Neuroscience 601 (2026) 45–57

Contents lists available at ScienceDirect

Neuroscience

journal homepage: www.elsevier.com/locate/nsc

Trained immunity in neuroinflammation: emerging evidence, clinical perspectives, and future directions☆

Enis Guso [a,b,1], Alessia Lupoli [a,1], Emanuele Olivieri [b], Alessia Bottoni [a], Maira Gironi [a], Davide M. Missarelli [a], Ahmed T. Toosy [d,e], Elena Rossi [a,*], Roberto Furlan [a,c]

[a] Clinical Neuroimmunology Unit, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milan, Italy
[b] Department of Clinical and Experimental Sciences, University of Brescia 25100 Brescia, Italy
[c] Vita e Salute San Raffaele University, Milan, Italy
[d] Queen Square MS Centre, Department of Neuroinflammation, Queen Square Institute of Neurology, University College London, London, UK
[e] UCL Hawkes Institute, University College London, London, UK

ARTICLE INFO

Keywords:
Trained immunity
Neuroinflammation
Neuroimmunology
Ischemic stroke
Neurodegeneration
Cell metabolism
Epigenetic remodelling
Innate immune memory

ABSTRACT

Trained immunity is the ability of the innate immune system to mount a heightened response to an environmental stimulus after a previous encounter with a noxious trigger. This effect is mediated by metabolic rewiring and epigenetic reprogramming in innate immune cells. In the context of neuroinflammation, trained immunity may represent a major contributor to the pathogenesis of neurological diseases, exerting both detrimental and potentially beneficial effects. While the general mechanisms and systemic implications of trained immunity are widely discussed, evidence in central nervous system (CNS) diseases remains fragmented and largely confined to individual pathological conditions. As a result, a comprehensive framework integrating these findings and identifying shared mechanisms across neurological disorders is still lacking. In this review, we explore the concept of trained immunity with a focus on neuroinflammatory and neurodegenerative diseases, synthetizing evidence from multiple CNS pathologies, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, and cerebrovascular disorders. We first critically examine preclinical and experimental studies addressing innate immune memory in the CNS and subsequently integrate these findings with emerging clinical evidence, aiming to identify convergent mechanisms and disease-relevant immune memory signatures. Finally, we discuss potential therapeutic targets identified in preclinical settings and outline key unresolved issues, including the nature of triggering stimuli, thresholds, and temporal dynamics shaping innate immune memory in the CNS. By highlighting current limitations and defining critical questions for future research, this review presents a unifying

Abbreviations: Aβ, amiloid beta; AD, Alzheimer's Disease; APP-transgenic mice, amyloid precursor protein- transgenic mice; ApoE-ε4, apolipoprotein E-epsilon 4; BBB, blood–brain barrier; BCG, Bacille Calmette-Guérin; C.Albicans, Candida Albicans; ChIP seq, Chromatin immunoprecipitation sequencing; CMV, Cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; DAMPs, Damage-Associated Molecular Patterns; EBV, Epstein Barr virus; FHTE, Fascicola hepatica total extract; GLP1R, Glucagon like peptide 1 receptor; H3K27ac, histone 3 lysine 27 acetylation; H3K4me3, histone 3 lysine 4 trimethylation; H3K9me2, histone 3 lysine 9 dimethylation; HDAC, histone deacetylase; HIF-1α, Hypoxia-Inducible Factor 1-alpha; HSCs, hematopoietic stem cells; HSV-1, Herpes simplex virus 1; IFN-γ, interferon-gamma; IGF1R, Insulin-like growth factor 1 receptor; IL, interleukin; iNOS, inducible nitric oxide synthase; IPLs, immune gene-priming long non-coding RNAs; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; M.Tuberculosis, Mycobacterium Tuberculosis; MRI, Magnetic Resonance Imaging; MS, Multiple Sclerosis; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; NK, natural killer; NLRP3, NOD-like receptor protein 3; NRa1, nicotinic receptor-associated protein 1; oxLDL, oxidized low-density lipoprotein; PAMPs, Pathogen-Associated Molecular Patterns; PBMCs, peripheral blood mononuclear cells; PD, Parkinson's Disease; PET, positron emission tomography; Poly I:C, Polyinosinic:polycytidylic acid; PPAR-α, peroxisome proliferator-activated receptor alpha; PRR, pattern-recognition receptors; pwMS, people with multiple sclerosis; RAP1, Repressor activator protein 1; shRNA, short hairpin RNA; ST2, suppression of tumorigenicity 2; TADs, topologically associated domains; TCA cycle, trycarboxylic acid cycle; TNF-α, tumor necrosis factor-alpha; TRAF6, TNF receptor-associated factor 6; 3xTg-AD mice, triple transgenic AD mice.

☆ This article is part of a special issue entitled: 'Infection, Immunity and Inflammation' published in Neuroscience.

* Corresponding author.
E-mail address: rossi.elena@hsr.it (E. Rossi).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.neuroscience.2026.02.047
Received 16 September 2025; Accepted 27 February 2026
Available online 3 March 2026

perspective on trained immunity in neurological diseases and underscores the translational potential to modulate neuroinflammation and to influence disease progression.

Introduction

Neuroinflammation can be conceptualized as the Central Nervous System's (CNS) attempt to respond to an injury that disrupts its homeostasis and contributors to this phenomenon are both innate and adaptive CNS immunity (Huang et al., 2025). The primary line of defence in the CNS (i.e. innate immunity) is largely orchestrated by the activation of resident cells, namely microglial cells and astrocytes. This process can either protect the CNS or, if dysregulated, exacerbate further damage. As evidence of this dual role, neuroinflammation is recognized to be detrimental in Multiple Sclerosis (MS) (Heß et al., 2020; Titus et al., 2020) Alzheimer's Disease (AD) (Ising et al., 2019; Pomilio et al., 2020; Wang et al., 2021, 2022; Xu et al., 2021) and Parkinson's Disease (PD) (Sarkar et al., 2020), whereas it could be considered beneficial at the beginning of these neurodegenerative disorders, when, for example, microglia help to clear misfolded proteins (Zhang et al., 2005; Keren-Shaul et al., 2017; Venezia et al., 2017; Heckmann et al., 2019; Choi et al., 2020; McAlpine et al., 2021). Overall, neuroinflammation is widely recognised as a defining feature across a broad spectrum of neurological diseases (Wilson et al., 2023a), driving their progression and often preceding pathological hallmarks such as protein deposits in the context of neurodegeneration (Galiano-Landeira et al., 2020; Chen et al., 2023; Wilson et al., 2023b).

Both preclinical and clinical studies have shown that a systemic inflammatory event can influence the development of CNS pathologies (Zhang et al., 2023). Indeed, systemic inflammation, induced by exogenous events like infections (Kamer et al., 2009; Wang et al., 2014, 2020; Ishida et al., 2017; Matheoud et al., 2019), or arising from conditions known for their associations with chronic inflammation like diabetes (Crane et al., 2013; Bahniwal, Little and Klegeris, 2017), obesity (Litwiniuk et al., 2021), and atherosclerosis (Walker et al., 2019; Jin, Liu and Wei, 2025), may precede the onset and potentially drive the growth of neurodegeneration. Evidence has challenged the traditional view of the CNS as an immune-privileged region providing a pathobiological framework to explain the connection between systemic inflammation and neurological diseases. Firstly, inflammatory mediators such as cytokines can disrupt the blood–brain barrier (BBB), enter the brain and activate microglial cells and astrocytes sparking a cascade of improper responses that converge towards a sustained and altered neuroinflammation (Banks, Kastin and Broadwell, 1995; Chen et al., 2019; Hauptmann et al., 2020). Likewise, peripheral immune cells can infiltrate the CNS, activate resident brain cells and determine analogous results (Fiala et al., 2002; Ferretti et al., 2016; Cai et al., 2021). Secondly, the CNS is now understood to engage in constant dialogue with the peripheral immune system through a series of interactive barriers – for instance the BBB, the blood-cerebrospinal fluid (CSF) barrier (comprising by the choroid plexus and the arachnoid meningeal layer) and the meningeal lymphatic vessels. This neuroimmune crosstalk occurs not only in pathological states, where these apparent boundaries are compromised, but also under physiological conditions, thus facilitating the relationship between central and peripheral immunity (Kipnis et al., 2025; Smyth and Kipnis, 2025).

The immune system exhibits remarkable plasticity, once thought to be limited to adaptive immunity through T and B cell memory. Accumulating evidence, however, shows that innate immune cells, including monocytes, macrophages, and microglia, can also retain memory of prior stimuli and mount enhanced responses upon re-exposure. This phenomenon, defined as trained immunity, encompasses a process by which innate immune cells, following ligand binding to their pattern-recognition receptors (PRRs), undergo long-term epigenetic reprogramming guided by metabolic mechanisms that persist after the initial stimulus fades (Netea, Quintin and van der Meer, 2011; Netea, et al., 2020).

In humans, evidence for this mechanism emerged from studies showing that the live attenuated Bacillus Calmette-Guérin (BCG) vaccine confers protection against subsequent infections by other pathogens (Higgins et al., 2016; Prentice et al., 2021). Building on these observations, it became evident that, unlike the precise activation and targeting of adaptive immunity, trained immunity is distinguished by its ability to be triggered by a wide range of stimuli, establishing a broad and robust immune defence that "primes" the system for a swifter, more effective response to future challenges (Vuscan et al., 2024). Experimental models show that microbial components (e.g., β-glucan, muramyl dipeptide, flagellin) and endogenous mediators such as interleukin (IL)-1, oxidized lipoproteins, and catecholamines can induce trained immunity through metabolic and epigenetic reprogramming, enhancing resistance to infections (Di Luzio and Williams, 1978; Krahenbuhl et al., 1981; Muñoz et al., 2010; Marakalala et al., 2013). Beyond infection, trained immunity contributes to diverse pathologies, including cardiovascular, autoimmune, allergic, oncologic, and metabolic diseases (Vuscan et al., 2024). For instance, monocytes from atherosclerosis patients exhibit a pro-inflammatory profile that promotes plaque formation (Bekkering et al., 2013).

Based on these data, trained immunity can be regarded as a double-edged sword, in the sense that, depending on the triggering stimulus, it can be beneficial or detrimental to human health. With this view, ageing, one of the primary risk factors for most neurological disorders, could serve as another example to demonstrate the detrimental impact of trained immunity. Indeed, this process manifests as a convergence of mechanisms that lead to chronic low-grade inflammation, termed inflammaging (Franceschi et al., 2000), and may be sustained by the occurrence of a maladaptive remodelling of innate immune cells. With ageing, monocytes and macrophages start secreting specific inflammatory molecules known to be involved in trained immunity-related mechanisms, thus contributing to escalated systemic inflammation (Qian et al., 2012; Metcalf et al., 2015; Franceschi et al., 2017). Consequently, trained immunity likely plays a fundamental role in the pathogenesis of neurological diseases, provided the involvement of both systemic and CNS inflammatory mechanisms (Zhang et al., 2023; Shi and Yong, 2025).

This review offers a comprehensive synthesis of the current evidence on the involvement of trained immunity in neurological disorders characterized by neuroinflammation, including MS, cerebrovascular diseases, AD and PD. Specifically, we examine the underlying cellular and molecular mechanisms, the immune cell populations implicated, and evidence derived from both experimental and clinical studies, thereby outlining the current state of knowledge in this emerging field. Furthermore, we address existing limitations and knowledge gaps, while considering the potential of trained immunity to yield novel biomarkers and therapeutic strategies capable of modifying the course of neurological diseases. For the purpose of this review, and while we acknowledge that mechanistic distinctions exist between priming, tolerance, differentiation and trained immunity as adaptive programs of innate immune cells (Divangahi et al., 2021), we will employ the terms cellular priming and training interchangeably. In this context, priming refers to the effect of an initial stimulus that alters the functional state of a cell such that it does not return to baseline before a second challenge, often leading to additive or enhanced responses (i.e., the ability of one stimulus to induce a change in immune cells so they respond differently upon a second stimulus).

Cellular mechanisms of trained immunity

Trained immunity refers to the property of innate immune cells to produce an enhanced inflammatory response after returning to resting state following initial exposure to a pathogenic stimulus, thus indicating that, contrary to what previously assumed to be a lymphocyte prerogative, innate immune cells can recall, recognize, and demonstrate enhanced responses to further exposure to similar stimuli. After the established role of live vaccines such as BCG in inducing a heightened nonspecific response by innate immune cells against subsequent infections (Blanden, Lefford and Mackaness, 1969), studies have investigated the mechanisms behind this enhanced secondary response. Indeed, mice immunized with BCG vaccine or exposed to mild dose of *C. albicans* were protected from a secondary infection by *C. albicans* or *Mycobacterium tuberculosis*, respectively (Netea et al., 2020). Key mechanisms include altered cellular metabolism and epigenetic reprogramming through chromatin remodelling, DNA methylation, transcription of long non-coding RNAs (lncRNAs). Although the full molecular basis remains unclear, current evidence suggests that these regulatory mechanisms converge to enhance the transcriptional response of specific inflammatory genes (Mantovani and Netea, 2020).

Metabolic alterations

Innate immunity recognizes noxious stimuli through Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) ligands binding to PRRs, activating a pro-inflammatory response. This mechanism induces the activation and modulation of metabolic pathways, increasing aerobic glycolysis, fatty acid metabolism, tricarboxylic acid (TCA) cycle, and amino acid metabolism in immune cells (Keating and El-Osta, 2015a; Viola et al., 2019a). Persistently increased glycolysis promotes two essential pathways implicated in the determination of trained immunity, namely Hypoxia-Inducible Factor 1-alpha (HIF-1α) via succinate, and mammalian target of rapamycin (mTOR) mainly through mevalonate (an intermediate in cholesterol biosynthesis) fuelling inflammatory response with production of IL-1β (Cheng et al., 2014; Bekkering et al., 2018). Additionally, dectin-1 activation by ligands, such as β-glucans and fungi polysaccharides, stimulates calcium entry in the cell and involvement of nuclear factor of activated T cells (NFAT) pathway with resultant activation of inflammatory gene transcription (Quintin et al., 2012a; Mata-Martínez, Bergón-Gutiérrez and del Fresno, 2022a). Moreover, the shift from oxidative phosphorylation to aerobic glycolysis, driven by the Akt/mTOR/HIF-1α pathway, is essential for β-glucan-induced training (Cheng et al., 2014). Trained monocytes exhibit increased glucose uptake and glycolytic activity, facilitating production of proinflammatory cytokines and improving effector functions such as phagocytosis (Cheng et al., 2014). This metabolic switch is not exclusive to β-glucan, a similar glycolytic upregulation has been observed following BCG and oxidized low-density lipoprotein (oxLDL) stimulation (Keating et al., 2020). A hallmark of this glycolytic shift is the increased conversion of glucose to lactate, a feature consistently seen in trained cells (Bekkering et al., 2021). Pyruvate generated from glycolysis also feeds into the TCA cycle via conversion to acetyl-CoA, leading to elevated mitochondrial activity and ATP production. Glutamine metabolism is also enhanced to support the TCA cycle, with glutamate entering the cycle either via α-ketoglutarate or, alternatively, through succinate semialdehyde leading to succinate production (Arts et al., 2016). Cholesterol metabolism has also emerged as a critical pathway in trained immunity. Inhibition of cholesterol synthesis using statins prevents the induction of trained immunity by β-glucan, BCG, and oxLDL, underscoring its essential role (Porta et al., 2009). Further, findings also attribute a significant role in trained immunity to the complement system. C1q, a key subunit of the classical complement pathway, has been shown to induce immune tolerance, similarly to lipopolysaccharide (LPS)-induced tolerance (Porta et al., 2009). Indeed, C1q-treated monocytes showed reduced glycolysis and inhibition of the mTOR and MYC signalling (crucial to the trained immunity phenotype (Jonkman et al., 2025), making C1q a suitable target for a disease-modifying therapy.

Epigenetic reprogramming

These metabolic pathways directly influence the other milestone of trained immunity: epigenetics. The most common epigenetic sequelae of trained immunity on histones are the acetylation of the histone 3 lysine 27 (H3K27ac) at distal enhancers and the trimethylation of the histone 3 lysine 4 (H3K4me3) at the promoters (Netea, Domínguez-Andrés, Barreiro et al., 2020).

It is well established that epigenetic reprogramming is closely linked to metabolic rewiring, as key metabolites derived from processes such as oxidative phosphorylation and the TCA cycle can directly modulate the activity of chromatin modifying enzymes. For example, elevated acetyl-CoA levels promote histone acetylation, a key feature of transcriptionally active chromatin. Moreover, TCA cycle metabolites, such as α-ketoglutarate, function as cofactors for DNA and histone demethylases (Lu et al., 2012). Conversely, accumulation of succinate or fumarate inhibits these enzymes. It was shown how fumarate itself can induce a trained immunity phenotype, by promoting histone marks such as H3K4me3 and H3K27ac (Arts et al., 2016). These effects mirror, at least in part, the epigenetic signatures observed following β-glucan stimulation, suggesting fumarate acts downstream of the metabolic rewiring initiated by a training stimulus (Xiao et al., 2012). Once the priming molecule (BCG or β-glucan) binds to PRRs on the myeloid cell, the inflammatory genes gain acetylation at distal enhancers of specific conserved topologically associated domains (TADs), where several classes of innate immune genes are contained and where they interact within multigene complexes. Acetylation of TADs promotes chromatin opening and, together with the activation and nuclear translocation of NFAT, initiates the transcription of immune gene-priming lncRNAs (IPLs). These lncRNAs are expressed at physiologically repressed immune loci, converting immune cells from a quiescent to a primed state. A paradigmatic example of IPL involvement in trained immunity is UMLILO, contained within the super-enhancer of the inflammatory CXCL chemokine's locus. Once UMLILO is transcribed, its mRNA binds to trimethylation complexes, exploiting 3D looping, bringing them close to the nearby innate immune genes, allowing their methylation. Once the TADs acquire the H3K4me3 mark, the chromatin becomes more accessible to transcription of inflammatory genes, making the response to a second stimulus faster and more robust, leaving what was then called an "epigenetic scar" determined by changes in the long-term responsiveness of the cell (Fanucchi et al., 2019). Taken together, these studies demonstrate that metabolic and epigenetic reprogramming are core characteristics of trained immunity. Understanding and harnessing these adaptations may enable the development of strategies to emulate the prompt and robust responses of trained cells to harmful stimuli into disease-relevant contexts.

Where and how: the hub of trained immunity

Trained immunity can occur in bone marrow progenitor cells (central trained immunity) as well as in blood monocytes and tissue macrophages (peripheral trained immunity) (Netea et al., 2020). The bone marrow, as the site of haematopoiesis, is where haematopoietic stem cells (HSCs) undergo asymmetric division to generate the full spectrum of myeloid and lymphoid cells. Monocytes derived from trained HSCs migrate to peripheral organs and differentiate into macrophages with enhanced antimicrobial functions. Kaufmann et al. demonstrated that HSCs can be reprogrammed to imprint mononuclear phagocytes with a trained phenotype. Indeed, BCG vaccination reshapes the bone marrow microenvironment through cytokine and PAMPs release, leading to transcriptional and epigenetic reprogramming of HSCs and progenitors (Kaufmann et al., 2018). These changes are maintained in multipotent

progenitors and bone marrow–derived macrophages, resulting in heightened reactivity against *M. tuberculosis* and increased production of interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), and IL-1β (Kaufmann et al., 2018).

In the periphery, circulating and resident monocytes, macrophages, and natural killer (NK) cells not only inherit trained signatures from their precursors but can also acquire memory locally. Early evidence showed that macrophages exposed to LPS developed tolerance, with transient silencing of inflammatory genes to prevent excessive inflammation, while antimicrobial genes remained active (Foster, Hargreaves and Medzhitov, 2007). Such epigenetically mediated regulation enabled a more rapid and robust response to subsequent LPS challenges. The duration and character of trained immunity depend on multiple factors, particularly stimulus intensity: moderate antigen exposures induce trained signatures, whereas high-dose or repeated stimuli favour immune tolerance, leading to suppressed responses to secondary insults (van der Meer et al., 2015; Seeley and Ghosh, 2017; Netea et al., 2019; Ochando et al., 2023).

Table 1
Metabolic and epigenetic reprogramming underlying trained immunity in neuroinflammatory contexts.

Stimulus	Mechanism of action	Type of cell	Metabolic modifications	Epigenetic modifications	Phenotype	Reference
β-glucans, fungi polysaccharides	Dectin-1 → Akt/ mTOR/HIF-1α	Macrophages Microglia	↑ aerobic glycolysis	↑ H3K4me3 in promoters ↑ acetylation at enhancers (e.g. H3K27ac) ↑ transcription of immune gene-priming lncRNAs (IPLs)	Trained	Marakalala et al., 2013;Mata-Martínez, et al., 2022;Quintin et al., 2012;van der Meer et al., 2015
BCG vaccine	TLRs/NOD2 signaling	Macrophages	↑ aerobic glycolysis	↑ H3K4me3 in promoters ↑ acetylation at enhancers (e.g. H3K27ac) ↑ transcription of immune gene-priming lncRNAs (IPLs)	Trained	Keating and El-Osta, 2015; Kaufmann et al., 2018;Van der Meer et al., 2015;Murphy, Mills and Basdeo, 2021;Tiwari et al., 2024;
Microbial components e.g. LPS, Candida Albicans, muramyl dipeptide, flagellin	TLR4 activation	Macrophages Microglia Astrocytes	↑ aerobic glycolysis ↑ production of ATP-citrate lyase (ACLY) in astrocytes	↑ H3K4me3 in promoters ↑ acetylation at enhancers (e.g. H3K27ac) ↑ transcription of immune gene-priming lncRNAs (IPLs) ↑ p300 activity in astrocytes	Trained (acute exposure)	Krahenbuhl et al., 1981;Muñoz et al., 2010;Foster, Hargreaves and Medzhitov, 2007;van der Meer et al., 2015;Seeley and Ghosh, 2017
Damage-Associated Molecular Patterns (DAMPs) e.g. HMGB1, protein aggregates, oxLDL, lipid soluble ligands	Pattern Recognition Receptors (PRRs) activation	Macrophages Microglia Astrocytes	↑ aerobic glycolysis ↑ production of ATP-citrate lyase (ACLY) in astrocytes	↑ H3K4me3 in promoters ↑ acetylation at enhancers (e.g. H3K27ac) ↑ transcription of immune gene-priming lncRNAs (IPLs) ↑ p300 activity in astrocytes	Trained	(Viola et al., 2019b) Wang et al., 2024;Keating and El-Osta, 2015;Ren et al., 2025
Endogenous mediators e.g. Catecholamines, cytokines	PRR-linked downstream signaling	Macrophages Microglia Astrocytes	↑ aerobic glycolysis ↑ production of ATP-citrate lyase (ACLY) in astrocytes	↑ H3K4me3 in promoters ↑ acetylation at enhancers (e.g. H3K27ac) ↑ transcription of immune gene-priming lncRNAs (IPLs) ↑ p300 activity in astrocytes	Trained-like	Reviewed in Lee et al., 2024
C1q	TLR4 modulation; negative regulators	Macrophages Microglia Astrocytes	↓ aerobic glycolysis → inhibition of the mTOR and MYC signalling	↓ p300 activity in astrocytes ↓ H3K27ac at promoters of inflammatory genes (TNF, IL1B)	Tolerogenic	Jonkman, Maaike M.E. Jacobs, et al., 2025
Repeated administrations of LPS	Activation of TLR4 Upregulation of negative regulators	Macrophages Microglia Astrocytes	↓ aerobic glycolysis → inhibition of the mTOR and MYC signalling	↓ p300 activity in astrocytes ↓ H3K27ac at promoters of inflammatory genes (TNF, IL1B)	Tolerogenic	Wendeln et al., 2018
Microinfarcts	NLRP3 inflammasome	Microglia	Interaction with MLL1	↑ H3K4me3 in promoters of inflammatory genes	Trained-like	Feng et al., 2024

Adding to this complexity, trained immunity can yield contrasting outcomes depending on the priming stimulus and differentiation state of the cell. For example, β-glucan priming of human monocytes enhances IFN-α and IL-6 expression, whereas LPS suppresses them. Moreover, upon LPS stimulation, monocytes exhibit stronger IL-1β responses than differentiated macrophages, highlighting intrinsic differences between immune training and tolerance (Saeed et al., 2014). These functional changes are underpinned by dynamic chromatin remodelling, particularly H3K27 acetylation at promoter and enhancer regions, followed by stabilized H3K4me1 marks that help sustain innate immune memory. Better definition of the duration and functional outcomes of trained immunity will be crucial for its translation onto clinical settings.

The power of surrounding stimuli to imprint a metabolic signature in cells patrolling the CNS affects secondary challenges. In these terms, whilst there is consensus that trained immunity is rooted in the response of innate immune cells (Bromuro et al., 2002; Polonelli et al., 2003), a collaborative and intricate relationship exists between innate and adaptive immune responses. Extensively explored by Murphy et al., 2021 (Murphy, Mills and Basdeo, 2021), a plethora of molecular triggers from BCG, β glucan, LPS, or PHTE, can induce trained immunity by promoting the release of various cytokines by myeloid cells which in turn stimulate different subtypes of T helper or regulatory cells. This leads to multiple outcomes and is particularly relevant for autoimmunity (Quinn et al., 2019). This crosstalk between innate and adaptive immunity may indeed determine the development and progression of disease in the context of neuroinflammation.

Trained immunity in neuroinflammation: macrophages, microglia and astrocytes

While the concept of trained immunity can be applied to a variety of cell types, macrophages, microglia, and astrocytes are the main cell types involved during neuroinflammation (Table 1).

Macrophages

Within the CNS, peripheral trained immunity significantly contributes to neuroinflammation and neurodegeneration. Inflammatory cues can reprogram microglia and astrocytes, imprinting long-lasting changes. Among peripheral blood mononuclear cells (PBMCs), monocytes and macrophages are the most extensively studied and consistently implicated in innate immune memory, with characteristic inflammatory signatures and epigenetic modifications in line with the above-discussed mechanisms (Shnyra et al., 1998; Palmieri et al., 2020; Haimerl et al., 2021; Lechner et al., 2022; Hartana et al., 2023; Kandalla et al., 2023). Normally patrolling the blood–brain barrier (BBB), monocytes/macrophages gain full access to the CNS when the barrier is disrupted by trauma, disease, or aging (Blau et al., 2012), where they amplify inflammation and microglial activation (Girard et al., 2013; Costello et al., 2016). In neurological disorders such as MS, AD, PD, and ischemic stroke, macrophages, microglia and astrocytes act as central drivers of both inflammatory and protective signalling, with indication of priming behaviour depending on the environment and secreted factors consistent with trained immunity. Distinguishing infiltrating macrophages from resident microglia remains challenging, as their reciprocal interactions are not fully understood (Amici, Dong and Guerau-de-Arellano, 2017; Minogue, 2017), however evidence exists to support their differential contribution during CNS injury. In mice, for example, peripheral macrophages are found to be primed by ischemia-induced microglial peroxisome proliferator-activated receptor-alpha (PPARα), a nuclear receptor activated by soluble ligands, with well-known anti-inflammatory effects. After ischemic stroke, PPARα becomes down-regulated in microglia, leading to pro-inflammatory activity and increased CNS infiltration by monocyte-macrophages. Intriguingly, PPARα overexpression in microglia alleviates ischemic brain injury (Ren et al., 2025). On the other hand, alternative activation of monocytes/macrophages was reported in mice via IL-33/ST2 signalling by glial cells after CNS acute ischemic and traumatic injury, supporting priming of these cells towards a beneficial phenotype guarantying a smaller lesion volume, both ischemic and traumatic, and a more prominent BBB integrity (Gadani et al., 2015; Wang et al., 2024).

Microglia

Contrary to monocytes-macrophages, microglia are long-lived cells, with a lifespan of about 4–20 years in humans and up to 15 months in mice (Askew et al., 2017; Füger et al., 2017). As pointed by Neher and Cunningham (Neher and Cunningham, 2019), microglial immune memory may arise long time before the secondary stimulus, for instance by maternal immune activation or early exposure to inflammatory events (Mattei et al., 2017; Loayza et al., 2023), which would determine a primed and rapid phenotypic shift once re-exposed to a distant inflammatory insult. This would support the ability of microglia to undergo immune training and maintain a long-term epigenetic shift even after developmental migration during embryogenesis (Ginhoux et al., 2010).

Wendeln and colleagues (2018) reported not only that peripheral LPS stimulation was able to induce microglial activation, but also that different patterns of repeated stimulations conferred contrasting effects in inducing a trained or tolerant innate immune phenotype, further complicating the landscape described in Section 2.3. These effects were evident when comparing cytokine levels in blood versus brain tissues (Cheng et al., 2014). Indeed, acute LPS stimulation in APP-transgenic mice – an experimental model of AD – was associated with induced trained immunity by enhancing HIF-1α and consequent glycolysis elevation. In contrast, repeated (4x) LPS stimulations determined RAP1-mediated microglial tolerance beneficial for amyloid-β (Aβ) phagocytosis (Wendeln et al., 2018). Similarly, in animal models of brain ischemia, repeated (4x) LPS-preconditioning stimulations (1 month before the hypoxic insult) compared with single (1x) LPS stimulation and with controls generated lower levels of microglial activation and neuronal damage were reported for brain ischemia in LPS-preconditioned animals compared with controls highlighting timing- and context-dependent immune memory modulation (Wendeln et al., 2018).

Temporal dynamics of challenge-rechallenge are also relevant. Indeed, whilst short temporal lag (e.g. 2 days) between inflammatory stimulation by LPS or β-glucan resulted in immune training after systemic secondary stimulation by LPS, a 7-day interval between preconditioning and stimulation induced immune tolerance with suppression of inflammatory activity. Interestingly, the authors reported alternative responses between in vitro and *in vivo* microglia, such that *in vivo* administration elicited microglial activation via increased expression of dectin-1, rather than increasing inflammatory cytokines as observed in vitro (Heng et al., 2021). In ischemic stroke mice models, pre-treatment with LPS induced higher pro-inflammatory cytokine production, increased H3K4me1 epigenetic mark, contributing to wider infarct sizes (Feng et al., 2020). Moreover, both LPS and β-glucan preconditioning induced immune tolerance in the periphery with lower levels of IL-1β, IFN-γ and IL-6 compared with PBS-preconditioned control, pointing to relevant differential contributions of peripheral innate immune cells and brain-resident macrophages. Epigenetic reprogramming in microglial memory and immune regulation was also observed in vitro and *in vivo* model of PD, as well as in postmortem human PD brain. In fact, suppressing histone acetylation at inflammatory genes, through inhibition of H3K27ac, lead to a shift toward a less pro-inflammatory microglial phenotype, by decreasing iNOS and increasing anti-inflammatory and pro-reparative genes (Huang et al., 2023a). Evidence for beneficial memory training in macrophages and microglia has also been demonstrated in a demyelination mouse model in the context of aging. Microglial regenerative function is impaired with epigenetic modifications consequent to the cited inflammaging. Indeed, BCG

preconditioning followed by lysolecithin-induced demyelination was associated with reduced demyelination, lower numbers of Iba1$^+$ microglia cells, and enriched H3K27ac and H3K4me3 marks at regions corresponding to genes associated to lipid metabolism (Tiwari et al., 2024). These data were further confirmed by genetic ablation of HDAC1/2 enzymes, known for their role in controlling histone acetylation, which resolved in lower lesion damage with higher numbers of CC1$^+$ oligodendrocytes and lower Iba1$^+$ cells (Tiwari et al., 2024). Taking advantage of recent advances in single-cell epigenomic technologies, including scATAC-seq, snRNA-seq, and multiome profiling, researchers have begun to reveal the heterogeneity of human microglial states and identify poised enhancers and transcription factor networks that may underlie microglial immune memory (Huang et al., 2023) Indeed, as already mentioned, inflammatory stimuli can remodel chromatin and histone marks such as H3K27ac, priming transcriptional programs for enhanced responsiveness or tolerance in the innate immune memory—or trained immunity—of microglia (Martins-Ferreira et al., 2021; Zhang et al., 2022; Scholz, Brösamle, Yuan, Beyer, et al., 2024; Scholz, Brösamle, Yuan, Neher, et al., 2024). While direct evidence of trained immunity in living human microglia remains limited due to ethical and technical constraints, analyses of post-mortem brain tissue, surgical samples, and iPSC-derived microglia using these single-cell approaches indicate that microglial epigenetic landscapes can retain signatures of prior inflammatory exposures. Complementary single-cell epigenomic studies in peripheral human immune cells show that systemic stimuli, such as vaccination or infection, can induce durable chromatin remodeling, supporting the idea that systemic signals may contribute to microglial training in humans (Wimmers et al., 2021; You, Chen, Zhang, Zhao, Chen, E.-Q. Qin, et al., 2021; Schlüter et al., 2025).

These findings underscore the remarkable plasticity of microglia and their context-dependent immune memory. However, most evidence derives from murine or in vitro models, leaving open questions about the relevance and safety of targeting microglial epigenetic programming in humans. Translating these insights into therapeutic strategies will require careful evaluation of timing, stimulus type, and systemic effects.

Astrocytes

Despite their different lineage compared with immune cells, astrocytes immune behaviour in CNS immunity has gained over the years particular interest in the context of neuroinflammation. Being the most abundant glial cells in the brain, astrocytes carry a plethora of roles within the mammalian CNS by supporting neuronal and oligodendrocyte metabolism and function, surveillance of the synaptic and perivascular environments, contribution to the homeostasis of CNS and involvement in repair responses upon injury (Allen and Lyons, 2018). Astrocytes reactivity during CNS disease and neuroinflammation is complex and context-dependent and involves interaction with neurons, oligodendrocytes, microglia, macrophages, endothelial cells and pericytes (Verkhratsky et al., 2023). Upon injury, astrocytes respond to released cytokines, chemokines, reactive oxygen species, and neurotransmitters to orchestrate an appropriate reaction that may protect the brain from further damage. Triggered by the exposure to these proinflammatory factors, astrocytes assume a reactive state during which their homeostatic signature is lost with morphological and functional alterations (Linnerbauer, Wheeler and Quintana, 2020). Recent studies suggest that astrocytes, similarly to immune cells, may also develop a memory towards pathogens and inflammatory stimuli, with relevant patterns of trained immunity. Lee and coworkers (2024) reported trained immunity-like responses by astrocytes to stimulation with IL-1β and TNF-α both *in vivo* and in vitro, with enhanced increase of pro-inflammatory genes expression (Il-6, Ccl2, Nos2) upon re-exposure compared with single exposure to the stimulus. Epigenetic mechanisms behind this phenomenon were ascribed to Acly (an enzyme for the synthesis of Acetyl-CoA)-dependent p300 regulation with consequent acetylation at H3K27ac. Indeed, CRISPR-Cas9 LV Ep300 inactivation at a GFAP promoter resulted in amelioration of EAE clinical score, confirming a trained memory profile of astrocytes in a model of neuroinflammation (Lee et al., 2024). Astrocytes priming role has also been demonstrated in AD. Poly I:C or cytokine cocktail-primed astrocytes carrying the ApoE-ε4 risk allele, compared with non-carriers, showed reduced response upon Aβ exposure, which resulted in impaired microglial phagocytosis (Lee et al., 2025), highlighting the relevance of genetics in guiding cellular behaviour. Furthermore, astrocyte dual role has been extensively discussed in reference to neurodegenerative diseases like AD pointing to both beneficial or detrimental effects of these cells on the CNS structure and function strictly dependent on the microenvironment (Kim et al., 2024). Thus, astrocytes display memory-like, epigenetically driven responses, but their dual and context-dependent roles caution against simplistic therapeutic targeting in neuroinflammation.

Collectively, these studies underscore the central role of metabolic and epigenetic reprogramming in shaping trained immunity across microglia, astrocytes, and macrophages, highlighting both their therapeutic potential and context-dependent effects (Murphy, Mills and Basdeo, 2021). However, most evidence comes from animal and in vitro models, making it critical to validate these mechanisms in human studies to uncover real-life relevance, biomarkers, and translational insights.

Trained immunity in neurological diseases

Trained immunity mechanisms are implied in numerous conditions in humans, both in physiological and pathological conditions, such as infectious, autoimmune and neurological diseases (Fig. 1). Dissecting their favourable and detrimental role in these diseases may help evaluate candidate targets for future tailored therapies. However, the paucity of clinical data, the lack of standardized, operational definitions of trained immunity and immune tolerance, and the absence of reliable blood-based and imaging biomarkers collectively contribute to substantial heterogeneity across research pathways. Whilst an exhaustive review of the literature is beyond the scope of this work, an overview of the prevalent conditions associated with neuroinflammation aims to guide some reflective thoughts on the emerging concepts of trained immunity.

Multiple sclerosis

Multiple Sclerosis (MS) is a demyelinating, neurodegenerative, autoimmune disease driven by altered adaptive and innate immune system cells. Monocytes, macrophages and microglia are found in MS lesions and play a pivotal role in disease pathogenesis. Trained immunity signatures do exist in people with MS (pwMS) compared with healthy controls, showing a higher number of non-classical monocytes (Haschka et al., 2020) with higher expression of activation markers (Chuluundorj et al., 2017), higher cytokines secretion (Fransson et al., 2024) and a metabolic shift towards enhanced glycolytic pathways (Zahoor et al., 2022) (Fig. 1A).

However, evidence confirming trained immunity remains elusive due to inconsistent outcomes in clinical studies. For instance, a phase 2–3 trial reported the effects of BCG vaccination in a Clinically Isolated Syndrome cohort, which slowed the development of new gadolinium-enhancing lesions on brain Magnetic Resonance Imaging (MRI) for a 6-month period and reducing the conversion to Clinically Defined Multiple Sclerosis over a 5-year period (Ristori et al., 2013). In contrast, in a large Canadian epidemiological study, BCG vaccination failed to show benefits as a preventive treatment for the incidence of MS (Corsenac et al., 2022).

During the history of the disease, BCG vaccination, a well-described trained immunity-inducer, has been tried as a disease modifying treatment and as a preventive strategy for MS, based on the protective action

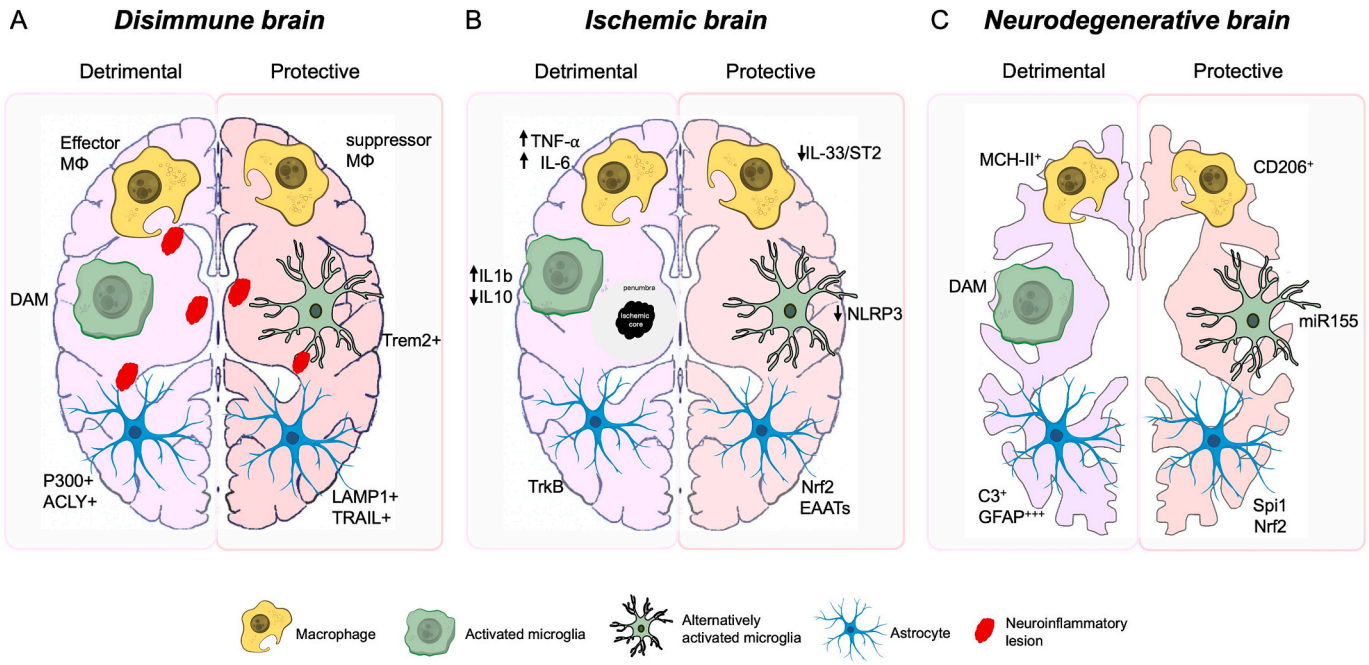

Fig. 1. Trained infiltrating macrophages, microglia, and astrocytes can modulate, positively or negatively, pathological processes like neuroinflammation (A), stroke (B), and neurodegeneration (C). Protective and detrimental roles of these cell type have been widely explored, but not always in the context of trained immunity. Instructive is the case of stroke, where in animal models it has been shown that previous training influences the outcome of both the acute phase of stroke as well as its sequelae. This might explain the known association of infectious training events with worse outcome in future stroke, or the well-established link between infectious evens and the risk to develop neurodegenerative diseases. Created using elements from https://scidraw.io/ (CC BY 4.0).

of the adjuvants in modulating experimental models of autoimmune diseases.

As a preventive strategy for MS, a *meta*-analysis of six case-control studies in 2011 (Farez and Correale, 2011) found no significant association between prior BCG vaccination and subsequent MS risk (BCG: OR 0.96, 95% CI 0.69–1.34), although the underlying observational studies were characterized by small sample sizes and limited validity (e.g.: a self-reported BCG vaccination status). Instead, in 2022, in a large Canadian population-based birth cohort (n = 400,563), BCG vaccination was associated with a modestly increased hazard of incident MS when considering all cases (adjusted HR 1.16, 95% 1.05–1.28), mainly driven by vaccinations administered before 1 year of age (Corsenac et al., 2022). Some limitations must be considered: the limited definition of Relapsing-Remitting MS (RRMS) used, the impossibility to assess presence of RRMS in a large portion of the population (30%), the lower sensitivity of MS diagnostic criteria in the periods considered (1983–1996 and 1997–2014), thus underestimating the total cases of MS. Clearly defining whether BCG vaccination could reduce or increase MS risk would benefit from broader methodological standardization.

As a potential therapy, (Ristori et al., 1999) showed in 12 pwMS a reduction in the frequency of new lesions on brain Magnetic Resonance Imaging (MRI); in 2013 the same group demonstrated again fewer gadolinium-enhancing brain MRI lesions over the first 6 months in a placebo-controlled, randomized clinical trial in a Clinically Isolated Syndrome cohort, in addition to fewer conversions to clinically defined MS over a 5-year period (Ristori et al., 2013). It is important to specify BCG vaccine has pleiotropic immunomodulatory effects: in vitro, it can induce IL-10-producing dendritic cells (Madura Larsen et al., 2007) and it determines epigenetic modifications enhancing Treg-mediated immune balance amongst the others (Keefe et al., 2021). Due to unstandardised operational definitions and lack of assays of trained immunity for routine clinical use, quantification at the individual level remains challenging, whether BCG alters innate immune memory *in vivo* and to what extent such changes causally mediate measurable MRI or clinical outcomes in MS is yet unanswered.

In MS, C1q constitutes a critical mediator in the interplay between neurons, astrocytes and microglia (Absinta et al., 2021; Jonkman et al., 2025). In fact, an increase in C1q deposition has been found at synapses in MS brain, responsible for microglia-mediated phagocytosis of labelled synapses (Michailidou et al., 2015) and related to cognitive dysfunction (Ramaglia et al., 2021). C1q inhibitors may thus be a validate candidate as Disease-Modifying Therapy. However, as suggested by Jonkman and colleagues (Jonkman et al., 2025), C1q may act as a trained immunity-inhibitor; its pharmacological inhibition may lead to a disinhibition of those trained immunity footprints discussed above, potentially worsening the auto-innate immune damage. It must be said that no major safety concerns have been identified so far in the ongoing trials of C1q inhibitors for Guillain Barrè Syndrome (Kroon et al., 2025) and Huntington's Disease (Kumar et al., 2023). In line with the crosstalk between innate and adaptive immunity, an intriguing study (Jacobs et al., 2024) demonstrated that T lymphocytes mediate monocyte activation through CD40L, enabling TRAF6, bound to the intracellular domain of CD40, to promote increased cellular metabolic activity, chromatin remodelling and a heightened pro-inflammatory cytokine response after a second stimulus. Frexalimab, a monoclonal antibody targeting CD40L, showed effectiveness in a phase 2 trial in reducing new gadolinium enhancing lesions in pwMS (Vermersch et al., 2024). Beyond its established interference with the CD40-CD40L costimulatory pathway, the benefits from this drug might be also attributed to the modulation of trained immunity.

Overall, while molecular and cellular features consistent with trained immunity are detectable in pwMS, direct evidence linking these signatures to clinically meaningful outcomes remain limited and, at times, contradictory. The pleiotropic effects of interventions such as BCG vaccination, the lack of standardized assays to quantify innate immune memory *in vivo*, and the complex interplay between complement pathways and adaptive immunity make causal inference particularly challenging. Clarifying whether trained immunity represents a driver of MS pathology, a context-dependent modifier, or an epiphenomenon will require mechanistically grounded longitudinal studies

and harmonized clinical readouts before credibly considered a therapeutic target.

Cerebrovascular diseases

In cerebrovascular diseases, evidence of trained immunity is limited. Compared with MS, trained immunity pathways can develop as sequelae of acute ischemic stroke and to the severity and progression of cerebral small vessel disease (a pathological process affecting arterioles, capillaries and venules leading to ischemic and haemorrhagic damage). In fact, in subjects affected by cerebral small vessel disease, blood monocytes exhibit heightened pro-inflammatory cytokine production, secreting higher levels of IL-8 and IL-17 at basal conditions and IL-6 after stimulation with Pam3Cys (a toll-like receptor agonist). The progression of the disease as evaluated 9 years later by MRI correlated with the trained immunity features of circulating monocytes, without influence of immunomodulator drugs, inflammatory conditions and diabetes (Noz et al., 2018).

In mice, Feng and coworkers (Feng et al., 2024) demonstrated how a single cortical microinfarct can considerably worsen the outcomes of a subsequent stroke. The mechanism is likely attributed to a typical trained immunity epigenetic mark, the H3K4 methylation, leading to increased NLRP3 activity in microglia, priming proinflammatory genes, even in the contralateral cortex (Fig. 1B). NLRP3 knockout alleviated the heightened innate immune response, protecting from the secondary event and posing this gene as a potential therapeutic candidate to mitigate the worse outcomes of recurrent stroke in humans with cortical microinfarcts (Wei et al., 2020). Further insights from mice models emerged from Tze-Yen Lin and colleagues' work (Lin et al., 2023), elucidating the impact of high-salt diet on brain recovery after intracerebral haemorrhage, through the downregulation of NR4α protein family in HSCs. Specific knockout of NR4a1 in macrophages replicated high-salt diet-induced effects, whilst its overexpression or activation determined better haemorrhagic stroke outcomes, adding another possible therapeutic target, coming from trained immunity.

An interesting study from Simats and colleagues (2024) highlighted the aforementioned crosstalk between districts, showing how the effects of innate immune memory may determine remote organ dysfunction after ischemic brain damage, previously considered immunologically privileged. Mice affected by experimental brain ischemic stroke showed persistent pro-inflammatory epigenetic signatures (assessed as chromatin accessibility with ChIP seq evaluating H3K4me1, H3K4me3 and H3K27ac) in monocytes and macrophages in multiple organs, lasting up to 3 months after the acute event. These were driven by IL-1β and led to the mobilization and differentiation of myeloid precursors to the heart, inducing cardiac remodelling, leading to diastolic dysfunction and pro-arrhythmic changes. Interestingly, post-stroke cardiac dysfunction was prevented with CCR2/5 inhibition or IL-1β blockade. The pathological findings were confirmed in humans, revealing marked cardiac fibrosis and increased trained monocytic recruitment in the hearts of stroke patients[101]. In a recent phase 1/2 trial in patients with ischemic stroke due to large vessel occlusion, the administration of a TLR4 antagonist, a receptor involved in innate immune responses, resulted in reduced infarct volume, decreased NIHSS score, and improved disability at 90 days (Hernández-Jiménez et al., 2023).

Targeting trained immunity epigenetic and metabolic changes may, once again, be associated with better long-term outcomes and less complications, although more evidence is necessary.

Neurodegenerative diseases

Alzheimer's disease

Alzheimer's Disease (AD) is the most common form of dementia, characterized by accumulation of Aβ plaques, neurofibrillary tangles and neuroinflammation, the latter mediated by innate immunity, microglia and astrocytes (Fig. 1C).

A recent study (Saaoud et al., 2025) hypothesized AD as an auto-innate immune disease, after discovering with bioinformatic approaches in the 3xTg-AD mice model an upregulation of genes involved in inflammasome, immunometabolism and trained immunity pathways. A set of these genes was orchestrated by trained immunity modulation like the knockdown of the promoter SET-7 and the overexpression of the anti-inflammatory cytokine IL-37, which may represent a key element for innate immunity (Saaoud et al., 2025).

LPS-trained microglia appear to exert a deleterious effect on AD progression. Indeed, LPS may play a pivotal role in AD pathogenesis (Zhan, Stamova and Sharp, 2018), as indicated by increased plasma LPS concentrations in patients with AD compared with cognitively healthy controls (Zhang et al., 2009). LPS-trained microglial cells have been shown to promote a switch in astrocytic phenotype to the neurotoxic A1 (Liddelow et al., 2017), through TNF-α, IL-1α and complement C1q, leading to neuronal loss (Sfera et al., 2018), indicative of deleterious effects of trained immunity in this context. But this mechanism, as above discussed, seems additionally dependent from the number of LPS exposure. Deleterious effects from single acute exposure to LPS (i.e. trained immunity) were reverted after repeated exposure (i.e. tolerance) (Wendeln et al., 2018). The switch from trained immunity to tolerance with associated harmful vs beneficial outcomes is strongly suggestive of a memory-like mechanism of innate immune and glial cells that may underline crucial unclear pathogenic mechanisms and novel therapeutic targets. To this end, clinical trials are already exploring ways to mitigate microglial-astrocyte crosstalk by looking at GLP1R agonist analogues that could block the conversion from trophic to pro-inflammatory astrocytes (Yun et al., 2018; Cummings et al., 2025).

As already mentioned, epigenetic manipulation comprises, among the others, acetylating (e.g. H3K27ac) and deacetylating modifications of DNA and histone proteins. Histone Deacetylase Inhibitors (HDACi) can lower LPS-induced microglial training (Durham, Grigg and Wood, 2017). Thus, lowering the Aβ burden through HDACi-induced microglia tolerization (Wendeln et al., 2018a; Gofrit et al., 2019), could become a concrete option for treating AD.

Clinically, C1q increase in CSF of pre-dementia AD patients (Brosseron et al., 2022), with associated induction of microglia-mediated excessive phagocytosis and synaptic clearance in AD patients (Neniskyte, Neher and Brown, 2011; Neher, Neniskyte and Brown, 2012) points towards a pathological role of this complement subunit in AD. On the other hand, the inhibitory role of C1q on innate immune memory responses, including metabolic and epigenetic modifications associated with immune tolerance (Jonkman, et al., 2025), is indicative of a complex interplay of factors involving differential pathological substrates. Currently, more studies are needed to address these contrasting roles, understand the multifaceted mechanisms behind C1q in neuroinflammation and how it could be related to Aβ accumulation or clearance.

The clinical relevance of trained immunity in AD emerged in 2019 from a large longitudinal study investigating BCG therapy for bladder cancer (Gofrit et al., 2019) which proposed an alternative perspective to classical vaccination paradigms. After eight years of follow-up, the authors reported a four-fold higher risk of developing AD in patients who had not received BCG treatment. Subsequent investigations yielded heterogeneous hazard ratios; however, a *meta*-analysis integrating these data demonstrated a pooled hazard ratio of 0.55 (95% CI: 0.42–0.73) for dementia risk in BCG-treated versus non-treated bladder cancer patients (Han et al., 2023). In parallel, studies assessing BCG vaccination in cognitively healthy individuals at high risk for AD—defined by APOE genotype, age, and plasma Aβ42/Aβ40 ratio—reported a modest increase in the plasma amyloid ratio following intervention. Although this biomarker is recognised to be less robust compared with CSF measures (Hansson et al., 2022), it is associated with cerebral Aβ deposition assessed by amyloid-PET (Janelidze et al., 2016). Together, these findings suggest that modulation of innate immune memory at the population level may influence AD-related pathological processes.

These observations indicate that key regulators of trained immunity represent promising therapeutic targets in AD, particularly with the aim of shifting innate immune responses from a maladaptive trained state toward a controlled tolerogenic phenotype. The apparent protective association of BCG exposure further supports the concept that long-term reprogramming of innate immunity may translate into clinical benefit. Nevertheless, substantial gaps remain in our understanding of how trained immunity interacts with Aβ accumulation, complement activation, epigenetic remodelling, and microglia–astrocyte crosstalk. A more comprehensive mechanistic framework will be essential to determine whether targeting trained immunity can be developed into a safe and effective disease-modifying strategy for AD.

Parkinson's disease

PD is a neurodegenerative disorder primarily characterized by the loss of dopaminergic neurons in the nigrostriatal system due to the aggregation of misfolded α-synuclein. Neuroinflammation is thought to be a key player in the pathogenesis of PD, with contribution from both innate and adaptive immunity (Tansey and Romero-Ramos, 2019). The concept of trained immunity is strongly relevant for PD. In mice models, BCG vaccination preserved striatal integrity and prevented microglial activation (Yong et al., 2011). In humans, a multicentred cohort study showed a 28% reduction in the incidence of PD in BCG-treated bladder cancer patients (Klinger et al., 2021). Additional evidence strengthens the putative role of a mechanism of trained immunity in PD, however with contrasting findings. Indeed, in a murine model of the disease, HIF-1α was necessary to train microglia, together with one of the main neuroinflammatory pathways in the striatum involved in PD pathogenesis. HIF-1α knockout mice displayed reduced trained phenotype and lower PD-like pathology (Dong et al., 2024), indicating a mechanism of trained immunity in this neurological disorder.

Contrarily, among pathogenetic mechanisms, aggregated α-synuclein induces IL-1β production through microglial NLRP3 perpetuating neuroinflammation, similarly to what is reported for cerebrovascular diseases (Feng et al., 2024b). In a phase 1b open-label study, inhibition of microglial NLRP3, potentially responsible for the downregulation of microglial phagocytosis in PD, showed a progressive reduction in plasma and CSF pro-inflammatory cytokine levels (Clarke et al., 2025), highlighting potential key mediators as potential therapeutic targets. Despite the available studies, results are confounding, and whilst suggestive of a trained immunity mechanism in PD, more research is necessary to understand whether its role is beneficial, detrimental, or more complex, substrate- and time-dependent.

Discussion

Trained immunity has gained strong attention in immunology as a crucial response mechanism towards pathogens and antigenic threats. Shared mechanisms among peripheral and resident CNS immune cells have been proposed, with many studies supporting priming and cellular memory in response to signalling factors that recall trained immunity. Although extensively investigated over the past few decennia, substantial knowledge gaps remain, not only in the molecular and cellular mechanisms underpinning trained immunity in neuroinflammation, but also for its translational power into clinical applications.

The most relevant limitation is our incomplete understanding of the real-life stimuli responsible for its induction. Laboratory evidence strongly demonstrates the involvement of trained immunity profiles acquisition by innate immune cells in neuroinflammation, with extensive literature supporting the involvement of many stimuli like BCG vaccination or treatment, β-glucans and LPS, contributing to altered response upon secondary insult. However, experimental models typically rely on high-dose or artificially controlled exposures, and we still have gaps regarding which stimuli can meaningfully induce trained immunity. How does this established mechanism truly reflects neuroinflammatory diseases has only started to emerge. Potentially a wide range of stimuli could prime the innate immune system, from viral infections, exposure to pollutants, to sugar-rich diets, childhood obesity, to teratogens (Alfredsson and Olsson, 2019; Boyd et al., 2022; Ahmed, Chaudhary and K. Agrawal, 2024; Livingston et al., 2024).

Epstein Barr Virus (EBV) is strongly linked to higher risk of MS (Bjornevik et al., 2022), Cytomegalovirus (CMV) on the contrary seems to be associated with lower risk of MS (Grut et al., 2021). Herpes simplex virus 1 (HSV-1) has consistently been associated with increased risk of AD and mild cognitive impairments (Duarte et al., 2019). Additionally, viral infections are a leading cause of encephalitis (Rocamonde et al., 2023), which may be a potential trigger for macrophages and resident immune cells priming. This, combined with a specific genetic predisposition may result in altered response to protein aggregation, impaired phagocytosis, demyelination and neurodegeneration (Duarte et al., 2019; Harms, Ferreira and Romero-Ramos, 2021; Popa, Cheval and Zujovic, 2025). Similarly, bacterial infections could recapitulate trained immunity-like mechanisms associated with tolerance and inefficient immune response (Tohidpour et al., 2017), BBB disruption via endothelin-1 signalling (Palmer, 2011; Freeman et al., 2014), promoting CNS parenchymal damage. Dietary habits could contribute to fuel trained immunity in predisposed subjects. Indeed, western diets and high glucose intake have been linked to elevated risk of MS (Hoffman et al., 2023), AD (Więckowska-Gacek et al., 2021), PD (Zapała et al., 2022), putatively mediated by inflammatory pathways such as NRLP3 inflammasome (Christ et al., 2018). Additionally, gut microbiota alterations could contribute to both initiate or support neuroinflammation via the gut-brain axis like in the established case of PD (El Aidy, Dinan and Cryan, 2014). Finally, childhood obesity, whether due to inherited traits and/ or dietary habits, has been associated with higher risk of neuroinflammation (Tait et al., 2022; Li et al., 2023; Hagman et al., 2025). Similarly traumatic childhood trauma has been associated with epigenetic modification leading to long term consequences potentially attributable to trained immunity (Thumfart et al., 2022). The conundrum is self-explanatory, how many stimuli do we encounter in life? Which one is the fatal stimulus that may drive or support chronic neuroinflammation? When in life do these potential triggers have the most impact? Do these different stimuli have additive effects on our genetics? Most likely so, and in this case, is there a threshold for triggering trained immunity associated with neuroinflammation? In the context of reprogramming events, the threshold levels, exposure durations, and qualitative determinants required for this process remain undefined. Furthermore, cell type–specific differences, tissue microenvironments, and host conditions in which trained immunity manifests are still poorly characterized. These observations suggest that trained immunity may not represent a universal phenomenon, as distinct stimuli can disrupt discrete epigenetic and functional memory programs. Collectively, these knowledge gaps underscore the need for mechanistic studies to delineate the pathways governing this complex immunological process in real-life disease, as current models of trained immunity remain oversimplified (O'Farrell et al., 2025).

Another fundamental problem underlying the definition of trained immunity is its dual role in immune-mediated disorders, enhancing protection against infections but, when dysregulated, driving chronic inflammation, immune tolerance, or tumor-promoting effects. Evidence from epidemiological and observational studies links BCG vaccination to reduced COVID-19 severity and lower seroprevalence of SARS-CoV-2 antibodies (Klinger et al., 2021; Hu et al., 2022), while single-cell epigenomic analyses show infection itself can induce trained immunity (You, Chen, Zhang, Zhao, Chen, E. Q. Qin, et al., 2021). Beyond infection, BCG remains the gold-standard therapy for noninvasive bladder cancer, partly through trained immunity mechanisms (Cardillo et al., 2021); yet maladaptive trained immunity has also been associated with oncogenic mutations in monocyte/macrophage populations (Netea and Joosten, 2024a, 2024b). These contrasting effects underscore the context-dependent nature of trained immunity (Netea, et al., 2020) and the need for standardized methodologies and biomarker discovery (Vuscan et al., 2024) to advance its therapeutic application in the field of

neuroinflammation.

Future perspectives

Indeed, missing details about the onset of metabolic and epigenetic changes create an important obstacle before the application of trained immunity to clinical relevance, but they should not obviate the need for biomarker discovery or treatment strategies. For instance, measuring the levels of an upstream regulator of trained immunity, such as long non-coding RNA, could represent a valuable research direction to pursue; however, low abundance and nuclear localization may make it unsuitable as a circulating biomarker (Fanucchi et al., 2019b). Similarly, blood pro-inflammatory cytokines or complement factors may also be unsuitable, due to highly variable levels in disease (Kany, Vollrath and Relja, 2019). Measuring DNA methylation and acetylation levels, the metabolic propensity to engage in glycolytic activity rather than oxidative phosphorylation may provide precise markers of trained immunity, but this approach would be time-consuming, expensive and restricted to specialist laboratories. A more promising option might be to measure the propensity to produce pro-inflammatory and anti-inflammatory cytokines after the stimulation with standardized stimuli (e.g. LPS, BCG etc.). In this regard, standardized tests exploiting overnight cultures and analysis of expressed factors of interests could be feasible (Duffy et al., 2014; Sugrue et al., 2022; Gynthersen et al., 2023).

A critical challenge moving forward is the development of imaging biomarkers capable of detecting trained immunity *in vivo*. To date, no modality has been specifically developed for this purpose. Hyperpolarized^13C MRI (Marakalala et al., 2013) enables spatially resolved assessment of pyruvate-to-lactate conversion, potentially reflecting the enhanced glycolytic reprogramming that characterizes trained immunity. However, its biological specificity remains to be established and requires validation through comparative studies integrating established markers of innate immune activation, such as TSPO-based imaging of microglial activity.

With the likelihood of multiple possible therapeutic targets to modulate trained immunity, in the future, CRISPR-mediated DNA methylation editing may become a candidate tailored strategy. In preclinical studies it has shown the possibility of modulating the inflammatory response to noxious stimuli (Valcárcel et al., 2025). In addition, many signatures associated with trained immunity result from inflammatory processes but only a few may be predictive when analysed in prospective clinical studies (Netea and Joosten, 2024b). Furthermore, future studies should strive to discriminate, if possible, the nature of epigenetic changes by environmental factors (Mallick and Duttaroy, 2023) and how to distinguish between the definitions of trained immunity and epigenetics itself. It is thus imperative to produce new evidence to address the knowledge gaps spanning from defining the timing of onset, the threshold, the duration, the number of stimuli necessary that may induce trained immunity in the context of neuroinflammation. These answers are needed not only from lab-based research but also from mechanistic clinical studies for specific neurological diseases, to pioneer biomarker discovery and treatment strategies.

Funding

This work has been supported by the Ministry of Health, project PNRR-MAD-2022-12375634, CUP code C43C22001060008.

CRediT authorship contribution statement

Enis Guso: Writing – original draft, Visualization, Writing – review & editing. **Alessia Lupoli:** Writing – original draft, Visualization, Writing – review & editing. **Emanuele Olivieri:** Writing – original draft, Visualization, Writing – review & editing. **Alessia Bottoni:** Writing – review & editing. **Maira Gironi:** Writing – review & editing, Conceptualization. **Davide M. Missarelli:** Writing – original draft. **Ahmed T. Toosy:** Writing – review & editing. **Elena Rossi:** Writing – original draft, Conceptualization, Supervision, Visualization, Writing – review & editing. **Roberto Furlan:** Writing – review & editing, Supervision, Writing-original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Absinta, M., et al., 2021. A lymphocyte–microglia–astrocyte axis in chronic active multiple sclerosis. Nature 597 (7878), 709–714. https://doi.org/10.1038/s41586-021-03892-7.

Ahmed, Z., Chaudhary, F., Agrawal, K.D., 2024. Epidemiology, pathophysiology, and current treatment strategies in stroke. Cardiol. Cardiovascular Med. 8 (4). https://doi.org/10.26502/fccm.92920399.

El Aidy, S., Dinan, T.G., Cryan, J.F., 2014. Immune modulation of the brain-gut-microbe axis. Front. Microbiol. 5. https://doi.org/10.3389/fmicb.2014.00146.

Alfredsson, L., Olsson, T., 2019. Lifestyle and environmental factors in multiple sclerosis. Cold Spring Harb. Perspect. Med. 9 (4), a028944. https://doi.org/10.1101/cshperspect.a028944.

Allen, N.J., Lyons, D.A., 2018. Glia as architects of central nervous system formation and function. Science 362 (6411), 181–185. https://doi.org/10.1126/science.aat0473.

Amici, S.A., Dong, J., Guerau-de-Arellano, M., 2017. Molecular mechanisms modulating the phenotype of macrophages and microglia. Front. Immunol. 8. https://doi.org/10.3389/fimmu.2017.01520.

Arts, R.J.W., et al., 2016. Glutaminolysis and fumarate accumulation integrate immunometabolic and epigenetic programs in trained immunity. Cell Metab. 24 (6), 807–819. https://doi.org/10.1016/j.cmet.2016.10.008.

Askew, K., et al., 2017. Coupled proliferation and apoptosis maintain the rapid turnover of microglia in the adult brain. Cell Rep. 18 (2), 391–405. https://doi.org/10.1016/j.celrep.2016.12.041.

Bahniwal, M., Little, J.P., Klegeris, A., 2017. High glucose enhances neurotoxicity and inflammatory cytokine secretion by stimulated human astrocytes. Curr. Alzheimer Res. 14 (7). https://doi.org/10.2174/1567205014666170117104053.

Banks, W.A., Kastin, A.J., Broadwell, R.D., 1995. Passage of cytokines across the blood-brain barrier. Neuroimmunomodulation 2 (4), 241–248. https://doi.org/10.1159/000097202.

Bekkering, S., et al., 2013. Trained innate immunity and atherosclerosis. Curr. Opin. Lipidol. 24 (6), 487–492. https://doi.org/10.1097/MOL.0000000000000023.

Bekkering, S., et al., 2018. Metabolic induction of trained immunity through the mevalonate pathway. Cell 172 (1–2), 135–146.e9. https://doi.org/10.1016/j.cell.2017.11.025.

Bekkering, S. *et al.* (2021) 'Trained immunity: reprogramming innate immunity in health and disease keywords', 54. 10.1146/annurev-immunol-102119.

Bjornevik, K., et al., 2022. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science 375 (6578), 296–301. https://doi.org/10.1126/science.abj8222.

Blanden, R.V., Lefford, M.J., Mackaness, G.B., 1969. The host response to calmette-guérin bacillus infection in mice. J. Exp. Med. 129 (5), 1079–1107. https://doi.org/10.1084/jem.129.5.1079.

Blau, C.W., et al., 2012. The age-related deficit in LTP is associated with changes in perfusion and blood-brain barrier permeability. Neurobiol. Aging 33 (5), 1005.e23–1005.e35. https://doi.org/10.1016/j.neurobiolaging.2011.09.035.

Boyd, R.J., et al., 2022. Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases. J. Neuroinflammation 19 (1), 223. https://doi.org/10.1186/s12974-022-02584-x.

Bromuro, C., et al., 2002. Interplay between protective and inhibitory antibodies dictates the outcome of experimentally disseminated candidiasis in recipients of a *Candida albicans* vaccine. Infect. Immun. 70 (10), 5462–5470. https://doi.org/10.1128/IAI.70.10.5462-5470.2002.

Brosseron, F., et al., 2022. Soluble TAM receptors sAXL and sTyro3 predict structural and functional protection in Alzheimer's disease. Neuron 110 (6), 1009–1022.e4. https://doi.org/10.1016/j.neuron.2021.12.016.

Cai, H.-Y., et al., 2021. Adjusting vascular permeability, leukocyte infiltration, and microglial cell activation to rescue dopaminergic neurons in rodent models of Parkinson's disease. npj Parkinson's Disease 7 (1), 91. https://doi.org/10.1038/s41531-021-00233-3.

Cardillo, F., et al., 2021. Bacillus Calmette–Guérin immunotherapy for cancer. Vaccines 9 (5), 439. https://doi.org/10.3390/VACCINES9050439.

Chen, A.-Q., et al., 2019. Microglia-derived TNF-α mediates endothelial necroptosis aggravating blood brain–barrier disruption after ischemic stroke. Cell Death Dis. 10 (7), 487. https://doi.org/10.1038/s41419-019-1716-9.

Chen, X., et al., 2023. Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy. Nature 615 (7953), 668–677. https://doi.org/10.1038/s41586-023-05788-0.

Cheng, S.-C., et al., 2014. mTOR- and HIF-1α–mediated aerobic glycolysis as metabolic basis for trained immunity. Science 345 (6204). https://doi.org/10.1126/science.1250684.

Choi, I., et al., 2020. Microglia clear neuron-released α-synuclein via selective autophagy and prevent neurodegeneration. Nat. Commun. 11 (1), 1386. https://doi.org/10.1038/s41467-020-15119-w.

Christ, A., et al., 2018. Western Diet Triggers NLRP3-Dependent innate immune reprogramming. Cell 172 (1–2), 162–175.e14. https://doi.org/10.1016/j.cell.2017.12.013.

Chuluundorj, D., et al., 2017. Glatiramer acetate treatment normalized the monocyte activation profile in MS patients to that of healthy controls. Immunol. Cell Biol. 95 (3), 297–305. https://doi.org/10.1038/icb.2016.99.
Clarke, N., et al., 2025. 'Anti-neuroinflammatory and anti-inflammatory effects of the NLRP3 inhibitor NT-0796 in subjects with Parkinson's disease', movement disorders [Preprint]. 10.1002/mds.30307.
Corsenac, P., et al., 2022. Bacillus Calmette–Guerin vaccination and multiple sclerosis: a population-based birth cohort study in Quebec, Canada. Eur. J. Neurol. 29 (6), 1791–1804. https://doi.org/10.1111/ENE.15290;WGROUP:STRING:PUBLICATION.
Costello, D.A., et al., 2016. The age-related neuroinflammatory environment promotes macrophage activation, which negatively impacts synaptic function. Neurobiol. Aging 43, 140–148. https://doi.org/10.1016/j.neurobiolaging.2016.04.001.
Crane, P.K., et al., 2013. Glucose levels and risk of dementia. N. Engl. J. Med. 369 (6), 540–548. https://doi.org/10.1056/NEJMoa1215740.
Cummings, J.L., et al., 2025. evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease. Alzheimer's Res. Therapy 17 (1), 1–12. https://doi.org/10.1186/S13195-024-01666-7/FIGURES/2.
Divangahi, M., et al., 2021. Trained immunity, tolerance, priming and differentiation: distinct immunological processes. Nat. Immunol. 22 (1), 2–6. https://doi.org/10.1038/s41590-020-00845-6.
Dong, H., et al., 2024. Hypoxia inducible factor-1α regulates microglial innate immune memory and the pathology of Parkinson's disease. J. Neuroinflammation 21 (1). https://doi.org/10.1186/s12974-024-03070-2.
Duarte, L.F., et al., 2019. Herpes simplex virus type 1 infection of the central nervous system: insights into proposed interrelationships with neurodegenerative disorders. Front. Cell. Neurosci. 13. https://doi.org/10.3389/fncel.2019.00046.
Duffy, D., et al., 2014. Functional analysis via standardized whole-blood stimulation systems defines the boundaries of a healthy immune response to complex stimuli. Immunity 40 (3), 436–450. https://doi.org/10.1016/j.immuni.2014.03.002.
Durham, B.S., Grigg, R., Wood, I.C., 2017. Inhibition of histone deacetylase 1 or 2 reduces induced cytokine expression in microglia through a protein synthesis independent mechanism. J. Neurochem. 143 (2), 214–224. https://doi.org/10.1111/JNC.14144.
Fanucchi, S., et al., 2019. Immune genes are primed for robust transcription by proximal long noncoding RNAs located in nuclear compartments. Nat. Genet. 51 (1), 138–150. https://doi.org/10.1038/s41588-018-0298-2.
Farez, M.F., Correale, J., 2011. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. J. Neurol. 258 (7), 1197–1206. https://doi.org/10.1007/s00415-011-5984-2.
Feng, Y., et al., 2024. Cortical microinfarcts potentiate recurrent ischemic injury through NLRP3-dependent trained immunity. Cell Death Dis. 15 (1), 36. https://doi.org/10.1038/s41419-023-06414-7.
Feng, Y.W., et al., 2020. hUCMSCs mitigate LPS-induced trained immunity in ischemic stroke. Front. Immunol. 11. https://doi.org/10.3389/fimmu.2020.01746.
Ferretti, M.T., et al., 2016. T-cell brain infiltration and immature antigen-presenting cells in transgenic models of Alzheimer's disease-like cerebral amyloidosis. Brain Behav. Immun. 54, 211–225. https://doi.org/10.1016/j.bbi.2016.02.009.
Fiala, M., et al., 2002. Cyclooxygenase-2-positive macrophages infiltrate the Alzheimer's disease brain and damage the blood–brain barrier. Eur. J. Clin. Invest. 32 (5), 360–371. https://doi.org/10.1046/j.1365-2362.2002.00994.x.
Foster, S.L., Hargreaves, D.C., Medzhitov, R., 2007. Gene-specific control of inflammation by TLR-induced chromatin modifications. Nature 447 (7147), 972–978. https://doi.org/10.1038/nature05836.
Franceschi, C., et al., 2000. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908 (1), 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.
Franceschi, C., et al., 2017. Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. Front. Immunol. 8. https://doi.org/10.3389/fimmu.2017.00982.
Fransson, J., et al., 2024. Multiple sclerosis patient macrophages impaired metabolism leads to an altered response to activation stimuli. Neurol.: Neuroimmunol. & Neuroinflammation 11 (6), e200312. https://doi.org/10.1212/NXI.0000000000200312.
Freeman, B.D., et al., 2014. Endothelin-1 and its role in the pathogenesis of infectious diseases. Life Sci. 118 (2), 110–119. https://doi.org/10.1016/j.lfs.2014.04.021.
Füger, P., et al., 2017. Microglia turnover with aging and in an Alzheimer's model via long-term in vivo single-cell imaging. Nat. Neurosci. 20 (10), 1371–1376. https://doi.org/10.1038/nn.4631.
Gadani, S.P., et al., 2015. The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury. Neuron 85 (4), 703–709. https://doi.org/10.1016/j.neuron.2015.01.013.
Galiano-Landeira, J., et al., 2020. CD8 T cell nigral infiltration precedes synucleinopathy in early stages of Parkinson's disease. Brain 143 (12), 3717–3733. https://doi.org/10.1093/brain/awaa269.
Ginhoux, F., et al., 2010. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 330 (6005), 841–845. https://doi.org/10.1126/science.1194637.
Girard, S., et al., 2013. Microglia and macrophages differentially modulate cell death after brain injury caused by oxygen-glucose deprivation in organotypic brain slices. Glia 61 (5), 813–824. https://doi.org/10.1002/glia.22478.
Gofrit, O.N., et al., 2019. Bacillus Calmette-Guérin (BCG) therapy lowers the incidence of Alzheimer's disease in bladder cancer patients. PLoS One 14 (11), e0224433. https://doi.org/10.1371/JOURNAL.PONE.0224433.
Grut, V., et al., 2021. Cytomegalovirus seropositivity is associated with reduced risk of multiple sclerosis-a presymptomatic case-control study. Eur. J. Neurol. 28 (9), 3072–3079. https://doi.org/10.1111/ENE.14961.
Gynthersen, R.M.M., et al., 2023. Exploration of the induced cytokine responses in European Lyme neuroborreliosis: a longitudinal cohort study. Ticks Tick-borne Dis. 14 (1). https://doi.org/10.1016/j.ttbdis.2022.102057.
Hagman, E., et al., 2025. Association between adolescent obesity and early adulthood healthcare utilization—a two-cohort prospective study. BMC Med. 23 (1), 1–10. https://doi.org/10.1186/S12916-025-03866-W/TABLES/3.
Haimerl, P., et al., 2021. Inflammatory macrophage memory in nonsteroidal anti-inflammatory drug–exacerbated respiratory disease. J. Allergy Clin. Immunol. 147 (2), 587–599. https://doi.org/10.1016/j.jaci.2020.04.064.
Han, C., et al., 2023. The role of Bacillus Calmette-Guérin administration on the risk of dementia in bladder cancer patients: a systematic review and meta-analysis. Front. Aging Neurosci. 15, 1243588. https://doi.org/10.3389/FNAGI.2023.1243588/BIBTEX.
Hansson, O., et al., 2022. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alzheimer's and Dementia 18 (12), 2669–2686. https://doi.org/10.1002/ALZ.12756.
Harms, A.S., Ferreira, S.A., Romero-Ramos, M., 2021. Periphery and brain, innate and adaptive immunity in Parkinson's disease. Acta Neuropathol. 141 (4), 527–545. https://doi.org/10.1007/s00401-021-02268-5.
Hartana, C.A., et al., 2023. IL-15-dependent immune crosstalk between natural killer cells and dendritic cells in HIV-1 elite controllers. Cell Rep. 42 (12), 113530. https://doi.org/10.1016/j.celrep.2023.113530.
Haschka, D., et al., 2020. Expansion of neutrophils and classical and nonclassical monocytes as a hallmark in relapsing-remitting multiple sclerosis. Front. Immunol. 11, 507993. https://doi.org/10.3389/FIMMU.2020.00594/BIBTEX.
Hauptmann, J., et al., 2020. Interleukin-1 promotes autoimmune neuroinflammation by suppressing endothelial heme oxygenase-1 at the blood–brain barrier. Acta Neuropathol. 140 (4), 549–567. https://doi.org/10.1007/s00401-020-02187-x.
Heckmann, B.L., et al., 2019. LC3-associated endocytosis facilitates β-amyloid clearance and mitigates neurodegeneration in murine alzheimer's disease. Cell 178 (3), 536–551.e14. https://doi.org/10.1016/j.cell.2019.05.056.
Heng, Y., et al., 2021. Systemic administration of β-glucan induces immune training in microglia. J. Neuroinflammation 18 (1), 57. https://doi.org/10.1186/s12974-021-02103-4.
Hernández-Jiménez, M., et al., 2023. Safety and efficacy of ApTOLL in patients with ischemic stroke undergoing endovascular treatment. JAMA Neurol. 80 (8), 779. https://doi.org/10.1001/jamaneurol.2023.1660.
Heß, K., et al., 2020. Lesion stage-dependent causes for impaired remyelination in MS. Acta Neuropathol. 140 (3), 359–375. https://doi.org/10.1007/s00401-020-02189-9.
Higgins, J.P.T., et al., 2016. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ (Online) 355. https://doi.org/10.1136/BMJ.I5170.
Hoffman, K., et al., 2023. Gut microbiome-modulated dietary strategies in EAE and multiple sclerosis. Front. Nutr. 10. https://doi.org/10.3389/fnut.2023.1146748.
Hu, Z., et al., 2022. Trained immunity: A Yin-Yang balance. MedComm 3 (1). https://doi.org/10.1002/MCO2.121.
Huang, M., et al., 2023. Microglial immune regulation by epigenetic reprogramming through histone H3K27 acetylation in neuroinflammation. Front. Immunol. 14. https://doi.org/10.3389/fimmu.2023.1052925.
Huang, Y., et al., 2025. Innate and adaptive immunity in neurodegenerative disease. Cell. Mol. Life Sci. 82 (1), 68. https://doi.org/10.1007/s00018-024-05533-4.
Ishida, N., et al., 2017. Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice. npj Aging Mech. Dis. 3 (1), 15. https://doi.org/10.1038/s41514-017-0015-x.
Ising, C., et al., 2019. NLRP3 inflammasome activation drives tau pathology. Nature 575 (7784), 669–673. https://doi.org/10.1038/s41586-019-1769-z.
Jacobs, M.M.E., et al., 2024. Trained immunity is regulated by T cell-induced CD40-TRAF6 signaling. Cell Rep. 43 (9). https://doi.org/10.1016/j.celrep.2024.114664.
Janelidze, S., et al., 2016. Plasma β-amyloid in Alzheimer's disease and vascular disease. Sci. Rep. 6 (1), 1–11. https://doi.org/10.1038/SREP26801;SUBJMETA=1689,378,53,631,692;KWRD=BIOMARKERS, DISEASES+OF+THE+NERVOUS+SYSTEM.
Jin, Z., Liu, N., Wei, H., 2025. Atherosclerosis is associated with amyloid and tau pathology via blood–brain barrier dysfunction in the hippocampus of aged human brains. PLoS One 20 (6), e0324652. https://doi.org/10.1371/journal.pone.0324652.
Jonkman, I., Jacobs, M.M.E., et al., 2025. C1q reprograms innate immune memory. Front. Immunol. 16. https://doi.org/10.3389/fimmu.2025.1515127.
Kamer, A.R., et al., 2009. TNF-α and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. J. Neuroimmunol. 216 (1–2), 92–97. https://doi.org/10.1016/j.jneuroim.2009.08.013.
Kandalla, P.K., et al., 2023. M-CSF directs myeloid and NK cell differentiation to protect from CMV after hematopoietic cell transplantation. EMBO Mol. Med. 15 (11). https://doi.org/10.15252/emmm.202317694.
Kany, S., Vollrath, J.T., Relja, B., 2019. Cytokines in inflammatory disease. Int. J. Mol. Sci. 20 (23), 6008. https://doi.org/10.3390/IJMS20236008.
Kaufmann, E., et al., 2018. BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. Cell 172 (1–2), 176–190.e19. https://doi.org/10.1016/j.cell.2017.12.031.
Keating, S.T., et al., 2020. Rewiring of glucose metabolism defines trained immunity induced by oxidized low-density lipoprotein. J. Mol. Med. 98 (6), 819–831. https://doi.org/10.1007/s00109-020-01915-w.

Keating, S.T., El-Osta, A., 2015. Epigenetics and metabolism. Circ. Res. 116 (4), 715–736. https://doi.org/10.1161/CIRCRESAHA.116.303936.
Keefe, R.C., et al., 2021. BCG therapy is associated with long-term, durable induction of Treg signature genes by epigenetic modulation. Sci. Rep. 11 (1), 14933. https://doi.org/10.1038/s41598-021-94529-2.
Keren-Shaul, H., et al., 2017. A unique microglia type associated with restricting development of Alzheimer's disease. Cell 169 (7), 1276–1290.e17. https://doi.org/10.1016/j.cell.2017.05.018.
Kim, J., et al., 2024. Pathological phenotypes of astrocytes in Alzheimer's disease. Exp. Mol. Med. 56 (1), 95–99. https://doi.org/10.1038/s12276-023-01148-0.
Kipnis, J., et al., 2025. Resolving the mysteries of brain clearance and immune surveillance. Neuron 113 (23), 3908–3923. https://doi.org/10.1016/j.neuron.2025.10.036.
Klinger, D., et al., 2021. Bladder cancer immunotherapy by BCG Is associated with a significantly reduced risk of Alzheimer's disease and Parkinson's disease. Vaccines 9 (5), 491. https://doi.org/10.3390/VACCINES9050491/S1.
Krahenbuhl, J.L., et al., 1981. Effects of muramyl dipeptide treatment on resistance to infection with Toxoplasma gondii in mice. Infect. Immun. 31 (2), 716–722. https://doi.org/10.1128/iai.31.2.716-722.1981.
Kroon, H.-A., et al., 2025. Efficacy and safety of targeted immunotherapy with ANX005 in treating guillain-barré syndrome: a phase 3 multicenter study (PL5.006). Neurology 104 (7_Supplement_1), 4954. https://doi.org/10.1212/WNL.0000000000212033.
Kumar, R., et al., 2023. A Phase 2 open-label study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous ANX005 in Patients with, or at risk of, manifest huntington's disease (HD) (S32.009). Neurology 100 (17_supplement_2), 3366. https://doi.org/10.1212/WNL.0000000000203217.
Lechner, A., et al., 2022. Macrophages acquire a TNF-dependent inflammatory memory in allergic asthma. J. Allergy Clin. Immunol. 149 (6), 2078–2090. https://doi.org/10.1016/j.jaci.2021.11.026.
Lee, H.-G., et al., 2024. Disease-associated astrocyte epigenetic memory promotes CNS pathology. Nature 627 (8005), 865–872. https://doi.org/10.1038/s41586-024-07187-5.
Lee, S.-I., et al., 2025. Astrocyte priming enhances microglial Aβ clearance and is compromised by APOE4. Nat. Commun. 16 (1), 7551. https://doi.org/10.1038/s41467-025-62995-1.
Li, Z.A., et al., 2023. Childhood obesity is linked to putative neuroinflammation in brain white matter, hypothalamus, and striatum. Cereb. Cortex Comm. 4 (2). https://doi.org/10.1093/texcom/tgad007.
Liddelow, S.A., et al., 2017. Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541 (7638), 481. https://doi.org/10.1038/NATURE21029.
Lin, T., et al., 2023. Trained immunity induced by high-salt diet impedes stroke recovery. EMBO Rep. 24 (12), 10.15252/embr.202357164.
Linnerbauer, M., Wheeler, M.A., Quintana, F.J., 2020. Astrocyte crosstalk in CNS inflammation. Neuron 108 (4), 608–622. https://doi.org/10.1016/j.neuron.2020.08.012.
Litwiniuk, A., et al., 2021. Inflammasome NLRP3 potentially links obesity-associated low-grade systemic inflammation and insulin resistance with alzheimer's disease. Int. J. Mol. Sci. 22 (11), 5603. https://doi.org/10.3390/ijms22115603.
Livingston, G., et al., 2024. Dementia prevention, intervention, and care: 2024 report of the lancet standing commission. Lancet 404 (10452), 572–628. https://doi.org/10.1016/S0140-6736(24)01296-0.
Loayza, M., et al., 2023. Maternal immune activation alters fetal and neonatal microglia phenotype and disrupts neurogenesis in mice. Pediatr. Res. 93 (5), 1216–1225. https://doi.org/10.1038/s41390-022-02239-w.
Lu, C., et al., 2012. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature 483 (7390), 474–478. https://doi.org/10.1038/nature10860.
Di Luzio, N.R., Williams, D.L., 1978. Protective effect of glucan against systemic Staphylococcus aureus septicemia in normal and leukemic mice. Infect. Immun. 20 (3), 804–810. https://doi.org/10.1128/iai.20.3.804-810.1978.
Madura Larsen, J., et al., 2007. BCG stimulated dendritic cells induce an interleukin-10 producing T-cell population with no T helper 1 or T helper 2 bias *in vitro*. Immunology 121 (2), 276–282. https://doi.org/10.1111/j.1365-2567.2007.02575.x.
Mallick, R., Duttaroy, A.K., 2023. Epigenetic modification impacting brain functions: effects of physical activity, micronutrients, caffeine, toxins, and addictive substances. Neurochem. Int. 171, 105627. https://doi.org/10.1016/j.neuint.2023.105627.
Mantovani, A., Netea, M.G., 2020. Trained innate immunity, epigenetics, and covid-19. N. Engl. J. Med. 383 (11), 1078–1080. https://doi.org/10.1056/nejmcibr2011679.
Marakalala, M.J., et al., 2013. Dectin-1 plays a redundant role in the immunomodulatory activities of β-glucan-rich ligands in vivo. Microbes Infect. 15 (6–7), 511–515. https://doi.org/10.1016/j.micinf.2013.03.002.
Martins-Ferreira, R., et al., 2021. Microglial innate memory and epigenetic reprogramming in neurological disorders. Prog. Neurobiol. 200, 101971. https://doi.org/10.1016/J.PNEUROBIO.2020.101971.
Mata-Martínez, P., Bergón-Gutiérrez, M., del Fresno, C., 2022. Dectin-1 signaling update: new perspectives for trained immunity. Front. Immunol. 13. https://doi.org/10.3389/fimmu.2022.812148.
Matheoud, D., et al., 2019. Intestinal infection triggers Parkinson's disease-like symptoms in Pink1−/− mice. Nature 571 (7766), 565–569. https://doi.org/10.1038/s41586-019-1405-y.
Mattei, D., et al., 2017. Maternal immune activation results in complex microglial transcriptome signature in the adult offspring that is reversed by minocycline treatment. Transl. Psychiatry 7 (5), e1120–e. https://doi.org/10.1038/tp.2017.80.
McAlpine, C.S., et al., 2021. Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. Nature 595 (7869), 701–706. https://doi.org/10.1038/s41586-021-03734-6.
van der Meer, J.W.M., et al., 2015. Trained immunity: A smart way to enhance innate immune defence. Mol. Immunol. 68 (1), 40–44. https://doi.org/10.1016/j.molimm.2015.06.019.
Metcalf, T.U., et al., 2015. Global analyses revealed age-related alterations in innate immune responses after stimulation of pathogen recognition receptors. Aging Cell 14 (3), 421–432. https://doi.org/10.1111/acel.12320.
Michailidou, I., et al., 2015. Complement C1q-C3-associated synaptic changes in multiple sclerosis hippocampus. Ann. Neurol. 77 (6), 1007–1026. https://doi.org/10.1002/ana.24398.
Minogue, A.M., 2017. Role of infiltrating monocytes/macrophages in acute and chronic neuroinflammation: effects on cognition, learning and affective behaviour. Prog. Neuropsychopharmacol. Biol. Psychiatry 79, 15–18. https://doi.org/10.1016/j.pnpbp.2017.02.008.
Muñoz, N., et al., 2010. Mucosal administration of flagellin protects mice from *Streptococcus pneumoniae* lung infection. Infect. Immun. 78 (10), 4226–4233. https://doi.org/10.1128/IAI.00224-10.
Murphy, D.M., Mills, K.H.G., Basdeo, S.A., 2021. The effects of trained innate immunity on T cell responses; clinical implications and knowledge gaps for future research. Front. Immunol. 12. https://doi.org/10.3389/fimmu.2021.706583.
Neher, J.J., Cunningham, C., 2019. Priming microglia for innate immune memory in the brain. Trends Immunol. 40 (4), 358–374. https://doi.org/10.1016/j.it.2019.02.001.
Neher, J.J., Neniskyte, U. and Brown, G.C., 2012. 'Primary phagocytosis of neurons by inflamed microglia: potential roles in neurodegeneration', Front. Pharmacol., 3 FEB. 10.3389/FPHAR.2012.00027,.
Neniskyte, U., Neher, J.J., Brown, G.C., 2011. Neuronal death induced by nanomolar amyloid β is mediated by primary phagocytosis of neurons by microglia. J. Biol. Chem. 286 (46), 39904–39913. https://doi.org/10.1074/jbc.M111.267583.
Netea, M.G., et al., 2019. Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. Cell Host Microbe 25 (1), 13–26. https://doi.org/10.1016/j.chom.2018.12.006.
Netea, M.G., Domínguez-Andrés, J., Barreiro, L.B., Chavakis, T., Divangahi, M., Fuchs, E., Joosten, L.A.B., et al., 2020. Defining trained immunity and its role in health and disease. Nat. Rev. Immunol.. Nat. Res. 375–388. https://doi.org/10.1038/s41577-020-0285-6.
Netea, M.G., Joosten, L.A.B., 2024a. Trained immunity in the bone marrow: hub of autoimmunity. Cell Stem Cell 31 (11), 1555–1557. https://doi.org/10.1016/j.stem.2024.10.008.
Netea, M.G., Joosten, L.A.B., 2024b. Trained innate immunity: concept, nomenclature, and future perspectives. J. Allergy Clin. Immunol. 154 (5), 1079–1084. https://doi.org/10.1016/j.jaci.2024.09.005.
Netea, M.G., Quintin, J., van der Meer, J.W.M., 2011. Trained immunity: a memory for innate host defense. Cell Host Microbe 9 (5), 355–361. https://doi.org/10.1016/j.chom.2011.04.006.
Noz, M.P., et al., 2018. Trained immunity characteristics are associated with progressive cerebral small vessel disease. Stroke 49 (12), 2910–2917. https://doi.org/10.1161/STROKEAHA.118.023192.
Ochando, J., et al., 2023. Trained immunity — basic concepts and contributions to immunopathology. Nat. Rev. Nephrol. Nat. Res. 23–37. https://doi.org/10.1038/s41581-022-00633-5.
O'Farrell, A., et al., 2025. 'Innate immune memory is stimulus specific', *bioRxiv*, p. 2025.01.22.634275. 10.1101/2025.01.22.634275.
Palmer, A.M., 2011. The role of the blood brain barrier in neurodegenerative disorders and their treatment. J. Alzheimer's Dis.: JAD 24 (4), 643–656. https://doi.org/10.3233/JAD-2011-110368.
Palmieri, E.M., et al., 2020. Nitric oxide in macrophage immunometabolism: hiding in plain sight. Metabolites 10 (11), 429. https://doi.org/10.3390/metabo10110429.
Polonelli, L., et al., 2003. Therapeutic activity of an engineered synthetic killer antiidiotypic antibody fragment against experimental mucosal and systemic candidiasis. Infect. Immun. 71 (11), 6205–6212. https://doi.org/10.1128/IAI.71.11.6205-6212.2003.
Pomilio, C., et al., 2020. Microglial autophagy is impaired by prolonged exposure to β-amyloid peptides: evidence from experimental models and Alzheimer's disease patients. GeroScience 42 (2), 613–632. https://doi.org/10.1007/s11357-020-00161-9.
Popa, E., Cheval, H., Zujovic, V., 2025. Cues of trained immunity in multiple sclerosis macrophages. Cells 14 (14), 1054. https://doi.org/10.3390/cells14141054.
Porta, C., et al., 2009. Tolerance and M2 (alternative) macrophage polarization are related processes orchestrated by p50 nuclear factor κB. Proc. Natl. Acad. Sci. 106 (35), 14978–14983. https://doi.org/10.1073/pnas.0809784106.
Prentice, S., et al., 2021. BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: an investigator-blind randomised controlled trial. Lancet Infect. Dis. 21 (7), 993–1003. https://doi.org/10.1016/S1473-3099(20)30653-8.
Qian, F., et al., 2012. Age-associated elevation in TLR5 leads to increased inflammatory responses in the elderly. Aging Cell 11 (1), 104–110. https://doi.org/10.1111/j.1474-9726.2011.00759.x.
Quinn, S.M., et al., 2019. Anti-inflammatory trained immunity mediated by helminth products attenuates the induction of T cell-mediated autoimmune disease. Front. Immunol. 10 (MAY). https://doi.org/10.3389/fimmu.2019.01109.
Quintin, J., et al., 2012. Candida albicans infection affords protection against reinfection via functional reprogramming of monocytes. Cell Host Microbe 12 (2), 223–232. https://doi.org/10.1016/j.chom.2012.06.006.

Ramaglia, V., et al., 2021. Complement-associated loss of CA2 inhibitory synapses in the demyelinated hippocampus impairs memory. Acta Neuropathol. 142 (4), 643–667. https://doi.org/10.1007/s00401-021-02338-8.
Ren, T., et al., 2025. Targeting microglial PPARα ameliorates the outcome of ischemic stroke by enhancing interaction with infiltrating peripheral monocytes/macrophages. Cell Rep. 44 (7), 115875. https://doi.org/10.1016/j.celrep.2025.115875.
Ristori, G., et al., 1999. Use of bacille calmette-guerin (BCG) in multiple sclerosis. Neurology 53 (7), 1588–1589. https://doi.org/10.1212/WNL.53.7.1588/ASSET/D36F42CA-BAFE-4D80-A13E-0074EB83C761/ASSETS/GRAPHIC/53_7_1558_T1.GIF.
Ristori, G., et al., 2013. Effects of Bacille Calmette-Guérin after the first demyelinating event in the CNS. www.neurology.org.
Rocamonde, B., et al., 2023. Viral-induced neuroinflammation: different mechanisms converging to similar exacerbated glial responses. Front. Neurosci. 17. https://doi.org/10.3389/fnins.2023.1108212.
Saaoud, F., et al., 2025. Alzheimer's disease as an auto-innate immune pathology with potential cell trans-differentiation and enhanced trained immunity in 3xTg-AD mouse model. J. Alzheimer's Dis. 105 (2), 550–572. https://doi.org/10.1177/13872877251329583.
Saeed, S., et al., 2014. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. Science 345 (6204). https://doi.org/10.1126/science.1251086.
Sarkar, S., et al., 2020. Molecular signatures of neuroinflammation induced by αsynuclein aggregates in microglial cells. Front. Immunol. 11. https://doi.org/10.3389/fimmu.2020.00033.
Schlüter, T., et al., 2025. Trained immunity: induction of an inflammatory memory in disease. Cell Res. 35 (11), 792–802. https://doi.org/10.1038/s41422-025-01171-y.
Scholz, R., Brösamle, D., Yuan, X., Neher, J.J., et al., 2024a. 'Combined analysis of mRNA expression and open chromatin in microglia', pp. 543–571. 10.1007/978-1-0716-3437-0_35.
Scholz, R., Brösamle, D., Yuan, X., Beyer, M., et al., 2024. Epigenetic control of microglial immune responses. Immunol. Rev. 323 (1), 209–226. https://doi.org/10.1111/imr.13317.
Seeley, J.J., Ghosh, S., 2017. Molecular mechanisms of innate memory and tolerance to LPS. J. Leukoc. Biol. 101 (1), 107–119. https://doi.org/10.1189/jlb.3MR0316-118RR.
Sfera, A., et al., 2018. 'Rusty microglia: trainers of innate immunity in Alzheimer's disease'. Front. Neurol. Frontiers Media S.A. 10.3389/fneur.2018.01062.
Shi, F.-D., Yong, V.W., 2025. Neuroinflammation across neurological diseases. Science 388 (6753). https://doi.org/10.1126/science.adx0043.
Shnyra, A., et al., 1998. Reprogramming of lipopolysaccharide-primed macrophages is controlled by a counterbalanced production of IL-10 and IL-12. J. Immunol. 160 (8), 3729–3736. https://doi.org/10.4049/jimmunol.160.8.3729.
Simats, A., et al., 2024. Innate immune memory after brain injury drives inflammatory cardiac dysfunction. Cell [Preprint]. https://doi.org/10.1016/j.cell.2024.06.028.
Smyth, L.C.D., Kipnis, J., 2025. 'Redefining CNS immune privilege', *Nature Reviews Immunology* [Preprint]. Nature Research. https://doi.org/10.1038/s41577-025-01175-0.
Sugrue, J.A., et al., 2022. Enhanced TLR3 responsiveness in hepatitis C virus resistant women from the Irish anti-D cohort. Cell Rep. Med. 3 (11). https://doi.org/10.1016/j.xcrm.2022.100804.
Tait, J.L., et al., 2022. Longitudinal associations of childhood fitness and obesity profiles with midlife cognitive function: an Australian cohort study. J. Sci. Med. Sport 25 (8), 667–672. https://doi.org/10.1016/J.JSAMS.2022.05.009.
Tansey, M.G., Romero-Ramos, M., 2019. Immune system responses in Parkinson's disease: Early and dynamic. Eur. J. Neurosci. 49 (3), 364–383. https://doi.org/10.1111/EJN.14290.
Thumfart, K.M., et al., 2022. Epigenetics of childhood trauma: Long term sequelae and potential for treatment. Neurosci. Biobehav. Rev. 132, 1049–1066. https://doi.org/10.1016/j.neubiorev.2021.10.042.
Titus, H.E., et al., 2020. Pre-clinical and clinical implications of "inside-out" vs. "outside-in" paradigms in multiple sclerosis etiopathogenesis. Front. Cell. Neurosci. 14. https://doi.org/10.3389/fncel.2020.599717.
Tiwari, V., et al., 2024. Innate immune training restores pro-reparative myeloid functions to promote remyelination in the aged central nervous system. Immunity 57 (9), 2173–2190.e8. https://doi.org/10.1016/j.immuni.2024.07.001.
Tohidpour, A., et al., 2017. Neuroinflammation and infection: molecular mechanisms associated with dysfunction of neurovascular unit. Front. Cell. Infect. Microbiol. 7. https://doi.org/10.3389/fcimb.2017.00276.
Valcárcel, G., et al., 2025. Modulating immune cell fate and inflammation through CRISPR-mediated DNA methylation editing, Sci. Adv. https://www.science.org.
Venezia, S., et al., 2017. Toll-like receptor 4 stimulation with monophosphoryl lipid A ameliorates motor deficits and nigral neurodegeneration triggered by extraneuronal α-synucleinopathy. Mol. Neurodegener. 12 (1), 52. https://doi.org/10.1186/s13024-017-0195-7.
Verkhratsky, A., et al., 2023. Astrocytes in human central nervous system diseases: a frontier for new therapies. Signal Transduct. Target. Ther. 8 (1), 396. https://doi.org/10.1038/s41392-023-01628-9.
Vermersch, P., et al., 2024. Inhibition of CD40L with frexalimab in multiple sclerosis. N. Engl. J. Med. 390 (7), 589–600. https://doi.org/10.1056/nejmoa2309439.
Viola, A., et al., 2019. The metabolic signature of macrophage responses. Front. Immunol. 10. https://doi.org/10.3389/fimmu.2019.01462.
Vuscan, P., et al., 2024. Trained immunity: general and emerging concepts. Immunol. Rev. 323 (1), 164–185. https://doi.org/10.1111/IMR.13326.
Walker, K.A., et al., 2019. Systemic inflammation during midlife and cognitive change over 20 years. Neurology 92 (11). https://doi.org/10.1212/WNL.0000000000007094.
Wang, C., et al., 2022. Microglial NF-κB drives tau spreading and toxicity in a mouse model of tauopathy. Nat. Commun. 13 (1), 1969. https://doi.org/10.1038/s41467-022-29552-6.
Wang, H., et al., 2020. Bacterial, viral, and fungal infection-related risk of Parkinson's disease: Meta-analysis of cohort and case–control studies. Brain and Behavior 10 (3). https://doi.org/10.1002/brb3.1549.
Wang, J., et al., 2021. Nogo receptor impairs the clearance of fibril amyloid-β by microglia and accelerates Alzheimer's-like disease progression. Aging Cell 20 (12). https://doi.org/10.1111/acel.13515.
Wang, M., et al., 2024. IL-33/ST2 signaling in monocyte-derived macrophages maintains blood-brain barrier integrity and restricts infarctions early after ischemic stroke. J. Neuroinflammation 21 (1), 274. https://doi.org/10.1186/s12974-024-03264-8.
Wang, X.-L., et al., 2014. Helicobacter pylori filtrate induces alzheimer-like tau hyperphosphorylation by activating glycogen synthase kinase-3β. J. Alzheimer's Dis. 43 (1), 153–165. https://doi.org/10.3233/JAD-140198.
Wei, Y., et al., 2020. Cortical microinfarcts associated with worse outcomes in patients with acute ischemic stroke receiving endovascular treatment. Stroke 51 (9), 2742–2751. https://doi.org/10.1161/STROKEAHA.120.030895/SUPPL_FILE/STR_STROKE-2020-030895_SUPP1.PDF.
Wendeln, A.-C., et al., 2018. Innate immune memory in the brain shapes neurological disease hallmarks. Nature 556 (7701), 332–338. https://doi.org/10.1038/s41586-018-0023-4.
Więckowska-Gacek, A., et al., 2021. Western diet as a trigger of Alzheimer's disease: from metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. Ageing Res. Rev. 70, 101397. https://doi.org/10.1016/j.arr.2021.101397.
Wilson, D.M., et al., 2023. Hallmarks of neurodegenerative diseases. Cell 186 (4), 693–714. https://doi.org/10.1016/j.cell.2022.12.032.
Wimmers, F., et al., 2021. The single-cell epigenomic and transcriptional landscape of immunity to influenza vaccination. Cell 184 (15), 3915–3935.e21. https://doi.org/10.1016/j.cell.2021.05.039.
Xiao, M., et al., 2012. Inhibition of α-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors. Genes Dev. 26 (12), 1326–1338. https://doi.org/10.1101/gad.191056.112.
Xu, Y., et al., 2021. Autophagy deficiency modulates microglial lipid homeostasis and aggravates tau pathology and spreading. Proc. Natl. Acad. Sci. 118 (27). https://doi.org/10.1073/pnas.2023418118.
Yong, J., et al., 2011. BCG vaccine-induced neuroprotection in a mouse model of parkinson's disease. PLoS One 6 (1), e16610. https://doi.org/10.1371/JOURNAL.PONE.0016610.
You, M., Chen, L., Zhang, D., Zhao, P., Chen, Z., Qin, E.-Q., et al., 2021. Single-cell epigenomic landscape of peripheral immune cells reveals establishment of trained immunity in individuals convalescing from COVID-19. Nat. Cell Biol. 23 (6), 620–630. https://doi.org/10.1038/s41556-021-00690-1.
Yun, S.P., et al., 2018. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. Nat. Med. 24 (7), 931–938. https://doi.org/10.1038/S41591-018-0051-5.
Zahoor, I., et al., 2022. 'Blood-based untargeted metabolomics in relapsing-remitting multiple sclerosis revealed the testable therapeutic target'. 10.1073/pnas.
Zapała, B., et al., 2022. The role of the western diet and oral microbiota in parkinson's disease. Nutrients 14 (2), 355. https://doi.org/10.3390/nu14020355.
Zhan, X., Stamova, B., Sharp, F.R., 2018. 'Lipopolysaccharide associates with amyloid plaques, neurons and oligodendrocytes in Alzheimer's disease brain: a review'. Front. Aging Neurosci. Frontiers Media S.A. 10.3389/fnagi.2018.00042.
Zhang, R., et al., 2009. Circulating endotoxin and systemic immune activation in sporadic amyotrophic lateral sclerosis (sALS). J. Neuroimmunol. 206 (1–2), 121–124. https://doi.org/10.1016/J.JNEUROIM.2008.09.017.
Zhang, W., et al., 2023. Role of neuroinflammation in neurodegeneration development. Signal Transduct. Target. Ther. 8 (1), 267. https://doi.org/10.1038/s41392-023-01486-5.
Zhang, W., et al., 2005. Aggregated α-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. FASEB J. 19 (6), 533–542. https://doi.org/10.1096/fj.04-2751com.
Zhang, X., et al., 2022. Epigenetic regulation of innate immune memory in microglia. J. Neuroinflammation 19 (1). https://doi.org/10.1186/S12974-022-02463-5.