Metabolic challenges produced as a result of Maternal Immune Activation and Compensatory Hyper-Connected connected Brain Regions

Metabolic challenges from maternal immune activation and hyperconnected brain networks

Maternal immune activation (MIA) alters offspring metabolism at multiple levels (mitochondria, glucose, lipids), while compensatory hyperconnectivity in brain networks increases local energy demand. Together, they suggest a brain that is both developmentally at risk and metabolically "expensive" to run.

Metabolic Effects of Maternal Immune Activation

Mitochondrial dysfunction and oxidative stress

- Prenatal LPS-induced MIA in rats causes **increased NOX activity and ROS**, early **mitochondrial membrane depolarization** and **reduced ATP**, progressing in adolescence to persistent ROS overproduction, downregulated electron transport chain complexes, and neuroinflammation, forming a "vicious cascade" of mitochondrial damage and oxidative stress in brain (Cieślik et al., 2023).
- Poly(I:C)-MIA in mice leads in adult offspring to **increased mitochondrial respiration and mass** in prefrontal cortex and amygdala, but **reduced coupling efficiency and higher leak respiration**, indicating compensatory but inefficient mitochondria and sex-dependent vulnerability (Hahn et al., 2020).
- Review work links MIA to **mitochondrial dysfunction, oxidative stress, and metabolic disease** risk in offspring (Shimizu et al., 2023).

Glucose and systemic metabolic programming

- In rats, LPS-MIA disrupts **maternal glucose homeostasis** and, postpartum, drives increased hepatic gluconeogenesis, impaired pancreatic function, and higher plasma glucose; NAC partially corrects early but not late alterations (Afşar et al., 2026).
- Human birth-cohort data show higher **placental inflammatory and oxidative stress markers** associated with higher fasting glucose and prediabetes in 5–6-year-old children, implicating intrauterine immune/oxidative milieu in long-term **glucose dysregulation** (Zhou et al., 2024).
- A primate MIA model shows widespread changes in **lipid, amino acid, and nucleotide metabolism** across plasma, CSF, gut tissues, with links to behavior and cytokines, supporting broad metabolic reprogramming (Boktor et al., 2022).

Broader metabolic disease risk

- MIA is associated with offspring **cardiovascular and metabolic diseases** in addition to neurodevelopmental and immune disorders (Shimizu et al., 2023).
- Reviews of gestational metabolic conditions (e.g., gestational diabetes) describe **insulin signaling disruption, mitochondrial dysfunction, oxidative stress, and chronic inflammation**, mechanisms overlapping with MIA-related pathways (Torres-Torres et al., 2024).

Key offspring metabolic challenges after MIA

Level	Main challenge	Citations
Brain mitochondria	Persistent ROS, low ATP, inefficient respiration	(Cieślik et al., 2023; Hahn et al., 2020; Shimizu et al., 2023)
Glucose control	↑ hepatic gluconeogenesis, beta-cell dysfunction, prediabetes risk	(Afşar et al., 2026; Zhou et al., 2024)
Systemic metabolism	Altered lipid/amino acid profiles, immunometabolic reprogramming	(Boktor et al., 2022; Alharithi et al., 2025; Shimizu et al., 2023)

FIGURE 1 Core metabolic disturbances linked to MIA

Metabolic Costs of Compensatory Hyperconnectivity

- After brain injury, **hyperconnectivity** (increased functional coupling) is a common adaptive response but must negotiate a trade-off between **metabolic cost and communication efficiency**; hubs are used because they are relatively efficient, yet chronic hyperconnectivity may expose them to **elevated metabolic stress** and secondary pathology over the lifespan (Hillary & Grafman, 2017).
- Longitudinal TBI data show early widespread **increased network strength and cost**, then more focal hyperconnectivity in default-mode and attentional hubs, where **higher connection cost predicts worse cognition**, indicating that compensation comes with sustained energy demands (Roy et al., 2017).
- Functional and metabolic imaging in healthy adults shows that during demanding tasks, **reconfiguration of functional networks tightly couples to increased regional glucose consumption**, especially in feedforward task-relevant pathways (Gasser et al., 2024).
- Resting-state work shows that **connector hubs** (linking networks) have higher glucose uptake than other regions, underscoring that highly connected areas are energetically expensive (Palombit et al., 2022).
- Ageing studies demonstrate that supporting hub connectivity consumes a **large fraction of a limited glucose budget**, and reallocation of this cost is linked to cognitive decline (Deery et al., 2024).

Intersection: MIA, Metabolism, and Hyperconnected Networks

- MIA produces a brain with **fragile mitochondrial function, oxidative stress, and altered systemic metabolism** (Cieślik et al., 2023; Boktor et al., 2022; Hahn et al., 2020; Shimizu et al., 2023).
- Hyperconnected or hub-heavy network organization, even when compensatory, **raises local energy demands and metabolic stress** in precisely the regions critical for integration (Hillary & Grafman, 2017; Roy et al., 2017; Gasser et al., 2024; Deery et al., 2024; Palombit et al., 2022).
- Together, this suggests that individuals exposed to MIA may face **reduced metabolic reserves** at the cellular and systemic level while needing to sustain **high-cost network configurations** to maintain function, potentially increasing vulnerability to neurodevelopmental disorders and later-life neurodegeneration (Cieślik et al., 2023; Boktor et al., 2022; Hahn et al., 2020; Deery et al., 2024; Shimizu et al., 2023).

Conclusion

Research indicates that maternal immune activation programs long-lasting **mitochondrial dysfunction, oxidative stress, and glucose and lipid abnormalities** in offspring. Separately, compensatory hyperconnectivity and hub-centered network organization are **metabolically costly**, concentrating glucose use and stress in key brain regions. The convergence of these processes implies that brains shaped by MIA may be forced to operate demanding, hyperconnected networks on an already compromised metabolic foundation, heightening risk for cognitive and psychiatric difficulties across the lifespan.

References

Afşar, E., Öz, M., Özkan, E., & Eranıl, I. (2026). Maternal Immune Activation Disrupts Autophagy and Glucose Homeostasis: Experimental Evidence for the Protective Effects of N-Acetylcysteine on Maternal and Offspring Outcomes in a Rat Model. *Journal of Applied Toxicology, 46*, 1372 - 1388. https://doi.org/10.1002/jat.70063

Alharithi, Y., Phillips, E., Wilson, T., Couvillion, S., Nicora, C., Darakjian, P., Rakshe, S., Fei, S., Counts, B., Metz, T., Searles, R., Kumar, S., & Maloyan, A. (2025). Metabolomic and transcriptomic remodeling of bone marrow myeloid cells in response to maternal obesity.. *American journal of physiology. Endocrinology and metabolism*. https://doi.org/10.1152/ajpendo.00333.2024

Boktor, J., Adame, M., Rose, D., Schumann, C., Murray, K., Bauman, M., Careaga, M., Mazmanian, S., Ashwood, P., & Needham, B. (2022). Global metabolic profiles in a non-human primate model of maternal immune activation: implications for neurodevelopmental disorders. *Molecular Psychiatry*, 1 - 15. https://doi.org/10.1038/s41380-022-01752-y

Cieślik, M., Zawadzka, A., Czapski, G., Wilkaniec, A., & Adamczyk, A. (2023). Developmental Stage-Dependent Changes in Mitochondrial Function in the Brain of Offspring Following Prenatal Maternal Immune Activation. *International Journal of Molecular Sciences, 24*. https://doi.org/10.3390/ijms24087243

Deery, H., Liang, E., Siddiqui, M., Murray, G., Voigt, K., Di Paolo, R., Moran, C., Egan, G., & Jamadar, S. (2024). Reconfiguration of metabolic connectivity in ageing. *Communications Biology, 7*. https://doi.org/10.1038/s42003-024-07223-0

Gasser, E., Schaer, R., Mueller, F., Bernhardt, A., Lin, H., Arias-Reyes, C., & Weber-Stadlbauer, U. (2024). Prenatal immune activation in mice induces long-term alterations in brain mitochondrial function. *Translational Psychiatry, 14*. https://doi.org/10.1038/s41398-024-03010-x

Hahn, A., Breakspear, M., Rischka, L., Wadsak, W., Godbersen, G., Pichler, V., Michenthaler, P., Vanicek, T., Hacker, M., Kasper, S., Lanzenberger, R., & Cocchi, L. (2020). Reconfiguration of functional brain networks and metabolic cost converge during task performance. *eLife, 9*. https://doi.org/10.7554/elife.52443

Hillary, F., & Grafman, J. (2017). Injured Brains and Adaptive Networks: The Benefits and Costs of Hyperconnectivity.. *Trends in cognitive sciences, 21 5*, 385-401. https://doi.org/10.1016/j.tics.2017.03.003

Palombit, A., Silvestri, E., Volpi, T., Aiello, M., Cecchin, D., Bertoldo, A., & Corbetta, M. (2022). Variability of regional glucose metabolism and the topology of functional networks in the human brain. *NeuroImage*, 119280. https://doi.org/10.1016/j.neuroimage.2022.119280

Roy, A., Bernier, R., Wang, J., Benson, M., French, J., Good, D., & Hillary, F. (2017). The evolution of cost-efficiency in neural networks during recovery from traumatic brain injury. *PLoS ONE, 12*. https://doi.org/10.1371/journal.pone.0170541

Shimizu, Y., Sakata-Haga, H., Saikawa, Y., & Hatta, T. (2023). Influence of Immune System Abnormalities Caused by Maternal Immune Activation in the Postnatal Period. *Cells, 12*. https://doi.org/10.3390/cells12050741

Torres-Torres, J., Monroy-Muñoz, I., Pérez-Durán, J., Solís-Paredes, J., Camacho-Martinez, Z., Baca, D., Espino-Y-Sosa, S., Martínez-Portilla, R., Rojas-Zepeda, L., Borboa-Olivares, H., & Reyes-Muñoz, E. (2024). Cellular and Molecular Pathophysiology of Gestational Diabetes. *International Journal of Molecular Sciences, 25*. https://doi.org/10.3390/ijms252111641

Zhou, J., Teng, Y., Ouyang, J., Wu, P., Tong, J., Gao, G., Yan, S., Tao, F., & Huang, K. (2024). Associations of Placental Inflammation and Oxidative Stress Biomarkers with Glucolipid Metabolism in Children: A Birth Cohort Study in China. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease, 13*. https://doi.org/10.1161/jaha.124.035754