Molecular Psychiatry (2019) 24:18–33
https://doi.org/10.1038/s41380-018-0017-5

EXPERT REVIEW

Depression and obesity: evidence of shared biological mechanisms

Yuri Milaneschi[1] · W. Kyle Simmons[2,3] · Elisabeth F. C. van Rossum[4] · Brenda WJH Penninx[1]

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

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/m^2 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).

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

✉ Brenda WJH Penninx
B.Penninx@vumc.nl

1 Department of Psychiatry, Amsterdam Neuroscience and Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, The Netherlands

2 Laureate Institute for Brain Research, Tulsa, OK, USA

3 School of Community Medicine, The University of Tulsa, Tulsa, OK, USA

4 Department of Internal Medicine, Division of Endocrinology, Erasmus University Medical Center Rotterdam, and Obesity Center CGG, Rotterdam, The Netherlands

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 >95th 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]	Symptoms	BMI ≥ 30	1.29 (1.18–1.42)		
	$N = 8$ [176,510]	Clin Diag	BMI ≥ 30	1.16 (1.02–1.32)		
Longitudinal evidence from meta-analyses				**OBES→DEP**	**DEP→OBES**	
Blaine (2008) [13]	$N = 23$ [33,690]	Combined sympt. or Clin Diag	BMI weight change or onset of BMI ≥ 30	1.19 (1.14–1.24)		
Luppino et al. (2010) [4]	$N = 5$ [52,421]	Symptoms	BMI ≥ 30	1.36 (1.03–1.80)		
	$N = 3$ [2966]	Clin Diag	BMI ≥ 30	2.15 (1.48–3.12)		Adolescent and adult samples
	$N = 5$ [3643]	Symptoms	BMI ≥ 30		1.48 (1.17–1.87)	
	$N = 4$ [2991]	Clin Diag	BMI ≥ 30		1.71 (1.33–2.19)	
Mannan et al. (2016) [11]	$N = 12$ [126,594]	Combined sympt. or Clin Diag[a]	BMI ≥ 30	1.18 (1.04–1.35)		Adult samples only
	$N = 9$ [85,358]	Combined sympt. or Clin Diag[a]	BMI ≥ 30		1.37 (1.17–1.48)	
Mannan et al. (2016) [12]	$N = 6$ [20,855]	Combined sympt. or Clin Diag[a]	BMI ≥ 30	1.40 (1.16–1.70)		Adolescent samples only
	$N = 7$ [16,373]	Combined sympt. or Clin Diag[a]	BMI ≥ 30		1.70 (1.40–2.07)	

[a]Number/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/m^2) than when applying the BMI cut-off of 30 kg/m^2, and are positive but less strong and not always significant for overweight (BMI 25–30 kg/m^2) [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, immuno-inflammatory 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.

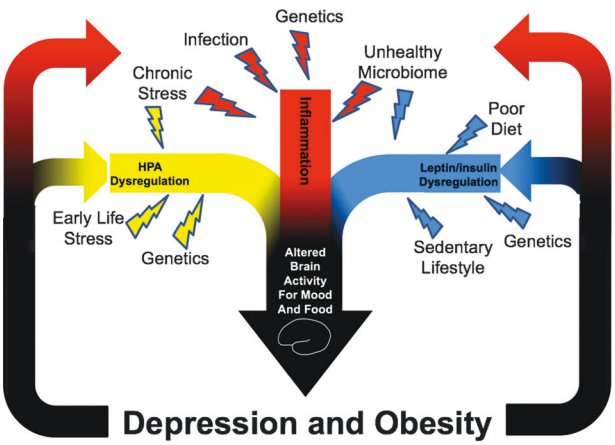

Fig. 1 Overview of the shared biological pathways influencing depression and obesity

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

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 ("hypercortisolistic 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 'hypercortisolistic' obese patients may be more prone to the metabolic sequela 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-βHSD) 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 5α-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 sequela of abdominal obesity. Interestingly, evidence is also accumulating of links between NAFLD and depression [63].

HPA-axis hyperactivation represent 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 quinolic acid, resulting in hippocampal neuronal damage [71, 72]. Quinolic 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

behaviors in mice [80]. Furthermore, upregulation of the NLRP3 inflammasome may determine a caspase-mediated cleavage of GR, impairing its responsivity and therefore contributing to chronic activation of HPA axis [81].

A role for immuno-inflammatory dysregulation in depression has been confirmed by a large body of evidence: from clinical studies on cytokine-induced depression [66] to large meta-analyses reporting on higher levels of inflammatory markers in depressed persons versus controls [82–86]. More recently, pathway analyses of MDD GWAS results [41, 87] identified significant associations with gene clusters involved in cytokine and immune response. Similarly, transcriptome studies showed that MDD is associated with expressions of genes in pathways related to innate and adaptive immunity [88, 89].

Clinical heterogeneity may impact the complex interplay between depression, obesity, and inflammation. Three large cohort studies found higher C-reactive protein (CRP) concentrations in MDD patients with increased neurovegetative features, as compared to other patients and healthy controls [21, 90, 91]. Consistently, a recent large collaborative study [31] showed that depressed patients endorsing increased appetite/weight during an active episode carried a higher number of genetic risk variants for high BMI and CRP.

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.

Neuroendocrine regulators of energy metabolism

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 leptin central signaling. For instance, CRP has been shown to directly inhibit the binding of leptin to its receptors [97]. Moreover, central inflammation can impair hypothalamic leptin receptors activity through the activation of inhibitory signals from multiple negative-feedback circuits[96].

Leptin also has an impact on mood. In animal models, peripheral and central administration of leptin produces antidepressant-like effects in behavioral tests and reverse depressive-like behavior induced by chronic unpredictable stress [98, 99]. Leptin effects on mood may be exerted via different pathways: direct action on neurons via receptors expressed in the hippocampus and amygdala, enhancement of neurogenesis and neuroplasticity in hippocampus and cortex, and modulation of HPA axis and immune system [100–102]. It has been hypothesized that leptin resistance (peripheral hyperleptinemia due to reduced central signaling) may constitutes a phenotype risk for depression [103]. Consistently, genetic deletions of leptin receptor in the hippocampus and cortex of mice causes hyperleptinemia with depression-like phenotypes [104] and resistance to treatment with fluoxetine and desipramine [105]. Results from previous observational studies in humans were hampered by small samples and clinical heterogeneity. A recent study [30] based on more than 2000 participants showed that current MDD patients with increased neurovegetative symptoms (in particular appetite and weight) had higher circulating leptin as compared to healthy controls, independently from BMI. Moreover, among current MDD patients, higher leptin was associated, independently from BMI, with hyperphagia and increased weight. Finally, a recent study [31] on >25,000 samples showed that only MDD characterized by increased appetite/weight symptoms was associated with polygenic risk scores for circulating leptin.

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 prediabetic 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].

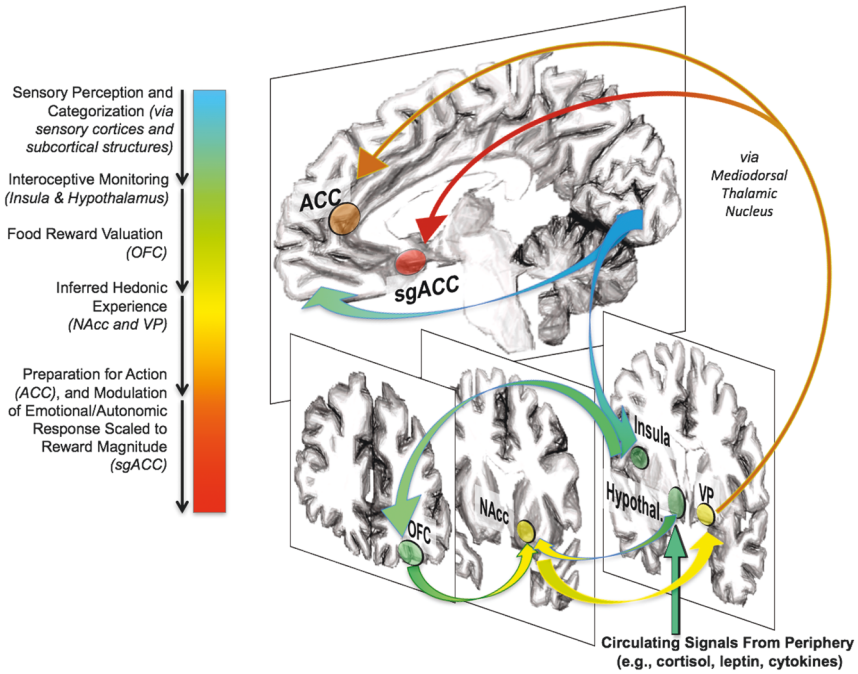

Fig. 2 Brain circuitry involved in perception, cognition, and action related to potentially rewarding stimuli

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

with remitted depression exhibit decreased ventral striatum and vmPFC activity to the taste of chocolate. Likewise, at-risk young adults with a depressed parent exhibit decreased OFC activity to the taste of chocolate [168].

Considering depression heterogeneity is crucial when tracing its neural substrates. Simmons et al. [169] asked unmedicated depressed subjects to undergo fMRI while viewing pictures of food cues. Depressed subjects with *decreased* appetite exhibited decreased activity in a region of the mid-insula that is critical for monitoring the body's internal homeostatic state (interoceptive cortex), while depressed subjects with *increased* appetite exhibited increased orbitofrontal, striatal, and ventral pallidum activity while viewing food pictures. These findings help us to understand the behavioral heterogeneity among depression subtypes, with *hypo*-activity in a key interoceptive/homeostatic monitoring region in individuals whose depression manifests with a failure to meet their energy needs, and *hyper*-activity of reward regions in individuals whose depression manifests with increased eating.

Other mechanisms

Our review mainly discusses biological mechanisms linking depression and obesity. Nevertheless, it cannot be ignored that these proximal mechanisms may be heavily influenced by more distal behavioral and psychosocial factors. Over the past decades, adoption of sedentary lifestyles, reduction of time spent in physical activity, increased consumption of high caloric palatable food, and reduction in sleeping hours have constituted the main drivers of the secular trend toward increasing obesity in developing countries. Clustering of these risk factors is common in depressed persons, who are more likely engaging in behaviors such as smoking, excessive alcohol use, poor nutrition, poor sleep hygiene, and sedentariness [170, 171]. Furthermore, such behavioral factors are associated with biological dysregulations of depression and obesity. For instance, inadequate sleep has been linked with increased cortisol, inflammatory markers, leptin and reduced insulin sensitivity, and with increased risk of development of both depression and obesity [172, 173]. Also psychological factors play a prominent role in maintaining this detrimental link. For example, emotional eating (the tendency to eat in response to negative emotions) has been associated with depression [174] and obesity [175]. Behavioral and psychological risk factors remain a key target, accessible, and modifiable, for treatments aimed at breaking down the depression–obesity spiral.

Clinical and research implications

As described, depression and obesity are closely interconnected and interact causing a progressive downward spiral in a persons' health status. This observation has important clinical implications. On the one hand, this co-occurrence may represent a major obstacle in the treatment of each conditions separately. Indeed, in depressed patients, obesity-related biological dysregulations have been associated with a more chronic course [176] and poor response to standard antidepressant treatments [177]. Similarly, comorbid depression may disrupt adherence to treatments aimed at obesity and related conditions via reduced adherence to medication and lifestyle prescriptions [178]. On the other hand, this link may represent an important leverage in treating patients with comorbid depression and obesity: for this specific subgroup, the toolbox of available interventions may be widened to include treatments with evidence of positive effects in both conditions.

Treatment strategies targeting the shared mechanisms described in the present review could be beneficial for improving both depression and obesity. For example, lifestyle modifications aimed at modifying dietary habit and physical activity are effective in reducing body weight, improving related biological dysregulations and depressive symptoms [179, 180]. Further trials should systematically tackle important methodological issues, such as long-term weight re-gain and identification of the most effective protocol of exercise and nutritional programs, combined with behavioral interventions. Most importantly, such trials should be designed for patients with comorbid depression and obesity.

Another promising shared biological mechanism to be targeted is inflammation. A recent meta-analysis [181] including 14 randomized placebo-controlled trials showed that anti-inflammatory treatment effectively reduced symptoms in depressed patients. Nevertheless, substantial heterogeneity was found, indicating the need to identify subgroups in which the effect of the treatment could be maximized. Intriguingly, post-hoc analyses of a previous trial [182] showed that infliximab (the monoclonal antibody against tumor necrosis factor-α) exerted antidepressant effects only in patients with higher baseline CRP and higher BMI. These findings suggest that (adjunctive) anti-inflammatory treatment may be especially relevant for depressed patients with obesity.

In addition, treatment strategies with established efficacy in one condition could be extended and tested to the other. A promising example of this extension is represented by bupropion, an antidepressant that inhibits dopamine and norepinephrine reuptake and increases pro-opiomelanocortin neuron activity. Bupropion is one of the few antidepressants producing weight loss [15]; the combination of bupropion and naltrexone, an antagonist of opioid receptor system (modulating hedonic evaluation of food) has been approved for obesity treatment by FDA and EMA. Intriguingly, a recent study [183] showed that genes shared between MDD and BMI are overrepresented among

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-βHSD1 inhibitors or selective GR antagonists may specifically target hypercortisolistic 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 characterized 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.

References

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–96.
2. Effects H. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377:13–27. http://www.nejm.org/doi/10.1056/NEJMoa1614362
3. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med. 2017;376:254–66. http://www.nejm.org/doi/10.1056/NEJMra1514009
4. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. Psychiatry Res. 2010;178:230–5. https://doi.org/10.1016/j.psychres.2009.04.015.
5. Jung SJ, Woo H, Cho S, Park K, Jeong S, Lee YJ, et al. Association between body size, weight change and depression: systematic review and meta-analysis. Br J Psychiatry. 2017;211:14–21. http://www.ncbi.nlm.nih.gov/pubmed/28428339 [cited 4 Sep 2017]
6. Quek Y-H, Tam WWS, Zhang MWB, Ho RCM. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. Obes Rev. 2017;18:742–54. http://doi.wiley.com/10.1111/obr.12535 [cited 4 Sep 2017]
7. Abou Abbas L, Salameh P, Nasser W, Nasser Z, Godin I. Obesity and symptoms of depression among adults in selected countries of the Middle East: a systematic review and meta-analysis. Clin Obes. 2015;5:2–11. http://www.ncbi.nlm.nih.gov/pubmed/25504829
8. Xu Q, Anderson D, Lurie-Beck J. The relationship between abdominal obesity and depression in the general population: a systematic review and meta-analysis. Obes Res Clin Pract. 2011;5:e267–360. http://linkinghub.elsevier.com/retrieve/pii/S1871403X11000275 [cited 20 April 2017].
9. Pereira-Miranda E, Costa PRF, Queiroz VAO, Pereira-Santos M, Santana MLP. Overweight and obesity associated with higher depression prevalence in adults: a systematic review and meta-

analysis. J Am Coll Nutr. 2017;36:223–33. http://www.ncbi.nlm.nih.gov/pubmed/28394727 [cited 30 Aug 2017].
10. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, obesity, and depression. Arch Gen Psychiatry. 2010;67:220 http://www.ncbi.nlm.nih.gov/pubmed/20194822 [cited 20 Apr 2017]
11. Mannan M, Mamun A, Doi S, Clavarino A. Is there a bi-directional relationship between depression and obesity among adult men and women? Systematic review and bias-adjusted meta analysis. Asian J Psychiatr. 2016;21:51–66. https://doi.org/10.1016/j.ajp.2015.12.008.
12. Mannan M, Mamun A, Doi S, Clavarino A. Prospective associations between depression and obesity for adolescent males and females—a systematic review and meta-analysis of longitudinal studies. PLoS ONE. 2016;11:e0157240. http://dx.plos.org/10.1371/journal.pone.0157240
13. Blaine B. Does depression cause obesity? J Health Psychol. 2008;13:1190–7. http://journals.sagepub.com/doi/10.1177/1359105308095977
14. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518:197–206. http://www.ncbi.nlm.nih.gov/pubmed/25673413
15. Serretti A, Mandelli L. Antidepressants and body weight. J Clin Psychiatry. 2010;71:1259–72. http://www.ncbi.nlm.nih.gov/pubmed/21062615 [cited 30 Aug 2017]
16. Bet PM, Hugtenburg JG, Penninx BWJH, Hoogendijk WJG. Side effects of antidepressants during long-term use in a naturalistic setting. Eur Neuropsychopharmacol. 2013;23:1443–51. https://doi.org/10.1016/j.euroneuro.2013.05.001.
17. Gibson-Smith D, Bot M, Milaneschi Y, Twisk JW, Visser M, Brouwer IA, et al. Major depressive disorder, antidepressant use, and subsequent 2-year weight change patterns in the Netherlands Study of Depression and Anxiety. J Clin Psychiatry. 2016;77:e144–51. http://www.psychiatrist.com/jcp/article/pages/2016/v77n02/v77n0203.aspx [cited 20 Apr 2017]
18. Vogelzangs N, Kritchevsky SB, Beekman ATF, Newman AB, Satterfield S, Simonsick EM, et al. Depressive symptoms and change in abdominal obesity in older persons. Arch Gen Psychiatry. 2008;65:1386 http://www.ncbi.nlm.nih.gov/pubmed/19047525 [cited 4 Sep 2017]
19. Jokela M, Hamer M, Singh-Manoux A, Batty GD, Kivimäki M. Association of metabolically healthy obesity with depressive symptoms: pooled analysis of eight studies. Mol Psychiatry. 2014;19:910–4. http://www.nature.com/doifinder/10.1038/mp.2013.162
20. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiatry. 2015;20:32–47. http://www.nature.com/doifinder/10.1038/mp.2014.163
21. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman ATF, Penninx BWJH. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Mol Psychiatry. 2013;18:692–9. http://www.nature.com/doifinder/10.1038/mp.2012.144 [cited 21 Apr 2017]
22. Lamers F, Beekman ATF, van Hemert AM, Schoevers RA, Penninx BWJH. Six-year longitudinal course and outcomes of subtypes of depression. Br J Psychiatry 2016;208:62–8. http://bjp.rcpsych.org/cgi/doi/10.1192/bjp.bp.114.153098[cited 20 Apr 2017]
23. Sullivan PF, Prescott CA, Kendler KS. The subtypes of major depression in a twin registry. J Affect Disord. 2002;68:273–84. http://www.ncbi.nlm.nih.gov/pubmed/12063155 [cited 21 Apr 2017]
24. Cizza G, Ronsaville DS, Kleitz H, Eskandari F, Mistry S, Torvik S, et al. Clinical subtypes of depression are associated with specific metabolic parameters and circadian endocrine profiles in women: the power study. PLoS ONE. 2012;7:e28912.
25. Levitan RD, Davis C, Kaplan AS, Arenovich T, Phillips DIW, Ravindran AV. Obesity comorbidity in unipolar major depressive disorder: refining the core phenotype. J Clin Psychiatry. 2012;73:1119–24. http://article.psychiatrist.com/?ContentType=START&ID=10007866 [cited 21 Apr 2017]
26. Lasserre AM, Glaus J, Vandeleur CL, Marques-Vidal P, Vaucher J, Bastardot F, et al. Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study. JAMA Psychiatry. 2014;71:880–8. http://www.nature.com.e.bibl.liu.se/ng/journal/vaop/ncurrent/full/ng.3404.html%5Cn
27. Lasserre AM, Strippoli M-PF, Glaus J, Gholam-Rezaee M, Vandeleur CL, Castelao E, et al. Prospective associations of depression subtypes with cardio-metabolic risk factors in the general population. Mol Psychiatry 2017;22:1026–1034. https://doi.org/10.1038/mp.2016.178
28. Milaneschi Y, Lamers F, Peyrot WJ, Abdellaoui A, Willemsen G, Hottenga J-J, et al. Polygenic dissection of major depression clinical heterogeneity. Mol Psychiatry 2016;21:516–22. http://www.nature.com/doifinder/10.1038/mp.2015.86
29. Lamers F, Milaneschi Y, de Jonge P, Giltay EJ, Penninx BWJH. Metabolic and inflammatory markers: associations with individual depressive symptoms. Psychol Med. 2017 1–11. https://www.cambridge.org/core/journals/psychological-medicine/article/metabolic-and-inflammatorymarkers-associations-with-individual-depressive-symptoms/912CA2359F039231EA1E963602835624
30. Milaneschi Y, Lamers F, Bot M, Drent ML, Penninx BWJH. Leptin dysregulation is specifically associated with major depression with atypical features: evidence for a mechanism connecting obesity and depression. Biol Psychiatry. 2017;81:807–14. https://doi.org/10.1016/j.biopsych.2015.10.023.
31. Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, et al. Genetic association of major depression with atypical features and obesity-related immunometabolic dysregulations. JAMA Psychiatry. 2017 ;74:1214–25.
32. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157:1552–62. http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.157.10.1552 [cited 30 Aug 2017]
33. Robinson MR, English G, Moser G, Lloyd-Jones LR, Triplett MA, Zhu Z, et al. Genotype-covariate interaction effects and the heritability of adult body mass index. Nat Genet. 2017;49:1174–81. http://www.nature.com/doifinder/10.1038/ng.3912 [cited 27 Jul 2017]
34. Pigeyre M, Yazdi FT, Kaur Y, Meyre D. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci. 2016;130:943–86. http://clinsci.org/cgi/doi/10.1042/CS20160136
36. Finucane HK, Bulik-Sullivan BK, Gusev A, Trynka G, Reshef Y, Loh P-R, et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. Nat Genet. 2015;47:1228–35. http://www.nature.com.e.bibl.liu.se/ng/journal/vaop/ncurrent/full/ng.3404.html%5CnCn
37. Hek K, Demirkan A, Lahti J, Terracciano A, Teumer A, Cornelis MC, et al. A genome-wide association study of depressive symptoms. Biol Psychiatry. 2013;73:667–78.
38. Okbay A, Baselmans BML, De Neve J-E, Turley P, Nivard MG, Fontana MA, et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet. 2016;48:1–13. http://www.nature.com/doifinder/10.1038/ng.3552
39. Cai N, Bigdeli TB, Kretzschmar W, Li Y, Liang J, Song L, et al. Sparse whole-genome sequencing identifies two loci for major

depressive disorder. Nature. 2015;523:588–91. http://www.nature.com/doifinder/10.1038/nature14659
40. Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat Genet. 2016;48:1031–6. https://doi.org/10.1038/ng.3623
41. Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Identification of 44 genetic associations for major depressive disorder. bioRxiv [Internet]. 2017. http://www.biorxiv.org/content/early/2017/07/24/167577
42. Howard DM, Adams MJ, Shirali M, Clarke T, Marioni RE, Coleman JRI, et al. Genome-wide association study of depression phenotypes in UK Biobank (n=322, 580) identifies the enrichment of variants in excitatory synaptic pathways. bioRxiv 2017. https://www.biorxiv.org/content/early/2017/08/01/168732
43. Wheeler E, Huang N, Bochukova EG, Keogh JM, Lindsay S, Garg S, et al. Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. Nat Genet. 2013;45:513–7 [Internet]. http://dx.doi.org/10.1038/ng.2607
44. Pearce LR, Atanassova N, Banton MC, Bottomley B, Van Der Klaauw AA, Revelli JP, et al. XKSR2 mutations are associated with obesity, insulin resistance, and impaired cellular fuel oxidation. Cell . 2013;155:765–77.
45. Hashimoto T, Maekawa S, Miyata S. IgLON cell adhesion molecules regulate synaptogenesis in hippocampal neurons. Cell Biochem Funct. 2009;27:496–8.
46. Schäfer M, Bräuer AU, Savaskan NE, Rathjen FG, Brümmendorf T. Neurotractin/kilon promotes neurite outgrowth and is expressed on reactive astrocytes after entorhinal cortex lesion. Mol Cell Neurosci. 2005;29:580–90.
47. Lee AWS, Hengstler H, Schwald K, Berriel-Diaz M, Loreth D, Kirsch M, et al. Functional inactivation of the genome-wide association study obesity gene neuronal growth regulator 1 in mice causes a body mass phenotype. PLoS ONE. 2012;7:e41537.
48. Boender AJ, van Rozen AJ, Adan RaH. Nutritional state affects the expression of the obesity-associated genes Etv5, Faim2, Fto, and Negr1. Obesity. 2012;20:1–6.
49. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008;31:464–8.
50. McEwen BS. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol Rev. 2007;87:873–904.
51. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. Nat Rev Neurosci. 2009;10:423–33 [Internet]. http://www.nature.com/doifinder/10.1038/nrn2651
52. Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N, et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Mol Psychiatry. 2016;22:900–9 [Internet]. http://www.nature.com/doifinder/10.1038/mp.2016.60
53. Sonino N, Fava GA. Psychiatric disorders associated with Cushing's syndrome. Epidemiology, pathophysiology and treatment. CNS Drugs. 2001;15:361–73. http://www.ncbi.nlm.nih.gov/pubmed/11475942
54. Wester VL, Staufenbiel SM, Veldhorst MAB, Visser JA, Manenschijn L, Koper JW, et al. Long-term cortisol levels measured in scalp hair of obese patients. Obesity. 2014;22:1956–8.
55. Noppe G, van den Akker ELT, de Rijke YB, Koper JW, Jaddoe VW, van Rossum EFC. Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body fat distribution. Int J Obes (Lond). 2016;40:1–22. http://www.ncbi.nlm.nih.gov/pubmed/27339603
56. Fardet L, Fève B. Systemic glucocorticoid therapy: a review of its metabolic and cardiovascular adverse events. Drugs. 2014;74:1731–45.
57. Pace TWW, Miller AH. Cytokines and glucocorticoid receptor signaling. Ann NY Acad Sci. 2009;1179:86–105. http://www.ncbi.nlm.nih.gov/pubmed/19906234 [cited 7 Jun 2017]
58. Stimson RH, Walker BR. The role and regulation of 11β-hydroxysteroid dehydrogenase type 1 in obesity and the metabolic syndrome. Horm Mol Biol Clin Investig. 2013;15:37–48. http://www.ncbi.nlm.nih.gov/pubmed/25436731 [cited 30 Aug 2017]
59. Poór V, Juricskay S, Gáti A, Osváth P, Tényi T. Urinary steroid metabolites and 11beta-hydroxysteroid dehydrogenase activity in patients with unipolar recurrent major depression. J Affect Disord. 2004;81:55–9. http://linkinghub.elsevier.com/retrieve/pii/S016503270300199X [cited 30 Aug 2017]
60. Fouad Mansour M, Pelletier M, Tchernof A. Characterization of 5α-reductase activity and isoenzymes in human abdominal adipose tissues. J Steroid Biochem Mol Biol. 2016;161:45–53 [Internet]. https://doi.org/10.1016/j.jsbmb.2016.02.003.
61. Irwig MS. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. J Clin Psychiatry. 2012;73:1220–3. http://article.psychiatrist.com/?ContentType=START&ID=10007988 [cited 30 Aug 2017]
62. Ahmed A, Rabbitt E, Brady T, Brown C, Guest P, Bujalska IJ, et al. A switch in hepatic cortisol metabolism across the spectrum of non alcoholic fatty liver disease. PLoS ONE. 2012;7:e29531.
63. Huang X, Liu X, Yu Y. Depression and chronic liver diseases: are there shared underlying mechanisms? Front Mol Neurosci. 2017;10:134 http://www.ncbi.nlm.nih.gov/pubmed/28533742%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC542056
64. van Rossum EFC. Obesity and cortisol: new perspectives on an old theme. Obesity. 2017;25:500–1.
65. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med. 2012;18:363–74. http://www.ncbi.nlm.nih.gov/pubmed/22395709
66. Capuron L, Miller AH. Immune system to brain signaling: Neuropsychopharmacological implications. Pharmacol Ther. 2011;130:226–38 [Internet]. https://doi.org/10.1016/j.pharmthera.2011.01.014.
67. Dinel A-L, André C, Aubert A, Ferreira G, Layé S, Castanon N. Cognitive and emotional alterations are related to hippocampal inflammation in a mouse model of metabolic syndrome. PLoS ONE. 2011;6:e24325. http://dx.plos.org/10.1371/journal.pone.0024325
68. Pistell PJ, Morrison CD, Gupta S, Knight AG, Keller JN, Ingram DK, et al. Cognitive impairment following high fat diet consumption is associated with brain inflammation. J Neuroimmunol. 2010;219:25–32. https://doi.org/10.1016/j.jneuroim.2009.11.010.
69. Erion JR, Wosiski-Kuhn M, Dey A, Hao S, Davis CL, Pollock NK, et al. Obesity elicits interleukin 1-mediated deficits in hippocampal synaptic plasticity. J Neurosci. 2014;34:2618–31. http://www.ncbi.nlm.nih.gov/pubmed/24523551
70. Pavlov VA, Tracey KJ. Neural regulation of immunity: molecular mechanisms and clinical translation. Nat Neurosci. 2017;20:156–66.
71. Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G, et al. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-α: relationship to CNS immune responses and depression. Mol Psychiatry. 2010;15:393–403. http://www.nature.com/doifinder/10.1038/mp.2009.116

72. Campbell BM, Charych E, Lee AW, Moller T. Kynurenines in CNS disease: regulation by inflammatory cytokines. Front Neurosci. 2014;8:1–22.
73. Dantzer R, Walker AK. Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression? J Neural Transm. 2014;121:925–32.
74. Hardingham GE, Fukunaga Y, Bading H Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. Nat Neurosci 2002 [Internet]. http://www.nature.com/doifinder/10.1038/nn835
75. Strowig T, Henao-mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. Nature. 2012;481:278–86.
76. Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav Immun. 2013;31:105–14.
77. Yin Z, Deng T, Peterson LE, Yu R, Lin J, Hamilton DJ, et al. Transcriptome analysis of human adipocytes implicates the NOD-like receptor pathway in obesity-induced adipose inflammation. Mol Cell Endocrinol. 2014;394:80–7 [Internet]. https://doi.org/10.1016/j.mce.2014.06.018.
78. Stienstra R, Joosten LAB, Koenen T, Van Tits B, Van Diepen JA, Van Den Berg SAA, et al. The inflammasome-mediated caspase-1 activation controls adipocyte differentiation and insulin sensitivity. Cell Metab. 2010;12:593–605.
79. Alcocer-Gómez E, de Miguel M, Casas-Barquero N, Núñez-Vasco J, Sánchez-Alcazar JA, Fernández-Rodríguez A, et al. NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder. Brain Behav Immun. 2014;36:111–7.
80. Wong M-L, Inserra A, Lewis MD, Mastronardi CA, Leong L, Choo J, et al. Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition. Mol Psychiatry. 2016;21:1–9 [Internet]. http://www.nature.com/doifinder/10.1038/mp.2016.46
81. Paugh SW, Bonten EJ, Savic D, Ramsey LB, Thierfelder WE, Gurung P, et al. NALP3 inflammasome upregulation and CASP1 cleavage of the glucocorticoid receptor cause glucocorticoid resistance in leukemia cells. Nat Genet. 2015;47:607–14. http://www.nature.com/doifinder/10.1038/ng.3283
82. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-Analysis. Psychosom Med. 2009;71:171–86. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006842-200902000-00006
83. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67:446–57. https://doi.org/10.1016/j.biopsych.2009.09.033.
84. Hiles SA, Baker AL, de Malmanche T, Attia J. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. Psychol Med. 2012;42:2015–26. http://www.journals.cambridge.org/abstract_S0033291712000128
85. Liu Y, Ho RCM, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012;139:230–9. https://doi.org/10.1016/j.jad.2011.08.003.
86. Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand. 2017;135:373–87.
87. The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. Nat Neurosci. 2015;18:199–209.
88. Jansen R, Penninx BWJH, Madar V, Xia K, Milaneschi Y, Hottenga JJ, et al. Gene expression in major depressive disorder. Mol Psychiatry. 2016;21:444–444. http://www.nature.com/doifinder/10.1038/mp.2015.94
89. Leday GGR, Vértes PE, Richardson S, Greene JR, Regan T, Khan S, et al. Replicable and coupled changes in innate and adaptive immune gene expression in two case-control studies of blood microarrays in major depressive disorder. Biol Psychiatry. 2017;83:70–80.
90. Glaus J, Vandeleur CL, von Känel R, Lasserre AM, Strippoli MPF, Gholam-Rezaee M, et al. Associations between mood, anxiety or substance use disorders and inflammatory markers after adjustment for multiple covariates in a population-based study. J Psychiatr Res. 2014;58:36–45.
91. Hickman RJ, Khambaty T, Stewart JC. C-reactive protein is elevated in atypical but not nonatypical depression: data from the National Health and Nutrition Examination survey (NHANES) 1999-2004. J Behav Med. 2014;37:621–9. http://link.springer.com/10.1007/s10865-013-9510-0[cited 21 Apr 2017]
92. Van Der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. Cell. 2015;161:119–32 [Internet]. https://doi.org/10.1016/j.cell.2015.03.008.
93. Licinio J, Caglayan S, Ozata M, Yildiz BO, de Miranda PB, O'Kirwan F, et al. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proc Natl Acad Sci. 2004;101:4531–6. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=384781&tool=pmcentrez&rendertype=abstract
94. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. N Engl J Med. 2007;356:237–47 [Internet]. http://www.nejm.org/doi/abs/10.1056/NEJMoa063988
95. Farooqi IS, Keogh JM, Yeo GSH, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003;348:1085–95 [Internet]. http://www.nejm.org/doi/abs/10.1056/NEJMoa022050 [31 Aug 2017]
96. Cui H, López M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. Nat Rev Endocrinol. 2017;13:338–51 [Internet]. http://www.nature.com/doifinder/10.1038/nrendo.2016.222%5Cn. http://www.ncbi.nlm.nih.gov/pubmed/28232667
97. Chen K, Li F, Li J, Cai H, Strom S, Bisello A, et al. Induction of leptin resistance through direct interaction of C-reactive protein with leptin. Nat Med. 2006;12:425–32.
98. Garza JC, Guo M, Zhang W, Lu X-Y. Leptin restores adult hippocampal neurogenesis in a chronic unpredictable stress model of depression and reverses glucocorticoid-induced inhibition of GSK-3β/β-catenin signaling. Mol Psychiatry. 2012;17:790–808. http://www.nature.com/doifinder/10.1038/mp.2011.161 [cited 21 Apr 2017]
99. Yamada N, Katsuura G, Ochi Y, Ebihara K, Kusakabe T, Hosoda K, et al. Impaired CNS leptin action is implicated in depression associated with obesity. Endocrinology. 2011;152:2634–43 [Internet]. https://academic.oup.com/endo/article-lookup/doi/10.1210/en.2011-0004 [cited 21 Apr 2017]
100. Farr OM, Tsoukas MA, Mantzoros CS. Leptin and the brain: Influences on brain development, cognitive functioning and psychiatric disorders. Metabolism. 2015;64:114–30. http://www.sciencedirect.com/science/article/pii/S0026049514001991 [cited 21 Apr 2017]
101. Bouret SG. Neurodevelopmental actions of leptin. Brain Res. 2010;1350:2–9. http://www.sciencedirect.com/science/article/pii/S000689931000819X [cited 21 Apr 2017]

102. Licinio J, Mantzoros C, Negrão AB, Cizza G, Wong ML, Bongiorno PB, et al. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. Nat Med. 1997;3:575–9. http://www.ncbi.nlm.nih.gov/pubmed/9142131 [cited 21 Apr 2017]
103. Lu X-Y. The leptin hypothesis of depression: a potential link between mood disorders and obesity? Curr Opin Pharmacol. 2007;7:648–52. http://www.ncbi.nlm.nih.gov/pubmed/18032111 [cited 21 Apr 2017]
104. Guo M, Huang T-Y, Garza JC, Chua SC, Lu X-Y. Selective deletion of leptin receptors in adult hippocampus induces depression-related behaviours. Int J Neuropsychopharmacol. 2013;16:857–67. http://www.ncbi.nlm.nih.gov/pubmed/22932068 [cited 2 May 2017]
105. Guo M, Lu X-Y. Leptin receptor deficiency confers resistance to behavioral effects of fluoxetine and desipramine via separable substrates. Transl Psychiatry. 2014;4:e486. http://www.ncbi.nlm.nih.gov/pubmed/25463972 [cited 2 May 2017]
106. Ueki K, Kondo T, Kahn CR. Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms. Mol Cell Biol. 2004;24:5434–46. http://www.ncbi.nlm.nih.gov/pubmed/15169905 [cited 5 Sep 2017]
107. Kawazoe Y, Naka T, Fujimoto M, Kohzaki H, Morita Y, Narazaki M, et al. Signal transducer and activator of transcription (STAT)-induced STAT inhibitor 1 (SSI-1)/suppressor of cytokine signaling 1 (SOCS1) inhibits insulin signal transduction pathway through modulating insulin receptor substrate 1 (IRS-1) phosphorylation. J Exp Med. 2001;193:263–9. http://www.ncbi.nlm.nih.gov/pubmed/11208867 [cited 5 Sep 2017]
108. Bendtzen K, Mandrup-Poulsen T, Nerup J, Nielsen JH, Dinarello CA, Svenson M. Cytotoxicity of human pI 7 interleukin-1 for pancreatic islets of Langerhans. Science. 1986;232:1545–7. http://www.ncbi.nlm.nih.gov/pubmed/3086977 [cited 5 Sep 2017]
109. Rasgon NL, Kenna HA, Wroolie TE, Williams KE, DeMuth BN, Silverman DHS. Insulin resistance and medial prefrontal gyrus metabolism in women receiving hormone therapy. Psychiatry Res. 2014;223:28–36 [Internet]. Available from10.1016/j.pscychresns.2014.04.004
110. Kenna H, Hoeft F, Kelley R, Wroolie T, DeMuth B, Reiss A, et al. Fasting plasma insulin and the default mode network in women at risk for Alzheimer's disease. Neurobiol Aging. 2013;34:641–9 [Internet]. 10.1016/j.neurobiolaging.2012.06.006
111. Rasgon NL, Kenna HA, Wroolie TE, Kelley R, Silverman D, Brooks J, et al. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol Aging. 2011;32:1942–8 [Internet]. Available from10.1016/j.neurobiolaging.2009.12.005
112. Rasgon NL, McEwen BS. Insulin resistance—a missing link no more. Mol Psychiatry. 2016;21:1648–52.
113. Kan C, Silva N, Golden SH, Rajala U, Timonen M, Stahl D, et al. A systematic review and meta-analysis of the association between depression and insulin resistance. Diabetes Care. 2013;36:480–9.
114. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care. 2008;31:2383–90.
115. Knol MJ, Twisk JWR, Beekman ATF, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia. 2006;49:837–45. http://link.springer.com/10.1007/s00125-006-0159-x
116. Rotella F, Mannucci E. Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. Diabetes Res Clin Pract. 2013;99:98–104 [Internet]. Available from10.1016/j.diabres.2012.11.022
117. Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. J Clin Psychiatry. 2013;74:31–7.
118. Kan C, Pedersen NL, Christensen K, Bornstein SR, Licinio J, MacCabe JH. et al. Genetic overlap between type 2 diabetes and depression in Swedish and Danish twin registries. Mol Psychiatry. 2016;21:903–9. http://www.nature.com/doifinder/10.1038/mp.2016.28.
119. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012;489:220–30. http://www.nature.com/doifinder/10.1038/nature11550
120. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444:1027–131. http://www.nature.com/doifinder/10.1038/nature05414
121. Cani PD, Bibiloni R, Knauf C, Neyrinck AM, Delzenne NM. Changes in gut microbiota control metabolic diet-induced obesity and diabetes in mice. Diabetes. 2008;57:1470–81.
122. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57:1470–81. http://diabetes.diabetesjournals.org/cgi/doi/10.2337/db07-1403 [cited 5 Sep 2017]
123. Lin P, Ding B, Feng C, Yin S, Zhang T, Qi X, et al. Prevotella and Klebsiella proportions in fecal microbial communities are potential characteristic parameters for patients with major depressive disorder. J Affect Disord. 2017;207:300–4 [Internet]. Available from10.1016/j.jad.2016.09.051
124. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun. 2015;48:186–94 [Internet]. 10.1016/j.bbi.2015.03.016
125. Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res. 2016;82:109–18 [Internet]. 10.1016/j.jpsychires.2016.07.019
126. Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol Psychiatry. 2016;21:1–11. http://www.nature.com/doifinder/10.1038/mp.2016.44%5Cn [Internet]. http://www.ncbi.nlm.nih.gov/pubmed/27067014
127. Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science (80-). 2016;352:565–9.
128. Rogers GB, Keating DJ, Young RL, Wong M-L, Licinio J, Wesselingh S. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol Psychiatry. 2016;21:1–11. http://www.nature.com/doifinder/10.1038/mp.2016.50
129. Martin A. The Representation of Object Concepts in the Brain. Annu Rev Psychol. 2007;58:25–45. http://www.ncbi.nlm.nih.gov/pubmed/16968210 [cited 5 Sep 2017]
130. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 2002;3:655–66. http://www.ncbi.nlm.nih.gov/pubmed/12154366 [cited 5 Sep 2017]
131. Rudebeck PH, Murray EA. Balkanizing the primate orbitofrontal cortex: distinct subregions for comparing and contrasting values.

Ann NY Acad Sci. 2011;1239:1–13 [Internet]. Available from: http://doi.wiley.com/10.1111/j.1749-6632.2011.06267.x
132. Berridge KC, Kringelbach ML. Neuroscience of affect: brain mechanisms of pleasure and displeasure. Curr Opin Neurobiol. 2013;23:294–303. http://linkinghub.elsevier.com/retrieve/pii/S0959438813000330 [cited 5 Sep 2017]
133. Rudebeck PH, Putnam PT, Daniels TE, Yang T, Mitz AR, Rhodes SEV, et al. A role for primate subgenual cingulate cortex in sustaining autonomic arousal. Proc Natl Acad Sci USA. 2014;111:5391–6 [Internet]. http://www.pnas.org/cgi/doi/10.1073/pnas.1317695111 [cited 5 Sep 2017]
134. Shenhav A, Cohen JD, Botvinick MM. Dorsal anterior cingulate cortex and the value of control. Nat Neurosci. 2016;19:1286–91. http://www.ncbi.nlm.nih.gov/pubmed/27669989 [cited 5 Sep 2017]
135. Berthoud H-R, Morrison C. The Brain, Appetite, and Obesity. Annu Rev Psychol. 2008;59:55–92. http://www.ncbi.nlm.nih.gov/pubmed/18154499 [cited 5 Sep 2017]
137. Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. Psychiatr Clin North Am. 1998;21:293–307. http://www.ncbi.nlm.nih.gov/pubmed/9670227 [cited 5 Sep 2017]
138. van Santen A, Vreeburg SA, Van der Does AJW, Spinhoven P, Zitman FG, Penninx BWJH. Psychological traits and the cortisol awakening response: results from the Netherlands Study of Depression and Anxiety. Psychoneuroendocrinology. 2011;36:240–8. http://linkinghub.elsevier.com/retrieve/pii/S0306453010001836 [cited 5 Sep 2017]
139. Wang S-S, Kamphuis W, Huitinga I, Zhou J-N, Swaab DF. Gene expression analysis in the human hypothalamus in depression by laser microdissection and real-time PCR: the presence of multiple receptor imbalances. Mol Psychiatry [Internet]. 2008;13:786–99, 741. http://www.nature.com/doifinder/10.1038/mp.2008.38 [cited 2017 Sep 5].
140. Avery JA, Gotts SJ, Kerr KL, Burrows K, Ingeholm JE, Bodurka J, et al. Convergent gustatory and viscerosensory processing in the human dorsal mid-insula. Hum Brain Mapp. 2017;38:2150–64 [Internet]. http://doi.wiley.com/10.1002/hbm.23510 [cited 5 Sep 2017]
141. Avery JA, Kerr KL, Ingeholm JE, Burrows K, Bodurka J, Simmons WK. A common gustatory and interoceptive representation in the human mid-insula. Hum Brain Mapp. 2015;36:2996–3006 http://doi.wiley.com/10.1002/hbm.22823 [cited 5 Sep 2017]
142. Craig ADB. Topographically organized projection to posterior insular cortex from the posterior portion of the ventral medial nucleus in the long-tailed macaque monkey. J Comp Neurol. 2014;522:36–63 [Internet]. http://doi.wiley.com/10.1002/cne.23425 [cited 5 Sep 2017]
143. Morel A, Gallay MN, Baechler A, Wyss M, Gallay DS. The human insula: architectonic organization and postmortem MRI registration. Neuroscience [Internet]. 2013;236:117–35. http://linkinghub.elsevier.com/retrieve/pii/S0306452213000419 [cited 5 Sep 2017]
144. Hoffman HH, Schnitzlein HN. The numbers of nerve fibers in the vagus nerve of man. Anat Rec. 1961;139:429–35. http://www.ncbi.nlm.nih.gov/pubmed/13963923 [cited 5 Sep 2017]
145. Barrett LF, Simmons WK. Interoceptive predictions in the brain. Nat Rev Neurosci. 2015;16:419–29. http://www.nature.com/doifinder/10.1038/nrn3950 [cited 5 Sep 2017]
146. Craig ADB. How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;10:59–70. http://www.nature.com/doifinder/10.1038/nrn2555 [cited 5 Sep 2017]
147. Kroemer NB, Krebs L, Kobiella A, Grimm O, Vollstädt-Klein S, Wolfensteller U, et al. (Still) longing for food: insulin reactivity modulates response to food pictures. Hum Brain Mapp. 2013;34:2367–80 [Internet]. http://doi.wiley.com/10.1002/hbm.22071 [cited 5 Sep 2017].
148. Page KA, Seo D, Belfort-DeAguiar R, Lacadie C, Dzuira J, Naik S, et al. Circulating glucose levels modulate neural control of desire for high-calorie foods in humans. J Clin Invest. 2011;121:4161–9. http://www.jci.org/articles/view/57873 [cited 5 Sep 2017]
149. Simmons WK, Rapuano KM, Kallman SJ, Ingeholm JE, Miller B, Gotts SJ, et al. Category-specific integration of homeostatic signals in caudal but not rostral human insula. Nat Neurosci. 2013;16:1551–2. http://www.nature.com/doifinder/10.1038/nn.3535 [cited 5 Sep 2017]
150. Führer D, Zysset S, Stumvoll M. Brain activity in hunger and satiety: an exploratory visually stimulated FMRI study. Obesity (Silver Spring). 2008;16:945–50 [Internet]. http://doi.wiley.com/10.1038/oby.2008.33 [cited 5 Sep 2017]
151. LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav Neurosci. 2001;115:493–500. http://www.ncbi.nlm.nih.gov/pubmed/11345973 [cited 5 Sep 2017]
152. Goldstone AP, Prechtl de Hernandez CG, Beaver JD, Muhammed K, Croese C, Bell G, et al. Fasting biases brain reward systems towards high-calorie foods. Eur J Neurosci. 2009;30:1625–35 [Internet]. http://doi.wiley.com/10.1111/j.1460-9568.2009.06949.x [cited 5 Sep 2017]
153. Dimitropoulos A, Tkach J, Ho A, Kennedy J. Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. Appetite. 2012;58:303–12. http://linkinghub.elsevier.com/retrieve/pii/S0195666311006222 [cited 5 Sep 2017]
154. Paulus MP, Stein MB. An insular view of anxiety. Biol Psychiatry. 2006;60:383–7. http://linkinghub.elsevier.com/retrieve/pii/S0006322306004768 [cited 5 Sep 2017]
155. Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. Psychosom Med. 2003;65:528–33. http://www.ncbi.nlm.nih.gov/pubmed/12883101 [cited 5 Sep 2017]
156. Lepine J-P, Briley M. The epidemiology of pain in depression. Hum Psychopharmacol Clin Exp. 2004;19(S1):S3–7. http://www.ncbi.nlm.nih.gov/pubmed/15378670 [cited 5 Sep 2017]
157. Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H. A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. Neuroimage. 2012;61:677–85 [Internet]. http://linkinghub.elsevier.com/retrieve/pii/S1053811912003862 [cited 5 Sep 2017]
158. Su L, Cai Y, Xu Y, Dutt A, Shi S, Bramon E. Cerebral metabolism in major depressive disorder: a voxel-based meta-analysis of positron emission tomography studies. BMC Psychiatry. 2014;14:321 [Internet]. http://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-014-0321-9 [cited 5 Sep 2017]
159. Berridge KC, Ho C-Y, Richard JM, DiFeliceantonio AG. The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Res. 2010;1350:43–64. http://linkinghub.elsevier.com/retrieve/pii/S0006899310008115 [cited 5 Sep 2017]
160. Clithero JA, Rangel A. Informatic parcellation of the network involved in the computation of subjective value. Soc Cogn Affect Neurosci. 2014;9:1289–302. https://academic.oup.com/scan/article-lookup/doi/10.1093/scan/nst106 [cited 5 Sep 2017]
161. Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. Obes Rev. 2012;13:43–56. Internet: http://doi.wiley.com/10.1111/j.1467-789X.2011.00927.x [cited 5 Sep 2017]

162. Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE. The contribution of brain reward circuits to the obesity epidemic. Neurosci Biobehav Rev. 2013;37(Pt A):2047–58. http://linkinghub.elsevier.com/retrieve/pii/S0149763412002102 [cited 5 Sep 2017]
163. Martin-Soelch C. Is depression associated with dysfunction of the central reward system? Biochem Soc Trans. 2009;37:313–7. http://www.ncbi.nlm.nih.gov/pubmed/19143654 [cited 5 Sep 2017]
164. Price JL, Drevets WC. Neurocircuitry of mood disorders. Neuropsychopharmacology. 2010;35:192–216. http://www.ncbi.nlm.nih.gov/pubmed/19693001 [cited 5 Sep 2017]
165. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–55. http://linkinghub.elsevier.com/retrieve/pii/S0149763410001120 [cited 5 Sep 2017]
166. Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. Curr Opin Psychiatry. 2015;28:7–12. http://www.ncbi.nlm.nih.gov/pubmed/25415499 [cited 5 Sep 2017]
167. McCabe C, Cowen PJ, Harmer CJ. Neural representation of reward in recovered depressed patients. Psychopharmacology (Berl). 2009;205:667–77. http://www.ncbi.nlm.nih.gov/pubmed/19529923 [cited 5 Sep 2017]
168. McCabe C, Woffindale C, Harmer CJ, Cowen PJ. Neural processing of reward and punishment in young people at increased familial risk of depression. Biol Psychiatry. 2012;72:588–94. http://linkinghub.elsevier.com/retrieve/pii/S0006322312004465 [cited 5 Sep 2017]
169. Simmons WK, Burrows K, Avery JA, Kerr KL, Bodurka J, Savage CR, et al. Depression-related increases and decreases in appetite: dissociable patterns of aberrant activity in reward and interoceptive neurocircuitry. Am J Psychiatry. 2016;173:418–28 [Internet]. http://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2015.15020162
170. van Gool CH, Kempen GIJM, Penninx BWJH, Deeg DJH, Beekman ATF, van Eijk JTM. Relationship between changes in depressive symptoms and unhealthy lifestyles in late middle aged and older persons: results from the longitudinal aging study Amsterdam. Age Ageing. 2003;32:81–7.
171. van Gool CH, Kempen GIJM, Bosma H, van Boxtel MPJ, Jolles J, van Eijk JTM. Associations between lifestyle and depressed mood: longitudinal results from the Maastricht Aging Study. Am J Public Health. 2007;97:887–94. http://www.ncbi.nlm.nih.gov/pubmed/16735630 [cited 5 Sep 2017]
172. Beccuti G, Pannain S. Sleep and obesity. Curr Opin Clin Nutr Metab Care. 2011;14:402–12. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00075197-201107000-00016 [cited 2017 Aug 31]
173. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011;135:10–9. http://www.ncbi.nlm.nih.gov/pubmed/21300408 [cited 5 Sep 2017]
174. van Strien T, Winkens L, Toft MB, Pedersen S, Brouwer I, Visser M, et al. The mediation effect of emotional eating between depression and body mass index in the two European countries Denmark and Spain. Appetite. 2016;105:500–8 [Internet]. 10.1016/j.appet.2016.06.025
175. Lazarevich I, Irigoyen Camacho ME, Velázquez-Alva MDC, Zepeda Zepeda M. Relationship among obesity, depression, and emotional eating in young adults. Appetite. 2016;107:639–44.
176. Vogelzangs N, Beekman ATF, Boelhouwer IG, Bandinelli S, Milaneschi Y, Ferrucci L, et al. Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. J Clin Psychiatry. 2011;72:598–604.
177. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: a meta-analysis. Eur Neuropsychopharmacol. 2015;25:1532–43.
178. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Arch Intern Med. 2000;160:2101. http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.160.14.2101 [cited 5 Sep 2017]
179. American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel, 2013. Expert panel report: guidelines (2013) for the management of overweight and obesity in adults. Obesity. 2014;22(S2):S41–410. http://www.ncbi.nlm.nih.gov/pubmed/24227637 [cited 5 Sep 2017].
180. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. BMC Psychiatry. 2014;14:107 http://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-14-107
181. Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, Mors O, et al. Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects. JAMA Psychiatry. 2014;71:1381 http://www.ncbi.nlm.nih.gov/pubmed/25322082 [cited 21 Apr 2017]
182. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70:31–41. http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/2013.jamapsychiatry.4 [cited 21 Apr 2017]
183. Wong BC, Chau CK, So H Genetic overlap of depression with cardiometabolic diseases and implications for drug repurposing for comorbidities. 2017;1–28. https://www.biorxiv.org/content/early/2017/08/23/140590
184. McElroy SL, Guerdjikova AI, Kim DD, Burns C, Harris-Collazo R, Landbloom R, et al. Naltrexone/Bupropion combination therapy in overweight or obese patients with major depressive disorder. Prim Care Companion CNS Disord. 2013 20;15 [Internet]. http://www.ncbi.nlm.nih.gov/pubmed/24171147
185. Paz-Filho G, Mastronardi CA, Licinio J. Leptin treatment: Facts and expectations. Metabolism. 2015;64:146–56 [Internet]. 10.1016/j.metabol.2014.07.014