Relationships among Microglial dysregulation, Hyper and Hypo Connected Brain Networks and Mitochondrial Dysfunction and Glutamate Excitotoxicity

Microglia, Network Connectivity, Mitochondria and Glutamate: How They Interact

Research across neurodevelopmental and psychiatric/degenerative disorders converges on a shared theme: **microglial dysregulation, glutamatergic imbalance, mitochondrial dysfunction, and network hyper/hypoconnectivity are tightly interlinked** rather than separate problems.

Microglial Dysregulation and Network (Hyper/Hypo) Connectivity

- Microglia regulate **synaptic pruning, maturation, and excitatory synapse properties**, so altered signaling can yield defective functional connectivity and silent or immature synapses (Furlan et al., 2024; Paolicelli & Ferretti, 2017; Basilico et al., 2018; Mordelt & De Witte, 2023; Matuleviciute et al., 2023).
- Perturbed microglia during development produce long-lasting **synaptic defects and network vulnerability** typical of ASD, ADHD, schizophrenia and other NDDs (Furlan et al., 2024; Iovino et al., 2020; Paolicelli & Ferretti, 2017; Lukens & Eyo, 2022; Mordelt & De Witte, 2023; Matuleviciute et al., 2023).
- In MDD and AD, in vivo microglial activation correlates with **reduced structural integrity, small-worldness and local efficiency** of networks, and with abnormal insula–subgenual ACC connectivity (Cakmak et al., 2022; Leng et al., 2022).

Examples of Microglia–Connectivity Links

Context	Microglial change	Network effect	Citations
MDD (PET–MRI)	↑ TSPO signal (sgACC)	Altered sgACC–insula connectivity	(Cakmak et al., 2022)
AD	↑ microglial activation	↓ structural & functional efficiency	(Leng et al., 2022)
NDD models	Developmental microglial perturbation	Impaired FC reminiscent of autism	(Paolicelli & Ferretti, 2017; Mordelt & De Witte, 2023)

FIGURE 1 Associations between microglia and network connectivity

Glutamate Excitotoxicity, Mitochondria and Microglia

- Loss of glutamate homeostasis → **extrasynaptic glutamate rise**, Ca^{2+} overload, mitochondrial abnormalities, oxidative stress, and neuronal atrophy/death (excitotoxicity) (Nicosia et al., 2024; McGrath et al., 2022; Olloquequi et al., 2018; Vaglio-Garro et al., 2024; Wu et al., 2025; Verma et al., 2022).
- Mitochondrial TCA enzyme **OGDHC** is inhibited by inflammatory NO/ROS, reducing mitochondrial glutamate uptake and **promoting toxic (extrasynaptic GluN2B) glutamate signaling**, ferroptosis and further mitochondrial dysfunction (Vaglio-Garro et al., 2024).
- Microglia and astrocytes control glutamate clearance; their dysfunction causes **spillover, extrasynaptic NMDA/AMPA activation, neuroinflammation and network dysregulation** (Zádori et al., 2018; McGrath et al., 2022; Zhu et al., 2023; Vaglio-Garro et al., 2024; Czapski & Strosznajder, 2021).
- In AD, kynurenine pathway metabolite **quinolinic acid** promotes glutamate excitotoxicity, ROS, lipid peroxidation, and microglial neuroinflammation, directly linking mitochondria-related tryptophan metabolism to glutamate toxicity and microglial activation (Zádori et al., 2018).

From Cellular Pathology to Hyper/Hypoconnected Circuits

- Excess glutamate and impaired microglial pruning can drive **aberrant E/I balance** and "homeostasis network collapse," contributing to both hyper- and hypoconnected states seen in AD and psychiatric illnesses (McGrath et al., 2022; Czapski & Strosznajder, 2021).
- Microglial dyshomeostasis alone (not just as a response to damage) can initiate **synaptic and connectivity abnormalities** and behavioral phenotypes across NDD and neurodegenerative models (Furlan et al., 2024; Iovino et al., 2020; Mordelt & De Witte, 2023; Matuleviciute et al., 2023).

Conclusion

Across conditions, **microglial dyshomeostasis, mitochondrial impairment, and glutamate excitotoxicity form a feed-forward loop that disrupts synaptic pruning, glutamatergic balance, and network organization**. This loop can manifest as both hyper- and hypoconnected brain networks, helping unify cellular pathology with large-scale connectivity changes in neurodevelopmental and psychiatric disorders.

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