Brain-immune crosstalk in the treatment of major depressive disorder

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Abstract
A growing number of studies are pointing out the need for a conceptual shift from a brain-centered to a body-inclusive approach in mental health research. In this perspective, the link

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1. Introduction

1.1. Major depression and antidepressant therapy

Major Depressive Disorder (MDD) is a chronic, recurring and potentially life-threatening illness with a multitude of triggers and causes. MDD affects over 300 million people, i.e., around 5 percent of the global population, is the leading cause of years lost owing to disability worldwide and the third overall contributor to the burden of disease, projected to be the biggest contributor by 2030 (WHO, 2017). MDD represents a substantial proportion of the economic burden on health care systems worldwide.

The first-line treatment for MDD is the administration of antidepressant drugs, whose use has steadily increased after the introduction of selective serotonin reuptake inhibitor (SSRI) in the early 1990s. Though antidepressants are so commonly prescribed, their efficacy is variable and incomplete (Trivedi et al., 2006), calling for the development of novel and more effective therapeutic strategies. Regrettably, this process is facing several important difficulties whose reasons include our current conceptual and technical limitations in identifying selected neurobiological substrates as potential targetable processes to achieve mental health (Berk and Nierenberg, 2015; Leboyer et al., 2016a). Therefore, there is an increasing need for an innovative approach able to overcome these limitations.

Psychopathology is still perceived as a phenomenon emerging predominantly - if not exclusively - from the brain. However, (Branchi, 2011; Bullmore, 2018; Milaneschi et al., 2020; Pariante, 2016; Thibaut, 2018; Viglione et al., 2019) increasing preclinical and clinical findings implicate the entire body as a key determinant in the onset and treatment of psychiatric disorders - from MDD to schizophrenia (Branchi, 2011; Bullmore, 2018; Milaneschi et al., 2020; Pariante, 2016; Thibaut, 2018; Viglione et al., 2019). Moreover, tackling the complexity of mental health in a comprehensive mind-body perspective is opening new venues for a deeper comprehension of the biological processes defining brain function per se (Kendler, 2001).

In this perspective, the interplay between the immune system and the brain has recently emerged as one of the most important novel developments in mental health research (Benedetti et al., 2016; Dantzer et al., 2008; Miller and Raison, 2016). The brain and the rest of the body are deeply interconnected and continuously interact, and inflammation is widely implicated in such communication. Therefore, targeting inflammatory processes could lead to breakthroughs in the prevention and treatment of psychiatric disorders such as depression and psychosis (Bullmore and Lynall, 2014; Leboyer et al., 2016a; Pariante, 2017).

1.2. The rise of immunopsychiatry

The link between the immune system and the brain has been systematically explored since the 1970s when the field of psychoneuroimmunology was born. First, it was found that the brain influences the immune system activity, demonstrating that classical behavioral conditioning affects immune processes (Ader and Cohen, 1975). Afterward, the bidirectional nature of this interaction was demonstrated, showing that the immune response to antigens leads to increased activity of hypothalamic neurons (Besedovsky et al., 1983). One of the most significant pieces of evidence of the role of the immune system in modulating brain function is the behavioral response to infection, which involves a set of behavioral changes such as anhedonia, decreased appetite, disturbed sleep, decreased activity and social withdrawal. These changes, overall named sickness behavior, overlap to part of the symptoms of MDD (Dantzer, 2004) and have been hypothesized to have an adaptive function to cope with illness and infection (Raison and Miller, 2011). It is worth noting that, though the time course and magnitude of the immune system activation do not fully overlap, the molecular signature of sickness behavior and depression involves a rise of the levels of the same pro-inflammatory cytokines, such as Interleukin (IL)-1, IL-6 and Tumor Necrosis Factor (TNF)α (Dowlati et al., 2010).

More recently, the link between disturbances in the immuno-inflammatory system and the etiology and
pathophysiology of several psychiatric disorders has been specifically explored, making the field of immunopsychiatry rise (Dantzer et al., 2008; Leboyer et al., 2016a, 2016b; Parriante, 2017). The evidence supporting this new field is rapidly growing. For instance, the administration of agents increasing immune system activation has been demonstrated to lead to a depressive state in healthy volunteers and patients affected by chronic inflammatory diseases or treated with the pro-inflammatory factor interferon-alpha have an increased likelihood to show depressive symptoms (Bonaccorso et al., 2002; Capuron et al., 2002; Dickens and Creed, 2001). In addition to MDD, a role for infection, inflammation and autoimmunity has been found for a number of psychiatric disorders, including schizophrenia (Khandaker and Dantzer, 2016) and bipolar disorder (Benedetti et al., 2020). These disorders have been associated with an alteration in both the innate and adaptive immune system (Haapakoski et al., 2016; Medina-Rodriguez et al., 2018), and autoimmune phenomena were evident in both disorders (Leboyer et al., 2016b). Furthermore, the prevalence of organ-specific autoimmunity (thyroid, gastric and islet) has been found raised in bipolar disorder (Kupka et al., 2002; Leboyer et al., 2016b; Padmos et al., 2004).

In the last decades, pharmacological interventions able to modulate the immune response have been proposed as therapeutic strategies for psychiatric disorders (Leboyer et al., 2016a). The most investigated compounds are the non-steroidal anti-inflammatory drugs (NSAID), such as celecoxib and acetylsalicylic acid. The results of different clinical trials showed that the administration of celecoxib as add-on (adjunctive) therapy to different classes of antidepressants improves the symptomatology in depressed patients (Akhdzadeh et al., 2009; Colpo et al., 2018; Muller et al., 2006), though it is not effective in bipolar depression (Husain et al., 2020b), and treatment with acetyl-salicylic acid in combination with lithium reduces medication events in bipolar patients (Colpo et al., 2018; Stolk et al., 2018). Selected agents with anti-inflammatory properties showed efficacy also in schizophrenia, demonstrating beneficial effects on symptom severity in first episode psychosis and early-phase schizophrenia (Cakici et al., 2019; Fond et al., 2014).

The innovative theoretical framework of immunopsychiatry represents one of the most promising approaches for developing novel and effective treatments for psychiatric disorders. The reported alterations in the immune system playing a role in psychiatric disorders (Leboyer et al., 2016a; Muller, 2017) represent novel and targetable biological processes (Colpo et al., 2018; Jha and Trivedi, 2018; Leboyer et al., 2016b; Wetsman, 2017). Immunological therapeutics have already been proven successful in several biomedical fields and many drugs affecting immune response are already available and can be repurposed into psychiatry. In addition, immunopsychiatry holds the promise to contrast the withdrawal of several major pharmaceutical companies from key areas of neuroscience and psychopharmacology occurred in the last decades (Leboyer et al., 2016a). Given the incomplete and variable efficacy of currently available treatment strategies, a renewed interest from pharmacological industries might also give new hope to patients and their families.

### 1.3. Inflammation in major depression

An increasing number of clinical evidence demonstrates a link between excessive immune system activation and onset and progression of MDD (Blume et al., 2011; Maes et al., 1999, 2009). Depression is common in individuals affected by autoimmune or infectious diseases, such as rheumatoid arthritis or hepatitis (Benros et al., 2013; Dickens and Creed, 2001), and elevated levels of peripheral pro-inflammatory markers, such as IL-1β, IL-6, TNFα and C-reactive protein (CRP), have been reported in depressed patients (Goldsmith et al., 2016; Haapakoski et al., 2016; Howren et al., 2009). Although most clinical studies assessed the immune response at peripheral level, recent studies found high levels of IL-6 and TNFα, associated with an increased microglial activation, in the cerebrospinal fluid (CSF) and brain parenchyma in depression (Enache et al., 2019). Moreover, an intravenous administration of an endotoxin able to activate the immune system response induces, in healthy volunteers, a significant increase in CSF IL-6 level that was associated with the severity of mood impairment (Engler et al., 2017). In addition, patients receiving pro-inflammatory agents, including IL-2 and INF-α, because afflicted with somatic diseases such as hepatitis C or cancer, show a significant cytokine increase associated with the onset of depressive symptoms (Capuron and Miller, 2011; Eggermont et al., 2008; Friebe et al., 2010; Madeeh Hashmi et al., 2013). Pre-treatment with Paroxetine is effective in counteracting the depressive symptomatology caused by the administration of IFN-α (Kraus et al., 2002; Musselman et al., 2001).

Though the association between the immune system and MDD has been clearly described, its aetiologic role is still debated (Kohler et al., 2016). Some authors have hypothesized that an increase in inflammatory markers occurs before the onset of the depressive symptoms, suggesting that the immune system activation precedes the psychopathology (Gimeno et al., 2009; Liu et al., 2019; Pasco et al., 2010). Others propose an opposite temporal relationship, suggesting that psychiatric disorders cause an impairment in immunocompetence, leading to an increased vulnerability to infectious diseases (Copeland et al., 2012; Dantzer, 2012) or reported a lack of correlation (Levine et al., 1999). In addition, only 30% of depressed patients show high inflammatory levels (Miller and Raison, 2016; Raison et al., 2006) and, in turn, depression does not always follow an immune activation (Raison and Miller, 2011). Since stress increases both immune response and the risk of psychiatric disorders, exposure to stressful conditions, including childhood adversity, has been hypothesized to represent the common factor triggering the increase in both inflammatory markers and the likelihood of depression (Benros et al., 2013; Garcia-Bueno et al., 2008; Muller et al., 2019). A further hypothesis proposes that the correlation between immune system activation and MDD is not readily evident because it concerns only specific symptom domains, such as anhedonia and altered motor activity (Miller and Raison, 2016) or atypical, energy-related symptoms (Lamers et al., 2020; Milaneschi et al., 2020). The identification of a specific set of depressive symptoms associated with alterations in inflammatory processes led to name this subtype of depression as
immunometabolic depression (Milaneschi et al., 2020; for further details, see paragraph Metabolism and immune system interplay in the treatment of depression).

2. The interaction between antidepressant drugs and inflammation

2.1. Antidepressant drugs affect immune system activation

Antidepressant drugs have been suggested to decrease immune system activation (Galecki et al., 2018). Evidence supporting this hypothesis comes from in vitro studies. For instance, tricyclic antidepressants, such as clomipramine and imipramine, act as antagonists of prostaglandin E2, inhibit prostaglandin synthesis and decrease nitric oxide and TNF flow in microglia and astrocyte cultures (Wang et al., 2017). SSRIs attenuate cyclooxygenase (COX)-2 expression and reduce levels of cytokines such as TNFα (Taler et al., 2007). A wide range of antidepressants, including imipramine, clomipramine, venlafaxine, fluoxetine, sertraline and trazodone, modify the pro-/anti-inflammatory ratio in favor of a reduction of inflammatory markers in human blood samples (Kopschina Feltes et al., 2017). Several clinical studies confirmed these in vitro findings, showing that SSRIs, such as fluoxetine, significantly reduce the peripheral concentration of IL-6 and IL-1β in depressed patients (Basterzi et al., 2005; Hannestad et al., 2011; Song et al., 2009). However, other studies found discordant results, reporting that the administration of antidepressants does not affect the immune system activation (Haastrup et al., 2012; Jazayeri et al., 2010; Kim et al., 2013) or even produce a pro-inflammatory action (Chen et al., 2010; Kagaya et al., 2001). Overall, antidepressant effect appears not consistent and may depend on other factors (Alboni et al., 2016; Golia et al., 2019). To reconcile these apparently contradictory results, it has been recently proposed that basal inflammatory levels define the action of antidepressant drugs on the immune system: antidepressant action is pro- or anti-inflammatory when basal levels are, respectively, low or high. This regulation appears to be associated to the increase in neural plasticity induced by drug administration that normalizes immune function (Alboni et al., 2016; for further details, see paragraph Interplay between inflammation and neural plasticity).

2.2. Immune system activation affects antidepressant drug efficacy

Since antidepressant drugs affect the immune system activation, it has been recently postulated that part of their action might be mediated by inflammatory processes. Indeed, increased inflammatory levels reduce antidepressant drug efficacy (Carvalho et al., 2013; Colpo et al., 2018; Haroon et al., 2018; Pariante, 2017). In particular, high expression levels of genes related to immune system activation, such as IL-6, TNFα, macrophage migration inhibitory factor, and IL-1β, in patients’ blood predict a lack of response to different classes of antidepressant drugs (Arteaga-Henriquez et al., 2019; Cattaneo et al., 2016; Eller et al., 2008; Lanquillon et al., 2000; Tuglu et al., 2003) or a general refractoriness to SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) beneficial effects (Vogelzangs et al., 2014; Yoshimura et al., 2009). In addition, a lack of decrease in TNFα blood levels during antidepressant treatment was found in patients not responding to treatment (Lanquillon et al., 2000) and specific variances of the IL-1β gene polymorphism predict non-response to antidepressants (Baune et al., 2010; Yu et al., 2003). Finally, CRP levels, considered an overall index of patient’s inflammatory status (Felger et al., 2018), has been reported to be increased in depressed patients and more so in treatment-resistant individuals (Chamberlain et al., 2019). Overall, these findings indicate that immune system activation affects antidepressant drug efficacy and suggest that the stratification of depressed patients according to their inflammatory biomarker profile has the potential to disentangle responders and non-responders, thus increasing the efficacy of antidepressant interventions. Otherwise, the administration of anti-inflammatory drugs appears as an alternative strategy to treat depression.

2.3. Use of anti-inflammatory drugs to treat MDD

Depressed patients show high levels of inflammatory markers (Dowlati et al., 2010; Howren et al., 2009; Liu et al., 2012; Maes et al., 1995, 2009; Yirmiya et al., 2015), the administration of pro-inflammatory drugs leads to the onset of depressive symptomatology (Bonaccorso et al., 2002; Capuron et al., 2002; Madeeh Hashmi et al., 2013) and antidepressant efficacy is reduced by excessive immune system activation (Carvalho et al., 2013; Eller et al., 2008; Haroon et al., 2018; Huang et al., 2018; Lanquillon et al., 2000; Powell et al., 2013; Strawbridge et al., 2015). Based on these observations, it has been postulated that anti-inflammatory drugs represent promising therapeutic strategies for the treatment of MDD. Therefore, an increasing number of studies is exploring anti-inflammatory drugs as a stand-alone treatment or as an add-on to standard antidepressant administration (Fourrier et al., 2018; Kohler et al., 2014; Kopschina Feltes et al., 2017; Muller, 2019; Rosenblat et al., 2014; Tying et al., 2006).

Compounds able to inhibit both COXs and thus reducing inflammation, such as NSAIDs, have been widely investigated as a possible treatment for depression (Baune, 2016). Celecoxib, one of the most used COX-2 inhibitors, has been reported to be, in combination with traditional antidepressants such as reboxetine, sertraline, and fluoxetine, more effective than the antidepressants alone or placebo (Abbasi et al., 2012; Akhondzadeh et al., 2009; Kohler et al., 2014, 2016; Muller et al., 2006; Na et al., 2014), and several clinical trials showed its antidepressant effect also as monotherapy (Iyengar et al., 2013). Although selective COX-2 inhibitors have a stronger anti-inflammatory activity compared to the non-selective ones (Riendeau et al., 1997), the latter exert an antidepressant action as well. For instance, acetyl salicylic acid is an inhibitor of both COX-1 and COX-2 and its administration reduces pro-inflammatory cytokines expression level (Muller, 2019). The use of acetyl salicylic acid reduces the rate of depression (Berk et al., 2013; Kessing et al., 2019), and its administration with SSRIs
increases the rate of response and remission (Mendlewicz et al., 2006). Other NSAIDs as naproxen and ibuprofen administered as monotherapy have been reported to produce antidepressant effects in patients with active osteoarthritis (Iyengar et al., 2013).

A different class of anti-inflammatory agents is the biotherapeutic monoclonal antibodies, compounds able to block the activity of different immune players including cytokines, cytokine receptors, or immune checkpoints. Stand-alone treatment with TNFα antagonists, such as Etanercept or Infliximab (Grattendick et al., 2008) has been shown to decrease depressive symptoms in patients with autoimmune disorders (Tyring et al., 2006; Wichers et al., 2006). The administration of adalimumab, a humanized antibody against TNFα, has been reported to reduce depressive symptoms in individuals affected by psoriasis (Menter et al., 2010; Schmitt and Wozel, 2009). A systematic review and meta-analysis conducted by Kappelmann and colleagues showed that anti-cytokine treatments, such as adalimumab, etanercept, infliximab, and tocilizumab, led to a pronounced improvement of depressive symptoms (Kappelmann et al., 2018).

Minocycline is a second-generation tetracycline antibiotic with antioxidant, anti-inflammatory and neuroprotective effects, which render it a potential new promising therapy in psychiatry, and in particular to treat depression (Dean et al., 2012; Pae et al., 2008; Soczynska et al., 2012). Although a large number of clinical trials to evaluate the antidepressant efficacy of minocycline, both as an add-on and stand-alone treatment, are still missing, a study published in 2012 showed that the use of minocycline as adjuvant improves depressive symptoms (Miyakoa et al., 2012). Recently, an interesting review exploring the efficacy of minocycline as antidepressant monotherapy has reported a large antidepressant effect compared to placebo (Rosenblat and McIntyre, 2018). However, in a randomized, placebo-controlled trial, minocycline was not more effective than placebo in bipolar depression, indicating that this drug cannot be exploited to treat all types of mood disorders (Husain et al., 2020a).

Among the potential novel treatments for depression could be included the omega-3 polyunsaturated fatty acids (PUFAs). Indeed, these dietary fatty acid exhibit anti-inflammatory effects (Calder, 2008) and results from different meta-analyses indicate that omega-3 supplementation is beneficial in depressed patients (Appleton et al., 2010) when they also receive antidepressants (Mocking et al., 2016). Recently, statins, which are commonly used for hypercholesterolemia and have anti-inflammatory properties, have also been proposed as a treatment for MDD, alone or in combination with SSRIs. These compounds have been found to not harm non-depressed individuals but to significantly improve depressive symptoms in patients (Kohler-Forsberg et al., 2020; Yatham et al., 2019).

The overall efficacy of anti-inflammatory drugs in treating MDD has been illustrated in many studies and meta-analyses (Bai et al., 2020; Kappelmann et al., 2018; Kohler et al., 2014; Yatham et al., 2019). However, many others had contrasting results, reporting no (Almeida et al., 2010; Fields et al., 2012; Fond et al., 2014; Fourrier et al., 2018; Wittenberg et al., 2019) or even detrimental effects (Warner-Schmidt et al., 2011). For instance, Greengard and collaborators found that anti-inflammatory treatments, including ibuprofen and acetylsalicylic acid, reduce or even inhibit SSRI antidepressant action (Warner-Schmidt et al., 2011). These conflicting findings suggest that the beneficial effects of anti-inflammatory drugs might be dependent on patients’ heterogeneity and thus one or more moderating factors may determine treatment outcome (Kraemer et al., 2006). In addition, the available studies have relevant design differences, are limited in number and are in part small-scaled, raising the need for further and larger studies in the field.

An increasing number of studies suggest that baseline inflammatory components may be used to identify specific groups of depressed patients who differently respond to anti-inflammatory drugs. Indeed, the efficacy of these drugs appears to be high mainly in patients showing at baseline an excessive immune system activation. TNFα inhibitor Infliximab produces an improvement of depressive symptoms only in those treatment-resistant patients with high baseline levels of CRP (Raison et al., 2013). Further studies are currently exploring whether anti-inflammatory pharmacotherapy has to be tailored based on the immune profile of the patient. The efficacy of celecoxib as an add-on treatment to vortioxetine is measured according to baseline CRP levels in an ongoing randomized double-blind placebo-controlled study (Fourrier et al., 2018). Another ongoing clinical trial (Eudract 2015-003413-26), which is stratified, randomized, placebo-controlled, is testing the efficacy of minocycline as an add-on treatment to an SSRI in depressed patients according to the patients’ baseline CRP levels. The potential involvement of elevated inflammatory levels in the reduced response to antidepressant treatment is supported by (i) the about one-third of all depressed patients having elevated serum CRP levels (>3 mg L⁻¹; (Wium-Andersen et al., 2013) that overlaps with the one-third of patients showing treatment resistance (Nemeroff, 2007), (ii) the elevated inflammatory markers predicting poor antidepressant response (Carvalho et al., 2013; Yoshimura et al., 2009) and (iii) treatment-resistance being associated to lack of reduction of cytokine levels following treatment (Kappelmann et al., 2018; Maes et al., 1995; O’Brien et al., 2007).

It is worth noting that, in addition to being beneficial in patients with high baseline CRP levels, anti-inflammatory treatment as infliximab appears to lead to a worse outcome, compared to placebo, in patients with low baseline CRP levels (Raison et al., 2013). This suggests that the beneficial antidepressant effects of anti-inflammatory drugs might not be simply associated with a reduction of immune activation but to its normalization.

3. Mechanisms underlying the interaction between antidepressant action and immune system

A number of molecular and cellular mechanisms have been hypothesized to link the immune system function with the efficacy of therapeutic approaches to treat depression. The following ones are among the most widely investigated and
better elucidated. These can be either alternative or complementary.

3.1. Kynurenine pathway

Tryptophan, the essential amino-acid precursor of serotonin, can be processed along two alternative pathways (Fig. 1). The first and most common one involves tryptophan hydroxylase and leads to the production of serotonin. Alternatively, especially in inflammatory conditions associated with increased levels of TNFα and IFNγ, tryptophan is processed by the enzyme indoleamine 2,3-dioxygenase (IDO) that catalyzes the first and rate-limiting step of tryptophan metabolism along the kynurenine pathway (Haroon et al., 2020). Kynurenine is subsequently metabolized to kynurenic acid (KA) in astrocytes, oligodendrocytes, and neurons or to 3-hydroxykynurenine (3-HK), anthranilic acid, 3-hydroxyanthranilic acid, and ultimately quinolinic acid (QA) in microglia, macrophages, and monocytes. The latter metabolites stimulate N-methyl-D-aspartate receptors and promote oxidative stress (Haroon et al., 2020; Schwarz et al., 2012; Schwarz and Stone, 2017). Accordingly, subjects afflicted with conditions that are associated with increased inflammatory processes (e.g., chronic diseases, aging, inflammatory disorders) show an activation of the kynurenine pathway leading to the production of QA (Capuron and Miller, 2011; O’Farrell and Harkin, 2017; Schwarz and Stone, 2017). Recently, another enzyme, the tryptophan 2,3-dioxygenase (TDO), has been found to play a key role overlapping to that of IDO in the kynurenine pathway. However, its activation produces partially different neurobehavioral effects (Dantzer, 2017).

In the last two decades, the kynurenine pathway has been involved in neuropsychiatric disorders and suggested to represent a key mechanism linking inflammation to depression (Dantzer et al., 2008; Haroon et al., 2020; Vancassel et al., 2018). Consistent with this notion, kynurenine pathway activation was shown to correlate with the severity of neuropsychiatric symptoms in clinical populations (Parrott et al., 2016b; Raison et al., 2010; Savitz et al., 2015a, 2015b). Special attention has been paid to IDO since its activation has been found to be associated with increased levels of depression-like phenotypic markers in several mouse models of depression and inflammation (Andre et al., 2014; Dinel et al., 2014; O’Connor et al., 2009a, 2009b). Interestingly, genetic or systemic inhibition of IDO was found to prevent emotional alterations in mice submitted to immune/inflammatory challenge, stretching further the causal role of IDO in inflammation-induced depressive-like behavior (O’Connor et al., 2009a, 2009b; Salazar et al., 2012). In addition, manipulations able to activate the kynurenine pathway in the brain induce depressive-like behavior in rodents (Castanon et al., 2015; Dobos et al., 2012; Godbout et al., 2008). The mechanisms potentially underlying the role of IDO in mood disorders are twofold. The first implies the reduction of serotonin synthesis as a consequence of processing tryptophan along the kynurenine pathway, though this appears not to be a direct relationship since some studies found no change in serotonin levels when IDO activation is modified (Kim et al., 2012). The second implies the generation of neurotoxic metabolites, such as 3-hydroxykynurenine (3-HK) and quinolinic acid (QA), which can stimulate the glutamatergic system and correlate to the severity of mood symptoms in several clinical studies (Bay-Richter et al., 2015; Capuron and Miller, 2011; Haroon et al., 2017; Schmitt et al., 2017). This mechanism is in line with the structural and functional alterations reported in psychiatric conditions associated with immune activation (Dantzer and Walker, 2014) and potentially involves the activation of NMDA receptors whose involvement in mood disorders is demonstrated in several reports (Dantzer and Walker, 2014; Haroon et al., 2016, 2017; Henter et al., 2018). 3-HK has been found to be related to depression-like behavior in a dose-dependent manner (Parrott et al., 2016a, 2016b), while the lack of IDO protects against NMDA receptor-mediated excitotoxicity (Mazarei et al., 2013). Similarly, NMDA receptor blockade was found to prevent the inflammation-induced depressive-like phenotype (Walker et al., 2013) and the synthesis of...
the NMDA receptor agonist QA (Laumet et al., 2017; Parrott et al., 2016b). Accordingly, postmortem studies found increased microglial QA levels in brain regions of depressed patients (Steiner et al., 2011). Interestingly, and relevant to antidepressant response, recent findings indicate that the response to escitalopram is increased in depressed patients exhibiting higher baseline levels of serotonin together with lower markers of kynurenine pathway activation (Sun et al., 2020). Altogether, these findings strongly support the role of IDO and related kynurenine pathway activation in underlying the relationship between inflammatory processes and the development of depressive symptoms and the antidepressant response. It is worth noting that the kynurenine pathway is only a part of a large complex regulatory system of the inflammatory processes. For instance, emerging data have shed light on the role of the ligand-activated transcription factor aryl hydrocarbon receptor in transducing the effects imparted by IDO1 and TDO2 on the immune system function (Cheong and Sun, 2018).

3.2. Metabolism and immune system interplay in the treatment of depression

Metabolic dysregulation cannot be ignored when trying to understand the link between immune activation and psychiatric disorders such as depression (Fig. 2) since this interplay emerges in a large part of patients, ranging from 15% to 29% (Milaneschi et al., 2020). White adipose tissue, especially in the abdominal area, is an active endocrine organ producing inflammatory cytokines and hormones (e.g. leptin) and, therefore, a major contributor to pathogenic immune-metabolic responses both in the central nervous system as well as in the rest of the body (Chait and den Hartigh, 2020). Activation of pro-inflammatory response stimulates the release of lipids in the bloodstream determining a reduction in high-density lipoprotein (HDL) cholesterol and phospholipids and an increase in triglycerides. In addition, inflammatory activation induces insulin resistance and alters glucose metabolism acting directly on pancreatic β cells. It also stimulates the leptin-melanocortin pathway that has an important role in lipid and glucose homeostasis as it is a key neuroendocrine regulator of energy homeostasis. More indirectly, inflammation favors the development of leptin and insulin resistance by crippling the functionality of their receptors in the brain (Cui et al., 2017). So, immune activation shows a strong, bidirectional interplay with metabolic and endocrine homeostasis systems that regulate energy homeostasis. This is evident as well from the significant and quite strong associations found between inflammatory markers, such as CRP and IL-6, with higher body mass index fat mass, triglyceride levels, and lower HDL cholesterol in large-scale cohorts. Consequently, metabolic and immune dysregulation are partly two sides of the same coin (see Fig. 3), and that is why some research now uses combined immune-metabolic dysregulation scores and consider both dysregulations simultaneously (Lamers et al., 2020).

A clinically relevant concept is Metabolic syndrome (MetS), defined by a combination of central obesity, high blood pressure, low HDL cholesterol, elevated triglycerides, and hyperglycemia. MetS indicates a preclinical state for the development of cardiovascular disease and diabetes (Mottillo et al., 2010). The MetS prevalence is 58% higher in psychiatric patients as compared to the general population (Vancampfort et al., 2015). The risk for MetS was similarly elevated in those with schizophrenia, bipolar disorder, and major depressive disorder, which suggests that MetS is a general comorbidity seen in different psychiatric patient groups. A systematic review involving 155,333 subjects found depression and MetS to be modestly associated (Odds Ratio = 1.34; (Pan et al., 2012), and a dose-response relationship between severity of depression and MetS has been confirmed (van Reedt Dortland et al., 2010). Prospective evidence does confirm a bidirectional relationship with depression predicting the onset of MetS, and MetS predicting the onset of depression over time (Pan et al., 2012). Most consistent evidence exists between depression and obesity-related components (abdominal obesity, low HDL cholesterol, hypertriglyceridemia; (Bot et al., 2020), whereas associations with hyperglycemia and hypertension are less often confirmed (Penninx, 2017; Vancampfort et al., 2015). Three longitudinal patient studies confirmed that a combination of multiple metabolic dysregulations contributes to sustained chronicity of depression (Marijnissen et al., 2017; Vogelzangs et al., 2011, 2014). Unhealthy lifestyle, imbalances in the microbiome, genetic risk patterns and potential psychotropic medication effects are all likely to contribute to metabolic dysregulations seen in depressed patients (see Fig. 2).

Several studies illustrate antidepressants to impact on (subtle) metabolic dysregulations, that could thus also indirectly impact on immune dysregulation. In a meta-analysis of treatment trials, Serretti and Mandelli evaluated...
short-term weight change after antidepressant treatment and found that amitriptyline, mirtazapine and paroxetine lead to a greater risk of weight gain (Serretti and Mandelli, 2010). In contrast, weight loss occurred with fluoxetine (in acute phase only) and bupropion. Other compounds were found to have a transient or negligible effect on body weight in the short term. In a 6-year observational study with three assessment waves, antidepressant use was consistently associated with metabolic dysregulation at all assessment waves, and it exerted a negative, longitudinal impact on subsequent metabolic health (Hiles et al., 2016). Compared with antidepressant nonusers, the use of most types of antidepressants (tricyclic antidepressants, SSRIs, SNRs) was associated with higher waist circumference, triglycerides and number of MetS abnormalities. As this study also included drug-naive depressed patients, it could illustrate that symptom severity and antidepressant use both exerted independent effects on MetS: also patients without antidepressant medication have an increased MetS risk. In line with this, more metabolic dysregulation was confirmed in a recent meta-analysis among first-episode drug-naive depressed patients (Cakici et al., 2020).

Finally, it is important to point out that the prevalence and relevance of MetS abnormalities may partly depend on the specific depression symptom profile. Recent studies point towards more MetS abnormalities in especially depressed persons with many atypical, energy-related neurovegetative symptoms including hyperphagia, hypersomnia, lack of energy, and leaden paralysis (Lamers et al., 2012; Lasserre et al., 2014; Penninx, 2017). In line with this, also elevated immune markers (IL-6, TNFα and CRP) were found to be specifically linked to these atypical, energy-related symptoms in various large-scale studies (Lamers et al., 2020; Milaneschi et al., 2020). This has raised awareness of the existence of immunometabolic depression (Milaneschi et al., 2020). This is a subtype of depression, that is prominent in roughly a quarter of all depressed patients, in which there is a clustering of disrupted energy-regulating neuroendocrine and metabolic signaling (e.g., leptin, insulin, dyslipidemia) and systemic low-grade inflammation that map more consistently to atypical behavioral symptoms reflecting altered energy intake/expenditure balance (hyperphagia, weight gain, hypersomnia, fatigue, and leaden paralysis). It needs to be examined in future studies whether immunometabolic depression moderates the antidepressant effects of standard (e.g. antidepressants) or novel (e.g., anti-inflammatory or lifestyle-targeted) therapeutic approaches. A relevant step towards precision psychiatry.

3.3. Regulation of immune imbalance in the treatment of depression

The immune system provides continual surveillance and regulation of a wide number of key brain processes, ranging from neuroplasticity to neurogenesis, white matter growth and the coping response to stress (Ziv and Schwartz, 2008). Dysregulation of the balance between innate and adaptive immunity but also between the pro-inflammatory and the anti-inflammatory/regulatory arm of the immune system may lead to alterations in these processes and in brain function in general. Indeed, accumulating evidence suggests that cell-mediated immunity plays an active role in the pathogenesis of MDD (Beumer et al., 2012; Miller, 2010; Tohen and Baune, 2015).

The initiation and resolution phases of both innate and adaptive immunity are orchestrated by the myeloid lineage, composed of monocyte-macrophages and dendritic cells (Murray, 2017), which through the production of cytokines and cell-to-cell interactions both positively and negatively regulate and recruit T cells. Whereas, altered

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**Fig. 3** Imbalance in immune responses. The immune system regulates a wide number of neural processes and its dysregulation leads to alterations in brain function. Environmental factors such as stressful conditions directly activate the kynurenine pathway (through TDO) and the HPA axis and promote the production of cytokines. Similarly, also the metabolic syndrome and other factors promotes the production of cytokines which, in turn, can activate the kynurenine pathway (through IDO), the HPA axis and the adaptive immune system in an attempt to restore homeostasis. However, the alterations in the regulatory systems potentially trigger a chronic low-grade inflammatory state which leads to mental illness and immune dysfunction. HPA, Hypothalamus-Pituitary-Adrenal; IDO, Indoleamine 2,3-dioxygenase; TDO, Tryptophan 2,3-dioxygenase.
monocyte number, activation state and gene expression suggest a state of monocyte inflammatory activation in at least a sub-group of MDD patients (Grosse et al., 2015; Nowak et al., 2019; Schieweck et al., 2020), a decrease in the response of T cells, and in particular in T regulatory cells (T regs), has been reported in both stressed and depressed individuals (Irwin and Miller, 2007; Zorrilla et al., 2001). T regs control inflammation by secreting anti-inflammatory cytokines and inhibiting pro-inflammatory responses (Sakaguchi et al., 2008). Similarly, natural killer (NK) cells, which have been found to be decreased in MDD (Patas et al., 2018), attenuate microglial inflammatory activity and brain inflammation (Shi et al., 2011). When NK and T regs are reduced, episodes of excessive inflammatory macrophage activation can occur.

Joining results on cytokines and on T cells subsets, two divergent sets of observations have emerged in MDD. Several studies described MDD as associated to immune dysregulation due to reduced proliferative T cell responsiveness, reduced NK and T reg levels and activity (Grosse et al., 2016b; Miller, 2010). Other studies suggest an immune hyperactivation in MDD, as indicated by increased production of pro-inflammatory cytokines (Dowlati et al., 2010), enhanced proliferation of T cells (Toben and Baune, 2015), increased CD4/CD8 ratio (Di Rosso et al., 2016), and an increased percentage of activated T cells (Patas et al., 2018). These alterations have been hypothesized to be part of the same pathophysiological process: a dysregulation of some parts of the immune system leading to hyperactivation of other parts. Such dysregulation fits best with the concept of premature aging of the T cell system, leading to the so-called “inflammaging” (Squassina et al., 2019). Characteristics of premature immune aging are an excessive memory T cell formation (due to e.g. chronic viral infection, such as cytomegalovirus) with the formation of senescent poor-reactive T memory and at the expense of the number of naïve reactive T cells. Such T cell aging-induced low responsiveness would lead to a compensatory high level of low-grade chronic inflammation of monocytes/macrophages and Th1 and Th17 cells (“inflammaging”). The condition is further characterized by a poor activity of T cell tolerance mechanisms, opening the gateway to autoimmune reactions. Accordingly, pre-clinical and clinical studies reported depression associated with an increase in Th17 cells and a decrease in T regs, leading to a raised Th17/Treg cell ratio (Beurel et al., 2013; Chen et al., 2011) but also to a lower percentage of NK cells and higher percentages of B and T cells (Schieweck et al., 2020). These immune alterations may vary at different time points in the course of the disease and are under the control of various influences such as the state of chronic infections and the presence of childhood adversity (Ford et al., 2020). Accordingly, a lower percentage of Th2 cells, together with a lower expression of monocyte inflammatory genes have been reported in MDD patients aged < 30 years while, in patients aged >30 years, reduced Th17, T reg and NK cells were observed together with a monocyte pro-inflammatory activation (Grosse et al., 2016b). Also, pro-inflammatory activation of monocytes was found in MDD patients with a history of childhood adversity (Schieweck et al., 2020), while childhood adversity also induced a higher rate of cytomegalovirus infection, which induced a state of premature T cell aging (Ford et al., 2020).

The relevance of T cells in MDD is further corroborated by the changes in T cell number and percentage following antidepressant treatment. Administration of drugs acting on serotonin and noradrenaline neurotransmitter systems induce a rise in T regs (Grosse et al., 2016a; Himmerich et al., 2010) while decreasing IL-1β and IL-6 production (Himmerich et al., 2010). Furthermore, high CD8+ percentages and reduced NK percentages have been reported to predict non-response to SSRI and SNRIs (Grosse et al., 2016a). In addition, several endocrine mechanisms have been hypothesized to modulate T cell action in MDD, such as the antagonism by leptin. Metabolic syndrome is highly prevalent in MDD (Kahl et al., 2012) and adipose tissue secretes leptin in proportion to its mass. In turn, leptin controls immune cells promoting a pro-inflammatory status (Matarese et al., 2010). Repeated exposure to such inflammatory stimuli would lead later in life also to premature immune-senescence, however, also stress and alterations in the glucocorticoid system can anticipate this process (Bauer, 2008) affecting frequencies, subset distribution and functional competence of T regs (Jagger et al., 2014). Indeed, elevated cortisol levels during major depression have been proposed as an important potential mechanism modulating immune system activity (Cubala and Landowski, 2014). However, the immunosuppressive effect of glucocorticoids seems to be insufficient to reduce inflammation in MDD, possibly because inflammation induces glucocorticoid resistance and enhances the release of the corticotropin releasing factor by the hypothalamus (Perrin et al., 2019). Steroid resistance, with a reduced number of glucocorticoid receptors, is common to both lymphocytes and monocytes, thus contributing to the inflammatory phenotype and to immune imbalance (Carvalho et al., 2014; Hasselmann et al., 2018).

Other systems besides the endocrine system can participate in the regulation of the cell-mediated immune response in MDD, most notably the tryptophan catabolic pathway, though there is some debate on whether this regulation is fine enough to actually regulate immune system. Since tryptophan is essential for effector T cells proliferation, its depletion through IDO or TDO activation, induced by pro-inflammatory cytokines and/or the exposure to stressful conditions, potentially cause apoptosis of T cells (Beissert et al., 2006; Mellor et al., 2003), leading to the T cell dysfunction observed in MDD. In addition, serotonin and the activation of the immune system exert a mutual control because serotonin influences the function of macrophages, NK, and T cells, and, in turn, T cells have been reported to synthesize and release serotonin (Roumier et al., 2019). Accordingly, MDD patients show a decreased expression of serotonergic receptors on T regs together with reduced T regs and serotonin serum levels (Li et al., 2010) and mice with low levels of T regs show reduced serotonin levels (Jankord and Herman, 2008).

Finally, an alteration in T cells number and activity with increased cytokine levels may participate in white and gray matter deficit as suggested by recent studies showing an association between Th17, Treg, NK cells, and cytokines with brain structure and function of regions part of the cortico-limbic circuit involved in mood and emotion regulation (Benedetti et al., 2016; Furlan et al., 2019; Poletti et al., 2017, 2019).
In agreement with the idea that MDD could derive from a defect of the regulatory arm of the immune system which would lead to chronic inflammation, novel treatment strategies could be aimed at recovering the immune balance. Accordingly, clinical trials are currently targeting T regs though the administration of low dose IL-2 with the aim of restoring the balance between pro-inflammatory/regulatory cells (EUDRACT: 2019-001696-36).

3.4. Interplay between inflammation and neural plasticity

A more recent view of the interplay between the immune system, brain function and novel therapeutic strategies to treat depression is centered on the regulatory action exerted by the immune system on neural plasticity. This view proposes that immune system activation should be in a physiological range to allow for neural plasticity processes, which are key in brain rewiring leading to recovery (Branchi et al., 2014; Golia et al., 2019; Yirmiya and Goshen, 2011).

Neural plasticity is defined as the capability of the brain to keep remodeling through continuous structural and functional changes that allow the individual to respond and adapt to external stimuli, modifying the behavioral outcome (von Bernhardi et al., 2017). Major depression has been associated with impaired neural plasticity (Liu et al., 2017) and a significant alteration of plasticity markers. Reduced levels of Brain Derived Neurotrophic Factor (BDNF), the neurotrophic factor most involved in plasticity process (Castren and Hen, 2013), impaired long-term potentiation (LTP), a form of synaptic plasticity, and decreased neurogenesis (Lucassen et al., 2010) have been widely described in depressed patients and preclinical models of depression. In addition, exposure to stress, considered one of the main factors triggering the psychopathology (Cohen et al., 2007), results in plasticity impairment (Pittenger and Duman, 2008) and most therapeutic strategies effective in treating depression, such as SSRI administration, enhance neural plasticity (Branchi, 2011; Castren and Hen, 2013; Maya Vetencourt et al., 2008). In addition, several studies have demonstrated the ability of pro-inflammatory cytokines, which are reported to trigger MDD, to reduce plasticity markers in both animal and human studies (Borsini et al., 2015). Indeed, a recent in vitro study found that demonstrated that the degenerative cytokine, interferon-alpha, decreases hippocampal neurogenesis through upregulation of the interferon-stimulated genes, ISG15 and USP18 (Borsini et al., 2018). Decreased neurogenesis might well be a key mechanism by which high levels of inflammation induces depression, as antidepressant strategies, including omega-3 fatty acids, reverse these effects (Borsini et al., 2017). Moreover, the serum of patients treated with interferon-alpha who go on to develop depression can reduce neurogenesis in vitro (Borsini et al., 2019).

Recently, the action of the immune system in the brain has been reconsidered from being deleterious to be deeply implicated in the physiological functioning (Branchi et al., 2014; Morganti-Kossmann et al., 2002; Yirmiya and Goshen, 2011). Neural plasticity involves several processes such as growing and pruning of dendrites and axons, shaping of synapses and associated structures, apoptosis and neurogenesis, that produce neuritic debris. The immune system removes this debris, keeping neural homeostasis and thus allowing brain tissue remodeling. Therefore, the physiological immune system activity is beneficial (Golia et al., 2019; Hewett et al., 2012; Santello and Volterra, 2012; Yirmiya and Goshen, 2011), however any deviation towards an extreme activation or suppression would lead to an impairment in neural plasticity. Accordingly, recent results showed that pro- and anti-inflammatory compounds, such as lipopolysaccharide and ibuprofen, produce, as expected, opposite effects on physiological endpoints and immune response, but have an overlapping effect on plasticity at molecular and cellular levels, since both compounds significantly reduce plasticity markers such as BDNF levels and LTP amplitude (Golia et al., 2019). Thus, to keep high neural plasticity levels, which are a prerequisite to recovering from depression (Branchi, 2011; Carhart-Harris et al., 2018; Duman, 2002; Viglione et al., 2019; Branchi and Giuliani, 2021), the immune system activation should be tightly regulated (Fig. 4).

A relevant theoretical consequence of the present view is that the ultimate therapeutic effect of drugs affecting the immune system response is determined by the baseline inflammatory condition of the individual since the beneficial impact should be evaluated according to the drug capability to normalize or exacerbate the inflammatory balance (Golia et al., 2019). For instance, anti-inflammatory treatment is expected to be beneficial mainly in depressed patients showing high baseline levels of inflammatory markers because, in this case, it leads to a normalization of the immune system activation. Accordingly, a study examining the effects of the anti-inflammatory compound infliximab showed that patients with high baseline levels of peripheral inflammation profit from the treatment, while...
those with low baseline inflammation show even a worse outcome compared to patients receiving placebo (Raison et al., 2013). Several preclinical studies and clinical trials are currently in progress to corroborate such a hypothesis (Arteaga-Henriquez et al., 2019; Fourrier et al., 2018; Eudract 2015-003413-26). This view reconciles apparently discordant findings including those by Greengard and collaborators, demonstrating that anti-inflammatory drugs counteract the effect of SSRIs in treating depression (Warner-Schmidt et al., 2011). This discrepancy could be explained hypothesizing that patients receiving the SSRI and the anti-inflammatory drug had low immune system activation at baseline, which leads to an excessive immune suppression that is detrimental to plasticity. Accordingly, it has been suggested that subgroups of depressed individuals, selected according to their baseline inflammatory profile, may even benefit from an acute stimulation of certain aspects of the inflammatory response (Golia et al., 2019; Raison, 2017). Overall, in the framework of the crosstalk between the immune system and the brain, inflammatory processes have to be tightly controlled to instate the neural and behavioral plasticity needed to recover from depression. It is worthy of note that SSRIs, which reportedly increase plasticity, in turn, affect immune system activation, suggesting that plasticity and inflammation are mutually regulating processes (Alboni et al., 2016).

4. Conclusions

The knowledge about the interplay between the immune system and the brain in the treatment of depression has been growing and important advances have been made in recent years. The emerging field of immunopsychiatry is transforming our understanding of mental illness and is allowing for the exploration of innovative diagnostic and therapeutic approaches (Leboyer et al., 2016; Pariante, 2017). On the one side, the prediction of treatment outcome according to immune parameters is a potentially fruitful field of clinical research and, on the other, the use of immune modulation holds the promise to improve the efficacy of the next generation of antidepressant compounds. In this perspective, a precise/personalized medicine approach, taking into account the patient’s baseline immune condition, appears warranted for designing successful interventions. Thus, the next fundamental step for the immunopsychiatry is to exploit the inflammatory blueprint, relevant to define subtypes of mental illnesses, to finally develop novel, reliable, and effective treatments for psychiatric disorders. However, some aspects require further development. Insufficient data and a still limited understanding of the biological processes and mechanisms underlying the immune pathogenesis of the psychopathology hamper to readily implement treatment protocols in the clinics and warrant further studies. Moreover, a better definition of the time course and the magnitude of the immune system activation in depression would help better unravel the interplay between inflammation and depressive symptomatology.

Finally, it is worth noting that the immunopsychiatric approach implies a broadening of our view in the study of mental health, moving our focus from the brain only to the entire body and the living environment. Such a shift in perspective has one major conceptual and practical implications. First, it implies the study of psychiatric disorders at the interface between the brain, the body and the environment, pointing out to the relevance of the physiological and environmental context in addition to the details of the molecular and cellular mechanisms (Alboni et al., 2016; Golia et al., 2019; Raison et al., 2013; Branchi and Giuliani, 2021). Second, it implies a greater number of pharmacologically targetable disease mechanisms, which do not involve only the nervous but also the immune system, to be exploited to develop novel effective treatments for psychiatric disorders. Since knowledge of disease mechanism was asserted as one of the most important factors in decisions to invest in a particular human condition, this may renew the interest of pharmaceutical companies in investing in the fields of neuroscience, psychiatry and psychopharmacology. Third, a replicable set of findings increasingly paints a consistent picture of how the immune system is key in identifying depression subtypes, which has the potential to impact the efforts of pharmaceutical industries to refine the population target, finally increasing the success rate of novel treatments.

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Conflict of Interest

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Supplementary material

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