What are the tensions between Mitochondrial Bioenergetics, Hyper and Hypo Brain Connectivity and Neuro=Developmental and Psychiatric Disorders and Aging?

How energy, connectivity, and lifespan brain disorders pull against each other

Across neurodevelopment, adulthood, and aging, the brain must balance **limited mitochondrial energy supply** with the costs of maintaining large-scale networks. The "tensions" arise when mitochondrial bioenergetics can no longer fully support patterns of hyper- and hypoconnectivity seen in neurodevelopmental and psychiatric disorders and in aging brains.

Energy Demands of Brain Hubs and Long-Range Connectivity

- High-degree hubs (default mode, multisensory, association networks) have **dense synapses, long axons and high ATP demand**, making them especially vulnerable when mitochondrial number/function decline with age (Watanabe et al., 2021; Yang et al., 2023; Valenti & Vacca, 2023).
- Glucose hypometabolism and degraded mitochondrial metabolism are consistent signatures of aging and major neurodegenerative diseases, particularly in connectomic hubs (Yang et al., 2023; Valenti & Vacca, 2023; Cheng et al., 2022).
- Between-network and long-range connectivity consume more energy than local connections; mitochondrial dysfunction or mtDNA variants preferentially reduce these links, especially between dorsal attention and language networks in young adults, suggesting early "premature aging" of cognition-related circuits (Marečková et al., 2026).

Energy–Connectivity Trade-offs

Situation	Connectivity pattern	Mitochondrial / metabolic tension	Citations
Healthy aging	Global metabolic connectivity ↓; hubs preserved structurally but metabolically stressed	Mitochondrial number/function decline, risk of hub failure	(Watanabe et al., 2021; Mertens et al., 2022; Yang et al., 2023; Valenti & Vacca, 2023)
Neurodegeneration	Mixed hyper+hypoconnectivity, mainly hypoconnectivity	Hyperconnectivity as short-term compensation but metabolically costly	(Yang et al., 2023; Herzog et al., 2022; Hillary & Grafman, 2017; Aswendt & Hoehn, 2022)
Young "at-risk" adults	Selective between-network hypoconnectivity	Higher mtDNA functional impact + epigenetic aging	(Marečková et al., 2026)

FIGURE 1 Energy limits shaping hub and network connectivity across life.

Neurodevelopmental and Psychiatric Disorders: Shared but Divergent Pressures

- In Down, Rett, and Fragile X syndromes, mitochondrial bioenergetic dysfunction is proposed as an **early, causal contributor** to impaired neuroplasticity and circuit formation, underlying intellectual disability and atypical connectivity (Fernandez et al., 2019).
- In 22q11.2 deletion, mitochondrial oxidative stress in layer 2/3 neurons reduces long-range cortical projections, producing **cortical under-connectivity and cognitive impairment**; antioxidant rescue of mitochondria normalizes connectivity and behavior (Kim et al., 2019).
- Large cross-diagnostic fMRI work in ASD, ADHD and schizophrenia finds a **shared abnormal connectivity pattern** plus disorder-specific directions (hypoconnectivity in ASD vs hyperconnectivity in ADHD), with implicated genes enriched for synaptic, immune-metabolic and **mitochondrial** pathways (Diao et al., 2026).
- Major psychiatric disorders show impaired oxidative phosphorylation, altered mitochondrial dynamics and brain energy deficits; authors propose **circuit-specific mitochondrial dysfunction at sensitive developmental stages** as a driver of distinct connectivity phenotypes (Kim et al., 2019; Nunes et al., 2025).

Hyper- vs Hypoconnectivity as Adaptive vs Maladaptive Under Energy Constraints

- Following injury or degeneration, **functional hyperconnectivity** can be a compensatory response that improves communication but **raises metabolic load** on hubs; chronic hyperconnectivity may over time contribute to secondary pathology and eventual hypoconnectivity (Hillary & Grafman, 2017; Aswendt & Hoehn, 2022; Herzog et al., 2022).
- High-order connectivity analyses in Alzheimer's disease and frontotemporal dementia reveal **co-existing hyper- and hypoconnectivity**, with hyperconnectivity often focal in hubs (amygdala, insula, frontal regions) and hypoconnectivity dominating overall—consistent with early over-engagement followed by energy-limited failure of broader networks (Herzog et al., 2022).
- In depression, distinct hypoconnectivity and hyperconnectivity subtypes centered on default-mode epicenters show different molecular signatures (glial vs neuronal genes, distinct transmitter systems), highlighting that similar symptoms can emerge from **different connectivity–metabolism configurations** (Li et al., 2025).

Aging, Neurodevelopmental Disorders, and "Premature" Aging

- Axonal and synaptic mitochondria show region-specific aging changes: reduced numbers and impaired ATP/Ca^{2+} handling in hippocampal boutons vs increased numbers in more resilient regions, pointing to **uneven energy stress across circuits** (Yang et al., 2023).
- Reviews on brain aging in NDDs argue that early mitochondrial dysfunction, oxidative stress and inflammation may **shift aging trajectories**, contributing to earlier cognitive decline and vulnerability to classic neurodegenerative diseases (De Aguiar Da Costa et al., 2026; Fernandez et al., 2019).
- mtDNA variants with higher functional impact are linked to **lower between-network connectivity and accelerated epigenetic aging** in young adults, suggesting mitochondrial bioenergetics can embed aging pressures into connectivity decades before overt disease (Marečková et al., 2026).

Tensions in Summary

The core tensions highlighted by these studies are:

- **Energy supply vs network complexity:** Mitochondrial decline (or genetically impaired bioenergetics) clashes with the high energetic cost of maintaining and flexibly reconfiguring large-scale networks, especially hubs and long-range connections (Yang et al., 2023; Fernandez et al., 2019; Valenti & Vacca, 2023; Marečková et al., 2026).
- **Short-term compensation vs long-term vulnerability:** Hyperconnectivity may temporarily preserve function after insult or in early disease but imposes extra metabolic stress on already fragile mitochondria, contributing to later hypoconnectivity and degeneration (Hillary & Grafman, 2017; Aswendt & Hoehn, 2022; Herzog et al., 2022).
- **Shared mechanisms vs heterogeneous outcomes:** Across neurodevelopmental and psychiatric disorders, mitochondrial dysfunction and oxidative stress recur, yet produce diverse patterns of hyper- and hypoconnectivity depending on circuit, developmental timing, and aging, complicating diagnosis and treatment (Diao et al., 2026; Kim et al., 2019; Fernandez et al., 2019; Nunes et al., 2025; Payares et al., 2024; De Aguiar Da Costa et al., 2026).

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