How could recognition and treatment of Developmental Dysregulation of Innate Immunity and Mitochondrial Dysfunction in Justice-Involved People with Neurodevelopmental and Psychiatric Disorders improve outcomes?

Targeting innate immune and mitochondrial dysfunction could improve neurodevelopmental, psychiatric, and justice-related outcomes through early recognition and precision interventions

Justice-involved people with neurodevelopmental and psychiatric disorders show elevated rates of immune dysregulation, mitochondrial dysfunction, and developmental adversity, yet these biological substrates remain largely unrecognized in criminal justice settings (Borschmann et al., 2020; Rice et al., 2023; Crole-Rees et al., 2025). The evidence base spans three interconnected facets: innate immune dysregulation in neurodevelopment, mitochondrial dysfunction as a shared mechanism, and screening and treatment gaps in justice-involved populations.

Innate Immune Dysregulation in Neurodevelopmental Disorders

Dysfunction in innate immune signaling pathways — including Toll-like receptors, cytokines, inflammasomes, and microglial phagocytic signals — has been functionally linked to autism, schizophrenia, and other neurodevelopmental disorders (Zengeler & Lukens, 2021). Repeated evidence of aberrant innate cellular function, neuroinflammation, and microglia activation has been observed in both human and animal models of ASD, often correlating with worsening behaviors (Hughes et al., 2022). Innate immune dysfunction also overlaps transdiagnostically across psychotic and affective disorders, with elevated inflammatory cytokines and altered monocyte function found in schizophrenia, bipolar disorder, and major depressive disorder (Hughes & Ashwood, 2020).

Developmental stressors — including immune challenge, psychosocial stress, and drug exposure — induce long-lasting innate immune memory in microglia through epigenetic reprogramming, priming the brain for later disease (Carloni et al., 2021). Childhood maltreatment, prevalent among justice-involved populations, produces a consistent transdiagnostic increase in pro-inflammatory immune markers in psychiatric patients, with IL-6 identified as a significant mediator between early trauma and adult psychiatric diagnosis (Van Den Noortgate et al., 2025).

Immune Mechanism	Disorder Association	Evidence Type
Microglial synaptic pruning	Autism, schizophrenia	Human and animal (Zengeler & Lukens, 2021)
TLR/cytokine hypo-responsiveness	PANS, neurodevelopmental	PBMC stimulation assay (Han et al., 2025)
Maternal immune activation	ASD, ADHD, schizophrenia	Preclinical models (Yong et al., 2025)
Childhood maltreatment → IL-6 elevation	Transdiagnostic psychiatric	Meta-analysis (n=12,141) (Van Den Noortgate et al., 2025)

FIGURE 1 Innate immune mechanisms linked to neurodevelopmental and psychiatric disorders across developmental stages.

Mitochondrial Dysfunction as a Shared Mechanism

Mitochondrial dysfunction is a critical factor in the etiology of ASD, ADHD, and Rett syndrome, characterized by impaired mitochondrial dynamics, oxidative stress, and defective mitophagy (Yang et al., 2025). Inflammatory mediators from activated microglia alter mitochondrial function, while damaged mitochondria release DAMPs — including mitochondrial DNA, TFAM, and cardiolipin — that further activate pro-inflammatory microglial processes in a self-perpetuating cycle (Gevezova et al., 2023; Cieślik et al., 2023; Yong et al., 2025). This "mitoflammation" cascade links innate immune dysregulation and mitochondrial dysfunction as mutually reinforcing pathological processes (Cieślik et al., 2023; Zawadzka et al., 2021).

Maternal immune activation produces developmentally staged mitochondrial damage: early ROS generation via NADPH oxidase in fetuses and neonates transitions to persistent mitochondrial membrane depolarization, reduced ATP, and electron transport chain downregulation in adolescence (Cieślik et al., 2023). Clinical features of mitochondrial dysfunction in ASD include neurodevelopmental regression triggered by inflammatory events, seizures, motor delays, and fatigue — presentations that may be misattributed to behavioral noncompliance in justice settings (Rose et al., 2018).

Several therapeutic approaches show preclinical promise:

- **Antioxidants and biogenesis stimulators** — resveratrol and curcumin induce mitochondrial biogenesis and alleviate oxidative stress (Yang et al., 2025)- **PGC-1α and NRF2 pathway targeting** — regulators of mitochondrial biogenesis and antioxidant defense show promise in preclinical models (Yang et al., 2025)- **Mitophagy enhancement** — preserving fusion-fission cycles or enhancing mitophagy reduces accumulation of defective mitochondria (Yang et al., 2025)- **IVIG treatment** — reversed dysregulated ribosomal, epigenetic, and immune signaling pathways in PANS patients (Han et al., 2025)## Screening and Treatment Gaps in Justice-Involved Populations

People with neurodevelopmental conditions are over-represented in criminal justice settings, yet PTSD and other comorbidities remain under-detected and under-treated, with prevalence estimates ranging from 4.6% to 80% due to inconsistent screening (Crole-Rees et al., 2025). Comprehensive assessment appears superior to brief screening for identifying neurodevelopmental disorders in youth justice populations (Holland et al., 2021). Justice-involved young people experience disproportionate rates of mental illness compounded by developmental adversity, yet community mental health services remain largely inaccessible to them (Rice et al., 2023).

Detained adolescents show high lifetime prevalence of mental disorders (up to 95%), substance use disorders (22–96%), self-harm (12–65%), and neurodevelopmental disabilities (2–47%), with social and structural drivers of poor health overlapping with factors associated with justice involvement (Borschmann et al., 2020). Improving detection of mental and physical disorders, providing appropriate interventions during detention, and optimizing transitional health care after release could improve health outcomes for these vulnerable young people (Borschmann et al., 2020).

Gap	Current State	Potential Improvement
Immune/microbial screening	Not performed in justice settings	Biomarker-guided early identification (Yang et al., 2025)
Mitochondrial assessment	Non-specific biomarkers, under-recognized	Buccal enzymology, fatty acid biomarkers (Rose et al., 2018)

Gap	Current State	Potential Improvement
Trauma-informed immune care	IL-6 mediation unaddressed	Anti-inflammatory/immune-modulating therapies (Van Den Noortgate et al., 2025)
Transitional care	Fragmented post-release	Integrated mental health and justice services (Rice et al., 2023)

FIGURE 2 Screening and treatment gaps for immune and mitochondrial dysfunction in justice-involved populations.

Recognizing innate immune and mitochondrial dysfunction in justice-involved people with neurodevelopmental and psychiatric disorders could enable biomarker-guided screening, immune-modulating and mitochondria-targeted treatments, and integrated transitional care — addressing biological substrates that current justice and mental health systems entirely overlook (Novellino et al., 2020; Yang et al., 2025; Rice et al., 2023).

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