RESEARCH PAPER

Precision Psychopharmacology in Schizophrenia: Integrating Neurotransmitter Signatures and Sympathetic Nervous System Biomarkers for Personalized Treatment

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Abstract

Schizophrenia is a heterogeneous syndrome and nearly one third of patients gain no benefit from dopamine antagonist therapy. This systematic review interrogates whether neurotransmitter signatures and sympathetic nervous system biomarkers can stratify treatment responsivity and thereby guide precision psychopharmacology. Five studies were synthesized after a structured screening cascade reported through a PRISMA workflow. Dopaminergic and glutamatergic indices showed divergent associations with antipsychotic outcome and elevated anterior cingulate glutamate distinguished nonresponders with an area under the curve of 0.59. Resting vagal tone was markedly attenuated in schizophrenia with a pooled Hedges g of −0.98 for high frequency heart rate variability. Inflammatory and epigenetic markers including interleukin 6 and methylation panels reached discriminative accuracy up to 0.92. The convergent evidence supports a neuroimmunoautonomic framework in which glutamatergic refractoriness autonomic hypotonia and cytokine dysregulation jointly sculpt treatment resistance. Multimodal biomarker integration appears indispensable because no solitary index attains clinical separability.

Keywords: schizophrenia precision psychiatry dopamine glutamate heart rate variability inflammation treatment resistance endophenotype

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1. Introduction

Schizophrenia affects approximately one percent of the world's population and has a significant impact on cognitive, affective and functional domains (McCutcheon et al., 2020). Pharmacological cornerstone is dopamine D2 receptor antagonism and this mechanism targets primarily the positive symptom cluster, with little modification of negative and cognitive deficits (McCutcheon et al., 2019). A significant proportion of people (around 1/3) remain treatment resistant and continue to have disabling symptoms after sufficient attempts at treatment with antipsychotics (Demjaha et al., 2014; Lieberman et al., 2005; Kahn et al., 2008). This dichotomy of responsivity suggests that the disorder is not a single entity, but rather a collection of biologically distinct subtypes (Comai et al., 2025).

For decades, the dopamine hypothesis has been the focus of mechanistic thinking. In established illness, positron emission tomography (PET) shows increased presynaptic striatal dopamine synthesis capacity with a large effect size (McCutcheon et al., 2019). But this dopaminergic excess is not consistently associated with responders vs. nonresponders and a refractory subset of patients has normal striatal dopamine function (Demjaha et al., 2014; Kim et al., 2017; Avram et al., 2019; Jauhar et al., 2019). These observations have sparked a glutamatergic reconceptualization that has led to the concept of NMDA receptor hypofunction causing a broader symptom spectrum (McCutcheon et al., 2020). Treatment resistant cohorts show increased glutamate in the anterior cingulate cortex using proton magnetic resonance spectroscopy (Mouchlianitis et al., 2016; Egerton et al., 2018; Iwata et al., 2019; Tarumi et al., 2020). These two observations inspire a signature based reading where different neurotransmitter signatures correspond to different therapeutic pathways.

There are two general types of glutamate modulating strategies. One class augments NMDA receptor signaling while the other curtails excess synaptic glutamate (McCutcheon et al., 2020). The presence of these classes demonstrates the mechanistically tractable nature of the glutamatergic signature, not just

its descriptive nature. This is supported by genetic evidence as risk genes for example GRIN2A, GRIA1 and GRM3 encode subunits of glutamate receptors (McCutcheon et al., 2020). This genetic anchoring takes glutamate from the passive correlate to a potential causal node in intractable disease.

The ANS provides an alternative lens into pathophysiology beyond central neurotransmission. The neurovisceral integration model suggests that the prefrontal inhibitory control over cardiac vagal outflow represents self regulatory capacity (Thayer & Lane, 2000; Thayer et al., 2009, 2012). Thus, decreased HRV could be a peripheral endophenotype linking central dysregulation to cardiovascular morbidity (Clamor et al., 2016). Schizophren patients have significantly higher cardiovascular mortality risk and autonomic dysfunction is likely a contributing factor to this excess mortality (Hennekens et al., 2005).

Inflammation provides a third line of weakness. Surface transdiagnostically and correlate with refractory illness, elevated levels of interleukin 6 and cognate cytokines (Comai et al., 2025). The vulnerability stress model suggests that genetic and environmental loads interact on common neurobiological substrates to trigger psychosis (Zubin & Spring, 1977; Nuechterlein & Dawson, 1984; Van Os et al., 2010; Howes et al., 2017). Precision psychiatry aims to break down this heterogeneity into actionable biosignatures instead of considering the syndrome as one (Comai et al., 2025).

The aim of the present review is to have three goals. First, it describes dopamine and glutamate signatures, and their differential association with treatment response. Second, it evaluates endophenotypic biomarkers of the sympathetic and autonomic nervous system like heart rate variability and inflammatory markers. Third, it constructs integrative causal pathways and reciprocal dynamics between neurotransmitter imbalance, autonomic dysregulation, and treatment resistance. We hypothesize that there is no single biomarker capable of clinical separability and multimodal integration is necessary for effective stratification.

2. Methods

2.1 Protocol and design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses framework. The procedure proceeded through identification screening eligibility and inclusion phases as depicted in Figure 1. The review questions were specified a priori around neurotransmitter autonomic and immune biomarkers of antipsychotic response.

2.2 Search strategy

A structured search was executed across five electronic databases comprising PubMed Scopus Web of Science Embase and PsycINFO. The temporal window extended from database inception to early 2025. Boolean strings combined disorder descriptors with biomarker and treatment descriptors. Table 1 enumerates the database specific strings and their record yields. Table 2 specifies the eligibility criteria applied during screening.

Database	Search string	Records
PubMed	("schizophrenia" OR "psychosis") AND ("dopamine" OR "glutamate" OR "biomarker" OR "heart rate variability")	31
Scopus	("treatment resistant schizophrenia" OR "refractory psychosis") AND ("biomarker" OR "neuroimaging" OR "autonomic")	26
Web of Science	("schizophrenia") AND ("precision psychiatry" OR "endophenotype" OR "inflammation")	22
Embase	("antipsychotic response") AND ("dopamine" OR "glutamate" OR "vagal")	11
PsycINFO	("schizophrenia") AND ("personalized treatment" OR "biomarker")	7
Database subtotal	Total records returned by database querying	97
Other sources	Hand searching of reference lists	23

Table 1. Database search strategy with Boolean strings and record yields.

Domain	Inclusion criterion	Exclusion criterion
Population	Adults with schizophrenia or psychosis	Non psychotic disorders

Exposure	Neurotransmitter autonomic or inflammatory biomarker	No biomarker quantified
Outcome	Treatment response or endophenotypic status	No outcome reported
Design	Peer reviewed review meta analysis or cohort	Case report or conference abstract
Language	English language full text	Non English without translation

Table 2. Inclusion and exclusion criteria applied across screening and eligibility.

2.3 Study selection

A further 23 records were identified in the hand search of reference lists and 97 records were found in the database search. Once the duplicates had been removed the rest of the pool was moved on to the title and abstract screening. At this stage 21 records were screened out. Then a total of 52 full text articles were evaluated for their eligibility and 45 were excluded because they were not within the scope, and/or had insufficient methodological detail, and/or were of limited rigour. Five studies met all the criteria and were included in the qualitative synthesis. The entire selection process is described in figure 1.

2.4 Data extraction and synthesis

Two classes of variables were extracted comprising study characteristics and quantitative outcomes. Hedges g standardized mean differences, odds ratios and area under the curve values were recorded as effect sizes. Where studies reported analysis of covariance the F statistic and partial eta squared were captured. Due to the diversity of designs, a narrative synthesis with tabulated effect sizes was used instead of a pooled meta analysis. Translational readiness was evaluated using the sensitivity and specificity of the biomarkers and the area under the curve. The main quantitative results of the studies included are summarized in Table 3.

2.5 Quality appraisal

Methodological quality was considered when deciding to include or exclude studies. Primary studies were included if they provided explicit biomarker quantification in a transparent way and had defined outcome measures. Reviews that synthesized primary quantitative evidence were kept, not opinion. This appraisal led to the exclusion of full text articles because of the lack of rigorous evidence, lack of detail or mismatch of topics as indicated in Figure 1.

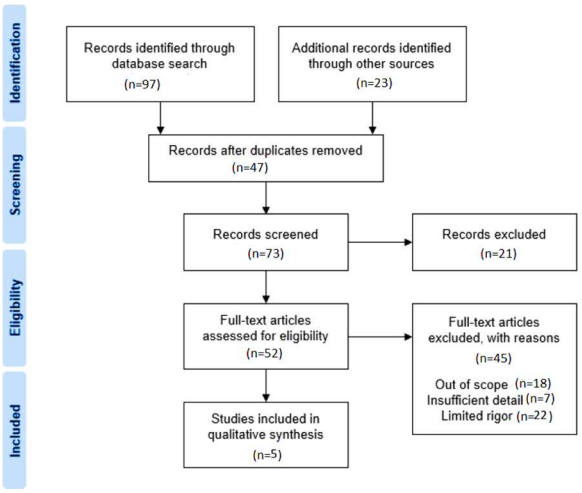

Figure 1. PRISMA flow diagram of the study selection process.

3. Results

3.1 Overview of included studies

The five studies that were included were one narrative review on dopamine and glutamate biology, one multicenter study using neuroimaging, one meta analysis of heart rate variability, one systematic review of treatment resistance biomarkers and one narrative review of precision psychiatry. The aggregate evidence is a series of questions that addresses the same question in different modalities. Table 3 summarises the main quantitative results.

3.2 Dopamine and glutamate signatures and treatment response

McCutcheon et al. (2020) combined converging evidence that presynaptic striatal dopamine is increased in schizophrenia. The pooled positron emission tomography data showed a large effect (Hedges g ~ 0.7) for increased dopamine synthesis capacity (McCutcheon et al., 2020). Dopaminergic excess that was localized to the dorsal striatum was correlated with positive symptom severity (McCutcheon et al., 2020; Radua et al., 2015; Jauhar et al., 2017; Egerton et al., 2017). The same review noted a parallel abnormality of glutamatergic system. Increased Glx (g = 0.4) and increased glutamate (g = 0.6) were found in the basal ganglia and increased thalamic glutamine (g = 0.6) (McCutcheon et al., 2020). Positive symptoms were alleviated in approximately two-thirds of patients and one-third of patients were refractory to antipsychotics

(McCutcheon et al., 2020). Importantly, the responsivity signature (McCutcheon et al., 2020) seemed to be related to glutamatergic as opposed to dopaminergic pathology.

This dissociation has been directly tested in the STRATA study (Egerton et al., 2021). In total, 92 participants completed the spectroscopy and 54 completed both the spectroscopy and dopamine positron emission tomography (Egerton et al., 2021). Anterior cingulate glutamate was higher in antipsychotic nonresponders after adjustment for age and sex with an F statistic of 4.99 across degrees of freedom 1 and 81 and a P value of .03 and a partial eta squared of 0.06 (Egerton et al., 2021). The level of discriminative accuracy was moderate with an area under the curve of 0.59 (Egerton et al., 2021). The best cut point was found to be 0.73 sensitivity and 0.49 specificity (Egerton et al., 2021). The mean of striatal glutamate did not differ between groups with an F of 0.96 and a P of .33 (Egerton et al., 2021). Similarly, striatal dopamine function was not able to differentiate responders from nonresponders (F = 1.24, P = .27, and area under the curve = 0.59, Egerton et al., 2021). The positive coupling between anterior cingulate glutamate and striatal dopamine was only observed in nonresponders with an r of .37 and a P of .05 (Egerton et al., 2021). The results confirm a glutamatergic signature of refractoriness and demonstrate that there is no clinical separability between single metrics (Egerton et al., 2021).

The glutamatergic account is well-mechanistically based. Administration of NMDA receptor antagonists induces positive negative and cognitive symptoms in healthy volunteers which recapitulates the full syndrome (McCutcheon et al., 2020). Reduced dendritic arborization spine density and synaptophysin expression is seen in post mortem tissue in frontal and temporal regions (McCutcheon et al., 2020). These structural deficits dovetail with the spectroscopic elevations and frame glutamatergic pathology as both molecular and morphological (McCutcheon et al., 2020).

3.3 Sympathetic nervous system biomarkers as endophenotypic indicators

Clamor and colleagues (2016) meta analyzed resting vagal activity from 34 studies. High frequency heart rate variability was substantially reduced in schizophrenia with a pooled Hedges g of −0.98 and a 95% confidence interval from −1.56 to −0.41 and a P value of .0008 (Clamor et al., 2016). The root mean square of successive differences was in parallel deficit with a g of −0.91, a confidence interval of −1.19 to −0.62 and a P below .0001 (Clamor et al., 2016). Both indices reflect cardiac vagal tone and large negative values indicate significant autonomic hypotonia (Clamor et al., 2016; Task Force of the European Society of Cardiology, 1996). There was extreme heterogeneity as I squared was 98 percent, indicating significant between study variance (Clamor et al., 2016). A deficit was found in the medicated groups with a g around −0.95 but was reduced toward the null in unmedicated groups (Clamor et al., 2016). In samples with chronic illness, the g was increased by the high frequency reduction, to −1.418, while in samples with first episode, the g was −0.500 (Clamor et al., 2016). The gradient indicates that with the progression of illness, the vagal withdrawal increases (Clamor et al., 2016). The authors conceptualized reduced variability as a potential endophenotype that connects schizophrenia with EDD and cardiovascular risk (CVR) (Clamor et al., 2016; Hansen et al., 2003; Castro et al., 2008).

Meta regression confirmed the autonomic deficit's strength. The reduction of HRV was not significantly affected by age or duration of illness (Clamor et al., 2016). Significant decreases were seen in both inpatient and outpatient settings in subgroup analysis (Clamor et al., 2016). The uniformity of the moderators supports the endophenotypic interpretation of the deficit (Clamor et al., 2016).

Pisanu and colleagues compiled a list of biomarkers of treatment resistant schizophrenia from 75 studies (Pisanu et al., 2024). The most consistent signal was inflammatory dysregulation, which showed an odds ratio of 24.7 and an adjusted P of .014 (Pisanu et al., 2024). Catalase activity associated with resistance with an odds ratio of 1.58 and a P of .046 (Pisanu et al., 2024). Despite the schizophrenia polygenic risk score predicting resistance with an odds ratio of 1.09 and P value of .003, single nucleotide polymorphism heritability was still modest, between 1 and 4 percent (Pisanu et al., 2024). The most discriminatory methylation panels had area under the curve between 0.83 and 0.92, and accuracy as high as 87.3 percent and sensitivity as high as 90 percent (Pisanu et al., 2024). These epigenetic and immune indices performed better on separability than neurotransmitter measures, but require independent replication (Pisanu et al., 2024).

3.4 Integrative biomarkers for precision psychiatry

Comai and colleagues surveyed multimodal biomarkers from neuroimaging (EEG), protein immunology (kynurenine), and genomics (Comai et al., 2025). Neurofilament light chain was found to be between 1.2 and 2.5 times higher than normative levels, and was associated with poorer outcomes in

schizophrenia (Comai et al., 2025). Interleukin 6, tumor necrosis factor alpha and high sensitivity C reactive protein increased across the diagnoses during acute phases (Comai et al., 2025). Comai et al. (2025) showed that treatment resistant schizophrenia exhibited greater kynurenine pathway activity compared to first line responders. The most matured translational tool was pharmacogenetic genotyping of cytochrome enzymes such as CYP2D6 and CYP2C19 (Comai et al., 2025). The authors concluded that there is no one biomarker that encompasses the disorder, and integration is necessary, which can be achieved by computational modeling and machine learning (Comai et al., 2025).

Table 3 Qualitative Analysis

Study	Design	Neurotransmitter Findings	Autonomic/Inflammatory Findings	Key Implication
McCutcheon et al. (2020)	Narrative Review	Striatal dopamine elevated (g=0.7); glutamate NMDA hypofunction explains wider symptoms	Environmental factors influence dopaminergic dysfunction	TRS shows glutamatergic rather than dopaminergic dysfunction
Egerton et al. (2021)	Cross-Sectional	ACC glutamate higher in NR (P=.03; AUC=.59); no striatal dopamine difference (P=.27)	None measured	Single neurotransmitter measures cannot distinguish responder status
Clamor et al. (2016)	Meta-Analysis	None measured	HRV reduced in SZ (g=-0.98; P<.0001); robust across medication status	Reduced vagal activity is potential endophenotype
Pisanu et al. (2024)	Systematic Review	Glutamate genes (GRIN1, GRIN2A) support glutamatergic dysfunction	IL-6 most replicated TRS marker (OR=24.7; P=.014); kynurenine pathway altered	Inflammation/cytokine imbalance is most promising TRS biomarker pathway
Comai et al. (2025)	Narrative Review	Focus on biomarkers across domains	IL-6, TNF-α, hs-CRP elevated transdiagnostically; kynurenine metabolites linked to treatment response	No single biomarker sufficient; multimodal integration essential

The review also catalogued physiological and neural predictors. Reduced alpha power and increased theta activity associated with poor antipsychotic response while mismatch negativity and the P300 event related potential indexed cognitive dysfunction (Comai et al., 2025). Gray matter volume and functional connectivity predicted response to clozapine and to neurostimulation (Comai et al., 2025). Machine learning models that fused electroencephalographic features approached near perfect classification accuracy (Comai et al., 2025). These observations reinforce that predictive power accrues from feature fusion rather than from any isolated channel (Comai et al., 2025).

Table 3. Summary of principal quantitative findings across the five included studies. ACC anterior cingulate cortex. NR nonresponder. R responder. HRV heart rate variability. RMSSD root mean square of successive differences. TRS treatment resistant

schizophrenia. PRS polygenic risk score. AUC area under the curve.

Study	Design	Sample	Key measure	Effect size	P
McCutcheon et al. 2020	Narrative review	Pooled PET	Dopamine synthesis capacity	g ≈ 0.7	–
McCutcheon et al. 2020	Narrative review	Pooled MRS	Basal ganglia glutamate	g = 0.6	–
Egerton et al. 2021	Cross sectional	92 MRS	ACC glutamate NR vs R	F = 4.99; η^2 = 0.06	.03
Egerton et al. 2021	Cross sectional	54 PET	Striatal dopamine NR vs R	F = 1.24	.27
Egerton et al. 2021	Cross sectional	92 MRS	ACC glutamate AUC	AUC = 0.59	–
Clamor et al. 2016	Meta analysis	1353 SZ; 1702 HC	High frequency HRV	g = −0.98	.0008
Clamor et al. 2016	Meta analysis	1016 SZ; 1469 HC	RMSSD	g = −0.91	<.0001
Pisanu et al. 2024	Systematic review	75 studies	IL-6 and TRS	OR = 24.7	.014
Pisanu et al. 2024	Systematic review	40 TRS; 40 non	Methylation AUC	AUC = 0.83–0.92	–
Pisanu et al. 2024	Systematic review	10,501 TRS	SZ PRS and TRS	OR = 1.09	.003
Comai et al. 2025	Narrative review	Multimodal	Neurofilament light chain	1.2–2.5×	–

4. Discussion

This synthesis expands on a three-part argument. The neurotransmitter axis shows a dopaminergic glutamatergic dissociation such that responsivity is associated with dopaminergic mechanisms and refractoriness with glutamatergic excess (McCutcheon et al., 2020). The dissociation was operationalized in the STRATA, which showed higher glutamate levels in the anterior cingulate in nonresponders but demonstrated the ceiling of single marker discrimination at an AUC of 0.59 (Egerton et al., 2021). The autonomic axis showed very strong vagal hypotonia with effect magnitudes close to unity, indicating that HRV is a strong endophenotypic indicator (Clamor et al., 2016). The immune and epigenetic axis emerged interleukin 6 elevation and methylation signatures, which had significantly better separability (Pisanu et al., 2024).

A coherent causal architecture emerges when these axes are interlaced. The anterior cingulate is glutamatergic and dysfunction of inhibitory circuits in prefrontal cortex to subcortical and brainstem circuits (McCutcheon et al., 2020). The neurovisceral integration model proposes that prefrontal dysfunction is linked to cardiac vagal outflow, and therefore, the same prefrontal dysfunction that maintains refractory psychosis could also lead to the loss of vagal tone (Thayer et al., 2009). This decrease in vagal activity, in turn, allows for a proinflammatory environment, as vagal activity normally inhibits cytokine release (Clamor et al., 2016). The resulting increase in interleukin 6 then acts as a negative feedback on central glutamatergic and dopaminergic transmission, and reinforces resistance (Pisanu et al., 2024). This reciprocal loop is a rephrasing of treatment resistance as a self-reinforcing neuroimmunoautonomic state instead of a static lesion (Comai et al., 2025).

This integrative reading is reinforced by the dopaminergic glutamatergic coupling that was only found in nonresponders (Egerton et al., 2021). In refractory patients, anterior cingulate glutamate correlated positively with striatal dopamine,

suggesting an abnormal (dysregulated) cortico-subcortical pathway that is not seen in responders (Egerton et al., 2021). Cross system coupling could be a phenoconversion to a resistant endophenotype (Comai et al., 2025). Thus, a candidate biosignature lattice for stratification is the convergence of glutamatergic excess autonomic withdrawal and cytokine elevation (Comai et al., 2025).

The implications for translation are significant. The multimodal panel combining the spectroscopic glutamate autonomic variability with inflammatory and epigenetic markers may achieve greater separability than any of the single markers alone (Pisanu et al., 2024). Methylation panels are already close to the area under the curve of 0.92, and might be used to anchor such a lattice (Pisanu et al., 2024). Pharmacogenetic genotyping might be used to optimize dosage, and autonomic monitoring might identify cardiovascular risk (Comai et al., 2025). If a glutamatergic resistant signature can be identified early in the illness, it may be appropriate to start treatment with clozapine instead of sequential trials with dopamine antagonists (McCutcheon et al., 2020).

It is important to note that these markers are dynamic. The increase in vagal withdrawal from first episode to chronic illness suggests that autonomic dysregulation is not static, but rather evolves over time (Clamor et al., 2016). A progressive endophenotype calls for early intervention because the biosignature may be most modifiable prior to consolidation (Comai et al., 2025). The continued reduction of variability in the medicated groups further supports this, as the vagal deficit is not a drug effect but a property of the disorder (Clamor et al., 2016). This intrinsic property makes HRV a suitable trait marker for stratification (Clamor et al., 2016).

There are some caveats to these inferences. The studies included were of varying design, ranging from narrative review to meta analysis and did not allow for a single pooled estimate. The heart rate variability literature is heterogeneous with an I squared of 98 percent that limits precision (Clamor et al., 2016). The accuracy of neurotransmitter markers was close to chance at 0.59 (Egerton et al., 2021). The definition of treatment resistance was different in primary studies and decreased the comparability of biomarkers (Pisanu et al., 2024). There is limited evidence of prospective validation of integrated panels (Comai et al., 2025).

5. Conclusion

The need for precision psychopharmacology in schizophrenia calls for a change from a one-size-fits-all approach of dopamine blockade to a biosignature-informed approach. The evidence suggests that the mechanisms of glutamatergic excess are related to refractoriness, and dopaminergic mechanisms are related to responsivity. A peripheral endophenotype is autonomic hypotonia (low HRV). The inflammatory and epigenetic markers that were most discriminatory were led by interleukin 6 and methylation panels. A multimodal neuroimmunoautonomic lattice is required for clinical separability, which no single index can achieve. Integrated panels need to be validated in future prospective cohorts to achieve personalized treatment.

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