THE DEPRESSION CONTINUUM

Major Depressive Disorder as the Reversible-State Phenotype of the Multi-Axis Collapse that Sustains as Alzheimer's Disease

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in dialogue with Tsai, Venturino, Ribeiro, Bredesen, and the Collapse quartet

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A First-Principles thesis. Companion to the Collapse quartet — Convergent Synaptic Collapse, Homeostatic Microglial Collapse, Bioenergetic Collapse, and Terminal Collapse — and to The Ketamine Paradox and The Tryptophan Partition Node.

Contents

Abstract

The Collapse quartet established that Alzheimer's disease arises from the convergent failure of five mechanistically distinct but molecularly coupled axes: synaptic NMDA-PV+ excitatory-inhibitory dysregulation, microglial homeostatic-state collapse with NLRP3-driven inflammatory amplification, bioenergetic and quality-control failure at the mitochondrial substrate, tryptophan partition shift from serotonergic to kynurenine and NAD+ branches, and extracellular matrix degradation at the perineuronal net. The framework was developed to explain a neurodegenerative phenotype whose hallmark is irreversibility. This thesis argues that the same five axes, observed at lower cumulative damage and in a state where neuronal death has not yet occurred, produce the clinical phenotype that psychiatry calls major depressive disorder, and that the boundary between the two diseases is not categorical but a function of time, dose, and the reversibility of damage to the substrate.

The argument proceeds through six convergent lines of evidence. First, the canonical rapid-antidepressant mechanism — NMDA receptor blockade on PV+ interneurons, transient disinhibition of pyramidal neurons, glutamate surge, AMPA receptor activation, BDNF release, TrkB activation, mTORC1-mediated synaptogenesis — is the same molecular cascade that the Convergent Synaptic Collapse thesis identifies as the extrinsic-pole death pathway of Alzheimer's disease. The difference is that in depression the cells survive and the cascade is reversible, while in advanced AD the same circuit-level pathology terminates in excitotoxic death of PV+ interneurons whose perineuronal nets have already been degraded.

Second, the inflammation hypothesis of depression — chronic peripheral inflammation drives indoleamine 2,3-dioxygenase induction, which depresses central serotonin synthesis through tryptophan substrate withdrawal while elevating kynurenine-pathway metabolites — invokes precisely the molecular nodes that the Homeostatic Microglial Collapse thesis identifies as the bridge between mitochondrial damage and pathological microglial effector activity: NLRP3-derived IL-1β, IDO-driven kynurenine shift, microglial reactive-state transitions. The cytokines of sickness behavior and the cytokines of microglial collapse are the same cytokines; only their cumulative time-integral differs.

Third, the metabolic psychiatry framework formalized by Picard, Sarnyai, and Sethi in their 2026 Nature Mental Health review argues that mitochondria are the central organelle on which chronic stress, metabolic burden, and chronic inflammation converge to produce both psychiatric and neurodegenerative phenotypes. The Bioenergetic Collapse thesis arrived at the same conclusion from the neurodegenerative direction. The two literatures converge on a single mitochondrial-substrate model whose intervention space — ketogenic metabolic therapy, intermittent fasting, metformin, GLP-1 receptor agonists, NAD+ precursors, mitophagy enhancers — is identical across the diseases the conventional taxonomy treats as distinct.

Fourth, the perineuronal net, identified by the Collapse quartet as the master vulnerability switch of Alzheimer's disease, is also the structural substrate of fear-memory persistence, social-memory durability, and the sustained antidepressant effect of ketamine. The Phoumthipphavong eNeuro 2016 demonstration that hippocampal PNN integrity is required for sustained ketamine antidepressant action establishes the same structure as the gate of both psychiatric resilience and neurodegenerative resilience. The PNN is not a neurodegeneration-specific node; it is the structural substrate of all forms of late-acquired plasticity stability.

Fifth, the locus coeruleus — whose Braak pre-tangle pathology begins in the first decades of life and whose noradrenergic loss correlates with the earliest depressive and sleep-related symptoms of pre-clinical AD — provides the anatomical bridge between the depressive and dementing phenotypes. Tau pathology in the LC produces depression before it produces dementia, because the LC's noradrenergic projections shape mood, arousal, and circuit-level vigilance long before cortical synaptic loss becomes measurable.

Sixth, adult hippocampal neurogenesis — the canonical cellular substrate of antidepressant action through the 5-HT BDNF granule-cell-genesis pathway — is the same neurogenic process whose age-related and inflammation-driven failure the Tryptophan Partition Node thesis identifies as a contributor to cognitive decline. The neurogenic substrate of depression and the neurogenic substrate of resilience to dementia are the same substrate.

The thesis concludes that the depression-dementia continuum is the most direct test of the Collapse framework's predictive validity. The framework predicts that depressive endophenotypes detectable in midlife — elevated kynurenine-to-tryptophan ratio, reduced heart-rate variability, mild PNN signal attenuation on advanced imaging, reduced gamma-band coherence, and subtle anhedonia — will predict late-life cognitive decline at population scale, that interventions targeting the convergent multi-axis substrate will produce simultaneous benefit on mood and on long-term cognitive trajectory, and that the failure of unimechanistic antidepressants (SSRIs, SNRIs) in subgroups whose pathology has shifted predominantly to the inflammatory or kynurenine axis is the same failure mode as the failure of unimechanistic neuroprotective agents (memantine, donepezil) in advanced AD. Both failures arise from the same architectural error: addressing one axis of a five-axis pathology with one-target pharmacology.

1. Introduction: One Substrate, Two Time-Slices

The conventional taxonomy of clinical psychiatry treats major depressive disorder as a primary disease of mood, defined by phenomenological criteria (DSM-5: persistent sadness or anhedonia, sleep and appetite disturbance, fatigue, concentration impairment, suicidal ideation) and treated

through a pharmacological program whose principal targets are the monoaminergic neurotransmitter systems. The conventional taxonomy of clinical neurology treats Alzheimer's disease as a primary disease of cognition, defined by the accumulation of amyloid and tau pathology and the loss of episodic memory, treated through a pharmacological program whose principal targets are the cholinergic system (donepezil, rivastigmine), NMDA receptor (memantine), and, more recently, amyloid clearance (lecanemab, donanemab). The two diseases occupy separate clinical specialties, separate diagnostic frameworks, separate trial enterprises, and largely separate research literatures.

This separation has resisted the accumulating evidence that the diseases are not separate. Late-life depression precedes dementia in a substantial fraction of cases, with hazard ratios for subsequent dementia diagnosis in the range of 1.5 to 2.5 across cohorts. Mid-life depression, with onset before age 50, is associated with elevated late-life dementia risk even when controlling for the recurrence of depressive episodes in later decades, suggesting that the depressive episodes themselves are not the causal mechanism but the early clinical manifestation of an underlying process whose later manifestation is cognitive decline. The post-mortem brains of patients with histories of major depression show elevated neuroinflammatory markers, reduced perineuronal net coverage, reduced adult hippocampal neurogenesis, mitochondrial DNA damage, and elevated kynurenine-pathway metabolites — precisely the molecular substrate that the Collapse quartet identifies as the pathological substrate of Alzheimer's disease.

The argument of this thesis is that the relationship between depression and dementia is not one of comorbidity, shared risk factor, or causal precedence, but of *identity at the substrate level*. The five axes the Collapse quartet identifies — synaptic, microglial-inflammatory, bioenergetic, tryptophan-partition, and ECM/PNN — are jointly necessary and individually insufficient for either phenotype. When the cumulative damage to the substrate is low and the dysregulation is recent, the phenotype is mood disturbance whose biology is reversible. When the cumulative damage is high and the dysregulation has been sustained for decades, the phenotype is cognitive decline whose biology is no longer reversible. The two phenotypes are time-slices of the same trajectory.

This identity claim has consequences. It predicts that the most effective depression treatments are those that engage the multi-axis substrate, not those that target a single neurotransmitter system. It predicts that the most effective AD prevention strategies will be those that operate on the same multi-axis substrate, deployed early enough that the damage is still reversible. It predicts that the failure modes of unimechanistic interventions in depression (SSRI non-response in approximately one-third of patients, recurrence in approximately half) and in AD (memantine and cholinesterase-inhibitor monotherapy producing modest, time-limited symptomatic benefit without altering disease trajectory) have the same architectural origin: addressing one axis of a five-axis pathology with one-target pharmacology. It predicts that the interventions that succeed in

depression and the interventions that succeed in AD prevention will be the same interventions, applied at different stages of the trajectory.

The thesis is structured around the five axes the Collapse quartet identified, with each axis examined for its depressive-state manifestation, its dementia-state manifestation, and the molecular mechanism that connects them. The argument concludes with a unified case history showing how the same individual, observed across midlife and late life, traces the same biology through the two clinical states, and with a set of falsifiable predictions that distinguish the continuum framework from alternative accounts.

2. The Clinical Observation: Late-Life Depression as Prodrome

2.1 The epidemiological signal

The association between depression and subsequent dementia has been documented across more than fifty independent cohort studies spanning four decades. The 2017 Lancet Commission on dementia prevention and the 2020 update both identified depression as a modifiable risk factor for dementia, with population-attributable fractions in the range of 4–6%. Meta-analyses pooling longitudinal data from approximately 100,000 participants estimate hazard ratios for subsequent dementia in patients with prior depressive episodes between 1.65 and 2.30, with the higher estimates corresponding to studies that specifically isolated depression with late-life onset.

The interpretation of this signal has been contested for decades. Three accounts have competed in the literature. The first, the "reverse causality" account, argues that early depression is a *consequence* of the pre-clinical dementia process — that the inflammation, neurogenic loss, and synaptic dysregulation of pre-symptomatic AD produce depressive symptoms before they produce measurable cognitive decline. On this account, depression is a marker rather than a cause. The second, the "shared risk factor" account, argues that the diseases share common upstream determinants — cerebrovascular disease, chronic inflammation, metabolic syndrome, social isolation — and that the association reflects this common cause rather than any direct mechanistic link. The third, the "causal" account, argues that the depressive episodes themselves produce neurobiological damage — through chronic cortisol elevation, hippocampal atrophy, reduced neurogenesis, sustained inflammation — that accelerates the dementia process.

The Collapse framework dissolves this dichotomy by proposing that all three accounts are partially correct because they are partially the same account. The pre-clinical dementia process and the depressive episodes are not in a causal relationship but in an identity relationship: they are the same biology observed at different time-slices and different cumulative damage levels. The "shared risk factors" are not separately upstream of two separate diseases but jointly upstream of a single multi-axis substrate whose state determines the phenotype. The "reverse causality" intuition that depression marks pre-clinical AD is correct but the framing is wrong: there is no reversal of causality because there are not two diseases in temporal sequence; there is one biology whose milder expression is depression and whose later expression is dementia.

2.2 The midlife signal and the cumulative-exposure hypothesis

The most informative subset of the epidemiological literature concerns midlife depression — depressive episodes occurring before age 50 — and its relationship to dementia diagnosed two or three decades later. If the late-life depression-dementia association were entirely explained by reverse causality (depression as a marker of pre-clinical AD), midlife depression should show no association with dementia, because the AD process has not yet begun in most cases at that age. The data show the opposite. The Whitehall II cohort, the Framingham Offspring Study, the Honolulu-Asia Aging Study, and the Health and Retirement Study have each documented elevated dementia hazard in individuals with midlife depressive episodes, with hazard ratios in the range of 1.4 to 1.8 — lower than the late-life signal, but robust to controlling for vascular comorbidities, education, and apolipoprotein E genotype.

The midlife signal cannot be explained by reverse causality because the AD process is not detectable in most cases at midlife. It cannot be entirely explained by shared risk factors because the association persists after statistical adjustment for the principal candidate shared factors. It can be explained by the identity account: midlife depression is the early manifestation of a multi-axis dysregulation whose continued operation over the subsequent two decades produces dementia in those individuals whose substrate is most vulnerable. The depressive episodes are not causing the dementia; they are *announcing* the trajectory of the substrate.

This framing predicts that the most informative midlife biomarkers will be substrate-level markers — inflammatory cytokines, kynurenine-to-tryptophan ratio, heart-rate variability as a marker of autonomic-mitochondrial integration, gamma-band EEG coherence as a marker of PV+/PNN function, advanced MRI markers of perineuronal net coverage and adult neurogenesis. The clinical depressive phenotype is one readout of the substrate; the biomarkers are others. The biomarkers should outperform the clinical phenotype in predicting late-life dementia, because they measure the substrate directly rather than measuring the noisy clinical reflection.

2.3 The treatment-response signal

A second informative subset of the literature concerns treatment-resistant depression — defined operationally as failure to respond to two or more adequately dosed antidepressant trials of different mechanistic classes — and its relationship to dementia risk. Treatment-resistant depression is associated with elevated dementia risk relative to treatment-responsive depression, with hazard ratios approaching 2.0 in some cohorts. The conventional interpretation is that treatment-resistant depression is "worse" depression, with greater cumulative neurobiological damage.

The Collapse framework supplies a more specific interpretation. The pharmacological mechanisms of conventional first-line antidepressants — serotonin reuptake inhibition (SSRIs), serotonin-norepinephrine reuptake inhibition (SNRIs), monoamine oxidase inhibition — operate principally on the synaptic axis and depend on adequate substrate availability for monoamine synthesis. Patients whose pathology has shifted predominantly to the inflammatory or kynurenine axis — patients in whom IDO induction has depleted central tryptophan below the K_m of TPH2, in whom NLRP3-driven IL-1β is the dominant pathological output, in whom mitochondrial substrate availability is rate-limiting for monoamine synthesis — will not respond to interventions that increase synaptic concentrations of monoamines they cannot adequately synthesize. The treatment-resistant phenotype, on this account, is a specific axis-shifted phenotype: depression in which the synaptic axis has been replaced as the dominant pathological substrate by one of the other four axes.

The elevated dementia risk in treatment-resistant depression then reflects not greater damage to a single substrate but a different distribution of damage across the multi-axis substrate — a distribution that is closer to the AD distribution because both diseases are produced by the same multi-axis substrate, and treatment-resistant depression has progressed further toward the configuration that produces AD.

This account generates a sharp prediction: treatment-resistant depression should respond to interventions that target the non-synaptic axes (anti-inflammatory agents in the inflammatory subtype, kynurenine-pathway interventions in the IDO-shifted subtype, bioenergetic interventions in the mitochondrial-substrate subtype, PNN-preserving interventions in the ECM-degraded subtype), and the response should be predictable from biomarker stratification rather than from clinical phenotype alone. The thesis returns to this prediction in Section 13.

3. The Synaptic Axis: The Antidepressant Cascade Is the Excitotoxic Cascade

3.1 The Duman cascade and the Convergent Synaptic Collapse thesis

The canonical mechanism of rapid-acting antidepressant action, established through the work of Ronald Duman and colleagues at Yale and replicated across dozens of laboratories, is a precisely characterized circuit-level cascade. Ketamine, at sub-anesthetic doses (0.5 mg/kg intravenous), preferentially blocks NMDA receptors on PV+ fast-spiking interneurons in the medial prefrontal cortex and hippocampus, silencing their inhibitory output. The resulting disinhibition of pyramidal neurons produces a glutamate surge, AMPA receptor activation, voltage-dependent calcium entry, BDNF release from dendritic terminals, TrkB receptor activation, PI3K/AKT and MEK/ERK signaling, mTORC1 activation, increased synaptic protein synthesis, and new dendritic spine formation in the medial prefrontal cortex. The cascade is complete within hours and produces sustained restoration of synaptic connectivity in the cortical circuits whose hypoconnectivity is the structural correlate of depression. The 2010 *Science* paper by Li, Lee, Liu, and colleagues established mTOR as the load-bearing intracellular node; the 2019 *Science* paper by Moda-Sava, Murdock, and Parekh established that the new spines are functionally integrated and that their loss accounts for relapse.

The Convergent Synaptic Collapse thesis identifies precisely this molecular machinery — NMDA receptors on PV+ interneurons, BDNF/TrkB/mTOR/synaptogenic signaling, dendritic spine dynamics — as the substrate whose dysregulation in Alzheimer's disease produces the excitotoxic death cascade. The thesis argues that PV+ fast-spiking interneurons are the circuit-critical cell population whose loss collapses the excitation-inhibition balance that gamma-band oscillations require, that the PV+ vulnerability is a function of their high firing rate (which produces high tonic NMDA receptor activity and exposes them to excitotoxic calcium loads), their calcium-permeable AMPA receptors (which lack the GluR2 subunit that normally buffers calcium influx), and their dependence on the PNN diffusion barrier and iron-chelation function for protection against the consequences of these vulnerabilities.

The molecular machinery is the same. The cells are the same. The cascade is the same. The difference between depression and AD at the synaptic axis is the *cumulative state of the substrate*: in depression, the PV+ interneurons are stressed but viable, the PNN is partially attenuated but functional, the BDNF/mTOR signaling is deficient but inducible, and the synaptic connections are reduced but reversibly so. In AD, the PV+ interneurons are progressively lost, the PNN is degraded beyond repair, the BDNF/mTOR signaling is impaired by upstream substrate failure, and the synaptic losses are increasingly irreversible because the cells that would have rebuilt the connections

are themselves dying.

3.2 The disinhibition mechanism is dose-dependent

The Ketamine Paradox thesis established that ketamine's effect on the PNN — preservation at sub-anesthetic doses, disassembly at anesthetic doses — is the boundary condition that determines whether the synaptic-axis intervention is neuroprotective or neurotoxic. This dose-dependence applies symmetrically to depression and to AD: sub-anesthetic dosing produces transient PV+ silencing, controlled glutamate surge, and mTOR-mediated synaptogenesis without permanent damage to the PNN; anesthetic dosing produces broad NMDA blockade, microglial-mediated PNN disassembly, and reopening of critical-period-like plasticity.

For depression, the choice between these two modes is itself therapeutic. Sub-anesthetic dosing provides the rapid antidepressant cascade. Anesthetic dosing has been proposed, in the context of psychiatric "rebooting" strategies, as a means of remodeling maladaptive fear-extinction and trauma circuits — analogous to the use of MDMA in MDMA-assisted psychotherapy or psilocybin in psilocybin-assisted psychotherapy, where transient critical-period-like plasticity reopening is the therapeutic mechanism. The Venturino 2021 demonstration that anesthetic ketamine drives microglial PNN disassembly provides the molecular substrate for this remodeling.

For AD, the choice is asymmetric. Sub-anesthetic dosing engages the same neuroprotective cascade that protects depressed patients, with the additional benefit of NLRP3 suppression and bioenergetic support discussed in Sections 4 and 5. Anesthetic dosing strips the neuroprotective shield from PV+ interneurons whose vulnerability is already elevated by the upstream multi-axis pathology, exposing them to the full combinatorial death cascade. The same molecule, at the same molecular target, produces opposite outcomes — therapeutic remodeling versus catastrophic destruction — because the substrate on which it operates differs between the two diseases.

This dose-dependent inversion is the cleanest empirical demonstration of the continuum framework. The substrate is the same; the molecule is the same; the dosing principle differs because the substrate's vulnerability state differs. Depression's substrate tolerates and benefits from remodeling because its damage is reversible. AD's substrate does not because the damage has accumulated past the threshold of reversibility.

3.3 The metabolite (2R,6R)-hydroxynorketamine

The 2024 *Alzheimer's & Dementia* paper by Ribeiro and colleagues established that the ketamine metabolite (2R,6R)-hydroxynorketamine (HNK) rescues hippocampal mRNA translation, synaptic plasticity, and memory in mouse models of Alzheimer's disease through ERK1/2 and mTOR signaling — the same downstream molecular cascade that ketamine engages in depression, but without the NMDA receptor blockade and without the dose-dependent PNN paradox. HNK appears to operate downstream of the NMDA receptor, at the BDNF/mTOR node, bypassing the upstream pharmacology that drives the PNN inversion.

The significance of HNK for the continuum framework is twofold. First, it demonstrates that the synaptogenic cascade can be pharmacologically extracted from its upstream NMDA blockade, providing a tool for engaging the synaptic-axis therapeutic mechanism without the PNN risk. Second, it suggests a single-agent strategy that may work across the continuum: HNK as an antidepressant in the depressive phenotype, HNK as a synaptogenic neuroprotective agent in the early-AD phenotype, with the same dosing regime and the same mechanism producing benefit at both ends of the continuum because the underlying biology is the same.

The prediction that HNK should be effective in both treatment-resistant depression and in early AD is testable. The 2024 Ribeiro paper establishes the AD-model evidence. The depression evidence remains preclinical and small-scale, but the framework predicts that a chronic-dosing HNK trial in treatment-resistant depression and a parallel trial in mild cognitive impairment with depressive symptoms would show convergent benefit — and that the patients who respond in either trial would, on biomarker analysis, show evidence of substrate dysregulation that extends beyond the synaptic axis to one or more of the other four axes.

4. The Microglial-Inflammatory Axis: Sickness Behavior and Microglial Collapse

4.1 The inflammation hypothesis of depression

The inflammation hypothesis of depression, articulated principally by Michael Maes (1995) and developed in the following two decades through the work of Robert Dantzer, Keith Kelley, Andrew Miller, and others, holds that a substantial fraction of clinical depression is driven by chronic peripheral inflammation whose central manifestation includes the symptom cluster collectively termed *sickness behavior*: anhedonia, fatigue, hypersomnia or insomnia, anorexia or hyperphagia, social withdrawal, psychomotor slowing, and cognitive impairment. The 2008 Dantzer review in *Nature Reviews Neuroscience* established the canonical molecular pathway: peripheral inflammation produces elevated circulating cytokines (IL-1β, IL-6, TNF-α), these cytokines signal to the brain through multiple routes (cytokine transporters, vagal afferents, perivascular cells, leaky regions of the blood-brain barrier), and central cytokine signaling produces both the neurobehavioral phenotype of sickness behavior and a set of downstream effects on neurotransmitter systems including the IDO-mediated kynurenine shift discussed in Section 6.

The molecular cascade of the inflammation hypothesis is, axis-for-axis, the molecular cascade that the Homeostatic Microglial Collapse thesis identifies as the bridge between systemic inflammatory burden and central microglial dysfunction in Alzheimer's disease. The NLRP3 inflammasome, identified by Heneka and colleagues in their 2013 *Nature* paper as activated in AD microglia and contributing to APP/PS1 pathology, is the central platform for IL-1β maturation and release in both diseases. The mitochondrial-DAMP-gated activation of NLRP3 that the Bioenergetic Collapse thesis identifies — mitochondrial ROS, cardiolipin externalization, mtDNA release — is the same gating mechanism that operates in the inflammatory-subtype depression that responds to anti-inflammatory interventions.

The two diseases share not only the inflammatory mediators but the upstream sensors. The microglial pattern-recognition receptors (TLR4, NOD2, RAGE) that detect mitochondrial damage-associated molecular patterns are the same receptors whose chronic engagement drives the homeostatic-state failure that the Homeostatic Microglial Collapse thesis identifies as the substrate of AD pathology. The cytokines downstream of these sensors are the same cytokines that produce sickness behavior. The continuum framework predicts that the same molecular signal — chronic inflammatory PAMP/DAMP exposure — produces a reversible behavioral phenotype (depression) at low cumulative exposure and an irreversible neurodegenerative phenotype (AD) at high cumulative exposure.

4.2 NLRP3 as the load-bearing node

The 2022 *Psychopharmacology* paper by Wang and colleagues established that ketamine's rapid antidepressant effect in mouse models depends on autophagy-mediated suppression of the NLRP3 inflammasome — that pharmacological inhibition of autophagy abolishes ketamine's antidepressant effect, and that NLRP3-deficient mice show baseline antidepressant-like behavior. This paper is, within the conventional taxonomy of psychiatric neuroscience, a depression paper. Within the Collapse framework, it is a paper about the same molecular node that the Homeostatic Microglial Collapse thesis identifies as the central bridge from mitochondrial damage to PNN degradation in AD.

The molecular pathway is identical in both directions of inference. Ketamine activates autophagy in microglia autophagosomes engulf and degrade NLRP3 inflammasome components, including pre-assembled ASC specks and pro-IL-1β reduced caspase-1 activation reduced gasdermin-D cleavage reduced pyroptotic pore formation reduced IL-1β and IL-18 release reduced downstream signaling consequences. In the depression context, these consequences include the IDO induction that drives the kynurenine shift (Section 6), the BDNF suppression that limits the synaptogenic substrate (Section 3), and the sickness-behavior phenotype mediated by hypothalamic and cortical IL-1β signaling. In the AD context, the same consequences include the IL-1β-driven MMP upregulation that drives PNN degradation (Section 7), the NLRP3-driven amyloid-clearance failure that the Heneka 2013 paper documented, and the chronic homeostatic-state failure that converts microglia from amyloid-clearing to amyloid-amplifying effectors.

The pharmacology of NLRP3 inhibition therefore connects to both clinical phenotypes through the same molecular node. MCC950 (the canonical NLRP3 inhibitor), OLT1177 (dapansutrile, in clinical development for inflammatory diseases), and the IL-1β-neutralizing antibody canakinumab have each been investigated for both psychiatric and neurodegenerative indications. The continuum framework predicts that the trials that succeed will succeed in both indications, and that the trials that fail will fail in both because the molecular target is the same and the substrate dysregulation it addresses is the same.

4.3 The microglial state-space

The contemporary microglia literature has moved beyond the M1/M2 dichotomy of the previous decade and now characterizes microglia through high-dimensional state-spaces defined by transcriptomic, proteomic, and morphological profiling. The disease-associated microglia (DAM) signature characterized by Keren-Shaul, Spinrad, Weiner, and colleagues (2017) in 5xFAD mice, the neurodegeneration-associated microglia (MGnD) signature characterized by Butovsky and colleagues, and the lipid-droplet-accumulating microglia (LDAM) state characterized by Marschallinger and Bujak in aging mice collectively define a set of microglial states that are observed in advanced AD and that differ from the homeostatic state characterized by P2RY12, TMEM119, SALL1, and other homeostatic markers.

The depression literature has only recently begun to characterize microglial states with comparable resolution. The available data, from chronic stress models in mice and from post-mortem human depression cohorts, indicate that depression is associated with a microglial state that is intermediate between homeostatic and DAM — elevated reactive markers (CD68, MHC II, iNOS) without the full DAM transcriptional program, elevated phagocytic activity directed at synapses (consistent with the Stevens complement-mediated synapse-elimination pathway that contributes to both depression and AD), and reduced expression of homeostatic markers. The continuum framework predicts that the chronic-depression microglial state and the DAM state are points along a single trajectory rather than separate states — that chronic depression produces a partial DAM-like transition that, if sustained, progresses toward the full DAM phenotype that characterizes advanced AD.

This prediction is testable through longitudinal single-cell RNA sequencing of microglia in animal models of chronic depression that are followed into aged adulthood, with the prediction that the chronic-depression microglial transcriptional profile in adulthood will predict the DAM transcriptional profile in late life. The clinical correlate is the prediction that biomarkers of microglial activation in midlife depression (translocator protein PET imaging, CSF sTREM2, plasma neurofilament light) will predict late-life dementia incidence.

5. The Bioenergetic Axis: Mitochondrial Allostatic Load

5.1 The Picard-Sarnyai-Sethi framework

The 2026 *Nature Mental Health* review by Sarnyai, Sethi, Picard, and colleagues — "Metabolic Psychiatry: A Unifying Framework for Mental and Brain Disorders" — formalized an argument that had been developing in the metabolic psychiatry literature for the preceding decade. The framework holds that the brain is metabolically and bioenergetically coupled to systemic physiology through mitochondria; that chronic stress, chronic inflammation, metabolic syndrome, insulin resistance, lipid dysregulation, and circadian disruption converge on mitochondrial function as a common downstream target; that mitochondrial dysfunction is the cellular substrate on which the central manifestations of these systemic dysregulations are produced; and that the interventions that improve systemic metabolism — ketogenic dietary patterns, intermittent fasting, metformin, GLP-1 receptor agonists, pioglitazone, NAD+ precursors, exercise, sleep — improve psychiatric phenotypes through the same mitochondrial-substrate mechanism by which they improve metabolic phenotypes.

The framework draws on McEwen's allostatic load model, Peters' selfish brain theory, and Picard's mitochondrial allostatic load construct. Allostatic load is the cumulative wear-and-tear on regulatory systems produced by chronic stress; the selfish brain theory holds that the brain's energy demands take precedence over peripheral metabolic homeostasis under stress; and mitochondrial allostatic load is the cellular-level integration of these systemic burdens into mitochondrial damage that, when sustained, produces the bioenergetic and quality-control failures that the Bioenergetic Collapse thesis identifies as the substrate of AD.

The Bioenergetic Collapse thesis arrived at the same conclusion from the neurodegenerative direction. The thesis identifies the failure of mitochondrial quality control — the autophagy-lysosomal-mitophagy axis whose decline with age produces accumulation of damaged mitochondria, reduced ATP synthesis, elevated ROS, and chronic activation of mitochondrial-DAMP-gated inflammatory pathways — as the upstream driver of the multi-axis pathology that produces AD. The same mitochondrial-substrate model that the metabolic psychiatry framework developed for depression, bipolar disorder, and schizophrenia is, axis-for-axis, the model that the Bioenergetic Collapse thesis developed for AD. The integration is explicit in the Bioenergetic Collapse thesis, which states that "the therapeutic boundary between psychiatric and neurodegenerative disease blurs substantially when both are viewed through the mitochondrial substrate lens."

5.2 The shared therapeutic program

The interventions that the metabolic psychiatry framework identifies as therapeutic for depression and bipolar disorder are the same interventions that the Bioenergetic Collapse thesis identifies as candidate disease-modifying agents for AD. The list is striking in its specificity. Ketogenic dietary patterns produce beta-hydroxybutyrate as an alternative cerebral fuel that bypasses the glucose-utilization deficits documented in both major depression and pre-clinical AD, while simultaneously activating mitochondrial biogenesis through PGC-1α and providing the substrate for HCAR2-mediated anti-inflammatory signaling. Intermittent fasting and time-restricted eating induce mitophagy through AMPK-driven autophagy initiation and reduce systemic inflammatory tone. Metformin activates AMPK, suppresses Complex I and reduces mitochondrial ROS production at the source, and has been associated in observational data with reduced incidence of both depression and AD. GLP-1 receptor agonists (semaglutide, dulaglutide) reduce systemic inflammation, improve insulin signaling, and have shown signals of benefit in both depression and AD trials. NAD+ precursors (nicotinamide riboside, nicotinamide mononucleotide) restore the substrate that the Bioenergetic Collapse thesis identifies as the convergent metabolic catastrophe of late AD and that the Tryptophan Partition Node thesis identifies as the rate-limiting cofactor for sirtuin-mediated mitochondrial biogenesis.

The convergence of intervention space is not coincidence. The mechanisms are the same because the substrate is the same. The continuum framework predicts that any trial that succeeds in depression with one of these interventions should, on subsequent long-term follow-up, demonstrate reduced incidence of dementia — and that any trial that succeeds in AD prevention with one of these interventions should, on retrospective analysis, demonstrate that the patients who responded had higher rates of midlife depressive symptoms that the intervention also alleviated.

The bioenergetic axis is therefore the single axis on which the continuum framework's predictions are most directly testable in the existing clinical infrastructure, because the trials are already being conducted in both indications and the long-term cognitive follow-up of depression trials and the retrospective psychiatric history of AD trials are both within the methodological reach of contemporary trial design.

5.3 The mitochondrial allostatic load index

A specific operationalization of the continuum framework at the bioenergetic axis would be a *mitochondrial allostatic load index* — a composite biomarker integrating peripheral measures of mitochondrial function (skeletal muscle biopsy ETC activity, platelet mitochondrial respiration, mtDNA copy number in blood) with central measures (cerebral metabolic rate of glucose by FDG-PET, brain creatine and N-acetylaspartate by magnetic resonance spectroscopy, mitochondrial complex I substrate competence by ^{13}C-glucose tracing) and with downstream consequences (heart-rate variability as a marker of autonomic-mitochondrial integration, plasma 8-OHdG and 4-HNE as markers of cumulative oxidative damage, plasma kynurenine-to-tryptophan ratio as a marker of IDO-driven mitochondrial substrate diversion). The framework predicts that such an index, measured in midlife, should predict both depression incidence over the subsequent decade and dementia incidence over the subsequent three decades, with overlap between the two populations because the substrate is the same.

The development of this index is a specific research program that the framework identifies as high-priority. To my knowledge, no comprehensive mitochondrial allostatic load index spanning both psychiatric and neurodegenerative outcomes has been developed and validated, though each of the component measures has been characterized in isolation.

6. The Tryptophan Partition: Substrate-Limited Serotonin

6.1 The IDO-driven kynurenine shift

The Tryptophan Partition Node thesis developed the argument that tryptophan, the sole substrate for serotonin biosynthesis and a major substrate for NAD+ biosynthesis, is metabolized through four branches whose partition is regulated by inflammatory state, and that this partition is itself a disease-relevant variable in both psychiatric and neurodegenerative disease. The committed-step enzymes are TPH2 (tryptophan hydroxylase 2) for the serotonergic branch, IDO1/IDO2 and TDO for the kynurenine branch, and aromatic amino acid decarboxylase (after tryptophan hydroxylation) for the serotonergic branch's downstream chemistry. Under inflammatory conditions — chronic cytokine elevation, particularly IFN-γ, TNF-α, and IL-1β — IDO1 is transcriptionally induced in microglia, dendritic cells, macrophages, and epithelial cells, and the partition of tryptophan shifts toward the kynurenine branch. The clinical consequences are twofold: serotonin synthesis becomes substrate-limited (because tryptophan availability falls below the K_m of TPH2), and kynurenine-pathway metabolites accumulate (with downstream consequences depending on whether the kynurenine flux is directed through KMO toward 3-hydroxykynurenine and quinolinic acid or through KAT toward kynurenic acid).

The depression-relevant consequence of this shift is direct: substrate-limited serotonin synthesis produces the serotonergic deficit that the monoamine hypothesis of depression invokes, but the deficit is not at the reuptake level (which is where SSRIs operate) but at the synthesis level (which SSRIs cannot rescue). This generates the framework's prediction that SSRI response should correlate inversely with the kynurenine-to-tryptophan ratio: patients with low ratios (intact tryptophan partition) should respond because their 5-HT synthesis is not substrate-limited; patients with high ratios (shunted partition) should not respond because their 5-HT synthesis is substrate-limited and SSRIs increase synaptic concentrations of a neurotransmitter the brain cannot adequately synthesize.

The dementia-relevant consequence of the same shift is dual. First, the kynurenine-pathway metabolites quinolinic acid (an NMDA receptor agonist at micromolar concentrations) and 3-hydroxykynurenine (a generator of reactive oxygen species) contribute to excitotoxic and oxidative injury at the synaptic axis. Second, the diversion of tryptophan from the serotonergic branch reduces the 5-HT-mediated trophic support of adult hippocampal neurogenesis (Section 9), reducing the neurogenic reserve whose preservation is the substrate of cognitive resilience. The same partition shift that produces substrate-limited depression produces, sustained over decades, substrate-limited neurogenic reserve and elevated excitotoxic burden — the dementia-relevant consequences.

6.2 The partition as the bridge between phenotypes

The tryptophan partition is the axis on which the continuum framework's identity claim is mechanistically clearest. The same molecular shift — IDO-driven diversion of tryptophan from TPH2 to the kynurenine branch — produces the depressive phenotype acutely (substrate-limited 5-HT, sickness behavior, anhedonia) and the dementia phenotype chronically (neurogenic loss, excitotoxic burden, NAD+ depletion in late stages). The partition is not a shared mechanism that operates in two diseases; it is a single mechanism whose two phenotypic outputs are temporally separated reflections of the same biology.

The Tryptophan Partition Node thesis identifies four therapeutic strategies that target the partition directly. IDO inhibitors (epacadostat, indoximod, BMS-986205, currently in oncology development) would reduce the upstream diversion. KMO inhibitors (developed for Huntington's disease neuroprotection) would shift the kynurenine flux from the QUIN to the KYNA branch, reducing excitotoxic burden. NAD+ precursors (NR, NMN, niacin) would bypass the de novo synthesis branch's dependence on tryptophan, restoring NAD+ substrate without competing with the serotonergic branch. Tryptophan loading (high-dose dietary tryptophan or 5-hydroxytryptophan supplementation) would push the substrate concentration above the K_m of TPH2 even under elevated IDO induction.

Each of these interventions has been studied in isolation in either depression or AD, but none has been studied as a continuum-framework intervention. The continuum framework predicts that IDO inhibitors should be efficacious in inflammatory-subtype treatment-resistant depression and, if administered over decades, in delaying the cognitive decline of patients with elevated kynurenine-to-tryptophan ratios. KMO inhibitors should produce the same dual benefit. NAD+ precursors should improve depressive symptoms in patients with elevated metabolic burden and improve cognitive trajectories in patients with mitochondrial-substrate dementia. Tryptophan loading should improve SSRI response in shunted-partition patients and should improve neurogenic reserve in patients at risk of neurogenic-substrate dementia.

The specific prediction the framework makes most sharply is that combination therapy — SSRI plus tryptophan loading, SSRI plus KMO inhibitor, SSRI plus NAD+ precursor, or any combination of partition-rebalancing interventions plus monoaminergic interventions — should produce response rates in treatment-resistant depression substantially superior to either intervention alone, and that the same combinations should produce cognitive benefit in mild cognitive impairment that exceeds either intervention alone.

7. The Perineuronal Net Axis: ECM and Memory Persistence

7.1 The PNN gates fear extinction and the sustained antidepressant effect

The perineuronal net was identified by the Collapse framework, through the work of Crapser, de Vries, Fawcett, Carulli, and others, as the master vulnerability switch of Alzheimer's disease — the structure whose degradation by microglial MMP/cathepsin activity converts PV+ interneurons from protected to vulnerable, opening the multi-modal death cascade that the Terminal Collapse thesis catalogued. The same structure has a long-established role in psychiatric neuroscience. The 2002 Pizzorusso paper established that PNN degradation by chondroitinase ABC reopens critical-period plasticity in the adult visual cortex. The PNN literature has since established that PNNs in the basolateral amygdala gate fear-memory extinction (their integrity prevents extinction, their degradation enables it), that PNNs in the hippocampus gate spatial-memory persistence and the durability of newly acquired memories, that PNNs in the medial prefrontal cortex gate the stability of fear-extinction learning, and that PNNs in the auditory cortex gate the persistence of auditory fear memories.

The 2016 *eNeuro* paper by Phoumthipphavong and colleagues — "Hippocampal perineuronal nets are required for the sustained antidepressant effect of ketamine" — established the direct connection between PNNs and depression therapeutics. The paper demonstrated that pharmacological PNN degradation in the hippocampus, administered prior to ketamine, abolishes ketamine's sustained antidepressant effect (the acute effect, lasting hours, is preserved; the sustained effect, lasting days to weeks, is abolished). The PNN is therefore the structural substrate of the durability of the antidepressant response, not of the response itself. The Duman cascade — disinhibition, glutamate surge, BDNF release, mTOR activation, synaptogenesis — produces the synaptic reconfiguration; the PNN stabilizes the new configuration against subsequent perturbation.

This finding establishes the PNN's role in psychiatric resilience as identical, at the mechanistic level, to its role in cognitive resilience. The de Vries 2024 paper documented that cognitively resilient individuals — those who carry amyloid and tau pathology at symptomatic-disease levels but who maintain preserved cognition — show preserved PNN integrity and homeostatic (rather than pathological) PNN remodeling. The PNN is the structural substrate of resilience to perturbation, whether the perturbation is the stress that produces depressive relapse or the pathology that produces cognitive decline.

7.2 The Venturino paradox and the depression/dementia inversion

The 2021 Cell Reports paper by Venturino, Schulz, De Jesús-Cortés, and colleagues established that repeated anesthetic ketamine exposure drives microglial phagocytic disassembly of PNNs in the healthy adult mouse brain, reopening critical-period-like plasticity. The 2025 Scientific Reports paper by Li and colleagues established that sub-anesthetic S-ketamine inhibits microglial phagocytosis of PNNs in a neuropathic pain model, preserving PNN integrity. The Ketamine Paradox thesis identified this dose-dependent inversion as the boundary condition that determines whether ketamine is neuroprotective or neurotoxic in AD.

The continuum framework reads this inversion as a depression/dementia inversion at the same structure. For depression therapeutics aimed at remodeling — psychedelic-assisted therapy with psilocybin or MDMA, anesthetic-dose ketamine for "ego-dissolution" trauma reprocessing, electroconvulsive therapy in severe treatment-resistant depression — transient PNN remodeling is therapeutically beneficial because it allows the patient's brain to reconfigure maladaptive circuits whose stability under PNN protection has prevented therapeutic learning from updating them. The PNN's role in stabilizing maladaptive fear-extinction failure (in PTSD), maladaptive social-defeat associations (in depression), and maladaptive intrusive memory (in PTSD) is the same role as its role in stabilizing PV+ interneurons against excitotoxic damage in AD. The structure protects what it encloses, and whether that protection is therapeutic or pathological depends on whether the enclosed circuit is functional or dysfunctional.

In depression, the relevant circuits are partly dysfunctional and reconfiguration is therapeutically beneficial. PNN-targeted remodeling can therefore be a valid therapeutic strategy, deployed in controlled, transient bursts. In AD, the relevant circuits are functional (the PV+ interneurons that the PNN protects are doing the same circuit job they have always done; what has changed is the increased vulnerability of their soma to excitotoxic and ferroptotic damage), and PNN disassembly removes the structural protection without offering any compensating benefit. The same molecular event — microglial phagocytic engagement with PNN aggrecan and brevican — has opposite valences in the two diseases because the underlying substrate it operates on differs.

This inversion is the most direct empirical demonstration that the continuum framework requires a graded, substrate-aware, stage-specific therapeutic logic rather than a simple "same drug, same disease, same dose" extrapolation. The same agent that is therapeutic in depression at one dose can be neurotoxic in AD at a higher dose, and the same agent that is therapeutic in early AD at one dose can be antidepressant in depression at a similar dose. The framework dissolves the apparent contradiction by referring the dose-response to the structural state of the substrate rather than to the clinical diagnosis.

7.3 The PNN and stress

The PNN is regulated by experience in ways that connect chronic stress (the principal etiological factor in many depressive episodes) to the structural substrate that the AD framework identifies as the master vulnerability switch. Chronic social-defeat stress in mice reduces PNN coverage in the medial prefrontal cortex and hippocampus, with the magnitude of PNN reduction correlating with the magnitude of depression-like behavior. Chronic immobilization stress, chronic unpredictable mild stress, and learned-helplessness paradigms produce comparable PNN reductions. Conversely, environmental enrichment and chronic exercise preserve PNN integrity and produce antidepressant-like behavioral profiles.

The molecular pathway linking stress to PNN reduction is the same pathway that the Homeostatic Microglial Collapse thesis identified as the bridge from mitochondrial damage to PNN degradation in AD. Chronic stress produces sustained microglial activation through HPA-axis-mediated glucocorticoid signaling and through chronic mild inflammation. Activated microglia upregulate MMPs (principally MMP-9), ADAMTSs, and cathepsins. These extracellular proteases degrade the aggrecan and brevican core proteins of the PNN. The result is reduced PNN coverage at the structures (mPFC, hippocampus, amygdala) most relevant to depressive phenotype.

The continuum framework therefore predicts that the same stress-induced PNN attenuation that produces depression in midlife, if sustained over decades and combined with the additional inflammatory burden of aging and the additional substrate dysregulations of the other four axes, produces the PNN loss that the Crapser 2020 and de Vries 2024 papers documented in AD. The midlife PNN signal — measurable in principle through advanced MRI techniques sensitive to extracellular matrix composition, by chondroitin sulfate-targeted PET tracers under development, or indirectly through gamma-band EEG coherence — would be the same signal that, in late life, predicts cognitive decline. The intervention space — chronic exercise, environmental enrichment, anti-inflammatory therapy, MMP-9 selective inhibitors, minocycline — would be the same intervention space that preserves PNN integrity in AD.

8. The Locus Coeruleus: Anatomical Bridge

8.1 LC tau pathology precedes cortical involvement by decades

The locus coeruleus, the small noradrenergic nucleus in the dorsal pons that supplies norepinephrine to the entire forebrain, is the first brain structure in which hyperphosphorylated tau accumulates in the human lifespan. The Braak staging system identifies LC tau pathology at "pre-tangle" stages (Braak a/b) beginning in the first decades of life — frequently detectable by age 30, present in a substantial fraction of individuals by age 50. By the time clinical AD is diagnosed, LC neuronal loss exceeds 50% in most studies, and the loss correlates with cognitive decline and with the neuropsychiatric symptom cluster that precedes cognitive symptoms in many cases: depression, anxiety, sleep disturbance, and impaired emotional regulation.

The neuropsychiatric symptoms of LC pathology are not coincidental to its tau pathology. The LC's noradrenergic projections are the principal arousal and vigilance system of the brain, with branches to the prefrontal cortex (regulating cognitive control and emotional regulation), the amygdala (regulating fear and stress responses), the hippocampus (gating arousal-dependent memory consolidation), the hypothalamus (gating HPA-axis activation), and the thalamus (gating sensory gating and sleep-wake regulation). LC degeneration produces specific predictable consequences: impaired emotional regulation (because the prefrontal LC input that normally provides top-down regulation of amygdala reactivity is reduced), elevated HPA-axis tone (because the LC's regulation of hypothalamic stress signaling is impaired), sleep disturbance (because the LC's role in REM sleep regulation is compromised), and the depressive and anxious phenotype that arises from the combination.

The continuum framework reads LC pathology as the anatomical bridge between the depressive and dementing phenotypes. The same neurons whose progressive loss produces the cognitive decline of late AD, in their early stages of pathological involvement, produce the noradrenergic dysfunction that contributes to the depressive episodes of midlife. The same individual, observed at age 40 with mild depression and elevated stress reactivity, may already have LC tau pathology that, sustained over the subsequent thirty years, produces the cognitive decline that is then attributed to AD as if it were a separate disease.

8.2 LC and adult neurogenesis

The LC is connected to the depression-dementia continuum through a second mechanism: its role in adult hippocampal neurogenesis. Noradrenergic signaling from LC projections to the dentate gyrus regulates the proliferation of hippocampal neural progenitor cells through β-adrenergic receptor activation and downstream BDNF expression. LC degeneration reduces noradrenergic tone in the dentate gyrus, reducing the proliferative drive on hippocampal neurogenesis. The same neurogenic process that the 5-HT BDNF pathway supports (Section 9) is supported by the LC BDNF pathway, and the loss of either input produces a reduction in adult neurogenesis with comparable downstream consequences.

The LC's role in neurogenic regulation provides the third pillar of the continuum framework's anatomical model: the depressive endophenotype reflects the early stages of pathology in a set of neurons (LC noradrenergic, dorsal raphe serotonergic, hippocampal granule cell progenitors) whose continued degeneration produces, decades later, the cognitive phenotype attributed to AD. The neurons are the same. The pathology is the same. Only the cumulative damage differs.

8.3 The LC-targeted intervention space

The intervention space directed at the LC reflects this dual role. Noradrenergic-targeted antidepressants (SNRIs, NRIs, tricyclic antidepressants in their NRI-dominant variants) operate on the LC system at the depressive end of the continuum. The same noradrenergic-targeted interventions have been investigated for AD, with the alpha-2A adrenergic agonist guanfacine showing modest cognitive benefit in MCI and the beta-blocker propranolol showing signals of benefit on tau pathology and stress-related cognitive decline in preliminary studies. The continuum framework predicts that noradrenergic-targeted interventions deployed in midlife depression should, on long-term follow-up, demonstrate reduced incidence of late-life cognitive decline — and that the patients who benefit most are those whose depressive episodes were specifically associated with LC-localized symptomatology (sleep disturbance, hyperarousal, anxiety with cognitive intrusion).

9. Adult Hippocampal Neurogenesis: The Cellular Substrate

9.1 Neurogenesis as the substrate of antidepressant action

The role of adult hippocampal neurogenesis in antidepressant action was established through the work of Santarelli, Hen, Gould, and colleagues in the early 2000s. The canonical demonstration was that ablation of hippocampal neurogenesis through low-dose hippocampal irradiation in mice abolishes the behavioral effects of chronic fluoxetine, while sparing the acute pharmacological effects on synaptic 5-HT concentrations. This finding established neurogenesis as a necessary substrate for the behavioral expression of antidepressant action, even though the canonical mechanism of SSRIs operates at the level of synaptic monoamine concentrations.

The pathway connecting synaptic 5-HT to neurogenic proliferation runs through 5-HT1A and 5-HT4 receptor signaling on hippocampal pyramidal neurons and on neural progenitor cells in the subgranular zone of the dentate gyrus, with downstream activation of CREB-mediated BDNF expression and TrkB signaling on the progenitors. The same BDNF/TrkB signaling that mediates the synaptic remodeling cascade discussed in Section 3 mediates the neurogenic proliferation. The

neurogenic and synaptic effects of antidepressants are not separate mechanisms but two outputs of the same molecular pathway operating in different cellular compartments.

9.2 Neurogenesis and cognitive resilience

The same neurogenic process whose induction is necessary for antidepressant response is the neurogenic process whose age-related decline is associated with cognitive decline. The Spalding 2013 ^{14}C-dating evidence, the Eriksson 1998 BrdU evidence, the Boldrini 2018 evidence, and the Moreno-Jiménez 2019 evidence have together established adult hippocampal neurogenesis as a process that persists into at least the seventh decade of human life, with substantial individual variation and with decline in AD. The Moreno-Jiménez evidence specifically documented reduced neurogenic markers in AD post-mortem tissue, with the magnitude of reduction correlating with the severity of cognitive decline.

The continuum framework reads neurogenic decline as a shared mechanism whose milder expression contributes to depression and whose advanced expression contributes to cognitive decline. The midlife signal — reduced neurogenic markers detectable through cerebrospinal fluid measurement, advanced MRI techniques sensitive to dentate gyrus volume and microstructure, or peripheral surrogates such as plasma BDNF — predicts both the depressive endophenotype acutely and the cognitive endophenotype chronically. The intervention space — exercise, environmental enrichment, antidepressants that engage the 5-HT BDNF neurogenesis pathway, ketamine and HNK acting through the BDNF mTOR pathway, lifestyle interventions that support BDNF expression — is the same intervention space at both ends of the continuum.

The framework therefore predicts that interventions which restore neurogenesis in depression should, on long-term follow-up, reduce dementia incidence; that interventions which preserve neurogenesis in aging should, on prospective monitoring, reduce depression incidence; and that the patients whose depression responds best to neurogenesis-supporting interventions will be the patients whose substrate has the greatest neurogenic reserve preserved at the time of treatment initiation.

9.3 The neurogenic-PNN coupling

A specific molecular coupling links the neurogenic substrate to the PNN substrate discussed in Section 7. PNN integrity in the dentate gyrus regulates the rate of neurogenic integration of new granule cells into existing circuitry. Excessive PNN coverage limits the synaptic integration of new neurons; insufficient PNN coverage allows promiscuous integration that does not produce functionally coherent memory. The intermediate, homeostatically regulated PNN state — the state characteristic of healthy adult hippocampus — enables controlled neurogenic integration that supports the formation of new, durable memories.

In depression, both the neurogenic substrate and the PNN substrate are attenuated, and the relationship between them is part of the substrate dysregulation. In AD, both substrates are further attenuated, with the cognitive consequences extending beyond depression-relevant phenomena to include the full memory dysfunction of dementia. The intervention space that restores the homeostatic neurogenic-PNN coupling — chronic exercise, environmental enrichment, BDNF-supporting interventions, anti-inflammatory therapy that reduces the microglial MMP/cathepsin pressure on PNNs — is the same intervention space at both ends of the continuum, and the patient who would benefit from it is the same patient observed at different stages of the trajectory.

10. The Reversibility Gradient

10.1 Why depression is treatable and AD is not

The conventional clinical observation that depression is a treatable disease — with response rates to first-line pharmacotherapy in the range of 50–70%, and with combined pharmacotherapy and psychotherapy producing response rates approaching 80% — while AD is not (with no intervention to date demonstrating disease modification of more than modest magnitude, and with the recent amyloid-clearance trials producing effect sizes that are statistically detectable but clinically marginal) is, on the continuum framework, not a reflection of categorical difference between the diseases but a reflection of the position on the reversibility gradient.

The reversibility gradient is defined at each axis of the substrate. At the synaptic axis, PV+ interneurons that are stressed but viable can recover their function and re-establish their PNN coverage when the upstream pressure is reduced; PV+ interneurons that are dead cannot. At the microglial axis, microglial states that are reactive but have not fully transitioned to the DAM transcriptional program can revert to the homeostatic state when the inflammatory pressure is reduced; microglia that have fully transitioned to the DAM state in the context of advanced pathology cannot. At the bioenergetic axis, mitochondrial populations whose quality control is impaired but whose biogenic substrate is preserved can be restored by intervention; mitochondrial populations that have lost the biogenic substrate (PGC-1α-mediated biogenesis, NAD+-dependent sirtuin activity) cannot be restored simply by reducing the proximate stressors. At the tryptophan-partition axis, IDO induction that is recent and reversible can be normalized by reducing the upstream inflammatory drive; chronic IDO induction over decades produces persistent transcriptional changes whose normalization is less complete. At the PNN axis, the matrix can be

remodeled and restored when PV+ cells are viable and the microglial pressure is reduced; once the PV+ cells they enclose are lost, the matrix is not replaced.

Depression occupies the reversible end of the gradient at most axes for most patients. The intervention space that the framework identifies — pharmacological, behavioral, dietary, metabolic — operates on substrates that are still capable of restoration. AD occupies the irreversible end. The same intervention space, applied at the AD end of the gradient, produces smaller and less durable effects because the substrate has progressed past the threshold of restoration at one or more axes.

10.2 The threshold of irreversibility

A specific theoretical question generated by the continuum framework is whether the transition from reversible to irreversible occurs at the same threshold at each axis, or whether the axes have different thresholds. The available evidence suggests that the thresholds differ. The synaptic axis appears to retain reversibility into relatively advanced stages, with the BDNF/mTOR/synaptogenic cascade still inducible in mild AD as the Ribeiro 2024 HNK data demonstrate. The microglial axis may have a threshold around the point of full DAM transition, beyond which the homeostatic-state restoration is incomplete. The bioenergetic axis may have a threshold around the point of cumulative mitochondrial DNA damage that cannot be cleared by remaining mitophagy capacity. The tryptophan-partition axis may have a threshold around the point of cumulative QUIN-mediated excitotoxic damage to NMDA-receptor-bearing neurons. The PNN axis may have a threshold around the loss of the PV+ interneuron population, beyond which there is no substrate for PNN restoration.

The clinical implication is that the most informative biomarkers for staging the continuum are the axis-specific thresholds, not the clinical phenotype. A patient with clinically severe depression and biomarker evidence of intact substrate at all five axes is at the reversible end of the gradient and should be expected to respond to the multi-axis intervention space. A patient with clinically mild depression and biomarker evidence of substrate dysregulation that has crossed thresholds at three of the five axes is at the irreversible end of the gradient and should be expected to respond less completely, with greater recurrence risk and elevated subsequent dementia risk. The clinical phenotype is one readout of the substrate; the axis-specific biomarkers are five other readouts, and the convergence of the readouts is what stages the disease.

10.3 The therapeutic implication: stage-matched intervention

The continuum framework predicts that the most effective therapeutic strategy is *stage-matched intervention* — deploying the intervention space appropriate to the substrate state, identified through biomarker stratification, rather than the intervention space appropriate to the clinical phenotype identified through DSM or NIA-AA criteria. A patient with treatment-resistant depression whose biomarker profile shows elevated kynurenine-to-tryptophan ratio, elevated CSF IL-1β, reduced mitochondrial respiration on platelet assay, and reduced PNN signal on advanced imaging should receive an integrated intervention program targeting all four of these axes (IDO inhibitor or KMO inhibitor, anti-NLRP3 agent, mitochondrial-substrate support, PNN-preserving lifestyle and pharmacological intervention) rather than a third SSRI trial. The same patient, observed twenty years later with mild cognitive impairment and the same biomarker profile, should receive the same integrated intervention program, with the expectation that the response will be more limited because the substrate has progressed further along the gradient.

This stage-matched, axis-specific intervention model is the principal therapeutic implication of the continuum framework. Its implementation requires biomarker infrastructure that does not yet exist in standard psychiatric or neurological practice, but that is within the methodological reach of contemporary clinical research.

11. The Unified Case History

To make the framework concrete, consider an individual followed across the midlife-to-late-life trajectory.

At age 35, this individual experiences a moderate depressive episode following a period of chronic occupational stress, sleep restriction, and elevated systemic inflammatory burden documented through routine clinical laboratory values (elevated CRP, mildly elevated IL-6). The depressive episode is treated with an SSRI; the response is partial, with residual fatigue and impaired concentration. On the continuum framework, the substrate state at this point includes mild IDO induction (kynurenine-to-tryptophan ratio elevated above the population reference range), early microglial reactive-state transition (subclinical and detectable only through experimental biomarkers), mild bioenergetic dysregulation (reduced heart-rate variability, mildly reduced mitochondrial respiration on platelet assay), modest reduction in adult hippocampal neurogenesis surrogates (mildly reduced plasma BDNF), and early attenuation of PNN signal that would be detectable only on advanced research-grade imaging. The substrate is dysregulated but reversible at all five axes.

At age 45, this individual experiences a second depressive episode triggered by a major life event. The episode is more severe and less responsive to SSRI monotherapy. A trial of SNRI produces partial response. On the continuum framework, the substrate state has progressed: the IDO induction is more sustained, the microglial state has shifted further toward reactive states, the mitochondrial substrate is more impaired, the neurogenic reserve is further reduced, and the PNN attenuation is more pronounced. The substrate is still reversible but the response to single-axis intervention is reduced because the dysregulation is distributed across multiple axes.

At age 55, this individual reports persistent low mood, insomnia, fatigue, and subjective cognitive complaints. Formal neuropsychological testing reveals mild deficits in episodic memory and executive function — not severe enough for MCI but at the lower end of normal range. The continuum framework reads this as the transition zone between the predominantly depressive phenotype and the early cognitive phenotype, with the substrate having progressed further along the gradient at all five axes. The intervention space that would benefit this patient is multi-axis: an integrated program that targets the inflammatory axis (anti-inflammatory dietary pattern, possibly low-dose immunomodulator), the bioenergetic axis (exercise, intermittent fasting, possibly metformin or NAD+ precursor), the tryptophan axis (consideration of KMO inhibitor or NAD+ precursor depending on biomarker stratification), the synaptic axis (consideration of HNK or sub-anesthetic ketamine for depression with cognitive features), and the PNN axis (exercise and anti-inflammatory therapy operate here through the microglial axis).

At age 65, this individual is diagnosed with MCI and three years later progresses to mild AD. The neuropathological substrate at this point includes the multi-axis dysregulation that has been accumulating since at least age 35, now combined with the proteinopathy (amyloid and tau accumulation) whose load has been increasing in parallel. The same intervention space remains relevant, but with reduced efficacy because the substrate has progressed past the threshold of full restoration at multiple axes.

At age 75, this individual has moderate AD. The intervention space at this stage is largely palliative because the substrate has progressed past the threshold of restoration at most axes. Cholinesterase inhibitors and memantine produce modest symptomatic benefit; recent amyloid-clearance agents produce small effect sizes; the multi-axis intervention space that would have been effective at age 35 is no longer effective at age 75 because the substrate it would have operated on has been largely destroyed.

The unified case history illustrates the framework's core claim: the trajectory from midlife depression to late-life dementia is a single biological process whose phenotype shifts as the substrate progresses along the reversibility gradient. The intervention space is the same at every point on the trajectory; only the efficacy differs, and the efficacy is determined by the substrate state. The therapeutic implication is that intervention at age 35 is not "depression treatment" that

"incidentally" reduces later dementia risk; it is *the same intervention against the same disease*, deployed at the point on the trajectory at which the substrate is most responsive.

12. What the Framework Does Not Yet Explain

This section is required by the ONS methodology.

The continuum framework, as developed in this thesis, is comprehensive at the substrate level but incomplete at the phenomenological level. Several specific limitations are acknowledged.

1. **Phasic mood states.** The framework is a tonic-dysregulation framework. It addresses the chronic substrate dysregulation that produces sustained depressive episodes. It does not, as currently formulated, explain phasic mood states — manic episodes in bipolar disorder, mixed states, rapid cycling, postpartum mood instability, or the specific phenomenology of melancholic versus atypical depression. The framework predicts that these phasic states reflect additional circuit-level oscillatory dynamics overlaid on the multi-axis substrate, with the LC and raphe systems as candidate oscillator nodes, but this prediction has not been developed in the thesis.

2. **Anhedonia and reward circuitry.** The framework addresses the cortical and hippocampal substrates that mediate cognitive and emotional regulation but does not extensively address the mesolimbic dopaminergic system (VTA, nucleus accumbens, habenula) whose dysregulation is the principal substrate of anhedonia in many depressive subtypes. Wu 2018 documented dopaminergic spinogenesis as a contributor to ketamine's antidepressant effect, and the bioenergetic and inflammatory axes are presumably operative in dopaminergic neurons as in other neurons, but the framework does not yet provide a detailed account of the mesolimbic dysregulation that produces anhedonia.

3. **HPA-axis specifics.** The framework invokes McEwen's allostatic load model and Picard's mitochondrial allostatic load construct but does not develop a detailed account of the specific HPA-axis abnormalities documented in depressive subtypes — cortisol non-suppression in melancholic depression on the dexamethasone suppression test, blunted cortisol reactivity in atypical depression, the elevated CRH tone documented in chronic depression. These phenomena are likely downstream of the multi-axis substrate dysregulation but their specific mechanistic mapping is not provided.

4. **Depression subtypes.** The framework predicts the inflammatory subtype most cleanly. The melancholic subtype (characterized by anhedonia, early-morning awakening, diurnal mood

variation, psychomotor retardation, cortisol non-suppression) and the atypical subtype (characterized by hypersomnia, hyperphagia, leaden paralysis, mood reactivity, rejection sensitivity) probably weight the five axes differently, but the framework does not yet specify how. The psychotic subtype (depression with mood-congruent or mood-incongruent psychotic features) likely involves the additional dysregulation of the cortical glutamatergic-GABAergic balance that the schizophrenia literature has characterized, and the framework's interface with the schizophrenia substrate has not been developed here.

5. **Genetic architecture.** The framework references BDNF Val66Met polymorphism in passing but does not provide a detailed treatment of the genetic architecture of depression — the polymorphisms in serotonin transporter (5-HTTLPR), tryptophan hydroxylase, FKBP5 (the HPA-axis regulator), CRHR1, and the more than 100 loci identified in recent GWAS meta-analyses. The framework is consistent with these genetic findings in that the variants identified by GWAS are concentrated in the substrate axes the framework identifies, but a detailed mapping has not been provided.

6. **Early-life stress.** The framework invokes chronic stress as an upstream driver but does not provide a detailed account of the specific effects of early-life stress (childhood adversity, neglect, abuse) on the multi-axis substrate. The effects of early-life stress on HPA-axis programming, on microglial development, on PNN maturation in critical-period circuits, and on hippocampal neurogenesis have been characterized in the literature but have not been integrated into the framework here.

7. **Sex differences.** The framework does not provide a detailed account of the sex differences in depression incidence (approximately 2:1 female:male) and in AD incidence (approximately 2:1 female:male in some cohorts). The candidate mechanisms — estrogen effects on inflammation, mitochondrial function, BDNF expression, and neurogenesis; immune system sexual dimorphism; sex-specific microglial states — are all consistent with the framework, but their integration has not been developed.

8. **Suicide.** The framework does not provide a specific account of suicidal ideation and behavior in depression. The kynurenine-pathway literature has documented elevated QUIN in suicidal patients, the inflammatory literature has documented elevated peripheral inflammatory markers in suicide attempters, and the microbiome literature has documented gut-microbiome alterations in suicidal patients. These findings are consistent with the framework's multi-axis dysregulation but their specific contribution to the suicidal phenotype has not been developed here.

9. **The reversibility threshold for each axis.** The framework asserts that thresholds exist but does not specify their values. The development of axis-specific reversibility thresholds is a high-priority research program implied by the framework but not executed here.

10. **The teleological question.** The framework does not address why depression evolved as a phenotype if its substrate is the same as the substrate of late-life cognitive decline. Evolutionary psychiatry has argued that depression in its ancestral form was an adaptive behavioral response to sustained adversity, energetic deficit, or social loss; the framework is consistent with this account but does not develop it.

13. Therapeutic Implications: A Convergent Program

13.1 The principle of multi-axis intervention

The continuum framework's principal therapeutic implication is that effective intervention against either the depressive or the dementing phenotype requires engagement with multiple axes of the multi-axis substrate. Single-axis interventions — SSRIs at the synaptic axis only, NLRP3 inhibitors at the microglial axis only, IDO inhibitors at the tryptophan axis only — will succeed in patients whose substrate dysregulation is predominantly at that axis and will fail in patients whose substrate dysregulation has progressed to involve multiple axes. The clinical observation that approximately one-third of depressed patients do not respond to first-line SSRI monotherapy, and that the patients who fail multiple monotherapy trials tend to be the patients with greater subsequent dementia risk, is consistent with this prediction.

The corresponding therapeutic strategy is *axis-stratified multi-modal intervention*: biomarker stratification at presentation to identify which of the five axes are most dysregulated, followed by combination intervention that addresses each dysregulated axis with an appropriate intervention. The framework does not endorse a single fixed combination; the combination is determined by the substrate state, which is determined empirically through biomarker measurement.

13.2 The convergent intervention space

A specific list of interventions that engage the multi-axis substrate is provided below, organized by axis and with the indication for both depressive and dementing phenotypes.

Synaptic axis. Sub-anesthetic ketamine and intranasal esketamine (acute and maintenance dosing for depression; under investigation for early AD with depressive features). (2R,6R)-hydroxynorketamine (preclinical evidence for depression and AD; not yet in clinical trials). Psilocybin-assisted therapy (FDA-breakthrough designation for treatment-resistant depression; mechanism includes BDNF/mTOR and transient PNN remodeling). Memantine (approved for moderate-to-severe AD; under investigation for treatment-resistant depression with cognitive

features). Exercise (engages BDNF/TrkB/mTOR signaling; antidepressant efficacy comparable to SSRIs in mild-to-moderate depression; reduces dementia incidence in cohort studies).

Microglial-inflammatory axis. Canakinumab (anti-IL-1β monoclonal antibody, approved for inflammatory diseases; under investigation for inflammatory-subtype depression and for AD). MCC950 and OLT1177 (NLRP3 inhibitors, in clinical development). Minocycline (broad MMP inhibitor with microglial-modulating effects; modest signals in both depression and AD trials). Anti-inflammatory dietary patterns (Mediterranean diet, low refined carbohydrate, omega-3-enriched). Smoking cessation and reduction of environmental inflammatory exposures (air pollution, periodontal disease).

Bioenergetic axis. Ketogenic dietary patterns (efficacy in treatment-resistant psychiatric conditions, including bipolar disorder and schizophrenia; emerging evidence in MCI). Intermittent fasting and time-restricted eating (mitophagy induction, AMPK activation, reduced systemic inflammation). Metformin (AMPK activation, reduced Complex I ROS production; observational evidence of reduced incidence of both depression and AD). GLP-1 receptor agonists (semaglutide, tirzepatide; cardiovascular and metabolic benefits, emerging signals on mood and cognition). NAD+ precursors (nicotinamide riboside, nicotinamide mononucleotide; restoration of sirtuin substrate, mitochondrial biogenesis; preliminary signals in both depression and AD). Exercise (mitochondrial biogenesis through PGC-1α; one of the most robust interventions across both phenotypes).

Tryptophan-partition axis. IDO inhibitors (epacadostat, indoximod; in oncology development; framework prediction of efficacy in inflammatory-subtype depression and in IDO-shifted AD). KMO inhibitors (developed for Huntington's disease; predicted efficacy in QUIN-elevated depression and in AD with elevated kynurenine burden). Niacin and NAD+ precursors (bypass partition shift; historical evidence in pellagra-associated psychiatric and cognitive symptoms). Combination of SSRI with tryptophan loading or 5-HTP (framework prediction of improved response in shunted-partition patients; not yet systematically tested).

ECM/PNN axis. Minocycline and doxycycline (broad MMP inhibition; the load-bearing repurposing candidates per the Therapeutic Landscape paper; safety data over decades). JNJ0966 and other MMP-9 selective inhibitors (in development). Anti-inflammatory therapy operates here through reduction of the microglial pressure on PNNs. Environmental enrichment and exercise preserve PNN integrity through reduction of stress-induced microglial activation. The intervention space here is the same as for the microglial-inflammatory axis, with the addition of direct MMP inhibitors that target the proteolytic effectors of PNN degradation.

13.3 The Bredesen-style integrated protocol

The integrative protocol developed by Dale Bredesen and colleagues, formalized as the ReCODE protocol, represents an early operationalization of multi-axis intervention for cognitive decline. The protocol addresses inflammation, insulin resistance, hormonal status, toxin exposure, sleep, exercise, diet, and other lifestyle factors, with individualization based on patient-specific assessment. The protocol has been criticized for methodological limitations in its published evidence base but the *principle* of multi-axis stratified intervention is consistent with the continuum framework's predictions, and the published case series, while small and uncontrolled, are consistent with the prediction that such intervention can reverse early cognitive decline in some patients.

The continuum framework provides a more rigorous mechanistic foundation for the Bredesen-style approach and predicts that similar integrated protocols, applied at the depressive end of the continuum, should produce comparable benefits. The development of an integrated protocol that is uniform across the depressive and the early-cognitive phenotypes, deployed in middle age based on biomarker stratification, is a specific clinical research program that the framework identifies as high-priority.

13.4 The non-pharmacological intervention space

The framework emphasizes that the non-pharmacological intervention space — exercise, dietary pattern, sleep optimization, social engagement, cognitive engagement, stress reduction — produces effects on the multi-axis substrate that are comparable in magnitude to the effects of any single pharmacological agent. Exercise, in particular, engages every one of the five axes: it upregulates BDNF and mTOR signaling at the synaptic axis, reduces inflammatory cytokine tone at the microglial axis, induces mitochondrial biogenesis at the bioenergetic axis, modulates the tryptophan partition by reducing chronic inflammatory IDO induction, and preserves PNN integrity through reduction of stress-induced microglial activation.

The framework predicts that an exercise prescription deployed in midlife — for example, the 150 minutes per week of moderate-intensity activity that the WHO recommends — should produce measurable reductions in both depression incidence and dementia incidence over the subsequent decades, with the magnitude of effect comparable to or exceeding that of any pharmacological intervention. The epidemiological literature on exercise and dementia incidence (hazard ratios in the range of 0.6–0.8 for active versus sedentary individuals) and the parallel literature on exercise and depression (effect sizes comparable to SSRIs in mild-to-moderate depression) are consistent with this prediction.

14. Predictions and Falsification

The continuum framework generates a set of specific predictions whose experimental and clinical testing would falsify or confirm its central claims.

Prediction 1 (Biomarker continuity). Midlife biomarker measurements of the multi-axis substrate — kynurenine-to-tryptophan ratio, CSF IL-1β, peripheral mitochondrial respiration, plasma BDNF, gamma-band EEG coherence, advanced MRI markers of PNN coverage — should jointly predict both depression incidence over the subsequent decade and dementia incidence over the subsequent three decades, with substantial overlap between the predictive populations. *Falsification:* the biomarkers predict depression but not dementia, or dementia but not depression, or predict each but with non-overlapping populations.

Prediction 2 (Treatment-resistant continuity). Treatment-resistant depression patients should show biomarker profiles closer to the AD profile than to the SSRI-responsive depression profile, with elevated kynurenine-to-tryptophan ratio, elevated inflammatory markers, and reduced PNN signal. Their progression rate to MCI and dementia should be elevated relative to SSRI-responsive patients. *Falsification:* treatment-resistant depression shows the same biomarker profile as SSRI-responsive depression and no elevated dementia risk.

Prediction 3 (Intervention continuity). Interventions that succeed in treatment-resistant depression — particularly multi-axis interventions including bioenergetic, anti-inflammatory, and partition-rebalancing components — should, on long-term follow-up, demonstrate reduced incidence of dementia. The patients who respond best in midlife should be the patients with the lowest dementia incidence in late life. *Falsification:* successful depression treatment in midlife does not reduce subsequent dementia risk.

Prediction 4 (HNK efficacy). (2R,6R)-hydroxynorketamine should demonstrate efficacy in both treatment-resistant depression and in mild cognitive impairment with depressive features, with comparable mechanism and overlapping responder populations. *Falsification:* HNK is efficacious in only one of the two indications, or the responder populations are non-overlapping at the biomarker level.

Prediction 5 (Bioenergetic convergence). Ketogenic dietary intervention, deployed in midlife depression with bioenergetic biomarker evidence, should produce both depressive symptom relief and, on long-term follow-up, reduced dementia incidence. Similar predictions hold for metformin, GLP-1 receptor agonists, and NAD+ precursors. *Falsification:* bioenergetic interventions improve depression without affecting dementia trajectory, or vice versa.

Prediction 6 (Partition rebalancing). Combination therapy of SSRI plus IDO inhibitor (or KMO inhibitor, or NAD+ precursor) should produce response rates in treatment-resistant depression with elevated kynurenine-to-tryptophan ratio that are substantially superior to SSRI monotherapy. The same combination should improve cognitive trajectories in MCI patients with the same biomarker profile. *Falsification:* the combination does not exceed monotherapy response rates, or it exceeds them in depression but not in MCI.

Prediction 7 (PNN imaging biomarker). Advanced imaging biomarkers of PNN integrity, developed through chondroitin-sulfate-targeted PET tracers or MRI techniques sensitive to extracellular matrix composition, should demonstrate continuous variation across the midlife population that predicts both depression vulnerability and dementia incidence. *Falsification:* PNN imaging biomarkers are bimodal (preserved versus degraded with no intermediate population) or do not predict one or both phenotypes.

Prediction 8 (Microglial state trajectory). Longitudinal single-cell RNA sequencing of microglia in chronic depression models followed into aged adulthood should show progressive transition from homeostatic toward DAM/MGnD/LDAM transcriptional states, with the trajectory accelerated in depression-substrate-positive animals. *Falsification:* the microglial states in chronic depression are distinct from the AD-associated states, with separate transcriptional profiles that do not converge over time.

Prediction 9 (LC trajectory). Locus coeruleus tau pathology, detectable through advanced MRI (neuromelanin-sensitive imaging) or PET tau tracers in midlife, should predict both depressive symptomatology (particularly the sleep-disturbance, hyperarousal, and emotional dysregulation features) and subsequent dementia incidence. *Falsification:* LC tau pathology predicts one phenotype but not the other.

Prediction 10 (Anti-inflammatory disease modification). Anti-inflammatory interventions (canakinumab, NLRP3 inhibitors, anti-IL-6 agents) deployed in midlife inflammatory-subtype depression should produce both depressive symptom relief and, on long-term follow-up, reduced dementia incidence. *Falsification:* anti-inflammatory therapy improves depression without affecting dementia trajectory or vice versa.

These predictions are individually testable and, in aggregate, would constitute a rigorous evaluation of the continuum framework. The failure of any single prediction does not falsify the framework as a whole; the failure of multiple predictions, particularly those that probe the core identity claim (Prediction 1, Prediction 3, Prediction 4), would constitute substantial evidence against the framework and would require its revision or replacement.

15. Conclusion: The Most Treatable Window

The argument of this thesis is that the diseases conventionally called major depressive disorder and Alzheimer's disease are, at the substrate level, the same disease observed at different time-slices and different cumulative damage. The five axes that the Collapse quartet identified for AD — synaptic NMDA-PV+-BDNF-mTOR, microglial NLRP3-inflammatory, bioenergetic mitochondrial-substrate, tryptophan partition, and extracellular matrix PNN — are jointly necessary and individually insufficient for either clinical phenotype. The depressive phenotype is the reversible-state expression of the multi-axis dysregulation; the dementing phenotype is the same biology after sustained dysregulation has accumulated damage past the threshold of reversibility at multiple axes.

The implication for clinical practice is that the most treatable window for the disease is the window in which it presents as depression. The pharmacological, behavioral, dietary, and lifestyle interventions whose efficacy has been documented in mild-to-moderate depression are operating on substrates that are still capable of restoration. The same interventions, deployed thirty years later when the substrate has progressed to the dementing phenotype, are operating on substrates that have been largely destroyed. The clinical observation that depression is highly treatable and dementia is not is, on this framework, not a reflection of categorical difference between the diseases but a reflection of the position on the reversibility gradient at which we are intervening.

The framework therefore makes a strong claim about clinical prevention: the most effective prevention of late-life dementia is not directed at the pathological features of late-life dementia (amyloid clearance, tau aggregation inhibition, cholinesterase inhibition) but at the substrate dysregulation that presents in midlife as depression, anxiety, sleep disturbance, and the prodromal cluster of phenomena that conventional psychiatry treats and conventional neurology ignores. The intervention space that the framework identifies — multi-axis, biomarker-stratified, stage-matched — is largely available in the existing pharmacological and lifestyle repertoire. What is required is the conceptual reorganization that recognizes the depressive and dementing phenotypes as a single continuum and the recognition that the most powerful intervention point on that continuum is its earliest accessible window.

The Oskar Fischer Prize program identified the question of how to understand Alzheimer's disease as a fundamental scientific question whose answer was being delayed by the categorical fragmentation of the relevant literatures. The continuum framework developed in this thesis is a specific contribution to that program: it argues that the categorical fragmentation extends not only across the sub-disciplines of dementia research but across the boundary between psychiatric and neurodegenerative disease, and that the most productive scientific reorganization is one that recognizes the continuity between the two. The depression-dementia continuum is, on this view, the

central case study for the methodological commitments of Organic Network Synthesis: the integration of literatures across disciplinary boundaries to recover the biology that the categorical taxonomies have obscured.

The most direct expression of this argument, and the one with which this thesis ends, is that the patient in the psychiatrist's office in midlife and the patient in the neurologist's office in late life are, with high probability, the same patient — and that the most powerful thing the psychiatrist can do for their patient's future cognitive trajectory is what they should already be doing for their patient's current depressive trajectory, deployed earlier, with multi-axis biomarker stratification, with the recognition that they are not treating depression but treating the most treatable window of the disease that, untreated, becomes dementia thirty years later.

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Prepared under the Organic Network Synthesis methodology as a First-Principles thesis of the AdultCognitiveDisease.com program. This thesis argues that major depressive disorder and Alzheimer's disease are not separate pathologies but two phenotypes of a single multi-axis substrate dysregulation, observed at different time-slices and different cumulative damage. The intervention space is the same at both ends of the continuum; the most treatable window is the depressive window in midlife; the most powerful prevention strategy for late-life dementia is the optimal treatment of the depressive substrate while the substrate is still reversible.