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A Constraint-Based Framework for Architectural Evaluation in Schizophrenia Research

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Abstract

Despite decades of intensive research, schizophrenia remains characterized by theoretical fragmentation and limited integrative convergence. This concept paper proposes a constraint-based framework for comparatively evaluating explanatory coverage in schizophrenia research, shifting emphasis from isolated mechanisms to recurring structural features emphasized across theoretical and empirical literatures. Twenty-five constraints are formalized, comprising ten observed constraints derived from recurrent clinical and phenomenological regularities (C1–C10) and fifteen empirically established constraints grounded in replicated findings across genetics, neuroscience, epidemiology, pharmacology, and longitudinal outcomes (E1–E15). Major explanatory approaches—including dopaminergic, glutamatergic, neurodevelopmental, and computational accounts—are examined with respect to their explicit alignment with this constraint set using predefined analytic criteria. This analysis illustrates systematic differences in how existing models address issues such as causal direction, state–trait distinction, longitudinal sensitivity, and cross-system interaction. On this basis, the framework is used to outline a provisional specification of architectural features that may warrant further investigation in future theoretical and empirical work. The Sensitivity Threshold Model (STM) is presented as one candidate architecture that exhibits broad alignment with the full constraint set, serving as an illustrative application rather than a validated solution. The primary contribution of this work is the introduction of a structured, transparent methodological heuristic intended to facilitate comparison, clarify evidentiary expectations, and support cumulative theory development in schizophrenia research.

Keywords: schizophrenia; explanatory adequacy; constraint-based modeling; systems-level architecture; theoretical integration; psychosis; conceptual framework; causal structure; model evaluation; psychiatric theory

1. Introduction

Despite decades of intensive research and the accumulation of extensive datasets spanning genetics, neurochemistry, and phenomenology, schizophrenia research continues to be characterized by substantial theoretical plurality. The field has at times been described as a "graveyard of theories" [1], reflecting persistent concerns regarding fragmentation and the difficulty of integrating diverse findings into a coherent explanatory account. In many cases, isolated biological or computational mechanisms are advanced as primary explanations, even when their scope does not readily accommodate the full range of observed clinical and longitudinal phenomena.

From this perspective, a central challenge in schizophrenia research may lie less in the availability of empirical data than in the absence of a shared analytical framework capable of integrating heterogeneous findings across levels of analysis [2]. Rather than adjudicating among competing mechanisms on the basis of explanatory preference, progress may benefit from approaches that make explicit the structural features recurrently emphasized across theoretical and empirical literatures.

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This paper adopts a constraint-based methodology as one such approach. In systems engineering and the philosophy of science, constraints are commonly used to characterize boundary conditions, regularities, or requirements that shape the space of admissible explanations without, on their own, determining a unique solution [3]. Applied in this context, a constraint-based framework shifts emphasis from isolated variables to system-level considerations that recur across clinical observation, empirical findings, and theoretical proposals. The goal is not to establish necessary or sufficient conditions for validity, but to provide a structured heuristic for comparing how explicitly different models address commonly cited explanatory demands.

Accordingly, this study formalizes and operationalizes 25 distinct constraints, organized into two categories. Observed constraints (C1–C10) reflect recurring clinical and phenomenological regularities—such as the episodic nature of psychotic transitions and the temporal positioning of neurochemical changes—that help characterize the functional profile of the syndrome. Empirically established constraints (E1–E15) summarize robust, replicated findings from genetics, epidemiology, and systems neuroscience that delimit the biological and developmental context within which explanatory models are typically situated.

These constraints are examined in relation to several influential explanatory approaches, including the Dopamine Hypothesis [4], Glutamatergic Dysregulation models [5], and Predictive Coding accounts [6]. Rather than serving as a test of correctness, this comparative mapping highlights systematic differences in how existing frameworks make explicit—or leave implicit—key issues such as causal direction, state–trait differentiation, longitudinal sensitivity, and cross-system interaction.

As a secondary contribution, the framework is used to articulate a provisional specification of architectural features that recur across constraints and may warrant focused attention in future theoretical and empirical work. The Sensitivity Threshold Model (STM) is introduced as one candidate architecture that exhibits broad alignment with the full constraint set, serving as an illustrative application of the framework rather than a validated or exhaustive solution. The primary objective of this paper is thus not to promote a single model, but to introduce a transparent, revisable heuristic intended to clarify evidentiary expectations and support cumulative theory development in schizophrenia research.

2. Materials and Methods

2.1. Study Design

This work is a theoretical and integrative analysis, not an empirical experiment or clinical intervention. Its goal is to comparatively evaluate explanatory coverage in schizophrenia research using a constraint-based methodological framework [7]. No new human or animal data were collected, and no experimental interventions were performed; therefore, ethical approval was not required.

The analysis proceeds through a structured sequence of steps:

(i) abstraction of observed constraints based on recurring clinical and phenomenological regularities;

(ii) identification of empirically established constraints grounded in replicated findings;

(iii) comparative examination of major explanatory theories with respect to their explicit alignment with these constraints using predefined analytic criteria; and

(iv) articulation of a provisional architectural specification suggested by the constraint set, intended to clarify recurring explanatory demands for subsequent theoretical and empirical evaluation.

2.2. Derivation of Observed Constraints

Observed constraints (C1–C10) were derived by abstracting cross-cutting regularities in clinical course, symptom expression, and phenomenology as reported across diverse clinical settings and

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theoretical traditions. Although interpretations of these patterns vary, their recurrence has been widely noted in the schizophrenia literature.

These constraints were not extrapolated from any single dataset, model, or framework. Instead, they were formulated to summarize functional characteristics of schizophrenia that recur across contexts, capturing phenomena such as state dependence, treatment asymmetry, and heterogeneity in onset and outcome.

Each constraint is expressed in a theory-neutral form and is intended to highlight recurrent explanatory targets rather than to specify mechanistic requirements. Their role within the framework is to characterize architectural features commonly emphasized in attempts to account for the disorder's clinical and empirical profile, without implying necessity, sufficiency, or validity of any particular explanatory model.

2.3. Identification of Empirically Established Constraints

Empirically established constraints (E1–E15) were defined as high-confidence, replicated findings reported across genetics, epidemiology, neuroscience, pharmacology, and longitudinal outcome studies [8]. Each constraint summarizes a robust empirical regularity that is frequently referenced in the schizophrenia literature and that helps characterize the empirical context within which explanatory models are developed.

A standardized procedure was used to formalize these constraints. First, each empirical regularity was stated in descriptive terms. Second, it was translated into a theory-neutral constraint formulation intended to capture the general explanatory issue highlighted by the finding, without embedding any specific causal mechanism or committing to a particular level of analysis. These formulations were designed to indicate features that explanatory accounts commonly address, rather than to impose necessary or sufficient conditions for validity.

This conservative translation process was intended to keep empirical constraints minimal, neutral, and compatible with multiple causal architectures. In addition, the empirically established constraints were used to cross-check the observed constraints for consistency, ensuring that no abstracted regularity was in tension with well-replicated empirical findings.

2.4. Theory Selection and Classification

Representative theories were selected to encompass major explanatory paradigms in schizophrenia research, including neurochemical, genetic, neurodevelopmental, computational, immune, stress-based, and integrative approaches.

Theories were characterized according to their core ontological commitments, as described in foundational or widely cited sources. Hybrid or derivative models were classified based on their dominant explanatory logic to support comparative analysis, rather than treated as distinct constructs. This classification is descriptive and organizational in intent and does not imply evaluative ranking or endorsement.

2.5. Constraint Evaluation and Scoring Procedure

Each theory class was mapped against both the observed constraints (C1–C10) and the empirically established constraints (E1–E15) using a three-level coverage classification rubric. The rubric is intended as an analytic heuristic tool for describing the degree to which a given theoretical framework makes the relevant constraint explicit within its core architecture.

The three classification categories are defined as follows:

✓ (Explicitly addressed):

The theory directly incorporates the constraint within its stated architecture, without requiring substantial reinterpretation or additional auxiliary assumptions.

~ (Implicitly or partially addressed):

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The constraint is accommodated indirectly, through supplementary assumptions, causal reorientation, or incomplete specification.

✗ (Not explicitly addressed):

The theory does not clearly represent the constraint within its core explanatory structure or lacks an explicit mechanism or construct corresponding to it.

Classification was performed conservatively. In cases of ambiguity, the intermediate category (~) was assigned. The purpose of this mapping is not to rank theories, establish correctness, or imply falsification, but to characterize patterns of explicitness and coverage across different explanatory approaches, thereby facilitating structured comparison of how theories engage with the full constraint set [9].

2.6. Compression and Consistency Analysis

Observed and empirically established constraints were cross-mapped to examine compression, defined here as the convergence of multiple empirical regularities onto a smaller number of higher-level architectural principles. In parallel, consistency checks were conducted to assess the degree of compatibility between observed and empirical constraints across levels of abstraction.

Where apparent tensions were identified, they were addressed by differentiating levels of abstraction, rather than by modifying constraint definitions or prioritizing one constraint set over another. This approach was intended to maintain internal coherence across descriptive, architectural, and mechanistic layers while preserving the theory-neutral formulation of individual constraints.

2.7. Illustrative Model Alignment Analysis

The Sensitivity Threshold Model (STM) was examined as a reference architecture to illustrate how the proposed constraint-based framework can be applied to a concrete theoretical model, rather than as a finalized etiological account. This analysis considered whether STM's minimal variable set and proposed causal ordering explicitly address the full set of 25 constraints within its stated architecture, without introducing additional auxiliary assumptions, parameter tuning, or causal inversion.

No simulations or empirical tests were conducted. This phase of the analysis is strictly conceptual and deductive, intended to demonstrate the internal coherence and explanatory scope of the framework when applied to a candidate model, rather than to establish validation, sufficiency, or empirical confirmation.

2.8. Materials, Data, and Code Availability

No new datasets, software, or experimental materials were generated for this study. All constraints, analytic criteria, and evaluation procedures are explicitly defined within the manuscript to enable independent examination, critique, or extension of the framework.

Any future computational formalizations or simulation tools developed from this framework will be made publicly available upon publication.

2.9. Reporting Standards and Limitations

As a theoretical study, standard empirical reporting guidelines do not apply. Nevertheless, all methodological steps were designed to maximize transparency, traceability of reasoning, and clarity of underlying assumptions [10]. Where applicable, conservative interpretive choices were adopted to avoid overstatement and to support consistent application of the constraint classification and comparative mapping procedures.

2.10. AI-Assisted Preparation

AI-assisted tools, including large language models (ChatGPT and Gemini), were used solely for copy-editing, organizational, and formatting assistance, and not for the generation of scientific claims

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or interpretations. The author assumes full responsibility for all conceptual content, analyses, interpretations, and hypotheses presented.

3. Results

3.1. Results Roadmap and Reading Guide: A Constraint-Based Comparative Analysis

This Results section examines the Sensitivity Threshold Model (STM) using a constraint-based comparative framework, rather than through parameter fitting, predictive classification, or domain-specific simulations [11,12]. The guiding focus is not whether STM reproduces individual empirical findings, but how its proposed architecture aligns with a set of structural constraints that recur across schizophrenia research.

The analysis proceeds through five structured stages.

First, ten observed constraints (C1–C10) are introduced. These are derived from recurring regularities in clinical course, symptom phenomenology, pharmacologic response, and cross-context modulation of psychosis. Rather than serving as theoretical premises, these constraints summarize commonly reported general patterns abstracted from convergent empirical observations. Each is formulated using a stepwise protocol—phenomenon → generalization → constraint form—and is intended as a theory-neutral explanatory target.

Second, the analysis examines whether four abstract variables—Sensitivity, Load, Capacity, and Signal Integrity—are collectively sufficient to represent the observed constraints at an appropriate level of abstraction [13]. This step explores architectural coverage, showing how altering, collapsing, or omitting variables limits the ability to preserve features such as causal directionality, state–trait distinction, or generality across constraints. The aim at this stage is minimal structural expressiveness, rather than biological completeness.

Third, STM and other major theory classes are comparatively mapped against the observed constraint set. Using a predefined analytic rubric, theories are characterized according to the degree to which each constraint is explicitly, partially, or not explicitly addressed within their stated architectures, without introducing auxiliary assumptions that substantially alter their core explanatory commitments. This analysis is comparative and descriptive; constraints are treated as external reference points, not as theoretical preferences.

Fourth, fifteen empirically established constraints (E1–E15) are introduced, drawing on robustly replicated findings from epidemiology, neuroscience, pharmacology, longitudinal outcomes, and systems-level analyses. These constraints undergo the same abstraction procedure as the observed constraints. Theory-by-constraint alignment is again characterized using the same analytic rubric to support consistency across domains.

Fifth, the observed and empirical constraint sets are integrated. This integration illustrates how the observed constraints organize and compress multiple empirical regularities into higher-level architectural considerations without internal inconsistency. From this process, a provisional architectural specification is articulated, summarizing structural features that recur across constraints and that may warrant particular attention in future theoretical work. Within this context, Constraint C3—the downstream positioning of neurochemical abnormalities—emerges as a highly discriminative constraint, as it places strong demands on causal ordering and poses challenges for a range of otherwise influential models [14].

Summary Outputs

The primary analytic products of this section are presented as a series of schematic matrices and tables:

- Table 3.2 – Observed Constraints and STM Variables
- Table 3.3 – Mapping of Observed Constraints (C1–C10) to STM Variable Set
- Table 3.4 – Theory × Observed Constraint Matrix (C1–C10)
- Table 3.5 – Empirical Constraint Summary (E1–E15)
- Table 3.6 – Mapping of Empirical Constraints (E1–E15) to Observed Constraints (C1–C10)

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- Table 3.7 – Theory × Empirical Constraint Matrix (E1–E15)
- Box 3.1 – Provisional Architectural Specification

Reading Guide

- Readers interested in comparative explanatory coverage may focus on Tables 3.4 and 3.7, which present theory-by-constraint mappings for observed and empirical domains.
- Readers focused on model architecture and abstraction logic may consult Section 3.3, Tables 3.2–3.3, and Box 3.1.
- Readers prioritizing empirical anchoring and cross-domain integration may consult Table 3.5, Sections 3.5–3.6, and Table 3.6.

3.2. The Ten Observed Constraints (C1–C10): Derivation, Corroboration, and Comparative Relevance

This section introduces a set of ten observed constraints (C1–C10) that summarize recurrent structural considerations commonly emphasized in explanatory accounts of schizophrenia. These constraints are not derived from the Sensitivity Threshold Model (STM), nor are they proposed as theoretical postulates. Rather, they are formulated as non-idiosyncratic regularities, abstracted from recurring empirical patterns in the clinical, phenomenological, pharmacological, and contextual expression of psychosis [15].

The purpose of this section is twofold. First, it makes explicit a set of theory-neutral explanatory targets that recur across the schizophrenia literature, independent of any particular mechanistic proposal. Second, it illustrates how existing theories vary in the degree to which these targets are explicitly addressed, implicitly accommodated, or only partially represented within their stated architectures, sometimes requiring additional assumptions or reinterpretations that affect causal ordering or blur distinctions between state-level and trait-level phenomena [16,17].

In this sense, C1–C10 characterize a set of comparative considerations that are relevant to architectures such as STM, while remaining independent of any specific model's validity or correctness. Their role within the analysis is analytic and comparative, rather than justificatory or prescriptive.

Collectively, these constraints define what is referred to here as the observed constraint set. They are formulated to be model-agnostic, expressed at a level of abstraction that generalizes beyond individual studies while remaining grounded in repeatedly reported clinical and research findings.

Positioned at an intermediate level of abstraction, these constraints sit above empirical particulars (e.g., biomarkers or single-case reports) but below formal model variables [18]. This positioning allows them to:

- Support structured comparison between competing theory classes
- Avoid premature commitment to specific mechanistic explanations
- Maintain contact with the complexity and heterogeneity of real-world clinical phenomena

3.2.1. Derivation Protocol for the Observed Constraints

Each observed constraint (C1–C10) was derived using a fixed, transparent protocol designed to support traceability of reasoning and consistency across constraints. The aim of this protocol is to translate recurring clinical or phenomenological observations into explicit analytic reference points, while avoiding the introduction of model-specific logic, terminology, or assumptions.

For each constraint C_k, six standardized elements are presented:

(1) Phenomenon Statement

A plain-language description of a recurring pattern reported in schizophrenia or psychosis. This description is intentionally non-technical and theory-neutral, focusing on the structural features of the phenomenon rather than proposed mechanisms.

(2) Generalization Step

A justification for treating the phenomenon as a recurrent explanatory consideration. This step identifies the scope of recurrence (e.g., cross-patient, cross-context, cross-phase) and explains why the pattern is frequently emphasized across diagnostic categories or clinical trajectories.

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(3) Constraint Form

A theory-neutral formulation that expresses the phenomenon as a high-level explanatory consideration, phrased to indicate the type of representational challenge it poses for explanatory models, without asserting necessity, sufficiency, or validity. This formalization elevates the pattern from an isolated observation to a comparative analytic reference point.

(4) Corroboration Bundle

A brief summary of the types of evidence that jointly support the relevance of the constraint (e.g., epidemiology, longitudinal course, pharmacologic asymmetries, cross-diagnostic analogs). Citations are provided for context, with emphasis placed on the complementary roles of different evidence classes rather than on individual findings.

(5) Representational Implications

An explanation of how explanatory accounts may be limited or distorted if the phenomenon is not explicitly represented. This may include issues such as circular explanation, mischaracterized causal ordering, or reduced capacity to account for clinically meaningful variability. The intent is to clarify the analytic significance of the constraint, not to imply falsification or failure.

(6) Link Forward to Model Variables

A brief forward reference indicating which STM variable(s) are relevant to representing the constraint and why. This serves as an orientation to Section 3.3, which examines the roles and interactions of STM variables in relation to the observed constraints, rather than as a derivation or proof.

This structured derivation protocol serves three epistemic purposes:

1. It supports independence of constraint formulation by ensuring that each constraint is motivated without reference to STM or any other specific model.
2. It enables readers to examine the constraints on their own terms before considering how different theoretical architectures engage with them.
3. It reinforces the role of observed constraints as external comparative considerations, rather than as internal model properties or reformulations of assumed mechanisms.

The ten constraints derived using this protocol are presented in Sections 3.2.2.1–3.2.2.10, each following the standardized six-part structure.

3.2.2. Observed constraints C1–C10

3.2.2.1. C1 — Stress Can Induce Psychosis (Non-Specificity of the Psychosis Generator)

1. Phenomenon Statement

Psychotic phenomena—including hallucinations, delusions, and disorganized thought—have been reported to emerge in response to acute or sustained stressors, even in individuals without a prior diagnosis of a psychotic disorder [19,20]. Such episodes have been observed following conditions including sleep deprivation, extreme psychosocial stress, sensory overload, medical illness, and high cognitive or emotional demand. In many cases, the resulting states exhibit formal similarities to schizophrenia-spectrum psychosis in content, structure, and severity.

2. Generalization Step

This phenomenon has been documented across diverse settings and populations, including medical inpatient units, military training environments, disaster-affected populations, and experimental paradigms involving sensory deprivation or circadian disruption. It appears across cultures and diagnostic categories. Across these contexts, the common feature is not the nature of the stressor itself, but the system's dynamic state under sustained or extreme load. This recurrence suggests that psychosis may arise as a general system-level response to excessive stress, motivating its treatment as a recurring explanatory consideration rather than as a context-specific anomaly [13,20].

3. Constraint Form

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This constraint highlights the need for explanatory accounts of schizophrenia to address how psychotic states may be precipitated by non-specific stressors, without relying exclusively on mechanisms that are unique to schizophrenia-spectrum conditions. It serves as a theory-neutral reference point for comparing how different models conceptualize the relationship between stress, system state, and psychotic expression.

4. Corroboration Bundle

Multiple lines of evidence support the relevance of this constraint, including:

- Clinical case reports and observational studies describing psychosis associated with sleep deprivation, intensive care unit stays, or acute medical stress.
- Longitudinal studies linking stress exposure to psychotic decompensation or relapse [21].
- Experimental paradigms demonstrating perceptual instability and cognitive disorganization under sustained overload [19,22].
- Phenomenological analyses documenting overlap in symptom content and structure between schizophrenia and transient stress-induced psychotic states [20].

5. Representational Implications

Explanatory models that posit a strictly schizophrenia-specific mechanism for psychosis may encounter difficulties accounting for the close phenomenological overlap between stress-induced psychosis and schizophrenia-spectrum presentations. Addressing this constraint often requires additional assumptions to segregate similar system states into distinct causal categories, which may complicate accounts of relapse, remission, and context-dependent symptom fluctuation under varying environmental or physiological load.

6. Link Forward to Model Variables

This constraint underscores the relevance of state-sensitive constructs that capture variations in external or internal load, along with mechanisms that allow for threshold-like transitions in system behavior. In the STM framework, this consideration is represented through the Load (L) variable, which accumulates stressors and interacts with Sensitivity (S) and Capacity (C) to influence system state. More generally, the constraint highlights the importance of dynamic system properties, which may be less readily captured by exclusively static or trait-based formulations.

3.2.2.2. C2 — Individual Sensitivity Modulates Threshold (Quantitative, Not Categorical Difference)

1. Phenomenon Statement

Individuals differ substantially in their susceptibility to psychosis when exposed to comparable stressors or environmental demands [23,24]. Some individuals exhibit psychotic symptoms under relatively mild perturbations, whereas others maintain stability even under intense or prolonged stress. This variability is observed both within schizophrenia-spectrum populations and across the general population, including individuals without formal psychiatric diagnoses.

2. Generalization Step

This pattern recurs across epidemiological, clinical, and experimental contexts. Vulnerability to psychosis is commonly reported as dimensionally distributed, rather than sharply dichotomized [25]. Subthreshold psychotic experiences, variability in stress tolerance, and differences in relapse thresholds often appear as stable, continuous traits rather than as discrete transitional stages [26]. The absence of a clear boundary between “affected” and “unaffected” individuals prior to onset suggests that psychosis risk may reflect quantitative modulation of system thresholds, rather than the binary presence or absence of a single underlying lesion or disease state [23,25]. This recurrence motivates its treatment as a general explanatory consideration.

3. Constraint Form

This constraint draws attention to the importance of representing individual differences in baseline vulnerability as continuous variations in system sensitivity or threshold. It serves as a theory-neutral reference point for comparing how different explanatory models conceptualize individual susceptibility to psychosis, particularly with respect to dimensional versus categorical formulations.

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4. Corroboration Bundle

Support for this constraint comes from multiple domains, including:

- Population-level studies showing a long-tailed continuum of psychotic-like experiences rather than a bimodal split.
- Dose–response relationships between psychosocial stress and symptom emergence, modulated by individual traits.
- Longitudinal findings demonstrating graded variation in onset timing and relapse likelihood rather than discrete transitions.
- Genetic studies indicating weak, polygenic contributions consistent with a sensitivity continuum [27].

5. Representational Implications

Explanatory models that conceptualize schizophrenia primarily as a categorical condition—such as one arising from a discrete lesion or irreversible switch—may encounter difficulties fully accounting for graded onset patterns, variable relapse trajectories, and the persistence of subthreshold symptoms. Addressing this constraint often requires additional assumptions to partition a continuous vulnerability spectrum into discrete states, which can complicate explanations of early warning signs, partial symptom presentations, and fluctuating remission across developmental trajectories.

6. Link Forward to Model Variables

This constraint highlights the relevance of trait-like parameters that modulate a system's proximity to threshold across individuals. In the STM framework, this role is represented by Sensitivity (S), a continuous variable that interacts with momentary Load (L) and underlying Capacity (C) to influence system state. More generally, the constraint underscores the importance of explicitly representing baseline susceptibility within explanatory architectures, which may be less readily captured by models relying exclusively on state-based triggers or downstream neurochemical effects.

3.2.2.3. C3 — Neurochemical Abnormalities Are State-Dependent and Context-Sensitive (Causal Direction Consideration)

1. Phenomenon Statement

Neurochemical abnormalities commonly associated with schizophrenia—most prominently alterations in dopaminergic signaling—vary with symptom state, environmental context, and treatment exposure [4,14]. These abnormalities often attenuate or partially normalize during remission and do not reliably distinguish schizophrenia from other psychotic or stress-related states [14]. As such, they are frequently observed as state-sensitive correlates rather than as fixed indicators of disease presence.

2. Generalization Step

This pattern recurs across multiple domains. Neurochemical changes tend to track symptom intensity more closely than diagnostic category, appear in non-schizophrenic psychotic states, and can be experimentally modulated through interventions that do not alter baseline vulnerability [4]. Pharmacological treatments often reduce specific symptoms without restoring premorbid cognitive or functional capacity, and similar neurochemical profiles have been reported across distinct conditions involving psychosis or extreme stress [2]. Together, these observations motivate treating neurochemical alterations as context-dependent components within broader system dynamics, rather than as singular initiating causes.

3. Constraint Form

This constraint highlights the importance of causal ordering in explanatory models of schizophrenia, drawing attention to whether neurochemical abnormalities are conceptualized as primary drivers, mediating processes, or downstream correlates within a larger system. It serves as a theory-neutral reference point for comparing how different models position neurochemical changes relative to vulnerability, environmental load, and system state.

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4. Corroboration Bundle

- Support for this constraint comes from converging lines of evidence, including:
- State-dependent associations between neurochemical markers and symptom severity.
- Overlap of neurochemical findings across schizophrenia and non-schizophrenic psychotic states.
- Treatment asymmetries in which symptom reduction occurs without full restoration of baseline cognitive or functional capacity.
- Longitudinal observations showing persistence of vulnerability despite partial neurochemical normalization.

5. Representational Implications

Explanatory models that treat neurotransmitter abnormalities as primary etiological drivers may encounter difficulties fully accounting for the recurrence of similar neurochemical patterns across distinct conditions, the dissociation between symptom fluctuation and fixed neurochemical states, and the often partial or asymmetric effects of pharmacological interventions. Addressing this constraint typically requires careful differentiation between mechanistic correlates and upstream contributors to system instability, in order to avoid circular explanatory loops in which downstream effects are mistaken for initiating causes [4].

6. Link Forward to Model Variables

This constraint underscores the relevance of architectural representations that preserve causal ordering, in which baseline vulnerability and system load precede downstream neurochemical dynamics. Within the STM framework, neurochemical processes are conceptualized as mediating or stabilizing influences operating downstream of Sensitivity, Load, Capacity, and Signal Integrity. More generally, the constraint highlights how different explanatory architectures vary in their treatment of neurochemical changes within multi-level system dynamics.

3.2.2.4. C4 — Symptoms Are State-Dependent and Environmentally Modulated

1. Phenomenon Statement

The severity, form, and prominence of psychotic symptoms are frequently observed to fluctuate in response to changes in both external environmental context and internal physiological or psychological state. Symptoms often intensify under conditions of heightened stimulation, acute stress, sleep disruption, or unpredictability, and may improve in calmer, more structured, or low-demand environments—even in the absence of changes to long-term vulnerability or formal diagnostic status [19,21].

2. Generalization Step

This pattern has been reported across inpatient, outpatient, and naturalistic settings. Within-individual symptom variability correlates with real-time environmental modulation, including changes in social load, sensory input, routine stability, and physiological factors such as fatigue or circadian disruption [24]. Similar dynamic coupling between symptom expression and contextual change has been documented across illness stages and across psychotic-spectrum conditions [20]. The recurrence of this pattern across diverse contexts supports its treatment as a general explanatory consideration rather than as an incidental or context-specific observation.

3. Constraint Form

This constraint draws attention to the importance of representing psychotic symptoms as state-dependent phenomena that are modulated by environmental and contextual factors. It serves as a theory-neutral reference point for comparing how different explanatory models conceptualize symptom variability, particularly with respect to the distinction between transient state dynamics and more stable trait-level vulnerability.

4. Corroboration Bundle

- Support for this constraint comes from converging sources of evidence, including:
- Clinical observations of symptom exacerbation during periods of stress, overstimulation, or disrupted routines.

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- Reports of symptom improvement in low-stimulation or highly structured environments (e.g., quiet inpatient settings or nature-based contexts).
- Relapse patterns associated with environmental destabilization, such as transitions or loss of routine [21].
- Experimental findings linking contextual manipulation to shifts in salience attribution, perception, and cognitive coherence [24].

5. Representational Implications

Explanatory models that conceptualize symptoms primarily as fixed outputs of an underlying disease entity may encounter difficulties accounting for rapid within-person variability and context-dependent symptom change. Addressing this constraint often requires additional mechanisms to explain how environmental modulation influences symptom expression, particularly in relation to remission, relapse, and moment-to-moment clinical dynamics.

6. Link Forward

This constraint highlights the relevance of time-varying, context-sensitive state variables that are distinct from baseline vulnerability. Within the STM framework, these considerations are represented by variables such as Load (L) and Signal Integrity (SI), which mediate how external input and internal state influence symptom expression. More generally, the constraint underscores the importance of distinguishing dynamic state processes from trait-level sensitivity in explanatory architectures, in order to capture the reversible and modulatory nature of psychotic states.

3.2.2.5. C5 — Onset Timing Is Variable and Context-Sensitive

1. Phenomenon Statement

The timing of psychosis onset in schizophrenia shows substantial variability across individuals and at-risk populations. Although incidence rates peak during adolescence and early adulthood, first-episode psychosis has also been reported in childhood, midlife, and later life [15,20]. Onset is frequently observed in association with contextual changes such as developmental transitions, major life stressors, sleep disruption, substance exposure, or cumulative environmental demand [13,21].

2. Generalization Step

This variability has been documented across epidemiological surveys, clinical cohort studies, and longitudinal follow-ups. No single age range, developmental milestone, or biological marker consistently predicts onset timing [15]. Instead, onset appears sensitive to interactions between environmental conditions and internal regulatory capacity, even among individuals with comparable trait-level vulnerability. The recurrence of this pattern across populations and cultural contexts motivates its treatment as a general explanatory consideration in schizophrenia research [20].

3. Constraint Form

This constraint highlights the importance of accounting for temporal variability in psychosis onset, with attention to how timing may depend on contextual factors and system state rather than being rigidly determined by fixed biological triggers. It provides a theory-neutral reference point for comparing how different explanatory models conceptualize the relationship between vulnerability, environmental exposure, and the timing of symptom emergence.

4. Corroboration Bundle

Evidence relevant to this constraint includes:

- Epidemiological findings showing broad, non-normal distributions of age at first psychosis onset.
- Longitudinal studies linking onset timing to psychosocial stressors, life transitions, or cumulative environmental burden.
- Observations of early or delayed onset associated with modifiable external factors such as migration, trauma, or substance exposure.
- Cross-cultural research demonstrating similar timing variability under differing societal and developmental norms.

5. Representational Implications

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Explanatory models that emphasize fixed developmental lesions, narrowly defined critical periods, or time-locked biological processes may encounter difficulties accounting for the full observed distribution of onset timing. Addressing this constraint often requires additional assumptions to reconcile early, typical, and late onset cases within a single framework, particularly when individuals with similar baseline vulnerability diverge markedly in the timing of symptom emergence.

6. Link Forward

This constraint underscores the relevance of state-dependent, time-varying processes whose interaction with trait-level vulnerability influences when psychotic instability emerges. Within the STM framework, these considerations are represented by the dynamic interaction of Load (L), Sensitivity (S), and Capacity (C), allowing onset to be conceptualized as a context-sensitive phase transition rather than as a fixed or biologically preordained event. More generally, the constraint highlights the importance of representing temporal dynamics in explanatory architectures of schizophrenia.

3.2.2.6. C6 — Cognitive and Sensory Changes Commonly Precede Psychosis (Prodromal Overload)

1. Phenomenon Statement

Prior to the emergence of overt psychotic symptoms, many individuals exhibit progressive changes in cognition, sensory processing, and everyday functioning [28,31]. These changes often include declines in attention, working memory, processing speed, sensory filtering, and adaptive behavior, and may be accompanied by subjective experiences of overload, confusion, or heightened perceptual sensitivity.

2. Generalization Step

This temporal pattern has been reported across prodromal-phase research, first-episode cohorts, retrospective clinical accounts, and studies of individuals at elevated risk for psychosis. Cognitive and sensory disturbances are frequently observed months or years before the onset of frank psychotic symptoms [28,29], and in some cases persist or evolve regardless of whether a full psychotic episode ultimately occurs [29,31]. The consistency of this early-phase pattern across methodologies and populations motivates its treatment as a general explanatory consideration regarding the temporal structure of psychosis development.

3. Constraint Form

This constraint draws attention to the temporal ordering of cognitive, sensory, and functional changes relative to the onset of psychotic symptoms. It serves as a theory-neutral reference point for comparing how different explanatory models conceptualize early system strain, prodromal dynamics, and the relationship between pre-psychotic changes and later symptom emergence.

4. Corroboration Bundle

Evidence relevant to this constraint includes:

- Longitudinal studies of high-risk and prodromal individuals demonstrating early neurocognitive decline.
- Neuropsychological assessments revealing impairments in working memory, attention, and executive function prior to psychosis onset.
- Sensory processing abnormalities (e.g., gating and filtering deficits) detected in at-risk populations [30].
- Functional deterioration in education, employment, and self-care preceding first-episode psychosis [31].

5. Representational Implications

Explanatory models that conceptualize psychosis as the initiating pathological event—whether neurochemical, perceptual, or computational—may encounter difficulties accounting for the systematic presence of early cognitive and sensory change. Addressing this constraint often requires additional mechanisms to integrate prodromal strain, early functional decline, and later symptom

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emergence within a single temporal framework, particularly when these early features are not easily reducible to downstream effects of psychosis or treatment.

6. Link Forward

This constraint highlights the relevance of processes that evolve prior to overt psychotic instability, distinguishing early system strain from later state-level collapse. Within the STM framework, these considerations are represented through limitations in Capacity (C) and the accumulation of Load (L), which precede and increase vulnerability to subsequent disruptions in Signal Integrity (SI). More generally, the constraint underscores the importance of representing the prodrome as a period of progressive system stress, rather than as a symptom-free waiting phase, within explanatory architectures of schizophrenia.

3.2.2.7. C7 — Symptom Content Is Meaningfully Linked to Experience (Structured Symptoms, Not Random Noise)

1. Phenomenon Statement

The content of psychotic symptoms—particularly delusions and hallucinations—has frequently been reported to show systematic connections to an individual's personal experiences, emotional concerns, cultural context, and prior beliefs [32,34]. Rather than appearing arbitrary, symptom content often centers on personally salient themes, recent stressors, or culturally available narratives [32], suggesting that psychotic experiences commonly retain structured and semantically meaningful organization.

2. Generalization Step

This pattern has been observed across cultures, historical periods, clinical subtypes, and diagnostic categories [33]. Although surface-level content varies, the internal logic, thematic organization, and experiential relevance of psychotic symptoms are often preserved. Even in acute or first-episode presentations—and across schizophrenia as well as other stress-related psychotic states—symptom content has been described as exhibiting coherent semantic structure [33,36]. The recurrence of this pattern across contexts motivates its treatment as a general explanatory consideration in models of psychosis.

3. Constraint Form

This constraint highlights the importance of accounting for the structured and experience-linked nature of psychotic symptom content, serving as a theory-neutral reference point for comparing how different explanatory models address semantic organization, meaning attribution, and the relationship between internal representations and lived experience.

4. Corroboration Bundle

Evidence relevant to this constraint includes:

- Phenomenological analyses documenting narrative and symbolic coherence in delusions and hallucinations.
- Cross-cultural studies demonstrating thematic adaptation of symptom content to local beliefs, threats, and sociocultural frameworks.
- Longitudinal research linking symptom emergence to specific stressors, traumas, or unresolved concerns [35].
- Cognitive neuroscience findings indicating partial preservation of semantic networks even during acute psychotic episodes.

5. Representational Implications

Explanatory approaches that emphasize undifferentiated neural noise, stochastic signal loss, or non-specific circuit disruption may encounter difficulties accounting for the consistent semantic organization observed in many psychotic experiences. Addressing this constraint often requires additional mechanisms to explain how meaning, narrative structure, and experiential relevance are maintained—even as cognitive control, precision, or stability becomes compromised.

6. Link Forward

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This constraint underscores the relevance of architectural features that allow representational structure to be altered without being entirely lost. Within the STM framework, these considerations are captured by the Signal Integrity (SI) variable, which reflects the coherence and organization of internal representations under varying levels of system load. More generally, the constraint highlights the importance of distinguishing between structured representational disruption and unstructured noise when comparing explanatory models of psychosis.

3.2.2.8. C8 — Antipsychotic Treatment Produces Symptom Dampening with Limited Functional Restoration

1. Phenomenon Statement

Antipsychotic medications are consistently reported to reduce the intensity and frequency of positive psychotic symptoms, such as hallucinations and delusions, in many individuals [4,37]. These effects are often partial, vary substantially across individuals, and are frequently not accompanied by corresponding improvements in cognitive performance, negative symptoms, or long-term functional capacity [2,38].

2. Generalization Step

This asymmetric treatment profile has been observed across medication classes, illness stages, diagnostic subgroups, and longitudinal studies. Symptom reduction commonly occurs without restoration of premorbid functioning, and relapse is frequently reported following medication discontinuation [37]. In addition, antipsychotics have demonstrated similar symptom-reducing effects in non-schizophrenic psychotic states, such as delirium or mania [39]. The recurrence of this pattern across conditions and contexts motivates its treatment as a general explanatory consideration regarding treatment response in psychosis.

3. Constraint Form

This constraint highlights the importance of distinguishing between symptom suppression and broader changes in baseline vulnerability or system organization. It serves as a theory-neutral reference point for comparing how different explanatory models interpret antipsychotic treatment effects, particularly with respect to whether symptom improvement is taken to reflect modulation of system state, alteration of upstream contributors, or both.

4. Corroboration Bundle

Evidence relevant to this constraint includes:

- Randomized controlled trials demonstrating consistent reduction of positive symptoms without proportional gains in cognitive function or real-world outcomes.
- High relapse rates following medication discontinuation, even after periods of clinical stabilization.
- Use of antipsychotics across diagnostic categories, including delirium, mania, and ICU-associated psychosis, suggesting non-specific effects on psychotic symptom expression [39–41].
- Longitudinal findings showing dissociation between short-term symptom control and long-term functional trajectory.

5. Representational Implications

Explanatory models that interpret antipsychotic response primarily as evidence of correction of an underlying etiological process may encounter difficulties accounting for persistent functional impairment, residual symptoms, and symptom recurrence following medication withdrawal. Addressing this constraint often requires maintaining a distinction between mechanisms of symptom modulation and mechanisms contributing to long-term vulnerability, in order to avoid conflating treatment effects with causal origins [2,4].

6. Link Forward

This constraint underscores the relevance of distinguishing between system stabilization and system repair within explanatory architectures. In the STM framework, antipsychotic effects are conceptualized as reducing system reactivity or filtering salience—thereby lowering acute overload—without necessarily increasing baseline Capacity (C) or restoring Signal Integrity (SI).

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More generally, the constraint highlights how different models conceptualize the trade-off between symptom dampening and long-term functional change when interpreting pharmacological interventions.

3.2.2.9. C9 — Repeated Episodes Are Associated with Increased Vulnerability Over Time (Sensitization / Progressive Vulnerability)

1. Phenomenon Statement

Following an initial psychotic episode, subsequent episodes are often reported to occur more readily, sometimes being triggered by lower-intensity stressors or environmental perturbations than those associated with the first episode [42,43]. Over time, relapse risk may increase, intervals between episodes may shorten, and recovery may appear less complete, even when baseline vulnerability factors seem relatively stable [43,44].

2. Generalization Step

This pattern has been documented across longitudinal studies, first-episode cohorts, relapse prediction models, and naturalistic follow-up data [43,44]. It is not fully accounted for by medication adherence, psychosocial stressors, or diagnostic progression alone. Similar sensitization-like effects have also been described in other stress-related and neurological conditions, supporting its interpretation as a general system-level phenomenon rather than as a schizophrenia-specific anomaly. The recurrence of this pattern across contexts motivates its treatment as a general explanatory consideration.

3. Constraint Form

This constraint highlights the importance of representing history-dependent changes in vulnerability, drawing attention to whether explanatory models treat psychotic episodes as isolated and fully reversible events or as experiences that may alter future system stability. It provides a theory-neutral reference point for comparing how different models conceptualize relapse risk, recovery, and long-term course.

4. Corroboration Bundle

Evidence relevant to this constraint includes:

- Longitudinal studies demonstrating increasing relapse risk following successive psychotic episodes [42,44].
- Findings linking longer duration of untreated psychosis (DUP) to poorer long-term outcomes, suggesting that early intervention may influence subsequent vulnerability trajectories [45].
- Observations of reduced stress tolerance and symptom reactivation at lower levels of environmental load following relapse.
- Analogous sensitization phenomena described in epilepsy, PTSD, mood disorders, and immune priming models, indicating a broader principle of progressive threshold change [46,47].

5. Representational Implications

Explanatory models that conceptualize psychotic episodes as discrete, fully reversible perturbations may encounter difficulties accounting for increasing relapse susceptibility and incomplete recovery over time. Addressing this constraint often requires additional mechanisms to capture path-dependent dynamics, particularly when worsening course cannot be attributed solely to external stressors or to progressive structural damage.

6. Link Forward

This constraint underscores the relevance of history-sensitive processes through which prior episodes influence future system stability. Within the STM framework, these considerations are represented as progressive reductions in effective Capacity (C) or cumulative changes in Signal Integrity (SI), which narrow the margin between stability and destabilization. More generally, the constraint highlights how different explanatory architectures represent the long-term impact of repeated episodes on vulnerability, without presupposing irreversible damage or fixed deficit models.

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3.2.2.10. C10 — Schizophrenia Is Associated with Cross-System Coupling Between Neural, Immune, and Stress-Regulatory Processes

1. Phenomenon Statement

Psychotic disorders, including schizophrenia, have frequently been reported to co-occur with indicators of immune dysregulation, systemic inflammation, and heightened physiological stress sensitivity [48,49]. Individuals with schizophrenia show elevated rates of autoimmune conditions, increased inflammatory marker levels, and amplified biological responses to stress, often concurrent with or predictive of neuropsychiatric symptom expression [48].

2. Generalization Step

These patterns have been documented across epidemiological surveys, clinical case–control cohorts, and biomarker studies, and are not confined to a single illness phase or patient subgroup. Similar associations between immune activity, stress regulation, and symptom expression have been reported in episodic conditions such as depression, PTSD, and bipolar disorder, suggesting that schizophrenia may participate in a broader class of systemically coupled disorders [50]. The recurrence of these associations across conditions and systems motivates their treatment as a general explanatory consideration, rather than as incidental comorbid findings.

3. Constraint Form

This constraint highlights the importance of considering coupled dynamics across neural, immune, and stress-regulatory systems when evaluating explanatory models of schizophrenia. It serves as a theory-neutral reference point for comparing how different models conceptualize cross-system interactions, as opposed to attributing symptom emergence solely to brain-isolated mechanisms or single-pathway processes.

4. Corroboration Bundle

Evidence relevant to this constraint includes:

- Elevated prevalence of autoimmune and inflammatory conditions among individuals diagnosed with schizophrenia.
- Associations between pro-inflammatory markers (e.g., cytokines) and symptom severity or relapse risk [49].
- Findings linking stress–immune system interactions, including maternal immune activation, to increased schizophrenia susceptibility [51,52].
- Cross-diagnostic studies reporting relationships between immune dysregulation and psychiatric instability, consistent with shared pathways of systemic vulnerability.

5. Representational Implications

Explanatory models that focus narrowly on isolated neural circuits or neurotransmitter-specific processes may encounter difficulties accounting for the consistent interaction between immune activation, physiological stress, and symptom modulation reported across studies. Addressing this constraint often requires additional mechanisms to integrate immune and stress-related influences with neural dynamics, rather than treating such findings as secondary or unrelated phenomena.

6. Link Forward

This constraint underscores the relevance of systems-level representations in which load is not limited to neural information processing, but also encompasses physiological, immunological, and endocrine stressors. Within the STM framework, these influences are incorporated as non-neural load vectors interacting with Sensitivity (S) and Capacity (C), enabling cross-system coupling without presupposing a single etiological pathway. More generally, the constraint highlights how different explanatory architectures integrate—or compartmentalize—multi-system influences in models of schizophrenia.

3.2.2.11. Consolidated Summary of Observed Constraints (Table 3.2)

Table 3.2 provides a consolidated summary of the ten observed constraints (C1–C10), outlining their formulation, corroboration domains, and their implications for explanatory model architectures.

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Constraint # / Name	Constraint summary	Derivation notes	Corroboration tags	Comparative implications for model architectures	Forward link (STM variables)
C1 — Stress-induced psychosis	Psychotic states are frequently observed in response to non-specific stressors across contexts, not exclusively in disease-specific conditions.	Psychosis under sleep loss, stress, overload; phenomenological similarity across contexts	stress-psychosis, relapse, cross-context	Highlights the relevance of state-dependent instability mechanisms beyond disease-specific generators	Load (L), Sensitivity (S), Capacity (C)
C2 — Quantitative vulnerability	Susceptibility to psychosis varies continuously across individuals rather than presenting as a categorical condition.	Graded risk and threshold variation; continuum of subthreshold phenomena	epidemiology, genetics, course	Poses challenges for strictly binary or fixed-lesion disease models	Sensitivity (S)
C3 — Downstream neurochemistry	Neurochemical abnormalities are commonly observed as state-dependent mediators rather than invariant initiating causes.	State tracking of dopamine; non-specificity across psychoses	pharmacology, state-dependence	Draws attention to causal ordering and the distinction between mediators and upstream contributors	Signal Integrity (SI), Load (L)
C4 — State-dependent symptoms	Symptom expression fluctuates with environmental and internal state rather than remaining fixed across contexts.	Contextual worsening/improvement; within-person variability	course, environment, stress	Highlights the importance of dynamic state variables in symptom modeling	Load (L), Signal Integrity (SI)
C5 — Variable onset timing	Psychosis onset occurs across a wide temporal range and is sensitive to contextual and developmental factors.	Wide age-of-onset distribution; trigger-linked first episodes	epidemiology, life events	Challenges models based on rigid developmental clocks or time-locked lesions	Load (L) × Sensitivity (S)
C6 — Prodromal overload	Cognitive, sensory, and functional changes commonly precede overt psychosis.	Early cognitive decline; pre-psychotic functional changes	prodrome, cognition, perception	Highlights the need to represent early system strain preceding symptom collapse	Capacity (C), Load (L)
C7 — Structured symptom content	Psychotic symptoms frequently retain meaningful, experience-linked structure rather than appearing as random noise.	Thematic delusions/hallucinations; cultural and experiential coupling	phenomenology, cross-cultural	Draws attention to representational coherence under instability	Signal Integrity (SI)
C8 — Medication asymmetry	Antipsychotic treatment commonly reduces positive symptoms without proportional restoration of	Positive symptom reduction; limited cognitive restoration	pharmacology, outcomes	Highlights the distinction between symptom stabilization and long-term vulnerability	Sensitivity (effective), Load (L)

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	cognitive or functional capacity.				
C9 — Sensitization over time	Recurrent episodes are often associated with increased relapse susceptibility and reduced resilience.	Increased relapse risk; reduced recovery after episodes	longitudinal course, relapse	Emphasizes the importance of history-dependent dynamics	Capacity (C), Signal Integrity (SI)
C10 — Cross-system coupling	Schizophrenia is frequently associated with immune and stress-regulatory system interactions.	Immune/inflammatory overlap; stress–physiology coupling	immune, stress, cross-diagnostic	Highlights cross-system integration beyond brain-isolated mechanisms	Load (L), Sensitivity (S)

Table 3.2. This consolidated table closes the observed-constraint arc of the Results section. In the following section (3.3), these constraints are used to examine how a small set of abstract variables can jointly represent C1–C10 while preserving causal ordering, state–trait distinction, and generality at the level of abstraction considered. C1 [17,19,21,22,24], C2 [20,23,25–27], C3 [4,5,14], C4 [19,24], C5 [21,26,31], C6 [28,29,31], C7 [32–35], C8 [37,38,45], C9 [42–44,46,47], C10 [48–52]

3.3. Rationale for Proposing a Four-Variable STM Architecture to Represent the Observed Constraints

The ten observed constraints summarized in Section 3.2 place multiple, and in some cases competing, demands on explanatory architectures. Considered individually, several of these constraints can be addressed within existing theoretical models. Considered jointly, however, they highlight recurring challenges related to abstraction level, causal ordering, and the distinction between stable vulnerability and dynamic state processes.

The purpose of this section is to examine whether a small set of abstract variables—Sensitivity, Load, Capacity, and Signal Integrity—is collectively adequate to represent the full observed constraint set (C1–C10) at the level of abstraction considered, without internal inconsistency or reliance on ad hoc auxiliary constructs. This analysis is intended as a conceptual and architectural examination, rather than as a biological derivation or formal mathematical proof.

Across prior theoretical approaches, three recurring representational challenges motivate this examination.

First, explanatory frameworks with overly collapsed variable structures often blur causal ordering, particularly with respect to downstream neurochemical processes (Constraint C3) [4,5,14]. When baseline vulnerability, dynamic instability, and neurochemical mediation are represented at a single causal level, neurotransmitter changes may implicitly assume an initiating role rather than being treated as context-dependent mediators. This representational compression can complicate alignment with state dependence, non-specificity across psychotic conditions, and treatment asymmetry.

Second, reduced-variable formulations frequently conflate stable individual vulnerability with fluctuating contextual burden, creating tension with Constraints C2, C4, and C5 [20,23–27,31]. Without distinct representations of trait-like sensitivity and time-varying load, it becomes difficult to simultaneously account for quantitative differences in susceptibility, context-dependent symptom modulation, and variability in onset timing. Attempts to address this gap often rely on loosely defined modifiers (e.g., “stress,” “severity,” or “stage”) that function descriptively but lack explicit architectural status.

Third, explanatory accounts that do not explicitly represent representational coherence or integrity encounter challenges in addressing Constraint C7 [32–35]. In such cases, the structured and experience-linked content of psychotic symptoms may be treated as incidental, epiphenomenal, or

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external to the model's ontology, requiring additional assumptions to reconcile phenomenological organization with underlying mechanisms.

The Sensitivity Threshold Model addresses these challenges by introducing four abstract variables at a level of generality intended to preserve separation between vulnerability, dynamic load, system capacity, and representational coherence. Each variable contributes distinct explanatory roles across multiple constraints, and exploratory comparison suggests that collapsing or omitting any one of them tends to reintroduce one or more of the representational challenges outlined above. Conversely, introducing additional abstract variables at this level does not obviously increase coverage of the observed constraint set, and may instead introduce redundancy or unnecessary complexity.

In the subsections that follow, we first outline concise operational characterizations of the four variables (Section 3.3.1). We then examine how each variable contributes to representing specific constraints (Section 3.3.2), followed by a systematic mapping between constraints and variables (Section 3.3.3). The section concludes with a non-redundancy analysis that explores why alternative formulations with fewer or merged variables encounter difficulties in representing C1–C10 coherently at the same level of abstraction (Section 3.3.4).

Taken together, this analysis motivates the four-variable STM architecture as a parsimonious and internally consistent representational framework for organizing the observed constraints, without implying biological completeness, exclusivity, or finality.

3.3.1. Operational Characterization of the Four STM Variables

To organize the observed constraint set (C1–C10) at a common level of abstraction, the Sensitivity Threshold Model introduces four abstract variables. These variables are defined functionally and operationally rather than as direct biological substrates. Their role is to support comparative analysis by carrying recurring constraint-relevant distinctions, rather than to specify mechanisms or etiological pathways (Constraints C1–C10 supported by [17–36,42–52]).

Each variable is introduced based on three guiding considerations:

1. It contributes to representing multiple observed constraints within a single architectural framework.
2. It captures a distinction that becomes difficult to preserve when variables are collapsed or conflated.
3. It can, in principle, be mapped to downstream biological or computational mechanisms without altering its abstract representational role.

The four variables are characterized as follows.

V1. Sensitivity (S)

Sensitivity is a trait-like gain or responsivity parameter that reflects how strongly a system reacts to internal or external perturbations. Higher sensitivity implies that a given input—whether sensory, cognitive, emotional, or physiological—has a larger effective impact on system stability. Sensitivity varies continuously across individuals, remains relatively stable over time compared to state-dependent factors, and influences baseline proximity to instability. Rather than generating symptoms directly, Sensitivity modulates how readily fluctuations in Load influence system state [20,23,25–27].

V2. Load (L)

Load is a state-dependent, cumulative burden acting on the system. It encompasses acute and chronic demands arising from environmental stressors, sensory stimulation, cognitive and emotional effort, sleep disruption, substance exposure, physiological illness, and immune or metabolic activation. Load fluctuates over time, may accumulate or dissipate, and is closely associated with transitions between relatively stable and unstable system states. Load is conceptually distinct from Sensitivity: similar levels of demand may be tolerated by one system while destabilizing another [17,19,21,22,24,48–52].

V3. Capacity (C)

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Capacity refers to the system's available processing, buffering, and compensatory resources—its functional reserve for maintaining stability under load. It includes integrative ability, inhibitory control, adaptive flexibility, and resilience to perturbation. Unlike Sensitivity, Capacity can vary over time as a function of development, stress exposure, recovery processes, or repeated destabilizing episodes. Capacity constrains both tolerance to load and the extent of recovery following instability [28,29,31,42–47].

V4. Signal Integrity (SI)

Signal Integrity is a representational quality parameter describing the clarity, coherence, and reliability of internal and external signals. High signal integrity corresponds to stable signal-to-noise ratios and coherent inference, whereas degraded signal integrity reflects noisy, ambiguous, or unstable representations. Signal Integrity is symptom-proximal: alterations in its quality are closely associated with hallucinations, delusions, and disorganization. Reduced signal integrity can also increase effective load by requiring greater processing effort to resolve ambiguity, creating feedback between representational degradation and system instability [32–36].

Together, these variables provide a structured way to distinguish between baseline vulnerability, time-varying demand, buffering capacity, and representational coherence. Exploratory comparison suggests that when any of these distinctions is omitted or collapsed, specific observed constraints become more difficult to represent coherently at the same level of abstraction.

In the following section, we examine how each variable contributes to representing particular observed constraints, and how alternative formulations that merge or omit variables encounter recurring representational challenges (Section 3.3.2).

3.3.2. Constraint–Variable Contribution Analysis

This section examines how each of the four STM variables contributes to representing specific observed constraints, and how alternative formulations that omit or collapse variables encounter recurring representational challenges. Rather than establishing formal necessity, the analysis is intended to clarify which distinctions appear difficult to preserve when particular variables are not explicitly represented, given the observed constraint set.

Sensitivity (S): Representing Quantitative Vulnerability Differences

Observed Constraint C2 highlights that vulnerability to psychosis varies quantitatively across individuals rather than categorically [20,23,25–27]. This heterogeneity is relatively stable over time and shapes how individuals respond to comparable perturbations.

In formulations that do not explicitly distinguish a trait-like vulnerability dimension, susceptibility is typically encoded either as a categorical disease state or as an indirect function of exposure history. Categorical encodings struggle to reflect the observed continuum of vulnerability, while exposure-based encodings make it difficult to explain why similar perturbations yield divergent outcomes across individuals.

Introducing a Sensitivity parameter provides a straightforward way to represent graded differences in baseline responsivity while maintaining a separation between vulnerability and momentary state. Comparative analysis suggests that this distinction becomes harder to preserve when Sensitivity is collapsed into other variables, particularly without introducing additional assumptions.

Load (L): Representing Dynamic State Pressure

Observed Constraints C1, C4, and C5 emphasize that psychosis can be precipitated, modulated, and temporally patterned by environmental and contextual factors such as stress, sleep disruption, or stimulation [17,19,21,22,24,26,31]. These influences are transient, cumulative, and reversible, suggesting a driver that varies over time.

In models without an explicit state-dependent load dimension, contextual effects are often absorbed into shifting vulnerability parameters or treated as secondary modifiers. Such approaches can blur the distinction between trait and state, and complicate unified representation of acute spikes, remission, and cumulative burden.

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Explicitly representing Load allows these state-dependent influences to be tracked without conflating them with baseline vulnerability, and helps maintain coherence across constraints involving onset timing, symptom fluctuation, and relapse dynamics.

Capacity (C): Representing Prodrome and Sensitization

Observed Constraints C6 and C9 indicate that systems can undergo progressive strain prior to overt psychosis (prodrome) and exhibit altered resilience following destabilizing episodes (sensitization) [28,29,31,42–47]. These patterns imply a dimension that can degrade, partially recover, and evolve over time.

When no explicit capacity-like variable is included, prodromal changes are often reinterpreted as early symptoms or fixed traits, while sensitization effects are attributed to unmodeled degenerative processes. These strategies make it difficult to represent gradual, history-dependent changes in tolerance within a unified framework.

Including Capacity as a distinct dimension provides a way to represent evolving system resources and recovery dynamics without collapsing early strain into symptom expression or invoking additional mechanisms.

Signal Integrity (SI): Representing Structured Symptom Content and Causal Ordering

Observed Constraints C7 and C3 jointly emphasize that psychotic symptoms exhibit structured, experience-linked content, while neurochemical changes are typically state-dependent and downstream [4,5,14,32–36].

Variables governing load magnitude or tolerance do not directly capture representational quality. In formulations without an explicit coherence-related dimension, symptom structure is often treated as incidental or embedded within neurochemical processes, which can complicate preservation of causal ordering.

Introducing Signal Integrity allows representational degradation to be modeled directly, while maintaining neurochemical modulation as a downstream stabilizing influence rather than an initiating cause.

Summary and Scope

Across these comparisons, each variable appears to support a distinct representational role tied to specific observed constraints. When variables are omitted or collapsed, recurring difficulties arise in preserving causal ordering, state–trait separation, or phenomenological structure at the same level of abstraction. Conversely, introducing additional abstract variables at this level does not obviously resolve these difficulties and may introduce redundancy.

Addendum: Constraint C10 and Cross-System Scope

Observed Constraint C10 does not introduce an additional abstract variable, but places scope requirements on existing ones. In particular, Load and Capacity must be defined broadly enough to accommodate non-neural physiological processes, including immune and metabolic activity [48–52]. Restricting these variables to brain-internal mechanisms complicates representation of cross-system coupling observed in schizophrenia and related conditions.

3.3.3. Representation of Observed Constraints at a Common Level of Abstraction

Introduction to Table 3.3 (Results text)-

Building on the preceding variable definitions and comparative analyses, this section examines how the observed constraint set (C1–C10) can be represented at a common level of abstraction using the four STM variables. Table 3.3 maps each observed constraint to one or more STM variables—Sensitivity (S), Load (L), Capacity (denoted here as K to avoid confusion with constraint labels), and Signal Integrity (I)—indicating which variables play primary or supporting roles in representing each constraint [17–27,31–35,37,38,42–52].

This mapping step serves two analytic purposes. First, it illustrates how the same small set of abstract variables contributes to representing multiple, independent constraints, rather than being introduced in a one-constraint-per-variable manner. Second, it provides a transparent account of how

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distinctions such as causal ordering, state–trait separation, and phenomenological structure are preserved at the chosen level of abstraction.

The table should be read as a comparative representational aid, not as a proof of exclusivity or optimality. It is intended to clarify how different constraints place representational demands on explanatory architectures, and how those demands can be jointly organized using a limited number of abstract dimensions.

Table 3. 3 Observed constraints (C1–C10) → STM variables {S, L, K, I}.

Notation: S = Sensitivity, L = Load, K = Capacity (used instead of C to avoid confusion with constraint labels C1–C10), SI or I = Signal Integrity.			
Constraint (Ck)	Primary carrier variable(s)	Secondary carrier(s)	Mapping justification (why these variables must carry it)
C1 — Stress can induce psychosis	L, S	K, I	Stress, sleep loss, and overload are most naturally represented as state-dependent load (L) acting on baseline vulnerability (S). Capacity (K) influences tolerance to stress, while Signal Integrity (I) reflects downstream destabilization as overload increases.
C2 — Individual sensitivity modulates threshold	S	K	Quantitative variation in vulnerability is readily captured by a trait-like gain parameter (S). Capacity (K) can influence tolerance margins, but does not on its own capture stable interindividual differences without blurring trait–state distinctions.
C3 — Neurochemical abnormalities downstream	L, K *(upstream)*; I *(symptom-proximal)*	S	This constraint highlights the importance of causal ordering: increasing load (L) interacting with limited capacity (K) precedes instability, while Signal Integrity (I) reflects symptom-proximal coherence changes. Neurochemical processes are treated as downstream mediators rather than initiating variables.
C4 — Symptoms are state-dependent, environmentally modulated	L, I	K, S	Environmental modulation is readily represented by a state variable tracking context (L) together with a variable tracking representational coherence (I). Capacity (K) influences stability under changing load, while Sensitivity (S) modulates amplification without accounting for within-person state fluctuation on its own.
C5 — Onset timing variable and context-sensitive	L	S, K	A wide and context-sensitive onset distribution aligns with dynamic load trajectories (L), including spikes and accumulation, interacting with baseline sensitivity (S) and buffering capacity (K). Trait vulnerability alone does not capture timing variability.

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C6 — Cognitive & sensory symptoms precede psychosis	K, L	I, S	Prodromal cognitive and sensory changes are readily represented as capacity strain (K) under rising load (L) prior to overt psychosis. Signal Integrity (I) begins to degrade near threshold, while Sensitivity (S) modulates the impact of early load.
C7 — Symptom content is structured, not random	I	L, S	Experience-linked and semantically structured symptom content is naturally associated with a representational or coherence dimension (I). Load (L) may increase noise and Sensitivity (S) may amplify salience, but neither alone captures structured content without an integrity-related construct.
C8 — Antipsychotics reduce sensitivity (dampening tradeoff)	S (effective) *(and/or L_effective)*	I, K	Medication effects are readily represented as reductions in effective gain (S_effective) and/or effective load, stabilizing symptoms without restoring baseline capacity (K). Improvements in Signal Integrity (I) follow downstream as instability decreases.
C9 — Repeated episodes lower future thresholds	K	I, L, S	Sensitization over time aligns with history-dependent erosion of functional reserve (K) and/or persistent reductions in Signal Integrity (I), narrowing tolerance to future load. Apparent changes in Sensitivity (S) may occur state-wise, but the key distinction involves degradable system resources.
C10 — Overlap with immune & stress illness	L	S, K	Cross-system coupling is readily accommodated when load (L) includes immune, inflammatory, and physiological stressors in addition to psychological demands. Sensitivity (S) captures generalized reactivity, while Capacity (K) reflects system-level reserve influenced by non-neural burdens.
The mapping shown in Table 3.3 does not assign a unique variable to each constraint. Instead, each STM variable contributes to representing multiple independent constraints (e.g., Load contributes to C1, C4, C5, C6, and C10; Sensitivity contributes to C2 and modulates several others; Capacity contributes to C6 and C9; Signal Integrity contributes to C7 and supports causal ordering in C3 and C4). This reuse highlights abstraction at a common architectural level rather than bespoke, one-to-one constructions.			

Interpretive Notes

Table 3.3 shows how each observed constraint is associated with one or more STM variables at the level of abstraction considered. For each constraint, the table identifies primary carrier variables—those most directly involved in representing the constraint—as well as secondary variables that modulate or support that representation. Neurochemical abnormalities are treated as downstream mediators rather than primary variables, consistent with the causal-direction considerations emphasized in Constraint C3.

To avoid notational ambiguity, Capacity is denoted as K throughout this subsection (K ≡ Capacity as defined in Section 3.3.1), while Sensitivity, Load, and Signal Integrity are denoted as S, L, and I, respectively.

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This mapping highlights how the STM variables are reused across constraints, rather than tailored to individual phenomena, helping to distinguish systematic abstraction from bespoke patching. It does not imply that alternative variable sets could not represent similar mappings, nor that the STM formulation is unique or final.

While Table 3.3 illustrates one way in which the observed constraints can be organized using the four STM variables, representational adequacy alone does not settle questions of parsimony or redundancy. In principle, alternative formulations involving additional variables or partial collapses could also be explored. The following section (3.3.4) therefore examines how reduced or merged variable formulations encounter recurring representational challenges when attempting to preserve causal ordering, state–trait distinction, and phenomenological coherence at the same level of abstraction.

3.3.4. Representational Implications of Reduced or Collapsed Variable Sets

The analyses above motivate a four-variable STM architecture by examining how different abstract distinctions contribute to representing the observed constraints at a common level of abstraction. As a complementary step, this section explores how reduced or collapsed variable formulations encounter recurring representational challenges when applied to the same constraint set.

Rather than establishing formal failure or optimality, the purpose here is to clarify which distinctions become difficult to preserve when fewer than four abstract variables are explicitly represented. These challenges are structural in nature and recur across different modeling choices, rather than depending on specific parameter values or implementation details.

Omission of Signal Integrity (I)

When Signal Integrity is not explicitly represented, accounting for the structured and experience-linked content of psychotic symptoms (Constraint C7) becomes more difficult. In such formulations, symptom coherence must either be treated as incidental or imported from outside the model's core ontology. This can complicate integration with constraints involving phenomenological structure and downstream mediation, particularly where representational degradation plays a central role [32–35].

Collapsing Sensitivity (S) into Capacity (K)

When trait-like Sensitivity is merged with Capacity, distinctions between stable individual vulnerability and time-varying tolerance become blurred. This can introduce tension with constraints emphasizing quantitative interindividual differences (C2) alongside state-dependent modulation and timing variability (C4, C5). Models adopting this collapse often require additional descriptive modifiers to recover these distinctions, increasing architectural complexity without making them explicit.

Treating Load (L) as an Implicit Environmental Factor

When Load is treated informally as "environment" rather than as an explicit state variable, representing cumulative burden, acute spikes, remission, and relapse dynamics becomes less transparent. Constraints emphasizing temporal dynamics and context sensitivity (C1, C4, C5, C9, C10) are then addressed indirectly, often through auxiliary assumptions rather than a unified state representation.

Summary of Reduction Effects

Across these comparisons, reduced or collapsed formulations tend to encounter predictable representational tensions related to causal ordering, state–trait separation, history dependence, or phenomenological structure. Introducing additional descriptive elements can partially address these tensions, but often at the cost of reintroducing distinctions implicitly rather than representing them directly.

This analysis does not imply that alternative variable sets are invalid or unusable. Instead, it highlights why the four-variable STM formulation provides a parsimonious and transparent way to

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organize the observed constraints at the abstraction level adopted in this manuscript, without presupposing uniqueness, exclusivity, or finality.

More detailed comparisons of reduced variable subsets against both observed and empirical constraints are provided in Appendix D, where the same analytic rubric is applied for transparency and completeness.

3.4. Mapping the ten observed constraints across theories (STM included): comparative explanatory adequacy

The preceding sections introduced a set of ten observed constraints (C1–C10) and examined how these constraints can be represented within a four-variable Sensitivity Threshold Model (STM) architecture at a common level of abstraction [3,7–9,12,16]. Building on this foundation, the present section examines how a range of existing explanatory frameworks in schizophrenia research relate to the same observed constraints.

The purpose of this analysis is not to rank theories by historical influence, clinical uptake, or empirical breadth. Instead, the comparison is organized around a shared analytic question: to what extent do different theoretical frameworks explicitly address, accommodate, or leave unarticulated the observed constraints as formulated here, given their stated core variables and causal commitments [3,7,9,12].

For each theory class, the analysis focuses on its core ontology—the primary variables, processes, and relationships emphasized in foundational or widely cited formulations [8,16]. The observed constraints are treated as theory-external reference points, derived independently of any single model, and are used to facilitate systematic comparison across frameworks. This approach follows prior work emphasizing constraint-based evaluation and theory comparison in complex, multilevel psychiatric phenomena [3,9,12,16].

Throughout this section, constraint alignment is interpreted in a descriptive and comparative sense, rather than as a judgment of correctness, validity, or empirical adequacy. A theory may align closely with certain constraints, address others indirectly, or leave some constraints only partially articulated within its existing structure. Where additional assumptions or reinterpretations would be required to accommodate a constraint, this is noted as a representational consideration rather than as a theoretical deficiency [9,12,16].

This comparative mapping completes the observed-constraint portion of the Results by clarifying patterns of overlap, divergence, and complementarity across explanatory approaches. It is intended to support transparent cross-theoretical comparison and to highlight how different models distribute explanatory emphasis across recurring features of schizophrenia phenomenology and course, without adjudicating between them [3,7–9,12,16].

3.4.1. Scoring Rubric: Explicit Decision Rules

To support transparency and reproducibility, theory–constraint alignment is described using a standardized three-level rubric. The rubric is intended as an analytic aid for comparative mapping, not as a measure of empirical validity, theoretical correctness, or scientific merit.

Theory–constraint alignment is described using the following symbolic notation, applied uniformly across all observed constraints:

- ✓ Explicitly represented — The theory's stated variables and relationships include an explicit representation of the constraint as formulated, without requiring auxiliary assumptions or reinterpretation of causal ordering.
- ~ Indirectly or partially represented — The constraint can be accommodated only through auxiliary assumptions, interpretive extension, or incomplete specification within the theory's core ontology.
- ✗ Not explicitly represented — The theory's primary constructs do not directly represent the constraint as formulated, and addressing it would require non-trivial extension beyond the theory's stated architecture.

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These symbols denote representational explicitness under the present analytic framing, not empirical validity, theoretical correctness, or scientific merit [3,7–9,12,16].

Table 3.4 Comparative mapping of explanatory frameworks to observed constraints (C1–C10)

Representation key (analytic rubric):

✓ = explicitly represented in the theory's core ontology

~ = indirectly or partially represented (via auxiliary assumptions or interpretive extension)

✗ = not explicitly represented within the stated architecture

Interpretive note:

Table entries indicate whether a theory's primary constructs and relationships, as defined in foundational or widely cited formulations, can represent each observed constraint as formulated, without auxiliary assumptions that alter causal direction, abstraction level, or state–trait separation.

Symbols denote representational explicitness under the present analytic framing, not empirical validity, theoretical correctness, or scientific merit [3,7,9,12,16,17,24,26,31].

Reference architecture note:

The Sensitivity Threshold Model (STM) is included as a reference architecture demonstrating that simultaneous representation of all observed constraints is achievable within a single coherent framework. Its inclusion does not imply validation, superiority, or exclusivity.

Theory-Model / Constraint	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Dopamine-centric	~	✗	✗	~	~	~	✗	~	✗	✗
Glutamate / NMDA	~	✗	✗	~	~	~	✗	✗	✗	✗
Other monoamines	~	✗	✗	~	~	✗	✗	~	✗	✗
Polygenic (GWAS)	✗	~	✗	✗	~	✗	✗	✗	✗	~
Rare variants / CNVs	✗	✗	✗	✗	~	✗	✗	✗	✗	~
Gene × environment / epigenetic	~	~	~	✓	✓	~	✗	✗	~	~
Neurodevelopmental	✗	~	~	~	~	✓	✗	✗	~	~
Dysconnection	~	~	~	~	~	✓	~	✗	✗	✗
E/I imbalance	~	✗	~	~	~	~	✗	✗	✗	✗
Synaptic pruning	✗	~	~	~	✓	✓	✗	✗	~	✓
Predictive coding	✓	~	~	✓	✓	✓	✓	~	✗	✗
Aberrant salience	~	✗	✗	~	~	~	~	✓	✗	✗
Source monitoring	~	✗	✗	~	~	~	✓	~	✗	✗
Sensory gating	~	~	✗	~	~	✓	✗	~	✗	✗
Stress–diathesis	✓	~	~	✓	✓	~	✗	✗	~	~
Trauma / dissociation	~	~	~	✓	~	✓	✓	✗	~	~
Social defeat	~	~	✗	✓	~	~	~	✗	✗	✗
Substance-induced	✓	~	✗	✓	✓	~	~	✗	~	✗
Immune / inflammatory	~	~	~	✓	✓	~	✗	✗	~	✓
Prenatal infection	✗	✗	✗	~	✓	~	✗	✗	✗	✓
Neurodegenerative	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗
Psychodynamic-only	✗	✗	✗	~	✗	~	~	✗	✗	✗
Sensitivity Threshold Model (STM)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Color shading is used solely to aid visual parsing of representational coverage and does not imply empirical strength, correctness, or theoretical priority.

3.4.2. Theory × Observed Constraints Matrix (Table 3.4)

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Table 3.4 presents the theory × constraint coverage matrix for the ten observed constraints (C1–C10), mapping the Sensitivity Threshold Model (STM) alongside representative theory classes commonly invoked in schizophrenia research. The matrix summarizes patterns of representational coverage under a shared analytic rubric and should be interpreted as an assessment of architectural alignment with the observed constraint set, rather than as a point-by-point critique of individual theories or an evaluation of empirical validity.

STM is included not as the only possible framework capable of engaging these constraints, but as a reference construction demonstrating that simultaneous representation of all ten observed constraints is achievable within a single coherent, system-level formulation.

Discriminative Role of Specific Constraints

Across the matrix, certain constraints appear to function as particularly informative discriminators among explanatory architectures, particularly those that distinguish dynamic, system-level formulations from models centered on fixed pathology or single mechanisms. In particular:

- C3 (causal direction constraint),
- C2 (quantitative, continuous vulnerability),
- C9 (history-dependent sensitization), and
- C10 (cross-system physiological coupling)

tend to differentiate models based on whether their core ontology explicitly represents dynamic progression, trait–state separation, and multi-system interaction [4,14,20,23,25–27,42–52].

Recurring Patterns Across Common Frameworks

Several systematic patterns of partial or indirect representation recur across widely discussed theory classes:

- Neurochemical models (e.g., dopamine-centric or monoaminergic accounts) often represent symptom-proximal correlates effectively, but do not explicitly encode the causal-direction constraint (C3), as neurochemical changes are frequently positioned as initiating factors rather than as state-dependent mediators within the model's primary architecture [4,14].
- Stress–diathesis formulations capture contextual modulation and vulnerability interactions (C1, C4), but typically lack formal architectural elements required to represent longitudinal sensitization (C9) or enforce causal ordering constraints such as C3, leaving these dimensions descriptively specified rather than structurally encoded [17,21,24,26,31,42–47].
- Predictive-coding and related computational approaches exhibit strong alignment with inference-related constraints (notably C7), yet often represent psychotic episodes as locally bounded inferential disruptions, without explicitly modeling longer-term course dynamics (C9) or cross-system coupling (C10) within their core formulation [6,42–52].

Taken together, these patterns suggest that many leading frameworks achieve partial coverage by representing specific mechanisms or domains (e.g., inference, stress responsiveness, neurochemical modulation), while leaving other observed constraints under-specified at the architectural level.

STM as a Reference Architecture

The Sensitivity Threshold Model (STM) is included in Table 3.4 as a constraint-complete reference architecture with respect to the observed constraint set (C1–C10), in the sense that it was explicitly constructed to represent these constraints simultaneously, without introducing auxiliary assumptions that alter causal direction, abstraction level, or state–trait separation

In particular, STM explicitly encodes the causal ordering emphasized by C3, representing neurochemical changes as downstream mediators within a broader instability process:

Input → Overload → System Instability → Neurochemical Change [4,14]

Within this architecture:

- Capacity supports representation of progressive vulnerability and sensitization over time,
- Load provides a shared representational dimension for environmental, physiological, and contextual pressures,

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- Signal Integrity accounts for structured symptom content without collapsing causal hierarchy, and
- Sensitivity preserves stable, trait-level modulation of threshold.

These variables together form a minimal system-level structure capable of representing the full observed constraint set, serving as a concrete illustration of how phenomenological fidelity and biological compatibility can be jointly maintained within a single explanatory framework.

3.4.3. Empirically Established Constraints — Transition and Scope

The analysis in Section 3.3 completes the first half of the Results by evaluating competing theories against the observed constraint set (C1–C10)—a set derived from recurring regularities in clinical course, phenomenology, and contextual modulation. Under the present analytic rubric, these constraints appear to be architecturally discriminative, in the sense that they differentially engage explanatory frameworks depending on whether state-dependent dynamics, trait-level vulnerability, and history-sensitive processes are explicitly represented. Within this framing, systems-level models with explicit state-, trait-, and history-dependent components may be required to satisfy these constraints simultaneously [3,7,12,17,24,26,31,42–47].

However, the observed constraints alone are not intended to guarantee alignment with the broader empirical literature. To ensure that the constraint set is not an artifact of selective abstraction or phenomenological emphasis, the next section anchors the analysis in a second, independent requirement set: fifteen empirically established constraints (E1–E15), derived from well-replicated findings across epidemiology, neuroscience, pharmacology, developmental trajectories, and longitudinal outcomes [7,9,12,16].

Section 3.5 applies the same constraint-based procedure—derivation, formalization, and theory × constraint mapping—to this empirically anchored set. Conducting the analysis in parallel allows for systematic comparison between observed and empirical constraints, clarifying areas of convergence and divergence in representational coverage across theories under a consistent evaluative framework.

3.5. The Fifteen Empirically Established Constraints (E1–E15): Definition, Significance, and Derivation from the Field

The observed constraints examined in Sections 3.2–3.4 were derived by abstracting recurring regularities across clinical course, phenomenology, and contextual modulation [8,10]. While these constraints are useful for comparative evaluation of theoretical models, they are intended to be situated within the broader empirical literature to reduce the risk of selective abstraction or model-contingent framing [7,9].

This section introduces a second, independent constraint set: fifteen empirically established constraints (E1–E15). These constraints are derived from well-replicated findings across multiple domains, including epidemiology, neuroscience, genetics, pharmacology, developmental studies, and longitudinal outcome research in schizophrenia and related psychotic conditions [10].

The role of E1–E15 is not to catalogue individual empirical findings, but to distill what those findings, considered collectively, imply at the level of architectural requirements for explanatory models [11,12]. Each constraint is formulated as a high-confidence empirical regularity, such that accommodating it requires engagement with converging evidence across studies and methodologies, rather than reliance on isolated results or single theoretical interpretations [8,9].

Collectively, the E1–E15 constraints serve two complementary functions. First, they anchor the constraint-based evaluation in externally replicated empirical evidence, ensuring that the framework is not dependent on internal coherence alone [7]. Second, they enable systematic comparison with the observed constraint set (C1–C10), supporting analysis of overlap, compression, and divergence across constraint types in later sections [12].

3.5.1. Constraint Extraction and Validation Notes

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3.5.1.1. Extraction Logic and Empirical Validation

Each empirical constraint (Ei) was derived using a standardized two-step procedure designed to minimize interpretive bias and maximize generality [7,9].

First, an empirical basis was identified [10]. This consists of findings that are:

(i) replicated across multiple studies or methodologies,

(ii) observed across independent samples or contexts, and

(iii) widely acknowledged within the field, even where interpretation remains contested [8,9].

These findings span epidemiology, neurobiology, pharmacology, genetics, developmental studies, and longitudinal clinical research [10].

Second, each finding was reformulated into constraint form using a standard analytic template:

"An adequate explanatory framework for schizophrenia should be able to account for…" [12]

This step formalizes the empirical pattern into a high-confidence empirical requirement, without embedding any specific mechanistic interpretation or architectural commitment [7,12].

Importantly, this procedure does not privilege any single empirical domain [10]. Constraints are extracted only where multiple domains converge on the same structural implication, even when they do so at different descriptive or explanatory levels [10]

3.5.1.2. Selection Scope and Inclusion Criteria

The empirical constraint set (E1–E15) was not constructed by selecting findings that support a particular theory or framework [7,9]. Instead, it reflects cross-domain convergence across domains that are frequently siloed in schizophrenia research [8]. For example, epidemiological regularities are evaluated alongside pharmacological asymmetries, developmental timing effects, and longitudinal outcome patterns.

Findings were excluded from constraint formulation if they:

- relied primarily on single studies or unreplicated effects,
- involved domain-specific measurements without general relevance across levels [10],
- or collapsed logically into broader constraints already included in the set [12].

As a result, the E1–E15 constraints represent structural requirements imposed by the empirical field as a whole—not by any one paradigm, dataset, or theoretical tradition [7,8]. This makes them suitable for evaluating explanatory adequacy across diverse models using the same rubric previously applied to the observed constraints in Section 3.3 [12].

In the subsections that follow, each empirical constraint (E1–E15) is presented in turn, with its empirical basis, constraint formulation, and significance for theory evaluation made explicit [7].

3.5.2.1. E1 — Schizophrenia as a Heterogeneous Syndrome

Empirical basis (field-accepted regularity).

Schizophrenia exhibits marked heterogeneity across symptom profiles, age of onset, clinical course, cognitive impairment, treatment response, and long-term outcomes [2,15,20]. Historically, multiple diagnostic subtypes were proposed (e.g., paranoid, disorganized, catatonic), but these were ultimately collapsed into a single category due to poor subtype reliability and extensive clinical overlap [1,2]. To date, no single biomarker, lesion, or etiological pathway has been shown to define schizophrenia across cases [2,4,5]. As a result, schizophrenia is widely characterized as a syndrome encompassing heterogeneous manifestations rather than a single disease entity with a unified cause [2,15].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to account for substantial heterogeneity within a single diagnostic syndrome, without requiring a unique causal pathway for each presentation or dissolving the syndrome into unrelated disease entities.

Significance for theory evaluation.

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This constraint places strong architectural pressure on models that posit a single necessary and sufficient cause—such as a fixed lesion, specific neurotransmitter imbalance, or monogenic defect—as a universal explanation for schizophrenia [2,4,5]. It also constrains approaches that address heterogeneity primarily through proliferation of subtypes without a unifying explanatory framework, as such strategies shift explanatory burden from mechanism to classification and leave cross-case coherence underspecified.

Link forward to observed constraints.

E1 aligns most directly with C2 (quantitative vulnerability across individuals) and C5 (variable, context-sensitive onset), and secondarily with C1 (psychosis inducible by non-specific stressors). Together, these observed constraints illustrate how heterogeneity can arise from continuous variation in vulnerability and dynamic system-level interactions, rather than from the presence of multiple unrelated disease processes.

3.5.2.2. E2 — Absence of a Single Defining Biomarker

Empirical basis (field-accepted regularity).

Despite decades of investigation, no blood test, neuroimaging marker, neurotransmitter level, genetic variant, or physiological measure has demonstrated sufficient diagnostic utility for schizophrenia [2,14]. Proposed biomarkers—whether molecular, structural, functional, or genomic—exhibit substantial overlap with healthy controls and with individuals diagnosed with other psychiatric or neurological conditions [14,27]. Findings are frequently statistically significant at the group level but lack the specificity or sensitivity required for reliable individual-level diagnosis [2,11].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to account for the absence of a single defining biomarker and must not rely on a localized lesion, molecule, or pathway as a necessary and sufficient cause of the disorder [2,4,5].

Significance for theory evaluation.

This constraint places strong architectural pressure on models that posit a unique biological signature—such as a specific neurotransmitter imbalance, circumscribed brain abnormality, or monogenic variant—as the central explanatory basis of schizophrenia [2,27]. It also constrains reductionist frameworks that infer individual-level diagnostic mechanisms directly from group-level statistical associations [11], or that privilege a single measurement domain (e.g., dopamine signaling or neuroimaging findings) without integrating cross-domain variability and overlap.

Link forward to observed constraints.

E2 aligns most directly with C2 (continuous rather than categorical vulnerability) and C3 (neurochemical abnormalities as downstream or mediating factors rather than primary causes). It also reinforces C1 (psychosis inducible by non-specific stressors), supporting the broader inference that schizophrenia is not defined by a disease-specific marker, but by system-level vulnerability and instability dynamics.

3.5.2.3. E3 — Polygenic Risk Is Real but Weak

Empirical basis (field-accepted regularity).

Large-scale genome-wide association studies (GWAS) consistently show that schizophrenia risk is influenced by thousands of common genetic variants, each contributing a very small effect size [27]. Polygenic risk scores (PRS) are statistically associated with schizophrenia at the population level, but they explain only a modest proportion of variance and have limited predictive value at the individual level [25,31]. No single variant—or small set of variants—accounts for a substantial fraction of risk [27].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to incorporate diffuse, small-effect genetic influences as modulators of vulnerability, without assuming strong genetic determinism or reliance on a limited set of high-impact causal variants [2].

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Significance for theory evaluation.

This constraint places strong architectural pressure on models that treat genetic liability as near-deterministic or that anticipate convergence on a small number of mechanistically decisive genetic pathways [2]. It also constrains frameworks that equate statistical association with direct causation [11], or that fail to represent the substantial gap between genetic loading and clinical manifestation—particularly in the absence of interacting environmental, developmental, or contextual factors [25,31].

Link forward to observed constraints.

E3 aligns most directly with C2 (continuous vulnerability) and C5 (context-sensitive onset timing), and reinforces C1 (psychosis inducible by non-specific stressors). Together, these observed constraints clarify how polygenic architecture shapes baseline susceptibility rather than defining a disease-specific pathway, and why phenotypic expression depends critically on load, context, and system-level interaction.

3.5.2.4. E4 — Environmental Factors Have Large Effect Sizes

Empirical basis (field-accepted regularity).

Multiple environmental exposures show substantial and replicable associations with schizophrenia risk across epidemiological and longitudinal studies [20,21]. These include urban upbringing, minority and migrant status, childhood adversity, social defeat, and cannabis use—particularly during adolescence [20,21]. In many analyses, the effect sizes associated with these exposures equal or exceed those of individual genetic variants [21,27], and risk frequently scales with exposure intensity, duration, or cumulative burden [24].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to explain how environmental exposures exert significant, state-dependent effects on system stability and illness risk [20]. Environmental contributions cannot be treated solely as incidental background factors, but must be represented as causally relevant influences on vulnerability and instability.

Significance for theory evaluation.

This constraint places strong pressure on models that privilege intrinsic biological mechanisms while relegating environmental influences to minor, symbolic, or unspecified roles [21]. It also challenges frameworks that invoke "environment" only as a descriptive backdrop rather than as a quantifiable and dynamically potent source of system load. Adequate explanatory architectures must therefore include mechanisms by which environmental burden alters system dynamics and modulates proximity to instability over time [24].

Link forward to observed constraints.

E4 aligns most directly with C1 (psychosis inducible by non-specific stressors) and C4 (state-dependent, environmentally modulated symptoms), and reinforces C5 (context-sensitive and variable onset timing). Taken together, these observed constraints support models in which environmental inputs contribute directly to load accumulation and system destabilization, without requiring disease-specific triggers or singular causal events.

3.5.2.5. E5 — Onset Is Developmentally Patterned but Not Fixed

Empirical basis (field-accepted regularity).

Epidemiological studies consistently show a peak incidence of schizophrenia in late adolescence and early adulthood, with well-documented sex-specific differences in onset timing [29,31]. At the same time, robust cases of both childhood-onset and late-onset schizophrenia have been reported, and the overall age-of-onset distribution is broad and continuous rather than sharply bounded [20,25,44]. These findings indicate that while developmental stage modulates risk, onset is not confined to a single fixed window or developmental milestone [45].

Constraint statement (analytic requirement).

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Any valid theory of schizophrenia must be able to explain why onset shows developmental patterning while remaining variable and context-sensitive across individuals [31]. Onset therefore cannot be modeled solely as the deterministic expression of a fixed early developmental lesion.

Significance for theory evaluation.

This constraint places strong limits on models that conceptualize schizophrenia as the inevitable outcome of a prenatal or early developmental insult whose effects simply manifest at a predetermined age [44]. It also challenges frameworks that treat adolescence as a uniform or fixed trigger point independent of state variables, environmental context, or individual variability [45]. More generally, it favors explanatory architectures in which developmental sensitivity modulates vulnerability without rigidly fixing the timing of illness emergence, allowing later-life exposures and system dynamics to influence onset [25,31].

Link forward to observed constraints.

E5 aligns most directly with C5 (variable, context-sensitive onset timing) and C2 (continuous vulnerability), and secondarily with C1 (psychosis inducible by non-specific stressors). Together, these observed constraints support models in which developmental stage shapes—but does not dictate—the conditions under which threshold crossing occurs.

3.5.2.6. E6 — Prodromal Phase Is Common and Measurable

Empirical basis (field-accepted regularity).

Longitudinal and retrospective studies consistently identify a prodromal phase preceding first-episode psychosis in a substantial proportion of individuals later diagnosed with schizophrenia [25,31]. This phase includes measurable changes such as cognitive decline, attentional deficits, social withdrawal, anxiety, and subtle perceptual disturbances [19,28,29]. These features often emerge months to years before overt psychotic symptoms [29,31] and have been detected across clinical high-risk cohorts, first-episode samples, and population-based studies [25,28].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to account for the frequent presence of a progressive prodromal phase preceding psychosis, and therefore cannot treat psychotic symptoms alone as the sole initiating event in the disorder's trajectory [31].

Significance for theory evaluation.

This constraint places strong limits on explanatory models that conceptualize schizophrenia as an abrupt-onset condition or that treat pre-psychotic cognitive, functional, or perceptual changes as incidental or epiphenomenal [28]. It also challenges frameworks that attribute early deterioration exclusively to emerging psychosis or to treatment effects, without representing an earlier phase of system strain [19,29]. More generally, the constraint favors architectures capable of representing gradual degradation, cumulative instability, or declining system tolerance prior to overt psychotic collapse [28,31].

Link forward to observed constraints.

E6 aligns most directly with C6 (cognitive and sensory symptoms precede psychosis) and supports C9 (history-dependent sensitization), insofar as early instability may alter subsequent vulnerability and recovery dynamics. It also reinforces C5 (variable and context-sensitive onset timing), as the duration, slope, and phenomenological profile of the prodromal phase vary substantially across individuals and contexts [25,31].

3.5.2.7. E7 — Cognitive Deficits Are Core and Persistent

Empirical basis (field-accepted regularity).

Individuals with schizophrenia consistently exhibit impairments in working memory, processing speed, attention, and executive function [18,38]. These cognitive deficits are detectable prior to the onset of psychosis [28,29], are present during first-episode illness [44], and typically persist even when positive symptoms remit [38]. Cognitive impairment is strongly associated with

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long-term functional outcomes [45] and is observed across illness stages, treatment contexts, and diagnostic subgroups [18,44].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to account for enduring cognitive dysfunction as a central component of the disorder's clinical profile, rather than treating such deficits solely as secondary consequences of hallucinations, delusions, or medication effects [18,38].

Significance for theory evaluation.

This constraint places substantial pressure on models that prioritize positive symptoms as the primary locus of pathology or that treat cognitive impairment as incidental to psychotic expression or treatment response [18]. It also challenges frameworks that emphasize perceptual or inferential disruption without explicitly representing persistent limitations in cognitive capacity or information-processing resources. More generally, explanatory architectures must be capable of accounting for both the temporal stability and functional impact of cognitive deficits across illness phases [44,45].

Link forward to observed constraints.

E7 aligns most directly with C6 (cognitive and sensory symptoms precede psychosis) and supports C9 (history-dependent sensitization), insofar as enduring reductions in cognitive capacity may influence both vulnerability to destabilization and recovery following episodes. It also reinforces C8 (medication asymmetry), as cognitive deficits typically show limited improvement despite effective suppression of acute psychotic symptoms [38].

3.5.2.8. E8 — Psychotic Symptoms Are State-Dependent

Empirical basis (field-accepted regularity).

Across clinical, epidemiological, and longitudinal studies, psychotic symptoms are observed to fluctuate in response to internal and external state variables [24,44], including stress, sleep disruption, substance use, social context, and environmental stimulation [19,21]. Remission and relapse are common [42], and symptom severity can vary substantially within individuals over time [44,45], even in the absence of detectable permanent structural change [44].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to account for the episodic and state-dependent expression of psychotic symptoms [24], rather than treating symptom expression as the invariant manifestation of a fixed defect or lesion.

Significance for theory evaluation.

This constraint places strong pressure on models that conceptualize psychosis primarily as a static, trait-like phenomenon [44]. It also highlights limitations in frameworks that lack explicit state variables capable of representing temporal fluctuation, recovery, and relapse dynamics [42]. In the absence of such variables, symptom variability tends to be addressed descriptively or attributed primarily to external intervention, rather than being represented as an intrinsic feature of the disorder's dynamics [45].

Link forward to observed constraints.

E8 aligns most directly with C4 (symptoms are state-dependent and environmentally modulated) and supports C1 (non-specific psychosis generators), reinforcing that diverse and transient state perturbations can precipitate or attenuate symptoms [21,24]. It also complements C8 (medication asymmetry) by emphasizing the distinction between modulating state expression and altering baseline vulnerability.

3.5.2.9. E9 — Antipsychotics Reduce Positive Symptoms but Not Cognitive Deficits

Empirical basis (field-accepted regularity).

Antipsychotic medications reliably reduce positive symptoms—particularly hallucinations and delusions—during both acute treatment and maintenance phases [37]. In contrast, their effects on cognitive performance, motivation, negative symptoms, and long-term functional outcomes are weak, inconsistent, or negligible [38,44]. Cognitive deficits typically persist despite effective

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suppression of positive symptoms [38], and functional recovery often lags behind symptomatic improvement [45].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to explain why dopamine-targeting treatments suppress positive symptoms without reliably restoring cognitive function or broader system capacity [4,14]. This pattern implies a dissociation between symptom-proximal modulation and underlying vulnerability or functional architecture.

Significance for theory evaluation.

This constraint places strong pressure on models that interpret dopamine dysregulation as the sole or primary etiological driver of schizophrenia [4]. It also highlights limitations in frameworks that infer causal primacy from treatment responsiveness alone, thereby conflating symptom suppression with correction of upstream system dysfunction [11]. Adequate explanatory models must distinguish between mechanisms that stabilize acute expression and those that account for persistent cognitive and functional impairment [14].

Link forward to observed constraints.

E9 aligns most directly with C3 (neurochemical abnormalities are downstream rather than primary) and C8 (antipsychotics reduce sensitivity rather than correcting root vulnerability). It also supports C7 (structured symptom content), insofar as medication effects may attenuate salience or instability without reconstructing the representational architecture underlying cognition and long-term functional capacity.

3.5.2.10. E10 — Treatment Response Is Highly Variable

Empirical basis (field-accepted regularity).

Clinical outcomes following treatment for schizophrenia are markedly heterogeneous [43,44]. Approximately one-third of individuals exhibit treatment-resistant symptoms [37], while others achieve sustained remission with minimal or intermittent pharmacological support [43]. Relapse can occur despite full adherence [37,42], and conversely, some individuals remain stable with limited or no ongoing medication [44]. This variability is observed across illness stages, treatment modalities, and healthcare settings [43,45].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to account for substantial inter-individual variability in treatment response [44]. Frameworks that posit a single dominant causal pathway must therefore explain why modulation of that pathway yields heterogeneous therapeutic outcomes across individuals.

Significance for theory evaluation.

This constraint places pressure on models that assume uniform clinical improvement when a presumed primary mechanism is targeted [37]. It also highlights limitations in explanations that attribute treatment non-response primarily to adherence, access, or external confounds [42]. Adequate explanatory architectures must allow for interacting sources of vulnerability and resilience [43,44]—such as baseline sensitivity, fluctuating system load, and functional reserve—such that treatment effects vary as a function of individual system configuration and history.

Link forward to observed constraints.

E10 aligns most directly with C2 (quantitative vulnerability rather than categorical disease) and C8 (antipsychotics reduce effective sensitivity rather than correcting root vulnerability). It also supports C9 (history-dependent sensitization), insofar as prior episodes and cumulative system strain may shape subsequent treatment responsiveness and stability over time.

3.5.2.11. E11 — Stress and Sleep Deprivation Can Induce Psychosis

Empirical basis (field-accepted regularity).

Psychotic symptoms can reliably emerge in individuals without a schizophrenia diagnosis when exposed to extreme stress, prolonged sleep deprivation, or severe physiological overload [21,22,47].

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This phenomenon has been documented in experimental sleep-deprivation paradigms as well as in real-world settings such as military operations, disaster zones, intensive care units, and severe medical illness [21,40,46]. In addition, substances such as amphetamines and corticosteroids can precipitate psychotic states [14,51], often with phenomenology overlapping that observed in schizophrenia-spectrum disorders [14].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to account for psychosis as a general, state-dependent brain-system failure that is not exclusive to schizophrenia as a diagnostic category [47]. Explanatory frameworks must therefore explain how similar psychotic phenomena can arise under diverse upstream perturbations.

Significance for theory evaluation.

This constraint places pressure on models that conceptualize psychosis as arising solely from a schizophrenia-specific lesion, molecular pathway, or diagnostic identity [14]. It also highlights limitations in frameworks that require fixed, disease-specific mechanisms to explain psychotic symptoms, as such accounts struggle to accommodate the emergence of comparable phenomena in individuals without schizophrenia under conditions of sufficient stress, sleep disruption, or pharmacological challenge.

Link forward to observed constraints.

E11 aligns most directly with C1 (stress-induced psychosis / non-specificity of the psychosis generator) and supports C3 (neurochemical abnormalities as downstream rather than primary processes), insofar as similar psychotic states can arise via multiple upstream perturbations [21,22]. It also complements C4 (state-dependent and environmentally modulated symptoms) by illustrating how transient system overload can produce psychotic expression without requiring disease-specific pathology [40,46].

3.5.2.12. E12 — Brain Differences Are Subtle, Distributed, and Non-Specific

Empirical basis (field-accepted regularity).

Neuroimaging studies consistently report small effect sizes for structural and functional brain differences in individuals diagnosed with schizophrenia [2,15]. Reported findings include modest cortical thinning, ventricular enlargement, and regional activity differences [15]; however, these alterations are spatially distributed rather than focal, variable across individuals, and show substantial overlap with other psychiatric conditions such as bipolar disorder and major depressive disorder [2,14]. To date, no single brain region, spatial pattern, or imaging-derived marker has demonstrated sufficient specificity to characterize schizophrenia at the individual level [2,4].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be compatible with the empirical observation that brain differences associated with the disorder are subtle, distributed, and non-specific [15], rather than presupposing a focal lesion, localized structural defect, or uniformly progressive neurodegenerative process.

Significance for theory evaluation.

This constraint places limits on models that treat schizophrenia as arising primarily from large-scale, localized brain damage or as a classical neurodegenerative disorder [14]. It also highlights challenges for explanatory frameworks that infer causal mechanisms directly from group-level neuroimaging differences without accounting for their modest effect sizes, heterogeneity, and cross-diagnostic overlap [2]. More broadly, it favors models capable of accommodating system-level dysregulation that manifests as diffuse and variable brain alterations, rather than as anatomically specific or degenerative pathology [4].

Link forward to observed constraints.

E12 aligns most directly with C3 (neurochemical abnormalities as downstream rather than primary processes) and C10 (cross-system coupling), insofar as distributed brain differences are consistent with system-wide instability or load-related dysregulation rather than disease-specific

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structural lesions. It also supports C2 (quantitative vulnerability) by reinforcing the interpretation of graded, population-level variation rather than categorical anatomical markers [20].

3.5.2.13. E13 — Inflammation and Immune Signals Are Elevated in Subsets

Empirical basis (field-accepted regularity).

A subset of individuals diagnosed with schizophrenia exhibit elevated inflammatory markers, including increased circulating cytokines [49], as well as higher rates of autoimmune comorbidities relative to the general population [48]. Epidemiological and preclinical studies further implicate maternal immune activation during pregnancy as a risk factor for later development of psychotic disorders in offspring [52]. Importantly, immune-related findings are heterogeneous: they are observed in identifiable subsets of cases rather than being uniformly present across all individuals diagnosed with schizophrenia [50].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be able to accommodate immune and inflammatory processes as modulators of vulnerability, symptom expression, or illness course, without treating immune dysfunction as a necessary or universal cause of the disorder [50].

Significance for theory evaluation.

This constraint places limits on explanatory frameworks that position immune dysfunction as a singular or universally primary causal pathway in schizophrenia [48]. It also highlights limitations in accounts that treat immune findings as either globally determinative or entirely incidental. More generally, it favors models capable of representing immune activity as one of several interacting contributors to system stability, threshold sensitivity, or symptom exacerbation in a subset of cases [51], without redefining schizophrenia as a uniformly immune-mediated condition [50].

Link forward to observed constraints.

E13 aligns most directly with C10 (cross-system coupling), supporting the interpretation that immune processes can contribute to systemic load or destabilization. It also supports C1 (non-specific psychosis generators) and C2 (quantitative vulnerability), insofar as immune activation may shift risk or lower thresholds for instability in some individuals without serving as a uniform initiating mechanism.

3.5.2.14. E14 — Outcome Is Highly Variable

Empirical basis (field-accepted regularity).

Long-term outcomes in schizophrenia are highly heterogeneous [42,44]. While some individuals achieve sustained remission and meaningful functional recovery, others experience persistent symptoms and significant disability [43,44]. Longitudinal research consistently indicates that environmental and contextual factors—such as social support, housing stability, and access to care—exert substantial influence on outcome trajectories [21,45], in many cases rivaling or exceeding biological predictors in explanatory strength [45].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be compatible with the wide variability observed in long-term outcomes and therefore cannot rely on assumptions of intrinsic uniform progression or inevitable degenerative course [44].

Significance for theory evaluation.

This constraint places limits on models that presuppose schizophrenia follows a uniformly deteriorating trajectory driven by fixed pathology or irreversible damage [44]. It also highlights challenges for explanatory frameworks that overemphasize early biological insults while underrepresenting the modifying roles of environmental load, buffering factors, and recovery processes over time [21,45]. More broadly, valid models must be capable of representing divergent outcome trajectories under shared diagnostic labels, including resilience, stabilization, and partial or sustained recovery [42,43].

Link forward to observed constraints.

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E14 aligns most directly with C9 (history-dependent sensitization), insofar as prior episodes influence—but do not rigidly determine—future outcomes. It also supports C4 (state-dependent and environmentally modulated symptoms) and C5 (variable onset and course), reinforcing the need for models that represent long-term dynamics as contingent on interactions among sensitivity, load, and system-level buffering capacity.

3.5.2.15. E15 — Cross-Diagnostic Overlap Is Extensive

Empirical basis (field-accepted regularity).

Schizophrenia exhibits substantial overlap with other psychiatric conditions across genetic, cognitive, neurobiological, and symptomatic domains [53,54]. Polygenic studies consistently reveal shared risk architecture with bipolar disorder, major depressive disorder, autism spectrum conditions, and other mood and neurodevelopmental syndromes [27,54,55]. Likewise, cognitive impairments and neural differences associated with schizophrenia frequently parallel those observed in adjacent diagnostic categories, with boundaries that appear continuous rather than sharply categorical [20,53,56].

Constraint statement (analytic requirement).

Any valid theory of schizophrenia must be compatible with extensive cross-diagnostic overlap and therefore cannot rely on assumptions of categorical biological isolation or strict etiological exclusivity [54].

Significance for theory evaluation.

This constraint places limits on explanatory frameworks that conceptualize schizophrenia as a singular, closed disease system with uniquely specific causal mechanisms or rigid diagnostic boundaries [53,55]. It also highlights challenges for diagnostic-essentialist accounts that infer biological discontinuity primarily from nosological tradition, despite converging evidence for transdiagnostic genetic, cognitive, and neurobiological continuity. More generally, explanatory models must be capable of representing shared vulnerability architectures and partially overlapping mechanisms that span traditional psychiatric categories [54,56].

Link forward to observed constraints.

E15 aligns most directly with C2 (quantitative vulnerability rather than categorical disease) and C10 (cross-system coupling), reinforcing the placement of schizophrenia within a broader continuum of psychiatric vulnerability. It also supports C1 (non-specific psychosis generators), insofar as shared system-level failure modes can give rise to overlapping symptom expressions across diagnostic constructs.

Table 3.5. Empirically established constraints (E1–E15): summary

Purpose: Provide a compact, reviewer-accessible overview of the empirical constraint set, analogous to Table 3.2 for observed constraints.

Ei	Short name	Core empirical regularity	Constraint statement (analytic requirement)
E1	Syndrome, not disease	Extreme heterogeneity across symptoms, course, outcomes	Any valid theory must accommodate substantial heterogeneity within a single syndrome without fragmenting schizophrenia into unrelated disease entities.
E2	No single biomarker	No diagnostic blood, imaging, genetic, or molecular marker	Any valid theory must account for the absence of a single defining biomarker and cannot rely on a localized lesion, molecule, or pathway as a necessary and sufficient cause.
E3	Weak polygenic risk	Thousands of variants with tiny effects; low variance explained	Genetic factors must be represented as diffuse contributors to vulnerability rather than as deterministic drivers of onset, timing, or severity.

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E4	Large environmental effects	Urbanicity, adversity, cannabis, social defeat	Any valid theory must formally integrate environmental exposures as causally potent, state-dependent contributors to system instability.
E5	Patterned but flexible onset	Peak in adolescence with early and late cases	Any valid theory must explain developmentally patterned yet variable and context-sensitive onset, rather than assuming a fixed developmental trigger.
E6	Common prodrome	Cognitive, social, perceptual changes precede psychosis	Any valid theory must account for a progressive prodromal phase preceding psychosis, rather than treating psychosis as the initiating pathology.
E7	Persistent cognitive deficits	Stable impairments before and after psychosis	Any valid theory must represent enduring cognitive dysfunction as a core feature, not solely as a consequence of acute psychotic symptoms or treatment.
E8	State-dependent psychosis	Fluctuation with stress, sleep, environment	Any valid theory must represent psychotic symptoms as state-dependent and episodic rather than as static trait expressions.
E9	Medication asymmetry	Strong positive-symptom effect, weak cognitive effect	Any valid theory must explain why dopamine-targeting treatments suppress positive symptoms without restoring core cognitive or functional capacity.
E10	Variable treatment response	Resistance, remission, relapse despite adherence	Any valid theory must accommodate substantial inter-individual variability in treatment response rather than assuming a single uniformly effective pathway.
E11	Stress-induced psychosis	Sleep deprivation, disaster, ICU, substances	Any valid theory must account for psychosis as a general, state-dependent brain-system failure that can arise under diverse upstream perturbations.
E12	Subtle brain differences	Small, distributed, non-specific neuroimaging effects	Any valid theory must be compatible with subtle, distributed, and non-specific brain differences rather than presupposing focal or degenerative pathology.
E13	Immune effects in subsets	Cytokines, autoimmunity, maternal immune activation	Any valid theory must accommodate immune and inflammatory processes as modulators of vulnerability or symptom expression in subsets of cases.
E14	Variable outcome	Recovery vs chronic disability; social context matters	Any valid theory must be compatible with wide variability in long-term outcomes, including resilience, stabilization, and recovery.
E15	Cross-diagnostic overlap	Shared genetics and cognition with other disorders	Any valid theory must be compatible with extensive cross-diagnostic overlap rather than assuming strict etiological or biological isolation.

3.6. Conceptual Mapping of Empirical Constraints (E1–E15) to Observed Constraints (C1–C10)

The observed constraints (C1–C10) were derived by abstracting recurring regularities across clinical presentation, phenomenology, and illness course [8]. The empirical constraints (E1–E15), by contrast, were extracted directly from well-replicated findings spanning epidemiology, neuroscience, genetics, pharmacology, and longitudinal outcome research [10]. This section links these two levels by examining how multiple empirical constraints converge and compress into fewer observed constraints at a higher level of abstraction [12].

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This mapping serves three related purposes. First, it demonstrates that the observed constraint set is not independent of the empirical literature, but can be understood as a principled reorganization of it [8]. Second, it shows that compression preserves explanatory content rather than discarding domain-specific evidence [12]. Third, it supports the use of observed constraints as a useful abstraction level for comparative theory evaluation, while empirical constraints function as an external anchoring reference for validation and scope control [11,16].

3.6.1. Compression Logic

Compression refers to cases in which multiple empirical constraints—originating from distinct empirical domains—converge on the same underlying structural requirement for explanatory models [8,12]. For example, E4 (large environmental effects), E8 (state-dependent psychotic symptoms), and E11 (stress-induced psychosis) converge on the requirement that psychosis be explainable as a state-dependent instability process [12], which is captured by observed constraints C1 and C4.

Similarly, E1 (syndrome heterogeneity), E2 (absence of a single biomarker), E3 (weak polygenic risk), and E15 (cross-diagnostic overlap) jointly motivate C2, which requires a quantitative vulnerability architecture rather than categorical disease entities [8].

This convergence is not incidental. Rather, it reflects the fact that explanatory models are typically evaluated based on their ability to satisfy shared structural requirements implied by diverse empirical findings, rather than on their capacity to explain isolated observations in a domain-specific manner [11,16].

3.6.2. Mapping Overview (conceptual)

How to read Table 3.6

Table 3. 6. Conceptual mapping of empirical constraints (E1–E15) to observed constraints (C1–C10).

Empirical constraint	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
E1 — Syndrome, not disease	~	✓			~					~
E2 — No single biomarker		✓	✓							
E3 — Weak polygenic risk	~	✓			✓					
E4 — Large environmental effects	✓			✓	✓					
E5 — Patterned but flexible onset		✓			✓					
E6 — Common prodrome						✓			✓	
E7 — Persistent cognitive deficits						✓	~		✓	
E8 — State-dependent psychosis	✓			✓						
E9 — Medication asymmetry			✓				~	✓		
E10 — Variable treatment response		✓						✓	✓	
E11 — Stress/sleep-induced psychosis	✓		✓	✓						~
E12 — Subtle, non-specific brain differences		✓	✓							~
E13 — Immune effects in subsets	~	✓								✓
E14 — Highly variable outcomes				✓	~				✓	
E15 — Cross-diagnostic overlap	~	✓								✓

- Rows represent empirically established constraints that cannot be denied without contradicting replicated evidence [10].
- Columns represent observed constraints that operate at a higher level of abstraction [8].
- Compression is evident where multiple Ei converge on a single Cj, indicating that the observed constraint captures a common structural requirement [12] shared across diverse empirical domains.

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- Every observed constraint is grounded in empirical findings, and each empirical constraint maps onto at least one observed constraint [16], indicating bidirectional coverage between the two levels of analysis.

This table completes the empirical ↔ observed constraint bridge for the purposes of the present analysis, setting up the final step of the Results section: the derivation of the adequate solution specification and identification of C3 as the keystone constraint.

At a high level, the mapping proceeds as follows:

- C1 (non-specific psychosis generators) compresses E4, E8, and E11.
- C2 (quantitative vulnerability) compresses E1, E2, E3, and E15.
- C3 (downstream neurochemistry) compresses E9 and E12.
- C4 (state-dependent symptoms) compresses E4, E8, and E14.
- C5 (variable onset timing) compresses E3, E4, and E5.
- C6 (prodromal overload) compresses E6 and E7.
- C7 (structured symptom content) is supported indirectly by E7 and E9.
- C8 (medication asymmetry) compresses E9 and E10.
- C9 (sensitization and history dependence) compresses E6, E7, E10, and E14.
- C10 (cross-system coupling) compresses E13 and E15.

Consistency check: absence of constraint contradictions

Crucially, the mapping in Table 3.6 is not only comprehensive but also internally consistent. No observed constraint (C1–C10) is found to contradict any empirically established constraint (E1–E15) under the present abstraction [16]. Where a potential tension might appear—such as between heterogeneity (E1) and structured symptom content (C7), or between downstream neurochemistry (C3) and medication efficacy (E9)—the relationship resolves at the level of abstraction. Empirical constraints specify what must be true in the world, whereas observed constraints specify how explanatory models must be structured [11,12] to accommodate those truths. Apparent conflicts therefore reflect differences in descriptive level rather than logical incompatibility [8].

Illustrative potential conflicts and resolutions

• E1 (syndrome heterogeneity) vs. C7 (structured symptom content): heterogeneity concerns between-individual variation, whereas C7 constrains within-episode representational structure; the two operate at different scales and are compatible.

• E9 (dopamine-targeting efficacy) vs. C3 (downstream neurochemistry): symptom suppression by dopamine modulation is consistent with a downstream stabilizing role and does not imply etiological primacy.

• E13 (immune effects in subsets) vs. C10 (cross-system coupling): subset-specific immune modulation is precisely the form of interaction C10 requires, not a contradiction of it.

3.6.3. Significance of Compression

This mapping demonstrates that the observed constraints are not selective reinterpretations, but principled abstractions that emerge when heterogeneous empirical findings are reorganized by their shared structural implications for explanatory architecture [8,12]. Importantly, no observed constraint lacks empirical grounding, and no major empirical regularity is left unrepresented under the present level of abstraction [10].

The compression step therefore completes the internal logic of the Results section:

- empirical constraints establish what cannot be denied without contradicting replicated evidence [16],
- observed constraints establish what explanatory models must be able to represent [8], and
- STM variables specify how those explanations must be structured at the architectural level [11,12].

Together, these steps lay the foundation for the final synthesis: the explicit specification of properties required by any explanatory framework aiming to account for psychosis and schizophrenia under the present constraint-based analysis [16].

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3.7. Mapping the Empirical Constraints Across Theories (STM Included)

The preceding sections established two independent constraint sets: the observed constraints (C1–C10), derived from recurring clinical and phenomenological regularities, and the empirically established constraints (E1–E15), extracted directly from replicated findings across epidemiology, neuroscience, genetics, pharmacology, and longitudinal outcome studies. Section 3.6 demonstrated that these two sets are internally consistent and structurally aligned.

This section completes the Results by evaluating how major explanatory frameworks engage the empirical constraint set itself [16]. Whereas Section 3.4 assessed theories against the observed constraints as an abstraction-level test, the present analysis functions as an external-validity assessment: it asks whether each theory's core ontology can accommodate what the field has already established empirically, under a shared analytic framing.

The goal is not to adjudicate which theory is "true," but to assess constraint coverage [12]. Empirical constraints are treated as fixed requirements imposed by the literature. Theories are evaluated solely on whether their foundational assumptions can represent these requirements without reliance on auxiliary assumptions that alter causal direction, collapse abstraction levels, or reposition downstream correlates as primary causes [8,11].

3.7.1. Theory × Empirical Constraints Matrix (Table 3.7)

Table 3.7 presents the theory × empirical constraints matrix, evaluating representative theory classes against the empirically established constraint set (E1–E15). Evaluation uses the same three-level rubric introduced in Section 3.4 and reflects architectural representational coverage rather than empirical popularity, historical influence, or claims of theoretical correctness [12,16].

Table 3.7. Theory × Empirically Established Constraints (E1–E15)

Scoring rubric (applied uniformly):

✓ = explicitly represented

~ = indirectly or partially represented

✗ = not explicitly represented

Scores indicate whether a theory's core ontology can accommodate a given empirical constraint without auxiliary assumptions that alter causal direction, collapse abstraction levels, or reposition downstream correlates as primary causes [8,11].

Theory / Constraint	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E13	E14	E15
Dopamine-centric	~	✗	~	~	~	~	✗	~	✓	~	~	~	✗	~	~
Glutamate / NMDA	~	✗	~	~	~	~	~	~	~	~	~	~	~	~	~
Other monoamines	~	✗	~	~	~	✗	~	~	~	~	~	~	✗	~	~
Polygenic (GWAS)	✓	✓	✓	~	~	~	~	~	~	~	~	✓	~	~	✓
Rare variants / CNVs	~	✓	~	~	~	~	~	~	~	~	~	✓	~	~	~
Gene × environment / epigenetic	✓	✓	✓	✓	✓	~	~	~	~	~	~	✓	~	✓	✓
Neurodevelopmental	✓	✓	✓	~	~	✓	✓	~	~	~	~	✓	~	~	✓
Dysconnection	✓	✓	~	~	~	✓	✓	~	~	~	~	✓	~	~	✓
E/I imbalance	~	✓	~	~	~	~	✓	~	~	~	~	✓	~	~	~
Synaptic pruning	~	✓	✓	~	✓	✓	✓	~	~	~	~	✓	✓	~	✓
Predictive coding	✓	✓	~	✓	✓	✓	✓	✓	~	~	✓	✓	~	✓	✓
Aberrant salience	~	✓	~	~	~	~	~	✓	✓	~	~	✓	✗	~	~
Source monitoring	~	✓	~	~	~	~	~	✓	~	~	~	✓	✗	~	~
Sensory gating	~	~	~	~	~	✓	~	~	~	~	~	~	✗	~	~

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Stress–diathesis	✓	✓	✓	✓	✓	~	~	✓	~	~	✓	✓	~	✓	✓
Trauma / dissociation	~	✓	~	✓	~	✓	~	✓	~	~	✓	✓	~	✓	~
Social defeat	~	✓	~	✓	~	~	~	✓	~	~	~	✓	✗	✓	~
Substance-induced	~	✓	~	✓	✓	~	~	✓	~	~	✓	✓	~	✓	~
Immune / inflammatory	✓	✓	~	✓	✓	~	~	✓	~	✓	~	✓	✓	✓	✓
Prenatal infection	~	✓	~	~	✓	~	~	~	✗	~	✗	✓	✓	~	~
Neurodegenerative	✗	✓	~	✗	✗	✗	~	✗	✗	~	✗	✗	~	✗	✗
Psychodynamic-only	✗	✓	✗	~	✗	~	~	~	✗	✗	~	✓	✗	~	✗
Sensitivity Threshold Model (STM)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Interpretation.

This table summarizes empirically established constraints that frameworks aiming to provide a comprehensive account of schizophrenia commonly seek to engage, based on convergent and widely replicated findings across genetics, neurodevelopment, neurobiology, cognition, and clinical course. The table is intended to clarify coverage of a shared empirical constraint space rather than to rank theories or adjudicate correctness. The Sensitivity Threshold Model (STM) is included as a reference construction demonstrating that simultaneous representation of all listed constraints is achievable within a single coherent system-level framework; the table does not imply that STM is the only possible framework capable of doing so.

The table is intended to support comparative assessment of architectural adequacy rather than to assert truth claims or adjudicate theoretical correctness [16].

3.7.2. Pattern-Level Results: Architectural Coverage and Gaps

The constraint-coverage patterns in Table 3.7 suggest consistent architectural signatures across theory classes. Most models succeed within their domain of emphasis but systematically struggle to satisfy constraints that require integration across domains—indicating structural incompleteness rather than gaps in empirical support [10,12].

Result statement A — Single-pathway neurochemical models.

Single-pathway neurochemical theories (e.g., dopamine-centric and related monoamine accounts) perform best on medication-linked constraints, particularly those related to acute symptom suppression (E9). However, they consistently struggle to explicitly represent constraints involving heterogeneity (E1), absence of diagnostic biomarkers (E2), and cross-diagnostic overlap (E15). These limitations reflect the absence of a principled distinction between upstream vulnerability, state-dependent destabilization, and downstream symptom modulation, increasing the risk of causal inversion when treatment response is interpreted as etiological evidence [8,11].

Result statement B — Genetic and neurodevelopmental models.

Genetic, polygenic, and neurodevelopmental frameworks capture important aspects of risk architecture, distributed biological findings, and developmental patterning (E1, E3, E5, E12). However, they often struggle to account for state dependence, episodic instability, and variable treatment response (E8–E11) unless supplemented with explicit load- or state-based mechanisms [16]. As a result, these models often provide only partial representational coverage of constraints that require dynamic transitions rather than static predisposition..

Result statement C — Computational and systems-adjacent models.

Computational approaches, including predictive coding and related frameworks, perform well on constraints involving structured symptom content and state dependence (E7, E8), and tend to exhibit stronger alignment than single-pathway models on causal organization. Nonetheless, they

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often leave treatment response variability, sensitization, and outcome divergence (E9, E10, E14) underspecified, reflecting limited anchoring to longitudinal course and intervention asymmetries [1].

Result statement D — Integrative stress and systems-level models.

Stress–diathesis, trauma-related, immune-modulatory, and other integrative models capture environmental sensitivity and variability (E4, E8, E11), but typically lack a unified architecture capable of representing heterogeneity, history dependence, and recovery trajectories simultaneously. As a result, they satisfy relevant constraints locally but fail to generalize across the full empirical constraint set.

Result statement E — Sensitivity Threshold Model as a unification scaffold.

The Sensitivity Threshold Model is included in Table 3.7 as a constraint-complete reference architecture. Its role is not to assert etiological finality, but to demonstrate that it is possible, in principle, for a single systems-level explanatory model to satisfy all empirically established constraints simultaneously without auxiliary assumptions or causal inversion [16]. STM functions as a unification scaffold capable of hosting genetic, developmental, environmental, neurochemical, and computational components while preserving causal direction, state–trait separation, and outcome variability.

Together, these pattern-level results complete the external-validity evaluation of the Results section. They support the interpretation that explanatory limitations stem not from missing data, but from insufficient architectural capacity to integrate heterogeneity, dynamics, and history—setting the stage for the final synthesis of required model properties [12].

3.8. Derived "Final Solution Specification" and Why STM Satisfies It (C3 as the Driver)

The preceding sections established two key results:

i. the empirical constraint set (E1–E15) cannot be denied without contradicting replicated findings, and

ii. the observed constraints (C1–C10) represent necessary abstractions that compress these findings without loss.

Together, these constraint sets logically constrain the space of admissible explanations [12,16].

This section makes that restriction explicit. Rather than proposing a specific mechanism, it derives a solution-level specification: a minimal set of architectural properties that an explanatory model aiming to account for all constraints simultaneously would be required to satisfy under the present analytic framing [8]. These requirements are not design preferences; they follow from the constraint structure itself [16], with C3 (causal direction: downstream neurochemistry) acting as the keystone that prevents causal inversion [11].

As demonstrated in Sections 3.3–3.7, the Sensitivity Threshold Model instantiates each element of this specification directly through its four-variable architecture, without auxiliary assumptions or causal inversion; STM is therefore referenced here as a concrete realization of the derived requirements rather than as an independent explanatory or privileged explanatory claim.

3.8.1. Constraint-Derived Requirements

Box 3.1 — Provisional Architectural Specification

A model is considered constraint-adequate under the present analytic framing if it satisfies all seven requirements simultaneously.

#	Requirement	Description
1	Dynamic State Representation	Schizophrenia must be represented as a dynamically evolving condition (e.g., fluctuation, remission, relapse), rather than as a static defect. (Forced by E8; supported by E11 and E14; formalized by C4.)
2	Load-Sensitive Threshold Behavior	Onset and exacerbation must be representable as threshold-crossing events driven by cumulative and acute load, allowing for variable timing and triggers. (Grounded in E5; formalized by C1 and C5.)

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3	Quantitative Heterogeneity without Fragmentation	The model must account for wide-spectrum variation in presentation and outcome without fragmenting schizophrenia into unrelated diseases. (Grounded in E1; formalized by C2.)
4	Absence of Single-Biomarker Expectation	The model must accommodate subtle, distributed, and non-specific biological effects, rather than require a unique lesion. (Grounded in E2; reinforced by E12.)
5	Explicit Trait × State Interaction	Stable vulnerability factors must interact with dynamic environmental and physiological stressors to produce instability. (Grounded in E3–E4; formalized by C2 and C4.)
6	Progressive Vulnerability with Partial Reversibility	The model must account for history-dependent sensitization while preserving the possibility of recovery and system re-stabilization. (Grounded in E14; formalized by C9.)
7	Preservation of Causal Ordering (Keystone Requirement)	Neurochemical abnormalities must be represented as downstream effects of system instability rather than as primary causes. (Formalized by C3; required to accommodate E9, E11, and E12.)

Interpretive note

A model that satisfies all seven conditions in Box 3.1 may be regarded as structurally adequate under the consolidated constraint set. Models that satisfy only subsets of these requirements may offer domain-specific insight but lack the architectural scope required for a general explanatory framework.

Why C3 functions as the keystone constraint

Among the observed constraints, C3 (neurochemical abnormalities are downstream, not primary) plays a stabilizing role in preserving causal coherence. In its absence, explanatory models frequently invert causality—interpreting state-correlated features such as dopamine dysregulation or medication response as etiological drivers. This inversion leads to predictable difficulties accommodating E9 (medication asymmetry), E11 (stress-induced psychosis), and E14 (variable outcomes), and collapses critical distinctions between vulnerability, state destabilization, and symptom expression.

Preserving causal ordering—upstream vulnerability and load → state destabilization → downstream expression—is therefore a central architectural requirement. C3 prevents explanatory shortcuts that conflate symptomatic suppression with etiological resolution.

This constraint-derived specification delineates the architectural properties required of any model aiming to satisfy the full constraint set. In the following section, the Sensitivity Threshold Model is referenced as a reference architecture illustrating how these requirements can be jointly satisfied—not by stipulation, but by construction.

3.8.2. Why C3 Is Critical (The Keystone Forcing Constraint)

Among the observed constraints, C3—that neurochemical abnormalities are downstream, not primary—plays a uniquely restrictive and stabilizing role. While other constraints specify what must be represented (e.g., heterogeneity, state dependence, or outcome variability), C3 specifies how causality must be ordered. It therefore functions as a keystone constraint: when it is not enforced, models may appear to accommodate other constraints, but only by implicitly inverting cause and effect.

C3 as a Causal-Direction Requirement

C3 requires that neurochemical abnormalities—particularly dopaminergic alterations—be modeled as state-sensitive and context-dependent consequences of system instability, rather than as initiating lesions. Under this requirement, neurochemical dynamics track variations in load and vulnerability, rather than defining the disorder's root cause.

This directional constraint is supported by convergent empirical findings, including:

- E9 (medication asymmetry): antipsychotics suppress positive symptoms without restoring cognitive or functional capacity;

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- E11 (stress- and sleep-induced psychosis): phenomenologically similar psychotic states can arise in non-schizophrenic contexts under sufficient load;
- E12 (non-specific brain differences): neuroimaging abnormalities are subtle, distributed, and highly cross-diagnostic.

Together, these findings indicate that similar neurochemical patterns can arise from diverse upstream perturbations, placing strong limits on interpretations that posit a fixed biochemical etiology.

What C3 Constrains

By enforcing causal ordering, C3 places stringent constraints on neurotransmitter-first models when they are proposed as root-cause explanations. In particular, such models struggle to account for:

- the inducibility of psychosis by non-disease stressors (E11),
- the dissociation between symptom suppression and functional recovery (E9), and
- the persistence of highly variable long-term outcomes despite neurochemical intervention (E14).

C3 does not deny the relevance of neurochemistry. Rather, it repositions neurochemical mechanisms as symptom-proximal modulators and treatment levers operating downstream of broader system dynamics, rather than as primary etiological drivers.

What C3 Forces into the Solution Space

Once causal inversion is ruled out under the present analytic framing, C3 necessitates that viable models include an upstream regulatory architecture capable of generating state instability without invoking a fixed lesion. Such an architecture must be able to:

- integrate cumulative and acute load,
- represent capacity limits and erosion,
- allow threshold-crossing events with variable timing, and
- support feedback, sensitization, and partial recovery across episodes.

In effect, C3 favors systems-level architectures in which neurochemical signals are embedded within broader dynamics of vulnerability, regulation, and adaptation, rather than isolated at the origin of disease.

C3 as the Stabilizer of the Full Constraint Set

When C3 is not enforced, many theories appear to satisfy portions of the constraint set by reinterpreting downstream correlates as causes. When C3 is enforced, these apparent solutions lose coherence, revealing unresolved tensions elsewhere in the architecture.

In this sense, C3 stabilizes the full constraint set by preserving distinctions between:

- trait-level vulnerability,
- state-level destabilization, and
- downstream symptom expression.

Conclusion: C3 as a Forcing Constraint

C3 is therefore not merely one constraint among many. It functions as a forcing constraint that strongly shapes the space of candidate explanatory architectures, favoring those capable of satisfying all constraints simultaneously while preserving causal ordering, state–trait distinction, and the empirically supported role of neurochemistry.

3.8.3. STM Satisfaction Demonstration (Closing Results Statements)

The preceding sections derived a constraint-forced solution specification independent of any specific model. This final subsection evaluates whether the Sensitivity Threshold Model (STM) satisfies that specification at the level of explanatory architecture. The goal is not empirical finality, but conceptual sufficiency under the full constraint set.

Constraint-Level Sufficiency

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STM satisfies the full set of derived architectural requirements (Box 3.1) under the present analytic framing, because its core variables naturally instantiate the needed properties—without auxiliary assumptions or causal inversion:

- Dynamic state behavior is modeled through load-dependent instability and recovery, satisfying E8 and C4.
- Load-sensitive thresholds allow for variable onset and relapse, satisfying E5 and C5.
- Quantitative heterogeneity without fragmentation arises from continuous variation in Sensitivity and Capacity, satisfying E1 and C2.
- Absence of a single biomarker is explained by distributed, state-dependent degradation of signal integrity rather than a fixed lesion, satisfying E2 and E12.
- Explicit trait × state interaction is formalized via stable Sensitivity interacting with dynamic Load, satisfying E3, E4, and C4.
- Progressive vulnerability with partial reversibility is captured through Capacity erosion and history-dependent threshold shifts, satisfying E14 and C9.

These features arise directly from STM's four-variable structure, rather than being introduced as auxiliary additions, and preserve causal directionality throughout.

C3 Satisfaction (Causal Direction Preserved)

STM satisfies the keystone constraint C3—that neurochemical abnormalities are downstream, not primary—by design. Neurochemical changes are modeled as state-tracking modulators of Signal Integrity, not as initiating lesions or identity markers.

This preserves:

- Consistent causal order (vulnerability → load → destabilization → symptom),
- Internal consistency across constraints,
- Compatibility with E9 (medication asymmetry), E11 (stress-induced psychosis), and E14 (variable outcomes).

STM thus avoids the causal inversion that can arise in otherwise promising models when downstream correlates are treated as primary causes.

STM as a Minimal Constraint-Consistent Architecture

STM is not proposed as the final truth about schizophrenia. Its significance is structural: it represents one minimal architecture that satisfies the full set of constraints simultaneously—including heterogeneity, dynamics, history, and causal order.

While other theories capture important fragments of this space, Table 3.7 demonstrates that they do so incompletely or with unresolved tensions. STM's contribution is to show that full constraint coverage is possible without incoherence or overfitting.

Anchoring to Field Consensus

Current consensus across psychiatry, neuroscience, and epidemiology holds that:

- Schizophrenia is multifactorial,
- No single gene, lesion, or pathway explains it,
- Its expression depends on interactions between vulnerability and environment.

The results here do not challenge that consensus—they make it architecturally explicit.

When these field-admitted facts are treated as constraints, they demand a model that:

- Preserves heterogeneity without fragmentation,
- Represents state dependence and context-sensitive onset,
- Maintains consistent causal direction,
- Allows for divergent long-term trajectories.

STM meets this demand by providing a constraint-adequate, causally ordered, and dynamically stable explanatory architecture.

Conclusion

Schizophrenia, under the full constraint set, is most coherently represented as a state-dependent systems instability—arising from the interaction of distributed vulnerability and cumulative load, rather than a fixed lesion or single-pathway disease.

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The Sensitivity Threshold Model is presented as a minimal explanatory architecture fully consistent with both this representation and the broader scientific consensus: not a final mechanism, but a structurally adequate platform for one.

4. Discussion

4.1. Summary of Principal Findings

This work did not begin with a new etiological claim about schizophrenia. Instead, it asked a prior structural question:

What must any adequate explanatory model look like, given what the field already knows?

To address this, we:

- Formalized well-established empirical findings as constraints (E1–E15),
- Compressed them into a set of higher-level observed constraints (C1–C10), and
- Evaluated existing theories against this combined constraint set.

From this process, a constraint-derived specification of explanatory adequacy emerged.

Three principal findings followed:

1. Most influential theories satisfy some—but not all—constraints.

Their limitations are architectural rather than empirical: they lack the structural capacity to integrate heterogeneity, state dynamics, and causal ordering simultaneously.

2. A small subset of constraints are disproportionately discriminative.

Most notably:

- C3 (causal direction),
- State dependence, and
- Outcome variability.

These constraints place strong limits on entire classes of models that might otherwise appear sufficient under narrower evaluative criteria.

3. A unified, constraint-consistent model is possible in principle.

The Sensitivity Threshold Model (STM) demonstrates that it is possible to absorb the full constraint set without contradiction, inversion, or overfitting. As demonstrated in Appendix D, the STM can be interpreted as a minimally sufficient architecture under the present constraint set: removal of any single variable produces a structural inability to satisfy one or more key clinical or empirical constraints.

Taken together, these results suggest that the field's theoretical fragmentation reflects not irreducible complexity, but incomplete integration at the architectural level.

4.2. Relation to Previous Studies and Working Hypotheses

The conclusions of this study are broadly consistent with current field consensus: schizophrenia is multifactorial, shaped by interactions between genetic vulnerability and environmental stressors, with no single causal pathway or diagnostic biomarker. This view has emerged independently across genetics, epidemiology, neuroscience, and clinical research.

However, much of the existing literature has remained descriptively convergent but architecturally underspecified—relying on broad terms such as gene–environment interaction, neurodevelopmental risk, or dopamine dysregulation without explicitly specifying how these elements must be causally organized to account for the full clinical phenotype.

The present findings help clarify why this gap has persisted. Many dominant hypotheses were not wrong in what they identified—but were limited in what they could accommodate simultaneously.

- Dopamine dysregulation, for example, is well supported as a symptom-linked mediator. However, it becomes insufficient as a standalone root cause once medication asymmetry, stress-induced psychosis, and variable outcomes are taken into account.

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- Genetic and neurodevelopmental models effectively capture distributed vulnerability, but struggle to explain state-dependent fluctuation, remission, and sensitization without importing additional dynamic mechanisms.
- Computational models—particularly predictive processing accounts—advance further by addressing symptom structure and representational instability. Yet these approaches often remain weakly anchored to longitudinal course, treatment variability, and partial recovery.

Taken together, these limitations suggest that ongoing disagreement in the field stems less from conflicting empirical evidence than from mismatched abstraction levels—where systems-level behavior is often explained using component-level ontologies that lack the capacity to integrate dynamics, history, and causal ordering simultaneously.

4.3. Implications of the Constraint-Based Approach

A central implication of this work is that schizophrenia may be more productively understood not as a disease defined by a specific lesion, molecule, or pathway, but as a state-dependent systems instability.

The constraint-derived solution specification points toward classes of explanatory architectures that model:

- threshold behavior,
- load accumulation and dissipation,
- capacity limits and depletion,
- and history-dependent sensitization,

while preserving consistent causal direction and maintaining a clear separation between trait-level vulnerability and state-level fluctuation.

Crucially, this shift in framing does not invalidate component-level research. Findings related to:

- genetic variants,
- neurotransmitter systems,
- immune processes,
- and circuit-level alterations

remain highly relevant. Under a constraint-based lens, however, these features are more naturally understood as contributors to vulnerability, load, or signal integrity, rather than as standalone etiologies.

This reframing offers a principled architectural basis for integrating findings across biological and psychological domains—without relying on premature reduction or causal inversion.

A second implication concerns diagnosis and classification. Constraints related to:

- heterogeneity (E1, C2),
- cross-diagnostic overlap (E15, C10),
- and outcome variability (E14, C9)

collectively suggest that rigid categorical boundaries may obscure aspects of the shared architecture of psychiatric vulnerability.

A constraint-consistent perspective therefore supports emerging dimensional and transdiagnostic approaches, while preserving schizophrenia as a coherent syndrome—defined not by a unitary cause, but by a characteristic pattern of state-dependent instability.

4.4. Why Causal Direction Matters

Among all constraints, the requirement that neurochemical abnormalities be treated as downstream and state-tracking—rather than as primary causes—(C3) emerged as especially constraining. This helps explain why many models appear plausible when evaluated in isolation, yet encounter difficulties under integration.

Causal inversion allows short-term explanatory success, but often at the cost of long-term coherence.

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Preserving consistent causal direction helps resolve several long-standing puzzles:

- why antipsychotics suppress positive symptoms without reliably restoring cognition or function,
- why psychosis can be induced in non-schizophrenic individuals under extreme stress or sleep deprivation,
- and why outcomes diverge so widely despite similar diagnoses and treatment regimens.

These phenomena are difficult to reconcile within neurotransmitter-first etiologies when such mechanisms are treated as primary causes, but they follow naturally from models in which neurochemistry modulates symptom expression rather than defining core vulnerability.

4.5. Future Research Directions

The constraint-based framework introduced here suggests several priorities for future investigation:

1. Model testing and falsification

Future work should evaluate candidate models not merely for internal fit or empirical replication, but for constraint compliance. This may enable clearer identification of failure modes and support principled comparisons across competing frameworks.

2. Longitudinal and state-sensitive measurement

Many constraints highlight the importance of tracking load, capacity, and instability over time. This supports expanded use of intensive longitudinal designs, ecological momentary assessment, and dynamic systems modeling to capture temporal patterns and state transitions.

3. Mechanistic instantiation of abstract variables

While this work focused on architecture, future studies can explore how specific biological mechanisms instantiate constraint-required variables—for example, how immune activation, sleep disruption, or synaptic alterations contribute to load accumulation, capacity erosion, or signal degradation.

4. Clinical translation and intervention design

Constraint-consistent models may help inform interventions that go beyond symptom suppression—targeting load reduction, capacity preservation, and sensitization prevention. This shift in focus could yield improved long-term outcomes, particularly for treatment-resistant or high-risk populations.

4.6. Limitations

This study is conceptual in nature and does not directly test models against empirical data. The approach focuses on evaluating architectural adequacy under a defined constraint set, rather than on fitting or predicting specific outcomes. While all constraints were derived from replicated findings across multiple domains, their selection and formulation necessarily involve interpretive judgment—particularly in abstracting empirical regularities into non-negotiable architectural requirements.

Moreover, although the Sensitivity Threshold Model is shown to satisfy the full constraint set under the present analysis, this does not imply that it is the only possible architecture capable of doing so. Alternative models may also meet the same requirements if they preserve the necessary causal ordering, abstraction level, and variable separation. The STM is therefore offered not as a definitive theory, but as a minimal working solution demonstrating that full constraint satisfaction is achievable in principle.

5. Conclusions

This work reframes schizophrenia research as a problem of explanatory adequacy under constraint, rather than as a contest between isolated hypotheses. By formalizing what any viable model must satisfy—based on what the field already knows—it helps explain why theoretical progress has remained limited despite decades of empirical discovery.

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The key result is not that one model is "correct," but that the constraint structure itself substantially constrains the space of admissible explanations. This recognition transforms ambiguity into guidance: it suggests that theoretical progress may depend less on identifying additional causal components, and more on developing explanatory architectures capable of integrating the components already supported by the literature.

Working within these constraints may enable the field to move beyond fragmentation—toward principled synthesis and deeper understanding.

Within this framework, the present work distinguishes between the architectural requirements imposed by the empirical constraint structure and any particular model that instantiates them. The derived solution specification defines the necessary properties of an adequate explanatory architecture, independent of specific mechanisms. The Sensitivity Threshold Model is presented as a reference implementation that demonstrates the feasibility of satisfying these requirements simultaneously. STM is not proposed as a unique or final explanation, but as a proof-of-concept showing that a coherent, causally ordered, and constraint-consistent model is possible in principle. Other models may also occupy this admissible space, provided they preserve the same core structural properties implied by the constraint set.

The future of schizophrenia theory may therefore depend less on identifying new causes, and more on building architectures capable of honoring the constraints we already understand.

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Abbreviations

STM	Sensitivity Threshold Model
S	Sensitivity (one of the four abstract variables of the STM)
L	Load (one of the four abstract variables of the STM).
C	Capacity (one of the four abstract variables of the STM).
K	Capacity (alternate notation for the Capacity variable used in tables to avoid confusion with constraint labels)
SI	Signal Integrity (one of the four abstract variables of the STM).
I	Signal Integrity (alternate notation for Signal Integrity).

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C1–C10	Observed Constraints (ten clinical and phenomenological regularities formalized in the study).
E1–E15	Empirical Constraints (fifteen robust findings from genetics, neuroscience, and epidemiology used as boundary conditions).
GWAS	Genome-Wide Association Study (used in the context of polygenic risk).
CNVs	Copy Number Variants (used in the context of rare genetic variants).
NMDA	N-methyl-D-aspartate (referring to the glutamatergic receptor/theory).
E/I	Excitation/Inhibition (as in "E/I imbalance" models).
ICU	Intensive Care Unit (mentioned in the context of stress-induced psychosis).
Ei	Empirical constraint index (used when mapping individual empirical findings).
Cj	Observed constraint index (used when mapping individual clinical observations).

Appendix A

Heuristic and Conceptual Origin: The Observational Constraints (OC1–OC11)

The observational prototypes listed here (OC1–OC11) represent the inductive origins of the formal architectural constraints later defined in Table 3.2. They emerged through exploratory reasoning methods — including narrative construction, analogical modeling, and theoretical thought experiments — rooted in sensitivity theory, stress biology, systems neuroscience, and computational overload metaphors. These prototypes served as conceptual scaffolding for the subsequent formalization of the architectural constraint set (C1–C10). Each OC reflects an insight that appeared repeatedly across STM narrative case studies and metaphor-driven reasoning, and is traceable to a specific empirical or experiential domain.

These prototypes are presented solely to document the conceptual and heuristic origins of the formal constraint set; they are not offered as empirical evidence, diagnostic claims, or generalizable observations.

Observed Constraint ID	**Prototype Insight**	**Narrative and Theoretical Origin**
OC1	Psychotic symptoms emerge under conditions of extreme cognitive and sensory overload.	Derived from documented extreme stress and sensory deprivation paradigms (e.g., military training reports, experimental sleep-deprivation studies), interpreted through information-theoretic overload metaphors.
OC2	Individuals with heightened sensitivity are more susceptible to overload-related breakdown.	Core STM hypothesis; draws from individual-difference models of sensory sensitivity (e.g., HSP literature) and IT systems with high-sensitivity thresholds.
OC3	Reducing environmental input can mitigate or reverse psychotic symptoms.	Observations from clinical and environmental settings involving reduced stimulation (e.g., inpatient units, controlled environments), interpreted through load-reduction analogies.
OC4	Even non-vulnerable individuals can experience transient psychosis under sufficient overload.	Universality of overload response demonstrated through sleep deprivation, extreme sensory deprivation, and stress-induced hallucinations in healthy individuals.
OC5	Cognitive overload precedes neurochemical dysregulation, not the reverse.	Contrasts with dopamine-first interpretations by modeling input saturation → system instability → neurochemical compensation.

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OC6	Psychosis reflects a system-level failure due to exceeded processing thresholds.	Central to the IT crash metaphor; failure emerges not from damaged parts, but from overwhelmed integrative functions and feedback loop collapse.
OC7	Highly sensitive individuals exhibit exaggerated reactivity under stress.	Individual-difference models of sensory and affective sensitivity (e.g., HSP literature), interpreted through systems-theoretic amplification frameworks.
OC8	Sensory gating failure results in cognitive flooding by unfiltered stimuli.	Inspired by extreme sensory deprivation and high-noise conditions; aligns with STM's neuroscience modeling of impaired signal filtering under overload.
OC9	Antipsychotic medications function by reducing neuronal sensitivity and input processing.	Pharmacological effects interpreted heuristically as reducing effective system gain or responsivity within the STM load-based framework.
OC10	Resilience and buffering prevent breakdown in sensitive systems.	Emphasizes protective effects of sleep, withdrawal from high-load environments, and supportive contexts — all of which increase tolerance thresholds.
OC11	First psychotic episodes frequently follow identifiable life stressors rather than occurring randomly or strictly developmentally.	Onset narratives in STM highlight situational overload — trauma, transitions, or sudden increases in input — rather than age-based triggers.

Appendix B

From Narrative-Derived Prototypes (OC1–OC11) to Formal Architectural Constraints (C1–C10)

This appendix illustrates how the inductive insights developed in Appendix A (OC1–OC11) were formally abstracted into the empirical constraint architecture outlined in Table 3.2. Each mapping illustrates the formal abstraction of exploratory narrative insights into a structurally explicit constraint framework for modeling schizophrenia as a load-sensitive, dynamically regulated system. Some constraints arise directly from single narrative prototypes, while others emerge through convergent synthesis across multiple narratives, highlighting their strength as general design principles for modeling complex psychiatric syndromes.

The mappings presented here document the conceptual abstraction process and do not constitute empirical validation of the resulting constraints.

OC → C	Formal Constraint (C)	Justification for Mapping
OC1 → C1	Stress-induced psychosis	Narrative examples of hallucinations under extreme sensory and cognitive load support psychosis as a state, not a trait—triggered by acute overload rather than intrinsic disease.
OC4 → C1	Stress-induced psychosis	Demonstrates universality: even non-diagnosed individuals can manifest psychotic states under extreme load, reinforcing that schizophrenia reflects a load-threshold interaction, not a unique brain lesion.
OC2 → C2	Quantitative vulnerability	Trait-level sensitivity, as conceptualized in individual-difference models of responsivity and STM narratives, is treated as a continuous variable—enabling a graded risk architecture rather than categorical liability.
OC7 → C2	Quantitative vulnerability	Amplified reactivity under stress further supports graded susceptibility, not binary pathology. Degree of sensitivity modulates risk across a spectrum.

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OC5 → C3	Downstream neurochemistry	STM contrasts with dopamine-first interpretations by modeling neurochemical dysregulation as a downstream effect of overload.
OC3 → C4	State-dependent symptoms	Symptoms remit in low-stimulation environments, implying psychosis is context-sensitive — a reversible system state modulated by environmental input.
OC8 → C4	State-dependent symptoms	Sensory gating failures occur under load, not permanently. Supports the idea that filtering breakdown is state-contingent, not a fixed hardware defect.
OC6 → C1 / C4	Stress-induced psychosis / State dependence	Collapse occurs when systemic thresholds are breached — not due to pre-existing structural damage. This explains both the onset of psychosis and its fluctuation.
OC9 → C8	Medication asymmetry	Antipsychotics are interpreted heuristically as reducing effective system responsivity, suppressing symptoms without resolving underlying vulnerability.
OC10 → C6	Prodromal overload	STM's buffering model maps to pre-psychotic states that reflect overload accumulation. Narratives describe resilience and recovery via environmental withdrawal before collapse.
OC11 → C5	Variable onset timing	First-episode psychosis often follows discrete life stressors, not a developmental milestone, supporting a threshold-based timing model rather than a time-locked neurodevelopmental model.
(Implicit narrative) → C7	Structured symptom content	Narrative synthesis suggests that symptom content often reflects recent salient stressors, motivating the constraint that psychotic symptoms exhibit structured, experience-linked organization rather than random noise.
(Cross-narrative synthesis) → C9	Sensitization over time	Repeated overload events lower the threshold for subsequent breakdowns — establishing a temporal vulnerability gradient consistent with stress-sensitization models.
(Cross-narrative synthesis) → C10	Cross-system coupling	STM integrates stress, immune, endocrine, and neurocognitive domains. Multiple narratives motivate the inclusion of coupled system interaction, where stress propagates across biological domains.

Multiple observational prototypes may converge on a single architectural constraint, reinforcing its conceptual robustness and structural coherence. Conversely, certain constraints—especially those involving systemic coupling or long-term sensitization—emerge only through cross-narrative integration, rather than from any single origin story. This mapping formalizes the translation process by which narrative-derived insights were abstracted into a falsifiable, systems-level constraint framework capable of engaging both clinical phenomena and biological mechanisms within a unified explanatory architecture.

Appendix C

Empirical Alignment: Mapping Established Constraints (E1–E15) onto STM Architecture

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This appendix documents how the empirically established constraints (E1–E15)—derived from replicated findings across psychiatry, neuroscience, immunology, and cognitive systems research—map onto the architectural variables of the Sensitivity Threshold Model (STM).

The purpose of this mapping is not to empirically validate STM as a correct or complete model, but to demonstrate structural compatibility between the model's core variables and the high-consensus empirical regularities already established in the literature. Each constraint is treated as an external requirement, and STM is evaluated solely on whether its architecture can accommodate these requirements without contradiction, causal inversion, or auxiliary assumptions.

Constraint ID	Name & Description	Structural Importance (The "Why")	Constraint Interpretation within STM Architecture
E1	Syndrome, not disease (Extreme heterogeneity)	Rules out single-lesion models; requires a framework for diverse failure modes.	STM conceptualizes schizophrenia as a common endpoint of multiple overload pathways in highly sensitive systems. Heterogeneity reflects convergence on a shared failure state arising from different combinations of vulnerability and stress, rather than a uniform causal mechanism.
E2	No single biomarker (No diagnostic marker found)	Supports that schizophrenia is a systems-level organizational failure, not a localized organic defect.	STM models psychosis as arising from dynamic systemic dysregulation rather than a fixed lesion. Functional impairment emerges from interactions across multiple regulatory processes, supporting an emergent rather than localized origin.
E3	Weak polygenic risk (Thousands of tiny variants)	Limits genetic determinism; necessitates a distributed Sensitivity parameter.	STM interprets polygenic effects as small contributions to baseline system sensitivity. These distributed influences shape overall vulnerability without specifying a single causal pathway, consistent with cumulative risk modulation rather than gene-specific determinism.
E4	Large environmental effects (Urbanicity, adversity)	Forces inclusion of a state-dependent Load variable.	STM integrates environmental exposures such as urban stress, trauma, and sensory overload as contributors to cumulative cognitive and physiological load, particularly in sensitive individuals. Sustained input burden progressively reduces system resilience.
E5	Patterned/Flexible onset (Adolescent peak)	Rules out fixed-insult models; requires interaction between Load and developmental Sensitivity.	STM models psychosis onset as a threshold event arising when increasing cognitive and social demands exceed available regulatory capacity during development, rather than as the delayed expression of a fixed early lesion.
E6	Common prodrome (Changes precede psychosis)	Shows psychosis is a late-stage manifestation.	STM interprets early symptoms such as anxiety, sleep disruption, and sensory sensitivity as indicators of progressive regulatory strain, reflecting system destabilization prior to overt psychosis rather than early psychotic expression itself.
E7	Persistent cognitive deficits (Stable trait)	Distinguishes stable Capacity from fluctuating psychotic State.	STM differentiates enduring limitations in cognitive capacity from transient overload states. Stable deficits reflect long-term constraints in processing resources, while psychotic symptoms reflect acute system overload.

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E8	State-dependent psychosis (Fluctuates with stress)	Supports threshold-crossing logic over static defect models.	STM treats psychosis as a state transition triggered by excessive load. Stress, sleep disruption, or sensory saturation can temporarily exceed system thresholds, producing unstable processing without implying a permanent defect.
E9	Medication asymmetry (Positive symptoms vs. Cognition)	Confirms consistent causal direction (downstream neurochemistry).	STM frames antipsychotics as modulators of system sensitivity that reduce acute symptom expression without restoring baseline processing capacity, consistent with a downstream, stabilizing role for dopamine.
E10	Variable treatment response (Resistance/Remission)	Highlights multiple interacting system variables.	STM's multidimensional architecture predicts that treatment outcomes depend on which system components are most compromised. Different failure profiles produce different response patterns.
E11	Stress-induced psychosis (Sleep deprivation/ICU)	Shows psychosis is not disease-specific.	STM explains stress- or sleep-related psychosis as a general consequence of excessive load on regulatory systems, demonstrating that psychotic states can emerge in the absence of schizophrenia-specific pathology.
E12	Subtle brain differences (Non-specific imaging)	Rules out gross neurodegeneration models.	STM supports a model of functional dysregulation without permanent structural damage. Neural alterations reflect transient or distributed system instability rather than localized neurodegeneration.
E13	Immune effects in subsets (Cytokines/Maternal risk)	Expands Load to include physiological stressors.	STM incorporates immune activation as a contributor to overall system load. Inflammatory processes increase regulatory burden and reduce signal fidelity without constituting a primary causal mechanism.
E14	Variable outcome (Recovery is possible)	Rules out inexorably degenerative models.	STM interprets recovery as restoration of regulatory balance through load reduction, capacity support, and environmental stabilization, allowing systems to re-establish functional equilibrium.
E15	Cross-diagnostic overlap (Shared genetics/cognition)	Supports transdiagnostic architectures.	STM treats psychiatric syndromes as different expressions of shared vulnerability interacting with domain-specific stressors. Phenotypic differences arise from pathway dynamics rather than distinct etiologies.

Summary: From Narrative Hypotheses to Empirically Anchored Architecture

The STM framework originated through inductive hypothesis generation informed by high-stress psychotic states, computational analogies, and real-world accounts of sensory and emotional overload. These narrative-derived insights were formalized as observational constraints and

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subsequently abstracted into a systems-level architectural model. When this architecture is mapped onto empirically established constraints, it exhibits broad structural compatibility with high-consensus findings across psychiatry and systems neuroscience.

This iterative translation process — from narrative prototype to formal constraint to empirical anchoring — illustrates a bottom-up model-building methodology capable of unifying heterogeneous empirical phenomena within a coherent, falsifiable systems framework. Rather than fitting a theory post hoc to existing data, STM demonstrates how structured narrative reasoning can identify latent regularities and generate integrative explanatory architectures.

Appendix D

Exploratory Variable-Subset Comparisons

This appendix demonstrates that the constraint-level adequacy of the Sensitivity Threshold Model (STM) is not reducible to any proper subset of its variables. Each STM variable subset is evaluated against the same observed and empirical constraints used throughout the manuscript, using the identical three-level rubric.

The purpose of this analysis is not to optimize variable count, but to demonstrate structural non-substitutability: each variable contributes a distinct architectural function required by the consolidated constraint set.

Scoring rubric (unchanged)

- ✓ Satisfies — Constraint follows directly from the subset's core ontology
- ~ Partially satisfies — Constraint can be accommodated only via auxiliary assumptions or ambiguity
- ✗ Fails — Constraint cannot be represented structurally

(Variables: S=Sensitivity, L=Load, K=Capacity, I=Signal Integrity.)

STM subset	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
S	✗	✓	✗	✗	✗	✗	✗	~	✗	✗
L	~	✗	✗	~	✓	~	✗	~	✗	✓
K	✗	✗	✗	✗	✗	~	✗	✗	✓	✗
I	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗
S+L	✓	✓	✗	~	✓	~	✗	~	✗	✓
S+K	✗	✓	✗	✗	✗	~	✗	✓	✓	✗
S+I	✗	✓	✗	✗	✗	✗	✓	~	✗	✗
L+K	~	✗	✗	~	✓	✓	✗	✓	✓	✓
L+I	~	✗	~	✓	✓	~	✓	~	✗	✓
K+I	✗	✗	~	✗	✗	~	✓	✗	✓	✗
S+L+K	✓	✓	✗	~	✓	✓	✗	✓	✓	✓
S+L+I	✓	✓	~	✓	✓	~	✓	~	✗	✓
S+K+I	✗	✓	~	✗	✗	~	✓	✓	✓	✗
L+K+I	~	✗	✓	✓	✓	✓	✓	✓	✓	✓
S+L+K+I	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Constraint failures under variable removal (non-redundancy analysis):

- Dropping I collapses C7 (structured symptom content) and weakens downstream/coherence requirements inside C3/C4.
- Dropping K collapses C9 (history-dependent threshold lowering) and makes medication asymmetry (C8) at best partial (you can "dampen," but can't represent *why cognition/capacity doesn't restore*).

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- Dropping L collapses state/context requirements (C1/C4/C5/C10) because there is no formal time-varying burden driver.

This table uses the document's empirical→observed compression map (Table 3.6) to derive what each empirical constraint *structurally requires* of an explanatory model (e.g., E4/E8 require the state-instability architecture behind C1 & C4; E6 requires the C6 & C9 structure; etc.).

STM subset	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E13	E14	E15
Table 3.6 Logic	C2	C2, C3	C2, C5	C1, C4, C5	C2, C5	C6, C9	C6, C9	C1, C4	C3, C8	C2, C8, C9	C1, C3, C4	C2, C3	C2, C10	C4, C9	C2, C10
S	~	✗	~	✗	~	✗	✗	✗	✗	~	✗	✗	~	✗	~
L	~	~	~	~	~	~	~	~	~	✗	~	~	~	~	~
K	✗	~	✗	✗	✗	~	~	✗	✗	~	~	~	✗	~	✗
I	✗	~	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
S+L	✓	~	✓	~	✓	~	~	~	~	~	~	~	✓	~	✓
S+K	~	~	~	✗	~	~	~	✗	✗	✓	~	~	~	~	~
S+I	~	~	~	✗	~	✗	✗	✗	✗	~	✗	~	~	✗	~
L+K	~	~	~	~	~	✓	✓	~	~	~	~	~	~	~	~
L+I	~	~	~	~	~	~	~	~	~	✗	~	~	~	~	~
K+I	✗	~	✗	✗	✗	~	~	✗	✗	~	~	~	✗	~	✗
S+L+K	✓	~	✓	~	✓	✓	✓	~	~	✓	~	~	✓	~	✓
S+L+I	✓	~	✓	✓	✓	~	~	✓	~	~	~	~	✓	~	✓
S+K+I	~	~	~	✗	~	~	~	✗	~	✓	~	~	~	~	~
L+K+I	~	~	~	~	~	✓	✓	~	~	~	~	~	~	✓	~
S+L+K+I	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Appendix D shows that STM's full constraint satisfaction is not reducible to any proper subset of its variables. Each variable plays a non-substitutable structural role, and only the complete four-variable system satisfies all observed and empirical constraints without auxiliary assumptions.

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