Neuroscience Applied 3 (2024) 103923

Contents lists available at ScienceDirect

Neuroscience Applied

journal homepage: www.journals.elsevier.com/neuroscience-applied

Review

# Breaking free from the inflammatory trap of depression: Regulating the interplay between immune activation and plasticity to foster mental health

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ARTICLE INFO

*Keywords:*
Inflammation
Antidepressant
Environment
Context
Immunopsychiatry
Neural plasticity

ABSTRACT

Immune alterations have been widely implicated in the onset, progression, and treatment of major depressive disorder. However, our comprehension of the intricate link between immune function and psychopathology remains fragmented and limited. Here we propose that the interplay between immune function and neural plasticity is key in the transition from psychopathology to mental wellbeing. In particular, any deviation toward an extreme immune activation or suppression leads to a dysregulation in the molecular machinery underlying neural plasticity. Therefore, pro–inflammatory conditions in depressed patients are associated with impaired plasticity, limiting the potential to recover. Patient's confinement within their pathological state is here referred to as an *inflammatory trap of depression*. The normalization of immune activation reinstates plasticity, thereby restoring the capacity to attain mental wellbeing. Since growing evidence is showing that reinstating plasticity does not lead to an improvement *per se* but increases the likelihood of recovery, combining the normalization of immune activity with environmental conditions promoting wellbeing is critical to achieve a beneficial outcome. This theoretical framework allows to reconcile key conceptual discrepancies in immunopsychiatry such as the *egg and chicken* and the *nor sufficient nor necessary* issues. Overall, we propose that tuning the immune system to promote neural plasticity is a promising approach to refine and develop innovative therapeutic strategies for depression, leading to personalized and highly effective treatments.

## 1. Introduction

When investigating psychiatric disorders, brain functioning cannot be explored without considering its relationship with the whole body (Pariante, 2016; Thibaut, 2018). In this context, the immune system plays a key role (Branchi, 2011; Bullmore, 2018; Milaneschi et al., 2020). Indeed, starting from the 1970s, extensive research has methodically unveiled the functional link between the immune and the central nervous system (Ader and Cohen, 1975; Besedovsky et al., 1983). More recently, immune dysregulation has been implicated in the vulnerability and onset of psychiatric disorders, leading to the establishment of the field of immunopsychiatry (Dantzer et al., 2008; Leboyer et al., 2016; Pariante, 2017). Immune alterations have been found in association with many psychiatric conditions, including Major Depressive Disorders (MDD) (Dantzer et al., 2008; Miller and Raison, 2016), schizophrenia (Khandaker and Dantzer, 2016), bipolar disorder (Benedetti et al., 2020), and autism spectrum disorder (Croonenberghs et al., 2002). In addition, epidemiological evidence has suggested an etiological link between schizophrenia, viral infections, and autoimmune diseases (Benros, 2015; Brown and Derkits, 2010; Eaton et al., 2006). Similarly, a potential connection between infections experienced during fetal life and an increased risk to develop autism spectrum disorder in offspring has been reported (Jiang et al., 2016; Tioleco et al., 2021).

An increasing number of therapeutic strategies targeting the immune system have been proposed and tested (Leboyer et al., 2016; Muller, 2017), with highly encouraging results (Cakici et al., 2019; Kohler et al., 2014; Muller et al., 2006; Nettis et al., 2021; Raison et al., 2013; Stolk et al., 2010), to treat psychiatrist disorders. Nonetheless, the specific mechanisms linking the immune system to mental health remains elusive. In this review, we will examine evidence concerning the interaction between immune function and MDD and propose a theoretical

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https://doi.org/10.1016/j.nsa.2023.103923
Received 11 September 2023; Received in revised form 31 October 2023; Accepted 3 November 2023
Available online 8 November 2023

framework positing the involvement of the immune system in neural plasticity, i.e. the ability to change brain functioning and behavior according to experiences, which is key in the transition from psychopathology to wellbeing (Branchi, 2022). This framework allows to reconcile potential conceptual discrepancies in the immunopsychiatry field and paves the way for innovative therapeutic strategies in psychiatry.

## 2. The crosstalk between immune activation and major depressive disorder

Though MDD is a chronic and recurring psychiatric illness affecting over 300 million people worldwide, standing among the three highest contributors to the overall burden of disease (WHO, 2017), the therapeutic strategies currently available have variable and incomplete efficacy (Trivedi et al., 2006). This can be attributed to the limited understanding of the mechanism of action and to the difficulties in identifying neurobiological substrates as potential targetable processes to restore mental health (Berk and Nierenberg, 2015; Leboyer et al., 2016). The urgent demand for novel and improved therapeutic approaches has prompted an extensive exploration of the pathological mechanisms underlying depression. In this perspective, exploring the crosslink between the immune and the central nervous systems appears to be one of the most promising avenues (Branchi et al., 2021; Miller and Raison, 2016).

### 2.1. Immune overactivation is associated with depression

An increasing body of clinical evidence indicates a link between immune overactivation and the onset and progression of depression (Blume et al., 2011; Lamers et al., 2020; Maes et al., 1995; Milaneschi et al., 2020; Pariante, 2017). Intravenous administration of pro-inflammatory agents is associated with the appearance and severity of depressive symptoms (Capuron and Miller, 2011; Eggermont et al., 2008; Engler et al., 2017; Friebe et al., 2010; Lasselin et al., 2020; Madeeh Hashmi et al., 2013). Accordingly, chronic immune-mediated inflammatory diseases, such as rheumatoid arthritis and cardiovascular disease (Dickens et al., 2002; Hare et al., 2014) and other conditions with low-grade inflammation, are associated with a significantly higher risk of depression (Goldsmith et al., 2016; Zalli et al., 2016). In addition, around thirty percent of depressed patients show high levels of inflammatory markers in the blood (Miller and Raison, 2016; Osimo et al., 2019; Raison et al., 2006, 2013) such as Interleukin (IL)-1β, IL-6, Tumor necrosis factor (TNF)-α and C-reactive protein (CRP) (Benros et al., 2013; Dickens and Creed, 2001). A recent meta-analysis, which includes 30 studies, has revealed that the prevalence of low-grade inflammation (CRP >3 mg/L) in individuals with depression is 27%, while the majority of depressed individuals (58%) exhibit CRP levels over 1 mg/L (Osimo et al., 2019). It has also been suggested that the onset and progression of mood disorders may involve an imbalance between heightened innate immunity, characterized by increased expression of pro-inflammatory genes in monocytes/macrophages, and reduced adaptive immunity, marked by premature aging and senescence of T cells (Grosse et al., 2016; Simon et al., 2021; Snijders et al., 2016).

### 2.2. Immune modulation of antidepressant treatment response

Recent studies have demonstrated that immune dysfunction reduces the efficacy of antidepressant drugs (Benedetti et al., 2021; Carvalho et al., 2013; Colpo et al., 2018; Haroon et al., 2018; Pariante, 2017; Strawbridge et al., 2015), suggesting that inflammatory processes are also involved in antidepressant action. On the one hand, patients with high expression levels of genes associated with immune activation, such as IL-6, TNF-α, macrophage migration inhibitory factor, and IL-1β, in their blood, respond less to different classes of antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or tricyclic antidepressants (Arteaga-Henriquez et al., 2019; Cattaneo et al., 2016; Eller et al., 2008; Lanquillon et al., 2000; Tuglu et al., 2003). On the other hand, a recent meta-analysis has shown that antidepressant treatment significantly decreased TNF-α levels in responders only (Liu et al., 2020). Moreover, MDD patients who respond to antidepressant treatment have lower baseline IL-8 levels compared to non-responders (Liu et al., 2020). Finally, the IL-1β gene polymorphism has been found to predict non-response to antidepressants (Baune et al., 2010; Yu et al., 2003).

The differential response to antidepressant treatments according to baseline immune activation offers a novel strategy to enhance treatment efficacy through stratification of patients based on their inflammatory profile (Drevets et al., 2022; Ioannou et al., 2021; Milaneschi et al., 2020, 2021). Stratification criteria encompass a combination of variables such as treatment resistance, CRP levels, and anhedonia-related symptoms (Inamdar et al., 2014; McIntyre et al., 2019). Indeed, some studies have shown that baseline CRP levels identify which patients will respond or not to antidepressant treatment (Chamberlain et al., 2019; Nettis et al., 2021; Raison et al., 2013). However, other studies have reported discordant results (Baune et al., 2021), suggesting that, though immune profiling is highly relevant, it might not be the only factor determining antidepressant treatment outcome. Several ongoing clinical trials are further exploring this hypothesis (Arteaga-Henriquez et al., 2019; Fourrier et al., 2018; Nettis et al., 2021).

### 2.3. Anti-inflammatory drugs for the treatment of depression

Since high levels of inflammatory markers have been extensively documented in depressed patients (Dowlati et al., 2010; Howren et al., 2009; Liu et al., 2012; Maes et al., 1995, 2009), an increasing number of studies are investigating the use of anti-inflammatory drugs either as a standalone treatment or as an adjunct to standard antidepressant administration (Fourrier et al., 2018; Kohler et al., 2014; Kopschina Feltes et al., 2017; Muller, 2019; Rosenblat et al., 2014; Tyring et al., 2006).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), which can inhibit both Cyclooxygenases (COXs) and reduce inflammation, have been extensively investigated as potential treatments for depression (Baune, 2016). Celecoxib, a widely used COX-2 inhibitor, when combined with traditional antidepressants like reboxetine, sertraline, and fluoxetine, has been reported to be more effective than the antidepressants alone or placebo (Abbasi et al., 2012; Akhondzadeh et al., 2009; Kohler et al., 2014, 2016; Muller et al., 2006; Na et al., 2014). Celecoxib has been demonstrated to have an antidepressant effect even when used as monotherapy (Iyengar et al., 2013). While non-selective COX-2 inhibitors generally exhibit weaker anti-inflammatory activity compared to selective ones (Riendeau et al., 1997), these have been also reported to possess antidepressant properties. For instance, acetylsalicylic acid, which inhibits both COX-1 and COX-2, has been associated with a reduced incidence of depression (Berk et al., 2013; Kessing et al., 2019), and its administration in combination with SSRIs enhances the rate of response and remission (Mendlewicz et al., 2006). Minocycline, a second-generation tetracycline antibiotic with antioxidant, anti-inflammatory, and neuroprotective effects is a promising therapy for depression (Dean et al., 2012; Pae et al., 2008; Soczynska et al., 2012) as clinical studies have shown its efficacy as an adjunctive treatment (Miyaoka et al., 2012; Nettis et al., 2021).

While many studies and meta-analyses have demonstrated the overall efficacy of anti-inflammatory drugs in treating depression (Bai et al., 2020; Kappelmann et al., 2018; Kohler et al., 2014; Yatham et al., 2019), others have reported no or even detrimental effects (Almeida et al., 2010; Fields et al., 2012; Fond et al., 2014; Fourrier et al., 2018; Wittenberg et al., 2019). For instance, some studies have indicated that anti-inflammatory drugs, including ibuprofen and acetylsalicylic acid, might reduce or inhibit the action of SSRIs (Husain et al., 2020; Warner-Schmidt et al., 2011). These conflicting findings indicate that the

beneficial effects of the anti-inflammatory drugs may depend on patient heterogeneity as well as the involvement of moderating factors that determine treatment outcomes, such as the current living conditions or past adverse events experienced during early life or at adulthood (Kraemer et al., 2006; Musillo et al., 2022).

## 3. The plot thickens: open theoretical issues in linking immune activation and depression

Though a clear association between immune alterations and MDD has been established, the causal relationship between them remains not understood. Indeed, as elegantly pointed out by Pariante (2016), a number of theoretical issues in the immunopsychiatry field are still open and have yet to be resolved. Here, five issues among the most relevant are described:

(i) the *egg and chicken scenario*. It is unclear whether immune overactivation temporarily precedes depression or vice versa (Rengasamy et al., 2021). On the one hand, a number of longitudinal studies reported that high levels of inflammatory markers, such as increased plasma IL-6, CRP, and TNFα, predict the onset of MDD over the subsequent months or years in otherwise healthy individuals (Baune et al., 2012; Dowlati et al., 2010; Gimeno et al., 2009; Khandaker et al., 2014; Lamers et al., 2019; Milaneschi et al., 2009; Miller et al., 2019; Smith et al., 2018; Valkanova et al., 2013). In addition, as mentioned above, interventions that trigger immune overactivation induce neuropsychiatric symptoms, ranging from transient sickness behavior to clinically significant depression (Capuron and Miller, 2004, 2011; Harrison et al., 2009; Lasselin et al., 2020; Mazza et al., 2023). The high comorbidity of autoimmune diseases and depression further suggests the role of inflammation in the onset of the psychopathology (Euesden et al., 2017). On the other hand, it has been reported that cumulative depression episodes predict future peripheral IL-6, CRP or other cytokine elevation (Copeland et al., 2012; Huang et al., 2018; Mac Giollabhui et al., 2021; Prather et al., 2009).

(ii) *neither necessary nor sufficient.* Immune dysregulation and depression are not inextricably associated with each other. Only around 30% of depressed patients show elevated levels of inflammatory markers (Osimo et al., 2019) while most people with increased immune activation do not develop the psychopathology.

(iii) *no temporal overlapping.* The onset of psychopathology and the immune overactivation do not occur simultaneously, even in those individuals which are both depressed and displaying high levels of inflammatory markers.

(iv) *neither too much nor too little.* An increasing number of studies is suggesting that immune function has to be tightly regulated to foster mental wellbeing as both excessive immune activation or suppression can have detrimental effects (Branchi & Giuliani, 2021; Raison et al., 2013; Yirmiya and Goshen, 2011). Accordingly, some studies suggest that anti-inflammatory treatments can even slow or hamper the recovery from depression (Raison et al., 2013; Warner-Schmidt et al., 2011).

(v) *bidirectional action of antidepressant drugs on the immune system*. Many studies have reported anti-inflammatory effects of antidepressant drugs (Galecki et al., 2018). *In vitro* investigations have shown that tricyclic antidepressants, such as clomipramine and imipramine, exert their effects by acting as inhibitors of prostaglandin synthesis, and reducing nitric oxide and TNF-α production in cultures of microglia and astrocytes (Wang et al., 2017). SSRIs are reported to attenuate the expression of COX-2 and reduce the levels of cytokines like TNF-α (Taler et al., 2007). Antidepressants, such as imipramine, fluoxetine, sertraline, and trazodone, have a demonstrated ability to shift the pro-/anti-inflammatory balance in favor of reducing inflammation in human blood samples (Kopschina Feltes et al., 2017). Clinical studies corroborated these findings by indicating a significant reduction in the peripheral concentrations of IL-6 and IL-1β in depressed patients treated with the SSRI fluoxetine (Basterzi et al., 2005; Hannestad et al., 2011). However, contradictory evidence exists. In contrast to the anti-inflammatory effects observed in these studies, others have reported no discernible effect (Haastrup et al., 2012; Jazayeri et al., 2010; Kim et al., 2013), or indicated even a pro-inflammatory action (Chen et al., 2010; Kagaya et al., 2001).

Understanding these open issues and inconsistencies will allow to better comprehend the link between the immune and the central nervous system and further exploit the potential of the immunopsychiatry approach in the development of novel and effective treatments for mental health.

## 4. Interplay between immune activation and neural plasticity

### 4.1. Plasticity in mental health

Plasticity refers to the ability of the brain and behavior to adapt and change in response to experiences. Its effects are evaluated by measuring the extent of change over time in specific neural and/or behavioral features, ranging from synaptic strength to learned responses (Humeau and Choquet, 2019). Plasticity is gaining increasing recognition as a fundamental concept in psychiatry and mental health as it has an essential role in the reorganization of neural circuits and behavioral responses during the transition from psychopathology to mental health (Branchi, 2022; Duman et al., 1999; Lindenberger et al., 2017; Price and Duman, 2020). However, high plasticity is not inherently beneficial because, though it makes the brain, and thus behavior, more susceptible to change, it does not give a direction to such change (Branchi, 2011; Delli Colli et al., 2022). Conversely, the direction can be set by contextual factors, such as living conditions and psychotropic or environmental interventions. In particular, it has been shown that, when neural plasticity is high, supportive environmental conditions lead toward a beneficial outcome, while adverse events may even worsen mental conditions (Belsky et al., 2009; Branchi, 2011). Therefore, increasing plasticity levels is therapeutically relevant only when combined with a favorable context. This concept is exemplified by the results obtained with plasticity-enhancing treatments, such as SSRIs, psychedelics, and ketamine, that can effectively promote wellbeing when combined with favorable contextual conditions (Bottemanne et al., 2022; Carhart-Harris et al., 2018; Chiarotti et al., 2017; Golia et al., 2019; Lepow et al., 2021). It has been shown that the combination of psychotherapy with antidepressants is more effective than administering the drug alone (Cuijpers et al., 2020). Similarly, different levels of plasticity associated to the polymorphism of the serotonin-transporter-linked promoter region (5-HTTLPR) produce outcomes that depend on contextual factors (Belsky et al., 2009; Delli Colli et al., 2022). It has to be considered that neural plasticity is largely age-dependent and organized in temporal windows, which involve different underlying molecular mechanisms (Sale et al., 2014). This implies that different pharmacological approaches may have distinct effects on plasticity across the lifespan (Maya Vetencourt et al., 2008).

### 4.2. Both extreme activation and suppression of the immune system impair neural plasticity

Recent perspectives on the connections between the immune system and the brain highlight the regulatory action of the immune function on neural plasticity. It has been proposed that maintaining immune activation within a physiological range is key for neural plasticity which, in turn, plays a pivotal role in brain rewiring underlying the recovery process (Branchi & Giuliani, 2021; Golia et al., 2019; Yirmiya and Goshen, 2011).

The immune system is involved in the molecular mechanisms

underlying neural plasticity and tissue remodeling such as removing debris and keeping brain homeostasis (Yirmiya and Goshen, 2011). Accordingly, any dysregulation of its function due to deviations toward either extreme activation or suppression leads to an impairment in plasticity (Golia et al., 2019; Hewett et al., 2012; Santello and Volterra, 2012; Yirmiya and Goshen, 2011). Recent results indeed have shown that pro- and anti-inflammatory compounds, such as lipopolysaccharide and ibuprofen, though producing opposite effects on physiological endpoints and immune response, have an overlapping detrimental impact on plasticity at molecular and cellular levels, significantly reducing plasticity markers such as BDNF levels and long-term potentiation (LTP) amplitude (Golia et al., 2019). This is corroborated by increasing evidence showing that immune abnormalities are associated with impaired plasticity. On the one hand, pro-inflammatory cytokines (i.e., IL-1β and TNF-α) reduce neurogenesis in both animal and human studies (Borsini et al., 2015). The administration of Interferon-α, a depressogenic cytokine, leads to a decrease of hippocampal neurogenesis by upregulating interferon-stimulated genes, ISG15 and USP18, as demonstrated in an in vitro study in human hippocampal stem cells (Borsini et al., 2018). On the other, reduced or lack of expression of pro-inflammatory cytokines impairs synaptic plasticity as well. Knockouts for IL-1β and TNF-α show impaired LTP (Avital et al., 2003) and long-term depression (Albensi and Mattson, 2000). TNF-α derived from glial cells significantly modulates homeostatic plasticity by stimulating the exocytosis of AMPA receptors and suppressing astrocytic glutamatergic transporters at the synaptic site (Stellwagen et al., 2005; Stellwagen and Malenka, 2006).

Overall, given the need of a tight regulation of immune function to promote neural plasticity and the context-dependent outcome of plasticity, therapeutic strategies for MDD based on the modulation of the immune system should take into considerations both the level of immune activation and the potential contextual factors driving the patient toward mental wellbeing.

### 4.3. *Microglia as effector of neural plasticity*

Microglia, the resident immune cells in the brain (Tremblay et al., 2011), play a pivotal role in regulating brain activity and neural processes associated to plasticity. They closely interact with neurons through the expression of receptors for neurotransmitters and neuropeptides, allowing them to rapidly respond to changes in neural activation. In turn, they directly influence neural activity and synaptic plasticity through actions such as phagocytosing spines or synapses and releasing cytokines to modulate the activity of voltage-gated channels and receptors. Additionally, they play a crucial role in regulating synaptic scaling and homeostasis (Sancho et al., 2021). These processes often involve close interactions with astrocytes. Indeed, activated microglia can induce a neurotoxic reactive phenotype in astrocytes, causing them to lose their ability to promote neuronal synaptogenesis (Liddelow et al., 2017). Furthermore, microglia are involved in regulating the growth and integrity of myelin as they can activate a pro-regenerative phenotype that contributes to remyelination following insults (McNamara et al., 2023; Ronzano et al., 2021). Abnormal microglial activation may disrupt interactions between neurons and oligodendrocytes at the synapse and compromise white matter integrity throughout the brain (Peferoen et al., 2014).

Current models of microglia activation in neurological and psychiatric disorders suggest a continuum of intermediate phenotypes. This continuum ranges from a pro-inflammatory phenotype, which releases inflammatory mediators and induces inflammation and neurotoxicity, to an anti-inflammatory phenotype that releases anti-inflammatory mediators capable of fostering neuroprotection. For instance, in vivo imaging (i.e., Positron Emission Tomography) human studies reported activated microglia in many psychiatric disorders, including mood disorders and psychosis, and obsessive-compulsive disorder (Hellwig and Domschke, 2019; Meyer et al., 2020). In addition, post-mortem studies in suicide patients with mood disorders and schizophrenia reported high microglia density (Steiner et al., 2008), and activated microglia phenotypes not responding to regulatory signaling (Naggan et al., 2023).

It is worth noting that microglia have been proposed as an important effector linking immune activation and neural plasticity (Alboni et al., 2016; Branchi et al., 2014; Yirmiya et al., 2015) as they are involved in a range of phenomena from synaptic pruning to learning and memory performance, and brain modifications according to environmental stimuli (Maggi et al., 2011; Pickering and O'Connor, 2007; Rogers et al., 2011). In addition, the states of activated microglia have been shown to be modulated by contextual factors like aging, presence of pathogens and stress proteins, as well as the exposure to stressful conditions (Singhal and Baune, 2017; Wang et al., 2022). Indeed, these cells exhibit a high sensitivity to neural changes and modify their structure and activity accordingly (Dheen et al., 2007). Interestingly, it has been postulated that MDD, largely associated to low levels of neural plasticity, might be directly associated to either intense inflammatory activation or by decline and senescence of microglial cells and antidepressant and anti-inflammatory treatments can improve depressive symptoms by modulating microglial activation (Branchi et al., 2014; Yirmiya et al., 2015).

## 5. Implementation in the clinical practice

### 5.1. *Both excessive immune activation and suppression hinder recovery*

The view of a tightly regulated immune activation as a pivotal factor in neural plasticity that, in turn, controls the transition from psychopathology to wellbeing (Fig. 1A), holds important implications in terms of future clinical applications. First, the therapeutic efficacy of the drugs affecting the immune response depends on the individual's baseline inflammatory condition as the beneficial effects emerge from restoring the inflammatory balance and not by dampening it (Branchi & Giuliani, 2021) (Fig. 1B). For instance, anti-inflammatory treatment is expected to be beneficial for patients with high baseline inflammatory levels,

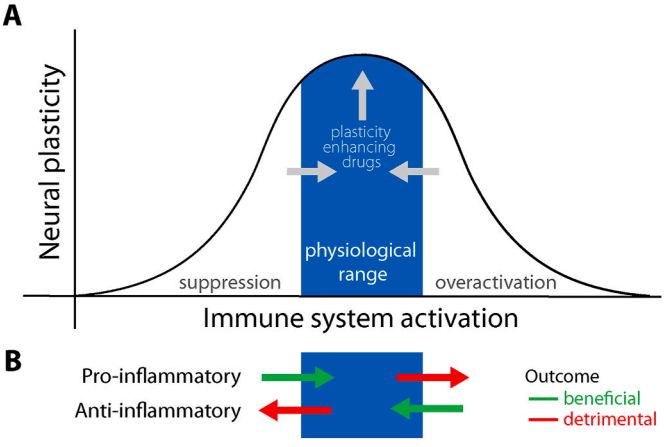


**Fig. 1. The interplay between the immune system and neural plasticity.** (A) Immune activation within the physiological range (blue colored area) enables neural plasticity, a crucial factor for the rewiring of brain circuits underlying the transition from depression to mental health. Any deviation from such range results in plasticity impairment. Because of a mutual regulation, psychoactive drugs known to enhance neural plasticity (e.g., SSRIs) have been shown to drive immune activation within the physiological range. (B) Pro- and anti-inflammatory agents produce effects that depend on their potential for restoring the physiological range of inflammation. In particular, their effectiveness relies on the ability to counteract excessive suppression or overactivation of inflammation, according to the patient's baseline inflammatory levels. Figure adapted from (Branchi & Giuliani, 2021). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

since it can help normalize immune activation. Conversely, patients with low baseline inflammation may experience a worse outcome because their anti-inflammatory status is exacerbated (Raison et al., 2013). Indeed, it has been shown that patients' stratification according to baseline inflammatory markers might markedly increase the efficacy of drugs acting on immune regulation (Carvalho et al., 2013; Chamberlain et al., 2019; Nettis et al., 2021; Pariante, 2017). Second, the view here proposed reconciles seemingly contradictory findings, including studies demonstrating that anti-inflammatory drugs can either worsen mental health (Raison et al., 2013) or counteract the effects of SSRIs in treating depression (Warner-Schmidt et al., 2011). When inflammatory markers are excessively low, depressed individuals might even benefit from the acute stimulation of at least certain aspects of the immune response in order to restore the physiological immune function (Alboni et al., 2016; Raison, 2017). Also in case of an imbalance between innate and adaptive immunity (Grosse et al., 2016; Simon et al., 2021; Snijders et al., 2016), immuno-modulatory interventions are aimed at restoring the disrupted immune function to promote the transition toward recovery.

### 5.2. *The inflammatory trap of depression*

Distinct levels of immune activation are associated with specific degrees of plasticity which, in turn, differently affect the likelihood of transitioning from psychopathology to wellbeing (Fig. 2). Immune activation within the physiological range enables neural plasticity, promoting the potential for recovery (Fig. 2A). By contrast, any deviation from this range, such as a pro-inflammatory state, results in an

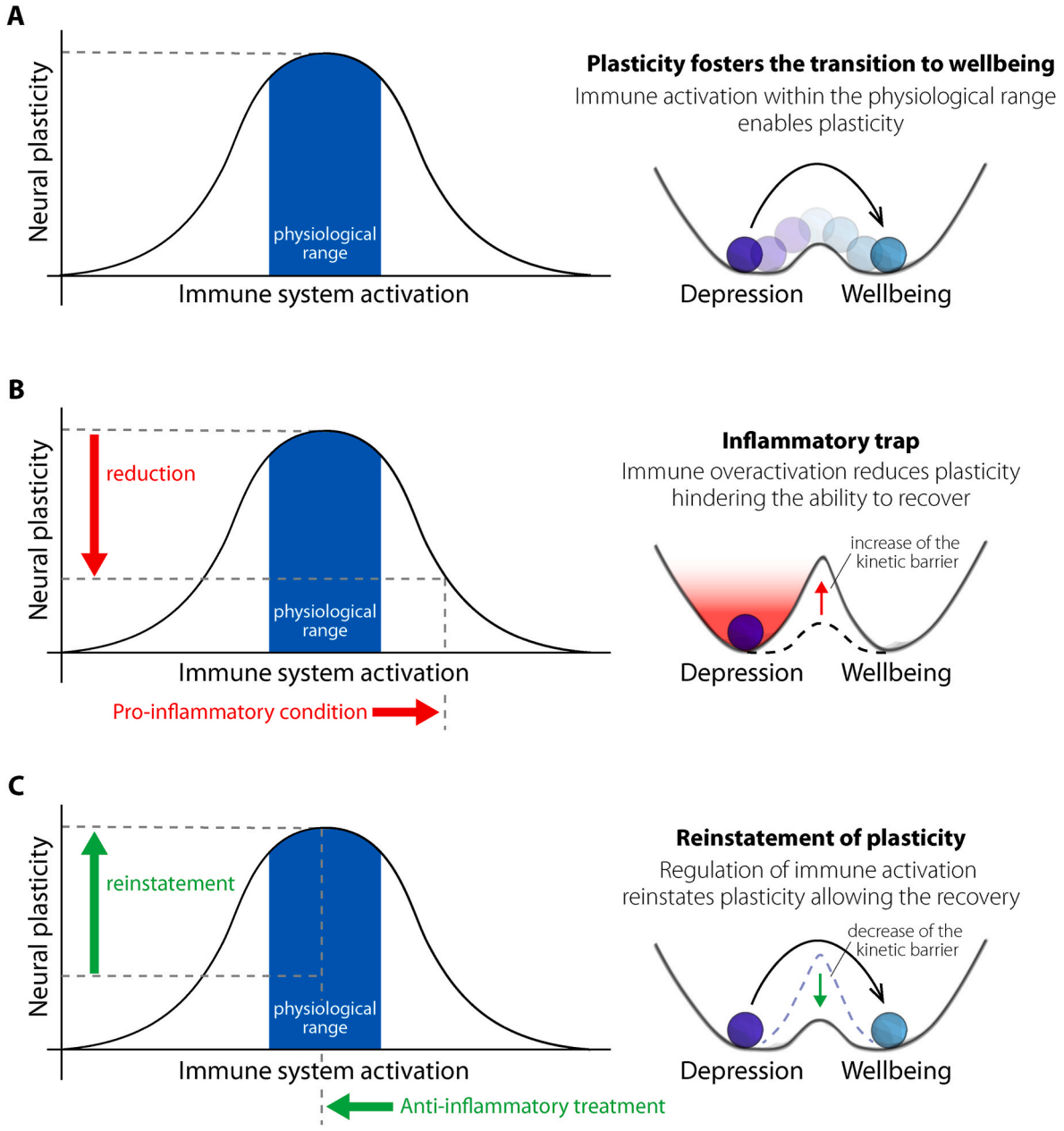


**Fig. 2. The inflammatory trap of depression**. (A) Neural plasticity levels enabled by immune activation within the physiological range (blue colored area) is critical for the transition from depression to wellbeing. (B) Pro-inflammatory conditions reduce plasticity, dampening the likelihood of the transition from depression to wellbeing. This results in an *inflammatory trap* that confines the patient to their pathological state. (C) Anti-inflammatory treatments, by contrast, are expected to normalize immune activation in inflamed patients, reinstating neural plasticity and, thus, restoring the capability to recover. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

impairment of plasticity, leading to a reduced capability to achieve mental wellbeing. Such a condition, named *inflammatory trap of depression*, confines the patients in their pathological state (Fig. 2B). Anti-inflammatory treatments, such as NSAIDs, which normalize immune activation in inflamed patients, reinstate neural plasticity, thus restoring the patient's capability to recover (Fig. 2C). In a clinical perspective, immune alterations should be normalized to allow patients to break free from the inflammatory trap and recover.

### 5.3. The relevance of context

Since immune regulation promotes plasticity (Golia et al., 2019), and the outcomes of plasticity are contingent on the context (Belsky et al., 2009; Branchi & Giuliani, 2021; Delli Colli et al., 2022), the ultimate outcome of immune regulation is expected to be context-dependent as well. Specifically, realigning the immune response within the bounds of the physiological range, through the administration of anti-inflammatory agents, can reinstate neural and behavioral plasticity which, in turn, enables the transition from psychopathology to mental health. However, as mentioned above, the likelihood of such transition is associated to the concomitant conditions or actions capable of promoting wellbeing (Bottemanne et al., 2022; Branchi, 2022; Klobl et al., 2022) (Fig. 3). Therefore, the efficacy of anti-inflammatory treatments is predicted to be higher either when administered to patients experiencing a supportive environment, psychotherapy and environmental interventions promoting a favorable subjective appraisal of the living conditions (Fig. 3A). Accordingly, not only an immune dysregulation that impairs plasticity but also the lack of conditions fostering mental health may limit the efficacy of therapeutic strategies (Fig. 3B). Consequently, the information concerning psychosocial and socio-demographic features is key when assessing the efficacy of drugs or interventions regulating the immune function. Neglecting the drug-by-environment interaction may account, at least partially, for the high variability in the response to anti-inflammatory pharmacological interventions (Baune et al., 2021; Husain et al., 2020; Liu et al., 2020; Nettis et al., 2021), generating considerable controversy within the field (Berk et al., 2020; Miller and Pariante, 2020). In addition, it may represent one of the causes contributing to the low trial sensitivity which has resulted in a progressive decline in the investments for the development of new therapeutic drugs for mental health. Hence, the present view strongly encourages forthcoming clinical trials in the psychiatry field to consistently collect data pertaining to income, education, occupation, and broader socio-environmental aspects for a comprehensive description of the living conditions, thus increasing the understanding of treatment effects.

### 5.4. The relevance of time

Neural plasticity is a dynamic process producing effects that differ according to, not only context, but also time (Branchi, 2022). For instance, the gene by environment interaction involving the 5-HTTLPR polymorphism, which has been deeply involved in the regulation of neural plasticity (Belsky et al., 2009), produces effects that are time-dependent (Delli Colli et al., 2022). In particular, at short time intervals (i.e., less than one year from the stressful event), the individuals bearing that *s* allele, associated to higher plasticity, are more vulnerable to depression than those bearing the *l* allele. However, at longer time intervals the two alleles lead to equal vulnerability.

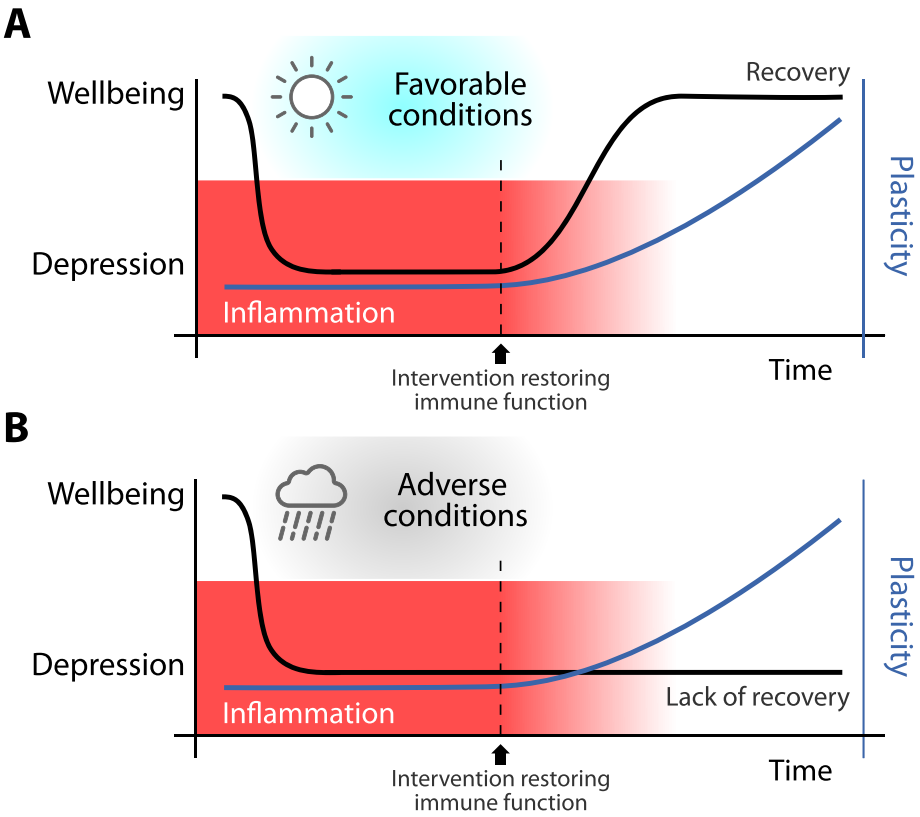


**Fig. 3. The therapeutic efficacy of immune modulatory interventions depends on the concomitant exposure to conditions promoting wellbeing.** Since immune regulation facilitates plasticity, and the consequences of plasticity are context-dependent, the ultimate outcome of immune regulation is influenced by contextual factors. Specifically, realigning the immune response within the physiological range via pharmacological (e.g., anti-inflammatory agents) or environmental interventions (e.g., psychotherapy) reinstates neural plasticity, increasing the odds of recovery. However, (A) reinstating plasticity is not sufficient, but the transition toward a healthy state occurs when the patient is also concomitantly exposed to conditions or interventions that promote wellbeing. (B) Accordingly, recovery is hampered by the experience of adverse conditions.

Therefore, reinstating neural plasticity through immune regulation does not produce a defined effect, but opens a window of opportunity for outcomes that are contingent to both context and time. The duration of the window of opportunity is critical in determining the therapeutic outcome. Achieving immune regulation over a short period of time results in limited opportunities for improvement as it might not be sufficient for the reorganization of brain function and behavior. By contrast, a long-lasting immune regulation increases the likelihood and the magnitude of such recovery. This intricate interplay serves as a further potential explanation for the lack of temporal overlap between immune regulation and the recovery from mental illness.

It is important to acknowledge that the time-dependent effects of plasticity are driven by dynamic processes that encompass their molecular and cellular substrates, including microglia. For instance, stress exposure initially triggers a phase of microglial activation and proliferation, followed by a subsequent phase of apoptosis and decline. The timing of these events is crucial and blocking the initial activation mitigates the subsequent microglial decline that is associated to the onset of depressive-like behavior (Kreisel et al., 2014). This highlights the dynamic nature of microglial functioning and emphasizes the importance of considering the specific temporal phases to understand the vulnerability to stress-induced depressive disorder.

## 6. Revisiting the open theoretical issues in immunopsychiatry in the light of the interplay between the immune system and plasticity

The interplay between immune activation and neural plasticity described here offers potential speculative considerations for addressing the open theoretical issues in immunopsychiatry described in section 3. The view of immune activation as regulator of plasticity, which is not inherently beneficial or detrimental, but producing an outcome dependent on context, calls for a novel theoretical framework which advocates for permissive, rather than instructive, causality (Branchi & Giuliani, 2021). In instructive causal relationships, cues do produce specific events (e.g., the rain wets the floor), while, in permissive relationships, cues do not produce specific events but increase or decrease the likelihood of another cue to produce an event (e.g., opening the door increases the likelihood to enter the room but does not imply entering the room) (Branchi & Giuliani, 2021). The immune system acts through permissive causality: it does not directly affect mood but, by regulating plasticity, amplifies or dampens the impact of instructive factors (e.g., living conditions and/or psychotherapy) on mood (Branchi, 2022). In particular, immune activity within the physiological range enables plasticity that, in turn, increases the likelihood of the transition from psychopathology to wellbeing. The latter can be achieved when patients concomitantly experience conditions promoting mental health.

The permissive causality linking immune function and depression allows to potentially explain why immune overactivation is *neither necessary nor sufficient* in triggering MDD. Indeed, the presence of one condition does not imply but just favors the other (Fig. 4A–B). Similarly, it offers a possible explanation of why there is *no temporal overlapping* between the rise in immune markers and the onset of psychopathology. The fact that both an excessive activation and a suppression of immune response hamper plasticity may explain why immune activation has to be *neither too much nor too little* to promote recovery from depression (Alboni et al., 2016; Branchi & Giuliani, 2021; Raison, 2017; Raison et al., 2013; Yirmiya and Goshen, 2011; Yirmiya et al., 2015). The *bidirectional action of antidepressant drugs on the immune response*, which can result either in a reduction (Basterzi et al., 2005; Hannestad et al., 2011; Song et al., 2009) or in an increase (Chen et al., 2010; Kagaya et al., 2001) in inflammation, could arise from the mutual regulation

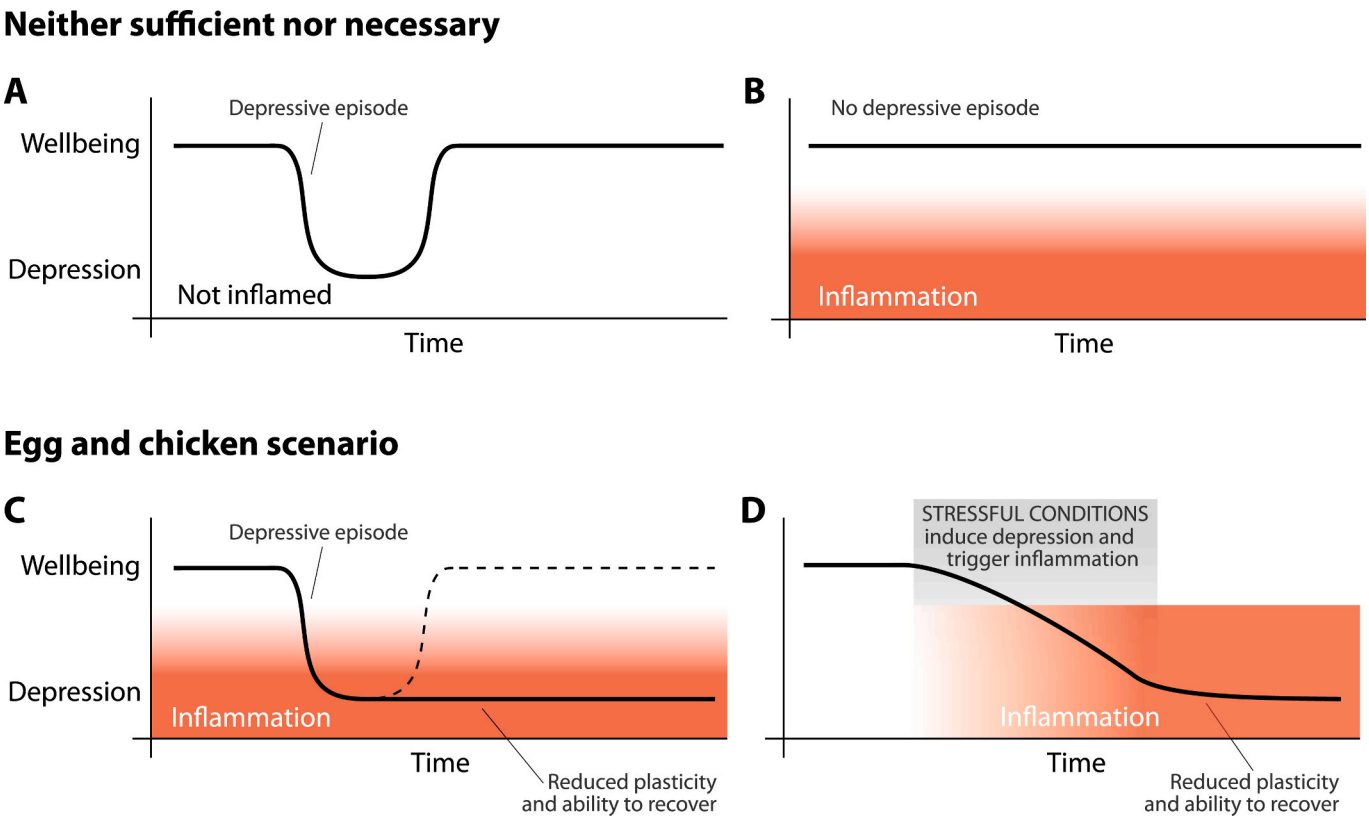


**Fig. 4. Linking immune regulation and depression: a permissive relationship**. (A–B) *Neither sufficient nor necessary*. Depression (A) and inflammation (B) can occur independently from each other. (C–D) *Egg and chicken scenario*. Both conditions can precede the other. (C) When a depressive episode develops in a condition of inflammation, it hampers the patient's ability to recover, reducing neural plasticity. Alternatively, (D) psychopathology can precede immune dysregulation because conditions that trigger depression, such as chronic stress, have been reported to raise inflammatory markers.

between immune function and plasticity: the enhancement of plasticity induced by antidepressants may regulate the underlying molecular mechanisms, including inflammatory processes, leading to an anti-inflammatory action when inflammation is too high, or to a proinflammatory action when immune activation is too low (Fig. 1).

Finally, the hypothesis of a permissive relationship between the immune system and depression may explain the *egg and chicken* scenario, suggesting that both conditions can precede the other (Fig. 4C–D). Immune dysregulation can precede psychopathology as the associated diminished plasticity impairs the individual's capacity to recover after being exposed to conditions that trigger depression (Fig. 4C). Alternatively, psychopathology can precede immune dysregulation because conditions that trigger depression, such as chronic stress, have been reported to raise inflammatory markers (Fig. 4D) (Allen et al., 2014; Rohleder, 2014; Slavich and Irwin, 2014).

## 7. Conclusions

The emerging field of immunopsychiatry is revolutionizing our comprehension of mental illnesses, providing novel theoretical frameworks and paving the way for innovative diagnostic and therapeutic approaches (Leboyer et al., 2016; Pariante, 2017).

Here we focused on the interplay between immune activation and neural plasticity that is emerging as pivotal in mental health (Branchi & Giuliani, 2021). We proposed that the immune system regulates neural plasticity which, in turn, is necessary for the transition from psychopathology to mental wellbeing. In particular, pro–inflammatory conditions are associated with impaired plasticity, reducing the potential for recovery. This gives rise to a condition named the *inflammatory trap of depression* that is the patient's confinement within their pathological state. The normalization of immune activation reinstates plasticity, thereby restoring the capacity to attain mental wellbeing. However, since reinstating plasticity does not directly improve mood but increases the likelihood of recovery (Branchi, 2022; Branchi & Giuliani, 2021), immune regulation has an effective therapeutic power when combined with contextual conditions fostering wellbeing such as a supportive living environment or psychotherapy. This theoretical framework entails several important implications. Among these, it highlights the importance of studying psychiatric disorders at the interface between the brain, body, and environment, emphasizing the relevance of the immune regulation of brain functions, such as neural plasticity, to advance our understanding of mental wellbeing (Alboni et al., 2016; Golia et al., 2019; Raison et al., 2013). Second, it urges for a precise/personalized medicine approach that takes into account not only the patient's baseline immune profile but also contextual factors, such as the living environment, to finally develop novel, reliable, and effective treatments for psychiatric disorders.

## Role of funding source

Supported by the Italian Ministry of Health PNRR-MAD-2022-12375716 - Immune4Plasticity -and by the Istituto Superiore di Sanità, ISS20-4f4dcc4bf1bc TUNEIMMUNE, both to IB, and European Union H2020 Grant 754740 "MoodStratification" to FB. Funders had no role in the preparation, review, or approval of the manuscript and decision to submit the manuscript for publication.

## Declaration of competing interest

IB, AV, BV, FC, FB, SP declare no competing financial interests.

## Acknowledgements

The European College of Neuropsychopharmacology (ECNP) Immuno-NeuroPsychiatry Network has supported this paper as both IB and BV are members of the Network.

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