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Synaptic Pruning in Schizophrenia: Manifestations and Antecedents

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Abstract:
Schizophrenia (SCZ) is a complex neurodevelopmental disorder characterised by structural and functional abnormalities in the brain. The synaptic pruning (SP) hypothesis, originally proposed by Irvin Feinberg (1982), suggests that excessive SP during adolescence contributes to the pathogenesis of SCZ. SP is a normal neurodevelopmental process wherein redundant synapses are eliminated to refine neural circuits. However, in SCZ, SP is aberrant and manifests as widespread grey matter depletion, reduced dendritic spine density, and cognitive deficits. This paper explores the structural and functional consequences of abnormal SP in SCZ and its potential antecedents, such as complement component 4 (C4) overexpression, neuroinflammation, NMDA receptor dysfunction, genes, and environmental deprivation and insults. Understanding the interplay between SP and schizophrenia pathophysiology may provide crucial insights into its neurodevelopmental origins and novel treatment strategies, especially for children showing early signs of psychosis.

Keywords: Cognitive, grey matter, schizophrenia, synaptic pruning

I. INTRODUCTION

S chizophrenia (SCZ) is a complex neurodevelopmental psychiatric disorder that affects how a person thinks, feels, and behaves. It is characterised by a range of symptoms broadly categorised as positive, negative, and cognitive. Positive symptoms refer to the presence of abnormal behaviours or experiences that are not typically seen in healthy individuals. These include hallucinations (auditory or visual perceptions without external stimuli); delusions (firmly held false beliefs despite contradictory evidence); disorganised thinking and speech (manifested as loose associations, tangentiality, and in severe cases, incoherence); and grossly disorganised or abnormal motor behaviour (ranging from childlike silliness to unpredictable agitation to catatonia). Conversely, negative symptoms involve a diminution or absence of typical behaviours and functions. These encompass avolition (lack of motivation), blunted affect (reduced emotional expression), asociality (social withdrawal), anhedonia (inability to experience pleasure), and alogia (poverty of speech). Cognitive symptoms of SCZ impact memory, attention, working memory, problem-solving, processing speed, and social cognition [1]. Not all symptoms need to be exhibited and the combination thereof varies among patients. Centuries of research on the aetiopathogenesis of SCZ have revealed it to be incredibly complex, with multiple intersecting hypotheses and models having been

proposed to explain it. One such hypothesis is the synaptic pruning hypothesis put forth by Irvin Feinberg [2].

During the early prenatal stages, the brain normally forms more synapses than it will require to function optimally. This overabundance allows the brain's circuits to be finely tuned to the demands of any environment it is exposed to. This fine-tuning is termed synaptic pruning (SP), a process responsible for the large-scale remodelling of the developing brain that culminates in the highly precise and efficient wiring that characterises mature neural circuits [3]. Neural activity, including that occurring in response to environmental stimuli, guides SP, such that less frequently used synapses are eliminated and more frequently used ones are preserved and strengthened. Such synaptic elimination (including in the prefrontal cortex [4]) happens primarily through phagocytosis by microglia, the resident macrophages of the central nervous system (CNS). Like cellular debris and pathogens, synapses that need to be removed are tagged (or opsonised) by molecules such as complement component 3. Microglia then recognise these tags and engulf the marked synapses.

The brain's neural circuitry is largely pruned during two developmental stages: the first two postnatal years and adolescence [5]. Abnormal pruning at both times is associated with several neuropsychiatric conditions [6–14]. More specifically, the SP hypothesis of SCZ states that excessive SP during adolescence contributes to the aetiopathogenesis of SCZ [2]. The hypothesis connects to abnormal SP several observations about SCZ patients, such as broad structural and functional abnormalities in their brains and the symptoms of psychosis typically emerging after the second wave of SP [2,15]. This paper explores the literature pertaining to aberrant SP in SCZ, including its structural and functional manifestations, and potential antecedents and mechanisms.

II. MANIFESTATIONS OF ABERRANT SYNAPTIC PRUNING IN SCHIZOPHRENIA

A. Smaller Brain Volume

Structural imaging research has indicated reduced whole brain volumes during the prodromal phase, at the onset of psychosis, and in chronic illness [16–20]. For instance, a meta-analysis involving over 18,000 subjects revealed that both medicated and antipsychotic-naive patients exhibit decreased intracranial and total brain volumes, with the most pronounced reductions observed in grey matter (GM) structures such as the frontal and temporal lobes, cingulate and insular cortex, and the thalamus [21]. An eight-year longitudinal MRI study revealed that individuals with a high genetic risk for SCZ possess smaller whole brain, PFC, and temporal lobe volumes over time than those without genetic risk. Additionally, those who eventually developed SCZ exhibited even greater PFC volume reduction [22]. Smaller hippocampal volumes have also been observed in the early stages of the illness [23–24], consistent with the temporal lobe findings. Volume reduction in SCZ is particularly notable in cortical areas, whereas structural imaging studies of the basal ganglia [25–27] and cerebellum [28–30] have shown mixed results. GM depletion is considered the primary phenomenon underlying these brain volume reductions in SCZ patients [31–32].

B. Grey Matter Depletion

Over the course of brain maturation, regressive events such as SP reduce GM density; whereas concomitant progressive events such as myelination increase white matter (WM) density [33–34]. Excessively reduced GM has been observed widely across the cerebral cortex, especially in the frontal and temporal lobes of individuals at high risk for SCZ who eventually develop psychosis [22, 35–39], individuals experiencing their first psychosis episode [18, 40–43], and patients diagnosed with SCZ [18, 44–49]. Thompson et al. [50] conducted multiple MRI scans on 12 adolescents with SCZ and 12 without

over five years. They observed a gradual GM loss in those with SCZ, initially affecting the parietal association areas and later extending to the parietal, motor, temporal, and prefrontal regions.

Further, a longer duration of illness [51–52] and the severity of negative symptoms [44, 52] are correlated with lower GM volume in several areas including the left dorsomedial prefrontal cortex (PFC), right middle frontal cortex [51] frontotemporal region [44], the superior temporal gyrus, and anterior cingulate cortex [52]. Conversely, improved cognitive symptoms in domains such as working memory, attention, and psychomotor speed are observed in SCZ patients with a greater GM volume [51].

These abnormal GM reductions are attributed to exaggerated regressive brain maturational events such as SP because of the temporal [40] and spatial [42] coincidence of pathological and non-pathological cortical thinning in SCZ patients and controls, respectively. In other words, it is the frontal lobes, the areas pruned during adolescence and young adulthood, that display the most significant GM depletion in SCZ, whose symptoms are also known to emerge during adolescence and young adulthood. Furthermore, the overactivity of microglia, the cells that phagocytose synapses, also depletes GM [53–54].

While appropriate GM reductions are perturbed by synaptic over-pruning, the brain WM of SCZ patients, especially within the frontal and temporal lobes, also appears less dense and of poorer structural integrity [55–57]. Abnormal myelination has also been inferred, as measured by the grey-to-white matter contrast [58], with improvement correlating with the duration of antipsychotic intake [41]. Akin to SP, myelination also occurs in a posterior-to-anterior direction, with the frontal and temporal lobes myelinating during adolescence, among other life stages [59–60]. Once again, microglia seem to be involved in the aforementioned WM anomalies as activated microglia have been found near dystrophic and apoptotic oligodendrocytes, demyelinating and dysmyelinating axons in SCZ patients [61]. Oligodendrocytes are the glial cells mainly responsible for myelinating axons in the CNS. Other contributing factors include morphological abnormalities in oligodendrocytes and attenuated expression of oligodendrocyte- and myelin-related proteins in SCZ patients [61].

C. Dendritic Spine and Neuropil Depletion

Glausier & Lewis [62] ascribe smaller GM volumes in SCZ to neuropil shrinkage instead of neuronal death [63–65]. Neuropil is a region, most prominently occurring in the brain, that comprises unmyelinated axons, axon terminals, dendritic shafts, and dendritic spines. Particularly, dendritic spines are distinct morphological and biochemical structures that extend from the dendritic shafts of pyramidal cells in the cortex and hippocampus, among other brain areas. Spines are the substrate for 80–95% of excitatory synapses in the CNS [66–68], with each spine typically receiving one glutamatergic synapse [69]. Therefore, spine density marks the amount of excitatory input a neuron gets [70].

In SCZ, there is a notable reduction in spine density and size across various cortical regions, such as the striatum, the subiculum, the temporal, auditory, and prefrontal cortices [62, 71–78]. Notably, lower spine density is observed in layer 3 pyramidal neurons (PNs) of the dorsolateral PFC [73], an anomaly absent in deeper cortical layers, such as layers 5 and 6 [79]. Further evidence, although indirect, comes from experimental studies wherein reduced dendritic spines were linked to deficits in sociability, sensorimotor processing, working memory, and attention, also commonly seen in SCZ [80–81]. Such a decrease in dendritic spine density seems to result from a combination of overpruning, impaired spinogenesis, genes, and cytoarchitectural defects [82].

Dendritic spines have been implicated in the aetiogenesis of SCZ since they increase during childhood and prominently decrease during adolescence [83–87]. Moreover, dendritic spines have dynamic shapes and change form slightly throughout their existence [88]. Although the different shapes exist on a

continuum [89], two have been commonly studied in relation to SCZ and SP. Firstly, small, thin spines are transient and dynamic and, therefore, important for learning, which requires rapid plasticity via new connections [88, 90–91]. Secondly, large, mushroom spines, being more mature and persistent, participate in long-term activity-dependent synaptic plasticity and memory retention [92–93].

Studies on rats show that during adolescent SP, thinner, more immature spines and precursors thereof (filopodia) are the principal targets of elimination in the neocortex, sparing larger, more enduring spines [4, 94]. These findings align with the activity-dependent nature of SP that follows a use-it-or-lose-it principle [95–96]. Thus, it may be speculated that thin spines are selectively compromised in SCZ, but the reason for this is unclear. Indeed, two postmortem studies have found a preferential decrease in smaller spines, but these investigations are limited to the primary auditory cortex. One showed its association with altered calcium channel signalling involving the SCZ risk gene CACNB4, ultimately hindering spinogenesis [97]. Another associated it with reduced microtubule-associated protein 2 (MAP2) immunoreactivity, suggesting cytoskeletal abnormalities that may underlie synaptic dysfunction [98]. However, two more studies contradict these findings. Cai et al. [99] observed that a specific gene variant associated with SCZ risk preferentially decreased mushroom spine density in cultured primary hippocampal neurons of rats. Sánchez-González et al. [100] found increased thin spine density in frontal cortex PNs in a rat strain presenting schizophrenia-like traits, reflecting immature synaptic states.

Additionally, Gonzalez-Burgos et al. [101] obtained findings that contrast with the theory that smaller spines are preferentially eliminated during adolescent SP. They showed that in layer 3 PNs in monkeys' DLPFC, weaker synapses (with small spines) get eliminated just as much as stronger synapses, thus supporting uniform pruning across the entire distribution of synaptic strengths. Given these findings, they inferred that the selective elimination of small spines, as observed by MacDonald et al. [97] and McKinney et al. [98], suggests an abnormal pruning process where strong synapses are eliminated normally while weak synapses are eliminated excessively, which disrupts the normal distribution of synaptic strengths and reduces the excitatory drive to layer 3 PNs. Thus, there is an apparent lack of consensus concerning the morphological type of dendritic spines in SCZ and its relation with SP.

D. Cognitive Symptoms

Cognitive symptoms, including deficits in attention, psychomotor speed, information processing, learning, memory, abstract thinking, planning, and problem-solving, are a widespread and disruptive domain of SCZ symptomatology [102]. These denote a trait marker for SCZ since they appear even before the onset of the illness [103–104]. They seem to stem from a combination of disrupted neuroplasticity (NP) [105–112] and abnormal brain connectivity [114–115]. This is reflected in functional neuroimaging findings in SCZ such as aberrant frontotemporal activity and connectivity, thought to contribute to deficits in verbal memory and encoding; abnormal activation in sensory pathways in response to complex stimuli, indicating faulty sensory integration; and unbalanced top-down and bottom-up processes during information-processing (summarised in Boland & Verduin [1]). Conversely, interventions such as cognitive remediation therapy (CRT) target NP and neural rewiring, improving cognitive performance, both globally and in specific domains, such as social cognition, verbal working memory, and daily functioning [42, 116–119]. These positive outcomes are also reflected in neuroimaging studies reporting increased frontal and temporal activation, enhanced resting-state functional connectivity, and lesser GM loss post-intervention, accompanied by improved performance on various cognitive tasks [118, 120].

Synaptic Pruning and Neuroplasticity. We present four lines of evidence that relate to both NP and SP. Firstly, long-term potentiation (LTP) and long-term depression (LTD), at two complementary scales,

underlie NP and SP. LTP strengthens synaptic connections to enhance inter-neuronal communication by promoting spine turnover and synapse stabilisation [121- 122]. On the other hand, LTD weakens synaptic connections by inducing spine shrinkage and loss, increased varicosities turnover, and increased separation of varicosities from dendritic spines [121, 123–125]. At an immediate and microcircuit level, LTP and LTD allow NP by adjusting synaptic strength at individual synapses, enabling rapid, activity-dependent changes critical for processes like learning and memory [126–127]. At a developmental and microcircuit level, these phenomena play a vital role in SP and shaping neural circuitry [128].

The few investigations on LTP in SCZ have reported impaired LTP-like plasticity in the patients' motor [129–131] and visual [132] cortices in response to non-invasive stimulation. Two studies particularly found impaired focal LTP-like plasticity rather than the non-focal type, indicating subdued plasticity and signal integration at the synapse level [129–130, 133]. Further, one study established a relationship between subdued LTP-like plasticity in the motor cortex and patients' deficits in rotary pursuit motor learning [131]. Such faulty LTP is seen as a result of dysfunction of glutamatergic and dopaminergic neurotransmission, N-methyl-D-aspartate (NMDA) receptors, and inhibitory regulation comprising the gamma-aminobutyric acid (GABA)-synthesising enzyme glutamic acid decarboxylase and GABAergic neurotransmission [111, 129, 134–138]. Abnormal density, trafficking, and subunit expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors may also play a role, although the findings are inconclusive [139]. Even fewer investigations on LTD in SCZ also indicate abolished LTD-like plasticity [130, 140].

The second line of evidence pertains to dendritic spines, which contain NMDA and AMPA receptors, making them the anatomical substrate for NP. As explained in the previous subsection, these appear to be depleted in patients with SCZ, likely due to excessive elimination or pruning. Thirdly—and more generally—the 108 SCZ-associated genetic loci analysed by Ripke et al. [113] are those that encode synaptic proteins essential to synaptic plasticity, such as NMDA, AMPA, the voltage-dependent calcium channel, and dopamine receptor D2. Lastly, environmental factors also influence synaptic plasticity and SP: early-life stress and cognitive deprivation form the two common themes among the environmental risk factors of SCZ, as explained later. In both animal and human studies, these are linked to quicker brain maturation and reduced NP, further tied to cognitive impairments akin to those seen in SCZ [141].

Synaptic Pruning and Neural Wiring. Enfeebled LTP and LTD would mean that the required synaptic connections are not formed/strengthened, and the trivial ones are not removed/weakened. This may obfuscate the utility of specific brain networks, a crucial determinant for the process of SP. Normally, SP optimises circuitry, manifesting as superior functional outcomes and signal-to-noise ratio (SNR) of neural transmission [142–145]. However, in the brains of SCZ patients, such disturbed SP may explain the widespread hypoconnectivity observed within and among several key networks using resting-state functional connectivity, namely the default mode network, auditory network, core network, somatomotor network, salience network, and the self-referential network [114]. These findings support the dysconnectivity hypothesis of SCZ by Stephan et al. [146].

This explains the abnormal functional neuroimaging findings obtained in SCZ patients, such as faulty sensory integration, and top-down and bottom-up processing during information processing [1]. Specifically, the following have been reported: abnormal activation in the dorsal visual pathway in response to complex stimuli conditions, despite normal activation in basic sensory and motor regions in response to simple stimuli; faulty inhibitory P300 for a no-go condition, indicating reduced inhibition by the PFC; in event-related potential (ERP) studies with oddball tasks, aberrant activation in patients

correlates with symptom severity: attenuated response to targets is thought to reflect insufficient top-down activation of target circuitry, whereas attenuated evoked response to novel distractors may reflect overprocessing of bottom-up events [1]. Additionally, a lower SNR has been observed, with dopamine, glutamate, and GABA dysfunction as possible antecedents [147], which are already known to be involved in the aetiology of SCZ. This reduced SNR manifests (in SCZ patients and, to a lesser extent, in their non-diagnosed siblings) as insufficient prefrontal activation during cognitive tasks in fMRI data and variability in prefrontal ERPs in EEG data [147]. Further, [148] proposed neural network abnormalities in SCZ due to pathological SP as the reason for a conflict between the excitatory and inhibitory processes in the brains of SCZ patients. This was manifested in their EEG results as either a simultaneous increase or decrease in ERP latency and amplitude when shown neutral and threatening images.

III. POTENTIAL ANTECEDENTS TO ABERRANT SYNAPTIC PRUNING IN SCHIZOPHRENIA

A. Immune and Microglial Dysfunction

Immune Dysregulation and Neuroinflammation Drive Microglial Overactivation: Since microglia are the resident macrophages of the CNS, their role in synaptic elimination also constitutes the neuroinflammation hypothesis of SCZ, which posits that dysregulation of the immune system and inflammatory processes play a significant role in the pathophysiology of SCZ [149]. SCZ risk is elevated by prenatal and childhood infections [150], and autoimmune disorders independently and in combination with infections [151]. Next, inflammatory mediators are involved in SP [152] and are associated with SCZ [148, 153–156]. Thus, the link between neuroinflammation and SCZ might be mediated by microglial overactivation and the resulting hyperfunctioning, including aggressive SP [157], indicated by activated microglia found in postmortem studies of SCZ patients [158–160].

C4 Overexpression Aggravates Microglia-Driven Synaptic Elimination: Genome-wide association studies (GWAS) have uncovered common genetic variants associated with a heightened risk of SCZ [161]. The most robust findings involve the major histocompatibility complex (MHC) locus on chromosome 6 [113, 162]. Particularly, repeated copy numbers of the complement component 4 (C4) gene result in increased expression of the C4A (but not C4B) isoform of C4, an immune system signalling molecule [162, 163]. C4A participates in SP by activating complement component (C3), which opsonises dendritic spines of weak or less active synapses for phagocytosis by microglia [164]. In vitro models have shown that microglia-mediated SP and synaptic engulfment are more aggressive in SCZ when either the microglia or neurons in cell culture are derived from patients, in comparison to healthy controls [165]. This aligns with observations of reduced spine density in SCZ, suggesting a mechanism of excessive synaptic elimination.

Moreover, C4A expression in humanised mouse models [166] and patient-derived cultures [87, 167] directly correlates with increased microglial engulfment and neuronal complement deposition. However, although C4A concentration is elevated in the cerebrospinal fluid (CSF) of first-episode psychosis patients who develop SCZ, this increase is not fully explained by genetic risk variance at the C4 locus [168]. Contributing towards a more comprehensive explanation, Gracias et al. [168] discovered that cytokines interleukin (IL)-1β and IL-6 in patient-derived cellular models and IL-1β in patient-derived CSF selectively enhance C4A mRNA expression in neurons, even after controlling for genetically predicted C4A mRNA expression. Prasad et al. [169] also found a positive correlation between IL-6 in the peripheral blood and catabolites of membrane phospholipids in the thalamus of the brains of early-course SCZ

patients. These catabolites were thought to reflect neuropil depletion, likely due to excessive pruning. They further cite evidence indicating that smaller thalamic volume is associated with negative and positive symptoms and hindered cognitive performance. Additional indirect evidence (summarised in Pearson & Iadecola [170]) comes from studies that have established associations between maternal infections, interleukins, and SCZ.

Potential Treatments: Studies on potential treatment drugs consistent with these mechanisms have shown that minocycline, an antibiotic, reduces microglial engulfment of synapses and thereby reduces the risk of SCZ [89] as well as negative and cognitive symptoms [171]. Previous meta-analyses had also demonstrated the drug's effectiveness and safety in treating the negative symptoms ([172–173]; cf. Deakin et al. [174]; see also Inta et al. [175]). Wangemann [166] also found that oridonin, a targeted NLRP3 inflammasome inhibitor, exhibits anti-inflammatory properties in human induced pluripotent stem cells (iPSC)-derived microglia. It suppressed synaptosome phagocytosis and enhanced synaptic density in C4A overexpressing iPSC-derived cortical neurons when co-cultured with microglia. Suppression of microglial activity through anti-inflammatory agents also enhances the antipsychotic effect for treating negative and cognitive symptoms [171, 176–178]. Furthermore, various antipsychotic agents attenuate microglial secretion of pro-inflammatory substances such as nitric oxide and interleukins [179–183].

B. Excitatory-Inhibitory Dysfunction

Glutamate Surge in the Cortex Exacerbates Synaptic Pruning: Glutamate and GABA are the brain's primary excitatory and inhibitory neurotransmitters, respectively. The glutamate hypothesis of SCZ posits that hypofunction of the NMDA glutamate receptor (NMDAR) causes hypoactivation of GABAergic interneurons that express parvalbumin (PV+ interneurons), consequently producing disinhibition of excitatory glutamatergic PNs, which contributes to SCZ symptoms [184–186]. PV+ interneurons are fast-spiking and synchronise the activity of PNs, which constitute about 80% of all cerebrocortical neurons and generate the gamma band oscillations necessary for optimal cognitive function. Parellada & Gasso [82] review several lines of evidence that align with the glutamate hypothesis (see also Howes & Shatalina [187]), including the psychotomimesis induced in healthy subjects by NMDAR antagonists such as ketamine and phencyclidine and dysfunction of the PV+ interneurons in the PFC and hippocampus. Additionally, Orhan et al. [188] reported elevated kynurenic acid, an endogenous NMDAR antagonist, in patients' brains, which decreased neuronal activity and promoted microglial synaptic elimination.

Parellada & Gasso [82] also combine the glutamate hypothesis with the well-known dopamine hypothesis of SCZ by proposing that aberrant excitation of PV+ GABAergic inhibitory interneurons triggers (a) a disinhibited and excessive glutamate release by glutamatergic cerebrocortical PNs; and (b) hyperdopaminergic subcortical areas, for which the disinhibition of long-range pyramidal cortical projection to the ventrotegmental area may also be responsible. They further explain that the glutamate surge and calcium overload through glutamate receptors can initiate excitotoxicity and rapid dendritic pruning (or non-lethal synaptic apoptosis) by locally activating the mitochondrial apoptosis pathway and the caspase-3 cascade, resulting in a reduced density of dendritic spines. Parellada & Gasso [82] cite evidence showing that apoptotic dendrites are more likely to be eliminated by microglia because they release certain "find me" (e.g., glutamate levels) and "eat me" (e.g., complement cascade proteins such as C1q and C3) signals for the microglia. Thus, the hyperglutamatergic state and its consequences are tied to reduced NP, dysfunctional brain regions, and the negative and cognitive symptoms of SCZ.

Since dendritic spines form the principal microstructure of glutamate synapses [189] and their density is often reduced in the brains of SCZ patients [73], this could initiate the vicious cycle of NMDAR—and

therefore GABAergic interneuron—hypoactivation, followed by the uninhibited glutamate surge in the cortex, and excessive spine elimination or death. The possible antecedents to NMDAR dysfunction in SCZ are outside the scope of this paper, but research indicates a genetic basis [190, 113] in addition to a controversial auto-immunological basis [191–192].

Besides modulating the activity of GABAergic interneurons, a general function of NMDAR activation is to control cytoskeletal dynamics and the expression of structural proteins and neurotrophins like brain-derived neurotrophic factor (BDNF) that aid in synapse stabilisation, and to recruit AMPA receptors to help maintain spine integrity [193–194]. Therefore, alterations to these receptors may compromise the structural integrity of dendritic spines and reduce their activity levels, making them more susceptible to either death or elimination by microglia.

Disrupted GABA Neurotransmission May Drive Synaptic Pruning: Along with NMDAR, the GABA receptors form a crucial part of the excitatory-inhibitory balance in the brain. The role of $GABA_A$ receptors—particularly the α4βδ isoform—in SP was demonstrated by Smith et al. [195], who injected its orthosteric agonist, gaboxadol, into male mice for 14 days, starting at the onset of puberty. They observed a 50% reduction in the dendritic spine density in layer 3 pyramidal cells of the prelimbic PFC and impaired temporal order recognition—a PFC-dependent cognitive deficit reported in SCZ. The α4βδ isoform is found on extrasynaptic sites in the forebrain and partakes in tonic inhibition, wherein the receptor isoform, when activated, remains open for a longer time, providing a lasting inhibitory tone [196]. Tonic inhibition is crucial for synaptic plasticity, neurogenesis [197-198], and cognitive functions [199-200]. The reduced spine density observed by Smith et al. [195] may be attributed to the increased probability of elimination of inhibited and relatively inactive neurons [201-203]. This may also be why administering NMDAR antagonist MK801 [204] and genetically deleting the NR1 subunit of NMDARs [205] reduces spine density in cortical PNs, since activation of NMDARs on a neuron excites the neuron. Furthermore, similar to how gaboxadol elicited impaired temporal order recognition, NMDAR antagonists also elicit the positive, negative, and cognitive symptoms of SCZ [206-207]. However, whether gaboxadol, like NMDAR antagonists, selectively disrupts GABA-related functioning [208–209] or also directly impacts glutamate neurotransmission is unknown. Moreover, the cortical PNs affected by NMDAR antagonists and gaboxadol also extend connections to the ventral tegmental area—a crucial part of the mesolimbic dopamine pathway that is thought to produce excessive dopamine and positive symptoms in SCZ.

Rabinovitch et al. [210] put forth a model suggesting that the genetic predisposition to SCZ leads to an overproduction of GABAergic neurons, possibly prenatally. However, in the adult brain, either (a) the excitatory-inhibitory (E/I) balance is skewed towards glutamatergic neurons due to the over-pruning of GABAergic neurons by homeostasis-maintaining glial cells; or (b) the E/I ratio is balanced but the power of both neuron types is diminished, a result of the glial cells also over-pruning glutamatergic synapses to re-establish the equilibrium disrupted by E/I imbalance towards glutamatergic power. The authors also propose a mathematical model and graph to represent this process.

Potential Treatments: Given that the hypoactivation of NMDAR contributes to SCZ symptoms, glutamatergic drugs or NMDAR agonists have been proposed as treatments. Orhan et al. [188] found that the decrease in spine density caused by kynurenic acid in excitatory neurons developed from iPSCs was reversed by adding NMDA and the endogenous co-agonist D-serine. A Cochrane review also reported a moderate effect of D-serine and glycine when complementing antipsychotics but pointed out the inconsistent data and small sample size [211]. However, D-cycloserine, a partial agonist of NMDAR's glycine site, did not improve symptoms. Reduced levels of D-aspartate, an endogenous NMDAR agonist

[212]; quinolinic acid, an endogenous NMDAR agonist [213]; and LY379268, an agonist of mGluR2/3, a group II metabotropic glutamate receptor [214], have also been implicated in SCZ. Engel et al. [214], in mice models, showed that LY379268 restores the excitatory-inhibitory balance disrupted in SCZ and that it does so with efficiency comparable to olanzapine. Similarly, [215] genetically and pharmacologically elevated D-aspartate levels in mice. This increased NMDAR activity, improved cognitive and memory functions, and attenuated schizophrenia-related deficits in sensorimotor gating induced by amphetamine and MK-801. In light of studies implicating deficient GABA neurotransmission in SCZ and its upregulation in the regulation of the onset and duration of pre-adolescent SP, preliminary evidence suggests that tiagabine, a GABA reuptake inhibitor that blocks the GABA transporter 1 (GAT-1), may improve cognitive symptoms in early course of SCZ by modulating PFC functions, as shown in fMRI scans taken as subjects performed working memory tasks [216–217]. Although the aforementioned drugs by themselves may not be enough to treat a disorder as multifaceted as SCZ, further translational and clinical research is nevertheless needed to determine their therapeutic effectiveness.

C. Genes

RELN. Arkhipov et al. [148] implicate the RELN gene in synaptic elimination. The RELN gene codes for reelin, an extracellular matrix protein that modulates the formation of neural systems and synaptogenesis through its trophic and signalling role [218–219]. In addition, reelin plays an active role in regulating glutamatergic neurotransmission and aids in the development of dendritic spines, which helps maintain optimal synaptic plasticity [218, 220–221]. The binding of reelin to receptors triggers cascades contributing to dendritic proliferation, dendritic growth, and branching in the cortex [222–226]. Arkhipov et al. observed abnormally high levels of reelin in patients' peripheral blood due to decreased methylation (repression) of the promoter region of the RELN gene. Given that methylation in peripheral blood is inversely proportional to that in the brain [227], they state that reelin levels must be reduced in patients' brains (previously confirmed by Impagnatiello et al. [228]) due to the hypermethylation of the RELN gene. They theorise that the reduced reelin may result in indirect connections, insufficient synaptic elimination, and abnormal neural processing evident in their EEG data, which depicted an imbalance of excitation and inhibition processes in the brain. However, part of the results obtained by Arkhipov et al. [148] are inconsistent with previous studies that found a reduction in RELN mRNA expression [229] and heightened methylation of the RELN promoter [230] in SCZ patients' peripheral blood (see also Markiewicz et al. [231])

Boksa [232] purports that the reduction in dendritic spine density in reelin-deficient rodents may result from reelin's role in cytoskeleton stability. She explains that "phosphorylation of the F-actin binding protein, n-cofilin, inhibits its actin-severing activity, leading to stabilisation of the cytoskeleton, & it has been shown that signalling by reelin is required for n-cofilin phosphorylation [233]. Thus, in patients, reduced reelin may reduce cytoskeleton stability & dendritic spine density via a decrease in n-cofilin phosphorylation" (p. 2). Unsurprisingly, decreased reelin expression in the brain has been considered a vulnerability factor within the 2-hit model of SCZ aetiology [228]. Moreover, RELN supplementation may have a trophic effect on synaptic plasticity as it helps recover deficits in dendritic spine density, synaptic function, and cognitive performance that are associated with reduced RELN expression [234].

RhoGTPases. Certain genes & their respective proteins that have been implicated in SCZ are also involved in dendritic spine stability and elimination. For example, a family of small RhoGTPases (RhoA, Rac1, Cdc42) regulates the actin cytoskeleton that determines the morphology and, therefore, the synaptic function of dendritic spines. The mRNAs for Cdc42 and Duo (orthologous to Kailrin-7) are reduced in the

DLPFC of SCZ patients, and their expression correlates with spine density in the same region [235]. In the same study [235], the mRNA expression of Cdc42 and Duo was unaltered in monkeys chronically exposed to the antipsychotics haloperidol or olanzapine.

DISC1. Hayashi-Takagi et al. [236] explain the interactions among various proteins that influence dendritic spine stability, and ultimately, the probability of their elimination. Kalirin-7 (Kal-7) binds to and activates Rac-1, which is needed for spine growth, but its overexpression (and underexpression; see [235]) hampers spines. DISC1 (Disrupted-in-Schizophrenia 1), often associated with SCZ, prevents Kal-7 from binding to Rac-1 by confining the former's access to the latter, while the expression of DISC1 itself is inhibited by NMDAR activation. DISC1 is required for appropriate spine maintenance, but its overexpression leads to spine shrinkage. Thus, both over- and under-expression of DISC1 can be implicated in SCZ. Such interaction of DISC1 with proteins governing the actin cytoskeleton may account for the loss of dendritic length & spine density seen in DISC1 mutant mice [237]. Thus, the gene affects NP [238–239], which underlies the cognitive symptoms of SCZ, as explained previously. Various polymorphisms of DISC1 have been associated with SCZ [240–243]. DISC1 acts as a scaffold protein, and (a) as shown by Hayashi-Takagi [236], regulates many other proteins governing signalling and cytoskeletal structure; (b) regulates neurodevelopmental processes such as neurogenesis, migration, neurite outgrowth, and spine development; and (c) is involved in dopamine neurotransmission, which is generally aberrant in SCZ [244]. Since Bellon et al. [245] found that monocyte-derived-neuronal-like cells (MDNCs) from medicated patients prune more primary neurites after exposure to dopamine, DISC1 may play an indirect role in SP in SCZ. Besides DISC1, several other genes associated with SCZ are involved in overlapping processes such as SP, synaptic plasticity, and dendritic spine dynamics. These include Neuregulin 1 (NRG 1), Akt1, CACNA1C, and DTNBP1 [106].

DLG1, NOS1, THBS4, FADS1. Cocchi et al. [246] identified proteins associated with pruning by reviewing literature from 1995 to 2013 and using databases like PubMed and GeneMania. Genetic association with SCZ was tested using a sample of 9,490 subjects from the Psychiatric Genomics Consortium. Their genetic analyses found the following four genes to be relevant in SP and SCZ: DLG1 (Discs, large homolog) subserves synaptogenesis, signal transduction, cell proliferation, adherens junction assembly, and alteration of neuronal environment through glutamatergic and astrocyte activation. NOS1 (Nitric oxide synthase) codes for an enzyme that produces nitric oxide, which acts as a neurotransmitter and regulates neuron environment modifications and pruning. The gene is also associated with structural changes in the brain in SCZ. THBS4 (Thrombospondin) encodes an extracellular adhesive glycoprotein involved in cellular interactions, including migration (which is involved in pruning), neuronal development, and response to CNS injury. The protein also binds to ECM components important in SCZ and pruning. FADS1 (Fatty acid desaturase) catalyses the biosynthesis of highly unsaturated fatty acids, maintaining membrane structure and playing a role in pruning and SCZ. Through cell line and regional brain expression analysis, these genes were found to be primarily expressed in (a) the neuropil, to which the brain volume shrinkage found in SCZ is usually attributed [65, 261–263]; and (b) hippocampus, where notable differences manifest early in life between normal individuals, those at-risk, and those who will be diagnosed with SCZ in the future [264–265].

MHC. Certain other genes have also been recently linked to SCZ because of their role in microglial SP. The MHC on chromosome 6 forms the genetic platform for innate and adaptive immune processes. Its relation with SCZ has been explained in a previous section. The MHC encompasses the prominent human leucocyte antigen (HLA) region, whose variations are associated with SCZ [247–250]. Such variations

are also linked to a smaller thalamus [251], which further correlates with negative and positive symptoms [252] and cognitive performance [253]. Marco et al. [8] observed that the HLA-C and HLA-DRA genes showed significantly more single-nucleotide polymorphisms in 24% and 17% of the sample of SCZ patients, respectively. These genes involved in immunity and inflammation can alter microglial functions, potentially affecting neuronal and axonal remodelling, apoptosis, and SP. This harkens back to the neuroinflammation/immunity theory of SCZ described before.

Kynurenic Acid. Also mentioned before, Orhan et al. [188] found that kynurenic acid, an endogenous NMDAR antagonist usually elevated in the brains of SCZ patients, decreases neural activity and increases microglial SP. Additionally, by integrating large transcriptomic and genetic datasets, they demonstrated that the gene co-expression networks for KYNA-producing enzymes, namely the kynurenine aminotransferases (KATs), are independently enriched for genes involved in synaptic activity (including those coding for NMDAR subunits and α7nAchR) and common genetic risk variants for SCZ.

CYFIP1. The CYFIP1 gene, located in the 15q11.2 neurodevelopmental risk locus, encodes a protein that regulates actin cytoskeletal dynamics and is involved in dendritic complexity maintenance and mature spine stabilisation; it is also associated with SCZ [254]. Sheridan et al. [165] investigated its role in human microglial function by generating multiple CRISPR knockouts in patient-derived microglia models. They found that loss of CYFIP1 significantly reduced synaptic vesicle phagocytosis, altered microglial morphology to a more ramified (resting or surveillant) state, and decreased microglial motility. Drew et al. [255] also reported that conditional knockout of CYFIP1 in mice microglia led to impaired surveillance due to reduced mobility. However, they also reported decreased process ramification and increased activation marked by elevated CD68 expression. Additionally, CYFIP1 deletion or haploinsufficiency in mice results in defective neuronal morphology, plasticity and connectivity [254, 256–260].

D. Environmental Factors

Psychosocial. Among the most well-known postnatal environmental risk factors for SCZ are psychosocial. These include low socioeconomic status, first- or second-generation migrant status, social and material deprivation, social adversity, stressful life events, and adverse childhood experiences such as emotional, physical, and sexual abuse, mental illness in household members, bullying and collective violence, and emotional neglect [2, 15, 266]. Sheridan & McLaughlin [267] conceptualise such adverse experiences on two dimensions: threat and deprivation, which we shall consider as the primary themes among these overlapping factors. Although there is a paucity of studies that directly correlate these risk factors with markers of SP, specifically in SCZ patients, the impact of threat and deprivation on neurodevelopment—particularly SP—has been widely studied, allowing only indirect inference of associations between the aforementioned risk factors and SP.

Deprivation is defined by Sheridan & McLaughlin [267] as “the absence of expected environmental inputs in cognitive (e.g., language) and social domains as well as the absence of species- and age-typical complexity in environmental stimulation” (p. 13). Such deprivation may be experienced by children, preteens, and adolescents exposed to limited educational and recreational resources due to poverty; and few or poor social interactions due to discrimination, language barriers, or parental/caregiver neglect. Given the importance of neural activity for activity-dependent SP [3], both animal and human studies have shown that such deprivation accelerates and intensifies synaptic elimination, resulting in markedly reduced synapses per neuron, dendritic branching, and cortical thickness [141, 268–270]. As discussed before, these structural changes co-occur with deficits in learning and memory also found in SCZ patients.

A threat, according to Sheridan & McLaughlin [267] involves "the presence of an atypical (i.e., unexpected) experience characterised by actual or threatened death, injury, sexual violation, or other harm to one's physical integrity" (p. 13). SCZ risk factors such as social adversity, community violence, stressful life events, and physical or sexual abuse, combined with the resulting stress response, may confer significant deviations from normal neurodevelopment, which align with results from neuroimaging data from SCZ patients. Exposure to threat, stress, and fear has been linked, in both animal and human models, to faster brain maturation [2, 141, 267]; reduced hippocampal volume, dendritic branching, and spine density in the hippocampus and PFC [141, 267]; blunted LTP in the hippocampus [267]; and aggravated microglial synaptic elimination in the PFC (but attenuated in the hippocampus [271–272]) through microglial overactivity and elevated C3 [274]. Exposure to early-life adversity and deprivation also impairs cognitive flexibility and associative learning [268, 270, 273], deficits that are also observed in SCZ patients [275–276] and may be a consequence of heightened SP at the cost of synaptic plasticity. Early childhood adversity can also make individuals more sensitive to stress during adolescence (see Smith & Pollak [277] for a detailed discussion), amplifying its deleterious effects on SP and contributing to the onset of SCZ. Furthermore, besides the valence of these psychosocial experiences, their frequency also influences SP. Chronic and repeated exposure to the same set of stimuli also trades synaptic plasticity with SP as the brain's circuits refine to handle the (unvarying) demands of the environment [141]. During early development, inhibitory neurotransmission progressively increases [278]. The heightened plasticity characteristic of a critical neurodevelopmental period concludes when PV+ inhibitory interneurons mature and perineuronal nets (PNNs) form [279]. Exposure to early-life adversity decreases the number of PV+ interneurons and later leads to increased PNN accumulation around these cells, indicating reduced plasticity [280–281]. A reduction of PV+ interneurons was also found in the PFC of SCZ patients in a meta-analysis of post-mortem studies [282]. Moreover, as discussed earlier, Parellada and Gassó [82] theorised that the hypoactivation of said interneurons plays a crucial role in heightened synaptic elimination and the aetiology of SCZ.

Immunological. Another class of SCZ risk factors implicates the immune system, encompassing prenatal infections and prenatal exposure to maternal infections, the risk for which may be elevated by urban upbringing and gestation in the winter, also considered SCZ risk factors [283]. This association may be explained by immune system activation (including induction of immunity-related genes such as the MHC; [284]), resulting in heightened microglial reactivity and, subsequently, microglial engulfment of synapses [285–288]. In addition, increased pro-inflammatory genes in the cortex and hippocampi of SCZ patients may predispose their microglia to abnormally high activation [285]. A more permeable blood-brain barrier, microglial activation, and increased IL-6 and IL-1β (also implicated in SP, as mentioned previously) may mediate the relationship between maternal immune activation and SCZ [170]. IL-1β activates the pro-inflammatory M1 state of microglia, also triggered following neuronal injury ([289]; thereby also partly explaining the relationship between foetal hypoxia or other obstetric complications and SCZ risk [283, 290–291]). The dominance of the M1 state, coupled with an extended inflammatory response, results in the overproduction of pro-inflammatory cytokines and reactive oxygen species, ultimately causing synaptic loss and neuronal death [292]. Further, consistent with the diathesis-stress hypothesis of SCZ, perinatal activation of microglia may also make them vulnerable to overactivation by stressors experienced later in life, ultimately encouraging a shift to a pro-inflammatory M1 state [289].

In addition to disease and injury, social stress can also trigger the immune system and microglia-mediated SP in frontocortical and limbic circuits [293–295], whereupon the psychosocial and immunological risk

factors converge. Social stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, both of which influence microglia and their reaction to stress [296–297], including heightened reactivity to later stress due to prior stress [298]. The adrenal cortex releases glucocorticoids in response to HPA axis activation. Since microglia express glucocorticoid receptors, high glucocorticoid levels can activate microglia, while mediators released by activated microglia can stimulate the HPA axis, producing a vicious cycle [299]. Further, elevated glucocorticoid levels correlate with the release of pro-inflammatory cytokines such as the interleukins [298], whose role in SP and SCZ was explained previously. At least two mechanisms link stress, microglia, and SP [298]. First, CX3CR1, the fractalkine receptor on microglia, is increasingly expressed in the cortex as a result of stress, while CX3CR1 knockout in mice enhances microglial engulfment and prevents further stress-induced modulation. Its deletion disrupts hippocampus-mPFC connectivity, impairs social interaction, and links microglia-driven SP to neuropsychiatric disorders. CX3CR1 is significantly downregulated in SCZ patients' blood and brain [300]. Second, and as stated previously, C3–C3R signalling tags synapses for microglial engulfment. Chronic stress elevates C3 and C3R levels, accelerating synaptic elimination [298]. Additional neurobiological effects of chronic stress include loss of dendritic spines and synapses, and these effects are associated with stress-induced cognitive-behavioural impairments such as anhedonia and working memory deficits (summarised in [156]).

Treatments. Several interventions for SCZ, such as cognitive remediation therapy (CRT), cognitive enrichment therapy (CET), and social skills training, aim to alleviate cognitive deprivation and promote synaptic plasticity. In early-course psychosis patients, CET preserves GM volume in the left hippocampus, parahippocampal gyrus, and fusiform gyrus and these neuroprotective effects correlate with improved cognitive outcomes [301]. CRT improves verbal fluency and increases hippocampal volume [302]. It is also associated with better functional neuroimaging outcomes, such as enhanced frontal, parietal, and occipital activation and resting-state functional connectivity [120]. Environmental enrichment has been linked to enhanced plasticity and cortical remodelling through microglial engulfment of PNNs; socially-driven oxytocin boosts; and secretion of dopamine, serotonin, and noradrenaline [141]. Thus, these interventions may reverse excessive synaptic loss and/or prevent further deterioration. Interventions targeting stress and well-being have also been investigated, with integrated coping awareness therapy, mindfulness-based stress reduction, and cognitive-behavioural therapy showing promising results [303–305]. However, investigations on the neural and cognitive changes resulting from these therapies are rare. One such trial reported that differences in brain activations between patients and controls were ameliorated by CBT targeting 'jumping to conclusions' and attributional biases, a prominent cognitive style in patients that can produce delusions [306]. Additionally, whether the aforementioned interventions mitigate excessive peri-adolescent SP is unknown. Longitudinal studies should follow a sample of healthy children, children showing early signs of psychosis without treatment, and children with early signs of psychosis receiving the aforementioned therapies into late adolescence and compare the structural, functional, and cognitive outcomes of these three groups.

IV. CONCLUSION

This paper narrates the literature on a variety of factors and mechanisms related to SP to various degrees of closeness. We aspired to delineate the broad span of this hypothesis and thereby the ideas it offers to future investigations. SCZ is a complex disorder with several evidence-based theories explaining it, but no single unified framework has been developed to date. Thanks to its diffuse nature, SP seems to be a

point of convergence for some of the aetiologic mechanisms proposed so far, namely genes, immune dysfunction, neuroinflammation, neural dysconnectivity, compromised plasticity, hyper- and hypo-glutamatergic states, and environmental influences. However, the same diffuse nature also allows it to overlap with competing mechanisms that may manifest similarly, such as deficient synaptogenesis, high synaptic apoptosis, excitotoxicity, and enfeebled cytoarchitecture. It is important to note that SP cannot yet be directly observed in vivo; our current understanding relies largely on indirect measures from neuroimaging and postmortem studies. Nonetheless, the developmental basis of SP gives us hope that attempts to correct it in children at risk or showing early signs of psychosis may lead to a less severe and debilitating form of SCZ. For SP to become a reliable target of interventions, future research would need to disentangle it from competing mechanisms and fortify its importance in SCZ by investigating it through a variety of tools and designs, especially longitudinal studies.

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