THE KETAMINE PARADOX

NMDA Receptor Blockade, Perineuronal Net Dynamics, and the Death-Modality Spectrum of Alzheimer's Disease

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in dialogue with Butovsky, Crapser, de Vries, Olney, and the Collapse quartet

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Companion to the Collapse quartet: Convergent Synaptic Collapse, Homeostatic Microglial Collapse, Bioenergetic Collapse, and Terminal Collapse

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Abstract

The Collapse quartet established that Alzheimer's disease produces neuronal death through two mechanistically distinct but coupled pathways: an intrinsic quality-control failure (autophagy-lysosomal collapse, mitophagy failure, PANTHOS) that kills pyramidal neurons from within, and an extrinsic circuit-driven assault (excitotoxicity, ferroptosis, phagoptosis) that kills parvalbumin-positive fast-spiking interneurons from without. The perineuronal net was identified as the structure whose degradation converts the extrinsic pathway from latent vulnerability to active execution. This thesis examines ketamine — a dissociative anesthetic and NMDA receptor antagonist with rapid antidepressant properties — through the lens of this death-modality spectrum, and discovers that its pharmacology engages both ends of the axis simultaneously, but with a central paradox that may define the boundary conditions of its therapeutic utility in neurodegeneration.

At the extrinsic end of the spectrum, sub-anesthetic ketamine blocks extrasynaptic NMDA receptors on PV+ interneurons, reducing excitotoxic calcium influx through the same mechanism that memantine exploits but with greater potency and additional downstream signaling consequences. This blockade preferentially silences PV+ interneuron firing, producing a transient disinhibition of pyramidal neurons that triggers a glutamate surge, AMPA receptor activation, BDNF release, and mTORC1-mediated synaptogenesis — the molecular cascade responsible for ketamine's rapid antidepressant effect. The 2024 demonstration by Ribeiro and colleagues that the ketamine metabolite (2R,6R)-hydroxynorketamine rescues hippocampal synaptic plasticity and memory in Alzheimer's disease mouse models through ERK1/2 and mTOR signaling establishes direct preclinical evidence that this cascade is operative in AD.

At the intrinsic end, ketamine activates autophagy and suppresses the NLRP3 inflammasome through a mechanism that proceeds via autophagy-mediated degradation of inflammasome components, reducing IL-1β and IL-18 release — the specific pyroptotic output that the Homeostatic Microglial Collapse thesis identified as the bridge between mitochondrial damage signals and destructive microglial effector activity. The suppression of NLRP3 simultaneously addresses the inflammatory amplification loop and reduces the MMP upregulation that drives perineuronal net degradation.

The paradox emerges at the perineuronal net itself. Anesthetic-dose ketamine activates microglia to disassemble perineuronal nets through phagocytic engulfment, as demonstrated by the 2021 Cell Reports study by Venturino, Schulz, De Jesús-Cortés, and colleagues. This disassembly reopens critical-period plasticity — a property with therapeutic potential in psychiatric indications — but in the context of Alzheimer's disease, it is precisely the pathological event that the Collapse quartet identifies as the master vulnerability switch. A 2025 Scientific Reports study then demonstrated the opposite: S-ketamine at sub-anesthetic doses inhibits microglial phagocytosis of perineuronal nets in a neuropathic pain model, preserving

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PNN integrity and reducing neuroinflammation. The paradox is therefore dose-dependent and enantiomer-specific: the same molecule that protects PNNs at sub-anesthetic doses destroys them at anesthetic doses, and the S-enantiomer and R-enantiomer may diverge in their net effects on the PNN–PV+ axis.

This thesis integrates these findings into the death-modality framework and proposes that sub-anesthetic ketamine — and more specifically, its metabolite (2R,6R)-hydroxynorketamine — occupies a unique pharmacological position as the only characterized agent that simultaneously addresses excitotoxic death (through NMDA receptor blockade), pyroptotic amplification (through NLRP3 suppression via autophagy), synaptic loss (through BDNF/mTOR-mediated synaptogenesis), and the feed-forward excitotoxic cascade (through transient PV+ silencing that paradoxically reduces network hyperexcitability by interrupting the pathological excitation-inhibition spiral). It further proposes that the dose-dependent PNN paradox defines a therapeutic window whose boundaries must be respected: sub-anesthetic dosing that preserves PNN integrity while engaging the neuroprotective cascade, versus anesthetic dosing that destroys the very structure the Collapse quartet identifies as the critical substrate of resilience.

1. Introduction: A Drug at Both Ends of the Spectrum

The death-modality spectrum proposed in the Terminal Collapse thesis organized the characterized cell death mechanisms of Alzheimer's disease along an axis from intrinsic quality-control failure to extrinsic circuit-driven assault. At the intrinsic pole, PANTHOS — neuronal death through autophagy-lysosomal failure producing inside-out plaque formation — kills pyramidal neurons through the accumulation of their own undegradable cargo. At the extrinsic pole, excitotoxicity — glutamate-mediated NMDA receptor hyperactivation producing calcium overload — kills PV+ fast-spiking interneurons through environmental assault enabled by perineuronal net degradation. Between these poles, ferroptosis, pyroptosis, necroptosis, phagoptosis, and parthanatos each combine intrinsic and extrinsic elements in proportions that vary by cell type, disease stage, and local biochemical context.

The therapeutic implication of this spectrum was that effective neuroprotection would require simultaneous engagement with multiple death pathways — that no single-target intervention could address the full width of the axis. This thesis tests that prediction against a specific pharmacological case: ketamine, the dissociative NMDA receptor antagonist whose pharmacology turns out to engage both ends of the spectrum through mechanisms that are individually well-characterized but have not previously been integrated within a single neurodegeneration-oriented framework.

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Ketamine is not a conventional Alzheimer's disease therapeutic candidate. It has been developed and deployed primarily in two contexts: as a surgical anesthetic at doses of 1–2 mg/kg intravenous, and as a rapid-acting antidepressant at sub-anesthetic doses of 0.5 mg/kg intravenous (or intranasal esketamine at comparable bioavailability). Its mechanism of action in depression — preferential blockade of NMDA receptors on PV+ interneurons, producing transient disinhibition of pyramidal neurons, a glutamate surge, AMPA receptor activation, BDNF release, and mTORC1-mediated synaptogenesis — was established principally through the work of Ronald Duman at Yale and has been confirmed and extended by multiple laboratories. Its mechanism of action in anesthesia — broad NMDA receptor blockade producing dissociative unconsciousness — operates at higher receptor occupancy and through a less selective pharmacological profile.

The discovery that motivates this thesis is that these two dosing regimes produce opposite effects on the structure that the Collapse quartet identifies as the master vulnerability switch in Alzheimer's disease: the perineuronal net. At anesthetic doses, ketamine activates microglia to phagocytically disassemble PNNs, reopening critical-period plasticity but stripping the neuroprotective shield from PV+ interneurons. At sub-anesthetic doses, S-ketamine inhibits microglial phagocytosis of PNNs, preserving the structure that the Collapse quartet argues must be preserved to prevent the multi-modal death cascade. This dose-dependent inversion, demonstrated across two independent studies using different model systems, different ketamine enantiomers, and different experimental paradigms, is the empirical foundation of the paradox this thesis examines.

The question the thesis addresses is not whether ketamine should be administered to Alzheimer's disease patients — that question requires clinical evidence this thesis cannot supply. The question is what ketamine's pharmacology reveals about the death-modality spectrum itself, and whether the convergence of ketamine's multiple mechanisms on the specific nodes identified by the Collapse quartet constitutes evidence that the quartet's framework is capturing real biology rather than imposing artificial coherence on a disparate literature.

2. Ketamine at the Extrinsic Pole: Excitotoxicity and the PV+ Interneuron

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2.1 The disinhibition mechanism

The canonical mechanism of sub-anesthetic ketamine's action, established through the work of Duman and colleagues and now replicated across dozens of laboratories, proceeds through a specific circuit-level sequence. Ketamine, as a low-affinity uncompetitive NMDA receptor antagonist, preferentially blocks NMDA receptors that are tonically active — that is, receptors held in an open or semi-open state by sustained glutamate exposure. In cortical circuits, the neurons with the highest tonic NMDA receptor activity are the PV+ fast-spiking interneurons, whose high firing rate and strong excitatory drive produce sustained NMDA receptor opening at their postsynaptic densities. Ketamine therefore preferentially reduces excitatory drive to PV+ interneurons, silencing their inhibitory output and producing a transient disinhibition of the pyramidal neurons they normally restrain.

This disinhibition generates a burst of pyramidal neuron activity — a glutamate surge — that activates AMPA receptors on the disinhibited pyramidal neurons, producing a cascade of intracellular signaling: voltage-dependent calcium entry through AMPA and voltage-gated calcium channels → BDNF release from pyramidal neuron dendrites → TrkB receptor activation → PI3K/AKT and MEK/ERK signaling → mTORC1 activation → increased synaptic protein synthesis → new dendritic spine formation → restored synaptic connectivity. The entire cascade, from NMDA blockade to new spine formation, is complete within hours, producing the rapid antidepressant effect that distinguishes ketamine from all prior antidepressant pharmacology.

2.2 The excitotoxic protection

Within the death-modality framework, ketamine's NMDA receptor blockade on PV+ interneurons has a second and previously underappreciated significance: it is directly neuroprotective for those same cells. The Terminal Collapse thesis established that PV+ interneurons are uniquely vulnerable to excitotoxic death because their GluR2-lacking AMPA receptors and high-frequency firing produce calcium loads that exceed parvalbumin's buffering capacity when the PNN diffusion barrier is lost. Ketamine's blockade of NMDA receptors on these cells reduces one of the two major calcium-entry routes (the other being the calcium-permeable AMPA receptors), lowering the total calcium influx per unit time and extending the window before mitochondrial calcium overload triggers the excitotoxic death cascade.

This is the same mechanism that memantine exploits, but ketamine operates at it from a different pharmacological angle. Memantine is a low-affinity, voltage-dependent blocker that preferentially occupies the channel during tonic activation and exits during phasic synaptic events. Ketamine is a higher-affinity blocker with a slower off-rate, meaning it provides more sustained channel blockade but also more interference with normal synaptic NMDA transmission. The therapeutic window for neuroprotection is therefore narrower for ketamine than for memantine: too little blockade provides insufficient calcium reduction; too much blockade impairs the synaptic

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NMDA signaling that Hardingham demonstrated is neuroprotective through the CREB survival pathway. Sub-anesthetic dosing sits within this window; anesthetic dosing exceeds it.

2.3 Interrupting the feed-forward loop

The excitotoxic feed-forward loop described in the Terminal Collapse thesis — PV+ death → reduced inhibition → increased pyramidal firing → more glutamate → more PV+ death — is self-sustaining once initiated. Ketamine's PV+ silencing mechanism suggests a counterintuitive intervention strategy: by transiently silencing PV+ interneurons pharmacologically, ketamine may paradoxically interrupt the feed-forward loop by replacing pathological PV+ hyperactivation (driven by excessive excitatory input after PNN loss) with a controlled pharmacological pause. The transient silencing is followed by a rebound in which BDNF and mTOR signaling strengthen the surviving synaptic connections, potentially restoring a more stable excitation-inhibition balance than existed before the intervention.

This framing predicts that sub-anesthetic ketamine should be most effective in early-stage AD, when the feed-forward excitotoxic loop is initiating (detectable as subclinical EEG hyperexcitability and gamma-band abnormalities) but before the PV+ interneuron population is depleted beyond recovery. At later stages, when PV+ cells are already lost, there are no interneurons left to protect or to silence, and the disinhibition mechanism produces glutamate surges without the compensatory rebound — potentially accelerating pyramidal neuron death rather than preventing it. The therapeutic window is therefore both dose-dependent and stage-dependent.

3. Ketamine at the Intrinsic Pole: Autophagy, NLRP3, and the Quality-Control Axis

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3.1 Autophagy activation and NLRP3 suppression

The discovery that ketamine induces autophagy in microglia — increasing LC3B levels and decreasing p62 protein in the prefrontal cortex and hippocampus — and that this autophagy activation suppresses NLRP3 inflammasome assembly, connects ketamine directly to the intrinsic end of the death-modality spectrum. The Bioenergetic Collapse thesis identified NLRP3 as the mitochondrial-ROS-gated amplifier through which failed mitophagy becomes destructive microglial effector output. The Homeostatic Microglial Collapse thesis identified NLRP3-derived IL-1β as the cytokine that upregulates MMP expression and potentiates glutamatergic signaling at the PNN–PV+ axis. Ketamine's autophagy-mediated NLRP3 suppression therefore addresses the specific molecular node that connects mitochondrial quality-control failure to PNN degradation.

The mechanism proceeds as follows: ketamine activates autophagy in microglia autophagosomes engulf and degrade NLRP3 inflammasome components (including 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 MMP upregulation in surrounding cells reduced PNN degradation preserved PV+ interneuron neuroprotective shielding. This is a causal chain that runs from the intrinsic pole (autophagy and inflammasome biology) to the extrinsic pole (PNN integrity and excitotoxic vulnerability), and ketamine engages it at the upstream autophagy step rather than at any of the downstream effector steps.

The significance of this mechanism is that it is autophagy-dependent, not merely anti-inflammatory. Autophagy inhibitors block ketamine's NLRP3-suppressive effect, demonstrating that ketamine does not simply suppress inflammation but restores a quality-control function — autophagosomal clearance of inflammasome components — whose failure is part of the broader quality-control collapse that the Bioenergetic thesis described. Ketamine is, on this reading, a partial quality-control restorer rather than a conventional anti-inflammatory agent, and its mechanism of NLRP3 suppression is more aligned with the therapeutic strategy the Collapse quartet recommends (restore quality-control competence) than with the conventional anti-inflammatory strategy the quartet criticizes (silence the downstream output).

3.2 mTOR: The double-edged signal

Ketamine's activation of mTORC1 is central to its synaptogenic antidepressant mechanism: mTORC1 drives the synaptic protein synthesis that produces new dendritic spines and restores connectivity. But mTORC1 activation also suppresses autophagy through phosphorylation and cytoplasmic retention of TFEB, the master transcription factor for lysosomal biogenesis and autophagy gene expression. The Bioenergetic Collapse thesis identified TFEB-mediated lysosomal biogenesis as essential for autophagy-lysosomal competence, and mTOR inhibition (via rapamycin) as a strategy for rescuing autophagy in AD models.

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This creates a pharmacological tension within ketamine's own mechanism: the mTORC1 activation that drives synaptogenesis simultaneously suppresses the TFEB-mediated autophagy that clears NLRP3 components and maintains lysosomal competence. How can ketamine activate both autophagy and mTOR?

The resolution appears to be temporal and compartmental. The autophagy activation that suppresses NLRP3 operates in microglia; the mTORC1-mediated synaptogenesis operates in pyramidal neurons. Different cell types may respond to the same drug through different downstream cascades. Furthermore, the initial NMDA blockade produces an energy-sensing signal (reduced calcium-dependent ATP consumption transient AMPK activation) that activates autophagy in the first minutes, while the subsequent glutamate surge and BDNF release activate mTORC1 over the following hours. The temporal sequence — autophagy first, mTOR second — may allow both mechanisms to operate in the same brain without mutual cancellation, though their long-term interaction under repeated dosing remains an unresolved question.

4. The Perineuronal Net Paradox

4.1 Anesthetic ketamine disassembles PNNs

The 2021 Cell Reports study by Venturino, Schulz, De Jesús-Cortés, and colleagues demonstrated that repeated anesthetic ketamine (three exposures at surgical-anesthetic doses) strongly reduces PNN coating in the healthy adult mouse brain and promotes juvenile-like plasticity. The mechanism is microglial: following ketamine exposure, microglia engage with PV+ neurons in a layer-specific manner and phagocytically remodel the PNN matrix. The disassembly is not an artefact of NMDA blockade per se but is mediated by microglial activation, as pharmacological depletion of microglia prevents the PNN loss.

This finding is directly relevant to the Collapse quartet because it demonstrates that the same molecular event the quartet identifies as the master vulnerability switch — microglial phagocytic degradation of PNNs around PV+ interneurons — can be pharmacologically induced by ketamine at anesthetic doses. The functional consequence documented in the Venturino study is the reopening of critical-period plasticity, which is therapeutically interesting for psychiatric and developmental indications but which, within the Collapse framework, is the biological equivalent of removing the neuroprotective shield that prevents excitotoxic, ferroptotic, and phagoptotic death of the exposed cell.

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The Venturino study also identified a remarkable specificity: 60-Hz light flicker entrainment produces the same microglia-mediated PNN disassembly as anesthetic ketamine, but 40-Hz flicker — the frequency used by Li-Huei Tsai's laboratory to drive microglial amyloid clearance in AD models — does not. This frequency-specific divergence suggests that the microglial programs for PNN remodeling and for amyloid clearance are distinct, and that stimulation paradigms designed for one purpose may inadvertently engage the other. The 60-Hz finding has not been replicated in AD models and its relevance to human disease is unknown, but it demonstrates that PNN disassembly is an actively regulated microglial program rather than a passive consequence of neuroinflammation.

4.2 Sub-anesthetic S-ketamine preserves PNNs

The 2025 Scientific Reports study demonstrated that sub-anesthetic S-ketamine (10 mg/kg intraperitoneal in mice) inhibits microglial phagocytosis of perineuronal nets in a chronic constriction injury model of neuropathic pain. In the injury model, spinal cord microglia are activated and phagocytically degrade PNNs, contributing to pain signaling. S-ketamine treatment attenuated microglial reactivity, reduced the number of lysosomes within microglia, and inhibited microglial engulfment of WFA-positive PNN material, resulting in preserved PNN integrity and improved pain thresholds.

The contrast with the Venturino result is striking. Anesthetic ketamine (high dose, racemic, repeated) drives microglial PNN disassembly. Sub-anesthetic S-ketamine (low dose, single enantiomer, single or repeated) inhibits microglial PNN phagocytosis. The inversion is dose-dependent and possibly enantiomer-dependent, with the S-enantiomer (esketamine, the form approved as Spravato for treatment-resistant depression) showing the PNN-protective profile at sub-anesthetic doses.

4.3 Resolution of the paradox

The dose-dependent PNN inversion can be understood within the disinhibition framework as follows. At sub-anesthetic doses, ketamine preferentially blocks NMDA receptors on PV+ interneurons, producing the disinhibition cascade (glutamate surge BDNF mTOR synaptogenesis) and simultaneously suppressing microglial NLRP3 activation through autophagy induction. The anti-inflammatory effect on microglia — reduced NLRP3, reduced IL-1β, reduced MMP expression — is anti-phagocytic with respect to PNNs. Microglia in the sub-anesthetic ketamine environment are shifted toward a less reactive, less phagocytically aggressive state, and their engagement with PNNs is reduced rather than enhanced.

At anesthetic doses, the pharmacological picture changes. Broad NMDA receptor blockade silences not only PV+ interneurons but the entire excitatory network, producing a fundamentally different circuit state. The compensatory upregulation that follows — an attempt by the brain to

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restore excitatory signaling in the face of global NMDA blockade — may involve microglial remodeling of the extracellular matrix to facilitate new synaptic connections, and PNN disassembly is one such remodeling event. The microglial state at anesthetic doses is not the suppressed, anti-inflammatory state of sub-anesthetic exposure but an actively remodeling state that engages PNNs as substrates for plasticity-promoting clearance.

The implication for Alzheimer's disease is that the dosing regime determines whether ketamine is neuroprotective or neurotoxic with respect to the Collapse quartet's master vulnerability switch. Sub-anesthetic ketamine, by preserving PNN integrity while blocking excitotoxic NMDA receptor activation and suppressing NLRP3-mediated inflammatory amplification, addresses multiple nodes of the death-modality cascade without compromising the neuroprotective shield. Anesthetic ketamine, by driving PNN disassembly, strips the shield and exposes PV+ interneurons to the full combinatorial death cascade the Terminal Collapse thesis described.

5. The Metabolite Gateway: (2R,6R)-Hydroxynorketamine

The most therapeutically promising development in ketamine pharmacology for neurodegeneration is the characterization of (2R,6R)-hydroxynorketamine (HNK), a ketamine metabolite that retains the synaptogenic and neuroprotective properties of the parent compound while lacking its NMDA receptor-blocking, dissociative, and abuse-liability properties. The 2024 Alzheimer's & Dementia paper by Ribeiro and colleagues demonstrated that HNK rescues hippocampal mRNA translation, synaptic plasticity, and memory in mouse models of Alzheimer's disease through ERK1/2 and mTOR signaling — the first direct demonstration that the ketamine pharmacological cascade produces disease-relevant cognitive rescue in AD.

The significance of HNK for the death-modality framework is that it potentially dissociates the beneficial synaptogenic mechanism from both the NMDA blockade (which carries the dose-dependent PNN paradox) and the dissociative anesthetic properties (which limit clinical dosing). If HNK activates BDNF/mTOR-mediated synaptogenesis without the NMDA blockade that drives the PNN paradox, it may provide the synaptogenic and anti-inflammatory benefits of ketamine without the dose-dependent risk of PNN disassembly. The prediction from the Collapse framework is that HNK should preserve PNN integrity (because it does not produce the global NMDA blockade that drives anesthetic-dose PNN disassembly) while restoring synaptic connections in the prefrontal cortex and hippocampus (because it retains the mTOR-mediated synaptogenic cascade).

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HNK has not been tested for its effects on perineuronal nets, on microglial phagocytic behavior, or on the NLRP3 inflammasome in AD models. These experiments are among the most direct predictions the Collapse framework generates for the ketamine pharmacological program, and their outcomes would be decisive for the framework's validity.

6. Ketamine and the Ferroptotic Gateway

The Terminal Collapse thesis identified ferroptosis as the oxidative-damage gateway that determines whether bioenergetic stress produces recoverable adaptation (mitohormesis) or irreversible death, with GPX4/glutathione status as the gating variable. Ketamine's relationship to this gateway is indirect but mechanistically significant.

Ketamine's antidepressant mechanism involves increased energy metabolism, augmented antioxidant defense, and upregulation of Nrf2-responsive genes, the same transcriptional program that Maher's geroneuroprotective compounds (J147, CMS121) engage to prevent ferroptotic death. If sub-anesthetic ketamine upregulates the antioxidant defense system in neurons and microglia — increasing glutathione synthesis, GPX4 expression, and superoxide dismutase activity — it may raise the ferroptotic threshold in PV+ interneurons whose PNNs are partially degraded, extending the window between PNN loss and ferroptotic death.

This prediction is speculative but testable. The experiment would measure GPX4 expression, glutathione levels, and lipid peroxidation markers (4-HNE, MDA) in PV+ interneurons of AD model mice treated with sub-anesthetic ketamine versus vehicle, with PNN integrity as the co-primary endpoint. A positive result — preserved ferroptotic defenses in ketamine-treated animals with partially degraded PNNs — would establish ketamine as an agent that addresses both the extrinsic excitotoxic pathway (through NMDA blockade) and the ferroptotic gateway (through antioxidant upregulation) simultaneously.

7. Ketamine and NAD+ Metabolism

The Terminal Collapse thesis identified NAD+ depletion as the convergent metabolic catastrophe where parthanatos (PARP-1 hyperactivation), Wallerian degeneration (SARM1 activation), and

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bioenergetic collapse (age-related NAD+ biosynthetic decline) all meet. Ketamine's relationship to NAD+ metabolism has been documented but not integrated into the neurodegeneration framework.

Ketamine's antidepressant effect involves energy metabolism engagement that increases cellular NAD+/NADH ratios through enhanced glycolysis and oxidative phosphorylation. The SIRT1 upregulation documented in ketamine-treated cells is NAD+-dependent and connects to PGC-1α-mediated mitochondrial biogenesis — the same pathway the Bioenergetic Collapse thesis identified as essential for maintaining the mitochondrial population quality that homeostatic microglial function requires. If ketamine increases NAD+ availability in neurons and microglia, it may simultaneously suppress parthanatos (by providing substrate that competes with PARP-1 for NAD+ consumption), delay Wallerian degeneration (by maintaining the NAD+ pool that keeps SARM1 inactive), and support mitochondrial biogenesis (by fueling the SIRT1/PGC-1α pathway).

This is the intrinsic-pole therapeutic mechanism: ketamine does not block any specific death pathway but supports the metabolic substrate whose depletion enables three of them. Combined with its extrinsic-pole mechanism (NMDA blockade of excitotoxic calcium entry) and its PNN-interface mechanism (NLRP3 suppression reducing microglial PNN degradation), this gives ketamine engagement with at least five of the eight death modalities catalogued in the Terminal Collapse thesis — a breadth of coverage that no other single pharmacological agent provides.

8. The Therapeutic Window: Dose, Timing, and Enantiomer

The integration of ketamine's multiple mechanisms within the death-modality framework generates specific predictions about the boundary conditions of its therapeutic utility in Alzheimer's disease.

Dose. Sub-anesthetic dosing (0.1–0.5 mg/kg IV, or equivalent intranasal esketamine) is predicted to be neuroprotective through PNN preservation, excitotoxic protection, NLRP3 suppression, and synaptogenic rescue. Anesthetic dosing (1–2 mg/kg IV, repeated) is predicted to be neurotoxic through PNN disassembly, stripping the neuroprotective shield from PV+ interneurons and exposing them to the full combinatorial death cascade. The therapeutic window is therefore narrow and its boundaries are defined by the PNN response rather than by conventional tolerability endpoints.

Timing. Sub-anesthetic ketamine is predicted to be most effective in early-stage AD (MCI or pre-clinical), when the excitotoxic feed-forward loop is initiating (detectable as EEG hyperexcitability), PV+ interneurons are stressed but not yet dead, and PNNs are partially degraded

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but not yet eliminated. At later stages, when PV+ interneurons are depleted and PNNs are absent, the target cells for both the neuroprotective and synaptogenic mechanisms no longer exist, and ketamine's glutamate surge may accelerate pyramidal neuron death through the same excitotoxic mechanisms it would have prevented at an earlier stage.

Enantiomer. S-ketamine (esketamine, approved as Spravato) has demonstrated PNN-protective effects at sub-anesthetic doses and has greater NMDA receptor affinity than R-ketamine. R-ketamine has shown greater and more sustained antidepressant effects in some preclinical models and may have a more favorable mTOR/BDNF signaling profile. The optimal enantiomer for AD neuroprotection may differ from the optimal enantiomer for antidepressant efficacy, and the selection should be guided by PNN integrity endpoints rather than by mood endpoints.

Metabolite. (2R,6R)-Hydroxynorketamine, which retains synaptogenic and cognitive-rescue properties without NMDA receptor blockade or dissociative effects, may bypass the PNN paradox entirely by operating downstream of the NMDA receptor at the BDNF/mTOR node. If HNK preserves PNN integrity (predicted by the framework but not yet tested), it would be the preferred agent for chronic AD neuroprotection because it provides the synaptogenic and metabolic benefits without the dose-dependent risk of PNN disassembly.

9. What the Paradox Reveals About the Framework

The ketamine paradox is not merely a pharmacological curiosity. It is a test of the Collapse quartet's central architecture. If the quartet's framework is correct — if the PNN is indeed the master vulnerability switch whose integrity determines whether the multi-modal death cascade activates — then any intervention that affects PNN integrity should produce predictable effects on downstream pathology. Ketamine provides exactly this test, because its dose-dependent PNN effects (preservation at sub-anesthetic doses, disassembly at anesthetic doses) generate opposite predictions that are experimentally verifiable.

Prediction 1. Sub-anesthetic ketamine administered chronically to 5xFAD or APP/PS1 mice should preserve PNN integrity (WFA staining), maintain PV+ interneuron density, reduce NLRP3 activation markers (ASC specks, cleaved caspase-1, IL-1β), preserve E/I balance (gamma-band oscillation power), and delay cognitive decline relative to vehicle — with PNN integrity as the readout that correlates most tightly with cognitive preservation.

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Prediction 2. Anesthetic ketamine administered repeatedly to the same models should degrade PNNs, reduce PV+ interneuron density, and accelerate cognitive decline — despite providing the same BDNF/mTOR synaptogenic cascade at the molecular level — because the PNN disassembly opens the multi-modal death cascade that overwhelms the synaptogenic rescue.

Prediction 3. (2R,6R)-Hydroxynorketamine administered chronically should preserve PNNs (because it does not block NMDA receptors and therefore does not trigger the anesthetic-dose microglial remodeling program), provide the synaptogenic rescue (because it activates ERK/mTOR independently of NMDA blockade), and produce cognitive rescue (as Ribeiro 2024 demonstrated) — and the cognitive rescue should correlate with PNN integrity more tightly than with amyloid or tau burden.

Prediction 4. If any of these predictions fail — if sub-anesthetic ketamine degrades PNNs rather than preserving them, or if PNN degradation does not predict cognitive outcome — the quartet's framework requires revision at the point of failure.

These predictions are experimentally tractable with existing tools (WFA histochemistry for PNNs, PV immunostaining for interneuron density, ASC speck quantification for NLRP3 activation, EEG for gamma-band oscillatory power, standard behavioral paradigms for cognitive endpoints). The ketamine paradox is therefore not only a pharmacological question but an experimental program for validating or falsifying the Collapse quartet's central claims.

10. Therapeutic Implications Beyond Ketamine

The analysis of ketamine within the death-modality framework generates principles that extend beyond the specific drug to the design of neuroprotective strategies in general.

Principle 1: PNN integrity as a gate for all neuroprotective interventions. Any intervention that inadvertently degrades PNNs while providing other neuroprotective benefits will produce diminishing returns as PNN loss opens death pathways faster than the intervention can close them. This principle applies not only to ketamine at anesthetic doses but to any PNN-remodeling intervention, including chondroitinase ABC (used experimentally to enhance plasticity) and potentially to some anti-inflammatory agents that alter microglial phagocytic behavior.

Principle 2: The disinhibition–protection balance. Interventions that silence PV+ interneurons (whether pharmacologically, through optogenetics, or through circuit-level

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neuromodulation) transiently reduce inhibitory output and increase excitatory drive. In the healthy brain, this produces beneficial plasticity. In the AD brain, where surviving PV+ interneurons are already stressed and PNNs are partially degraded, the same disinhibition may accelerate the feed-forward excitotoxic loop. The balance between disinhibition-mediated plasticity and excitotoxic risk is disease-stage-dependent and must be assessed through E/I balance biomarkers rather than through mood or behavioral endpoints alone.

Principle 3: Multi-mechanism agents over single-target agents. Ketamine's unusual breadth of engagement across the death-modality spectrum — excitotoxic protection, NLRP3 suppression, synaptogenic rescue, metabolic support, and (at appropriate doses) PNN preservation — illustrates why single-target neuroprotective agents have failed in AD trials. The disease operates through multiple concurrent death pathways, and an agent that addresses only one (memantine for excitotoxicity, canakinumab for IL-1β, complement inhibitors for phagoptosis) leaves the others operational. The most promising therapeutic candidates are those that, like ketamine at sub-anesthetic doses, engage multiple nodes of the cascade through a single pharmacological mechanism.

Principle 4: Metabolites as separable therapeutic payloads. The dissociation of (2R,6R)-hydroxynorketamine from the parent compound's NMDA blockade demonstrates that the synaptogenic and neuroprotective mechanisms can be pharmacologically separated from the receptor-blocking mechanism that carries the PNN paradox. This separation principle — identifying the active metabolite or downstream effector that provides the therapeutic benefit without the mechanism that produces the risk — is generalizable to other pharmacological programs and may be especially important for chronic dosing in neurodegenerative indications where the acute psychiatric dosing paradigm (single infusion, rapid onset, self-limiting effect) is replaced by sustained pharmacological exposure.

II. What This Analysis Cannot Determine

This section is required by the ONS methodology.

1. Whether sub-anesthetic ketamine preserves PNN integrity in AD models. The 2025 S-ketamine PNN-preservation finding was demonstrated in a neuropathic pain model, not in an AD model, and the microglial states in the two conditions may differ.

2. Whether the PNN-protective effect of sub-anesthetic S-ketamine extends to racemic ketamine or to R-ketamine. Enantiomer-specific PNN effects have not been systematically

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compared.

3. Whether (2R,6R)-hydroxynorketamine affects PNN integrity in any model. This is the most direct prediction the framework generates and it has not been tested.

4. Whether ketamine's autophagy-mediated NLRP3 suppression operates in AD microglia specifically, or only in the LPS-stimulated and stress models in which it was demonstrated.

5. Whether ketamine's mTOR activation in neurons and autophagy activation in microglia are truly cell-type-specific and temporally separated, or whether the two mechanisms interfere with each other under chronic dosing conditions.

6. Whether the clinical dosing paradigm for treatment-resistant depression (0.5 mg/kg IV, typically 6 infusions over 2–3 weeks) is appropriate for AD neuroprotection, or whether chronic low-dose maintenance would be required.

7. Whether ketamine's antioxidant and metabolic effects are of sufficient magnitude to meaningfully shift the ferroptotic threshold in PV+ interneurons in the aged, iron-loaded AD brain.

8. Whether the Ribeiro 2024 HNK cognitive rescue in AD mice reflects synaptogenic restoration, anti-inflammatory action, metabolic support, or a combination — and which of these is the load-bearing therapeutic mechanism.

9. Whether ketamine at any dose or enantiomer modifies amyloid or tau pathology directly, or whether its effects are entirely mediated through the circuit-level and microglial mechanisms described here.

10. Whether any of the predictions in Section 9 will survive experimental testing in AD models, or whether the framework's application to ketamine will require revision.

12. Conclusion

Ketamine's pharmacology maps onto the death-modality spectrum of Alzheimer's disease with a precision that no other single agent matches. At the extrinsic pole, it blocks excitotoxic NMDA receptor activation on the specific cell type (PV+ interneurons) that the Collapse quartet identifies as circuit-critical. At the intrinsic pole, it activates autophagy and suppresses the NLRP3 inflammasome through a mechanism that addresses the specific molecular node (mitochondrial-DAMP-gated pyroptotic amplification) that bridges bioenergetic failure to microglial

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effector output. At the PNN interface — the structure the quartet identifies as the master vulnerability switch — it preserves integrity at sub-anesthetic doses and destroys it at anesthetic doses, revealing a dose-dependent paradox whose resolution defines the therapeutic window.

The paradox is the thesis's central finding. It demonstrates that the PNN is not merely a conceptual construct within the Collapse framework but a pharmacologically responsive structure whose manipulation produces predictable downstream consequences for the death-modality cascade. An agent that preserves the PNN should protect PV+ interneurons from multi-modal death; an agent that degrades the PNN should expose them to it. Ketamine does both, depending on dose, and the specificity of this dose-response to PNN integrity is evidence that the framework is capturing real biology.

The metabolite (2R,6R)-hydroxynorketamine offers the possibility of extracting the synaptogenic and neuroprotective mechanisms from the NMDA receptor blockade that carries the PNN paradox, and the Ribeiro 2024 demonstration of cognitive rescue in AD mice provides the first direct evidence that the ketamine pharmacological cascade is operative in AD. Whether HNK can be developed as a chronic neuroprotective agent for early AD — preserving PNNs, restoring synaptic connections, suppressing inflammatory amplification, and supporting bioenergetic competence — is an experimental question whose answer would simultaneously validate the Collapse quartet's framework and open a new therapeutic class for Alzheimer's disease.

The broader lesson is that the death-modality spectrum is not merely a descriptive taxonomy but a predictive framework. It predicts that agents engaging multiple death pathways will outperform single-target interventions. It predicts that PNN integrity will be the most informative biomarker of therapeutic success. It predicts that dose, timing, and enantiomer selection must be guided by PNN endpoints rather than by conventional amyloid or tau readouts. And it predicts that the greatest therapeutic opportunities will be found in agents whose pharmacology spans the full width of the intrinsic-extrinsic axis — agents that, like ketamine at its best, address both the cell that is dying from within and the cell that is dying from without.

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Prepared under the Organic Network Synthesis methodology as a companion analysis to the Collapse quartet. This thesis examines ketamine's pharmacology as a test case for the death-modality spectrum framework, revealing a dose-dependent paradox at the perineuronal net that simultaneously validates the framework's central claims and defines the boundary conditions of its most promising therapeutic candidate.

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