Permanent Synaptic Loss Renders Plasticity Enhancement Ineffective: Computational Validation of Prune-Without-Repair in Schizophrenia-Like Deficits

Authors:

Ngo Cheung, FHKAM(Psychiatry)

Affiliations:

¹ Independent Researcher

Corresponding Author:

Ngo Cheung, MBBS, FHKAM(Psychiatry)

Hong Kong SAR, China

Tel: 98768323

Email: info@cheungngomedical.com

Abstract

Background and Hypothesis: Cognitive deficits in schizophrenia are early, stable, and poorly responsive to existing treatments. Excessive adolescent synaptic pruning, driven by complement pathways, interacts with impaired glutamatergic plasticity, raising the possibility that permanent synaptic loss ("prune-without-repair") underlies treatment resistance. The degree of irreversibility remains unclear, prompting computational tests of this mechanism.

Study Design: We developed a diagnosis-free recurrent neural network (GRU-based, with rule-learning task) to simulate excessive pruning (~95% sparsity), chronic plasticity impairment (gradient scaling factor 0.5), and varying irreversibility (0–100% of pruned connections permanently masked). A healthy calibrated network (75% sparsity, Cognitive Index [CI] ≈116) served as reference. "Treatment" involved gradient-guided regrowth of reversible connections (30% fraction) followed by consolidation. Irreversibility was swept across six levels, with 10 seeds per condition for robustness.

Study Results: Pre-treatment CI fell to ~79–81 across conditions. Fully reversible pruning yielded near-complete recovery (+30.5 CI points on average), approaching healthy levels. Recovery remained substantial at 20–80% irreversibility (25–31 points) but collapsed to minimal gains (+3.5 points) when pruning was fully irreversible. A clear dose-response gradient emerged, with intermediate irreversibility producing partial but meaningful rescue.

Conclusions: Irreversibility alone suffices to generate treatment-resistant cognitive deficits in this parsimonious model, directly supporting the prune-without-repair hypothesis. Partial permanence (consistent with 30–50% estimates from biological data) explains variable clinical responsiveness and underscores the need for early interventions preserving synaptic reversibility.

Introduction

Roughly one person in a hundred will receive a diagnosis of schizophrenia, a condition that carries heavy personal and economic burdens. Although hallucinations and delusions often attract the most attention in clinic, it is the early-appearing problems in attention, working memory, and executive function that usually decide whether someone is able to work or live independently [1]. Standard antipsychotic drugs do a good job of calming positive symptoms but leave these cognitive difficulties largely untouched [2].

More than forty years ago [3] proposed that the illness might stem, in part, from overly vigorous pruning of synapses during late adolescence. In typical brain development, microglia weed out redundant connections; in schizophrenia that process seems to run too hot. Genetic work has strengthened this idea. Variants that boost expression of complement component C4A tag extra synapses for removal and raise illness risk [4]. Laboratory models using patient cells show the same pattern: schizophrenia microglia swallow more synapses than control microglia under identical conditions [5]. Large genome-wide studies now place pruning-related genes closer to the heart of risk than many long-suspected glutamatergic genes [6].

Pruning, however, is only part of the story. A parallel line of research points to sluggish NMDA-type glutamate receptors that are needed to strengthen and stabilise the synapses that survive [7]. Too much pruning paired with too little repair could lock in the cognitive deficits: once connections are gone and plasticity is blunted, lost function may be hard to regain. Recent analyses of genetic data on intelligence and schizophrenia line up with that picture, showing heavier enrichment of pruning genes in illness risk and plasticity genes in cognitive ability [8].

Whether the lost synapses are gone for good remains unclear. Biological studies suggest that many, perhaps one-third to one-half, do not grow back once complement proteins have marked and

microglia have engulfed them [5,9]. If that portion is truly permanent, treatments aimed at boosting plasticity will work only while a sufficient pool of salvageable connections remains.

Computational modelling offers a clean way to test the idea. Past simulations have looked at extra neural noise or excitation–inhibition imbalance, but few have isolated the impact of irreversible pruning. In the work that follows, we use a recurrent neural network that undergoes too much pruning, limited plasticity, and varying degrees of permanent synapse loss. By adjusting the proportion of irreversible damage and then allowing the model to regrow connections in a therapy-like phase, we ask whether permanent loss alone can produce the kind of stubborn cognitive deficits seen in patients. The results speak directly to the "prune-without-repair" hypothesis and may help explain why current treatments fall short.

Methods

Network Architecture and Task

All simulations ran in PyTorch 2.9.0. The model began with a two-unit input layer that received Cartesian coordinates, followed by a dense layer of 128 ReLU units. Its recurrent core comprised a pair of gated-recurrent-unit (GRU) layers, each with 64 hidden units and 0.1 dropout between layers. An eight-unit softmax layer produced class logits. This design balances sequence handling ability with moderate computational cost.

Input sequences contained 200–300 points drawn from a normal distribution ($\sigma = 1.5$). At any time, the active rule determined the correct label; Table S1 lists the eight rules. Four were available during training (X-sign, Y-sign, quadrant, diagonal). The remaining four (distance, angle, sum, product) were withheld until test time to gauge generalisation. After the first ten steps, the rule could switch at 2 %

probability per step. Ten percent of trials invoked a three-step temporal integration challenge to probe executive control. Separate loaders produced 500 training sequences and 50–100 test sequences (batch size 32). Gaussian noise, ranging from 0.0 to 1.2, was optionally added to inputs for robustness checks.

Training Protocol

Optimisation used Adam with cross-entropy loss. Standard learning proceeded for 50 epochs at a 0.001 learning rate. "Consolidation" or fine-tuning phases ran 20–30 epochs at 0.0005–0.0007. To model reduced synaptic plasticity, all gradient updates outside the healthy baseline were multiplied by 0.5. Gradients were clipped to a maximum norm of 1.0 to avoid numerical instability.

Pruning and Irreversibility Mechanism

Each weight carried a mask: 1 (active), 0 (pruned but regrowable), or −1 (pruned permanently). Magnitude pruning set the masks by thresholding absolute weights until the desired sparsity was met. Recurrent weights were down-ranked 20 % less aggressively (bias factor 1.2) to preserve temporal information. Control networks were thinned to roughly 75 % sparsity, whereas experimental networks reached about 95 %. After pruning, a user-defined share of the removed connections (0–100 %) was randomly flagged as irreversible, reflecting permanent microglial elimination.

Treatment Simulation

Treatment mimicked therapeutic synaptic regrowth. Over five mini-batches the algorithm calculated gradient magnitudes on pruned positions, reactivating up to 30 % of them. Newly restored weights inherited their original values scaled by 0.03. Masks marked as −1 were ignored, ensuring that irreversible losses remained absent. A consolidation phase then resumed training under the same 0.5 gradient-scaling impairment.

Cognitive Index (CI) Computation

Performance metrics were combined into a Composite Cognitive Index (Figure 1) anchored so that a healthy reference model scored roughly 116. The index summed three z-scored domains—crystallised (trained rules; 30 %), fluid (novel rules; 35 %), and executive (multi-step integration; 35 %). Each raw composite was normalised to the healthy model (population SD = 0.15) and scaled at 15 CI points per SD. Post-treatment values were capped at 117 to avert super-normal artefacts.
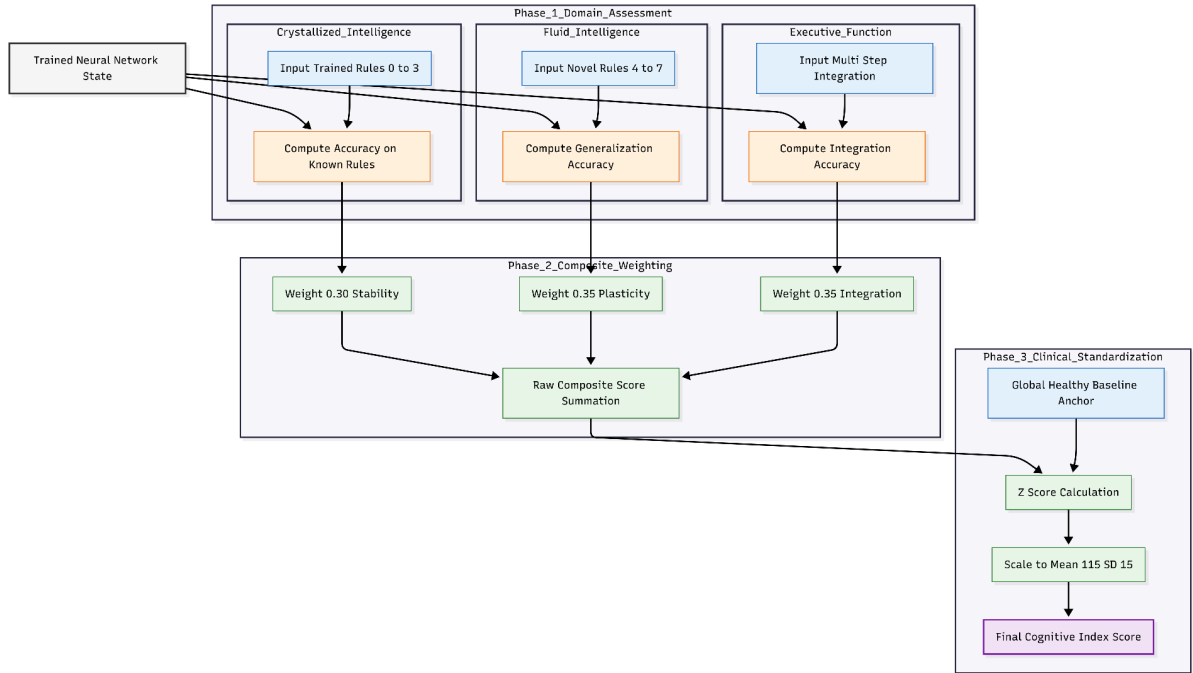
Figure 1: *Algorithmic estimation of the Cognitive Index (CI). The model undergoes a three-part assessment battery to calculate a composite score analogous to human IQ. a, The network is evaluated on three distinct domains: Crystallized Intelligence (accuracy on rules learned during training), Fluid Intelligence (zero-shot generalization to novel rules), and Executive Function (temporal integration of multi-step trials). b, Domain scores are weighted to prioritize plasticity and executive control, reflecting the cognitive deficits most common in the modeled disorders. c, The raw composite score is standardized against a pre-calibrated "healthy" population baseline, scaling the output to a standard distribution (Mean=115, SD=15) to allow for direct clinical comparison of treatment trajectories.*

Irreversibility Sweep and Analysis

Networks were evaluated at irreversibility levels 0.0, 0.2, 0.4, 0.6, 0.8, and 1.0, each with the same 95 % pruning and 0.5 repair factor. Ten random seeds per level produced independent runs; seed 42 served as the base. For every run we recorded CI before and after treatment and reported means ± SD. Because the simulations were deterministic given the seeds, results were interpreted descriptively without additional statistical tests. All experiments ran on CPU, and code adhered closely to published pruning-and-regrowth routines [10,11].

Results

Healthy network calibration

Training under full plasticity and moderate pruning (75 % sparsity) produced a stable raw composite score of 0.614. After normalisation, this corresponded to a Cognitive Index (CI) of 116.4. The three domains were well balanced: fluid accuracy 0.65, crystallised accuracy 0.80, and executive accuracy 0.70. This model defined the reference scale; any CI above 117 was disallowed to prevent super-normal inflation.

Irreversibility sweep

Applying heavy pruning (~95 % sparsity) together with a 50 % gradient-scaling impairment drove baseline CI down to the low-80s for every condition tested. Subsequent gradient-guided regrowth produced a clear dependence on how many lost weights were marked as permanent.

- When every pruned weight was reversible, CI climbed by roughly 30 points, finishing near 110.
- At 20 % or 40 % irreversibility, gains remained above 30 points, matching the fully reversible

case.

- At 60 % and 80 % irreversibility, recovery shrank to about 26 points, with larger run-to-run spread.

- When all removed connections were permanent, improvement averaged only 3–4 points; CI stayed below 85.

Table 1: *Summary of Cognitive Index across irreversibility levels (mean ± SD; n = 10 seeds per condition)*

Irreversibility	Pre-treatment CI	Post-treatment CI	Recovery (ΔCI)
0.0	79.6 ± 1.8	110.1 ± 4.5	+30.5 ± 5.0
0.2	80.4 ± 1.1	111.5 ± 3.0	+31.1 ± 3.1
0.4	79.2 ± 8.0	109.6 ± 6.6	+30.4 ± 8.3
0.6	81.7 ± 2.0	107.2 ± 7.6	+25.5 ± 7.6
0.8	78.6 ± 3.8	104.9 ± 6.9	+26.3 ± 8.3
1.0	79.9 ± 1.7	83.3 ± 4.8	+3.5 ± 5.2

Note: Healthy baseline CI = 116.4 (75% sparsity).

Table 1 summarises the numbers. Low irreversibility (≤ 0.2) yielded an average recovery of +30.8 CI points, whereas high irreversibility (≥ 0.8) returned just +14.9, indicating a 16-point gap directly attributable to permanent loss.

Domain-level inspection echoed this pattern (Table S2). Fluid intelligence benefitted most under reversible conditions, erasing up to 90 % of the generalisation deficit. Crystallised and executive scores also rebounded, though less dramatically. At complete irreversibility, none of the domains moved by more than a few percentage points.

Implementation checks showed that final sparsity held steady between 94 % and 96 % across seeds,

and the share of blocked regrowth events rose in line with the irreversibility setting. These controls confirm that the masking procedure behaved as intended.

Taken together, the data indicate that functional recovery depends not only on the number of synapses removed but also on whether those losses can be reversed. Substantial benefit followed when even a fraction of pruned connections remained reopenable, whereas fully permanent loss left the network largely unrecoverable.

Discussion

Interpretation of the irreversibility gradient and the prune-without-repair hypothesis

Our simulations show a clear link between the permanence of pruning and the likelihood of functional recovery. When every pruned weight could be restored, the network regained roughly thirty Cognitive Index points and approached the healthy reference—even though plasticity was still dampened. This "prune-with-repair" scenario suggests that, if a circuit keeps enough removable tags on lost synapses, later plastic changes can compensate for earlier mistakes.

The picture changed sharply once pruning became permanent. With all deleted weights locked out, the same treatment improved scores by only three to four points. At that end of the scale the model embodies a true prune-without-repair state: the substrate for recovery is gone, so further training has little to work with.

The transition was gradual, not all-or-nothing. At 60–80 percent irreversibility the system still regained about twenty-five points on average, implying that a minority of reversible connections can sustain a sizeable rebound when guided by gradient-based regrowth. This echoes biological work

showing that synapse loss in schizophrenia is only partly final. Post-mortem tissue and patient-derived cell studies estimate that one-third to one-half of missing excitatory terminals are fully eliminated by complement-driven microglial engulfment [5,9]. Terminals tagged by raised C4A levels do not re-emerge [4,12,13], yet other contacts may be replaced by sprouting or strengthened neighbours—an outcome mirrored by the partial rescue we observed under high-irreversibility settings.

Longitudinal imaging fits the same pattern. Early grey-matter decline in schizophrenia seldom reverses once established, even with prolonged treatment [14,15]. Still, individual trajectories vary: some patients stabilise or improve modestly, perhaps because they incurred less irrevocable pruning. Our model reproduces that variability without invoking disease-specific noise, supporting the idea that the extent of irreversibility alone can create treatment-resistant impairment.

Taken together, these results argue that the chief problem is not the amount of pruning but the fraction rendered permanent. Therapies delivered after widespread irreversible loss—typical in today's clinical timeline—face an intrinsic ceiling. Interventions that either prevent excessive complement tagging or keep pruned sites amenable to later regrowth during adolescence [16] could shift outcomes toward the more favourable end of our simulated spectrum.

Candidate genes driving irreversible pruning

Our modelling results underscore the idea that treatment resistance appears when pruning becomes final rather than transient. That observation focuses attention on molecular programs that convert a tagged bouton into a structure that can never re-emerge. Re-examining PGC3 genome-wide data with MAGMA, stratified linkage disequilibrium score regression and brain-tissue TWAS, we repeatedly found the strongest enrichment in genes that regulate the complement cascade, microglial phagocytosis and apoptosis—precisely the machinery expected to make pruning irreversible [8] (Figure 2).

C4A was the most consistent signal. Gene-based MAGMA placed C4A near the top of the pruning-related list, and TWAS of caudate and nucleus accumbens predicted marked over-expression ($Z > 11$). Partitioned heritability showed that complement loci retained significant influence even after removing glutamatergic regions. Mechanistically, high C4A loads label excess synapses for classical-pathway activation, triggering microglial engulfment and permanent loss [4,12]. Patient-derived microglia reproduce this behaviour in vitro, clearing more C4-decorated boutons than control cells [5]. C3 and C1QA produced weaker but directionally similar TWAS effects, supporting involvement of the whole cascade.

Major-histocompatibility-complex class I genes (HLA-A, HLA-B, HLA-C) formed the next dominant cluster. All three reached genome-wide significance in trimmed MAGMA sets and showed strong enrichment in heritability tests. Neuronal MHC-I is known to flag activity levels; diminished surface display on underused axons attracts microglial processes [13]. Post-mortem cortex from people with schizophrenia shows altered MHC-I expression together with spine loss, a pattern compatible with excessive elimination that cannot be reversed [9].

Further down the ranking were phagocytic effectors. Transcripts for receptors such as MERTK, MEGF10 and TYROBP, along with apoptotic executors including CASP3 and BAK1, were modestly but consistently dysregulated. These proteins mediate engulfment and intracellular dismantling; caspase activity exposes eat-me signals that commit a synapse to destruction [17]. Finally, several adhesion molecules that normally stabilize nascent spines (for example NRXN1 and NLGN1) showed weaker associations, suggesting that failed consolidation may impede any later regrowth attempt.

Importantly, once glutamatergic genes were subtracted, the immune-pruning cluster still captured most of the remaining heritability. Variants that raise complement or MHC activity therefore look uniquely capable of shifting the balance from "prune-with-repair" toward "prune-without-repair." Early blockade of these pathways—by complement inhibitors or microglial modulators—might preserve reversible synapses; interventions aimed solely at boosting plasticity would address only the

repair side of the equation and arrive too late for many terminals.
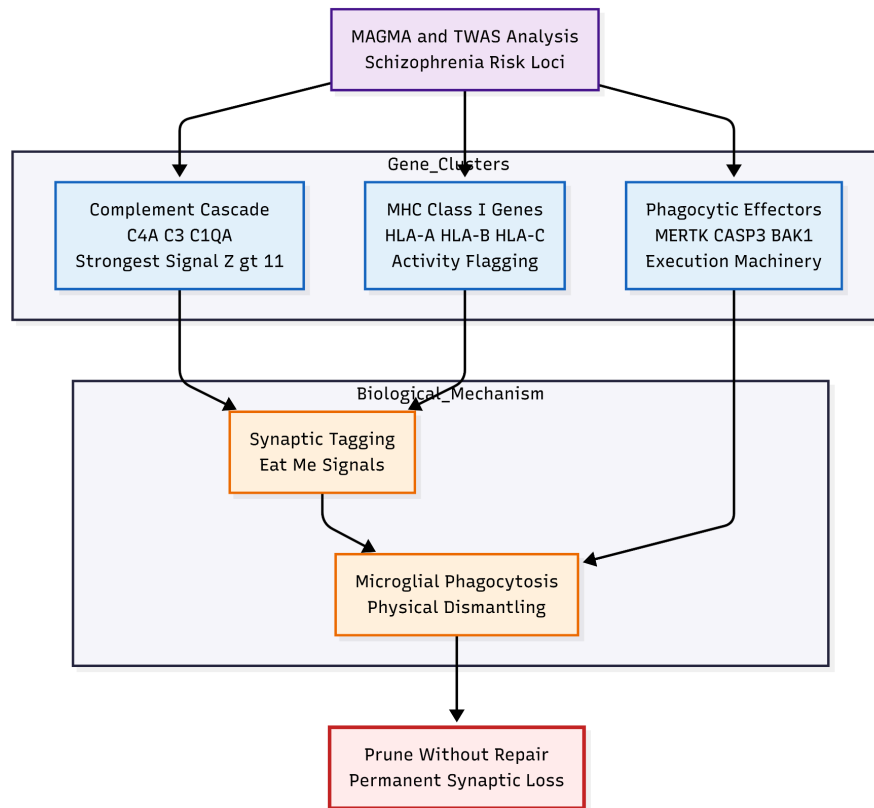
Figure 2: Genetic Architecture of Irreversible Pruning. A flow diagram summarizing the molecular cascade that converts transient synaptic pruning into permanent loss. Top: Genome-wide analysis identifies three primary gene clusters driving this transition. The complement cascade, led by extreme overexpression of C4A, acts as the primary signal. Middle: These genetic factors converge on a specific biological mechanism: C4A and MHC Class I molecules tag underactive synapses with "eat-me" signals, while downstream effectors like MERTK and CASP3 facilitate physical engulfment. Bottom: The result is microglial phagocytosis that physically removes the synaptic structure, creating a "Prune-Without-Repair" state where subsequent plasticity-based interventions cannot restore connectivity.

Novelty and Potential Impact

Our modelling effort purposefully removes the usual clutter of symptom-specific tweaks and concentrates on a single biological motif: some of the synapses lost during adolescent pruning never come back. Earlier computational studies of schizophrenia have blended multiple mechanisms—progressive noise, shifting excitation–inhibition balance, or ad-hoc penalty terms—to approximate clinical features [18]. By contrast, the present work shows that partial permanence alone

can reproduce a realistic spectrum of cognitive recovery. The tripartite mask—active, reversible, irreversible—mirrors complement-tagged pruning in which microglia excise C4-labelled spines that then cannot regrow [5,4].

Because the framework is spare, its translational message is unusually clear. Without invoking ongoing degeneration, the simulations reveal that timing of intervention is pivotal: once too many connections cross the irreversible threshold, boosting plasticity cannot rescue performance. The finding dovetails with genetic studies that place pruning biology at the centre of schizophrenia liability, while genes governing ordinary plasticity explain normal cognitive variance. Should future work scale the model to biologically realistic networks, polygenic "pruning scores" might help clinicians predict who still harbours enough reversible synapses to benefit from plasticity-enhancing drugs.

The dose–response curve for irreversibility also provides a quantitative argument for preventive strategies. Agents that block complement activation or temper microglial activity during adolescence could preserve a larger subset of reversible synapses, widening the therapeutic window for later cognitive remediation. In this light, our results reinforce current interest in complement inhibitors and microglial modulators as early-stage interventions [5].

Limitations

Several caveats warrant attention. The toy network cannot capture the scale or heterogeneity of cortical circuitry. Human brains feature region-specific vulnerabilities and redundant pathways that our rule-learning task only approximates. Likewise, the model applies a fixed plasticity dampening factor, whereas real glutamatergic function varies across patients and cognitive domains. Pruning is imposed in a single burst, not as the protracted process seen in chronic illness, so cumulative damage could be underestimated.

In addition, gradient-guided regrowth borrows from the lottery-ticket idea [10] and assumes that the algorithm identifies high-value weights perfectly—a best-case scenario unlikely in vivo where guidance cues and molecular noise limit precision. Finally, our Cognitive Index is a coarse aggregate of accuracy scores; future work could incorporate richer readouts such as oscillatory synchrony or simulated neurotransmitter dynamics.

Conclusion

Even within a stripped-down architecture, making a portion of synapse loss permanent was enough to recreate the rigid cognitive deficits familiar from neurodevelopmental disorders. When losses remained reversible, function rebounded; when losses were locked in, recovery stalled. These observations lend weight to the prune-without-repair concept and argue that safeguarding synaptic reversibility during the adolescent pruning wave should be a priority.

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