How are Neuro-Chemistry, Bio-Mechanics, and Bio-Energetics all needed to adequately understand Neurodevelopmental and Psychiatric Disorders?

Neuro-chemistry, bio-mechanics, and bio-energetics jointly explain neurodevelopmental and psychiatric disorders.

Neurodevelopmental and psychiatric disorders arise from converging disruptions across neurotransmitter signaling, cellular mechanics, and energy metabolism rather than from any single domain (Diao et al., 2026; Gupta et al., 2026; Valenti & Vacca, 2023). Each perspective captures a distinct layer of pathophysiology that the others cannot explain alone.

Neuro-Chemistry: Synaptic and Circuit-Level Signaling

Neurochemical dysregulation — spanning glutamatergic, dopaminergic, and serotonergic systems — represents the most established axis of psychiatric and neurodevelopmental pathophysiology (Sarnyai & Ben-Shachar, 2024; Bertollo et al., 2025). Schizophrenia has long been conceptualized through neurotransmitter imbalance models, which form the basis for current antipsychotic pharmacotherapy (Sarnyai & Ben-Shachar, 2024). Across autism, ADHD, and schizophrenia, disorder-specific connectivity deviations map onto distinct neurotransmitter signatures: glutamatergic plasticity and immune activation in ASD, dopaminergic regulation and glia-neuron interactions in ADHD, and broad synaptic dysregulation in SCZ (Diao et al., 2026). Receptor dysregulation, abnormal intracellular signaling cascades, and ion channel dysfunction produce widespread network dysconnectivity that manifests as cognitive, emotional, and behavioral deficits (Gupta et al., 2026). Glutamatergic neurotransmission alterations co-occur with mitochondrial dysfunction across ASD, schizophrenia, bipolar disorder, and major depression, and these functions are intrinsically interdependent (Kim et al., 2019). The kynurenine metabolic system — linking tryptophan metabolism to neuroactive metabolites — has emerged as a neurochemical target bridging neurodevelopmental pathology and neuroprotection across multiple psychiatric conditions (Tanaka et al., 2022).

Bio-Mechanics: Cellular Architecture and Circuit Formation

Bio-mechanical processes — including cytoskeletal remodeling, axon guidance, and synaptic structural dynamics — are essential for constructing the neural circuits whose disruption underlies these disorders (He et al., 2025; Valenti & Vacca, 2023). Shared transdiagnostic connectivity patterns across ASD, ADHD, and schizophrenia involve genes enriched for **cytoskeletal remodeling** and synaptic development, expressed in midbrain and deep-layer cortical neurons (Diao et al., 2026). NDD-causing genetic variants frequently converge on pathways governing synaptic plasticity and function, suggesting that structural synaptic mechanics are a common substrate (Parenti et al., 2020). The bioenergetic cost of neurodevelopment serves largely synaptic transmission and **actin cytoskeleton dynamics**, directly coupling mechanical processes to energy demands (Bülow et al., 2022). Neural tube closure, cell migration, and differentiation — mechanical events fundamental to brain morphogenesis — are disrupted when bioenergetic support falters, producing structural defects such as microcephaly and brain dysgenesis (Rajan & Fame, 2024). Altered connectivity in the prefrontal cortex and amygdala, observed across both neurodevelopmental and mood disorders, reflects disrupted circuit-level architecture that emerges from aberrant neurodevelopmental mechanics (Bertollo et al., 2025).

Bio-Energetics: Mitochondrial Function and Metabolic Homeostasis

Disorder	Bioenergetic Finding	Citation
Schizophrenia	20–22% reduction in ATP synthesis; 18–35% reduced Complex I activity	(Ricci et al., 2026)
Autism	Elevated lactate; reduced phosphocreatine-to-ATP ratios; Complex I, III, V deficits	(Ram et al., 2026)
Down/Rett/Fragile X	Shared mitochondrial bioenergetic deficits as common pathogenesis factor	(Valenti & Vacca, 2023)
ADHD	Mitochondrial dysfunction and oxidative stress linked to cognitive deficits	(Yang et al., 2025)

FIGURE 1 Bioenergetic abnormalities across specific neurodevelopmental and psychiatric disorders

Mitochondrial dysfunction is increasingly understood not as a downstream consequence but as an **upstream causal event** in neurodevelopmental pathology (Valenti & Vacca, 2023; Yang et al., 2025). The developing brain's peak bioenergetic demand coincides with the typical age of onset for neurodevelopmental disorders (~5 years), suggesting that energy supply failures are causative rather than incidental (Bülow et al., 2022). Schizophrenia has been re-conceptualized as a disease of impaired **dynamic metabolic flexibility**, reconciling peripheral and central glucose metabolism abnormalities along the disease course (Sarnyai & Ben-Shachar, 2024). In first-episode antipsychotic-naïve schizophrenia patients, comparable bioenergetic abnormalities appear, confirming primary pathophysiology rather than medication effects (Ricci et al., 2026). Mitochondrial dynamics — fusion, fission, and mitophagy — maintain neuronal energy homeostasis, and their dysregulation causes accumulation of damaged mitochondria, exacerbating oxidative damage across ASD, ADHD, and Rett syndrome (Yang et al., 2025). Metabolic pathways including glycolysis, lipid metabolism, and amino acid metabolism provide the energy and substrates for neurotransmitter synthesis, myelination, and cell proliferation, directly linking bioenergetics to neurochemical function (He et al., 2025).

Convergence Across All Three Domains

- **Neurochemistry and bioenergetics are interdependent**: mitochondrial oxidative phosphorylation sustains neurotransmission, and glutamatergic transmission relies on intact mitochondrial function, making it difficult to determine which is the primary driver of psychiatric phenotypes (Kim et al., 2019).
- **Bio-mechanics requires bioenergetic support**: actin cytoskeleton dynamics and synaptic structural remodeling — the mechanical processes driving circuit formation — consume the bulk of the brain's bioenergetic output (Bülow et al., 2022; Valenti & Vacca, 2023).
- **Transdiagnostic convergence**: mitochondrial dysfunction, oxidative stress, and redox imbalance serve as unifying features across autism, schizophrenia, bipolar disorder, and major depressive disorder, linking all three domains to shared pathophysiology (Kim et al., 2019; Nunes et al., 2025).
- **Therapeutic integration**: interventions targeting mitochondrial pathways, metabolic balance, and synaptic signaling together may address the multiscale mechanisms that single-domain treatments miss (Valenti & Vacca, 2023; He et al., 2025; Yang et al., 2025).

Adequate understanding of neurodevelopmental and psychiatric disorders requires all three perspectives because neurochemical signaling, bio-mechanical circuit construction, and bioenergetic metabolism are mutually dependent: neurotransmission consumes ATP, cytoskeletal dynamics demand energy, and mitochondrial function is itself regulated by signaling pathways that control neuroplasticity (Valenti & Vacca, 2023; Kim et al., 2019).

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