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Review Article

Severe psychiatric disorders and general medical comorbidities: inflammation-related mechanisms and therapeutic opportunities

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Individuals with severe psychiatric disorders, such as mood disorders and schizophrenia, are at increased risk of developing other medical conditions, especially cardiovascular and metabolic diseases. These medical conditions are underdiagnosed and undertreated in these patients contributing to their increased morbidity and mortality. The basis for this increased comorbidity is not well understood, possibly reflecting shared risks factors (e.g. lifestyle risk factors), shared biological mechanisms and/or reciprocal interactions. Among overlapping pathophysiological mechanisms, inflammation and related factors, such as dysbiosis and insulin resistance, stand out. Besides underlying the association between psychiatric disorders and cardiometabolic diseases, these mechanisms provide several potential therapeutic targets.

Introduction

Psychiatric disorders are a heterogeneous group of conditions primarily marked by behavioral and cognitive symptoms. These conditions are prevalent and associated with significant disability. According to the Global Burden of Disease, psychiatric disorders are among the leading causes of the world's disease burden [1]. Moreover, while the last decades have witnessed a reduction in disability-adjusted life-year—a measure of the gap between the health of a specific population compared with a normative standard—from communicable, maternal, neonatal and nutritional diseases, there was an increase in burden due to injuries and non-communicable diseases, including psychiatric disorders [2].

Compared with the general population, individuals with severe psychiatric disorders, especially schizophrenia and bipolar disorder, also referred in the literature as 'severe mental illness' (SMI), are at risk for increased morbidity with other medical conditions. Patients with SMI have high levels of cardiovascular risk factors and are at increased risk of cardiovascular diseases, including ischemic heart disease, stroke and premature mortality [3–5]. Despite these patients exhibit higher rates of unnatural deaths, such as suicide and accidents, than the general population, medical conditions account for approximately 70% of their causes of death, with cardiovascular diseases contributing approximately 20% to the reduction in their overall life expectancy [6]. Individuals diagnosed with schizophrenia, for instance, have a life expectancy 15–20 years shorter than the observed in the general population. Besides affecting life expectancy, medical comorbidities are implicated in worse clinical outcomes, including increased psychiatric readmissions [7]. Furthermore, metabolic syndrome, diabetes and hypertension are significantly associated with cognitive impairment in people with SMI [8].

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The biological basis for the increased comorbidity between psychiatric disorders and medical conditions, especially metabolic and cardiovascular diseases, is incompletely understood, possibly reflecting shared socioeconomic, lifestyle and biological risks factors, operative pathophysiological mechanisms and/or reciprocal interactions. It is worth mentioning that psychiatric disorders are complex pathophysiological processes, with the involvement of multiple physiological systems beyond the central nervous system (CNS). In this context, psychiatric disorders have been conceptualized not only as the result of brain dysfunction/disease but also as a systemic disorder [9,10].

Recognizing the increased comorbidity and the shared drivers between psychiatric disorders and medical conditions, its impact on clinical outcomes and understanding of its pathophysiological underpinnings have several implications. Clinically, this knowledge can guide diagnostic (e.g., laboratory tests), preventative and therapeutic decisions (e.g., risk factor mitigation, medication selection and non-pharmacological prescriptions) regarding the management of these patients. From health service and policy perspective, it might support systems integration and rational resources allocation. From a research standpoint, it might contribute to identify novel therapeutic targets predicated on identified common operative pathways.

In this manuscript, our goals are to highlight the meaning of medical comorbidities in severe psychiatric disorders or SMI and to discuss their pathophysiological bases focusing on immune/inflammatory mechanisms and related pathways.

Medical comorbidities in psychiatry: an overview

Comorbidity can be defined as the presence of more than one distinct disorder or disease in the same individual. There are related constructs, such as multimorbidity and burden of disease, that are often loosely used interchangeably [11]. While all these concepts share the notion of concurrent diseases, the construct of comorbidity implies an index disease to which other condition(s) is (are) associated. Therefore, from a medical specialty (e.g., psychiatric) standpoint, it makes sense to use the concept of comorbidity instead of others that do not prioritize any condition.

In a person with a psychiatric disorder, the coexistence of one or more medical conditions raises two main questions: (i) what is the clinical impact in terms of management and outcomes? (ii) do they share risk pathways and pathophysiological mechanisms? Regarding the former, comorbid medical conditions, especially metabolic and cardiovascular diseases, are understood to negatively influence the morbidity and mortality of patients with SMI. This also has practical implications for patient management, as the physician must be aware of potential drug–drug interactions, and carefully monitor for emerging symptoms and side effects. It is worth mentioning that people with SMI are usually undertreated and under-investigated for primary and secondary prophylaxis of medical comorbidities, especially cardiovascular diseases [12–15]. This might reflect socioeconomic disadvantage, health system flaws, such as fragmented clinical care, health literacy barriers and negative attitudes from non-mental health clinicians towards 'psychiatric patients' that contribute to worse clinical outcomes in these patients.

In terms of potential pathophysiological commonalities, there are different models by which a psychiatric disorder and a medical disease may be linked. In the causation model, the presence of a medical disease and/or its treatment can cause a psychiatric disorder. Examples of this model include interferon-induced depression, corticosteroid-induced mood disorders (e.g. Cushing's disease and prednisone-induced mania) and behavioral changes due to focal lesions [16–19]. More recently, a great attention has been directed to psychiatric presentations of autoimmune processes, such as autoimmune encephalitis [20]. In these examples, behavioral symptoms are secondary to the medical condition, and usually do not reflect the typical presentation of primary psychiatric disorders, representing only a minor proportion of cases.

Other explanatory models of comorbidity include shared risk factors and overlapping pathophysiological mechanisms. These models are better fitted to explain the complex interactions, frequently involving bidirectional influences, among psychiatric and medical conditions. Obesity, for instance, can be seen as a risk factor for both mood disorders and cardiovascular diseases, and itself shares risk determinants with common mental disorders [21–23]. Through habit changes, including decreased physical activity and increased eating behaviors, different psychiatric disorders are associated with weight gain and obesity. Some eating disorders, such as binge-eating disorder, are even characterized by increased eating behaviors that can lead to obesity and other metabolic conditions. Obesity is an important component of several psychiatric conditions, but currently it is not conceptualized as one [24]. Psychotropic drugs, especially mood stabilizers and antipsychotics, can also induce weight gain and metabolic diseases [25]. Regarding mechanisms, inflammation has been implicated in the pathophysiology of both psychiatric disorders and medical conditions, including obesity, diabetes, atherosclerosis and heart diseases [26,27]. Other operative pathways that are shared between common mental disorders and medical comorbidities include oxidative, endoplasmic reticulum and nitrosative stress, mitochondrial dysfunction and apoptosis. More recently, studies investigating polygenic

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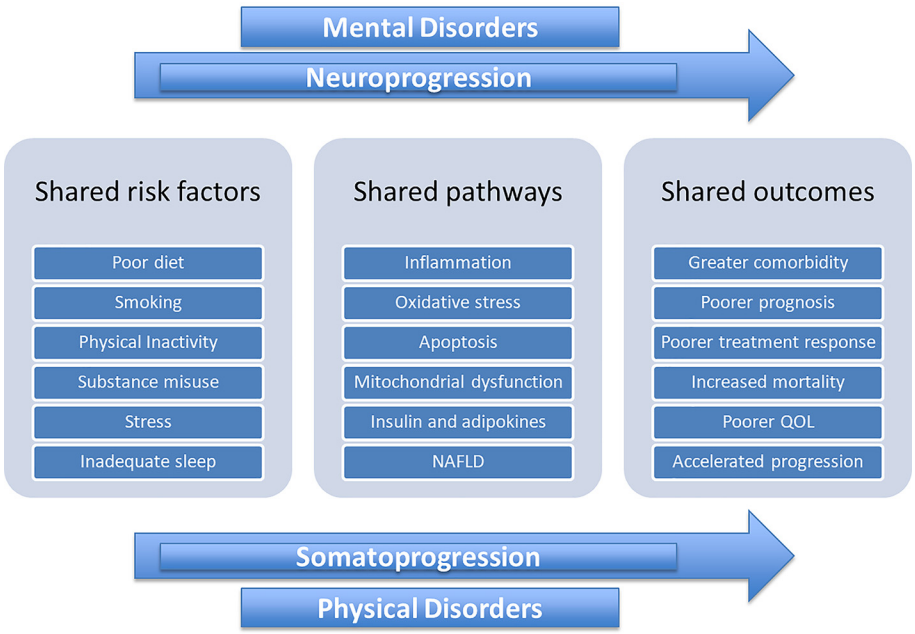

Figure 1. Shared mechanisms between neuroprogression and somatoprogression

Risk factors and pathways that drive the progression of psychiatric (or mental) disorders, termed neuroprogression, overlap with those driving medical comorbidity, termed somatoprogression. Abbreviations: NAFLD, non-alcoholic fatty liver disease; QOL, quality of life.

risk scores have shown genetic overlap between SMI and primarily inflammatory/immune-based diseases, such as inflammatory bowel disease and psoriasis [28,29], and also cardiovascular and metabolic phenotypes [30,31]. In sum, the pathways that drive the progression of neuropsychiatric disorders, termed neuroprogression, overlap substantively with those driving medical comorbidity, termed somatoprogression [32] (Figure 1).

Inflammation as an underlying mechanism and potential therapeutic target

Current evidence linking inflammation to the pathophysiology of SMI

Multiple lines of evidence, from clinic-epidemiological to molecular/genetic, implicate chronic low-grade inflammation in the pathophysiology of severe psychiatric disorders or SMI (Table 1). In mood disorders, for instance, the observed inflammation can be regarded as a prototypical inflammatory response, including abnormal function of sterile inducers, sensors, inflammatory mediators and target tissues (e.g., brain) [33]. High levels of pro-inflammatory cytokines (e.g. tumor necrosis factor alpha [TNF], interleukin 1 beta [IL-1β], IL-6, IL-17 and IL-33), chemokines, soluble cytokine receptors (e.g. sTNFR1) and acute-phase reactants (e.g. C-reactive protein, CRP) have been reported in plasma and cerebrospinal fluid (CSF) of patients with major depressive disorder (MDD) or bipolar disorder (BD), especially during mood episodes [34,35]. A recent cohort study evaluating 737 patients with schizophrenia and 895 patients with BD reported higher plasma levels of IL-18, and increased expression of inflammasome-related genes (NLRP3 and NLRC4) in the blood of patients relative to controls [36]. Polymorphisms in pro-inflammatory cytokine genes, including those encoding IL-1β and TNF, have also been associated with depression and treatment response [37]. These inflammatory changes are termed 'sterile' as they are not associated with specific infections and are best understood as indicating the role of immune mediators as wide-ranging stress response pathways beyond 'bug fighting' functions.

Notwithstanding that inflammation is not universally present in all people with SMI, it plays important roles in their pathophysiology, and systemic levels of related biomarkers have been associated with their clinical progression and severity. Increased serum levels of CRP and IL-6 predicted the development of depressive symptoms in MDD [38], while remission of MDD was linked with a normalization of inflammatory markers [9]. Similarly, serum cytokine concentrations, like IL-6, were associated with disease severity, duration and antipsychotic therapy in schizophrenia

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Table 1 Current evidence linking chronic low-grade inflammation in the pathophysiology of severe psychiatric disorders (e.g. mood disorders)

Molecular	● Increased expression and polymorphisms of immune-related genes (e.g. IL-1β, TNF-α and CRP) ● Activation of intracellular pathways (e.g. MAPK and NF-κB) ● Activated sensors (e.g. TLRs and inflammasome)
Peripheral blood or CNS	● High levels of pro-inflammatory cytokines (e.g. TNF-α, IL-1β, IL-6, IL-17, IL-33) ● High levels of soluble cytokine receptors (e.g. sTNFR1 and sTNFR2) ● High levels of chemokines (e.g. CCL11, CCL2, CCL3, CCL20, IL-8) ● High levels of acute phase proteins (e.g. CRP) ● More endothelial cell activation markers ● Increased levels of adipokines ● More oxidative stress markers ● High levels of autoantibodies
Clinical	● Increased prevalence of autoimmune diseases ● Increased prevalence of general medical comorbidities (cardiovascular diseases, diabetes mellitus and obesity) ● Pro-inflammatory mediators associated with symptomatology, clinical progression and treatment response ● Remission associated with normalization of inflammatory markers

Abbreviations: CRP, C-reactive protein; IL-1β, interleukin 1β; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TLR, Toll-like receptors; TNF-α, tumor necrosis factor α.

[39–41]. In addition, Th17 cells (which are main sources of IL-17) may contribute to neuroinflammation in mood and psychotic disorders through activation of microglia and astrocytes [42]. Inflammation has also been associated with early childhood trauma, a risk factor for diverse psychiatric illnesses as well as treatment non-responsiveness [43]. A double-blind, placebo-controlled, randomized clinical reported that 45% of MDD patients with non-response to antidepressants had a CRP > 3 mg/L, which is an accepted cut-off point for elevated inflammation [44]. Despite promising, the relationship between clinical improvement and peripheral inflammation should be further investigated in longitudinal studies [45,46].

An important question is: how do peripheral cytokines contribute to changes in mood, cognition and behavior? Several pathways through which peripheral inflammatory molecules can be transmitted from the periphery to the brain have been investigated. Peripheral cytokines can reach the CNS and cross the blood–brain barrier (BBB) through transport channels and/or its permeable areas, activating microglia and hence contributing to neuroinflammation. Neuroinflammation is an important mechanism involved in the pathophysiology of several (if not all) psychiatric disorders. The activation of microglia may lead, among other effects, to a positive feedback loop in which cytokines released by activated microglia can further increase inflammation and activate new microglial cells [47]. Inflammation and associated reactive oxygen and nitrogen species can disrupt the BBB, prompting more circulating mediators to reach the brain [48]. Once in the brain, these inflammatory mediators can influence the levels of neurotransmitters and neurotrophic factors, and, as consequence, affect neural circuits implicated in cognition, emotion, and behavior [49]. Indeed, peripheral levels of specific inflammatory cytokines are likely associated with cognitive function [50] and neuroanatomic changes [51]. Pro-inflammatory cytokines may also sensitize afferent sensory nerves (e.g. vagus nerve) innervating peripheral tissues and conveying important information of inflammation into the brain [52].

As not all patients have heightened inflammation, the hypothesis of an 'inflammatory phenotype' subgroup of mood disorders has been explored. Penninx and colleagues, for example, have posited an 'immunometabolic' subtype of depression, associated with atypical clinical features [53]. In theory, patients with immune activation should be more responsive to anti-inflammatory treatments than others [54], although in practice, this has not been borne out as clearly as hoped [55]. Therefore, it remains of theoretical importance to identify patients who would benefit most from anti-inflammatory interventions (see section *Targeting inflammation and related mechanisms for psychiatric treatment and to prevent comorbidities: pharmacological approaches*). Presented as guidance in this context, several risk factors are associated with heightened inflammation, and may constitute an indirect way to assess patient's inflammatory phenotype: older age, early-life stress, medical comorbidities, atypical depression, recurrent depression, obesity, poor sleep, unhealthy diet, sedentary lifestyle, fatigue, pain, smoking, alcohol dependence, vitamin D insufficiency and gender (woman) [56,57]. In a psychiatric context, these seemingly diverse risk factors, including medical comorbidities, are ultimately transduced by immune pathways, emphasising the broad functions of the immune system.

Inflammation as common denominator to SMI and general medical comorbidities

Chronic low-grade inflammation is similarly thought to contribute significantly to the development of medical comorbidities in SMI, including cardiovascular and metabolic diseases [58,59]. Cardiovascular disease is the leading cause of death in BD [60], and patients with BD have significantly higher rates of myocardial infarction [61], stroke [61], atherosclerosis [62] and hypertension [63] than the general population [47,58]. In addition, higher rates of metabolic syndrome [64,65], Type II diabetes mellitus [66,67], dyslipidemia [68], gout [69], osteoporosis [70,71], cancer [72] and chronic obstructive pulmonary disease [73,74] have also been observed in patients with mood disorders. Similar scenario has been described for patients with schizophrenia [8–10]. Conversely, in patients with chronic diseases, the lifetime prevalence of MDD is 2- to 3-fold higher than in general population, reaching up to 40% [59]. One in four adults with Type II diabetes experienced depression [66].

These clinical facts highlight a strong association between SMI and inflammation-related chronic medical conditions. However, they do not provide evidence of causality: it is largely unclear whether SMI increases the risk for these conditions, whether a pre-existing inflammatory condition increases the risk for developing SMI or whether both are consequent to shared risk factors that drive inflammation. This interaction may be bidirectional, with SMI and inflammation-related conditions fueling each other [47], with specific genetic and environmental factors (including early-life stress) increasing the risk for each of them.

Association of autoimmune diseases and autoantibodies with SMI

People with mood disorders, notably those with BD, have increased frequency of autoimmune conditions, such as rheumatoid arthritis and thyroid diseases [75]. Conversely, patients with systemic autoimmune diseases have an increased risk for developing mood disorders [76].

Previous cohort studies have further indicated the link between autoimmunity and BD. Following 3.57 million births and identified 10,000 patients with BD, a cohort study revealed that a history of Crohn's disease, Guillain–Barré syndrome or autoimmune hepatitis was associated with greater risk for developing BD [77]. The prevalence of BD among patients with systemic lupus erythematosus (SLE) was greater than matched controls [78], while women with SLE may present a 6-fold increase in the incidence of BD [79]. Similarly, the prevalence of depression was much higher in multiple sclerosis and rheumatoid arthritis compared to the general population [80,81]. Patients with multiple sclerosis also have up to 30-fold increase in the incidence of BD [82]. It is worth emphasizing that, in clinical contexts, depression cannot be solely explained as a psychological reaction to an illness. In multiple sclerosis, for example, structural damage of the brain accounts for at least 40% of the estimated frequency/severity of depressive symptoms [80]. Furthermore, the overall prevalence of autoimmune and allergic diseases was around 45% in BD patients [83], almost 2-fold higher than the estimated prevalence in the general population. Atopic disorders, and asthma, in particular, are associated with a higher risk for developing BD [84,85]. It is plausible that the same immune pathways that are involved in the progression of autoimmune diseases may also be responsible for developing comorbid mood disorders.

Thyroid diseases are often associated with psychiatric disorders. Previous studies have reported that patients with MDD or BD had higher frequency of autoimmune thyroiditis [86,87]. A higher lifetime prevalence of depression was reported in patients with subclinical thyroid dysfunction [88], while increased thyroid peroxidase antibodies associated with increased lifetime diagnosis of MDD [89]. There is also evidence of increased prevalence of circulating thyroid autoantibodies in BD [87], independent of lithium exposure [90]. Several other autoantibodies have been identified higher in comparison with controls, including autoantibodies against gliadin [91] and N-methyl-d-aspartate receptor (NMDAR) [92]. The co-occurrence of thyroid and anti-brain antibodies in MDD and schizophrenia were associated with clinical progression and reduced treatment response following 6 weeks [93]. There is evidence that oxidatively damaged epitopes can form immunogenic neo-epitopes that drive the process of autoimmunity [94]. Taken together, these findings suggest a link between autoimmunity and SMI, especially mood disorders.

Putative mechanisms underlying inflammation in SMI

Several mechanisms can explain the inflammatory phenotype reported in SMI which have been confirmed by clinical and preclinical studies [95]. First, it should be noted that inflammatory mediators are physiologically produced by different tissues, including immune cells, adipose tissue (i.e., adipokines), muscle fibers (i.e., myokines), gut and brain. Therefore, it is likely that multiple mechanisms contribute to the chronic low-grade inflammation observed in SMI (Figure 2).

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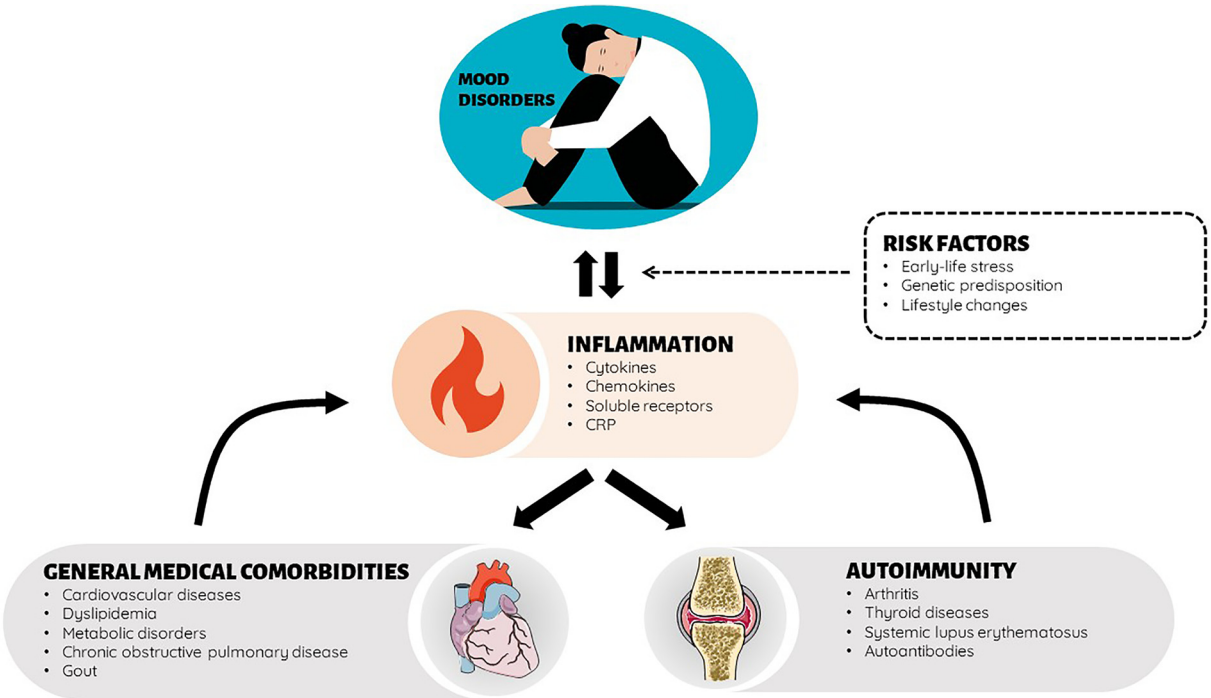

Figure 2. The central role played by inflammation in the comorbidity between severe psychiatric disorders (e.g. mood disorders) and general medical conditions

Peripheral biomarkers of inflammation (e.g., C reactive protein, CRP; cytokines) are found elevated in these patients, implicating inflammatory mechanisms in their pathophysiology. Inflammatory mechanisms are also involved in the pathogenesis of other medical conditions, especially cardiovascular, metabolic and autoimmune diseases.

Lifestyle-related changes

The association between severe psychiatric and metabolic disorders is bidirectional and involves multiple interconnected mechanisms. The direction of causation is a matter of debate, and actually may vary in individual cases. Patients with SMI frequently have negative lifestyle habits that predispose to systemic inflammation [96]. These lifestyle changes include a sedentary lifestyle, poor sleep, unhealthy diet, and smoking—all of which are important risk factors for non-communicable diseases and can induce chronic low-grade inflammation [97]. Some of these lifestyle changes, including sedentary and eating behaviors, alongside medication can also promote weight gain [25]. Carbohydrate craving, for instance, is a symptom commonly reported by patients with seasonal affective disorder who increase the consumption of ultra-processed foods during periods of mood symptoms, usually in the Fall and Winter, with subsequent weight gain and risk of obesity [98]. Furthermore, antipsychotics, particularly certain first- (e.g. chlorpromazine, thioridazine) and second-generation (e.g. olanzapine and clozapine) drugs, can induce marked weight gain and increased adiposity as side effects [99]. Antidepressants also have complex effects on body weight and metabolic parameters. Antidepressants can promote weight gain and increase the risk of developing obesity-related metabolic changes, such as diabetes mellitus Type 2 [100]. As for antipsychotics, this association seems to depend on treatment duration and the subclass of the antidepressant used [101]. Monoamine oxidase inhibitors and tricyclics can cause weight gain and favor the development of obesity-related metabolic complications, including worse glycemic control [100,102,103], while serotonin re-uptake inhibitors (SSRIs) can promote short-term weight loss [103,104]. Despite these general tendencies, the results of clinical trials on the effect of antidepressants on weight are not homogeneous, and vary according to the study design, the sample characteristics, the use of combination therapy, and even different drugs in the same subclass [105–107].

Relevant to this discussion, obesity and mood disorders share key inflammatory mechanisms, and both are characterized by oxidative stress and mitochondrial dysfunction [108,109]. Obesity is marked by chronic inflammation with high plasma levels of TNF-α, IL-6, and CRP, with up to 30% of circulating IL-6 derived from adipose tissue [110]. Proinflammatory cytokines secreted by adipose tissue cells can stimulate the hypothalamic–pituitary (HPA)

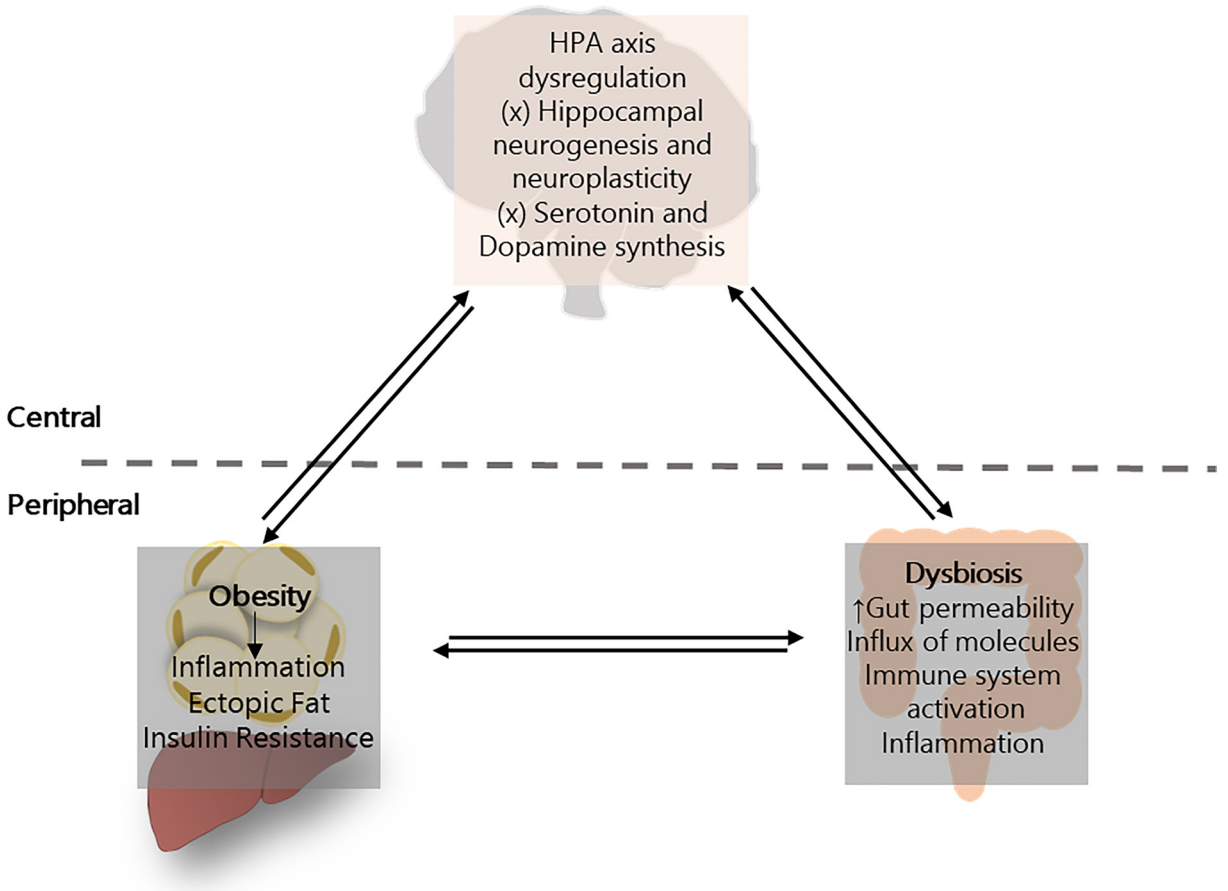

Figure 3. Mechanisms underlying the link between obesity and severe psychiatric disorders

Obesity is characterized by a low-grade chronic inflammation which favors the development of insulin resistance and ectopic fat accumulation. Individuals with obesity-related metabolic complications and/or psychiatric disorders exhibit alterations in gut microbiota composition (so-called dysbiosis), associated with an increase in gut permeability and activation of the immune system. Dysbiosis, inflammation and insulin resistance can cause dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, impair hippocampal neurogenesis and neuroplasticity, and influence neurotransmitters synthesis, favoring the development of psychiatric disorders. Symbols: (x) impairment

axis, leading to metabolic imbalances, such as hypercortisolemia, that can increase adipose tissue mass [96]. In addition, poor diet and obesity have been associated with marked microbiota changes that may contribute to chronic low-grade inflammation (as discussed below) (Figure 3).

Inadequate physical activity is also a well-known risk factor for several medical conditions (e.g., cardiovascular disease, diabetes, cancer, osteoporosis, etc.) and mood disorders. Individuals who are physically active present lower inflammation levels than sedentary ones [111]. Moreover, mounting evidence supports the notion that exercise has antidepressant effects [112]. Sleep loss has also been associated with increased production of proinflammatory cytokines and related cellular inflammatory signaling [113].

Insulin resistance and metabolic changes

The activation of inflammatory pathways, a common denominator to psychiatric and metabolic disorders, favors insulin resistance development through the activation of serine kinases (e.g., c-Jun N-terminal kinase (JnK) and IκB kinase b (IKKβ)) by pro-inflammatory cytokines with subsequent phosphorylation of insulin receptor substrate-1 and blockage of its intracellular signaling [114]. Insulin resistance is a critical factor in the pathophysiology of obesity-related metabolic complications, and has been associated with unfavorable outcomes in patients with SMI [115]. For instance, patients with BD and insulin resistance and/or diabetes mellitus Type 2 (DM2) have higher rates of rapid cycling, lithium-refractory treatment, and disability compared with euglycemic BD patients [116,117]. The

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coexistence of DM2 and mood disorders increases the rate of cardiovascular events and, as a consequence, the mortality rate [118,119]. Insulin resistance is more prevalent among patients with BD than the general population, even in newly diagnosed and drug naïve patients [115,120].

Hypothalamic deficiency in insulin signaling has been implicated in HPA axis dysregulation, which can influence the physiological response to stress, including enhanced inflammatory response [121]. Patients with DM2 have an altered diurnal pattern of cortisol levels when compared with individuals without DM2, with a flatter cortisol decline slope during the day and higher levels in the evening [122]. Insulin resistance can impair hippocampal neurogenesis and neuroplasticity [123], phenomena frequently associated with the pathophysiology of severe psychiatry disorders [124–126].

It is worth mentioning that patients with SMI may display other metabolic alterations. Elevated uric acid levels, for example, have been described in patients with BD, especially during manic states [127]. Depression is also associated with dysregulated adipokine signaling, which is likely a linking element with metabolic dysfunction [128,129].

Persistent activation of the stress system

Psychiatric disorders, notably anxiety and mood disorders, have been conceptualized as chronic stress disorders given their long-lasting dysfunctional changes of the stress system. Exposure to daily life stressors is associated with activation of the stress system, eliciting evolutionary conserved neuroendocrine responses aimed to restore homeostasis. The stress responses involve the activation of the HPA axis and the sympathetic nervous system with consequent release of glucocorticoids (cortisol) and catecholamines (norepinephrine and epinephrine), respectively. If these evolutionary conserved responses are inadequate, excessive, or prolonged, they can impair the functioning of the brain, metabolism, and immune response [130].

The constant and/or recurrent exposure to high cortisol levels observed in chronic stress disorders, as in anxiety and mood disorders, may lead to steroid resistance (insensitivity) to the suppressive effects of glucocorticoids [33]. Indeed, high cortisol concentrations have been consistently reported in mood disorders, especially MDD, but patients display hyporesponsive glucocorticoid receptor (GR) in the brain and peripheral tissues [131–133]. Without the adequate inhibitory control of glucocorticoids, the net result is enhanced immune responses, as shown by increased levels of activated cells and higher production of pro-inflammatory cytokines [33]. In addition, pro-inflammatory cytokines are known to up-regulate the HPA axis, increasing systemic cortisol levels [130], as well as inducing glucocorticoid resistance by disrupting GR expression and function, leading to unrestrained inflammatory responses [134]. Accordingly, euthymic BD patients exposed to acute psychosocial stress (i.e., Trier Social Stress Test, TSST) had significantly attenuated stress responses, as shown by reduced salivary cortisol levels and blunted heart rate in comparison to healthy controls [133]. Furthermore, enhanced activated immune responses were observed in BD following stress as compared to controls, in line with steroid resistance. In conclusion, failure to develop adequate stress-related neuroendocrine responses could lead to overshooting of immune responses and, hence, underlie the immune imbalance observed in SMI.

Immune activation and impaired immunoregulation

It has been suggested that chronic low-grade inflammation may also result from activated innate and adaptive (T and B lymphocytes) immune responses and impaired immunoregulation [26]. Those with mood disorders, for example, display higher counts of innate immune cells (ex., CD14+ monocytes and neutrophils), increased neutrophil–lymphocyte ratios, activated macrophages and T cells, as well as intracellular signaling involved with inflammation, cell activation and proliferation [135,136]. Patients with BD also have increased mRNA M1-like signature (IL-6 and IL-1β) in contrast with decreased M2-like signature (CCL22 and IL-10) in peripheral blood compared with healthy controls [137]. The M1/M2 paradigm defines classically activated (M1-type) and alternatively activated (M2-type) macrophages. The M1-type macrophages have been associated with pro-inflammatory responses in several disease models whereas the M2-type profile has been related to anti-inflammatory state or tissue remodeling. A recent study reported that a major dysfunction of NK cells in first-episode psychosis (schizophrenia and BD) correlated with psychotic, manic and depressive symptoms [138]. Previous studies have shown that lymphocytes of BD subjects stimulated *in vitro* produced higher levels of pro-inflammatory (Th1/Th17) cytokines than healthy controls [139]. These findings concur with recent data in MDD, indicating increased numbers of CD4+ T cells expressing IL-17 and TNF-α [140].

Most of the current literature on this topic reported immune changes at baseline—i.e., without the influence of realistic psychosocial stressors that are important triggers of clinical progression and presentation. To overcome this limitation, a previous study reported that euthymic BD patients following the TSST had lower proportions of regulatory T cells than controls, and this could partially explain the activated T-cell profile observed in these patients

[133]. Psychosocial stress may activate intracellular pathways involved in immune activation and inflammation. One candidate pathway is the NF-κB, a master transcription factor for pro-inflammatory genes. A seminal study reported increased NF-κB signaling in peripheral blood mononuclear cells (PBMCs) of healthy volunteers following TSST, which was mediated via adrenergic stimulation [141]. Cells of patients with MDD or BD had overactivated NF-κB and MAPK intracellular cascades following TSST [133,142], which were associated with increased plasma levels of IL-6. Therefore, stress-related disorders engage evolutionary conserved transcription pathways implicated in inflammatory response.

In addition, mounting evidence indicates that impaired immunoregulatory mechanisms may also play a role in this activated immune profile, as reviewed elsewhere [26]. Patients with mood disorders have low numbers of innate (e.g. myeloid-derived suppressor cells) and adaptive regulatory cells (e.g. CD4+CD25+FoxP3+ or Tregs). In addition, Treg cells were predictors of treatment response in MDD, as they were found increased in patients responsive to antidepressants [143]. A lowered proportion of IL-10-expressing Treg cells was observed in BD [144], indicating impaired function, since IL-10 is a potent regulatory cytokine. These steady state immunoregulatory mechanisms are important to controlling activated immune responses, preventing autoimmunity and to refrain chronic low-grade inflammation. For instance, experimental ablation of Tregs in mice leads to persistent inflammation [145]. These data strongly indicate an activated T-cell profile, partly explaining the higher risk of autoimmune diseases in mood disorders

Imbalanced neurotransmitter systems

Immune activation and inflammation increase the activity of enzymes that participate in the kynurenine (KP) and tetrahydrobiopterin (BH4) pathways, influencing the metabolism of serotonin and dopamine [146]. Inflammatory cytokines can induce the expression and activity of the enzyme GTP-cyclohydrolase 1 (GTP-CH1), the rate-limiting enzyme in the synthesis of tetrahydrobiopterin (BH4), an essential cofactor for nitric oxide synthase isoforms (NOS) and the phenylalanine, tyrosine and tryptophan hydroxylases (PAH, TH and TPH, respectively) responsible for the synthesis of monoamines. GTP-CH1 catalyzes the conversion of guanosine triphosphate (GTP) into 7,8-dihydroneopterin triphosphate (NH2TP), which is converted by 6-pyruvoyl-tetrahydropterin synthase (PTPS) to 6-pyruvoyltetrahydrobiopterin (6-PTP) that will form BH4 by sepiapterin reductase. In humans, the activation of GTP-CH1 leads to an accumulation of NH2TP and production of neopterin at the expense of BH4 due to a relative deficiency of PTPS [147]. Furthermore, the activation of inducible NOS by inflammatory mediators can deviate BH4 away from monoamine hydroxylases influencing the synthesis of dopamine and serotonin [146] (Figure 4).

KP is the main route of tryptophan metabolism, the precursor of serotonin. Pro-inflammatory cytokines upregulate the enzyme indoleamine 2,3-dioxygenase (IDO), which catalyzes the conversion of tryptophan (TRP) into kynurenine (KYN). Downstream this first rate-limiting step, the KP segregates into two major branches. The first branch is catalyzed by kynurenine aminotransferases (KATs) that convert KYN into kynurenic acid (KYNA), with reportedly neuroprotective roles [148]. The second branch is catalyzed by kynurenine-3-monooxygenase (KMO) that converts kynurenine into 3-hydroxykynurenine (3-HK) and other neurotoxic metabolites, including hydroxyanthranilic acid (3-HAA) and quinolinic acid (QUIN) [146]. KMO is also up-regulated by inflammatory stimuli, suggesting that inflammation can divert tryptophan from the synthesis of serotonin to the synthesis of neurotoxic metabolites [149,150]. A recent meta-analysis of clinical studies assessing KP metabolites in patients with mood disorders and schizophrenia showed an increased KYN:TRP ratio in the serum/plasma of patients with MDD and schizophrenia, and a decreased KYNA:QUIN ratio in patients with MDD and BD, corroborating the view of a shift in the TRP metabolism away from serotonin to the KP and, more specifically, its 'neurotoxic branch' in these SMI [151].

Inflammaging and immunosenescence

Mood disorders and schizophrenia are associated with several features of accelerated aging [152,153]. These features encompass cell senescence, immune and structural/neuroanatomical changes resembling those found during physiological aging. As consequence, SMI are independent risk factors of aging-related diseases, including Alzheimer's disease and related dementias (ADRD) [154].

Biological aging can be defined by different hallmark changes, including cellular senescence, telomere attrition, mitochondrial dysfunction, impaired nutrient sensing, genomic instability, epigenetic alterations, stem cell exhaustion, loss of proteostasis and altered intercellular communication [155]. These hallmarks of biological aging have been observed prematurely in adults with mood disorders and schizophrenia, indicating these conditions as models of accelerated aging [154,156]. One strong candidate marker of altered intercellular communication is the 'inflammaging' concept, which postulates that there is a gradual increase in chronic low-grade sterile inflammation associated with

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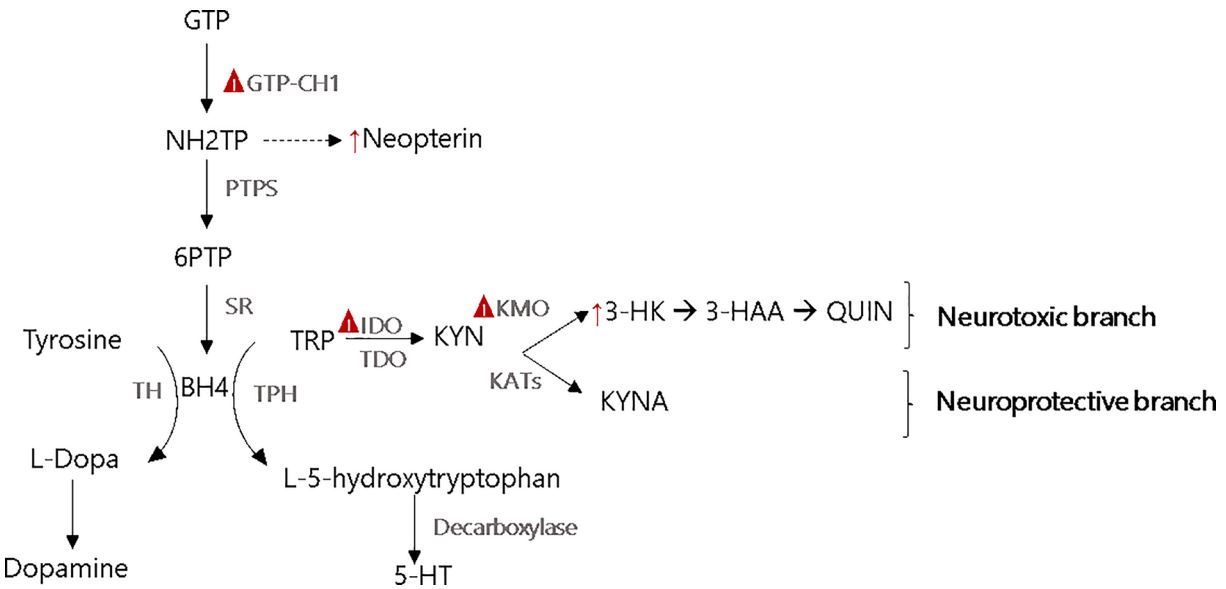

Figure 4. Tetrahydrobiopterin (BH4) and kynurenine (KP) pathways under inflammatory stimuli

Immune activation and inflammatory stimulation increases the enzyme GTP-cyclohylase 1 (GTP-CH1) activity that catalyzes the conversion of guanosine triphosphate (GTP) into 7,8-dihydroneopterin triphosphate (NH2TP). NH2TP is converted by 6-pyruvoyl-tetrahydropterin synthase (PTPS) to 6-pyruvoyltetrahydrobiopterin (6PTP) that will form BH4 (a cofactor of tryptophan hydroxylase [TPH] and tyrosine hydroxylase [TH]). In humans, the activation of GTP-CH1 leads to an accumulation of NH2TP and production of neopterin at the expense of BH4, decreasing the production of dopamine and serotonin. Inflammatory cytokines also activate the enzymes indoleamine 2,3-dioxygenase (IDO) and kynurenine-3-monooxygenase (KMO), deviating tryptophan (TRP) from the synthesis of serotonin to the synthesis of neurotoxic metabolites: 3-hydroxykynurenine (3-HK), hydroxyanthranilic acid (3-HAA), and quinolinic acid (QUIN). Abbreviations: 5-HT, 5-hydroxytryptamine; KAT, kynurenine aminotransferase; KYNA, kynurenic acid; SR, sepiapterin reductase; TDO, tryptophan 2,3-dioxygenase.

increased age-related morbidity and mortality [157]. Inflammaging and immunosenescence are thought as important biological drivers for the age-related morbidity observed in psychiatric conditions.

At the cellular level, aging translates into telomere shortening. Indeed, telomere attrition is one of the most robust markers of replicative cellular senescence. When the telomere length reaches a critical length, cell functioning becomes unstable, leading to cellular senescence. Many studies reported a greater telomere erosion in patients with mood disorders and schizophrenia [153,158,159]. Telomere shortening in BD, as compared to healthy controls, represented 13 years of accelerated aging [160]. This is not far from the shorter lifespan observed in people with the disorder, as females and males with BD died, respectively, 9.0 and 8.5 years earlier than the general population [161]. In addition, non-affected siblings of BD patients had shorter telomere length compared to unrelated controls [162], suggesting that telomere attrition and cellular senescence are possible trait characteristics of BD. Patients with MDD had greater telomere erosion in a 2-year follow up than healthy controls [163]. Intriguingly, inflammation and telomere shortening show a bidirectional association: a pro-inflammatory state seems to contribute to aging and telomere dysfunction, and telomere attrition is able to induce low-grade inflammation [164]. Several features of premature aging have been reported in adults with chronic medical conditions as well, including as cardiovascular, metabolic, autoimmune, neurodegenerative diseases and cancer [165]. These features involve inflammaging, oxidative stress, telomere shortening, immunosenescence and cellular senescence—which were found predictive of poor clinical outcomes. It is important to be proactive in conceptualising this domain since frontline therapies such as lithium are associated with longer telomere length [166]. Previous preclinical studies have shown that lithium treatment decreased oxidative stress and increased telomerase activity [167]. However, there is no clear mechanistic evidence linking lithium-related molecular effects, its clinical efficacy and the modulation of telomere dynamics. Future studies should integrate the mechanistic effects using human-derived cell lines with data obtained from longitudinal studies to shed light on the potential association between telomere attrition, lithium mechanisms of action and its therapeutic efficacy.

High numbers of late-differentiated $CD8^+CD28^-$ T cells were also reported in parallel with shortened telomere length in peripheral blood mononuclear cells (PBMCs) of patients with BD, suggesting premature immunosenescence

[139,158]. Increased numbers of $CD8^+CD28^-$ T cells are similarly observed during healthy aging [168], in chronic viral infections, and in autoimmune disorders like rheumatoid arthritis and multiple sclerosis [158,169]. These cells are defined as senescent (i.e. reached replicative senescence) and possess various cytotoxic and inflammatory properties which may contribute to inflammaging by secreting large amounts of interferon (IFN)-γ, TNF-α, IL-1β and IL-6 upon stimulation [170]. The higher counts of senescent T cells may contribute to relevant pathophysiological changes in these psychiatric conditions, such as cognitive impairment. Interestingly, increased counts of senescent $CD8^+CD28^-$ T cells were associated with poor memory performance in rheumatoid arthritis [171]. The mechanism by which senescent T cells regulate cognition is largely unknown, but there is preliminary evidence showing that senescent effector memory T cells can activate microglia [172].

Targeting inflammation and related mechanisms for psychiatric treatment and to prevent comorbidities: pharmacological approaches

As discussed above, inflammation is an important aspect of the pathophysiology of psychiatric disorders, not only being strongly associated with medical comorbidities, but also having direct and indirect effects on brain cells and thus on cognitive, emotional and behavioral symptoms. In this context, it is reasonable to postulate that anti-inflammatory interventions may be of great therapeutic value for psychiatric patients with medical comorbidities. While this perspective has not been specifically addressed, preclinical and clinical studies have shown the potential therapeutic benefit of anti-inflammatory based strategies in the treatment of psychiatric disorders.

Traditional pharmacological treatments for mood disorders have anti-inflammatory effects. Antidepressants (e.g. selective serotonin reuptake inhibitors, SSRIs) and lithium have well-established anti-inflammatory effects, decreasing the production of pro-inflammatory cytokines (TNF-α, IL-1 and IFN-γ), increasing the release of anti-inflammatory cytokines (IL-10), attenuating cyclooxygenase (COX)-2 expression and inhibiting NF-κB activity [173–175]. Accordingly, clinical benefits of these drugs might be achieved by 'normalization' of neurochemical imbalances, and by 'normalization' of systemic inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs) and monoclonal antibodies targeting cytokines have been investigated for the treatment of mood disorders and schizophrenia, with promising but inconsistent results. A recent meta-analysis showed that nonsteroidal anti-inflammatory drugs (e.g., celecoxib—a selective COX-2 inhibitor) reduced depressive symptoms compared with placebo, and MDD patients with higher levels of inflammatory markers at baseline benefited most [176]. This potential therapeutic effect of an anti-inflammatory strategy in a subgroup of MDD patients with an 'inflammatory phenotype' was confirmed in a trial with anti-TNF antibody [44]. A double-blind, randomized, placebo-controlled study with BD patients treated with celecoxib revealed that intervention yielded a faster decrease in depression scores compared with placebo [177]. Another randomized clinical trial showed that modulation of the inflammation via celecoxib had clinical benefits for treatment-resistant BD [178]. In contrast, the largest clinical trial of an anti-inflammatory therapy to date using aspirin showed that it worsened depression [179], despite the fact that meta-analyses have shown that aspirin and statins have antidepressant efficacy [180,181]. Besides conflicting results, the effect size of the positive treatments is small and their potential for clinical translation remains to be determined.

Previous studies with experimental rodent models of depression and mania also demonstrated therapeutic effects of COX-2 inhibition [182–184]. As there is no well-established animal model of BD, preclinical studies rely on independent depression and mania models, especially the latter [185]. Multiple mechanisms have been implicated in the observed therapeutic responses, including protection against neuronal injury through reduction of oxidative stress and pro-inflammatory cytokines. For instance, the efficacy of lithium treatment in a rat model of mania induced by dextroamphetamine was related to reduced circulating and brain levels of pro-inflammatory cytokines [182]. Together these pieces of evidence suggest that anti-inflammatory therapies have potential in the management of severe psychiatric disorders.

Given the common mechanisms underlying severe psychiatric and metabolic diseases pathophysiology, some therapeutic strategies may be beneficial to both conditions. Previous studies have suggested the positive effects of antidiabetic drugs as a therapeutic strategy for patients with mood disorders [186–188]. Guo et al. [2014] observed that patients with MDD and DM2 treated with metformin (1,000 mg/day) for 24 weeks had a concomitant and more significant reduction in depressive symptoms and HbA1c plasma levels, an estimate of the average glucose blood levels over the previous 3 months, when compared with those who received placebo [188]. Furthermore, depressive symptoms, as measured by the Hamilton Rating Scale for Depression, positively correlated with HbA1c plasma

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level [188]. Abdallah et al. [2020] observed higher response and remission rates of depression with metformin (1,000 mg/day) as an adjunct strategy to antidepressant treatment with fluoxetine (20 mg). Calkin et al. showed that in patients with BD who were treated with metformin and whose insulin resistance improved, there was a substantial and parallel improvement of mood symptoms [189]. More recently, clinical trials have shown antidepressant effect of novel antidiabetic and weight-reducing drugs, such as thiazolidinediones (peroxisome proliferator-activated, PPAR γ agonists) [190] and glucagon-like peptide 1 (GLP-1) functional agonists [191]. Besides peripheral effects on insulin resistance, these drugs can cross the blood–brain barrier and play central roles, such as preventing neuronal apoptosis and improving neuronal structuring, which can contribute to antidepressant effects [191].

Antidiabetic drugs have also been suggested as a strategy to prevent the metabolic effects of antipsychotics [192]. Despite the limited number of high quality and/or large randomized controlled trials, meta-analyses have suggested the positive effect of metformin to prevent weight gain and improve glucose parameters in patients with schizophrenia and/or BD taking antipsychotics [193–195]. A better result in preventing antipsychotic-induced weight gain can be achieved when metformin is associated with lifestyle and dietary interventions. A randomized controlled trial involving 128 first-episode schizophrenia patients taking antipsychotics found that the group that received lifestyle-plus-metformin had superior effect on reducing weight, BMI, and waist circumference compared with groups that received placebo or metformin alone. Lifestyle interventions included changes in diet and physical activity, in addition to psychoeducational program focused on lifestyle and behavioral techniques to weight management [196]. These findings highlight the relevance of lifestyle changes along with psychoeducational approaches as adjunct strategies to the pharmacological treatment of medical comorbidities in psychiatric disorders. It is worth highlighting that psychosocial interventions are established non-pharmacological strategies for patients with SMI but frequently overlooked in the context of cardiometabolic treatment [197].

Targeting inflammation and related mechanisms for psychiatric treatment and to prevent comorbidities: non-pharmacological approaches

Non-pharmacological approaches can benefit both psychiatric disorders and medical comorbidities. Dietary intervention and regular physical activity, common non-pharmacological approaches in the management of metabolic diseases, can prevent and/or improve psychiatric conditions [198,199]. A relatively limited number of randomized clinical trials have been carried out to specifically evaluate the therapeutic effect of dietary interventions in psychiatric disorders, and most of them focused on mood disorders.

The consumption of a dietary pattern called the 'Mediterranean diet' was effective in preventing and treating MDD [200–202]. Two randomized controlled trials observed significant reduction in depressive symptoms in patients with MDD treated with a dietary intervention based on the Mediterranean diet with [201] or without [200] omega-3 supplementation when compared with psychosocial support. The Mediterranean diet is an established cardiovascular protective diet characterized by high consumption of olive oil and nuts, fruits, vegetables, and whole grains, which are sources of monounsaturated fats, flavonoids, and dietary fiber, all components supposedly responsible for inducing an anti-inflammatory profile [203,204]. A recent randomized clinical trial involving patients with BD observed a reduction in variability in mood, energy, irritability, and pain, as measured by a twice-daily, 12-week ecological momentary analysis paradigm, in a group of patients that received a diet containing a high omega-3: omega-6 ratio [205].

In contrast, diet exhibiting a pro-inflammatory profile, as measured by the Dietary Inflammatory Index (DII), was associated with an increased risk of MDD [206]. DII calculation considers the effect of 45 food or food components (nutrients and bioactive components) on six serum inflammatory markers (IL-1β, IL-4, IL-6, IL-10, TNF, and CRP). Each food parameter is classified as pro-inflammatory (when significantly increased IL- 1β, IL-6, TNF, or CRP or decreased IL-4 or IL-10) or anti-inflammatory (when significantly decreased IL- 1β, IL-6, TNF, or CRP or increased IL-4 or IL-10) getting a predetermined score. A positive score (+1) means a pro-inflammatory effect and a negative [-1] score means an anti-inflammatory effect [207]. Among food parameters with a positive score are carbohydrates, cholesterol, saturated and *trans* fatty acids, all present in high quantity in ultra-processed and animal foods [207]. Of note, it is well-known that increased consumption of dietary sources of these nutrients is associated with a higher risk of cardiovascular diseases [208].

Besides diet, regular physical activity have well documented benefits to mental health [199,209]. A large cross-sectional epidemiological study involving more than one million American adults found that people who had physical activity had a reduction in approximately 40% of the number of days of negative self-reported mental health

[209]. The mechanisms underlying the exercise-induced antidepressant effects remain elusive, being proposed increase in the production of brain-derived neurotrophic factor (BDNF), a neurotrophin implicated in neurogenesis, neuroplasticity, and mood disorders pathophysiology, improved mitochondrial bioenergetic efficiency and activation of the endocannabinoid system [210].

A growing number of studies have shown the pivotal role of human microbiota (i.e., the microorganism community that inhabits our body) in health, with greater attention to the gut microbiota [211]. Developments in gene sequencing methods and analyses made the investigation of microbiota composition possible and affordable contributing to the recent advance of the field [211]. Compared with healthy individuals, patients with severe psychiatric disorders exhibit marked alterations in microbiota with an imbalance in their composition and diversity, a phenomenon called 'dysbiosis' [212]. Dysbiosis can contribute to the pathophysiology and/or be the consequence of biological and behavioral processes implicated in SMI. The gut microbiota of patients with mood disorders and schizophrenia have reduced amount of bacteria genus associated with the production of short-chain fatty acids (SCFAs, such as acetate, propionate, and butyrate) (e.g., *Faecalibacterium* and *Coprococcus*) and an increase in genus associated with pro-inflammatory pathways (e.g., *Eggerthella*) [213]. Similarly, individuals with obesity and related metabolic diseases, such as DM2 and nonalcoholic fatty liver disease (NAFLD), exhibit distinct gut microbiota signatures. A large metagenome-wide association study showed that patients with DM2 have a decrease of butyrate-producing bacteria in their gut microbiota (e.g., *Clostridiales sp. SS3/4, Eubacterium rectale, Faecalibacterium prausnitzii, Roseburia intestinalis*, and *Roseburia inulinivorans*) and increase in opportunistic pathogens bacteria (e.g., *Bacteroides caccae, Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum, Eggerthella lenta* and *Escherichia coli*) [214]. Another study showed association between gut microbiota composition and progression of NAFLD since patients with advanced fibrosis exhibited significant changes in phylum and species of gut bacteria community compared with patients with mild/moderate NAFLD [215]. In this context, it is noteworthy that NAFLD is disproportionately more common in people with diverse mental health problems and is a neglected element of the metabolic syndrome in such people, where it serves as an amplifier of information as well as other dysregulated metabolic pathways [216].

From a pathophysiological perspective, dysbiosis has been associated with an increase in gut permeability and influx of molecules (e.g., LPS) from the lumen, activating immune cells and inflammatory response [217–219]. Microbiota also participates in mechanisms associated with cognition and emotion regulation. Therefore, microbiota modulation strategies can ameliorate gut permeability, prevent or minimize inflammatory response and help regulate brain-mediated processes. For example, the lack of microbiota observed in germ-free (GF) mice impairs the synthesis of serotonin [220,221] and HPA axis reactivity [222,223]. Moreover, GF mice exhibit behavioral changes, including reduced anxiety- and depression-like behaviors [220,222]. In preclinical studies, the use of probiotics (i.e., live microorganisms that confer a health benefit on the host) has already been associated with down-regulation of HPA axis activity [224], increased production of the neurotransmitter gamma-aminobutyric acid (GABA; an effect observed in certain pharmacological antidepressant treatments) [225,226] and TRP [227].

In clinical studies, gut microbiota modulating strategies, such as probiotics, dietary fiber consumption and fecal microbiota transplantation (FMT), influenced positively obesity-related metabolic complications, such as DM and dyslipidemia [228–230]. The use of probiotics was also able to reduce circulating levels of inflammatory (CRP and IL-10) and oxidative stress (malondialdehyde) biomarkers, and decrease depressive symptoms in patients with psychiatric disorders [231]. This potential antidepressant effect of probiotics is more evident among patients with mood disorders (compared with people from the general population without a formal psychiatric diagnosis) and in studies using multiple strains of bacteria [232,233]. The use of prebiotics (i.e. nutrients for beneficial microorganisms) [234] was also more effective when given to individuals with depression compared with people without psychiatric diagnosis [235]. Besides using specific strains of bacteria, other strategies, especially FMT, i.e. transference of microorganisms from stool samples of a healthy donor, showed positive effects in the treatment of mood disorders [236–239]. However, the results were relatively short lasting (approximately 3–6 months) given the high costs and complex procedures involved [236]. Recently, Meyyappan et al. [2022] showed the promising effect of Microbial Ecosystem Therapeutics-2 (MET-2), an alternative to FMT, in a phase 1, open-label trial involving 12 adults diagnosed with MDD and/or generalized anxiety disorder. MET-2 determined a significant reduction in depressive and anxiety symptoms over ten weeks of follow-up (8 weeks of treatment). MET-2 consists of oral ingestion of capsules composed of 40 different strains of gut bacteria from a healthy donor [240].

In sum, pharmacological or non-pharmacological strategies that target the prevention and treatment of metabolic abnormalities seem to improve psychiatric symptoms, especially mood symptoms. Further studies are necessary to define better therapeutic strategies (e.g. type and duration of physical activity, diet pattern, probiotics vs. FMT vs.

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others; single vs. multiple bacteria strains), especially taking into account long-term outcomes, also investigating their potential influence on both psychopathological and metabolic parameters.

Conclusions and perspectives

Patients with severe psychiatric disorders are at increased risk of developing medical comorbidities, especially metabolic disorders and cardiovascular diseases. These medical conditions are underdiagnosed and undertreated in these patients contributing to their increased morbidity and mortality. Multiple levels of factors seem to play a role in this context, from shared risk factors (e.g. unhealthy life style) to health system flaws, also encompassing common pathophysiological pathways and bidirectional interactions.

Inflammation and related mechanisms, notably insulin resistance and dysbiosis, seem to be major players underlying the comorbidity between psychiatric disorders and medical conditions, as reviewed here. The understanding of the pathogenesis and the specific contribution of each one of these processes to the comorbidity scenario is still in its infancy. HPA axis dysfunction leading to hypercortisolism and corticosteroid receptor downregulation contribute to the low-grade inflammation observed in mood disorders and schizophrenia, but other factors, such as dysbiosis and immune dysregulation towards autoimmunity propensity, can also 'fuel' a pro-inflammatory profile. Conversely, inflammation (or insulin resistance or dysbiosis) is not observed in all patients, but in subgroups. The possibility of investigating subsets of patients presenting specific phenotypes (e.g. 'inflammatory phenotype') remains to be better explored therapeutically, as these patients might be more responsive to specific strategies (e.g. anti-inflammatory treatment) than others [27,54]. It also remains to be defined whether a treatment toward shared pathophysiological mechanisms between a psychiatric disorder and a medical comorbidity can influence both conditions. Preliminary studies with metformin and statins, for instance, have been encouraging, but their long-term impacts remain uncertain. This also applies to anti-hypertensive drugs, such as angiotensin converting enzyme inhibitors and angiotensin receptor 1 antagonists [241].

In the context of worldwide aging population, there has been a marked increase in the prevalence of neurodegenerative diseases, especially Alzheimer's disease and related dementias (ADRD). Severe psychiatric disorders have been regarded as risk factors of ADRD [242]. The mechanisms underlying this association remain to be established, but might be related to the increase frequency of cardiovascular diseases and diabetes—established risk factors of ADRD—and overlapping mechanisms, especially low-grade inflammation [243]. It remains to be determined whether the treatment of both psychiatric and medical conditions would result in synergistic neuroprotective effect and the potential role of anti-inflammatory strategies,

In sum, medical comorbidities are a matter of concern in the management of psychiatric patients. The existent gaps in the understanding and treatment of these comorbid conditions in psychiatry are challenging but also bring opportunities, as new therapeutic approaches can emerge from this field of investigation.

Data Availability

Not applicable.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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CRediT Author Contribution

Antonio L. Teixeira: Conceptualization, Writing—original draft, Writing—review & editing. **Lais B. Martins:** Writing—original draft. **Michael Berk:** Conceptualization, Writing—review & editing. **Moisés E. Bauer:** Conceptualization, Writing—review & editing.

Abbreviations

5-HT, 5-hydroxytryptamine; BD, bipolar disorder; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; FMT, fecal microbiota transplantation; IL-1β, interleukin 1β; KAT, kynurenine aminotransferase; KYNA, kynurenic acid; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; SR, sepiapterin reductase; TDO, tryptophan 2,3-dioxygenase; TLR, Toll-like receptors; TNF-α, tumor necrosis factor α; MET-2, Microbial Ecosystem Therapeutics-2; MDD, major depressive disorder; NAFLD, non-alcoholic fatty liver disease; QOL, quality of life; SMI, severe mental illness.

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