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NEUROPLASTICITY AND CHRONIC STRESS: MECHANISMS OF BRAIN DAMAGE AND PATHWAYS TO RECOVERY

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Abstract

Major depressive disorder (MDD) is increasingly recognized as a systemic pathology of impaired homeostatic neuroplasticity induced by chronic stress. This review synthesizes current evidence demonstrating how hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis triggers glucocorticoid neurotoxicity and the profound downregulation of Brain-Derived Neurotrophic Factor (BDNF). Structurally, these molecular shifts precipitate an 8–10% volumetric deficit in the hippocampus (Videbech & Ravnkilde, 2004), alongside dendritic retraction and a reduction in synaptic density within the prefrontal cortex (PFC).

We highlight how the depletion of synaptic vesicle protein 2A (SV2A), now measurable *in vivo* via PET imaging (Holmes et al., 2019), serves as an objective biomarker for this structural decay. The onset of treatment resistance in refractory patients is directly linked to this morphological degradation, where the "neuroplasticity gap" prevents standard monoaminergic drugs from achieving clinical efficacy.

Ultimately, achieving true clinical remission requires a shift toward rapid-acting neurorestorative interventions, such as NMDA receptor antagonists, which

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bypass traditional signaling delays to activate the mTORC1 pathway. By physically reconstructing damaged neural networks and restoring the biological mechanisms of resilience (Russo et al., 2012), these therapies move the clinical goal from simple neurotransmitter elevation to the active restoration of the central nervous system's structural integrity.

Keywords: Major depressive disorder (MDD); Neuroplasticity; Chronic stress; BDNF; Hippocampal atrophy; SV2A; mTORC1; Synaptogenesis; HPA axis; Neurorestoration; Treatment-resistant depression; Biological resilience.

Introduction

Major depressive disorder (MDD) is a severe psychiatric illness representing a systemic pathology of impaired neuroplasticity. Neuroplasticity refers to the physiological capacity of the central nervous system to reorganize synaptic architecture in response to environmental stimuli. Exposure to chronic stress disrupts these adaptive mechanisms, precipitating synaptic loss and structural modifications within neural networks (Duman R.S. & Aghajanian G.K., 2012). According to the World Health Organization, depression affects over 300 million individuals globally and remains a primary driver of non-fatal health loss and disability (WHO, 2023).

Neuroimaging and post-mortem analyses demonstrate that MDD is associated with volumetric deficits in the hippocampus and prefrontal cortex, alongside functional dysregulation of the amygdala. These regional alterations compromise emotional stability, memory processing, and executive cognitive functions (Videbech P. & Ravnkilde B., 2004). On a molecular level, the primary drivers of this maladaptive remodeling include the downregulation of Brain-Derived Neurotrophic Factor (BDNF) and prolonged glucocorticoid toxicity stemming from hypercortisolemia (Sapolsky R.M., 2000).

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Identifying these neurobiological shifts is critical, as morphological degradation and the inhibition of neurogenesis explain the onset of treatment resistance and chronic cognitive deficits observed in refractory patients (Pittenger C. & Duman R.S., 2008).

The aim of this review is to synthesize the clinical and molecular mechanisms underlying impaired neuroplasticity in MDD and evaluate the therapeutic potential of neurorestorative interventions.

Overview of Neuroplasticity in the Healthy Brain

Neuroplasticity is defined as the fundamental and intrinsic capacity of the central nervous system to reorganize its structural, functional, and connectional architecture in response to a continuous stream of internal or environmental stimuli (Fuchs E. & Flügge G., 2014). In the healthy adult brain, this process is far from static; rather, neural circuits undergo perpetual remodeling to facilitate complex cognitive processes such as learning, memory consolidation, and behavioral adaptation. This dynamic capability is driven by two primary, interlinked mechanisms: structural plasticity and functional plasticity. Structural plasticity involves the physical, morphological remodeling of the neuronal tree, including the elongation or retraction of dendrites and the de novo formation or elimination of dendritic spines, which serve as the primary postsynaptic sites for excitatory input (Duman R.S. & Aghajanian G.K., 2012). Complementing this, functional plasticity modulates the efficacy and strength of existing synaptic transmission, primarily through activity-dependent changes such as Long-Term Potentiation (LTP) and Long-Term Depression (LTD), which adjust the weight of neural connections based on the temporal patterns of neuronal firing.

At the cellular and systems levels, adaptive neural remodeling is not uniform across the encephalon but is heavily concentrated in highly plastic regions, most notably the hippocampus and the prefrontal cortex (PFC). These areas are critical

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for executive cognitive functions, spatial navigation, and the complex regulation of emotional states. Within the hippocampus, a unique form of neuroplasticity persists throughout adulthood in the form of neurogenesis. This process occurs in the subgranular zone (SGZ) of the dentate gyrus, where neural stem cells undergo a rigorous cycle of proliferation, differentiation, and eventual integration into the pre-existing functional circuitry (Pittenger C. & Duman R.S., 2008). These newborn neurons contribute significantly to pattern separation — the ability to distinguish between highly similar memories — and provide a structural basis for the brain's resilience against environmental stressors.

The maintenance of synaptic density and the survival of these newborn neurons in the dentate gyrus are strictly dependent on the presence and activity of neurotrophic factors, the most prominent of which is Brain-Derived Neurotrophic Factor (BDNF) (Duman R.S. & Li N., 2012). In a physiological state, BDNF serves as a primary mediator of synaptogenesis and neuronal health. It exerts its biological effects by binding with high affinity to the Tropomyosin receptor kinase B (TrkB) receptors located on the neuronal membrane. This ligand-receptor interaction induces TrkB dimerization and autophosphorylation, which subsequently triggers several major intracellular signaling pathways. The MAPK/ERK (Mitogen-Activated Protein Kinase) pathway is primarily responsible for the regulation of protein synthesis and the promotion of complex dendritic arborization, ensuring the growth and branching of the neuronal tree. Simultaneously, the PI3K/Akt (Phosphoinositide 3-kinase) pathway plays a critical role in promoting neuronal survival by inhibiting pro-apoptotic signaling and stabilizing mitochondrial function. Furthermore, the PLCγ (Phospholipase C-gamma) pathway facilitates the rapid release of intracellular calcium, which is essential for the immediate enhancement of synaptic strength and the induction of functional plasticity (Pittenger C. & Duman R.S., 2008).

These signaling cascades collectively regulate the transcription and translation of essential synaptic proteins, such as Synapsin I, which is involved in

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neurotransmitter release, and PSD-95, which provides the structural scaffolding necessary for the maturation and stabilization of new dendritic spines (Duman R.S., 2012). Through these intricate molecular events, healthy neuroplasticity creates a homeostatic buffer that preserves cognitive integrity and emotional stability, allowing the individual to mount an effective and flexible response to acute stress without falling into pathological states of neural degradation.

Structural Brain Changes in Major Depressive Disorder

Recurrent Major Depressive Disorder (MDD) is robustly associated with an 8% to 10% reduction in total hippocampal volume, a finding that has been consistently validated through extensive neuroimaging meta-analyses involving thousands of clinical subjects (Videbech P. & Ravnkilde B., 2004). This significant decline in grey matter volume is not merely a global consequence of cell death, but rather a complex, region-specific manifestation of cellular atrophy and suppressed regenerative capacity. Detailed high-resolution MRI studies indicate that this atrophy is most pronounced in the CA1 and CA3 subfields, which are critical for memory processing and spatial navigation. The primary drivers of this structural degradation include widespread dendritic retraction, a marked loss of excitatory mushroom-shaped synaptic spines, and the profound suppression of adult neurogenesis within the dentate gyrus (Sapolsky R.M., 2000; Pittenger C. & Duman R.S., 2008). In a healthy state, the hippocampus maintains a delicate homeostatic balance of synaptic turnover; however, under the pathological conditions of chronic stress, the rate of synaptic pruning and dendritic "withering" far outpaces the brain's innate ability to generate new connections.

Beyond the loss of neuronal complexity, the structural pathology of MDD involves a critical reduction in the density and functionality of glial cells, particularly astrocytes and oligodendrocytes, within the medial and dorsolateral prefrontal cortex (PFC) (Duman R.S. & Aghajanian G.K., 2012). Astrocytes are

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responsible for maintaining the blood-brain barrier and regulating the uptake of excess glutamate; their depletion leads to a state of "excitotoxicity," where neurons are over-stimulated and eventually damaged by their own neurotransmitters. This loss of glial support directly compromises the metabolic integrity of the PFC, leading to a measurable thinning of the cortical layers. Because the PFC is responsible for high-order executive functioning and the "top-down" inhibitory control over subcortical emotional centers, this structural thinning represents a catastrophic failure of the brain's executive regulatory system (Pittenger C. & Duman R.S., 2008).

When these inhibitory cortical projections wither, the amygdala — the brain's primary emotional alarm system — escapes regulatory oversight and enters a state of pathological hyper-reactivity. Neuroimaging data shows that in MDD patients, the amygdala responds disproportionately to negative or even neutral environmental stimuli, effectively "highjacking" the brain's attention. This circuit-level imbalance manifests clinically as persistent emotional dysregulation, heightened anxiety, and a pathological inability to shift cognitive focus away from depressive ruminations. Furthermore, as the atrophied hippocampus fails to provide necessary contextual feedback, the hyper-reactive amygdala begins to interpret safe environments as threatening, further locking the patient into a self-perpetuating cycle of stress and neural degradation (Goadsby P.J. et al., 2017).

Ultimately, these structural deficits explain why chronic MDD is often associated with long-term cognitive and memory impairments that persist even between depressive episodes. The morphological degradation of the hippocampus and PFC suggests that depression is a progressive neurobiological process; the longer a patient remains in an untreated state of hypercortisolemia, the more "fixed" these structural modifications become (Fuchs E. & Flügge G., 2014). This understanding is critical for clinical practice, as it shifts the therapeutic goal from merely "balancing chemicals" to the physical reconstruction of damaged neural

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networks. Without addressing the underlying dendritic retraction and synaptic loss, true clinical remission remains elusive for many refractory patients.

Molecular Mechanisms of Impaired Neuroplasticity

The molecular pathology underlying Major Depressive Disorder (MDD) is primarily driven by the chronic downregulation of Brain-Derived Neurotrophic Factor (BDNF), a critical neurotrophin that functions as the primary mediator of neuronal growth, survival, and synaptic maintenance (Duman R.S. & Li N., 2012). In a healthy physiological state, BDNF supports the structural integrity of the brain; however, in the presence of chronic stress, a significant deficiency in this protein inhibits de novo synaptogenesis and triggers a cascade of pathological synaptic pruning. This loss of neurotrophic support means that neural networks essentially lose their "repair kit," becoming unable to fix cellular damage inflicted by the physiological correlates of environmental or psychological stress. Over time, this results in a progressive weakening of circuit connectivity, where the brain's ability to adapt to new information is severely compromised (Duman R.S. & Aghajanian G.K., 2012; Pittenger C. & Duman R.S., 2008).

This molecular deficit is significantly compounded by the sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to systemic hypercortisolemia. Under normal conditions, the HPA axis follows a precise negative feedback loop that terminates the stress response; in MDD, this loop is disrupted, leading to a "flooding" of the brain with glucocorticoids (Sapolsky R.M., 2000). Elevated glucocorticoids are inherently neurotoxic when present in high concentrations for extended periods. They actively disrupt metabolic glucose transport in neurons, effectively starving the cells of energy and making them highly vulnerable to oxidative stress and mitochondrial dysfunction. This metabolic failure prevents neurons from maintaining their complex dendritic trees, forcing them to "withdraw" or retract their branches to conserve energy,

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which directly contributes to the volumetric loss observed in the hippocampus (Fuchs E. & Flügge G., 2014).

Furthermore, the prolonged presence of high cortisol levels triggers a state of persistent neuroinflammation, characterized by the activation of microglia — the brain's resident immune cells. Once activated, microglia release pro-inflammatory cytokines such as IL-1beta and TNF-alpha, which further suppress adult neurogenesis in the dentate gyrus and interfere with BDNF signaling pathways. This inflammatory environment creates a "vicious cycle" where the brain is stuck in a state of maladaptive plasticity. Instead of reorganizing to recover from stress, the neural circuits become "locked" into a rigid, dysfunctional architecture that is increasingly resistant to standard pharmacological interventions (Goadsby P.J. et al., 2017).

The onset of MDD is therefore fundamentally tied to this pathological shift in the brain's internal environment. As excess circulating glucocorticoids penetrate the blood-brain barrier, they exert direct toxic effects on vulnerable limbic structures, particularly the hippocampus and the prefrontal cortex. This hormonal toxicity not only arrests the birth of new neurons but also triggers the physical "withering" of existing ones. Consequently, the brain loses its fundamental capacity to habituate to psychological stressors, resulting in a permanent state of neural and emotional fragility where even minor stress triggers a disproportionate depressive response (Sapolsky R.M., 2000; Fuchs E. & Flügge G., 2014).

Neuroplasticity and Treatment Resistance

Structural deficits and suppressed synaptogenesis serve as the primary biological drivers of Treatment-Resistant Depression (TRD), a clinical state where patients fail to achieve symptomatic remission despite multiple adequate trials of antidepressant therapy. Approximately 30% of clinical cases are classified as TRD, failing to respond to standard monoaminergic interventions, such as Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin-Norepinephrine

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Reuptake Inhibitors (SNRIs) (Duman R.S. & Aghajanian G.K., 2012). This widespread therapeutic failure occurs primarily because conventional medications are designed to modulate neurotransmitter concentration within the synaptic cleft, but they cannot rapidly reverse severe, long-term morphological damage. In patients with chronic MDD, the "neuroplasticity gap"—the distance between chemical signaling and physical circuit repair—becomes too wide for traditional monoamine-based drugs to bridge effectively.

This resistance is deeply rooted in the "lag-time" of standard antidepressants. While SSRIs increase synaptic serotonin levels within hours of the first dose, the clinical antidepressant effect typically takes three to six weeks to manifest. This delay corresponds to the time required for the brain to initiate the intracellular signaling cascades—specifically the upregulation of BDNF and the activation of the mTOR (mammalian target of rapamycin) pathway—needed to physically reconstruct retracted dendrites and lost synaptic spines (Pittenger C. & Duman R.S., 2008). In TRD, however, the degree of hippocampal volume loss and deep synaptic pruning in the prefrontal cortex may be so advanced that the standard neurotrophic signal generated by SSRIs is insufficient to overcome the pro-atrophic environment created by chronic hypercortisolemia.

Furthermore, the structural integrity of the **glutamatergic system** appears to be compromised in resistant cases. Because the prefrontal cortex loses a significant portion of its glutamatergic synapses, the "top-down" connectivity required for emotional regulation is physically severed. Standard antidepressants rely on a relatively intact neural architecture to transmit their therapeutic signals; if the "hardware" of the brain is too degraded, adjusting the "software" of neurotransmitters yields little clinical benefit. Consequently, patients with advanced structural atrophy require a fundamental shift in treatment strategy—moving away from slow-acting monoaminergic modulation toward rapid-acting neuroplastic agents or neuromodulation techniques that can bypass these standard signaling delays (Duman R.S. & Li N., 2012).

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True clinical remission in TRD, therefore, requires the physical reconstruction of damaged neural networks rather than simple neurotransmitter elevation. Rapid-acting agents, such as NMDA receptor antagonists (e.g., ketamine), work by triggering a sudden "burst" of glutamate that immediately activates synaptogenic pathways, effectively "rebooting" the circuit connectivity in the prefrontal cortex within hours. This approach targets the structural deficit directly, offering a pathway to recovery for patients whose neural architecture has become resistant to traditional homeostatic repair mechanisms. Identifying these structural "tipping points" through neuroimaging may eventually allow for precision psychiatry, where patients with significant atrophy are moved immediately to neurorestorative therapies rather than enduring months of ineffective monoaminergic trials (Goadsby P.J. et al., 2017).

Neurorestorative Therapeutic Strategies

The clinical resolution of Major Depressive Disorder requires therapeutic interventions that move beyond simple neurochemical modulation to directly stimulate synaptogenesis and dendritic arborization. Standard monoaminergic antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs), initiate a complex cascade of intracellular signals that gradually upregulate the expression of Brain-Derived Neurotrophic Factor (BDNF) (Duman R.S. & Li N., 2012). This process is mediated by the activation of the cAMP-response element-binding protein (CREB), a transcription factor that slowly enhances the synthesis of neurotrophic proteins. While effective for many patients, this genomic mechanism requires several weeks of sustained treatment to physically alter the neural circuitry. The delayed therapeutic onset reflects the time needed for newborn neurons to mature and for retracted dendritic branches to physically regrow and re-establish functional synaptic connections within the prefrontal cortex and hippocampus.

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In stark contrast, rapid-acting antidepressants, most notably NMDA receptor antagonists like ketamine, provide an immediate synaptogenic effect by bypassing these traditional signaling delays (Duman R.S. & Aghajanian G.K., 2012). Ketamine functions by triggering a transient "glutamate burst" in the prefrontal cortex, which leads to the rapid activation of the mTORC1 (mammalian target of rapamycin complex 1) signaling pathway. This pathway acts as a molecular "engine" for protein synthesis, specifically targeting the translation of essential synaptic proteins like PSD-95 and GluA1. Within hours of administration, this mechanism can physically restore the density of dendritic spines that were previously lost due to chronic stress, offering a promising avenue for reversing acute structural atrophy even in highly refractory patients who have failed multiple trials of traditional medication.

Beyond pharmacological interventions, the stabilization of hippocampal volume and the promotion of neural repair are significantly enhanced by lowering the systemic burden of cortisol-induced toxicity. Evidence suggests that sustained clinical remission is contingent upon the brain's capacity to restore homeostatic neuroplasticity, a state where neural circuits can once again habituate to psychological stressors (Sapolsky R.M., 2000). To achieve this, modern treatment protocols are increasingly focusing on "environmental enrichment" and lifestyle adjustments, such as aerobic physical exercise. Exercise has been shown to directly stimulate the release of BDNF in the dentate gyrus, acting synergistically with antidepressants to accelerate the integration of newborn neurons into existing functional networks (Fuchs E. & Flügge G., 2014).

Ultimately, the future of neurorestorative therapy lies in identifying the precise molecular "tipping points" where structural damage becomes reversible. By combining rapid-acting agents that provide immediate circuit "rebooting" with long-term pharmacological and cognitive interventions that stabilize these new connections, clinicians can facilitate a more robust and lasting recovery. This shifting focus from mere symptom management to the active physical restoration

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of the brain's "hardware" remains the most critical objective in modern psychiatry. Understanding these pathways to recovery not only provides a roadmap for treating treatment-resistant depression but also offers hope for preventing the long-term cognitive decline often associated with recurrent depressive episodes (Duman R.S. & Li N., 2012; Goadsby P.J. et al., 2017).

Potential for Neural Recovery

Evidence from longitudinal neuroimaging studies suggests that the structural and volumetric deficits observed in Major Depressive Disorder are not necessarily permanent, but are partially, and in some cases fully, reversible through targeted intervention. The biological key to this recovery lies in the brain's inherent, albeit suppressed, capacity for homeostatic neuroplasticity. Sustained pharmacological and cognitive-behavioral interventions facilitate the stabilization of hippocampal volume primarily by lowering the systemic "toxic load" of cortisol-induced hypercortisolemia (Sapolsky R.M., 2000). When the hypothalamic-pituitary-adrenal (HPA) axis is successfully recalibrated, the reduction in circulating glucocorticoids allows the hippocampus to exit its self-preservation "atrophy mode." This metabolic shift re-opens the window for neural repair, as the previously starved neurons regain the ability to transport glucose and synthesize the proteins necessary for dendritic regrowth.

Beyond standard medical treatments, environmental enrichment and specific lifestyle adjustments act as powerful non-pharmacological catalysts for neurogenesis. Physical exercise, in particular, has been identified as a primary driver of neuronal proliferation in the dentate gyrus (Fuchs E. & Flügge G., 2014). During aerobic activity, the body produces peripheral growth factors, such as IGF-1 (Insulin-like Growth Factor 1), which cross the blood-brain barrier and work synergistically with central BDNF to enhance the survival and functional integration of newborn neurons. This process does not merely add "more cells"

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to the brain; it physically strengthens the structural buffer of the limbic system, making the individual more resilient to future psychological stressors.

The physical reconstruction of these functional networks is the true biological hallmark of clinical remission. While a patient may show symptomatic improvement through neurotransmitter modulation, achieving a deep and lasting recovery is contingent upon the brain's capacity to rebuild the "hardware" that was damaged during the depressive episode. This involves the stabilization of new synaptic spines and the restoration of the complex dendritic arborization in the prefrontal cortex (PFC). As these circuits are repaired, the PFC regains its ability to provide top-down inhibitory control over the amygdala, effectively "resetting" the emotional thermostat of the brain. This structural restoration explains why patients who maintain long-term treatment and healthy lifestyle habits show a significantly lower risk of relapse compared to those who stop treatment prematurely before neural repair is complete.

Ultimately, the neuroplasticity model of recovery shifts the clinical focus from a "deficit-based" perspective to a "growth-based" strategy. It underscores that the brain is a dynamic organ capable of profound structural transformation even after severe periods of chronic stress. By understanding that recovery is a physical process of reconstruction — a "neuro-rehabilitation" — clinicians can better tailor interventions to maximize the brain's innate regenerative potential. This perspective provides a powerful biological basis for hope, illustrating that even after years of morphological degradation, the pathways to recovery remain physiologically accessible through the persistent application of neurorestorative strategies (Sapolsky R.M., 2000; Duman R.S. & Li N., 2012).

Future Directions

The future of depression research lies in identifying objective biomarkers of neural plasticity to transition psychiatry toward a rigorous, neurobiological diagnostic framework. Advanced neuroimaging, such as Positron Emission

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Tomography (PET) using novel radioligands for synaptic vesicle protein 2A (SV2A), now allows for the real-time visualization of synaptic loss and recovery *in vivo* (Goadsby P.J. et al., 2017). These tools provide the foundation for "precision psychiatry," enabling clinicians to identify individuals at high risk for structural atrophy before clinical symptoms manifest. By detecting these shifts early, medicine can move from reactive symptom management to proactive, aggressive neuroprotective interventions.

Simultaneously, pharmacological development is shifting toward non-monoaminergic agents that bypass the limitations of traditional reuptake inhibitors. Current research focuses on drugs that directly stimulate neurotrophic factor release or modulate the glutamatergic system to trigger immediate synaptogenesis (Duman R.S. & Li N., 2012). By targeting intracellular engines like the mTORC1 pathway, these therapeutics aim to "reboot" circuit connectivity in the prefrontal cortex within hours. This is critical for treatment-resistant patients whose monoamine pathways are structurally too degraded to respond to standard medications.

Ultimately, integrating these molecular mechanisms into clinical diagnostics will enable personalized, neurorestorative interventions. Future protocols will involve mapping a patient's "plasticity profile" to align their specific morphological needs with rapid-acting agents and neuromodulation. This evolution redefines clinical remission: moving from the mere suppression of emotional distress to the active, physical reconstruction of the central nervous system's structural integrity and biological resilience.

Conclusion

Major Depressive Disorder (MDD) is defined by a systemic failure of homeostatic neuroplasticity, where chronic HPA-axis activation and hypercortisolemia drive a "hardware" collapse. This structural decay manifests as profound dendritic retraction, synaptic pruning, and an 8–10% reduction in

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hippocampal volume (Sapolsky R.M., 2000; Videbech P. & Ravnkilde B., 2004). Because these deficits compromise the prefrontal cortex's inhibitory control over the amygdala, the brain becomes locked in a self-perpetuating cycle of emotional dysregulation and treatment resistance.

True clinical remission requires shifting focus from neurotransmitter levels to the physical reconstruction of neural networks. While standard SSRIs rely on a slow genomic increase in BDNF, rapid-acting agents like ketamine bypass these delays by directly activating the mTORC1 pathway to restore synaptic density within hours (Duman R.S. & Li N., 2012). This neurorestorative approach, combined with lifestyle factors like exercise that boost IGF-1, provides the only reliable pathway to reversing structural atrophy and restoring long-term biological resilience.

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