prevalence in women (29). Furthermore, striking sex differences have been observed in eating behaviours and food cravings, resulting in an increased risk for obesity (30–32). For example, women with obesity report higher food addiction behaviours, cravings, comorbidity and reward sensitivity than men with obesity (33–35). Other clear sex differences are reflected in the greater number in women of unsuccessful attempts to maintain weight loss and in the higher progressive weight gain ('yo-yo effect') (29,32,36–38).

Neuroimaging studies have identified some of the brain mechanisms associated with obesity and food addiction (39,40), demonstrating alterations in the core reward network (e.g. nucleus accumbens) and the extended reward network (i.e. emotion regulation, executive control, salience and somatosensory networks) (41–43). Beyond identification of anatomical and functional alterations of brain regions, recent neuroimaging studies have shifted their focus on identifying alterations in brain network properties (44). Within the framework of complex network analysis via graph theory, brain regions can be characterized by their 'centrality' or contribution to the functional integrity and information flow in the entire brain network (45–48). Regions with high centrality are considered essential for information flow and integrative processing (46,49,50). Previous work has shown that individuals who are overweight demonstrate increased centrality between reward network regions and regions of the executive control, emotional regulation and somatosensory networks (41); sex-specific brain alterations have also been reported in obesity and ELA studies (11,51–57). These findings underscore the importance of studying ELA and sex-related differences in the alterations of core and extended reward networks in obesity.

Previous studies have explored the interaction between body mass index (BMI), brain centrality and food addiction (58). This study expands on previous work and investigates commonalities and differences between

men and women in the relationship between ELA and alterations in the extended reward network of the brain, within the context of food addiction. Three hypotheses are tested: (1) increased ELA is associated with greater functional measures of centrality between core and extended reward regions in individuals with high BMI compared with individual with normal BMI. (2) The observed ELA–brain associations are greater with food addiction levels in individuals with high BMI compared with individuals with normal BMI. (3) In women with high BMI, greater ELA is associated with increased centrality of reward and emotion regulation regions but decreased centrality of salience regions. In contrast, in men with high BMI, greater ELA is associated with increased centrality of somatosensory regions.

Materials and methods

Participants

Participants between the ages of 18 and 50 years were recruited through the University of California, Los Angeles, and local community advertisements. A nurse practitioner performed a clinical assessment of all participants, which included a mini-mental state exam (59,60). The sample was composed of 186 right-handed participants (84 men and 102 women), with the absence of significant medical or psychiatric conditions. Participants were excluded for the following: pregnant or lactating, illicit drug use and substance abuse including alcohol abuse as specified by DSM criteria, abdominal surgery, tobacco dependence (half a pack or more daily), extreme strenuous exercise (>8 h of continuous exercise per week), current or past psychiatric illness and major medical or neurological conditions. Participants taking medications that interfere with the CNS or regular use of analgesic drugs were excluded. Because female sex hormones such as oestrogen are known to affect brain structure and function, only women who were in premenopausal with regular menstrual cycles and who were scanned during the follicular phase of their menstrual cycles (i.e. 4–12 d after the first day of the last menstrual period) were included in this study.

Participants with hypertension, diabetes, metabolic syndrome, eating disorders, such as anorexia or bulimia, substance abuse, tobacco dependence and psychiatric illnesses were excluded to minimize confounding effects. Participants were also excluded if they had undergone any bariatric surgery. The BMI cut-offs are as follows: the normal BMI group consisted of individuals with BMI < 25, and the high BMI group consisted of individual with BMI \geq 25 (overweight and obese). Previous work has shown that the overweight and obese brain shows similar

alterations in reward networks of the brain (41). No participants exceeded 400 lb because of magnetic resonance imaging scanning weight limits.

All procedures complied with the principles of the Declaration of Helsinki and were approved by the Institutional Review Board at UCLA's Office of Protection for Research Participants. All participants provided written informed consent.

Questionnaires

Participants filled out the Yale Food Addiction Scale (YFAS) questionnaire, a 25-item scale developed to measure food addiction by assessing signs of substance dependence symptoms in eating behaviour (61). This scale is based upon the substance dependence criteria found in the DSM-IV (19) (e.g. tolerance [marked increase in amount; marked decrease in effect], withdrawal [agitation, anxiety and physical symptoms] and loss of control [eating to the point of feeling physical ill]) (61). Although food addiction is often measured using the diagnostic criteria with a YFAS cut-off score of 3 to indicate a dichotomous 'diagnosis', we used the symptom count measure for our tripartite analysis (described in the succeeding texts), as this analysis functions best with continuous variables. For our study, higher YFAS symptom scores indicate greater addiction-like criteria. The YFAS has displayed a good internal reliability $\alpha = 0.86$ (61). The internal reliability for the study sample for YFAS was $\alpha = 0.73$. Subjective socio-economic status was measured using the MacArthur Scale of Subjective Social Status, a tool that has been previously used in large epidemiological studies conducted in the USA (62).

Early life adversity was measured using the Early Traumatic Inventory – Self Report (ETI-SR) (63), a 27-item (total score 0–27) questionnaire. This questionnaire assesses the histories of childhood traumatic and adverse life events that occurred before the age of 18 years old and covers four domains: general trauma (11 items), physical punishment (five items), emotional abuse (five items) and sexual abuse (six items). General traumatic events comprise a range of stressful and traumatic events that can be mostly secondary to chance events. Sample items on this scale include death of a parent, discordant relationships or divorce between parents or death or sickness of a sibling or friend. Physical abuse involves physical contact, constraint or confinement, with intent to hurt or injure. Sample items on the physical abuse subscale include being spanked by hand or being hit by objects. Emotional abuse is verbal communication with the intention of humiliating or degrading the victim. Sample items on the ETI-SR emotion subscale include the following, 'Often put down or ridiculed' or 'Often told that one is

no good'. Sexual abuse is unwanted sexual contact performed solely for the gratification of the perpetrator or for the purposes of dominating or degrading the victim. Sample items on the sexual abuse scale include being forced to pose for suggestive photographs, to perform sexual acts for money or to coerce anal sexual acts against one's will. Each subscale score was calculated based on the number of items receiving a positive response. The ETI-SR was the instrument chosen because of its psychometric properties, ease of administration, time efficiency and ability to measure ELAs in multiple domains (63). Each ETI-SR subscale has good reliability ($\alpha = 0.70$ – 0.87) and validity ($r = 0.32$ – 0.44) (63). The internal reliability for the study sample for the ETI-SR total scale was $\alpha = 0.70$.

Magnetic resonance imaging acquisition

Whole brain structural and functional (resting state) data were acquired using a 3.0 T Siemens Prisma MRI scanner (Siemens, Erlangen, Germany). Women were scanned during the follicular phase of their menstrual cycle. Detailed information on the standardized acquisition protocols, quality control measures and image preprocessing are provided in previously published studies (11,41,56,57,64,65).

Structural magnetic resonance imaging

High-resolution T1-weighted images were acquired: echo time/repetition time = 3.26 ms/2,200 ms, field of view = 220 × 220 mm, slice thickness = 1 mm, 176 slices, 256 × 256 voxel matrices and voxel size = 0.86 × 0.86 × 1 mm.

Functional magnetic resonance imaging

Resting-state scans were acquired with eyes closed and an echo planar sequence with the following parameters: echo time/repetition time = 28 ms/2,000 ms, flip angle = 77°, scan duration = 10m0s–10m6s, field of view = 220 mm, slices = 40 and slice thickness = 4.0 mm, and slices were obtained with whole-brain coverage.

Preprocessing of images

Preprocessing and quality control was performed using Statistical Parametric Mapping-8 (SPM8) software and involved bias field correction, coregistration, motion correction, spatial normalization, tissue segmentation and Fourier transformation for frequency distribution. Data were then spatially normalized to the Montreal Neurological Institute template using the structural scans; previous

studies suggest that this is adequate for reliable functional connectivity estimates (66–68). The average temporal signal-to-noise ratio was 50.4, as assessed by the MRIQC toolbox (69). A temporal signal-to-noise ratio of 50.4 is at least comparable with that in many published large-scale studies (70).

Magnetic resonance imaging processing

Structural image parcellation

T1-image segmentation and cortical and subcortical regional parcellation were conducted using FREESURFER v.5.3.0 (71–73) following the nomenclature described in the Destrieux and Harvard–Oxford subcortical atlas (74,75). This parcellation results in the labelling of 165 regions, 74 bilateral cortical structures, seven subcortical structures, the midbrain and the cerebellum (76).

Functional brain construction

Functional brain networks were constructed as previously described (11). To summarize, linear measures of region-to-region functional connectivity (Pearson's correlations) were computed using the CONN toolbox (77). The resting-state images were filtered using a bandpass filter ($0.008/s < f < 0.08/s$) to reduce the low-frequency and high-frequency noises. A component-based noise correction method, aCompCor (77), was applied to remove nuisances for better sensitivity and specificity of the analysis. Six motion realignment parameters and their first-order temporal derivatives along confounds for white matter and cerebrospinal fluid (based on aCompCor results) were removed using regression. Although the influence of head motion cannot be completely removed, aCompCor has been shown to be particularly effective for dealing with residual motion relative to other methods (78). The connectivity between the 165 brain regions was indexed by a matrix of Fisher z-transformed correlation coefficients reflecting the association between average temporal BOLD time series signals across all voxels in each brain region. The connectivity matrix was then smoothed with a 4-mm isotropic Gaussian kernel. Functional connections were retained at $z > 0.3$, and all other values were set to 0. The magnitude of the z-score represents the weights in the functional network.

Brain regions of interest

Based on previous research (11,79–81), regions of interest were restricted to core regions of the 'reward network' (basal ganglia: caudate, pallidum, nucleus accumbens and brainstem, including the substantia nigra [SN] and

ventral tegmental area [VTA]) and the extended reward network, which includes the 'emotional regulation network' (amygdala, hippocampus, subgenual anterior cingulate cortex and anterior cingulate cortex [ACC]), the 'salience network' (anterior insula [aINS] and anterior mid-cingulate cortex), the 'executive control network' (dorsolateral prefrontal cortex [dlPFC], ventrolateral prefrontal cortex [vlPFC], medial prefrontal cortex [mPFC] and orbital frontal gyrus [OFG]) and the 'somatosensory network' (putamen and thalamus) (Table 1, which contains a list of the regions and their Atlas labels).

Computing network metrics

The Graph Theory GLM toolbox (www.nitrc.org/projects/metalab_gtg) and in-house MATLAB scripts were used to calculate and analyse the brain network properties and organization from the participant-specific functional brain networks for the brain regions of interest. Regions with high centrality are highly influential, communicate with many other regions, facilitate functional integration and play a key role in network resilience to insult (48). Three indices of centrality were computed: (1) *degree*

strength (DS) reflects the number of other regions a brain region interacts with functionally (local prominence), (2) *betweenness centrality* (BC) reflects the ability of a region to influence information flow (signalling) between two other regions and (3) *eigenvector centrality* (EC), where higher values indicate the region is directly connected to other highly connection regions reflective of the global (versus local) prominence of a region.

Statistical analysis

Tripartite network analysis was performed to integrate information from (1) ELA (ETI-SR questionnaire), (2) food addiction (YFAS questionnaire) and (3) functional network metrics characterizing the centrality regions of interest. Spearman correlations were computed between all data types controlling for age and sex for between disease group comparisons and for age for within sex comparisons in MATLAB version R2015b. Results were adjusted for multiple testing using a false discovery rate of 5% and thresholded for significance at an adjusted p of $q < 0.05$. Next, nodes (ELA scores, YFAS scores and brain centrality metrics) and edges (significant z values)

Table 1 Regions of interest from the Destrieux and Harvard–Oxford atlas

Region	Full destrieux name	Destrieux abbreviation
Reward network		
1	Basal ganglia	Caudate Nucleus accumbens Pallidum Ventral tegmental area/substantia nigra
		CaN NAcc Pal VTA–SN
Emotional regulation network		
1	Amygdala	Amygdala
2	Hippocampus	Hippocampus
3	ACC	Anterior part of the cingulate gyrus and sulcus
4	sgACC	Subcallosal area and subcallosal gyrus
		Amg Hip ACgG_S SbCaG
Salience network		
1	aINS	Anterior segment of the circular sulcus of the insula Horizontal ramus of the anterior segment of the lateral sulcus (or fissure) Vertical ramus of the anterior segment of the lateral sulcus (or fissure) Short insular gyri Superior segment of the circular sulcus of the insula
		ACirIns ALSHorp ALSVerp ShoInG SupCirIns
2	aMCC	Middle–anterior part of the cingulate gyrus and sulcus
		MACgG_S
Executive control network		
1	OFG	Medial orbital sulcus (olfactory sulcus) Orbital gyri
		MedOrS OrG
2	dlPFC	Middle frontal gyrus (F2) Inferior frontal sulcus
		MFG InfFS
3	vlPFC	Orbital part of the inferior frontal gyrus Triangular part of the inferior frontal gyrus
		InfFGOrp InfFGTrip
4	mPFC	Transverse frontopolar gyri and sulci Straight gyrus and gyrus rectus
		TrFPoG_S RG
Somatosensory network		
1	Basal ganglia	Putamen
		Pu
2	Thalamus	Thalamus
		Tha

were imported into CYTOSCAPE v.3.5.1 for visualization. The layout results in nodes that are connected with similar associations grouped together. This technique allows one to see clusters or patterns in the data.

The results are described in terms of direct effects (nodes connected by an edge) or indirect effects (nodes that are connected to other regions via the edges of other nodes but that do not share an edge). The analysis presumes that associations present in one group, which are missing in another, not only differentiate the groups but also indicate potential clues to the functionality of the system; this approach has been used previously (58,82). Comparisons were made between all the brain networks representing each group in order to identify disease and sex effects: (1) the high BMI group versus the normal BMI group (disease effect) and (2) the women with high BMI group versus the men with high BMI group (sex effect). Each group was examined in how they differ in the areas of significant associations between ETI-SR, brain connectivity and food addiction scores (YFAS).

Results

Participant characteristics

Participant characteristics are summarized in Tables 2A and 2B. Participants with high BMI (BMI ≥ 25 kg/m²: mean BMI = 30.12, standard deviation [SD] = 4.51, range = 25.00–47.54 kg/m²) consisted of 54 men (mean = 28.71, SD = 3.19, range = 25.00–37.68 kg/m²) and 53 women (mean = 31.56, SD = 5.18, range = 25.09–47.54 kg/m²). Of these participants, 65 were overweight (BMI = 25.00–29.99 kg/m²; men = 40 and women = 25) and 42 were obese (BMI ≥ 30 kg/m²; men = 14 and women = 28). Participants with normal BMI (BMI < 25 kg/m²: mean BMI = 22.12, SD = 1.70, range = 17.90–24.88 kg/m²) consisted of 30 men (mean = 22.46, SD = 1.65, range = 17.90–24.80 kg/m²) and 49 women (mean = 21.91, SD = 1.71, range = 18.80–24.88 kg/m²).

Participants with high BMI reported higher scores on ETI-SR general ($p = 0.02$), emotional ($p = 0.0006$) and total ($p = 0.00007$). Although there were no significant differences in YFAS scores among the groups, men and women with high BMI, on average, showed higher scores than men and women with normal BMI (4.00 and 3.98 vs. 1.70 and 2.29, respectively). Similarly, all participants with high BMI, regardless of sex, had higher levels of YFAS than participants with normal BMI (3.98 vs. 2.04, respectively). A total of 17.4% of participants with high BMI reported a diagnostic (≥ 3) YFAS score, compared with 0% of participants with normal BMI ($p = 0.032$). A total of 8.0% of men with high BMI reported a diagnostic YFAS

score, compared with 22.7% of women with high BMI ($p = 0.188$). There were no significant differences in subjective socio-economic status among any of the groups.

Comparing the association networks of the high body mass index group with the normal body mass index group

Results are summarized in Tables 3 and 4 and depicted in Figure 1.

Impact of early life adversity

Only the normal BMI group showed numerous positive associations between ETI-SR total score and centrality of brain regions in the executive control network: left dlPFC (EC: $r = 0.30$, $q = 0.02$), bilateral OFG (EC left: $r = 0.34$, $q = 0.02$; EC right: $r = 0.37$, $q = 0.003$) and bilateral mPFC (EC left: $r = 0.26$, $q = 0.049$; EC right: $r = 0.39$, $q = 0.003$). No significant associations were found in the high BMI group with centrality of executive control regions.

The normal BMI group also showed a negative association between ETI-SR total and centrality of a somatosensory region: left thalamus (BC: $r = -0.28$, $q = 0.03$). In contrast, the high BMI group showed a positive association between ETI-SR physical and centrality of a different region of the somatosensory network: right putamen (BC: $r = 0.26$, $q = 0.02$). Both groups showed negative associations between ETI-SR physical and centrality of the left aINS (high BMI BC: $r = -0.25$, $q = 0.04$; normal BMI DS: $r = -0.31$, $q = 0.03$).

Associations of brain networks with food addiction scores

Compared with the normal BMI group, those with high BMI showed negative associations between YFAS and centrality of bilateral thalamus (DS right: $r = -0.36$, $q = 0.006$; DS left: $r = -0.38$, $q = 0.003$; and EC left: $r = -0.27$, $q = 0.049$).

Association of early life adversity with alterations in the extended reward network and with food addiction

The high BMI group showed an indirect association between ELA and food addiction scores through centrality of VTA-SN (ETI-SR physical BC VTA-SN: $r = -0.22$, $p = 0.02$; BC VTA-SN-YFAS: $r = 0.28$, $p = 0.02$). The normal BMI group showed numerous indirect associations between numerous indices of ELA with food addiction through centrality of right mPFC (ETI-SR total EC mPFC:

Table 2 A.) Study demographics and clinical behavioural measures for individuals in the normal and high BMI groups. B.) Comparisons of study demographics and clinical behavioural measures

Measurement	Normal BMI (<25)								
	Men N = 30			Women N = 49			Total N = 79		
	Mean or count	SD or %	N	Mean or count	SD or %	N	Mean or count	SD or %	N
Age (years)	29.70	12.13	30	28.49	10.60	49	28.95	11.15	79
BMI (kg/m ⁻²)	22.46	1.65	30	21.91	1.71	49	22.12	1.70	79
SES	5.43	2.15	7	5.83	1.27	12	5.68	1.60	19
ETI									
General score	1.53	1.72	30	1.31	1.26	48	1.40	1.44	78
Physical score	1.67	1.73	30	0.77	1.22	48	1.12	1.49	78
Emotional score	0.63	1.19	30	0.52	1.32	48	0.56	1.26	78
Sexual score	0.07	0.25	30	0.25	0.67	48	0.18	0.55	78
Total score	3.90	3.58	30	2.85	2.96	48	3.26	3.23	78
YFAS									
YFAS score	1.70	0.95	10	2.29	1.07	14	2.04	1.04	24
Measurement	High BMI (>25)								
	Men N = 54			Women N = 53			Total N = 107		
	Mean or Count	SD or %	N	Mean or count	SD or %	N	Mean or count	SD or %	N
Age (years)	34.33	12.59	54	32.49	8.69	53	33.42	10.83	107
BMI (kg/m ⁻²)	28.71	3.19	54	31.55	5.18	53	30.12	4.51	107
SES	6.11	2.19	18	5.95	1.08	42	6.00	1.48	60
ETI									
General score	1.60	1.71	53	1.85	1.85	53	1.73	1.78	106
Physical score	1.54	1.70	52	1.45	1.46	53	1.50	1.58	105
Emotional score	0.98	1.61	52	1.21	1.74	53	1.10	1.67	105
Sexual score	0.21	0.80	52	0.72	1.34	53	0.47	1.13	105
Total score	4.41	4.34	51	5.23	4.73	53	4.83	4.54	104
YFAS									
YFAS score	4.00	4.70	21	3.98	2.55	42	3.98	3.38	63
Measurement	High BMI vs. normal BMI			High BMI vs. normal BMI			High BMI vs. normal BMI		
	<i>t</i>			d.f.			<i>p</i>		
Age (years)									
SES									
ETI									
General score									
Physical score									
Emotional score									
Sexual score									
Total score									
YFAS									
YFAS score									
Measurement	Men with high BMI vs. women with high BMI			Men with high BMI vs. women with high BMI			Men with high BMI vs. women with high BMI		
	<i>t</i>			d.f.			<i>p</i>		
Age (years)									
SES									
ETI									
General score									
Physical score									
Emotional score									
Sexual score									
Total score									
YFAS									
YFAS score									

BMI, body mass index; ETI, Early Traumatic Inventory; SD, standard deviation; SES, socio-economic status; YFAS, Yale Food Addiction Survey.

Table 3 Tripartite associations (all significant association for the high BMI, normal BMI, women with high BMI, and men with high BMI groups)

High BMI						
Functional connectivity region	Network	Network metric	<i>r</i>	<i>p</i>	<i>q</i>	d.f.
ETI						
General (ETI)						
Left nucleus accumbens	Reward	Eigenvector centrality	-0.21158	0.03108	0.12432	105
Physical (ETI)						
VTA-SN	Reward	Betweenness centrality	-0.22425	0.02277	0.09109	104
Left ACC (ACgG_S)	Emotional regulation	Betweenness centrality	0.25437	0.00952	0.03807	104
Left aINS (ALSHorp)	Saliency	Betweenness centrality	-0.24943	0.01106	0.04424	104
Left dlPFC (InfFS)	Executive control	Betweenness centrality	-0.23944	0.01486	0.04457	104
Left vlPFC (InfFGOrp)	Executive control	Betweenness centrality	0.25144	0.01041	0.04457	104
Right vlPFC (InfFGOrp)	Executive control	Betweenness centrality	0.22067	0.02510	0.15058	104
Left vlPFC (InfFGTrip)	Executive control	Eigenvector centrality	-0.20013	0.04268	0.25606	104
Right putamen	Somatosensory	Betweenness centrality	0.25644	0.00893	0.01786	104
Emotional (ETI)						
Left caudate	Reward	Strength	0.23053	0.01914	0.07658	104
Right caudate	Reward	Strength	0.21073	0.03263	0.09788	104
Left amygdala	Emotional regulation	Eigenvector centrality	-0.22497	0.02233	0.08933	104
Left aINS (ALSHorp)	Saliency	Betweenness centrality	-0.20663	0.03625	0.14501	104
Left OFG (OrG)	Executive control	Eigenvector centrality	-0.25464	0.00944	0.05664	104
Right mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	-0.19674	0.04639	0.23541	104
Left dlPFC (MFG)	Executive control	Betweenness centrality	0.19392	0.04967	0.29803	104
Sexual (ETI)						
Right vlPFC (InfFGTrip)	Executive control	Eigenvector centrality	0.19944	0.04341	0.26047	104
Total (ETI)						
Left ACC (ACgG_S)	Emotional regulation	Betweenness centrality	0.25688	0.00915	0.03661	103
Left aINS (ALSHorp)	Saliency	Betweenness centrality	-0.21341	0.03127	0.12506	103
Left dlPFC (InfFS)	Executive control	Betweenness centrality	-0.20259	0.04114	0.12343	103
Left vlPFC (InfFGOrp)	Executive control	Betweenness centrality	0.23843	0.01581	0.09485	103
YFAS						
VTA-SN	Reward	Betweenness centrality	0.28396	0.01987	0.07950	68
Left thalamus	Somatosensory	Betweenness centrality	-0.26677	0.02909	0.05819	68
Left thalamus	Somatosensory	Eigenvector centrality	-0.27464	0.02450	0.04900	68
Right thalamus	Somatosensory	Eigenvector centrality	-0.25214	0.03955	0.07911	68
Left thalamus	Somatosensory	Strength	-0.37559	0.00174	0.00347	68
Right thalamus	Somatosensory	Strength	-0.35845	0.00290	0.00579	68
Normal BMI						
Functional connectivity region	Network	Network metric	<i>r</i>	<i>p</i>	<i>q</i>	d.f.
ETI						
General (ETI)						
Left vlPFC (InfFGOrp)	Executive control	Betweenness centrality	-0.25546	0.02593	0.15558	77
Right mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	0.28340	0.01311	0.07867	77
YFAS			-0.43797	0.03231	0.19386	25
Physical (ETI)						
VTA-SN	Reward	Eigenvector centrality	0.28254	0.01340	0.05361	77
Left aINS (ACirIns)	Saliency	Strength	-0.30798	0.00680	0.02720	77
Right aINS (SholnG)	Saliency	Strength	-0.27447	0.01642	0.06569	77
Right MACC (ACgG_S)	Saliency	Strength	-0.22919	0.04643	0.08517	77
Right OFG (OrG)	Executive control	Eigenvector centrality	0.25668	0.02521	0.07562	77
Right mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	0.26485	0.02077	0.07562	77
Left thalamus	Somatosensory	Betweenness centrality	-0.25321	0.02732	0.05464	77
Emotional (ETI)						
Left OFG (OrG)	Executive control	Eigenvector centrality	0.31112	0.00623	0.02331	77
Right OFG (OrG)	Executive control	Eigenvector centrality	0.25295	0.02748	0.06028	77

Continues

Table 3. Continued

Left dlPFC (InffS)	Executive control	Betweenness centrality	-0.31798	0.00512	0.03074	77
Right vlPFC (InffGTrip)	Executive control	Eigenvector centrality	0.24891	0.03014	0.06028	77
Left mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	0.30315	0.00777	0.02331	77
Right mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	0.32717	0.00392	0.02350	77
Sexual (ETI)						
Left dlPFC (InffS)	Executive control	Eigenvector centrality	-0.27239	0.01729	0.10374	77
Total (ETI)						
VTA-SN	Reward	Eigenvector centrality	0.23457	0.04139	0.16556	77
Right OFG (OrG)	Executive control	Eigenvector centrality	0.37108	0.00097	0.00290	77
Left OFG (OrG)	Executive control	Eigenvector centrality	0.34240	0.00246	0.01479	77
Left dlPFC (MFG)	Executive control	Eigenvector centrality	0.30315	0.00777	0.02331	77
Left mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	0.25798	0.02445	0.04891	77
Right mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	0.39134	0.00047	0.00284	77
Left thalamus	Somatosensory	Betweenness centrality	-0.27569	0.01593	0.03186	77
YFAS						
Right OFG (OrG)	Executive control	Eigenvector centrality	-0.43718	0.03266	0.10019	25
Right mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	-0.42578	0.03804	0.10019	25

Women with High BMI

Functional connectivity region	Network	Network metric	<i>r</i>	<i>p</i>	<i>q</i>	d.f.
ETI						
General (ETI)						
Right caudate	Reward	Eigenvector centrality	0.27956	0.02473	0.03710	52
Right nucleus accumbens	Reward	Eigenvector centrality	0.34203	0.01307	0.03710	52
Left aINS (ALSHorp)	Salience	Betweenness centrality	-0.28469	0.04080	0.16321	52
Physical (ETI)						
Left aINS (ALSHorp)	Salience	Betweenness centrality	-0.28425	0.00112	0.00449	52
Left putamen	Somatosensory	Strength	0.35131	0.01066	0.02131	52
Right putamen	Somatosensory	Strength	0.32796	0.01762	0.03524	52
Emotional (ETI)						
Right nucleus accumbens	Reward	Eigenvector centrality	0.27592	0.00771	0.02313	52
Left ACC (ACgG_S)	Emotional regulation	Eigenvector centrality	0.28694	0.01916	0.03833	52
Right ACC (ACgG_S)	Emotional regulation	Eigenvector centrality	0.30690	0.00690	0.02759	52
Left sgACC (SbCaG)	Emotional regulation	Eigenvector centrality	0.29556	0.01340	0.03833	52
Left aINS (ALSHorp)	Salience	Betweenness centrality	-0.29431	0.00419	0.01675	52
Sexual (ETI)						
Right aINS (ALSHorp)	Salience	Betweenness centrality	0.31814	0.02154	0.08615	52
Total (ETI)						
Right nucleus accumbens	Reward	Eigenvector centrality	0.28201	0.02282	0.06845	52
Left aINS (ALSHorp)	Salience	Betweenness centrality	-0.29581	0.03324	0.13295	52
Left putamen	Somatosensory	Strength	0.30922	0.02571	0.05142	52
Right putamen	Somatosensory	Strength	0.29247	0.03538	0.07075	52
YFAS						
VTA-SN	Reward	Betweenness centrality	0.38368	0.01109	0.04436	43
Right dlPFC (InffS)	Executive control	Betweenness centrality	-0.33333	0.00894	0.05366	43
Left vlPFC (InffGTrip)	Executive control	Betweenness centrality	-0.31484	0.00575	0.03449	43
Right mPFC (TrFPoG_S)	Executive control	Eigenvector centrality	0.36598	0.01580	0.09478	43
Left thalamus	Somatosensory	Betweenness centrality	-0.39129	0.00947	0.01894	43

Men with High BMI

Functional connectivity region	Network	Network metric	<i>r</i>	<i>p</i>	<i>q</i>	d.f.
ETI						
General (ETI)						
Left amygdala	Emotional regulation	Betweenness centrality	0.34465	0.01235	0.04939	52
Physical (ETI)						
Right caudate	Reward	Eigenvector centrality	0.30781	0.02799	0.08398	51

Continues

Table 3. Continued

Left nucleus accumbens	Reward	Betweenness centrality	-0.30109	0.03179	0.12718	51
Left hippocampus	Emotional regulation	Strength	-0.28141	0.04545	0.18179	51
Left dlPFC (InFFS)	Executive control	Betweenness centrality	-0.33094	0.01769	0.05306	51
Left vlPFC (InFFGOrp)	Executive control	Betweenness centrality	0.34037	0.01453	0.05306	51
Right vlPFC (InFFGOrp)	Executive control	Betweenness centrality	0.36065	0.00933	0.05596	51
Left vlPFC (InFFGTriP)	Executive control	Eigenvector centrality	-0.37116	0.00733	0.04399	51
Left vlPFC (InFFGTriP)	Executive control	Strength	-0.30609	0.02893	0.17356	51
Emotional (ETI)						
Right caudate	Reward	Strength	0.29087	0.03839	0.11516	51
Left OFG (OrG)	Executive control	Eigenvector centrality	-0.33562	0.01606	0.09633	51
Sexual (ETI)						
Left caudate	Reward	Strength	0.30712	0.02837	0.05674	51
Right caudate	Reward	Strength	0.30599	0.02898	0.08695	51
Left pallidum	Reward	Eigenvector centrality	0.30104	0.03182	0.12730	51
Left pallidum	Reward	Strength	0.31946	0.02231	0.05674	51
Left aINS (ACirlns)	Saliency	Betweenness centrality	-0.29324	0.03676	0.14706	51
Left dlPFC (MFG)	Executive control	Eigenvector centrality	0.29915	0.03297	0.19781	51
Left dlPFC (MFG)	Executive control	Strength	0.28943	0.03940	0.12281	51
Right vlPFC (InFFGTriP)	Executive control	Eigenvector centrality	0.33575	0.01601	0.09607	51
Right vlPFC (InFFGTriP)	Executive control	Strength	0.30069	0.03203	0.14355	51
Left mPFC (TrFPoG_S)	Executive control	Strength	0.28730	0.04094	0.12281	51
Left thalamus	Somatosensory	Strength	0.31168	0.02599	0.05197	51
Right thalamus	Somatosensory	Strength	0.36990	0.00755	0.01510	51
YFAS			-0.49862	0.01545	0.09267	23
Total (ETI)						
Right caudate	Reward	Eigenvector centrality	0.36146	0.00991	0.02972	50
Right caudate	Reward	Strength	0.28914	0.04170	0.12509	50
Left dlPFC (InFFS)	Executive control	Betweenness centrality	-0.28229	0.04701	0.14103	50
Left vlPFC (InFFGOrp)	Executive control	Betweenness centrality	0.30287	0.03252	0.14103	50
Right vlPFC (InFFGOrp)	Executive control	Betweenness centrality	0.29583	0.03699	0.22195	50
Left vlPFC (InFFGTriP)	Executive control	Eigenvector centrality	-0.30251	0.03274	0.19642	50
YFAS						
VTA-SN	Reward	Eigenvector centrality	-0.51955	0.00927	0.03708	24
VTA-SN	Reward	Strength	-0.59150	0.00233	0.00933	24
Left hippocampus	Emotional regulation	Betweenness centrality	0.68360	0.00023	0.00092	24
Left ACC (ACgG_S)	Emotional regulation	Eigenvector centrality	-0.44378	0.02983	0.11933	24
Right ACC (ACgG_S)	Emotional regulation	Eigenvector centrality	-0.46504	0.02203	0.08814	24
Left ACC (ACgG_S)	Emotional regulation	Strength	-0.46347	0.02255	0.05417	24
Right ACC (ACgG_S)	Emotional regulation	Strength	-0.49237	0.01452	0.05808	24
Left sgACC (SbCaG)	Emotional regulation	Strength	-0.45070	0.02709	0.05417	24
Right aINS (SholnG)	Saliency	Strength	-0.42519	0.03834	0.07667	24
Left MACC (ACgG_S)	Saliency	Eigenvector centrality	-0.47111	0.02014	0.08056	24
Left MACC (ACgG_S)	Saliency	Strength	-0.52871	0.00790	0.03161	24
Right MACC (ACgG_S)	Saliency	Strength	-0.61368	0.00143	0.00570	24
Left OFG (OrG)	Executive control	Betweenness centrality	0.49154	0.01471	0.04413	24
Right dlPFC (MFG)	Executive control	Strength	-0.52306	0.00872	0.05234	24
Right vlPFC (InFFGOrp)	Executive control	Strength	-0.41754	0.04234	0.12703	24
Left vlPFC (InFFGTriP)	Executive control	Betweenness centrality	0.50666	0.01152	0.04413	24
Right putamen	Somatosensory	Strength	-0.43769	0.03243	0.03243	24
Right thalamus	Somatosensory	Betweenness centrality	0.44878	0.02783	0.05566	24
Left thalamus	Somatosensory	Eigenvector centrality	-0.50496	0.01185	0.02369	24
Right thalamus	Somatosensory	Eigenvector centrality	-0.43718	0.03266	0.06532	24
Left thalamus	Somatosensory	Strength	-0.58316	0.00278	0.00556	24
Right thalamus	Somatosensory	Strength	-0.53695	0.00682	0.01364	24

This table summarizes the key findings from Table 3, comparing disease effect (high BMI group vs. normal BMI group) and sex effect (women with high BMI group vs. men with high BMI group). Cells highlighted in grey represent that at least one association remained significant following multiple hypothesis correction ($q < 0.05$).

BMI, body mass index; ETI, Early Traumatic Inventory; YFAS, Yale Food Addiction Survey.

Table 4 Summary of adverse life event–brain associations

Functional connectivity region	High BMI vs. normal BMI	Women with high BMI vs. men with high BMI
Reward network		
General (ETI)		
Left caudate		
Right caudate		Women with high BMI: ↑
Left nucleus accumbens	High BMI: ↓	
Right nucleus accumbens		Women with high BMI: ↑
Physical (ETI)		
Right caudate		Men with high BMI: ↑
Left nucleus accumbens		Men with high BMI: ↓
VTA–SN		
	High BMI: ↓	
	Normal BMI: ↑	
Emotional (ETI)		
Left caudate	High BMI: ↑	
Right caudate	High BMI: ↑	Men with high BMI: ↑
Right nucleus accumbens		Women with high BMI: ↑
Sexual (ETI)		
Left caudate		Men with high BMI: ↑
Right caudate		Men with high BMI: ↑
Left pallidum		Men with high BMI: ↑
Total (ETI)		
Right caudate		Men with high BMI: ↑
Right nucleus accumbens		Women with high BMI: ↑
VTA–SN		
	Normal BMI: ↑	
YFAS		
Left caudate		
Right nucleus accumbens		
VTA–SN	High BMI: ↑	Women with high BMI: ↑
		Men with high BMI: ↓
Emotional regulation network		
General (ETI)		
Left amygdala		Men with high BMI: ↑
Left sgACC		
Physical (ETI)		
Left amygdala		
Right amygdala		
Left hippocampus		Men with high BMI: ↓
Left ACC	High BMI: ↑	
Left sgACC		
Emotional (ETI)		
Left amygdala	High BMI: ↓	
Right amygdala		
Left ACC		Women with high BMI: ↑
Right ACC		Women with high BMI: ↑
Left sgACC		Women with high BMI: ↑
Sexual (ETI)		
Left sgACC		
Right sgACC		
Total (ETI)		
Left amygdala		
Left ACC	High BMI: ↑	
YFAS		
Left hippocampus		Men with high BMI: ↑
Right hippocampus		
Left ACC		Men with high BMI: ↓
Right ACC		Men with high BMI: ↓

Continues

Table 4. Continued

Functional connectivity region	High BMI vs. normal BMI	Women with high BMI vs. men with high BMI
Left sgACC		Men with high BMI: ↓
Saliency network		
General (ETI)		
Left aINS		Women with high BMI: ↓
Right aINS		
Physical (ETI)		
Left aINS	High BMI: ↓ Normal BMI: ↓	Women with high BMI: ↓
Right aINS	Normal BMI: ↓	
Right aMCC	Normal BMI: ↓	
Emotional (ETI)		
Left aINS	High BMI: ↓	Women with high BMI: ↓
Sexual (ETI)		
Left aINS		Men with high BMI: ↓
Right aINS		Women with high BMI: ↑
Total (ETI)		
Left aINS	High BMI: ↓	Women with high BMI: ↓
YFAS		
Left aINS		
Right aINS		Men with high BMI: ↓
Left aMCC		Men with high BMI: ↓
Right aMCC		Men with high BMI: ↓
Executive control network		
General (ETI)		
Left vIPFC	Normal BMI: ↓	
Right vIPFC		
Right mPFC		
Physical (ETI)		
Right OFG	Normal BMI: ↑	
Left dIPFC	High BMI: ↓	Men with high BMI: ↓
Right dIPFC		
Left vIPFC	High BMI: ↑	Men with high BMI: ↓
Right vIPFC	High BMI: ↑	Men with high BMI: ↑
Right mPFC	Normal BMI: ↑	
Emotional (ETI)		
Left OFG	High BMI: ↓ Normal BMI: ↑	Men with high BMI: ↓
Right OFG	Normal BMI: ↑	
Left dIPFC	High BMI: ↑ Normal BMI: ↓	
Right vIPFC	Normal BMI: ↑	
Left mPFC	Normal BMI: ↑	
Right mPFC	High BMI: ↓ Normal BMI: ↑	
Sexual (ETI)		
Left dIPFC	Normal BMI: ↓	Men with high BMI: ↑
Right vIPFC	High BMI: ↑	Men with high BMI: ↑
Left mPFC		Men with high BMI: ↑
Total (ETI)		
Left OFG	Normal BMI: ↑	
Right OFG	Normal BMI: ↑	
Left dIPFC	High BMI: ↓ Normal BMI: ↑	Men with high BMI: ↓
Left vIPFC	High BMI: ↑	Men with high BMI: ↓
Right vIPFC		Men with high BMI: ↑
Left mPFC		

Continues

Table 4. Continued

Functional connectivity region	High BMI vs. normal BMI	Women with high BMI vs. men with high BMI
Right mPFC	Normal BMI: ↑	
YFAS		
Left OFG		Men with high BMI: ↑
Right dlPFC		Women with high BMI: ↓
		Men with high BMI: ↓
Left vIPFC		Women with high BMI: ↓
		Men with high BMI: ↑
Right vIPFC		Men with high BMI: ↓
Right mPFC		Women with high BMI: ↑
Somatosensory network		
General (ETI)		
Right putamen		
Physical (ETI)		
Left putamen		Women with high BMI: ↑
Right putamen	High BMI: ↑	Women with high BMI: ↑
Left thalamus	Normal BMI: ↓	
Sexual (ETI)		
Right putamen		
Left thalamus		Men with high BMI: ↑
Right thalamus		Men with high BMI: ↑
Total (ETI)		
Left putamen		Women with high BMI: ↑
Right putamen		Women with high BMI: ↑
Left thalamus	Normal BMI: ↓	
YFAS		
Left putamen		
Right putamen		Men with high BMI: ↓
Left thalamus	High BMI: ↓	Women with high BMI: ↓
		Men with high BMI: ↓
Right thalamus	High BMI: ↓	Men with high BMI: ↓

BMI, body mass index; ETI, Early Traumatic Inventory; YFAS, Yale Food Addiction Survey.

$r = 0.39$, $q = 0.003$; ETI-SR emotional EC mPFC: $r = 0.33$, $q = 0.02$; ETI-SR physical EC mPFC: $r = 0.26$, $p = 0.02$; ETI-SR general EC mPFC: $r = 0.28$, $p = 0.01$; and EC mPFC-YFAS: $r = -0.43$, $p = 0.04$) and right OFG (ETI-SR total EC OFG: $r = 0.37$, $q = 0.003$; ETI-SR emotional EC OFG: $r = 0.25$, $p = 0.03$; ETI-SR physical EC OFG: $r = 0.26$, $p = 0.03$; and EC OFG-YFAS: $r = -0.44$, $p = 0.03$). This group also showed a direct negative association between ETI-SR general trauma score and food addiction ($r = -0.44$, $p = 0.03$).

Comparing the association networks of women with high body mass index with men with high body mass index

Results are summarized in Tables 3 and 4 and depicted in Figure 2.

Impact of early life adversity

Both men and women with high BMI showed positive associations between ETI-SR and centrality of reward

regions: right caudate (men | ETI-SR total: EC $r = 0.36$, $q = 0.03$; women | ETI-SR general: EC: $r = 0.28$, $q = 0.04$) and right nucleus accumbens (women | ETI-SR emotional: EC: $r = 0.28$, $q = 0.02$; women | ETI-SR general: EC: $r = 0.34$, $q = 0.04$). Similarly, both groups also showed positive associations between ETI-SR and centrality of emotion regulation regions: bilateral ACC (women | ETI-SR emotional: EC left: $r = 0.29$, $q = 0.04$; EC right: $r = 0.31$, $q = 0.03$), left subgenual ACC (women | ETI-SR emotional: EC: $r = 0.30$, $q = 0.04$) and left amygdala (men | ETI-SR general: BC: $r = 0.34$, $q = 0.049$). Both groups also showed positive associations between ETI-SR and centrality of somatosensory regions: right thalamus (men | ETI-SR sexual: DS: $r = 0.37$, $q = 0.02$) and bilateral putamen (women | ETI-SR physical: DS left: $r = 0.35$, $q = 0.02$; DS right: $r = 0.33$, $q = 0.04$). Only the men with high BMI showed a negative association between ETI-SR physical and centrality of an executive control region: left vIPFC (EC: $r = -0.37$, $q = 0.04$), while no significant associations were found in the women with high BMI with centrality of executive control regions.

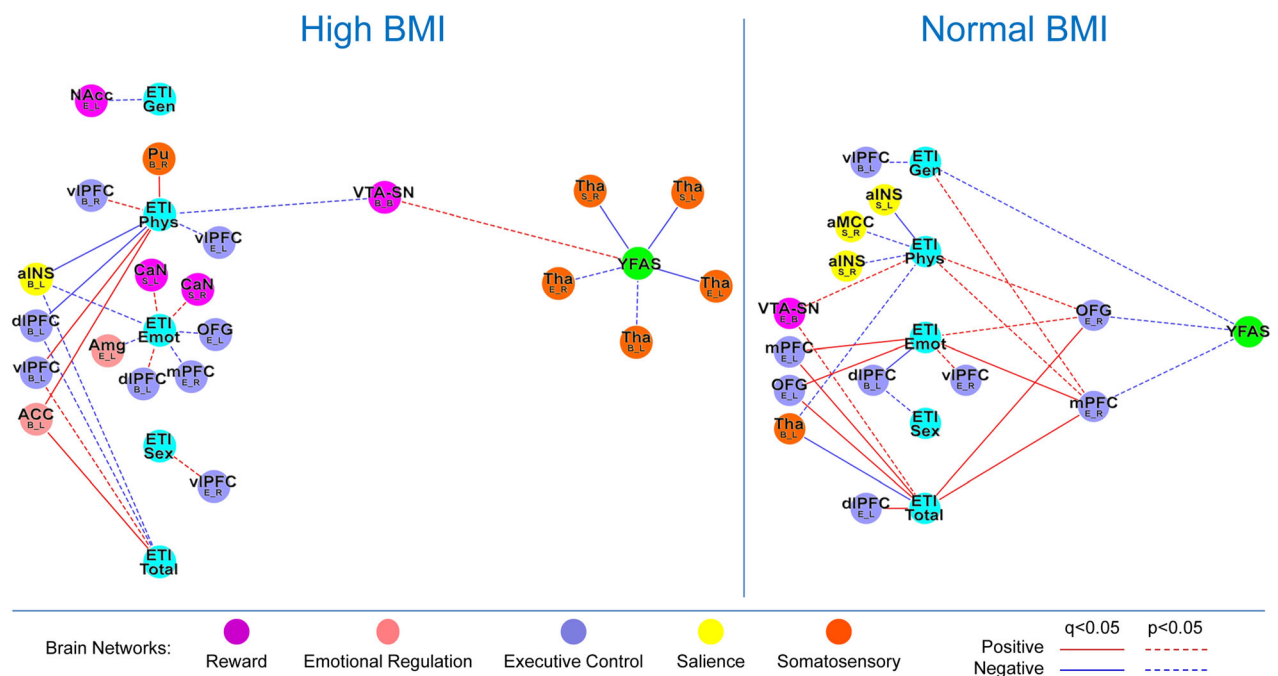


Figure 1 Tripartite association network of the high body mass index (BMI) and normal BMI groups. This figure demonstrates the tripartite association network of the high BMI and normal BMI groups to underscore disease effect. Functional brain connectivity of regions of interest is presented with the region of interest noted in a larger font, with the connectivity measure and lateralization indicated below in the form X_Y, where X indicated a connectivity measure (B, betweenness centrality; E, eigenvector centrality; S, degree strength) and Y indicates lateralization (B, bilateral; L, left; R, right). ACC, anterior cingulate; aINS, anterior insula; Amg, amygdala; CaN, caudate; dlPFC, dorsal lateral prefrontal cortex; ETI Emot, early traumatic inventory subscale emotion score; ETI Gen, early traumatic inventory subscale general scores; ETI Phys, early traumatic inventory subscale physical scores; ETI Sex, early traumatic inventory subscale sex scores; ETI Total, early traumatic inventory subscale total scores; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; OFG, orbital frontal gyrus; Pu, putamen; Tha, thalamus; vlPFC, ventral lateral prefrontal cortex; VTA–SN, ventral tegmental area/substantia nigra; YFAS, Yale Food Addiction Survey.

Associations of brain networks with food addiction scores

Women showed a *positive* association between YFAS and centrality of VTA–SN (BC: $r = 0.38$, $q = 0.04$), while men showed *negative* associations between YFAS and centrality of the same reward region (DS: $r = -0.59$, $q = 0.009$; EC: $r = -0.52$, $q = 0.04$). Women showed a *negative* association between YFAS and centrality of left vlPFC (BC: $r = -0.31$, $q = 0.03$). In contrast, men group showed *positive* associations between YFAS and centrality of the same executive control region (BC: $r = 0.51$, $q = 0.04$) and left OFG (BC: $r = 0.49$, $q = 0.04$).

Only male participants showed a positive association between YFAS and centrality of emotional regulation and saliency regions: left hippocampus (BC: $r = 0.68$, $q = 0.0009$) and bilateral anterior mid-cingulate cortex (left DS: $r = -0.53$, $q = 0.03$; right DS: $r = -0.61$, $q = 0.006$). Both men and women showed negative association between YFAS and centrality of somatosensory regions: left thalamus (women BC: $r = -0.39$, $q = 0.02$; men EC: $r = -0.50$, $q = 0.02$; and men left DS: $r = -0.58$,

$q = 0.006$), right thalamus (men DS: $r = -0.54$, $q = 0.01$) and right putamen (men DS: $r = -0.44$, $q = 0.03$).

Early life adversity is associated with alterations in the extended reward network and with food addiction

Men showed an indirect association between ELA and food addiction through centrality of right thalamus (ETI-SR sexual DS right thalamus: $r = 0.37$, $q = 0.02$; DS right thalamus YFAS: $r = -0.54$, $q = 0.01$) and left thalamus (ETI-SR sexual DS left thalamus: $r = 0.31$, $p = 0.03$; DS left thalamus YFAS: $r = -0.58$, $q = 0.006$).

Discussion

The goal of the current study was to investigate the association of ELA with measures of connectivity in the core and extended reward network of the brain and with a measure of food addiction. In addition, this study aimed to determine if these associations differ according to sex. Individuals with high BMI had positive associations

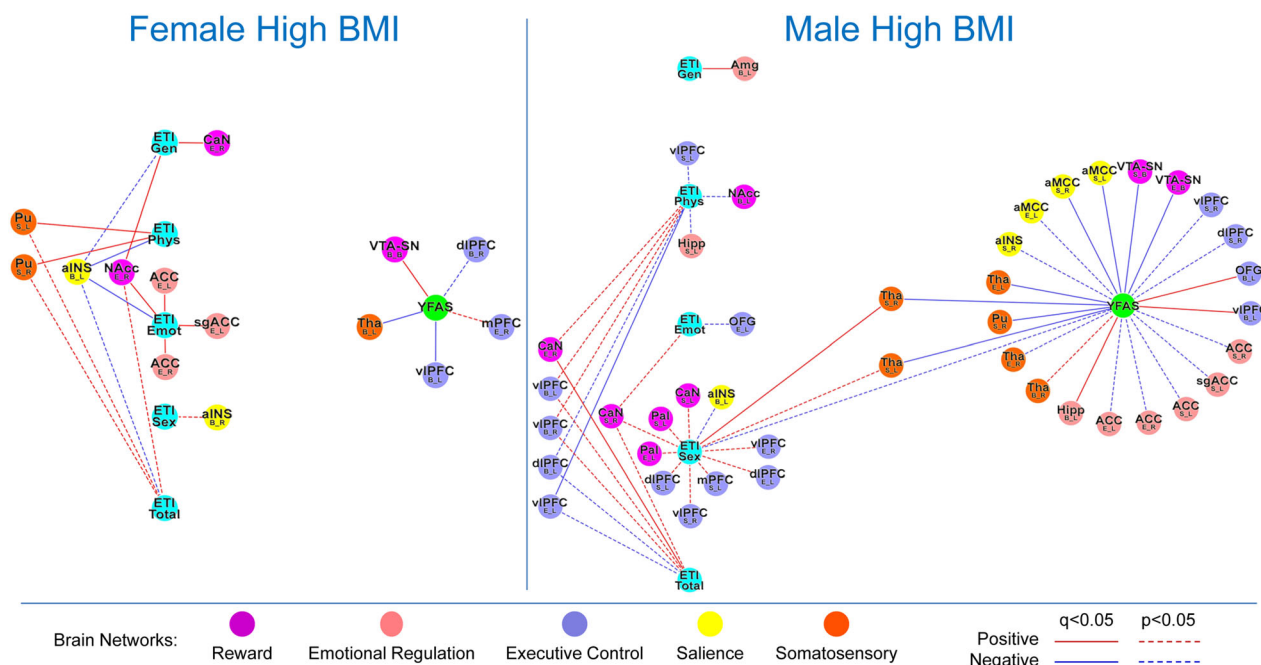


Figure 2 Tripartite association network of the women with high body mass index (BMI) and men with high BMI groups. This figure demonstrates the tripartite association network of the women with high BMI and men with high BMI groups to underscore sex effect. Functional brain connectivity of regions of interest is presented with the region of interested noted in a larger font, with the connectivity measure and lateralization indicated below in the form X_Y, where X indicated a connectivity measure (B, betweenness centrality; E, eigenvector centrality; S, degree strength) and Y indicates lateralization (B, bilateral; L, left; R, right). ACC, anterior cingulate; aINS, anterior insula; aMCC, middle anterior cingulate; Amg, amygdala; CaN, caudate; dlPFC, dorsal lateral prefrontal cortex; ETI Emot, early traumatic inventory subscale emotion score; ETI Gen, early traumatic inventory subscale general scores; ETI Phys, early traumatic inventory subscale physical scores; ETI Sex, early traumatic inventory subscale sex scores; ETI Total, early traumatic inventory subscale total scores; Hipp, hippocampus; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; OFG, orbital frontal gyrus; Pal, pallidum; Pu, putamen; sgACC, subgenual anterior cingulate; Tha, thalamus; vlPFC, ventral lateral prefrontal cortex; VTA-SN, ventral tegmental area/substantia nigra; YFAS, Yale Food Addiction Survey.

of ELA with centrality of emotion regulation regions; these associations were accompanied by increased food addiction scores. Participants with normal BMI showed positive associations between ELA and centrality of executive control regions. BMI-related differences are influenced by sex; women with high BMI showed positive associations between ELA and centrality of reward regions, emotion regulation regions and food addiction scores. Men with high BMI showed associations of ELA with food addiction through centrality of somatosensory regions. These results support the hypothesis that ELA events during childhood may alter connectivity of brain regions in the extended reward network, perhaps contributing to increased vulnerability for food addiction and obesity in adulthood, with these vulnerabilities differing by sex. This is the first study to investigate the role of ELA on brain networks, obesity and food addiction within the context of a comprehensive, systems biology based model that integrates sex differences.

Higher levels of ELA (physical and total) were positively associated with both emotion regulation (amygdala and ACC) and somatosensory (putamen) regions. In contrast,

negative associations were observed with salience (aINS) and executive control (dlPFC) regions. In comparison, individuals with normal BMI had positive associations between ELA (emotional and total) and executive control regions (mPFC) and negative associations with ELA (physical and total) and salience (aINS) and somatosensory (thalamus) regions. The study hypotheses, though, were only partially supported as the positive association between ELA and centrality in reward regions in participants with high BMI did not survive correction for multiple comparisons.

Alterations in reward and emotion regulation regions have been previously demonstrated in individuals with obesity (41,56,57). The basal ganglia and the related corticostriatal pathways, in particular, play a crucial role. The nucleus accumbens is a central part of the dopamine system, regulating reward sensitivity and controlling processes underlying food intake and food addiction (39). The reward deficiency model suggests that in obesity, the presence of decreased dopamine signalling in the striatum reinforces the rewarding properties of food and disrupts corticostriatal communication between the basal

ganglia (core reward) and the extended reward system (83,84). Similar to other addictive disorders in which perturbations in brain regions within the core and extended reward networks have been reported, a less responsive dopamine system leads to a greater propensity towards obesity (40,85–88). The extended reward system involves regions associated with salience and cortical inhibition (prefrontal control) networks (39,89–91). In obesity, the salience network integrates salient information to make decisions regarding food intake (92–95) and, together with the executive control network, inhibits reward impulses (96,97). When viewed together with these reports, the study results suggest that in individuals with high BMI, ELAs may further increase the engagement of emotion regulation and reward regions, perhaps contributing to increased food seeking behaviours, as measured by YFAS.

In participants with high BMI, levels of food addiction were negatively associated with centrality of the thalamus (somatosensory network). These study results are consistent with previous studies, which have demonstrated decreased functional activation and anatomical connectivity of somatosensory regions in obesity (40,41,53,56,57,98,99). Food addiction has been implicated in obesity as a result of alterations in the extended reward network (39,40,94); the somatosensory network represents an important component of the extended reward network, playing a key role in interoceptive and sensory awareness and generating appropriate motor responses (41,100,101). These findings may reflect reduced dopamine signalling in the thalamus and perhaps the striatum as a whole, which has been associated with reinforcing the rewarding properties of food and, in individuals with high BMI but not normal BMI, with increased metabolism in somatosensory cortical regions (83).

In participants with high BMI, ELA (physical) scores showed increased associations with food addiction through increased centrality of reward regions (VTA–SN, an important hub of dopaminergic signalling (102)). These associations were not seen with other ELA subscores. In individuals with normal BMI, higher levels of all ELA subscores were associated with lower food addiction through increased centrality of the executive control regions (OFG and mPFC).

The relationships between different types of ELA and alterations in functional and anatomical brain connectivity measures has been explored previously (11). ELA (general) may not be as severe or personal in nature as other ELAs and may actually serve as a source of increased resilience (11). Participants with normal BMI showed associations between food addiction and ELA (general), reflecting associations that may be protective. Participants with high BMI (high BMI group and men with high

BMI) showed associations between food addiction and other, non-general ELAs (physical and sexual), perhaps reflecting the more deleterious nature of these ELAs. Individuals with a history of general ELA (as opposed to physical or sexual) may be more likely to translate these experiences into adulthood resiliency, which may explain the potentially protective nature of these experiences (103). These findings provide a more nuanced understanding of the relationship between ELA and food addiction.

The basal ganglia (regions within the reward network) receive input from several cortical (including sensory, motor and executive control), limbic, salience and midbrain regions. The basal ganglia are involved in a range of learning behaviours related to the anticipation and motivation associated with ingestive behaviours (39,104,105). The study results demonstrate evidence that ELA may increase food addiction through increased centrality of core reward regions. Although causality remains to be determined, these findings suggest that in addition to obesity, ELA plays a role in alterations in the extended reward regions, which are associated with food addiction. ELA may contribute to disruptions in the topology of these brain regions and increase vulnerability to develop food addiction, relative to changes seen in obesity alone. Longitudinal studies will need to determine if obesity and its associated metabolic changes cause rewiring in brain architecture or if genetic factors and ELA are the primary drivers in shaping brain networks and predisposing an individual to develop maladaptive eating behaviours.

In women with high BMI, higher food addiction scores were associated with greater centrality in the core reward regions; however, in men with high BMI, higher food addiction scores were associated with decreased centrality of core reward and salience regions. Additionally, the network of women with high BMI revealed a negative association between food addiction and centrality of the executive control network (vlPFC), whereas in the network of men with high BMI, this association was positive (OFG and vlPFC). These differences are consistent with previous work describing increased post-prandial activations in reward regions in women and somatosensory regions in men (53,56,57,98,106–109). In women with high BMI, greater engagement of reward regulation networks, combined with reduced engagement of executive control regions, may increase susceptibility to cravings for certain foods, especially sugar (53,108–110). Furthermore, disruptions to these regions in women have been shown to result in hyperphagia (53,107,108).

These findings at the brain level are consistent with epidemiological studies that show sex-related differences in food addiction related to the types of foods craved and the intensity and frequency of the cravings (31,32). For

example, women crave sweets such as chocolates, while men crave savoury foods. Additionally, women report more trait-related and state-related cravings, finding it more difficult to cognitively regulate or restrain food cravings (31,32). On the other hand, men consume larger bite sizes and chew faster and more forcefully compared with women (32). This is consistent with the study results, which show an association between ELA (sex) and food addiction through centrality in somatosensory (thalamus) regions only in men with high BMI. These ingestive patterns could translate to women eating more often and men consuming larger meals in response to ELA.

Compared with men with high BMI, women with high BMI report higher food addiction behaviours, cravings, comorbidity, reward sensitivity and repeated unsuccessful attempts to maintain weight loss (33–35). The findings reported here, which suggest that men with high BMI differ from their female counterparts in the processing and modulation of rewarding food stimuli, may be attributed to the ability of oestrogen to modulate dopaminergic and serotonergic signalling (40,111). 17-Beta-estradiol has been shown to directly potentiate dopamine release in the rat nucleus accumbens (112). It is also important to note that serotonergic neurons in the midbrain differentiate early during CNS development, with sex differences in the serotonergic system of the rat brain established as early as the second postnatal week, likely mediated by intracellular oestrogen receptors (113,114). These developmental sex differences may set the stage for enhanced corticolimbic responsiveness to emotional stimuli in women (115). Alternatively, the sex-specific interactions between ELA, brain connectivity and food addiction behaviours may be a result of differential activation of the hypothalamic–pituitary–adrenal axis. Although at times conflicting, data from numerous studies have demonstrated notable sex differences with respect to stress-induced cortisol levels (116–118). It is important to note, though, that sex differences may not represent exclusively fundamental biological differences, as hedonic food intake may also be influenced by cultural differences in societal expectations from men and women (119,120).

The cross-sectional nature of the study did not enable us to address questions of causality between the observed brain changes, clinical/behavioural outcomes, self-reported ELA and obesity. Future studies will need to determine if the observed alterations in the brain's extended reward network in obesity represent a pre-obesity state, increasing the risk of developing maladaptive eating patterns during stress. Alternatively, they may be a consequence of remodelling of the brain as a consequence to ELA or obesity. Another limitation of the cross-sectional nature of this study is that it is not possible to discern whether the differences in brain circuitry,

which are influenced by ELA, contribute to food addiction or if the food addiction behaviours themselves contribute to the observed differences in the brain. Although BMI, which expresses the relationship between height and weight and is the most widely used measure of obesity, is not ideal as it does not translate to the presence of disease. Therefore, future studies may consider other measures of obesity such as waist–hip ratio or visceral adiposity in order to validate the current BMI studies. Future studies, which are appropriately powered, may benefit from three group subanalysis, further dividing the high BMI group into 'overweight' and 'obese' categories.

To measure ELA, ETI-SR was used, which does not capture the age at which the ELA occurs. Future studies may benefit from incorporating other measures of ELA that capture this information or include it into the weight of the ELA score or that quantify severity such as the Adverse Childhood Experiences questionnaire (121). ETI-SR may also be limited by recall accuracy; future, long-term longitudinal studies would likely more accurately reflect ELA that may be missed with self-report questionnaires. Additionally, future studies may benefit from less stringent exclusion criteria, including individuals who have experienced ELAs but are less healthy and suffer from other forms of addictive disorders. To assess for food addiction, we used the original YFAS (19), which is based on the DSM-IV. Future studies may benefit from using the YFAS 2.0, which is based on the DSM-5 criteria (122). Larger samples are needed with a wider range of clinical and behavioural symptoms in order to assess subgroup differences (e.g. obese versus overweight versus normal weight or high food addiction versus low food addiction; different ethnicities). Future studies with larger sample sizes will also allow for mediation and moderation analyses to be conducted. Although various trends in the data were observed, some of these trends may be due to a limited sample size, especially with respect to subgroup differences. Assessments for depression and anxiety, which are often comorbid conditions in obesity, will help to characterize obesity states. When treating YFAS as a dichotomous variable (using the accepted threshold of ≥ 3), YFAS was associated with having a higher BMI, although no statistically significant differences in YFAS scores by BMI status emerged when treating YFAS as a continuous variable; our results should be interpreted within this context. In addition, multimodal imaging will provide a better understanding of these findings. As systemic inflammatory markers (123) and metabolites such as those derived from the gut microbiota have been associated with obesity and food addiction, future mechanistic studies that integrate these mediators are also of value.

This study builds on previous work exploring the relationship between ELA, obesity and food addiction.

Participants with high BMI showed higher positive associations between ELA and centrality of emotional regulation regions and food addiction scores. In contrast, participants with normal BMI showed higher positive associations between ELA and centrality of executive control regions. These ELA–brain interactions differed substantially by sex, contributing to a more nuanced understanding of the forces driving the pathophysiology of obesity and food addiction. Women with high BMI showed positive associations with ELA and centrality of *reward* and *emotional* regulation regions and with food addiction. In contrast, men with high BMI showed associations with ELA and centrality of *somatosensory* regions and food addiction. These findings may have implications for more effective, sex-specific and behavioural treatments for obesity, especially for individuals whose obesity may be driven primarily by food addiction. For clinicians treating patients with obesity and food addiction, a more personalized treatment plan, incorporating patient sex and history of ELA, may be of value especially when treatment includes brain-directed therapies such as cognitive behavioural therapy.

Conflict of Interest Statement

No conflicts of interest exist.

Research involving human participants and informed consent

All procedures complied with the principles of the Declaration of Helsinki and were approved by the Institutional Review Board at UCLA's Office of Protection for Research Participants. All participants provided written informed consent.

Funding

This research was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases including K23 DK106528 (A. G.), R01 DK048351 (E. A. M.), P50 DK064539 (E. A. M.) and P30 DK041301, and pilot funds were provided for brain scanning by the Ahmanson-Lovelace Brain Mapping Center. Preliminary data were reported in an abstract presented as a poster at Digestive Diseases Week (DDW), Washington DC, 2018.

References

- Williamson DF, Thompson TJ, Anda RF, Dietz WH, Felitti V. Body weight and obesity in adults and self-reported abuse in childhood. *Int J Obes Relat Metab Disord* 2002 Aug; **26**: 1075–1082.
- Felitti VJ, Jakstis K, Pepper V, Ray A. Obesity: problem, solution, or both? *Perm J* 2010 Spring; **14**: 24–30.
- Farr OM, Ko BJ, Joung KE, et al. Posttraumatic stress disorder, alone or additively with early life adversity, is associated with obesity and cardiometabolic risk. *Nutr Metab Cardiovasc Dis* 2015 May; **25**: 479–488.
- Hemmingson E. Early childhood obesity risk factors: socioeconomic adversity, family dysfunction, offspring distress, and junk food self-medication. *Curr Obes Rep* 2018 Jun; **7**: 204–209.
- Hemmingson E, Johansson K, Reynisdottir S. Effects of childhood abuse on adult obesity: a systematic review and meta-analysis. *Obes Rev* 2014 Nov; **15**: 882–893.
- Grilo CM, Masheb RM, Brody M, Toth C, Burke-Martindale CH, Rothschild BS. Childhood maltreatment in extremely obese male and female bariatric surgery candidates. *Obes Res* 2005 Jan; **13**: 123–130.
- Fink K, Ross CA. Adverse childhood experiences in a post-bariatric surgery psychiatric inpatient sample. *Obes Surg* 2017 Dec; **27**: 3253–3257.
- Thomason ME, Marusak HA. Toward understanding the impact of trauma on the early developing human brain. *Neuroscience* 2017 Feb 7; **342**: 55–67.
- Saleh A, Potter GG, McQuoid DR, et al. Effects of early life stress on depression, cognitive performance and brain morphology. *Psychol Med* 2017 Jan; **47**: 171–181.
- Cohen RA, Grieve S, Hoth KF, et al. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry* 2006 May 15; **59**: 975–982.
- Gupta A, Mayer EA, Acosta JR, et al. Early adverse life events are associated with altered brain network architecture in a sex-dependent manner. *Neurobiol Stress* 2017 Dec; **7**: 16–26.
- Heany SJ, Groenewold NA, Uhlmann A, Dalvie S, Stein DJ, Brooks SJ. The neural correlates of Childhood Trauma Questionnaire scores in adults: a meta-analysis and review of functional magnetic resonance imaging studies. *Dev Psychopathol* 2017 Dec; **11**: 1–11.
- Marusak HA, Thomason ME, Peters C, Zundel C, Elrahal F, Rabinak CA. You say 'prefrontal cortex' and I say 'anterior cingulate': meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomology. *Transl Psychiatry* 2016 Nov 8; **6**: e944.
- Calem M, Bromis K, McGuire P, Morgan C, Kempton MJ. Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. *Neuroimage Clin* 2017; **14**: 471–479.
- Berens AE, Jensen SKG, Nelson CA 3rd. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Med* 2017 Jul 20; **15**: 135.
- Teicher MH, Anderson CM, Ohashi K, Polcari A. Childhood maltreatment: altered network centrality of cingulate, precuneus, temporal pole and insula. *Biol Psychiatry* 2014 Aug 15; **76**: 297–305.
- Gearhardt AN, Corbin WR, Brownell KD. Food addiction: an examination of the diagnostic criteria for dependence. *J Addict Med* 2009 Mar; **3**: 1–7.
- Gearhardt AN, Grilo CM, DiLeone RJ, Brownell KD, Potenza MN. Can food be addictive? Public health and policy implications. *Addiction* 2011 Jul; **106**: 1208–1212.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn: Washington, DC: American Psychiatric Association, 2013.

20. Carter A, Hendrikse J, Lee N, et al. The neurobiology of “food addiction” and its implications for obesity treatment and policy. *Annu Rev Nutr* 2016 Jul 17; **36**: 105–128.
21. Leigh SJ, Lee F, Morris MJ. Hyperpalatability and the generation of obesity: roles of environment, stress exposure and individual difference. *Curr Obes Rep* 2018 Mar; **7**: 6–18.
22. Cottone P, Sabino V, Roberto M, et al. CRF system recruitment mediates dark side of compulsive eating. *Proc Natl Acad Sci U S A* 2009 Nov 24; **106**: 20016–20020.
23. Raymond C, Marin MF, Majeur D, Lupien S. Early child adversity and psychopathology in adulthood: HPA axis and cognitive dysregulations as potential mechanisms. *Prog Neuropsychopharmacol Biol Psychiatry* 2018 Jul 13; **85**: 152–160.
24. Pagoto SL, Spring B, McChargue D, et al. Acute tryptophan depletion and sweet food consumption by overweight adults. *Eat Behav* 2009 Jan; **10**: 36–41.
25. Sato W, Sawada R, Kubota Y, Toichi M, Fushiki T. Homeostatic modulation on unconscious hedonic responses to food. *BMC Res Notes* 2017 Oct 26; **10**: 511.
26. Blundell JE, Finlayson G. Is susceptibility to weight gain characterized by homeostatic or hedonic risk factors for overconsumption? *Physiol Behav* 2004 Aug; **82**: 21–25.
27. Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research? *JAMA* 2016 Nov 08; **316**: 1863–1864.
28. Gartner DR, Taber DR, Hirsch JA, Robinson WR. The spatial distribution of gender differences in obesity prevalence differs from overall obesity prevalence among US adults. *Ann Epidemiol* 2016 Apr; **26**: 293–298.
29. Garawi F, Devries K, Thorogood N, Uauy R. Global differences between women and men in the prevalence of obesity: is there an association with gender inequality? *Eur J Clin Nutr* 2014 Oct; **68**: 1101–1106.
30. Lalitha V, Pal GK, Pal P, Parija SC, Murugaiyan SB. Gender difference in the role of posterodorsal amygdala on the regulation of food intake, adiposity and immunological responses in albino Wistar rats. *Annal Neurosci* 2016 Mar; **23**: 6–12.
31. Hallam J, Boswell RG, DeVito EE, Kober H. Gender-related differences in food craving and obesity. *Yale J Biol Med* 2016 Jun; **89**: 161–173.
32. Park S, Shin WS. Differences in eating behaviors and masticatory performances by gender and obesity status. *Physiol Behav* 2015 Jan; **138**: 69–74.
33. Loxton NJ, Tipman RJ. Reward sensitivity and food addiction in women. *Appetite* 2017 Aug 1; **115**: 28–35.
34. Ruddock HK, Dickson JM, Field M, Hardman CA. Eating to live or living to eat? Exploring the causal attributions of self-perceived food addiction. *Appetite* 2015 Dec; **95**: 262–268.
35. Jastreboff AM, Gaiser EC, Gu P, Sinha R. Sex differences in the association between dietary restraint, insulin resistance and obesity. *Eat Behav* 2014 Apr; **15**: 286–290.
36. Mauvais-Jarvis F. Epidemiology of gender differences in diabetes and obesity. *Adv Exp Med Biol* 2017; **1043**: 3–8.
37. Tronieri JS, Wurst CM, Pearl RL, Allison KC. Sex differences in obesity and mental health. *Curr Psychiatry Rep* 2017 Jun; **19**: 29.
38. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)* 2008 Sep; **32**: 1431–1437.
39. Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci* 2011 Jan; **15**: 37–46.
40. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev* 2013 Jan; **14**: 2–18.
41. Gupta A, Mayer EA, Sanmiguel CP, et al. Patterns of brain structural connectivity differentiate normal weight from overweight subjects. *Neuroimage Clin* 2015; **7**: 506–517.
42. Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE. The contribution of brain reward circuits to the obesity epidemic. *Neurosci Biobehav Rev* 2013 Nov; **37**: 2047–2058.
43. Lee PC, Dixon JB. Food for thought: reward mechanisms and hedonic overeating in obesity. *Curr Obes Rep* 2017 Dec; **6**: 353–361.
44. Crossley NA, Mechelli A, Scott J, et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain* 2014 Aug; **137**: 2382–2395.
45. Sporns O. From simple graphs to the connectome: networks in neuroimaging. *Neuroimage* 2012 Aug 15; **62**: 881–886.
46. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 2009 Mar; **10**: 186–198.
47. Irimia A, Chambers MC, Torgerson CM, van Horn JD. Circular representation of human cortical networks for subject and population-level connectomic visualization. *Neuroimage* 2012 Apr 2; **60**: 1340–1351.
48. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 2010 Sep; **52**: 1059–1069.
49. Bullmore E, Sporns O. The economy of brain network organization. *Nat Rev Neurosci* 2012 Apr 13; **13**: 336–349.
50. Betzel RF, Avena-Koenigsberger A, Goni J, et al. Generative models of the human connectome. *Neuroimage* 2016 Jan 1; **124**: 1054–1064.
51. Haase L, Green E, Murphy C. Males and females show differential brain activation to taste when hungry and sated in gustatory and reward areas. *Appetite* 2011 Oct; **57**: 421–434.
52. Cornier MA, Salzberg AK, Endly DC, Bessesen DH, Tregellas JR. Sex-based differences in the behavioral and neuronal responses to food. *Physiol Behav* 2010 Mar 30; **99**: 538–543.
53. Geliebter A, Pantazatos SP, McQuatt H, Puma L, Gibson CD, Atalayer D. Sex-based fMRI differences in obese humans in response to high vs. low energy food cues. *Behav Brain Res* 2013 Apr 15; **243**: 91–96.
54. Ruigrok AN, Salimi-Khorshidi G, Lai MC, et al. A meta-analysis of sex differences in human brain structure. *Neurosci Biobehav Rev* 2014 Feb; **39**: 34–50.
55. Cosgrove KP, Mazure CM, Staley JK. Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biol Psychiatry* 2007 Oct 15; **62**: 847–855.
56. Gupta A, Mayer EA, Hamadani K, et al. Sex differences in the influence of body mass index on anatomical architecture of brain networks. *Int J Obes (Lond)* 2017 Aug; **41**: 1185–1195.
57. Gupta A, Mayer EA, Labus JS, et al. Sex commonalities and differences in obesity-related alterations in intrinsic brain activity and connectivity. *Obesity (Silver Spring)* 2018 Feb; **26**: 340–350.
58. Osadchiy V, Labus JS, Gupta A, et al. Correlation of tryptophan metabolites with connectivity of extended central reward network in healthy subjects. *PLoS ONE* 2018; **13**: e0201772.
59. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 Nov; **12**: 189–198.

60. van Patten R, Britton K, Tremont G. Comparing the mini-mental state examination and the modified mini-mental state examination in the detection of mild cognitive impairment in older adults. *Int Psychogeriatr* 2018 Jul; **19**: 1–9.
61. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. *Appetite* 2009 Apr; **52**: 430–436.
62. Adler N, Singh-Manoux A, Schwartz J, Stewart J, Matthews K, Marmot MG. Social status and health: a comparison of British civil servants in Whitehall-II with European- and African-Americans in CARDIA. *Soc Sci Med* 2008 Mar; **66**: 1034–1045.
63. Bremner JD, Bolus R, Mayer EA. Psychometric properties of the Early Trauma Inventory – Self Report. *J Nerv Ment Dis* 2007 Mar; **195**: 211–218.
64. Labus JS, van Horn JD, Gupta A, et al. Multivariate morphological brain signatures predict patients with chronic abdominal pain from healthy control subjects. *Pain* 2015 Aug; **156**: 1545–1554.
65. Labus JS, Naliboff B, Kilpatrick L, et al. Pain and Interoception Imaging Network (PAIN): a multimodal, multisite, brain-imaging repository for chronic somatic and visceral pain disorders. *Neuroimage* 2015 Apr 19; **124**: 1232.
66. Birn RM, Molloy EK, Patriat R, et al. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage* 2013 Dec; **83**: 550–558.
67. van Dijk KR, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *J Neurophysiol* 2010 Jan; **103**: 297–321.
68. Gonzalez-Castillo J, Handwerker DA, Robinson ME, et al. The spatial structure of resting state connectivity stability on the scale of minutes. *Front Neurosci* 2014; **8**: 138.
69. Esteban O, Birman D, Schaer M, Koyejo OO, Poldrack RA, Gorgolewski KJ. MRIQC: advancing the automatic prediction of image quality in MRI from unseen sites. *PLoS ONE* 2017; **12**: e0184661.
70. Adhikari BM, Jahanshad N, Shukla D, et al. A resting state fMRI analysis pipeline for pooling inference across diverse cohorts: an ENIGMA rs-fMRI protocol. *Brain Imaging Behav* 2018 Sep 6. <https://doi.org/10.1007/s1168>
71. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002 Jan 31; **33**: 341–355.
72. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. *Neuroimage* 1999 Feb; **9**: 195–207.
73. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage* 1999 Feb; **9**: 179–194.
74. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006 Jul 1; **31**: 968–980.
75. Destrieux C, Fischl B, Dale A, Haglren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage* 2010 Oct 15; **53**: 1–15.
76. Irimia A, van Horn JD. The structural, connectomic and network covariance of the human brain. *Neuroimage* 2012 Oct 29; **66C**: 489–499.
77. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect* 2012; **2**: 125–141.
78. Ciric R, Wolf DH, Power JD, et al. Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *Neuroimage* 2017 Jul 1; **154**: 174–187.
79. Li G, Ji G, Hu Y, et al. Bariatric surgery in obese patients reduced resting connectivity of brain regions involved with self-referential processing. *Hum Brain Mapp* 2018 Jul 31; **39**: 4755–4765.
80. Belfort-DeAguiar R, Seo D, Lacadie C, et al. Humans with obesity have disordered brain responses to food images during physiological hyperglycemia. *Am J Physiol Endocrinol Metab* 2018 May 1; **314**: E522–E529.
81. Sinha R. Role of addiction and stress neurobiology on food intake and obesity. *Biol Psychol* 2018 Jan; **131**: 5–13.
82. Labus JS, Osadchiy V, Hsiao EY, et al. Evidence for an association of gut microbial *Clostridia* with brain functional connectivity and gastrointestinal sensorimotor function in patients with irritable bowel syndrome, based on tripartite network analysis. *Microbiome* 2019 Mar 21; **7**: 45.
83. Volkow ND, Wang GJ, Telang F, et al. Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. *Neuroimage* 2008 Oct 1; **42**: 1537–1543.
84. Gaiser EC, Gallezot JD, Worhunsky PD, et al. Elevated dopamine D_{2/3} receptor availability in obese individuals: a PET imaging study with [¹¹C](+)-PHNO. *Neuropsychopharmacology* 2016 Dec; **41**: 3042–3050.
85. Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philos T R Soc B* 2008 Oct 12; **363**: 3191–3200.
86. Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. *Biol Psychiatry* 2013 May 1; **73**: 811–818.
87. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Baler R. Food and drug reward: overlapping circuits in human obesity and addiction. *Curr Top Behav Neurosci* 2012; **11**: 1–24.
88. Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philos Trans R Soc Lond B Biol Sci* 2008 Oct 12; **363**: 3191–3200.
89. Mayer EA. Gut feelings: the emerging biology of gut–brain communication. *Nat Rev Neurosci* 2011 Aug; **12**: 453–466.
90. Kenny PJ. Reward mechanisms in obesity: new insights and future directions. *Neuron* 2011 Feb 24; **69**: 664–679.
91. Bartholdy S, Dalton B, O'Daly OG, Campbell IC, Schmidt U. A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. *Neurosci Biobehav Rev* 2016 May; **64**: 35–62.
92. Morrow JD, Maren S, Robinson TE. Individual variation in the propensity to attribute incentive salience to an appetitive cue predicts the propensity to attribute motivational salience to an aversive cue. *Behav Brain Res* 2011 Jun 20; **220**: 238–243.
93. Garcia-Garcia I, Jurado MA, Garolera M, et al. Alterations of the salience network in obesity: a resting-state fMRI study. *Hum Brain Mapp* 2013 Nov; **34**: 2786–2797.
94. Volkow ND, Baler RD. NOW vs LATER brain circuits: implications for obesity and addiction. *Trends Neurosci* 2015 Jun; **38**: 345–352.
95. Wijngaarden MA, Veer IM, Rombouts SA, et al. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. *Behav Brain Res* 2015; **287**: 127–134.

96. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct* 2010 Jun; **214**: 655–667.
97. Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Rev* 2003 Jan; **41**: 88–123.
98. Atalayer D, Pantazatos SP, Gibson CD, et al. Sexually dimorphic functional connectivity in response to high vs. low energy-dense food cues in obese humans: an fMRI study. *Neuroimage* 2014 Oct 15; **100**: 405–413.
99. Wang GJ, Tomasi D, Backus W, et al. Gastric distention activates satiety circuitry in the human brain. *Neuroimage* 2008 Feb 15; **39**: 1824–1831.
100. Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. *J Neurosci Off J Soc Neurosci* 2011 Mar 23; **31**: 4360–4366.
101. Olivo G, Wiemerslage L, Nilsson EK, et al. Resting-state brain and the FTO obesity risk allele: default mode, sensorimotor, and salience network connectivity underlying different somatosensory integration and reward processing between genotypes. *Front Hum Neurosci* 2016; **10**: 52.
102. Rinaldi R. Dopamine and reward seeking: the role of ventral tegmental area. *Rev Neurosci* 2014; **25**: 621–630.
103. Kentner AC, Cryan JF, Brummelte S. Resilience priming: translational models for understanding resiliency and adaptation to early life adversity. *Dev Psychobiol* 2019 Apr; **61**: 350–375.
104. Balleine BW, Delgado MR, Hikosaka O. The role of the dorsal striatum in reward and decision-making. *J Neurosci Off J Soc Neurosci* 2007 Aug 1; **27**: 8161–8165.
105. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacol Off Publ Am College Neuropsychopharmacol* 2010 Jan; **35**: 4–26.
106. Coveleskie K, Gupta A, Kilpatrick LA, et al. Altered functional connectivity within the central reward network in overweight and obese women. *Nutr Diabetes* 2015 Jan 19; **5**: e148.
107. Stice E, Burger KS, Yokum S. Relative ability of fat and sugar tastes to activate reward, gustatory, and somatosensory regions. *Am J Clin Nutr* 2013 Dec; **98**: 1377–1384.
108. Connolly L, Coveleskie K, Kilpatrick LA, et al. Differences in brain responses between lean and obese women to a sweetened drink. *Neurogastroenterol Motil* 2013 Jul; **25**: 579–e460.
109. Kilpatrick LA, Coveleskie K, Connolly L, et al. Influence of sucrose ingestion on brainstem and hypothalamic intrinsic oscillations in lean and obese women. *Gastroenterology* 2014 May; **146**: 1212–1221.
110. Li P, Shan H, Liang S, et al. Sleeve gastrectomy recovering disordered brain function in subjects with obesity: a longitudinal fMRI study. *Obes Surg* 2018 Mar; **2**.
111. Rapuano KM, Huckins JF, Sargent JD, Heatherton TF, Kelley WM. Individual differences in reward and somatosensory-motor brain regions correlate with adiposity in adolescents. *Cereb Cortex* 2016 Jun; **26**: 2602–2611.
112. Thompson TL, Moss RL. Estrogen regulation of dopamine release in the nucleus accumbens: genomic- and nongenomic-mediated effects. *J Neurochem* 1994 May; **62**: 1750–1756.
113. Jarzab B, Dohler KD. Serotonergic influences on sexual differentiation of the rat brain. *Prog Brain Res* 1984; **61**: 119–126.
114. McEwen BS, Alves SE. Estrogen actions in the central nervous system. *Endocr Rev* 1999 Jun; **20**: 279–307.
115. Domes G, Schulze L, Bottger M, et al. The neural correlates of sex differences in emotional reactivity and emotion regulation. *Hum Brain Mapp* 2010 May; **31**: 758–769.
116. Uhart M, Chong RY, Oswald L, Lin PI, Wand GS. Gender differences in hypothalamic-pituitary-adrenal (HPA) axis reactivity. *Psychoneuroendocrinology* 2006 Jun; **31**: 642–652.
117. Kudielka BM, Kirschbaum C. Sex differences in HPA axis responses to stress: a review. *Biol Psychol* 2005 Apr; **69**: 113–132.
118. Bangasser DA, Valentino RJ. Sex differences in stress-related psychiatric disorders: neurobiological perspectives. *Front Neuroendocrinol* 2014 Aug; **35**: 303–319.
119. Estima CC, Bruening M, Hannan PJ, et al. A cross-cultural comparison of eating behaviors and home food environmental factors in adolescents from São Paulo (Brazil) and Saint Paul – Minneapolis (US). *J Nutr Educ Behav* 2014 Sep-Oct; **46**: 370–375.
120. Pollard J, Kirk SF, Cade JE. Factors affecting food choice in relation to fruit and vegetable intake: a review. *Nutr Res Rev* 2002 Dec; **15**: 373–387.
121. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) Study. *Am J Prev Med* 2019 Jun; **56**: 774–786.
122. Gearhardt AN, Corbin WR, Brownell KD. Development of the Yale Food Addiction Scale version 2.0. *Psychol Addict Behav* 2016 Feb; **30**: 113–121.
123. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm* 2010; **2010**.