Schizophrenia as Ordered Synaptic Fragility: A Causal Hierarchy from Development to Psychosis

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Abstract

Schizophrenia is proposed as an ordered failure of synaptic development and maintenance within the unusually prolonged, plastic, and densely interconnected architecture that supports human association, self-modeling, and social cognition. The sapiens-specific claim is a scoping commitment about the integrated architecture and phenomenology, not a claim that every component mechanism is human-unique. Distributed common and rare variation biases synaptic construction and maintenance in mature neuronal populations; prenatal regulatory perturbations create vulnerability; adolescent and, in some cases, later normal loss of reserve exposes it. Complement-dependent microglial pruning is proposed as a privileged but nonexclusive developmental amplifier, competing with astrocytic MEGF10/MERTK-mediated elimination and conditioned by neuronal activity, NMDA receptor-dependent plasticity, inhibitory maturation, and mitochondrial reserve. The predicted anatomy is reduced neuropil and dendritic-spine density without commensurate neuronal death. Chronic cohorts show lower presynaptic SV2A binding, whereas an early-course study found no large corrected deficit, making timing and medication dependence empirical questions. Dysconnection degrades excitation-inhibition balance and neural synchrony; hippocampal hyperactivity and cortical disinhibition recruit striatal dopamine dysregulation. The account adopts Kapur's aberrant-salience bridge from dopamine to psychotic conviction but departs from the dopamine hypothesis version III by treating presynaptic striatal dopamine as a downstream, potentially bypassable amplifier rather than the obligatory final common pathway. Failures of corollary discharge, predictive updating, and social metarepresentation shape psychotic content. Liability persists through recurrent deleterious variation across a vast mutational target rather than adaptive psychosis. Seven prespecified programs test complement-mediated pruning, temporal ordering of dopamine, synaptic loss, human-lineage genomic concentration, evolutionary persistence, attractor dynamics, and inhibitory-oscillatory failure.

Keywords: schizophrenia, synaptic pruning, complement, astrocytes, dysconnection, excitation-inhibition balance, neural oscillations, dopamine, aberrant salience, neurodevelopment, human evolution, falsifiability

The Central Claim

Schizophrenia is best understood as an inherent vulnerability surface of the human brain: a predictable class of failure modes produced by the same architectural and regulatory innovations that make Homo sapiens cognition possible. The syndrome is not reducible to dopamine excess, NMDA receptor hypofunction, inflammation, mitochondrial dysfunction, abnormal pruning, or a focal circuit lesion. Those findings occupy different levels of one causal hierarchy. Schizophrenia begins as distributed developmental fragility in the synaptic apparatus, is amplified by adolescent or later remodeling, and becomes clinically visible when dysconnected association networks recruit hippocampal-striatal dopamine systems and lose the ability to distinguish self from other, signal from noise, and inference from evidence.

The central mechanism is a genetically loaded susceptibility to maladaptive synaptic selection. Prenatal disturbances in neuronal differentiation, migration, transcription, splicing, synapse formation, and metabolic support produce circuits that are functional but precarious. During adolescence, when the cortex must eliminate redundant connections while stabilizing efficient ones, complement-dependent microglial pruning magnifies small differences in synaptic fitness. Vulnerable or mistagged synapses are preferentially removed; inhibitory and excitatory systems lose their calibrated reciprocity; neuropil contracts; NMDA receptor-dependent plasticity becomes unreliable; and large-scale integration fails. Dopamine dysregulation is neither the initiating lesion nor, in this account, an obligatory final common pathway. It is a downstream gain mechanism that converts dysconnected inference into psychotic conviction. This ordering agrees with Howes and Kapur (2009) that diverse hits lie upstream of

presynaptic striatal dopamine but rejects their stronger funnel-point claim; it adopts Kapur's (2003) aberrant-salience framework as the bridge from dopaminergic gain to psychotic experience.

Animal models are used here to test conserved component mechanisms—complement-mediated refinement, inhibitory timing, mitochondrial reserve, and hippocampal control of dopamine—not to claim that a rodent or nonhuman primate reproduces the integrated human syndrome or its language- and self-model-dependent phenomenology.

This theory is not a list of abnormalities. It is a sequence. Its explanatory force depends on keeping six propositions distinct and ordered.

1. The architectural substrate. Human association cortex, frontotemporal and frontoparietal connectivity, hippocampal-prefrontal integration, and social-metarepresentational systems mature unusually late and remain unusually dependent on experience-guided synaptic refinement (Burns, 2004; Weinberger, 1987).

2. The genetic liability. Hundreds of common variants, recurrent copy-number variants, and ultra-rare coding variants converge on synaptic organization, glutamatergic signaling, calcium regulation, chromatin control, and neuronal development rather than on a single schizophrenia-specific pathway (International Schizophrenia Consortium, 2009; Marshall et al., 2017; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Trubetskoy et al., 2022).

3. The developmental timing. Risk is planted predominantly during prenatal construction, can produce measurable but subclinical childhood deviations, and is often exposed when adolescent pruning, myelination, inhibitory maturation, and prefrontal specialization make circuit precision rate-limiting. Later hormonal transitions, immune-metabolic burden, or normal age-related loss of reserve can expose the same liability after the modal onset window; this is not a claim of illness-specific neurodegeneration (Feinberg, 1982; Howes & Murray, 2014; Jaffe et al., 2018; Jones et al., 1994; Murray & Lewis, 1987; Reichenberg et al., 2010; Weinberger, 1987).

4. The execution mechanism. Complement tagging and microglial phagocytosis provide a candidate privileged selection system capable of turning subtle neuronal weakness into actual synapse loss; mitochondrial and homeostatic reserve determine whether that selection remains adaptive or destructive. Astrocytic MEGF10/MERTK-mediated pruning is a competing route, so "privileged" means a greater causal contribution in a prespecified subgroup and window, not exclusivity (Chung et al., 2013; Sekar et al., 2016; Sellgren et al., 2019; Stevens et al., 2007; Yilmaz et al., 2021).

5. The circuit expression. Reduced neuropil and impaired NMDA receptor-dependent plasticity create dysconnection. Inhibitory calibration and the beta- and gamma-band synchrony that depend on it degrade; prefrontal and temporal systems lose signal fidelity; hippocampal hyperactivity recruits mesostriatal dopamine; and failures of self-monitoring and social inference supply the phenomenological content of psychosis (Lewis et al., 2005; Lodge & Grace, 2007; Stephan et al., 2009; Uhlhaas & Singer, 2010).

6. The evolutionary persistence. The human cognitive architecture was selected; schizophrenia-risk alleles were not. Deleterious variation persists because the mutational target is enormous and recurrent structural and sequence variation continually replenishes liability. Evidence that some allele-frequency trajectories have recently declined is evidence of directional selection, not proof that the present system is at mutation-selection equilibrium (Burns, 2004; Keller & Miller, 2006).

The closest existing synaptic synthesis is the synaptic hypothesis of schizophrenia version III, which identifies synaptic dysfunction as a master mechanism linking genetic and environmental risk to symptoms (Howes & Onwordi, 2023). The primary dopaminergic foil is the dopamine hypothesis version III, which likewise places diverse hits upstream but designates presynaptic striatal dopamine as the final common pathway to psychosis (Howes & Kapur, 2009). The present theory accepts synaptic convergence and Kapur's aberrant-salience account but rejects dopamine as an obligatory funnel point. It adds five commitments: an ordered hierarchy separating neuronal liability, glial execution, and dopaminergic amplification; a sapiens-specific scope for the architecture and phenomenological content that fail; an explicit evolutionary-persistence model; operational dynamical-systems predictions for an attractor transition; and prespecified experiments whose null results would force abandonment of load-bearing claims. Table 1 maps these commitments and the six propositions to seven decisive tests.

Table 1. Crosswalk from propositions to falsification programs

Proposition	Distinguishing commitment or claim	Decisive test(s)
1. Architectural substrate	Sapiens-specificity is a scope claim about integrated association, language, self-modeling, and social architecture.	Test 4: human-lineage genomic enrichment and comparative component program.
2. Genetic liability	Distributed common and rare variation converges on synaptic systems without a deterministic schizophrenia gene.	Tests 3–5: anatomical lesion, lineage concentration, and replenishing mutation.
3. Developmental timing	Prenatal vulnerability is exposed by adolescent or later loss of reserve; sex shifts the timing of transition.	Tests 1–3, 6, and 7.
4. Execution mechanism	Complement-microglial pruning is privileged but nonexclusive relative to astrocytic MEGF10/MERTK pruning.	Test 1: target-engaged blockade plus microglia/astrocyte comparison.
5. Circuit expression	Dysconnection and E/I failure precede dopamine amplification and can enter a nonlinear attractor.	Tests 2, 3, 6, and 7.
6. Evolutionary persistence	Recurrent deleterious mutation, not hidden advantage, maintains liability.	Test 5.

Genetic Architecture: Polygenicity as Functional Convergence

The allelic architecture of schizophrenia decisively excludes a common, high-penetrance schizophrenia gene. Current genomic evidence instead describes a continuous spectrum: hundreds of common loci of individually trivial effect, recurrent rare copy-number variants of moderate or large effect, and ultra-rare coding variants with larger but still incomplete penetrance (Chick et al., 2025; Owen et al., 2023; Singh et al., 2022; Sullivan et al., 2024; Trubetskoy et al., 2022). Even the strongest variants appear in unaffected people. Genetic liability therefore changes probability, developmental stability, and compensatory demand; it does not encode a fixed clinical destiny.

This polygenic model is not a recent inference; it was established directly. In a genome-wide association study of European-ancestry cases and controls, the International Schizophrenia Consortium (2009) showed that aggregate scores built from thousands of common alleles at liberal significance thresholds predicted case status in independent samples, that the same scores predicted bipolar disorder but none of six nonpsychiatric diseases, and that forward simulations placed the variance in liability captured by common markers at roughly one third. That result reframed the field: the object of genetic inquiry became a distributed liability rather than a gene.

The crucial result is not merely polygenicity but convergence. The first large Psychiatric Genomics Consortium analysis to identify more than 100 schizophrenia loci found associations at DRD2 and at genes involved in glutamatergic transmission and synaptic plasticity, including GRM3, GRIN2A, SRR, and GRIA1, as well as multiple voltage-gated calcium-channel genes. The same study found that most credible causal variation was regulatory rather than protein-altering and detected independent enrichment in brain and immune enhancers (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Later fine-mapping and exome studies strengthened the same pattern: receptors, channels, endocytic machinery, synaptic organizers, transcriptional regulators, and chromatin-looping factors converge on the construction, signaling, and maintenance of synapses even when their immediate molecular functions differ (Chick et al., 2025; Singh et al., 2022; Trubetskoy et al., 2022).

Rare structural variation reaches the same endpoint by a different route. In 21,094 cases and 20,227 controls, schizophrenia was associated with an excess of rare exonic copy-number variants, especially ultra-rare deletions. The strongest gene-set enrichment involved synaptic genes and the activity-regulated cytoskeleton-associated protein complex; gains were enriched in the NMDA receptor complex. Genome-wide significant loci included deletions at 1q21.1, NRXN1, 3q29, 15q13.3, distal 16p11.2, and 22q11.2, and gains at 7q11.23 and proximal 16p11.2 (Marshall et al., 2017). Common variants subtly retune expression and developmental timing; rare variants remove or duplicate larger pieces of the same machinery. The packaging differs. The systems consequence does not.

Cross-disorder genomics further shows that the liability is not contained by diagnostic categories. Across eight psychiatric disorders, the strongest genetic correlation was between schizophrenia and bipolar disorder ($r_g = .70$), approximately three quarters of lead cross-disorder signals were pleiotropic, and the most broadly shared locus, near DCC, was associated with all eight disorders. Pleiotropic loci were

enriched in neurodevelopmental processes, glutamate signaling, calcium channels, cortical glutamatergic neurons, and genes whose expression peaked in the second prenatal trimester (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). These findings do not dissolve schizophrenia into nonspecific distress. They establish that schizophrenia is assembled from broadly used developmental machinery and becomes distinct only at the level of timing, cell-type weighting, circuit configuration, and systems dynamics.

Cell-Type Resolution: Neuronal Liability, Glial Execution

Cell-type mapping clarifies a point that otherwise appears contradictory. Common-variant risk is concentrated primarily in mature neurons, whereas a central proposed execution mechanism is microglial. In the first rigorous integration of schizophrenia GWAS data with single-cell transcriptomic taxonomies, risk enrichment localized to hippocampal CA1 pyramidal neurons, cortical pyramidal neurons, striatal medium spiny neurons, and cortical interneurons. Embryonic, progenitor, and glial populations showed no comparable enrichment (Skene et al., 2018). More recent brain-wide mapping has refined the neuronal signal to specific SST and PAX6 interneuron populations, layer-specific excitatory neurons, hippocampal neurons, and subcortical cell classes in amygdala, thalamus, and related integration hubs (Duncan et al., 2025).

This is not evidence against an immune or microglial mechanism. It defines the direction of causation. The genetically vulnerable object is often the neuron or synapse: its activity, molecular composition, developmental age, complement tagging, or capacity for repair. Microglia are the developmental selection machinery that reads those differences and converts them into retention or elimination. A predominantly neuronal genetic signal can therefore produce a microglia-dependent anatomical lesion. Indeed, patient-derived pruning models indicate contributions from both sides of the synapse-microglia interaction: schizophrenia-derived microglia engulf more synaptic material, and schizophrenia-derived synaptic material is more avidly engulfed even by control microglia (Sellgren et al., 2019).

The theory therefore assigns different causal roles to different cell populations. Neurons carry much of the inherited liability; microglia implement a crucial developmental decision; oligodendrocytes, vascular cells, and peripheral immune signals shape the conditions under which it is made. Astrocytes are not passive context: they directly engulf excitatory and inhibitory synapses through MEGF10 and MERTK pathways (Chung et al., 2013). Microglia are privileged here only because the schizophrenia-specific evidence chain from C4A genetics to complement tagging and microglial engulfment is currently stronger. That comparative claim is tested rather than assumed below.

Developmental Timing: Prenatal Construction, Adolescent Exposure

The developmental proposition has deep roots. Weinberger (1987) argued that a fixed early lesion could remain clinically latent until the late maturation of prefrontal and limbic systems made those circuits indispensable. In the same year, Murray and Lewis (1987) independently argued that schizophrenia is, in a substantial subset of cases, a neurodevelopmental disorder: the ventricular enlargement seen in patients is present at first episode, is largely non-progressive, follows a variety of early cerebral insults, and correlates with obstetric complications, winter birth, and anomalous cerebral lateralization, while the long latency to onset reflects the delayed functional maturation of the affected systems. Feinberg (1982) proposed that schizophrenia could arise from a fault in the programmed elimination of synapses during adolescence—too many, too few, or the wrong connections removed. Together these theories identified the two ends of the causal interval: prenatal vulnerability and adolescent decompensation. Modern genomics now fills in the interval between them.

Human frontal-cortex transcriptomics demonstrates that development is not a simple change in the amount of gene expression. It is a large-scale reconfiguration of isoforms, splice junctions, and previously unannotated transcribed sequence. Jaffe et al. (2018) identified developmental isoform shifts in 6,672 genes, enriched for synaptic transmission, neuronal development, cell communication, and dopaminergic and glutamatergic pathways. Genes undergoing these shifts were substantially more likely to reside in schizophrenia GWAS loci. In adult schizophrenia cortex, replicated expression differences disproportionately resembled persistence of a fetal-like program: features normally high prenatally remained elevated, whereas features normally high postnatally were reduced. Schizophrenia risk

therefore lies not only in which genes are expressed, but in when, where, and in what transcript form they are expressed.

Recent fetal regulatory analyses reinforce this conclusion. Schizophrenia-associated regulatory activity is especially prominent in the first two trimesters, with risk-gene expression concentrated in immature excitatory neurons; placental expression provides an additional prenatal pathway through which maternal-fetal conditions can alter liability (Birnbaum & Weinberger, 2024). The prenatal contribution is not only a matter of when brain genes switch on; it includes the placenta as a distinct causal surface.

The most direct test of a placental gene-by-environment mechanism remains Ursini et al. (2018), but its replication is contested. In the discovery sample, a schizophrenia polygenic score built from variants at genome-wide-significant thresholds explained 11.2% of case-control variance (Nagelkerke R^2) among participants with early-life complications versus 0.8% among those without, and the highest risk quintile showed an odds ratio of 8.36 versus 1.55. These unusually stringent scores are ordinarily less predictive than scores built from broader variant sets. Vassos et al. (2022) found no significant polygenic-risk-by-obstetric-complication interaction across five independent samples (effective N = 2,110) and no enrichment of the reported placental pathways in the full Swedish cohort of 5,001 cases and 6,243 controls. When Ursini and colleagues reclassified their discovery sample with the shorter Lewis-Murray scale, roughly one third of complication-positive participants changed category and the interaction disappeared ($t = 1.048$, $p = .295$). Ursini and Weinberger (2022) argued that the replication used less complete exposure measurement; Vassos and Murray (2022) replied that the pathway null remained. The placental result is therefore provocative and mechanistically relevant, but not established.

Compensation does not mean normal childhood function. Prospective birth-cohort work shows subtle cognitive, motor, language, and social deviations years before psychosis, compatible with a network that functions but carries reduced reserve (Jones et al., 1994; Reichenberg et al., 2010). Adolescence remains the modal stress test because synapses are selected, inhibitory networks mature, association tracts are myelinated, hormones alter neuromodulatory tone, and social-cognitive demands rise sharply. Yet it is a gate, not a universal deadline. Association-cortex maturation continues into the third decade, and later-onset cases may cross the same stability boundary when normal aging, immune-metabolic burden, or hormonal change erodes compensation. The male-predominant earlier onset and female second incidence peak are first-order predictions: sex- and pubertal-stage differences in pruning, myelination, inhibitory maturation, and gonadal-hormone modulation should shift the stability boundary. If those biological trajectories do not mediate sex differences in age at onset after accounting for exposure and ascertainment, Proposition 3 is weakened (Häfner, 2019; Howes & Murray, 2014).

Longitudinal imaging supports peri-onset remodeling, but the magnitude and regional map must be calibrated. Cannon et al. (2015) reported large right-prefrontal thinning effects in a small converter subgroup and an exploratory cytokine-thinning association. In the ENIGMA clinical-high-risk mega-analysis (N = 3,169), baseline cortical thinning was widespread but small (mean $d = -0.13$), and conversion was associated most consistently with fusiform, superior temporal, and paracentral thinning (mean $d = -0.22$), not a uniquely right-prefrontal pattern; the authors explicitly warned that small samples can inflate earlier effects (Jalbrzikowski et al., 2021). NAPLS3 then supplied stronger longitudinal evidence: 338 nonconverters, 42 converters, and 62 controls completed up to five scans over eight months, with accelerated prefrontal, temporal, and parietal thinning preceding conversion and a change-based classifier reaching an area under the curve of .74 (Collins et al., 2023). Peri-onset cortical remodeling is therefore reproducible, but no single discovery-sample effect size or region should carry the theory.

Synaptic Pruning as the Developmental Gate

The complement system provides a molecular bridge from developmental vulnerability to actual loss of connectivity. In the developing retinogeniculate system, C1q and C3 participate in activity-dependent elimination of weak inputs (Stevens et al., 2007). Sekar et al. (2016) supplied the schizophrenia-specific link: C4 structural alleles predict brain C4A expression, risk tracks predicted C4A expression, and C4 localizes to synaptic processes. Yilmaz et al. (2021) then supplied causal overexpression evidence in humanized mice: C4A bound synapses more efficiently than C4B, increased microglial engulfment, and reduced cortical synapse and spine density. Yet C4-null mice had normal cortical synapse counts.

Pathological C4A elevation can therefore be sufficient for over-elimination without establishing that complement is necessary for all normal cortical pruning or that the same process occurs in every patient.

Nomenclature is mechanistic, not cosmetic: C4 denotes the complement component and locus, C4A a gene/isotype and protein product, and C4a the small cleavage fragment released during activation (Heurich et al., 2024). In patient-derived systems, schizophrenia microglia-like cells engulfed more synaptosomes, schizophrenia synaptosomes were preferentially engulfed, C4AL copy number correlated with C3 deposition and uptake, and CR3 blockade abolished excess elimination (Sellgren et al., 2019). Recent peripheral work found C4 protein concentrated in neutrophils and monocytes and a C4A-copy-number association with neutrophil C4 in schizophrenia, but the patient neutrophil analysis was only n = 15 and does not demonstrate central pruning (Howes et al., 2026; Kalinowski et al., 2026).

Astrocytes provide the strongest alternative execution route. They actively eliminate synapses through MEGF10 and MERTK in development and adulthood (Chung et al., 2013). Microglial privilege is therefore a comparative, stage- and subgroup-specific claim: complement/CR3 perturbation should account for more pathological synapse loss than astrocytic-pathway perturbation in the biomarker-defined state. Test 1 makes that comparison explicit.

Human evidence remains convergent but indirect. The small, exploratory NAPLS cytokine-thinning association is compatible with immune-linked peri-onset remodeling, whereas larger structural studies show smaller and differently distributed effects (Cannon et al., 2015; Collins et al., 2023; Jalbrzikowski et al., 2021). No existing human study directly demonstrates complement-dependent synapse loss.

Pruning must also be understood as selection rather than indiscriminate destruction. In a healthy brain, it improves computational efficiency by removing low-value connections and strengthening retained ones. In a vulnerable brain, the ranking function is corrupted. The wrong synapses look weak, the wrong signals acquire complement, and transient developmental instability is converted into durable circuit underconnectivity. Feinberg’s (1982) original insight was therefore correct in its essential form: the adolescent developmental program is not incidental to schizophrenia. It is the gate through which latent liability becomes structural disease.

Neuropil Loss: The Anatomical Signature

The predicted anatomy is a cortex with too little connectional tissue, not a cortex emptied of neurons. The reduced-neuropil hypothesis was formulated to explain smaller cortical volume, increased neuronal packing density, and relative preservation of neuronal somata (Selemon & Goldman-Rakic, 1999). Neuropil comprises dendrites, axon terminals, spines, synapses, glial processes, and extracellular matrix; it is not merely interstitial “space.” Unbiased stereology found no significant global deficit in total prefrontal neuron number, although focal or cell-type-specific losses remain possible (Thune et al., 2001). Schizophrenia is, in this sense, a disorder of the connectional apparatus surrounding neuronal somata rather than wholesale loss of those somata.

Direct postmortem evidence is laminar and circuit-specific. In dorsolateral prefrontal area 46, Glantz and Lewis (2000) found a 23% reduction in dendritic-spine density on deep layer 3 pyramidal neurons in schizophrenia relative to controls. The effect was not reproduced in psychiatric comparison cases, was not explained by antipsychotic exposure, and was not a nonspecific whole-cortex phenomenon. Deep layer 3 is precisely where local recurrent excitation, long-range corticocortical input, and thalamocortical communication must be integrated. A selective reduction there is not a generic sign of illness. It is a lesion in the substrate of association.

SV2A positron-emission tomography has moved the presynaptic claim into living brains, but the literature is stage-dependent. Chronic and largely medicated samples showed lower SV2A binding across frontal, cingulate, hippocampal, and other regions (Onwordi et al., 2020; Radhakrishnan et al., 2021). By contrast, Onwordi et al. (2024) studied 21 early-course patients recruited from first-episode services and 21 controls and found no corrected group difference in most regions. Two patients were antipsychotic-naïve and 19 had prior exposure, with a mean drug-free interval of approximately 180 days and a minimum of 41 days. Effect sizes ranged from $d = 0.0$ to 0.7; uncorrected temporal-lobe and anterior-cingulate findings did not survive multiple-comparison correction, and the study was powered to detect only effects of $d \geq 0.9$. The

result directly contradicts a universal large presynaptic deficit early in illness, while leaving smaller effects, subregional postsynaptic changes, and loss developing after onset unresolved.

Medication remains a serious confound, but the evidence is mixed rather than exculpatory. Greater cumulative antipsychotic exposure predicts some longitudinal gray- and white-matter change (Fusar-Poli et al., 2013; Ho et al., 2011). In rats, 28 days of haloperidol or olanzapine did not lower SV2A, and chronic human SV2A studies found no simple exposure-binding association (Onwordi et al., 2020; Radhakrishnan et al., 2021). The long washout in the early-course null study also argues against an immediate drug effect, but prior treatment was nearly universal and cumulative human exposure was not randomized (Onwordi et al., 2024). The defensible conclusion is therefore narrower: antipsychotics can affect bulk brain measures, a direct SV2A-lowering effect has not been demonstrated, and disease-intrinsic presynaptic loss remains plausible but not settled.

This licenses only a disciplined use of the word progressive. Schizophrenia is not a classical neurodegenerative disease, and the evidence does not support inexorable illness-specific neuronal destruction after onset (Zipursky et al., 2013). NAPLS3 indicates that accelerated cortical thinning can precede conversion over intervals of months, whereas the early-course SV2A null and long-term outcome literature argue against assuming a large universal presynaptic lesion at first episode or relentless decline thereafter (Collins et al., 2023; Onwordi et al., 2024). The theory therefore predicts heterogeneous, developmentally timed remodeling that can continue through transition and then plateau at a lower level of reserve—not a fixed right-prefrontal effect and not inevitable lifelong deterioration.

This anatomical formulation explains how symptoms can be severe despite subtle gross pathology. A neuron need not die to become computationally isolated. Small reductions in dendritic arbor, spine number, recurrent excitation, or inhibitory input can destroy the timing and gain relationships on which working memory, context maintenance, self-monitoring, and social inference depend. Preserved neurons leave open the possibility of functional recovery; preserved cell bodies do not imply preserved networks.

From Synaptic Fragility to Dysconnection

Synapse loss becomes psychopathology through dysconnection. Stephan et al. (2009) argued that schizophrenia reflects abnormal functional integration caused by impaired NMDA receptor-dependent synaptic plasticity under faulty neuromodulatory control. The distinction is crucial. The lesion is not simply too little NMDA signaling. Dopamine, acetylcholine, and serotonin regulate NMDA receptor phosphorylation, trafficking, subunit composition, and the insertion or removal of AMPA receptors. A circuit can therefore transmit signals yet fail to update the strength and timing of its connections in response to experience. Dysconnection is abnormal coupling (sometimes reduced, sometimes pathologically increased) rather than literal disconnection.

This framework unifies transmitter theories that are often treated as competitors. Glutamate supplies much of the fast excitatory architecture and plasticity substrate. GABA determines temporal precision and gain control. Dopamine regulates salience, reinforcement, and the population of neurons available for phasic response. Acetylcholine and serotonin alter the conditions under which plasticity occurs. Complement and microglia alter which synapses remain available to be plastic at all. These are not rival causes. They are interacting control layers in one developmental learning system.

The inhibitory limb of this control system has a specific and reproducible pathology, and it converts synaptic fragility into a measurable failure of cortical timing. Primary postmortem studies found reduced GAD67 expression without loss of the neurons that express it, reduced GAT1 expression in a subset of prefrontal GABA neurons, and preferential deficits in parvalbumin-associated transcripts (Akbarian et al., 1995; Hashimoto et al., 2003; Volk et al., 2001). These findings support altered function in fast-spiking chandelier and basket-cell systems rather than simple interneuron death. The review by Lewis et al. (2005) integrates this pattern with reduced chandelier-cell cartridges, compensatory postsynaptic receptor changes, and impaired neurotrophin signaling.

Because parvalbumin interneurons generate the rhythmic inhibition that organizes beta- and gamma-band oscillations, their dysfunction degrades exactly the synchrony on which perceptual grouping, attentional selection, working-memory maintenance, and spike-timing-dependent plasticity depend (Uhlhaas & Singer, 2010). Patients show reduced power and phase-locking of the 40-Hz auditory steady-state

response, diminished task-evoked gamma, and reduced long-range phase synchronization during perceptual organization; these deficits are heritable, are present in unmedicated first-episode patients and in first-degree relatives, and are only modestly attenuated by antipsychotics, and therefore cannot be reduced to chronic illness or medication (Uhlhaas & Singer, 2010). Critically, the maturation of these very oscillations across the transition from late adolescence to adulthood coincides with the typical window of onset, tying the physiological signature back to the developmental gate: a circuit already compromised by imprecise inhibition may be unable to support the high-frequency, long-range coding regime that normally consolidates at this transition, precipitating decompensation (Uhlhaas & Singer, 2010).

That the inhibitory abnormality may be organizational rather than a uniform regional deficiency is suggested, not established, by Lukow et al. (2026; published online 2025). In 22 clinical-high-risk participants, 10 first-episode patients, and 23 controls, hippocampal α5-containing GABA-A receptor availability was flatly null, $F(2, 50) = 0.25$, $p = .78$; pairwise effects ranged from $d = 0.01$ to 0.67. A novel perturbation-covariance analysis detected brain-wide and hippocampal-centered organizational deviations. Because the first-episode group was $n = 10$ and the covariance method is unreplicated, this is hypothesis-generating support for a systems-level lesion, not a quantitative anchor or proof against regional-deficit models.

The same mechanism helps explain characteristic positive symptoms. Normally, an action or thought is accompanied by an efference copy predicting its sensory consequences. When frontotemporal plasticity and timing are unreliable, that prediction no longer attenuates self-generated input: inner speech can be experienced as an external voice, and intention as alien control. In the primary electrophysiological study, patients—especially those prone to hallucinations—failed to show the normal increase in low-frequency frontal-temporal coherence during talking relative to listening (Ford et al., 2002). This operational failure of self-monitoring complements the broader dysconnection account of Stephan et al. (2009). Psychosis is not random mental noise; it is a systematic failure of generative models that normally identify agency.

Dysconnection is not confined to gray matter. Long-range integration depends on myelinated cortico-cortical and thalamocortical tracts, and the earliest genome-wide expression study of the schizophrenia prefrontal cortex found coordinated downregulation of oligodendrocyte- and myelination-related genes, including transcripts governing compact-myelin structure (MAL, CNP, MAG) and the neuregulin receptor ERBB3 (Hakak et al., 2001). Deficient oligodendrocyte support degrades conduction velocity and the temporal precision of distant coupling, and the protracted myelination of association tracts through adolescence places this axis, like the synaptic one, under maximal strain during the window of onset. Gray-matter synaptic loss and white-matter conduction failure are complementary routes to the same endpoint: a cortex whose distributed computations no longer cohere in time.

Dysconnection also accounts for cognitive and negative symptoms. Reduced recurrent excitation and impaired inhibitory tuning lower prefrontal signal-to-noise ratio, destabilize working-memory representations, and weaken the capacity to maintain goals across delay. Aberrant reinforcement learning then prevents positive outcomes from being converted into future action, even when consummatory pleasure remains intact (Marder & Umbricht, 2023). The same synaptic lesion can thus produce executive failure, avolition, disorganization, and psychosis depending on which circuit and computational operation is most affected.

The Hippocampal-Striatal Dopamine Cascade

The dopamine abnormality in schizophrenia is real, but its causal status is disputed. Howes and Kapur (2009) place multiple genetic, developmental, environmental, and circuit hits upstream yet designate presynaptic striatal dopamine dysregulation as the final common pathway to psychosis. The present theory agrees that dopamine is downstream of heterogeneous risk and closely linked to psychosis, but makes a stronger ordering claim: synaptic/circuit instability and hippocampal overdrive precede dopamine escalation, and dopamine is an amplifying node rather than an obligatory funnel point. Lodge and Grace (2007) provided a causal circuit model in which pathologically elevated ventral hippocampal activity increases the number of spontaneously active ventral tegmental dopamine neurons through a ventral hippocampus–nucleus accumbens–ventral pallidum–VTA pathway. In the methylazoxymethanol acetate model, temporary hippocampal inactivation normalized dopamine-neuron population activity and reduced

amphetamine hypersensitivity. The dopamine system was being driven into a high-gain state by an abnormal upstream circuit.

This circuit corrects an oversimplified cortical-to-striatal account. Prefrontal disinhibition can contribute to aberrant striatal drive, but hippocampal hyperactivity supplies a powerful regulator of how many dopamine neurons are available for phasic recruitment. Human findings of hippocampal hypermetabolism, glutamate-GABA imbalance, and structural change identify a plausible ignition point (Howes et al., 2024; Mancini et al., 2023). The link is not yet secure: in a multimodal clinical-high-risk study, striatal dopamine synthesis capacity was not significantly related to hippocampal glutamate and did not predict transition (Howes et al., 2020). This null is a genuine challenge to a strict hippocampus-to-dopamine ordering and motivates the longitudinal and interventional tests below.

Kapur (2003) supplies the brain-to-mind bridge. Dopamine does not determine the semantic content of a delusion or hallucination; dysregulated release confers aberrant salience on external events and internal representations, while cognitive and sociocultural schemas shape delusions and hallucinations (Howes & Murray, 2014; Kapur, 2003). In this theory, dysconnected cortical and hippocampal systems generate anomalous experiences and prediction errors; dopamine assigns urgency, confidence, and behavioral force. This division of labor explains why D2 blockade can reduce positive symptoms without repairing cognition, negative symptoms, or the underlying synaptic lesion. It also explains why xanomeline-trospium can be antipsychotic without direct D2 blockade: central M1/M4 agonism alters cortical-hippocampal computation and restrains striatal dopamine release through muscarinic control (Kaul et al., 2024).

The syndrome therefore contains at least two coupled physiological failures: an underconnected, noisy association cortex and an overresponsive hippocampal-striatal salience system. Their interaction is more explanatory than either alone. Cortical dysconnection without dopaminergic amplification may produce cognitive vulnerability and odd experiences; dopaminergic amplification without the characteristic dysconnected generative models need not produce schizophrenia. Full psychosis emerges when malformed inference and excessive salience lock together.

Environmental Amplification: Threshold Modulators, Not Separate Etiologies

Environmental risk factors are often presented as an etiologically miscellaneous list: obstetric complications, prenatal infection, urban upbringing, migration and social defeat, psychosocial stress, cannabis exposure, and immune-metabolic disturbance. These associations are established at different levels of evidence, including urbanicity, social defeat, and high-potency cannabis (Di Forti et al., 2019; Krabbendam & van Os, 2005; Selten & Cantor-Graae, 2005). The theory replaces the list with a mechanistic criterion. An exposure matters to the extent that it perturbs complement expression, glial state, NMDA receptor-dependent plasticity, inhibitory maturation, hippocampal excitability, blood-brain barrier function, or mitochondrial reserve during a sensitive developmental window (Howes & Murray, 2014; Rantala et al., 2022; Stephan et al., 2009).

Prenatal infection can alter fetal neural development (Brown & Derkits, 2010); chronic social adversity can sensitize stress and dopamine systems (Howes & Murray, 2014; Selten & Cantor-Graae, 2005); high-potency cannabis is associated with greater psychosis risk and perturbs endocannabinoid-glutamatergic signaling (Di Forti et al., 2019); and centrally elevated kynurenic acid antagonizes NMDA and α7 nicotinic receptors (Plitman et al., 2017). These exposures do not write separate environmental forms of schizophrenia. They lower the threshold at the same developmental gate. Effects depend on timing, dose, genetic background, and compensatory reserve.

The placental polygenic-risk-by-obstetric-complication result remains the contested example detailed above: mechanistically relevant, but not established and not a quantitative anchor for the environmental claim (Ursini et al., 2018; Vassos et al., 2022).

The microbiota-gut-brain axis is best placed within this broader category rather than treated as an independent cause. Reported dysbiosis, reduced short-chain-fatty-acid production, increased lipopolysaccharide signaling, and altered tryptophan metabolism can amplify peripheral inflammation and kynurenine-pathway activity, thereby converging on microglial and NMDA receptor mechanisms already

central to the theory (Su et al., 2025; Zhu et al., 2025). The relevant variable is not the name of the exposure. It is the molecular route by which the exposure changes synaptic selection or circuit gain.

Gene-environment interaction is mechanistically expected but not guaranteed to appear as a large statistical interaction in any particular cohort. A vulnerable circuit can remain compensated in a favorable developmental environment, while a modest exposure can become decisive near the stability boundary; severe insults can also push lower inherited liability toward the same failure regime. Measurement error, scale choice, selection, and low interaction power make empirical G×E estimates fragile. The theory therefore predicts pathway convergence and timing-dependent effect modification, while treating any single reported multiplicative coefficient as provisional.

The 22q11.2 Deletion: A Compressed Model of Distributed Fragility

The 22q11.2 deletion is the clearest natural experiment in the theory. It is one of the strongest recurrent copy-number risk loci for schizophrenia (Marshall et al., 2017), yet only a minority of carriers develop psychosis (Murphy et al., 1999; Schneider et al., 2014). The deletion therefore concentrates liability without determining outcome. It reveals the same architecture found in idiopathic schizophrenia: distributed perturbation of synaptic proteins, inhibitory transmission, dopamine regulation, immune signaling, and mitochondrial function, followed by variable compensation.

Several deleted genes map directly onto the proposed cascade. MRPL40 haploinsufficiency impairs mitochondrial ATP production and calcium buffering, disproportionately threatening fast-spiking interneurons with exceptional metabolic demands (Devaraju & Zakharenko, 2017; Li et al., 2019). PRODH-related proline accumulation can inhibit GAD-dependent GABA synthesis (Crabtree et al., 2016), while DGCR8-related microRNA disruption can alter dopamine and glutamate receptor expression (Zinkstok et al., 2019). In vivo, deletion carriers show hippocampal glutamate-GABA imbalance, with greater glutamatergic abnormality in those with psychotic symptoms (Mancini et al., 2023).

Variable penetrance appears to depend in part on mitochondrial quality control. Carriers with psychosis show older, depolarized mitochondrial populations and impaired mitophagy, whereas nonpsychotic carriers show stronger compensatory mitochondrial biogenesis (Li et al., 2021; Stronati et al., 2024). This finding supplies a missing dimension of the pruning theory. A synapse must be metabolically maintained in order to compete successfully during refinement. Mitochondrial reserve can therefore determine whether a vulnerable connection survives a normal developmental challenge.

The deletion neither establishes complement as the universal initiating lesion nor proves convergence; incomplete penetrance requires probabilistic language. It is a concentrated natural experiment consistent with disruption of multiple upstream systems converging on synaptic, inhibitory, hippocampal, and dopaminergic endpoints. Genes dysregulated in 22q11.2 deletion neurons overlap idiopathic schizophrenia genomic signals, supporting the view that rare concentrated haploinsufficiency and diffuse polygenic liability differ partly in packaging without establishing mechanistic identity (Nehme et al., 2022). The syndrome emerges when compensation fails, not when any one gene is lost.

Why the Syndrome Is Human: Association Cortex, Self-Modeling, and the Social Brain

The phrase sapiens-specific must be defined precisely. It does not mean that every risk gene is unique to humans, that no nonhuman animal can display psychosis-relevant behavior, or that a single mutation created schizophrenia at speciation. It means that the characteristic syndrome depends on a human-specific configuration of prolonged cortical development, elaborated association networks, language-mediated inner speech, autobiographical self-modeling, and social metarepresentation. Nonhuman systems can test conserved components of the causal chain; they cannot, without those architectures, instantiate the full phenomenological syndrome. The specificity claim is therefore strongest at the level of integrated architecture and weakest as a near-term experimental proposition.

Burns (2004) located schizophrenia vulnerability in the evolution of frontotemporal and frontoparietal connectivity supporting the social brain and theory of mind. The present theory retains that core insight but supplies the missing molecular and developmental mechanism. Extended postnatal maturation creates a

long interval during which experience must stabilize recently elaborated networks. The same heterochronic expansion that permits flexible social learning also exposes those networks to mutations, transcriptional mistiming, metabolic failure, and maladaptive pruning. Human cognition is powerful because its circuits are not finished at birth. Schizophrenia is possible for the same reason.

The phenomenology follows directly. Auditory verbal hallucinations exploit inner speech; thought insertion and delusions of control exploit agency attribution; paranoia and ideas of reference exploit social inference; disorganization exploits the coordination of language and context; and negative symptoms erode the motivational and affiliative machinery required for human group life. Stephan et al.'s (2009) corollary-discharge account explains how self-generated events become alien, while Burns's (2004) social-brain account explains why the resulting errors are saturated with intention, identity, status, threat, and meaning. Human specificity is visible not only in the evolutionary substrate but in the content of the symptoms.

Human-lineage-specific regulatory and structural innovations provide plausible genomic substrates for this fragility, and the molecular-evolution evidence is now direct. Schizophrenia-associated variation is enriched near human-accelerated regulatory regions, and recurrent schizophrenia copy-number hotspots overlap segmental duplications that expanded during human evolution and remain vulnerable to nonallelic homologous recombination (Sandroni & Chaumette, 2025). At the level of individual genes, several of the best-replicated schizophrenia loci bear signatures of positive Darwinian selection on the human and primate lineages: comparative-genomic analyses detected accelerated nonsynonymous substitution and selective-sweep signals at genes including DISC1, NRG1, and DTNBP1, with a pronounced peak of human-lineage selection falling precisely within the schizophrenia-associated region of DISC1 (Crespi et al., 2007). At the level of polygenic architecture, schizophrenia risk variants are enriched in genomic regions that underwent positive selection in modern humans after divergence from Neanderthals, a signature not shared by other psychiatric or neurological traits (Srinivasan et al., 2016).

These findings are frequently misread as support for a hidden-advantage account. They are not. Crespi and colleagues framed their own result as evidence that schizophrenia is a costly by-product of adaptive cognitive evolution, not an adaptation in itself; Srinivasan and colleagues framed theirs as polygenic overlap between risk and the machinery of human-specific traits. What both establish is that the genomic regions in which schizophrenia liability is concentrated are disproportionately the regions that human cortical evolution most recently and rapidly rebuilt. The architecture in which deleterious variants arise was itself a target of selection. The deleterious variants were not.

Crow (2000) was therefore right about the level of the problem and wrong about the unit of explanation. Schizophrenia vulnerability is yoked to a species-defining cognitive innovation, but the mechanism is not a single sex-linked language gene. It is distributed across the regulatory, synaptic, metabolic, and structural systems required to build a late-maturing association brain. The unit is the developmental architecture.

Why It Persists: Mutation-Selection Balance, Not Hidden Advantage

A severe, heritable disorder that reduces survival and reproduction creates an evolutionary paradox only if one assumes that the same common alleles must have been maintained because they were beneficial. Keller and Miller (2006) showed why that assumption is unnecessary and usually implausible. Balancing-selection accounts require compensating fitness advantages large enough to offset the substantial costs of schizophrenia, yet reliable evidence for heterozygote advantage, creativity-related reproductive benefit, or frequency-dependent advantage is weak. The disorder is among the least plausible candidates for a hidden-benefit explanation because its fitness costs are so large.

Mutation-selection balance provides the better solution. Human behavior and cognition sit downstream of thousands of genes and regulatory elements involved in neurogenesis, migration, synaptogenesis, pruning, receptor trafficking, metabolism, and plasticity. This creates a vast mutational target. Each generation introduces new deleterious variants at many points in the system; selection removes them, but it cannot drive their aggregate frequency to zero because new mutations continually replenish the pool (Keller & Miller, 2006). Rare copy-number variants generated by segmental-duplication architecture make this process visible at larger scale (Marshall et al., 2017; Sandroni & Chaumette, 2025).

Molecular-evolution signatures at schizophrenia loci do not imply that risk alleles were favored. Deep-time positive-selection signals near some loci may reflect selection on linked variants or on the broader architecture in which risk arises (Crespi et al., 2007; Srinivasan et al., 2016). In contemporary UK Biobank data, common schizophrenia liability confers no reproductive advantage large enough to sustain prevalence by balancing selection (Escott-Price et al., 2019). Akbari et al. (2026) add a different observation: over the past ten millennia in West Eurasia, polygenic predictors of schizophrenia and bipolar disorder declined while measures of cognitive performance increased. Their method was designed to identify directional selection and distinguish it from migration, population structure, and non-adaptive purifying or stabilizing selection. The schizophrenia result is therefore directional, not “purifying,” and it is not schizophrenia-specific given the parallel bipolar signal and the high genetic correlation between the disorders.

The finding must also be calibrated. The trait predictors were derived in industrialized societies, and the authors explicitly note that their relation to phenotypes adaptive in the past is uncertain. Directional selection accounted for only a small fraction—approximately 2%—of total allele-frequency change, even though the aggregate polygenic trajectory approached one contemporary standard deviation. Most importantly, a sustained decline over ten millennia is a non-equilibrium observation. It argues against a hidden-advantage account for the measured predictors, but it does not by itself demonstrate mutation-selection balance, which is an equilibrium model of continual mutational input and selective removal.

Mutation-selection balance remains the proposed persistence mechanism for a separate reason: schizophrenia liability has an enormous mutational target, and new point mutations, indels, and recurrent copy-number variants continually enter that target while selection removes deleterious alleles (Keller & Miller, 2006; Marshall et al., 2017). The ancient-DNA trajectory constrains this account by showing that at least one recent selective regime was directional and not at equilibrium. A complete model must therefore allow changing environments and selective regimes while testing whether recurrent mutational input is quantitatively sufficient to replenish what selection removes. The architecture/allele distinction survives; the claim that ancient DNA directly confirms equilibrium does not.

Schizophrenia therefore persists neither because psychosis benefits groups nor because risk alleles secretly improve creativity. It persists because eliminating every route to synaptic failure would require eliminating the genomic and developmental complexity that produces human cognition. The price is architectural, not adaptive.

Diagnostic Boundaries and the Schizophrenia Attractor

The theory predicts that diagnostic boundaries will be biologically porous. Cross-disorder genomics identifies correlated liability dimensions rather than one psychiatric factor or eight isolated diseases. Schizophrenia and bipolar disorder share especially strong common-variant liability, while pleiotropic loci influence mood, psychotic, compulsive, and neurodevelopmental phenotypes through overlapping developmental pathways (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019). A categorical nosology imposed at the level of symptoms cannot map cleanly onto a many-to-many genetic architecture.

Schizophrenia is not a discrete molecular species; it is proposed as a coherent systems-level attractor that emerges when shared neurodevelopmental liability is weighted toward association-cortex dysconnection, impaired self-monitoring, hippocampal overdrive, striatal salience amplification, and sufficient loss of functional reserve. “Attractor” is not used metaphorically. It predicts multistability under similar external conditions, hysteresis or path dependence after transition, and critical slowing as the boundary is approached—rising temporal autocorrelation, variance, and recovery time after perturbation. Densely sampled clinical-high-risk data should therefore show early-warning signals before psychosis beyond simple increases in mean symptom severity. Their reliable absence, together with smooth, fully reversible state change under the prespecified Test 6 conditions, would falsify the nonmetaphorical attractor claim while leaving the broader synaptic hierarchy open.

This formulation also explains heterogeneity within schizophrenia. Different individuals can enter the same attractor through different combinations of common variants, rare variants, prenatal disturbances, environmental amplifiers, metabolic reserve, and developmental timing. Once the system crosses the stability boundary, however, the downstream relationships become more stereotyped: synaptic loss,

dysconnection, excitation-inhibition imbalance, hippocampal-striatal dysregulation, and failure of inference. Etiological heterogeneity and syndromic coherence are therefore not opposites. They are expected properties of a complex system with many routes into a limited set of failure states.

Falsifiability: Decisive Tests That Could Break the Theory

A theory that accommodates every possible observation explains nothing. The hierarchy proposed here makes ordered claims and must state which observations would break them. The seven programs below distinguish target failure from theory failure, specify the population and developmental window to which each claim applies, and avoid treating every negative study as either decisive or irrelevant after the fact. Table 1 provides the proposition-to-test crosswalk. Some programs are feasible now; others are explicitly long-horizon.

Test 1. Complement-dependent microglial pruning is the privileged developmental amplifier.

Claim at risk. Complement tagging and microglial phagocytosis are a privileged mechanism converting distributed synaptic vulnerability into structural underconnectivity during a defined peri-onset window—not merely one correlate among many and not assumed to dominate astrocytic pruning in every state.

Prediction. In biomarker-enriched high-risk individuals who show active classical-complement signaling and measurable synaptic decline, selective suppression of the relevant complement axis before conversion will slow SV2A loss and reduce transition; complement/CR3 perturbation will also suppress pathological engulfment more strongly than MEGF10/MERTK perturbation in matched cellular systems.

Design. Development would proceed through phase I safety and target-engagement studies before a prevention trial. The decisive stratum would require both (i) active classical-pathway signaling, defined by two pretreatment samples with a preregistered, analytically validated activation composite (for example, C4d/C4 together with C3a or iC3b) above an age- and site-specific threshold, and (ii) synaptic decline, defined by a negative slope across two pretreatment [11C]UCB-J scans 8–12 weeks apart that exceeds scanner-specific least-significant change in a preregistered cortical composite. Gene/isotype C4A and activation fragment C4a would be kept distinct (Heurich et al., 2024). Approximately 200 participants per arm would receive a CNS-penetrant C1q, C3, or CR3-pathway intervention for 12–24 months. Co-primary outcomes would be SV2A slope and 24-month transition under a joint-success rule: full support requires benefit on both at familywise α; an SV2A-only benefit falsifies the claim that preserved synapses mediate transition reduction, whereas a transition-only benefit falsifies SV2A decline as the proposed mediator. Infection-risk mitigation, vaccination, medical exclusions, surveillance, and independent stopping rules are prerequisites. Parallel patient-derived neuron–microglia and neuron–astrocyte co-cultures would compare complement/CR3 blockade with MEGF10/MERTK perturbation.

Falsifying result. With adequate exposure and confirmed target engagement, no benefit on either co-primary falsifies complement as the privileged amplifier in the prespecified stratum. Discordant co-primaries are interpreted by the rules above rather than adjudicated after the fact. In the cellular arm, complete complement blockade that leaves pathological engulfment intact or shows astrocytic flux to be dominant falsifies microglial privilege even if complement remains a correlate.

Current state. Sekar et al. (2016), Sellgren et al. (2019), and Yilmaz et al. (2021) establish genetic, cellular, and mouse-causal plausibility; Heurich et al. (2024) clarifies the relevant entities, and recent PNAS work extends the candidate biology to peripheral immune cells while remaining small and indirect for brain pruning (Howes et al., 2026; Kalinowski et al., 2026). BeneMin found no benefit of nonspecific, post-onset minocycline for negative symptoms or imaging biomarkers (Deakin et al., 2018), a null that lowers confidence but is not the target-engaged prevention test. No complement-specific prevention trial with a synaptic endpoint has met these conditions.

Test 2. Dopamine dysregulation is strictly downstream of synaptic and hippocampal dysconnection.

Claim at risk. Striatal dopamine dysregulation is a downstream gain mechanism recruited by upstream cortical and hippocampal dysconnection and hippocampal hyperactivity, not the initiating lesion. This is the

theory's most exposed ordering claim and its direct alternative to dopamine hypothesis version III's obligatory final common pathway.

Prediction. (a) In individuals who convert to psychosis, cortical and hippocampal synaptic loss and hippocampal hyperactivity temporally precede the rise in striatal dopamine synthesis capacity. (b) Experimentally reducing ventral-hippocampal hyperactivity lowers striatal dopamine synthesis capacity and psychotic symptoms.

Design (a): temporal precedence. At the NAPLS3 conversion rate of 42/380 (11%) and 85% retention, approximately 1,070 clinical-high-risk participants would be needed to retain about 100 converters; a 600-person cohort should instead expect roughly 55–60. The decisive study would therefore be a multisite adult consortium of approximately 1,100, with baseline and one follow-up paired [18F]FDOPA and [11C]UCB-J wave at 9 months or within four weeks of transition, whichever occurs first—four PET scans maximum, not six. Participants younger than 18 would contribute MRI/EEG but not the paired PET protocol. Published estimates imply roughly 5–6 mSv per paired brain-PET wave before site-specific adjustment ([18F]FDOPA PET/CT 2.8–3.7 mSv; 370 MBq [11C]UCB-J <2.0 mSv), so two waves would be about 10–12 mSv plus attenuation correction (Cawthorne et al., 2021; Kaushik et al., 2013). Each site would require protocol-specific organ dosimetry, ultra-low-dose or MR attenuation correction where available, cumulative-dose caps, and ALARA review. Quarterly arterial-spin-labeling or resting-state functional MRI would index hippocampal activity. Preregistered within-person change-point and cross-lagged models would test which measure departs first and whether synaptic or hippocampal change predicts later dopamine change beyond symptoms, medication, and cannabis exposure.

Design (b): interventional causal chain. Approximately 150 high-risk or early-psychosis participants would be randomized to placebo or an agent that reduces hippocampal hyperactivity at a dose with prespecified arterial-spin-labeling target engagement. [18F]FDOPA and symptoms would be measured before and after treatment. The agent need not be levetiracetam, but the trial must verify the hippocampal perturbation rather than infer it from dose.

Falsifying result. The ordering claim fails if striatal dopamine synthesis capacity reliably rises before any detectable synaptic loss or hippocampal hyperactivity, or if a well-powered intervention that clearly normalizes hippocampal activity leaves dopamine synthesis and psychotic symptoms unchanged. Either result would place dopamine at the leading edge or sever the proposed causal link.

Current state. Striatal dopamine synthesis capacity can be elevated before onset (Howes et al., 2011), but ordering remains unresolved. The multimodal clinical-high-risk null—no significant dopamine–hippocampal-glutamate relationship and no prediction of transition—already exposes the proposed chain (Howes et al., 2020). Existing SV2A studies are cross-sectional, including the early-course null summarized above (Onwordi et al., 2024). Completed levetiracetam studies measured hippocampal or clinical outcomes but not [18F]FDOPA, so neither closes the hippocampus-to-dopamine loop. A longitudinal multimodal study or target-engaged intervention with dopamine imaging remains decisive.

Test 3. The lesion is lost neuropil and synapses with preserved neurons, and the synaptic deficit is not produced by antipsychotics.

Claim at risk. The structural signature is reduced dendritic-spine and synaptic density with relative preservation of neuronal number, and this synaptic reduction is disease-intrinsic rather than a medication artifact.

Prediction. Large presynaptic deficits need not be universal at first episode, but individuals crossing the proposed developmental transition should show declining synaptic markers before or after onset without proportional loss of neuronal somata. After careful control of illness severity and indication, cumulative antipsychotic exposure should not explain most of that decline.

Design. Recruit antipsychotic-naïve clinical-high-risk and first-episode participants and obtain baseline SV2A PET before clinically indicated treatment whenever feasible. Do not randomize patients to a harmful delay in treatment. Repeat imaging at short intervals under genuine clinical equipoise and thereafter within usual care, recording dose, adherence, symptom burden, substance use, and inflammatory-metabolic covariates; use target-trial emulation, propensity methods, and within-person analyses to estimate treatment effects. Pair imaging with a neuronal-integrity measure. In parallel, apply unbiased stereology

and single-nucleus quantification to a large postmortem cohort with detailed exposure histories, and use a controlled nonhuman-primate antipsychotic arm for direct pharmacological calibration.

Falsifying result. The theory fails if well-powered longitudinal studies repeatedly show no synaptic decline across transition or chronicity in the subgroup the theory identifies; if early, symptom-linked loss is primarily loss of neuronal somata rather than synapses and processes; or if clinically relevant antipsychotic exposure produces a reproducible, dose-dependent SV2A reduction in previously drug-naïve humans and experimentally treated primates sufficient to explain the patient-control signal.

Current state. Global prefrontal neuron number is generally preserved in unbiased stereology, although focal exceptions remain possible (Thune et al., 2001). Chronic cohorts show lower SV2A, and rodent antipsychotic exposure did not reproduce it (Onwordi et al., 2020; Radhakrishnan et al., 2021). The important early-course null and its sample, exposure, and power limitations are summarized above (Onwordi et al., 2024). The missing experiment is longitudinal and must separate illness stage from treatment without imposing an unethical duration of untreated psychosis.

Test 4. Human-lineage genomic concentration is testable now; sapiens-specific phenomenology is a long-horizon comparative program.

Claim at risk. Schizophrenia liability is disproportionately concentrated in recently evolved or structurally labile parts of the human genome, while the integrated syndrome depends on human association, language, self-modeling, and social-cognitive architecture.

Prediction. Properly controlled partitioned-heritability analyses will show enrichment in human-accelerated regulatory regions, human-lineage selection annotations, and segmental-duplication/nonallelic-recombination-prone loci beyond matched genomic expectation.

Design. Test the genomic prediction in the largest available schizophrenia GWAS with linkage-disequilibrium-aware models, ancestry-specific sensitivity analyses, matched annotations, and negative-control traits. A separate cross-species program should ask how homologous high-effect variants alter conserved synaptic, inhibitory, oscillatory, mitochondrial, and dopaminergic components. It should not be presented as a near-term test of human delusions, inner speech, or social metarepresentation in an animal lacking the relevant architecture.

Falsifying result. A precise, adequately powered absence of enrichment across preregistered human-lineage regulatory and structural annotations would falsify the genomic concentration claim. The broader sapiens-specific phenomenology claim is presently the theory's least directly falsifiable component; comparative models can delimit necessary component mechanisms, but they cannot now provide a decisive yes-or-no reproduction of the full syndrome. Treating that limitation openly is more credible than labeling an infeasible primate experiment "decisive."

Current state. Existing analyses report enrichment near human-divergent, post-Neanderthal selected regions, human-accelerated elements, and expanded segmental duplications (Crespi et al., 2007; Sandroni & Chaumette, 2025; Srinivasan et al., 2016). These findings justify a rigorous replication test but do not settle annotation dependence, linkage, ancestry, or specificity. Animal and cellular models remain valuable for conserved components only.

Test 5. Persistence is due to mutation-selection balance, not selection favoring the risk alleles.

Claim at risk. Recurrent deleterious mutation across a vast target, rather than compensating advantage of schizophrenia-risk alleles, is sufficient to explain persistence; the selective regime may change through time and need not be at equilibrium in any observed interval.

Prediction. Risk-increasing alleles will show no aggregate balancing-selection signal or reproductive advantage sufficient to offset affected individuals' fitness costs; de novo and recurrent structural variation will make a measurable contribution to replenishment; and ancient trajectories will be compatible with changing directional selection rather than assumed equilibrium.

Design. Combine (i) ancient-DNA time series in multiple regions and epochs; (ii) direct completed-fertility estimates in contemporary natural-fertility populations; (iii) de novo mutation and recurrent-copy-number-

variant rate estimates linked to liability; and (iv) haplotype-level tests distinguishing selected risk alleles from linked beneficial variants. Quantitative forward models should ask whether measured mutational input can maintain observed liability under the estimated, time-varying selection coefficients.

Falsifying result. Mutation-selection balance should be rejected if risk alleles themselves show robust balancing or positive selection with a fitness advantage large enough to sustain prevalence, or if empirically measured mutational input is far too small to replenish liability under realistic selective costs. A directional decline in one historical interval neither falsifies nor confirms the model by itself; it supplies a boundary condition the model must reproduce.

Current state. Contemporary data provide little evidence for a compensating reproductive advantage (Escott-Price et al., 2019). Akbari et al. (2026) detected directional declines in predictors of schizophrenia and bipolar disorder, but emphasized industrialized-society phenotype definitions and a method distinct from purifying selection. The approximately one-standard-deviation trajectory, against a background in which directional selection explains only a small fraction of allele-frequency change, is a strong non-equilibrium constraint. Direct measurements of replenishing mutational input and completed fertility in natural-fertility populations are still missing.

Test 6. Psychosis transition has attractor dynamics rather than smooth symptom accumulation.

Claim at risk. “Attractor” denotes a genuine nonlinear state transition with multistability, critical slowing, and hysteresis, not a metaphor for severe illness.

Prediction. Within individuals who convert, prespecified early-warning statistics—rising lag-1 autocorrelation, variance, cross-domain coupling, and recovery time after perturbation—will increase before transition beyond any rise in mean symptom level; after remission, the return path will differ from the entry path.

Design. Follow approximately 400 clinical-high-risk participants for 18 months with six smartphone prompts per day, continuous sleep/activity sensing, weekly brief cognitive probes, and monthly 14-day intensified sampling; trigger eight prompts per day for 21 days when symptom slope or sleep disruption crosses a preregistered threshold. Primary estimands are within-person. Time series would be detrended for slow mean change, diurnal and weekly cycles, medication, cannabis, and missingness; rolling-window choices, minimum observations, and early-warning thresholds would be fixed before analysis. Recovery time would be estimated after naturalistic stressors and a standardized, low-burden challenge. Models would be trained in one cohort and tested in held-out participants and an external cohort; between-person averages would not substitute for individual dynamics.

Falsifying result. The nonmetaphorical attractor claim is falsified if well-sampled converters repeatedly transition without any preregistered early-warning signal, recovery does not slow, and remission follows the same smooth and fully reversible path after adequate control of trends and measurement error. A group-level association without within-person warning does not rescue the claim.

Current state. The manuscript’s multistability, hysteresis, and critical-slowing predictions are presently untested in schizophrenia. Dense experience sampling makes this a feasible prospective test, but it requires sustained adherence and independent replication.

Test 7. Excitation-inhibition failure produces a peri-onset oscillatory signature.

Claim at risk. Impaired inhibitory calibration is a load-bearing circuit mechanism, not an incidental correlate of chronic illness or treatment.

Prediction. Reduced 40-Hz auditory steady-state power and phase locking, impaired task-evoked gamma, and weakened long-range synchronization will be present before or at first episode, worsen within converters, and covary with cognitive instability and dysconnection independently of antipsychotic exposure.

Design. A harmonized multisite study would recruit approximately 350 clinical-high-risk participants, 150 antipsychotic-naïve or minimally exposed first-episode patients, and 200 controls. High-density EEG would measure 40-Hz auditory steady-state responses, visual/task gamma, resting beta-gamma coupling,

hearing thresholds, vigilance, and movement at baseline, six months, and transition; a subset would undergo MEG and MRS for spatial and E/I calibration. Analyses would preregister power, intertrial phase coherence, source-level long-range coupling, site harmonization, and within-person change. Sex and pubertal stage would be modeled explicitly because Proposition 3 predicts timing differences.

Falsifying result. Proposition 5 is falsified in this limb if adequately powered, harmonized studies repeatedly find normal ASSR/gamma measures in unmedicated converters and first-episode patients, or if all abnormalities are explained by hearing, attention, medication, or chronicity and show no relationship to dysconnection or cognition.

Current state. ASSR and gamma abnormalities are among the most tractable physiological predictions in the paper and have been reported in unmedicated first-episode patients and relatives (Uhlhaas & Singer, 2010). What is missing is a preregistered longitudinal test across transition.

These seven programs differ in immediacy. Complement target engagement, oscillatory phenotyping, dense experience sampling, and longitudinal multimodal imaging are technically conceivable now but vary greatly in ethical, financial, and statistical burden; the human-lineage genomic test is straightforward, and comparative phenomenology remains long-horizon. A theory that survived the properly powered, prespecified tests would not be proven. It would have earned credibility by stating in advance which nulls count, which nulls do not, and why.

Synthesis

Schizophrenia begins with distributed liability across synaptic, regulatory, calcium-signaling, immune, chromatin, and mitochondrial systems. The burden is heavily neuronal but recruits microglial, astrocytic, oligodendroglial, vascular, and peripheral immune mechanisms. Common and rare variants differ in scale, not in creating deterministic destiny; pleiotropy is expected because the same developmental machinery is reused across psychiatric conditions.

Vulnerability is planted largely during prenatal construction and exposed when adolescent—or later normal—loss of reserve makes circuit precision rate-limiting. Complement-microglial pruning is a privileged but nonexclusive amplifier; astrocytic MEGF10/MERTK pruning, inhibitory maturation, myelination, and metabolic competition provide parallel mechanisms. The anatomical prediction is reduced spine density and neuropil with relative preservation of neuronal somata. Chronic SV2A deficits support presynaptic loss in some stages, whereas the early-course null forbids treating a large onset deficit or medication independence as universal. Sex differences in remodeling and hormonal timing should shift age at onset.

The physiological consequence is dysconnection: unstable recurrent activity, degraded beta/gamma synchrony, hippocampal overdrive, and striatal dopamine amplification. The theory adopts Kapur’s aberrant-salience account but differs from dopamine hypothesis version III by placing dopamine after synaptic/circuit failure and denying it obligatory funnel-point status. Dysconnected generative models produce anomalous experiences; dopamine gives them salience and behavioral force; corollary-discharge and social-inference failures shape their content. Cognitive and negative symptoms arise from the same connectional deficit in circuits for working memory, learning, motivation, and affiliation.

Environmental exposures matter when they converge on pruning, plasticity, inhibition, hippocampal excitability, or metabolic support. The placental G×E result remains provocative but contested. The 22q11.2 deletion is a concentrated, incomplete-penetrance example consistent with distributed upstream disruption and variable compensation, not proof of any universal initiating lesion.

The sapiens-specific claim is a scope statement: the integrated syndrome depends on late-maturing human association, language, self-modeling, and social architecture, while conserved components remain experimentally accessible in animals and cells. Persistence is attributed to recurrent deleterious variation across a vast mutational target, not hidden advantage; recent ancient-DNA decline constrains but does not prove mutation-selection balance.

Schizophrenia is therefore proposed as ordered synaptic fragility: predominantly prenatal in vulnerability, commonly exposed by adolescent or later remodeling, connectional in anatomy, dysconnective and oscillatory in physiology, dopaminergic in amplification, and social-inferential in phenomenology. The

hierarchy is exposed to seven prespecified failures, including complement, dopamine ordering, attractor dynamics, and E/I oscillations.

The therapeutic implication follows directly but must respect prior failures. Treatment cannot remain confined to suppressing downstream dopamine after psychosis consolidates, yet “restoring NMDA plasticity” is not a novel proposal: large trials of the glycine-transporter inhibitor bitopertin and the mGlu2/3 agonist pomaglumetad did not establish efficacy for persistent negative symptoms (Bugarski-Kirola et al., 2017; Stauffer et al., 2013). Those failures argue for stage-specific, biomarker-stratified interventions rather than indiscriminate glutamatergic augmentation. Xanomeline-trospium demonstrates that acute antipsychotic efficacy can be achieved without direct D2 blockade (Kaul et al., 2024). The theory therefore prioritizes temporally targeted preservation of vulnerable synapses, complement intervention only with verified target engagement and safety, stabilization of inhibitory networks, reduction of hippocampal overdrive, and support of mitochondrial quality control before underconnectivity becomes entrenched.

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