The Coerulean Interface

Vagal Inflammatory Load, Noradrenergic Restraint, and the Microglial Fate of the Locus Coeruleus in Alzheimer's Disease

How the Nucleus That Fails First Is Also the Brake on Microglial Inflammation — and How the Afferent Vagus Drives It: A Coerulean–Microglial Spiral Joining the Bioenergetic and Microglial Axes of the Collapse Trilogy

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience. Companion volume to the Collapse trilogy and to The Vagal Interface; the

Alzheimer-and-locus-coeruleus-focused treatment of the vagal inflammatory load and the noradrenergic restraint of microglia.

“The locus coeruleus is the nucleus that fails first and the brake whose failure lets the fire spread. Its bioenergetic collapse and the disinhibition of the microglia are not two events but one, seen from two sides.”

— ONS Methodology Working Notes, 2026

For Michael Heneka, who showed that the locus coeruleus governs Alzheimer's pathology through the noradrenergic control of microglia, and for Heiko Braak, who showed that the same nucleus is where the disease is first written.

THE COLLAPSE TRILOGY — COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition · The Vascular Phasing · The Vagal Interface

V. The Coerulean Interface ☐ this volume

This volume is the Alzheimer-and-locus-coeruleus-focused face of the vagal interface. Where the companion volume *The Vagal Interface* develops the full bidirectional conduit and its synucleinopathy-propagation function, the present volume concentrates on the inflammation-to-microglia mechanism: the afferent vagus as a chronic inflammatory load on the locus coeruleus, coerulean noradrenaline as an endogenous brake on microglia, and the self-amplifying coerulean–microglial spiral that joins the bioenergetic and microglial axes of the trilogy at a single brainstem nucleus — the one that fails first.

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Abstract

The locus coeruleus is the earliest site of Alzheimer's disease pathology. Hyperphosphorylated tau appears in this small pontine noradrenergic nucleus before it appears anywhere in the cortex — on autopsy evidence, in the first three decades of life, decades before symptoms — and the locus coeruleus is also the brain's sole source of cortical and hippocampal noradrenaline, a neuromodulator that, beyond its classical roles in arousal and attention, is a potent endogenous suppressor of microglial inflammation. This dissertation advances the thesis that the locus coeruleus occupies a uniquely catastrophic position in Alzheimer's disease because it is simultaneously the brain's first point of bioenergetic failure, the brain's principal anti-inflammatory brake on microglia, and the central recipient of the vagal afferent signal that reports the inflammatory state of the body. These three properties are not independent. The afferent vagus delivers a chronic inflammatory drive to the locus coeruleus through the nucleus tractus solitarius; the locus coeruleus answers peripheral and central inflammation with a noradrenergic restraint of microglia; and the bioenergetic cost of sustaining that answer, in a nucleus already operating at the edge of its metabolic ceiling, is part of what makes the locus coeruleus fail first. When it fails, the noradrenergic brake on microglia is released, neuroinflammation is disinhibited, and the disinhibited inflammation feeds back onto the surviving locus coeruleus neurons — a self-amplifying loop that this thesis names the *coerulean–microglial spiral*.

The thesis is organised in seven analytical chapters. Chapter I establishes the locus coeruleus as ground zero, consolidating the Braak pretangle evidence, the neuromelanin-MRI and stereological correlations between locus coeruleus integrity and cognitive trajectory, and the intrinsic bioenergetic vulnerability characterised by the Bioenergetic Collapse thesis. Chapter II develops the central and underappreciated fact that locus coeruleus noradrenaline is an endogenous anti-inflammatory, integrating the Heneka programme — in which experimental locus coeruleus lesioning worsens amyloid pathology, suppresses microglial amyloid clearance, and amplifies neuroinflammation — into the microglial axis of the

Collapse trilogy. Chapter III treats the afferent vagus as the conduit through which the inflamed periphery imposes a chronic activating load on the locus coeruleus, drawing the nucleus tractus solitarius □ locus coeruleus projection through the sickness-behaviour and inflammaging literatures. Chapter IV develops the cholinergic anti-inflammatory pathway as a second, parallel restraint on microglia, proposing a three-pillar model of microglial homeostasis — TGF-β/SMAD transcriptional identity, noradrenergic β-adrenergic restraint, and cholinergic α7-nicotinic restraint — of which two pillars are vagally and coeruleanly controlled. Chapter V formalises the coerulean–microglial spiral and derives its kinetics. Chapter VI synthesises the argument into the claim that the locus coeruleus is the hub at which the bioenergetic and microglial axes of the trilogy are physically joined, and that the vagus is the peripheral lever on that hub. Chapter VII develops therapeutic implications — noradrenergic augmentation, α7-nicotinic agonism, transcutaneous vagal stimulation, and the use of locus coeruleus neuromelanin MRI and heart-rate variability as a paired biomarker — and the falsifiable predictions that distinguish the framework from the cephalocentric default.

The dissertation concludes that the earliest event in Alzheimer's disease and the central event in its neuroinflammation are the same event seen from two sides: the locus coeruleus is the nucleus that fails first *and* the brake whose failure releases the microglia, and the vagus is how the body's inflammatory state reaches it. Neuroinflammation in Alzheimer's disease is not only a consequence of the disease; through the loss of the noradrenergic brake, it is one of its engines.

Keywords: locus coeruleus, noradrenaline, Alzheimer's disease, neuroinflammation, microglia, β-adrenergic receptor, α7 nicotinic acetylcholine receptor, cholinergic anti-inflammatory pathway, vagus nerve, nucleus tractus solitarius, pretangle tau, neuromelanin MRI, heart-rate variability, inflammaging

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1. Introduction

1.1 The Research Problem

Alzheimer's disease is conventionally understood as a disease of the cortex and hippocampus — the regions whose degeneration produces the amnestic syndrome that defines the clinical diagnosis. Yet the neuropathological evidence has, for two decades, pointed insistently to a different origin. The earliest deposits of abnormal, hyperphosphorylated tau in the human brain are found not in the entorhinal cortex, where Braak's cortical staging begins, but caudal to it, in the locus coeruleus — the small, bilateral, pigmented noradrenergic nucleus of the dorsal pons. Braak and Del Tredici's examination of large autopsy series, including young individuals, established that "pretangle" tau material appears in locus coeruleus neurons in childhood and adolescence, years to decades before cortical tau and before any clinical sign, and that the locus coeruleus is affected in essentially all cases that go on to develop cortical pathology. The locus coeruleus is, on this evidence, the first domino.

The Bioenergetic Collapse thesis of the Collapse trilogy took up this fact and asked why a small brainstem nucleus, rather than the cortex it supports, should fail first, and answered in terms of intrinsic bioenergetic vulnerability: the locus coeruleus neuron fires tonically, sustains one of the most diffusely projecting fields in the brain, operates a catecholaminergic biochemistry that generates oxidative and

proteostatic stress, and runs consequently at the edge of its metabolic ceiling, where it is exquisitely sensitive to any additional demand. That account is intrinsic and substrate-level, and it is the foundation on which the present dissertation builds. But it is incomplete in two respects that this thesis takes as its problem.

First, the intrinsic account does not incorporate the locus coeruleus's role as a *regulator of inflammation*. Noradrenaline released from locus coeruleus terminals is, in addition to its arousal and plasticity functions, one of the brain's principal endogenous suppressors of microglial activation — a fact established by Heneka, Feinstein, and colleagues but not integrated into the trilogy's microglial axis. The degeneration of the locus coeruleus therefore does not merely remove a source of arousal and a metabolically vulnerable cell population; it removes a brake on neuroinflammation, with consequences for the microglial state transition that the Homeostatic Microglial Collapse thesis places at the centre of the disease. Second, the intrinsic account treats the activating drive on the locus coeruleus as given, without asking what sustains the tonic firing whose metabolic cost is the nucleus's undoing. This dissertation proposes that a substantial and modifiable part of that drive is the afferent vagal signal of peripheral inflammation, relayed through the nucleus tractus solitarius — that the inflamed body, read by the vagus, is one of the things that keeps the locus coeruleus working beyond its means.

The thesis advanced is therefore a coupling thesis: the locus coeruleus is simultaneously the first site of bioenergetic failure, the principal anti-inflammatory brake on microglia, and the central recipient of the vagal inflammatory signal, and these three roles interlock into a self-amplifying loop. The loss of the noradrenergic brake disinhibits microglia; the disinhibited microglia raise the central inflammatory load; the raised load, together with the afferent vagal load from the periphery, drives the surviving locus coeruleus neurons harder; and the additional demand accelerates their bioenergetic failure. The locus coeruleus is the hub at which the bioenergetic and microglial axes of the trilogy are physically joined, and the vagus is the peripheral lever on that hub.

1.2 Significance

The significance of this reframing is fourfold. First, it identifies the locus coeruleus not as one early-affected nucleus among several but as the *mechanistic pivot* of Alzheimer neuroinflammation. If coerulean noradrenaline restrains microglia, then the earliest pathological event of the disease — locus coeruleus dysfunction — is also the releasing event for its neuroinflammation, and the long-standing question of whether neuroinflammation is cause or consequence of Alzheimer's disease acquires a precise answer: through the loss of the noradrenergic brake, it is both, in a loop, with the locus coeruleus as the point at which cause becomes consequence and back again.

Second, the framework supplies a unifying interpretation of an otherwise puzzling set of observations: that noradrenergic denervation worsens amyloid pathology in animal models; that locus coeruleus neuronal density at autopsy predicts the rate of cognitive decline in the years before death; that the "cognitive reserve" associated with education and engagement has a plausible noradrenergic substrate; and that sleep disruption, which is both an early symptom of and a risk factor for Alzheimer's disease, is tightly coupled to the locus coeruleus through its control of arousal state and, through noradrenaline, of glymphatic clearance and microglial surveillance. Each of these becomes a facet of a single coerulean account.

Third, the framework makes neuroinflammation *modifiable from the periphery and from the brainstem* rather than only at the parenchymal microglion. If a chronic afferent vagal inflammatory load contributes to locus coeruleus drive, then reducing peripheral inflammation reduces central noradrenergic burden; and if the cholinergic anti-inflammatory pathway supplies a parallel central brake on microglia through α7-nicotinic receptors, then vagal tone is a lever on microglial state independent of the noradrenergic pillar. The framework thus situates two of the three pillars of microglial restraint — the noradrenergic and the cholinergic — under vagal and coerulean control, and makes both accessible to intervention.

Fourth, the framework reorganises the biomarker landscape. Locus coeruleus integrity is now measurable in living humans by neuromelanin-sensitive MRI, and vagal tone is measurable by heart-rate variability; the framework predicts that these two inexpensive, non-invasive measures should be coupled, and that their joint decline should precede and predict the neuroinflammatory and cognitive trajectory more strongly than either alone. It proposes a paired brainstem–autonomic

biomarker for the earliest, pre-amyloid phase of the disease.

1.3 Scope and Limitations

This dissertation is a synthetic review centred on Alzheimer's disease. It draws the vagus and the locus coeruleus into the AD-focused Collapse framework and is deliberately narrower than its companion volume *The Vagal Interface*, which treats the full bidirectional conduit and its synucleinopathy-propagation function. The α-synuclein gut-to-brain route, the truncal-vagotomy epidemiology, and the body-first/brain-first dichotomy that are central to the Parkinson's-weighted reading of the vagus are treated here only briefly, in §2.7, as a boundary that locates the present argument; readers seeking that material are referred to the companion volume. The present thesis is concerned specifically with the locus coeruleus, with noradrenaline as an anti-inflammatory, and with the vagal inflammatory load as a driver of the nucleus — the Alzheimer-relevant, inflammation-to-microglia face of the vagal interface.

The thesis cannot resolve the direction of first causation. It does not claim that vagal inflammatory load initiates locus coeruleus tau pathology; the pretangle tau of the first decades of life appears before any plausible chronic inflammatory load and is most parsimoniously intrinsic. The thesis claims, more modestly, that vagal inflammatory load and the loss of the noradrenergic brake *condition and accelerate* a process whose earliest seed is intrinsic — that they convert a slow, possibly subclinical intrinsic vulnerability into a progressive disease by adding demand and removing restraint. The framework is therefore a thesis about progression and amplification more than about initiation, and it is stated as such. It also does not claim that noradrenaline is the dominant determinant of microglial state; it claims that noradrenergic tone is one of three restraining pillars, and that its coerulean source makes its loss an early and inevitable feature of the disease.

2. Literature Review

2.1 The Locus Coeruleus as the First Site of Alzheimer Pathology

The neuropathological priority of the locus coeruleus rests primarily on the work of Braak and Del Tredici. Their staging of subcortical tau pathology, set out across a series of papers culminating in the 2011 *Acta Neuropathologica* analysis, demonstrated that abnormal, non-argyrophilic "pretangle" tau material accumulates in the locus coeruleus and a small number of other subcortical nuclei before it is detectable in the transentorhinal cortex where their earlier cortical staging began. The pretangle material was found in individuals as young as children and adolescents, was essentially ubiquitous by middle age, and preceded the cortical neurofibrillary pathology in a manner consistent with the locus coeruleus being the origin rather than an early casualty. Whether or not one accepts the strong interpretation that tau pathology spreads transsynaptically from the locus coeruleus to its cortical targets — a claim that remains debated — the descriptive priority of the locus coeruleus is among the most robust facts in Alzheimer neuropathology.

This priority is matched by functional and structural correlations in living and recently deceased humans. Wilson and colleagues, in a 2013 clinicopathological study, reported that locus coeruleus neuronal density measured at autopsy predicted the rate of cognitive decline over the preceding years, independent of cortical pathology. The advent of neuromelanin-sensitive MRI, which exploits the paramagnetic neuromelanin pigment that accumulates in catecholaminergic neurons, has made locus coeruleus integrity measurable in vivo; Betts, Düzel, and others have shown that the neuromelanin-MRI locus coeruleus signal declines with age and is reduced in Alzheimer's disease and in those at risk, and that it correlates with memory performance. Mather and Harley's 2016 synthesis in *Trends in Cognitive Sciences* consolidated the case that locus coeruleus integrity is a determinant of cognitive resilience in the ageing brain. Weinshenker's 2018 review in *Trends in Neurosciences* — "the long road to ruin" — placed noradrenergic dysfunction at the centre of the neurodegenerative process across diseases.

2.2 The Intrinsic Bioenergetic Vulnerability of the Locus Coeruleus

The Bioenergetic Collapse thesis develops the intrinsic account of why the locus coeruleus fails first, and it is recapitulated here as background. The locus coeruleus neuron is autonomously pacemaking and tonically active even at rest; it sustains long, thin, largely unmyelinated axons, projecting noradrenaline throughout the cortex, hippocampus, cerebellum, and spinal cord from a nucleus of only some tens of thousands of neurons per side; and it must propagate and recover action potentials along those unmyelinated fibres continuously. The catecholaminergic biochemistry compounds the cost: the synthesis, vesicular packaging, and oxidative metabolism of noradrenaline generate reactive quinones and hydrogen peroxide, and the auto-oxidation that produces neuromelanin is a chronic source of oxidative and proteostatic stress. The combination — autonomous pacemaking, high tonic firing, and an intrinsically stressful transmitter — places the locus coeruleus neuron close to its bioenergetic ceiling, where NAD□ supply, mitochondrial quality control, and autophagic capacity are chronically taxed and where any sustained increase in demand cannot be met without attrition. This intrinsic vulnerability is the substrate on which the extrinsic, vagal and inflammatory, drive of the present thesis acts.

2.3 Noradrenaline as an Endogenous Anti-Inflammatory: The Heneka Programme

The fact on which this dissertation turns is that noradrenaline suppresses microglial inflammation. This was established principally by Heneka, Feinstein, and colleagues over two decades. In vitro, noradrenaline acting on β-adrenergic receptors suppresses the induction of inflammatory genes — inducible nitric oxide synthase, interleukin-1β, tumour necrosis factor — in microglia and astrocytes exposed to amyloid-β or lipopolysaccharide. In vivo, the experimental lesioning of the locus coeruleus, achieved with the noradrenergic neurotoxin DSP-4, amplifies neuroinflammation and worsens pathology. The decisive demonstration came in Heneka and colleagues' 2010 *Proceedings of the National Academy of Sciences* study, which showed that DSP-4 lesioning of the locus coeruleus in an APP-transgenic mouse model increased amyloid plaque burden, elevated inflammatory markers, and — critically — impaired the ability of microglia to migrate to and phagocytose amyloid-β, while also reducing the expression of amyloid-degrading enzymes. Noradrenaline, in other words, both restrains the inflammatory phenotype of microglia and promotes their beneficial, amyloid-clearing functions; its loss does double damage, releasing the harmful phenotype and disabling the protective one.

The receptor mechanisms have been progressively clarified. β2-adrenergic receptor signalling on microglia raises intracellular cyclic AMP and suppresses NF-κB-driven transcription, paralleling the cyclic-AMP-dependent anti-inflammatory effect of other Gs-coupled receptors. More recent work has shown that noradrenaline, through β2-adrenergic receptors, also governs the dynamic surveillance behaviour of microglia: Stowell and colleagues (2019) and Liu and colleagues (2019), in paired *Nature Neuroscience* papers, demonstrated that noradrenergic tone — high during wakefulness — suppresses the motility and process dynamics of microglia, and that the reduction of noradrenergic tone during sleep releases microglial surveillance. This couples the noradrenergic anti-inflammatory function to arousal state and to sleep, and connects it to the glymphatic clearance that is itself noradrenaline- and sleep-dependent. The locus coeruleus thus governs microglial state across multiple axes: the inflammatory phenotype, the phagocytic function, the surveillance dynamics, and, through sleep and glymphatics, the clearance environment in which microglia operate.

2.4 The Microglial Axis of the Collapse Trilogy and the Place of Noradrenaline

The Homeostatic Microglial Collapse thesis frames the microglial axis as the loss of a TGF-β/SMAD-maintained homeostatic identity — the transition from a surveillant, homeostatic microglion to a disease-associated, pro-inflammatory one, with mitophagy competence sorting the post-homeostatic cells into distinct downstream fates. The present thesis proposes that noradrenergic tone is a second pillar of homeostatic restraint, parallel to and partly independent of the TGF-β/SMAD pillar. Where the transcriptional programme sets the homeostatic baseline through a slow, identity-defining mechanism, the noradrenergic pillar provides a fast, dynamically adjustable, receptor-mediated brake whose strength tracks locus coeruleus activity and integrity. The two pillars are complementary, and the microglial transition is most permissive when both are weak — when the TGF-β/SMAD programme is failing and, simultaneously, the locus coeruleus has degenerated enough to withdraw the noradrenergic brake. Because locus coeruleus degeneration is the earliest event of the disease, the withdrawal of the noradrenergic pillar is predicted to be an early and possibly initiating contributor to the microglial transition — earlier than the failure of the transcriptional pillar, which the microglial thesis associates with later disease.

2.5 The Afferent Vagus, the Nucleus Tractus Solitarius, and the Drive on the Locus Coeruleus

The locus coeruleus does not fire in a vacuum; its tonic and phasic activity is shaped by its afferents, prominent among which is the input relayed from the nucleus tractus solitarius (NTS), the brainstem terminus of the afferent vagus. The afferent vagus is the brain's principal sensor of peripheral inflammation, established by the sickness-behaviour literature of Watkins, Maier, Goehler, and Dantzer: peripheral interleukin-1β and lipopolysaccharide drive fever, anorexia, and lethargy through a vagally-mediated pathway, and subdiaphragmatic vagotomy attenuates these responses. The NTS integrates this afferent inflammatory signal with humoral signals sampled at the adjacent area postrema and projects, directly and through the ventrolateral medulla, to the locus coeruleus. A peripheral inflammatory state is therefore transduced into a sustained excitatory drive on the locus coeruleus.

The relevance to chronic disease is that the low-grade systemic inflammation of ageing — "inflammaging" — and the many peripheral inflammatory states the corpus

records as Alzheimer risk factors (metabolic syndrome, periodontal disease, gut dysbiosis, chronic infection) constitute a chronic afferent vagal load. This load drives the locus coeruleus continuously, adding to the tonic firing whose bioenergetic cost the intrinsic account identifies as the nucleus's undoing. The afferent vagus is thus a candidate source of the otherwise-unexplained sustained demand on the locus coeruleus, and a modifiable one: unlike the intrinsic firing properties, the peripheral inflammatory load can be reduced.

2.6 The Cholinergic Anti-Inflammatory Pathway as a Parallel Brake

The efferent arm of the vagus supplies a second, mechanistically distinct restraint on inflammation: the cholinergic anti-inflammatory pathway of Tracey and colleagues. Vagal efferent activity, relayed through the splenic nerve and a population of acetylcholine-synthesising T cells, suppresses macrophage tumour necrosis factor production through the α7 nicotinic acetylcholine receptor (Borovikova et al., 2000; Wang et al., 2003; Rosas-Ballina et al., 2011). The α7 receptor is also expressed on microglia, and Shytle and colleagues (2004) demonstrated that acetylcholine, acting through microglial α7 receptors, suppresses NF-κB activation and cytokine release. There is therefore a central cholinergic anti-inflammatory mechanism, distinct from the noradrenergic one, operating on the same microglia. The two vagally-related brakes — the noradrenergic, sourced from the locus coeruleus that the afferent vagus drives, and the cholinergic, carried by the efferent vagus and its α7 effector — together place microglial restraint substantially under vagal and coerulean control. This is the basis of the three-pillar model developed in Chapter IV.

2.7 Boundary: The Synucleinopathy Reading and Its Separation from the Present Argument

For completeness the present thesis notes its boundary with the synucleinopathy-weighted reading of the vagus. In Parkinson's disease and related synucleinopathies, the vagus functions additionally as a physical route for the caudo-rostral propagation of misfolded α-synuclein from the enteric nervous system to the brainstem — the Braak dual-hit hypothesis, the Holmqvist and Kim demonstrations of gut-to-brain transport, and the truncal-vagotomy epidemiology that supplies quasi-experimental human evidence for the route. That propagation function passes through the same brainstem nuclei the present thesis discusses (the dorsal motor nucleus, and at Braak stage 2 the locus coeruleus itself), but it is a distinct mechanism — a conduit for pathology rather than a signal of inflammation — and it is developed in the companion volume *The Vagal Interface*. The present dissertation concerns the Alzheimer-relevant functions: the afferent inflammatory load on the locus coeruleus, the noradrenergic restraint of microglia, and the loop that joins them. The two readings share an anatomy and diverge in mechanism.

2.8 Gaps in the Literature

Four gaps motivate the present synthesis. First, the Heneka programme on noradrenergic control of microglia and the Braak evidence on locus coeruleus pathological priority are rarely integrated; the field knows both that the locus coeruleus fails first and that noradrenaline restrains microglia, but it has not drawn the inference that the first event is the releasing event for the neuroinflammation. Second, the autonomic-ageing literature on heart-rate variability and the brainstem literature on locus coeruleus integrity have developed independently, despite both indexing the same vagal–coerulean system. Third, the inflammaging and gut–brain literatures emphasise humoral and vascular routes of peripheral-to-central inflammation and underdevelop the afferent-vagal-to-locus-coeruleus route. Fourth, the noradrenergic and cholinergic anti-inflammatory pathways are studied separately and have not been combined with the TGF-β/SMAD account into a unified model of microglial restraint. This dissertation addresses all four.

3. Methodology

This dissertation employs the Organic Network Synthesis (ONS) methodology of the AdultCognitiveDisease.com corpus, applied across the Collapse trilogy and its companion volumes. ONS treats the published literature as a network of mechanistic claims and seeks the convergence nodes at which independently developed frameworks make contact, on the premise that the convergence nodes carry the explanatory leverage of a systems account.

The method as applied here proceeds in four steps. First, *hub identification*: the selection of the locus coeruleus as the candidate hub on the basis of its dual status as the earliest site of Alzheimer pathology and the source of an anti-inflammatory neuromodulator, a coincidence that the trilogy's separate bioenergetic and microglial analyses each touch but neither integrates. Second, *literature triangulation*: the assembly of four literatures that do not ordinarily cite one another — the Braak/neuromelanin locus coeruleus pathology literature, the Heneka noradrenaline-and-microglia literature, the Tracey inflammatory-reflex literature, and the Watkins/Maier vagal-sickness-behaviour literature. Third, *loop construction*: the assembly of these into the coerulean–microglial spiral, with explicit attention to the sign and the kinetics of each arc, so that the loop is stated as a falsifiable dynamical claim rather than a metaphor. Fourth, *prediction derivation*: the statement of predictions that distinguish the framework from the default, weighted toward those for which paired locus-coeruleus-MRI and heart-rate-variability data, noradrenergic-augmentation trials, and α7-agonist trials already exist or are obtainable.

The methodology has the limitations inherent to synthetic review. It cannot establish causation, and the coerulean–microglial spiral, in particular, is a hypothesised positive-feedback loop whose existence in humans is inferred from its separately evidenced arcs rather than demonstrated as a whole. The thesis foregrounds the contested status of transsynaptic tau spread from the locus coeruleus, the species gap between the DSP-4 mouse lesion models and human disease, and the modest and not uniformly replicated clinical evidence for noradrenergic and vagal interventions, rather than suppressing them; Chapter VII states the conditions under which the framework would be falsified.

4. Chapter I — The Locus Coeruleus as Ground Zero

4.1 The Descriptive Priority

The empirical foundation of this dissertation is the descriptive priority of the locus coeruleus in Alzheimer pathology, established in §2.1 and elaborated here. The strength of the Braak pretangle evidence lies in its developmental dimension: the pretangle tau material is present in the locus coeruleus of individuals far too young to have any cortical pathology or clinical sign, and it is present with a prevalence that rises monotonically with age until it is essentially universal. The locus coeruleus is not merely affected early in symptomatic patients; it is affected first in the population, decades before disease. Whatever initiates Alzheimer's disease acts on the locus coeruleus before it acts anywhere else that can be seen.

This priority reframes the disease's natural history. The decades-long preclinical phase of Alzheimer's disease, conventionally described in terms of accumulating amyloid, can be redescribed as a decades-long period during which the locus coeruleus is the principal site of pathology and the cortex is still intact. The clinical disease, on this reading, is the late phase of a brainstem process — the point at which the consequences of locus coeruleus dysfunction, propagated and amplified, finally reach and overwhelm the cortical circuits whose failure produces symptoms. The locus coeruleus is the long fuse of the disease.

4.2 The Functional Consequences of Coerulean Decline

The locus coeruleus supplies noradrenaline to the entire forebrain, and its decline therefore has consequences across every function noradrenaline serves. It modulates attention and arousal; it gates the signal-to-noise ratio of cortical processing; it is required for certain forms of synaptic plasticity and memory consolidation, including the noradrenergic enhancement of hippocampal long-term potentiation; and it participates in the regulation of cerebral blood flow and the neurovascular coupling that the Vascular Phasing thesis examines. The progressive loss of these functions over the preclinical decades supplies a parsimonious account of several otherwise-disparate prodromal features of Alzheimer's disease — the subtle attentional and sleep changes, the loss of cognitive resilience — and connects the locus coeruleus to the synaptic axis of the trilogy through its plasticity-supporting role. But the function on which this thesis concentrates is the one least represented in the classical picture: the control of microglia.

4.3 The Bioenergetic Reading and Its Extension

The intrinsic bioenergetic vulnerability of the locus coeruleus, recapitulated in §2.2, explains the nucleus's susceptibility but not the trajectory of its failure. A vulnerability is a standing condition; a disease is a process. To convert the standing vulnerability into a progressive process requires a sustained or escalating demand that the vulnerable neuron cannot meet. The intrinsic account locates this demand in the neuron's own firing and biochemistry, which are constant rather than escalating, and therefore explains susceptibility better than progression. The present thesis supplies the escalating term: the afferent vagal inflammatory load (Chapter III), which rises with age as inflammaging advances, and the disinhibited central inflammation that follows the loss of the noradrenergic brake (Chapter V), which rises as the disease progresses. These two escalating demands convert the standing bioenergetic vulnerability into a progressive collapse, and they are the subject of the chapters that follow.

5. Chapter II — Coerulean Noradrenaline as an Endogenous Anti-Inflammatory

5.1 The Core Mechanism

The central mechanism of this dissertation, established in the literature by the Heneka programme (§2.3), is that noradrenaline released from locus coeruleus terminals suppresses the inflammatory activation of microglia and promotes their beneficial functions. The mechanism operates principally through β2-adrenergic receptors expressed on microglia, whose Gs coupling raises intracellular cyclic AMP and thereby suppresses NF-κB-dependent transcription of the inflammatory cytokines and inducible nitric oxide synthase, while simultaneously supporting the migratory and phagocytic functions through which microglia clear amyloid-β and debris. Noradrenaline is, in effect, a tonic instruction to microglia to remain in or return toward their surveillant, non-inflammatory, clearance-competent state — an instruction broadcast continuously across the forebrain by the tonically active locus coeruleus.

5.2 The Evidence from Coerulean Lesioning

The strongest causal evidence comes from experimental lesioning. The noradrenergic neurotoxin DSP-4 destroys locus coeruleus terminals and depletes forebrain noradrenaline, and its application in amyloid-bearing transgenic mice reproducibly worsens the disease: amyloid plaque burden increases, inflammatory markers rise, microglial recruitment to plaques and phagocytic clearance of amyloid decline, and amyloid-degrading enzyme expression falls (Heneka et al., 2010; Jardanhazi-Kurutz et al., 2010; Kalinin et al., 2007). The lesion experiments establish that noradrenergic tone is not an epiphenomenon of locus coeruleus activity but a functionally necessary restraint: removing it is sufficient to amplify neuroinflammation and impair amyloid clearance in a model that otherwise progresses more slowly. The translational caveat — that DSP-4 produces an acute, complete lesion unlike the slow partial attrition of human disease — is real and is stated; but the direction of the effect, and its consistency across laboratories, make the anti-inflammatory function of coerulean noradrenaline among the better-established facts in the experimental neuroinflammation literature.

5.3 The Surveillance and Sleep Dimension

The 2019 demonstrations by Stowell and by Liu that noradrenaline, through β2-adrenergic receptors, suppresses microglial process motility and surveillance — and that the fall of noradrenergic tone during sleep releases that surveillance — add a temporal and a sleep dimension to the coerulean control of microglia. In the healthy brain, this produces a daily rhythm: high noradrenergic tone during wakefulness holds microglia in a restrained, less-motile state, and the nightly fall of tone permits a surveillance and clearance phase coordinated with glymphatic flow. In the diseased brain, the loss of locus coeruleus neurons flattens this rhythm — chronically low noradrenergic tone removes the daytime restraint, while the disrupted sleep architecture of Alzheimer's disease degrades the nightly clearance phase. The result is a microglial population that is both chronically disinhibited and ineffectively scheduled, losing both the restraint that noradrenaline imposes and the coordinated clearance that its rhythmic withdrawal once permitted. The coerulean control of microglia is thus not only tonic but temporal, and both dimensions fail together as the nucleus degenerates.

5.4 Integration with the Microglial Axis

The integration of this chapter with the Homeostatic Microglial Collapse thesis is the proposition that the loss of the noradrenergic brake is an early driver of the microglial state transition — earlier, in the disease's natural history, than the failure of the TGF-β/SMAD transcriptional pillar that the microglial thesis emphasises. Because the locus coeruleus is the first site of pathology, its anti-inflammatory output begins to wane during the long preclinical phase, while the cortical microglia are still transcriptionally homeostatic. The framework therefore predicts a sequence: noradrenergic restraint declines first, partially disinhibiting microglia and raising the inflammatory set-point during the preclinical decades; the raised set-point, together with accumulating amyloid and the failing transcriptional pillar, then drives the full microglial transition in the symptomatic phase. The noradrenergic pillar is the early-warning pillar, the one whose decline tracks the earliest pathology of the disease.

6. Chapter III — The Afferent Vagus and the Inflammatory Load on the Locus Coeruleus

6.1 The Afferent Vagus as Inflammation Sensor, Revisited for the Locus Coeruleus

Chapter II established what the locus coeruleus does to inflammation; this chapter establishes what inflammation does to the locus coeruleus. The afferent vagus, the brain's principal sensor of peripheral inflammation (§2.5), delivers its signal to the NTS, and the NTS projects to the locus coeruleus. The consequence is that a peripheral inflammatory state becomes a central drive on the locus coeruleus: the nucleus that restrains inflammation is itself driven by inflammation, in a feedforward arrangement that is adaptive in the acute case — peripheral infection raises locus coeruleus activity, which mobilises arousal and, through noradrenaline, restrains the central inflammatory response — but maladaptive when the peripheral inflammatory signal becomes chronic.

6.2 The Chronic Load of Inflammaging

The peripheral inflammatory state of the ageing body is not acute and self-limiting but chronic and progressive. Inflammaging — the low-grade, sterile, systemic inflammation that accompanies ageing — raises the basal afferent vagal inflammatory signal across the adult lifespan, and the specific peripheral inflammatory conditions the corpus records as Alzheimer risk factors add to it. The locus coeruleus therefore experiences, over the same decades during which its intrinsic vulnerability is playing out, a slowly rising afferent inflammatory drive. The framework's claim is that this rising drive is one of the escalating demands (§4.3) that converts the locus coeruleus's standing bioenergetic vulnerability into a progressive failure: the nucleus is driven harder, for longer, by an inflamed periphery it is wired to respond to, and the additional tonic activity exacts a bioenergetic cost the already-marginal neuron cannot sustain indefinitely.

6.3 The Modifiability of the Afferent Load

The distinctive feature of the afferent vagal load, relative to the intrinsic firing properties, is that it is modifiable. The intrinsic pacemaking and catecholaminergic biochemistry of the locus coeruleus neuron are fixed properties of its identity; the afferent inflammatory load is a function of the peripheral inflammatory state, which is amenable to intervention through anti-inflammatory, metabolic, microbiome, and lifestyle measures. The framework therefore predicts that reducing peripheral inflammation should reduce the afferent vagal drive on the locus coeruleus and, by lowering one of the escalating demands, slow the nucleus's bioenergetic attrition. This supplies a brainstem-level mechanism for the corpus's repeated observation that anti-inflammatory and lifestyle interventions modulate Alzheimer risk, and it locates part of the benefit of those interventions in the protection of the locus coeruleus rather than only in the cortex.

6.4 The Convergence of Drive and Disinhibition

The afferent inflammatory load of this chapter and the loss of the noradrenergic brake of Chapter II converge on the same nucleus from opposite directions. The afferent load drives the locus coeruleus harder; the loss of the brake means that the inflammation the locus coeruleus is failing to restrain rises, adding a central inflammatory load to the peripheral one. As the locus coeruleus degenerates, it is simultaneously driven more (by rising peripheral and central inflammation) and able to do less (because fewer neurons remain to supply the restraining noradrenaline). This convergence is the substance of the coerulean–microglial spiral, formalised in Chapter V.

7. Chapter IV — The Cholinergic Anti-Inflammatory Pathway and the Three Pillars of Microglial Restraint

7.1 The Three Pillars

This dissertation proposes that microglial homeostasis in the adult brain rests on three restraining pillars, of which the Collapse trilogy has previously developed only one. The first pillar is the TGF-β/SMAD transcriptional programme characterised by the Homeostatic Microglial Collapse thesis — the slow, identity-defining signalling that maintains the surveillant microglial phenotype. The second pillar is the noradrenergic β-adrenergic restraint developed in Chapter II — the fast, tonic, receptor-mediated brake supplied by the locus coeruleus. The third pillar is the cholinergic α7-nicotinic restraint supplied by the cholinergic anti-inflammatory pathway (§2.6) — a second fast, receptor-mediated brake, carried by the efferent vagus and its acetylcholine effector. The three pillars differ in timescale (transcriptional versus receptor-mediated), in source (paracrine versus coerulean versus vagal), and in receptor (SMAD versus β-adrenergic versus α7-nicotinic), and they are partly redundant — a virtue in a homeostatic system, since the failure of one pillar can be buffered by the others.

7.2 The Vagal and Coerulean Control of Two Pillars

The framework's organising observation is that two of the three pillars are under vagal and coerulean control. The noradrenergic pillar is sourced from the locus coeruleus, which the afferent vagus drives; the cholinergic pillar is carried by the efferent vagus directly. Only the TGF-β/SMAD pillar is independent of the vagal–coerulean system. This means that the vagus and the locus coeruleus together govern the dynamically adjustable, receptor-mediated component of microglial restraint, while the transcriptional component is set elsewhere. The consequence for disease is that the early failure of the locus coeruleus and the age-related withdrawal of vagal tone weaken two of the three pillars simultaneously and early, leaving microglial restraint dependent on the single transcriptional pillar — which the microglial thesis identifies as itself failing in the symptomatic phase. The disease, on this reading, is in part the sequential loss of the three pillars, with the vagally and coeruleanly controlled pillars failing first.

7.3 Why Redundancy Delays and Then Accelerates Collapse

The three-pillar model explains a characteristic feature of the disease's natural history: its long latency followed by a relatively rapid clinical decline. During the preclinical decades, the early loss of the noradrenergic pillar (as the locus coeruleus declines) and the gradual withdrawal of the cholinergic pillar (as vagal tone falls with age) are buffered by the intact TGF-β/SMAD pillar, which maintains microglial homeostasis despite the weakening of the faster brakes. The system tolerates the loss of one or two pillars because the third compensates — and the disease remains subclinical. When the transcriptional pillar finally begins to fail, however, there are no remaining brakes to compensate, and the microglial transition proceeds rapidly. The redundancy of the three-pillar architecture both delays the onset of clinical disease and, by exhausting the compensatory reserve before the final pillar fails, sharpens the decline once it begins. This is the microglial-restraint analogue of the cognitive-reserve phenomenon, and it predicts that the rate of clinical progression should depend on the order and spacing in which the pillars fail.

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8. Chapter V — The Coerulean–Microglial Spiral

8.1 The Loop Stated

The central dynamical claim of this dissertation is a positive-feedback loop joining locus coeruleus failure to microglial activation, which this thesis names the coerulean–microglial spiral. The loop has four arcs. First, locus coeruleus degeneration reduces forebrain noradrenaline. Second, reduced noradrenaline disinhibits microglia — releasing the inflammatory phenotype and impairing amyloid clearance (Chapter II). Third, the disinhibited, activated microglia raise the central inflammatory load, producing cytokines and reactive species that are toxic to neurons, including to the surviving locus coeruleus neurons, which are among the most vulnerable in the brain. Fourth, the raised inflammatory load — together with the afferent vagal load from the inflamed periphery (Chapter III) — drives the surviving locus coeruleus neurons harder and exposes them to a more inflammatory milieu, accelerating their degeneration and returning the loop to its first arc with fewer neurons remaining.

Each arc of the loop is separately evidenced: the noradrenergic anti-inflammatory mechanism (arc two) by the Heneka programme; the neurotoxicity of activated microglia (arc three) by the broad neuroinflammation literature; and the vulnerability of locus coeruleus neurons to inflammatory and oxidative stress (arc four) by the bioenergetic account. The novel claim is not any single arc but their closure into a loop, and the prediction that the loop's gain — the degree to which each cycle amplifies the next — determines the rate of progression once the spiral is engaged.

8.2 The Kinetics and the Tipping Point

The spiral is a positive-feedback loop, and positive-feedback loops have a characteristic dynamical signature: a slow, sub-threshold phase in which the loop gain is below unity and perturbations decay, followed, once the gain crosses unity, by a rapid, self-amplifying phase. The framework maps this signature onto the natural history of Alzheimer's disease. During the long preclinical phase, the loop gain is below unity — the intact TGF-β/SMAD pillar and the still-substantial locus coeruleus population keep the disinhibition mild and the locus coeruleus loss slow, so that the loop does not run away. The transition to clinical disease corresponds to the loop gain crossing unity, at which point each increment of locus coeruleus loss produces enough microglial disinhibition to drive more than an equal increment of further locus coeruleus loss, and the spiral accelerates. This mapping is the framework's account of why Alzheimer's disease has a tipping point — why decades of slow, tolerated change give way to years of progressive decline — and it locates the tipping point in the crossing of the spiral's gain threshold.

8.3 Where to Break the Loop

A positive-feedback loop can be broken at any arc, and the spiral's four arcs define four points of therapeutic intervention. Arc one (locus coeruleus loss) can be addressed by protecting the nucleus, including by reducing the afferent inflammatory load (Chapter III). Arc two (noradrenergic disinhibition of microglia) can be addressed by noradrenergic augmentation, replacing the failing coerulean output pharmacologically. Arc three (microglial inflammatory output) can be addressed by the cholinergic pillar — α7-nicotinic agonism or vagal stimulation — supplying an alternative brake when the noradrenergic one has failed. Arc four (inflammatory drive on the locus coeruleus) can be addressed by reducing both the central inflammatory load and the peripheral one. The framework predicts that interventions at different arcs should be synergistic, because breaking any one arc lowers the loop gain and amplifies the effect of breaking the others — a prediction that is the dynamical formalisation of the trilogy's recurring conclusion that combination therapy at coupled points outperforms monotherapy.

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9. Chapter VI — Synthesis: The Locus Coeruleus as the Hub of the Bioenergetic and Microglial Axes

9.1 The Hub

The synthesis of this dissertation is that the locus coeruleus is the hub at which the bioenergetic and microglial axes of the Collapse trilogy are physically joined. The bioenergetic axis identifies the locus coeruleus as its earliest and most vulnerable point; the microglial axis identifies the loss of homeostatic restraint as its central event; and the locus coeruleus is the source of the noradrenergic restraint whose loss is, this thesis argues, an early driver of that microglial event. The two axes are therefore not merely correlated through shared downstream pathology; they are joined at a single nucleus, where the bioenergetic failure of that nucleus is the same event as the withdrawal of the microglial brake. The locus coeruleus is the anatomical point at which "the bioenergetic substrate fails" and "the microglia are disinhibited" become two descriptions of one process.

9.2 The Vagus as the Peripheral Lever

The vagus is the peripheral lever on this hub. Its afferent arm sets part of the activating load on the locus coeruleus, and its efferent arm supplies the cholinergic pillar that can substitute for the failing noradrenergic one. The vagus does not replace the locus coeruleus in the framework; it modulates it and backs it up. The afferent vagus determines how hard the inflamed periphery drives the nucleus, and therefore how fast the intrinsic vulnerability is converted into progressive failure; the efferent vagus determines how much cholinergic restraint remains to hold the microglia when the noradrenergic restraint has gone. Through these two arms, a peripheral immunometabolic state — the variable the corpus's "systemic disease" frameworks identify as upstream — acts on the central hub of the disease. The vagus is the channel that makes the periphery matter to the locus coeruleus.

9.3 The Relation to the Companion Volumes

This thesis stands in a definite relation to its companion volumes. *The Vascular Phasing* identifies the neurovascular unit as the gateway through which the aged systemic milieu reaches the parenchyma humorally; the present thesis identifies the afferent vagus as the parallel neural channel through which the inflamed periphery reaches the locus coeruleus, and the two are complementary routes to the same brainstem target. *The Tryptophan Partition* identifies a shared metabolic substrate whose inflammatory shunt depletes neuroprotective branches; the inflammatory IDO induction it describes is part of the peripheral and central inflammatory state that drives the afferent vagal load and the microglial disinhibition of the present framework. *The Vagal Interface* develops the full bidirectional conduit and its synucleinopathy-propagation function; the present thesis is its Alzheimer-and-locus-coeruleus-focused face, sharing the anatomy and concentrating on the inflammation-to-microglia mechanism. The companion volumes converge: a shared substrate, a shared vascular gateway, a shared neural conduit, all reaching the same small pontine nucleus that fails first.

10. Chapter VII — Therapeutic Implications and Experimental Predictions

10.1 The Therapeutic Surface

The framework generates a therapeutic surface organised around the four arcs of the coerulean–microglial spiral (§8.3): protect the locus coeruleus, augment noradrenergic restraint, supply cholinergic restraint, and reduce the inflammatory drive. These targets are unusually accessible, comprising approved or repurposable drugs (noradrenergic agents, cholinergic agents), a non-invasive device intervention (transcutaneous vagal stimulation), and modifiable peripheral inflammation, and they are unusually measurable, through paired locus-coeruleus-MRI and heart-rate-variability biomarkers.

10.2 Noradrenergic Augmentation

The most direct implication of the noradrenergic anti-inflammatory mechanism is that augmenting noradrenergic signalling should restrain microglia and slow the spiral. The noradrenaline reuptake inhibitor atomoxetine, and the partial substitute provided by the noradrenaline-precursor and β-agonist literature, supply candidate interventions; atomoxetine has been examined in early Alzheimer trials with biomarker but not yet robust clinical endpoints, and the framework predicts that noradrenergic augmentation should be most effective early, while enough locus coeruleus terminals remain to deliver the augmented signal, and less effective late, once the projection has degenerated. This timing prediction parallels the one developed for vagal stimulation and is a recurring feature of the framework: interventions that support a failing brake work while the brake still exists and fail once it is gone.

10.3 Cholinergic Restraint: A New Reading of an Old Drug Class

The cholinergic pillar supplies a new reading of the cholinesterase inhibitors, the mainstay symptomatic treatment for Alzheimer's disease. Their modest benefit is conventionally attributed entirely to the augmentation of basal-forebrain cholinergic neurotransmission at the synapse. The three-pillar model suggests that part of their effect may operate through the augmentation of cholinergic anti-inflammatory tone on microglia — that by raising acetylcholine they strengthen the α7-nicotinic pillar of microglial restraint, independent of their synaptic action. The framework predicts that selective α7-nicotinic agonists, which would engage the anti-inflammatory pillar without the synaptic and peripheral effects of global cholinesterase inhibition, should reduce neuroinflammatory markers, and it reframes the cholinergic system in Alzheimer's disease as a restraint on microglia and not only a substrate of memory.

10.4 Transcutaneous Vagal Stimulation

Transcutaneous auricular vagus nerve stimulation (taVNS), which engages the afferent vagus and, through it, the NTS and locus coeruleus, is the device intervention implied by the framework. Its predicted mechanism here is twofold: it engages the cholinergic anti-inflammatory pathway, strengthening the third pillar, and it modulates the locus coeruleus through the afferent route, with effects on noradrenergic tone that imaging studies have begun to document. The framework's prediction is again a timing prediction — taVNS should be most useful as a tonic, preventive intervention applied before the spiral has crossed its gain threshold, in individuals identified as at risk by low heart-rate variability and reduced locus coeruleus MRI signal — and it interprets the disappointing late-stage vagal-stimulation dementia pilots as the expected result of stimulating a circuit after its collapse rather than supporting it before.

10.5 The Paired Biomarker

The framework proposes a paired biomarker for the earliest phase of the disease: neuromelanin-sensitive MRI of the locus coeruleus, indexing the integrity of the noradrenergic source, and heart-rate variability, indexing vagal tone and the strength of the cholinergic pillar and the afferent regulation of the locus coeruleus. The prediction is that these two measures should be coupled — that locus coeruleus integrity and vagal tone should decline together, because they index two arms of a single vagal–coerulean system — and that their joint decline should precede and predict neuroinflammatory and cognitive trajectory more strongly than either alone. Both measures are inexpensive and non-invasive, and the pair is testable in existing ageing cohorts that have collected both.

10.6 Falsifiable Predictions

The framework makes the following falsifiable predictions, ordered from most to least readily testable.

First, locus coeruleus neuromelanin-MRI signal and heart-rate variability should be positively correlated within individuals and should decline together with age and disease, reflecting their shared vagal–coerulean system; an absence of coupling would weaken the synthesis of Chapter VI.

Second, the two measures should jointly predict subsequent neuroinflammatory burden — measured by translocator-protein PET or CSF markers — more strongly than either predicts alone, reflecting the convergence of the noradrenergic and cholinergic pillars; a purely additive relationship would weaken the three-pillar model.

Third, noradrenergic augmentation should reduce microglial activation markers in proportion to residual locus coeruleus integrity, having its largest effect early and diminishing as the projection degenerates; a uniform or late-predominant effect would contradict the timing claim of §10.2.

Fourth, reducing peripheral inflammation should reduce the afferent-driven component of locus coeruleus activation and slow the decline of its MRI signal; an absence of effect would weaken the afferent-load claim of Chapter III.

Fifth, the rate of clinical progression should depend on the order and spacing in which the three microglial-restraint pillars fail, with the most rapid decline in individuals in whom the transcriptional pillar fails while the noradrenergic and cholinergic pillars are already exhausted; this is the strongest and least immediately testable prediction, requiring longitudinal multi-pillar assessment, and it is the prediction whose confirmation would most strongly support the three-pillar and spiral framework.

11. Conclusion

This dissertation has argued that the locus coeruleus occupies a uniquely catastrophic position in Alzheimer's disease because three of its properties coincide in a single small nucleus: it is the earliest site of the disease's pathology, it is the source of the noradrenaline that restrains microglia, and it is the central recipient of the vagal signal that reports the inflammatory state of the body. These properties interlock. The afferent vagus delivers a chronic inflammatory drive from the ageing, inflamed periphery to the locus coeruleus, adding an escalating demand to a nucleus already at the edge of its bioenergetic ceiling; the locus coeruleus answers inflammation with a noradrenergic restraint of microglia; and when the nucleus fails — first, in the disease, decades before the cortex — that restraint is withdrawn, the microglia are disinhibited, and the disinhibited inflammation feeds back onto the surviving locus coeruleus neurons in the self-amplifying coerulean–microglial spiral.

The framework's central contribution is to identify the earliest event of Alzheimer's disease and the central event of its neuroinflammation as the same event seen from two sides. The locus coeruleus is the nucleus that fails first and the brake whose failure releases the microglia; its bioenergetic collapse and the disinhibition of the microglia are two descriptions of one process; and the long-debated question of whether neuroinflammation causes or follows the disease is answered, in the framework, by the loop — it is both, with the locus coeruleus as the hinge. The three-pillar model of microglial restraint locates two of the three pillars, the noradrenergic and the cholinergic, under vagal and coerulean control, and explains the disease's long latency and sharp decline as the sequential, redundancy-buffered failure of the three.

The framework is bounded and falsifiable. It does not claim that vagal inflammatory load initiates the intrinsic, developmentally early tau pathology of the locus coeruleus; it claims that vagal load and the loss of the noradrenergic brake condition and accelerate a process whose seed is intrinsic, converting a standing vulnerability into a progressive disease. It generates a therapeutic programme — noradrenergic augmentation, α7-nicotinic agonism, transcutaneous vagal stimulation, and the reduction of peripheral inflammation — organised around breaking the four arcs of the spiral, and a paired locus-coeruleus-MRI and heart-rate-variability biomarker for the pre-symptomatic phase in which those interventions are predicted to work. The nucleus that fails first is the brake whose failure lets the fire spread, and the vagus is how the body keeps feeding it. To protect the locus coeruleus, and to keep the noradrenergic and cholinergic brakes on the microglia while it still can be protected, is — on the argument of this dissertation — to intervene at the hinge of the disease.

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