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Review Article

Linking atypical depression and insulin resistance-related disorders via low-grade chronic inflammation: Integrating the phenotypic, molecular and neuroanatomical dimensions

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ABSTRACT

Insulin resistance (IR) and related disorders, such as T2DM, increase the risk of major depressive disorder (MDD) and vice versa. Current evidence indicates that psychological stress and overeating can induce chronic low-grade inflammation that can interfere with glutamate metabolism in MDD as well as insulin signaling, particularly in the atypical subtype. Here we first review the interactive role of inflammatory processes in the development of MDD, IR and related metabolic disorders. Next, we describe the role of the anterior cingulate cortex in the pathophysiology of MDD and IR-related disorders. Furthermore, we outline how specific clinical features of atypical depression, such as hyperphagia, are more associated with inflammation and IR-related disorders. Finally, we examine the regional specificity of the effects of inflammation on the brain that show an overlap with the functional and morphometric brain patterns activated in MDD and IR-related disorders.

1. Introduction

Major depressive disorder (MDD) is a common and highly disabling condition, which affects more than 20% of the population in the US (Hasin et al., 2018). The WHO ranked MDD as the third-leading cause of burden of disease worldwide and projected that the disease will rank first by 2030 (Malhi and Mann, 2018). Moreover, this mental illness is associated with higher prevalence of many somatic disorders, such as metabolic, cardiovascular and autoimmune diseases (Ali et al., 2006; González and Tarraf, 2013; Euesden et al., 2017). For example, type 2 diabetes mellitus (T2DM) can be observed 1.2–2.3 times more often in patients who suffer from depressive symptoms or are diagnosed with MDD compared to the general population (Arroyo et al., 2004; Knol et al., 2006; Mezuk et al., 2008; Mommersteeg et al., 2013). In turn, the prevalence of MDD is higher in T2DM patients (Ali et al., 2006; Roy and Lloyd, 2012). Moreover, patients with an impaired metabolic status,

Abbreviations: ACC, anterior cingulate cortex; aMCC, anterior midcingulate cortex; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATPase, adenosine triphosphatase; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CNS, central nervous system; CRP, C-reactive protein; CUMS, chronic unpredictable mild stress; dACC, dorsal anterior cingulate cortex; DC, degree centrality; DLPFC, dorsolateral prefrontal cortex; DSM, diagnostic and statistical manual of mental disorders; EAAT, excitatory amino-acid transporter; ELS, early-life stress; FC, functional connectivity; GSK3b, glycogen synthase kinase-3b; GLUT-4, glucose transporter type; HFD, high-fat diet; HOMA, homeostasis model assessment; HPA axis, hypothalamic-pituitaryadrenal axis; IDO, indoleamine 2,3 dioxygenase; IL, interleukin; IR, insulin resistance; KYNA, kynurenic acid; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MCT, monocarboxylat-transporter; MDD, major depressive disorder; MetS, metabolic syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NMDAR, N-methyl-D-aspartate receptor; NLRP3, NLR family pyrin domain containing 3; PAMP, pathogen-associated molecular pattern; pgACC, pregenual anterior cingulate cortex; pro-IL-1β, pro-interleukin-1β; QUIN, quinolinic acid; sgACC, subgenual anterior cingulate cortex; SSRI, selective serotonin receptor inhibitor; TCA, tricarboxylic acid cycle; TLR, toll-like receptor; TNF, tumor necrosis factor; T2DM, type 2 diabetes mellitus; xCT, cystine/glutamate antiporter.

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such as obesity or insulin resistance (IR), which are strongly associated with the pre-diabetic stage]11\, suffer more frequently from MDD (Luppino et al., 2010; Pearson et al., 2010). Because of their close association to IR (2. Classification and diagnosis of diabetes: Standards of medical care in diabetesd, 2019), we will refer to T2DM, obesity and metabolic syndrome (MetS) as IR-related disorders.

Even though psychological and behavioral factors, such as the burden of being chronically ill or poor personal care, may provide alternatives to explain the bidirectional association between MDD and T2DM to some extent, some shared underlying pathological processes, such as chronic low-grade inflammation, deserve closer attention (Chan et al., 2019; Lamers et al., 2018; Leonard and Wegener, 2019). It can be proposed that psychosocial stress or overeating-related nutrient-induced inflammation invokes a vicious cycle that can affect metabolism, the bodily stress response, brain activation patterns and the vegetative behavior of the individual. It has now been suggested that a particular subtype of MDD, namely the atypical subtype, can be associated with chronic low-grade inflammation, which also co-occurs with pre-diabetes or T2DM (Lamers et al., 2016; Penninx et al., 2013).

Although classical definitions of MDD involve lack of reactivity to pleasurable stimuli, loss of appetite and/or weight and insomnia, some MDD patients show a considerable amount of reactivity in mood and have increased appetite and hypersomnia. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, (DSM)-5, the latter group of patients is diagnosed with MDD with atypical features (atypical depression). The reported prevalence of atypical features within MDD patients varies between 18 and 43% depending on the diagnostic criteria, sample characteristics and design of the study (Akiskal and Benazzi, 2005; Angst et al., 2002; Gili et al., 2012; Horwath et al., 1992; Novick et al., 2005). Many studies reported that atypical depression is more common in females (Angst et al., 2002; Novick et al., 2005; Benazzi, 2003; Blanco et al., 2012), more often associated with a history of early-life stress (ELS) (Matza et al., 2003), an early onset of MDD (Angst et al., 2002; Horwath et al., 1992; Rodgers et al.., 2015) and a chronic course of the disease (Gili et al., 2012; Matza et al., 2003). The role of chronic low-grade inflammation in the etiology of MDD was particularly described for atypical depression (Lamers et al., 2016; Haapakoski et al., 2015; Hickman et al., 2014; Rudolf et al., 2014; Yoon et al., 2012). In line with this, a corresponding regional specificity of the correlates of neuroinflammation in the anterior cingulate cortex (ACC) that corresponds to clinical features in atypical depression has been recently introduced (Woelfer et al., 2019).

Poorer treatment response to selective serotonin reuptake inhibitors (SSRIs) (Stewart et al., 2010) and tricyclic antidepressants (Henkel et al., 2006) were reported in MDD with atypical features. Considering also the metabolic side effects of pharmacological antidepressant agents, such as weight gain (Blumenthal et al., 2014) or MetS (Van Reedt Dortland et al., 2010), new treatment strategies are needed for this patient group. In a recent study, atypical features predicted better antidepressant response to physical exercise (Rethorst et al., 2016). Given that hypersomnia and elevations in body mass index (BMI) were also associated with better treatment response to physical exercise (Rethorst et al., 2013; Toups et al., 2011), estimating the patient's metabolic risk would be beneficial for the development and assignment of individualized therapies of MDD patients.

In this review, we highlight a possible role of chronic low-grade

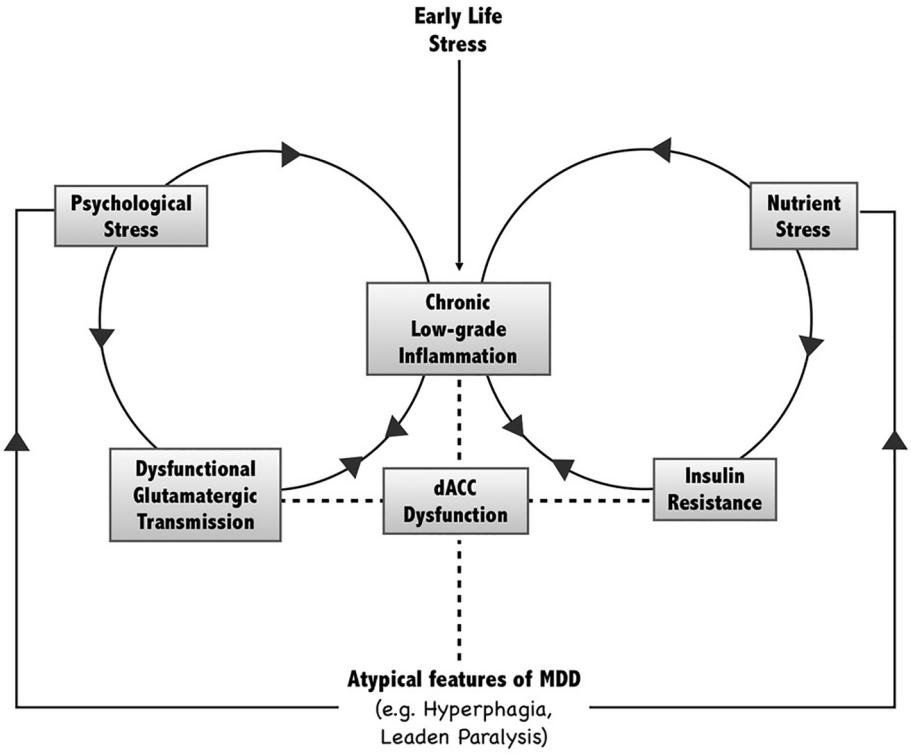

Fig. 1. Chronic low-grade inflammation mediates the bidirectional relationship between MDD with atypical features and insulin resistance (IR). Early-life stress has persistent effects on the systemic and cellular stress response and creates susceptibility for a dysregulated inflammatory response in the presence of additional stressors, such as psychological or nutrient stress. In turn, proinflammatory cytokines can interfere with the function of the hypothalamus–pituitaryadrenal (HPA) axis, energy and glutamate metabolism in astrocytes, N-methyl-D-aspartate receptor (NMDAR) activity, as well as insulin action on the targeted cells. Higher energy demands of NMDAR-rich synaptic units and inflammation-induced production of the NMDAR agonist quinolinic acid in the microglia can lead to dysfunctional glutamatergic activity, which in turn enhances the inflammatory activity. The dorsal anterior cingulate cortex (dACC) is a relatively NMDAR-rich region, which was often shown to have an abnormal functioning in major depressive disorder (MDD) as well as in IR-related disorders, such as obesity and type 2 diabetes mellitus (T2DM). Woelfer and colleagues (32) have proposed that the region-specific neuroinflammation pattern and the activity as well as connectivity changes in dACC could explain atypical features of MDD, such as hyperphagia or leaden paralysis. Overeating and insufficient physical activity related to leaden paralysis can also exacerbate inflammation and related IR as well as psychological burden. We propose that chronic low-grade inflammation might manifest itself in different pathological aspects (indicated by the dashed lines in the scheme) and might underlie the comorbidity of MDD and IR-related metabolic disorders. We suggest that they all together constitute a vicious cycle, with converging alteration in the region of the dACC, where risk factors and their clinical and cellular consequences potentiate one another and enhance the pro-inflammatory state.

inflammation in the pathogenesis of the comorbidity between MDD with atypical features and IR as well as related metabolic disorders and discuss the findings indicating shared abnormalities in brain activation patterns (Fig. 1). First, we introduce the involvement of inflammatory processes in the development of MDD, IR and related metabolic disorders. We then discuss the role of pro-inflammatory factors in the comorbidity between atypical depression and IR-related disorders. Furthermore, we review the role of the dACC in the pathophysiology of MDD and metabolic disorders. Importantly, we will summarize published results supporting the idea of regional convergence of metabolic deviation in MDD at the level of the dACC. Finally, we will integrate multilevel evidence of behavioral, molecular and neuroimaging traits to examine the syndromal relevance of the regional specificity of the effects of neuroinflammation with regionally overlapping brain patterns for the comorbidity of depression and IR-related disorders, such as T2DM. This shall lead to a new understanding why patients with a certain phenotype fall into the subtype of atypical depression that is further characterized by inflammatory and metabolic abnormalities.

2. The link between inflammation and MDD

The interaction between the elements of the immune system and the central nervous system (CNS) in the development of MDD has been extensively studied and discussed in several reviews (Iwata et al., 2013; Duman, 2014; Haroon et al., 2017; Raison and Miller, 2017; Himmerich et al., 2019). On one hand, a systemic inflammatory response to an infectious agent or cytokine administration can be communicated via inflammatory cytokines or immune cells to the CNS and thereby induce sickness behavior, which refers to infection-related behavioral changes, such as fatigue, anhedonia and anorexia (Dantzer et al., 2008; Capuron and Cytokines, 2004). On the other hand, both acute and chronic psychosocial stressors can also be transduced to immune signaling within brain parenchyma and modulate systemic immune activity as well as intra- and inter-regional communication within the brain, and thereby, effect mental functions and behaviors (Iwata et al., 2013; Duman, 2014).

Several comprehensive studies have revealed the mechanisms of the translation of systemic immune activity to an immune activation in the

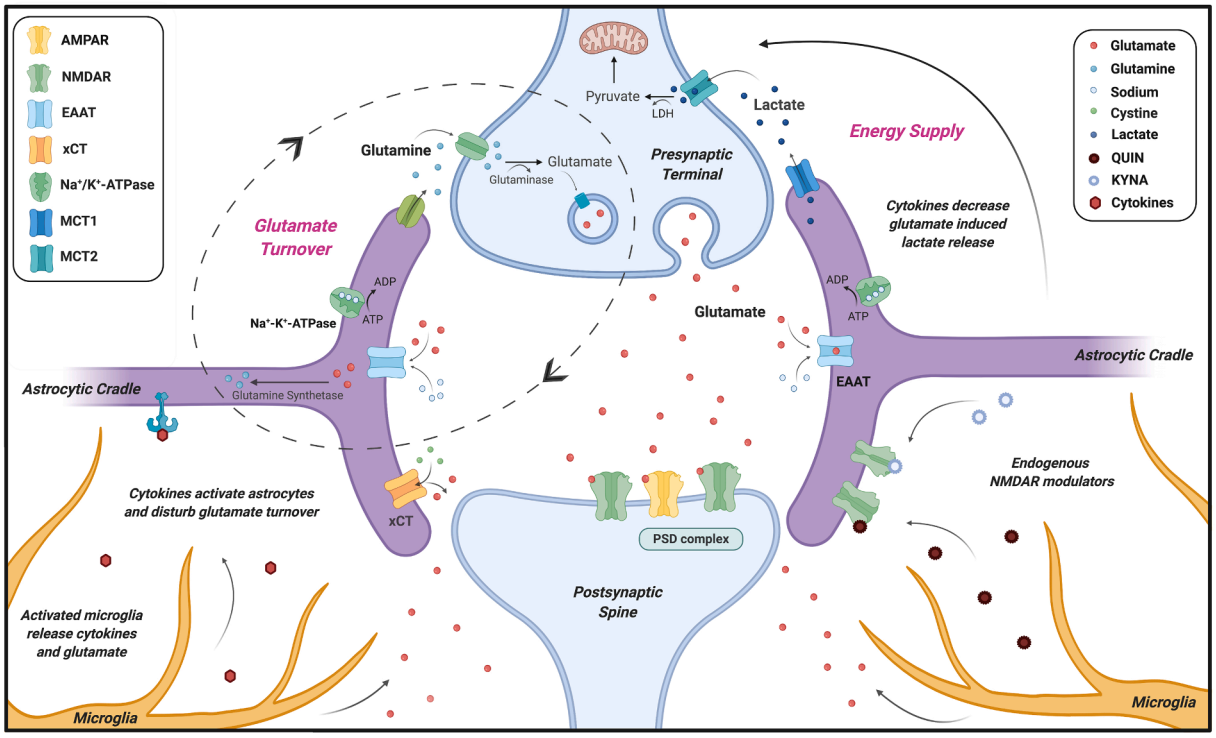

Fig. 2. Glutamatergic transmission and glutamate turnover in the pro-inflammatory state. Astrocytic cradles of protoplasmic astrocytes encircle synapses and together with presynaptic and postsynaptic neurons form the tripartite synapse (Araque et al., 1999). The low level of intrasynaptic glutamate is maintained by active transmembrane transport by excitatory amino-acid transporters (EAAT1 and EAAT2) (Danbolt, 2001). In astrocytes, glutamine synthetase converts glutamate to glutamine (Martinez-Hernandez et al., 1977) that is subsequently provided to neurons. In contrast to astrocytes, neurons are not able to synthesize glutamate de novo and therefore dependent on astrocyte-derived-glutamine for the synthesis of glutamate (Yu et al., 1983; Shank et al., 1985). Neurons convert glutamine to glutamate by glutaminase (Kvamme et al., 2000) and repack it into synaptic vesicles (Fremeau et al., 2004). More recently, the concept of the tripartite synapse was expanded to the concept of the quadri-partite synapse to also acknowledge the interaction of astrocytes and neurons with microglia (Schafer et al., 2013). Activated microglia release glutamate via cystine/glutamate antiporter (xCT) (Mesci et al., 2015; Kitagawa et al., 2019) futhermore glutamatergic compounds such as QUIN are secreted that increase the glutamatergic load (Stone and Perkins, 1981; Schwarcz et al., 1983; Guillemin et al., 2005). Activated microglia also release pro-inflammatory cytokines that activate astrocytes (Bezzi et al., 2001; Liddelow et al., 2017), which can induce glutamate release from astrocytes (Bezzi et al., 2001; Casamenti et al., 1999) and interfere with glutamate uptake (Hyvärinen et al., 2019; Hu et al., 2000; Mandolesi et al., 2013). Astrocytes convert kynurenine to kynurenic acid (KYNA), an N-methyl-D-aspartate receptor (NMDAR) antagonist (Schafer et al., 2013). The amount of KYNA production as well as the buffering capacity of astrocytes is linked to the functional capacity of astrocytes and the given metabolic resources (Schwarcz et al., 2012). Since the clearance of intrasynaptic glutamate via EAATs is realized by co-transport of glutamate and sodium, this process is coupled to the activity of Na+/K + adenosine triphosphatase (ATPase) (Voutsinos-Porche et al., 2003; Langer and Rose, 2009). Increased adenosine triphosphate (ATP) consumption increases glucose uptake in the endfeet, which enhances the glycolytic rate as well as lactate production (Pellerin and Magistretti, 1994; Chatton et al., 2000; Porras et al., 2008). Pyruvate is converted to lactate by lactate dehydrogenase (LDH) and is transported to the extracellular space via monocarboxylat-transporter (MCT)1. Neurons take up lactate via MCT2, where lactate is converted back to pyruvate to be used in the tricarboxylic acid cycle (TCA) (Magistretti and Cellular, 2015). Pro-inflammatory cytokines decrease glutamate-stimulated glucose uptake and lactate release (Gavillet et al., 2008; Bélanger et al., 2011). AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; PSD: postsynaptic density complex. *Created with BioRender.com.*

CNS (Himmerich et al., 2019; Dantzer, 2018; Miller et al., 2017). In the CNS, pro-inflammatory cytokines can interfere with the synthesis of monoaminergic neurotransmitters, with the serotonergic transmission and can enhance glutamatergic activity through several mechanisms (e.g. by activation of kynurenine pathway or by interfering with the tetrahydrobiopterin pathway) that have been extensively reviewed elsewhere (Iwata et al., 2013; Haroon et al., 2017; Raison and Miller, 2017; Capuron et al., 2017). Similar immune mediators were also shown to be associated to MDD (Haapakoski et al., 2015; Howren et al., 2009; Dowlati et al., 2010). Current evidence points to a more prominent role of inflammation in MDD with atypical features (Lamers et al., 2016; Milaneschi et al., 2016; Hickman et al., 2014; Rudolf et al., 2014; Yoon et al., 2012), though also contradictory findings were reported with some studies finding associations between melancholic depression and inflammation as well (Anisman et al., 1999; Glaus et al., 2014; Karlović et al., 2012a; 2012b;; Yang et al., 2018).

It has been posed that increased blood levels of pro-inflammatory cytokines may be trait markers in atypical depression, whereas in melancholic subtype this increase rather represents a state marker (Karlović et al., 2012a; 2012b).

3. The effect of inflammation on glutamatergic synapses - shared maladaptive alterations in MDD and IR-related disorders

Glutamatergic neurotransmission and glutamate turnover are tightly regulated processes that require a fine tuned interplay between neurons and glia (Fig. 2). The maintenance of glutamatergic synapses are energy demanding (Magistretti and Cellular, 2015). Therefore, a metabolic mismatch may occur in a pro-inflammatory state that increases the glutamtatergic load within the synapse. Besides the more general inflammatory processes involved in MDD that were introduced in section 2, current evidence indicates immune-mediated abnormalities specifically in glutamatergic neurotransmission and glutamate turnover in the pathophysiology of MDD (Haroon et al., 2017; Martín-Hernández et al., 2019; Li et al., 2019; Yang et al., 2013). Similar abnormalities reported in animal models of T2DM (Tsai et al., 2018a, 2018b; Liu and Zheng, 2019; Spinelli et al., 2017; Zheng et al., 2016, 2017; Arnold et al., 2014) may suggest common immune-mediated disturbances in glutamatergic synapses during the course of the two diseases. In the following paragraphs, immune-mediated changes in glutamatergic neurotransmission, glutamate turnover and neurometabolic coupling are introduced. Furthermore, findings of existing literature of animal models of MDD and T2DM are discussed.

Immune mediators can interfere with glutamate transmission by decreasing its clearance (Takahashi et al., 2003; Takaki et al., 2012) or inducing non-neuronal glutamate release (Takeuchi et al., 2006; Ida et al., 2008). The ‘spillover’ of glutamate into the extrasynaptic space can lead to stimulation of extrasynaptic glutamate receptors that eventually results in the loss of synaptic fidelity and disruption of neural circuitries (Fellin et al., 2004; Weng et al., 2007). Activated microglia (Mesci et al., 2015; Kitagawa et al., 2019; Takaki et al., 2012; Takeuchi et al., 2006) and astrocytes (Bezzi et al., 2001; Ida et al., 2008) release glutamate into the synaptic cleft and rapidly increase the extracellular glutamate levels (Takaki et al., 2012). Pro-inflammatory cytokines decrease the expression of excitatory amino-acid transporters (EAATs) in astrocytes (Sitcheran et al., 2005; Korn et al., 2005). In line with this, chronic unpredictable mild stress (CUMS)-induced depressive behavior is associated with decreased expression of glial EAATs in the hippocampus and cerebral cortex (Martín-Hernández et al., 2019; Banasr et al., 2010). Postmortem studies in MDD patients also indicated a decreased expression of EAATs in the ACC and dorsolateral prefrontal cortex (DLPFC) (Choudary et al., 2005) as well as in the hippocampus (Medina et al., 2016). Moreover, reduced EAAT1 and EAAT2 expression was reported in the hypothalamus (Liu and Zheng, 2019) and the hippocampus (Martín-Hernández et al., 2019; Li et al., 2019), for a contradictory finding see (Takeuchi et al., 2006) of HFD-mice.

Microglia display EAAT1 and EAAT2 only after immune activation and utilize glutamate in exchange for cystine for the production of the antioxidant GSH (Van Landeghem et al., 2001; Persson et al., 2007). Pro-inflammatory cytokines increase the expression of cystine/glutamate antiporter (xCT) and induce glutamate release from microglia (Mesci et al., 2015; Kitagawa et al., 2019). Moreover, upon activation, microglia secrete neurotoxic metabolites produced during tryptophan metabolism, which increase the burden on glutamatergic synapses (O’Connor et al., 2009; Stone and Perkins, 1981; Schwarcz et al., 1983; Guillemin et al., 2005). Pro-inflammatory cytokines induce indoleamine 2,3-dioxygenase (IDO) activity in microglial cells (Wang et al., 2010), which oxygenates tryptophan to kynurenine. Furthermore, kynurenine is converted into quinolinic acid (QUIN) in activated microglia, which is an N-methyl-D-aspartate receptor (NMDAR) agonist (Guillemin et al., 2001). Animal studies showed that CUMS induced increased IDO expression and QUIN levels (Martín-Hernández et al., 2019), while a blockade of IDO activation (O’Connor et al., 2009) or NMDARs (Walker et al., 2013) attenuates the lipopolysaccharide (LPS)-induced depression-like behavior. Accordingly, IFN-α treatment was found to be associated with IDO activity and with depressive symptoms in cancer patients (Capuron et al., 2002). Steiner et al. (Steiner et al., 2011) showed increased levels of QUIN in the ACC of depressed patients (Steiner et al., 2011). Activation of the kynurenine pathway has also been associated with obesity and MetS (Mangge et al., 2014; Brandacher et al., 2007; Favennec et al., 2015). Moreover, the LPS-induced depression-like behavior in obese mice was found to be associated with IDO activity (André et al., 2014; Dinel et al., 2014). Accordingly, HFD induces microglial activation in the hypothalamus (Thaler et al., 2012; Valdearcos et al., 2014; Baufeld et al., 2016) and hippocampus (Hao et al., 2016; Kang et al., 2016). Of note, in astrocytes kynurenine is converted to kynurenic acid, which is an NMDAR antagonist (Guillemin et al., 2001). Presumably, in the case of abnormal energy metabolism, astrocytes cannot balance the activity of IDO in activated microglia, therefore glutamatergic and pro-inflammatory activity cannot be controlled.

The extent of the immune activation on glutamatergic transmission may depend on the buffering capacity of astrocytes and the spatial arrangement of extra-synaptic glutamate receptors (Haroon et al., 2017; Weng et al., 2007; Rusakov and Kullmann, 1998; Tzingounis and Wadiche, 2007). Since astrocytic buffering capacity of astrocytes is also linked to available energy resources, such as glycogen (Sickmann et al., 2009; DiNuzzo et al., 2012; Schousboe et al., 2010), consequently a metabolic mismatch can emerge consequently towards excessive or prolonged glutamatergic activity. This can emerge especially in NMDAR-rich synapses, when the metabolic demand to maintain glutamate metabolism and the transmembrane gradients of K^+ and $Ca2^+$ are considered (Aubert et al., 2007). Protoplasmic astrocytes project their processes around arterioles and capillaries and form so-called “astrocytic endfeet” (Magistretti and Cellular, 2015). Glutamatergic transmission activates glucose uptake from the abluminal side of the astrocytic endfeets as well as glucose and glycogen derived lactate production in astrocytes to meet the increased energy demand (Sickmann et al., 2009; Schousboe et al., 2010; Pellerin and Magistretti, 1994; Chatton et al., 2000; Porras et al., 2008). Glycogenolysis in astrocytes contributes to the de novo synthesis of glutamate and glutamine (Sickmann et al., 2005; Gibbs et al., 2007). CUMS was shown to impair glycogen metabolism in the CNS. Even though glycogen synthase expression was enhanced in the brain, glycogenolysis was impaired and glycogen stores could not be used (Zhao et al., 2017). Interestingly, lactate infusion could improve depression-like behavior in a rodent experiment (Carrard et al., 2018). Of note, the utilization of brain glycogen was shown to be altered in Zucker Diabetic Fatty rats (Sickmann et al., 2012). Functional and structural impairments in hippocampal astrocytes were reported in high-fat diet (HFD)-fed mice (Cano et al., 2014), the utilization of brain glycogen was shown to be altered and glutamatergic transmission was observed to differ from standard

diet, which was possibly related to a reduced function in glutamate transporters (Fritz et al., 2018). Moreover, reduced lactate concentration was associated to reduced EAATs expression in the hippocampus of HFD-fed mice (Tsai et al., 2018).

Metabolic mismatch can induce a neuroinflammatory response and metabolic uncoupling in synaptic units can be increased by the additional effect of triggering conditions, such as sleep deprivation (Kilic et al., 2018). Furthermore, acute and chronic stress can lower the threshold for inflammatory responses via α2-adrenergic and glucocorticoid receptors in mice (Yapıcı-Eser et al., 2018), suggesting an additive effect of different stressors. In line with this, acute psychosocial stress induction induced a larger inflammatory response in subjects with known MDD risk factors, such as ELS (Pace et al., 2006; Carpenter et al., 2010). These findings may suggest an additive effect of distinct stressors, either cellular or psychosocial, on the inflammatory response in susceptible regions of the brain, presumably in relatively NMDAR-rich regions, such as the dACC (Palomero-Gallagher et al., 2009a; 2009b). Indeed, IFN-α administration resulted in increased glutamate/creatine ratio in the dACC, which was correlated with the severity of depressive symptoms in patients infected with the hepatitis C virus (Haroon et al., 2014). Interestingly, atypical depression was proposed to be associated with altered activity in the dACC, whereas melancholic depression was suggested to be more associated with changes in the pregenual ACC (pgACC), which is a relatively α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-rich region (Woelfer et al., 2019). It is worth noting though that typhoid vaccination induced deterioration in mood was correlated with the increased activation in sgACC and decreased connectivity of sgACC to bilateral nucleus accumbens and medial prefrontal cortex in healthy male participants (Harrison et al., 2009).

4. The association of inflammation with central and systemic insulin resistance (IR)

Obesity and obesity-associated IR are some of the most important predisposing factors for T2DM (2. Classification and diagnosis of diabetes: Standards of medical care in diabetesd, 2019). IR is defined as an insensitivity of target tissues to physiological levels of insulin. Metabolic inflammation has been put forward to underlie IR-related disorders and to link obesity to IR and T2DM (Chan KL, Cathomas F, Russo SJ. Central and peripheral inflammation link metabolic syndrome and major depressive disorder. Vol. 34, Physiology. American Physiological Society;, 2019; Hotamisligil et al., 1993). In addition to the infiltration of immune cells into adipose tissue (Hotamisligil et al., 1993; Wu et al., 2007) or the liver (Morinaga et al., 2015), elevated serum levels of various pro-inflammatory cytokines have been detected in patients with obesity (Capuron et al., 2011; Lasserre et al., 2014), IR (Festa et al., 2000), MetS (Santos et al., 2005) and T2DM (Mirza et al., 2012). Furthermore, their blood levels were associated with risk of MetS (Han et al., 2002) and T2DM (Lainampetch et al., 2019), especially in women (Han et al., 2002; Hong et al., 2020).

Several mechanisms underlying nutrient-induced IR were proposed. Glucose and lipid toxicity associated chronic mild systemic inflammation has received much attention, while the exact mechanisms are under active research and extensively reviewed elsewhere (Chan KL, Cathomas F, Russo SJ. Central and peripheral inflammation link metabolic syndrome and major depressive disorder. Vol. 34, Physiology. American Physiological Society;, 2019; Kennedy et al., 2009; Coope et al., 2016; Petersen and Shulman, 2018). However, for the purpose of the current review, we shortly mention the proposed link between overeating and inflammation. Excessive amount of free fatty acids can trigger a mitochondrial and endoplasmic stress response that induces production and secretion of pro-inflammatory cytokines and activates tissue macrophages in adipocytes (Özcan et al., 2006; Schaeffler et al., 2009). Cytokines, such as TNF-α or IL-1β, can interfere with insulin action in adipocytes and increase adipocyte lipolysis and turnover of non-esterified fatty acid and glycerol (Uysal et al., 1997; McGillicuddy et al., 2011; Wen et al., 2011). This further induces IR as well as inflammation also in hepatocytes and myocytes and results in peripheral IR (Roden et al., 2000; Reyna et al., 2008; Fuchs and Sanyal, 2012). In addition to lipid-induced IR, systemic inflammation induced by other triggering factors can also induce IR in susceptible individuals because of the interfering effect of pro-inflammatory cytokines on intracellular insulin action in target tissues, a process called inflammation-induced IR (Petersen and Shulman, 2018).

In the CNS, IR manifests itself with impairment in neuroplasticity, regulation of receptor trafficking and neurotransmitter release, but also with impairment in glucose uptake in neurons expressing glucose transporter type 4 (GLUT-4), the homeostatic response regulated by the hypothalamus (for a detailed discussion of central IR, see reviews (Petersen and Shulman, 2018; Pomytkin et al., 2018). Animal models showed that HFD can trigger expression of pro-inflammatory cytokines in the hypothalamus (De Souza et al., 2005; Thaler et al., 2012; Milanski et al., 2009) and can lead to central insulin and leptin resistance, which in turn can results in increased food intake and weight gain (Milanski et al., 2009; Howard et al., 2004). Moreover, HFD can induce increased immune cell infiltration into the CNS (Valdearcos et al., 2017; Lee et al., 2018; Buckman et al., 2014), microglial accumulation and activation in the hypothalamus in rodent models (Thaler et al., 2012; Valdearcos et al., 2014; Yi et al., 2012) Hypothalamic inflammation may also represent an early event that promotes obesity, since HFD-induced obesity and metabolic changes can be prevented by blocking hypothalamic inflammation (Milanski et al., 2009; Zhang et al., 2008). Moreover, hypothalamic inflammation could be detected weeks before inflammation and expansion in adipose tissue (Thaler et al., 2012). This suggests that hypothalamic inflammation contributes to the development of HFD-induced obesity and is not only a consequence of metabolic inflammation (Chan KL, Cathomas F, Russo SJ. Central and peripheral inflammation link metabolic syndrome and major depressive disorder. Vol. 34, Physiology. American Physiological Society;, 2019).

5. The mediatory role of inflammation between MDD with atypical features and IR-related disorders

Findings from animal models of obesity and T2DM suggest that immune activity plays a role in the comorbidity of these disorders and MDD. In addition to an increase in body weight and hyperglycemia, anxiety and depression-like behaviors were repeatedly observed in rodent models of T2DM (Dutheil et al., 2016; Grillo et al., 2011; Kleinridders et al., 2015; Sharma et al., 2010), while exercise-induced weight loss attenuated anxiety and depression-like behaviors (Park et al., 2017). Dutheil and colleagues (Dutheil et al., 2016) reported HFD-induced anxiety and depression-like behavior, an increase in the expression of IL-1β, IL-6, TNF-α and toll-like receptor (TLR)-4 in the hippocampus, alongside glucose intolerance. The blockage of inflammasome activation prevented the HFD-induced anxiety and depression-like behavior, suggesting that inflammatory mediators link metabolic and behavioral consequences of HFD (Dutheil et al., 2016). Supporting the additive effect of different stressors on the pro-inflammatory state of the brain, diet-induced obesity is also associated with an exacerbated peripheral and central inflammatory response to systemic LPS administration (Pohl et al., 2009; Chuang et al., 2010). Moreover, Andre and colleagues (Pohl et al., 2009) showed that following a 20-week long western like diet, systemic LPS administration leads to a higher increase in the peripheral and central levels of pro-inflammatory cytokines and kynurenine as well as hippocampal and hypothalamic expressions of pro-inflammatory cytokines and IDO. Accordingly, another study showed that systemic LPS administration increased brain IL-1β as well as the ratio of kynurenine to tryptophan and decreased hippocampal BDNF expression (Dinel et al., 2014). These findings suggest a development of vulnerability to immune activators both in the periphery and in the CNS in the course of obesity.

The other way round, psychosocial stress can also contribute to

weight gain and metabolic alterations in the development of obesity (Pan et al., 2013; Aslani et al., 2015; García-Díaz et al., 2007; Su et al., 2017). In rats, CUMS induced glucose intolerance and hypothalamic IR, which both improved with fluoxetine administration (Aslani et al., 2015). In a recent study in mice, the antidiabetic drug glyburide, which also is a NLR family pyrin domain containing 3 (NLRP3)-inflammasome inhibitor, improved CUMS-induced depressive-like behavior as well as peripheral and central IR (Lutter et al., 2008). A possible mechanism that links the HFD-induced hypothalamic inflammation and affective symptoms is the dysregulation of the orexin system (Tsuneki et al., 2013; Brundin et al., 2007), which has been reported in MDD patients (Rainero et al., 2011; Lu et al., 2017; Hara et al., 2005) as well as in metabolic disorders, such as obesity (Nobunaga et al., 2014). HFD induced a reduction in the number of orexin neurons in the hypothalamus in mice (Duffy et al., 2015) possibly via microglial activation (Duffy et al., 2019). Reduction in orexin activity may create a further susceptibility to neuronal insults and neuroinflammation (Gecici et al., 2005).

Altogether, these findings may indicate a common role of immune activity in translation of both psychosocial and nutrient-stress to a systemic pro-inflammatory state as well as the co-enhancing effect of both stressors upon low-grade inflammation, which likely mediates the comorbidity between MDD and IR-related disorders. This link seems to be more evident in patients with atypical features of MDD, namely increased appetite and lethargy (Lamers et al., 2018; Rudolf et al., 2014). In addition, atypical depression and more specifically hyperphagia were found to be associated with elevated leptin levels in serum, which may indicate a resistance to the anorexigenic effect of leptin (Milaneschi et al., 2017a, 2017b). Furthermore, current evidence indicates a shared genetic base between IR-related disorders and atypical depression (Milaneschi et al., 2016, 2017; de Kluiver et al., 2019; Dallman et al., 2003). A study with more than 25.000 samples reported that MDD patients endorsing the atypical symptoms of hyperphagia and/or weight gain carry a significantly higher number of genetic risk variants for high BMI, high circulating levels of CRP, leptin and BMI-adjusted leptin (de Kluiver et al., 2019) and hyperphagia has furthermore been linked to inflammatory gene expression pathways in depression [201. Considering that HFD can induce hypothalamic inflammation and central insulin and leptin resistance, which in turn results in increased food intake and weight gain in rodents (De Souza et al., 2005; Thaler et al., 2012; Milanski et al., 2009), it can be suggested that hyperphagia mirrors inflammation-induced dysfunctional central insulin and leptin resistance in patients with atypical depression. In addition, hyperphagia and the tendency to immobilization due to leaden paralysis may exacerbate inflammation and related IR, constituting a vicious cycle. Hyperphagia is also reinforced as a form of self-consolatory behavior to cope with emotional distress induced by rejection sensitivity in social contexts (Thaler et al., 2010).

Although acute peripheral immune stimulation induces sickness behavior that is characterized by anorexia, atypical depression and more specifically hyperphagia was found to be associated with inflammation (Lamers et al., 2016; Hickman et al., 2014; Rudolf et al., 2014; Yoon et al., 2012). Hypothalamic inflammation is associated with both positive and negative energy balance depending on the affected hypothalamic region and cells as well as the type and time-course of the inflammatory stimuli (Kumar et al., 2013). Chronic stress models in rodents, especially when combined with HFD, can induce weight gain as well as abnormalities in lipid metabolism in rodents, which may respond to fluoxetine treatment (Pan et al., 2013; Whale et al., 2019). Of note, weight loss was reported in hepatitis C patients with depression receiving IFN- α treatment. (DiSabato et al., 2016). The distinctions between the effects of chronic and acute inflammation as well as between different degrees of chronic inflammation are still under investigation (Kumar et al., 2013; Bennett and Molofsky, 2019; Levitan et al., 2012).

Although the bidirectional relationship between IR-related disorders and atypical depression has been shown in longitudinal studies (Luppino et al., 2010; Lamers et al., 2016; Lasserre et al., 2014; Daly, 2013) and the existing evidence suggesting that this bidirectional relationship is mediated by inflammatory mediators (Emery et al., 2007; Milaneschi et al., 2020), the temporal relationship between chronic low-grade inflammation, the occurrence of IR-related disorders and atypical depression is yet to be estimated. According to the immunometabolic depression model, polygenic effects create a liability for immunometabolic dysregulations together with environmental (e.g., smoking, substance use or stressful life events) and epigenetic factors, which consequently increase the occurrence of atypical depression related symptoms, such as hyperphagia, hypersomnia, fatigue and leaden paralysis (Vogt et al., 1995). It can be postulated that the temporal sequence from a basal inflammation liability to IR-related disorders or atypical depression can vary across individuals depending on the presence of particular genetic, environmental and behavioral risk factors that co-enhance the development of each other. Future longitudinal clinical studies are needed to understand the complex temporal relationship between the elements of immunometabolic dysfunction and atypical depression.

6. The role of the ACC in in the pathophysiology of MDD

ACC anatomy as well as functions and connections of its subregions (ACC parcellation is depicted in Fig. 3) are described in short in Box 1.

The ACC is a key player implicated in the pathophysiology of depression, which is supported by several observations. Studies reported smaller ACC volumes (Auer et al., 2000), abnormal glutamatergic levels (Morinaga et al., 2015; Capuron et al., 2011; Lasserre et al., 2014), for review see (Li et al., 2019), as well as lower fractional anisotropy (Li et al., 2014) in the ACC of MDD patients.

Evidence for the involvement of the ACC in depression furthermore comes from studies investigating medical treatment options, e.g. SSRIs. ACC hypermetabolism, which was particularly observed in responders to antidepressant treatment and a relationship between higher ACC activity before treatment and clinical outcome was observed (Osuch et al., 2000; Graf et al., 2013). Furthermore, a unidirectional attenuation of fMRI-activations under SSRI treatment within the ACC, specifically the pgACC and the dACC was described (Steiner et al., 2008). The discrepancy in ACC activity and the different directions of reported glucose metabolism changes could be explained in the context of

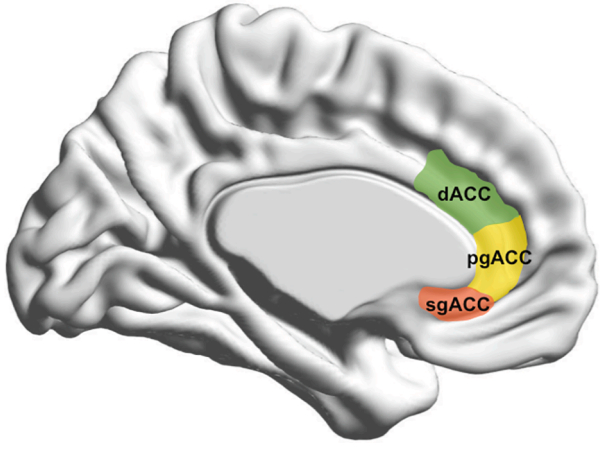

Fig. 3. Template of the human brain with a parcellation of the anterior cingulate cortex. sgACC, subgenual anterior cingulate cortex (orange); pgACC, pregenual anterior cingulate cortex (yellow); dACC, dorsal anterior cingulate cortex, also often referred to as anterior midcingulate cortex (green); derived with BrainNet viewer (231). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Box 1

ACC structure and receptor profile

The ACC includes Brodmann's areas 24, 25, 32, and 33. Based upon cytoarchitecture and functional connectivity, the ACC can be divided into a more ventral emotional component comprising the pregenual (pgACC) and the subgenual ACC (sgACC) and a more dorsal cognitive division, namely the dorsal ACC (dACC), also often referred to as anterior midcingulate cortex (aMCC)) (Vogt, 2005; Etkin et al., 2011; Bush et al., 2000; Palomero-Gallagher and Vogt, 2012; Vogt et al., 2003) (see Fig. 3). ACC subdivisions can be further delineated on the basis of their receptor profile (Palomero-Gallagher et al., 2009a, 2008; 2009b). The pgACC shows above average α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and below average N-methyl-D-aspartate receptor (NMDAR) densities (when compared to the whole cingulate cortex), whereas the inverse has been observed for the dACC, which can be considered an NMDAR-rich region. The ACC subregions furthermore show distinct cytoarchitectonic features, which are described in detail in (Mansouri et al., 2009).

Functions and connections of ACC subregions

dACC: The dACC is thought to be involved in cognitive processing, specifically in reward-based decision-making, conflict monitoring and adjustment of cognitive control (Vogt et al., 2005). It receives projections from the pain-related thalamic nuclei and is also strongly connected to the amygdala (Ghashghaei et al., 2007; Haber and Knutson, 2010). The dACC can furthermore stimulate the inhibitory function of the pgACC to the amygdala (Bush et al., 2000). The dACC orchestrates internal and external salient stimuli in a bottom-up manner and ensures necessary adaptive responses to salient stimuli, e.g. increasing attention by regulating other large-scale networks within the brain.

pgACC: Compared to the sgACC subregion, the pgACC has more widespread connections with the lateral prefrontal cortex (Haber and Knutson, 2010; Mayberg, 1997) and is mainly involved in processing emotions and regulating endocrine as well as autonomic responses to emotions.

sgACC: The sgACC as part of the limbic system is widely involved in emotion processing (Osuch et al., 2000; Pizzagalli, 2016; Chiba et al., 2001). The sgACC is connected with the amygdala and also projects to the ventral striatum and autonomic centers in the brainstem and hypothalamus (Haber and Knutson, 2010; Mayberg, 1997; Seminowicz et al., 2004). The sgACC is also involved in the cortico-basal ganglia circuit during reward processing (Mayberg, 1997) and furthermore was suggested to be one of the key structures during autonomic integration (Salience and Network [Internet]. Vol. 2, Brain Mapping: An Encyclopedic Reference. Elsevier Inc. , 2015). It was furthermore shown that sgACC activity and functional connectivity during evoked responses to emotional stimuli reflect inflammation-associated mood deterioration and can be modulated by peripheral cytokines (Harrison et al., 2009).

Together with the anterior insula the ACC is one of the two major player of the salience network, which is activated by salient stimuli (Öngür et al., 2003). Furthermore, the insula and ACC - specifically sgACC [to a lesser extend also pgACC and dACC (Kampe et al., 2009), which shows most pronounced connection - can be also referred to as 'ingestive cortex', receiving orexigenic input from the lateral hypothalamus either directly or via thalamic relays. This might constitute a neural pathway involved in the integration of information pertinent to taste and energy status as well as food related reward-processing (Xia et al., 2013).

established ACC subdivisions.

Moreover, the dACC seems to be more affected by inflammation in MDD. Examination of postmortem brain sections of patients who committed suicide showed elevated microglial density (Kraynak et al., 2018). Likewise, the expression of the NMDAR agonist microglial quinolinic acid was found to be increased in sgACC and dACC but not in pgACC in a human immunohistochemistry study comparing acutely depressed suicidal patients to healthy controls (Steiner et al., 2011). These alterations can lead to unbalanced glutamatergic activity in those regions, which in turn can enhance the inflammatory activity. In addition, there is extensive literature on inflammation sensitivity of dACC as reported in a *meta*-analysis by Kraynak (Cui et al., 2016), which summarizes the association of functional neuroanatomy of peripheral inflammatory physiology assessed by human neuroimaging studies. This *meta*-analysis revealed dACC as one of the consistently reported regions showing inflammatory sensitivity.

Based on these findings, Woelfer and colleagues (Woelfer et al., 2019) proposed that the region-specific correlates of neuroinflammation as well as the activity and connectivity changes in ACC could explain some atypical features of MDD. One clinical characteristic of MDD with atypical features is increased appetite causing an increase in weight, which is a risk factor to develop IR (2. Classification and diagnosis of diabetes: Standards of medical care in diabetesd, 2019). The following paragraph will elucidate the evidence for an involvement of the ACC in metabolic disorders and obesity.

7. Neuroimaging findings in patients with metabolic disorders and obesity

Several findings highlight the important role of dACC in T2DM. One study exploring whole-brain connectivity pattern in T2DM found that patients exhibit increased degree centrality (DC), which is defined as the number of links incident upon a brain region, in the right insula as well as the dACC (Liu et al., 2018). This finding was supported by a study performed by Liu and colleagues (Gold et al., 2007) who found that the DC values were higher in the left dACC in T2DM patients compared to healthy controls. Furthermore, in this study increased functional connectivity (FC) of the dACC was found in diabetic patients, which was correlated with higher fasting plasma glucose levels (Liu et al., 2018).

Besides the ACC, alterations in other regions were reported in patients with IR and related disorders. Hippocampal atrophy that correlated with cognitive dysfunction was described in diabetic patients (Keymeulen et al., 1995), which could be relevant for explaining the link to depression. Furthermore, particularly patients with long-standing diabetes showed changes in frontal perfusion and cerebral glucose metabolism (Ziegler et al., 1994; van Harten et al., 2006). The cerebral changes could be caused by chronic hyperglycemia, microvasculopathy, macrovasculopathy, episodes of hypoglycemia and possible direct effects of insulin on the brain (Hassenstab et al., 2012).

Studies also investigated the involvement of the dACC in obesity, which can be regarded as a prediabetic state. Considering alterations in obesity is important given the observation that patients with atypical depression tend to eat more. fMRI studies reported gray matter reductions in frontal regions, amongst others the dACC, which have been related to obesity (Raji et al., 2010; Wijngaarden et al., 2015).

Furthermore, decreased connectivity between the hypothalamus and the dACC after prolonged fasting in obese subjects was described while an increased connectivity in lean subjects was observed, supporting the idea that food reward and nutrient deprivation might be processed differently in obesity (Bénard et al., 2017). Obesity is furthermore associated with increased impulsivity, in particular due to stress, which was reported by a large sample human association study of impulsivity and weight status (Hu et al., 2015). The underlying brain structures for behavior control are considered to be striatal, frontal regions and the dACC (Vaidya and Stollstorff, 2008; Baker et al., 2011). Besides obesity-related alterations in the dACC, further regions deserve attention. Studies investigating animals under HFD described increased hypothalamic gliosis (Thaler et al., 2012; Berman et al., 2011); which was complimented by evidence of increased gliosis in the mediobasal hypothalamus of obese human subjects, as assessed by MRI (Berman et al., 2011). This might also affect the HPA-axis, a pathway well known to be involved in the etiology of depression. Furthermore, greater IR (assessed by homeostatic model assessment-IR (HOMA-IR)) in patients with T2DM was associated with reduced regional cerebral glucose metabolic rate in the posterior cingulate cortex/precuneus, parietal cortices, temporal/angular gyri, prefrontal and cingulate cortices (Bluhm et al., 2009), all of which are regions also implicated in the pathomechanism of depression (Walter et al., 2009; Bae et al., 2006; Ballmaier et al., 2004; Moran et al., 2013).

8. Neuroimaging findings at the interplay between MDD and IR-related disorders

To examine which brain regions are specifically involved in the bidirectional relationship between depression and metabolic disorders, neuroimaging results from patients with comorbidity of T2DM and MDD were of particular interest. A summary of studies investigating depressed diabetic patients and depressed patients with obesity or IR is provided in Table 1. It has to be noted that while the main focus of this review lies on atypical depression, the literature reported in Table 1 is not specifically investigating atypical depression, therefore information on this is not reported in the table. The summary contains findings from (Hasin et al., 2018) structural magnetic resonance imaging (MRI), (Malhi and Mann, 2018) functional MRI as well as (Ali et al., 2006) magnetic resonance spectroscopy (MRS).

ACC volumetric reductions, as reported in Table 1, were also reported in MDD and T2DM separately (Auer et al., 2000; Singh et al., 2019; Ajilore et al., 2007) and could reflect the disastrous effect of inflammation particularly on ACC brain morphometry in both diseases. The study by Singh and colleagues (Haroon et al., 2009) reported that youth with high IR and more food seeking behaviors demonstrated a greater level of dACC dysconnectivity to fronto-limbic reward networks. The authors hypothesized that the reported alterations in neural circuit underlie dysfunctional behavioral responses and increased sensitivity to rewarding intake of high calorie food, which leads to disinhibition of food intake even when the subjects are satiated. If these findings of disturbed inter-regional communication of the ACC and specifically of the dACC can be replicated, it will add to the understanding of the bidirectional link between depression and the development of metabolic disorders. The reported alterations in this region might also be involved in hyperphagia, which is a shared malfunction in IR-related disorders and MDD with atypical features.

In addition to changes in the ACC, other brain regions were implicated in the comorbidity of depression and metabolic disorders, which as well are reported in table 1. Of note regarding the reported studies of Alijore and colleagues (Geissler et al., 2003) and Haroon and colleagues (Mäkimattila et al., 2004), changes in myo-inositol levels have been associated with gliosis and neuropathy in diabetic (Järnum et al., 2011; Palomero-Gallagher et al., 2009a; 2009b) and depressed patients (Zhang et al., 2015).

9. Multilevel integration of molecular, behavioral and neuroimaging findings at the interplay of MDD and IR-related disorders

It is hypothesized that chronic low-grade inflammation plays a mediating role in the comorbidity of MDD and IR-related disorders (Leonard and Wegener, 2019; Lamers et al., 2016). This link seems more evident in patients who show atypical features of MDD, namely increased appetite and lethargy (Lamers et al., 2018; Rudolf et al., 2014). We claim that inflammation-mediated functional and morphometric abnormalities in dACC could be a shared feature in (atypical) depression and metabolic disorders.

The clinical and preclinical evidence presented in Section 5 indicates that there is an additive effect of distinct stressors, either cellular or psychosocial, on the peripheral and central inflammation as well as IR. Due to the structural and functional organization between neurons, astrocytes and microglia, the brain regions relatively rich in NMDAR, such as the dACC (Ding et al., 2019), might be more susceptible to the effects of inflammation in case of a metabolic mismatch (as discussed in Section 3). Given the abnormal dACC activity reported in obese individuals (e.g. (Vancassel et al., 2018)and the link between hyperphagia, atypical depression, MetS as well as low-grade inflammation, we claim that the dACC is involved in the comorbidity of atypical depression and IR-related disorders, which is in line with the postulation developed by Wölfer and colleagues (Woelfer et al., 2019).

In regard to our hypothesis, studies found a reduced volume in the dACC (Raji et al., 2010; Wijngaarden et al., 2015) as well as metabolic changes and an abnormal FC of the dACC, especially to regions involved in reward processing (Bénard et al., 2017; Baganz et al., 2013). Besides the dACC, other cortical and subcortical brain regions, particularly the hippocampus, basal ganglia and the prefrontal cortex indicate a more complex brain pattern in the bidirectional relationship between depression and diabetes. To our knowledge, there is no study that examines neuroimaging changes in a sample of patients who suffer from comorbid IR-related disorders and MDD with atypical features specifically. However, such a study would be necessary to fully test our hypothesis.

10. Limitations

In this review, we assessed the interfering effect of systemic or central inflammatory activity on synaptic transmission mainly focusing on glutamatergic synapses. Both depressive-like behavior in rodents and MDD in humans have also been associated with the effect of inflammation on dopaminergic as well as on serotonergic activity (for reviews see (Himmerich et al., 2019; Dantzer, 2018; Peng et al., 2016; Perugi et al., 2013). However, an exhaustive presentation of those results would have been beyond the scope of this work.

We shed light on some underlying pathomechanisms of MDD with atypical features, whereas it is worth mentioning, that atypical depressive episodes are also closely discussed in the context of bipolar II disorder (Akiskal and Benazzi, 2005; Alexopoulos, 2019; Simmons et al., 2018). This makes it important not to limit the reported observation on the assumed subtype of depression only, but also in bipolar disorder, and it could explain some contradictory findings in the literature. Of note, the cerebrovascular insufficiency developed in the course of IR-related disorders may also favor a certain form of late life-depression that develops in the elderly population and is characterized by executive dysfunction (Fugger et al., 2019).

Even though numerous studies indicate a link between MDD with atypical features and IR-related metabolic disorders (Lamers et al., 2018; Rudolf et al., 2014; Lasserre et al., 2014; Angst et al., 2006), a recent study in contrast reported that melancholic features were more pronounced in T2DM patients (Parker et al., 2002).

In line with this, while large cohort studies have found stronger associations with inflammatory and metabolic markers for atypical

Table 1

Author	Sample description (n, gender (male/female), mean age ± SD)	Method	Drug status	Duration of T2DM (in years*±SD) and/or disease onset information	Duration of MDD (in years*±SD) and/or disease onset information	Results
Functional findings – T2DM and MDD						
(Xia et al., 2013)	T2DM (n = 27, 16/11, 58.56 ± 6.60) T2DM + depressive mood (n = 25, 13/12, 56.76 ± 7.51) HC (n = 23, 10/13, 54.57 ± 6.29)	Rs-fMRI	T2DM: Varying combinations of insulin treatments, blood pressure loweing medication and/or cholesterol lowering medication. All patients were untreated for depression.	T2DM: 8.22 ± 4.25 T2DM + depressive mood: 9.26 ± 4.37	Not applicable	Decreased FC of left amygdala with left ACC, right inferior frontal gyrus, left fusiform gyrus and right precentral gyrus in T2DM + depressive mood. Association of amygdala FC in cingulate cortex with self-rating depression score in T2DM.
Structural findings - T2DM and MDD						
(Ajilore et al., 2010)	T2DM (n = 26, 8/18, 57.81 ± 8.49) T2DM + MDD (n = 26, 6/20, 55.0 ± 9.66) HC (n = 20, 5/15, 55.15 ± 8.23)	MRI	MDD: Drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control.	T2DM: 9.85 ± 8.24 T2DM + MDD: 10.50 ± 8.82	No history of depression prior to diabetes onset (as reported in Watari 2006)	Decreased cortical GM thickness in left ACC in T2DM and T2DM + MDD. Decreased cortical GM in bilateral prefrontal areas in T2DM + MDD.
(Ajilore et al., 2015)	T2DM (n = 24, 9/15, 58.88 ± 8.32) T2DM + MDD (n = 20, 4/16, 54.8 ± 10.71) HC (n = 32, 9/23, 53.47 ± 10.34)	MRI	MDD: Drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control.	T2DM: 9.75 ± 7.8 T2DM + MDD: 8.80 ± 7.6	Mean age of onset for MDD 49.3 ± 10.12 years old	Worse performance in T2DM + MDD in verbal list learning. Hippocampal volume as predictor of performance in HC. Age and hippocampal volume as predictors in T2DM. Age as predictor of verbal learning performance in T2DM + MDD.
(Desmidt et al., 2011)	T2DM (n = 13, 5/8, 65.5 ± 6.9) T2DM + MDD (n = 11, 3/8, 61.8 ± 7.5)	TPI	Not available	T2DM: 16.7 ± 10.3 T2DM + MDD: 16 ± 6.7	Not available	Lower brain tissue pulsatility in T2DM + MDD than in T2DM.
(Kumar et al., 2008)	T2DM (n = 26, 7/19, 57.85 ± 8.53) T2DM + MDD (n = 26, 6/20, 55.5 ± 9.66) HC (n = 25, 5/20, 53.24 ± 9.12)	MRI	MDD: Drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control.	T2DM: 118.15 ± 98.94 (in months) T2DM + MDD: 126 ± 105.83 (in months)	Not available	Smaller total brain GM and smaller GM volumes in ACC and orbitofrontal regions in T2DM and T2DM + MDD.
(Kumar et al., 2009)	T2DM (n = 22, 6/16, 60.7 ± 9.79) T2DM + MDD (n = 16, 2/14, 58.1 ± 10.71) HC (n = 30, 7/23, 54.9 ± 11.04)	MTI	MDD: No psychotropic medication for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control.	T2DM: 112.4 ± 97.4 (in months) T2DM + MDD: 156 ± 119 (in months)	Current episode of depression on average 16.4 ± 18.2 months (3 first episode, 7 had 1 prior depressive episode, 1 reported 2, and 1 reported 3. In 4 cases, insufficient information).	Smaller caudate nucleus head in T2DM + MDD. Reduced MTR in WM and GM regions in bilateral caudate nucleus in T2DM + MDD.
(Kumar et al., 2016)	MDD (n = 32, 9/23, 58.5 ± 12.6) T2DM (n = 21, 12/9, 65.1 ± 11.6) T2DM + MDD (n = 22, 10/12, 56.1 ± 10.0) HC (n = 38, 16/22, 62.6 ± 12.1)	MTI	MDD: Free of antidepressant and/or psychotropic medications for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control.	Not available	Not available	Lower MTR in globus pallidus in T2DM + MDD. Inverse correlation of biophysical measures in subcortical nuclei with measures of glycemic control, cerebrovascular burden and depression scores.
(Raffield et al., 2016)	T2DM (n = 461, 242/219, 66.8 + -9.7) Depressed T2DM (n = 104, 41/63, 62.5 ± 9.8) Anxious T2DM (N = 33, 12/21, 66.4 ± 8) Anxious + depressed T2DM (n = 57, 27/30, 61.4 ± 10.2)	fMRI/DTI	Antidiabetic medication (either hypoglycemic medications or insulin): T2DM: 84.4% Depressed T2DM: 83.7% Anxious T2DM: 75.8% Anxious + depressed T2DM: 77.2% Either antidepressant or antianxiety medication: T2DM: 12.6% Depressed T2DM: 14.4% Anxious T2DM: 27.3% Anxious + depressed T2DM: 14.0%	T2DM: 15.1 ± 8.1 Depressed T2DM: 14.7 ± 6.6 Anxious T2DM: 17.6 ± 8 Anxious + depressed T2DM: 13.3 ± 7.3	Not available	Poorer cognitive performance in T2DM with co-occuring anxiety and depression. Increased WM lesion volume, decreased GM volume and cerebral blood flow, higher mean diffusivity and lower FA in T2DM with co-occuring anxiety and depression.
(Watari et al., 2008)	T2DM (n = 23, 8/15, 58.74 ± 8.11) T2DM + MDD (n = 21, 6/15, 56.10 ± 10.64) HC (n = 22, 4/18, 52.64 ± 8.31)		MDD: No anti-depressant or psychotropic medications. T2DM: on varying combinations of oral hypoglycemic agents and insulin for blood sugar control.	T2DM: 10.13 ± 7.96 T2DM + MDD: 9.76 ± 7.77	Not available	Positive correlation of right orbitofrontal GM with executive functioning and attention/processing speed in T2DM + MDD. Attenuation of this effect in T2DM and HC.

(*continued on next page*)

Table 1 (*continued*)

Author	Sample description (n, gender (male/female), mean age ± SD)	Method	Drug status	Duration of T2DM (in years*±SD) and/or disease onset information	Duration of MDD (in years*±SD) and/or disease onset information	Results
(Yang, 2012)	MDD (n = 30, 14/16, 54.90 ± 13.67) T2DM (n = 18, 9/9, 56.11 ± 11.06) T2DM + MDD (n = 15, 6/9, 54.27 ± 8.32) HC (n = 32, 16/16, 55.13 ± 16.28)	MTI	Not available	Not available	Not available	Lower MTR in caudate nucleus head in MDD and T2DM + MDD. Lower MTR value in T2DM + MDD.
(Zhang et al., 2013)	MDD (n = 28, 8/20, 54.86 + 14.63) T2DM (n = 24, 14/10, 62.54 + 11.38) T2DM + MDD (n = 22, 11/11, 56.05 + 9.40) HC (n = 42, 20/22, 57.52 + 16.00)	DTI	MDD: Drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control.	T2DM: 113.88 ± 84.63 (in months) T2DM + MDD: 106.86 ± 87.59 (in months)	T2DM + MDD: No more than two major depressive episodes prior to the onset of diabetes.	Decreased FA and increase in radial diffusivity of right ALIC in MDD and T2DM + MDD. Lowest mean FA values in right ALIC in subjects with high depression ratings and high hemoglobin A1c levels.
MRS findings - T2DM and MDD						
(Ajilore et al., 2007)	T2DM (n = 24, 7/17, 58.13 ± 9.236), T2DM + MDD (n = 20, 5/15, 56.55 ± 10.2208) HC (n = 21, 5/16, 55.67 ± 9.8674)	MRS	MDD: Drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control.	Not available (description of subsample by Haroon et al. (261))	Five of the 20 subjects reported having an episode of depression prior to the onset of diabetes.	Reduced Glutamate and Glutamine in subcortical regions in T2DM + MDD. Increased myo-inositol levels in dorsolateral WM in T2DM + MDD and T2DM.
(Haroon et al., 2009)	T2DM (n = 20, 7/13, 57.70 ± 7.85) T2DM + MDD (n = 18, 5/13, 56.94 ± 10.64) HC (n = 19, 4/15, 54.47 ± 9.58)	MRS	MDD: Drug-naïve or free of antidepressant or anxiolytic medications for at least 2 weeks prior to the study. T2DM: Varying combinations of oral hypoglycemic agents and/or insulin for blood sugar control and several other medications including antihypertensive medications.	Age of onset: T2DM: 48.45 ± 11.00 T2DM + MDD: 47.22 ± 13.00	Age of onset: 51.28 ± 10.49	Association between myo-inositol and visuospatial impairment in right dlPFC in HC. Progressive weakening of this association in both diabetic groups.
Functional findings - IR/obesity and MDD						
(Ryan et al., 2012)	HC with range of BMI (n = 90, 46/44, 40.4 ± 6.4)	MRI	Not applicable	Not applicable	Not applicable	Co-varying higher levels of IR with increased connective strength between left VS to insula and dACC. dACC-VS connectivity predicting depressed mood.
(Singh et al., 2019)	Overweight/obese subjects with depressive symptoms (n = 42, 16/26,14.82 ± 1.86)	MRI	Youth were excluded if they were currently being treated for a mood disorde, had type 1 or type 2 diabetes or were taking medication that affected their weight or metabolism.	Not applicable	Not applicable	Greater IR and depression are related to increased ACC-hippocampal network connectivity
Structural findings - IR/obesity and MDD						
(Phillips et al., 2018)	Overweight subjects with depressive symptoms (n = 46, 18/28, 14.82 + -1.95)	MRI	Currently not taking medication or receiving psychotherapy for a mood disorder or medications that impair insulin action	Not applicable	Not applicable	Smaller whole brain volumes associated with IR.
(Singh et al., 2019)	Overweight/obese subjects with depressive symptoms (n = 42, 16/26, 14.82 ± 1.86)	MRI	Youth were excluded if they were currently being treated for a mood disorde, they had type 1 or type 2 diabetes or were taking medication that affected their weight or metabolism	Not applicable	Not applicable	Reduced hippocampal and ACC volumes in subjects with greater IR. Thinner ACC and smaller hippocampal volumes associated with more severe depressive symptoms. Opposite finding for low levels of IR.

Summary of neuroimaging findings in depressed diabetic/obese/IR patients.
ACC = anterior cingulate cortex, ALIC = anterior limb of internal capsule, dACC = dorsal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, DTI = diffusion tensor imaging, FA = fractional anisotropy, GM = grey matter, HC = healthy control, IR = Insulin resistance, MDD = major depressive disorder, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, MTI = magnetization transfer imaging, MTR = magnetization transfer ratio, T2DM = type 2 diabetes, TPI = tissue pulsatility imaging, VS = ventral striatum, WM = white matter. * if not stated otherwise

depression than for other subtypes of depression (Vogt et al., 1995), it cannot be ruled out that other inflammatory depression phenotypes exist. Studies assaying larger panels of inflammatory and metabolic markers and comprehensive phenotypic data are needed to further elucidate the associations between specific depression symptoms and subtypes.

In addition, some studies did not confirm the link between inflammation and the atypical subtype of depression (Anisman et al., 1999; Glaus et al., 2014; Karlović et al., 2012a; 2012b), which may be associated with the methods used to index inflammation, temporal trajectory of inflammation and sample characteristics. The DSM-IV definition of MDD with atypical features has been debated, as not all symptoms of the definition seem consistently correlated or do not share clinical profiles (Posternak and Zimmerman, 2002; Xu et al., 2011; Pan et al., 2012). There is some evidence showing that dysregulation of inflammatory and metabolic markers is most strongly linked to the more energy-regulation-related symptoms of atypical depression (e.g. hyperphagia/weight gain, hypersomnia and fatigue/leaden paralysis) (Lamers et al., 2018; Milaneschi et al., 2016). Based on this, it has been proposed that an 'immunometabolic depression' dimension might exist, which is characterized by these energy-related symptoms and immunometabolic dysregulation (Lamers et al., 2018; Vogt et al., 1995). This proposed depression dimension should be considered in future research.

Comorbidity of MDD and T2DM as well as obesity have been reported repeatedly and longitudinal studies confirm that MDD and T2DM are independent risk factors for each other (Ali et al., 2006; Arroyo et al., 2004; Knol et al., 2006; Mommersteeg et al., 2013; Roy and Lloyd, 2012; Luppino et al., 2010; Pearson et al., 2010). Nevertheless, causative knowledge as well as the temporal relationship still remains limited and the mediatory role of inflammation in the comorbidity of MDD - and specifically of atypical depression - and IR-related disorders still remains to be tested. It is worth noting that many of the studies that examined the comorbidity of IR-related disorders and MDD did not test the effect of current or previous use of antidepressant medications (Mezuk et al., 2008; Mommersteeg et al., 2013; Luppino et al., 2010; Kan et al., 2013; Stunkard et al., 2003; Patten et al., 2011; Grundy et al., 2014), even though antidepressants, especially tricyclic antidepressant and mirtazapine, are often associated with weight gain and obesity (Blumenthal et al., 2014; Van Reedt Dortland et al., 2010; Gramaglia et al., 2018; Yoon et al., 2013; Bhattacharjee et al., 2013; Kobrosly and van Wijngaarden, 2010). Meta-analyses indicate that antidepressants can increase the risk of T2DM depending on the dose and the duration of use (Bot et al., 2020; Vanhala et al., 2009). Side effects of medications may partially explain the alterations in energy metabolism and eating behavior, however, current evidence suggests that depressive symptoms associated to IR-related disorders seem to be independent from the side effects of antidepressant medication (Lamers et al., 2018, 2016; Peña et al., 2005; Hannestad et al., 2011; Vogelzangs et al., 2012). A further important aspect is that antidepressant medications have various effects on immune cells and inflammatory pathways (Park et al., 2012; Strawbridge et al., 2015; Di Rosso et al., 2016; Alcocer-Gómez et al., 2017; Dahl et al., 2014; Nigatu et al., 2015; Davies et al., 2020). Most studies reported a decrease of pro-inflammatory cytokine blood levels especially after SSRI treatment (Strawbridge et al., 2015; Di Rosso et al., 2016; Dahl et al., 2014; Davies et al., 2020; Xia et al., 2018). For this reason, we do not expect that increased levels of pro-inflammatory findings reported in atypical depression (Lamers et al., 2016; Hickman et al., 2014; Rudolf et al., 2014; Yoon et al., 2012) is a result of antidepressant medication.

Furthermore, the lack of reference to frequency and duration of depressive episodes in the reported studies should be discussed, since unfortunately, many studies in the literature did not control for these effects. However, Luppino and colleagues (Luppino et al., 2010) reported that the association between obesity and depression was stronger if the follow-up period is longer than 10 years in longitudinal studies, which indicates an effect of the duration of illness. Nigatu and colleagues (Ajilore et al., 2010) observed that obesity at baseline was associated to the onset of recurrent MDD but not to single depression episodes. Even though it seems legitimate to propose that the recurrent depressive episodes and longer duration of MDD are more strongly associated to immunometabolic dysfunction, the current evidence in MDD and atypical depression does not allow for a conclusive statement.

It is worth mentioning that besides dACC involvement in inflammatory sensitivity several other brain regions were repeatedly reported by Kraynak and colleagues (Cui et al., 2016). These regions include hippocampus, hypothalamus, striatum, insula, midbrain, and brainstem, as well as temporal cortices. Furthermore, sgACC activation was often reported making the dACC not the exclusive cingulate region involved in respective processes. Nevertheless, in contrast to the dACC involvement, the sgACC activations seem to be specific to the task type with emotion tasks eliciting greater absolute proportions of activations than cognitive or resting state tasks. Among the repeatedly activated brain regions, also the amygdala was identified as an important player. One recent study once suggested the amygdala to play a mechanistic role in inflammation-associated depressive symptoms, which was assessed by an fMRI study on pro- and anti-inflammatory therapies (Ajilore et al., 2015).

To fully prove our hypothesis, however, the distinction between MDD subtypes would be necessary and would be important to develop specific treatment strategies for different subtypes of MDD. At the moment, our hypothesis is supported by neuroimaging studies reporting dACC alterations in MDD, T2DM, obesity/IR as well as in depressed diabetic patients. Nevertheless, no definite conclusion about a *specific involvement* of the dACC in IR-pathomechanisms leading to the atypical subtype of depression can be drawn. However, our results strongly support further investigation of such a relationship.

11. Conclusion

Depression often co-occurs with diabetes, worsening the patients' prognosis and increasing overall costs associated with their treatment. Recent research indicates that (at least subgroups of) both diseases may share the same pathomechanisms, namely an involvement of chronic low-grade inflammation (18). Although no causative link is known, we found evidence for our hypothesis that depression and metabolic disorders share similar brain patterns and particularly the role of the dACC was highlighted. The functional neuroanatomy of the dACC explains a syndromal cluster of patients, often referred to as 'atypical', which are characterized by unaffected reward sensitivity, reactive affect and which present blood panels reflecting low-grade inflammation and IR. Our findings support a mechanistic link of the blood profile and phenotype via regionally specific effects at the level of the dACC. Given the metabolic side effects of some antidepressants as well as potential therapeutic alternatives, such a complex disease profile speaks for novel possibilities of integration of clinical characteristics into clinical decision trees.

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Conflict of interest

Prof. Walter performed studies with institutional research support from HEEL and from Janssen Pharmaceutical Research for an IIT on ketamine in patients with MDD, which is unrelated to this investigation.

Prof. Walter has not received any personal financial compensation from third parties. The other co-authors have no conflicts of interest to declare.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.12.020.

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