Structural Rebuilding Confers Superior Long-Term Resilience: A Unified Multi-Mechanism Computational Comparison of Antidepressants in Chronic Stress

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

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Abstract

Background: Major depressive disorder remains inadequately treated in many patients, with divergent onset speeds and durability across antidepressant classes. Emerging neuroplasticity frameworks emphasize synaptic loss, yet direct computational comparisons of glutamatergic (ketamine-like), monoaminergic (SSRI-like), and GABAergic (neurosteroid-like) mechanisms—particularly under chronic stress—are lacking.

Methods: We extended a pruning-plasticity model by applying 95% magnitude-based synaptic elimination to overparameterized feed-forward networks trained on Gaussian cluster classification. From identical pruned states, three interventions were tested across 10 stochastic seeds: ketamine-like gradient-guided regrowth (50% reinstatement) with consolidation; SSRI-like prolonged low-learning-rate refinement with gradual noise reduction; and neurosteroid-like global tonic inhibition (30% damping plus bounded activations). Outcomes included acute recovery, stress resilience (graded internal noise), acute relapse (additional 40% pruning), and longitudinal durability (eight cycles of 10% cumulative pruning with mechanism-specific maintenance).

Results: All treatments restored near-ceiling baseline performance, but resilience diverged: ketamine-like networks showed superior extreme-noise tolerance (81.7%) and zero acute/longitudinal relapse across seeds, despite rising sparsity. SSRI-like refinement yielded moderate gains (81.3% combined-stress acutely) but 40% seed relapse longitudinally. Neurosteroid-like inhibition matched early efficacy (97.8%) yet exhibited state-dependence and late-cycle vulnerability (20% seed relapse).

Conclusions: These simulations demonstrate mechanistically distinct routes—structural rebuilding (durable), gradual optimization (variable), reversible stabilization (rapid but fragile)—yielding predictive trade-offs in relapse risk. Findings support mechanism-based personalization, prioritizing synaptogenic agents for severe/chronic cases while rationalizing combinations for acute relief and

maintenance.

Introduction

Major depressive disorder (MDD) is one of the top drivers of global disability and carries heavy personal and financial costs [1]. Even with many drugs on the market, progress has stalled: only about a third of patients get well after an initial prescription, and roughly a third remain symptomatic after several different regimens [2]. Selective serotonin re-uptake inhibitors (SSRIs) still dominate routine care, yet these medicines often take weeks to work and may deliver only partial relief [3].

The hunt for faster and more dependable options has reshaped the field. Low-dose ketamine, an NMDA-receptor blocker, can lift mood within hours. The effect was known to be tied to bursts of synaptogenesis through BDNF- and mTOR-linked pathways [4,5]. Neuroactive steroids such as brexanolone and its oral analogue zuranolone increase tonic GABA_A inhibition and also act quickly, most clearly in postpartum depression [6]. These findings shift attention away from simple monoamine shortage toward problems in neural plasticity: chronic stress trims dendritic spines and synapses in prefrontal and hippocampal areas, leaving circuits fragile [7].

Computational models let researchers test how such circuit changes might play out. One influential idea treats depression as "too much pruning." The network still works under light load, but a small dose of extra noise makes it fail. Earlier work showed that letting the model regrow connections—an in-silico stand-in for ketamine—can restore stability without rebuilding every lost synapse [8]. What remains unclear is how different drug classes stack up when they are placed in the same framework. Do they differ in speed? Durability? Risk of pushing the system toward the opposite pole, as in a manic switch?

To explore those questions, we extended the pruning-plasticity model in a simple feed-forward classifier. From identical 95 % pruned starting points we applied three distinct interventions:

- a ketamine-like, gradient-guided regrowth routine;
- an SSRI-like, slow refinement with fading noise;
- a neurosteroid-like, global increase in tonic inhibition.

The protocol ran across ten random seeds and eight sequential "stress cycles," adding more pruning each time to mimic chronic relapse pressure. By following the same networks over time, we could compare recovery, stability, and switch liability side by side. The aim was to clarify how mechanism shapes outcome and to suggest when a given class might be the better clinical choice as rapid, plasticity-targeted treatments gain traction.

Methods

Network architecture and classification task

We built a small, fully connected feed-forward network to stand in for cortical circuitry. The model held two input units, three hidden layers (512, 512, 256 units) and four soft-max outputs. Hidden units used ReLU unless noted otherwise. After each hidden layer we could inject zero-mean Gaussian noise to mimic stress and, when needed, multiply activations by a global damping factor to imitate tonic inhibition.

The task was simple on purpose (Figure 1). Two-dimensional points were drawn from four Gaussian clouds centred at (−3, −3), (3, 3), (−3, 3) and (3, −3) with a standard deviation of 0.8. For every random seed we produced 12 000 training points, 4 000 noisy test points and 2 000 clean test points.

This layout let us watch accuracy fall as pruning and noise mounted, a laboratory version of latent vulnerability described in clinical work [8,7].

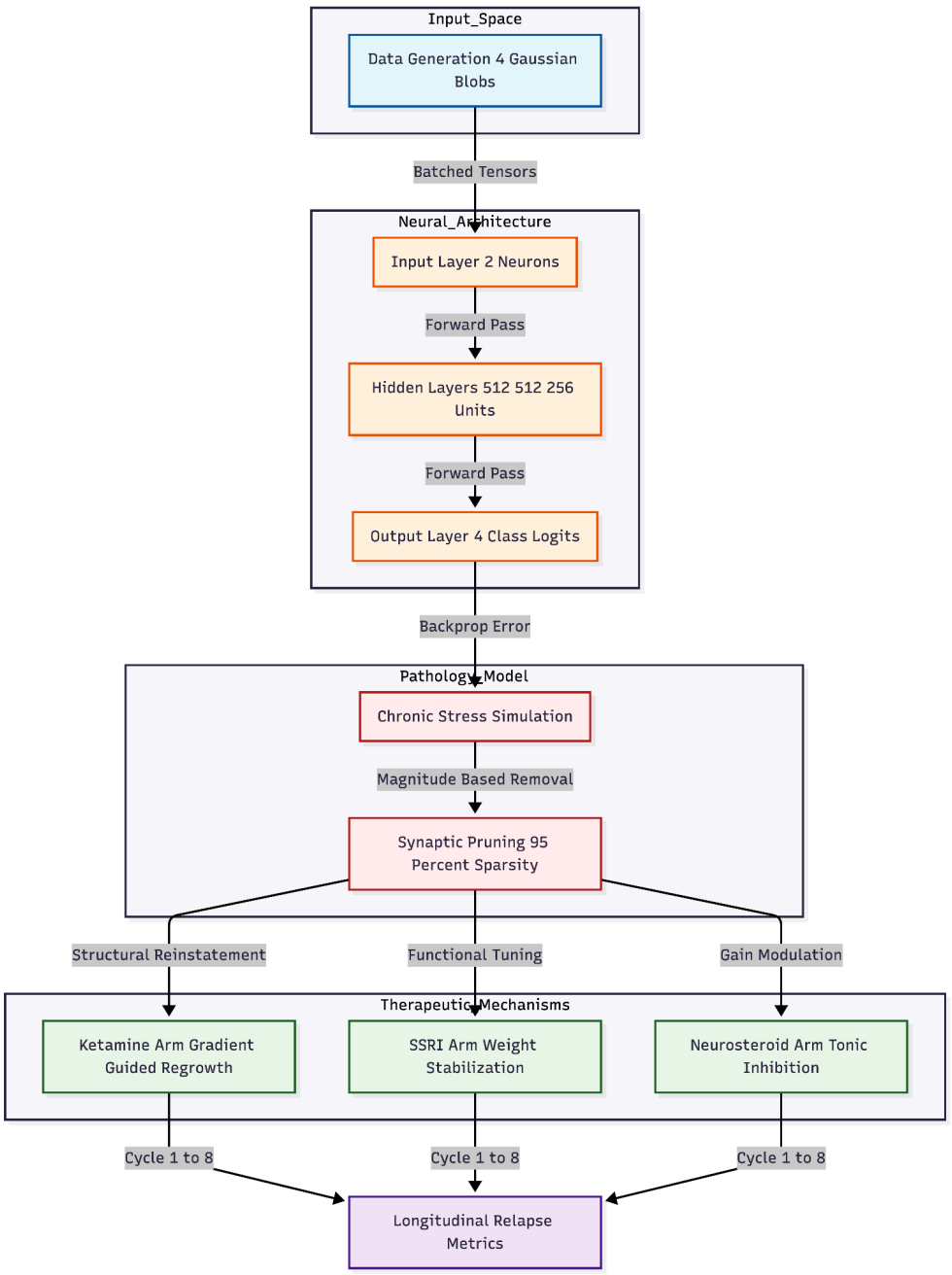

Figure 1: *Computational Architecture of the Multi-Mechanism Antidepressant Experiment. The diagram illustrates the information flow through the StressAwareNetwork. Synthetic classification data is fed into a feed-forward neural network. The "Pathology Model" simulates depression via chronic stress, resulting in severe synaptic pruning (95% sparsity). The network is then subjected to three distinct algorithmic interventions: Ketamine-like structural regrowth, SSRI-like functional weight stabilization, and Neurosteroid-like inhibitory modulation. The system evaluates the resilience of each mechanism against relapse over 8 longitudinal cycles of recurring stress.*

Baseline training and pruning

Weights were drawn from a small normal distribution and the network learned for 20 epochs with Adam (learning rate 0.001) on clean data. Once accuracy steadied, we lopped off the weakest 95 % of weights across all layers, leaving their sign intact. The result was a sparse "depressed" circuit that still did the job when inputs were noise-free but collapsed when perturbations appeared.

Antidepressant treatment protocols

Starting from identical pruned copies we imposed three separate recovery routines.

Ketamine-like synaptogenesis: For 30 mini-batches we collected gradient magnitudes at every pruned site. The top half of those locations were regrown with small random values (SD 0.03). Fifteen fine-tuning epochs followed (Adam, lr 0.0005) while the new sparsity mask stayed fixed.

SSRI-like gradual stabilisation: Sparsity remained at 95 %. The model trained for 100 epochs at a very low rate (1×10^{-5}). Internal noise began at σ 0.5 and faded linearly to zero, echoing the slow receptor and transcription shifts seen with monoaminergic drugs [9].

Neurosteroid-like tonic inhibition: We kept the 95 % mask but switched hidden activations to tanh and multiplied them by 0.7, reproducing the dampening effect of extrasynaptic GABA_A modulation. Ten consolidation epochs were run with Adam (lr 0.0005).

Evaluation metrics

After each intervention we measured accuracy on four test sets: clean, standard noisy, a combined-stress set (input noise σ 1.0 plus internal noise σ 0.5) and a sweep of internal noise from σ 0.0 to 2.5.

Acute relapse was probed by pruning a further 40 % of the remaining weights and retesting on the combined-stress set. For the neurosteroid condition we also checked accuracy after turning the damping factor off to see how much benefit depended on continued inhibition.

Long-term relapse under chronic stress

Durability was followed across eight stress cycles (Figure 2). Each cycle removed 10 % of the surviving weights, then applied a brief maintenance step that matched the original mechanism:

- ketamine-like, five fine-tuning epochs;
- SSRI-like, twenty very low-rate epochs with mild tapering noise;
- neurosteroid-like, ten epochs under active inhibition.

Combined-stress accuracy was recorded after every cycle. Dropping below 80 % marked a relapse.

Reproducibility and statistics

All experiments were repeated with 10 different random seeds that altered data draws, weight starts and noise streams. Means and standard deviations are reported; we also quote the range where it was informative. Code was written in PyTorch and run on a CPU; deterministic options were fixed whenever the library allowed.

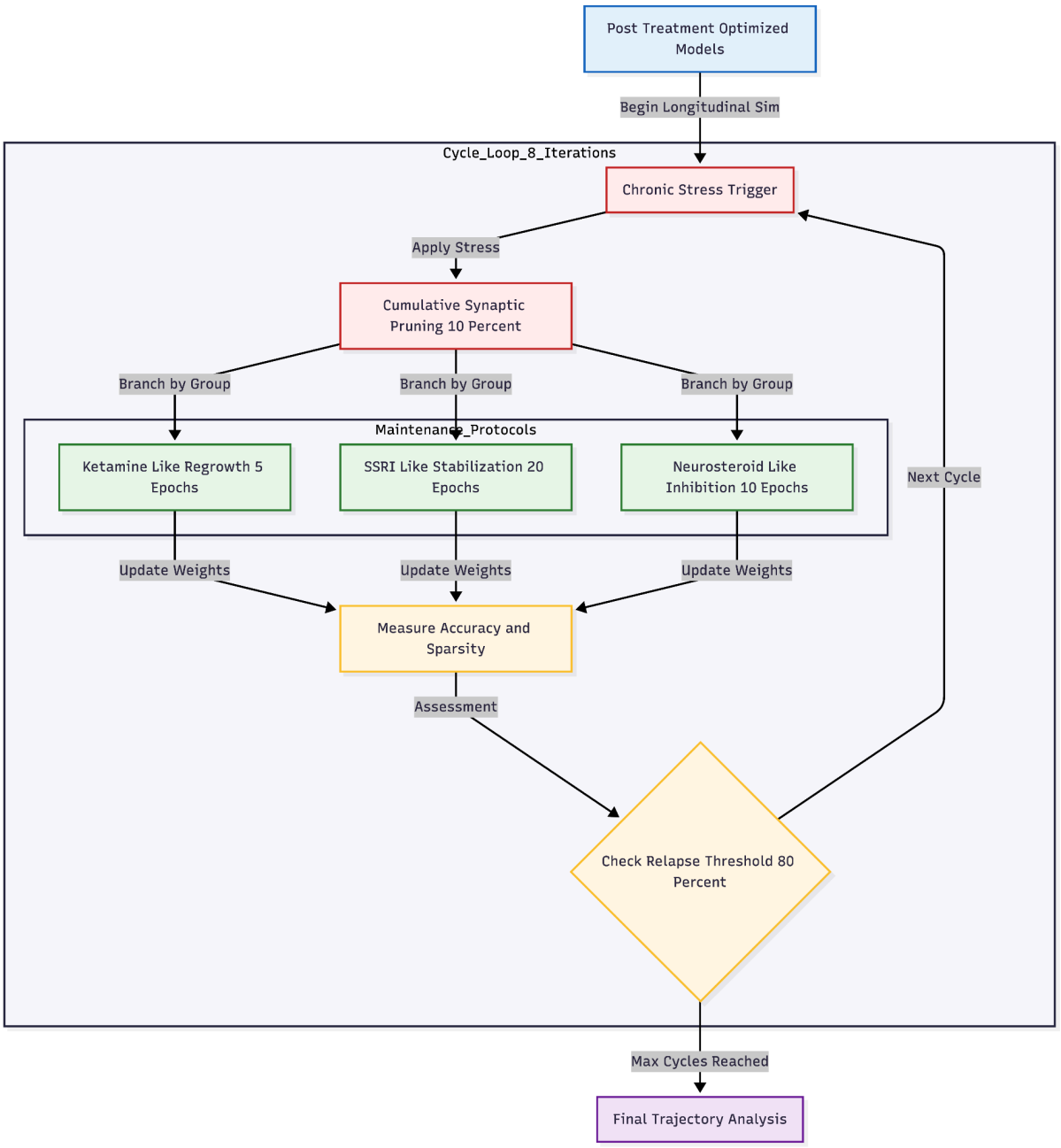

Figure 2: *Longitudinal Relapse Simulation Protocol. The diagram details the 8-cycle simulation used to evaluate long-term resilience. Initial post-treatment models enter a recursive loop representing the passage of time under adverse conditions. In every cycle, models undergo "Chronic Stress" (cumulative magnitude-based pruning removing 10% of remaining weights), followed by a mechanism-specific maintenance phase (periodic regrowth for Ketamine, stress-scheduled stabilization for SSRIs, or inhibitory consolidation for Neurosteroids). Relapse is defined as a drop in classification accuracy below 80%.*

Results

Post-treatment recovery and baseline efficacy

Before any rescue procedure the heavily pruned networks were barely functional: across ten seeds their accuracy under combined input and internal noise averaged 28.9 % (SD 2.4 %). Once an intervention was applied, performance on noise-free or mildly noisy data returned to ceiling levels. The ketamine-style regrowth and the neurosteroid-style tonic inhibition each produced perfect scores on both clean and standard noisy sets and almost full recovery under the combined-stress condition (97.3 % ± 0.2 and 97.8 % ± 0.1, respectively). The SSRI-style slow refinement helped far less. Although many seeds reached high values on clean inputs (mean 97.5 %, SD 7.6 %), their mean accuracy under combined stress was only 81.3 % (SD 8.8 %), revealing large between-seed spread (Table 1).

Table 1. *Post-Treatment Efficacy (Mean ± SD Across 10 Seeds)*

Treatment	Sparsity (%)	Clean (%)	Standard (%)	Combined Stress (%)
Untreated (pruned)	95.0 ± 0.0	32.1 ± 11.8	32.3 ± 11.0	28.9 ± 2.4
Ketamine-like	47.5 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	97.3 ± 0.2
SSRI-like	95.0 ± 0.0	97.5 ± 7.6	95.7 ± 8.0	81.3 ± 8.8
Neurosteroid-like	95.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	97.8 ± 0.1

Resilience to graded internal stress

When internal noise was increased stepwise, the three regimens separated sharply (Table 2). Ketamine-treated networks coped well even at the harshest perturbation level ($\sigma = 2.5$), still classifying 81.7 % (SD 3.0 %) of patterns correctly. The SSRI-treated and neurosteroid-treated models were similar up to moderate noise but both collapsed when noise became severe, each settling near 41–42 % accuracy. Untreated baselines hovered around chance throughout the sweep.

Table 2. *Stress Resilience Profile (Mean ± SD Accuracy)*

Treatment	No Noise (%)	Moderate (σ=0.5) (%)	High (σ=1.0) (%)	Severe (σ=1.5) (%)	Extreme (σ=2.5) (%)
Untreated (pruned)	32.3 ± 11.0	29.2 ± 2.8	29.2 ± 1.6	28.9 ± 1.5	27.8 ± 1.6
Ketamine-like	100.0 ± 0.0	99.9 ± 0.0	98.9 ± 0.7	95.3 ± 1.6	81.7 ± 3.0
SSRI-like	95.7 ± 8.0	85.0 ± 9.6	66.2 ± 7.7	53.8 ± 5.6	42.0 ± 3.1
Neurosteroid-like	100.0 ± 0.0	99.9 ± 0.1	91.6 ± 1.5	69.1 ± 2.0	41.2 ± 1.0

Acute relapse vulnerability

A sudden removal of 40 % of the surviving weights served as an acute relapse test. Ketamine-like models were almost unaffected, losing only 0.0 % on average (SD 0.4 %) from their combined-stress score. By contrast, SSRI-treated networks dropped 9.1 % (SD 5.8 %) and neurosteroid-treated networks dropped 6.9 % (SD 5.6 %).

Neurosteroid state-dependence

The benefit of the neurosteroid analogue depended on continued tonic damping. Once the damping factor was switched off, combined-stress accuracy fell sharply to 68.8 % (SD 9.9 %). Interestingly, tolerance of extreme internal noise improved slightly in this unmedicated state (51.9 % ± 2.8 versus 41.2 % ± 1.0 while medicated).

Longitudinal trajectories under chronic stress

Eight cycles of additional 10 % pruning, each followed by a mechanism-specific maintenance step, produced very different long-term pictures (Table 3). Ketamine-like networks held steady around 97.6 % combined-stress accuracy all the way to cycle 8 even though sparsity rose from 47.5 % to 77.4 %.

SSRI-treated models, which started low, improved slowly and finished at 93.2 % (SD 2.0 %). Neurosteroid-treated models looked excellent through the first five cycles but then diverged; by cycle 8 the group mean had slipped to 88.2 % with a wide 49.6–97.7 % range.

Table 3. *Combined-Stress Accuracy (%) by Cycle (Mean ± SD)*

Cycle	Ketamine	SSRI	Neurosteroid
0	97.5 ± 0.2	80.8 ± 8.7	97.7 ± 0.2
1	97.6 ± 0.2	84.7 ± 7.9	97.9 ± 0.3
2	97.7 ± 0.2	87.7 ± 5.4	97.8 ± 0.1
3	97.7 ± 0.3	90.1 ± 4.0	97.6 ± 0.4
4	97.6 ± 0.3	91.5 ± 3.4	97.5 ± 0.8
5	97.6 ± 0.4	92.1 ± 2.9	97.0 ± 0.9
6	97.5 ± 0.3	92.9 ± 2.4	95.6 ± 3.5
7	97.7 ± 0.3	92.6 ± 2.6	94.7 ± 2.8
8	97.6 ± 0.4	93.2 ± 2.0	88.2 ± 14.0

Long-term relapse risk

Table 4. *Longitudinal Relapse Summary*

Metric	Ketamine	SSRI	Neurosteroid
Total accuracy drop (cycle 0 to 8)	-0.1 ± 0.3%	-12.4 ± 8.3%	9.5 ± 14.0%
Final accuracy (cycle 8)	97.6 ± 0.4%	93.2 ± 2.0%	88.2 ± 14.0%
Seeds with relapse (<80%)	0/10	4/10	2/10
Seeds without relapse (≥80%)	10/10	6/10	8/10
Mean cycle at relapse (if relapsed)	N/A	0.0	8.0

None of the ketamine-treated seeds ever fell below the 80 % relapse threshold (Table 4). Four SSRI-treated seeds crossed that line immediately after the initial treatment, while two neurosteroid-treated seeds relapsed late, in cycle 8. Averaged across seeds, total loss of accuracy from cycle 0 to cycle 8 was −0.1 % for the ketamine analogue, −12.4 % for the SSRI analogue, and +9.5 %

for the neurosteroid analogue (the plus sign reflects the sharp late decline after earlier gains).

Overall, relative to the 28.9 % baseline, the ketamine-like and neurosteroid-like strategies each delivered an improvement of roughly 69 percentage points under combined stress, whereas the SSRI-like routine lifted accuracy by about 52 points and displayed the greatest variability and relapse liability.

Discussion

Interpretation of results

Placing three distinct recovery programmes inside the same wounded network revealed a set of trade-offs that echo real-world pharmacology (Figure 3). The ketamine-like routine, which reinstated half of the deleted synapses in an activity-guided way, produced almost immediate normalisation and—with or without further stress—barely budged thereafter. Even when another forty per cent of the remaining weights were cut and eight additional pruning rounds were imposed, accuracy stayed above 97 % and no seed relapsed. Clinically, a single ketamine infusion can trigger BDNF- and mTOR-dependent spine growth that outlasts drug exposure and holds up under subsequent stress [5,4]. The model suggests that durability arises not from a wholesale return to pre-morbid density but from selectively restoring high-value links, thereby rebuilding "reserve" that buffers later insults.

The SSRI-like schedule, by contrast, left the sparse architecture untouched and relied on slow parameter drift while internal noise tapered. Immediate gains were modest and uneven—some seeds barely moved off the 30 % baseline—yet most improved gradually and several reached the mid-90 % range by the final cycle. Four networks, however, never achieved a secure foothold and slipped below the 80 % relapse line early on. This mirrors the familiar picture of selective serotonin re-uptake

inhibitors: effectiveness that emerges over weeks, large patient-to-patient variability, and a sizeable minority of non-responders [10,9]. The simulation implies that when synaptic loss is severe, merely "tuning" existing weights may be insufficient unless accompanied by structural repair.

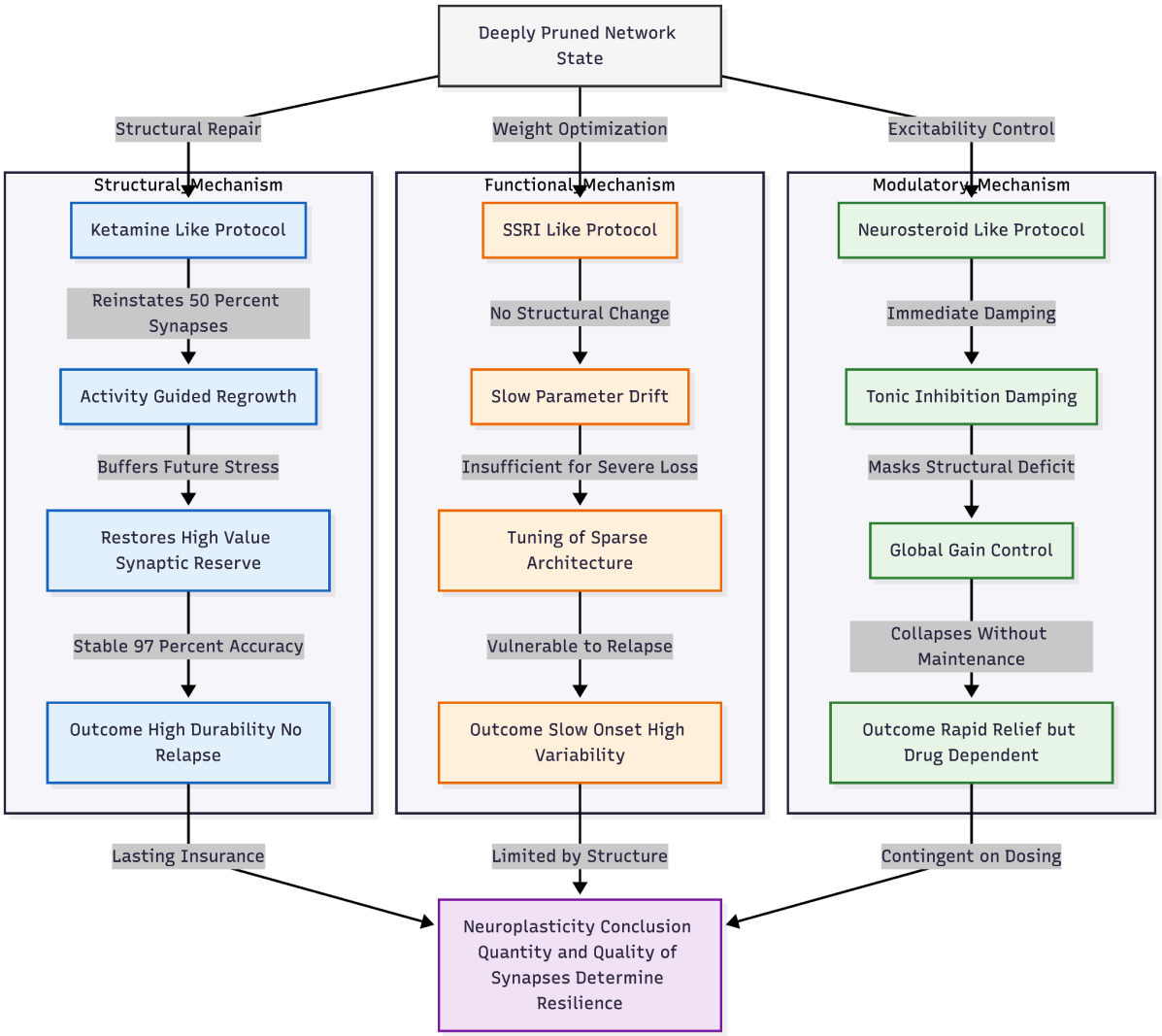

Figure 3: *Comparative Mechanisms of Action and Resilience Profiles. A schematic representation of the three distinct recovery pathways observed in the simulation. The Ketamine-like pathway (left, blue) confers lasting resilience by rebuilding synaptic "reserve" via activity-guided regrowth, mirroring BDNF-dependent structural repair. The SSRI-like pathway (center, orange) relies on tuning existing weights; while effective for some, it exhibits high variability and vulnerability when structural loss is too severe to be compensated by parameter drift alone. The Neurosteroid-like pathway (right, green) provides immediate functional relief via global gain control, but this benefit is contingent on the presence of the agent, failing to prevent relapse once the modulation is removed from a structurally deficient network.*

The neurosteroid-like intervention offered the quickest subjective relief—performance snapped back

to healthy levels the moment tonic damping was engaged—but the benefit proved contingent on continued inhibition. Removing the damping cut combined-stress accuracy by nearly thirty points, and two seeds collapsed during the last stress cycle despite maintenance sessions. Clinical experience with brexanolone and zuranolone is similar: fast symptom relief that can wane once dosing stops, particularly if underlying circuitry has not had time to rebuild [6]. In the model, global gain control contained excitability but, as pruning progressed, there were simply too few functional pathways left to stabilise.

Together, these findings support a neuroplasticity account of major depression in which both the quantity and the quality of synapses determine outcome [11]. When loss is extensive, agents that drive new growth confer lasting insurance; modulators that optimise or damp existing connections help only while enough structure remains—or while the drug is present. The wide seed-to-seed spread observed for monoaminergic and, later, neurosteroid conditions hints that individual differences in baseline pruning depth or excitability may underlie the heterogeneous responses seen in clinics.

Clinical decision-making and personalised sequencing

The simulation outcomes map neatly onto everyday prescribing dilemmas and suggest a triage logic based on underlying circuit damage and the urgency of symptom relief.

Profound structural loss—often seen in chronic, highly recurrent or treatment-resistant depression—appears best addressed with synaptogenic drugs. In the model, the ketamine analogue restored performance almost immediately, remained stable under extreme perturbation, and never relapsed even after further 30–40 % pruning. These features mirror clinical reports that a short ketamine course can trigger durable remission through rapid BDNF–mTOR-dependent spine formation [12]. For patients who repeatedly fail monoaminergic agents or present with marked cognitive blunting or anhedonia, glutamatergic treatments therefore deserve early consideration.

Situations demanding swift containment—postpartum depression, imminent suicide risk, or severe agitation—may profit from neurosteroid modulators. In silico, the GABAergic routine normalised accuracy in a single step and maintained high scores through the first stress cycles, echoing the clinical speed of brexanolone and zuranolone [6]. The sharp decline after damping withdrawal, however, cautions that such agents are bridges rather than stand-alone long-term solutions; follow-up therapy should be organised before discontinuation.

When illness is less entrenched and baseline circuitry largely intact, conventional SSRIs remain useful. Their simulated trajectory—slow but steady gains, substantial variability and occasional early failure—parallels real-world response curves. A poor initial trajectory may signal the need for augmentation rather than a prolonged wait-and-see approach.

Combined strategies emerge naturally from the model. Neurosteroids can cover the latency of SSRIs; ketamine-guided regrowth can be followed by low-dose SSRIs or psychotherapy to consolidate new connections; booster ketamine sessions can reinforce reserve in highly stress-exposed patients.

The contrasting relapse rates—zero for synaptogenic rescue versus 20–40 % for purely functional modulation—also argue for integrating biomarkers of synaptic loss or neuroinflammation into routine assessment so that clinicians can choose a mechanism informed by pathophysiology rather than by trial-and-error.

Novelty and translational potential

By embedding three fundamentally different antidepressant strategies inside one pruning-plasticity model, this study offers a clearer look at how treatment mechanism shapes both early response and long-term course (Figure 4). Previous in-silico work usually explored one pathway at a time—ketamine-like regrowth, slow monoaminergic adaptation, or global inhibitory damping—making cross-class comparisons indirect at best. Running the three approaches

side-by-side from identical, over-pruned baselines shows that the routes to recovery are not interchangeable.

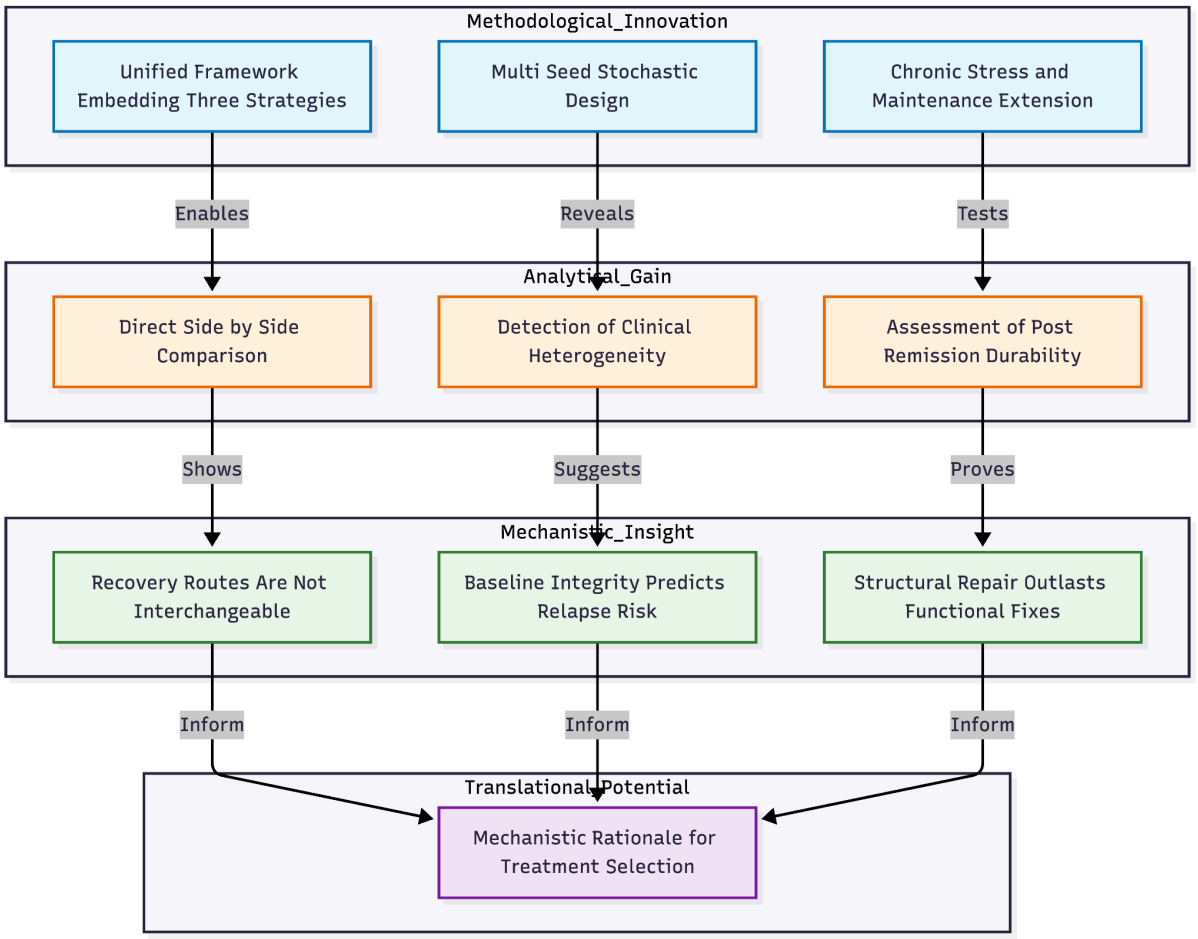

Figure 4: *Methodological Novelty and Translational Framework. This diagram illustrates how the study's specific design choices (blue) enable new analytical capabilities (orange), leading to distinct mechanistic insights (green) that culminate in clinical utility (purple). Unlike previous isolated studies, the Unified Framework allows for direct comparison, revealing that recovery pathways are distinct rather than interchangeable. The Multi-Seed Design captures stochastic variability, linking relapse to baseline circuit integrity rather than drug class alone. Finally, the Chronic Stress Extension demonstrates that while functional fixes can fail over time, structural repair offers lasting protection, providing a quantified rationale for selecting treatments based on the trade-off between speed, durability, and state-dependence.*

The multi-seed design is equally important. Introducing stochastic variation revealed patterns that a single deterministic run would miss: some "patients" on the SSRI schedule never cross a therapeutic threshold, whereas a minority on the neurosteroid schedule crash only after many stress cycles. Such divergence echoes clinical heterogeneity and suggests that baseline circuit integrity or excitability, rather than transmitter class per se, may determine who ultimately relapses.

The chronic-stress extension adds another layer. Few computational studies have asked what happens after the first remission; here, progressive pruning plus minimal "maintenance" demonstrates why structural rebuilding protects every seed, whereas purely functional fixes leave a tail of late failures. These findings dovetail with the growing view that major depression reflects circuit-level dysconnectivity, not merely monoamine shortage [11]. Quantifying the trade-offs—speed versus durability versus state-dependence—gives clinicians a mechanistic rationale for selecting ketamine, SSRIs, neurosteroids, or combinations according to individual risk profiles.

Limitations

Several caveats must temper direct biological inference. A feed-forward network cannot reproduce the reverberating loops of corticolimbic circuits; magnitude-based pruning is only a proxy for microglial or inflammatory synapse loss. The ketamine analogue grants faultless activity-guided regrowth, ignoring maladaptive sprouting; the SSRI routine sidesteps debates over serotonin depletion after long exposure [13]; the neurosteroid module dampens every hidden unit equally, whereas real extrasynaptic GABA_A receptors sit on select neurons.

Inter-seed variance arises from random data splits and weight initialisation, not from modelled genetic or hormonal modifiers. Maintenance schedules are sketched loosely on clinical practice—brief boosters for ketamine, longer courses for the others—but do not address dose, tolerability, or adherence. Adding recurrent dynamics, cell-type specificity, and empirically derived patient heterogeneity will be essential next steps.

Conclusion

Within these constraints, the simulations offer a coherent narrative: fragile circuits can be helped in three distinct ways—rebuilding lost links, patiently tuning what remains, or providing a temporary

brake on over-excitation—but only the first delivers uniform, lasting protection against future stress. A single framework that recreates these divergent trajectories narrows the gap between computational theory and bedside choice, supporting a shift toward mechanism-guided, plasticity-focused care as rapid-acting agents become mainstream [12].

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