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The brain-adipocyte-gut network: Linking obesity and depression subtypes

Carla M. Patist[1] · Nicolas J. C. Stapelberg[1,2] · Eugene F. Du Toit[3] · John P. Headrick[3]

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Abstract

Major depressive disorder (MDD) and obesity are dominant and inter-related health burdens. Obesity is a risk factor for MDD, and there is evidence MDD increases risk of obesity. However, description of a bidirectional relationship between obesity and MDD is misleading, as closer examination reveals distinct unidirectional relationships in MDD subtypes. MDD is frequently associated with weight loss, although obesity promotes MDD. In contrast, MDD with atypical features (MDD-AF) is characterised by subsequent weight gain and obesity. The bases of these distinct associations remain to be detailed, with conflicting findings clouding interpretation. These associations can be viewed within a systems biology framework—the psycho-immune neuroendocrine (PINE) network shared between MDD and metabolic disorders. Shared PINE subsystem perturbations may underlie increased MDD in overweight and obese people (obesity-associated depression), while obesity in MDD-AF (depression-associated obesity) involves more complex interactions between behavioural and biomolecular changes. In the former, the chronic PINE dysfunction triggering MDD is augmented by obesity-dependent dysregulation in shared networks, including inflammatory, leptin-ghrelin, neuroendocrine, and gut microbiome systems, influenced by chronic image-associated psychological stress (particularly in younger or female patients). In MDD-AF, behavioural dysregulation, including hypersensitivity to interpersonal rejection, fundamentally underpins energy imbalance (involving hyperphagia, lethargy, hypersomnia), with evolving obesity exaggerating these drivers via positive feedback (and potentially augmenting PINE disruption). In both settings, sex and age are important determinants of outcome, associated with differences in emotional versus cognitive dysregulation. A systems biology approach is recommended for further research into the pathophysiological networks underlying MDD and linking depression and obesity.

Keywords Major depressive disorder · Obesity · Systems biology · Psycho-immune neuroendocrine (PINE) network · Leptin · Gut microbiome

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✉ Nicolas J. C. Stapelberg
chris.stapelberg@health.qld.gov.au

Carla M. Patist
Carla.Patist@health.qld.gov.au

Eugene F. Du Toit
j.dutoit@griffith.edu.au

John P. Headrick
j.headrick@griffith.edu.au

[1] Gold Coast Hospital and Health Service, Southport, Australia

[2] Faculty of Health Sciences and Medicine, Bond University, Robina, Australia

[3] School of Medical Science, Griffith University Gold Coast, Southport, Australia

Introduction

Major depressive disorder (MDD) and obesity are highly significant, interlinked conditions—obesity increases risk of MDD, while depression with atypical features (MDD-AF) promotes obesity. The Global Burden of Disease Study 2010 ranked MDD 11th of 291 diseases and injuries worldwide (Murray et al., 2013), and MDD is among the top 20 causes of years lived with disability (Charlson et al., 2013). The ranking of MDD has increased since 1990 (Charlson et al., 2013) with recent estimates and projections (Vos et al., 2016) placing MDD as the second-leading cause of disability-adjusted life years (DALYs) through 2020, behind ischaemic heart disease (Murray & Lopez, 1997). The latter also is strongly associated with MDD (Stapelberg et al., 2015; Headrick et al., 2017). There has been a simultaneous increase in obesity, with overweight and obesity significant problems worldwide (Ng et al.,

2014). The proportion of adults with a body mass index (BMI) >25 increased substantially between 1980 and 2013: from 29% to 37% in men, and from 30% to 38% in women (Ng et al., 2014). Changes in childhood obesity are even more prominent (Bass & Eneli, 2015), with significant consequences for later illnesses, including MDD (Kelsey, Zaepfel, Bjornstad, & Nadeau, 2014). Overweight and obesity result in 3.8 DALYs lost and 3.4 million deaths worldwide (Ng et al., 2014). Importantly, obesity and MDD appear to be significantly linked (Wing et al., 1991; Sullivan et al., 1993; Friedman & Brownell, 1995; Barefoot et al., 1998; Roberts et al., 2000; Faith et al., 2002; Scott et al., 2008; Luppino et al., 2010; de Wit et al., 2010), with obesity increasing risk of MDD (Sullivan et al., 1993; Xu et al., 2011) and depression with atypical features (MDD-AF) promoting obesity (Hasler et al., 2004; Lasserre et al., 2014). Several physiological mechanisms may underlie development of depressive illness in obesity; major depression is associated with the metabolic syndrome and immune and endocrine dysfunction (Heiskanen et al., 2006; Richter, Juckel, & Assion, 2010; Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2015; Teixeira & Rocha, 2007), and both conditions share chronic low-grade inflammation, adipokine, autonomic nervous system (ANS), and gut microbiome changes.

Directionality of obesity-depression associations - importance of MDD subtype

A reciprocal or bidirectional association between MDD and obesity has been argued; some studies have concluded that depression also is a risk factor for obesity (Pine et al., 2001; Luppino et al., 2010; Vogelzangs et al., 2008). However, this bidirectionality is a simplification open to challenge (Lamers et al., 2010; Levitan et al., 2012; Hasler et al., 2004; Glaus et al., 2013) and inconsistent with the fact that MDD is most frequently characterized by decreased appetite and weight loss (Lamers et al., 2010; Levitan et al., 2012; Hasler et al., 2004; Glaus et al., 2013), whereas hyperphagia and weight gain are specifically associated with the MDD-AF subgroup (American Psychiatric Association, 2013), representing 15-35% of MDD. Because MDD remains a diagnostically unitary construct, incorporating several forms of depressive disorder such as MDD-AF and MDD with melancholic features (MDD-MF) as subtypes rather than distinct clinical entities (Levitan et al., 2012), many studies exploring MDD and obesity also consider depression as a unitary diagnosis (Levitan et al., 2012). This curtails more meaningful delineation of depressive illnesses, their pathogenesis and association with other diseases and risk factors, including obesity.

Faith et al. (2011) examined obesity-depression associations in 25 studies, of which 15 tested "depression-to-obesity" paths and 10 tested "obesity-to-depression" paths. Although limited by heterogeneity within the literature, 80% of the studies reported significant obesity-to depression associations (odds ratios 1.0-2.0), while 53% of analysed studies reported significant depression-to-obesity associations (Faith et al., 2011). They highlight methodological issues in the studies examined; 3 of 15 reviewed studies used measured weight and height together with interview assessments of depression. Recent meta-analysis by Mannan et al. (2016) suggests that directional relationships are strongest for MDD-to-obesity rather than obesity-to-MDD, particularly for women in the reproductive age group. However, a challenge in such studies remains identification of "directionality"—the unequivocal and singular preexistence of one disorder preceding later emergence of the other. This is exacerbated by unknowns regarding the mechanistic natures and temporal properties of disease development, and heterogeneities within disease cohorts.

Recent studies have attempted to identify subtypes of depressive illness based on methodologies such as latent class analysis (Lamers et al., 2010) or causative factors (Rudaz et al., 2017). Different depression subtypes have been identified, comparable to MDD-MF and MDD-AF; the latter exhibiting a stronger association with obesity (Lamers et al., 2010; Levitan et al., 2012; Hasler et al., 2004; Glaus et al., 2013). Association between atypical depression and obesity is further supported by longitudinal evidence (Hasler et al., 2004; Lasserre et al., 2014). It has been concluded that a depression-to-obesity association is driven solely by the MDD-AF subgroup (Lamers et al., 2013b; Sullivan et al., 1998; Hasler et al., 2004), although there also is evidence for overlap of MDD-AF and MDD-MF (Angst, Gamma, Benazzi, Ajdacic, & Rössler, 2007).

Detailed below, people with MDD-AF have different physiological responses of the PINE network compared with those with MDD-MF, with the latter associated with greater hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity and less immuno-inflammatory activity (e.g., tumour necrosis factor-α (TNF-α) changes). Those with MDD-AF exhibit decreased HPA axis activity even compared to nondepressed controls, yet greater proinflammatory activity than those with MDD-MF (Lamers et al., 2013a). Other studies demonstrate down-regulation of the HPA axis and CRH deficiency in MDD-AF, rather than the increased activity discussed with regards to MDD and an obesity-to-depression association (Gold & Chrousos, 2002). These distinctions are relevant to less prevalent depression-dependent obesity. Other factors, particularly age and sexual dimorphism, further complicate associations between obesity and depression (and their interpretation). For example, Roberts and Duong report no independent depression-to-obesity relationship in adolescents, with associations explained by body-image factors (Roberts & Duong, 2015), while Vittengl concludes that associations between obesity and depression

are significant only in females, involving emotional, social and physical dysfunctions (Vittengl, 2018).

General mechanisms linking obesity and depression

Two general mechanisms (not exclusive) can explain "typical" obesity-associated depression: i) obesity and MDD share fundamental biological mechanisms (inflammatory, neuroendocrine, metabolic, and gut-related), thus their perturbation in obesity predisposes to subsequent MDD; and ii) chronic psychological stress related to body-image associated with obesity contributes to dysregulation of this psycho-immune-neuroendocrine (PINE) network to promote MDD (Fig. 1). In this model, it is the physiological *consequences* of obesity that share in the pathogenesis of MDD: evolving low-grade inflammation, dysbiosis, ANS imbalance, leptin and ghrelin changes, together with image-related psychological stress. Considered within a systems biology framework, MDD is thought to arise via dysregulation of the PINE network by chronic stress, ultimately crossing a critical threshold or tipping point to an MDD disease state (PINE pathome) (Stapelberg et al., 2018; Stapelberg et al., 2015). This is supported by correlation of biomarkers of PINE network dysfunction and development of MDD (Verduijn et al., 2015). This progression and transition will be accelerated by additional chronic stressors and PINE dysregulation, for example arising in obesity (Fig. 1). Because obesity or its perception is psychologically stressful (Atlantis & Ball, 2008; Derenne & Beresin, 2006), with body image a well-established determinant of psychological health, obesity also poses a chronic psychological stressor exaggerating stress-dependent PINE dysfunction. Indeed, perception of body weight is a better predictor of MDD than actual obesity (with its metabolic and physiologic sequelae) and is implicated as a dominant basis of the association between obesity and MDD in adolescents (Roberts & Duong, 2013b, 2015). The severely obese are at high risk for depression, and severely obese younger women and those with poor body image are at further increased risk (Dixon, Dixon, & O'brien, 2003). While weight loss can improve psychometric measures of depression in the

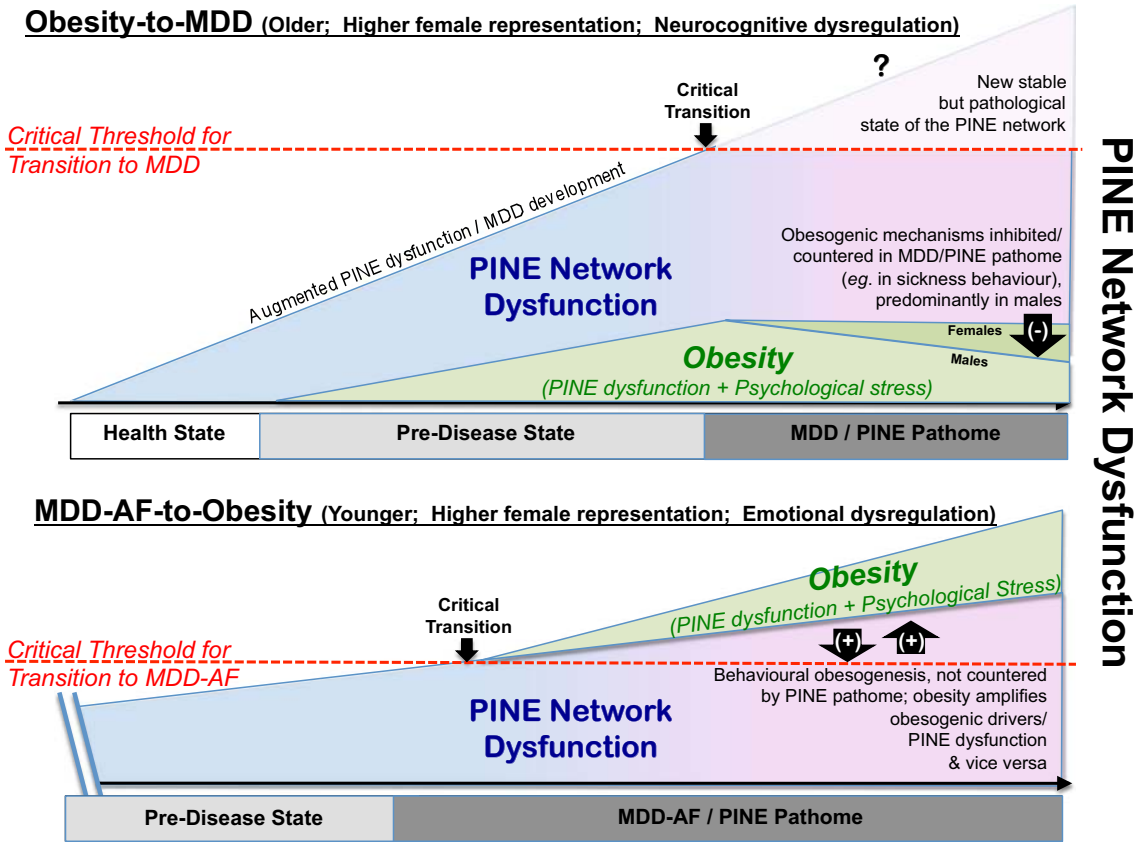

Fig. 1 General schemes of obesity-to-MDD and MDD-AF-to-obesity. Increased risk of MDD with obesity is driven by shared disruption of the PINE network, surpassing the threshold for transition from healthy or predisease states to MDD. Whether PINE dysregulation continues to evolve or stabilises in a new steady state is unclear. Transition to the PINE pathome (MDD) may counter obesogenic mechanisms, although females exhibit a tendency to retain obesity. In atypical depression (MDD-AF), emergence of obesity involves behavioural dysregulation (hyperphagia, hypersomnia, fatigue) associated with a hypersensitivity to interpersonal rejection, anxiety, and body-image factors. Obesity worsens behavioural drivers and PINE network dysfunction in a positive feedback manner, worsening depressive symptoms (linked to BMI). Age and sex are strong modifiers, with weight loss dominant in older/late-onset MDD in association with cognitive deficit, and weight gain in younger and female subjects in association with emotional dysregulation. Associations between obesity and MDD are generally stronger in females

severely obese, a fall in depression score also correlates with improvement in appearance evaluation (Dixon et al., 2003).

The PINE perturbation with obesity alone may be insufficient to transition the system across a critical threshold to the PINE pathome (MDD), unless coupled with chronic stress or preexisting network dysfunction. This mechanistic model nonetheless raises additional questions, not least why this sharing of PINE network subsystems does not in turn broadly promote obesity in MDD (a phenomenon specific to MDD-AF). Dominant weight loss in MDD implies that critical transition of the PINE network and emergence of MDD ultimately opposes or inhibits prior obesogenic mechanisms; however, obese people with MDD—especially women—may remain obese (Carpenter, Hasin, Allison, & Faith, 2000).

A third mechanism may explain the opposing directional relation of depression-associated obesity in MDD-AF: distinct behavioural responses, including chronically modified consolatory/reward responses in the context of long-standing hypersensitivity to interpersonal rejection, may fundamentally upset energy homeostasis to promote obesity (Fig. 1). The MDD-AF subtype is characterised by psycho-behavioural differences that include interpersonal rejection sensitivity, predominance of anxiety over mood symptoms, poor body image, hypersomnia, lethargy/fatigue, and hyperphagia. Altered eating and sleeping habits, fatigue, and poor body image may be multiple aspects of a single disorder (Silverstein & Angst, 2015), although MDD-AF could also reflect multiple conditions or a spectrum disorder (Parker et al., 2002). However, hypersensitivity to personal rejection appears to be a primary feature, promoting depression in response to stress and self-consolatory strategies of hyperphagia and hypersomnia (Parker et al., 2002). This hyperphagia, driven by rejection hypersensitivity and potentially involving disproportionate intake of sugar/fat rich "rewarding" foods (as observed with other forms of stress) (Epel, Lapidus, McEwen, & Brownell, 2001; Ng & Jeffery, 2003), coupled with fatigue and hypersomnia, underpin MDD-AF-associated obesity (Fig. 1). Emerging obesity may in turn reinforce and exaggerate behavioural determinants of MDD-AF and potentially worsen PINE network disruption, consistent with correlation of MDD-AF symptomology with BMI (Łojko, Buzuk, Owecki, Ruchała, & Rybakowski, 2015).

A biological basis for obesity-associated MDD

This paper focuses on plausible biological mechanisms leading from obesity to MDD (obesity-associated depression), before considering the less typical depression-to-obesity relationship (depression-associated obesity in MDD-AF). Mechanisms are presented using a systems biology framework, as employed previously in exploring physiological relationships between depressive illness and other comorbid conditions (Stapelberg et al., 2015; Stapelberg et al., 2011; Headrick et al., 2017). While obesity also is linked to other mental illnesses, for example anxiety symptoms (Sullivan et al., 1993; Wing et al., 1991) and disorders (Barry, Pietrzak, & Petry, 2008), these specific relationships are beyond the scope of the present discussion.

Relevance of a systems biology approach

Depression is recognised as having both a genetic (Hettema, 2010) and physiological basis (Stapelberg et al., 2015; Stapelberg et al., 2011). The relationship between depression and obesity is predominantly driven by these physiological processes (Stapelberg et al., 2015), although distinct psychological/behavioural changes may underpin a reverse association in MDD-AF (Parker et al., 2002). Nonetheless, emotional regulation is highly dependent on autonomic processes and is linked to physiological and metabolic regulatory processes described in the polyvagal (Porges, 1995, 1997, 1998, 2001, 2003) and neurovisceral integration theories (Thayer & Lane, 2000), and the PINE network model (Stapelberg et al., 2018; Stapelberg et al., 2015). Exploration of mechanistic relationships between depression and other medical conditions is facilitated by their conceptualisation within a systems biology framework (Stapelberg, Neumann, Shum, McConnell, & Hamilton-Craig, 2011; Stapelberg et al., 2018; Stapelberg et al., 2015).

Systems biology allows integrated analysis of complex interacting pathways or networks (Noorbakhsh, Overall, & Power, 2009) and is holistic rather than reductionist, which permits large numbers of elements (physiological processes) and their interrelationships to be identified, modelled, and tracked over time. This facilitates the evolution of new hypotheses regarding the organisation and function of complex biological systems (Alm & Arkin, 2003), and development of quantitative models (Barabasi & Oltvai, 2004). Examples of biological systems amenable to exploration using network theory include gene (Kitano, 2002; Alm and Arkin, 2003), protein and enzymatic (Nikolsky et al., 2005; Alm and Arkin, 2003), and metabolic networks (Kitano, 2002). Systems biology can also be applied to complex disease states involving multiple pathogenic determinants (Noorbakhsh et al., 2009) and highly interrelated mechanisms (Stapelberg et al., 2015; Stapelberg et al., 2011; Headrick et al., 2017).

The theory of allostasis (Sterling & Eyer, 1988) and the PINE network model (Stapelberg et al., 2015) both conceptualise depression as arising from chronic disruption of highly interlinked physiological pathways. The PINE model applies a systems biology approach to these processes, viewing them as a complex network

(Stapelberg et al., 2018). When this network or PINE physiome is progressively disrupted by chronic stress, homeostasis is perturbed beyond a critical threshold, giving rise to disease (Stapelberg et al., 2018). Disruption of the PINE network may promote several related diseases, with outcomes influenced by genetic predisposition, socioeconomics, and lifestyle - diathesis factors (Stapelberg et al., 2015). In this way, the PINE pathome encompasses pathologies, including obesity, the metabolic syndrome, atherosclerosis, hypertension, thrombosis, as well as coronary heart disease, type 2 diabetes, cerebrovascular accident, and depression (Stapelberg et al., 2015 and 2018). Within the PINE network depression is linked to obesity via several physiological pathways: metabolic and mood regulation via leptin and ghrelin, the ANS, thyroid and sex hormones and gut dysbiosis, which are linked by HPA axis and immuno-inflammatory function. These interrelationships have been synthesised into directional network diagrams, depicted in Figs. 2, 3, and 4.

Immuno-inflammatory Pathways Linking Obesity and MDD

Low-grade inflammation is shared across MDD and obesity, and appears causal in both, although whether as a precipitating versus reinforcing factor is unclear. Whether chronic low-grade inflammation alone is sufficient to induce chronic disease or requires additional disruptions of PINE network subsystems also is unclear. Nonetheless, cytokines, such as IFNγ and interleukin-6 (IL-6), increase with chronic stress (Stapelberg et al., 2015) and depression (Maes et al., 1993) and promote depression development (reviewed in Stapelberg et al., 2015). Indeed, IL-6 and CRP levels correlate with severity of depression (Elovainio et al., 2009; Frasure-Smith, Lespérance, Irwin, Talajic, & Pollock, 2009), are predictive of cognitive changes in depression (Gimeno et al., 2009), and are further enhanced by acute stress (Weinstein et al., 2010).

Systemic inflammation promotes neuroinflammation, resulting in a microglial proliferation and astrocyte decline (reviewed in Stapelberg et al., 2015), which promotes

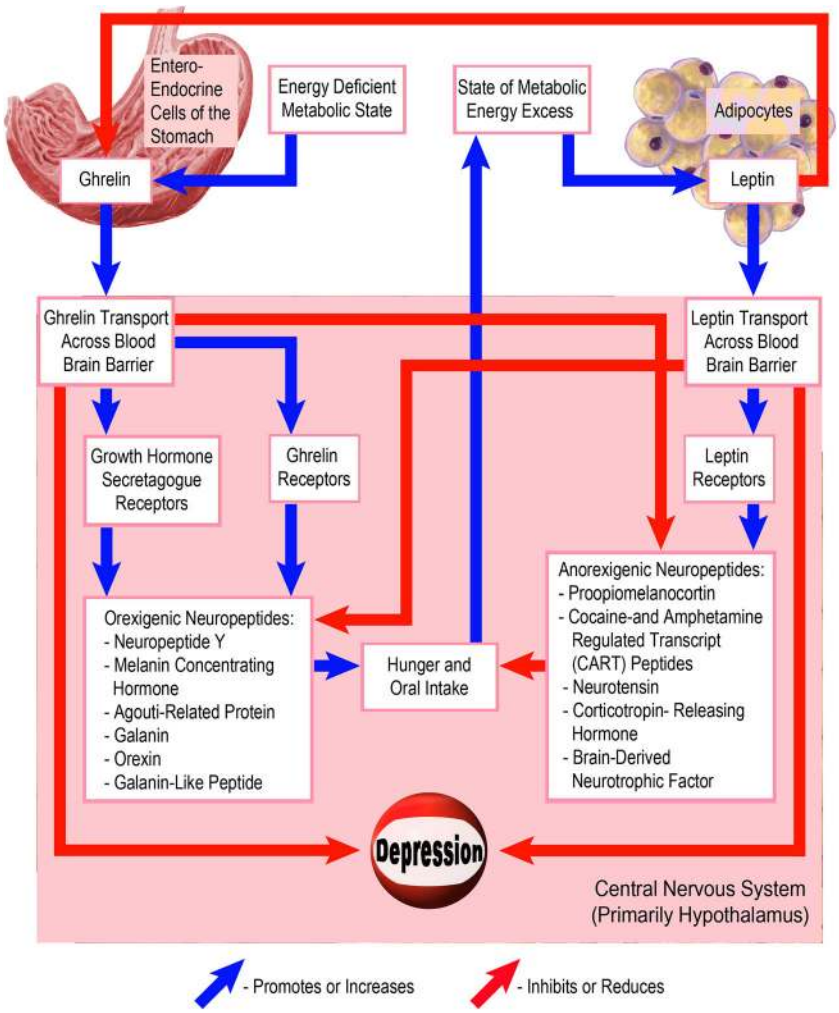

Fig. 2 A directional network diagram of the brain-adipocyte-gut network: immune, gut microbiome, and CNS interactions

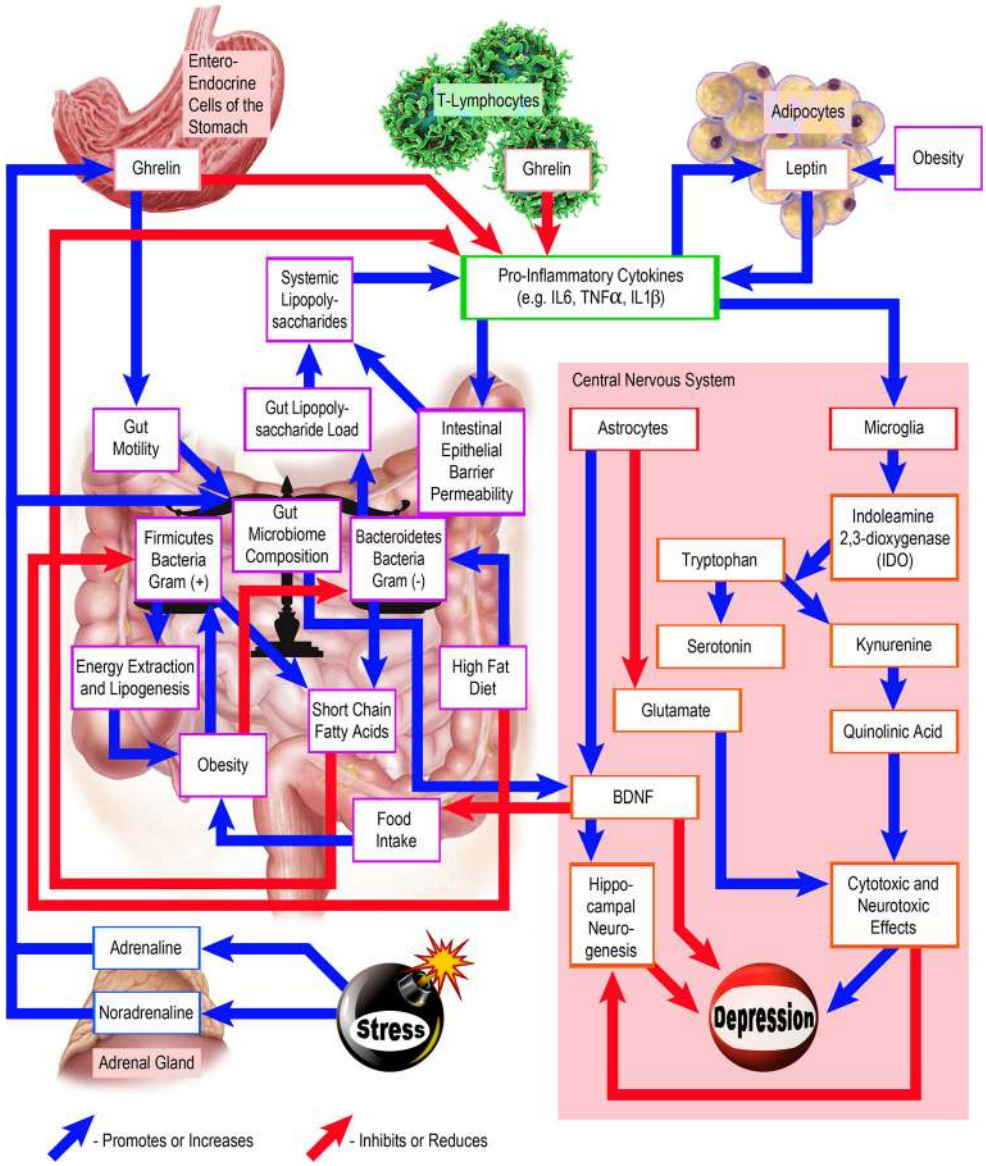

Fig. 3 A directional network diagram of the brain-adipocyte-gut network: interactions of leptin and ghrelin in energy and mood regulation

kynurenine pathway activity and reduces tryptophan availability for serotonin synthesis. This also decreases BDNF secretion and hippocampal neurogenesis, consistently linked to depression (Gould et al., 1998; McEwen, 1999; Duman et al., 1997; Brunoni et al., 2008). Depression is promoted by declining serotonin (Schildkraut, 1965) and generation of kynurenine-related neurotoxins that reduce trophic factors, such as BDNF, inhibiting neurogenesis (Stapelberg et al., 2015) (Fig. 2). Additional inflammatory activation in obesity can exaggerate or accelerate PINE network transition beyond a critical threshold to MDD (or the PINE pathome) (Fig. 1).

Cytokines, such as TNF-α and IL-6, are significantly elevated in obesity, and levels correlate significantly with body weight, BMI, waist and hip circumferences, and waist-hip ratio (Park, Park, & Yu, 2005). In addition, IL-6 levels are significantly related to visceral adiposity in obese people (Park et al., 2005) and to subcutaneous adiposity (together with CRP and TNF receptor 2) (Pou et al., 2007). Characteristic inflammation in obesity may increase gut permeability, leading to neurovegetative features of depression (Stapelberg et al., 2018). Positive feedback may emerge, with inflammation increasing permeability to induce further inflammation, while cytokines such as IL-6 stimulate the HPA axis to promote obesity, insulin-resistance, and hypertension (Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000). These mechanisms are implicated in development of MDD and are illustrated in Fig. 2, with roles of inflammation further discussed below in the context of shared PINE subsystems. Indeed, inflammatory changes in complex disorders, such as MDD and obesity, can be best understood through a systems

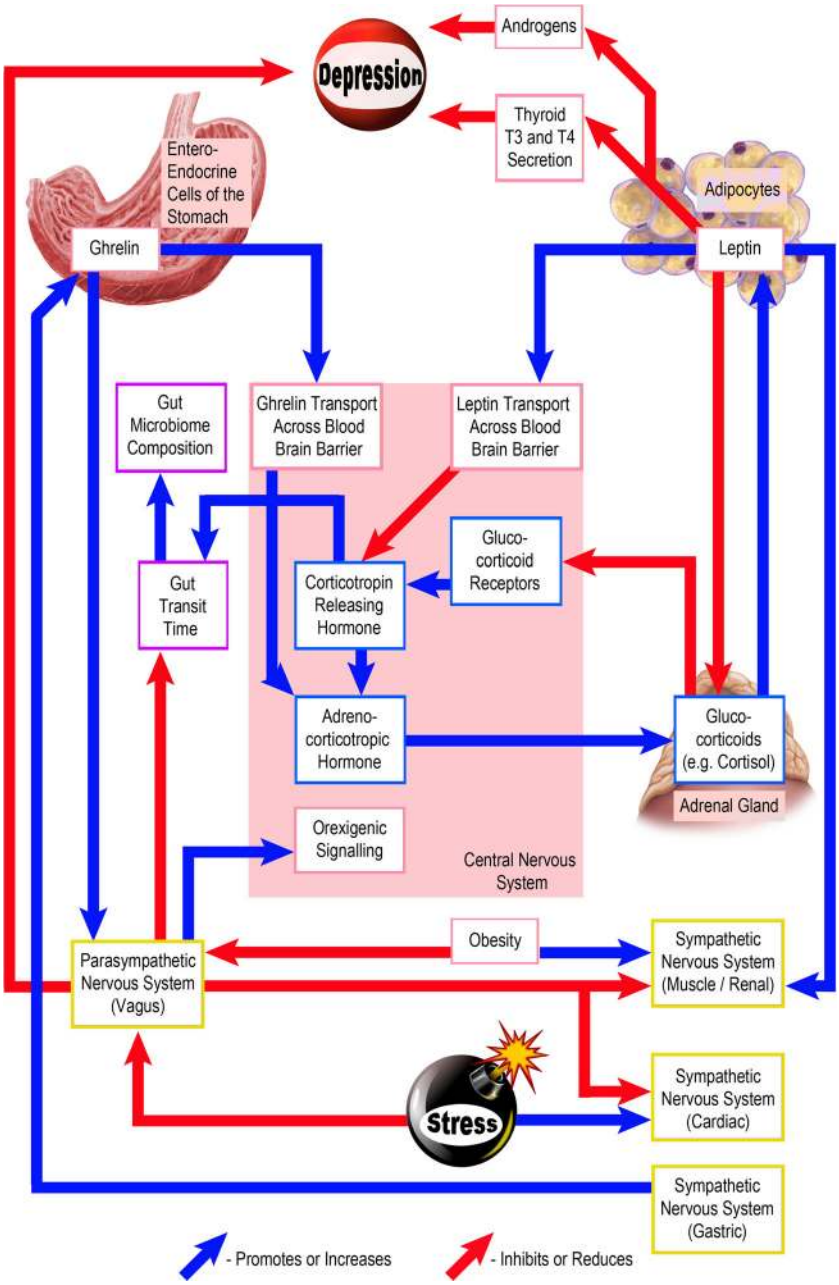

Fig. 4 A directional network diagram of the brain-adipocyte-gut network: endocrine and autonomic interactions

biology approach, driven and influenced by changes within interacting elements of the PINE network, including leptin-ghrelin, ANS, and gut-dependent mechanisms (Fig. 2).

Neuroendocrine Mechanisms Linking Obesity and MDD

Leptin and ghrelin

Dysregulation of the interacting leptin-ghrelin systems arises in obesity and may promote MDD, although conflicting observations render this a controversial subject. Both molecules are central regulators in the PINE network (Fig. 3), have independent links to mood regulation (Lu, 2007; Lutter & Elmquist, 2009; Schellekens, Finger, Dinan, & Cryan, 2012), and are implicated in MDD (Milaneschi, Lamers, Bot, Drent, & Penninx, 2017; Westling, Ahrén, Träskman-Bendz, & Westrin, 2004). Both are also modified in obesity, where they play a role in promoting energy imbalance through orexigenic, metabolic, and inflammatory effects. Dysregulation in obesity can thus predispose to MDD, augmenting the chronic PINE dysfunction that culminates in critical system transition to MDD (Stapelberg et al., 2018; Stapelberg et al., 2015).

Leptin is encoded by the obese (*ob*) gene and secreted from adipocytes (Lu, 2007; Zupancic and Mahajan, 2011; Zhang et al., 1994) to interact with hypothalamic leptin receptors to modulate energy homeostasis and trigger anorexic effects via orexigenic/anorexigenic neuropeptide changes, particularly in the arcuate nucleus (Brennan & Mantzoros, 2006; Elmquist, Bjørbæk, Ahima, Flier, & Saper, 1998; Klok, Jakobsdottir, & Drent, 2007). Energy-deficient states reduce leptin, leading to increased expression of orexigenic peptides, such as neuropeptide Y (NPY), melanin-concentrating hormone, agouti-related protein (AgRP), orexin, galanin, and galanin-like peptide (Klok et al., 2007; Morris et al., 2012), and thereby to increased food intake (Fig. 3). Conversely, energy excess increases leptin to up-regulate appetite suppressants, such as proopiomelanocortin (POMC) (Brennan & Mantzoros, 2006; Chan & Mantzoros, 2005), and suppress NPY and AgRP expression and neuronal activity, reducing feeding behaviour. In contrast to leptin, ghrelin is orexigenic and is synthesized in enteroendocrine cells of the stomach (Dixit et al., 2004). Ghrelin triggers growth hormone release (Petersenn, 2002) and activation of AgRP and NPY-producing neurons in the arcuate nucleus to stimulate food intake (Meier & Gressner, 2004), while also acting peripherally via afferent vagal activity (Date et al., 2002). Ghrelin blocks leptin actions in the hypothalamus via NPY receptor signalling and inhibition of POMC and corticotropin-releasing hormone (CRH) producing neurones (Inui, 2001; Klok et al., 2007; Shintani et al., 2001; Zarouna, Wozniak, & Papachristou, 2015), while leptin decreases ghrelin signalling by suppressing synthesis and release (Brennan & Mantzoros, 2006; Kalra, Ueno, & Kalra, 2005) and the activity of NPY and AgRP neurons (Baver et al., 2014). Thus, the two peptides have reciprocal counter-regulatory actions, as outlined in Fig. 3.

Leptin and ghrelin resistance. Increased leptin levels in obese subjects (Lu, 2007) reflect increased adiposity and adipocyte leptin production (Morris et al., 2012), coupled with evolving leptin-resistance (Brennan & Mantzoros, 2006). Negative feedback control of leptin (Banks, 2008) is disrupted by this resistance, increasing secretion and systemic levels (Brennan & Mantzoros, 2006; Lu, 2007). Central leptin resistance is evidenced by its inability to inhibit food intake in obese people (Heymsfield et al., 1999) or to inhibit persistent NPY neuronal activity in obesity (Baver et al., 2014). Central resistance may involve impaired blood brain barrier (BBB) transport (Banks, 2008), neuronal signalling defects, and induction of inhibitors of hypothalamic leptin-signalling (El-Haschimi & Lehnert, 2003), and leads to orexigenic outcomes while reducing leptin-related neuroprotection.

High systemic leptin inhibits ghrelin signalling by suppressing ghrelin release (Brennan & Mantzoros, 2006) and NPY and AgRP neuronal activity (Baver et al., 2014) coupled with decreased BBB transport (Banks, Burney, & Robinson, 2008). Central ghrelin resistance in obesity may be leptin-dependent, with suppression of AgRP and NPY expression (Cui, López, & Rahmouni, 2017) and neuronal activity (Briggs, Enriori, Lemus, Cowley, & Andrews, 2010)—effects inducible by leptin—considered primary determinants of resistance in obesity (Zigman, Bouret, & Andrews, 2016). Although impairment of ghrelin signalling may induce anorexigenic effects, potentially limiting food intake in obesity (Briggs et al., 2010), coexisting leptin-resistance inhibits this mechanism: leptin-resistance is associated with reduced systemic ghrelin in obesity (Tschöp et al., 2001; Zigman et al., 2016; Briggs et al., 2010). Central leptin and ghrelin resistance will also influence mood and cognition (Briggs et al., 2010), further influencing weight gain and obesity and promoting depression.

Influences of leptin and ghrelin on mood Ghrelin plays a role in stress responses and affects mood (Lutter et al., 2008) (Asakawa et al., 2001). Adrenaline elevates ghrelin levels during acute (de la Cour, Norlén, & Håkanson, 2007) and chronic stress in both animal models (Lutter et al., 2008; Ochi et al., 2008) and humans (Rouach et al., 2007), increasing hypothalamic CRH and circulating corticosterone (Asakawa et al., 2001). Lutter et al. (2008) propose this increase in ghrelin is protective, defending against depressive outcomes. Ghrelin does exhibit neuroprotective properties (Frago, Baquedano, Argente, & Chowen, 2011) and may increase hippocampal neurogenesis (Abizaid & Anisman, 2014), impairment of which promotes MDD (Sahay & Hen, 2007). Growth hormone secretagogue receptors in the ventral tegmental area and nucleus accumbens involved in reward and positive emotions additionally link ghrelin with stress regulation and anxiety (Sarker, Franks, & Caffrey, 2013) and depressive symptoms, such as anhedonia (Chuang et al., 2011). Obesity-dependent ghrelin resistance will suppress these antidepressant and neuroprotective effects (Lutter et al., 2008), promoting MDD. Recent animal studies indicate stress-related ghrelin resistance also contributes to amygdala hyperactivation and overconsolidation of fear memories, independent of appetite responses (Harmatz et al., 2017).

Leptin also affects mood (Lu, 2007), and while ghrelin and leptin have independent effects, they likely interact in influencing mood and depression (Abizaid & Anisman, 2014). Animal and human studies reveal correlations between depressed mood and reduced leptin (Jow, Yang, & Chen, 2006; Kim et al., 2006; Kraus, Haack, Schuld, Hinze-Selch, & Pollmächer, 2001; Lu, 2007; Lu, Kim, Frazer, & Zhang, 2006), and leptin administration reverses depressive behaviour in rodents (Kim et al., 2006; Lu et al., 2006). Nonetheless, findings in human studies are mixed, supporting either increased leptin in depression (Antonijevic et al., 1998;

Rubin, Rhodes, & Czambel, 2002), select elevations in depressed females (Rubin, Rhodes, & Czambel, 2002) or females with increased BMI (Ubani & Zhang, 2015), no such correlations (Deuschle et al., 1996), or a reduction in leptin levels independent of BMI (Jow et al., 2006; Kraus et al., 2001). Meta-analysis broadly supports elevation of leptin in mild/moderate MDD, and involvement of BMI in heterogeneity in leptin levels (Carvalho et al., 2014). Effects of leptin on mood are BMI dependent (Morris et al., 2012). Changes in systemic leptin with BMI are linked to leptin-resistance, which also modifies ghrelin signalling. Because the ability of leptin to induce effects at receptor and post-receptor levels is of physiological relevance (Morris et al., 2012; Zupancic & Mahajan, 2011), mood is more directly linked to leptin resistance than extracellular levels.

In summary, evidence supports a model whereby obesity and chronic modulation of leptin leads to resistance, increasing systemic leptin while reducing CNS levels and signalling. This attenuated central signalling, akin to leptin deficiency, reduces neuroprotection and promotes depressed mood, effects linked to and exacerbated by obesity-related central ghrelin resistance. These relationships are shown in Fig. 3.

Leptin-ghrelin system and inflammation Leptin and ghrelin influence inflammatory function, an important mediator of depression consistently dysregulated in obesity (Ferrante, 2007; Monteiro & Azevedo, 2010) (Fig. 2). Leptin promotes proinflammatory IL-6 and TNF-α release (Black, 2003; Loffreda et al., 1998; Matarese et al., 2005; Santos-Alvarez et al., 1999), whereas reduced leptin inhibits cellular immune responses (Lord, 2002). Miller et al. (2003) present a model in which depression promotes weight gain (relevant to MDD-AF), in turn activating inflammation through dual paths of adipose IL-6 release and leptin-dependent leukocyte IL-6 secretion. In a positive feedback loop, TNF-α may promote further leptin secretion (Black, 2003), linking inflammation to evolving leptin-resistance. C-reactive protein (CRP), a key inflammatory marker elevated in obesity (Visser, Bouter, McQuillan, Wener, & Harris, 1999) and depression (Dixon et al., 2008; Ladwig, Marten-Mittag, Löwel, Döring, & Koenig, 2003), is also an important "serum leptin-interacting protein," inhibiting leptin signalling and promoting resistance (Chen et al., 2006). Obesity-dependent increases in leptin may thus drive a systemic proinflammatory state to promote depression. In keeping with counter-regulatory effects of leptin and ghrelin, pro-inflammatory cytokine release is inhibited by ghrelin, a potential basis for its antidepressant effects (Dixit et al., 2004). Ghrelin and GHSR are also expressed in T lymphocytes and monocytes, where ghrelin inhibits expression of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α (Dixit et al., 2004). Impairment of ghrelin control in obesity will exaggerate inflammation, further promoting depression.

The HPA axis and the leptin-ghrelin system Dysregulation of the HPA axis is implicated in depression (Raison and Miller, 2003; Pariante & Lightman, 2008; Nemeroff & Vale, 2005), involving multiple molecular mechanisms (Stapelberg et al., 2015; reviewed in Stapelberg et al., 2011). Stress activates the axis via enhanced CRH secretion (Calogero et al., 1988, 1989; Oke & Tracey, 2009; Olofsson et al., 2012), triggering anterior pituitary adrenocorticotropic hormone (ACTH) production and subsequent release of glucocorticoids, such as cortisol (the "stress hormone") from the adrenal cortex. The network of mechanisms leading to and arising from HPA dysregulation is complex, involving in part resistance of glucocorticoid receptors to cortisol and disruption of the negative feedback that dampens HPA activity (Stapelberg et al., 2018; Stapelberg et al., 2015). Glucocorticoid resistance, in turn, drives inflammatory cytokine release (Raison, Capuron, & Miller, 2006) and suppresses inhibitory control of the sympathetic nervous system to further promote inflammation (Raison & Miller, 2003).

The leptin-ghrelin system is closely linked to HPA axis function (Fig. 4). Ghrelin facilitates neuroendocrine stress responses by promoting ACTH and cortisol release (Schmid et al., 2005), whereas leptin inhibits hypothalamic CRH release to suppress HPA activity (Heiman et al., 1997). Leptin also may directly inhibit cortisol production in adrenocortical cells (Bornstein, Uhlmann, Haidan, Ehrhart-Bornstein, & Scherbaum, 1997). Leptin resistance thus exaggerates elevations in glucocorticoid levels (Heiman et al., 1997). It has been argued that HPA axis overactivity with chronic stress contributes to obesity through inducing leptin secretion, with glucocorticoid excess promoting leptin resistance and obesity (Björntorp, 2001). The direction and temporal pattern of causality is unclear, although leptin resistance, increased leptin levels, and HPA activity are clearly linked. It is possible that positive feedback may arise with obesity-related leptin resistance, driving leptin and CRH secretion and increasing HPA axis activity. Increased HPA axis activity thus provides an added mechanistic link between obesity and depression. The HPA axis also inhibits gonadal steroid secretion (Sapolsky, Romero, & Munck, 2000), which promotes central obesity (Jazayeri & Meyer, 1988) (Fig. 4).

Sex and sex hormones in obesity and depression

Gonadal hormones and sex are critical factors in MDD and obesity. An association between obesity and depression appears to be more prominent in females versus males, although findings are mixed. Several studies identify associations specifically in females and not males. The longitudinal Northern Finland 1966 birth cohort study found females who are

overweight or obese in adolescence and adulthood are at increased risk for depression (Herva et al., 2005), with no association evident in males. Similarly, in a study of more than 40,000 individuals, Carpenter et al. (2000) reported a specific relationship between obesity and past year depression in women (odds ratio [OR] = 1.22) but not men (OR = 0.55). Meta-analysis of 23 long-term studies (33,000 participants) supports an increased risk of depressed female adolescents developing obesity (OR = 2.57), with no apparent risk in males (Blaine, 2008). Conversely, an epidemiological study of 40,790 adults established a relationship between obesity (BMI > 30.0) and MDD in both males and females (odds ratios 1.35–1.88) (Barry et al., 2008). Another large study (10,545 participants) found that obesity negatively predicted depression in males without predicting depression in females (Gariepy, Wang, Lesage, & Schmitz, 2010). Preiss et al. (2013) more recently examined 20 studies exploring sex as a moderating factor on the obesity-depression relationship: 8 found that sex was not a moderator, whereas 12 identified female sex as a significant moderator. Although some research (Atlantis & Baker, 2008; Markowitz, Friedman, & Arent, 2008) suggests only studies conducted in the United States find female sex to be associated with a depression-obesity relationship, this concept of population-based trends has been disputed (Preiss et al., 2013). Nonetheless, socioeconomic status does have an effect that appears to be sex-specific, particularly influencing women versus men (Beydoun & Wang, 2010; Everson, Maty, Lynch, & Kaplan, 2002; Goodman, Slap, & Huang, 2003).

Overall, evidence points to a stronger association between overweight or obesity and MDD in females, which is consistent with overrepresentation of females in MDD-AF (Rodgers et al., 2016; Schuch, Roest, Nolen, Penninx, & De Jonge, 2014). This dimorphism may involve physiological influences of sex hormones (described below), although it has been argued there is insufficient evidence to attribute differences to sex-related hormones rather than social, cultural, and physiological factors (Nolen-Hoeksema, 2001). Vittengl recently reported that obesity predicts depression (as in most MDD) and depression predicts obesity (as in MDD-AF) specifically in women, with emotional eating and physical impairment involved in both relations, and social dysfunction also contributing in the latter (Vittengl, 2018). This agrees with sexual dimorphism in MDD-AF and proposed roles of behavioural determinants of obesity in this atypical setting (Fig. 1).

Progesterone The relationship between sex-hormones and obesity has been investigated in the context of cancers, with obesity a risk factor for cancer (Calle & Thun, 2004; Pischon, Nöthlings, & Boeing, 2008). In a meta-analysis of 89 studies, Munsell et al. (2014) found obesity and its effect on breast cancer may be mediated by sex hormones. Zhang et al. (2009) showed that progesterone metabolites are produced in preadipocytes and mature lipid-storing adipocytes in women, consistent with progesterone effects on abdominal fat cell differentiation.

The effects of several hormones on depression, including progesterone, oestrogen, testosterone and cortisol, have been described in women suffering from postnatal depression (PND) (Bloch et al., 2000; Harris et al., 1989; Hendrick et al., 1998). Schiller et al. (2015) proposed that fluctuations in reproductive hormones trigger affective dysregulation in sensitive women. Limited data are available on the effects of progesterone on depression in patients who do not have mood disorders related to menstrual or reproductive events, although the role of oestrogen may be significant.

Oestrogens Oestrogens (estradiol, estriol, estrone) and their receptors play a key role in energy balance and glucose and lipid homeostasis. Reduced oestrogen in menopause modifies lipid profiles and promotes abdominal versus subcutaneous fat accumulation (Trujillo & Scherer, 2006), and oestrogen deficiency promotes visceral adiposity and insulin-resistance, increasing risks of type 2 diabetes, metabolic syndrome, and cardiovascular events in menopausal women (Carr, 2003). Low oestrogen also may promote depression. For example, bariatric surgery results in a rapid fall in oestrogen and increased rates of depression despite weight loss (Rutledge, Dorghazi, & Peralgie, 2006), an effect reversed with transdermal estradiol therapy in ~1/4 subjects. Oestrogen also exhibits serotoninergic functionality (Fink & Sumner, 1996; Halbreich, 1997), and depressed women with no past reproductive events have significantly lower plasma estradiol levels, particularly in the follicular phase of the menstrual cycle (Young, Midgley, Carlson, & Brown, 2000). The presence of oestrogen (17 beta estradiol and estrone) may protect against depression. Recently Skovlund et al. (2016) reported an association between depression and hormonal contraception in more than a million Danish women followed for several years in a prospective study: relative risk for first diagnosis of depression with combined oral contraceptive use was 1.23, and 1.34 in users of progestogen-only pills. Importantly, oestrogen and leptin receptors are also highly colocalised in the female hypothalamus (Diano, Kalra, Sakamoto, & Horvath, 1998), and estradiol modulates central leptin sensitivity (Clegg, Brown, Woods, & Benoit, 2006) and anorexigenic and weight loss effects of leptin (Marangon et al., 2014).

Testosterone An association between depression and low testosterone is evident in men, particularly older subjects (Seidman & Walsh, 2000). Men with borderline low testosterone are at increased risk of both depression and obesity (Westley, Amdur, & Irwig, 2015). However, there are inconsistencies in relationships between testosterone and depression, and a male subpopulation vulnerable to hypogonadism may contribute to risk of depression, confounding broader

associations between depression and testosterone (Amiaz & Seidman, 2008).

A reciprocal relationship exists between low serum testosterone, obesity, and metabolic syndrome. Low testosterone and sex hormone-binding globulin (SHBG) increase the risk of metabolic syndrome independently of age and obesity (Allan & McLachlan, 2010). A meta-analysis of 52 studies (Brand, Van Der Tweel, Grobbee, Emmelot-Vonk, & Van Der Schouw, 2011) concluded that males with metabolic syndrome have lower total and free testosterone, while testosterone levels are elevated in females with metabolic syndrome. A relationship also was evident between metabolic syndrome and lower SHBG levels (Brand et al., 2011). High serum leptin may contribute to decreased androgen levels in obese male patients (Isidori et al., 1999).

Thyroid function in obesity and depression

Depression and obesity can be additionally linked via the hypothalamic-pituitary-thyroid (HPT) system. Obesity can disrupt this system, promoting dysregulation in evolving MDD. Thyroid function is affected by weight gain, and obesity impacts the HPT regulatory system to elevate thyroid stimulating hormone (TSH) levels (Michalaki et al., 2006; Radetti et al., 2008). Obesity also produces physiological changes suggestive of hypothyroidism or chronic thyroiditis (Michalaki et al., 2006; Radetti et al., 2008). Hypothyroidism also has been associated with symptoms of depression (Garber et al., 2012), and alleviation of depressive symptoms with thyroid hormone treatment in hypothyroidism supports a thyroid-mood link (e.g., see Hennessey & Jackson, 1996). Interestingly, T3 hormone treatment of patients with depression increases nucleotide triphosphate levels, suggesting improved mitochondrial function and efficiency of ATP production (Iosifescu et al., 2008). However, both reductions and elevations in T4 levels have been linked with depression. A meta-analysis concludes that higher T4 levels in the normal range are associated with increased risk of depression (Williams et al., 2009). Itterman, Völzke, Baumeister, Appel and Grabe (2015) identified a positive relationship between depression and both diagnosed, untreated hypo- and hyperthyroidism in participants in the SHIP-1 and LEGEND studies.

Changes in thyroid function in obesity and MDD may involve shifts in leptin levels and signalling, which normally maintains hypothalamic TRH expression and thus influences TSH production (Feldt-Rasmussen, 2007; Flier, Harris, & Hollenberg, 2000). Central leptin resistance can disrupt the feedback loop between T4/T3 and the HPT axis, reducing T4/T3, TRH, and TSH (Flier et al., 2000). This provides an additional mechanistic link between leptin resistance and obesity, although these relationships require further study, e.g., testing whether leptin interacts with the HPT axis under physiological conditions or primarily during starvation or responses to illness when the axis is suppressed (Zimmermann-Belsing, Brabant, Holst, & Feldt-Rasmussen, 2003). These mechanisms are shown in Fig. 4.

Autonomic Dysfunction Linking Obesity and MDD

Obesity and depression are further linked via ANS dysregulation. Both depression (Esler et al., 1982; Veith et al., 1994) and obesity (da Silva et al., 2009; Lambert et al., 2010; Rahmouni, 2010; Masuo et al., 2001) involve sympathetic overactivity, although activation patterns may initially differ. With depression, total and cardiac sympathetic activities are elevated, whereas muscle sympathetic activity is unchanged or declines (Barton et al., 2007; Lambert & Schlaich, 2004). Increased cardiac sympathetic outflow also occurs with mental stress (Esler, Jennings, & Lambert, 1989) and is directly proportional to severity of depression symptoms (Light et al., 1998; Sheffield et al., 1998; Hughes & Stoney, 2000; Hamer et al., 2007). Elevated cardiac sympathetic activity has been linked to an increased risk of cardiac disease in those with depression (Scalco et al., 2009).

Contrasting depression, the pattern of sympathetic excitation in obesity appears specific to muscle and kidneys (da Silva, do Carmo, Dubinion, & Hall, 2009). Both animal (Prior et al., 2010) and human studies (Vaz et al., 1997) confirm relationships between obesity and renal sympathetic outflow. Sympathetic changes in obesity also have been linked to leptin (Haynes, 2000; Prior et al., 2010), which differentially regulates outflow to specific organ systems, particularly influencing renal function (da Silva et al., 2009; Rahmouni, 2010). Moreover, sympathetic outflow to the kidneys appears persistent, whereas other systems develop resistance to leptin (Rahmouni et al., 2008).

Parasympathetic function further links obesity and depression. Significant withdrawal of parasympathetic tone occurs in obesity (Hall et al., 2002; Van Vliet et al., 1995; Aronne et al., 1995), and is responsible for physiological changes such as increased heart rate (Aronne et al., 1995; Verwaerde et al., 1999; Van Vliet et al., 1995). Gut sensory information is also transmitted via afferent vagal fibres, terminating in hypothalamic nuclei with orexigenic functions (Rinaman, 2010). Ghrelin resistance has been linked to dysregulated vagal afferent activity in obesity (Naznin et al., 2015). Reduced vagal tone is central to the pathogenesis of depression, with removal of the parasympathetic "brake" compromising sympathetic control (Porges, Doussard-Roosevelt, & Maiti, 1994; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996) and promoting immunoinflammatory dysfunction by suppressing the cholinergic anti-inflammatory reflex (Martelli, McKinley, & McAllen, 2014). Vagal dysregulation therefore is shared between depression and obesity, facilitating sympathetic overactivity in both disorders. Withdrawal of parasympathetic tone in obesity may independently promote depression, because

poor parasympathetic tone is proposed as a key factor in depressive illness (Stapelberg et al., 2012).

Metabolic syndrome, endocrine, and immune mechanisms also may link obesity and depression through autonomic modulation. Changes in sympathetic outflow in obesity are linked to hypertension (da Silva et al., 2009), and chronic sympathetic dysfunction with overweight has been linked with declining insulin sensitivity, contributing to development of metabolic syndrome (Smith & Minson, 2012). Metabolic syndrome exacerbates sympathetic overdrive (Grassi et al., 1995, 2004; Lambert et al., 2010; Straznicky et al., 2005), related in part to increased circulating insulin and angiotensin II (Grassi et al., 1995). These shared mechanisms are shown in Fig. 4.

The Gut Microbiome and Dysbiosis in Obesity and MDD

The gut microbiome has been identified as an important factor in multiple chronic diseases (Forsythe, Sudo, Dinan, Taylor, & Bienenstock, 2010). The complex community of microorganisms (microbiome) in the human alimentary canal include ~40,000 species of bacteria, amounting to ~100 trillion individual organisms and weighing 1-2 kilograms (Forsythe et al., 2010; Frank & Pace, 2008; Gill et al., 2006). The gut microbiome exhibits incredible genetic diversity (e.g. Kurokawa et al., 2007) with the human host supporting an independent ecology (Costello, Stagaman, Dethlefsen, Bohannan, & Relman, 2012). The gut microbiome also represents a vast functional diversity in its commensal host interactions, ranging from digestion of complex polysaccharides, development and stimulation of the immune system, and regulation of homeostasis and energy metabolism (Costello et al., 2012; Nicholson et al., 2012; Foster and Neufeld, 2013; Boulangé et al., 2016). The latter functions related to energy regulation are implicated in obesity, while effects on CNS development, function and mental state are increasingly appreciated (Foster & Neufeld, 2013). Pathological alterations in the microbiome are termed dysbiosis. Mechanisms linking the CNS with gut function and dysbiosis prompted the concept of a "gut-brain axis" (Aziz & Thompson, 1998) and are shared across MDD and obesity (Fig. 2).

Gut dysbiosis links obesity and depression

Psychological stress can change gut microbiome composition, as demonstrated in rodents (Porter & Rettger, 1940; Tannock & Savage, 1974) and primates (Bailey & Coe, 1999). For example, noradrenaline secreted in gut mucosa and submucosa in response to stress (Stapelberg et al., 2015) may trigger rapid multiplication of gut bacteria, such as *Yersinia enterocolitica* and *Escherichia coli* (Keightley, Koloski, & Talley, 2015). Excessive noradrenaline or sympathetic activity thus modifies microbiome composition (Lyte, Vulchanova, & Brown, 2011). Dietary composition, which contributes to overweight and obesity, also affects the microbiome. Specific dietary factors altering the microbiome include fibre and digestible carbohydrate intake (Kashyap et al., 2013), together with the medium-chain fatty acid content of ingested lipids (Rial, Karelis, Bergeron, & Mounier, 2016), all of which can be altered in obesity. A diet high in fat increases the proportion of Gram-negative versus positive bacteria, increasing liberation of lipopolysaccharide (LPS) components of the former (Nicholson et al., 2012). This affects mood via inflammatory mechanisms, promoting sickness behaviour or depression. Imbalances in gut bacteria may be countered by administration of prebiotics, promoting growth of Gram-positive microbiota (Cani et al., 2007). Use of both pre- and probiotics is associated with reduced body weight and adiposity (John et al., 2018) while findings in depression are equivocal (Huang, Wang, & Hu, 2016; Ng, Peters, Ho, Lim, & Yeo, 2018).

Changes in the gut microbiome not only arise with metabolic disorders but appear causally involved. Because the microbiome influences host energy metabolism, dysbiosis can lead to weight gain and obesity (Boulangé, Neves, Chilloux, Nicholson, & Dumas, 2016). The microbiome promotes obesity independently of genetic predisposition (Turnbaugh et al., 2008; Bäckhed et al., 2007; Ley et al., 2006), and its composition differs in obese people, who have fewer *Bacteroidetes* and more *Firmicutes* species than nonobese people, for example. Because some classes of *Firmicute* microbes (e.g., *Mollicutes*) are more effective at energy extraction and promote lipogenesis, increased populations may drive lipogenesis and obesity (Ley, Turnbaugh, Klein, & Gordon, 2006; Turnbaugh, Bäckhed, Fulton, & Gordon, 2008). This has been confirmed by transplanting gut bacteria from obese into lean mice, inducing greater weight gain than bacteria from lean mice (Turnbaugh et al., 2008). Conversely, dietary restriction increases *Bacteroidetes* abundance, which is correlated with weight loss (Ley et al., 2006). There also is increasing attention to the pathobiological importance of short-chain fatty acid generation (acetate, propionate, butyrate) during fermentation of indigestible carbohydrates by anaerobic bacteria (e.g., *Firmicutes, Bacteroidetes*) (Sivaprakasam, Prasad, & Singh, 2016; Tan et al., 2014). These regulate intestinal physiology, immune function, inflammation and paracrine signalling, and participate in lipogenesis and gluconeogenesis (Fig. 2). The microbiome may also modify fat storage, influencing the fasting-induced adipose factor (FIAF) that inhibits lipoprotein lipase and thus lipid deposition in adipose tissue (Bäckhed et al., 2004). Gut microbes can additionally suppress the key regulatory enzyme adenosine monophosphate-activated protein kinase (AMPK), down-regulating hepatic fatty acid oxidation, and increasing cholesterol and triglyceride synthesis (Winder & Hardie, 1999).

The microbiome and gut transit time Autonomic function and diet can influence the microbiome via gut motility, thus transit time (Fig. 2). Because the ANS is the key regulator of the enteric nervous system (Keightley et al., 2015), increased sympathetic activity (da Silva et al., 2009; Lambert, Straznicky, Lambert, Dixon, & Schlaich, 2010; Masuo et al., 2001; Rahmouni, 2010) and withdrawal of parasympathetic tone in obesity (Aronne, Mackintosh, Rosenbaum, Leibel, & Hirsch, 1995; Hall, Crook, Jones, Wofford, & Dubbert, 2002; Van Vliet, Hall, Leland Mizelle, Montani, & Smith, 1995) will decrease motility. Similar ANS changes with chronic stress and depression also alter gut motility and secretion (Aggarwal et al., 1994). Resultant changes in transit time affect microbiome composition, which further influences motility (Kashyap et al., 2013). Microbiome modulation of gut motility will govern caloric extraction from gut contents (Abrams & Bishop, 1967; Musso, Gambino, & Cassader, 2011). Because ghrelin and CRH also increase gut motility (Meier & Gressner, 2004; Taché & Bonaz, 2007), changes in these factors with obesity and stress (potentially linked to leptin resistance) may modify microbiome composition to influence inflammation and development of depression.

Gut microbiome influences on the CNS

These effects on inflammation are the dominant mechanism by which the gut microbiome influences mood and stress responses, involving linkages between gut epithelial permeability, the HPA axis, and hippocampal BDNF expression (Fig. 2).

Gut permeability and inflammation linkages in obesity and depression The intestinal epithelial barrier allows fluid and nutrients to pass across the intestinal wall while preventing entry of gut organisms and larger toxic or antigenic molecules (Mass, Kubera, & Leunis, 2008). Within the barrier IgA secretion also prevents epithelial attachment of gut microorganisms (Mass et al., 2008). Inflammatory mediators, such as IFN-γ and IL-6, can compromise epithelial barrier function, enlarging intercellular spaces in the gut wall (Clark et al., 2005; Chavez et al., 1999; Yang et al., 2003)—the "leaky gut" (Mass et al., 2008)—to facilitate entry of immunogenic molecules such as LPS into the circulation and increase systemic cytokines (Maes et al., 2007; Dantzer et al., 1999). Increased circulating LPS is linked to symptoms of depression in animal models (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008) and humans (Wright, Strike, Brydon, & Steptoe, 2005). Behavioural changes in response to bacterial antigens/infection include fatigue, malaise, anorexia, altered sleep patterns, decreased physical activity, social withdrawal, and cognitive disturbance (Dantzer et al., 2008; Dantzer, 2009; Reichenberg et al., 2001)—"sickness behaviour" mirroring the neurovegetative features of depression (Dantzer, 2009).

The gut microbiome-HPA axis linkage Stress reactivity of the HPA axis is sensitive to the gut microbiome (Sudo et al., 2004). As an endocrine control mechanism, the HPA axis can be reprogrammed or reset early in life. Evidence of such effects stems from studies of childhood development disrupted by trauma (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). However, the HPA axis also may be developmentally influenced by the gut microbiome. Sudo et al. (2004) showed that mice reared without gut organisms (germ-free mice) exhibit an enhanced HPA axis reactivity that is countered by reconstitution with *Bifidobacterium infantis*. Microbial colonization of the gut and the subsequent immune response to commensal organisms in early life thus impacts on HPA axis responsiveness to stress (Sudo et al., 2004), in turn influencing propensity to disease in later life.

Dysbiosis and hippocampal BDNF Intestinal dysbiosis may promote depression via modulating hippocampal expression of BDNF, a trophic factor protecting against neuronal damage and maintaining cognitive function (Drapeau et al., 2003; Steffenach et al., 2002; Sugaya et al., 1996). Low BDNF is detrimental to memory, neural plasticity, and neurogenesis (Yirmiya & Goshen, 2011) and can result in depression (Stapelberg et al., 2015). Bercik et al. (2011) found that antimicrobials decrease hippocampal BDNF expression in mice, whereas colonisation of germ-free mice with gut microbiota increases hippocampal BDNF. This microbiome-dependent modulation of BDNF presents an additional gut-brain linkage relevant to MDD development (Fig. 2).

Weight loss within the PINE pathome and MDD

Reduction of appetite and weight loss have long been considered central neurovegetative features of depression (Beck & Alford, 2009; Schuyler, 1974), even though weight gain was also noted in some depressed patients (Bruch, 1974). Weight loss linked to reduced appetite is currently a recognised criterion of major depression (American Psychiatric Association, 2013). Disturbance of appetite has been physiologically linked to sickness behaviour (Dantzer, 2009; Dantzer et al., 1999; Dantzer et al., 1998) via the orexin system in the lateral hypothalamus (Gaykema & Goehler, 2009; Harris, Wimmer, & Aston-Jones, 2005). Sickness behaviour is a set of behaviours induced by proinflammatory cytokines (especially IL-1 in the CNS) to force an organism to conserve energy in the face of presumed infection. Raised proinflammatory markers in MDD also cause sickness behaviour, with energy-demanding behaviours, such as food seeking and feeding curtailed by a reduced appetite (Dantzer, 2009; Dantzer et al., 1999; Dantzer et al., 1998), promoting weight loss. Loss of weight in chronic stress and MDD also has been linked to anhedonia (loss of pleasure or reward with activity), with hypothesised perturbation of reward circuitry in the nucleus

accumbens disrupting perceived reward with food intake (Lim, Huang, Grueter, Rothwell, & Malenka, 2012), reducing intake and thus body weight. Thus, a majority of those with MDD will lose weight, despite stimulatory effects of preexisting obesity on MDD development. This implies that preexisting obesogenic mechanisms in a nondepressed (predisease) state are effectively countered by inflammation-induced sickness behaviour once transition to the PINE pathome and MDD occurs. However, sexual dimorphism also arises in this response, which appears to dominate in males whereas females may retain obesity after transition to MDD (Carpenter et al., 2000).

MDD-AF subtype and depression-associated obesity

The commonality of obesity outcomes and MDD mechanisms detailed above can explain increased risk of MDD with obesity. In contrast, this directionality is reversed in MDD-AF, which is strongly associated with subsequent obesity and metabolic disease. The description and clinical features of MDD-AF remain somewhat controversial, with a DSM-IV definition of mood reactivity plus ≥2 of increased appetite or weight gain, hypersomnia, "leaden paralysis," and hypersensitivity to interpersonal rejection. Whether a single or spectrum disorder (Parker, 2000; Parker et al., 2002), or involving multiple subtypes (Davidson, Miller, Turnbull, & Sullivan, 1982), is debated. Such controversies notwithstanding, common clinical features additional to depressed mood include a long-standing pattern of interpersonal rejection sensitivity, leaden paralysis or lethargy/anergia/fatigue, increased appetite, hypersomnia, weight gain, and higher female prevalence. Whether representing multiple MDD-AF comorbidities or elements of a single disorder (Silverstein & Angst, 2015), anxiety and eating disorders, poor body image, hypersomnia, and fatigue (separate from leaden paralysis) collectively provide a mechanistic basis for associations of both obesity and metabolic syndrome with MDD-AF (Lamers, Beekman, Van Hemert, Schoevers, & Penninx, 2016). The consistent hypersensitivity to interpersonal rejection presents a primary MDD-AF feature relevant to differing obesity risk in atypical versus melancholic subtypes of MDD, with associated emotional and self-consolatory dysregulation (Parker et al., 2002) underpinning an obesogenic energy imbalance—hyperphagia coupled with fatigue and hypersomnia. Hyperphagia also may involve increased intake of "rewarding" albeit detrimental foods, with stress increasing preference for high fat/sugar content foods (Epel et al., 2001; Ng & Jeffery, 2003). Evolving obesity may in turn induce positive feedback, exaggerating anxiety, body image, and self-consolatory abnormalities together with PINE network disruption (Fig. 1). Indeed, the symptoms of MDD-AF increase with BMI (Lamers et al., 2013b; Lasserre et al., 2014), and there is evidence of improved depressive symptomology with weight loss (Fabricatore et al., 2011). Nonetheless, weight loss is linked to worsening of MDD symptoms (Chaput, Arguin, Gagnon, & Tremblay, 2007), which may highlight the distinct relations and mechanisms linking weight and MDD subtypes. While weight loss is effective in countering feedback between obesity and MDD-AF, this may be more broadly counterproductive in MDD where weight loss is a pathological outcome.

Neurophysiological Features of MDD-AF

There is some evidence of neurophysiological distinctions between MDD-AF and MDD, although findings are equivocal with substantial overlap in features, and how these contribute to distinct behavioural and obesity outcomes in MDD-AF versus MDD-MF is unclear. There is evidence supporting the notion of relative HPA axis hyper- versus hypoactivity in MDD-MF versus MDD-AF, reflecting CRH hyper- and hyposecretion (Gold & Chrousos, 2002), and a relative hypocortisolemia in MDD-AF compared with MDD-MF (Stetler & Miller, 2011). Nonetheless, others argue that there is little support for reduced HPA activity or cortisol output, whereas a transition from CRH to arginine vasopressin control of the HPA axis arises with chronic or repeated stress (O'Keane, Frodl, & Dinan, 2012). As already detailed, leptin-resistance may play a key role in MDD pathogenesis and links obesity and depression (Lu, 2007). Leptin levels are elevated in patients with MDD-AF (Gecici et al., 2005) and strongly associated with obesity and obesigenic features of MDD-AF (hyperphagia, leaden paralysis) (Milaneschi et al., 2017).

Chronic low-grade inflammation, including elevations in IL-6, TNF-α, and CRP, is a mechanistic hallmark of MDD (Young, Bruno, & Pomara, 2014), and distinct inflammatory changes may arise in MDD-AF and MDD-MF. This includes differing cytokine profiles and greater inflammation in MDD-AF based on changes in CRP (Hickman, Khambaty, & Stewart, 2014), IL-6 (Rudolf, Greggersen, Kahl, Hüppe, & Schweiger, 2014), and IL-2 (Yoon, Kim, Lee, Kwon, & Kim, 2012), although findings are conflicting. Despite evidence of higher IL-6 in MDD-AF (Rudolf et al., 2014), others report greater elevations in IL-6 in MDD-MF while TNF-α is reduced in both MDD-AF and MDD-MF versus controls (although IL-6 and TNF-α correlate with MDD-AF and not MDD-MF) (Dunjic-Kostic et al., 2013). Similarly, MDD-AF has been associated with both increased (Yoon et al., 2012) and decreased IL-2 (Anisman, Ravindran, Griffiths, & Merali, 1999).

Neuroanatomically, there appear to be no significant differences in hippocampal volume (Greenberg, Payne, MacFall, Steffens, & Krishnan, 2008; Rusch, Abercrombie, Oakes, Schaefer, & Davidson, 2001) or white matter integrity (Ota

et al., 2015) between MDD-AF and MDD-MF, whereas regional differences in perfusion/activity may arise. Fountoulakis et al. (2004) report that MDD-AF is associated with increased frontal, temporal, and parietal versus decreased occipital perfusion, whereas MDD-MF was associated with decreased perfusion in most nonoccipital regions. MDD-AF may be associated with increased right hemispheric processing, with increased right parietal processing in MDD-AF versus increased left parietal processing in MDD-MF (Fountoulakis et al., 2004; Thase, 2009). Neurophysiological differences also emerge in MDD-AF versus MDD-MF. A distinction between MDD-AF and MDD-MF is supported in analysis of pattern-reversed visual evoked potentials, with differential shortening of N80 and P100 latency in atypical versus lengthening in melancholic patients (Fotiou, Fountoulakis, Iacovides, & Kaprinis, 2003). Additionally, the loudness dependence of auditory-evoked potentials appears stronger in MDD-AF than non-MDD-AF patients, which may reflect reduced serotonergic activity (Lee, Park, Yoon, Kim, & Hahn, 2014). In a more recent study employing transcranial magnetic stimulation, Veronezi et al. (2016) found those with MDD-AF presented a distinct pattern of decreased cortical inhibition (reflecting GABA-A receptor activity) and increased cortical facilitation (reflecting glutamate receptor activity), whereas MDD demonstrated decreased cortical silent period values (indicating GABA-B receptor activity).

These physiological distinctions warrant further study and, in some cases, are consistent with distinct linkages between obesity and depression in MDD-AF and MDD-MF. For example, a relative HPA hypoactivity could facilitate weight gain in MDD-AF (because the stress response is targeted at reducing feeding and food-seeking/exploratory behaviour and channelling energy to recovery). On the other hand, exaggerated inflammation might be predicted to favour sickness behaviour and reductions in feeding behaviour. Emotional dysregulation appears key (including anxiety and hypersensitivity to interpersonal rejection, and associated with younger and female subjects), with associated hyperphagia, hypersomnia, and fatigue primary determinants of the MDD-AF-to-obesity linkage. Obesity is thus favoured in the context of MDD-AF, likely involving positive feedback between evolving obesity, emotional determinants of disease, and PINE network disruption, consistent with BMI dependence of MDD-AF symptoms (Lamers et al., 2013b; Lasserre et al., 2014) (Fig. 1). Whether obesity in MDD-AF worsens PINE dysregulation is yet to be directly tested, and there is evidence that while evolution of MDD correlates with PINE network dysregulation, subsequent severity/progression of extant MDD may not (Verduijn et al., 2015). However, this analysis assessed MDD as a single entity and addressed limited biomarkers of the complex PINE network; it remains to be seen whether a lack of correlation holds for additional markers and across specific disease subtypes, such as MDD-AF.

Relevance of Age and Sex in MDD-AF

Both age and sex are important modifiers, with data suggesting the depression-to-obesity relation characteristic of MDD-AF is more specific to younger female patients in association with emotional dysregulation, whereas weight loss in later MDD occurs in both sexes in association with neurocognitive deficit. Females are overrepresented within the MDD-AF cohort and as demonstrated recently by Vittengl (2018), depression predicts obesity in women but not men (with more typical obesity-to-depression also apparent in females and not males). Early MDD onset also is more frequent in females (Park et al., 2014; Schuch et al., 2014) and in the MDD-AF subtype. Chen et al. (2009) showed that being a young female (18-39 years old) is significantly associated with obesity and depression, compared with older women, and work by Ma and Xiao (2010) further supports increased risk in the younger population (age 25 to 65 years). An early age of onset of MDD also is associated with significantly disrupted amygdala and cognitive control region connectivity (Luking et al., 2011; Clark et al., 2018), consistent with emotional dysregulation and distinct outcomes in younger *vs*. older MDD subjects (relevant to MDD-AF). Another large study followed 44,800 participants in the 2001 Behavioral Risk Factor Surveillance Survey (Heo, Pietrobelli, Fontaine, Sirey, & Faith, 2005), reporting that young overweight or obese women were significantly more at risk of having experienced depressed mood than nonoverweight and nonobese women (BMI <25). Young, obese women were particularly at risk of sustained depressed mood, whereas there was no association between depressed mood and obesity in "old" age groups, for either sex. Other studies also support an age-dependence of weight *loss* in depression, which appears greater in later versus early onset MDD (Charlton et al., 2013). Decreased appetite in late-life MDD is associated with neurocognitive deficits (Potter et al 2015) and appears linked to increased risk of dementia (Saha et al., 2016). There also is evidence for differing relationships between obesity and depression in younger adolescent subjects. Roberts and Duong (2013a) found no evidence of increased depression in obese youths, although obesity was increased in depressed youths. Later analysis revealed no independent association between depression and obesity in 11-17 year olds (Roberts & Duong, 2015), with the authors highlighting that etiologic linkage between MDD and body weight in adolescents likely involves body image factors.

Other studies indicate that the association between common mental disorders and obesity becomes stronger with maturing age (Kivimäki et al., 2009) or do not support any correlation between age and comorbid depression and obesity (McLaren, Beck, Patten, Fick, & Adair, 2008; Scott, McGee, Wells, & Oakley Browne, 2008). The latter may reflect the cross-sectional study designs, which are limited in the determination of causation (Mann, 2003). A large systematic

review of 204507 participants similarly did not find age to be a moderating factor (de Wit et al., 2010). However, this analysis included fewer studies in middle-aged and elderly participants (50 years and older).

Conclusions

A number of plausible, shared biological mechanisms may underlie the increased incidence of depression in overweight and obese people. We detail how interlinked obesity outcomes that are pathogenic mechanisms of MDD can mediate the dominant obesity-to-MDD linkage, with chronic stress related to body image additionally contributing (Roberts & Duong, 2015) (Fig. 1). Beyond the critical system transition to MDD, sickness behaviour and other PINE network dysregulation may counter obesogenesis and induce a potentially detrimental weight loss that appears to dominate in males versus females and is associated with cognitive decline. Conversely, distinct MDD-AF is more common in younger and female patients, in association with emotional dysregulation. Obesogenic mechanisms involve a combination of hyperphagia, hypersomnia, and fatigue linked to pathologically heightened sensitivity to interpersonal rejection, anxiety, and body-image concerns. Evolving obesity may induce detrimental positive feedback, amplifying these drivers and PINE network disruption to worsen depression symptoms. These distinct unidirectional relationships between obesity and depression have important implications and highlight the need for caution in prescribing weight loss to limit MDD symptomology. The complexity of the mechanistic network underpinning the incidence of depression in overweight and obese people demands further interrogation and clarification. Distinctions between depression subgroups (e.g., HPA hyper- vs. hypoactivation, differing immunoinflammatory changes) can shed further light on the critical mechanisms linking depression to metabolic and also cardiovascular disorders. A systems biology approach is recommended for further research into the pathophysiology of melancholic and atypical subtypes of depression. This applies especially to MDD-AF, which appears to have a distinct pathophysiology from that in MDD (Lamers et al., 2013b).

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