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White matter integrity and pro-inflammatory cytokines as predictors of antidepressant response in MDD

Sigrid Breit [a,c,*], Elena Mazza [a,b], Sara Poletti [a,b], Francesco Benedetti [a,b]

[a] Psychiatry and Clinical Psychobiology, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milano, Italy
[b] University Vita-Salute San Raffaele, Milano, Italy
[c] Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland

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ABSTRACT

Major depressive disorder (MDD) is a multifactorial, serious and heterogeneous mental disorder that can lead to chronic recurrent symptoms, treatment resistance and suicidal behavior. MDD often involves immune dysregulation with high peripheral levels of inflammatory cytokines that might have an influence on the clinical course and treatment response. Moreover, patients with MDD show brain volume changes as well as white matter (WM) alterations that are already existing in the early stage of illness. Mounting evidence suggests that both neuroimaging markers, such as WM integrity and blood markers, such as inflammatory cytokines might serve as predictors of treatment response in MDD. However, the relationship between peripheral inflammation, WM structure and antidepressant response is not yet clearly understood. The aim of the present review is to elucidate the association between inflammation and WM integrity and its impact on the pathophysiology and progression of MDD as well as the role of possible novel biomarkers of treatment response to improve MDD prevention and treatment strategies.

1. Clinical relevance of MDD

Major depressive disorder (MDD) is a prevalent and serious mental disorder that can lead to chronic recurrent symptoms and suicidal behavior. It is known to be one of the leading causes of disability worldwide and to pose several treatment challenges (Ferrari et al., 2013). A lifetime recurrence risk of respectively 60% after the first depressive episode and 90% after the third episode has been reported (Monroe and Harkness 2011). Studies showed that between 30% and 50% of patients do not respond to antidepressants (Bschor et al., 2012). Treatment resistant depression (TRD) is defined as resistance to at least two different antidepressants in the standard dose for a treatment duration of at least 6–8 weeks. It seems that an underlying immune dysregulation with elevated inflammatory levels might contribute to antidepressant treatment resistance (Strawbridge et al., 2015). Selective serotonin reuptake inhibitors (SSRIs) are usually first line therapy and represent the most commonly prescribed antidepressants in the treatment of MDD (Garnock-Jones and McCormack 2010). However, they show a lack of effectiveness, particularly in more severe forms of depression, with about 60–70% of patients not achieving remission (Trivedi et al., 2006; Yuan et al., 2020). The most effective treatment option in TRD is currently electroconvulsive therapy (ECT) with response rates of 50–70% and of even 90% in untreated patients (Greenberg and Kellner 2005). Nevertheless, relapse rates are high, particularly in the first 6 months after treatment (Jelovac et al., 2013). Given the heterogeneity of MDD, the high risk of chronification, including higher suicide risk, reduced quality of life as well as the enormous economic costs, that are related to numerous hospitalizations and protracted changes of treatment, there is a pressing need to identify novel biomarkers in order to develop more efficacious, rapid and personalized treatments.

2. The role of inflammation in MDD

The pathophysiology of MDD is still not clearly understood. To the best of our knowledge, its development involves social-environmental stress factors, genetic and biological factors as disturbances of the hypothalamic-pituitary adrenal axis (HPA)-axis and monoamine production, alterations in glutamate excitotoxicity, reduced neuroplasticity, as well as a dysregulation of the immune system with increased levels of pro-inflammatory cytokines. Cytokines are small proteins, produced by immune cells, as macrophages, lymphocytes and

* Corresponding author. University Hospital of Psychiatry and Psychotherapy University of Bern, Murtenstrasse 21, 3008, Bern, Switzerland.
E-mail address: sigrid.breit@upd.unibe.ch (S. Breit).

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mast cells. Essentially, cytokines can be divided into 5 main groups: interferons (IFN), interleukins (IL), colony stimulating factors (CSF), tumor necrosis factors (TNF) and chemokines. They are involved in cell signaling, regulating the proliferation and differentiation of other cells. As a part of immunological reactions and inflammatory processes, cytokines are particularly important for the balance of the immune system, that is essential for health and disease. A disruption of this balance caused by an excessive production of inflammatory cytokines can lead to the development of inflammatory disorders. Moreover, cytokines play an important role in brain function influencing neurotransmitter systems, neuroendocrine function and neuronal plasticity.

2.1. Inflammation and depression

Mounting evidence suggests the presence of a strong relationship between inflammation and depression. The exposure to chronic elevated inflammatory cytokines contributes to the development of mental disorders such as depression (Felger and Lotrich 2013). Exogenous administration of cytokines, for example IFN-α as treatment of cancers and viral infections, might induce depressive symptoms similar to MDD and elevate suicide risk by the activation of other central and peripheral inflammatory cytokines, interacting with monoamine metabolism (Raison et al., 2009; Lucaciu and Dumitrascu 2015; Felger et al., 2016).

Inflammatory cytokines can act as mediators of both environmental and genetic factors on the development of depression (Felger and Lotrich 2013). An important environmental contributing factor that goes along with chronically elevated levels of inflammation is childhood trauma. The exposure to adverse childhood experiences (ACE) is known to be a crucial risk factor for MDD and increased levels of pro-inflammatory cytokines, especially IL-6, have been reported in MDD patients with a history of ACE compared to depressed patients without ACE and healthy controls (Lu et al., 2013; de Punder et al., 2018; Muller et al., 2019; Gill et al., 2020). Accordingly, MDD patients with childhood trauma might represent a subgroup of depressed patients with a subtype of inflammatory MDD who could benefit more from an anti-inflammatory treatment (de Punder et al., 2018).

The presence of a link between inflammation and depression is corroborated also by mounting data showing a comorbidity of MDD with inflammatory medical illnesses. Up to 50% of patients with autoimmune disorders exhibit depression-like symptoms (Pryce and Fontana 2017) including rheumatoid arthritis (RA) (Vallerand et al., 2018), systemic lupus erythematosus (Bachen et al., 2009) and multiple sclerosis (MS) (Bruno et al., 2020). In these patients, levels of inflammatory markers correlate with depression severity (Koijma et al., 2009; Rossi et al., 2017; Herder and Hermanns 2019). Furthermore, it has been found that patients with autoimmune disorders who suffer depression respond less well to their anti-inflammatory treatment and that a successful treatment of depression might lead to an improvement of overall treatment outcome (Wenger and Calabrese 2021). Similar findings have been reported for other inflammatory diseases such as endocrine disorders (Fornaro et al., 2010), metabolic disorders (Luppino et al., 2010; Pan et al., 2012, Ambrósio et al., 2018) and cardiovascular disease (Shah et al., 2011; Halaris 2017). A chronic inflammatory state induced by medical illnesses that results in increased levels of pro-inflammatory cytokines that might enter the central nervous system (CNS) by breaking down the blood brain barrier (BBB) and activating glial cells, has been proposed as a possible underlying mechanism contributing to neuroinflammation and dysfunction of neurotransmitter systems involved in the pathophysiology of MDD (Sun et al., 2022) (see Fig. 1). Peripheral-induced inflammation might affect in particular specific brain regions as the hippocampus, cortex, amygdala and hypothalamus (Sun et al., 2022).

In physiological conditions, immune cells can enter into the CNS at specific sites, through the BBB and the choroid plexus in very low amount (Mapunda et al., 2022). However, conditions such as psychological stress can cause trafficking and recruitment of peripherally

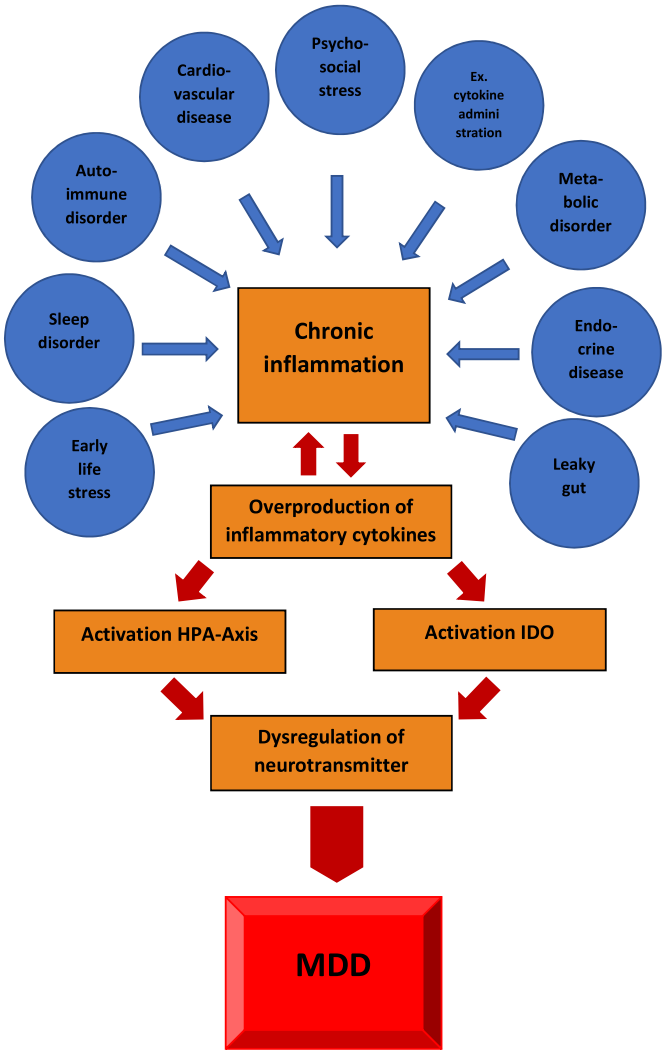

Fig. 1. Relationship between inflammation and depression.

derived monocytes to the brain where they differentiate into brain macrophages that promote inflammatory signaling (Wohleb et al., 2015). Recent studies investigated the relationship between plasma and cerebrospinal fluid (CSF) inflammatory markers and depressive symptoms in patients with MDD. A strong correlation was found between plasma and CSF CRP levels (Felger et al., 2020). High plasma CRP was associated with CSF inflammatory markers correlating with depression severity. This finding indicates the role of CRP as a potential peripheral biomarker reflecting peripheral and central inflammation in depression (Felger et al., 2020). Central neuroinflammation was found in perinatal depression (Miller et al., 2019). However, there was no strong correlation between plasma and CSF cytokine levels and no significant association between levels of peripheral cytokines and perinatal depression indicating that there is not always a link between central neuroinflammation and peripheral inflammation in MDD (Miller et al., 2019).

Inflammation is not specific for depression and is not relevant for all depressed patients. A recent meta-analysis of 30 studies indicated a prevalence of low-grade inflammation in depression of 27% and a prevalence of elevated CRP in depression of 58% (Osimo et al., 2019). Inflammatory depression can be considered as an important subtype of depression that is related to other inflammatory disorders, poorer response to antidepressants and treatment resistance (Suneson et al., 2021). Depressed patients without inflammatory alterations might show less treatment resistance and a better outcome after the treatment with conventional antidepressants. However, the focus on inflammation and

inflammatory parameters as predictors of treatment response might offer a great opportunity for patient stratification and the development of personalized treatments for MDD.

2.2. Immune alterations in MDD

Several meta-analyses and systematic reviews have indicated an association between MDD and increased levels of pro-inflammatory cytokines, mainly IL-6 (Howren et al., 2009; Dowlati et al., 2010; Liu et al., 2012; Haapakoski et al., 2015; Kohler et al., 2017; Yang et al., 2018), TNF-α (Dowlati et al., 2010; Liu et al., 2012; Kohler et al., 2017), IL-1β (Howren et al., 2009; Miller and Raison 2016; Yang et al., 2018) and the acute phase C-reactive protein (CRP) (Howren et al., 2009; Valkanova et al., 2013; Haapakoski et al., 2015) (see Table 1). Further, anti-inflammatory drugs could unfold small to moderate antidepressant effects whereas conventional antidepressants may have anti-inflammatory properties (Mosiolek et al., 2021) (see Table 3). A recent systematic review comprising 20 studies and 5063 participants showed improvement of depressive symptoms after anti-cytokine therapy (monoclonal antibody or cytokine inhibitor), emphasizing the possible causal role of cytokines in the pathogenesis of depression and cytokine modulators as potential future class of antidepressant drugs (Kappelmann et al., 2018). Also, improvement of depressive symptoms was accompanied by a reduction of IL-1β and TNF-α levels (Hannestad et al., 2011; Liu et al., 2020). The use of SSRIs might decrease levels of IL-6 and TNF-α (Hannestad et al., 2011; Wang et al., 2019) and IL-1β significantly (Wiedlocha et al., 2018; Wang et al., 2019). Another meta-analysis confirmed a decrease of IL-6 levels with antidepressant treatments, whereas treatment resistant patients showed increased TNF-α levels as well as higher baseline inflammation (Strawbridge et al., 2015). It can be concluded that SSRIs might have moderate immunomodulating effects (Wang et al., 2019) and that the best efficacy could be achieved by combining antidepressants with anti-inflammatory drugs in the case of initial treatment resistance to antidepressant therapy alone (Kopschina Feltes et al., 2017). Furthermore, ECT, that is applicated for the treatment of severe and TRD, has an impact on the neuroendocrine system, neurotransmitter levels and neuroplasticity as well as the immune system and cytokine levels (Rotter et al., 2013; Zincir et al., 2016; Gay et al., 2021), mainly acting on IL-6, TNF-α and CRP levels (Jarventausta et al., 2017; Kruse et al., 2018; Sorri et al., 2018).

Finally, a related group of cytokines particularly involved in neuroimmune processes, with receptors mainly expressed in the CNS, the so-called chemokines, may also play an important role in the pathophysiology of MDD. They are involved in synaptic transmission, neurogenesis and modulation of neuroinflammation by regulating the migration of monocytes and macrophages into the brain (Milenkovic et al., 2019). There is some evidence that chemokine levels might be increased in depressed patients and could be influenced by antidepressants, so that they might represent potential predictive markers and therapeutic targets in MDD (Eyre et al., 2016; Kohler et al., 2017, 2018; Milenkovic et al., 2019).

Most of the studies mentioned relate to peripheral cytokine levels. However, the inflammatory status in the CNS is of fundamental importance for brain function. Microglia are primary resident immune cells of the brain with a key function in neurogenesis, synapsis interactions, regulation of neuroinflammation and generation of inflammatory cytokines. Microglial cells are considered important contributing factors to the pathogenesis of depression (Yirmiya et al., 2015; Singhal and Baune 2017). In fact microglia, which can be activated amongst others by stress, neuronal injury, chronic inflammation and infection (Kreutzberg 1996; Streit et al., 1999; Sugama et al., 2009), induce an overproduction of pro-inflammatory cytokines, that may on the one hand trigger the activation of the HPA-axis and on the other hand the activation of the enzyme indoleamine-2,3-dioxygenase (IDO), stimulating the kynurenine pathway (Maes et al., 2011; Haroon et al., 2012). These pathophysiological mechanisms may lead to a dysregulation of serotonergic and noradrenergic systems and contribute to the pathophysiology of depression (Kopschina Feltes et al., 2017).

Furthermore, microglia cells considered as the main actors of stress-induced neuroinflammatory processes, seem to induce damage in other main glial cells such as astrocytes and oligodendrocytes, further contributing to the pathophysiology of depression (Czeh and Nagy 2018). Indeed, postmortem studies revealed reduced glial cell density, for example in the amygdala (Bowley et al., 2002) and in the anterior cingulate cortex (Cotter et al., 2001) in individuals with MDD and an evidence for disturbed glial gene expression in MDD has been described (Rajkowska et al., 2015; Pantazatos et al., 2017). Impaired functioning of oligodendrocytes, representing the main myelin forming cells of the CNS, may induce a disruption of neural networks, underlying mood regulation (Edgar and Sibille 2012). Whereas astrocyte dysfunction may lead to a dysregulation of glucose metabolism, neurotransmitter balance, synaptic development and BBB permeability. Altogether these alterations further contribute to the pathophysiology of depression.

3. White matter integrity and MDD

There is increasing evidence of the association between impaired WM integrity and depression, so that WM microstructural alterations have been proposed as potential biomarkers of MDD (Murphy and Frodl 2011; Zhu et al., 2011; Chen et al., 2016). The use of diffusion tensor imaging (DTI) allows a detailed insight into the microstructure of WM pathways. Tract Based Spatial Statistics (TBSS) is a voxel-wise approach, which allows analyses of WM microstructure across the entire brain. The TBSS method enables to obtain four DTI indexes: Fractional anisotropy (FA) which reflects axonal diameter, fiber density and myelination (Beaulieu 2002); Mean diffusivity (MD), a measure of the average mobility of water molecules independent of tissue directionality (Maffei et al., 2015); Axial diffusivity (AD) which reflects the magnitude of water diffusion in the direction of the fiber tract, representing an important correlate of axonal injury (Budde et al., 2009) as well as radial diffusivity (RD) which reflects the diffusion of water perpendicular to axonal fibers and increases with demyelination (Klawiter et al., 2011). Neurite orientation dispersion and density imaging (NODDI) and free-water (FW) imaging are advanced diffusion-weighted imaging techniques that are aimed at a biophysical characterization of WM microstructure and might offer greater sensitivity and specificity in the detection of WM integrity than the traditional DTI (Kraguljac et al., 2019). NODDI might enable a better differentiation of orientation dispersion and fiber density as shown in the example of MS (Schneider et al., 2017). FW imaging is used to measure the contribution of isotropic

Table 1
Inflammatory markers found to be altered in MDD (**meta-analysis/systematic review**).

CRP	IL-6	TNF-α	IL-1β	IL-8	INF-γ
Haapakoski et al., 2015; Valkanova et al., 2013; Howren et al., 2009	Perez-Sanchez et al., 2018; Yang et al., 2018; Kohler et al., 2017; Goldsmith et al., 2016 Haapakoski et al., 2015; Dahl et al., 2014; Liu et al., 2012; Dowlati et al., 2010; Howren et al., 2009	Perez-Sanchez et al., 2018; Kohler et al., 2017; Goldsmith et al., 2016; Liu et al., 2012; Dowlati et al., 2010	Perez-Sanchez et al., 2018; Yang et al., 2018; Chen et al., 2018; Miller and Raison, 2016; Dahl et al., 2014; Howren et al., 2009	Chen et al., 2018; Miller and Raison, 2016; Dahl et al., 2014	Chen et al., 2018; Perez-Sanchez et al., 2018; Kohler et al., 2017; Goldsmith et al., 2016; Dahl et al., 2014

FW to DTI metrics and might allow to differentiate between neurodegeneration and neuroinflammation (Kato et al., 2022). Neuroinflammation might lead to a volume increase of water in the extracellular spaces of the brain parenchyma, which is reflected by an increase of FW (Kraguljac et al., 2019). The application of a FW correction to DTI data might increase the sensitivity of DTI-based metrics for exploring clinical effects in depression (Bergamino et al., 2015). However, only few studies have used these advanced techniques to examine the association between inflammation and WM integrity compared to the TBSS method, which is most commonly used in the literature (Benedetti et al., 2016; Sugimoto et al., 2018; Green et al., 2021).

Neuroimaging studies revealed that depressed patients show WM alterations in different brain regions such as prefrontal and parietal cortex, the internal capsule and the left superior longitudinal fasciculus, the uncinate fasciculus and the supero-lateral medial forebrain bundle, as well as in limbic structures as the cingulum bundle (Ma et al., 2007; Kieseppa et al., 2010; Murphy and Frodl 2011; Zhu et al., 2011; Zuo et al., 2012; Aghajani et al., 2014; Bracht et al., 2015; Chen et al., 2016; Bhatia et al., 2018). Moreover, WM changes in the reward network, such as reduced myelination in the nucleus accumbens, have been reported highlighting its importance for the pathophysiology of depression (Sacchet and Gotlib 2017; Dillon et al., 2018). The exploration of WM integrity in young first episode and treatment-naïve patients indicates the presence of WM alterations in early stages of the disease, suggesting an influence on the pathophysiology of MDD (Zhu et al., 2011; Aghajani et al., 2014; Bessette et al., 2014; Chen et al., 2017). Furthermore, studies that investigated the effects of medication showed no difference between medicated and unmedicated patients, suggesting that WM changes in MDD are due to the disease process rather than to medication (Bessette et al., 2014; de Diego-Adelino et al., 2014; Jiang et al., 2017). As regard to different subtypes of MDD there are controversial findings. Ota et al. (2015) showed no significant difference of WM integrity between melancholic and atypical depression, whereas a study conducted by Bracht et al. (2014) found stronger alterations of the medial forebrain bundle in patients with the melancholic subtype of depression compared to non-melancholic MDD patients and healthy controls. In addition, Hyett and colleagues (Hyett et al., 2018) demonstrated WM alterations in the right anterior part of the internal capsule of melancholic MDD patients compared to non-melancholic depressed patients and healthy controls. This observation is associated with psychomotor slowing, the key symptom of the disorder. Another DTI-study that investigated the effect of family history and anhedonia on WM integrity, revealed decreased FA in the cingulum bundles, indicating the implication of cingulum WM impairments in the etiology of MDD (Keedwell et al., 2012). There is also evidence for a relationship between MDD symptoms severity and WM impairments. The more severe depressive symptoms, the more pronounced WM abnormalities, particularly in the corpus callosum (Cole et al., 2012).

4. Association of neuroinflammation and white matter microstructure in MDD

It is well known that neuroinflammation has an impact on WM microstructure (Favrais et al., 2011; Czeh and Nagy 2018; Sugimoto et al., 2018) even though the underlying mechanisms are not entirely understood and only few studies have been performed to examine directly the association between inflammation and WM integrity. A recent neuroimaging study that investigated the relationship between WM integrity and serum cytokine levels in MDD revealed microstructural alterations in the inferior fronto-occipital fasciculus and the genu of the corpus callosum that were associated with higher IL-1β levels in the early stage of the disease. The included patients were drug-naïve and at first depressive episode (Sugimoto et al., 2018). A very recent large-scale study has examined the serological and methylomic signatures of CRP and 189 structural neuroimaging phenotypes, including WM microstructure, and the interaction with depression in a sample of 880 individuals with MDD. Results showed that increased serum CRP levels were associated with increased depressive symptom severity, particularly somatic symptoms, as well as a decrease of entorhinal cortex thickness. DNAm CRP was related to a global cortical volume reduction and a decrease in WM integrity, with the greatest loss in the external capsule and the anterior limb of the internal capsule (Green et al., 2021). This study gives evidence for the central effects of peripheral inflammation from serological as well as epigenetic markers in brain regions implicated in depression, highlighting the important role of inflammation as treatment target for MDD (Green et al., 2021). Inflammatory cytokines influence WM integrity also in depressed patients with bipolar disorder (BD). A study, including 31 depressed patients with underlying BD, using a TBSS approach revealed an association of inflammatory cytokine- and growth factor levels with higher RD and MD and lower FA. The higher RD indicates a demyelination process, so that the results of this study suggest an inverse association of inflammation and the integrity of myelin sheaths (Benedetti et al., 2016).

Another important aspect is the impact of inflammatory cytokines on WM integrity in late life depression (LLD) and the relationship to vascular disease. A study investigating the influence of immunological biomarkers on brain structure in LLD showed a negative correlation of vascular endothelial growth factor (VEGF) and eotaxin with grey matter volume (Smagula et al., 2017). In addition, elevated levels of TNF-α were associated with greater white matter hyperintensities (WMHs) indicating multi-factorial pro-inflammatory processes that might contribute to both demyelination and vascular disease (Smagula et al., 2017). Immune dysregulation, overproduction of pro-inflammatory cytokines and endothelial dysfunction might induce rapid progression of atherosclerosis, increasing the risk of developing vascular disease in MDD (Tonhajzerova et al., 2020). Vascular depression is clinically characterized by cognitive impairment, disability and psychomotor retardation, accompanied by vascular risk factors as well as evidence of WMHs on MRI (Alexopoulos et al., 1997; Krishnan et al., 1997). On the one hand, the development of WMHs is associated with older age and vascular dysregulation, especially ischemia (Thomas et al., 2002). Inflammation might also play an important role in LLD (Penninx et al., 2003) and contribute to the proliferation of WMHs (Raz et al., 2012; Taylor et al., 2013).

The cause of reduced myelination in different brain regions of patients with MDD is not yet clear. One possible explanation is that psychosocial stress triggers inflammation leading to increased pro-inflammatory cytokines that can degrade myelin. There is evidence from mouse models that chronic social stress leads to an alteration of BBB facilitating the penetration of serum cytokines (Menard et al., 2017). Mice injected with IL-1β showed myelination defects that were correlated with reduced FA on DTI (Favrais et al., 2011). Another in vitro study demonstrated that recombinant human TNF-α induced damage to oligodendrocytes and myelin sheaths (Selmaj and Raine 1988). The crucial role of microglial cells for stress-induced neuroinflammation has already been elucidated. The activation of microglia might trigger a cascade of inflammatory processes, leading to a dysfunction of other important glial cells, as astrocytes and oligodendrocytes, that are responsible for the formation of myelin and the regulation of the BBB (Czeh and Nagy 2018). Peripheral pro-inflammatory cytokines can reach the CNS through leaky regions or by active uptake mechanisms across the BBB (Pan and Kastin 2003; Banks and Erickson 2010). They can also activate endothelial cells or perivascular macrophages to produce other inflammatory mediators (Miller 1999) or act directly on peripheral vagal nerve afferents. The vagus nerve represents an important mediator and a key player of the modulation of inflammation, projecting to the nucleus of the tractus solitarius and connecting further with regions of the CNS, such as the locus coeruleus, the rostral ventrolateral medulla, the amygdala, and the thalamus (Berthoud and Neuhuber 2000), that are important for the pathophysiology of MDD.

5. Association of neuroinflammation and grey matter in MDD

Mounting evidence from the literature suggests an association between inflammatory processes and brain structure and morphology related to the pathophysiology of MDD. As elucidated by Frodl et al. (2012), there is a relationship between a decreased hippocampal volume and increased IL-6 and CRP levels. Another recent neuroimaging study, comprising 514 patients with MDD, indicated a negative correlation between peripheral low-grade inflammation and grey matter volume in the prefrontal cortex and insula (Opel et al., 2019). Furthermore, a study investigating the association between immune markers and cortical thickness revealed a negative correlation between CRP levels and the thickness of the dorsal anterior cingulate cortex in unmedicated patients with MDD (Meier et al., 2016). The impact of activated microglia on neurogenesis might be disruptive by inducing neuronal apoptosis and suppressing neural stem cell proliferation (Chesnokova et al., 2016). Emerging evidence shows an association of MDD with small hippocampal volumes (MacQueen and Frodl 2011) and suggests that chronic inflammation might induce dysbalances of the HPA-axis and neurotransmitter systems increasing glutamate neurotransmission, which can affect hippocampal neurogenesis (Frodl et al., 2012; Troubat et al., 2021). However, the precise molecular mechanism of the impact of inflammation on grey matter and the relation to depression is yet not clear. A recent MS study points at a different pathophysiological mechanism with a distinct gene expression and a different inflammatory profile underlying demyelinated grey and WM areas (van Wageningen et al., 2022). In demyelinated WM lesions inflammation is generated by astrocyte T-cell interactions. Microglia in the demyelinated grey matter might induce a more anti-inflammatory activity without the infiltration of leucocytes suggesting a pathology that is less related to classical inflammation and more resistant to anti-inflammatory treatments as it is seen in patients who present with a cortical first phenotype of MS (van Wageningen et al., 2022). Taken together, there is evidence for the impact of inflammatory processes on grey matter contributing to the development of depression. However, we assume different neurobiological mechanisms underlying the association between WM integrity and inflammation in depression.

6. Predictors of treatment response in MDD

6.1. Inflammatory markers

A diverse profile of inflammatory cytokines might reflect a biological difference among patients with depression (Karlovic et al., 2012, Dunjic-Kostic et al., 2013), and lead to a different therapeutic response. Indeed, it is well established that patients with increased peripheral inflammation might have a poorer response to conventional antidepressants (Lanquillon et al., 2000; Yoshimura et al., 2009; Strawbridge et al., 2015; Amitai et al., 2016). This subgroup of patients that could be regarded as an inflammatory cytokine-associated subtype of MDD might benefit from anti-inflammatory treatments (Kopschina Feltes et al., 2017). Mounting evidence indicates that altered levels of peripheral cytokines might be related to antidepressant treatment outcome in MDD (Strawbridge et al., 2015; Liu et al., 2020; Benedetti et al., 2021). In particular, TNF-α (Liu et al., 2020), IL-6 (Yang et al., 2019; Dahl et al., 2014) and CRP (Uher et al., 2014) might represent potential predictors of response to treatment with antidepressants (see Table 2). IL-6 might also specifically predict response to SSRIs and SNRIs (Yoshimura et al., 2009; Carboni et al., 2019). A study investigating pro-inflammatory cytokine levels of 50 depressed patients before and after 12 weeks of antidepressant treatment indicated a decrease of most of the measured cytokines including IL-6, IL-8 and INF-y to normal levels correlating with recovery from depression (Dahl et al., 2014). Carboni et al. (2019) investigated a panel of peripheral biomarkers from two randomized placebo-controlled studies with depressed patients treated with paroxetine, venlafaxine or placebo. Response to paroxetine correlated with baseline IL-6, TNF-α and IL-10. Yoshimura et al. (2009) investigated a sample of 31 SSRI- or SNRI-responsive, 20 SSRI- or SNRI-refractory depressed patients and 30 healthy controls. Antidepressant treatment led to a significant reduction of IL-6 and TNF-α levels. The plasma IL-6 levels was higher in SSRI- and SNRI-refractory depressed patients than in SSRI- and SNRI-responsive depressed patients, indicating its potential role as predictor of response to SSRIs and SNRIs. Higher cytokine levels, in particular IL-6 and CRP levels, were associated with a better outcome in patients undergoing non-pharmacological treatments as ECT (Kruse et al., 2018; Carlier et al., 2019). Further, IL-6 might be the best predictor of treatment response to ECT, also in the long term (Jarventausta et al., 2017; Kruse et al., 2018) (see Table 2). However, there are studies indicating that changes in pro-inflammatory cytokine levels might be independent of antidepressant treatment outcome. A prospective, non-randomized, controlled study that investigated the ECT effect on pro-inflammatory cytokine levels in 50 patients with TRD compared with 30 healthy controls showed no significant difference between IL-6 levels before and after treatment and the alterations in the levels of other pro-inflammatory cytokines were not associated with treatment response (Zincir et al., 2016). A meta-analysis comprising 22 studies showed that SSRIs led indeed to a reduction of IL-6 and TNF-α levels, however, the use of other antidepressants, though effective on depressive symptoms, had no influence on cytokine levels (Hannestad et al., 2011). Another meta-analysis comprising 45 studies that examined levels of pro-inflammatory cytokines and chemokines in depressed patients during antidepressant treatment revealed a significant decrease in peripheral levels of IL-6 that was not associated with treatment response (Kohler et al., 2018). A recent review giving an overview on the effects of antidepressant treatment on peripheral biomarkers in depressed patients showed insufficient evidence because of inconsistent effects of antidepressants on pro-inflammatory cytokines, different treatment duration and small study samples (Mosiolek et al., 2021).

A study that investigated candidate gene expression revealed a dissociation between baseline predictor genes of treatment response and target genes that might change in the long term in responders. Non-responders showed higher baseline levels of the inflammation-related genes IL-1β, MIF and TNF-α, without any change in relation to treatment response. Instead, successful treatment response was related to a decrease in IL-6 levels (Cattaneo et al., 2013).

An mRNA-based biomarker approach suggests the identification of absolute mRNA values with the best predictive power and patients above the defined cut-offs could directly receive a more specific treatment with higher antidepressant dosages or switch to another antidepressant class and non-pharmacological treatment options (Cattaneo

Table 2
Inflammatory markers as predictors of response to antidepressants and ECT (**meta-analysis/systematic review**).

	CRP	IL-6	TNF-α	IL-1β	IL-8	INF-γ
Predictor of treatment response to **Antidepressants**	Yang et al., 2019; Uher et al., 2014; Tuglu et al., 2003	Yang et al., 2019; Carboni et al., 2019; Goldsmith et al., 2016; Dahl et al., 2014; Yoshimura et al., 2009; Leo et al., 2006	Liu et al.,2020; Carboni et al., 2019; Strawbridge et al., 2015; Fornaro et al., 2013; Leo et al., 2006; Tuglu et al., 2003; Lanquillon et al., 2000	Song et al., 2009; Leo et al., 2006	Dahl et al., 2014	Dahl et al., 2014
Predictor of treatment response to **ECT**	Carlier et al., 2019	Kruse et al., 2018; Jarventausta et al., 2017	Sorri et al., 2018; Pinna et al., 2018		Kruse et al., 2020	

et al., 2016).

6.2. White matter microstructure as marker

The use of multimodal structural and functional neuroimaging can provide different imaging markers that might indicate the treatment response profile and guide treatment selection. The limbic-cortical pathways are considered the main brain regions for directing antidepressant treatment (Fu et al., 2013). WM integrity might serve as a predictor of antidepressant treatment response in MDD (see Table 4). A recent DTI-study indicated that AD in the external capsule was significantly associated with antidepressant treatment response and further differences between responders and non-responders were found with a maximum of effect size in the cingulum-hippocampus region (Davis et al., 2019). Moreover, baseline FA in tracts of the right amygdala differ between responders and non-responders to escitalopram (Delorenzo et al., 2013). Connectivity alterations in the cingulum bundle and stria terminalis tracts might be putative predictors of response to antidepressant treatment with escitalopram, sertraline or venlafaxine (Korgaonkar et al., 2014; Grieve et al., 2016). Another interesting finding is that WM alterations indicate a vulnerability to treatment resistance and might serve as predictors of treatment-non-response. Several neuroimaging studies revealed significantly decreased FA in different fiber tracts, such as fornix, hippocampus, cingulum, corpus callosum, superior and inferior longitudinal fascicule, left middle frontal gyrus and ventromedial prefrontal cortex in patients with TRD compared to healthy controls as well as patients with MDD before treatment and with remitted-recurrent MDD (Zhou et al., 2011; de Diego-Adelino et al., 2014; Hoogenboom et al., 2014; Serafini et al., 2015).

The NMDA receptor antagonist ketamine is used as anesthetic, analgesic and antidepressant and mounting evidence indicates its anti-inflammatory properties (Kopra et al., 2021). A recent study that examined the effect of ketamine on WM microstructure in patients with MDD showed that higher pre-treatment FA in the left cingulum bundle and the left superior longitudinal fasciculus correlated with a greater improvement of depressive symptoms 24 h after ketamine administration. A rapid FA increase in numerous WM bundles was found 4 h after administration, which was significantly associated with an improvement in depressive symptoms (Sydnor et al., 2020).

To our best knowledge only one study has investigated whether WM microstructure may mediate the effect of treatment on depressive symptoms by reducing inflammation with an immunomodulatory drug. A recent study using FW imaging to explore the relationship between alterations in peripheral inflammation and WM integrity in MDD revealed an association between peripheral inflammation and FW across regions of interest and that cingulum WM predicts ketamine response (Langhein et al., 2022). However, other studies performed both in animal models and in patients with MS suggest that reducing inflammation with immunomodulatory agents may ameliorate WM microstructure (Gurevich et al., 2018; Saraste et al., 2021).

ECT has a direct effect on the CNS and electroconvulsive seizures have been suggested to decrease neuroinflammation by reducing microglial toxicity (Goldfarb et al., 2020). Thus, ECT might downregulate immune activation by reducing microgliosis and altering levels of pro-inflammatory cytokines. A clinically relevant mouse model of chronic MS demonstrated the inhibition of neuroinflammation by the application of electroconvulsive seizures leading to a reduction of demyelination and axonal loss (Goldfarb et al., 2020). In humans with depression ECT is known to induce an increase of hippocampal neurogenesis (Bolwig 2011; Bouckaert et al., 2014) as well as neuromodulatory and neurotrophic effects on WM integrity (Gryglewski et al., 2020; Repple et al., 2020). Patients with TRD demonstrated an increase of FA in dorsal fronto-limbic circuits that was related to ECT treatment response (Lyden et al., 2014). Right hippocampal pathways may also serve as a predictor of treatment response to ECT (Kubicki et al., 2019).

Finally, LLD is accompanied by age-related changes, such as brain volume atrophy, vascular changes of WM in the form of WMHs as well as altered functional connectivity (Aizenstein et al., 2014). Imaging markers as proliferation of WMHs in patients with LLD could have influence on therapy planning, indicating the need for a higher dosage of antidepressants from the beginning of treatment (Aizenstein et al., 2014).

Table 3
Influence of antidepressant treatment on cytokine levels (**meta-analysis/systematic review**).

	Change after SSRI	Change after SNRI/SSNRI/TCA	Change after AD in general
IL-6	↓ Wang et al., 2019; Carboni et al., 2019; Perez-Sanchez et al., 2018; Brunoni et al., (2013); Hannestad et al., 2011; Yoshimura et al., 2009; Leo et al., 2006; Basterzi et al., 2005	↓ Yoshimura et al., 2009	↓ **Kohler et al., 2018**; Wiedlocha et al., 2018; Goldsmith et al., 2016; Strawbridge et al., 2015; Dahl et al., 2014; Yoshimura et al., 2009
TNF-α	↓ **Wang et al., 2019**; Perez-Sanchez et al., 2018; Halaris et al., 2015; **Hannestad et al., 2011**; Leo et al., 2006	↓ Chen et al., 2018; Fornaro et al., 2013; Tuglu et al., 2003; Lanquillon et al., 2000	↓ **Kohler et al., 2018**; Yoshimura et al., 2009
IL-1β	↓ Wang et al., 2019; Wiedlocha et al., 2018; Perez-Sanchez et al., 2018; Hannestad et al., 2011; Song et al., 2009; Leo et al., 2006	↓ Chen et al., 2018	↓ **Hannestad et al., 2011**
IL-8		↓ Chen et al., 2018	↓ Dahl et al., 2014
INF-γ	↓ Perez-Sanchez et al., 2018; Brunoni et al., 2013	↓ Chen et al., 2018	↓ Dahl et al., 2014

7. Summary and conclusion

The presence of an immune dysregulation is an important contributing factor to the pathophysiology of depression. MDD is often associated with increased peripheral inflammation and for a subgroup of patients it might represent a pro-inflammatory condition, going along with a severe clinical course and treatment resistance. There is evidence for central effects of peripheral inflammation which could activate microglia which, in turn, might trigger a cascade of inflammatory processes leading to neurotransmitter imbalances. Glial dysfunction might also induce the overproduction of inflammatory cytokines and BBB alterations, facilitating the penetration into the CNS. In-vitro studies have indicated the demyelinating effects of pro-inflammatory markers on WM microstructure. Further, there is increasing evidence from recent neuroimaging studies for a direct association of inflammation parameters with WM microstructure alterations in patients with MDD and BD, also in the early stage of the illness (Benedetti et al., 2016; Sugimoto et al., 2018; Green et al., 2021). Differences have been found in the inflammatory profile and WM integrity of patients with different subtypes of depression and older age is associated with age-related changes of brain volume and WM integrity (Aizenstein et al., 2014; Bracht et al., 2014; Hyett et al., 2018). Finally, numerous studies indicated that both altered levels of peripheral inflammatory markers (Strawbridge et al., 2015; Liu et al., 2020; Benedetti et al., 2021), particularly TNF-α (Liu et al., 2020), IL-6 (Yang et al., 2019) and CRP (Uher et al., 2014; Yang et al., 2019) as

Table 4
WM integrity and the prediction of treatment response to antidepressants and ECT.

	Predictor of treatment response to Antide-pressants	References	Predictor of treatment response to ECT	References	Predictor of treatment resistance	References
White matter integrity	external capsule	Davis et al., 2019	dorsal fronto-limbic circuits	Lyden et al., 2014	hippo-campus	Zhou et al., 2011
	tracts to the right amygdala	Delorenzo et al., 2013	right hippo-campal pathways		cingulum corpus callosum superior and inferior longitud inalfascicule ventro-medial prefrontal cortex	de Diego-Adelino et al., 2014
	cingulum cingulate and stria terminalis	Korgaonkar et al., 2014		Kubicki et al., 2019	left middle frontal gyrus	Serafini et al., 2015
					fornix	Hoogenboom et al., 2014

well as WM integrity might predict antidepressant treatment outcome (Delorenzo et al., 2013; Korgaonkar et al., 2014, Davis et al., 2019). MDD patients who show elevated levels of pro-inflammatory cytokines may respond better to nonpharmacological therapeutic interventions, such as ECT (Kruse et al., 2018; Carlier et al., 2019) or vagus nerve stimulation (VNS), a novel therapy with modulatory effects on inflammatory cytokines that shows effectiveness in the treatment of patients with TRD with a long term benefit (Nahas et al., 2005; Schlaepfer et al., 2008; Berry et al., 2013). Nutritional components are becoming increasingly popular and are recommended in the treatment of milder forms of depression as adjunctive therapy. Psychobiotics, a class of probiotics, might exert some antidepressant and anti-inflammatory effects due to their impact on the vagus nerve through the interaction with gut microbiota (Dinan et al., 2013).

The hypothesis that the detrimental effects of altered immune/inflammatory setpoints, with persistent low-grade inflammation, on antidepressant response could be mediated by inflammation-induced alterations of WM microstructure is therefore tempting, but needs further research to be addressed. Despite mounting evidences on the role of the immune system and its effect on WM microstructure, no study has yet addressed the interaction between the two factors in influencing antidepressant response. Moreover, there is a lack of reproducible biomarkers predicting treatment response on an individual basis (Cattaneo et al., 2016). The availability of such biomarkers would enable more efficient and personalized treatments with faster treatment response, better prevention of treatment resistance, and improvement of life-quality as well as reduction of social and economic burden in the long term. Several clinical studies have been conducted using separately prognostic biomarkers as the subtype of depression, several neuroimaging and inflammatory markers. However, differences in the methods used for the analyses of inflammatory markers, the use of serum or plasma, and the methods used for WM analysis have hampered so far the individuation of biomarkers able to identify subgroups of patients needing more specific anti-inflammatory or immunomodulatory treatments. Further, considering that only about 30% of depressed patients report alterations of inflammatory markers, samples with a very high number of subjects are needed to stratify patients on the basis of their inflammatory and neuroimaging profiles. Finally, the analyses of inflammatory and neuroimaging markers involve a high number of intercorrelated data that need sophisticated statistical techniques also involving machine learning algorithms. Therefore, there is a need for further research using pooled data from different centers to identify markers to be used for the implementation of personalized treatment strategies and obtain the best possible treatment results.

Author statement

Herewith I certify that the manuscript was written by the authors and that all coauthors have agreed with its content.

The authors confirm contribution to the paper as follows:

Review conception and design: S. Breit, E. Mazza, S. Poletti, F. Benedetti.

Literature research, analysis and interpretation of the results: S. Breit.

Draft manuscript preparation: S. Breit, E. Mazza, S. Poletti, F. Benedetti.

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