Psychoneuroimmunology and Immunopsychiatry

CHAPTER 6

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HISTORY AND DEVELOPMENT OF PSYCHNEUROIMMUNOLOGY AND IMMUNOPSYCHIATRY

Psychoneuroimmunology broadly examines reciprocal interactions among psychological processes, the nervous system, and the immune system, whereas immunopsychiatry focuses more specifically on how inflammation and broader immune processes contribute to the pathophysiology and clinical manifestations of psychiatric disorders. Evidence for involvement of the immune system in brain pathologies dates back to the early twentieth century, when histopathological and immunological findings led several neurological diseases, such as multiple sclerosis, to be regarded as "neuroinflammatory" disorders[1,2]. In this context, 'neuroinflammation' reflected a reactive process, characterised by leukocyte infiltration into the CNS, gliosis, and marked increases in immune mediators[3]. Immune abnormalities were also reported during this period in psychiatric disorders[4]. However, findings in psychiatric conditions were less evident and less consistent than those observed in classical neuroinflammatory diseases. As a consequence, they were largely overshadowed by hypotheses centred on psychotropic mechanisms and neurotransmitters (e.g. dopamine, catecholamines)[5,6], and there was comparatively little research and development in the field of Immunopsychiatry.

Forty years ago, the first studies emerged showing that immune mediators such as cytokines could modulate the pituitary–adrenal axis[7], helping reshape our understanding of bidirectional immune-brain communication. Around the same time, pioneers such as Benjamin Hart[8] discovered that infection-associated changes in mood, motivation and cognition are not directly caused by pathogens themselves, but are instead driven by immune mediators. This opened the way to a broader body of research showing that pro- and likely also anti-inflammatory mediators can readily disrupt behaviour, cognitive and affective function[9,10]. The striking symptomatic overlap between "sickness behaviour" and clinical features of depression, coupled with the discovery that sustained therapeutic use of pro-inflammatory cytokines such as interferon-alpha can trigger de-novo depressive episodes[11] led to the re-emergence of interest in immunopsychiatry.

The mechanistic role of the immune system in psychiatry and neuropsychology has long been debated. Is immune system dysfunction sufficient alone to trigger psychiatric disorders or alter key cognitive functions, or is it generally only one of many contributing factors? Do they affect all patients or only specific subgroups? At present, these questions are yet to be fully resolved. However, in a limited number of psychiatric disorders, immune mechanisms are now believed to act as primary drivers of disease in discrete subsets of patients. Consequently, new nosological "(sub)categories" have begun to emerge in the psychiatric literature, notably "autoimmune psychosis" [12] and "immunometabolic" or "immune-driven" depression[13,14]. However, in other psychiatric disorders, immune dysfunction may better reflect a vulnerability to illness or a marker of disease severity.

The origins of immune dysfunctions contributing to psychiatric symptoms appear to be multifactorial. Genetic background may have a key role, as some psychiatric disorders are associated with single nucleotide polymorphisms (SNPs) located within immune-related genes, or loci that regulate their expression[15]. A clear illustration here comes from schizophrenia, where the SNP most strongly associated with the disorder lies within a locus containing complement C4 and HLA genes[16,17]. Beyond genetics, multiple other factors also likely contribute: maternal immune activation[18], infections with specific viruses across the lifespan[19,20], and factors involved in systemic low-grade inflammation[21], for instance low physical activity, poor diet, obesity and the social environment.

Regarding metabolic risk factors, the relationship between immunometabolic depression and overweight or obesity has been particularly investigated, in the context of whether weight gain may promote low-grade inflammation and thereby contribute to depression, or whether depression instead promotes weight gain through reduced physical activity, poorer diet, and related behavioural changes. Current evidence suggests that obesity and immunometabolic depression are not linked by a simple one-way causal relationship, but are initially associated and may then mutually reinforce each other over time[22–25].

EPIDEMIOLOGY

An important observation is that immune abnormalities are NOT present in ALL individuals with mental illness and are instead observed in only a subset of patients[26]. Current estimates suggest that clinically relevant immune-inflammatory alterations may be present in approximately one third of patients with psychiatric disorders[27]. However, precisely how these subgroups should be defined and the true prevalence of immune dysfunction across psychiatric disorders is has yet to be conclusively determined. For example, though mildly elevated high-sensitivity C-reactive protein (hsCRP) has emerged as a potentially useful proxy biomarker for identifying immunometabolic depression, no consensual pathological threshold has yet been established. Thus, according to one meta-analysis[28], 58% of patients with MDD could be classified as having immunometabolic depression if the hsCRP threshold is set above 1 mg/L, however this proportion would fall to 27% if a threshold of hsCRP > 3 mg/L is used. In autoimmune psychosis, differences in antibody detection methods, sample type (serum or CSF), and the antibody subunit targeted can markedly influence purported prevalences[29,30]. Nevertheless, in one of the largest studies of first-episode psychosis using live cell-based assays to detect several neuronal surface antibodies in serum (228 patients with first-episode psychosis and 105 controls), such antibodies were identified in 9% of patients compared with 4% of healthy controls, while anti-NMDAR antibodies were detected in 3% of patients and in none of the controls[31].

PATHOPHYSIOLOGY

CNS immune function can be broadly organized around three major effector components:

1. The highly dynamic blood–brain barrier (BBB);
2. Innate immune cells, consisting mainly of resident macrophages, namely microglia and perivascular macrophages. The meninges however, contain a broader range of innate immune cell types, including macrophages, eosinophils, and dendritic cells;
3. Adaptive immune cells, with diverse B-cell and, particularly, T-cell populations located in the meninges.

These components primarily communicate with one another, non-immune brain cells and the periphery through soluble immune mediators, particularly cytokines. As discussed earlier, components of the CNS immune system extends far beyond the identification, memory, and elimination of threats to bodily integrity and includes a range of fundamental homeostatic processes including synaptic plasticity, synapse elimination, and regulation of neurotransmitter synthesis.

Cytokines:

Within the brain parenchyma, cytokines such as IL-6, TNF and IFN-alpha can be produced by a range of non-classical immune cells including astrocytes (IL-6, TNF) and neurons (IL-6). They act on many different cell types, including neurons[32], astrocytes[33], endothelial cells[34] and microglia[35]. They can also originate from peripheral immune cells, and gain access to the CNS through expression of dedicated transporters in the BBB[36], or through regions where the BBB is naturally more permeable, such as the circumventricular organs. Finally, cytokines can also influence brain function without even entering the CNS by actions on visceral afferent fibres travelling in the Vagus and other autonomic nerves[37].

Within the brain, cytokines can directly modulate brain function through at least four partly distinct mechanisms: by directly modulating activity-dependent ion channels and neuronal excitability; by affecting the balance of neurotransmitter systems, notably glutamatergic, GABAergic, and dopaminergic signalling; by modulating synaptic plasticity and remodelling[9]; and by disrupting kynurenine pathways involved in serotonin synthesis and cellular metabolism[14]. Through these mechanisms, cytokines can regulate, and disrupt, motivation, executive function, mood and emotional regulation, pain processing, and sleep contributing to neuropsychiatric symptoms observed in sickness behaviour and immunometabolic depression (see below). Elevated circulating pro-inflammatory cytokines, notably IL-6 and TNF-α, have been linked in meta-analyses to MDD[38], BD[39], as well as acute and chronic schizophrenia patients[40]. This type of mild and restricted elevation in blood inflammatory markers is generally referred to as "low-grade inflammation" or "systemic chronic inflammation" and has multifactorial causes[21]. These observations prompted many researchers to consider that immunopsychiatric disorders may be secondary to systemic chronic inflammation, which could influence the brain through the pathways detailed above.

A key question remains regarding whether chronic inflammation in the body affects the brain directly through cytokines released by peripheral immune cells, or whether these mediators trigger inflammatory processes within the brain parenchyma, leading to neuroinflammation. While research has not precisely disambiguated the contributing effects of peripheral and central inflammation, microglial abnormalities identified in some psychiatric studies suggest that central immune processes are at least partly involved.

Microglia:

Microglia are highly plastic cells, which undergo a variety of structural and functional changes according to changes in their local environment. In addition to their role in inflammatory responses, microglia contribute to multiple homeostatic processes, including synapse formation, synaptic pruning, myelination, extracellular space surveillance, tissue remodelling, and ageing. Accordingly, they can adopt diverse states, each characterized by a particular combination of metabolic, gene- and protein-expression, morphological, and epigenetic features[41]. Among the various proteins expressed by microglia, translocator protein (TSPO) is particularly relevant, as its levels can be estimated using positron emission tomography (PET). Though TSPO is not specific to microglia (reflecting also astrocytic activity) and has been reported to be directly or indirectly sensitive to neuronal activity[42], elevated TSPO levels are frequently observed during acute inflammation and may suggest a shift from homeostatic toward injury-reactive glial states[43]. In schizophrenia, recent TSPO-PET studies have reported a reduced TSPO signal compared with healthy controls[44]. Interpretation of this in-vivo finding is currently unclear: it may reflect a shift in microglia states, and/or a decrease in neuronal activity. Nevertheless, these findings challenge the hypothesis of a generalized increase in neuroinflammation in schizophrenia. Post-mortem studies are consistent

with a possible shift in microglial states, having shown reduced expression of many microglia-associated markers (e.g. TLR10, TREM2, CX3CR1, C3)[45]. This expression pattern appears to be partly shared with bipolar disorder, but contrasts with autism spectrum disorder (ASD)[46]. In MDD, although findings remain heterogeneous, several lines of evidence point to microglial disturbances, particularly involving inflammatory signalling, NF-κB/NLRP3 pathway activation, oxidative stress, and kynurenine pathway dysregulation[47]. In addition, TSPO-PET studies have reported an increased TSPO signal[48], which may suggest a potential shift of microglia toward inflammatory states. These data indicate that microglial states may vary across disorders, potentially engaging distinct mechanisms within the CNS. For instance, in MDD, pathways associated with disease-related microglial states appear consistent with the symptom profile described in immunometabolic depression[13], suggesting that systemic chronic inflammation may contribute to immune-related changes within the brain, alongside the direct effects of cytokines. Conversely, in schizophrenia, certain disease-associated microglial states may exacerbate synaptic pruning during childhood and adolescence[49], a process suspected to contribute to vulnerability to the disorder[50].

Complement system:

The complement system is a ubiquitous and highly dynamic network of more than 50 proteins belonging to the innate immune system, organised as a sequential enzymatic cascade comprising three main pathways: the classical, lectin, and alternative pathways. Although the CNS is largely separated from the peripheral complement system by the BBB, complement proteins can be synthesized locally within the brain by several cell types, including microglia, astrocytes and neurons, with region- and time-dependent patterns of expression[51]. In the brain, complement functions extend beyond immune defence and inflammation, contributing more broadly to neuronal and synaptic homeostasis. A well-characterised example is complement-mediated synaptic refinement, in which C1q can tag weak or superfluous synapses, thereby facilitating their recognition and elimination by microglia. This mechanism occurs throughout life, but is particularly important during childhood and adolescence, when synaptic pruning supports the progressive maturation of brain circuits. Several studies have reported alterations in circulating and/or brain levels of complement components in BD[52], MDD[53], and autism spectrum disorder[54]. Similar increases have also been observed in schizophrenia[55,56], but in this disorder they may be partly explained by genetic variation within the C4 locus, particularly in C4A. Indeed, schizophrenia risk appears to be associated with configurations linked to higher C4A expression[16], and overexpression in mouse models has been shown to increase synaptic elimination and alter glutamatergic and GABAergic synaptic transmission[57–59]. Together, these findings support a model in which increased complement signalling, particularly involving C4A, may enhance synaptic elimination and thereby contribute to schizophrenia vulnerability.

Adaptive immune system:

In the CNS, most innate and adaptive immune cells are not normally found within the parenchyma in the absence of active inflammatory processes, but are mainly located in the meninges. Nevertheless, they closely interact with the brain and contribute to the maintenance of CNS homeostasis and cognitive function[60]. The involvement of adaptive immune cells is particularly evident in autoimmune psychosis, in which immunoglobulins secreted by plasma cells are thought to contribute to symptom development[12]. However, autoimmune psychosis will not be discussed in this or the following sections, as its pathophysiology, clinical presentation, assessment, and management largely overlap with those of autoimmune encephalitis, which is covered in another

chapter. This close overlap partly explains the ongoing debate regarding whether it should be maintained as a distinct category[61]. In the broader field of immunopsychiatry, although non-microglial immune cell populations are increasingly studied, current knowledge remains insufficient to provide an integrated view of their roles.

COMMON IMMUNE-MEDIATED NEUROPSYCHOLOGICAL AND PSYCHIATRIC PRESENTATIONS

Sickness behaviour:

Infections can rapidly induce a cluster of mood, motivational, and cognitive changes, collectively known as "sickness behaviours".

More precisely, the clinical presentation encompasses changes in mood, experienced as mild depression, anxiety, and fatigue[62], social withdrawal, heightened sensitivity to punishments[63], sleep disturbance, anorexia, psychomotor slowing[64,65] and cognitive disturbances such as subtle impairments in memory[66].

Sickness behaviours are typically short-lasting and rapidly resolve, following resolution of the infection.

Immunometabolic depression:

The clinical presentation of immunometabolic depression is closely related to that of sickness behaviour. It generally takes the form of a major depressive episode, but with atypical clinical features, mainly linked to metabolic regulation. It is often associated with symptoms related to energy balance, including asthenia, leaden paralysis, sleep disturbances, and reduced motivation[13,14]. Increased appetite is also frequently reported, sometimes accompanied by weight gain and, more broadly, by features of metabolic syndrome.

Little is known about the clinical course of immunometabolic depression itself. However, because chronic low-grade inflammation has repeatedly been associated with a broad range of medical conditions, including ischaemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease (NAFLD), autoimmune disorders, and neurodegenerative diseases, its course may be marked by multiple comorbidities[21].

ASSESSMENT AND DIAGNOSIS

Assessment of immunometabolic depression should first rely on a standard psychiatric interview to establish the diagnosis of MDD and to exclude relevant differential diagnoses. Particular attention should then be paid to atypical and energy-related features, as described above. The clinical assessment should also systematically explore medical comorbidities, especially features of metabolic syndrome, such as increased waist circumference and elevated blood pressure.

No biological criterion has yet been clearly established by consensus to support the diagnosis. Several cytokines, especially IL-6 and TNF-α, have frequently been reported to be elevated [38], but these markers are not easily available in routine clinical practice. HsCRP is also frequently elevated and is much more accessible clinically, but the optimal threshold remains debated.

Nevertheless, a cut-off around 3 mg/L is often used, partly because it appears to be more closely associated with response to immune-modulating treatments in MDD.

In addition, lipid profiling appears particularly relevant, both to identify potential dyslipidaemia and to complete the assessment of metabolic syndrome.

NEUROPSYCHIATRIC ASPECTS OF TREATMENT

Pharmacological treatment of immunometabolic depression:

Immunometabolic features may have important implications for treatment response in MDD. Indeed, elevated CRP, atypical energy-related symptoms, and higher BMI have been associated with poorer response to antidepressant treatment[67]. Among conventional treatments for MDD, electroconvulsive therapy (ECT) may be particularly relevant in this subgroup, as a recent meta-analysis found that higher baseline CRP and IL-6 levels were associated with greater antidepressant efficacy of ECT[68]. In addition, data from the CO-MED trial suggest that bupropion may be of interest as an add-on treatment, with SSRI–bupropion combination therapy showing better outcomes than SSRI monotherapy in patients with obesity[69] or elevated CRP[70].

Anti-inflammatory strategies have also been investigated in MDD. Several classes of compounds have been tested, including non-steroidal anti-inflammatory drugs, particularly celecoxib, antibiotics with immunomodulatory properties such as minocycline, anti-cytokine treatments targeting TNF-α, IL-6, or IL-2 pathways, and compounds with antioxidant and putative anti-inflammatory properties such as N-acetylcysteine (NAC). Overall, meta-analyses in MDD suggest a small-to-moderate antidepressant effect of anti-inflammatory agents, either as monotherapy or as add-on treatment[71–73]. However, most early trials included heterogeneous samples and did not stratify patients according to immunometabolic profile. Conversely, in patients with inflammatory medical conditions and depressive symptoms, anti-cytokine treatments have also been associated with greater reductions in depressive symptoms than placebo[74].

Some studies suggest that antidepressant effects of anti-inflammatory agents may depend on baseline inflammation, particularly CRP levels[75,76]. Others have even reported antidepressant effects only in patients with hsCRP >3 mg/L[77,78]. Larger stratified trials are ongoing and will be important to clarify these findings, as current evidence remains insufficient to define a clear treatment algorithm for immunometabolic depression.

Given the links between immunometabolic depression and BMI, statins have also been considered. Although a meta-analysis suggested a small antidepressant effect of statins compared with placebo[79], a recent larger RCT in patients with MDD and comorbid obesity found no superiority of add-on simvastatin over placebo for depressive symptoms[80].

Finally, antidiabetic agents with effects on obesity have also been investigated. According to one meta-analysis, pioglitazone was superior to placebo in reducing depressive symptoms, whereas metformin was not[81]. Similarly, a recent meta-analysis suggested an antidepressant effect of GLP-1 receptor agonists[82].

Lifestyle interventions:

Lifestyle interventions may be useful in immunometabolic depression because physical inactivity, poor diet, sleep disturbance, and metabolic dysfunction can promote low-grade inflammation. Exercise appears particularly relevant, with evidence suggesting benefits on depressive symptoms and inflammatory/metabolic markers, including reductions in CRP, leptin, and broader immunometabolic dysregulation[13,67].

Healthy dietary interventions, particularly Mediterranean-style diets, may also reduce depressive symptoms[83]. In contrast, evidence for anti-inflammatory supplements remains mixed, with inconsistent findings for probiotics and more promising but still inconclusive results for omega-3 fatty acids.

Psychoneuroimmunology broadly examines reciprocal interactions among psychological processes, the nervous system, and the immune system.

Immunopsychiatry examines how inflammation and broader immune processes contribute to the pathophysiology and clinical manifestations of psychiatric disorders

Immune abnormalities are not present in all psychiatric patients, but may define clinically relevant subgroups, currently estimated to involve approximately one third of patients.

Inflammation can affect brain function through several routes, including peripheral cytokine signalling, blood–brain barrier mechanisms, vagal pathways, microglial state changes, complement-mediated synaptic remodelling, and adaptive immune responses.Autoimmune psychosis illustrates a discrete immune-driven psychiatric subgroup, although its substantial overlap with autoimmune encephalitis continues to raise questions about its status as a distinct category.

Immunometabolic depression is characterised by major depressive episodes associated with low-grade inflammation, metabolic dysfunction, and atypical energy-related symptoms such as fatigue, sleep disturbance, increased appetite, weight gain, and reduced motivation.

HsCRP is a clinically accessible biomarker for immunometabolic depression, although the optimal threshold remains debated; a cut-off around 3 mg/L is often used in treatment-stratification studies.

Current treatment evidence suggests that immune and metabolic markers may help predict response to antidepressants, ECT, anti-inflammatory agents, and lifestyle interventions, but larger stratified trials are needed before clear treatment algorithms can be established.

References

1. Dawson, J. W. The Histology of Disseminated Sclerosis. *Edinb. Med. J.* **17**, 229–241 (1916).
2. Rivers, T. M., Sprunt, D. H. & Berry, G. P. OBSERVATIONS ON ATTEMPTS TO PRODUCE ACUTE DISSEMINATED ENCEPHALOMYELITIS IN MONKEYS. *J. Exp. Med.* **58**, 39–53 (1933).
3. Estes, M. L. & McAllister, A. K. Alterations in immune cells and mediators in the brain: it's not always neuroinflammation! *Brain Pathol. Zurich Switz.* **24**, 623–630 (2014).

4. Dameshek, W. White blood cells in dementia praecox and dementia paralytica. *Arch Neurol Psychiatry* **24**, 855 (1930).

5. Schildkraut, J. J. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am. J. Psychiatry* **122**, 509–522 (1965).

6. Meltzer, H. Y. & Stahl, S. M. The dopamine hypothesis of schizophrenia: a review. *Schizophr. Bull.* **2**, 19–76 (1976).

7. Besedovsky, H., del Rey, A., Sorkin, E. & Dinarello, C. A. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* **233**, 652–654 (1986).

8. Hart, B. L. Biological Basis of the Behavior of Sick Animals.

9. Martins, D. & Harrison, N. A. Cytokines as Neuromodulators: Insights From Experimental Studies With Humans and Nonhuman Primates. *Biol. Psychiatry* **99**, 971–982 (2026).

10. Feng, L., Wang, Y., Zeng, D., Wang, M. & Duan, X. Predictors of cognitive decline in older individuals without dementia: An updated meta-analysis. *Ann. Clin. Transl. Neurol.* **10**, 497–506 (2023).

11. Musselman, D. L. *et al.* Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa. *N. Engl. J. Med.* **344**, 961–966 (2001).

12. Pollak, T. A. *et al.* Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. *Lancet Psychiatry* **7**, 93–108 (2020).

13. Penninx, B. W. J. H. *et al.* Immuno-metabolic depression: from concept to implementation. *Lancet Reg. Health – Eur.* **48**, (2025).

14. Wessa, C., Simon, M. S. & De Picker, L. Current evidence on immune-driven depression. *Curr. Opin. Psychiatry* **39**, 8–18 (2026).

15. Le Clerc, S. *et al.* Immunogenetic Variants in Major Mental and Neurodevelopmental Disorders. *Biol. Psychiatry* **99**, 1002–1012 (2026).

16. Sekar, A. *et al.* Schizophrenia risk from complex variation of complement component 4. *Nature* **530**, 177–183 (2016).

17. Corvin, A. & Morris, D. W. Genome-wide association studies: findings at the major histocompatibility complex locus in psychosis. *Biol. Psychiatry* **75**, 276–283 (2014).

18. Estes, M. L. & McAllister, A. K. Maternal immune activation: Implications for neuropsychiatric disorders. *Science* **353**, 772–777 (2016).

19. Torrey, E. F. *Parasites, Pussycats and Psychosis: The Unknown Dangers of Human Toxoplasmosis*. (Springer International Publishing, Cham, 2022). doi:10.1007/978-3-030-86811-6.

20. Zheng, H. & Savitz, J. Effect of Cytomegalovirus Infection on the Central Nervous System: Implications for Psychiatric Disorders. *Curr. Top. Behav. Neurosci.* **61**, 215–241 (2023).

21. Furman, D. *et al.* Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* **25**, 1822–1832 (2019).

22. Milaneschi, Y. *et al.* Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations. *JAMA Psychiatry* **74**, 1214–1225 (2017).

23. de Kluiver, H., Jansen, R., Milaneschi, Y. & Penninx, B. W. J. H. Involvement of inflammatory gene expression pathways in depressed patients with hyperphagia. *Transl. Psychiatry* **9**, 193 (2019).

24. Zwiep, J. C. *et al.* Depression with immuno-metabolic dysregulation: Testing pragmatic criteria to stratify patients. *Brain. Behav. Immun.* **124**, 115–122 (2025).

25. Frank, P. *et al.* Overweight, obesity, and individual symptoms of depression: A multicohort study with replication in UK Biobank. *Brain. Behav. Immun.* **105**, 192–200 (2022).

26. Byrne, J. F. *et al.* Transdiagnostic inflammatory subgroups among psychiatric disorders and their relevance to role functioning: a nested case-control study of the ALSPAC cohort. *Transl. Psychiatry* **12**, 377 (2022).

27. Rietberg, T. *et al.* From non-specific biomarker to targeted action: transdiagnostic and sex-specific drivers of high-CRP status in severe mental illness across the FondaMental Advanced Centers of Expertise (FACE) cohorts. *Brain. Behav. Immun.* **134**, 106464 (2026).

28. Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B. & Khandaker, G. M. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol. Med.* **49**, 1958–1970 (2019).

et al.
Biol. Psychiatry
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30. Graus, F. *et al.* A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* **15**, 391–404 (2016).

31. Lennox, B. R. *et al.* Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. *Lancet Psychiatry* **4**, 42–48 (2017).

32. Schlüter, D., Deckert, M., Hof, H. & Frei, K. Toxoplasma gondii Infection of Neurons Induces Neuronal Cytokine and Chemokine Production, but Gamma Interferon- and Tumor Necrosis Factor-Stimulated Neurons Fail To Inhibit the Invasion and Growth of T. gondii. *Infect. Immun.* **69**, 7889–7893 (2001).

33. Choi, S. S., Lee, H. J., Lim, I., Satoh, J. & Kim, S. U. Human astrocytes: secretome profiles of cytokines and chemokines. *PloS One* **9**, e92325 (2014).

34. Johnson, R. H., Kho, D. T., O' Carroll, S. J., Angel, C. E. & Graham, E. S. The functional and inflammatory response of brain endothelial cells to Toll-Like Receptor agonists. *Sci. Rep.* **8**, 10102 (2018).

35. Hanisch, U.-K. Microglia as a source and target of cytokines. *Glia* **40**, 140–155 (2002).

36. Banks, W. A. From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery. *Nat. Rev. Drug Discov.* **15**, 275–292 (2016).

37. Jin, H., Li, M., Jeong, E., Castro-Martinez, F. & Zuker, C. S. A body–brain circuit that regulates body inflammatory responses. *Nature* **630**, 695–703 (2024).

38. Osimo, E. F. *et al.* Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain. Behav. Immun.* **87**, 901–909 (2020).

39. Solmi, M. *et al.* Peripheral levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-1β across the mood spectrum in bipolar disorder: A meta-analysis of mean differences and variability. *Brain. Behav. Immun.* **97**, 193–203 (2021).

40. Halstead, S. *et al.* Alteration patterns of peripheral concentrations of cytokines and associated inflammatory proteins in acute and chronic stages of schizophrenia: a systematic review and network meta-analysis. *Lancet Psychiatry* **10**, 260–271 (2023).

41. Paolicelli, R. C. *et al.* Microglia states and nomenclature: A field at its crossroads. *Neuron* **110**, 3458–3483 (2022).

42. Notter, T. *et al.* Neuronal activity increases translocator protein (TSPO) levels. *Mol. Psychiatry* **26**, 2025–2037 (2021).

43. Guilarte, T. R., Rodichkin, A. N., McGlothan, J. L., Acanda De La Rocha, A. M. & Azzam, D. J. Imaging neuroinflammation with TSPO: A new perspective on the cellular sources and subcellular localization. *Pharmacol. Ther.* **234**, 108048 (2022).

44. Plavén-Sigray, P. *et al.* Positron Emission Tomography Studies of the Glial Cell Marker Translocator Protein in Patients With Psychosis: A Meta-analysis Using Individual Participant Data. *Biol. Psychiatry* **84**, 433–442 (2018).

45. Gandal, M. J. *et al.* Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science* https://doi.org/10.1126/science.aat8127 (2018) doi:10.1126/science.aat8127.

46. Snijders, G. J. L. J. *et al.* A loss of mature microglial markers without immune activation in schizophrenia. *Glia* **69**, 1251–1267 (2021).

47. Wang, H. *et al.* Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. *J. Neuroinflammation* **19**, 132 (2022).

48. Gritti, D., Delvecchio, G., Ferro, A., Bressi, C. & Brambilla, P. Neuroinflammation in Major Depressive Disorder: A Review of PET Imaging Studies Examining the 18-kDa Translocator Protein. *J. Affect. Disord.* **292**, 642–651 (2021).

49. Sellgren, C. M. *et al.* Patient-specific models of microglia-mediated engulfment of synapses and neural progenitors. *Mol. Psychiatry* **22**, 170–177 (2017).

50. Faust, T. E., Gunner, G. & Schafer, D. P. Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS. *Nat. Rev. Neurosci.* **22**, 657–673 (2021).

51. Bohlson, S. S. & Tenner, A. J. Complement in the Brain: Contributions to Neuroprotection, Neuronal Plasticity, and Neuroinflammation. *Annu. Rev. Immunol.* **41**, 431–452 (2023).

52. Reginia, A. *et al.* Assessment of Complement Cascade Components in Patients With Bipolar Disorder. *Front. Psychiatry* **9**, 614 (2018).

53. Yao, Q. & Li, Y. Increased serum levels of complement C1q in major depressive disorder. *J. Psychosom. Res.* **133**, 110105 (2020).

54. Gunaydin, M. *et al.* Complement system dysfunction in autism spectrum disorder: evidence for altered C1q and C3 levels (complement system dysfunction in ASD). *Acta Neuropsychiatr.* **37**, e64 (2025).

55. Melbourne, J. K., Rosen, C., Feiner, B. & Sharma, R. P. C4A mRNA expression in PBMCs predicts the presence and severity of delusions in schizophrenia and bipolar disorder with psychosis. *Schizophr. Res.* **197**, 321–327 (2018).

56. Rey, R. *et al.* Overexpression of complement component C4 in the dorsolateral prefrontal cortex, parietal cortex, superior temporal gyrus and associative striatum of patients with schizophrenia. *Brain. Behav. Immun.* **90**, 216–225 (2020).

57. Comer, A. L. *et al.* Increased expression of schizophrenia-associated gene C4 leads to hypoconnectivity of prefrontal cortex and reduced social interaction. *PLoS Biol.* **18**, e3000604 (2020).

58. Druart, M. *et al.* Elevated expression of complement C4 in the mouse prefrontal cortex causes schizophrenia-associated phenotypes. *Mol. Psychiatry* **26**, 3489–3501 (2021).

59. Phadke, R. A. *et al.* The schizophrenia risk gene C4 induces pathological synaptic loss by impairing AMPAR trafficking. *Mol. Psychiatry* **30**, 796–809 (2025).

60. Kipnis, J. Multifaceted interactions between adaptive immunity and the central nervous system. *Science* **353**, 766–771 (2016).

61. Graus, F. & Dalmau, J. Autoimmune encephalitis or autoimmune psychosis? *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* **50**, 112–114 (2021).

62. Harrison, N. A. *et al.* Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol. Psychiatry* **66**, 407–414 (2009).

63. Harrison, N. A. *et al.* A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. *Biol. Psychiatry* **80**, 73–81 (2016).

64. Brydon, L., Harrison, N. A., Walker, C., Steptoe, A. & Critchley, H. D. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. *Biol. Psychiatry* **63**, 1022–1029 (2008).

65. Yirmiya, R. & Goshen, I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain. Behav. Immun.* **25**, 181–213 (2011).

66. Harrison, N. A., Doeller, C. F., Voon, V., Burgess, N. & Critchley, H. D. Peripheral inflammation acutely impairs human spatial memory via actions on medial temporal lobe glucose metabolism. *Biol. Psychiatry* **76**, 585–593 (2014).

67. Vreijling, S. R. *et al.* Features of immunometabolic depression as predictors of antidepressant treatment outcomes: pooled analysis of four clinical trials. *Br. J. Psychiatry* **224**, 89–97 (2024).

68. Dellink, A. *et al.* Inflammatory markers associated with electroconvulsive therapy response in patients with depression: A meta-analysis. *Neurosci. Biobehav. Rev.* **170**, 106060 (2025).

69. Jha, M. K. *et al.* Validating pre-treatment body mass index as moderator of antidepressant treatment outcomes: Findings from CO-MED trial. *J. Affect. Disord.* **234**, 34–37 (2018).

70. Jha, M. K. *et al.* Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology* **78**, 105–113 (2017).

71. Köhler-Forsberg, O. *et al.* Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatr. Scand.* **139**, 404–419 (2019).

72. Bai, S. *et al.* Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. *J. Neurol. Neurosurg. Psychiatry* **91**, 21–32 (2020).

73. Wittenberg, G. M. *et al.* Effects of immunomodulatory drugs on depressive symptoms: A mega-analysis of randomized, placebo-controlled clinical trials in inflammatory disorders. *Mol. Psychiatry* **25**, 1275–1285 (2020).

74. Kappelmann, N., Lewis, G., Dantzer, R., Jones, P. B. & Khandaker, G. M. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol. Psychiatry* **23**, 335–343 (2018).

75. Raison, C. L. *et al.* A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* **70**, 31–41 (2013).

76. Foley, É. M. *et al.* Interleukin 6 as a Treatment Target for Depression: A Proof-of-Concept Randomized Clinical Trial. *JAMA Psychiatry* https://doi.org/10.1001/jamapsychiatry.2026.1053 (2026) doi:10.1001/jamapsychiatry.2026.1053.

77. Porcu, M. *et al.* Effects of adjunctive N-acetylcysteine on depressive symptoms: Modulation by baseline high-sensitivity C-reactive protein. *Psychiatry Res.* **263**, 268–274 (2018).

78. Nettis, M. A. *et al.* Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **46**, 939–948 (2021).

79. Xiao, X., Deng, H., Li, P., Sun, J. & Tian, J. Statin for mood and inflammation among adult patients with major depressive disorder: an updated meta-analysis. *Front. Psychiatry* **14**, (2023).

80. Otte, C. *et al.* Simvastatin as Add-On Treatment to Escitalopram in Patients With Major Depression and Obesity: A Randomized Clinical Trial. *JAMA Psychiatry* **82**, 759–767 (2025).

81. Moulton, C. D., Hopkins, C. W. P., Ismail, K. & Stahl, D. Repositioning of diabetes treatments for depressive symptoms: A systematic review and meta-analysis of clinical trials. *Psychoneuroendocrinology* **94**, 91–103 (2018).

82. Chen, X., Zhao, P., Wang, W., Guo, L. & Pan, Q. The Antidepressant Effects of GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis. *Am. J. Geriatr. Psychiatry* **32**, 117–127 (2024).

83. Bizzozero-Peroni, B. *et al.* The impact of the Mediterranean diet on alleviating depressive symptoms in adults: a systematic review and meta-analysis of randomized controlled trials. *Nutr. Rev.* **83**, 29–39 (2025).