Schizophrenia as Sapiens-Specific Synaptic Fragility: A Unified Account of Origins, Mechanisms, and Persistence

Tyler M. Moore, Ph.D.

Originally published at https://www.mooremetrics.com/schizophrenia/

Abstract

Schizophrenia is proposed as a sapiens-specific failure mode of synaptic development: a recurrent breakdown of the unusually prolonged, plastic, and densely interconnected architecture that supports human association, self-modeling, and social cognition. The theory is hierarchical. Distributed common and rare genetic variation biases synaptic construction and maintenance in specific mature neuronal populations. Prenatal regulatory perturbations (including placenta-dependent pathways) create latent vulnerability; adolescent remodeling exposes it. Complement-dependent microglial pruning acts as a privileged developmental amplifier, with neuronal activity, NMDA receptor-dependent plasticity, inhibitory maturation, and mitochondrial reserve determining which synapses are retained or lost. The anatomical result is reduced neuropil and dendritic-spine density without commensurate neuronal death, and the loss of presynaptic terminals is not an artifact of antipsychotic exposure. The physiological result is dysconnection among prefrontal, temporal, hippocampal, thalamic, and striatal systems, expressed as impaired excitation-inhibition balance and degraded beta- and gamma-band synchrony. Hippocampal hyperactivity and cortical disinhibition recruit striatal dopamine dysregulation, while failures of corollary discharge, predictive updating, and social metarepresentation determine psychotic content. The same architecture explains cognitive and negative symptoms, cross-disorder pleiotropy, incomplete penetrance, and environmental sensitivity. Liability persists not because psychosis is adaptive, but because the human cognitive architecture was selected while deleterious variants are continually replenished across a vast mutational target by mutation-selection balance. This conclusion is now reinforced by ancient-DNA evidence of recent purifying selection against schizophrenia liability. Schizophrenia is therefore a coherent systems-level failure regime within a broader transdiagnostic neurodevelopmental liability. The account is offered not as an interpretive frame but as a falsifiable causal hierarchy, and decisive experiments capable of breaking it are specified.

Keywords: schizophrenia, synaptic pruning, complement, dysconnection, excitation-inhibition balance, neural oscillations, neurodevelopment, placenta, dopamine, 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 during adolescent circuit refinement, 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 not the initiating lesion. It is the downstream gain mechanism that converts dysconnected inference into psychotic conviction.

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 but often remains compensated until adolescent pruning, myelination, inhibitory maturation, and prefrontal specialization make circuit precision rate-limiting (Feinberg, 1982; Jaffe et al., 2018; Murray & Lewis, 1987; Weinberger, 1987).

4. The execution mechanism. Complement tagging and microglial phagocytosis provide a biological selection system capable of turning subtle neuronal weakness into actual synapse loss; mitochondrial and homeostatic reserve determine whether that selection remains adaptive or becomes destructive (Sellgren et al., 2019; Stevens et al., 2007).

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, recurrent structural variation is continually generated, and selection cannot eliminate the underlying architecture without eliminating the cognitive capacities built from it (Burns, 2004; Keller & Miller, 2006).

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 non-psychiatric 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, and the reproductive-fitness argument that common small-effect alleles largely escape strong purifying selection was already implicit in the data.

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; astrocytes, oligodendrocytes, vascular cells, and peripheral immune signals shape the local conditions under which that decision is made. Conflating genetic localization with mechanistic execution has obscured this architecture. Once the levels are separated, the apparent conflict disappears.

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.

Ursini et al. (2018) showed that the association between schizophrenia polygenic risk and case status is powerfully moderated by early-life complications. In their discovery sample, genome-wide significant risk alleles explained 11.2% of case-control variance among individuals with a history of obstetric complications but only 0.8% among those without, and the highest risk quintile carried an odds ratio of 8.36 in the complicated-pregnancy subgroup versus 1.55 otherwise. The interacting loci were disproportionately expressed in placenta, were enriched among genes dysregulated in pre-eclampsia and intrauterine growth restriction, and were more highly expressed in male than female placentae, supplying a candidate mechanism for the earlier onset and higher incidence of schizophrenia in males. Genetic liability, in part, is a liability of the fetal-placental stress response, not only of the fetal brain.

The seeds of illness are thus planted during circuit construction, often through molecular differences too small to prevent childhood function. Childhood compensation is possible because young networks are redundant and plastic. Adolescence removes that redundancy. Adolescence is not merely the age when symptoms happen to appear. It is the biological stress test built into the theory. Cortical synapses are being selected, inhibitory networks are maturing, prefrontal systems are becoming rate-limiting, long-range connections are being myelinated, gonadal and stress hormones are changing neuromodulatory tone, and social demands sharply increase. A circuit that was adequate while redundancy was high can fail when efficiency, precision, and stable self-other modeling become obligatory.

That the decisive change is concentrated around the transition itself is now visible in living brains. In the multisite North American Prodrome Longitudinal Study, individuals at clinical high risk who converted to psychosis showed accelerated thinning of right prefrontal cortex—right superior frontal, middle frontal, and medial orbitofrontal regions, with large effect sizes near $d = 1.0$—together with third-ventricle expansion, relative to non-converters and controls, and the steepest change occurred in those with the shortest prodrome (Cannon et al., 2015). The adolescent and peri-onset cortex is not a passive stage on which an earlier lesion is displayed. It is where the lesion is completed. Schizophrenia is therefore not an adult disease with a delayed onset. It is a developmental disease whose decisive lesion is often produced by normal maturation acting on an abnormal substrate.

Synaptic Pruning as the Developmental Gate

The complement system provides the molecular bridge from developmental vulnerability to actual loss of connectivity. In the developing retinogeniculate system, C1q localized to immature synapses, C3 participated downstream, and deletion of either component prevented normal elimination of weak inputs. Adult relay neurons in complement-deficient mice retained excessive numbers of functional inputs long after refinement should have been complete (Stevens et al., 2007). The significance of this work is conceptual as well as molecular: complement is not merely an inflammatory effector. In the developing brain it is part of an activity-sensitive synaptic selection algorithm.

Schizophrenia can exploit this normal algorithm in at least three ways. Vulnerable neurons can present weaker or abnormal synapses; complement tagging can be

increased or mistimed; and microglia can become intrinsically hyperphagocytic. Sellgren et al. (2019) demonstrated all three elements in patient-derived systems. Schizophrenia-derived microglia-like cells engulfed more synaptosomes, schizophrenia-derived synaptosomes were preferentially engulfed, neuronal C4A long-form copy number correlated with C3 deposition and synapse uptake, and blockade of microglial complement receptor 3 abolished the excess spine elimination. This is the critical transition from association to mechanism: genetic and cellular differences altered a defined pruning pathway and produced measurable synaptic loss.

Human in vivo evidence now converges with these cellular models. In the North American Prodrome Longitudinal Study, higher baseline levels of a proinflammatory cytokine index—tumor necrosis factor-alpha, interleukin-2, and interferon-gamma, markers associated with M1-like microglial signaling—predicted steeper subsequent right prefrontal thinning specifically in individuals who converted to psychosis, with the correlation reaching approximately -.65 among converters (Cannon et al., 2015). The authors interpreted the thinning as a marker of reduced integrated synaptic activity and proposed that inflammatory activation, potentially involving microglial synaptic pruning or dendritic retraction, contributes to accelerated peri-onset tissue change. This is the predicted signature of a selection mechanism operating too aggressively at the developmental gate: an immune-linked, medication-independent contraction of exactly the association cortex the theory places at the center of the syndrome.

The theory does not require every case to begin with a primary complement abnormality. Complement-mediated pruning is the dominant developmental amplifier, not the only upstream lesion. Any perturbation that weakens synapses, distorts activity-dependent competition, impairs NMDA receptor-dependent stabilization, reduces inhibitory coordination, or lowers metabolic reserve can cause the same pruning machinery to make systematically wrong decisions. The common endpoint is selective loss of connections that were already difficult to maintain. This is why genetic heterogeneity can coexist with mechanistic convergence.

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 the otherwise paradoxical combination of smaller cortical volume, increased neuronal packing density, and preserved total neuron number. Neuropil (dendrites, axon terminals, spines, synapses, and the extracellular space that supports them) can contract substantially while neuronal somata remain in place (Selemon & Goldman-Rakic, 1999). Schizophrenia is, in this sense, a disorder of the space between neurons.

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.

Contemporary synaptic imaging has moved this claim from postmortem inference to living brains. Using positron emission tomography for synaptic vesicle glycoprotein 2A (SV2A), a protein present in nearly all presynaptic terminals, independent groups found lower synaptic-terminal density across frontal and cingulate cortex, hippocampus, and multiple association regions in schizophrenia, with effect sizes near or above one standard deviation and reductions that survive partial-volume correction (Onwordi et al., 2020; Radhakrishnan et al., 2021). The reductions are not explained by regional atrophy: gray-matter volume did not differ enough, or covary with binding, to account for them (Onwordi et al., 2020; Radhakrishnan et al., 2021). Within patients, higher frontal SV2A availability tracked fewer positive symptoms, better emotion recognition, and faster processing speed (Radhakrishnan et al., 2021), tying the anatomical deficit directly to the cognitive and symptomatic phenotype.

The single most common objection to any structural account of schizophrenia is that patients are medicated and that antipsychotics themselves alter brain tissue. The objection must be met precisely rather than waved away, because part of it is correct. In the Iowa Longitudinal Study of first-episode schizophrenia, greater cumulative antipsychotic exposure independently predicted smaller gray-matter volumes and steeper white-matter and ventricular change across 674 scans, after simultaneous adjustment for illness severity, illness duration, and substance use (Ho et al., 2011); a meta-analysis of longitudinal MRI reached the same conclusion, with cumulative antipsychotic exposure predicting gray-matter decrement more strongly than illness duration or symptom severity (Fusar-Poli et al., 2013). Gross gray-matter volume is therefore a contaminated measure: some of its longitudinal decline is pharmacological. The synaptic signal is not. In a controlled experiment, rats receiving haloperidol or olanzapine for 28 days at clinically relevant plasma concentrations showed no reduction in SV2A by western blot, autoradiography, or immunofluorescence (Onwordi et al., 2020). The convergence is decisive in a way neither measure alone could be: the component of the anatomy that antipsychotics can produce (bulk gray- and white-matter volume) is dissociated from the component they cannot (presynaptic terminal density), and it is the latter that the theory requires. The synaptic lesion is a feature of the disorder, not of its treatment.

This licenses a disciplined use of the word *progressive*. Schizophrenia is not a classical neurodegenerative disease, and the evidence does not support an inexorable, illness-specific process of continuing neuronal destruction after onset (Zipursky et al., 2013). Much apparent post-onset progression in imaging cohorts is inflated by antipsychotic exposure, cannabis, alcohol and tobacco use, metabolic and stress physiology, and the sampling bias of chronically ill prevalence populations; cognitive performance, tellingly, is typically stable or improves after the first episode rather than declining, and roughly

40% of patients attain functional recovery while the proportion with persistently poor outcome remains stable across follow-up (Zipursky et al., 2013). What the theory posits instead is an accelerated and maladaptive remodeling, a peri-onset contraction of synaptic and neuropil volume (Cannon et al., 2015), that can continue through the transition to illness and then stabilize at a lower level of connectivity. The distinction is not semantic. A degenerative disease predicts relentless decline; a developmental loss of reserve predicts a fixed deficit compatible with plateau and partial recovery, which is what longitudinal outcome data show.

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 is the limb that converts synaptic fragility into a measurable failure of cortical timing. The most consistent molecular abnormality in the schizophrenia cortex is reduced expression of GAD67, the enzyme that synthesizes most cortical GABA. This GABA is concentrated in parvalbumin-expressing interneurons, the fast-spiking chandelier and basket cells that impose perisomatic inhibition on pyramidal neurons and thereby set the tempo of network activity (Lewis et al., 2005). These cells are not lost; roughly a quarter to a third of them lack detectable GAD67 transcript while the remainder are near-normal, and the same subset shows reduced GABA transporter (GAT1) expression, reduced chandelier-cell axon cartridges, and a compensatory upregulation of postsynaptic alpha-2 GABA-A receptors at the pyramidal axon initial segment that fails to restore control (Lewis et al., 2005). The proposed upstream driver

is deficient neurotrophin signaling through the TrkB receptor, which normally induces GAD67, GAT1, and parvalbumin, and whose graded reduction reproduces the same cellular pattern in mouse models (Lewis et al., 2005).

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 is organizational rather than a simple regional deficiency is underscored by molecular-network findings. In clinical high risk and first-episode psychosis, the availability of extrasynaptic GABA-A receptors containing the alpha-5 subunit (which mediate tonic inhibition and are concentrated in the hippocampus) showed no uniform regional reduction, yet its covariance across the brain, particularly between the hippocampus and the rest of the cortex, was significantly disrupted, with larger deviations in first-episode than in high-risk individuals (Lukow et al., 2026). The lesion is not everywhere a lower level of a receptor; it is a loss of the coordinated organization of inhibition across regions, which is precisely what a systems-level dysconnection account predicts and a simple regional-deficit account does not.

The same mechanism explains the characteristic positive symptoms. Normally, an action or thought is accompanied by an efference copy, a prediction of its sensory consequences. That prediction attenuates the response to self-generated speech, movement, and inner language. When frontotemporal plasticity and timing are unreliable, the predicted consequence no longer cancels the actual one. Inner speech can be experienced as an external voice; intention can be experienced as alien control; and internally generated associations can appear inserted, broadcast, or externally caused. Direct electrophysiology supports this reading: hallucinating patients fail to show the normal increase in frontal-temporal theta-band coherence that accompanies the generation, as opposed to the passive hearing, of one’s own speech, an operational failure to tag self-generated events as internal (Uhlhaas & Singer, 2010). Electrophysiological and imaging evidence reviewed by Stephan et al. (2009) likewise links hallucinations to impaired frontotemporal coherence and weakened self-monitoring. Psychosis is therefore 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 it is downstream. 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, both hippocampal firing and dopamine-neuron population activity were approximately doubled; temporary hippocampal inactivation normalized dopamine population activity and reduced amphetamine hypersensitivity. The dopamine system itself was not intrinsically broken. It 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 particularly powerful regulator of how many dopamine neurons are available for phasic recruitment. Human findings of hippocampal hypermetabolism, glutamate-GABA imbalance, and structural change in psychosis are therefore not parallel observations; they identify a plausible ignition point for dopamine dysregulation (Howes et al., 2024; Mancini et al., 2023). The cortex provides unstable models, the hippocampus drives contextual overactivation, and the striatum assigns abnormal motivational weight.

Dopamine does not determine the semantic content of a delusion or hallucination. Dysconnected cortical and hippocampal systems generate anomalous experiences and prediction errors; dopamine stamps those errors with salience, urgency, and confidence. 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 cholinergic interventions can be antipsychotic without direct D2 antagonism: striatal M4 receptors normally restrain dopamine release, while cortical and hippocampal muscarinic and nicotinic systems influence plasticity and cognitive precision (Saint-Georges et al., 2025).

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, psychosocial stress, cannabis exposure, and immune-metabolic disturbance. The theory replaces that list with a mechanistic criterion. An exposure matters to the extent that it perturbs complement expression, microglial state, NMDA receptor-dependent plasticity, inhibitory maturation, hippocampal excitability, blood-brain barrier function, or mitochondrial reserve during a sensitive developmental window (Rantala et al., 2022; Stephan et al., 2009).

Prenatal immune activation can alter fetal neuronal development and prime microglia; chronic stress can change glucocorticoid and cytokine signaling; cannabis can perturb endocannabinoid-NMDA interactions and adolescent plasticity; and kynurenine-pathway activation can reduce NMDA receptor function. These exposures do not write a separate environmental form of schizophrenia. They lower the threshold at the same developmental gate. Their effects depend on timing, dose, genetic background, and the capacity of the circuit to compensate.

The clearest demonstration that an exposure operates by modulating a genetic threshold, rather than by writing a separate disease, comes from obstetric complications. Their relationship to schizophrenia risk is not additive with polygenic liability but multiplicative: in exposed individuals, genome-wide significant risk alleles explained more than an order of magnitude more case-control variance than in unexposed individuals, and the interacting loci were concentrated in placental stress-response biology (Ursini et al., 2018). The exposure does not create risk de novo; it converts latent genetic liability into manifest disease at the developmental gate. Consistent with an immune route to the same gate, higher baseline proinflammatory cytokine levels predict accelerated peri-onset cortical thinning specifically in those who convert to psychosis (Cannon et al., 2015).

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 therefore obligatory rather than optional. A genetically vulnerable circuit can remain compensated in a favorable developmental environment, while a modest exposure can become decisive in a circuit already near the stability boundary. Conversely, severe developmental insults can push relatively low inherited liability toward the same failure regime. Heterogeneity of route is expected because the endpoint is a systems state, not a single lesion.

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 is not proof that complement is the initiating lesion in every case. It is stronger evidence than that: proof that concentrated disruption of multiple upstream systems can converge on the same synaptic, inhibitory, hippocampal, and dopaminergic endpoint. Genes dysregulated in 22q11.2 deletion neurons overlap idiopathic schizophrenia genomic signals, confirming that rare concentrated haploinsufficiency and diffuse polygenic liability differ chiefly in packaging (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-like 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, massively elaborated association networks, language-mediated inner speech, autobiographical self-modeling, and social metarepresentation. The failure mode is specific because the architecture that can fail in this way is specific.

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).

The molecular-evolution signatures at schizophrenia loci do not overturn this account, and the most recent evidence sharpens rather than softens it. That some risk-associated genes and regions bear signals of positive selection on the human lineage (Crespi et al., 2007; Srinivasan et al., 2016) speaks to the deep-time construction of the vulnerable architecture, not to ongoing selection favoring the risk-increasing alleles themselves. When the risk alleles are examined directly, the evidence points the other way. Analyses in the UK Biobank found no reproductive advantage to common schizophrenia risk alleles in unaffected carriers beyond a negligible, sex-dependent effect far too small to sustain prevalence by balancing selection (Escott-Price et al., 2019), consistent with the original demonstration that common schizophrenia alleles are precisely those small enough to escape strong purifying selection (International Schizophrenia Consortium, 2009). Most decisively, ancient-DNA time-series spanning the last ten millennia across West Eurasia reveal coordinated directional selection

acting to reduce the polygenic score for schizophrenia over time, in the same populations and by the same methods that detect rising scores for measures of cognitive performance (Akbari et al., 2026). Schizophrenia liability has been selected against in recent human history, not maintained by advantage. Its persistence despite that purifying pressure is exactly what mutation-selection balance predicts: selection removes deleterious variants, but a mutational target spanning thousands of genes, together with a genome architecture that continually regenerates recurrent structural variants, replenishes them faster than any realized selection coefficient can clear them.

The decisive evolutionary distinction is therefore between architecture and allele. The architecture of prolonged, plastic, socially specialized human neurodevelopment was selected. The damaging variants that destabilize it are under purifying selection. Burns (2004) described the vulnerability as a cost of elaborated social connectivity; Keller and Miller (2006) described how deleterious variation persists across a large mutational target; Akbari et al. (2026) now show that recent selection has been acting to reduce that variation. Combined, they yield a coherent account: selection built a high-performance system, and mutation-selection balance continually populates that system with low-frequency faults faster than selection can purge them.

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.

Porous boundaries do not make schizophrenia unreal. They locate its reality at the correct level. Schizophrenia is not a discrete molecular species; it is a coherent systems-level attractor. It 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. Other weightings of the same broad machinery yield bipolar disorder, autism, depression, or mixed phenotypes. Shared genes create overlapping vulnerability; circuit configuration creates the syndrome.

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 value of the hierarchy proposed here is that its levels make specific, ordered, and risky predictions, several of which could be shown to be false with experiments that are technically feasible today. This section specifies five such experiments. Each targets a load-bearing claim; each states the result the theory forbids; and each is designed so that a well-resourced team could execute it and, if the forbidden result obtained, refute the theory rather than merely qualify it. Where informative studies already exist, they are named, together with the reasons they are not yet decisive. The theory is offered in the expectation that it can be broken, and with an explicit account of how.

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

Claim at risk. Complement tagging and microglial phagocytosis are the dominant mechanism that converts distributed synaptic vulnerability into structural underconnectivity during the peri-onset window—not merely one correlate among many.

Prediction. Suppressing complement-mediated synaptic engulfment during the transition window will slow synaptic loss and reduce conversion in individuals at high risk.

Design. A randomized, double-blind, placebo-controlled prevention trial in clinical-high-risk individuals stratified for elevated combined risk (high polygenic score, attenuated psychotic symptoms, and functional decline). The active arm receives a central-nervous-system-penetrant inhibitor of the classical complement pathway, targeting C1q, C3, or the microglial complement receptor CR3/C3 axis, administered across the 12-to-24-month interval spanning expected transition. Co-primary outcomes are (a) the rate of decline in cortical synaptic-terminal density measured by serial SV2A positron emission tomography ([11C]UCB-J or [18F]SynVesT-1) in prefrontal, cingulate, and hippocampal regions, and (b) transition to a DSM/ICD psychotic disorder over 24 months. Target engagement is confirmed by reduction in cerebrospinal-fluid complement activation products (for example, C4a and C3 cleavage fragments). Power is set to detect a clinically meaningful reduction in conversion (for example, from 20% to 10%) and a between-group difference in SV2A slope of d approximately 0.5. An embedded mechanistic arm uses patient-derived induced pluripotent stem cells in a two-by-two co-culture (patient versus control neurons crossed with patient versus control microglia, each stratified by polygenic burden) to test whether pharmacological CR3/C3 blockade abolishes excess synaptosome engulfment across genotypes.

Falsifying result. With confirmed target engagement and adequate power, complement inhibition does not slow the SV2A decline and does not reduce conversion relative to placebo; and, in the co-culture arm, excess synaptic engulfment persists despite

complete complement blockade, or is driven entirely by microglial genotype independent of neuronal genotype. Either outcome would show that complement-microglial pruning is not the privileged amplifier the theory names and would demand a different execution mechanism.

Current state. The components exist; the decisive test does not. Patient-derived models show increased, complement-dependent microglial synapse elimination that minocycline blocks in vitro, and retrospective records associate adolescent tetracycline exposure with modestly reduced psychosis incidence (Sellgren et al., 2019). But the one completed randomized trial of a microglial inhibitor (minocycline in recent-onset psychosis, the BeneMin trial) was negative for negative symptoms and imaging biomarkers (Deakin et al., 2018), a result the theory anticipates rather than fears: minocycline is non-specific, and the trial intervened after onset, when the pruning window has largely closed. Complement-specific, CNS-penetrant agents are only now entering psychiatric development, and none has been tested in a high-risk cohort with a synaptic-density endpoint. The forbidden experiment has not been run.

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.

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. A longitudinal, densely sampled, multi-tracer imaging study in a large clinical-high-risk cohort. Each participant is scanned at 3-to-4-month intervals through the pre-onset period with (i) [18F]FDOPA positron emission tomography for striatal dopamine synthesis capacity, (ii) SV2A positron emission tomography for cortical and hippocampal synaptic density, and (iii) arterial-spin-labeling or resting-state functional MRI for hippocampal activity. Within converters, the analysis asks which measure departs from baseline first and whether the synaptic and hippocampal changes statistically lead the dopaminergic change.

Design (b): interventional causal chain. A randomized, placebo-controlled trial, in early psychosis or high risk, of an agent that reduces ventral-hippocampal hyperactivity at a target-engagement-confirmed dose (for example, low-dose levetiracetam, with hippocampal perfusion confirmed to fall by arterial spin labeling), with [18F]FDOPA measured before and after treatment.

Falsifying result. (a) Striatal dopamine synthesis capacity reliably rises before any detectable cortical or hippocampal synaptic loss or hippocampal hyperactivity in converters—that is, dopamine is the leading edge; or (b) confirmed normalization of hippocampal hyperactivity leaves striatal dopamine synthesis capacity and psychotic symptoms unchanged. Either result would invert or sever the causal chain the theory specifies.

Current state. The upstream and downstream measures have each been studied, but never together and never with the ordering resolved. Striatal dopamine synthesis capacity is elevated before onset in individuals who later transition and is greater in transitioners than non-transitioners, independent of antipsychotic treatment (Howes et al., 2011); but these dopamine studies cannot say whether the rise follows or leads synaptic and hippocampal change, and at least one multimodal study found striatal dopamine synthesis capacity unrelated to hippocampal glutamate and non-predictive of transition, a genuine crack in the assumed hippocampus-to-dopamine link. SV2A imaging in high-risk and first-episode samples exists but only cross-sectionally, and the field has explicitly called for longitudinal synaptic-density studies. On the interventional side, levetiracetam trials in early psychosis (for example, ClinicalTrials.gov NCT03129360 and NCT04317807) confirm that the drug can lower hippocampal activity and are testing symptom and volume outcomes, but they do not measure striatal dopamine synthesis capacity and so cannot test the specific causal prediction. No study has combined synaptic and dopaminergic tracers longitudinally through the transition, and none has closed the hippocampus-dopamine loop in humans. This is the single most decisive experiment the theory invites.

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. In antipsychotic-naive individuals, synaptic-terminal density is already reduced and declines around onset; total neuronal number is largely preserved; and the magnitude of synaptic reduction is uncorrelated with cumulative antipsychotic exposure.

Design. A two-part study. (i) In vivo: a longitudinal SV2A positron-emission-tomography study in antipsychotic-naive high-risk and first-episode individuals, with medication timing randomized where ethically permissible (immediate versus deferred antipsychotic initiation), and a co-registered index of neuronal integrity; the analysis tests whether synaptic-density reduction precedes and exceeds any neuronal loss and whether it tracks cumulative dose. (ii) Postmortem: in a large, well-matched cohort with detailed antemortem medication records, apply modern unbiased stereology and single-nucleus quantification to estimate absolute neuronal number and synaptic and spine density across association cortex and hippocampus, modeling cumulative antipsychotic exposure explicitly. A controlled non-human-primate arm administers chronic antipsychotics with serial SV2A imaging and terminal synaptic quantification.

Falsifying result. Robust, replicable primary neuronal loss—i.e., a reduction in total neuron number that is present early and proportional to symptom severity, rather than spine and synapse loss with preserved neurons; or a demonstration that the synaptic-density reduction is substantially produced by antipsychotic exposure, that is, a dose-dependent lowering of SV2A in previously drug-naive humans upon treatment and in chronically treated primates. Either result would break the claim that schizophrenia is

a loss of the space between neurons rather than a loss of neurons, and that the synaptic lesion is not a drug effect.

Current state. The available evidence supports the theory but has not been assembled into the decisive design. Unbiased stereology generally finds preserved cortical neuron number in schizophrenia; a controlled rodent experiment shows that chronic haloperidol and olanzapine do not lower SV2A (Onwordi et al., 2020), while longitudinal human data and meta-analysis show that antipsychotics do contribute to gross gray- and white-matter volume loss (Fusar-Poli et al., 2013; Ho et al., 2011), dissociating the drug-sensitive bulk-volume measure from the drug-insensitive synaptic measure. Peri-onset cortical thinning occurs in unmedicated converters (Cannon et al., 2015). What is missing is the randomized-medication-timing longitudinal synaptic study with a simultaneous neuronal-integrity readout, which would settle both halves of the claim at once.

Test 4. The syndrome depends on human-specific architecture, and its liability is concentrated in the human-lineage-elaborated genome.

Claim at risk. "Sapiens-specific" is a mechanistic statement: the characteristic syndrome requires human-specific cortical, self-modeling, and social-cognitive architecture, and schizophrenia's genetic liability is disproportionately located in the recently and rapidly evolved, structurally labile regions of the human genome.

Prediction. (a) Schizophrenia common-variant heritability is enriched in human-accelerated regions, human-lineage positively selected regions, and segmental-duplication and nonallelic-homologous-recombination-prone loci, beyond genomic-annotation expectation. (b) Introducing a substantial burden of human schizophrenia risk variation into a non-human system reproduces component endophenotypes (synaptic, oscillatory, dopaminergic) but not the integrated human-type syndrome with its self-monitoring and social-inferential phenomenology.

Design. (a) Partitioned-heritability analysis of the largest available schizophrenia GWAS against carefully constructed annotations of human-accelerated regions, ancient-DNA-derived human-lineage selection, and segmental-duplication architecture, with matched control annotations and proper linkage-disequilibrium modeling. (b) A cross-species program that engineers non-human primates, or the most humanized available models, to carry homologous high-effect copy-number variants (for example, the orthologue of the 22q11.2 deletion) and aggregated common-variant burden, and phenotypes them for the specific neural correlates the theory ties to psychosis: corollary-discharge and efference-copy failure, frontotemporal oscillatory coherence during self-generated action, and hippocampal-striatal dopamine dysregulation, alongside the synaptic and inhibitory endophenotypes.

Falsifying result. (a) Schizophrenia heritability shows no enrichment in human-lineage-specific regulatory or structural genome, being distributed indistinguishably from conserved, non-human-specific sequence; and (b) homologous risk-variant burden reproduces the full, integrated syndrome (including the neural signatures of impaired self-monitoring and social inference) in a non-human system that lacks human-specific association and social-cognitive architecture. Together these would falsify the human-architecture-specificity claim.

Current state. The genomic prediction is partly confirmed: schizophrenia risk is enriched in human-divergent, post-Neanderthal positively selected regions (Srinivasan et al., 2016) and near human-accelerated regions and expanded segmental duplications (Sandroni & Chaumette, 2025), with lineage-specific selection at individual loci (Crespi et al., 2007). A well-powered partitioned-heritability test could therefore either strengthen or break the claim. The cross-species prediction has been approached only piecemeal: existing 22q11.2-orthologous and risk-gene models reproduce synaptic, mitochondrial, inhibitory, and dopaminergic endophenotypes but have not been tested for the integrated self-monitoring and social-inferential phenotype, which is the crux of the specificity claim.

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

Claim at risk. Schizophrenia liability persists because deleterious variants are cleared by purifying selection but replenished across a vast mutational target, not because the risk-increasing alleles confer a compensating fitness advantage.

Prediction. The risk-increasing alleles as a class are under net purifying or directional selection and show no aggregate balancing-selection signal; unaffected carriers have no fitness advantage sufficient to sustain prevalence; and any selective-sweep signals at risk loci are attributable to linked beneficial variants rather than to the risk alleles themselves.

Design. A three-part evolutionary-genomic program. (i) High-density ancient-DNA time-series through the pre-industrial past, reconstructing the trajectory of the schizophrenia polygenic score and testing the direction of selection on the polarized risk-increasing allele set. (ii) Direct measurement of completed reproductive success as a function of schizophrenia polygenic score in large samples drawn from contemporary natural-fertility and high-fertility populations (not only post-demographic-transition industrialized cohorts, whose fertility patterns distort fitness estimates) to test whether unaffected high-liability individuals enjoy an advantage large enough to offset the fitness cost borne by affected individuals. (iii) Fine-scale haplotype dissection at risk loci that carry sweep signals, to determine whether the selected variant is the risk allele or a linked neighbor, together with formal tests for balancing selection (excess intermediate-frequency variants, elevated Tajima's D) on polarized risk alleles beyond the expectation from linked selection.

Falsifying result. The polarized risk-increasing alleles, as a class, show robust balancing selection or ongoing positive selection with a demonstrable and sufficient fitness advantage; or unaffected carriers in natural-fertility populations show a reproductive advantage large enough to sustain prevalence by balancing selection; or the sweep signals at risk loci are attributable to the risk alleles themselves rather than to linked variants. Any of these would replace mutation-selection balance with a hidden-advantage account.

Current state. The current balance of evidence favors the theory but leaves specific tests open. Ancient-DNA time-series across the last ten millennia show directional selection reducing the schizophrenia polygenic score (Akbari et al., 2026), and biobank analyses find no fitness advantage to common risk alleles in unaffected carriers beyond

a negligible effect (Escott-Price et al., 2019), consistent with mutation-selection balance and against cliff-edge or balancing accounts. The countervailing signals, positive selection at some risk loci over deeper time (Crespi et al., 2007; Srinivasan et al., 2016), have not been resolved to the level of the polarized risk allele, and completed-fertility measurements in natural-fertility populations are lacking. Until those are done, the door to a balancing account is not fully closed, and the theory's persistence claim remains genuinely falsifiable.

These five experiments do not exhaust the theory's exposure; they are the points at which it is most sharply at risk. Three of them—complement blockade in high-risk individuals with a synaptic endpoint, longitudinal dual-tracer imaging of the synapse-to-dopamine sequence, and the closing of the hippocampus-dopamine loop in humans—are within reach now and would, individually, either corroborate or overturn the theory's central mechanistic and ordering claims. A theory of schizophrenia that survived all five would not thereby be proven, but it would have earned the standing that the disorder's century of competing frameworks has lacked: it would have said in advance what could prove it wrong.

Synthesis

Schizophrenia begins with a distributed genetic burden across synaptic, regulatory, calcium-signaling, immune, chromatin, and mitochondrial systems. Common variants make small changes to expression and timing; rare variants make larger changes to dosage and structure. The burden is heavily neuronal, especially in mature pyramidal neurons, interneurons, hippocampal cells, and striatal populations, but it recruits glial and immune mechanisms during development. Because the same machinery is used across psychiatric conditions, pleiotropy is expected rather than anomalous.

The burden first acts during prenatal construction. It perturbs the quality, timing, and molecular identity of synapses—through fetal regulatory mistiming and through placental stress-response biology—without necessarily preventing childhood function. During adolescence, normal maturation becomes the decisive challenge. Complement-microglial pruning, inhibitory maturation, myelination, hormonal change, and rising social-cognitive demand remove redundancy and demand precision. Synapses that are weak, mistagged, metabolically underpowered, or poorly stabilized by NMDA receptor-dependent plasticity are selectively lost. The anatomical signature is reduced dendritic spine density and neuropil with relative preservation of neuronal number, and, because that signature is dissociable from the effects of antipsychotic medication, it is a feature of the disorder rather than of its treatment.

The physiological consequence is dysconnection. Prefrontal and temporal networks lose recurrent stability and timing; inhibitory control weakens and the beta- and gamma-band synchrony it supports degrades; hippocampal activity becomes excessive; and the ventral hippocampal-striatal-VTA system expands the pool of dopamine neurons available for phasic recruitment. Dysconnected generative models produce anomalous experiences and prediction errors. Dopamine assigns those errors salience and certainty. Corollary discharge fails, inner speech becomes alien, social inference becomes persecutory, and agency becomes unstable. Cognitive and negative symptoms

arise from the same connectional deficit in circuits for working memory, learning, motivation, and affiliation.

Environmental factors determine where an individual sits relative to the stability boundary. Prenatal infection, obstetric adversity, stress, cannabis, immune-metabolic disturbance, and other exposures matter when they converge on pruning, plasticity, inhibitory maturation, hippocampal excitability, or metabolic support, and the obstetric-complication-by-polygenic-risk interaction shows that such exposures act by multiplying genetic liability rather than by adding a separate one. The 22q11.2 deletion demonstrates the architecture in concentrated form: severe inherited vulnerability, incomplete penetrance, convergent synaptic and mitochondrial mechanisms, and outcome determined by compensation.

The syndrome is human because its defining failures occur in the late-maturing architecture of human association, language, self-modeling, and social cognition. It persists because selection favored that architecture, while mutation-selection balance continually replenishes deleterious variation across its enormous mutational target, and recent human history has been selecting that variation down, not up. Schizophrenia-risk alleles are not the hidden engine of genius. Schizophrenia is the recurrent failure cost of the machinery from which human cognitive flexibility is built.

Schizophrenia is therefore a sapiens-specific synaptic-fragility syndrome: prenatal in origin, adolescent in execution, connectional in anatomy, dysconnective in physiology, dopaminergic in amplification, social-inferential in phenomenology, and mutation-selection balanced in persistence. The theory does not ask one mechanism to explain every observation. It assigns each observation its place in a causal hierarchy. That hierarchy is the theory, and because it is a hierarchy of ordered causal claims rather than a catalogue of correlates, it can be tested and broken at each level.

The therapeutic implication follows directly. Once the disorder is understood as a developmental loss of synaptic and circuit reserve, treatment cannot remain confined to suppressing downstream dopamine after psychosis has consolidated. The decisive interventions will be temporally targeted and biologically stratified: preserving vulnerable synapses, normalizing complement-microglial selection, restoring NMDA receptor-dependent plasticity, stabilizing inhibitory networks, reducing hippocampal overdrive, and strengthening mitochondrial quality control before underconnectivity becomes entrenched.

Funding

This work received no specific external funding.

Use of generative artificial intelligence

Claude Opus 4.8, GPT-5.6 Sol, and Grok 4.3 were used in preparing initial drafts of the manuscript and for proofreading. The author reviewed and edited all output and takes responsibility for the content.

References

Akbari, A., Barton, A. R., Gazal, S., et al. (2026). Ancient DNA reveals pervasive directional selection across West Eurasia. *Nature*.

Birnbaum, R., & Weinberger, D. R. (2024). The genesis of schizophrenia: An origin story. *American Journal of Psychiatry, 181*(6), 482–492.

Burns, J. K. (2004). An evolutionary theory of schizophrenia: Cortical connectivity, metarepresentation, and the social brain. *Behavioral and Brain Sciences, 27*(6), 831–885. https://doi.org/10.1017/S0140525X04000196

Cannon, T. D., Chung, Y., He, G., Sun, D., Jacobson, A., van Erp, T. G. M., McEwen, S., Addington, J., Bearden, C. E., Cadenhead, K., Cornblatt, B., Mathalon, D. H., McGlashan, T., Perkins, D., Jeffries, C., Seidman, L. J., Tsuang, M., Walker, E., Woods, S. W., & Heinssen, R. (2015). Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biological Psychiatry, 77*(2), 147–157. https://doi.org/10.1016/j.biopsych.2014.05.023

Chick, S. L., et al. (2025). Whole-exome sequencing analysis identifies risk genes for schizophrenia. *Nature Communications, 16*, 7102.

Crabtree, G. W., Park, A. J., Gordon, J. A., & Gogos, J. A. (2016). Cytosolic accumulation of L-proline disrupts GABAergic transmission through GAD blockade. *Cell Reports, 17*(2), 570–582.

Crespi, B., Summers, K., & Dorus, S. (2007). Adaptive evolution of genes underlying schizophrenia. *Proceedings of the Royal Society B: Biological Sciences, 274*(1627), 2801–2810. https://doi.org/10.1098/rspb.2007.0876

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2019). Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell, 179*(7), 1469–1482. https://doi.org/10.1016/j.cell.2019.11.020

Crow, T. J. (2000). Schizophrenia as the price that Homo sapiens pays for language. *Brain Research Reviews, 31*(2–3), 118–129.

Deakin, B., Suckling, J., Barnes, T. R. E., et al. (2018). The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): A randomised, double-blind, placebo-controlled trial. *The Lancet Psychiatry, 5*(11), 885–894.

Devaraju, P., & Zakharenko, S. S. (2017). Mitochondria in complex psychiatric disorders: Lessons from mouse models of 22q11.2 deletion syndrome. *BioEssays, 39*(2), 1600177.

Duncan, L. E., et al. (2025). Mapping the cellular etiology of schizophrenia and complex brain phenotypes. *Nature Neuroscience, 28*(2), 248–258.

Escott-Price, V., Pardiñas, A. F., Santiago, E., Walters, J., Kirov, G., Owen, M. J., & O'Donovan, M. C. (2019). The relationship between common variant schizophrenia liability and number of offspring in the UK Biobank. *American Journal of Psychiatry, 176*(8), 661–666.

Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research, 17*(4), 319–334. https://doi.org/10.1016/0022-3956(82)90038-3

Fusar-Poli, P., Smieskova, R., Kempton, M. J., Ho, B. C., Andreasen, N. C., & Borgwardt, S. (2013). Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neuroscience and Biobehavioral Reviews, 37*(9), 1680–1691. https://doi.org/10.1016/j.neubiorev.2013.06.001

Glantz, L. A., & Lewis, D. A. (2000). Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Archives of General Psychiatry, 57*(1), 65–73.

Hakak, Y., Walker, J. R., Li, C., Wong, W. H., Davis, K. L., Buxbaum, J. D., Haroutunian, V., & Fienberg, A. A. (2001). Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences, 98*(8), 4746–4751. https://doi.org/10.1073/pnas.081071198

Ho, B.-C., Andreasen, N. C., Ziebell, S., Pierson, R., & Magnotta, V. (2011). Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry, 68*(2), 128–137.

Howes, O. D., Bose, S. K., Turkheimer, F., Valli, I., Egerton, A., Valmaggia, L. R., Murray, R. M., & McGuire, P. (2011). Dopamine synthesis capacity before onset of psychosis: A prospective [18F]-DOPA PET imaging study. *American Journal of Psychiatry, 168*(12), 1311–1317.

Howes, O. D., Bukala, B. R., & Beck, K. (2024). Schizophrenia: From neurochemistry to circuits, symptoms and treatments. *Nature Reviews Neurology, 20*(1), 22–35.

Howes, O. D., & Onwordi, E. C. (2023). The synaptic hypothesis of schizophrenia version III: A master mechanism. *Molecular Psychiatry, 28*(5), 1843–1856.

International Schizophrenia Consortium. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature, 460*(7256), 748–752. https://doi.org/10.1038/nature08185

Jaffe, A. E., Straub, R. E., Shin, J. H., Tao, R., Gao, Y., Collado-Torres, L., ... Weinberger, D. R. (2018). Developmental and genetic regulation of the human cortex transcriptome illuminate schizophrenia pathogenesis. *Nature Neuroscience, 21*(8), 1117–1125. https://doi.org/10.1038/s41593-018-0197-y

Keller, M. C., & Miller, G. (2006). Resolving the paradox of common, harmful, heritable mental disorders: Which evolutionary genetic models work best? *Behavioral and Brain Sciences, 29*(4), 385–452. https://doi.org/10.1017/S0140525X06009095

Lewis, D. A., Hashimoto, T., & Volk, D. W. (2005). Cortical inhibitory neurons and schizophrenia. *Nature Reviews Neuroscience, 6*(4), 312–324. https://doi.org/10.1038/nrn1648

Li, J., et al. (2019). Mitochondrial deficits in human iPSC-derived neurons from patients with 22q11.2 deletion syndrome and schizophrenia. *Translational Psychiatry, 9*(1), 302.

Li, J., et al. (2021). Association of mitochondrial biogenesis with variable penetrance of schizophrenia. *JAMA Psychiatry, 78*(8), 911–921.

Lodge, D. J., & Grace, A. A. (2007). Aberrant hippocampal activity underlies the dopamine dysregulation in an animal model of schizophrenia. *The Journal of Neuroscience, 27*(42), 11424–11430. https://doi.org/10.1523/JNEUROSCI.2847-07.2007

Lukow, P. B., Schubert, J. J., Severino, M., Knight, S. R., Kiemes, A., Livingston, N. R., ... Modinos, G. (2026). GABA-A receptor availability in clinical high-risk and first-episode psychosis: A [11C]Ro15-4513 positron emission tomography study. *Molecular Psychiatry, 31*, 987–996. https://doi.org/10.1038/s41380-025-03204-9

Mancini, V., et al. (2023). Excitatory/inhibitory imbalance underlies hippocampal atrophy in individuals with 22q11.2 deletion syndrome with psychotic symptoms. *Biological Psychiatry, 94*(7), 569–579.

Marder, S. R., & Umbricht, D. (2023). Negative symptoms in schizophrenia: Newly emerging measurements, pathways, and treatments. *Schizophrenia Research, 258*, 71–77.

Marshall, C. R., Howrigan, D. P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D. S., ... Sebat, J. (2017). Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nature Genetics, 49*(1), 27–35. https://doi.org/10.1038/ng.3725

Murphy, K. C., Jones, L. A., & Owen, M. J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry, 56*(10), 940–945.

Murray, R. M., & Lewis, S. W. (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal, 295*(6598), 681–682.

Nehme, R., et al. (2022). The 22q11.2 region regulates presynaptic gene-products linked to schizophrenia. *Nature Communications, 13*(1), 3690.

Onwordi, E. C., Halff, E. F., Whitehurst, T., Mansur, A., Cotel, M.-C., Wells, L., Creeney, H., Bonsall, D., Rogdaki, M., Shatalina, E., Reis Marques, T., Rabiner, E. A., Gunn, R. N., Natesan, S., Vernon, A. C., & Howes, O. D. (2020). Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. *Nature Communications, 11*, Article 246. https://doi.org/10.1038/s41467-019-14122-0

Owen, M. J., et al. (2023). Genomic findings in schizophrenia and their implications. *Molecular Psychiatry, 28*(12), 3638–3647.

Radhakrishnan, R., Skosnik, P. D., Ranganathan, M., Naganawa, M., Toyonaga, T., Finnema, S., Hillmer, A. T., Esterlis, I., Huang, Y., Nabulsi, N., Carson, R. E., & D'Souza, D. C. (2021). In vivo evidence of lower synaptic vesicle density in schizophrenia. *Molecular Psychiatry, 26*, 7690–7698. https://doi.org/10.1038/s41380-021-01184-0

Rantala, M. J., et al. (2022). Schizophrenia: The new etiological synthesis. *Neuroscience & Biobehavioral Reviews, 142*, 104894.

Saint-Georges, Z., et al. (2025). Cholinergic system in schizophrenia: A systematic review and meta-analysis. *Molecular Psychiatry, 30*, 3301–3315.

Sandroni, V., & Chaumette, B. (2025). Understanding the emergence of schizophrenia in the light of human evolution. *Genes, Brain and Behavior, 24*, e7013.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421–427. https://doi.org/10.1038/nature13595

Schneider, M., et al. (2014). Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome. *American Journal of Psychiatry, 171*(6), 627–639.

Selemon, L. D., & Goldman-Rakic, P. S. (1999). The reduced neuropil hypothesis: A circuit based model of schizophrenia. *Biological Psychiatry, 45*(1), 17–25.

Sellgren, C. M., Gracias, J., Watmuff, B., Biag, J. D., Thanos, J. M., Whittredge, P. B., Fu, T., Worringer, K., Brown, H. E., Wang, J., Kaykas, A., Karmacharya, R., Goold, C. P., Sheridan, S. D., & Perlis, R. H. (2019). Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. *Nature Neuroscience, 22*(3), 374–385. https://doi.org/10.1038/s41593-018-0334-7

Singh, T., et al. (2022). Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature, 604*(7906), 509–516.

Skene, N. G., Bryois, J., Bakken, T. E., Breen, G., Crowley, J. J., Gaspar, H. A., ... Hjerling-Leffler, J. (2018). Genetic identification of brain cell types underlying schizophrenia. *Nature Genetics, 50*(6), 825–833. https://doi.org/10.1038/s41588-018-0129-5

Srinivasan, S., Bettella, F., Mattingsdal, M., Wang, Y., Witoelar, A., Schork, A. J., ... Andreassen, O. A. (2016). Genetic markers of human evolution are enriched in schizophrenia. *Biological Psychiatry, 80*(4), 284–292. https://doi.org/10.1016/j.biopsych.2015.10.009

Stephan, K. E., Friston, K. J., & Frith, C. D. (2009). Dysconnection in schizophrenia: From abnormal synaptic plasticity to failures of self-monitoring. *Schizophrenia Bulletin, 35*(3), 509–527. https://doi.org/10.1093/schbul/sbn176

Stevens, B., Allen, N. J., Vazquez, L. E., Howell, G. R., Christopherson, K. S., Nouri, N., Micheva, K. D., Mehalow, A. K., Huberman, A. D., Stafford, B., Sher, A., Litke, A. M., Lambris, J. D., Smith, S. J., John, S. W. M., & Barres, B. A. (2007). The classical complement cascade mediates CNS synapse elimination. *Cell, 131*(6), 1164–1178. https://doi.org/10.1016/j.cell.2007.10.036

Stronati, E., et al. (2024). Schizophrenia in 22q11.2 deletion syndrome is associated with impaired neuronal mitophagy. *Molecular Psychiatry*. Advance online publication.

Su, B.-W., et al. (2025). The role of the microbiota-gut-brain axis in schizophrenia: An immunological perspective. *Frontiers in Immunology, 16*, 1711756.

Sullivan, P. F., Yao, S., & Hjerling-Leffler, J. (2024). Schizophrenia genomics: Genetic complexity and functional insights. *Nature Reviews Neuroscience, 25*(9), 611–624.

Trubetskoy, V., et al. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature, 604*(7906), 502–508.

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nature Reviews Neuroscience, 11*(2), 100–113. https://doi.org/10.1038/nrn2774

Ursini, G., Punzi, G., Chen, Q., Marenco, S., Robinson, J. F., Porcelli, A., Hamilton, E. G., Mitjans, M., Maddalena, G., Begemann, M., Seidel, J., Yanamori, H., Jaffe, A. E., Berman, K. F., Egan, M. F., Straub, R. E., Colantuoni, C., Blasi, G., Hashimoto, R., ... Weinberger, D. R. (2018). Convergence of placenta biology and genetic risk for schizophrenia. *Nature Medicine, 24*(6), 792–801. https://doi.org/10.1038/s41591-018-0021-y

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry, 44*(7), 660–669.

Zhu, B., et al. (2025). Multi-kingdom microbial changes and their associations with the clinical characteristics in schizophrenia patients. *Translational Psychiatry, 15*, 228.

Zinkstok, J. R., et al. (2019). Neurobiological perspective of 22q11.2 deletion syndrome. *The Lancet Psychiatry, 6*(11), 951–960.

This article was composed using a combination of the above-cited primary sources, Grok (grok.com), Claude (claude.ai), and my own editing. It can be cited as:

Moore, T. M. (2026). Schizophrenia as Sapiens-Specific Synaptic Fragility: A Unified Account of Origins, Mechanisms, and Persistence. Retrieved from https://mooremetrics.com/schizophrenia.