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Immune Conversations Gone Wrong: Crosstalk Mechanisms Driving Alzheimer's, Parkinson's, and Depression

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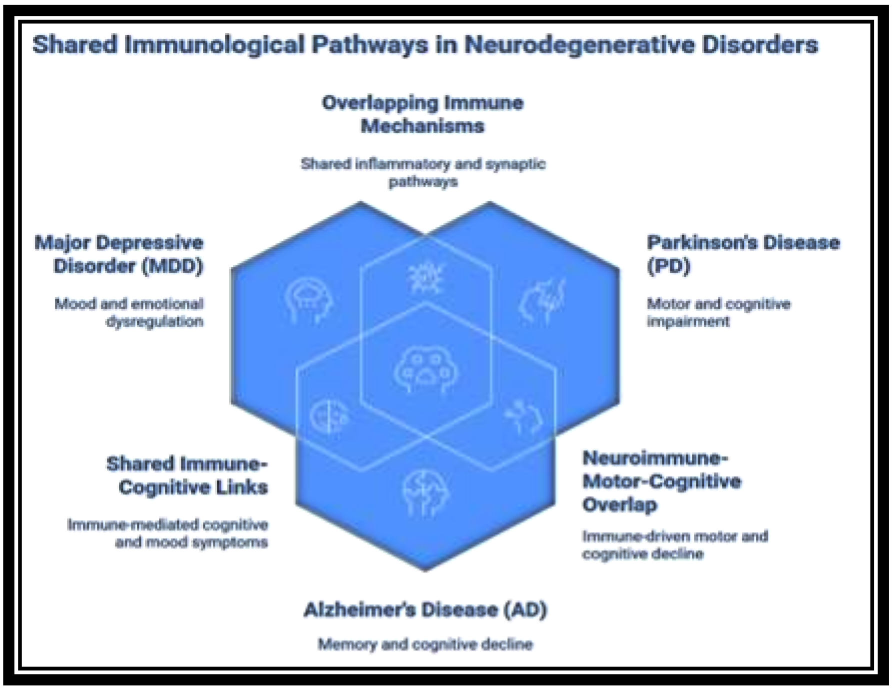
Abstract

Major depressive disorder (MDD), Parkinson's disease (PD), and Alzheimer's disease (AD) are examples of neurodegenerative and neuropsychiatric illnesses that have historically been seen through different pathological lenses. However, new research from 2018 to 2025 indicates that these disorders share a similar immunological foundation, characterized by an inappropriate interaction between the peripheral and central immune systems. Chronic neuroinflammation and synaptic failure result from this immunological dysregulation, which is caused by astrocytic reactivity, microglial priming, cytokine imbalance, and disruption of the gut-brain axis. The concept of "immune conversations gone wrong" underscores how neuroimmune communication, which is beneficial during homeostasis, becomes detrimental during illness. This review illustrates the interaction between innate and adaptive immune signaling networks in AD, PD, and MDD, incorporating recent multi-omics, neuroimaging, and clinical research findings. It highlights converging pathways such as NF-κB activation and interferon-mediated responses. Gaining insight into these common immune circuits could lead to the discovery of new treatment targets aimed at restoring equilibrium in neuroimmune interactions.

Graphical Abstract



Keywords: MDD, AD, PD, Neuroinflammation.

1. Introduction

Once thought to be an immune-privileged organ, the brain is now understood to be a site of dynamic immunological activity, controlled by peripheral immune cells, astrocytes, and microglia (Colonna et al., 2018). Synaptic pruning, debris removal, and neurotrophic signaling are all supported by neuroimmune interactions, which are essential for preserving neuronal health (Salter et al., 2021). However, chronic inflammation—a defining feature of neurodegenerative and mood disorders—is caused by ongoing immune activation and the failure of resolution mechanisms (Heneka et al., 2019).

Pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6, have been implicated as key mediators in the convergent inflammatory profiles observed in AD, PD, and depression over the past decade, according to transcriptome and proteomic studies (Becher et al., 2021). Immune dysfunction affects neuroplasticity and neurotransmitter modulation in all three disorders, in addition to neuronal death (Dantzer et al., 2020). As a result, these conditions can be viewed as distinct consequences of a common immunopathological environment.

Recent developments in spatial transcriptomics and single-cell RNA sequencing have demonstrated that microglial activation patterns in neurodegeneration and mood disorders are coincident (Masuda et al., 2022). The discovery of astrocytes (A1/A2 phenotypes) and disease-associated microglia (DAM) provides fresh insights into how maladaptive immune responses influence the progression of disease (Keren-Shaul et al., 2018; Liddelow et al., 2020).

For a long time, the main perspectives on neurodegenerative and neuropsychiatric conditions, including major depressive disorder (MDD), Parkinson's disease (PD), and Alzheimer's disease (AD), have been neuronal loss and neurotransmitter imbalance. However, dysregulated immune crosstalk—both within the central nervous system (CNS) and between the CNS and the periphery—has been shown to play a crucial role in their onset and progression over the past ten years (Heneka et al., 2019; Dantzer et al., 2020; Subramaniam et al., 2022).

Microglia, astrocytes, neurons, endothelial cells, and invading peripheral immune cells engage in a dynamic conversation at the neuroimmune interface. Under physiological conditions, this communication is precisely controlled, maintaining brain homeostasis, removing waste, and forming synaptic networks (Liddelow et al., 2017). However, these immune conversations "go wrong" in response to pathological stimuli, such as aging, infection, oxidative stress, or protein aggregation. This leads to maladaptive cytokine signalling and chronic neuroinflammation, which cause neuronal damage, synaptic dysfunction, and abnormal behaviour (Heppner et al., 2021; Miller & Raison, 2016).

Crucially, the concept of immunological crosstalk underscores that brain inflammation is rarely isolated; rather, it is a two-way dialogue influenced by peripheral immune responses, gut microbiota, metabolic changes, and stress hormones (Jiang et al., 2020). Because these systems are interrelated, immunological disruptions in one area, such as gut dysbiosis or peripheral cytokine storm, may affect microglial activation in the central nervous system (CNS) and potentially trigger neurodegenerative cascades.

Tau aggregation and amyloid-β accumulation in AD cause microglia to emit TNF-α, IL-6, and IL-1β, which prolongs neuroinflammation (Heneka et al., 2015). Similar proinflammatory loops involving T-cell infiltration and microglial hyperactivation are triggered by α-synuclein aggregation in Parkinson's disease (PD) (Sulzer et al., 2017). Conversely, in MDD, increased levels of TNF-α and IL-6 are associated with neurotransmitter dysregulation and hippocampus shrinkage, indicating inflammation-induced neuroplastic alterations (Miller & Raison, 2016; Dowlati et al., 2020).

When taken as a whole, these discoveries change our perspective of these illnesses from neuron-centric to immunological network-centric disorders, highlighting the potential benefits of therapeutic treatments that target glial regulation, cytokine signalling, and gut–brain axis restoration. The current review highlights translational targets for immunomodulatory therapeutics by integrating findings from 2018 to 2025 on how immunological crosstalk defects cause common and unique pathophysiological characteristics in AD, PD, and depression.

2. Mechanisms of Neuroimmune Crosstalk

2.1. Microglial Activation and Crosstalk

Neuroimmune signalling is mostly mediated by microglia, the CNS's resident macrophages. Microglia monitor the neuronal environment and maintain synaptic homeostasis in physiological conditions. However, they become persistently activated when exposed to misfolded proteins such as amyloid-β, α-synuclein, or stress-induced DAMPs (Hickman et al., 2018). Neuronal dysfunction is exacerbated by pro-inflammatory cytokines, reactive oxygen species, and complement factors released by activated microglia (Voet et al., 2019).

TREM2 signalling induces microglial activation in AD (Heneka et al., 2020). Similar to this, in Parkinson's disease (PD), microglia interact with aggregated α-synuclein through the NF-κB and STAT3 pathways, leading to chronic inflammation (Subramaniam et al., 2022). Chronic stress contributes to hippocampus shrinkage in depression by priming microglia toward a pro-inflammatory phenotype (Yirmiya et al., 2021). These results suggest that abnormal microglial crosstalk is a mechanism that unites neurodegeneration and mental disorders.

2.2. Astrocyte Reactivity and Cytokine Crosstalk

Traditionally thought to support glial cells, astrocytes actively participate in controlling the neuroimmune system. Astrocytes undergo phenotypic changes in inflammatory conditions, becoming reactive A1 astrocytes that release neurotoxic mediators (Liddelow et al., 2020). A2 astrocytes, on the other hand, generate neurotrophic factors that aid in healing. The A1 phenotype is driven by cytokines including IL-1α, TNF-α, and C1q, which connect glial toxicity and innate immunity (Clarke et al., 2021).

According to recent research, astrocyte-microglia interactions in AD and PD enhance inflammatory cascades via complement signalling and IL-6 (Escartin et al., 2021). There is a molecular connection between immunological dysregulation and mood symptoms in depression because astrocyte dysfunction lowers glutamate clearance and hinders serotonergic signalling (Wohleb et al., 2022).

2.3. Peripheral Immune Cell Infiltration

T lymphocytes, monocytes, and B cells can infiltrate the central nervous system (CNS) despite the blood–brain barrier's (BBB) ability to prevent immunological entry being compromised by chronic inflammation and vascular dysfunction (Da Mesquita et al., 2019). Peripheral monocytes that express CCR2 move to amyloid plaques in AD, aggravating inflammation (Mrdjen et al., 2021). According to Sulzer et al. (2020), CD4+ T lymphocytes in Parkinson's disease (PD) recognize α-synuclein epitopes and contribute to the death of dopaminergic neurons. BBB permeability and microglial activation are correlated with increased peripheral IL-6 and TNF-α in depression (Beurel et al., 2020).

Amyloid-β (Aβ) plaques, neurofibrillary tangles made of hyperphosphorylated tau, and gradual cognitive deterioration are the hallmarks of Alzheimer's disease (AD), the most prevalent kind of dementia. In addition to these traditional characteristics, a significant amount of research currently suggests that immunological dysregulation plays a crucial role in the development and course of disease (Heneka et al., 2019; De Strooper et al., 2021).

One of the first pathogenic characteristics of AD is microglial activation. Polymorphisms in immune-related genes such as TREM2, CD33, and CR1 have been found to increase vulnerability to AD by genome-wide association studies (Keren-Shaul et al., 2018; Gratuze et al., 2021). Microglial survival and phagocytic clearance of Aβ are supported by TREM2 signalling; however, long-term activation causes microglia to adopt a pro-inflammatory phenotype (Griciuc et al., 2019). When Aβ aggregates induce tau hyperphosphorylation and IL-1β release, a self-sustaining inflammatory loop is created (Heneka et al., 2020; Ising et al., 2021). By reacting to microglial cytokines, including IL-1α, TNF-α, and C1q, astrocytes also participate in immunological crosstalk by transforming into neurotoxic A1 astrocytes (Liddelow et al., 2020; Clarke et al., 2021). These reactive astrocytes contribute to synaptic loss by secreting complement components that mark synapses for microglial engulfment (Escartin et al., 2021).

Interferon and complement signalling pathways are increased in AD brains and peripheral blood, according to recent transcriptome studies (Rasmussen et al., 2022). Furthermore, through cytokine-mediated microglial priming, peripheral inflammation—such as that caused by infections or metabolic diseases—can hasten AD pathogenesis (Lim et al., 2023).

The gut-brain axis's significance in AD immunopathology is becoming more widely acknowledged. Immune cell infiltration into the brain is facilitated by gut dysbiosis, which increases systemic inflammation and BBB permeability (Zhao et al., 2022). Microglial activation and Aβ deposition are modulated by pro-inflammatory microbial metabolites such as lipopolysaccharide and short-chain fatty acid imbalances (Marizzoni et al., 2021; Kim et al., 2024). When glial cells and peripheral immunological players participate in maladaptive signalling that causes neurodegeneration, AD appears as a disease of misregulated immune dialogue.

3. Immune Crosstalk in Alzheimer's Disease

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4. Immune Crosstalk in Parkinson's Disease

Lewy bodies, which are an aggregation of α-synuclein, and dopaminergic neuronal loss in the substantia nigra are the hallmarks of Parkinson's disease (PD). Immune dysregulation has been identified in recent years as a key factor in the pathophysiology of Parkinson's disease (PD) (Subramaniam et al., 2022; Tansey et al., 2021). One of the most frequently observed immunological changes in Parkinson's disease is microglial activation. TNF-α, IL-1β, and nitric oxide are released by activated microglia, leading to oxidative stress and neuronal damage (Gao et al., 2021). As a DAMP, α-synuclein interacts with TLR2/4 receptors on microglia, activating NF-κB and initiating inflammasome signalling (Grotemeyer et al., 2023). The important immunological genes TREM2 and LRRK2 have been linked to microglial function and PD vulnerability (Cook et al., 2023).

Additionally, peripheral immune activation is crucial. Patients with Parkinson's disease (PD) have changed T-cell populations and elevated levels of circulating IL-6, IL-17, and TNF-α (Sulzer et al., 2020; Sommer et al., 2022). Both animal models and human postmortem tissues have shown evidence of CD4+ and CD8+ T cell infiltration into the substantia nigra (Brockmann et al., 2021). Dopaminergic cell loss is also influenced by autoimmune mechanisms, such as the identification of α-synuclein epitopes by adaptive immune cells (George et al., 2021). Additionally, astrocytes exacerbate neuroinflammation in Parkinson's disease (PD) by producing complement and S100β proteins, which attract microglia (Phani et al., 2022). A pro-inflammatory environment that is harmful to neuronal survival is maintained by this glial interaction.

Once more, the gut-brain axis appears as an upstream regulator. PD onset and severity have been linked to alterations in gut microbiota composition, characterized by a decrease in Prevotella and an increase in Enterobacteriaceae (Scheperjans et al., 2020). Endotoxins generated in the gut stimulate peripheral macrophages, which then spread inflammation to the central nervous system through the vagus nerve (Mulak et al., 2021). All things considered, Parkinson's disease (PD) is a prime example of how persistent immune activation, both peripheral and central, sustains neurodegeneration via maladaptive immunological communication.

5. Immune Crosstalk in Depression

Long thought to be a neurotransmitter disorder, depression is now recognized to have substantial neuroimmune changes (Miller et al., 2021). Major depressive disorder has been repeatedly linked to elevated peripheral cytokines such as CRP, TNF-α, and IL-6 (Dantzer et al., 2020). Microglial activation results from the ability of these molecules to traverse the blood-brain barrier or communicate via endothelial and vagal pathways (Yirmiya et al., 2021).

Long-term stress causes glucocorticoid resistance and activates the hypothalamic-pituitary-adrenal (HPA) axis, thereby prolonging the release of cytokines (Beurel et al., 2020). In response to this inflammatory environment, microglia and astrocytes decrease neurogenesis and impede synaptic plasticity (Wohleb et al., 2022). Elevated microglial activity in individuals with depressive disorders has been confirmed by recent neuroimaging studies using PET tracers for TSPO, a measure of glial activation (Setiawan et al., 2021). Concurrently, transcriptome analyses have revealed elevated NF-κB and interferon signalling in MDD brains (Dean et al., 2023).

Crucially, the immunological dysfunction associated with depression is also influenced by the gut-brain axis. Increased gut permeability and systemic inflammation result from dysbiosis, characterized by a decrease in Bifidobacterium and Lactobacillus species (Maji et al., 2022). Further highlighting the immunological connection, probiotic and anti-inflammatory therapies have shown modest benefits in alleviating depressive symptoms (Bharwani et al., 2024).

6. Therapeutic Implications and Future Directions

Interest in immunomodulatory techniques has increased since it was shown that AD, PD, and depression all share immune dysregulation. Early clinical trials have demonstrated promise in lowering neuroinflammatory indicators and enhancing cognitive and motor outcomes by targeting TNF-α and IL-1β (Wang et al., 2023).

The potential of biologics and small compounds that alter microglial activity, such as CSF1R inhibitors and TREM2 agonists, to restore immunological homeostasis is being investigated (Shi et al., 2023). Anti-inflammatory medications like minocycline and NSAIDs have the potential to be used as supplemental treatments for depression (Kappelmann et al., 2021). Restoring balanced immunological signalling is further aided by lifestyle therapies such as nutrition, exercise, and microbiome modification (Kim et al., 2024). Key molecular nodes for therapeutic targeting can be identified with the aid of artificial intelligence-driven network modeling (Zhou et al., 2025).

Alzheimer's disease (AD), Parkinson's disease (PD), and major depressive disorder (MDD) all share inflammatory cascades, according to recent discoveries about the immunopathological crosstalk underlying these conditions. This suggests that a network-based immunotherapeutic approach may be beneficial across historically different diagnostic boundaries (Heneka et al., 2019; Heppner et al., 2021). Researchers are currently investigating novel intervention pathways that extend far beyond traditional neurotransmitter- or protein-aggregate-based therapeutics by focusing on the dysregulated immunological signaling and glial cell activation that drive brain damage.

6.1. Immunomodulatory Therapies Targeting Glial Activation

Astrocytes and microglia play a key role in controlling CNS immunity. In AD and PD, their persistent activation causes neurotoxicity and neuronal death (Liddelow et al., 2017; Escartin et al., 2021). Currently undergoing preclinical or early clinical research are a number of medicines that target glial-mediated inflammation are CSF1R inhibitors, such as PLX3397, enhance neuronal survival in Parkinson's disease via regulating microglial proliferation.

In early PD and depression trials, minocycline, a tetracycline derivative, has shown neuroprotective effects by preventing microglial activation (Subramaniam et al., 2022). In AD and MDD models, astrocyte-specific modulators that target the STAT3 and NF-κB pathways may lessen proinflammatory cytokine production and glial reactivity.

6.2. Cytokine-Based and Anti-Inflammatory Therapeutics

The development of the disease and the intensity of its symptoms are closely linked to systemic inflammation and the increased production of cytokines, such as TNF-α, IL-1β, and IL-6 (Miller & Raison, 2016; Dowlati et al., 2020).

Therefore, cytokine blocking is a new treatment strategy. Anakinra and other IL-1 receptor antagonists have been tested for their ability to lessen the neuroinflammatory load associated with AD. There is evidence that TNF-α inhibitors, including etanercept and infliximab, can improve mood and cognitive symptoms in PD and MDD. By reducing peripheral-to-central inflammatory signaling, JAK/STAT pathway inhibitors and IL-6R antibodies (such as tocilizumab) may be beneficial (Pagani et al., 2022). Notwithstanding these developments, problems with the permeability of the blood–brain barrier (BBB) and the potential for systemic immunosuppression still persist.

6.3. Gut–Brain–Immune Axis Modulation

The gut microbiota is a crucial regulator of neuroinflammation and neurobehavioral consequences, according to growing data (Cryan et al., 2019; Kim et al., 2023). Through the vagus nerve and the secretion of systemic cytokines, dysbiosis and microbial metabolite imbalance can stimulate peripheral immune cells and encourage microglial overactivation.

Lactobacillus plantarum and *Bifidobacterium longum* are two examples of probiotics and prebiotics that can help improve microbial balance and alleviate symptoms of depression. Fecal microbiota transplantation (FMT) has shown some promise in reducing cognitive decline in AD models and motor impairments in Parkinson's disease (PD). Dietary strategies that lower oxidative stress and systemic inflammation, such as ketogenic and Mediterranean diets. Short-chain fatty acids (SCFAs) and postbiotics are being investigated as neuromodulators that reduce inflammation.

6.4. Nanotechnology and Targeted Drug Delivery

Nanotechnology-based medication delivery methods have received a lot of attention since the BBB restricts the efficacy of many neurotherapeutic drugs. Recent developments include polymeric nanoparticles that target microglia or astrocytes, which contain anti-inflammatory substances such as curcumin, resveratrol, or siRNA.

Mesenchymal stem cells (MSCs)-derived exosome-based delivery systems that move growth factors and anti-inflammatory miRNAs across the blood-brain barrier (Dwivedi et al., 2022). These methods offer decreased systemic toxicity, site-specific administration, and enhanced pharmacokinetics.

6.5. Epigenetic and Transcriptomic Therapeutic Targets

Immune gene expression profiles unique to disease have been identified in glial and immune cells thanks to developments in whole-genome and single-cell RNA sequencing (scRNA-seq)

Restoring immunological homeostasis while maintaining normal central nervous system function may be possible with epigenetic treatments.

6.6. Personalized and Precision Neuroimmunology

Precision medicine techniques are crucial since patients' immunological responses vary widely. To categorize patients according to their immunological status, biomarkers such as CSF cytokine profiles, PET imaging of TSPO (translocator protein) for microglial activation, and metabolomic fingerprints from gut microbiota are being investigated (Heppner et al., 2021; Sweeney et al., 2019). AI-driven network analysis, combined with multi-omics data (genomic, proteomic, and metabolomic), may soon enable customized immunomodulatory treatments based on specific immunological characteristics in AD, PD, and MDD.

6.7. Future Research Directions

Future research should focus on the following priority areas:

1. Temporal mapping of immune activation to differentiate between persistent pathogenic inflammation and early adaptive responses.
2. Systems biology modelling to comprehend feedback loops and intercellular signalling between peripheral immune cells, glia, and neurons.
3. Combination immunotherapy that incorporates glial reprogramming, microbiota repair, and cytokine regulation.
4. Longitudinal clinical research linking peripheral immune biomarkers to behavioural and cognitive outcomes.
5. The safe application of RNA-based immunotherapies and nanomedicine in clinical settings.

Over the next ten years, there is likely to be a trend toward holistic, cross-systemic immunotherapies that focus on restoring adaptive immunological homeostasis, in addition to reducing inflammation. This change will usher in a new era of immune-centered precision medicine for the treatment of neurodegenerative and mental conditions.

7. Conclusion

In the last ten years, there has been a paradigm change in our understanding of neurodegenerative and neuropsychiatric disorders. We now see them as immunologically networked pathologies rather than just neuron-centered disorders. Immune crosstalk dysregulation is a fundamental driver of pathology in Alzheimer's disease (AD), Parkinson's disease (PD), and major depressive disorder (MDD), according to evidence gathered between 2018 and 2025 (Heneka et al., 2019; Subramaniam et al., 2022; Miller & Raison, 2016).

A complex web of signaling pathways, including peripheral immune infiltration, microglial and astrocytic activation, blood–brain barrier impairment, and disturbance of the gut–brain–immune axis, causes a continuous state of inflammation in these illnesses that accelerates neuronal failure. The convergence of these mechanisms reveals common molecular inflammatory signs, such as altered complement pathways and increased cytokines including TNF-α, IL-1β, and IL-6 (Ising et al., 2019; Escartin et al., 2021).

Furthermore, neuroimmune communication is amplified by systemic immune factors, including circulating microRNAs, gut-derived metabolites, and chronic stress hormones, which cause maladaptive responses in the central nervous system (Cryan et al., 2019; Dwivedi et al., 2022). Together, our results show that neuroinflammation is a whole-body immunological phenomenon involving bidirectional signalling between the periphery and the central nervous system rather than an isolated brain event (Jiang et al., 2020).

This holistic understanding provides therapeutic opportunities for intervention. Preclinical and early clinical efficacy in lowering neuroinflammation and enhancing neurocognitive outcomes has been demonstrated by targeting the immune network through microglial modulators, cytokine inhibitors, immune checkpoint regulators, gut microbiota modulation, and nanoparticle-based anti-inflammatory delivery systems (Heppner et al., 2021; Kim et al., 2023). Personalized immunotherapy techniques are now possible because to multi-omics and single-cell sequencing investigations that reveal specific immune cell populations and signalling nodes implicated in each disease (Escartin et al., 2021).

Significantly, a unified immunological theory of neurodegeneration and mood disorders may be developing based on the overlap of neuroinflammatory signatures in AD, PD, and MDD. According to Sweeney et al. (2019) and Dowlati et al. (2020), this convergence supports the notion that chronic inflammation is a causative and sustaining role in the evolution of disease rather than just a secondary event. Therefore, the development of immunomodulatory treatments that can target this common pathogenic core, along with the identification of cross-disease indicators of immunological dysregulation, should be the primary goals of future research.

In conclusion, neurodegenerative and neuropsychiatric diseases stem from improper immune responses. We can advance toward a new era of integrative neuroimmunology by deciphering the precise molecular conversations between microglia, astrocytes, neurons, peripheral immune cells, and gut microbiota. In this new era, therapies aim to both rescue neurons and reprogram the brain's immune landscape toward homeostasis and repair. This strategy has the potential to revolutionize the way we identify, track, and manage some of the most crippling illnesses of our day.

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