

Dualistic Dynamics in Neuropsychiatry: From Monoaminergic Modulators to Multiscale Biomarker Maps

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1. Introduction: The Dualistic Lens

Neuropsychiatry lives at the crossroads of chemistry and cognition, where millisecond synaptic sparks sculpt decades-long stories of mood, memory, and identity [1–3]. The same organ then turns inward, making brain–body self-inquiry a central paradox now probed by advanced imaging, stimulation, and physiological modeling [4–6]. Modern data depict neurotransmission as a yin–yang choreography: glutamatergic bursts checked by gamma-aminobutyric acid (GABA) brakes and cortical volleys echoed by visceral afferents carrying gut, liver, and immune cues, while nanoscopic receptor tweaks reverberate through whole networks [7–9]. Mapping the harmonics of this loop may decode consciousness and its breakdown across neuropsychiatric and neurodegenerative disease, since equilibrium failure begets illness [10–12].

Within this framework, psychiatric and neurodegenerative disorders appear less like single-node breakdowns and more like systemic disequilibria [13–15]. When the delicate balance collapses, as in post-traumatic stress disorder (PTSD), dysregulated fear circuitry and hypothalamic–pituitary–adrenal (HPA) axis perturbations create neuroendocrine noise—cortisol volatility, monoaminergic surges, failed fear extinction, and intrusive memory loops [16–18]. Similarly, in Alzheimer’s disease (AD) or Parkinson’s disease, oxidative stress derails networks, yet antioxidant-rich diets and compounds modestly stabilize memory and action control in longitudinal human cohorts [17,19,20]. Complementing those longitudinal data, reviews show that phytochemicals—including polyphenols, alkaloids, and terpenoids—improve cognition and neuropsychiatric symptoms across AD and related disorders [21–23]. An expanding Topical Collection, “Neurodegeneration No More,” now assembles cutting-edge diagnostics, therapeutic targets, and integrative care models aimed at reversing disease trajectories, underscoring the urgency of interdisciplinary collaboration for neurodegenerative disease management [24]. Reinforcing this perspective, an increasing amount of evidence maps how medicinal plants inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) while activating nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, detailing dose windows and translational gaps across progressive neurodegenerative disease [25–27]. Nonetheless, three enduring translational gaps impede the conversion of conceptual advances into clinical benefit. The first is the bench-to-bedside divide: antioxidant interventions that show efficacy in rodent models or in silico screens rarely advance to well-powered clinical trials that rigorously account for sex, age, lifestyle



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factors, and comorbidities [27–29]. Second, a network-integration blind spot: investigations isolate single receptors, overlooking the multiplex cortisol–monoamine–immune crosstalk that governs resilience across organs and lifespan [30–32]. Third, the composite-biomarker vacuum: p-tau isoforms, circulating microRNAs, cortisol rhythms, or receptor-binding positron emission tomography (PET) signals remain unharmonized, limiting our ability to stratify patients, forecast trajectories, and personalize interventions [33–37].

This Special Issue, “Dualistic Equilibrium in Neurotransmission and Beyond,” is curated to illuminate that landscape, bridge its chasms, and chart future routes “https://www.mdpi.com/journal/biomedicines/special_issues/Neurotransmission (accessed on 12 June 2025)”. By uniting eight studies that journey from resveratrol-induced monoamine oxidase A (MAO-A) allostery and trace amine receptor agonism to orexin-orchestrated stress adaptation and isoform-specific tau diagnostics, the collection strives to translate basic insights, weave an empirically grounded system map, and lay scaffolds for next-generation composite biomarker panels. Together, these contributions aim to ignite interdisciplinary alliances spanning medicinal chemistry, network neuroscience, computational modeling, clinical psychiatry, policy makers, caregivers, and public health leaders worldwide, driving progress in basic science, clinical translation, and population health and steering lasting therapeutic innovation for patients across the globe.

2. Eight Windows on Equilibrium

Molecular docking, dynamics, and predator-stressed rats reveal resveratrol and its glucuronide occupy an allosteric pocket on MAO-A, dampening brain and liver enzyme activity and pointing dietary polyphenols toward anxiolytic monoaminergic therapy [38]. Shemiakova et al. synthesize evidence positioning trace amine-associated receptors (TAARs) as novel antidepressant targets [39] (Table 1). TAAR1–TAAR9 extend beyond smell, populating limbic circuits. The TAAR1 agonist ulotaront succeeds in phase 2/3 depression trials. Preclinical data show that TAAR2/TAAR5 shape emotion, monoamine signaling, and hippocampal neurogenesis, suggesting TAAR-targeted drugs could outpace monoamine therapies and cut side-effects in hard-to-treat depression populations.

Table 1. Thematic clustering of the eight contributions in the Special Issue “Dualistic Equilibrium in Neurotransmission and Beyond.” The table groups each paper under a shared mechanistic theme, lists its concise title, and links to the corresponding reference segment. This layout spotlights how the collection spans monoaminergic modulation, serotonergic/peripheral stress circuits, symptom-level and molecular modulators in psychiatric disorders, and biomarker discovery for neurodegeneration.

Group/Topic	Shared Idea	Paper	Ref.
Monoaminergic Targets for Mood Regulation	MAO-A or TAARs rebalance monoamines	Resveratrol as MAO-A allosteric modulator	[38]
		TAARs as novel antidepressant targets	[39]
Serotonergic and Peripheral Stress Systems	5-HT, CB1, orexin in stress and organs	Perinatal 5-HT enhancers alter gut–liver axis	[40]
		CB1–5-HT1A in stress-induced analgesia	[41]
		Orexin system in stress vigilance	[42]
		OCD symptoms worsen	[43]
Symptom Dynamics in Brain Disorders	Clinical/microRNA modulators of symptoms	depression in schizophrenia	[44]
Molecular Biomarkers for Neurodegeneration	Next-gen fluid markers for early AD diagnosis	miR-200b-3p antagonism reduces ADHD traits	[44]
		Plasma p-tau217/231 differentiation of AD	[45]

AD, Alzheimer’s disease; ADHD, attention-deficit/hyperactivity disorder; CB1, cannabinoid receptor type 1; 5-HT, 5-hydroxytryptamine; 5-HT1A, 5-hydroxytryptamine receptor type 1A; miR-200b-3p, microRNA 200b family subtype the 3’ strand; MAO-A, monoamine oxidase A; OCD, obsessive–compulsive disorder; p-tau217/231, phosphorylated tau protein at threonine 217 and threonine 231; TAARs, trace amine-associated receptors.

Perinatal exposure of rats to 5-hydroxytryptophan (5-HTP) or tranlycypromine induces adult-onset histomorphometric and metabolic alterations in the jejunum and liver, spotlighting how early hyperserotonemia imprints a persistent gut–liver serotonergic loop beyond the brain [40]. Pharmacological pairing of CB1 and 5-HT1A agonists or antagonists before versus after cold stress in rats showed serotonergic signaling maintains stress-induced analgesia pre-stress while cannabinoid modulation predominates post-stress, exposing time-specific crosstalk vital for designing anti-stress pain interventions [41]. A narrative review synthesizes evidence that orexin/hypocretin neurons act as master neuro-modulators coupling vigilance with autonomic, endocrine, and behavioral stress responses; highlights their roles in fear, anxiety, and learning; and surveys emerging orexin-based pharmacotherapies for sleep and stress disorders [42].

In 111 outpatients with schizophrenia, higher disorganized and obsessive–compulsive symptom scores independently predicted greater depressive severity, whereas a longer duration of untreated psychosis paradoxically correlated with milder depression, indicating that early circuit disorganization, rather than demographic factors, is the primary driver of comorbid depressive burden [43]. Striatal injection of a miR-200b-3p antagomir in spontaneously hypertensive rats alleviated inattention, reduced pro-inflammatory cytokines, and elevated antioxidant enzymes, spotlighting miR-200b-3p as a promising therapeutic microRNA target for attention-deficit/hyperactivity disorder (ADHD) [44].

A narrative review of 85 original studies concludes that plasma and cerebrospinal fluid (CSF) p-tau217 and p-tau231 outperform p-tau181 in detecting preclinical A β pathology, track tau-tangle progression, and differentiate AD from other dementias, positioning these isoform-specific assays as front-line, minimally invasive biomarkers for early diagnosis and staging [45].

3. Bridging the Gaps: How These Papers Move the Needle

Bridging conceptual insights to clinical utility requires proof that discoveries travel the full distance from molecules to networks to patients. The following three subsections illustrate this trajectory, showing how preclinical candidates acquire translational momentum, how receptor-centric views expand into circuit logic, and how layered biomarkers converge into actionable precision panels.

3.1. Translational Momentum of Rodent Leads

Three rodent-based investigations within the Special Issue push molecular leads toward the clinic. In chronically predator-stressed rats, resveratrol and its glucuronide occupied a newly charted monoamine-oxidase-A allosteric pocket, halved cortical and hepatic enzyme activity, and attenuated anxiety-like behavior, suggesting that a safe nutritional polyphenol could be repurposed for affective disorders [38]. Complementing this single-compound result, a recent narrative review shows that phytochemicals—from curcumin to flavonoids and alkaloids—concurrently quell neuroinflammation, oxidative stress, and mitochondrial dysfunction, easing major-depression phenotypes in preclinical and clinical studies [46]. Systemic delivery of the selective trace amine receptor-1 agonist RO5263397 reversed immobility in forced-swim and tail-suspension tests, normalized hippocampal neurogenesis, and reduced peripheral corticosterone, mechanistic outcomes echoed by the clinical-stage compound ulotaront now in phase 2/3 trials for depression and anxiety [39]. Meanwhile, CRISPR/Cas9 knockout of kynurenine-aminotransferase genes in mice suppressed cerebellar and hippocampal oxidative phosphorylation, highlighting kynurenine aminotransferase-dependent kynurenic control of mitochondrial respiration and energy metabolism in vivo [47,48]. Extending that axis, a quinoline-focused narrative review shows how halogenation, esterification, and in silico screening refine tryptophan-

derived metabolites into multi-target ligands that cross the blood–brain barrier and quell excitotoxic-immune cascades, steering rational design for next-generation quinoline-based mitochondrial therapeutics [49]. Finally, stereotaxic inhibition of striatal miR-200b-3p in spontaneously hypertensive rats restored attentional performance, suppressed interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha (α), and boosted superoxide-dismutase activity, delineating a microRNA–inflammation axis ripe for biomarker-guided antisense therapies that are advancing into first-in-human safety assessments [44]. Collectively, these convergent results validate target engagement, demonstrate behavioral rescue across independent models, and furnish biochemical read-outs that align seamlessly with ongoing or planned human studies, thereby shortening the bench-to-bedside journey.

3.2. From Receptor Islands to Circuit Continents—System-Level Integration

Perinatal elevation of systemic serotonin through 5-HTP or tranylcypromine resculpted adult gut–liver physiology: villus shortening, crypt hyperplasia, suppressed enterochromaffin 5-HT staining, and altered hepatic 5-HT-metabolizing enzymes, establishing a persistent peripheral serotonin circuit poised to influence brain mood circuits via the portal vein and vagus [40]. In an acute cold-stress model, bidirectional pharmacology revealed time-stamped reciprocity between CB1 and 5-HT1A signaling: co-agonism before stress magnified analgesia, whereas the identical cocktail after stress dampened it; selective antagonist pairings confirmed serotonergic dominance in stress initiation and cannabinoid control during recovery, underscoring a dynamic receptor handshake across limbic, periaqueductal-gray, and HPA nodes [41]. Complementing these rodent data, a comprehensive review positions orexin neurons as master switches that broadcast stress salience through widespread projections, coordinating vigilance, autonomic, and endocrine outputs while modulating monoamines, endocannabinoids, and neuropeptides, thereby offering a top-down scaffold for multi-target drug design [42]. Collectively, these findings shift the narrative from single-receptor pharmacology to network neuroscience, illuminating organ-to-brain loops and temporal hierarchies that future therapeutics must respect. A recent synthesis highlights that age-related vascular dysfunction, sarcopenic muscle loss, and neurodegenerative cognitive decline constitute a pathophysiological triad unified by oxidative stress and chronic inflammation [50].

3.3. Toward Composite Precision Panels

The Special Issue showcases how disparate biomarker layers can converge into patient-stratifying toolkits. A narrative synthesis of 85 studies reports that plasma and CSF p-tau217 and p-tau231 consistently outclass p-tau181, flagging pre-amyloid pathology with >90% accuracy, tracking Braak staging, and cleanly separating AD from frontotemporal and vascular dementias [45]. In a rodent model of ADHD, stereotaxic silencing of striatal miR-200b-3p rescued working-memory deficits, lowered IL-6 and TNF- α , and restored superoxide-dismutase activity, positioning this microRNA as both a mechanistic node and a peripheral read-out for neuro-immune dysregulation in ADHD [44]. Complementing these fluid signatures, a clinical cohort of 111 individuals with schizophrenia showed that disorganized and obsessive–compulsive symptom clusters, rather than demographic variables, predicted depressive load, while a longer untreated psychosis interval paradoxically attenuated it, nominating symptom network topology as a low-cost behavioral biomarker [43]. Together, isoform-specific tau assays, actionable microRNAs, and data-driven symptom lattices foreshadow multiplex panels capable of early detection, mechanistic staging, and personalized therapeutic steering across neuropsychiatric spectra.

4. Future Frontiers

Translating the mechanistic advances documented in this Special Issue into clinically transformative applications demands an integrated research agenda. We therefore outline five strategic imperatives—ranging from multi-omics imaging convergence to ethical governance—that together promise to consolidate molecular discoveries, refine patient stratification across the lifespan, and guide the deployment of network-targeted interventions.

4.1. Multi-Omics Coupling with In Vivo Imaging

Next-generation discovery hinges on stitching lipidomic, metabolomic and receptor-specific PET readouts within individuals [51–53]. Chemo-connectome scans link arachidonic acid flux or phospholipid turnover to network fragility [54–57]. To deepen interpretability, pipelines should also track brain-autonomic synchrony, capturing covariation between cortical activity and cardiac deceleration, charting loops that tie emotions to autonomic outflow [4,52,55]. Delivering this vision will require hybrid scanners, biofluid taps, and cloud analytics that fuse terabytes of omics spectra with voxel-wise binding maps in time [58–60].

4.2. Longitudinal, Sex-Balanced Cohorts

Most existing datasets are cross-sectional snapshots or male-skewed rodent lines [61–63]. We need cradle-to-senescence cohorts, stratified by chromosomal and hormonal sex, that collect neuroimaging, multi-omics, immune read-outs, and detailed life-event chronologies at repeated milestones [64–66]. Tracking the same individuals from perinatal stages through puberty, reproductive transitions, and neurodegenerative risk windows will reveal when gut–liver–brain loops or monoaminergic balances hit irreversible tipping points—and whether those inflections differ by sex, ancestry, or socio-environmental load [67–71].

4.3. Digital Phenotyping and Artificial Intelligence (AI) Biomarker Fusion

Wearables, smartphones, and ambient sensors convert gait micro-variability, sleep architecture, voice prosody, and social-touch signatures into continuous phenomic streams, illustrating the field's pivot from serendipitous drug discovery toward precision mental health research [72–76]. Parallel conceptual work urges replacing categorical Diagnostic and Statistical Manual of Mental Disorders (DSM)/International Classification of Diseases (ICD) diagnoses with dimensional Hierarchical Taxonomy of Psychopathology (HiTOP) and Research Domain Criteria (RDoC) taxonomies, integrating these phenomic streams into empirically anchored, biologically informed nosology [77–81]. Coupled with federated artificial intelligence (AI) that simultaneously ingests PET-omics, microRNA panels, and symptom lattices, these data lakes could generate personalized risk curves updated hourly [82–86]. Key priorities include open ontologies for feature harmonization, self-supervised algorithms that learn across modalities with minimal labels, and privacy-preserving architectures that keep raw data on-device while sharing encrypted embeddings for population-level modeling [87–89].

4.4. Network-Level Interventions

Insights from circuit-centric papers invite therapies that modulate entire networks rather than single receptors [90–92]. Closed-loop deep-brain or vagus nerve stimulators, guided by real-time neurochemical sensors, could nudge maladaptive oscillations back into equilibrium [90–92]. On the peripheral front, liver-targeted MAO-A inhibitors or gut-restricted 5-HT modulators may recalibrate central affect without crossing the blood–brain barrier, reducing systemic side-effects [68,93,94]. Combinatorial designs—such as

pairing orexin antagonists with anti-inflammatory microRNA mimics—should be tested in adaptive platform trials that can rapidly prune ineffective arms [95–98].

4.5. Ethical and Regulatory Horizon-Scanning

As datasets sprawl and interventions become closed-loop, guardrails must keep pace [99–101]. Regulators will need new guidelines for multi-omics companion diagnostics, AI-driven adaptive trials, and implantable devices that learn on the fly [102–104]. Equitable access requires subsidized genomic and imaging pipelines in low-resource settings and bias audits for machine learning models [101–103]. Finally, consent frameworks should allow participants granular control over which data layers—lipids, speech, location—enter shared repositories, ensuring progress does not outstrip public trust [99,100,104].

5. Conclusions: Toward a Convergent Neuropsychiatry

The studies collected in this Special Issue validate “dualistic equilibrium” as a unifying framework for neuropsychiatric science, showing that health depends on balanced interactions between excitation and inhibition, central and peripheral signaling, and molecular events and network dynamics. Each contribution shifts the discourse from isolated observations to a layered map that connects monoaminergic allostery, trace amine receptor pharmacology, orexin-regulated stress circuitry, microRNA-driven inflammation, and isoform-specific tau pathology. The resulting atlas is mechanistically precise, since it identifies actionable binding pockets, temporal receptor handshakes, and fluid biomarkers; translationally actionable, because several rodent leads already align with phase 2 or phase 3 trials; and ethically responsible, thanks to an explicit focus on sex-balanced cohorts, privacy-aware digital phenotyping, and equitable access to advanced diagnostics.

The next milestone is collective execution. Specialist silos must give way to consortia that integrate medicinal chemistry, imaging physics, multi-omics analytics, computational psychiatry, regulatory science, and patient advocacy. Shared protocols for hybrid PET-omics pipelines, harmonized outcome measures for adaptive trials, and interoperable data standards for wearable-derived phenomics will accelerate discovery while preventing duplication. Funding bodies should prioritize platforms that enroll cradle-to-senescence participants in diverse settings, ensuring that findings generalize across sex, ancestry, and socio-economic strata. Regulatory agencies can support this trajectory by creating pathways for composite biomarker approval and real-time neuromodulation devices.

Anchored in dualistic equilibrium, guided by a systems lens, and propelled by an ethic of inclusivity, the field is now positioned to transform fragmented mechanistic snapshots into integrated, patient-centered care paradigms. Progress will hinge not on isolated breakthroughs but on coordinated, transparent collaboration that keeps scientific ambition and societal responsibility in steady alignment.

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Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer’s disease
ADHD	attention-deficit/hyperactivity disorder
AI	artificial intelligence
CB1	cannabinoid receptor type 1
CSF	cerebrospinal fluid
HPA	hypothalamic–pituitary–adrenal
5-HT	5-hydroxytryptamine
5-HT1A	5-hydroxytryptamine receptor type 1A
5-HTP	5-hydroxytryptophan
IL	interleukin
MAO-A	monoamine oxidase A
miR-200b-3p	microRNA 200b family subtype the 3’ strand
OCD	obsessive–compulsive disorder
PET	positron emission tomography
p-tau217/231	phosphorylated tau protein at threonine 217 and threonine 231
TAARs	trace amine-associated receptors
TNF	tumor necrosis factor

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