The Vagal Interface

The Tenth Cranial Nerve as the Peripheral–Central Conduit of Neurodegenerative Collapse

How the Afferent, Efferent, and Propagative Functions of the Vagus Nerve Couple the Peripheral Immunometabolic State to the Bioenergetic, Microglial, and Synaptic Axes of Alzheimer's and Parkinson's Disease at a Single Brainstem Junction

ONS Methodology — Doctoral Thesis

AdultCognitiveDisease.com

June 2026

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience. Companion volume to the Collapse trilogy — Convergent Synaptic Collapse, Homeostatic Microglial Collapse, and Bioenergetic Collapse — and to The Tryptophan Partition and The Vascular Phasing.

“The nucleus that fails first is the nucleus that reads the body. Before the cortex forgets, the brainstem has spent a lifetime listening to the inflamed and hungry periphery — and the vagus is how it listens.”

— ONS Methodology Working Notes, 2026

For Kevin Tracey, whose discovery of the inflammatory reflex made the vagus a neuroimmune organ, and for Heiko Braak, whose caudo-rostral staging turned the dorsal medulla into the place where neurodegeneration is read to begin.

THE COLLAPSE TRILOGY — COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition · The Vascular Phasing

V. The Vagal Interface □ this volume

The trilogy's three principal volumes address distinct axes of neurodegenerative collapse — synaptic circuit, microglial state, and bioenergetic substrate. Where the earlier companion volumes identified couplings internal to the brain — a shared metabolic substrate (the tryptophan partition) and a shared vascular gateway (the neurovascular unit) — the present companion volume identifies the neural cable that couples the peripheral immunometabolic state to the brainstem. It runs outside the brain and back in: the vagus nerve, sensing, restraining, and in synucleinopathy conducting, the same peripheral state on which the trilogy's three axes converge.

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June 2026

Abstract

The vagus nerve is the longest of the cranial nerves and the only one that exits the cranium to innervate the thoracic and abdominal viscera; it is also the structure through which the largest share of the body's interoceptive traffic reaches the brain. Approximately four-fifths of its fibres are afferent, carrying continuous information about the mechanical, chemical, immune, and metabolic state of the gut, liver, pancreas, and heart to the nucleus tractus solitarius; the remaining efferent fifth carries parasympathetic and anti-inflammatory output from the dorsal motor nucleus and nucleus ambiguus back to the periphery. This dissertation advances the thesis that the vagus nerve is the principal *physical conduit* through which the peripheral immunometabolic state — the variable that the Collapse trilogy and its companion volumes have repeatedly identified as upstream of central neurodegeneration — is read by, and acts upon, the brainstem nuclei from which Alzheimer's disease and Parkinson's disease pathology first emerge. Where the trilogy's earlier volumes identified the *substrates* of collapse (bioenergetic, microglial, synaptic) and its companion volumes the *shared metabolic variable* (the tryptophan partition) and the *vascular gateway* (the neurovascular unit), the present volume identifies the *neural cable* that couples body to brain. The vagus is not one mechanism among many; it is the wire along which several of the trilogy's mechanisms are transmitted.

The thesis is organised in seven analytical chapters. Chapter I establishes the anatomy of the vagus as a bidirectional conduit, locating the afferent terminus at the nucleus tractus solitarius (NTS) and the efferent origin at the dorsal motor nucleus of the vagus (DMV) and nucleus ambiguus, and characterising the brainstem neighbourhood — NTS, DMV, area postrema, and the immediately adjacent locus coeruleus — in which the conduit meets the central nervous system. Chapter II treats the afferent arm as an interoceptive sensor of the inflamed and metabolically stressed periphery, integrating the Watkins–Maier sickness-behaviour literature with the gut-hormone and short-chain-fatty-acid signalling that the gut–brain axis concept already records. Chapter III treats the efferent arm as the cholinergic

anti-inflammatory pathway of Tracey and colleagues, and argues that vagal tone supplies a tonic brake on the microglial transition characterised by the Homeostatic Microglial Collapse thesis — that age-related vagal withdrawal is a permissive condition for that transition. Chapter IV treats the conduit as a highway, integrating the Braak caudo-rostral staging hypothesis, the Holmqvist–Kim demonstrations of gut-to-brain α-synuclein transport, and the Borghammer body-first/brain-first dichotomy with the truncal-vagotomy epidemiology that supplies the strongest available human evidence for a vagal route of pathology. Chapter V analyses the brainstem junction in detail, drawing the DMV–NTS–locus coeruleus triangle through the Bioenergetic Collapse thesis's identification of the locus coeruleus as the earliest site of Alzheimer pathology. Chapter VI synthesises the four arms into a single framework, deriving the claim that the vagus is the *peripheral operator* of the three collapse axes — the structure through which a peripheral state becomes a central trajectory. Chapter VII develops therapeutic implications and falsifiable predictions, including the cases for transcutaneous auricular vagus nerve stimulation, the interpretation of heart-rate variability as a vagal-tone biomarker of neurodegenerative risk, and the reconciliation of the disappointing vagus-stimulation dementia trials with the framework.

The dissertation concludes that the three axes of the Collapse trilogy are not only coupled through shared substrates and a shared vascular gateway; they are also *wired together through the body* by a single nerve whose afferent and efferent arms read and write the same peripheral immunometabolic variable. The vagal interface is the structure that makes "neurodegeneration is a systemic disease" a statement about anatomy rather than a metaphor.

Keywords: vagus nerve, inflammatory reflex, cholinergic anti-inflammatory pathway, α7 nicotinic acetylcholine receptor, nucleus tractus solitarius, dorsal motor nucleus of the vagus, Braak staging, α-synuclein propagation, body-first Parkinson's disease, truncal vagotomy, gut–brain axis, locus coeruleus, heart-rate variability, vagus nerve stimulation, neurodegeneration

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1. Introduction

1.1 The Research Problem

The neurodegenerative diseases are conventionally localised to the brain. The amyloid cascade hypothesis fixes attention on cortical and hippocampal Aβ; the synucleinopathy hypothesis on misfolded α-synuclein in the substantia nigra; the tauopathy hypothesis on neurofibrillary tangles whose distribution defines clinical staging. Each of these frameworks is *cephalocentric*: it takes the diseased brain as the unit of analysis and treats the periphery, where it appears at all, as a source of modifiable risk rather than as part of the disease apparatus. The Collapse trilogy of which this dissertation forms a companion volume — *Convergent Synaptic Collapse*, *Homeostatic Microglial Collapse*, and *Bioenergetic Collapse* — was an attempt to articulate the convergent infrastructure on which the disease-specific mechanisms run. The trilogy identified three axes: a synaptic-circuit axis (PV□ interneurons, perineuronal nets, gamma oscillations), a microglial-state axis (loss of TGF-β/SMAD-maintained homeostatic identity), and a bioenergetic-substrate axis (mitochondrial quality-control failure, NAD□ depletion, autophagy–lysosomal collapse). The companion volumes extended the framework toward shared variables: *The Tryptophan Partition* identified a single metabolic substrate whose allocation couples the three axes, and *The Vascular Phasing* identified the neurovascular unit as the gateway through which the aged systemic milieu reaches the parenchyma.

Each of these analyses repeatedly arrives at the same boundary and stops there. The microglial thesis identifies peripheral immune signals as drivers of the homeostatic-to-disease transition but treats their arrival in the brain as given. The bioenergetic thesis identifies the locus coeruleus as the earliest site of Alzheimer pathology but does not fully account for *why* a small brainstem nucleus, rather than the cortex it is supposed to be protecting, should fail first. The tryptophan thesis identifies the gut microbiota as a "peripheral partition operator" but leaves the mechanism by which the gut's metabolic state is communicated to the brainstem largely at the level of humoral signalling. The gut–brain axis concept in the knowledge base lists "neural (vagus nerve)" as the first of its four communication channels and then develops the immune, endocrine, and metabolic channels in detail while leaving the neural channel comparatively undeveloped. There is, in short, a recurring *missing cable* in the corpus: a structure that physically connects the

peripheral state to the brainstem nuclei that fail first.

This dissertation argues that the missing cable is the vagus nerve, and that its omission is not a minor lacuna but a structural blind spot of cephalocentric neurology. The thesis advanced is that the vagus nerve is the principal physical conduit coupling the peripheral immunometabolic state to the central nervous system, and that this coupling is *bidirectional and disease-relevant*: the afferent arm carries the inflamed and metabolically stressed peripheral state to the brainstem, where it is read first by the NTS and propagated to the locus coeruleus and beyond; the efferent arm carries an anti-inflammatory cholinergic output back to the periphery and, through central collaterals, supplies a tonic brake on microglial activation; and the conduit itself serves, in synucleinopathy, as a literal anatomical route for the caudo-rostral propagation of misfolded protein from the enteric nervous system to the brain.

1.2 Significance

The significance of this reframing is fourfold. First, it converts a metaphor into anatomy. The claim that "neurodegeneration is a systemic disease" — recorded in the knowledge base as a distinct framework and implicit across the corpus — is usually advanced at the level of correlation: systemic inflammation, metabolic syndrome, and microbiome composition track with disease risk. The vagal interface supplies the *mechanism of the correlation*. It identifies the specific nerve along which the systemic state is read and the specific nuclei at which it is first integrated, and it does so in a way that generates testable predictions about lesion effects, stimulation effects, and biomarker trajectories.

Second, the framework supplies a missing actor in the microglial-collapse account. The Homeostatic Microglial Collapse thesis identifies the loss of TGF-β/SMAD-maintained microglial identity as the central event of the microglial axis and characterises the peripheral immune signals that drive it. But it treats the brain's microglia as passively exposed to those signals. The cholinergic anti-inflammatory pathway supplies an *active, regulated brake*: vagal cholinergic tone, acting through α7 nicotinic acetylcholine receptors expressed on macrophages peripherally and on microglia centrally, suppresses NF-κB-driven cytokine production. Age-related decline in vagal tone — measurable as reduced heart-rate variability and well documented in the autonomic-ageing literature — therefore

removes a brake on the microglial transition. The framework reinterprets the microglial axis as a balance between an activating peripheral signal and a restraining vagal one, and predicts that the loss of the restraining signal is a permissive condition for collapse.

Third, the framework supplies the strongest available *human causal* evidence in the entire Collapse corpus. Most of the trilogy's mechanisms are supported by molecular and animal evidence and by human correlation; direct human causal evidence is rare because the relevant interventions cannot be performed experimentally. The vagus is an exception. Truncal vagotomy — the surgical transection of the vagus once performed routinely for peptic ulcer disease — constitutes an inadvertent human lesion experiment, and the epidemiological finding that full truncal vagotomy is associated with a reduced subsequent risk of Parkinson's disease, while selective vagotomy is not, is a quasi-experimental result of a kind the rest of the corpus cannot match. The vagal interface is the part of the framework where the human data are strongest.

Fourth, the framework reorganises the therapeutic landscape toward a target that is already clinically accessible. The vagus is stimulable, non-invasively, through the auricular branch that surfaces at the external ear; transcutaneous auricular vagus nerve stimulation (taVNS) is an inexpensive, well-tolerated intervention already in trials for inflammatory and affective conditions. The framework predicts that the relevant therapeutic variable is not stimulation per se but the *restoration of a tonic anti-inflammatory and interoceptive signal whose decline is itself part of the disease*, and it supplies an interpretation of the disappointing early vagus-stimulation dementia trials that turns on the difference between phasic stimulation of an already-collapsed circuit and the tonic support of a circuit before collapse.

1.3 Scope and Limitations

This dissertation is a synthetic review, not a report of original experimental data. Its contribution lies in the integration of literatures from neuroanatomy, neuroimmunology, autonomic physiology, the synucleinopathy-propagation field, and gut–brain axis biology into a single analytical schema centred on the vagus as the peripheral–central conduit. The work draws on both Alzheimer's disease and Parkinson's disease, because the vagal interface is differently weighted in each: the α-synuclein propagation route is most directly evidenced in PD and the related synucleinopathies, while the cholinergic anti-inflammatory and interoceptive arms are most directly relevant to the inflammatory and bioenergetic axes that the AD-centred trilogy develops. The thesis treats the two diseases as differently lit views of the same conduit rather than as a single uniform process.

The thesis cannot, and does not attempt to, resolve whether the vagus is a *causally originating* structure in neurodegeneration or a *conducting* one. The body-first/brain-first dichotomy that the framework adopts from Borghammer is explicitly a claim that the vagus is the originating route in only a subset of patients; in the brain-first subset, the same conduit may carry pathology in the opposite direction or play no originating role at all. The framework is consistent with the vagus being decisive in some patients and incidental in others, and Chapter IV treats this heterogeneity directly rather than suppressing it. The thesis also does not claim that the cholinergic anti-inflammatory pathway is the dominant determinant of microglial state; it claims that it is a regulated brake whose withdrawal is permissive, which is a weaker and more defensible position. Finally, the human vagotomy epidemiology, while the strongest causal evidence available, is observational and subject to confounding by the indication for surgery and by surveillance effects; the thesis weights it accordingly.

2. Literature Review

2.1 Historical Foundations: From Galen to the Inflammatory Reflex

The vagus nerve has been known since antiquity. Galen described the *par vagum* — the "wandering pair" — and demonstrated in his vivisection experiments that its section abolished the voice, establishing both its name and its motor function to the larynx. For most of the subsequent history of physiology the vagus was understood through Langley's parasympathetic framework as the principal efferent nerve of the "rest and digest" division of the autonomic nervous system: a cholinergic output that slows the heart, stimulates gastric secretion and motility, and opposes the sympathetic "fight or flight" response. The classical twentieth-century physiology of the vagus is overwhelmingly an efferent physiology, organised around its parasympathetic motor functions, and the surgical literature followed suit: truncal and selective vagotomy were developed by Dragstedt and others from the 1940s as treatments for peptic ulcer disease, on the rationale that cutting the vagal supply to the stomach would reduce acid secretion.

Two twentieth-century developments began to reorient the field. The first was the recognition, consolidated by Andrew and others, that the vagus is overwhelmingly an *afferent* nerve: roughly 80% of its fibres carry sensory information toward the brain rather than motor commands away from it. The afferent vagus terminates in the nucleus tractus solitarius, the brainstem's principal viscerosensory relay, and conveys information from arterial baroreceptors and chemoreceptors, pulmonary stretch receptors, and a dense array of gastrointestinal mechanoreceptors and chemoreceptors. This afferent dominance is the anatomical foundation of the modern view of the vagus as an *interoceptive* nerve — the structure through which the brain reads the state of the body's interior.

The second development, and the one most consequential for the present thesis, was the discovery of the *inflammatory reflex*. In 2000, Borovikova and colleagues demonstrated in *Nature* that electrical stimulation of the efferent vagus inhibits the production of tumour necrosis factor (TNF) by macrophages during endotoxaemia, and that this inhibition is mediated by acetylcholine acting on the macrophage. Tracey's 2002 *Nature* review named this circuit the inflammatory reflex and articulated its logic: the afferent vagus senses peripheral inflammation, and the efferent vagus, through the *cholinergic anti-inflammatory pathway*, restrains it — a

hard-wired neural reflex arc regulating innate immunity, analogous to a thermostat. Wang and colleagues identified in 2003 that the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR) is the essential macrophage receptor for this cholinergic restraint. The inflammatory reflex transformed the vagus from a purely autonomic-motor structure into the efferent arm of a neuroimmune regulatory circuit, and it is the molecular foundation on which Chapter III of this dissertation rests.

2.2 Vagal Neuroanatomy: Afferent Terminus, Efferent Origin, and the Brainstem Neighbourhood

The vagal afferents terminate in the nucleus tractus solitarius (NTS), which occupies the dorsomedial medulla and is somatotopically organised, with gastrointestinal afferents projecting to its caudal and medial subnuclei and cardiorespiratory afferents to more rostral and lateral regions. The NTS is the brainstem's integrative viscerosensory hub: it receives the afferent vagus, integrates it with humoral signals sensed at the adjacent area postrema (a circumventricular organ that lacks a blood–brain barrier and therefore directly samples the circulation), and projects onward to the parabrachial nucleus, the hypothalamus, the amygdala, and — critically for this thesis — the locus coeruleus and the dorsal raphe. The NTS is thus the first central station at which the peripheral state, carried by the afferent vagus, is read and distributed.

The vagal efferents arise from two nuclei. The dorsal motor nucleus of the vagus (DMV), lying immediately dorsal and lateral to the central canal in the medulla, supplies the preganglionic parasympathetic innervation of the gastrointestinal tract, providing most of the vagus's secretomotor and visceromotor output to the gut. The nucleus ambiguus, more ventral, supplies the cardiac and laryngopharyngeal motor output. The DMV is of particular importance to the present thesis because it is one of the two earliest sites of Lewy pathology in Parkinson's disease, and because its long, thin, unmyelinated efferent axons projecting to the enteric nervous system constitute a plausible anatomical substrate for the caudo-rostral transport of α-synuclein.

The decisive anatomical fact for the integration with the Collapse trilogy is *proximity*. The NTS and DMV lie in the dorsal medulla; the locus coeruleus lies just rostral, in the dorsal pons; and the dense reciprocal connections between the NTS and the locus coeruleus mean that the earliest central reader of the peripheral vagal

signal sits immediately adjacent to, and synaptically coupled with, the nucleus that the Bioenergetic Collapse thesis identifies as the earliest site of Alzheimer pathology. The brainstem neighbourhood in which the vagus meets the brain is the same neighbourhood in which both Alzheimer's and Parkinson's pathology first appear. This co-localisation is, in the framework of this dissertation, not a coincidence but the central anatomical clue.

2.3 The Cholinergic Anti-Inflammatory Pathway in Detail

The efferent arc of the inflammatory reflex is more anatomically complex than the original Borovikova experiments implied, and its elucidation is owed substantially to Rosas-Ballina, Olofsson, Tracey, and colleagues. The efferent vagus does not innervate the spleen — the principal reservoir of the TNF-producing macrophages — directly. Instead, the vagal signal is relayed through the coeliac–superior mesenteric plexus to the splenic nerve, which is catecholaminergic; the splenic nerve releases noradrenaline onto a specialised population of T lymphocytes that express choline acetyltransferase (ChAT) and the β2-adrenergic receptor; these ChAT□ T cells, stimulated by noradrenaline, synthesise and release acetylcholine; and the acetylcholine acts on α7nAChR expressed on splenic macrophages to suppress NF-κB nuclear translocation and the consequent production of TNF and other pro-inflammatory cytokines. The 2011 *Science* demonstration by Rosas-Ballina and colleagues that ChAT□ T cells are the proximal acetylcholine source resolved the apparent paradox that the spleen lacks direct cholinergic vagal innervation, and it established the inflammatory reflex as a hybrid neural–adaptive-immune circuit.

The relevance of this pathway to the central nervous system runs along two lines. The first is systemic: by restraining peripheral cytokine production, vagal tone lowers the systemic inflammatory load that, through the humoral and vascular channels, reaches the brain. The Vascular Phasing thesis identifies VCAM-1 induction at the brain endothelium as the gateway through which the aged systemic milieu acts on the parenchyma; the cholinergic anti-inflammatory pathway acts upstream of that gateway by lowering the circulating cytokine concentrations that drive endothelial activation. The second line is central and more direct: α7nAChR is expressed not only on peripheral macrophages but on microglia, and Shytle and colleagues demonstrated in 2004 that acetylcholine, acting through microglial α7nAChR, suppresses LPS-induced TNF release and inhibits microglial NF-κB activation. There is therefore a *central* cholinergic anti-inflammatory mechanism operating on the

very cell type whose state transition defines the microglial axis of the Collapse trilogy.

2.4 The Braak Caudo-Rostral Hypothesis and the Dorsal Motor Nucleus

The single most influential framework for the staging of Parkinson's disease pathology is the caudo-rostral scheme proposed by Braak and colleagues in 2003. On the basis of the distribution of α-synuclein-immunoreactive Lewy pathology across large autopsy series, Braak proposed that synucleinopathy in idiopathic PD does not begin in the substantia nigra — the site of the motor pathology — but in two caudal locations: the dorsal motor nucleus of the vagus in the medulla and the olfactory bulb. From these starting points, the pathology was proposed to ascend in a stereotyped caudo-rostral sequence: from the DMV through the lower brainstem (including, at stage 2, the locus coeruleus) to the substantia nigra (stage 3, at which motor symptoms typically emerge), and only later to limbic and neocortical regions (stages 4–6). The clinical corollary is that the prodromal, pre-motor phase of PD — characterised by constipation, REM sleep behaviour disorder, hyposmia, and dysautonomia — corresponds to the caudal stages, years to decades before the nigral pathology that produces the diagnosable motor syndrome.

Braak's scheme is contested. Not all PD cases conform to the caudo-rostral sequence; a substantial minority show pathology that does not follow the predicted order, and some authors have argued that the staging reflects selective vulnerability rather than spread. But two features of the scheme are robust and are the features on which this thesis relies. First, the DMV is, empirically, among the earliest and most consistently affected nuclei in PD, affected in the great majority of cases and frequently at the earliest stages. Second, the staging implies a *direction*: pathology that begins caudally and ascends. The combination of an early, consistently affected vagal motor nucleus and an ascending direction is precisely what a vagal-conduit hypothesis predicts, and it motivated Braak's own subsequent proposal — the "dual-hit" hypothesis, developed with Hawkes and Del Tredici — that an unknown pathogen or pathological agent enters the nervous system through two portals, the nasal (olfactory) and the gastric (vagal), and propagates centrally from each.

2.5 Gut-to-Brain α-Synuclein Propagation and the Vagotomy Epidemiology

The dual-hit hypothesis made a strong, testable prediction: that pathological α-synuclein can travel from the enteric nervous system to the brain along the vagus. Two lines of evidence have substantially confirmed it. Holmqvist and colleagues demonstrated in 2014 that α-synuclein, in various forms, injected into the rat intestinal wall is transported to the dorsal motor nucleus of the vagus, and that the transport has the characteristics of axonal transport along vagal fibres. Kim and colleagues, in a 2019 *Neuron* study that is the strongest single piece of evidence for the route, injected pathological α-synuclein preformed fibrils into the gut muscularis of mice and showed that the pathology spread in a caudo-rostral sequence — first to the DMV, then to the locus coeruleus, then to the substantia nigra and beyond — reproducing the Braak sequence and ultimately producing motor and non-motor deficits. Decisively, *truncal vagotomy prevented the spread*: cutting the vagus blocked the caudo-rostral propagation and the downstream pathology. The Kim study established the vagus as a sufficient anatomical route for gut-to-brain synuclein propagation in a mammalian model.

The human counterpart of the vagotomy experiment exists, fortuitously, because truncal vagotomy was once a common surgical treatment for peptic ulcer disease. Svensson and colleagues, in a 2015 *Annals of Neurology* study of Danish registry data, reported that patients who had undergone *full truncal* vagotomy had a reduced risk of subsequently developing Parkinson's disease relative to the general population, particularly when followed for more than five years, whereas patients who had undergone *selective* (super-selective, gastric-sparing-of-the-coeliac-branch) vagotomy did not show the same risk reduction. Liu and colleagues, in a 2017 Swedish registry study published in *Neurology*, reported a consistent finding: truncal vagotomy was associated with lower PD risk. The contrast between truncal and selective vagotomy is the crucial feature, because it is what a conduit hypothesis predicts — only the complete transection of the vagal trunk would be expected to interrupt an ascending pathological signal, while a selective gastric vagotomy that spares the broader trunk would not. The vagotomy epidemiology is observational and has not been uniformly replicated, but it constitutes the strongest available human evidence that the vagus is a route of PD pathology rather than merely a victim of it.

The Borghammer body-first/brain-first model, developed from 2019 onward, organises this evidence into a coherent heterogeneity. Borghammer proposed that idiopathic PD comprises (at least) two subtypes distinguished by the origin and initial spread of α-synuclein pathology. In the *body-first* subtype, pathology originates in the enteric or peripheral autonomic nervous system and ascends via the vagus to the brainstem, producing prodromal autonomic and REM-sleep-behaviour-disorder features that precede motor symptoms, and a relatively symmetric brainstem-first imaging signature. In the *brain-first* subtype, pathology originates within the CNS (possibly the olfactory route or the amygdala) and the autonomic involvement is later and the imaging signature more asymmetric. The body-first/brain-first model is important to this thesis because it specifies the *scope* of the vagal-conduit claim: the vagus is the originating route in the body-first subtype, and the framework does not require it to be decisive in every patient.

2.6 The Microbiota–Vagus Channel

The afferent vagus is also the neural arm of the gut–brain axis, and it is the structure through which the gut microbiota's metabolic state can be read by the brain in real time, on a timescale far faster than the humoral channels. Bravo and colleagues demonstrated in 2011 that chronic administration of *Lactobacillus rhamnosus* to mice altered GABA receptor expression in the brain and reduced anxiety- and depression-related behaviour, and that *these effects were abolished by vagotomy* — establishing the vagus as a necessary conduit for at least some microbiota-to-brain behavioural signalling. The afferent vagus expresses receptors for, and responds to, gut hormones (cholecystokinin, GLP-1, peptide YY, ghrelin, leptin) released by enteroendocrine cells in response to luminal contents, and recent work on neuropod cells has shown that enteroendocrine cells form direct synaptic-like contacts with vagal afferents, transducing luminal chemical information into vagal action potentials within milliseconds.

The microbiota–vagus channel connects this thesis directly to the gut–brain axis concept already recorded in the knowledge base and to *The Tryptophan Partition*. The knowledge base records the butyrate–LL-37–Aβ chaperone axis identified by Barron: butyrate produced by gut bacteria upregulates the antimicrobial peptide LL-37, which prevents Aβ fibrillation. Butyrate is also a vagal afferent signal — short-chain fatty acids activate vagal afferents both directly and through enteroendocrine intermediaries — so the same microbial metabolite that the

knowledge base identifies as a humoral anti-amyloid signal is simultaneously a neural signal carried by the vagus. *The Tryptophan Partition* identifies the gut microbiota as a "peripheral partition operator" whose tryptophan consumption and aryl-hydrocarbon-receptor-ligand output modulate the host's central tryptophan allocation; the vagus is one of the channels through which that peripheral operation is communicated centrally. The vagal interface is thus not a competitor to the gut–brain and tryptophan frameworks but the *neural substrate* they each presuppose.

2.7 The Locus Coeruleus and the Brainstem Monoaminergic Junction

The Bioenergetic Collapse thesis identifies the locus coeruleus (LC) as the earliest known site of Alzheimer pathology — the small pontine noradrenergic nucleus in which hyperphosphorylated tau appears, on autopsy evidence, before it appears anywhere in the cortex, often in the first three decades of life. The bioenergetic thesis develops a model in which LC neurons fail through a combination of their unique catecholaminergic biochemistry, high tonic firing rate, long unmyelinated projections, and consequent extreme metabolic demand, converging on PARP-1 hyperactivation, integrated-stress-response exhaustion, and NAD□ depletion. The present thesis adds an afferent dimension to that account.

The LC is densely and reciprocally connected with the NTS. Vagal afferent information, integrated at the NTS, is relayed to the LC, and the LC's tonic and phasic firing is modulated by visceral and immune signals arriving through this pathway. This connection has two consequences for the framework. First, it means that the LC is not only the earliest site of intrinsic bioenergetic failure but also a *recipient of the peripheral inflammatory and metabolic signal* carried by the vagus: an inflamed or metabolically stressed periphery drives, through NTS□LC projections, sustained LC activation, and sustained activation compounds the very metabolic demand that the bioenergetic thesis identifies as the LC's vulnerability. The afferent vagus is thus a candidate amplifier of LC bioenergetic stress. Second, in the synucleinopathy reading, the LC is *stage 2* of the Braak caudo-rostral sequence — the nucleus to which DMV pathology ascends — so the same locus coeruleus that the bioenergetic thesis identifies as Alzheimer's ground zero is, in Parkinson's disease, an early waypoint on the vagal propagation route. The LC is the convergence point at which the intrinsic-bioenergetic and the vagal-conduit accounts of brainstem-first neurodegeneration meet.

2.8 Gaps in the Literature

Five gaps in the existing literature motivate the present synthesis. First, the inflammatory-reflex literature and the neurodegeneration literature have developed largely in isolation: the cholinergic anti-inflammatory pathway is a mature field in sepsis, rheumatoid arthritis, and inflammatory bowel disease, but its application to the microglial state transition of chronic neurodegeneration is underdeveloped. Second, the α-synuclein propagation literature treats the vagus as an anatomical route for PD but has not been integrated with the broader systems framework of neurodegenerative collapse, nor connected to the bioenergetic account of brainstem vulnerability. Third, the autonomic-ageing literature documents the decline of vagal tone with age — and its association, through reduced heart-rate variability, with cognitive decline and dementia risk — but treats this as a cardiovascular or general-health correlate rather than as a mechanistic loss of an anti-inflammatory brake. Fourth, the gut–brain axis literature, including the corpus's own gut–brain concept, names the vagus as a channel but develops the humoral channels preferentially, leaving the neural channel comparatively unmechanised. Fifth, the therapeutic vagus-stimulation literature in dementia is small, early, and largely negative, and has not been reconciled with the mechanistic framework that would predict when and how stimulation should and should not work. This dissertation addresses all five gaps.

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3. Methodology

This dissertation employs the Organic Network Synthesis (ONS) methodology developed for the AdultCognitiveDisease.com corpus and applied across the Collapse trilogy and its companion volumes. ONS is a method of theoretical integration rather than of primary data generation: it 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 — rather than the individual frameworks — are where the explanatory leverage of a systems account resides.

The method as applied here proceeds in four steps. First, *conduit identification*: the selection of the vagus nerve as the candidate structure on the basis of its recurrence as a boundary condition across the trilogy's earlier analyses — the point at

which the microglial, bioenergetic, and tryptophan accounts each invoke a peripheral-to-central transmission they do not mechanise. Second, *literature triangulation*: the assembly of the relevant primary and review literatures from five distinct fields (neuroanatomy, neuroimmunology, autonomic physiology, synucleinopathy propagation, and gut–brain axis biology), with deliberate attention to the fields that do not ordinarily cite one another. Third, *convergence mapping*: the identification of the specific anatomical and molecular points at which the vagal conduit makes contact with each of the three collapse axes — the α7nAChR–microglia contact with the microglial axis, the NTS□LC projection with the bioenergetic axis, and the cholinergic and noradrenergic modulation of hippocampal plasticity with the synaptic axis. Fourth, *prediction derivation*: the statement of falsifiable predictions that distinguish the vagal-interface framework from the cephalocentric default, with particular weight on the predictions for which human lesion (vagotomy) and stimulation (VNS/taVNS) data already exist or are obtainable.

The methodology has the limitations inherent to synthetic review. It cannot establish causation; it can only identify where the existing causal evidence is strongest and organise it. It is vulnerable to confirmation bias in the selection of supporting literature, a vulnerability the corpus addresses through its standing quality-audit practice and which this thesis addresses specifically by foregrounding the contested status of the Braak staging scheme, the non-uniform replication of the vagotomy epidemiology, and the largely negative dementia-stimulation trials rather than suppressing them. Where the framework's predictions conflict with existing data, Chapter VII states the conflict and the conditions under which the framework would be falsified.

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4. Chapter I — Vagal Architecture: The Anatomy of a Bidirectional Conduit

The vagus nerve is best understood, for the purposes of this thesis, not as a nerve in the ordinary sense of a cable carrying signals in one direction but as a *bidirectional conduit* whose two arms read and write the same variable — the state of the peripheral interior — at the same brainstem location. This chapter establishes the architecture of that conduit.

4.1 The Afferent Dominance and Its Significance

The first and most consequential architectural fact about the vagus is its afferent dominance. Of the roughly tens of thousands of fibres in the cervical vagal trunk, approximately four-fifths are afferent, carrying sensory information toward the brain. This is the inverse of the intuitive picture of the vagus as a parasympathetic motor nerve, and it reframes the vagus as primarily a *sensory* structure — the principal channel of interoception, the sense of the body's own internal state. The afferent fibres are predominantly small-diameter and unmyelinated (C fibres) or thinly myelinated (Aδ), consistent with the slow, tonic, modulatory character of visceral sensation rather than the fast, discrete character of somatic sensation. Their cell bodies lie in the inferior (nodose) and superior (jugular) vagal ganglia, and their central processes terminate in the NTS.

The functional significance of afferent dominance is that the vagus is, in the first instance, a *measuring instrument*. It reports the mechanical state of the gut (distension, motility), the chemical state of the lumen (nutrients, microbial metabolites, pH), the immune state of the viscera (cytokines, and through paraganglia and direct mechanisms, the presence of inflammation), and the mechanical state of the cardiovascular and respiratory systems (baroreceptor and chemoreceptor input). The brain's continuous, real-time knowledge of the body's interior is to a large extent vagal knowledge. Any account of how a peripheral state becomes a central trajectory must pass through this measuring instrument.

4.2 The Nucleus Tractus Solitarius as the First Reader

The NTS is the central terminus of the afferent vagus and the first station at which the peripheral signal is read and integrated. Its architecture is suited to integration: it is somatotopically organised, it receives convergent input from multiple visceral systems, and it sits immediately adjacent to the area postrema, a circumventricular organ outside the blood–brain barrier that samples circulating signals directly. The NTS therefore integrates two streams — the *neural* stream carried by the afferent vagus and the *humoral* stream sensed at the area postrema — into a unified representation of the peripheral state. This dual sampling is architecturally important to the framework: it means that the NTS reads the periphery both through the fast neural channel and the slow humoral channel, and that the vagal interface and the humoral channels of the gut–brain axis converge at a single anatomical point.

From the NTS, the integrated signal is distributed. Ascending projections reach the parabrachial nucleus and thence the hypothalamus, thalamus, amygdala, and insular cortex — the interoceptive cortex in which the felt sense of bodily state is constructed. Of particular relevance to this thesis are the direct and indirect NTS projections to the locus coeruleus and the dorsal raphe, the brainstem's principal noradrenergic and serotonergic nuclei. The NTS is thus positioned to translate a peripheral inflammatory or metabolic signal into a modulation of the brain's two principal monoaminergic systems, and it is through this projection that the afferent vagus reaches the nucleus the bioenergetic thesis identifies as ground zero.

4.3 The Dorsal Motor Nucleus and the Efferent Gut Projection

The efferent parasympathetic supply to the gut arises from the DMV, whose preganglionic neurons project long, thin, largely unmyelinated axons through the vagal trunk to synapse on the enteric nervous system. These axons are remarkable for their length and their lack of myelination — properties that, in the bioenergetic framework, mark a neuron as metabolically vulnerable (the same properties characterise the LC's projection arbour), and that, in the propagation framework, provide a continuous axonal substrate along which misfolded protein could be transported. The DMV efferents do not innervate the gut musculature directly but synapse on enteric ganglia, which contain the intrinsic neurons of the gut — the same enteric neurons in which Lewy pathology is found early in PD, and which Holmqvist and Kim identified as the origin of vagal synuclein transport.

The architectural point is that the efferent DMV axon and the enteric neuron form a continuous, synaptically connected, anatomically defined path between the gut wall and the medulla. This path is the substrate for both the normal function of the conduit (parasympathetic control of digestion) and, in disease, its pathological function (the caudo-rostral transport of α-synuclein). The same wire carries the physiological signal downward and, in the body-first subtype, the pathological signal upward.

4.4 The Efferent Anti-Inflammatory Arc and Its Splenic Relay

The third architectural element is the efferent anti-inflammatory arc, which differs from the DMV gut projection in both origin and target. As established in §2.3, the cholinergic anti-inflammatory pathway reaches the spleen not by direct vagal innervation but through a relay: vagal efferents engage the coeliac–mesenteric plexus and the catecholaminergic splenic nerve, which acts on ChAT□ T cells, which release acetylcholine onto α7nAChR-bearing macrophages. This arc is architecturally distinct because it is *hybrid* — part neural, part adaptive-immune — and because its effector molecule, acetylcholine, acts at a receptor, α7nAChR, that is also expressed in the central nervous system on microglia. The architecture therefore provides both a peripheral effector (splenic macrophage restraint) and, through the same receptor system centrally, a candidate central effector (microglial restraint), unifying the peripheral and central anti-inflammatory functions of the vagus under a single receptor.

4.5 The Conduit as a Unit

Taken together, the four architectural elements — afferent dominance, the NTS as first reader, the DMV gut projection, and the splenic anti-inflammatory arc — define the vagus as a bidirectional conduit with a single functional purpose: to keep the brain and the peripheral interior in continuous mutual regulation. The afferent arm reports the peripheral state; the efferent arms act upon it, both viscerally (DMV) and immunologically (splenic arc); and the whole system is closed into a reflex at the NTS and DMV in the dorsal medulla, immediately adjacent to the locus coeruleus. The remainder of this dissertation examines what happens to this conduit, and to the brain it serves, when each of its arms is engaged by the disease process.

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5. Chapter II — The Afferent Arm: Interoceptive Sensing of the Inflamed and Metabolically Stressed Periphery

5.1 The Afferent Vagus as an Inflammation Sensor

The afferent vagus is the brain's principal sensor of peripheral inflammation. The foundational evidence comes from the sickness-behaviour literature developed by Watkins, Maier, Dantzer, and colleagues from the 1990s. Peripheral administration of the pro-inflammatory cytokine interleukin-1β, or of the bacterial endotoxin lipopolysaccharide, produces the stereotyped constellation of sickness behaviour — fever, anorexia, social withdrawal, lethargy, and hyperalgesia — that represents the brain's coordinated response to peripheral infection. Critically, *subdiaphragmatic vagotomy attenuates these responses*: cutting the abdominal vagus blocks or blunts the fever and sickness behaviour induced by intraperitoneal IL-1β, demonstrating that the afferent vagus is a necessary sensor for the brain's detection of, and response to, peripheral inflammation arising below the diaphragm. The vagal afferents sense cytokines both directly, through receptors on the afferent terminals and the nodose ganglion, and indirectly, through paraganglia and through the chemosensitive cells of the gut and liver.

The relevance to chronic neurodegeneration is that the same sensor that mediates acute sickness behaviour operates continuously. A chronically inflamed periphery — the low-grade systemic inflammation of ageing ("inflammaging"), of metabolic syndrome, of periodontal and gut dysbiosis, of the many peripheral

inflammatory states the corpus records as AD risk factors — produces a continuous afferent vagal signal of inflammation. This signal is integrated at the NTS and relayed to the hypothalamus (driving the HPA axis) and to the locus coeruleus and raphe (modulating the monoaminergic systems). The afferent vagus is thus the structure that converts a chronic peripheral inflammatory state into a chronic central neuromodulatory state, and it is the neural complement to the humoral and vascular channels by which the corpus's "systemic disease" frameworks reach the brain.

5.2 The Afferent Vagus as a Metabolic Sensor

Beyond inflammation, the afferent vagus is the brain's principal sensor of the gut's *metabolic* state. Vagal afferents express receptors for the gut hormones — cholecystokinin, glucagon-like peptide-1, peptide YY, ghrelin, and leptin — released by enteroendocrine cells in response to luminal nutrients, and they respond to the short-chain fatty acids produced by microbial fermentation of dietary fibre. The recent discovery of neuropod cells — enteroendocrine cells that form direct, glutamatergic, synaptic-like contacts with vagal afferents — established that the gut transduces luminal chemical information into vagal action potentials on a millisecond timescale, far faster than the diffusion of gut hormones through the circulation. The afferent vagus is therefore a high-bandwidth, real-time readout of the gut's nutritional and microbial state.

This metabolic-sensing function connects the afferent arm to the bioenergetic and tryptophan axes. Butyrate, the short-chain fatty acid that the knowledge base identifies (through Barron's work) as the upstream signal of the anti-amyloid LL-37 checkpoint, is simultaneously a vagal afferent signal; the gut microbiome's butyrate output is therefore read by the brain both humorally (LL-37 induction) and neurally (vagal afferent firing). The microbiota's tryptophan utilisation, identified in *The Tryptophan Partition* as a peripheral partition operation, alters the luminal chemistry that the afferent vagus reports. The afferent arm is thus the neural channel through which the gut–brain and tryptophan frameworks' peripheral operations become central signals.

5.3 The Cost of a Chronic Afferent Signal: Amplifying Locus Coeruleus Stress

The framework's distinctive prediction concerns the *cost* to the brainstem of reading a chronically abnormal periphery. The NTS relays the integrated afferent signal to the locus coeruleus, and inflammatory and stressful afferent input drives sustained LC activation. The Bioenergetic Collapse thesis establishes that the LC's vulnerability is fundamentally a vulnerability of metabolic demand: its neurons fire tonically, oxidise catecholamines continuously, and operate close to their bioenergetic ceiling, such that any sustained increase in firing compounds an already marginal NAD□ and ATP economy. A chronically inflamed or metabolically stressed periphery, read by the afferent vagus and relayed through the NTS, is therefore a chronic driver of the very LC activation that the bioenergetic thesis identifies as bioenergetically unsustainable. On this reading, the afferent vagus is not merely a passive reporter; it is an active amplifier of LC stress, converting a peripheral inflammatory state into an increment of central bioenergetic demand at the precise nucleus that fails first.

This is the framework's mechanistic bridge between the afferent arm and the bioenergetic axis, and it generates a specific prediction: interventions that reduce the *abnormality* of the afferent signal — by lowering peripheral inflammation, or by restoring a healthy microbial metabolic profile — should reduce the central monoaminergic burden and, by hypothesis, slow the bioenergetic attrition of the LC. The prediction is consistent with, and supplies a brainstem-level mechanism for, the corpus's existing observations that anti-inflammatory and dietary interventions modulate dementia risk.

6. Chapter III — The Efferent Arm: The Cholinergic Anti-Inflammatory Pathway and Microglial State

6.1 The Vagal Brake on Peripheral Inflammation

The efferent cholinergic anti-inflammatory pathway, established in §2.3, supplies a tonic neural restraint on peripheral cytokine production. Its physiological role is homeostatic: the inflammatory reflex closes the loop between the afferent sensing of inflammation and the efferent restraint of it, so that peripheral inflammation drives, through the brainstem, a compensatory anti-inflammatory output. The strength of this output — *vagal tone* — is a quantifiable physiological variable, indexed clinically by heart-rate variability (the beat-to-beat variation in heart rate that reflects parasympathetic, principally vagal, modulation of the sinoatrial node). High vagal tone corresponds to a strong inflammatory reflex and lower circulating cytokine concentrations; low vagal tone corresponds to a weak reflex and a higher inflammatory set-point.

The decline of vagal tone with age is one of the most robust findings in autonomic physiology. Heart-rate variability declines monotonically across the adult lifespan, and reduced heart-rate variability is associated, in large cohort studies, with elevated systemic inflammatory markers, with cognitive decline, and with incident dementia. The framework interprets this association mechanistically: age-related vagal withdrawal weakens the inflammatory reflex, raises the peripheral inflammatory set-point, and thereby increases the systemic inflammatory load that, through the vascular gateway of the Vascular Phasing thesis, reaches the brain. Reduced heart-rate variability is, on this reading, not merely a marker of poor cardiovascular health but a readout of a failing anti-inflammatory brake whose failure is upstream of central neuroinflammation.

6.2 The Central Cholinergic Brake on Microglia

The framework's central claim in this chapter goes beyond the peripheral effect to a direct central one. The α7 nicotinic acetylcholine receptor, the effector of the peripheral cholinergic anti-inflammatory pathway, is expressed on microglia, and acetylcholine acting through microglial α7nAChR suppresses NF-κB activation and the production of TNF and other pro-inflammatory cytokines (Shytle et al., 2004; De Simone et al., 2005). There is therefore a *central* arm of the cholinergic anti-inflammatory pathway operating directly on the cell type whose state transition defines the microglial axis of the Collapse trilogy.

The Homeostatic Microglial Collapse thesis frames the microglial axis as the loss of a TGF-β/SMAD-maintained homeostatic identity — a transition from a surveillant, homeostatic state to a disease-associated, pro-inflammatory one. The present framework adds the proposition that *cholinergic tone is a second pillar of homeostatic restraint, parallel to the TGF-β/SMAD pillar*. Where TGF-β/SMAD signalling maintains microglial identity through a paracrine and autocrine transcriptional programme, α7nAChR cholinergic tone restrains microglial activation through a fast, membrane-receptor-mediated suppression of NF-κB. The two pillars are complementary: the transcriptional pillar sets the homeostatic baseline; the cholinergic pillar provides a dynamically adjustable brake that tracks, through the vagus, the peripheral inflammatory state. The microglial transition, on this reading, is most permissive when *both* pillars are weakened — when the TGF-β/SMAD programme is failing *and* cholinergic tone has withdrawn.

6.3 Vagal Withdrawal as a Permissive Condition for the Microglial Transition

The synthesis of §6.1 and §6.2 is the framework's principal contribution to the microglial axis. Age-related vagal withdrawal weakens the cholinergic brake at two levels simultaneously: peripherally, it raises the inflammatory set-point and the systemic cytokine load that primes microglia through the vascular gateway; centrally, it reduces the direct α7nAChR restraint on microglial NF-κB. The two effects compound. A microglial population that is simultaneously more strongly primed (by a higher peripheral inflammatory load) and less strongly restrained (by lower central cholinergic tone) is a population poised for the transition that the microglial-collapse thesis describes. Vagal withdrawal does not, on this account, *cause* the microglial transition; it makes the transition more probable by removing a brake — it is a permissive, not a sufficient, condition.

This formulation has the virtue of being weaker and more defensible than a causal claim, and of generating a clear prediction: restoring cholinergic tone — pharmacologically through α7nAChR agonists, or physiologically through vagus nerve stimulation — should raise the threshold for the microglial transition and reduce neuroinflammatory markers. The prediction is partially borne out by the preclinical literature on α7nAChR agonists in AD models, which report reductions in microglial activation and amyloid burden, and it motivates the therapeutic analysis of Chapter VII. It also reframes a longstanding puzzle: the modest but real cognitive effects of cholinesterase inhibitors, the mainstay symptomatic treatment for AD, are conventionally attributed entirely to the augmentation of basal-forebrain cholinergic neurotransmission at the synapse; the present framework suggests that a portion of their effect may operate through the augmentation of cholinergic anti-inflammatory tone on microglia, a mechanism distinct from their synaptic action.

7. Chapter IV — The Conduit as Highway: α-Synuclein, Prion-like Propagation, and the Body-First Phenotype

7.1 The Vagus as an Anatomical Route, Not a Signal

The preceding two chapters treated the vagus as a *signalling* structure — afferent sensing and efferent restraint. This chapter treats it as something architecturally different: a physical *route* along which a pathological agent travels. In the synucleinopathy reading, the vagus is not transmitting information about the periphery; it is conducting misfolded α-synuclein from the enteric nervous system to the brainstem, in the manner of a highway rather than a wire. The distinction matters because the route function has its own evidence base, its own predicted lesion effect (vagotomy blocks it), and its own clinical phenotype (the body-first subtype).

The prion-like propagation framework, recorded extensively in the knowledge base as the expanded prion paradigm, holds that misfolded α-synuclein can act as a template that recruits and converts native α-synuclein in adjacent neurons, propagating in a self-amplifying, trans-synaptic, caudo-rostral sequence. The vagal route is the application of this general propagation mechanism to a specific anatomical substrate: the continuous, synaptically connected path from the enteric neuron through the DMV efferent axon to the medulla, established as architecture in Chapter I. The Kim 2019 demonstration — gut-injected fibrils ascending to DMV, then LC, then substantia nigra, with truncal vagotomy blocking the spread — is the proof of concept that this substrate can conduct pathology.

7.2 The Caudo-Rostral Sequence and the Brainstem Waypoints

The Braak caudo-rostral sequence, read as a propagation trajectory along and beyond the vagal route, passes through the same brainstem waypoints that the other chapters of this thesis have identified. Stage 1 involves the DMV (the efferent origin of the vagus) and the olfactory bulb. Stage 2 involves the locus coeruleus — the nucleus that the bioenergetic thesis identifies as Alzheimer's ground zero and that Chapter V will examine as the brainstem junction. Stage 3 reaches the substantia nigra and produces motor symptoms. The remarkable feature, from the standpoint of this synthesis, is that the synucleinopathy propagation route and the Alzheimer bioenergetic-vulnerability sequence pass through the *same nuclei in nearly the same order*: both diseases implicate the dorsal medulla and the locus coeruleus before they implicate the structures that produce their defining clinical syndromes. The vagal interface offers an account of why: these are the nuclei at which the peripheral interface meets the brain, and they are therefore both the first to receive a peripherally originating pathological agent (PD) and the first to bear the bioenergetic cost of reading a chronically abnormal periphery (AD).

7.3 The Vagotomy Experiment and the Strength of the Human Evidence

The truncal-vagotomy epidemiology, established in §2.5, is the empirical keystone of the route function and the strongest human causal evidence in the Collapse corpus. The logic is that of a natural lesion experiment: if the vagus is a route of ascending pathology, then transecting it should reduce the incidence of the disease it conducts, and the reduction should be specific to *complete* (truncal) transection, because a selective vagotomy that spares the broader trunk leaves the route partly intact. The Svensson and Liu registry studies report exactly this pattern — reduced PD risk after truncal but not selective vagotomy, emerging with sufficient follow-up time. The temporal requirement (the protection emerges only after years) is itself consistent with the framework, because the conduit hypothesis predicts a long prodromal ascent during which transection can still interrupt the trajectory.

The thesis weights this evidence carefully and states its limitations. The studies are observational; the indication for surgery (severe peptic ulcer disease) is itself associated with *Helicobacter pylori* infection and chronic inflammation, potential confounders of PD risk; the absolute risk reductions are modest; and replication has

not been uniform. But the specificity of the truncal-versus-selective contrast is difficult to explain by confounding, because confounding by the indication would apply equally to both surgical groups, whereas the protective signal is specific to the surgery that, on the conduit hypothesis, fully interrupts the route. The vagotomy epidemiology is the point in the framework where the human data most directly support a causal, anatomical role for the vagus.

7.4 The Body-First/Brain-First Dichotomy and the Scope of the Claim

The Borghammer body-first/brain-first model, established in §2.5, defines the scope of the route claim and protects it from over-extension. The framework does not assert that the vagus is the originating route in all, or even most, PD; it asserts that the vagus is the originating route in the *body-first* subtype, characterised by prodromal autonomic dysfunction, REM sleep behaviour disorder, and a relatively symmetric brainstem-first imaging signature. In the brain-first subtype, pathology originates centrally and the vagal route is not the origin. The dichotomy is important because it makes the framework falsifiable and bounded: it predicts that vagotomy protection, gut α-synuclein pathology, and prodromal autonomic features should cluster in the body-first subtype and be absent or attenuated in the brain-first subtype, and it predicts that the proportion of patients in whom vagal interventions are relevant is the body-first proportion, not the whole. The body-first/brain-first model converts the vagal-route hypothesis from an overreaching universal claim into a bounded claim about a definable subtype — which is the form in which it is most defensible and most useful.

8. Chapter V — The Brainstem Junction: DMV, NTS, and the Locus Coeruleus

8.1 The Convergence Triangle

The preceding chapters have repeatedly arrived at the same small region of the dorsal medulla and pons: the DMV (efferent origin), the NTS (afferent terminus), and the locus coeruleus (the bioenergetic ground zero and Braak stage-2 waypoint). This chapter examines the junction these three nuclei form. The thesis's central anatomical claim is that this triangle is the *interface itself* — the place where the peripheral conduit becomes a central trajectory — and that its identity as the interface explains why both major neurodegenerative diseases implicate it first.

The three nuclei are functionally and anatomically interlocked. The NTS receives the afferent vagus and projects to the LC; the DMV provides the efferent vagus and lies immediately adjacent to the NTS, sharing the dorsal vagal complex with it; and the LC, just rostral, receives the NTS afferent relay and projects diffusely throughout the brain, including back to the dorsal vagal complex. A peripheral signal entering the NTS is therefore read, relayed to the LC, and broadcast brain-wide within two synapses, while the DMV simultaneously issues the efferent response. The junction is a compact, densely interconnected, peripherally exposed node — and it is precisely the compactness and the peripheral exposure that, the framework argues, make it vulnerable.

8.2 Why the Locus Coeruleus Fails First: The Afferent Contribution

The Bioenergetic Collapse thesis explains the LC's primacy through intrinsic factors — its tonic firing, its long unmyelinated projections, its catecholaminergic biochemistry, its marginal NAD□ economy. The present thesis adds an *extrinsic* contribution that the intrinsic account does not include: the LC's position as the recipient of the afferent vagal signal. The LC does not fail in isolation; it fails while being chronically driven by the NTS relay of a peripheral state that, in the ageing and inflamed body, is chronically abnormal. The intrinsic bioenergetic vulnerability sets the LC's low ceiling; the extrinsic afferent drive raises the demand toward that ceiling. The two together — a nucleus that can least afford increased demand, positioned to receive the chronic increased demand of reading an inflamed periphery — provide a more complete account of LC primacy than either factor alone.

This integration also resolves a tension in the bioenergetic account. If the LC's vulnerability were purely intrinsic, one might expect its failure to be relatively uniform across individuals with similar genetics; but the LC's pathology is heterogeneous and correlated with peripheral and lifestyle factors that the intrinsic account does not naturally accommodate. The afferent contribution supplies the missing source of variance: individuals with a more inflamed periphery and lower vagal tone impose a heavier chronic afferent load on an equally vulnerable LC, and would be predicted to show earlier or more severe LC pathology. The framework thus predicts a measurable interaction between peripheral inflammatory status, vagal tone, and LC integrity — an interaction that is testable with existing LC-imaging (neuromelanin-sensitive MRI) and heart-rate-variability methods.

8.3 The DMV and the Olfactory Bulb as the Two Portals

The dual-hit hypothesis identifies two portals of entry — the gastric/vagal (DMV) and the nasal (olfactory bulb) — and the brainstem junction examined here is the central destination of the vagal portal. The framework notes the symmetry: both portals are sites of direct environmental exposure (the gut lumen and the nasal mucosa are the two largest interfaces between the nervous system and the external environment), both are sites of early Lewy pathology, and both bypass the blood–brain barrier through specialised anatomy (the enteric route via the vagus, the olfactory route via the olfactory nerve's direct projection). The vagal interface is the gut portal's central pathway, and the brainstem junction is where it arrives. The olfactory route is outside the scope of this thesis but is its natural complement; together the two portals define the peripheral-exposure architecture of synucleinopathy, of which the vagus is the larger and better-evidenced half.

9. Chapter VI — Synthesis: The Vagus as the Peripheral Operator of the Three Collapse Axes

9.1 Recapitulation of the Four Arms

The dissertation has examined four functions of the vagal conduit: the afferent arm as an interoceptive sensor of peripheral inflammation and metabolism (Chapter II); the efferent anti-inflammatory arm as a tonic brake on peripheral and central inflammation (Chapter III); the conduit as a physical route for α-synuclein propagation (Chapter IV); and the brainstem junction at which all of these meet the central nervous system (Chapter V). This chapter synthesises the four into a single claim: the vagus is the *peripheral operator* of the three collapse axes — the structure through which the peripheral immunometabolic state is translated into a central neurodegenerative trajectory.

9.2 The Vagus and the Microglial Axis

The vagus operates the microglial axis through the efferent cholinergic arm. The microglial transition is governed, in the synthesis of the microglial-collapse thesis and the present one, by a balance between an activating peripheral inflammatory signal and two restraining pillars — the TGF-β/SMAD transcriptional programme and the α7nAChR cholinergic brake. The vagus controls both sides of this balance: its afferent arm reports the activating signal, and its efferent arm supplies the cholinergic restraint, both peripherally (lowering the systemic load) and centrally (restraining microglial NF-κB directly). Vagal tone is therefore the single physiological variable that most directly sets the balance point of the microglial axis, and its age-related decline is a permissive condition for collapse. This is the framework's strongest and most mechanistically direct coupling.

9.3 The Vagus and the Bioenergetic Axis

The vagus operates the bioenergetic axis through the afferent arm and the brainstem junction. The afferent vagus, relaying a chronically abnormal peripheral state through the NTS to the locus coeruleus, supplies the extrinsic demand that compounds the LC's intrinsic bioenergetic vulnerability (Chapter V). The vagus does not cause the LC's marginal NAD□ economy — that is intrinsic — but it determines how heavily that economy is taxed, by setting the chronic afferent load. The bioenergetic axis's ground zero is, on this reading, also the afferent vagus's principal central target, and the coupling is anatomical: the nucleus that fails first is the nucleus that reads the periphery.

9.4 The Vagus and the Synaptic Axis

The vagus operates the synaptic axis least directly, through two routes. The first is the LC itself: the locus coeruleus is the brain's principal source of noradrenaline, and noradrenergic signalling modulates hippocampal synaptic plasticity, long-term potentiation, and memory consolidation; vagal afferent input to the LC therefore reaches the synaptic axis through LC□hippocampus projections. This is the mechanism of the long-known noradrenergic enhancement of memory consolidation by vagal afferent activation (the basis of the memory effects of vagus nerve stimulation reported since Clark and colleagues in the late 1990s). The second route is the α7nAChR itself, which is expressed at synapses and contributes to cholinergic modulation of cortical and hippocampal circuits, including the fast-spiking interneuron systems that the synaptic-collapse thesis identifies as central to gamma oscillations. The synaptic coupling is the weakest of the three and is developed here as a direction for future work rather than a load-bearing claim.

9.5 The Unifying Proposition

The unifying proposition of the dissertation is that the three axes of the Collapse trilogy are wired together *through the body* by the vagus. The earlier companion volumes identified couplings internal to the brain — a shared metabolic substrate (tryptophan), a shared vascular gateway (the neurovascular unit). The vagus is a coupling that runs *outside* the brain and back in: the same peripheral immunometabolic state is sensed by the afferent arm, acted upon by the efferent arm, and — in synucleinopathy — conducted as pathology along the conduit, with all three functions converging on the same brainstem junction. The vagus is the anatomical realisation of the corpus's recurring claim that neurodegeneration is a systemic disease. It is the wire that makes the claim literal.

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10. Chapter VII — Therapeutic Implications and Experimental Predictions

10.1 The Therapeutic Surface

The vagal interface generates a therapeutic surface distinct from those of the other collapse axes. Where the bioenergetic axis generates mitophagy inducers and NAD□ precursors, the microglial axis generates state stabilisers, and the synaptic axis generates perineuronal-net and gamma-entrainment interventions, the vagal interface generates a single cross-cutting target: *the restoration of vagal tone and the augmentation of the cholinergic anti-inflammatory pathway*. This target is unusual in being accessible both pharmacologically (α7nAChR agonists) and physically (vagus nerve stimulation), and in being measurable through an established biomarker (heart-rate variability).

10.2 Vagus Nerve Stimulation and the Transcutaneous Auricular Route

Vagus nerve stimulation (VNS) is an established therapy — implanted cervical VNS is FDA-approved for refractory epilepsy and depression — and the inflammatory-reflex literature has extended it to inflammatory conditions, with controlled evidence for cervical VNS in rheumatoid arthritis and inflammatory bowel disease. The development most relevant to a chronic, preventive, dementia-directed application is *transcutaneous auricular VNS* (taVNS), which stimulates the auricular branch of the vagus at the external ear non-invasively, without surgery, and is therefore suitable for the long-term, low-risk application that a neurodegeneration-prevention indication would require. taVNS has been shown to engage the NTS and LC (demonstrated by functional imaging), to modulate inflammatory markers, and to enhance memory consolidation in line with the noradrenergic mechanism of §9.4.

The framework's prediction is specific: taVNS should be most effective as a *tonic, preventive* intervention applied *before* the brainstem junction has collapsed, in individuals with low vagal tone and elevated peripheral inflammation, and its mechanism should be the restoration of the cholinergic brake on the microglial axis and the reduction of afferent inflammatory load on the LC. This prediction is distinct from, and largely untested by, the existing trials.

10.3 Reconciling the Negative Dementia-Stimulation Trials

The existing clinical evidence for VNS in Alzheimer's disease is small and largely unpersuasive: early open-label pilot studies (Sjögren and colleagues; the Merrill report) suggested modest cognitive stabilisation in small samples, but there is no robust controlled evidence of benefit, and the field has not advanced to large trials. The framework must reconcile this with its therapeutic optimism, and it does so through the timing distinction of §10.2. The early trials applied phasic cervical stimulation to patients with established, clinically diagnosed Alzheimer's disease — that is, to patients whose brainstem junction had, on the framework's own account, already collapsed, decades after the LC pathology began. The framework predicts that stimulating an already-collapsed circuit late in the disease should produce little benefit, exactly as observed, and that the relevant test of the framework is not the rescue of established disease but the *tonic support of the conduit before collapse* — a preventive application in at-risk, pre-symptomatic individuals identified by low heart-rate variability and elevated inflammatory markers. The negative late-stage trials are therefore consistent with the framework rather than a refutation of it, but the framework owes the field a positive preventive trial, and it specifies one in §10.5.

10.4 Heart-Rate Variability as a Risk Biomarker

The framework reinterprets heart-rate variability (HRV) as a readout of the vagal brake and therefore as a candidate biomarker of neurodegenerative risk. The prediction is that low HRV should precede and predict cognitive decline, independent of its cardiovascular significance, because it indexes the strength of the anti-inflammatory and interoceptive vagal functions that the framework identifies as upstream of central neuroinflammation and LC stress. The prediction is partially supported by existing cohort evidence linking reduced HRV to incident dementia, and it is cheaply testable at scale because HRV is measurable non-invasively, continuously, and with consumer-grade devices. The framework proposes HRV as a stratification variable for preventive vagal interventions: the individuals predicted to benefit from taVNS are those with low HRV and elevated peripheral inflammation, and HRV supplies the inexpensive screening tool to identify them.

10.5 Falsifiable Predictions

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

First, low heart-rate variability and elevated peripheral inflammatory markers should jointly predict subsequent locus coeruleus pathology, measurable by neuromelanin-sensitive MRI, more strongly than either predicts alone — the framework predicts a statistical interaction, not merely two main effects. Failure to find the interaction would weaken the afferent-amplification claim of Chapter V.

Second, the protective effect of truncal vagotomy on Parkinson's disease risk should be specific to the body-first subtype: when PD cases are stratified by body-first/brain-first features, the vagotomy protection should concentrate in the body-first cases. A finding that vagotomy protects equally across subtypes, or protects the brain-first subtype, would contradict the route claim of Chapter IV.

Third, α7nAChR agonists should reduce microglial activation markers in proportion to baseline vagal tone — having the largest effect in individuals with the lowest endogenous cholinergic tone, where the brake is most withdrawn. A uniform effect independent of baseline tone would weaken the permissive-brake formulation of Chapter III.

Fourth, tonic taVNS applied to pre-symptomatic individuals with low HRV and elevated inflammation should slow the accumulation of brainstem and limbic pathology and reduce neuroinflammatory CSF and imaging markers, whereas the same intervention applied to established disease should not. Benefit in established disease, or absence of benefit in the preventive application, would each bear on the timing claim of §10.3.

Fifth, gut-restricted reduction of peripheral inflammation (for example, by microbiome or anti-inflammatory dietary intervention) should reduce afferent vagal inflammatory signalling and, by hypothesis, central monoaminergic burden, measurable as a normalisation of the afferent-driven component of LC activation. This prediction links the vagal framework to the gut–brain and tryptophan frameworks and is testable through their shared interventions.

10.6 Therapeutic Integration with the Trilogy

The vagal therapeutic surface is complementary to, not competitive with, the other axes' surfaces. Because the vagus operates the microglial axis through the cholinergic brake and the bioenergetic axis through the afferent load, vagal interventions are predicted to *potentiate* axis-specific interventions rather than substitute for them: restoring the cholinergic brake should lower the microglial activation set-point against which a TGF-β/SMAD-directed state stabiliser acts, and reducing afferent inflammatory load should lower the bioenergetic demand against which an NAD□ precursor acts. The framework therefore predicts interaction effects in combination therapy, consistent with the trilogy's recurring conclusion that the convergent infrastructure of neurodegeneration is best addressed at multiple coupled points simultaneously rather than at any single one.

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11. Conclusion

This dissertation has argued that the vagus nerve is the missing cable of the Collapse corpus — the physical conduit through which the peripheral immunometabolic state, repeatedly identified across the trilogy and its companion volumes as upstream of central neurodegeneration, is read by, acts upon, and in synucleinopathy is conducted as pathology to the brainstem nuclei from which Alzheimer's and Parkinson's disease first emerge. The vagus is a bidirectional conduit whose afferent arm senses the inflamed and metabolically stressed periphery, whose efferent cholinergic arm restrains inflammation both peripherally and, through microglial α7nAChR, centrally, and whose physical axonal substrate serves, in the body-first subtype of Parkinson's disease, as the literal route of caudo-rostral α-synuclein propagation — with all of these functions converging on a single brainstem junction, the DMV–NTS–locus coeruleus triangle, that both diseases implicate first.

The framework's contribution to the trilogy is to make its central claim anatomical. Where the earlier companion volumes identified couplings internal to the brain — a shared metabolic substrate in the tryptophan partition, a shared vascular gateway in the neurovascular unit — the vagal interface identifies a coupling that runs through the body and back: the same peripheral state, sensed, acted upon, and conducted by one nerve, converging on the nucleus that fails first. The proposition that "neurodegeneration is a systemic disease" ceases, on this account, to

be a statement of correlation and becomes a statement about a specific nerve and a specific brainstem junction.

The framework is bounded and falsifiable. It does not claim the vagus is the originating cause of neurodegeneration; it claims the vagus is the conduit, decisive in the body-first subtype and permissive — through the withdrawal of the cholinergic brake — in the broader inflammatory and bioenergetic process. It is supported, at the route function, by the strongest human causal evidence in the corpus: the truncal-versus-selective vagotomy contrast, a natural lesion experiment that the rest of the trilogy's mechanisms cannot match. And it generates a therapeutic programme — preventive, tonic vagal support stratified by heart-rate variability — that is inexpensive, non-invasive, and immediately testable, together with an interpretation of the disappointing late-stage stimulation trials that turns on the difference between supporting a conduit before collapse and stimulating one after.

The locus coeruleus, the bioenergetic thesis's ground zero, is also the afferent vagus's central target and the synucleinopathy route's second waypoint. That three independent lines of evidence — bioenergetic vulnerability, interoceptive afferent load, and prion-like propagation — converge on the same small pontine nucleus is the central finding of this synthesis. The nucleus that fails first is the nucleus that reads the body. The vagus is how it reads.

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12. References

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