

Review

Huntington's Disease as a Neuroglial Systems Disorder: Mechanisms, Network Propagation, and Therapeutic Opportunities

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Abstract

Huntington's disease (HD) has traditionally been conceptualized as a neuron-centric disorder primarily attributed to cell-autonomous toxicity of mutant huntingtin (mHTT) in striatal medium spiny neurons. However, this framework inadequately explains the prolonged presymptomatic phase, selective network vulnerability, early non-motor manifestations, and limited success of neuron-targeted therapeutic interventions. Accumulating evidence from molecular biology, transcriptomics, neuroimaging, and preclinical therapeutics supports a reframing of HD as a disorder of neuroglial systems dysfunction. We synthesize data demonstrating that astrocytes, microglia, and oligodendrocyte lineage cells are not passive bystanders but play direct and interactive roles in HD pathogenesis through defined molecular mechanisms. Expression of mHTT in glial populations impairs synaptic homeostasis, metabolic coupling, immune resolution, and myelin integrity, generating self-amplifying pathological feedback loops that destabilize neural circuits long before overt neuronal death. Critically, we evaluate glial replacement therapy as a potential disease-modifying strategy. Preclinical studies demonstrate that transplantation of healthy human glial progenitor cells substantially ameliorates motor, cognitive, and neuropathological deficits in multiple HD models through oligodendroglial remyelination and lactate-mediated metabolic support, despite persistent neuronal mHTT expression. Effective HD therapy will likely require strategies that jointly target the genetic cause and the dysfunctional neuroglial microenvironment. By integrating systems neuroscience with glial biology and translational strategy, this review defines a neuroglial framework for HD that opens a plausible path toward meaningful disease modification and positions HD as a model disorder for glial-centric interventions in neurodegeneration.

Keywords: Huntington's disease; neuroglial systems; astrocytes; microglia; oligodendrocytes; neuroinflammation; white matter; glial replacement therapy



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1. Introduction

Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disorder caused by an expanded cytosine-adenine-guanine (CAG) trinucleotide repeat in the huntingtin gene, resulting in mutant huntingtin (mHTT) protein expression [1]. The disease manifests clinically as a progressive triad of motor abnormalities, cognitive decline, and psychiatric disturbances, typically emerging in mid-adulthood and progressing inexorably over 15 to 20 years [2]. Neuropathologically, HD is defined by selective degeneration of striatal medium spiny neurons (MSN) and progressive atrophy of cortical and subcortical regions [3,4].

For over three decades, a neuron-centric paradigm attributing pathogenesis primarily to neuron-intrinsic mHTT toxicity has dominated HD research. This framework encompasses dysregulated transcription, impaired mitochondrial function, disrupted proteostasis, altered synaptic signaling, and heightened excitotoxic susceptibility [5–9]. The neuron-centric model has been extraordinarily productive, yielding deep mechanistic insights into MSN vulnerability and providing the mechanistic foundation for huntingtin-lowering strategies that remain among the most promising disease-modifying approaches under investigation [10,11].

Although the neuron-centric model has substantially advanced the field, it does not fully explain several defining features of HD. First, although neuronal loss is a relatively late event, molecular, metabolic, and functional abnormalities are detectable years to decades before clinical onset in presymptomatic gene carriers, with the timing varying across biomarker modalities [12,13]. Large longitudinal cohorts such as PREDICT-HD and TRACK-HD have demonstrated that structural, cognitive, and neuropsychiatric alterations emerge years before an overt motor diagnosis is made. Longitudinal neuroimaging studies show that striatal volume loss accelerates predominantly in the 10 to 15 years preceding motor diagnosis, yet mHTT is ubiquitously expressed from conception [13–15]. Second, the spatial pattern of degeneration extends systematically beyond the striatum to cortical and subcortical regions. This progression follows anatomical connectivity and functional network architecture rather than regional mHTT expression levels [16,17]. And third, interventions that effectively reduce neuronal mHTT levels have thus far produced modest or variable clinical benefits in human trials [18,19]. Because of this limited efficacy, it is possible that downstream pathological processes will continue or change even after the primary genetic insult has been partially mitigated [20].

Notably, the unexpected ventricular enlargement and absence of clinical benefit observed in the Phase III trial of Tominersen [18] underscore the complexity of broadly suppressing mHTT within the central nervous system (CNS). These findings raise the possibility that intrathecal mHTT reduction may interact with neuroinflammatory or homeostatic processes in ways that remain incompletely understood. While multiple mechanistic explanations exist for this outcome—including off-target effects on wildtype huntingtin and delivery-related toxicity—the neuroglial systems framework proposed here offers one conceptual lens through which such interactions might be systematically investigated.

It should be noted, however, that the causal hierarchy between neuronal and glial pathology in humans remains unresolved. Much of the mechanistic evidence supporting early glial involvement derives from transgenic rodent models whose disease timelines, genetic architectures, and glial biology differ substantially from human HD. The discrepancies outlined above—between the timing of molecular pathology and clinical onset, the spatial pattern of neurodegeneration, and the limited efficacy of neuron-targeted interventions—highlight a fundamental gap between molecular pathology at the cellular level and systems-level disease expression. They suggest that HD progression is not governed solely by neuron-intrinsic toxicity but by the progressive destabilization of the

cellular environment in which neurons operate. Over the past decade, accumulating evidence has challenged the implicit assumption that neurons are the sole or even primary drivers of disease progression. It is now well established that mHTT is expressed across all major neural cell types, including astrocytes, microglia, and oligodendrocyte lineage cells [21,22]. Accumulating evidence indicates that mHTT expression in these glial populations is not biologically inert but induces cell-autonomous dysfunctions that impair essential homeostatic, metabolic, and immune-regulatory functions while simultaneously exerting non-cell-autonomous effects that amplify neuronal vulnerability [23–26].

Recent advances provide compelling support for this expanded view. Single-nucleus RNA sequencing studies reveal pronounced transcriptional dysregulation in glial populations that is consistent with early disease involvement and may precede widespread neuronal pathology [27,28]. Neuroimaging studies using diffusion tensor imaging and positron emission tomography demonstrate presymptomatic white matter microstructural abnormalities and microglial activation in gene carriers years before predicted motor onset [29,30]. Perhaps most strikingly, transplantation experiments show that replacement of diseased glia with healthy human glial progenitor cells can partially rescue motor, cognitive, and neuropathological deficits in HD mouse models despite the continued presence of mHTT in host neurons [25,31]. Instead of replacing the neuron-centered framework, we propose that HD should be conceptualized as a multilevel neuroglial systems disorder in which mHTT expression across neuronal and non-neuronal cell types generates progressive network instability. In this perspective, selective neuronal vulnerability emerges not solely from cell-autonomous toxicity but from distributed dysfunction across interacting cellular compartments. The term “neuroglial systems disorder” is used here to describe a state in which impaired homeostatic regulation, metabolic coupling, inflammatory signaling, and myelin integrity collectively destabilize corticostriatal circuits. This review is integrative and narrative in scope. Rather than performing a formal systematic meta-analysis, we synthesize converging genetic, molecular, cellular, and systems-level evidence to construct a mechanistically coherent framework and outline experimentally testable predictions. The framework proposed here should therefore be understood as a testable mechanistic hypothesis requiring longitudinal human validation rather than an established causal account.

2. The Neuroglial Unit: Functional Architecture and Pathological Transformation

Studying neuroglial cells is crucial for understanding the progression of HD, as their dysfunction may be an early and driving component of nervous system pathology. We use the term ‘neuroglial unit’ throughout this review as a working, integrative construct—conceptually related to established compartmental models such as the tripartite synapse and the neurovascular unit—to denote the functional ensemble formed by neurons, astrocytes, microglia, and oligodendrocytes that jointly sustain circuit homeostasis. This term is not yet standardized in HD literature and is proposed here as a heuristic framework rather than an established anatomical or molecular entity. Within this system, these cell types interact continuously to sustain synaptic stability, metabolic coupling, immune homeostasis, and network integrity [32]. Within the neuroglial unit, astrocytes regulate extracellular neurotransmitter and ion concentrations while providing metabolic substrates to neurons through mechanisms such as the astrocyte–neuron lactate shuttle [33,34]. Microglia continuously survey the neural environment, sculpt synaptic networks through activity-dependent pruning, and mediate immune responses to injury and stress [35,36]. Oligodendrocytes not only provide electrical insulation through myelination but also supply metabolic substrates to axons via monocarboxylate transporter 1, supporting the high energetic demands of action potential propagation [37,38].

Under physiological conditions, the neuroglial unit operates as a dynamic, adaptive system in which astrocytes, microglia, and oligodendrocytes trigger coordinated responses that act to restore homeostatic set points. Astrocytes rapidly buffer extracellular potassium and clear glutamate from the synaptic cleft, preventing excitotoxicity. Microglia detect and respond to neuronal stress signals, removing debris and modulating inflammatory tone. Oligodendrocytes adjust metabolic support in response to axonal activity patterns. This bidirectional communication helps ensure that local disturbances do not escalate into network-wide dysfunction [39,40].

In HD, homeostatic equilibrium is progressively compromised as mHTT expression dysregulates glial sensing, signaling, and effector functions. Instead of restoring homeostasis, glial responses often transition into maladaptive states characterized by positive feedback loops that amplify pathology over time [41]. Molecular, imaging, and experimental evidence highlight interlocking feedback mechanisms in model systems, suggesting that analogous processes may contribute to human pathology. It is important to acknowledge that these feedback loops are described here as conceptual constructs derived principally from experimental observations in rodent models and in vitro systems. Their operation in the human HD brain, and particularly their temporal sequence relative to neuronal pathology, has not yet been directly demonstrated. Computational modeling of these coupled nonlinear dynamics would represent a valuable methodological step toward formalizing their predicted behavior and generating quantitatively testable predictions. As detailed in Figure 1, homeostatic glial responses that would normally restore equilibrium instead trigger inflammatory and excitotoxic feedback loops in HD. First, a microglial–astrocyte inflammatory loop may develop in which primed microglia release pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) that drive astrocytes toward maladaptive reactive states characterized by reduced glutamate uptake capacity and impaired metabolic support functions [42,43]. Dysfunctional astrocytes may, in turn, fail to buffer synaptic activity adequately, releasing damage-associated molecular patterns that further activate microglia and perpetuate a cycle of chronic neuroinflammation [42–44]. Second, an astrocyte–neuron excitotoxic loop may emerge from astrocytic failure of glutamate clearance and potassium buffering. Downregulation of the astrocytic glutamate transporter (EAAT2) or glutamate transporter 1 (GLT1) [45] and alterations in inwardly rectifying potassium channels such as Kir4.1 are associated with elevated extracellular glutamate and potassium concentrations, contributing to neuronal hyperexcitability and calcium overload [46–48]. Stressed neurons may release excess glutamate and ATP, further impairing astrocytic function and reinforcing excitotoxic signaling. Over time, this loop may destabilize synaptic networks and erode neuronal resilience even in the absence of cell death [49,50]. Third, an oligodendrocyte–axon metabolic loop may arise from reduced oligodendroglial lactate support, potentially involving monocarboxylate transporter 1 (MCT1)-dependent mechanisms that are thought to be important for axonal energy homeostasis [51–53], and for which reduced expression has been reported in HD models [54]. Energetically compromised axons exhibit impaired conduction, dysregulated calcium handling, and increased vulnerability to degeneration. Axonal stress may generate abnormal electrical activity and metabolic byproducts that activate microglia and astrocytes, linking white matter pathology to inflammatory and synaptic dysfunction [55,56]. Together, these interconnected feedback mechanisms provide a coherent framework to interpret several enigmatic features of HD. They help account for the selective vulnerability of specific brain regions, as circuits with high metabolic demand, dense glutamatergic input, or extensive long-range projections may be particularly sensitive to disruptions in glial support [57,58]. They also offer a mechanistic basis that may contribute to the preferential propagation of dysfunction along functional networks. However, direct evidence distin-

guishing glial-driven propagation from neural connectivity-mediated or trans-synaptic mHTT spread remains to be established through longitudinal multimodal human studies [59,60]. Once established, these maladaptive configurations of the neuroglial unit may become progressively resistant to intervention. Even if neuronal mHTT toxicity is partially attenuated, the altered systems-level dynamics may persist, potentially contributing to the limited efficacy of late-stage therapeutic interventions targeting neurons alone [61,62]. This interaction network is summarized in Figure 1, which illustrates the self-reinforcing loops between glial dysfunctions and neuronal vulnerability.

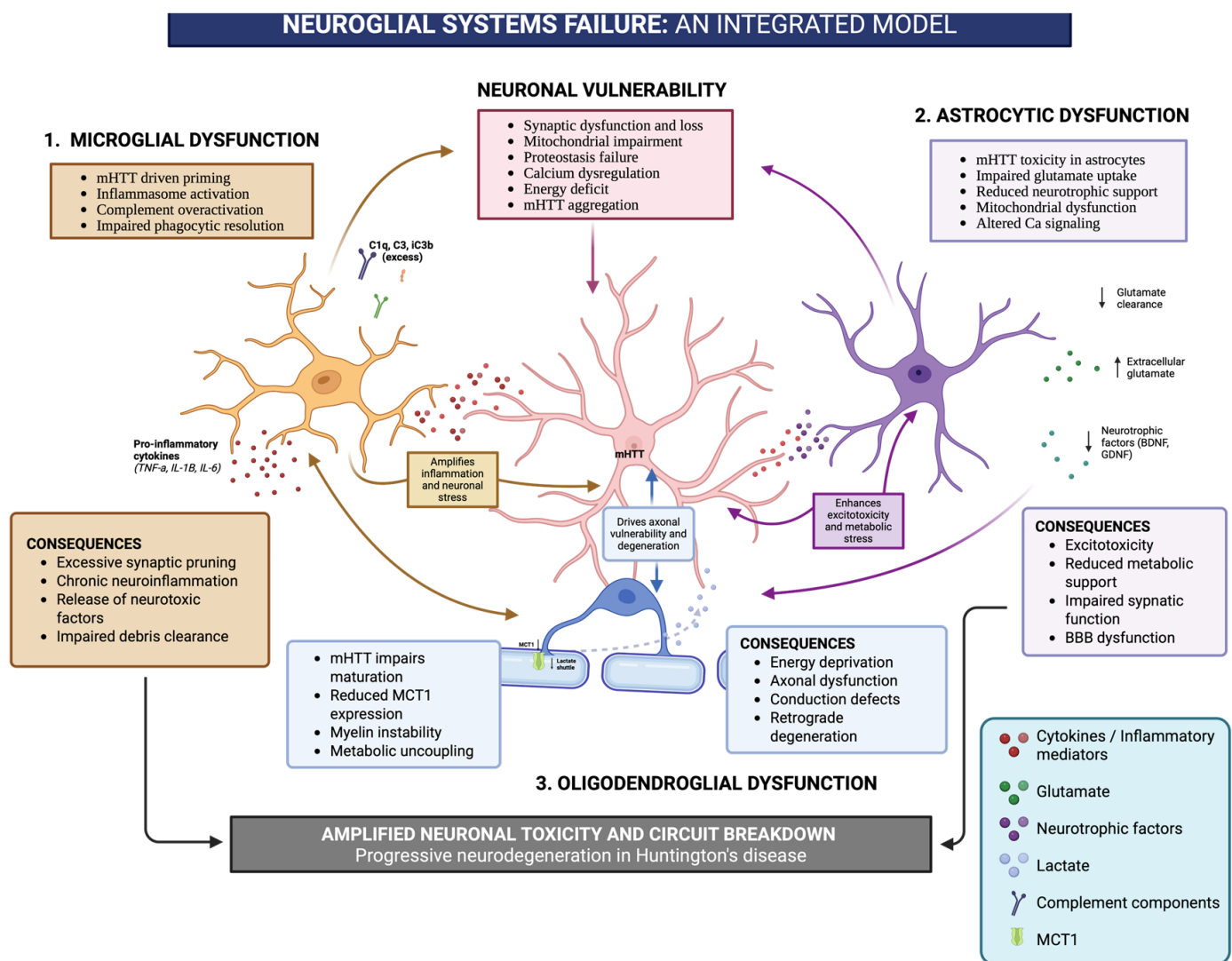


Figure 1. Integrated neuroglial systems failure model in Huntington's disease. Schematic representation of the bidirectional interactions between neuronal vulnerability, microglial dysfunction, astrocytic failure, and oligodendroglial metabolic uncoupling in HD. mHTT-driven glial dysfunction amplifies neuroinflammation, excitotoxicity, impaired metabolic support, complement activation, and axonal degeneration, generating self-reinforcing feedback loops that destabilize corticostriatal circuits and promote progressive neurodegeneration. Abbreviations: mHTT, mutant huntingtin; TNF- α , tumor necrosis factor-alpha; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; BBB, blood–brain barrier; MCT1, monocarboxylate transporter 1; C1q/C3/iC3b, complement cascade proteins. Abbreviations. $\uparrow$, increase; $\downarrow$, decrease.

This system-level perspective also illuminates the prolonged presymptomatic phase of HD. During this period, which can extend for decades, progressive glial dysfunction may degrade circuit efficiency and plasticity without causing immediate structural loss [63,64]. Early cognitive and psychiatric symptoms may therefore reflect functional network instability rather than neuronal death, consistent with observations that such symptoms often emerge years before motor manifestations and correlate with white matter integrity as well as striatal volume [65,66]. The neuroglial framework thus reframes early HD not as a clinically silent period preceding neuronal death but as an active process of systems-level destabilization that may create a critical window for therapeutic intervention.

The mHTT exerts both toxic gain-of-function effects and partial loss-of-normal-function consequences across multiple neural cell types. Although aggregation, transcriptional dysregulation, and impaired proteostasis have been most extensively characterized in neurons, transcriptomic and epigenomic studies demonstrate early and cell-type-specific molecular alterations in astrocytes, microglia, and oligodendrocytes [27,28]. These distributed changes suggest that the neuroglial unit is engaged as an active participant in HD pathogenesis from early stages, providing the cellular substrate through which the feedback mechanisms described above may operate.

3. Microglial Dysfunction: Immune Priming and Synaptic Destabilization

Microglia are the principal immune sentinels of the central nervous system and a core regulatory component of the neuroglial unit. In HD, microglial dysfunction represents an early, genetically driven, and potentially self-sustaining process that may reshape synaptic architecture, amplify neuronal stress, and destabilize neural networks prior to overt neurodegeneration [67–69]. This recognition fundamentally challenges the traditional view of microglia as passive responders to neuronal damage.

Microglia express mHTT from early developmental stages, and this expression exerts profound cell-autonomous effects on microglial physiology [68,69]. Transcriptomic analyses of human HD brain tissue and transgenic mouse models consistently reveal altered expression of genes involved in inflammatory signaling pathways, phagocytic function, and metabolic regulation [70,71]. These changes are not limited to late-stage disease but are detectable in presymptomatic animals and human tissue, indicating that microglial dysfunction likely contributes to early pathogenic processes rather than representing a secondary response solely.

Expression of mHTT interferes with key intracellular pathways regulating microglial activation thresholds, including dysregulation of NF- κ B signaling and impaired autophagic flux, which lower the threshold for activation and render microglia hypersensitive to otherwise benign stimuli [72,73]. One of the most compelling pieces of evidence for early microglial involvement comes from *in vivo* imaging studies using positron emission tomography (PET) with ligands targeting the translocator protein (TSPO), a marker of microglial activation.

Multiple independent studies using PET with TSPO ligands have reported elevated signal in presymptomatic HD gene carriers, with the degree of signal correlating with CAG repeat length and predicted time to disease onset [74,75]. It should be noted, however, that TSPO ligands do not exclusively bind activated pro-inflammatory microglia but also label homeostatic microglia, reactive astrocytes, and neurons under metabolic stress, limiting the mechanistic specificity of this readout [76,77]. With this caveat in mind, the detection of elevated TSPO signals in brain regions that do not yet show structural atrophy on conventional magnetic resonance imaging (MRI) supports the hypothesis that immune-related cellular changes may precede structural damage, though the precise cellular contributors and their functional significance remain to be determined [78,79]. Furthermore, it is

important to acknowledge that the myeloid compartment in the diseased CNS extends beyond parenchymal microglia to include border-associated macrophages (BAMs) residing in the meninges, choroid plexus, and perivascular spaces, as well as monocyte-derived macrophages that can infiltrate brain parenchyma under pathological conditions [80,81]. Many of the canonical markers used to study ‘microglial’ activation, such as TSPO, ionized calcium-binding adapter molecule 1 (Iba1), and cluster differentiation 68 (CD68), are also expressed by these macrophage populations, introducing a potential confound in bulk and imaging studies [76,77,81]. While single-nucleus RNA sequencing studies are beginning to resolve these distinct myeloid subsets [82], the specific contribution of BAMs and infiltrating macrophages to the neuroinflammatory milieu in HD remains an important and largely unexplored area for future investigations.

Post-mortem studies confirm these findings, demonstrating increased expression of microglial activation markers such as human leukocyte antigen DR isotype (HLA-DR) and CD68 in striatal and cortical tissue from individuals in early stages of disease [83,84]. These post-mortem findings should be interpreted with caution, however, given the confounds of agonal state, postmortem interval, and tissue pH, which can substantially alter glial gene expression profiles independently of disease-related changes.

While microglial populations in HD are transcriptionally heterogeneous, bulk analyses and post-mortem studies converge on a predominant pro-inflammatory bias, characterized by sustained production of mediators including IL-1 β , TNF- α , and IL-6 [85,86]. Unlike acute inflammatory responses that are tightly regulated and self-limiting, microglial cytokine release in HD is chronic and spatially diffuse, creating a low-grade neuroinflammatory milieu that pervades affected brain regions. This chronic inflammation exerts profound effects on neuronal function by modulating synaptic receptor trafficking, altering ion channel expression, and interfering with neurotrophic signaling pathways such as brain-derived neurotrophic factor signaling [87–89].

Over time, these effects degrade synaptic fidelity and plasticity, reducing the capacity of neural circuits to adapt to changing computational or behavioral demands. Importantly, chronic microglial activation also disrupts astrocytic and oligodendroglial functions, positioning microglia as important modulators within the broader cascade of neuroglial unit failure [45,90].

Beyond cytokine signaling, microglia play a direct role in shaping neural circuits through activity-dependent synaptic pruning mediated by complement cascade proteins [91,92]. In HD, this normally beneficial process becomes pathologically dysregulated. Evidence from animal models indicates that microglia excessively engulf synaptic elements, particularly within corticostriatal pathways that are critical for motor control and cognitive function [83,93]. Figure 2 illustrates this aberrant pruning mechanism in HD.

Altered expression and localization of complement proteins such as C1q and C3 contribute to inappropriate tagging of synapses for elimination, leading to progressive loss of functional connectivity that precedes neuronal death [94,95]. Two-photon imaging studies in living HD mice reveal increased frequency and duration of microglial contact with synapses and enhanced phagocytosis of synaptic material, providing direct visual evidence of aberrant synaptic pruning [96,97]. These multidimensional alterations—spanning activation threshold, cytokine secretion, complement-mediated pruning, metabolic reprogramming, and surveillance behavior—are systematically contrasted with homeostatic microglial properties in Table 1, which also situates each pathological change within the broader cascade of consequences that destabilize neural circuits prior to overt neurodegeneration.

The cascade of complement-mediated synaptic pruning is depicted in Figure 2, highlighting how C1q and C3b tag synapses for microglial engulfment.

Available evidence indicates that microglial dysfunction in HD extends to cellular metabolism. Expression of mHTT drives a metabolic shift toward glycolysis, which is characteristic of pro-inflammatory microglial states and limits the capacity of these cells to sustain homeostatic functions such as debris clearance and trophic support [98,99]. This metabolic reprogramming not only sustains chronic activation but may theoretically contribute to local energy imbalances in regions with high synaptic activity, though direct evidence for metabolic competition between microglia and neurons in the HD brain remains limited [100,101].

Aberrant Synaptic Pruning in Huntington's Disease

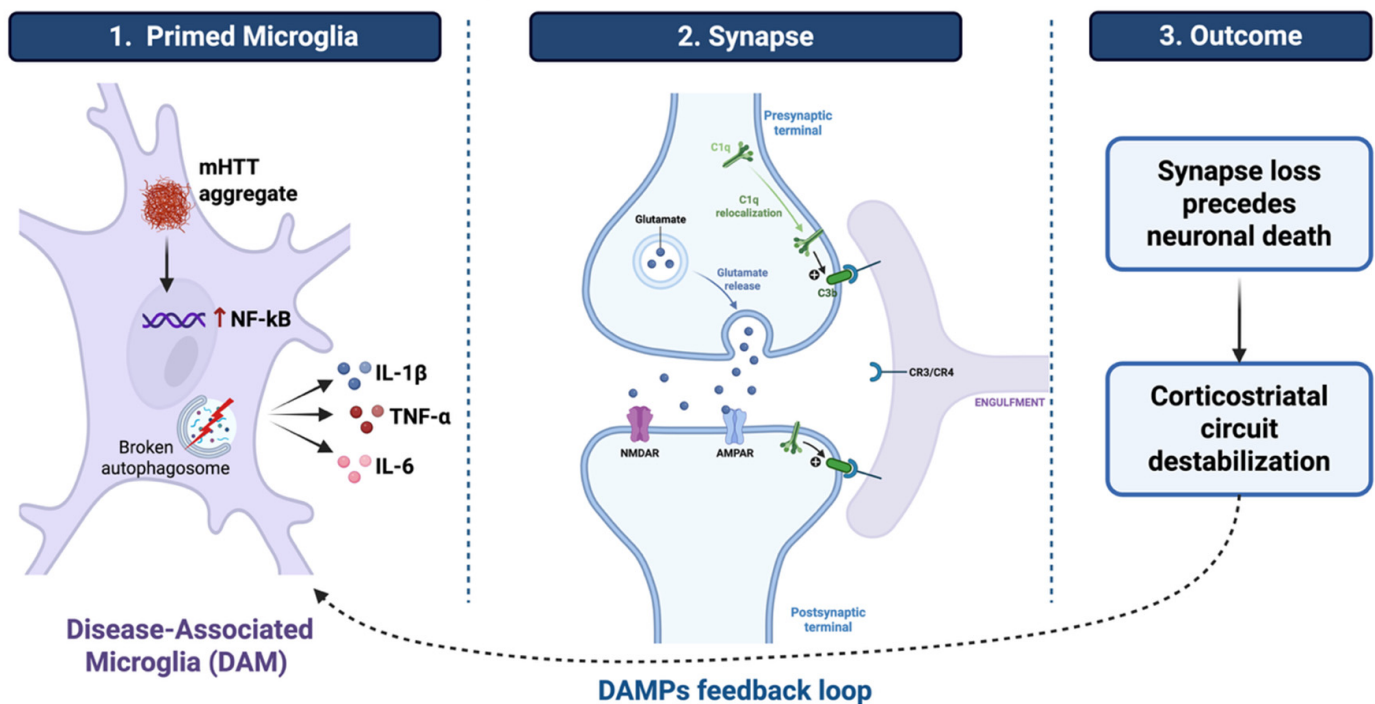


Figure 2. Aberrant complement-mediated synaptic pruning in Huntington's disease. mHTT-expressing disease-associated microglia (DAM) exhibit NF-κB activation, impaired autophagy, and increased pro-inflammatory cytokine release. Complement proteins C1q and C3b abnormally tag corticostriatal synapses, promoting excessive microglial engulfment through CR3/CR4 signaling. Progressive synapse loss destabilizes corticostriatal connectivity and precedes overt neuronal degeneration. Abbreviations: DAM, disease-associated microglia; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1β, interleukin-1 beta; C1q, complement component 1q; C3b, complement component 3b; CR3/CR4, complement receptors 3 and 4; NMDAR, N-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ↑, increasing; ↓, produces.

Notably, this central neuroinflammation does not occur in isolation: substantial evidence indicates a parallel, systemic inflammatory response in HD that may directly influence central glial activation, particularly under conditions of blood–brain barrier dysfunction. This peripheral dimension of HD pathology, including circulating biomarkers and immune cell alterations, is addressed in detail in Section 7.

Table 1. Microglial dysfunction in HD: homeostatic versus pathological states across functional domains.

Functional Consequence	Pathological State in HD	Homeostatic State	Feature	Key References
Chronic low-grade neuroinflammation; hypersensitivity to benign stimuli	Lowered by mHTT-driven NF- κ B dysregulation and impaired autophagic flux	High; requires DAMPs/PAMPs	Activation threshold	[64,66,68,69]
Disrupted synaptic receptor trafficking; impaired BDNF signaling; astrocyte A1 conversion	Sustained pro-inflammatory IL-1 β , TNF- α , IL-6 release	Anti-inflammatory; IL-10, TGF- β -dominant	Cytokine profile	[76–79,83]
Progressive loss of functional connectivity preceding neuronal death	Excess C1q/C3-mediated tagging; enhanced phagocytosis of corticostriatal synapses	Activity-dependent; selective and balanced via complement	Synaptic pruning	[74,86–90]
Potential contribution to local energy imbalance; exacerbation of local energy deficits in high-activity regions	Glycolytic shift driven by mHTT; limited capacity for debris clearance and trophic support	Oxidative phosphorylation; flexible substrate use	Metabolic state	[92–95]
Network-wide destabilization without overt neuronal death	Increased contact duration; biased toward inflammatory states; two-photon evidence of aberrant pruning	Continuous homeostatic monitoring; rapid process retraction/extension	Surveillance and synaptic contact	[45,88,90,91]
Associates with subsequent regional atrophy before structural MRI changes; not specific for pro-inflammatory states	Elevated in presymptomatic gene carriers; correlates with CAG repeat length and predicted onset	Low/baseline TSPO signal	In vivo activation (PET-TSPO)	[70–73]

Comparison of microglial properties under physiological homeostatic conditions and in the context of mHTT expression in HD, organized across six functional domains: activation threshold, cytokine secretion profile, synaptic pruning activity, metabolic state, surveillance behavior, and in vivo neuroimaging signal. Note that the PET-TSPO signal does not distinguish pro-inflammatory from homeostatic microglial activation states and should be interpreted accordingly. Abbreviations: DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; BDNF, brain-derived neurotrophic factor; TNF- α , tumor necrosis factor-alpha; TGF- β , transforming growth factor-beta; C1q/C3, complement cascade proteins; PET-TSPO, positron emission tomography with translocator protein ligand; mHTT, mutant huntingtin; CAG, cytosine-adenine-guanine repeat.

The therapeutic implications of microglial dysfunction are complex. Studies using colony-stimulating factor 1 receptor (CSF1R) inhibitors to deplete microglia in HD mouse models have yielded mixed results, with some studies reporting cognitive improvements while others find accelerated pathology, highlighting the context-dependent and potentially beneficial roles of microglia at different disease stages [102,103]. These findings argue against broad immunosuppression as a therapeutic strategy. Instead, effective interventions must aim to reprogram microglial states, restoring homeostatic surveillance and synaptic maintenance functions while limiting maladaptive pro-inflammatory activation [104,105]. The identification of specific microglial subpopulations that drive pathology versus those that support neuronal health remains an important area of ongoing investigation. Single-nucleus RNA sequencing has revealed that microglia are not a uniform population but encompass discrete transcriptional states, including disease-associated microglia (DAM) characterized by downregulation of homeostatic genes and upregulation of phagocytic and inflammatory programs [106–108]. Whether DAM and related subpopulations in HD exert net neurotoxic or neuroprotective effects, and how their representation evolves across

disease stages, are questions that the current review does not address but that are essential for designing subpopulation-targeted therapies.

4. Astrocytic Dysfunction: Metabolic and Homeostatic Collapse

Astrocytes, a major glial cell type in the CNS, are well-established regulators of neural circuit formation, function, and plasticity in both the developing and adult brain. They participate in this process through diverse mechanisms that induce the formation, elimination, and maturation of neuronal synapses [39,40]. Astrocytes are the primary regulators of extracellular homeostasis in the CNS, integrating metabolic support, neurotransmitter clearance, ion buffering, and synaptic modulation [109]. In HD, astrocytic dysfunction may represent a key transition point at which localized neuronal stress and microglial activation propagate into broader network instability [110]. Far from being passive structural cells, astrocytes expressing mHTT undergo profound functional reprogramming that undermines their capacity to sustain neuronal viability and synaptic function [111]. Astrocytes express mHTT throughout development and adulthood, and this expression induces cell-autonomous defects in key homeostatic pathways [112,113]. Transcriptomic and proteomic studies in HD models reveal extensive alterations in the expression of genes involved in glutamate transport, potassium channel function, mitochondrial metabolism, glycogen storage, and antioxidant defense [114–116]. These molecular changes translate into functional impairments that compromise the core homeostatic functions of astrocytes. Importantly, co-culture experiments demonstrate that astrocytic mHTT expression alone is sufficient in experimental systems to induce neuronal dysfunction even when neurons themselves do not express mHTT, providing evidence for non-cell-autonomous toxicity originating from astrocytes [22,23].

One of the most extensively characterized astrocytic defects in HD is impairment of glutamate clearance. Astrocytes normally maintain low extracellular glutamate concentrations through the high-affinity glutamate transporter EAAT2, also known as GLT-1, which is responsible for removing over 90% of synaptic glutamate [117]. In HD, EAAT2 expression and function are significantly reduced in both mouse models and human post-mortem tissue [118,119]. This reduction, which has been reported to reach 30 to 50% in striatal regions of R6/2 transgenic mice and in post-mortem human HD tissue [118,119], leads to prolonged elevation of synaptic glutamate concentrations. The consequences are twofold: sustained activation of NMDA and AMPA receptors increases intracellular calcium levels in neurons, promoting excitotoxic signaling cascades, and aberrant glutamate dynamics disrupt the temporal precision of synaptic transmission, degrading information processing within neural circuits [120,121]. The full spectrum of cell-autonomous homeostatic failures induced by mHTT expression in astrocytes—spanning glutamate clearance, potassium buffering, metabolic coupling, antioxidant defense, inflammatory modulation, and neurotrophic support—is systematically organized in Table 2, where each deficit is mapped to its molecular mediator and downstream consequence for neuronal viability and synaptic stability, underscoring how the convergence of these impairments generates a profoundly toxic microenvironment independently of direct neuronal mHTT toxicity.

Critically, EAAT2 dysfunction is detectable at early disease stages in rapidly progressing transgenic models such as R6/2 mice, before the appearance of an overt motor phenotype, and correlates with the severity of motor and cognitive deficits [122,123]; however, the compressed disease timeline of this model necessitates cautious interpretation when extrapolating these findings to the decades-long presymptomatic phase of human HD. Genetic or pharmacological enhancement of EAAT2 expression, for example through administration of ceftriaxone, ameliorates motor deficits and extends survival in HD mice, providing proof of principle that restoring astrocytic glutamate clearance can modify disease progression [124].

Astrocytes also play an essential role in regulating extracellular potassium concentrations through inwardly rectifying potassium channels, particularly Kir4.1 [117]. During neuronal activity, potassium ions are released into the extracellular space, and astrocytes rapidly buffer this potassium to prevent depolarization of neighboring neurons. In HD, Kir4.1 expression is significantly reduced in astrocytes, impairing activity-dependent potassium clearance [26,125]. The resulting elevation in extracellular potassium depolarizes neuronal membranes, increasing baseline excitability and lowering firing thresholds. This hyperexcitable state exacerbates the effects of glutamate dysregulation and amplifies synaptic instability [126,127]. Over time, chronic neuronal depolarization places additional metabolic stress on neurons, further eroding their functional resilience.

Beyond neurotransmitter and ion homeostasis, astrocytes are essential metabolic partners for neurons. Through mechanisms such as the astrocyte–neuron lactate shuttle, astrocytes take up glucose, convert it to lactate through glycolysis, and export lactate to neurons, where it is oxidized to support ATP production [34,128]. In HD, multiple aspects of astrocytic metabolism are disrupted. HD astrocytes exhibit mitochondrial dysfunction, reduced lactate production, impaired glycogen storage and mobilization, and compromised redox balance [129,130]. This metabolic uncoupling likely deprives neurons of critical energy substrates, particularly during periods of high synaptic activity when energy demands are greatest. Neurons operating under chronic energetic stress are less capable of maintaining ionic gradients, supporting synaptic transmission, and executing quality control mechanisms such as protein degradation and autophagy [131,132]. Moreover, metabolic deficits sensitize neurons to additional insults, including excitotoxic and inflammatory stressors, creating a state of heightened vulnerability.

Table 2. Astrocytic homeostatic failure in HD: molecular mediators, pathological impairments, and downstream neuronal consequences.

Downstream Effect on Neurons	Impairment in HD	Key Molecule	Homeostatic Function	Key References
Sustained NMDA / AMPA activation; calcium overload; excitotoxic cascades	30–50% expression reduction; detectable in presymptomatic R6/2 mice	EAAT2 (GLT-1)	Glutamate clearance	[45,47,48,106–108,112,113]
Neuronal membrane depolarization; increased baseline excitability; synergism with glutamate dysregulation	Significantly reduced expression; impaired activity-dependent clearance	Kir4.1 channel	Extracellular K ⁺ buffering	[25,115–117]
Energy substrate deprivation during synaptic activity; impaired proteostasis; heightened vulnerability to inflammatory stressors	Mitochondrial dysfunction; reduced lactate production; impaired glycogen mobilization	MCT1/MCT4, LDH, glycogen	Astrocyte–neuron lactate shuttle (ANLS)	[34,118–121,133]
Oxidative stress amplification; synergism with mitochondrial dysfunction	Compromised redox balance; reduced NRF2 target gene expression in mHTT astrocytes	NRF2, glutathione	Antioxidant defense	[104,119,121]

Table 2. Cont.

Downstream Effect on Neurons	Impairment in HD	Key Molecule	Homeostatic Function	Key References
Microglial re-activation; synaptic dysfunction. Inhibition of OPC differentiation; network repair failure	Predominantly pro-inflammatory reactive states (historically termed “A1-type”); reduced homeostatic gene expression; excess ECM secretion	Cytokines, DAMPs, ECM	Inflammatory modulation/ reactive astrocytosis	[26,27,41,47,122,123]
Reduced neuronal survival signaling; increased vulnerability of MSNs	Reduced trophic factor secretion; impaired BDNF release in mHTT-expressing astrocytes	BDNF, GDNF	Neurotrophic support	[83,101,103]
Summary of the six principal homeostatic functions maintained by astrocytes under physiological conditions, the molecular mediators responsible for each, the specific impairments induced by mHTT expression, and the resulting consequences for neuronal viability and synaptic stability. The convergence of these deficits generates a chronically toxic microenvironment that amplifies neuronal vulnerability independently of direct neuronal mHTT toxicity. Note: The term “A1-type” astrocytes is used here for historical reference. Current consensus guidelines discourage binary A1/A2 classification in favor of multidimensional and context-dependent phenotypic frameworks [133]. Abbreviations: EAAT2, excitatory amino acid transporter 2; GLT-1, glutamate transporter 1; Kir4.1, inwardly rectifying potassium channel 4.1; MCT, monocarboxylate transporter; LDH, lactate dehydrogenase; ANLS, astrocyte–neuron lactate shuttle; NRF2, nuclear factor erythroid 2-related factor 2; ECM, extracellular matrix; BDNF, brain-derived neurotrophic factor; GDNF, glial cell line-derived neurotrophic factor; DAMPs, damage-associated molecular patterns; OPC, oligodendrocyte progenitor cell; MSN, medium spiny neuron.				

Astrocytes in HD also exhibit reactive astrocytosis, a process characterized by morphological hypertrophy and transcriptional changes [134–137]. While some aspects of reactive astrocytosis may initially be protective, chronic activation drives astrocytes toward maladaptive phenotypes. Single-nucleus RNA sequencing studies of HD tissue reveal heterogeneous populations of reactive astrocytes with region-specific transcriptional signatures [138,139]. Current consensus frameworks distinguish multiple reactive astrocyte states that differ in their functional properties, neuroprotective capacity, and transcriptional signatures, underscoring that the terms “reactive” or “A1-type” inadequately capture the diversity of pathological astrocyte responses [133]. This complexity is summarized in Table 2, where the term ‘A1-type’ is retained solely for historical reference. In HD specifically, induced pluripotent stem cell (iPSC)-based modeling indicates that mHTT expression drives astrocytes toward aberrant developmental trajectories that may not map neatly onto canonical A1/A2 or neurotoxic/neuroprotective dichotomies [140]. Many reactive astrocytes in HD show reduced expression of genes associated with homeostatic functions and increased production of inflammatory mediators and extracellular matrix components. Rather than isolating damage and supporting repair, these chronically reactive astrocytes contribute to synaptic dysfunction, metabolic imbalance, and propagation of inflammation. Reactive astrocytosis in HD is particularly pronounced in the striatum, where astrocytes exhibit the most severe deficits in glutamate uptake and potassium buffering, aligning with the selective vulnerability of medium spiny neurons [141,142]. The regional specificity of astrocytic dysfunction reflects broader astrocytic heterogeneity. Astrocytes are not a uniform population but exhibit distinct transcriptional and functional profiles depending on their anatomical location [143,144]. In HD, striatal and cortical astrocytes display different patterns of gene expression changes and functional impairments, which may contribute to the characteristic pattern of regional vulnerability. Understanding this heterogeneity is essential for developing targeted therapeutic strategies that address region-specific as-

trocytic dysfunctions. Therapeutic strategies aimed at restoring astrocytic homeostasis represent promising avenues for disease modification. Beyond enhancing EAAT2 expression, approaches include restoring Kir4.1 function, correcting mitochondrial metabolism, replenishing glycogen stores, and modulating reactive astrogliosis to favor protective rather than harmful phenotypes [145,146]. Importantly, because astrocytic dysfunction contributes to creating a toxic microenvironment for neurons, interventions targeting astrocytes may provide benefits even in the presence of persistent neuronal mHTT expression. This principle is supported by glial replacement studies demonstrating that transplantation of healthy human glial progenitor cells can partially rescue neuronal function in HD models, although the magnitude and consistency of these effects vary across experimental conditions [25,147–149].

5. Oligodendrocyte Dysfunction: White Matter Degeneration and Metabolic Failure

For decades, HD was conceptualized primarily as a disorder of gray matter, with white matter changes considered secondary consequences of neuronal loss. This view is no longer fully supported by current evidence. Converging evidence from neuroimaging, transcriptomics, and experimental therapeutics now demonstrates that oligodendrocyte lineage dysfunction is an early and potentially causal contributor to disease progression [134,135]. The failure of oligodendrocytes to maintain myelin integrity and provide metabolic support precipitates an axonal energy crisis that destabilizes long-range neural connectivity well before overt neuronal death occurs. Longitudinal neuroimaging studies using diffusion tensor imaging have revealed that white matter abnormalities are among the earliest detectable brain changes in HD [29,138]. In premanifest gene carriers, DTI demonstrates reduced fractional anisotropy and increased radial diffusivity in major white matter tracts including the corpus callosum, internal capsule, and corticostriatal projections, with these changes appearing years or even decades before predicted motor onset [139,141]. These microstructural abnormalities correlate with measures of cognitive decline, CAG repeat length, and proximity to predicted phenoconversion, supporting the possibility that white matter pathology contributes to disease progression rather than representing a purely epiphenomenal consequence [150,151]. Critically, longitudinal studies demonstrate that white matter degeneration precedes and is associated with subsequent gray matter atrophy, challenging the traditional view that gray matter pathology drives disease progression [152,153].

At the cellular level, single-nucleus RNA sequencing studies of HD human post-mortem tissue and mouse models have revealed profound transcriptional dysregulation within the oligodendrocyte lineage [154,155]. Mature oligodendrocytes show consistent downregulation of core myelin structural genes, including myelin basic protein, proteolipid protein 1, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein [156]. Beyond structural components, oligodendrocytes exhibit dysregulation of lipid biosynthesis pathways essential for myelin membrane turnover and mitochondrial genes critical for ATP production [157]. This transcriptional reprogramming appears to shift oligodendrocytes into a metabolically compromised state, unable to meet the energetic demands of maintaining myelin sheaths over extensive axonal territories. Importantly, these transcriptional changes are not restricted to late-stage disease but are detectable in presymptomatic and early symptomatic stages, reinforcing the concept that oligodendroglial dysfunction contributes to early pathogenic processes [56,158]. Oligodendrocyte progenitor cells (OPC) represent the endogenous reservoir for myelin repair throughout adult life. In HD, OPC populations are numerically preserved or even expanded in affected brain regions, yet their capacity to differentiate into mature myelinating oligodendrocytes is markedly impaired [112,159,160]. Transcriptomic profiling reveals that HD OPCs display aberrant

activation of cellular stress pathways and repression of differentiation programs, creating a paradoxical state in which the brain contains abundant progenitors but lacks sufficient functional oligodendrocytes capable of sustaining axonal integrity [161,162]. The failure of OPC differentiation is further exacerbated by the inflammatory microenvironment generated by activated microglia and reactive astrocytes, which secrete factors that actively inhibit oligodendrocyte maturation [163,164]. This represents another example of how dysfunction in one glial cell type propagates to affect others within the integrated neuroglial unit. Pathological alterations affecting each stage of the oligodendrocyte lineage in HD—from the paradoxical differentiation block in numerically preserved OPCs, through the transcriptional collapse of mature myelinating cells, to the MCT1-dependent metabolic uncoupling that precipitates axonal energy crisis—are systematically delineated in Table 3, where each defect is aligned with its neuroimaging signature and clinical functional correlate, underscoring that oligodendrocyte lineage dysfunction is earlier and may be more mechanistically significant than previously appreciated.

Perhaps the most paradigm-shifting insight into oligodendroglial pathology in HD concerns the metabolic support function of oligodendrocytes. Beyond providing electrical insulation, oligodendrocytes are now recognized as essential metabolic supporters of axons [165,166]. Through expression of MCT1 in myelin sheaths, oligodendrocytes deliver lactate directly to axons, where it is imported via neuronal MCT2 and oxidized to fuel mitochondrial ATP production necessary for maintaining ionic gradients during action potential propagation [54,167]. This lactate-mediated metabolic coupling is particularly critical for long myelinated axons, which have limited access to blood-borne glucose and therefore depend heavily on oligodendrocyte-derived lactate. In HD, MCT1 expression is markedly reduced in oligodendrocytes in both mouse models and human tissue [54], a deficit that deprives axons of a key energy substrate and precipitates a state of axonal energy crisis (Figure 3). Chronically energy-deprived axons exhibit a cascade of pathological changes—including impaired action potential conduction, dysregulated calcium homeostasis, accumulation of abnormal cytoskeletal structures, and progressive degeneration in a dying-back pattern [150,151]—that directly link glial metabolic failure to the breakdown of neural circuit connectivity, independently of somatic neuronal death. The functional importance of oligodendrocyte-derived lactate has been demonstrated in non-HD systems through genetic experiments showing that selective disruption of MCT1 in oligodendrocytes is sufficient to cause axonal degeneration even in otherwise healthy tissue [38]. Whether analogous mechanisms operate with equivalent magnitude in the HD context remains to be directly established.

Clinical relevance of white matter pathology is suggested by studies reporting correlations between DTI metrics and cognitive performance in HD gene carriers [139,141], consistent with the hypothesis that disruption of long-range white matter tracts may contribute to the early cognitive and psychiatric manifestations of disease. Executive dysfunction, impaired processing speed, and behavioral dysregulation may reflect disruption of long-range connectivity mediated by white matter tracts rather than focal striatal pathology [168,169]. This observation is consistent with why cognitive and psychiatric symptoms often emerge as the earliest clinical manifestations of HD, preceding motor signs by years and causing substantial functional impairment.

The causal importance of oligodendroglial dysfunction in HD pathogenesis is strongly supported by glial replacement studies. Transplantation of healthy human glial progenitor cells into HD mouse models results in widespread engraftment and differentiation primarily into oligodendrocytes. This intervention restores myelin integrity, normalizes metabolic support through re-establishment of MCT1-mediated lactate delivery, and rescues motor and cognitive deficits [25,147]. Critically, these therapeutic benefits occur despite the con-

tinued presence of mHTT in host neurons, providing compelling functional evidence in preclinical systems that restoration of oligodendroglial support can non-cell-autonomously improve neuronal function and partially stabilize neural network activity. Recent mechanistic studies have identified oligodendroglial metabolic rescue as a major contributing mechanism underlying functional recovery in these experiments [31,52].

Experimental evidence in non-HD systems demonstrates that oligodendroglial MCT1 is essential for axonal metabolic support and that disruption of oligodendrocyte glycolysis can lead to secondary axonal degeneration [31,170]. In HD transplantation paradigms, the functional improvements observed following glial progenitor engraftment are consistent with restored metabolic coupling; however, direct loss-of-function MCT1 ablation studies within the specific context of HD glial transplantation remain limited. Thus, while MCT1-dependent lactate shuttling represents a mechanistically plausible mediator of rescue, definitive causal validation in HD models requires further targeted experimentation.

Table 3. Oligodendrocytes homeostatic failure in Huntington’s disease: molecular mediators, pathological impairments, and downstream neuronal consequences.

Neuroimaging/ Functional Correlate	HD-Associated Defect	Normal Rule	Cell Subtype	Key References
Paradoxical progenitor abundance without remyelination; no early structural MRI correlate	Numerically preserved/expanded but differentiation blocked; cellular stress pathway activation; maturation program repression	Reservoir for myelin repair; proliferation and differentiation on demand	OPC	[102,140–144]
Reduced FA and increased RD on DTI in corpus callosum and corticostriatal tracts; precedes gray matter atrophy	Downregulation of MBP, PLP1, MAG, MOG; impaired lipid biosynthesis; mitochondrial gene dysregulation	Electrical insulation via compacted myelin; maintenance of axonal conduction velocity	Mature myelinating oligodendrocyte	[26,28,51,130–132,137,138]
Impaired conduction; axonal Ca ²⁺ dysregulation; correlates with cognitive and psychiatric symptoms	Marked MCT1 reduction in HD models and human tissue; axonal energy crisis; dying-back degeneration pattern	Lactate delivery to axons via MCT1; critical support during action potential propagation	Metabolic oligodendrocyte (MCT1-expressing)	[38,49,50,165]
Longitudinal DTI changes precede volumetric loss; white matter abnormalities correlate with CAG repeat length	Transcriptional dysregulation detectable in presymptomatic and early symptomatic stages (snRNA-seq)	Transitional stage; initiates axonal contact and early myelination	Newly formed oligodendrocyte (NFO)	[26,52,137,139]

Characterization of the pathological alterations affecting each stage of the oligodendrocyte lineage in HD, from OPCs through newly formed and mature myelinating oligodendrocytes to the MCT1-expressing metabolic subtype. For each subtype, the table specifies its normal physiological role, the HD-associated molecular or cellular defect, and the corresponding neuroimaging or functional correlate. Collectively, these alterations establish that oligodendrocyte lineage dysfunction is an early, primary, and mechanistically decisive driver of white matter pathology and axonal energy failure in HD, preceding gray matter atrophy. Key references are provided for each subtype. Abbreviations: MBP, myelin basic protein; OPC, oligodendrocyte progenitor cell; PLP1, proteolipid protein 1; MAG, myelin-associated glycoprotein; MOG, myelin oligodendrocyte glycoprotein; MCT1, monocarboxylate transporter 1; DTI, diffusion tensor imaging; FA, fractional anisotropy; RD, radial diffusivity; snRNA-seq, single-nucleus RNA sequencing; Ca²⁺, calcium ions; NFO, newly formed oligodendrocyte; CAG, cytosine-adenine-guanine repeat.

MCT1-Dependant axonal metabolic uncoupling in Huntington's disease

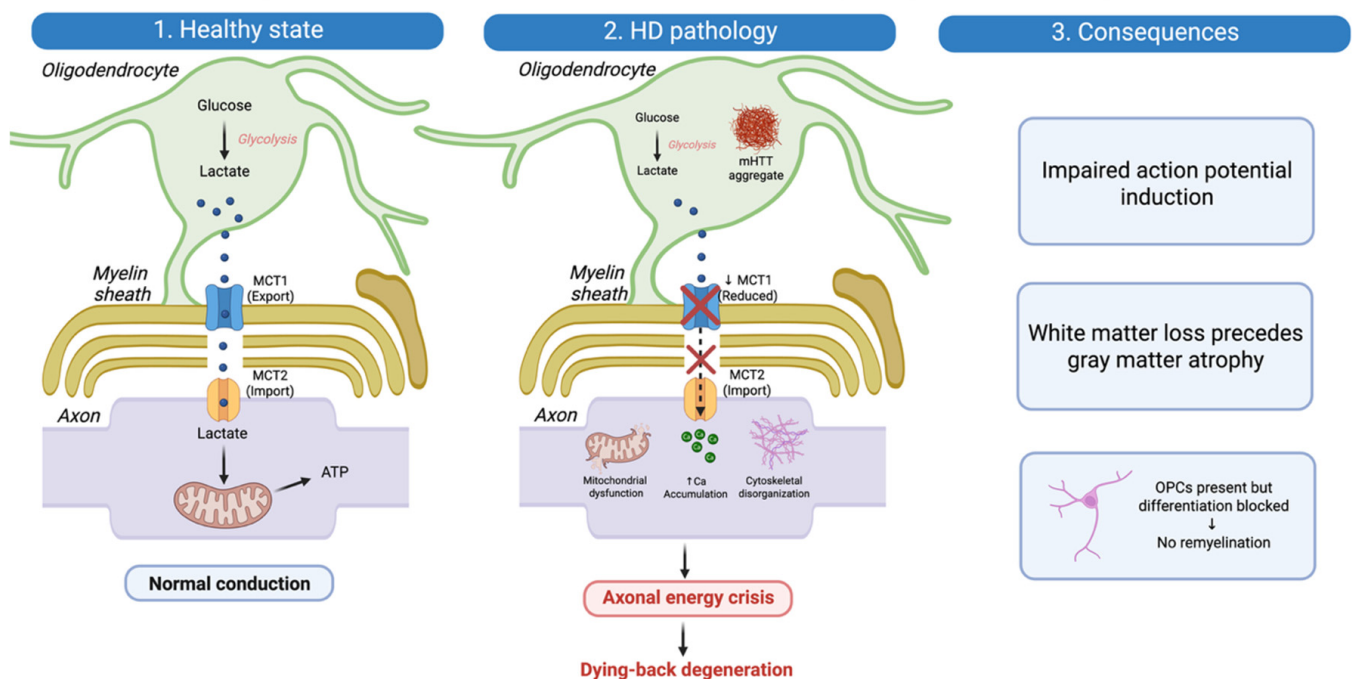


Figure 3. MCT1-dependent oligodendrocyte–axon metabolic coupling and axonal energy failure in Huntington's disease. Under physiological conditions, oligodendrocytes export lactate through MCT1 to support axonal ATP production via neuronal MCT2. In HD, mHTT-associated reduction in MCT1 impairs lactate delivery, promoting axonal energy crisis, mitochondrial dysfunction, Ca^{2+} dysregulation, cytoskeletal disorganization, and progressive dying-back degeneration. Consequences include impaired conduction, white matter loss, and failed remyelination due to blocked the oligodendrocyte progenitor cell (OPC) differentiation. Abbreviations: MCT1, monocarboxylate transporter 1; MCT2, monocarboxylate transporter 2; ATP, adenosine triphosphate; Ca^{2+} , calcium ion.

Within this systems-level framework, oligodendroglial metabolic support emerges as a key determinant of axonal stability and network coherence. Even modest disruptions in glial metabolic coupling may amplify synaptic and inflammatory stressors over time, contributing to progressive circuit destabilization. Collectively, the convergence of myelin structural failure, OPC differentiation block, and MCT1-dependent metabolic uncoupling positions oligodendrocyte lineage dysfunction as an early, mechanistically active, and therapeutically relevant contributor to HD pathogenesis. This perspective reframes HD not solely as a disorder of neuronal survival but as a long-evolving failure of neuroglial metabolic integration and directly motivates the evaluation of glial replacement strategies capable of restoring oligodendroglial function in the diseased brain, as examined in the following section.

6. Glial Replacement Therapy: From Proof of Principle to Clinical Translation

The recognition of HD as a disorder of neuroglial systems failure raises a critical therapeutic question: can replacing diseased glia with healthy cells rescue neuronal function and modify the disease course? This question has been addressed through a series of transplantation studies that collectively provide preclinical evidence for a functionally significant role of glial dysfunction in HD pathogenesis [25,31]. Human glial progenitor cells possess several biological properties that make them uniquely suited for therapeutic transplantation. When transplanted into neonatal or adult mouse brains, human glial progenitors demonstrate a competitive advantage over host mouse glia, progressively replacing en-

ogenous cells to generate chimeric brains with substantial human glial chimerism [171]. This competitive advantage likely reflects the larger size, more complex morphology, and enhanced signaling capacity of human glia compared to rodent glia [171,172].

Foundational proof-of-principle studies were conducted in the rapidly progressing R6/2 transgenic mouse model of HD. When healthy human glial progenitor cells were transplanted into neonatal R6/2 mice, donor cells migrated extensively and differentiated primarily into astrocytes and oligodendrocytes, achieving substantial glial chimerism in the striatum and cortex by adulthood [173]. In neonatal-engrafted R6/2 mice, transplantation of human glial progenitor cells resulted in widespread glial chimerization, delayed motor decline, and extended median survival by approximately 20–25% compared to non-engrafted littermates in the R6/2 model [25,171,174]. These findings should be interpreted in the context of the R6/2 model's compressed and artificially accelerated disease course, which limits direct extrapolation to human HD. Importantly, these benefits were observed in the context of early developmental engraftment, a condition that maximizes donor cell integration and may not directly extrapolate to adult-stage intervention. In addition, these benefits occurred despite the continued expression of mHTT in host neurons, providing strong preclinical evidence that correcting the glial microenvironment can non-cell-autonomously rescue neuronal function and modify disease progression at the organismal level.

Juvenile HD (JHD), defined as disease onset at ≤ 20 years of age, represents a rare and insufficiently characterized form of HD. Its clinical presentation differs from adult-onset disease, often with predominant behavioral and cognitive symptoms, which contributes to frequent misdiagnosis and significant diagnostic delay. These factors, together with JHD's low prevalence, have limited the availability of robust clinical and mechanistic data in this population. In this context, therapeutic approaches targeting the neuroglial component acquire relevance. Based on current preclinical evidence, glial replacement strategies may represent a plausible approach to modulating early network dysfunction and delaying disease progression, especially in forms with earlier onset [175]. Glial progenitor cell transplantation has been proposed as a disease-modifying strategy in HD; however, its application in JHD remains largely unexplored. The low incidence of the disease and the inherent challenges of designing clinical trials in pediatric populations have resulted in a significant gap in evidence. Additionally, the developing brain introduces variables that are not present in adult HD, including increased neuroplasticity, distinct microenvironmental dynamics, and ongoing neuroglial maturation. Within this framework, microglial-targeted or glial replacement approaches may be particularly relevant, given their role in synaptic regulation and immune homeostasis. Although direct evidence is currently lacking, these strategies represent a rational and promising avenue for future investigation in JHD [176].

A critical question for clinical translation is whether glial replacement can benefit already symptomatic brains rather than requiring intervention during development. This question was addressed using the more slowly progressing and genetically precise zQ175 knock-in mouse model. When human glial progenitors were transplanted into adult zQ175 mice after symptom onset, donor cells successfully migrated, differentiated, and integrated into host tissue despite the presence of pathology and neuroinflammation [177]. Transplanted animals showed significant improvements in motor coordination, reduced anxiety-like behaviors, and preservation of striatal volume compared to sham-transplanted controls [178]. These findings indicate that glial replacement can confer therapeutic benefits even after disease initiation, providing important proof of principle for adult intervention [31,177]. However, it should be acknowledged that engraftment efficiency, differentiation fidelity, and functional integration in symptomatic adult brains remain substantially inferior to neonatal conditions, and that the neuroinflammatory milieu

of the HD brain may further limit donor cell survival and function in ways not fully recapitulated by current models [31,155]. While early studies emphasized the contribution of astrocyte replacement to therapeutic benefit, recent mechanistic investigations have refined this view and identified oligodendroglial differentiation and metabolic rescue as major contributing mechanisms [25,31]. When transplanted glial progenitors differentiate in HD mouse brains, they preferentially adopt oligodendrocyte fates and remyelinate axons that have undergone demyelination [179]. Critically, donor-derived oligodendrocytes restore expression of MCT1 in myelin sheaths and re-establish lactate delivery to metabolically compromised axons [25,54]. This metabolic rescue normalizes axonal ATP levels, restores action potential conduction properties, and prevents axonal degeneration. Supporting evidence for the sufficiency and necessity of oligodendrocyte-mediated metabolic support comes from gain- and loss-of-function experiments in related systems: selective enhancement of MCT1 expression ameliorates relevant phenotypes, while genetic disruption of MCT1 in donor cells reduces therapeutic benefit [52]. However, definitive causal validation of this mechanism within the specific context of HD glial transplantation requires further targeted experimentation, as acknowledged in Section 5.

Beyond direct cellular replacement, transplanted glia exerts broader effects on the host brain microenvironment. Regions populated by donor cells show reduced microglial activation, normalization of astrocytic reactive states, and decreased expression of pro-inflammatory cytokines [42,165]. These changes suggest that healthy glia can reprogram the inflammatory milieu and interrupt the pathological feedback loops that perpetuate neuroglial unit failure. This systemic reprogramming likely contributes to therapeutic benefit beyond the direct effects of donor cell function. However, these preclinical results should be interpreted with appropriate caution. The R6/2 model employed in foundational studies overexpresses a truncated huntingtin fragment and displays an artificially rapid disease course not representative of human HD. Therapeutic benefits observed in neonatal chimeric models, where donor cells populate a highly plastic developing brain over weeks to months, may not be directly replicable in adult symptomatic brains where engraftment windows are narrower, the microenvironment is hostile, and the window for circuit repair may be partially closed [31,155]. These limitations reinforce the importance of adult-onset intervention studies and rigorous pre-clinical-to-clinical translation frameworks. Translation of glial replacement therapy to human HD faces substantial technical, biological, and regulatory challenges. The human brain volume of approximately 1400 cm³ vastly exceeds the mouse brain volume of approximately 0.4 cm³, representing a roughly 3500-fold difference in scale that poses fundamental challenges for achieving therapeutically meaningful glial chimerism through current delivery approaches [166]. Strategies to address this challenge include multisite stereotactic injection to broadly seed donor cells, intraventricular delivery combined with chemoattractant cues to guide migration, and development of biomaterial scaffolds that enhance cell survival and directed migration [54,167]. The full breadth of translational barriers that must be overcome before glial replacement therapy can advance to clinical application in HD—encompassing engraftment scale, immune compatibility, differentiation control, intervention timing, outcome measurement, and combination strategy—is critically appraised in Table 4, where each challenge is examined alongside its biological basis, proposed mitigation approaches, and an assessment of the current state of supporting evidence.

Table 4. Translational barriers and mitigation strategies for glial replacement therapy in HD.

Translational Challenge	Biological Basis	Proposed Strategies	Current Evidence Level	Key References
Engraftment scale	Human brain (about 1400 cm ³) vs. mouse brain (about 0.4 cm ³); need for widespread glial chimerism.	Multisite stereotactic injection; intraventricular delivery with chemoattractant cues; biomaterial scaffolds.	Preclinical only (mouse/NHP); no published human HD engraftment data.	[30,152–156,163,164]
Immune rejection	Allogeneic transplantation activates adaptive immunity; neuroinflammatory HD milieu may accelerate rejection.	HLA-matched donor cell banks; transient immunosuppression; autologous iPSC-derived glia with CRISPR CAG correction.	HLA banking: proof-of-concept; iPSC-CRISPR: in vitro/early preclinical.	[165–169]
Differentiation control and safety	Residual pluripotent cells risk teratoma; aberrant circuit integration could worsen function; neonatal vs. adult engraftment differ.	Rigorous differentiation protocols; negative selection against pluripotency markers; long-term follow-up registries.	Manufacturing protocols advancing; no long-term human safety data.	[151,168,169]
Timing of intervention	Self-sustaining pathological loops established before symptom onset; ethical concerns for invasive intervention in presymptomatic carriers.	Validated predictive biomarkers (NfL, DTI, TSPO-PET) for therapeutic window; risk-stratified trial design	Biomarker validation ongoing (TRACK-HD, PREDICT-HD cohorts).	[59,171,174,177–180]
Clinical outcome measures	Traditional motor scales (UHDRS) insufficiently sensitive to detect early systems-level repair or white matter changes.	DTI FA/RD, myelin water fraction imaging, fMRI connectivity, NfL and mHTT in CSF.	Biomarker-to-endpoint validation ongoing; regulatory guidance evolving.	[170–174,177]
Combination therapy integration	Glial replacement repairs microenvironment but does not eliminate neuronal mHTT toxicity; HTT-lowering does not restore established glial dysfunction	Sequential or concurrent HTT-lowering (ASOs, RNAi, CRISPR) plus glial replacement; mechanistic synergy studies needed	Conceptual framework established; no combined preclinical or clinical trial conducted	[181–183]

Appraisal of the six principal translational challenges that must be addressed before glial replacement therapy can advance to clinical application in HD: engraftment scale, immune rejection, differentiation control and safety, intervention timing, clinical outcome measurement, and integration into combination therapeutic strategies. For each challenge, the table identifies its biological basis, proposed mitigation approaches, and an honest assessment of the current level of supporting evidence. This framework underscores that glial replacement is best conceptualized not as a standalone intervention but as a component of combinatorial strategies that simultaneously address the genetic cause and the dysfunctional neuroglial microenvironment. Abbreviations: NHP, non-human primate; HLA, human leukocyte antigen; iPSC, induced pluripotent stem cell; CRISPR, clustered regularly interspaced short palindromic repeats; CAG, cytosine-adenine-guanine repeat; NfL, neurofilament light chain; DTI, diffusion tensor imaging; FA, fractional anisotropy; RD, radial diffusivity; fMRI, functional magnetic resonance imaging; CSF, cerebrospinal fluid; UHDRS, Unified Huntington's Disease Rating Scale; ASOs, antisense oligonucleotides; RNAi, RNA interference.

Immunological compatibility represents another major hurdle, as allogeneic cell transplantation risks immune rejection. Potential solutions include establishing HLA-matched donor cell banks, transient immunosuppression during the critical engraftment period, or generation of autologous cells through induced pluripotent stem cell technology combined with CRISPR-mediated correction of the CAG expansion [180,181]. Safety considerations are paramount. Ensuring complete differentiation of transplanted cells and eliminating any residual pluripotent cells that could give rise to teratomas requires rigorous cell manufacturing and quality control protocols [182]. Long-term safety monitoring over decades will

be essential to detect any late adverse effects, including tumorigenesis or aberrant circuit integration. Regulatory pathways for cell-based therapies are still evolving, and frameworks must be developed to evaluate interventions that aim to modify systems-level function rather than simply replacing lost cells [183]. Clinical trial design for glial replacement in HD must incorporate outcome measures appropriate for evaluating systems-level repair. Traditional motor rating scales such as the Unified HD Rating Scale, while important, may be insufficient to capture early improvements in network function, white matter integrity, or cognitive performance [184,185]. Neuroimaging biomarkers, including DTI metrics of white matter microstructure, myelin water fraction imaging to directly assess remyelination, and functional connectivity measures, may provide more sensitive readouts of therapeutic response [186,187]. Fluid biomarkers such as neurofilament light chain, which reflects axonal injury, and markers of metabolic function may complement imaging endpoints [188,189]. Patient selection and timing of intervention are critical strategic decisions. Given that glial dysfunction begins early and may establish self-reinforcing pathological loops, maximal therapeutic benefit may require intervention during premanifest or early symptomatic stages before substantial and potentially irreversible circuit dysfunction has occurred [63,170]. However, invasive cell transplantation in asymptomatic individuals raises significant ethical considerations regarding risk-benefit balance, informed consent, and appropriate patient counseling. Validated predictive biomarkers that identify individuals at imminent risk of phenoconversion will be essential for defining optimal therapeutic windows [190,191].

Importantly, glial replacement should not be viewed as a standalone therapy but as a component of combination strategies. Huntingtin-lowering therapies that reduce mHTT expression through antisense oligonucleotides, RNA interference, or gene editing address the genetic root cause but do not immediately repair established neuroglial dysfunction [10,192]. Conversely, glial replacement repairs the cellular microenvironment but does not eliminate ongoing mHTT toxicity in neurons. The optimal therapeutic approach likely involves combining genetic correction to prevent further damage with glial replacement to restore homeostasis and interrupt pathological feedback loops [193]. This dual strategy may provide synergistic benefits and offer significant potential for durable disease modification.

6.1. Mechanistic Integration with Huntingtin-Lowering Strategies

The neuroglial systems failure framework does not replace the centrality of mHTT as the initiating driver of pathology; rather, it reframes the therapeutic hierarchy. Huntingtin-lowering strategies aim to reduce the primary toxic insult across cell types, whereas glial-targeted interventions seek to restore the homeostatic environment required for circuit stability. These approaches are mechanistically complementary rather than competitive. Evidence from antisense oligonucleotide and RNA interference trials demonstrates that partial reduction in mHTT in humans is biologically feasible and can lower mutant protein levels in cerebrospinal fluid. However, the modest and sometimes inconsistent clinical responses observed to date suggest that reducing mHTT burden alone may not immediately reverse established systems-level dysfunction. Once inflammatory priming [42,43], astrocytic homeostatic collapse [111,114], and oligodendroglial metabolic uncoupling [54] are entrenched, circuit destabilization may persist despite partial mitigation of neuronal toxicity [10,18]. From a system's perspective, huntingtin-lowering may halt or slow further molecular damage, whereas glial-targeted interventions may be required to actively reconstitute metabolic coupling, normalize inflammatory tone, and restore synaptic stability. Sequential or concurrent therapeutic paradigms should therefore be explored in preclinical models, with careful evaluation of potential synergistic or antagonistic interactions [2,63]. Importantly, the optimal temporal sequence of such combination strategies remains unknown. Early

mHTT suppression could theoretically prevent the establishment of maladaptive neuroglial loops, while later-stage glial restoration may be necessary to repair already destabilized circuits. Determining the therapeutic window for each intervention represents a critical research priority [16,63].

6.2. Biological and Translational Limitations of Current Evidence

Although preclinical glial replacement studies provide compelling mechanistic support for the neuroglial systems failure model, several limitations must be explicitly acknowledged. First, foundational experiments were conducted primarily in transgenic mouse models, including R6/2 and zQ175. The R6/2 model overexpresses a truncated N-terminal huntingtin fragment and exhibits an accelerated disease course that does not recapitulate the decades-long prodromal phase of human HD. While zQ175 knock-in models provide improved genetic fidelity, species differences in glial biology, myelin dynamics, immune architecture, and brain size impose constraints on translational extrapolation [25,31,155]. Second, neonatal transplantation paradigms benefit from heightened developmental plasticity and reduced immune reactivity. Engraftment efficiency, differentiation fidelity, and long-range migration in adult symptomatic brains are substantially more limited. The inflammatory milieu present in established HD may further compromise donor cell survival and integration in ways not fully captured by current models [25,31,155]. Third, much of the human evidence supporting early glial involvement remains correlational. Neuroimaging, transcriptomic, and post-mortem studies strongly implicate glial dysfunction but do not yet provide definitive causal ordering between neuronal and glial pathology in vivo. Longitudinal multimodal biomarker studies will be required to resolve temporal relationships with greater precision [27–30,63]. These limitations do not invalidate the neuroglial framework; rather, they define the empirical work necessary to strengthen it.

6.3. Testable Predictions of the Neuroglial Systems Failure Model

A central strength of any systems-level framework lies in its capacity to generate falsifiable predictions. The neuroglial systems failure model yields several experimentally testable hypotheses: (1) Longitudinal reductions in oligodendroglial MCT1 expression would be expected to predict subsequent white matter microstructural decline and precede measurable gray matter atrophy in premanifest gene carriers; (2) Biomarkers reflecting astrocytic glutamate transport dysfunction or potassium buffering deficits should correlate more strongly with early cognitive impairment than with motor severity; (3) Microglial metabolic reprogramming toward glycolysis should temporally precede complement-mediated synaptic loss within corticostriatal circuits; (4) Combined huntingtin-lowering and glial restoration strategies should produce greater stabilization of white matter integrity and network connectivity than either intervention alone; and (5) Regions exhibiting the highest metabolic demand and densest long-range projections should display the earliest signatures of glial metabolic uncoupling. Failure of these predictions under rigorous longitudinal and mechanistic testing would require revision or refinement of the model. Their validation, conversely, would provide strong causal support for the neuroglial systems failure hypothesis.

7. Peripheral Immune and Inflammatory Alterations in HD

The evidence reviewed thus far has focused predominantly on the central nervous system; however, accumulating data indicate that peripheral systems may also contribute meaningfully to the neurodegenerative process in HD, and that peripheral measurements may offer an accessible window into the neuroglial milieu. Plasma glial fibrillary acidic

protein (GFAP), an astrocyte-specific intermediate filament protein, is elevated in HD patients across multiple disease stages [194], directly extending the neuroglial framework discussed throughout this review to a peripherally accessible biomarker. Plasma neurofilament light chain (NfL)—a core structural component of the neuronal cytoskeleton released into circulation following axonal injury—increases even more markedly than GFAP in the same patient cohorts [194], suggesting that axonal damage may be more readily detectable peripherally than astrocytic reactivity at comparable disease stages.

Peripheral immune alterations in HD were first reported in the 1980s, when changes in circulating and tissue-resident immune cell populations were documented in HD patients [195]. More recent work has identified alterations in circulating B- and T-lymphocyte populations that appear to scale with mutant huntingtin (mHTT) levels and to become more pronounced with advancing disease stage [196]. Notably, mHTT aggregates have been detected in peripheral organs—including the liver, kidney, spleen, and pancreas—in post-mortem analyses of HD patients, indicating that mHTT-associated proteotoxicity is not confined to the central nervous system, although this evidence remains limited to post-mortem material and warrants confirmation in living patients through accessible biomarkers [197].

The status of peripheral cytokines in HD remains a topic of active debate. There is substantial evidence for a parallel, systemic inflammatory response in HD, characterized by elevated plasma levels of pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β , even in premanifest gene carriers [198]. However, several studies have failed to detect consistent elevations of inflammatory markers in patient serum, whereas others report detectable plasma IL-6 and IL-8, with plasma IL-6 levels increasing progressively across disease stages [196,199,200]. In contrast, elevated levels of multiple interleukins have been consistently reported in experimental HD models [196], raising the possibility that peripheral cytokine signatures in human HD may be more variable or stage- and cohort-dependent than those observed in preclinical systems. Under conditions of blood–brain barrier (BBB) dysfunction, which has been documented in HD [69], these peripheral signals can directly activate or prime central glial cells, and proteomic profiling of plasma has revealed neuroinflammatory signatures that correlate with disease stage, offering a more accessible window into the neuroglial milieu than CSF or imaging-based methods [85].

Finally, the relationship between gut microbiota composition and peripheral cytokine production remains largely unexplored in HD; one study reported an association between specific bacterial taxa and increased IL-4 levels [201], raising the possibility of a gut–immune–brain axis that merits dedicated investigation in this disease. Taken together, these findings indicate that a comprehensive understanding of glial dysfunction in HD must integrate both central and peripheral immune compartments.

8. Conclusions and Future Directions

HD can be conceptualized as a progressive destabilization of the neuroglial ecosystem. Neuronal mHTT expression initiates molecular pathology, but converging preclinical and correlational human evidence suggests that the trajectory of regional vulnerability and clinical progression is substantially influenced by the functional integrity of astrocytes, microglia, and oligodendrocyte lineage cells. The convergence of synaptic dysregulation [23,25], chronic immune priming [44,198], and metabolic uncoupling [25,38] may generate self-reinforcing feedback loops that transform molecular perturbation into network-level dysfunction. While mechanistic and proof-of-principle evidence from animal models is substantial, converging human data from neuroimaging, transcriptomics, and biomarker studies increasingly support early glial involvement. Nevertheless, the precise causal ordering and temporal hierarchy between neuronal and glial pathology in humans re-

mains to be fully resolved, and continued integration of longitudinal human datasets [27,28] with mechanistic experimental systems [29,30,63] will be required to validate and refine the causal architecture of this framework. Experimental transplantation studies in HD models indicate that restoration of glial support can partially rescue neuronal and network dysfunction despite persistent neuronal mHTT expression [25,31]. Although these findings do not negate the central genetic cause of disease and must be interpreted with caution given the limitations of neonatal chimeric models and the compressed disease course of transgenic systems, they suggest that circuit-level stabilization may be achievable through repair of neuroglial interactions in contexts amenable to therapeutic intervention. Effective disease modification may ultimately require coordinated strategies that simultaneously attenuate mHTT toxicity and restore glial-mediated homeostasis. Huntingtin-lowering approaches [10,192] combined with interventions aimed at preserving white matter integrity, metabolic coupling, and inflammatory balance [193] may offer synergistic benefit.

A cross-cutting theme of this review is that glial dysfunction is not uniform across the brain but exhibits regional specificity that mirrors the selective vulnerability of neural circuits. For instance, striatal astrocytes display the most profound deficits in glutamate uptake (via EAAT2) and potassium buffering (via Kir4.1), directly exacerbating the excitotoxic stress on their synaptic partners, the medium spiny neurons [141,142]. In contrast, cortical astrocytes may exhibit a more pronounced reactive transcriptional shift, with increased expression of inflammatory mediators that compromise synaptic plasticity in corticostriatal projection neurons [138]. These divergent astrocytic phenotypes likely arise from region-intrinsic developmental programs, local neuronal signals, and differing metabolic demands. Similarly, the role of oligodendrocytes is most critical in long-range white matter tracts, such as the corpus callosum and internal capsule, where the failure of MCT1-mediated metabolic support precipitates an axonal energy crisis in vulnerable projections [150,151]. Comparing these regional gliodegenerative profiles suggests a model in which the unique ‘functional specialization’ of a glial cell, dictated by its local circuit, determines its primary mode of failure in HD: astrocytes failing at synaptic homeostasis in the striatum, and oligodendrocytes failing at metabolic support in white matter tracts. Understanding this regional interplay is crucial for designing circuit-targeted therapeutic interventions.

Looking forward, several priorities emerge. First, the development and validation of biomarkers that report on glial function, white matter microstructure, metabolic coupling, and inflammatory state will be essential for identifying therapeutic windows and monitoring response. Second, refinement of delivery technologies and cell engineering strategies will be necessary to determine whether glial replacement approaches can be safely translated to the adult human brain. Third, mechanistic studies using human-induced pluripotent stem cell-derived systems, organoids, and advanced in vivo models will be critical to clarify species-specific aspects of glial biology. Fourth, clinical trial design may benefit from incorporating systems-level endpoints, including network connectivity and metabolic imaging, rather than relying exclusively on measures of neuronal loss. And fifth, peripheral immune dysregulation and gut microbiota-derived metabolites have been shown to modulate central microglial activation in other neurodegenerative contexts [202,203], representing a comparatively underexplored dimension of neuroglial pathology in HD that warrants more systematic investigation. The neuroglial systems framework developed here proposes that HD is not solely a disorder of neuronal toxicity but may represent a progressive failure of integrated cellular homeostasis. Whether similar principles of metabolic coupling, inflammatory amplification, and circuit destabilization extend across other neurodegenerative disorders remains an open and testable question. By integrating glial biology, systems neuroscience, and translational strategy, the neuroglial framework developed here offers experimentally testable predictions and a mechanistically

grounded rationale for combination of therapeutic approaches. Whether similar principles of metabolic uncoupling, inflammatory amplification, and circuit destabilization extend across other neurodegenerative disorders remains an open question, positioning HD as a potential model disease for glial-centric intervention strategies.

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Abbreviations

The following abbreviations are used in this manuscript:

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANLS	astrocyte–neuron lactate shuttle
ASO	antisense oligonucleotide
ATP	adenosine triphosphate
BDNF	brain-derived neurotrophic factor
C1q	complement component 1q
C3	complement component 3
Ca ²⁺	calcium ion
CAG	cytosine-adenine-guanine trinucleotide repeat
CD68	cluster of differentiation 68
CNS	central nervous system
CRISPR	clustered regularly interspaced short palindromic repeats
CSF	cerebrospinal fluid
CSF1R	colony-stimulating factor 1 receptor
DAM	disease-associated microglia
DAMP	damage-associated molecular pattern
DTI	diffusion tensor imaging
EAAT2	excitatory amino acid transporter 2
ECM	extracellular matrix
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
GDNF	glial cell line-derived neurotrophic factor
GLT-1	glutamate transporter 1
HD	Huntington’s disease
HLA	human leukocyte antigen
HLA-DR	human leukocyte antigen DR isotype
HTT	huntingtin
IL-1 β	interleukin-1 beta
IL-6	interleukin-6
IL-10	interleukin-10
iPSC	induced pluripotent stem cell

K ⁺	potassium ion
Kir4.1	inwardly rectifying potassium channel 4.1
LDH	lactate dehydrogenase
MAG	myelin-associated glycoprotein
MBP	myelin basic protein
MCT1	monocarboxylate transporter 1
MCT2	monocarboxylate transporter 2
MCT4	monocarboxylate transporter 4
mHTT	mutant huntingtin
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MSN	medium spiny neuron
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NFO	newly formed oligodendrocyte
NfL	neurofilament light chain
NHP	non-human primate
NMDA	N-methyl-D-aspartate
NRF2	nuclear factor erythroid 2-related factor 2
OPC	oligodendrocyte progenitor cell
PAMP	pathogen-associated molecular pattern
PET	positron emission tomography
PLP1	proteolipid protein 1
RD	radial diffusivity
RNAi	RNA interference
snRNA-seq	single-nucleus RNA sequencing
TGF-β	transforming growth factor-beta
TNF-α	tumor necrosis factor-alpha
TSPO	translocator protein
UHDRS	Unified Huntington's Disease Rating Scale

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