



Depression and obesity: evidence of shared biological mechanisms

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Received: 11 September 2017 / Revised: 13 November 2017 / Accepted: 6 December 2017 / Published online: 16 February 2018
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Abstract

Depression and obesity are common conditions with major public health implications that tend to co-occur within individuals. The relationship between these conditions is bidirectional: the presence of one increases the risk for developing the other. It has thus become crucial to gain a better understanding of the mechanisms responsible for the intertwined downward physiological spirals associated with both conditions. The present review focuses specifically on shared biological pathways that may mechanistically explain the depression–obesity link, including genetics, alterations in systems involved in homeostatic adjustments (HPA axis, immuno-inflammatory activation, neuroendocrine regulators of energy metabolism including leptin and insulin, and microbiome) and brain circuitries integrating homeostatic and mood regulatory responses. Furthermore, the review addresses interventional opportunities and questions to be answered by future research that will enable a comprehensive characterization and targeting of the biological links between depression and obesity.

Introduction

Both depression and obesity are widespread conditions with major personal and public health implications [1–3]. As there is evidence that their prevalence and relative impact on public health will increase further over the next decade, both conditions deserve our full research and clinical attention. Clinically relevant depression could be defined either through self-reported symptoms (e.g. applying established cut-offs to questionnaire scores) or through an interview-based psychiatric diagnosis of major depressive disorder (MDD). Throughout this review, the term depression, if not otherwise specified, is used in its broadest meaning including both relevant self-reported symptoms and clinical syndromes. Where needed, the appropriate

terms of MDD diagnosis or self-reported symptoms are used to specifically distinguish the different definitions. Obesity is most often defined by a body mass index (BMI) ≥ 30 kg/m² according to WHO criteria. Many recent lines of scientific evidence indicate that depression and obesity are not independent. In fact, there is strong reason to believe that these conditions are interconnected through a vicious, mutually reinforcing cycle of adverse physiological adaptations. It is crucial to gain a better understanding of the mechanisms responsible for the interconnected downward spiral into both conditions. This review summarizes the epidemiological evidence linking depression and obesity (see Evidence for a bidirectional link between MDD and obesity). Then, the focus is on shared biological mechanisms that may explain the depression–obesity association at different levels, from genes and peripheral endocrine, immuno-inflammatory and metabolic mechanisms to brain (see Biological mechanisms linking depression and obesity). We conclude by discussing interventional opportunities and key issues to be addressed by future research (see Clinical and research implications).

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Evidence for a bidirectional link between MDD and obesity

Epidemiological evidence strongly supports an association between depression and obesity. Table 1 summarizes previous meta-analytic evidence; where feasible, pooled

Table 1 Overview of meta-analyses examining the association between depression and obesity

	Nr studies (sample size)	Depression definition	Obesity definition	Pooled effect sizeOdds ratio (95% CI)	Specific details
Cross-sectional evidence from meta-analyses					
De Wit et al. (2010) [5]	N = 8 [166,865]	Symptoms	BMI ≥ 30 or WC ≥ 88 (♂)/102 (♂)	1.23 (1.03–1.47)	
	N = 9 [37,638]	Clin Diag	BMI ≥ 30 or WC ≥ 88 (♀)/ ≥ 102 (♂)	1.14 (0.90–1.44)	
Xu et al. (2011) [9]	N = 12 [27,445]	Symptoms	WHR > 1 or WC ≥ 88 (♀)/ ≥ 102 (♂)	1.41 (1.22–1.64)	Only abdominal obesity indices
	N = 3 [7387]	Clin Diag	WHR > 1 or WC ≥ 88 (♀)/ ≥ 102 (♂)	1.30 (0.96–1.75)	
Abou Abbas et al. (2015) [8]	N = 8 [12,641]	Combined sympt. or SR disease or Clin Diag ^a	BMI ≥ 30 or WHR ≥ 0.84	1.27 (1.11–1.44)	Only studies from the Middle-East
Pereira-Miranda et al. (2015) [10]	N = 9 [171,701]	Combined sympt. or clin diag	BMI ≥ 30	1.32 (1.26–1.38)	
Quek et al. (2017) [7]	N = 7 [22,896]	Clin Diag	BMI $> 95^{\text{th}}$ p. or $>$ age-specific cut-offs	1.34 (1.10–1.64)	Only childhood or adolescent samples
Jung et al. (2017) [6]	N = 18 [371,897] N = 8 [176,510]	Symptoms Clin Diag	BMI ≥ 30 BMI ≥ 30	1.29 (1.18–1.42) 1.16 (1.02–1.32)	
Longitudinal evidence from meta-analyses					
Blaine (2008) [13]	N = 23 [33,690]	Combined sympt. or Clin Diag	BMI weight change or onset of BMI ≥ 30	OBES→DEP 1.19 (1.14–1.24) DEP→OBES	
Luppino et al. (2010) [4]	N = 5 [52,421] N = 3 [2966] N = 5 [3643] N = 4 [2991]	Symptoms Clin Diag Symptoms Clin Diag	BMI ≥ 30 BMI ≥ 30 BMI ≥ 30 BMI ≥ 30	1.36 (1.03–1.80) 2.15 (1.48–3.12) 1.48 (1.17–1.87) 1.71 (1.33–2.19)	Adolescent and adult samples
Mannan et al. (2016) [11]	N = 12 [126,594] N = 9 [85,358] N = 6 [20,855] N = 7 [16,373]	Combined sympt. or Clin Diag ^a Combined sympt. or Clin Diag ^a Combined sympt. or Clin Diag ^a Combined sympt. or Clin Diag ^a	BMI ≥ 30 BMI ≥ 30 BMI ≥ 30 BMI ≥ 30	1.18 (1.04–1.35) 1.37 (1.17–1.48) 1.40 (1.16–1.70) 1.70 (1.40–2.07)	Adult samples only Adolescent samples only

^aNumber/size of included studies not large enough to reliably separate effects. SR self-reported, Clin Diag clinical diagnosis using psychiatric criteria, WHR waist-hip ratio, WC waist circumference, BMI body mass index, CI confidence interval

estimates were presented separately for clinical diagnoses and self-reported symptoms of depression. Six meta-analyses [4–9] combining up to 26 cross-sectional studies all confirm a positive association between depression and obesity. Pooled cross-sectional odds ratios of depression among the obese ranged from 1.23 to 1.41 in studies based on self-reported symptoms, and from 1.14 to 1.30 in studies based on clinical diagnoses. Four longitudinal meta-analyses [10–13] confirm the existence of a bidirectional relationship: obesity longitudinally increases the risk of developing depression, and vice versa, depression increases the risk of subsequent obesity. As compared to cross-sectional meta-analyses, effect sizes tend to be higher in longitudinal analyses and one study [10] showed stronger bidirectional effects for MDD as compared to self-report symptoms. Overall, effect sizes are stronger when considering extreme obesity (class III: BMI ≥ 40 kg/m²) than when applying the BMI cut-off of 30 kg/m², and are positive but less strong and not always significant for overweight (BMI 25–30 kg/m²) [5, 10]. Sex has been shown to moderate the depression–obesity association as it was stronger in women than in men, but only in cross-sectional [5, 7, 10] and not in longitudinal meta-analyses. Finally, meta-analytic evidence shows that the depression–obesity association extends to bipolar depression [14], exists already in childhood and adolescence [6, 12], and is consistent across Western and non-Western countries [4, 5, 7].

Several meta-analyses provided effect sizes both unadjusted and adjusted for sociodemographic and lifestyle (e.g. smoking, activity) indicators. Overall, adjusted and unadjusted effect size estimates do not differ much [10–12], suggesting that these factors do not largely explain the depression–obesity link. One potentially important factor may be concurrent treatment by antidepressant medication, as indications exist that antidepressant treatment itself causes subsequent weight increase. Although this factor is often ignored in population-based studies, the prevalence of antidepressant medication in these studies is generally rather low and therefore it is unlikely that depression–obesity associations are completely attributable to antidepressant medication. In a meta-analysis examining body weight changes due to antidepressant use, Serretti and Mandelli [15] concluded that most antidepressants have transient and negligible effects on body weight in the short term. When side effects of antidepressants were examined over a longer term of 2–4 years in a study among ~1000 depressed patients, only mirtazapine use was associated with weight gain [16]. In a large-scale study among 2545 subjects, it was depression status and not antidepressant medication that predicted 2-year subsequent weight increase in multivariate analyses [17]. Overall, these findings suggest that, although few selective antidepressant medications cause (short term) weight gain, the

depression–obesity association likely is not explained by antidepressant medication.

Evidence exists that the association between depression and obesity is stronger for abdominal obesity. Abdominal obesity, characterized by visceral fat accumulation, has been more strongly linked to metabolic dysregulations. The meta-analysis of Xu et al. [8], confirmed that the association between abdominal obesity and depression was stronger than that between general obesity and depression reported by previous cross-sectional meta-analyses (Table 1). Also, the association between depressed mood with longitudinal change in abdominal visceral fat has been shown to be stronger than that with change in overall obesity [18]. The importance of metabolic dysregulation also becomes clear in an analysis among 30,337 obese persons [19]. Obese persons with a favorable metabolic profile had only a slightly increased depression risk compared to the non-obese, but the depression risk was greater when obesity is accompanied with an adverse metabolic profile (e.g. hypertension, dyslipidemia, high C-reactive protein, or insulin resistance).

Heterogeneity of depression

Depression's heterogeneity contributes to variability in the association with obesity; this association is stronger in certain subgroups of patients. Clinicians are well aware that patients with the same diagnosis of MDD may endorse very different symptom profiles. An important line of research on depression heterogeneity has classically focused on the distinction between two major clinical subtypes, melancholic and atypical. Melancholic depression is characterized by anhedonia, pronounced feelings of worthlessness, non-reactive mood, psychomotor disturbances, insomnia, loss of appetite and weight, diurnal mood variation, and impaired cognitive abilities, while atypical depression is characterized by lethargy, fatigue, excessive sleepiness, hyperphagia, weight gain, and mood reactivity. A comprehensive overview of the research on these clinical subtypes has been previously published in the *Mol Psychiatry* journal [20].

Emerging evidence suggests that the MDD link with obesity measures, and related metabolic and inflammatory dysregulations, is stronger for patients endorsing a symptom profile that previous studies often labeled as “atypical” [21–28]. However, these studies applied the same label of atypical to subgroups of patients selected based on different definitions: while some studies [24, 26, 27] strictly applied the DSM criteria for the atypical specifier, others [25, 28] used a simplified definition based on few symptoms (e.g. hyperphagia, hypersomnia, fatigue), or used classifications based on data-driven methods [21, 22, 28]. It is crucial therefore to indicate which of the atypical symptoms may constitute a major driver of the associations with obesity-

related features. In a large-scale study among MDD patients, it became clear that appetite upregulation in particular and to a lesser extent weight increase during a depressive episode were the symptoms most strongly associated with BMI and obesity-related inflammatory (high C-reactive protein and tumor necrosis factor alpha) and endocrine (high leptin) alterations [29, 30]. Other atypical symptoms showed weaker (leaden paralysis) or no (hypersomnia) associations with these markers [29, 30]. Together these findings suggest that the depression–obesity association is stronger in MDD patients with increased neurovegetative symptoms. It has been previously reported that while ~40–50% individuals lose their appetite and/or weight while depressed, a subgroup of ~15–25% of patients increases their appetite and/or weight during the active episode [28, 31]. The latter patients may represent a specific subgroup at higher risk for comorbid obesity.

Biological mechanisms linking depression and obesity

Biological, psychological, and behavioral factors may influence the bidirectional association between depression and obesity. Below we review biological pathways that may mechanistically explain the depression–obesity link (Fig. 1), starting from genetics. Then, we will consider alterations in systems involved in homeostatic adjustments (hypothalamic–pituitary–adrenal (HPA) axis, immunoinflammatory activation, neuroendocrine regulators of energy metabolism and microbiome) and brain circuitries integrating homeostatic and mood regulatory responses. These biological pathways may act in two, non-mutually exclusive, ways: as common underlying mechanisms influencing the liability to both depression and obesity, or as mediating mechanisms in causal relationships between the

two conditions. Finally, we will briefly mention other relevant behavioral and psychological mechanisms.

Genetics

Genetic factors influence similarly depression and obesity, with additive genetic effects explaining ~40% of phenotypic variation (heritability) for both MDD [32] and BMI [33].

Looking at the genetics of obesity, genome-wide association studies (GWAS) have identified more than two hundred loci reliably associated with BMI, obesity status, and fat distribution measures [34]. Complementary analyses based on transcriptomic data showed that genes near BMI-associated loci are highly expressed in brain regions involved in appetite and energy homeostasis (hypothalamus and pituitary gland) and mood regulation (hippocampus and limbic system) [35]. Relatedly, when considering cell type-specific annotations, the polygenic contribution to BMI heritability was found to be significantly enriched for brain cells as compared to other tissues [36]. These findings point towards the central role of specific brain regions in the regulation of body mass and energy homeostasis, which are overlapping with those involved in mood regulation.

With respect to the genetics of MDD, recent GWAS [37–42] uncovered more than 50 genetic loci reliably associated with depression phenotypes. Some of the strongest signals overlapped or were close to genes (*NEGR1*, neuronal growth regulator 1; *OLFM4*, olfactomedin 4; *KSR2*, kinase suppressors of ras 2) previously associated with BMI and severe early-onset obesity [35, 43, 44]. The function of *NEGR1* is emblematic of possible shared mechanisms linking depression to obesity. *NEGR1* modulates synaptic plasticity in brain areas crucial for mood and appetite regulation, such as cortex, hippocampus and hypothalamus [45–47]. Hypothalamic expression of *NEGR1* has been shown to be enhanced in animal models exposed to a restricted feeding schedule determining a reduction in body weight and in endocrine signals impacting on adiposity and mood (i.e. leptin, paragraph 3.3) [48]. Overarching analyses of all available GWA studies [41] confirmed that MDD polygenic architecture partially overlaps with obesity-related traits: estimates of genome-wide genetic correlations (determined by the number of genetic variants, and their level of concordance, shared between two traits) of MDD was 0.09 with BMI, 0.20 with obesity class III, 0.15 with body fat percentage, and 0.11 with waist circumference. It is important to consider the role of depression's heterogeneity when appraising the previous results. Recent large-scale analyses [31] involving >25,000 samples reported a strong genetic correlation (0.53) between BMI and MDD with increased appetite and/or weight gain.

Overall, emerging evidence suggests that the phenotypic relationship between depression and obesity is rooted in

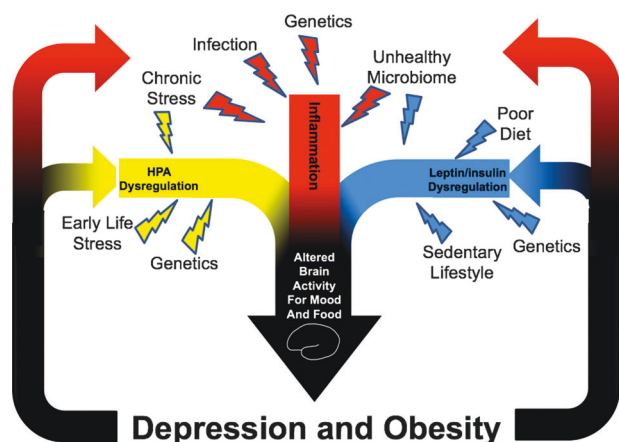


Fig. 1 Overview of the shared biological pathways influencing depression and obesity

partially overlapping genetic bases. This common genetic base is also reflected in most of the shared mechanisms described in the next paragraphs.

HPA axis

Hyperactivation of the HPA axis, determining a non-adaptive unabated release of cortisol, is one of the most consistent findings in biological psychiatry [49]. Long-term exposure to cortisol leads to neuronal damage and loss in limbic regions vulnerable to stress and associated with depression, such as the hippocampus and amygdala [50–52].

A natural model of prolonged cortisol exposure on mood is Cushing's syndrome (CS), characterized by endogenous hypercortisolism caused by a pituitary or adrenal adenoma or bilateral adrenal hyperplasia, which reverses after surgical removal or other treatments targeting the hypercortisolism. MDD occurs in 50–80% of CS patients with active disease [53]. Importantly, the onset of depressive symptoms with CS and their improvement after treatment of hypercortisolism demonstrates a causal role for cortisol in depression. Long-term HPA axis hyperactivation can also be found in nearly half of adult obese persons ("hypercortisolic obesity") [54]. Even at a young age, an almost 10-fold increased risk of obesity has been observed in children with the highest long-term cortisol levels [55]. Exposure to high cortisol may induce obesity through several mechanisms: (1) increase in appetite with a preference for energy-dense food; (2) promotion of adipogenesis and hypertrophy especially in visceral fat; (3) suppression of thermogenesis in brown fat with related reduction in energy expenditure [56]. It is conceivable that these 'hypercortisolic' obese patients may be more prone to the metabolic sequelae of obesity and to depression.

Several mechanisms influencing cortisol release and metabolism could play a role in obesity and MDD. Chronic inflammation typical of obesity may disrupt the functioning of glucocorticoid receptor (GR), the cortisol-binding receptor initiating the negative feedback and thereby suppressing HPA activity. Proinflammatory cytokines activate elements of cellular transduction cascades that impede GR nuclear translocation or interfere in GR interaction with response elements in promoters of genes [57]. Dysregulation of 11- β -hydroxysteroid dehydrogenase (11- β HSD) isozymes 2 and 1 (converting, respectively, bio-active cortisol into inactive cortisone and vice versa) is associated with disturbed cortisol metabolism in obesity [58] and MDD [59]. Furthermore, impaired 5 α -reductase activity (reducing glucocorticoids clearance) may potentiate accumulation of visceral adipose tissue [60] and influence the development of MDD [61]. Finally, the activity of hepatic enzymes responsible for cortisol clearance and regeneration

has been shown to be altered in patients with non-alcoholic fatty liver disease (NAFLD) [62], which is one of the metabolic sequelae of abdominal obesity. Interestingly, evidence is also accumulating of links between NAFLD and depression [63].

HPA-axis hyperactivation represents a potentially relevant mechanism connecting depression and obesity. As the involvement of hypercortisolism in obesity has been recently recognized [64], the exact extent of the overlap between depression and obesity around the HPA axis remains to be clearly established.

Immuno-inflammatory activation

Chronic low-grade inflammation is a hallmark of obesity. White adipocytes infiltrated by macrophages and other immune-cells produce proinflammatory cytokines [65]. This peripheral immune activation could be translated via humoral, neural, and cellular pathways [66] into brain inflammation, as indicated by higher hippocampal and cortical expression of cytokines in obesity animal models [67–69]. Different neural pathways are organized to provide a counter-response to central inflammation aimed at inhibiting its peripheral source: for instance, cytokine activation of afferent vagus nerve is mirrored by efferent signals inhibiting the release of cytokines [70]. Dysregulation of this circuit may contribute to the maintenance of obesity-related enhanced inflammation. Central inflammation impacts on established depression pathophysiological processes, such as monoaminergic neurotransmission alteration [66]. Cytokine-induced activation of the enzyme indoleamine 2,3-dioxygenase modulates tryptophan depletion and degradation towards neurotoxic end-products such as quinolinic acid, resulting in hippocampal neuronal damage [71, 72]. Quinolinic acid binds to glutamate receptor and, in synergy with cytokine-induced glutamate release and reuptake reduction, increases excitotoxicity and decreases neurotrophic factors synthesis [73, 74]. Finally, as described above, cytokines determine HPA-axis hyperactivation by disrupting its negative-feedback circuit [57].

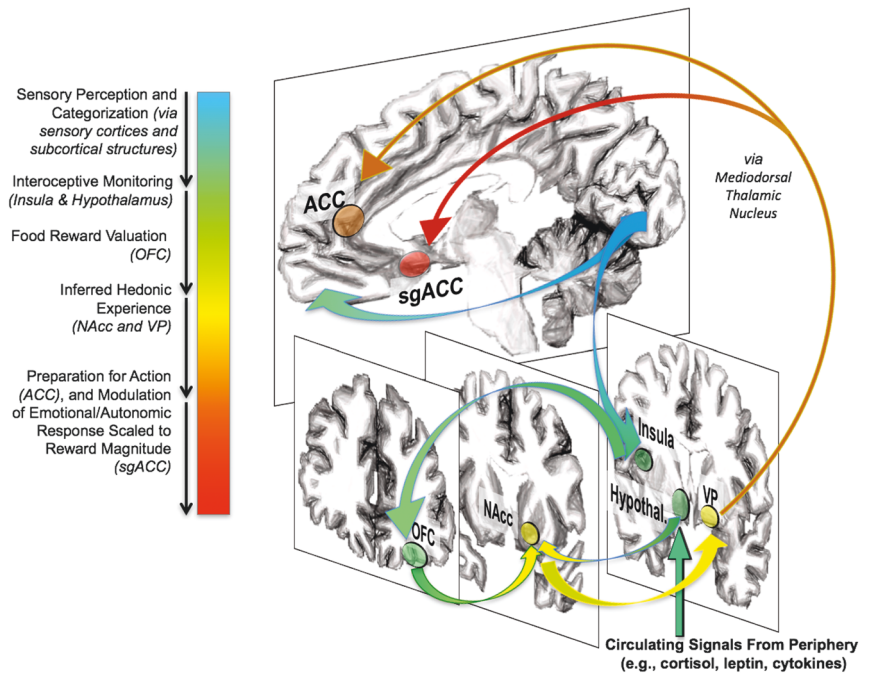
More recently, inflammasomes have gained increasing attention as important regulators of inflammatory activation. Inflammasomes are groups of protein complexes that are triggered by molecular patterns induced by physiological and psychosocial stress and cleave cytokines precursors into their active form via caspase-1 activation [75, 76]. It has been shown that expression of the NLRP3 inflammasome and caspase-1 is upregulated in adipocytes from obese patients [77], and caspase-1 inhibition reduced body weight and weight increase in obese mouse model [78]. Similarly, NLRP3 and caspase-1 expression was found to be increased in peripheral blood mononuclear cells of depressed patients [79], and caspase-1 inhibition decreased depressive-like

Increased inflammation is emerging as a central pathophysiological process in depression and obesity. Its centrality is also due to the widespread effect of chronic inflammation in altering other neuroendocrine systems hereby examined, including HPA axis and those involved in energy homeostasis described in the next paragraph.

The *leptin–melanocortin* pathway is a key neuroendocrine regulator of energy homeostasis. Leptin is produced by white adipose tissue in proportion to body fat and acts as an adiposity negative signal. Leptin binding to receptors expressed in the hypothalamus activates pro-opiomelanocortin neurons, which interact with other brain centers to integrate physiological and behavioral processes suppressing food intake and promoting energy expenditure [92]. Loss-of-function mutations in key genes of the pathway (*LEP*, leptin; *LEPR*, leptin receptor; *MC4R*, melanocortin 4 receptor) results in rare extreme forms of obesity, characterized by severe hyperphagia [93–95]. More common forms of obesity are associated with leptin resistance (a process comparable with insulin resistance in type 2 diabetes), blunting its anorexigenic effect and consequently disinhibiting feeding despite elevated circulating leptin. Central resistance is due to impaired leptin transport across the blood–brain barrier, reduced function of leptin receptors, and defects in leptin signal transduction [96]. Obesity-related inflammation plays a relevant role in disrupting

Obesity increases the risk of alterations of the *insulin* pathway regulating glucose metabolism, and ultimately leading to the development of type 2 diabetes (T2D). In the pre-diabetic stage tissues become unresponsive to insulin despite a peripheral increased release by pancreatic β -cell (insulin resistance). Again, inflammation plays a role in these alterations: raised concentrations of proinflammatory cytokines may lead to attenuate insulin receptor ability to propagate the signaling downstream (via increased activation of the same feedback mechanisms affecting leptin receptor) [106, 107] and to pancreatic β -cell apoptosis [108]. Insulin has significant effects in the brain, especially in the hippocampus and adjacent limbic structure in which insulin receptors are highly expressed. Alteration of regional cerebral metabolism due to insulin resistance has been associated with memory and executive functions impairment and neuronal damage in the hippocampus and medial prefrontal cortex [109–111]. Therefore, it has been postulated that insulin dysregulation may play a role in neuropsychiatric conditions such as dementia and depression [112].

Fig. 2 Brain circuitry involved in perception, cognition, and action related to potentially rewarding stimuli



Observational evidence sustains a link between depression and insulin-related conditions. A significant cross-sectional association between depression and insulin resistance was found in a recent meta-analysis [113]. Furthermore, several meta-analyses [114–117] indicate prospective bidirectional associations between depression and T2D. A previous study [118] based on national twin registries indicated that both genetic and environmental factors may explain a proportion of the phenotypic correlation between MDD and T2D. However, using molecular data, a large study [41] showed no significant genome-wide genetic correlation between MDD with glycemic traits or T2D. These data suggest that other factors beyond genetics may have a major impact on the interplay between insulin dysregulation and depression.

Overall, alteration of energy homeostasis mechanisms may represent a central link in the chain connecting depression and obesity. Experimental and observational evidence for leptin dysregulation suggests a common underlying mechanism influencing the two conditions at several levels, from genetics to behavior, resulting in the hyperphagia phenotype central for both obesity and depression with increased neurovegetative symptoms. Insulin dysregulation may likely represent a mediating mechanism in the obesity-depression relationship, highly influenced by environmental factors.

Microbiome

Microbiota of the gastro-intestinal tract is emerging as a key player in the pathophysiology of obesity. Gut microbiota, consisting of 40 trillion cells of hundreds of different

species (carrying 250 to 800 times more genes than humans) is a complex active network that directly affects host metabolic phenotypes [119]. Two bacterial phyla are predominant in humans, bacteroidetes and firmicutes, the latter producing more harvestable energy than the former. Obesity is characterized by an impaired bacteroidetes/firmicutes ratio, and experimental alteration of microbiota composition modulates the development of obesity [120, 121]. These alterations are also related to markers of local inflammation, which could increase gut permeability to bacteria that, in turn, contributes to onset and progression of systemic inflammation (metabolic endotoxemia) [122]. This inflammatory response may ultimately trigger inflammasomes and depression-related brain processes, creating a gut brain–microbiota axis potentially impacting on mood states.

Preliminary research showed that the microbiome and MDD are linked. In small observational studies [123, 124], MDD patients showed higher firmicutes and lower microbiota phylogenetic diversity as compared to controls. Moreover, microbiota transplantation from severely depressed patients induced depression-like behaviors in rats [125, 126]. Meta-genomic analyses of 1135 samples from a population-based cohort showed associations between the microbiome and several diseases and medications, including MDD and the use of tricyclic antidepressants and selective serotonin reuptake inhibitors [127].

The exact mechanisms linking microbiome activity to obesity and depression have yet to be fully elucidated. A previous expert review in *Mol Psychiatry* journal [128] examined in depth the role of gut microbiome in shaping

brain development and the potential mechanisms contributing to mental illness.

Brain mechanisms

The biological alterations described above influence the central nervous system's appetitive and homeostatic regulatory processes in ways that promote obesogenic and depressogenic behaviors. Peripheral signaling pathways communicate with the brain's circuitry involved in perception, cognition, and action related to potentially rewarding stimuli. This circuitry involves brain regions that support the mental representation of objects' and ideas' perceptual features (occipital and ventral temporal cortex [129]), their interoceptive/homeostatic significance (insula [130]), reward value (orbitofrontal cortex [131]), motivational salience and inferred hedonic potential (nucleus accumbens and ventral pallidum [132]), reward-relevant autonomic changes (ventral anterior cingulate cortex (ACC) [133]), and ultimately the executive control of behaviors necessary to acquire rewards (dorsal anterior cingulate cortex (ACC) [134]) (Fig. 2). Peripheral biological signals likely communicate with this infrastructure by initially altering activity in homeostatic/interoceptive regions, particularly the hypothalamus and insula.

Evidence from rodent and human research demonstrates that obesity is associated with changes in hypothalamic responses to metabolic signaling molecules [135]. The most well-studied of these phenomena is the development of obesity-related leptin resistance, which renders the hypothalamus relatively deaf to the leptin anorexogenic signal, thereby further promoting obesity. An extensive literature points to altered hypothalamic function associated with elevated cortisol [136–139] and leptin [30, 103] levels in animals exposed to depressogenic stress and depressed humans. The insula is another brain region involved in sensing peripheral body states that has been linked to obesity and depression. The insular cortex is the location of the primary interoceptive and gustatory cortices [140–143], and receives afferent projections from the vagus nerve via the solitary nucleus and thalamus [130]. Importantly, the largely unmyelinated vagus collects a wealth of visceral and inflammatory information from respiratory, cardiac, and gastric organs [135, 144]. Once this interoceptive information is received in the posterior and mid-insula, it is relayed back and forth along the insula's long axis in a process that ultimately results in higher-order integrated representations of the body's homeostatic state [145, 146]. Consistently with its role in visceral interoception, human neuroimaging studies have demonstrated that insula food-cue reactivity is sensitive to circulating markers of energy availability such as glucose and insulin [147–149], with insula activity typically decreasing markedly following

meals relative to when subjects are hungry [150–152]. Interestingly, obese adults do not exhibit the expected drop in insula activity to post-prandial food cues, suggesting that obesity is associated with *decreased* sensitivity to interoceptive signals of satiety [153]. Interestingly, other researchers have demonstrated that obese adults exhibit increased activity in the insula during experimentally induced hypoglycemia [148], suggesting that obesity may be associated with *increased* sensitivity to metabolic signals of hunger.

The central role of the insula in interoception is therefore key in obesity (associated with both increased sensitivity to hunger signals and decreased sensitivity to satiety signals), but extends also to other functions based on the perception/awareness of interoceptive signals, such as emotion regulation. Disorders such as depression partially arise from misperception and misattribution of interoceptive signals from the body [145, 154]. This accords well with the observation that some of the most pervasive symptoms of depression involve somatic disturbances and altered sense of body awareness [155, 156]. Consistently, altered insula activity is one of the most common findings across the neuroimaging literature in depression [157, 158].

Both the hypothalamus and insula have strong anatomical and functional connectivity to all the brain regions of the network depicted in Fig. 2. As a result, once peripheral dysregulations alter insula and hypothalamic activity, the consequences can easily propagate throughout the brain ultimately affecting mood and body weight. For example, through direct and polysynaptic connections, neurons in the hypothalamus and insula are able to influence the brain's dopaminergic reward system, including the striatum, ventral pallidum, orbitofrontal cortex (OFC), and medial prefrontal cortex (vmPFC). Within this pathway, the striatum (both ventral and dorsal) and ventral pallidum play critical roles in learning associations between external stimuli (such as food cues) and their hedonic consequences, as well as engendering those stimuli with motivational salience when they are likely to result in hedonic reward [132, 159]. The OFC and vmPFC use this information to compute reward valuations which then greatly influence behavior selection [131, 160]. Importantly, an extensive literature implicates all of these regions and processes in obesity [161, 162].

Likewise, a large literature demonstrates associations between depression and both abnormal reward representation, and abnormal activity within the dopaminergic reward system regions, particularly as it relates to anhedonia [163–166]. Although more research is required to precisely understand the extent to which depression-related alterations in the activity of reward neurocircuitry may be due to peripheral signals, there are clear examples that depression is associated with altered reward circuit activity specifically to food. McCabe et al. [167] demonstrated that individuals

those whose expression is induced by bupropion. Preliminary positive evidence [184] should be further extended to test whether naltrexone/bupropion combination may be specifically effective for patients with comorbid depression and obesity.

Another promising treatment may be the use of recombinant human leptin (metreleptin), which is highly effective in rare conditions characterized by severe obesity due to congenital leptin deficiency, inducing remarkable weight loss and improvement of related metabolic phenotypes [185]. Limited efficacy has been shown instead in common forms of obesity, characterized by leptin resistance. Based on established antidepressant-like effects, leptin-based treatments have been advocated for depression. In this effort, development of treatment effectively overcoming leptin resistance would be crucial. Finally, reducing hypercortisolism by using 11- β HSD1 inhibitors or selective GR antagonists may specifically target hypercortisolic patients with obesity and depression [64]. These potential treatments should be tested in future studies of sufficient methodological quality, duration, and sample size, including people with comorbid depression and obesity.

A major challenge in developing and testing new treatments for patients with depression and obesity will be represented by heterogeneity. As described, the relationship between depression and obesity is not consistent across patients, and not all patients similarly exhibit dysregulations in linking biological mechanisms. This observation underlines the need to identify more homogeneous subgroups of patients and to fully characterize them in clinical and biological terms. For this reason, ongoing research lines should be scaled-up and extended to include all 'omics' levels (e.g. microbiome, (epi)genomics, transcriptomics, proteomics, metabolomics) in order to provide an extensive characterization of all biological mechanisms connecting depression and obesity. Furthermore, an important step will be the delineation of causal connections in this complex network, especially between peripheral markers and brain activity. In the past decade progress has been made in linking aberrations in peripheral markers to altered activity in brain regions. Nevertheless, as yet there are no studies in humans that directly relate these peripheral dysregulations to changes in neural responses. This area of research faces the significant challenge of inferring the directionality of any observed effects between peripheral markers and central nervous system activity in depression and obesity. Answering these questions will require experimental studies where mood, appetite, and body composition are measured in the presence of experimental interventions that alter activity in basic biological signaling pathways.

Research along the lines indicated will enable the possibility to provide biologically based multi-level descriptions of patients with obesity and depression, and

the identification of patient subgroups at higher risk. Development of tailored treatments for persons selected based on their biological profile, in accordance with a personalized medicine approach, may ultimately benefit patients who suffer most under the weight of depression and obesity.

Acknowledgements WKS's contribution was supported by funding from the National Institute of Mental Health (K01MH096175) and National Institute of General Medical Services (P20GM109097). EFCvR is supported by a Vidi grant from the Netherlands Organization of Scientific Research NWO (grant number: 91716453) and an Erasmus MC research fellowship. BWJH's contribution was supported by the EU FP7 MooDFOOD project grant agreement no. 613598.

Compliance with ethical standards

Conflict of interest WKS is listed as a co-inventor on a patent regarding appetite change in depression. BWJHP has received research funding (non-related to the work reported here) from Jansen Research and Boehringer Ingelheim. The remaining authors declare that they have no conflict of interest.

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