Towards precision medicine

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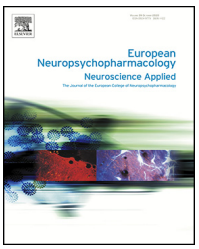

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Towards precision medicine: What are the stratification hypotheses to identify homogeneous inflammatory subgroups

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Abstract
Diverse lines of research testify a link, presumably causal, between immune dysregulation and the development, course and clinical outcome of psychiatric disorders. However, there is a large heterogeneity among the patients' individual immune profile and this heterogeneity prevents the development of precise diagnostic tools and the identification of therapeutic targets. The aim of this review was to delineate possible subgroups of patients on the basis of clinical dimensions, investigating whether they could lead to particular immune signatures and

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tailored treatments. We discuss six clinical entry points; genetic liability to immune dysregulation, childhood maltreatment, metabolic syndrome, cognitive dysfunction, negative symptoms and treatment resistance. We describe the associated immune signature and outline the effects of anti-inflammatory drugs so far. Finally, we discuss advantages of this approach, challenges and future research directions.

1. Introduction

Major psychiatric disorders such as major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia-spectrum disorders pose a significant burden on the individual, their caregivers and society in general (Alonso et al., 2004; Sobocki et al., 2006; Whiteford et al., 2013). Current front-line treatments include antidepressants, mood stabilizers and antipsychotics, often combined with psychotherapy and social support (Cipriani et al., 2011, 2018; "WHO | Antipsychotic Medications for Psychotic Disorders," 2015). However, a considerable fraction of patients across disorders respond only partly or are treatment resistant (Perlis et al., 2006; Sackeim, 2001; Saha et al., 2007). For this significant patient group, the development of new treatments is urgent. This development is hampered by high heterogeneity; patients with the same diagnosis may show large interindividual variation, and above that, nearly all symptoms may occur across different diagnostic categories. Current diagnostic classifications are largely based on groupings of subjectively experienced symptoms, which are assessed in the clinical interview. The aim of the field is to develop more objective measurable biomarkers related to the underlying pathophysiology of mental disorders (Insel and Cuthbert, 2015; Jentsch et al., 2015). In this regard, immune dysregulation may act as a pathophysiological "hub" that links divergent peripheral and central biochemical processes involved in several mental illnesses, at least in a considerable number of patients (Dantzer et al., 2008; Haroon et al., 2012; Müller and Schwarz, 2007).

The immune system is one of the body's central mechanisms, in constant interaction with the internal and external environment, and associations with different aspects of immune dysregulation have been found in relation to psychopathology. A subset of psychiatric patients with different diagnoses shows markers of immune dysregulation, with features similar to mild chronic inflammation (Goldsmith et al., 2016). Those markers tend to correlate with greater symptom severity and resistance to current treatments (Bulut et al., 2019; Carvalho et al., 2013; Fan et al., 2007; Haroon et al., 2018; Hope et al., 2013; Nothdurfter et al., 2019; Strawbridge et al., 2015). A number of studies point to the gut-brain axis, supporting the leaky gut hypothesis or the gut-microbiota-dysbiosis hypothesis (Berk et al., 2013; Genedi et al., 2019). Psychological stressors such as early life trauma and social stress may also induce immune dysregulation (Berk et al., 2013). Other sources of immune system aberrations might well be obesity, poor diet, low physical activity, disruption of sleep or smoking (Berk et al., 2013), auto-immune dysfunction (Eaton et al., 2010), and early life infections (Khandaker et al., 2012).

The identified mechanisms through which abnormal activation of the immune system may trans-diagnostically precipitate psychiatric symptoms are numerous (Raison and Miller, 2013; Rosenblat et al., 2014; Rosenblat and McIntyre, 2017; Stertz et al., 2013). In brief, proinflammatory cytokines passively or actively pass through the blood brain barrier (BBB) and induce microglia activation. Deviant microglia functioning could leave the brain tissue in suboptimal condition; with less modifiable synaptic connections, less efficient functional circuits and loss of plasticity (Eltokhi et al., 2020). These brain impairments may underlie impaired affective, cognitive and motivational functioning in people with major psychiatric illnesses. In addition to that, long-term increased immune activation results in abnormal hypothalamic–pituitary–adrenal (HPA) axis response, reduction of monoamine levels, increased production of neurotoxic glutamate, kynurenic catabolites and oxidative and nitrosative stress (O&NS).

While molecules produced by the immune system could regulate brain development and function, the brain also regulates the immune system. The predominant signaling pathways that have been involved in immune system modulation are the HPA axis and the sympathetic nervous system (Dantzer, 2018). The HPA axis is a major neuroendocrine system which controls responses to environmental stressors via the production of glucocorticoids, while glucocorticoids have a strong immunomodulatory effect. Exposure to psychological stressors, such as early life trauma, induces structural and functional alterations in the HPA axis and the associated brain areas (Van Bodegom et al., 2017). This results in long-term programming of the immune functions (Hong et al., 2020). In addition to the HPA axis-mediated communication between the brain and the immune system, immune cells also receive input directly from the sympathetic and parasympathetic nerve endings (Kenney and Ganta, 2014). Neurotransmitters released following the stimulation of the body's flight-or-fight responses bind to their respective receptors placed on the surface of immune cells, along with other target organs (Kenney and Ganta, 2014).

The fact that the immune and central nervous systems are reciprocally regulated opens the possibility that immune-modulating interventions may be beneficial for emotion regulation, cognition and other domains, while psychological and lifestyle interventions can affect and potentially restore immune function. In this review we will mainly focus on the immune-to-brain signaling pathways and the effects of immune-modulating interventions on psychiatric symptoms. Clinical trials thus far have shown mixed results

(Çakici et al., 2019; Köhler et al., 2014). This could theoretically be due to general study methodologies on heterogeneous patient groups. First and foremost, there is now evidence suggesting that not all patients show abnormal immune activation (Chamberlain et al., 2019; Raison and Miller, 2011), yet, in the majority of clinical trials participants are not pre-selected based on their baseline immune profile. Second, as with any other array of pathophysiological processes, the immune changes underlying different clinical symptoms are expected to be diverse and without doubt not universal. Therefore, we could not expect all patients to benefit from the same class of immune-modulating medication. Last, optimal dose and duration are not known, and some trials that came out negative may have missed optimal drug doses or provided it for a very short time period.

The potential that immune-modulating interventions hold is not trivial, considering the pressing need for new treatment options and the many therapeutics available in this field. However, a more personalized treatment approach towards the status of the immune state is warranted in order to increase the impact of immune system targeting medication, while keeping adverse effects acceptable. Towards this direction, the aim of this review was to identify subgroups of patients, on the basis of clinical dimensions, that have been associated with immune dysregulation and delineate their immune profile. We suggest six clinical entry points; genetic liability to immune dysregulation, childhood maltreatment, metabolic syndrome, cognitive dysfunction, negative symptoms and treatment resistance. We first describe the immune-related biomarkers that have been associated with each subgroup and we then outline the effects of immune-based interventions thus far. Finally, we discuss advantages of this approach, challenges and future directions.

1.1. Genetic liability to immune dysregulation in the development of psychopathology

Predisposition of an individual to abnormal immune responses has been suggested to play a role in the etiology of psychiatric disorders (Bufalino et al., 2013; Raison and Miller, 2013). In addition, patients with major psychiatric disorders have higher prevalence of autoimmune diseases, while a number of autoimmune diseases are associated with increased risk of psychopathology (Gibney and Drexhage, 2013; Jeppesen and Benros, 2019). Besides, a general (auto)immune disposition is further supported by findings of increased autoantibody levels and autoantibody reactivity in patients with MDD and schizophrenia even in the absence of known autoimmune disorders (Laske et al., 2008).

Both autoimmune and major psychiatric disorders are known to be heritable to some degree. Among the most consistent findings from genetic studies in psychiatric and autoimmune disorders are genetic loci associated with immune function. In addition, it has been hypothesized that patients with psychiatric disorders and in particular schizophrenia pose a genetic susceptibility to infections, while infection is a shared risk factor for the development of both psychopathology and autoimmune disorders (Benros and Mortensen, 2020; Jeppesen and Benros, 2019). Among the most studied genetic determinants of susceptibility towards psychopathology and autoimmune disorders are the major histocompatibility complex (MHC) class I and II regions and regions coding for the complement system (Castro and Gourley, 2010; Jeppesen and Benros, 2019; Sekar et al., 2016). MHC region is highly polymorphic and the product encoded is called human leukocyte antigen (HLA). In regard to the complement system, studies have shown excessive complement activity in relation to the development of schizophrenia (Sekar et al., 2016). The HLA and complement type can be detected in the clinic, with routine lab measurements, such us polymerase chain reaction, enzyme-linked immunosorbent assay, gel electrophoresis or more recent high-throughput nucleic acid detection methods (Castro and Gourley, 2010).

Another type of investigation, Mendelian randomization, uses genetic variation to provide evidence on the causality of the relationship between inflammatory biomarkers and major psychiatric disorders. Earlier this year, in a large UK population-based cohort study, Khandaker et al. showed that interleukin-6 (IL-6) and C-reactive protein (CRP) are likely causally associated with depression (Khandaker et al., 2020). In schizophrenia and schizoaffective disorder, CRP is suggested to have a protective effect, while soluble IL-6 receptor a risk increasing effect (Hartwig et al., 2017). A protective effect of CRP on schizophrenia was also shown in a meta-analysis by Ligthart et al. (Ligthart et al., 2018). In the same meta-analysis, counter to schizophrenia, CRP has been shown to have risk-increasing effect in BD (Ligthart et al., 2018). Analogously, in a large-scale cross-consortium Mendelian randomization study, the authors showed that genetically elevated CRP are potentially protective towards the risk of schizophrenia, while they observed a causal link between elevated CRP levels and BD (Prins et al., 2016). Last, Wium-Andersen et al. used genetic variants that influence the levels of CRP in a Mendelian randomization analysis to investigate whether CRP was associated with late onset BD in the general population. They conclude that indeed CRP is associated with late onset of the disease (Wium-Andersen et al., 2016).

Genetic liability to immune dysregulation may lead to precipitation and untoward prognosis of psychiatric disease though different pathways. Genetic susceptibility may result in abnormal number and activity of leucocytes and an aberrant level of pro-inflammatory cytokines in the serum, plasma and cerebral spinal fluid (Drexhage et al., 2010). The increased cellular and humoral immune response can trigger various neuroplastic changes, such as synaptic branching and neurogenesis, that on their term are also contributing mechanisms associated with psychiatric symptomatology (Eyre and Baune, 2012; Haarman et al., 2015). By looking at the different glial cells, such as microglia, astrocytes and oligodendrocytes various immunological effects on the brain of patients with mood disorders can be identified (Bhattacharya et al., 2016; B.C. Haarman et al., 2016). Recent studies reported increased activation of microglia in several areas of the brain in patients with MDD, BD and schizophrenia (Haarman et al., 2014; Ruhé et al., 2014). Microstructural white matter aberrations, involving oligodendrocytes, have been demonstrated quite robustly in patients with BD (Duarte et al., 2016; B.C. Haarman et al., 2016). Oxidative stress and kynurenine

pathways are thought to play an important role in the communication between immune cells, glial cells and neurons (Anderson et al., 2016; Wigner et al., 2017).

More genetic studies are needed, in order to establish the list of immune homologues that are most valuable predictors of the course of psychopathology. In addition, we need to estimate the combined effect of multiple genetic variants in order to treat clinically valuable quantitative thresholds of susceptibility towards immune dysregulation. But in the meanwhile, screening of patients for immune-related genetic variants that have been linked to psychopathology may help identify relevant clinical subtypes and possibly guide the development of tailored interventions and improve patients' prognosis.

1.2. Childhood maltreatment, immune dysregulation and the development of psychopathology

Childhood maltreatment (CM), defined as any abuse or neglect occurring before the age of 18 years, increases the risk to develop psychiatric disorders. CM is elevated in psychiatric populations, with a prevalence up to nearly 50% in major depression; childhood adversities, including CM, substantially increases the risk of psychosis (odds ratio: 2,8) (Varese et al., 2012). CM is also associated with an unfavorable course of illness and non-response to antipsychotic and antidepressant treatments (Misiak and Frydecka, 2016; Nelson et al., 2017). In BD, at least one type of CM is associated with an earlier age of onset, rapid cycling, more suicide attempts and mood episodes (Etain et al., 2013). CM is also associated with more physical and psychological comorbidities (Agnew-Blais and Danese, 2016; Hepgul et al., 2012; McIntyre et al., 2012; Misiak et al., 2015).

Interestingly, CM has been associated with immune disruption and as such inflammation could be conceived as a mediating factor between traumatic events and psychiatric disorders. Baumeister et al.(Baumeister et al., 2016) and Coelho et al. (Coelho et al., 2014), found in meta-analysis that CM is associated with elevated levels of circulating C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in both clinical and non-clinical samples. Regarding only studies on psychiatric patients, discrepant associations between CM and immune disruption have been reported. In a birth cohort with 32 years of follow-up, depressed participants with a history of CM had higher high sensitivity CRP (hsCRP) than controls, compared to depressed participants without a history of CM (Danese et al., 2008). In addition, in small samples of psychotic patients ($n = 40$) and first episode psychosis patients ($n = 24$), Dennison et al. (Dennison et al., 2012) and Di Nicola et al. (Di Nicola et al., 2013) reported proinflammatory phenotypes in patients with CM, including increased IL-6 and TNF-α or TNF-α only for first-episode. However, several discrepant results have also been published. Counotte et al. (Counotte et al., 2019) found no association between CM and any of the cytokines measured, including CRP, IL-6 and TNF$-\alpha$. No association was found in MDD either, despite 41 cytokines assayed (Palmos et al., 2019). By contrast, in a large population ($n = 1084$), Jonker et al. (Jonker et al., 2017) found an association between CM before 16 and psychopathology at 19 as well as between CM and CRP at 16, but the two were not related. Several factors could explain these discrepancies such as differences in cytokine's assays, in sample size, in assessment of CM or investigations of covariates.

The links between CM, immune system and psychopathology are complex, but CM appears as a key point since it impacts both clinical and immune features of psychiatric disorders. CM has huge implications for patients, caregivers and researchers, as it is relevant for stratification models: being highly prevalent in clinical populations and quite easy to assess, it would help to identify homogeneous subgroups of patients to whom immunomodulatory therapeutic strategies could be proposed.

1.3. Metabolic syndrome, immune activation and psychopathology

Metabolic syndrome represents a cluster of metabolic abnormalities that include hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia (Mottillo et al., 2010). It predisposes an individual to diabetes, cardiovascular disease (CVD), and dementia and is recognized as a leading cause of CVD-related mortality in the general population (Mottillo et al., 2010). In patients with severe psychiatric disorders, comorbid CVDs are known to be one of the most frequent causes of mortality, with a frequency well above that of suicide (Roshanaei-Moghaddam and Katon, 2009), resulting in life expectancy 10 to 20 years shorter compared to the general population (Chang et al., 2011). In a recent meta-analysis including individuals with BD, schizophrenia and depression, Vancampfort et al. reported a pool metabolic syndrome prevalence of 32.6% (95% confidence interval, 30.8–34.4) (Vancampfort et al., 2015). Metabolic syndrome is prevalent in other psychiatric comorbidities as well, such as anxiety and substance use disorders. The presence of metabolic syndrome is associated with an unfavorable course of illnesses, such as cognitive deterioration, relapse and poor treatment response. Several hypotheses have been suggested to explain this high prevalence including unhealthy and sedentary lifestyle and long-term exposure to psychotropic medication, particularly second-generation antipsychotics and some antidepressants. In addition, metabolic syndrome and psychiatric disorders probably share some pathophysiological features, including HPA axis and mitochondrial dysfunction, common genetic links, epigenetic interactions and neuroinflammation (Penninx and Lange, 2018).

A chronic prothrombotic and proinflammatory state appears to be the central mechanism underlying the pathophysiology of metabolic syndrome, characterized by increased inflammatory cytokine activity. White adipose tissue, especially in the abdominal area, is an active endocrine organ which produces inflammatory cytokines and hormones. It is therefore a major contributor to pathogenic immunometabolic responses in the central nervous system, as well as in the rest of the body (Lopresti and Drummond, 2013; Shelton and Miller, 2010). Several markers of chronic inflammation have been associated with both

obesity and metabolic syndrome in the general population (Saltiel and Olefsky, 2017). In individuals with psychiatric disorders, except for CRP level which have been extensively studied and globally found to be associated with metabolic syndrome or elevated body mass index (although with some inconsistent results) (Lasić et al., 2014; Marshe et al., 2017), other immune-related biomarkers have been much less investigated. In a study including 80 individuals with MDD, Martinac et al. found increased IL-6 serum levels and TNF-α in individuals with metabolic syndrome (Martinac et al., 2017). The levels of inflammatory markers (i.e. CRP and plasminogen activator inhibitor-1) were significantly higher among patients with metabolic syndrome, in another study including 62 inpatients with schizophrenia and 62 with recurrent depressive disorders (Lasić et al., 2014). In a 6-year follow up study, Lamers et al. investigated the association of four depression profilers with immuno-metabolic outcomes (Lamers et al., 2020). They found that atypical, energy-related symptom dimension was robustly associated with poorer immuno-metabolic health both cross-sectionally and longitudinally.

Studies in the general population suggest that anti-inflammatory strategies may be useful in individuals with cardiovascular risk factors, showing a promising lowering effect on some of the inflammatory markers among patients with metabolic syndrome and related disorders (Akbari et al., 2018; Tabrizi et al., 2019). In major mental disorders, several reviews and meta-analyses have examined the effectiveness and tolerance of anti-inflammatory drugs' add-on therapy. Overall, anti-inflammatory agents, mostly celecoxib, aspirin, minocycline, have shown significant effects, however, first they focused on psychiatric symptoms and severity not on cardiovascular risk and secondly they showed inconsistent results with different side effects among psychiatric disorders (Fond et al., 2014). Statins may be especially relevant, given their dual action in reducing cholesterol and inflammation. Statins that pass the BBB have been provided with effect on both metabolic syndrome and clinical symptom severity (Nomura et al., 2018). Physical exercise might also be promising, as it brings about a release of anti-inflammatory cytokines such as IL-10, IL-1 receptor antagonist and T cells (Gleeson et al., 2011; Petersen and Pedersen, 2005), affects adipose tissue (Ross and Bradshaw, 2009) and regulates components of HPA axis and mental health (Firth et al., 2018; Wegner et al., 2014). Extensive recent research also provides evidence that other non-pharmacological interventions, including motivational techniques and nutritional counselling have promising results to reduce cardiovascular risk factors (Cooper et al., 2016).

1.4. Cognitive dysfunction and immune dysregulation in major psychiatric disorders

Cognitive dysfunction is a common symptom in most psychiatric disorders which persists during remission and can vary from quite subtle, affecting only one domain to a global deterioration of most cognitive domains and a decline of up to ten IQ points. Immune dysregulation could be a general mechanism underlying impaired cognitive functioning in different psychiatric diagnoses.

A number of markers of subclinical chronic inflammation have been found to influence cognition across diagnostic boundaries, with IL-6 and CRP dominating the literature. In particular, in late-life depression, poor memory performance has been associated with circulating levels of IL-6 but not with TNF-α nor with IL-1β (Charlton et al., 2018). Likewise, in recurrent depressive disorder, lower immediate and delayed verbal recall performances were related to IL-6, but not TNF-α (Grassi-Oliveira et al., 2011). Association between cognitive dysfunction and IL-6 has also been shown in remitted patients with BD (Barbosa et al., 2018) and in patients with schizophrenia (Frydecka et al., 2015). In regard to schizophrenia, Frydecka et al. showed that higher IL-6 ($n = 151$) was associated with impairment of visual attention, visuomotor processing speed, memory, semantic memory, working memory, task-switching ability and executive control function (Frydecka et al., 2015). In a larger sample size ($n = 413$), Dickerson et al. showed that schizophrenia patients with CRP $\geq$5.0 mg/μl had significantly lower scores on a cognitive test battery than patients with CRP $<$5.0 mg/μl (Dickerson et al., 2007). CRP levels in regard to cognition have also been reported in BD patients. In 107 BD patients, CRP levels were inversely related to general cognitive functioning, and with immediate memory, attention, executive function and language (Dickerson et al., 2013). A number of other markers of subclinical chronic inflammation have been correlated with cognitive dysfunction, including cyclooxygenase-2 and prostaglandins (Cabrera et al., 2016), chemokines (Martínez-Cengotitabengoa et al., 2012), tryptophan metabolism mediators (Zhou et al., 2019) and markers of O&NS (Martínez-Cengotitabengoa et al., 2012).

In clinical trials that have assessed the effect of immune-modulating medication on cognition, some positive results have been found, though other studies report negative results. In schizophrenia and bipolar I/II depression for example, some studies found that minocycline could improve attention, executive functions, memory (Levkovitz et al., 2010; Liu et al., 2014) and psychomotor speed (Soczynska et al., 2017) respectively, but no effects on cognition were observed in other studies (Chaudhry et al., 2012; Deakin et al., 2018; Kelly et al., 2015; Weiser et al., 2019). Likewise, N-acetyl cysteine has been shown to enhance cognition and in particular attention, memory and executive functions (Rapado-Castro et al., 2017; Sepehrmanesh et al., 2018), but not in all trials (Breier et al., 2018; Dean et al., 2012). Pravastatin (Smith et al., 2016; Vincenzi et al., 2014) and varenicline (Smith et al., 2016) did not show beneficial effects on cognition. Infrequency of cognition as a primary outcome complicates the drawing of firm conclusions in current studies. In addition, the inclusion of patients with prominent baseline cognitive dysfunction in future studies is warranted in order to clarify whether immune-based treatments are of benefit for this group of psychiatric patients.

1.5. Negative symptoms and immune dysregulation in major psychiatric disorders

Negative symptoms –blunted affect, alogia, anhedonia, loss of motivation and asociality– have long been associated with chronic forms of schizophrenia, whereas they may be also observed in the early course of the disease (Guessoum et al., 2020; Mallet, 2020; Quattrone et al., 2019) or even precede diagnosis (Schmidt et al., 2017). They can also be found in schizoaffective disorder, in ultra-high-risk subjects (Fusar-Poli et al., 2020), in major depression, neurological diseases (Winograd-Gurvich et al., 2006), and even in the general population (Van Os and Reininghaus, 2016).

Pathophysiological hypotheses could be specific to each dimension of negative symptoms (Guessoum et al., 2020). The effect of peripheral inflammatory cytokines on the ventral striatum and other regions of the basal ganglia has been linked to deficits in reward processing and decreased motivation (Capuron et al., 2012). Inflammation leads to decreases in dopamine release and increased glutamate activity in some patients with major depression (Goldsmith and Rapaport, 2020). In schizophrenia-spectrum disorders, literature also demonstrates relationships between inflammatory cytokines and negative symptoms (TNF-α, IL-6, IL-1 levels mostly, IL-2, IL-8, IL-17) (Goldsmith and Rapaport, 2020), TNF-α and IL-6 levels are associated with blunted affect and alogia (Goldsmith et al., 2018). In drug naive first episode psychosis, negative symptoms are associated with high IL-6 and IL-10 levels (Goldsmith and Rapaport, 2020). Moreover, in ultra-high-risk subjects, baseline high TNF and IL-6 predict negative symptom trajectories (Goldsmith et al., 2019). CRP and its relation with negative symptoms gave conflicting results (Boozalis et al., 2018; Fernandes et al., 2016; Mitra et al., 2017; Steiner et al., 2020). It should be kept in mind that smoking and metabolic syndrome may act as confounding factors.

A recent study explored innate immune system activation (neutrophils, monocytes count, CRP) but found no association with the negative sub-scale of the Positive and Negative Syndrome Scale in first episode psychosis or schizophrenia patients (Steiner et al., 2020). In major depression, TNF-α and IL-6 are elevated (Dowlati et al., 2010), as CRP and IL-1 receptor antagonist, but no study specifically focuses on negative symptoms. High IL-8 levels are associated with schizophrenia and high negative symptoms (Rodrigues-Amorim et al., 2018), but were unchanged in depression (Köhler et al., 2017).

Negative symptoms in schizophrenia are relatively resistant to antipsychotics (Howes et al., 2017), and data are scarce in other diseases. Anti-inflammatory agents could therefore represent a valuable option. Minocycline, a tetracyclic drug that can cross the BBB, may relieve negative symptoms in schizophrenia and showed efficacy in major depression (Rosenblat & McIntyre, 2018). A recent meta-analysis of randomized controlled trials (RCTs) reported positive results on negative symptoms in schizophrenia for the following add-on anti-inflammatory agents: minocycline (ES=0.50; 95%CI=0.17-0.84; $p = 0.003$), N-acetyl-cysteine (ES=0.75; 95%CI=0.19-1.32; $p = 0.009$), and estrogen (ES=0.45; 95%CI=0.13-0.77; $p = 0.006$) (Çakici et al., 2019). In MDD, clinical trials with anti-inflammatory agents have indicated antidepressant treatment effects of both add-on treatment and monotherapy, with celecoxib add-on treatment showing improved antidepressant effects with little heterogeneity among studies (O. Köhler et al., 2014). Antidepressant effects of these agents on negative symptoms other than anhedonia and motivational deficits still need to be explored. Last, trials on the efficacy of the TNF antagonist infliximab in depression have shown conflicting results. Raison et al. showed a significant antidepressant effect in patients with baseline CRP levels of 5 mg/L or higher (Raison et al., 2013). In a follow-up study, though, McIntyre et al. did not find a significant anti-depressant effect in patients with bipolar depression and baseline immune system activation, as it was expected (McIntyre et al., 2019). A significant and sustained response was only observed in a subgroup of patients with a history of CM (McIntyre et al., 2019).

1.6. Immune dysregulation and treatment resistance

One third of patients treated for schizophrenia or mood disorders are considered resistant to treatment, commonly after the failure of two sequences of adequate treatment at a sufficient dosage and duration. Treatment resistant patients show elevated levels of pro-inflammatory cytokines compared to responsive patients, suggesting an interaction between immune moderators and treatment outcome.

In treatment resistant depression, a higher baseline inflammation is found with lower IL-4, vascular endothelial growth factor and monocyte chemoattractantprotein-1(MCP-1), increased levels of IL-6, IL-10, IL-17A, hsCRP, persistently elevated TNF-α, higher expression of IL-1β and migration inhibitory factor and polymorphism in immune genes (IL-1β, IL-11, and TNF-α) (Adzic et al., 2017; Carvalho et al., 2013; Cattaneoet al., 2013; Nothdurfter et al., 2019; Strawbridge et al., 2015). However, these results may differ across studies. In a recent literature review, the authors conclude that promising inflammatory biomarkers for the prediction of treatment resistant depression could be IL-6 and CRP/hsCRP (Yang et al., 2019). The level of expression of inflammation genes may also be considered as a candidate biomarker for antidepressant response (Cattaneoet al., 2013).

Elevated levels of IL-6 and CRP have been found in BD patients and particularly in patients with treatment resistant BD versus healthy controls suggesting that they may be a biomarker for BD (Edberg et al., 2018). Moreover, significantly higher plasma levels of TNF and soluble TNF receptor-2, elevated IL-1β and low kynurenine/tryptophan at baseline could be biomarkers of treatment resistant BD (Haroon et al., 2018; Murata et al., 2020). In treatment resistant manic patients, the white blood cells counts and carcinoembryonic antigen levels were significantly higher compared to treatment responsive manic patients and controls, and are associated with severity of disease in manic patients (Bulut et al., 2019). No difference in levels of hsCRP was found between the groups (Bulut et al., 2019). In patients with a poor lithium response, increased levels of TNF-α have

been found, suggesting the persistence of immune imbalance in treatment resistant mania (Guloksuz et al., 2012).

Specific immune-inflammatory profile has also been associated with treatment resistant schizophrenia. Specifically, immune-inflammatory response system and compensatory immune-regulatory reflex system activation that lead to increased levels of IL-6 and soluble IL-6 receptor were inversely associated with the anti-cytokine clara cell protein, increased level of soluble IL-1 receptor antagonist, IL-2, IL-10, soluble TNF receptor-1, soluble TNF receptor-2, CXCL-8, CCL-3 and polymorphism of CCL-2 (MCP-1 gene) and MCP-1 (Roomruangwong et al., 2020). Studies have also reported elevation of CRP levels in treatment resistant schizophrenia patients (Miller and Goldsmith, 2019). Drug resistance in schizophrenia could be associated with immune-inflammatory response system and HPA axis dysregulation, which could be modulated by antipsychotics treatment such as anti-inflammatory therapeutics (Altamura et al., 2005; B. et al., 2018).

The link between treatment resistant psychiatric disorders and inflammation is well reported, and therefore this would be a rational subgroup for stratification. The identification of biomarkers that predict response to treatment is necessary, firstly to guide treatment selection and also to serve as new therapeutic targets. In this regard, proinflammatory cytokines are promising to function as predictors of treatment response and as therapeutic targets (Halaris et al., 2020; A. H. Miller and Raison, 2016; Miller and Goldsmith, 2019; Raison et al., 2013; Shariq et al., 2018).

2. Discussion

In this review we present subgroups of patients with major psychiatric disorders that have been associated with immune dysregulation and would lead to a stratification model that better reflects the individual's immune state. These subgroups are based on the following relatively simple and easy to determine clinical entry points; genetic liability to immune dysregulation, childhood maltreatment, metabolic syndrome, cognitive dysfunction, negative symptoms, and treatment resistance.

The etiology of immune dysregulation in major psychiatric disorders, although complex, is becoming better understood. It is now well accepted that both genetic susceptibility and environmental triggers play a role (Raison and Miller, 2013). Genetic liability increases vulnerability and psycho-social factors may then trigger the immune system in a different way than in healthy individuals. Single nucleotide polymorphisms in immune-related genes are not only related to increased risk of psychopathology, but also with decreased responsiveness to conventional treatment (Bufalino et al., 2013). Therefore, identification of patients with genetic liability to immune dysregulation will facilitate clinicians to make more informed decisions on the treatment plan and expectedly minimize the need for lengthy periods of experimentation with various medications and dosages. In addition, it will allow directed screening and will hopefully improve our ability to predict untoward outcomes in the course of the disease.

When environmental stressors such as emotional or physical abuse and neglect, take place early in childhood, this increases the risk for the development of psychopathology (Varese et al., 2012) and somatic comorbidity (Hepgul et al., 2012; McIntyre et al., 2012; Misiak et al., 2015). Immune dysregulation has been postulated as a biological link of this relationship. In most, but not all, studies investigating this hypothesis, an association was found between IL-6, TNF-α and CRP and CM (Baumeister et al., 2016; Coelho et al., 2014; Counotte et al., 2019; Danese et al., 2008; Palmos et al., 2019). Further primary research as well as meta-analysis is warranted in order to clarify the observed inconsistencies and conceptualize whether this subgroup of patients has a homogenous inflammatory signature that could guide treatment. A question that still needs to be explored is whether the type and timing of trauma as well as the factors of resilience influence the immune phenotype. In addition, the assessment of important confounders (i.e. socioeconomic status) during childhood and adulthood has to be systematic. Finally, other biomarkers which have been associated with CM, such as aging markers, should be assessed (Aas et al., 2019).

For psychiatric patients with diagnosis of metabolic syndrome, a substantial amount of work suggests a causal link between metabolic syndrome and both inflammation and psychiatric illness. In this regard, targeting mutual disturbed biological pathways, for example inflammatory pathways, seems to be a focal point of intervention. Immunomodulatory interventions such as statins and physical exercise might be promising. Something that still needs to be clarified is whether the immuno-inflammatory signature of metabolic disturbances in the psychiatric population is different or the same compared to the general population. In addition, we should evaluate which anti-inflammatory strategies, aiming at improving cardiovascular risk factors in the general population, could be more effective for individuals with psychiatric disease. Last, when anti-inflammatory add-on therapies are being tested, it is important to evaluate the treatment effects on metabolic parameters and cardio-metabolic outcomes in addition to the effects on psychiatric symptomatology.

For patients presented with cognitive dysfunction and negative symptoms, immune biomarkers seem relevant for both diagnostic purposes and as treatment targets. There is evidence that mediators of the immune system interfere with specific neuronal circuits, namely circuits involved in reward processing and cognition (Capuron et al., 2012; Monje et al., 2003). In clinical samples, IL-6 seems to be associated with global cognitive functioning in general and with memory in particular across psychiatric disorders. This is consistent with studies in animal models showing that inflammation is a strong inhibitor of hippocampal neurogenesis and that IL-6 in particular is associated with poor learning and memory function (Monje et al., 2003). Other biomarkers, such as CRP, cyclooxygenase-2, prostaglandins, chemokines, tryptophan metabolism mediators and markers of O&NS stress are also potential biomarkers of cognitive dysfunction. In regard to negative symptoms and immune biomarkers, studies have mainly focused on schizophrenia, with TNF-α, IL-6, IL-1 being the most relevant. The infrequency of cognition and negative symptoms as primary outcome measures in studies precludes the drawing of fixed

conclusions on symptom-specificity of immune biomarkers. Future clinical trials with evidence-based selection of outcome measures will be decidedly informative. This need is not trivial, given that those are the symptoms usually resistant to current therapeutics (Howes et al., 2017).

Immune dysregulation might also be a moderator of the observed treatment resistance to current treatments. Based on the available evidence, the immune profile of treatment resistant patients tends to differ among studies even within the same pathology. Further stratification of patients based on the suspected origin of immune dysregulation might lead to more homogenous inflammatory subgroups. For instance, a potentially sound subgroup could be patients with poor gut health, such as increased gut permeability or dysbiosis in gut microbiome. This concept is rather promising, since there is a large repertoire of biomarkers to diagnose gut health such as lipoprotein binding protein, calprotectin and metagenomic shotgun sequencing and there are meaningful ways to restore gut health and the subsequent systemic immune dysregulation (Genedi et al., 2019).

The stratification model suggested in this review is based on the hypothesis that immune dysregulation appears in specific subgroups of patients with major psychiatric disorders. This hypothesis has been supported by studies showing that levels of immune biomarkers differ among patients (Chamberlain et al., 2019) and by studies showing that only patients with increased immune activation show a symptomatic response to an immune-modulating treatment (Rapaport et al., 2016). On the other hand, as shown by the authors of a recent meta-analysis, the relative variability of CRP and soluble IL-2 receptor is significantly lower in patients with depression compared to controls, implying that the immune marker elevation observed in depression is not due to an inflamed subgroup, but rather due to a change in the immune marker distribution (Osimo et al., 2020). Therefore, the discussion as to whether the observed immune activation appears in specific subgroups or is more general and homogeneous among patients is not conclusive. This question is currently under investigation in ongoing clinical trials (Khandaker et al., 2018). The validity of the inflamed-subgroup hypothesis will ultimately rest upon systematic investigation of immune biomarker patterns in large population-based studies and upon clinical trials showing a linear association between pre-treatment levels of immune markers and symptomatic response to immune-modulating intervention.

It should also be noted that most studies in the field were done in a cross-sectional design; hence prohibiting the elucidation of cause and effect relationships. The few longitudinal studies suggest a causal role of immune dysregulation in the development of clinical symptoms. In particular, baseline IL-6 and TNF-α have been found to predict negative symptoms slopes in individuals at clinical high risk for psychosis (Goldsmith et al., 2019), while IL-6 and CRP have been shown to predict the development of cognitive dysfunction in patients with MDD (Gimeno et al., 2009).Contrariwise,baseline levels of depression were not found to be predictive of immune activation at follow-up (Gimeno et al., 2009). Interestingly, serum hsCRP has been found to be predictive of depression over a decade, even in individuals with no prior history of depression at baseline (Pasco et al., 2010). Longitudinal studies are also necessary to clarify whether immune dysregulation or psychopathology precedes the immune dysregulation-psychopathology comorbidity observed in the subgroup of patients with experience of childhood maltreatment. The few studies in the field thus far show inconsistent results (Jonker et al., 2017; Miller and Cole, 2012).

Further research is needed, in order for the proposed model to be refined and tested in prospective clinical studies. Firstly, while the reviewed studies reported statistically significant associations between immune biomarkers and mental disorders compared to controls, this does not necessarily mean that these were large effects. Studies in the field have sometimes reported relatively small effect sizes, thus limiting the direct clinical relevance of the reported findings. Second, demonstrating statistical differences of a single immune biomarker between groups, for example IL-6, does not mean that measuring absolute IL-6 levels would be specific and sensitive enough to identify homogenous groups of patients. Instead, we suggest that the combination of biomarkers that represent each subgroup, the so-called "immune signature" could possibly have higher diagnostic and clinical value. The advantage of employing a panel of immune markers has been previously demonstrated in a proof of concept study by Rapaport et al. (Rapaport et al., 2016). Towards this direction, a wider array of immune biomarkers should be investigated. In future studies, attention should be brought to overlooked analytical and statistical methodological issues, as discussed in the next paper of this special issue by Glaichenhaus et al. (Glaichenhaus et al., In Press), as well as to confounding factors, such as the immune suppressing effects of psychotropics on the population under study (Chiu et al., 2013) and the various off-target effects of anti-inflammatory agents.

In conclusion, the stratification of patients in subgroups that better reflect the immune state of the patient is crucial when testing the viability of immune-based therapies. Indiscriminate treatment of psychiatric patients regardless of the baseline immune profile does not only run the risk of concealing the effect of treatment responders, but is possibly harmful for patients without immune dysregulation.

Contributors

M.L. conceived the presented stratification model. M.L., R.S., B.H. and M.I. developed the concept while M.I and R.S. drafted the overall manuscript of the review. E.S. and B.H. contributed in the drafting of the paragraph "Autoimmune liability in the development of psychopathology". M.F. drafted the paragraph "Childhood maltreatment, immune dysregulation and the development of psychopathology" and contributed in drafting part of the discussion. O.G. drafted the paragraph "Metabolic syndrome, immune activation and psychopathology". M.I. and I.S. drafted the paragraph "Cognitive dysfunction and immune dysregulation in major psychiatric disorders". J.M. and C.D. drafted the paragraph "Negative symptoms and immune dysregulation in major psychiatric disorders". E.T. drafted the paragraph "Immune dysregulation and treatment resistance". M.L., I.S., R.S., B.H. and M.I. provided critical revision. All

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