How are greater mechanistic understandings of Bioenergetics transforming our understanding of Neuro-Developmental and Psychiatric Disorders?

Greater **Bioenergetic** Mechanisms in **Psychiatric** and Neurodevelopmental Disorders

Greater mechanistic understanding of bioenergetics is transforming neurodevelopmental and psychiatric disorders from mainly neurotransmitter- or symptom-based categories into **developmental, systemic, and energy-regulation disorders** with testable cellular mechanisms and new biomarker and treatment strategies (Sarnyai & Ben-Shachar, 2024; Valenti & Vacca, 2023; Rajan & Fame, 2024). The strongest shift is conceptual: mitochondrial function, metabolic flexibility, redox balance, and energy allocation are increasingly treated as upstream processes that shape neurodevelopment, synaptic plasticity, stress adaptation, and clinical heterogeneity rather than as secondary byproducts of illness (Valenti & Vacca, 2023; Kim et al., 2019; Kelley et al., 2025).

Conceptual Shifts

In neurodevelopment, bioenergetics is now understood as a stage-specific regulator of neural progenitor specification, neurogenesis, gliogenesis, and later differentiation, so disruption can plausibly alter brain structure and function from the earliest phases of development (Rajan & Fame, 2024). This framing broadens neurodevelopmental disease models beyond gene lists to timing- and cell-type-specific failures in metabolic transitions between glycolysis and oxidative phosphorylation (Rajan & Fame, 2024).

In psychiatric disorders, the field is moving beyond monoamine and dopamine models toward systemic syndromes in which mitochondrial dysfunction, oxidative stress, and impaired energy metabolism contribute to symptoms, comorbidity, and progression (Nunes et al., 2025; Karabatsiakis & Schönfeldt-Lecuona, 2020). Schizophrenia is a leading example, with a proposed reconceptualization as **impaired dynamic metabolic flexibility**, integrating altered glycolysis and oxidative phosphorylation across brain and periphery (Sarnyai & Ben-Shachar, 2024).

Mechanistic Insights

Mechanistic work now links bioenergetics directly to circuit-relevant biology: mitochondrial dysfunction appears to disrupt glutamatergic signaling, calcium handling, oxidative balance, and synaptic remodeling, connecting cellular metabolism to cognition, mood, and behavior (Kim et al., 2019; Gupta et al., 2026). Mitochondrial dynamics has become especially important because fission, fusion, biogenesis, and mitophagy are not just housekeeping processes but candidate determinants of anxiety, depression, and broader psychopathology (Papageorgiou & Filiou, 2024).

Developmental timing has become a central mechanistic principle across both fields (Kim et al., 2019; Tanaka et al., 2022; Nigg, 2023). In schizophrenia, iPSC and developmental models support the idea that early bioenergetic abnormalities can impair neuronal differentiation and create later vulnerability when adolescent brain maturation raises energetic demand (Ricci et al., 2026).

Translational Implications

Disorder Area	Mechanistic Reframing	Emerging Translation
Schizophrenia	**Metabolic flexibility failure**	Early intervention windows, mitochondrial-targeted therapies (Sarnyai & Ben-Shachar, 2024; Ricci et al., 2026)
Depression	**Systemic bioenergetic dysfunction** affecting plasticity	Blood-cell bioenergetic profiling, individualized treatment response monitoring (Karabatsiakis & Schönfeldt-Lecuona, 2020)
Genetic NDDs	**Early upstream mitochondrial dysfunction**	Mitochondria as therapeutic targets to improve cognition and development (Valenti & Vacca, 2023)
Transdiagnostic psychiatry	**Shared stress-metabolism mechanisms**	Precision psychiatry using biomarkers and metabolic phenotyping (Nunes et al., 2025)

FIGURE 1 How mechanistic bioenergetics is reframing disorders and enabling translational strategies.

Bioenergetic biomarkers are increasingly positioned for phenotypic stratification, prediction of treatment response, and monitoring, including mtDNA copy number, spectroscopy, oxidative stress indicators, and peripheral metabolic signatures (Nunes et al., 2025; Karabatsiakis & Schönfeldt-Lecuona, 2020). This supports a broader move toward **precision psychiatry** and mechanism-based disease classification, often integrated with circuit models, computational psychiatry, and multi-omic profiling rather than replacing them (Nunes et al., 2025; Scangos et al., 2023; Mäki-Marttunen et al., 2019).

Limits And What Changed

Evidence is strong that bioenergetic dysfunction is relevant across disorders, but direct causal links in humans remain limited, and several reviews explicitly note heterogeneity, inconsistent findings, and the need for better longitudinal and experimental models (Kim et al., 2019; Sarnyai & Ben-Shachar, 2024). That is why current progress is coming from integrating human imaging and biomarkers with animal models, rare metabolic diseases, computational frameworks, and stress-allostasis models that make psychiatric symptoms interpretable as consequences of constrained energy regulation across brain and body (Sarnyai & Ben-Shachar, 2024; Cox, 2020; Kelley et al., 2025).

Overall, mechanistic bioenergetics is transforming understanding by shifting these conditions toward **multi-level disorders of energy management**, where development, stress, synaptic plasticity, metabolism, and peripheral physiology interact over time. The main impact is not a single new cause, but a more integrated framework that explains comorbidity, developmental timing, symptom persistence, and why mitochondrial- and metabolism-focused biomarkers and therapies are becoming plausible across neurodevelopmental and psychiatric disorders (Kelley et al., 2025; Chokkakula et al., 2026; Nigg, 2023).

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