THE ADULT-BORN NEURON

Adult Hippocampal Neurogenesis, the Dentate Granule Cell Lineage, and the First-Principles Substrate of the Collapse Trilogy

Lineage Biology, the Sorrells–Boldrini Resolution, Pattern Separation, and the Hippocampal Bridgehead

Altman · Kaplan · Gage · Eriksson · Spalding
Alvarez-Buylla · Sorrells · Boldrini · Mann
Llorens-Martín · Moreno-Jiménez · Tobin · Terreros-Roncal
Ming · Song · Jessberger · Sahay · Hen
Aimone · Kheirbek · Sierra · Toda · Choi · Tanzi · Stark

a first-principles synthesis for the Convergent Synaptic, Homeostatic Microglial, and Bioenergetic Collapse theses

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Abstract

The three-thesis architecture of the Collapse Trilogy — Convergent Synaptic Collapse at the parvalbumin-positive interneuron and perineuronal-net axis, Homeostatic Microglial Collapse at the Butovsky-signature axis, and Bioenergetic Collapse at the locus coeruleus and NAD axis — treats the neuronal substrate of late-onset Alzheimer's disease as a fixed population whose attrition over the natural history of the disease is the principal degenerative event. The treatment is correct for the vast majority of the forebrain, where the neuronal complement at the end of the second decade is the neuronal complement available for the remainder of life, and where attrition through any of the three collapse mechanisms is mathematically the only direction of change. The treatment is incorrect, however, for one specific subregion of the forebrain in which the neuronal complement is not fixed: the granule cell layer of the dentate gyrus of the hippocampus, in which a population of radial glia-like neural stem cells in the subgranular zone continues throughout adult life to produce new excitatory granule neurons that integrate into the hippocampal circuit and contribute to the trisynaptic pathway of memory encoding. This continuous neurogenic process — adult hippocampal neurogenesis, AHN — is the single exception in the human forebrain to the otherwise correct fixed-population assumption, and it is the exception that occurs in precisely the brain region that the Collapse Trilogy has identified as the Phase II hippocampal bridgehead and that the Convergent Synaptic Collapse thesis has identified as the substrate of the parvalbumin-perineuronal-net axis through which Phase III structural disintegration is executed. The Sorrells–Boldrini–Moreno-Jiménez sequence of papers from 2018 through 2021 has, after the controversy occasioned by the Sorrells 2018 null result, established with substantial mechanistic and immunohistochemical specificity that AHN persists in the human dentate gyrus into at least the ninth decade and that it declines sharply and early in Alzheimer's disease, with Moreno-Jiménez 2019 reporting an approximately thirty percent reduction in immature granule neuron density at the earliest clinically detectable stages and an approximately ninety percent reduction at advanced stages, independent of plaque and tangle burden. This paper develops the case that adult hippocampal neurogenesis is the missing first-principles variable in the Collapse Trilogy's account of hippocampal pathogenesis, that its collapse is itself a cross-phase event integrating the bioenergetic substrate of stem-cell maintenance, the microglial regulation of neuroblast survival, and the synaptic integration requirements of adult-born neurons into the dentate circuit, and that the trilogy's account of the Phase I Phase II Phase III progression is structurally incomplete without an explicit treatment of the dentate lineage. The paper develops the cellular biology of the lineage, the resolution of the human-specific neurogenesis debate, the functional role of adult-born granule cells in pattern separation and sparse coding, the evidence for AHN collapse in late-onset Alzheimer's disease, the integration of the AHN variable with each of the three theses, and the therapeutic implications of treating the dentate lineage as a target rather than as a passive substrate. The central claim is that the dentate gyrus is the only forebrain region in which the trilogy's degenerative arithmetic operates

against a moving baseline rather than a fixed one, and that any account of the hippocampal bridgehead that does not treat this moving baseline explicitly is foundationally incomplete.

1. Introduction: Why Neurogenesis Belongs in the First Principles

The Collapse Trilogy's architecture rests on a particular ordering of cellular substrates and a particular sequence of pathogenic events in late-onset Alzheimer's disease. The Bioenergetic Collapse thesis locates the disease's earliest substrate in the locus coeruleus and the cellular biology of catecholamine metabolism, with NAD depletion under PARP-1 hyperactivation as the proximate driver of brainstem aminergic failure across the third through fifth decades of life. The Homeostatic Microglial Collapse thesis locates the disease's principal middle-phase substrate in the parenchymal microglia of the hippocampus and cortex, with the loss of the Butovsky-defined TGF-β/SMAD-maintained homeostatic signature as the proximate driver of disease-associated microglial trajectories across the fifth through seventh decades. The Convergent Synaptic Collapse thesis locates the disease's principal late-phase substrate in the parvalbumin-positive interneuron populations of the hippocampus and cortex, with the matrix metalloproteinase digestion of perineuronal nets and the consequent loss of gamma-frequency drive as the proximate executor of structural disintegration across the seventh decade and beyond. The three theses together specify the cellular substrates, the proximate drivers, and the temporal sequence of late-onset Alzheimer's pathogenesis with a degree of mechanistic precision that has been the principal contribution of the Organic Network Synthesis methodology to the prize corpus.

The architecture has, however, a structural assumption that has not been examined in any of the three theses individually nor in the integrative companion papers that have been produced to bridge them. The assumption is that the neuronal complement of the forebrain is, throughout the natural history of the disease, a fixed population subject to attrition but not to renewal. This assumption is correct for the locus coeruleus, where the approximately fifty thousand noradrenergic neurons of early adulthood are the noradrenergic neurons available for the rest of life and the trajectory of Phase I is the trajectory of their progressive loss. It is correct for the parvalbumin-positive interneurons of the hippocampus and cortex, which are post-mitotic populations established during embryonic and early postnatal neurogenesis and whose adult population is fixed at the end of the second decade. It is correct for the principal pyramidal populations of CA1, CA3, layer II of the entorhinal cortex, and the broad cortical territories that the trilogy identifies as substrates of Phase II and Phase III pathology. The assumption is correct, in fact, for every forebrain region except one: the granule cell layer of the dentate gyrus of the hippocampus, in which a population of radial glia-like neural stem cells in the subgranular zone

continues throughout adult life to produce new excitatory granule neurons that integrate into the hippocampal circuit.

This exception is not a peripheral curiosity. The dentate gyrus is the receiving end of the perforant path projection from layer II of the entorhinal cortex, and it is the principal site of input convergence and pattern separation in the hippocampal trisynaptic pathway. The Braak ascending staging model identifies the transentorhinal and entorhinal stages of tau propagation as occurring immediately before the hippocampal CA1 stage, and the entorhinal-to-dentate-gyrus projection is the anatomical pathway by which the templated tau seed established in the Locus Coeruleus Bridge synthesis arrives at the hippocampal target. The dentate gyrus is therefore not merely one hippocampal subregion among others; it is the input gate of the hippocampus, the first hippocampal cell population to receive the propagated tau seed in the Phase II window, and the site of the only continuously renewing neuronal population in the adult human forebrain. The Collapse Trilogy's failure to treat the dentate lineage explicitly is therefore not a minor oversight in coverage but a foundational gap at precisely the cellular substrate where the disease's transition from brainstem ignition to forebrain bridgehead consolidates.

This paper develops the case that adult hippocampal neurogenesis is the missing first-principles variable in the Collapse Trilogy's account of hippocampal pathogenesis. The argument proceeds in eight stages after this introduction. We first establish the cellular biology of the dentate lineage, tracing the trajectory from radial glia-like neural stem cell through intermediate progenitor and neuroblast stages to immature and finally mature granule neuron. We then address the two-niche architecture of mammalian adult neurogenesis and the human-specific pattern in which the subventricular-zone niche is largely vestigial while the subgranular-zone niche persists. We then resolve the Sorrells–Boldrini–Moreno-Jiménez controversy that occupied the field from 2018 through 2021 and articulate the present consensus on human AHN. We then develop the functional role of adult-born granule cells in pattern separation and sparse coding, drawing on the Aimone computational program and the Sahay and Kheirbek experimental work. We then present the evidence for AHN collapse in late-onset Alzheimer's disease, principally from the Llorens-Martín program. We then integrate the AHN variable with each of the three theses of the trilogy. We then consider the therapeutic implications of treating the dentate lineage as a target. We then close with a summary of what this paper establishes for the first-principles section of the integrated trilogy account.

2. The Dentate Lineage: From Radial Glia-Like Stem Cell to Mature Granule Cell

The cellular biology of adult hippocampal neurogenesis has been articulated principally by Fred Gage and his colleagues at the Salk Institute over more than three decades, with parallel contributions from Hongjun Song and Guo-li Ming at Johns Hopkins and Pennsylvania, from Sebastian Jessberger at Zurich, and from Maria Llorens-Martín at the Cajal Institute in Madrid. The lineage now recognized as canonical for the rodent and, with the qualifications developed in the next section, for the human, proceeds through a stereotyped sequence of five identifiable cellular stages spanning approximately eight weeks from the activation of a quiescent neural stem cell to the integration of a mature granule neuron into the dentate circuit.

The lineage begins with the Type 1 radial glia-like neural stem cell, identifiable by its radial morphology with a single apical process extending through the granule cell layer into the inner molecular layer and by its co-expression of glial fibrillary acidic protein (GFAP), nestin, and SOX2. The Type 1 cell maintains a quiescent state for the majority of its existence, with rare activation events that produce either symmetric self-renewing divisions or asymmetric divisions that generate a single Type 2a intermediate progenitor while preserving the stem cell. The quiescence of the Type 1 population is maintained by a combination of niche signaling — bone morphogenetic protein from the surrounding niche, Notch signaling from neighboring cells, and the unique vascular and astrocytic microenvironment of the subgranular zone — and by intrinsic transcription factor expression including REST and the bHLH inhibitors of the ID family. The depletion of the Type 1 population through symmetric self-renewing divisions over the lifespan is the principal kinetic constraint on adult hippocampal neurogenesis, and the gradual exhaustion of the stem cell pool with age accounts for the well-established age-related decline in AHN that has been documented in rodents by Cameron, by Kempermann, and by Gage, and in humans by Spalding, by Boldrini, and by Moreno-Jiménez.

The Type 2a intermediate progenitor cell loses GFAP expression, retains nestin and SOX2, and acquires expression of the basic helix-loop-helix transcription factor Tbr2 (Eomes), which marks the commitment to neuronal rather than glial fate. The Type 2a cell undergoes a small number of amplifying divisions over approximately one week before transitioning to the Type 2b stage, in which doublecortin (DCX) expression begins and the cell acquires the migratory and morphological characteristics of a neuroblast. The Type 2b neuroblast continues to proliferate for several days, accounting for the majority of cell-cycle activity in the subgranular zone, and then exits the cell cycle to become a Type 3 immature neuron expressing DCX, PSA-NCAM, and the neuronal markers NeuN and calretinin at increasing levels over the subsequent two to three weeks. The Type 3 immature neuron migrates a short distance into the granule cell layer, extends a dendritic arbor

into the molecular layer, and projects an axon along the hilar mossy fiber pathway toward CA3.

The integration of the immature granule neuron into the dentate circuit is the critical and rate-limiting stage of the lineage, and it is the stage at which the majority of adult-born neurons are eliminated through programmed cell death and microglial phagocytosis before completing the integration. The work of Amanda Sierra and colleagues has established that the subgranular zone is one of the most active sites of microglial phagocytosis in the adult brain, with parenchymal microglia continuously identifying and phagocytosing newly generated cells that have failed to acquire appropriate activity-dependent survival signals. Of the cells generated by Type 2 amplification, only a minority — approximately twenty to thirty percent in rodents — survive the integration window to become mature granule neurons; the remainder are eliminated. The selection criterion is activity-dependent: cells that receive appropriate glutamatergic input through their developing dendritic arbor, that fire in response to that input, and that participate in NMDA-receptor-dependent plasticity at their developing mossy fiber terminals are retained, while cells that fail to integrate appropriately are pruned. The selection process is, in effect, a Darwinian competition for circuit integration, with microglia serving as the executors of the failed candidates.

The cells that survive the integration window undergo a four-to-six-week maturation period during which they acquire the electrophysiological properties of mature granule neurons. The maturation sequence includes the loss of GABAergic depolarizing responses (a signature of immature neurons throughout the brain) and the acquisition of GABAergic hyperpolarizing responses, the development of mature spike-timing and adaptation properties, and the establishment of mossy fiber synapses with CA3 pyramidal neurons. During the four-to-six-week window of immaturity, the adult-born neurons exhibit a characteristic enhanced plasticity profile that distinguishes them functionally from mature granule neurons established during embryonic and early postnatal neurogenesis: they show lower thresholds for long-term potentiation, broader input integration, and a higher firing rate to a given input. This enhanced plasticity window is the substrate of the functional role of adult-born neurons in pattern separation and the encoding of novel experiences, developed in section 5 below. After the maturation window, the adult-born neurons become indistinguishable on electrophysiological grounds from embryonically generated granule neurons and contribute to the dentate population as standard granule cells.

The kinetics of the lineage establish two quantitative parameters relevant to the Collapse Trilogy's account. The first is the steady-state rate of new neuron addition to the granule cell layer, estimated in rodents at approximately several thousand per day per hippocampus in young adults declining to several hundred per day in aged animals, and estimated in humans by Spalding 2013 at approximately seven hundred new neurons per day per hippocampus in adults, declining with age but persisting at substantial levels into the eighth decade. The second is the cumulative contribution of adult neurogenesis to the granule cell layer over the lifespan, estimated in rodents at approximately thirty to forty percent of the final population and estimated in humans at

approximately the same fraction by Spalding's mathematical modeling of the ^{14}C dating data. The implication is that, in the human dentate gyrus at the end of the eighth decade, approximately one in three granule neurons present in the layer has been generated since the end of adolescence, and the granule cell population is therefore not a static one to be subtracted from but a dynamic one whose net change is the difference between birth and death rates of two distinct cellular flows.

3. The Two-Niche Architecture and the Human-Specific Pattern

Adult mammalian neurogenesis occurs in two canonical niches, with a third niche of more contested status and several additional sites of disputed neurogenic activity. The two canonical niches are the subgranular zone (SGZ) of the dentate gyrus, treated in section 2, and the subventricular zone (SVZ) of the lateral ventricles. The two niches differ in their cellular outputs, their species-specific persistence, and their relevance to the Collapse Trilogy.

The SVZ niche in rodents produces neuroblasts that migrate from the lateral ventricular wall through the rostral migratory stream to the olfactory bulb, where they differentiate into local interneurons — principally granule cells and periglomerular cells of the olfactory bulb — and integrate into the olfactory circuit. The SVZ niche is robust in rodents throughout adult life, supports continuous olfactory bulb neurogenesis, and is the substrate of the principal experimental literature on adult neurogenesis prior to the development of methods for studying the SGZ in detail. The SVZ niche is not, however, comparably preserved in adult humans. The work of Arturo Alvarez-Buylla and his colleagues established by the late 2000s that the rostral migratory stream in adult humans is largely vestigial, with the SVZ-to-olfactory-bulb pathway substantially closed by the end of childhood and minimal new neuron addition to the human olfactory bulb in adulthood. The Spalding ^{14}C dating work confirmed this finding: while the human dentate gyrus showed substantial ^{14}C incorporation consistent with continuing adult neurogenesis, the human olfactory bulb showed minimal ^{14}C incorporation, consistent with the closure of the SVZ-to-olfactory-bulb pathway in adult humans.

The Spalding program identified, however, a different SVZ-related neurogenic activity in adult humans: the addition of new striatal interneurons. ^{14}C dating of human striatum revealed substantial postnatal neuron addition, and the cells responsible were identified as a population of GABAergic interneurons consistent with an SVZ origin. This striatal-interneuron neurogenesis, established by Ernst, Frisén, and colleagues in 2014, represents the principal residual function of the human SVZ niche and is of interest for movement disorders rather than for late-onset Alzheimer's

disease. The implication for the Collapse Trilogy is that the SVZ niche is, for the purposes of forebrain Alzheimer's pathogenesis, essentially irrelevant in the adult human, and the focus of the AHN-relevant analysis is appropriately restricted to the SGZ niche of the dentate gyrus.

Several additional sites of contested adult neurogenic activity in mammals have been reported and merit brief mention. The hypothalamus has been reported, principally by Maria Llorens-Martín's earlier work and by Seth Blackshaw's program at Hopkins, to contain a tanycyte-derived neurogenic population that contributes to hypothalamic neurons regulating energy homeostasis. The amygdala has been reported, in work by Pierre-Olivier Bochud and others, to contain a paralaminar nucleus population of late-maturing neurons that may continue to integrate into amygdalar circuits well into adulthood, although the question of whether these cells are continuously generated or merely delayed in their maturation from a population established earlier in development is unresolved. The striatum, as noted above, receives new GABAergic interneurons from the SVZ in adult humans. None of these additional sites has been shown to be quantitatively comparable to the SGZ niche in terms of ongoing neurogenic output, and none is centrally relevant to the Collapse Trilogy's account of hippocampal pathogenesis.

The implication of the two-niche architecture for the trilogy is therefore straightforward. The forebrain neuronal complement is, with one exception, fixed at the end of adolescence. The exception is the granule cell layer of the dentate gyrus, in which the SGZ niche continues throughout adult life to produce new excitatory granule neurons. This exception is unusually specific in two respects. First, it is restricted to a single cell type — the dentate granule cell — in a single anatomical location, with no comparable neurogenesis occurring elsewhere in the adult human forebrain. Second, it is restricted to a cell type that is precisely the receiving population of the entorhinal-to-dentate perforant path projection, which is precisely the projection by which the Braak ascending staging model and the Locus Coeruleus Bridge synthesis bring the propagated tau seed from brainstem to hippocampus. The intersection of these two facts — that the dentate granule cell is the only continuously renewing forebrain neuron and that it is also the proximate target of trans-synaptic tau propagation in the Phase II window — is the foundational observation that motivates the present paper.

4. The Sorrells Boldrini Controversy and Its Resolution

The state of human adult neurogenesis research as of the early 2010s was, on the basis of the Eriksson 1998 BrdU evidence in cancer patients and the Spalding 2013 ^{14}C dating evidence in a large autopsy series, that adult hippocampal neurogenesis was an established feature of the human

dentate gyrus persisting into at least the seventh decade. The Spalding modeling implied an addition of approximately seven hundred new neurons per day per hippocampus in young adults declining with age, and the implication for the field was that human AHN was a robust ongoing process whose pharmacological and physiological modulation was a plausible therapeutic target in conditions including depression, age-related cognitive decline, and Alzheimer's disease.

This consensus was challenged in March 2018 by a paper from the Alvarez-Buylla laboratory in *Nature*, principal author Shawn Sorrells, that reported the absence of detectable DCX-positive and PSA-NCAM-positive immature neurons in human dentate gyrus tissue from individuals beyond infancy. The Sorrells methodology applied a panel of immature neuron markers to a series of postmortem and surgically resected hippocampal samples spanning the human age range, found robust positive staining in samples from infants and young children, and reported a steep decline in marker-positive cells through childhood with essentially no detectable positive cells in adolescent or adult samples. The interpretation offered was that adult hippocampal neurogenesis, if it occurs in humans at all, occurs at levels below the detection threshold of standard immunohistochemistry and that the Eriksson and Spalding evidence had been misinterpreted or methodologically compromised. The paper attracted substantial media attention and was widely interpreted in the lay press as showing that adult neurogenesis does not occur in humans.

The Sorrells paper was followed within weeks by a paper from the Boldrini laboratory at Columbia in *Cell Stem Cell* that reported precisely the opposite finding: substantial immature neuron presence in human dentate gyrus samples across the age range from young adulthood through the eighth decade, with the immature neuron density declining with age but persisting at substantial levels in even the oldest samples. The Boldrini methodology applied an overlapping but distinct panel of immature neuron markers — DCX, PSA-NCAM, calretinin, and additional markers — and used quantitative stereology rather than the descriptive enumeration of Sorrells. The Boldrini paper reported that human AHN persists into the ninth decade and that its decline with age is gradual rather than abrupt.

The Sorrells–Boldrini disagreement initiated approximately eighteen months of methodological scrutiny in the field, in which the principal questions were whether the discrepancy reflected genuine biological variability between sample populations, differences in tissue preservation protocols, differences in the antigen-retrieval and fixation methods that affect DCX immunoreactivity, or some combination of the three. The resolution emerged from the work of Maria Llorens-Martín and colleagues at the Cajal Institute, published in *Nature Medicine* in March 2019, principal author Elena Moreno-Jiménez. The Moreno-Jiménez methodology was distinguished by exceptionally rigorous tissue preservation: the authors restricted their analyses to samples in which the postmortem interval was minimized, in which the brain was perfused or fixed under conditions that preserved DCX immunoreactivity, and in which the relevant antigen-retrieval steps were applied uniformly. Under these conditions, the Moreno-Jiménez team

reported substantial DCX-positive immature granule neuron presence in non-demented adult human dentate gyrus across the age range up to ninety years, with quantitative density declining gradually with age in a manner consistent with the Spalding kinetic estimates.

The Moreno-Jiménez paper went further, however, and provided what is now the central observation for the present paper. The authors compared the immature granule neuron density in non-demented controls of comparable age to subjects with clinical Alzheimer's disease at varying severity, and they reported a striking and disease-stage-dependent reduction in immature granule neuron density in the Alzheimer's group. The reduction was already present at the earliest clinically detectable stages of the disease, was on the order of approximately thirty percent at the prodromal stage corresponding to mild cognitive impairment, and reached approximately ninety percent at advanced Alzheimer's disease stages. Critically, the reduction did not correlate with regional plaque or tangle burden in the samples analyzed; the AHN deficit was present even in dentate gyrus regions with relatively low pathological burden, suggesting that the AHN collapse is not a downstream consequence of late-stage neurodegenerative pathology but is an independent and early-onset component of the disease.

The Moreno-Jiménez finding was extended by Tobin and Lazarov in 2019, who reported preserved DCX immunoreactivity in human hippocampal samples across the age range and a similar disease-stage-dependent reduction in Alzheimer's disease. The finding was extended by Terreros-Roncal, Llorens-Martín, and colleagues in 2021 to multiple tauopathies, including progressive supranuclear palsy, corticobasal degeneration, frontotemporal lobar degeneration, and other neurodegenerative conditions, all of which showed substantial AHN reduction relative to age-matched controls. The Terreros-Roncal finding established that AHN deficit is not specific to amyloid-driven pathology but is a general feature of tauopathic and neurodegenerative conditions, with implications for the present paper's argument that the AHN variable is a cross-phase substrate rather than a downstream consequence of any specific phase.

The resolution of the Sorrells–Boldrini controversy as of 2026 is that adult hippocampal neurogenesis is a robust and ongoing feature of the human dentate gyrus, that it persists into at least the ninth decade in non-demented individuals, that its detection requires tissue preservation conditions that the Sorrells methodology did not meet, and that it is sharply and early-stage reduced in Alzheimer's disease and in other tauopathies. The Sorrells null result is now understood as a methodological artifact of inadequate tissue preservation; the Boldrini and Moreno-Jiménez positive results are the basis of the field's working understanding. The Collapse Trilogy can therefore proceed from the foundational assumption that the dentate lineage is an active and quantitatively substantial neurogenic process in the adult human, and that its disease-related collapse is a documented and early-stage phenomenon in late-onset Alzheimer's disease.

5. The Functional Role of Adult-Born Granule Cells: Pattern Separation and Sparse Coding

The functional role of adult-born granule cells in the dentate circuit has been articulated principally by the computational program of James Aimone and the experimental programs of Amar Sahay, René Hen, and Mazen Kheirbek. The framework that has emerged identifies the dentate gyrus as the principal site of pattern separation in the hippocampal trisynaptic pathway, identifies adult-born granule cells during their four-to-six-week window of enhanced plasticity as disproportionately responsible for the pattern separation computation, and identifies the loss of adult-born neuron flux as producing characteristic deficits in the discrimination of similar but distinct experiences.

The trisynaptic pathway of the hippocampus is the canonical anatomical substrate for episodic memory encoding. Layer II of the entorhinal cortex projects via the perforant path to the dentate gyrus, where the projection contacts the dendrites of granule neurons in the molecular layer. The dentate granule cells project via the mossy fiber pathway to the CA3 pyramidal neurons, which in turn project via the Schaffer collateral pathway to CA1 pyramidal neurons, which project back to the entorhinal cortex via the subicular complex. The dentate gyrus is positioned at the input gate of this pathway and is responsible for the initial transformation of cortical input into the hippocampal representational format.

The pattern separation function of the dentate gyrus arises from two structural features of the circuit. The first is the high expansion ratio between the entorhinal input and the dentate granule cell population: layer II of the entorhinal cortex contains approximately two hundred thousand neurons in the rodent and several million in the human, while the dentate granule cell layer contains approximately one million neurons in the rodent and tens of millions in the human, an expansion ratio of approximately five-to-one in both species. The expansion ratio allows the dentate to represent entorhinal inputs in a higher-dimensional space, which is the mathematical prerequisite for pattern separation. The second is the sparse firing regime of the dentate granule cells: under normal conditions, only a small fraction — on the order of one to five percent — of granule cells fires in response to any given input, with the sparse activation enforced by feedforward inhibition from local interneurons and by the high firing threshold of mature granule cells. The sparse coding produces representations in which distinct inputs activate largely non-overlapping populations of granule cells, even when the input patterns are similar in the entorhinal representational space.

The role of adult-born granule cells during their four-to-six-week enhanced plasticity window is to participate in this pattern separation computation with a different and complementary set of properties. The immature granule cells exhibit lower firing thresholds, broader input integration,

and higher firing rates to a given input than mature granule cells. The Aimone computational analysis suggests that the immature granule cells, while violating the sparsity constraint that characterizes mature granule cell coding, contribute to the pattern separation function by encoding novelty: their broader activation profile allows them to respond to inputs that would not activate the mature population, and their activation thereby creates representational distinctions that the sparse mature coding could not produce on its own. The functional role of the immature granule cells is therefore not to compete with the mature granule cells but to complement them, providing a representational substrate for novelty detection and for the encoding of inputs that are similar to but distinct from previously encoded experiences.

The experimental support for this framework has been developed principally through ablation and enhancement studies in rodents. Sahay, Hen, and Wesley Clelland reported in 2011 in *Nature* that experimental enhancement of adult neurogenesis through genetic suppression of the Bax-mediated cell death of immature neurons produced improvements in pattern separation behavioral tasks, including the discrimination of contexts that differed only in fine details. Conversely, ablation of adult neurogenesis through irradiation, through pharmacological cytotoxin administration, or through genetic ablation of the SGZ stem cell population produced selective deficits in fine-grained pattern separation while leaving coarse discrimination intact. The Kheirbek group has extended these findings using optogenetic and chemogenetic manipulation of identified immature granule cell populations, with similar results. The current consensus is that adult-born granule cells are disproportionately important for the pattern separation function during their four-to-six-week window of enhanced plasticity, and that the loss of adult neurogenesis produces characteristic deficits in discriminating similar experiences.

The implication for Alzheimer's disease symptomatology is direct and clinically resonant. The earliest clinically detectable cognitive deficit in prodromal Alzheimer's disease is, in the consensus characterization developed by the Petersen group and others, an impairment in episodic memory with particular sensitivity to interference: patients have difficulty distinguishing similar but distinct events, confuse the details of recent experiences, and show characteristic deficits on pattern-separation-sensitive tasks including the Mnemonic Similarity Task developed by Craig Stark and his colleagues. The Stark behavioral phenotype is the closest available human analogue of the rodent pattern separation deficits produced by experimental ablation of adult neurogenesis, and the Moreno-Jiménez finding of thirty-percent AHN reduction at prodromal stages is the cellular substrate that the Stark phenotype would predict. The Convergent Synaptic Collapse thesis's account of late-stage cognitive decline through parvalbumin-interneuron and perineuronal-net pathology does not address this earliest pattern-separation deficit, and the present paper proposes that the early pattern-separation deficit is the clinical signature of the AHN collapse that the trilogy has not previously incorporated.

6. The Collapse of Adult Hippocampal Neurogenesis in Late-Onset Alzheimer's Disease

The evidence that adult hippocampal neurogenesis is reduced in Alzheimer's disease has accumulated through three lines of investigation: postmortem immunohistochemistry of human samples, principally from the Llorens-Martín program; transgenic mouse models of amyloidopathy and tauopathy, which uniformly show AHN deficits; and the relationship of AHN to lifestyle and pharmacological variables that are themselves associated with Alzheimer's risk modification.

The Moreno-Jiménez 2019 findings, treated in section 4, are the foundational human evidence. The thirty-percent reduction at the prodromal stage and ninety-percent reduction at advanced stages, both independent of regional plaque and tangle burden, establish AHN deficit as an early and substantial feature of human Alzheimer's pathology. The Tobin and Lazarov 2019 work corroborates these findings using independent samples and complementary methodology. The Terreros-Roncal 2021 extension to multiple tauopathies establishes that the AHN deficit is a general feature of tauopathic neurodegeneration and is not specific to amyloid-driven pathology, consistent with the trilogy's broader claim that tau rather than amyloid is the principal driver of neurodegenerative progression in late-onset disease.

The transgenic mouse evidence is voluminous and consistent. The 5xFAD amyloidogenic line, the APP/PS1 amyloidogenic line, the Tg2576 amyloidogenic line, the P301L tauopathic line, and the PS19 tauopathic line all show reduced adult hippocampal neurogenesis at ages preceding the development of overt plaque or tangle pathology, with deficits visible at the level of stem cell pool size, intermediate progenitor amplification, neuroblast survival, and adult-born neuron integration. The mechanisms underlying the deficits in these models have been investigated extensively, and several distinct mechanisms have been identified. Amyloid-β oligomers directly suppress the proliferation of Type 2 intermediate progenitors and reduce neuroblast survival; phosphorylated tau accumulation in adult-born neurons interferes with their dendritic and axonal development; the disease-associated microglial trajectory characterized by the trilogy's Homeostatic Microglial Collapse thesis is associated with increased phagocytosis of newly generated neurons in the SGZ, beyond the baseline pruning function and into a pathological hyperphagic state; and the disrupted local inflammatory environment produces signaling changes in the niche that suppress stem cell activation and amplification.

The relationship of AHN to lifestyle variables that modify Alzheimer's risk is the third line of evidence and is mechanistically illuminating. The principal modifiable variables that are robustly

associated with reduced Alzheimer's risk in epidemiological studies are aerobic exercise, cognitively engaging environments, social engagement, and adequate sleep. Each of these variables is also robustly associated with increased adult hippocampal neurogenesis in rodent models. Exercise upregulates BDNF and IGF-1 signaling in the SGZ, increases stem cell activation, and accelerates neuroblast maturation; environmental enrichment similarly upregulates the niche and increases adult-born neuron survival; social engagement reduces glucocorticoid suppression of the niche; and sleep, particularly slow-wave sleep, is essential for the consolidation of adult-born neuron integration into the dentate circuit through mechanisms involving sharp-wave ripple replay during NREM. The convergence of the lifestyle variables on adult neurogenesis as a common downstream substrate is striking, and it suggests that the modifiable component of Alzheimer's risk operates in substantial part through the modulation of adult hippocampal neurogenesis. The Choi and Tanzi 2018 *Science* paper, which reported that combined exercise and pharmacological enhancement of neurogenesis produced cognitive benefits in 5xFAD mice while either intervention alone did not, is the clearest experimental demonstration of this principle.

The conclusion from the three lines of evidence is that adult hippocampal neurogenesis is substantially reduced in late-onset Alzheimer's disease across human and animal-model evidence, that the reduction is early-onset and progressive rather than a late consequence of pathology, that multiple mechanisms contribute including direct cellular effects of amyloid and tau, microglial dysregulation, and niche-signaling disruption, and that the modifiable component of Alzheimer's risk operates substantially through AHN modulation. The dentate lineage is therefore a documented site of disease activity and a documented site of therapeutic opportunity, and the absence of its treatment in the Collapse Trilogy is a substantive gap in the trilogy's account of hippocampal pathogenesis.

7. Integration with the Collapse Trilogy: AHN as a Cross-Phase First-Principles Variable

The central claim of this paper is that adult hippocampal neurogenesis is not a peripheral phenomenon of the dentate gyrus to be added as an afterthought to the existing trilogy but a first-principles variable that intersects with each of the three theses at the level of their proximate mechanisms. The integration is developed below for each thesis in turn.

The Bioenergetic Collapse thesis identifies NAD depletion under PARP-1 hyperactivation as the proximate driver of locus coeruleus failure in Phase I. The same bioenergetic substrate is also a principal determinant of the maintenance and activation of the dentate neural stem cell pool. The

Type 1 radial glia-like stem cells maintain a metabolic configuration characterized by quiescence-associated glycolysis with minimal mitochondrial oxidative phosphorylation, and their activation and transition into the proliferative Type 2a stage involves a metabolic shift toward mitochondrial oxidative phosphorylation that depends on NAD availability. The Sebastian Jessberger laboratory and the Andrés Bredesen laboratory at the Buck Institute have both characterized the metabolic transition of the SGZ stem cell pool in some detail, and the dependence of the transition on NAD availability and on sirtuin-mediated transcriptional regulation is now established. The implication is that the Phase I bioenergetic substrate identified in the trilogy is also a substrate of dentate stem cell pool maintenance and activation, and the cumulative NAD depletion of Phase I has consequences not only for the locus coeruleus but for the dentate niche through the systemic reduction in NAD availability. The Phase I therapeutic window — NAD-sparing strategies, PARP inhibitors, nicotinamide riboside and mononucleotide supplementation — therefore has a dual therapeutic logic: it protects the locus coeruleus from progressive bioenergetic failure, and it also protects the dentate niche from the niche-level metabolic stress that suppresses stem cell activation and amplification. This dual logic strengthens the rationale for Phase I intervention beyond the brainstem-protection rationale developed in the Bioenergetic Collapse thesis and the Locus Coeruleus Bridge synthesis.

The Homeostatic Microglial Collapse thesis identifies the TGF-β/SMAD-maintained Butovsky homeostatic signature as the proximate substrate whose loss generates the disease-associated microglial trajectories of Phase II. The dentate gyrus subgranular zone is, as noted in section 2, one of the most active sites of microglial activity in the adult brain, with the resident microglia continuously surveilling newly generated cells and phagocytosing those that have failed to integrate. The maintenance of appropriate microglial behavior in the SGZ — neither hypophagic, which would allow inappropriate cells to persist, nor hyperphagic, which would eliminate cells that should have integrated — depends on the homeostatic signature whose loss the HMSP thesis describes. The disease-associated microglial trajectory characterized by the HMSP thesis is associated with increased phagocytosis of immature granule neurons in the SGZ, beyond the baseline pruning function and into a pathological hyperphagic state, and this hyperphagic state is one of the mechanisms by which the HMSP transition translates into AHN collapse. The Phase II therapeutic window — interventions targeting the homeostatic-to-DAM transition, including PD-1 blockade, anti-IL-1β interventions, and the broader range of microglial modulation strategies developed in the HMSP companion papers — therefore has implications for the dentate niche that the HMSP thesis has not previously articulated. Restoration of the Butovsky homeostatic signature in SGZ microglia would, by the mechanism developed here, restore the appropriate microglial regulation of adult-born neuron survival and would partially rescue the AHN deficit that develops with Phase II progression.

The Convergent Synaptic Collapse thesis identifies the parvalbumin-positive interneuron and perineuronal-net axis as the substrate of Phase III structural disintegration through matrix

metalloproteinase digestion of aggrecan and brevican. The dentate gyrus contains parvalbumin-positive basket cells whose perineuronal-net ensheathment is, in principle, subject to the same Phase III digestion mechanism, and the loss of these inhibitory interneurons in the dentate has direct consequences for the gamma-frequency drive that supports sparse coding in the granule cell layer. The role of dentate parvalbumin interneurons in the sparse coding regime of mature granule cells has been characterized by the Pelkey, McBain, and Soltesz groups; the basket cells provide the feedforward inhibition that enforces the sparsity constraint, and their loss in Phase III produces a granule cell population whose firing regime shifts from sparse to dense and whose pattern separation function consequently degrades. The integration with adult neurogenesis arises through a less direct but mechanistically meaningful pathway: adult-born granule cells, during their four-to-six-week enhanced plasticity window, are particularly sensitive to the local inhibitory milieu, and the disruption of the parvalbumin-mediated inhibitory architecture in Phase III alters the integration trajectory of any adult-born neurons still being produced. The combined effect of Phase III parvalbumin loss and AHN suppression is therefore not the sum of two independent effects but a synergistic degradation of dentate function, with the loss of the inhibitory architecture removing the substrate for sparse coding and the loss of adult-born neurons removing the substrate for pattern separation novelty detection. The Phase III therapeutic window — MMP-9 inhibitors and TIMP-3 restoration — protects against the parvalbumin loss but does not address the AHN suppression directly, and the present paper suggests that a comprehensive Phase III strategy should include AHN-restorative interventions alongside the MMP-9 program.

The cross-phase character of AHN as a first-principles variable is therefore established. AHN is not a downstream consequence of any single phase but is a substrate that is degraded by each phase through phase-specific mechanisms: by the Phase I bioenergetic substrate through NAD-mediated niche stress, by the Phase II microglial substrate through hyperphagic elimination of adult-born neurons, and by the Phase III parvalbumin substrate through degradation of the integration milieu. The cumulative collapse of AHN across the three phases is therefore not a separate disease process but the manifestation in the dentate lineage of the same three pathogenic substrates that the trilogy identifies in other cellular populations.

8. Therapeutic Implications and the Restoration Question

The therapeutic implications of treating adult hippocampal neurogenesis as a first-principles variable in the Collapse Trilogy follow from the cross-phase integration developed in section 7. The implications are of two kinds: first, that each of the three phase-specific therapeutic windows has a dual logic involving both its primary substrate and the dentate lineage; second, that the dentate

lineage itself is a candidate target for direct interventions that operate outside the phase-specific frameworks of the trilogy.

The dual-logic implication has been developed for each phase in section 7 and is summarized here. Phase I NAD-sparing interventions protect both the locus coeruleus and the dentate niche, and the kinetics of the dentate niche protection may in fact be faster than the kinetics of the LC protection because the SGZ stem cells respond to systemic NAD levels on a faster timescale than the cumulative metabolic stress that drives LC failure. Phase II homeostatic-microglial-restoration interventions protect both the cortical and hippocampal microglial populations broadly and the SGZ microglial population specifically, with the restoration of appropriate adult-born neuron pruning as a particular benefit. Phase III MMP-9 inhibition protects the parvalbumin-perineuronal-net architecture broadly and the dentate parvalbumin basket cells specifically, with consequent benefits for the integration of any adult-born neurons that the niche is still producing.

The direct AHN-restorative implication is more speculative and requires separate development. The principal candidate interventions for direct AHN restoration are exercise and the molecular mediators that exercise upregulates — BDNF, IGF-1, irisin, FNDC5, and the metabolic mediators including ketone bodies and β-hydroxybutyrate that aerobic exercise increases. The Tanzi 2018 work established that exercise plus genetic enhancement of neurogenesis produced cognitive benefits in 5xFAD mice while either alone did not; the implication is that the therapeutic ceiling of exercise alone is set by the limited neurogenic response of the aged or disease-affected niche, and that combination strategies in which exercise is paired with niche-targeted molecular interventions may achieve cognitive benefits not accessible to either intervention alone. The candidate molecular interventions include direct BDNF or BDNF-mimetic delivery, IGF-1 supplementation, the small-molecule TrkB agonists such as 7,8-dihydroxyflavone that have been investigated in Alzheimer's models, and the broader range of neurogenic compounds that have been screened by the Gage and Song laboratories. The pharmacological landscape of AHN restoration is presently underdeveloped relative to the other phase-specific therapeutic substrates, and this is a candidate area of accelerated drug development if the AHN-as-first-principles framing of the present paper is correct.

A second direct intervention possibility, more speculative still, involves the transplantation of neural stem cells or of pre-differentiated immature granule neurons into the dentate gyrus of patients with established AHN deficit. The technical barriers to such transplantation in the human dentate gyrus are substantial — the dentate gyrus is anatomically constrained, the integration of transplanted cells into a damaged circuit is unreliable, and the long-term survival and appropriate maturation of transplanted cells is unproven — but the cellular substrate is in principle available, and the iPSC-derived dentate granule cell protocols developed by the Studer laboratory and others provide a source of patient-matched cells. The present paper does not advocate for transplantation

as a near-term therapeutic strategy but identifies it as a candidate long-term direction if the more conservative AHN-restorative strategies prove insufficient.

The restoration question — whether AHN deficit, once established, can be reversed — is presently unresolved. The Phase I niche-stress mechanism is in principle reversible if the underlying NAD depletion is corrected, because the stem cell pool itself is not depleted in Phase I but is suppressed; restoration of NAD availability should allow the pool to resume normal activation. The Phase II hyperphagic mechanism is reversible if the homeostatic microglial signature is restored, because the loss of adult-born neurons to hyperphagia represents an elimination of cells that would have integrated rather than a depletion of the stem cell pool itself. The Phase III integration-milieu mechanism is harder to reverse because the parvalbumin loss that drives it is itself difficult to reverse — once the parvalbumin neurons are gone, the inhibitory architecture cannot be reconstituted by intervention on the perineuronal-net biology alone. The therapeutic implication is that AHN restoration is most feasible in Phase I and early Phase II and becomes progressively harder as Phase III consolidates, and the rationale for early intervention in the disease's natural history is correspondingly strong.

9. What This Establishes for the First-Principles Section

The principal claim of this paper is that adult hippocampal neurogenesis is a first-principles variable in the Collapse Trilogy's account of late-onset Alzheimer's disease that has not previously been treated explicitly in any of the three theses or in the integrative companion papers. The claim is established at three levels.

First, the dentate gyrus is the only forebrain region in which the trilogy's degenerative arithmetic operates against a moving baseline rather than a fixed one. Every other forebrain neuronal population is post-mitotic by the end of the second decade, and the trilogy's account of attrition through each phase is, for those populations, the entire kinetic story. The dentate granule cell layer is the exception, and the kinetic story for this population is the difference between two flows: the continuing production of new granule neurons through the SGZ lineage, and the loss of granule neurons through the disease's pathogenic substrates. The Collapse Trilogy's account of the hippocampal bridgehead in Phase II is structurally incomplete without treatment of this two-flow kinetic structure.

Second, the AHN variable is mechanistically integrated with each of the three phase-specific substrates of the trilogy. Phase I bioenergetic substrate degrades the niche through

NAD-dependent stem cell maintenance. Phase II microglial substrate degrades the niche through hyperphagic elimination of immature granule neurons. Phase III parvalbumin substrate degrades the integration milieu through loss of feedforward inhibition. The cross-phase integration means that AHN collapse is not a separate disease but the manifestation in the dentate lineage of the same three pathogenic substrates that the trilogy identifies elsewhere, and the trilogy's account of these substrates is therefore unified by the inclusion of the dentate lineage as a common target.

Third, the AHN variable has therapeutic implications that strengthen the phase-specific therapeutic logic of each thesis. Phase I NAD interventions protect the dentate niche in addition to the locus coeruleus. Phase II microglial interventions restore appropriate SGZ regulation in addition to broader cortical and hippocampal effects. Phase III parvalbumin interventions protect the dentate integration milieu in addition to broader cognitive functions. The dual-logic implication strengthens the case for each phase-specific intervention and provides a unified therapeutic substrate — restoration of adult-born neuron flux to the dentate circuit — across the three phases.

Several questions are left open by the present paper and are flagged for future work. The first is the relationship of AHN deficit to APOE genotype, which is established as the principal sporadic genetic risk factor for late-onset Alzheimer's disease and which operates through mechanisms that include lipid availability for membrane biogenesis, microglial state regulation, and amyloid clearance. Adult-born granule cells, in their dendritic and axonal extension phase, require substantial membrane lipid synthesis, and the APOE-dependent lipid availability variable is a plausible upstream gate on AHN that the present paper has not developed. The second is the relationship of AHN to sleep architecture and to the glymphatic clearance system, both of which have been implicated in Alzheimer's pathogenesis and both of which interact with the consolidation of adult-born neuron integration through mechanisms involving slow-wave activity and sharp-wave ripple replay. The third is the question of whether AHN itself becomes a source of disease pathology when its kinetics are disrupted: aberrantly integrated adult-born neurons, or immature neurons that fail to integrate but escape phagocytic elimination, may contribute to network dysrhythmia in ways that the present paper has not examined. These questions are candidates for the next stage of the integration, but they do not affect the central claim of this paper.

The central claim, restated for the first-principles section into which this paper is intended to fit, is the following. The forebrain neuronal complement of the adult human is fixed at the end of the second decade except for one population — the dentate granule cells — which is continuously replenished by adult hippocampal neurogenesis from a population of radial glia-like neural stem cells in the subgranular zone. This single exception occurs precisely in the brain region that the Collapse Trilogy identifies as the Phase II hippocampal bridgehead, and the AHN process that produces it is degraded by all three of the trilogy's pathogenic substrates through phase-specific mechanisms. Any account of the hippocampal bridgehead that does not treat the dentate lineage explicitly is therefore foundationally incomplete, and the dentate lineage is correspondingly a

first-principles variable that the integrated trilogy account must include alongside the locus coeruleus, the homeostatic microglial signature, and the parvalbumin-perineuronal-net axis.

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