Yes, dysregulated microglia can **cause mitochondrial dysfunction** in neurodevelopmental and psychiatric disorders, contributing to **metabolic impairment**, neuroinflammation, and disease pathology.

1. Introduction

Microglia, the brain's resident immune cells, are increasingly recognized as key regulators of neurodevelopment and contributors to the pathogenesis of neurodevelopmental and psychiatric disorders. Recent research demonstrates that dysregulated or overactivated microglia can directly impair mitochondrial function in neurons and glial cells, leading to metabolic disturbances, oxidative stress, and neuroinflammation. These processes have been implicated in disorders such as schizophrenia, autism spectrum disorder (ASD), depression, bipolar disorder, and Alzheimer's disease. Mechanistic studies reveal that microglial activation—triggered by genetic factors, environmental insults (e.g., maternal immune activation), or chronic stress—can disrupt mitochondrial bioenergetics, promote the release of reactive oxygen species (ROS), and alter synaptic function. Furthermore, impaired mitophagy in microglia exacerbates the accumulation of damaged mitochondria, amplifying inflammatory responses and neuronal injury (Park et al., 2020; He et al., 2021; Mora-Romero et al., 2024; Li et al., 2022; Zawadzka et al., 2021; Agrawal & Jha, 2020; Yang et al., 2025; Liu et al., 2025; Nakamura et al., 2025; Miao et al., 2025). The interplay between microglial dysfunction and mitochondrial impairment is thus a central theme in understanding the etiology of various brain disorders.

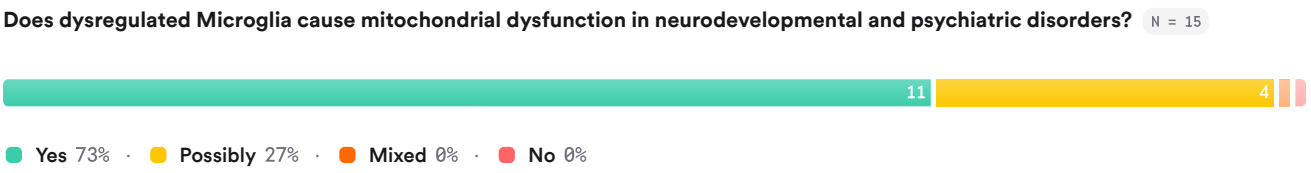

FIGURE 1 Consensus meter visualizing agreement on whether dysregulated microglia cause mitochondrial dysfunction in these disorders.

2. Methods

A comprehensive literature search was conducted across over 170 million research papers indexed in Consensus—including Semantic Scholar, PubMed, and other databases—to identify studies examining the relationship between microglial dysregulation and mitochondrial dysfunction in neurodevelopmental and psychiatric disorders. A total of 394,705 papers were initially identified; after multi-phase filtering for relevance and quality, 50 papers were included in this review.

Search Strategy

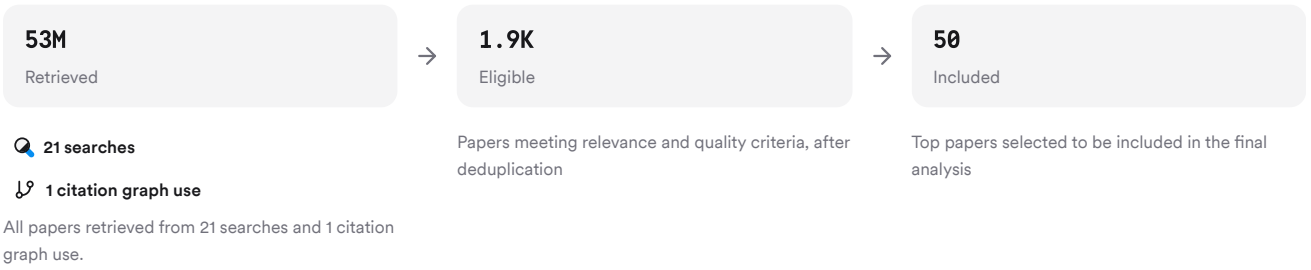

FIGURE 2 Flow diagram showing paper selection from identification to inclusion.

Six unique search strategies were used to capture foundational concepts, mechanistic pathways, alternate terminology, contrasting perspectives, related constructs (e.g., astrocyte involvement), and disorder-specific evidence.

3. Results

3.1 Evidence Linking Microglial Dysregulation to Mitochondrial Dysfunction

Multiple studies demonstrate that activated or dysregulated microglia can impair mitochondrial function in neurons and glial cells through several mechanisms:

- Activated microglia disturb metabolic pathways and impair mitochondrial function in cortical interneurons derived from both healthy controls and schizophrenia patients; these deficits are more persistent in schizophrenia-derived cells (Park et al., 2020).
- Disruption of signaling pathways (e.g., IL-33-ST2-AKT) impairs microglial metabolic adaptation during development, leading to dystrophy, impaired synaptic function, behavioral abnormalities, and increased seizure susceptibility (He et al., 2021).
- In animal models with targeted complex I deficiency in microglia, widespread glial dysfunction occurs alongside behavioral deficits and early lethality (Mora-Romero et al., 2024).

3.2 Mechanisms: Oxidative Stress & Mitophagy Defects

Microglial activation leads to increased production of ROS and pro-inflammatory cytokines:

- Mitochondrial DNA damage triggers further inflammation via TLR/NLRP3 inflammasome activation (Li et al., 2022; Zawadzka et al., 2021).
- Defective mitophagy results in accumulation of damaged mitochondria within microglia; this amplifies inflammatory signaling (e.g., cGAS-STING pathway) (Wang et al., 2023; Liu et al., 2022; Thangaraj et al., 2018).
- Environmental insults (e.g., maternal immune activation or chronic stress) induce a cycle of oxidative stress–mitochondrial dysfunction–neuroinflammation (Zawadzka et al., 2021; Ulecia-Morón et al., 2025).

3.3 Disorder-Specific Findings

- **Schizophrenia:** Persistent metabolic deficits due to activated microglia are more pronounced in patient-derived neurons; postmortem studies show reduced mitochondria number/volume in microglia (Park et al., 2020; Bast et al., 2025; Uranova et al., 2023; Uranova et al., 2024; Uranova et al., 2020; Laricchiuta et al., 2024).
- **Autism Spectrum Disorder:** Maternal immune activation induces microglial activation/oxidative stress/mitochondrial dysfunction; similar findings are reported for ASD brain tissue (Zawadzka et al., 2021; Gevezova et al., 2020; Sterben et al., 2025).
- **Depression & Bipolar Disorder:** Microglial metabolic reprogramming via mitochondrial dysfunction contributes to depressive-like behaviors; interventions targeting mitochondria can reverse some symptoms (Liu et al., 2025; Culmsee et al., 2019; Li et al., 2022; Cyrino et al., 2021).
- **Alzheimer's Disease:** Microglial mitochondrial dysfunction precedes neuroinflammation; targeting these pathways shows therapeutic promise (Li et al., 2022; Agrawal & Jha, 2020; Yang et al., 2025; Fairley et al., 2021; Li et al., 2024).

3.4 Bidirectional Interactions & Feedback Loops

There is evidence for a vicious cycle where:

- Mitochondrial dysfunction increases ROS production → activates microglia → further impairs mitochondria.
- Damaged mitochondria released from microglia propagate inflammation by activating astrocytes or neighboring neurons (Joshi et al., 2019).

Results Timeline

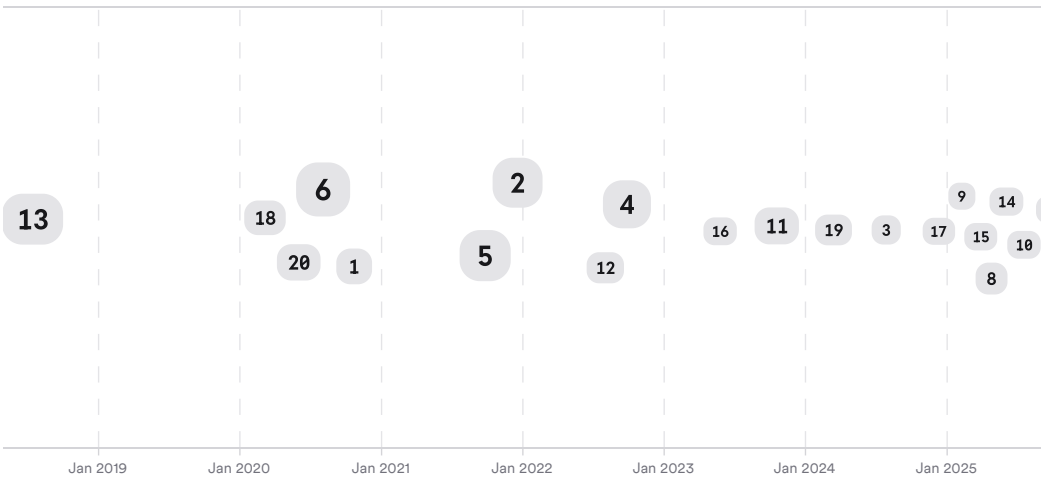

FIGURE 3 Timeline showing publication dates for key findings on the link between dysregulated microglia and mitochondrial dysfunction. Larger markers indicate more citations.

Top Contributors

Type	Name	Papers
Author	N. Uranova	(Fairley et al., 2021; ■ Joshi et al., 2019; Lukens & Eyo, 2022)
Author	Junnan Li	(■ Uranova et al., 2023)
Author	Yun Li	(Li et al., 2022)
Journal	*Frontiers in Psychiatry*	(Ulecia-Morón et al., 2025; Lukens & Eyo, 2022; ■ Hu et al., 2024)
Journal	*Nature neuroscience*	(Park et al., 2020; Culmsee et al., 2019)
Journal	*Journal of Neuroinflammation*	(Li et al., 2022; Thangaraj et al., 2018)

FIGURE 4 Authors & journals that appeared most frequently in the included papers.

4. Discussion

The reviewed literature provides strong evidence that dysregulated or overactivated microglia can cause or exacerbate mitochondrial dysfunction across multiple brain cell types—especially during critical periods of development or under pathological conditions such as infection or chronic stress (Park et al., 2020; He et al., 2021; ■ Zawadzka et al., 2021). This relationship is bidirectional: while dysfunctional mitochondria can activate inflammatory responses in microglia (and vice versa), persistent inflammation further damages mitochondria through oxidative stress mechanisms (Li et al., 2022; Sarkar et al., 2017). The consequences include impaired synaptic development/function (notably GABAergic signaling), altered neuronal connectivity (as seen in schizophrenia/ASD), cognitive decline (Alzheimer's), mood disturbances (depression/bipolar disorder), and even early lethality when glial energy metabolism is severely compromised (Park et al., 2020; ■ Mora-Romero et al., 2024; Agrawal & Jha, 2020).

However, some nuances remain: not all studies find identical patterns across cell types or disorders; genetic background modulates vulnerability to persistent metabolic deficits after inflammatory insults (Park et al., 2020). There is also emerging evidence that interventions targeting either mitochondrial health or inflammatory signaling can partially reverse these effects—suggesting potential therapeutic avenues but also highlighting the complexity of these interactions (■ Li et al., 2022).

Claims & Evidence Table

Claim	Evidence Strength	Reasoning	Papers
Dysregulated/activated microglia cause mitochondrial dysfunction	Strong	Multiple mechanistic studies show direct impairment of neuronal/glial mitochondria by activated microglia	(Park et al., 2020; He et al., 2021; ■ Mora-Romero et al., 2024)
Mitochondrial dysfunction amplifies neuroinflammation via ROS/NLRP3	Strong	Strong experimental support for feedback loop between ROS production/inflammasome activation	(Li et al., 2022; Sarkar et al., 2017)
Persistent metabolic deficits are more severe with genetic risk	Moderate	Schizophrenia-derived neurons show prolonged deficits after removal of activated-microglia-conditioned medium	(Park et al., 2020)
Mitophagy defects exacerbate inflammation/neurodegeneration	Moderate	Impaired clearance of damaged mitochondria leads to sustained inflammatory signaling	(Wang et al., 2023; ■ Liu et al., 2022)

Claim	Evidence Strength	Reasoning	Papers
Microglial-mitochondrial crosstalk is central across multiple disorders	Moderate	Evidence spans ASD/schizophrenia/depression/AD but with some heterogeneity	(Zawadzka et al., 2021; Agrawal & Jha, 2020; Gevezova et al., 2020)
Some aspects remain poorly understood/contradictory	Weak	Not all cell types/disorders show identical patterns; some null findings exist	(Lukens & Eyo, 2022)

FIGURE Key claims and support evidence identified in these papers.

5. Conclusion

Current evidence strongly supports a causal role for dysregulated microglia in inducing mitochondrial dysfunction within the context of neurodevelopmental and psychiatric disorders. This interaction drives a cascade involving oxidative stress, impaired synaptic development/function, chronic inflammation, and ultimately behavioral/cognitive pathology.

Research Gaps

Despite substantial progress elucidating these mechanisms—especially using animal models/cell cultures—gaps remain regarding human-specific pathways (especially longitudinal data), disorder specificity beyond ASD/schizophrenia/depression/AD, sex differences, developmental timing windows for vulnerability/resilience factors.

Research Gaps Matrix

Topic/Outcome	Animal Models	Human Postmortem Studies	Cell Culture/In Vitro	Genetic Risk Stratification
Microglial-induced mito dysfunction	18	7	12	5
Mitophagy defects	10	2	8	GAP
Disorder-specific findings	20	10	6	4
Sex differences	GAP	GAP	GAP	GAP

FIGURE Matrix showing study designs versus research topics/outcomes; gaps highlight underexplored areas such as sex differences.

Open Research Questions

Future research should focus on clarifying human-specific mechanisms—including longitudinal trajectories—and identifying precise molecular targets for intervention.

Question	Why
How do genetic risk factors modulate susceptibility to persistent metabolic deficits after early-life immune activation?	Understanding gene-environment interactions could inform personalized prevention/intervention strategies for at-risk individuals.

Question	Why
Can targeted therapies restoring mitophagy or reducing oxidative stress reverse established behavioral/cognitive symptoms?	Demonstrating reversibility would provide proof-of-concept for new treatments across multiple disorders.
What are the sex-specific differences in microglial-mitochondrial crosstalk during brain development?	Sex differences may explain variability in disorder prevalence/severity but remain largely unexplored experimentally.

FIGURE Open questions highlight future directions for mechanistic research on this topic.

In summary: Dysregulated microglia play a causal role in driving mitochondrial dysfunction across several neurodevelopmental and psychiatric conditions—a process central to disease pathogenesis but still requiring deeper mechanistic understanding for effective intervention strategies.

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