The Fermented Prodrome

The Gut Microbiome as the Ecological Origin of Depression, and Depression as the First Reversible Reading of the Collapse Continuum

The earliest cause of the disease and its earliest clinical reading — the gut's ecological drift and the depressive prodrome — are one event, and the depressive window is where they coincide.

ONS Methodology — Doctoral Thesis

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A Dissertation Submitted in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience. A bridge volume welding The Microbial Prologue to The Depression Continuum.

“Before the memory fails there is a mood; before the mood there is an ecology. The earliest complaint of a brain disease may be neither cognitive nor even neural — it may be the first legible sentence of an organ we ferment our food with.”

— ONS Methodology Working Notes, 2026

For the two prior volumes that each named a first and did not see they had named the same one — and for the clinicians who treat a mood in midlife without yet knowing they are rewriting a prologue.

A BRIDGE VOLUME — TWO FIRSTS, ONE EVENT

The Microbial Prologue — the gut ecology as the first cause, at the head of the vagal–coerulean cascade

The Depression Continuum — the depressive phenotype as the first window, at the head of the clinical trajectory

The Fermented Prodrome ☐ this volume: the two firsts are one event

One parent volume argued that the gut microbiome is the most upstream and most modifiable node of the causal chain that ends at the locus coeruleus; the other argued that major depressive disorder is the most reversible clinical window of the multi-axis collapse that becomes Alzheimer's disease. Each named a first. This bridge volume shows that the first cause and the first window coincide — the drift that begins the disease and the depression that first makes it legible occupy the same window of the same trajectory — so that rewriting the ecological prologue during the depressive window is the single highest-leverage act on the whole continuum.

Abstract

Two prior works of this programme each reached, from opposite ends of a single trajectory, for a claim about primacy. *The Microbial Prologue* argued that the resident microbial ecosystem of the gut is the most upstream and most modifiable variable in the causal chain that ends at the locus coeruleus — that "before the tangle there is the drift," and that the most upstream node on a causal chain is the one whose correction prevents the most downstream harm. *The Depression Continuum* argued that major depressive disorder is the reversible-state phenotype of the same multi-axis pathology that, sustained and accumulated, becomes Alzheimer's disease — that the most treatable window of that disease is the window in which it presents as depression. Each named a "first." Neither noticed that the two firsts are the same event.

This dissertation makes that identity its subject. Its central claim — the *double-first* — is that the gut's ecological drift and the depressive prodrome are not merely both early but are the *same early*: the drift is the earliest cause, the depressive phenotype is its earliest legible clinical reading, and the two coincide at the head of the trajectory. From this coincidence a therapeutic corollary follows that neither parent volume could state alone: the depressive window is doubly privileged, because the moment of maximal biological reversibility (the claim of *The Depression Continuum*) and the moment of maximal ecological modifiability (the claim of *The Microbial Prologue*) fall at the same point in time. The single highest-leverage intervention on the entire depression-to-dementia continuum is therefore the correction of the gut ecology while the person is still merely depressed.

The argument proceeds in eight chapters. Chapter I develops the double-first and states precisely what it does and does not assert. Chapter II supplies the upstream variable that *The Depression Continuum* left generic: it maps the gut microbiome onto each of that thesis's five axes — synaptic, microglial-inflammatory, bioenergetic, tryptophan-partition, and perineuronal — showing that the microbiome sets the tone of every one, and grading each weld from demonstrated to inferred. Chapter III reads sickness behaviour as the acute, experimentally induced prototype of the depressive prodrome, carried by the same vagal conduit *The Microbial Prologue* anatomised, and shows that faecal transplantation of a depressed human microbiome into a germ-free rodent transfers the depressive phenotype — the mood-side twin of the gut-to-brain proteinopathy transfer that anchors the Parkinson literature. Chapter IV

isolates the tryptophan fork as the keystone weld: the gut is the ecological controller of the very partition whose shift *The Depression Continuum* placed at the centre of its metabolic axis. Chapter V adds an ecological floor to the reversibility gradient. Chapter VI extends the gut–coerulean spiral into a gut–coerulean–mood spiral and locates the locus coeruleus as the shared hinge of both parent frameworks. Chapter VII draws the therapeutic consequences and states the falsifiable predictions that only the bridge can make. Chapter VIII is the required accounting of what the bridge does not yet explain.

The dissertation concludes with a reframing of clinical priority. The patient in the psychiatrist's office with a first inflammatory depression, the patient in the neurologist's office thirty years later with early cognitive decline, and the dysbiotic gut that has been drifting the whole while are, on this account, three views of one process — and the most hopeful of the three is the first, because a prologue written in an organ we ferment our food with can, unlike a tangle, still be rewritten.

Keywords: gut microbiome, microbiota-gut-brain axis, major depressive disorder, dysbiosis, butyrate, short-chain fatty acids, lipopolysaccharide, metabolic endotoxemia, tryptophan, kynurenine, indoleamine 2,3-dioxygenase, NLRP3 inflammasome, sickness behaviour, vagus nerve, locus coeruleus, faecal microbiota transplantation, reversibility gradient, prodrome, depression-dementia continuum, Alzheimer's disease.

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1. Introduction

1.1 The Two Firsts

Two of this programme's prior volumes converged, without either recognising the other's approach, on the concept of a first cause and a first window.

The Microbial Prologue is an origin volume. It followed the vagal–coerulean conduit that the companion brainstem volumes had mapped back past its terminus, into the abdomen, and argued that the resident microbial ecosystem of the gut is the upstream ecological variable that writes the inflammatory, metabolic, and proteinopathic signal the vagus then delivers to the locus coeruleus — the nucleus in which the first hyperphosphorylated tau of Alzheimer's disease appears, in autopsy series, before the third decade of life. Its governing principle was a principle about leverage: the most upstream node on a causal chain is the one whose correction prevents the most downstream harm, and the gut ecology is both the most upstream node of the chain it described and the most modifiable, because it is reachable through the lumen rather than across the blood-brain barrier. Its closing image was that "before the tangle there is the drift," and its most hopeful sentence was that a prologue, unlike a final chapter, can still be rewritten.

The Depression Continuum is a continuity volume. It argued that major depressive disorder is not a separate disease that happens to share mechanisms with dementia but the reversible-state expression of the same multi-axis pathology — the convergent dysregulation of five molecularly coupled axes (synaptic, microglial-inflammatory, bioenergetic, tryptophan-partition, and perineuronal) — observed earlier in life and at lower cumulative damage. Its governing principle was a principle about reversibility: the same intervention space operates at every point on the trajectory, and only its efficacy differs, because efficacy is set by how far the

substrate has progressed along a gradient from reversible to irreversible. Its most consequential claim was that the most treatable window of the disease is the window in which it presents as depression, because at that window the substrate is still capable of restoration.

Each volume named a first. *The Microbial Prologue* named the first *cause* — the ecological drift at the head of the causal chain. *The Depression Continuum* named the first *window* — the depressive phenotype at the head of the clinical trajectory. The volumes were written independently, in different registers, about diseases that the conventional taxonomy assigns to different specialties, and neither observed the coincidence that this dissertation exists to state: **the first cause and the first window are the same event.** The drift that begins the disease and the depression that first makes it legible occupy the same segment of the same trajectory. The gut is drifting while the patient is first becoming depressed, because the drift is one of the things that is making them depressed.

1.2 Significance

If the coincidence is real, three consequences follow, and each is a consequence that neither parent volume could reach from its own end.

First, *The Depression Continuum* acquires the upstream variable it left open. That thesis repeatedly invoked "chronic stress, chronic inflammation, metabolic burden, social isolation" as the upstream determinants of its five-axis substrate, but treated them as a generic bundle of exposures, and it listed, among the phenomena its framework did not yet explain, both the specific effects of early-life exposure on the substrate and the gut-microbiome alterations documented in its most severe patients. The present volume supplies exactly that missing variable: the microbiome is the concrete, measurable, and modifiable ecological factor that sets the inflammatory and metabolic tone of every one of the five axes, and it is the factor through which several of the generic "exposures" — diet above all — actually reach the substrate.

Second, *The Microbial Prologue* acquires its earliest human read-out. That thesis terminated its clinical claim at the neurodegenerative diseases — Alzheimer's and Parkinson's — and named depression only in passing, as one of the neuropsychiatric symptoms that locus-coeruleus pathology produces before it produces dementia. But if depression is not a symptom of the coming dementia but the same disease in its

reversible phase, then the depressive phenotype is the *earliest clinical signal of the gut-origin cascade itself* — the first thing that goes measurably wrong at the far, cerebral end of a chain that begins in the gut. The origin volume gains a prodrome.

Third, and most consequentially, the therapeutic surface and the therapeutic window coincide. *The Microbial Prologue* argued that the gut is the highest-leverage place to intervene because it is the most upstream. *The Depression Continuum* argued that the depressive window is the highest-leverage time to intervene because it is the most reversible. The double-first says these are the same intervention: correcting the gut ecology during the depressive window is simultaneously the most upstream and the most reversible move available, and it is therefore the single highest-leverage act on the entire continuum. The most powerful thing that can be done for a person's cognitive trajectory at seventy may be something done to their gut at forty, while they are merely depressed.

1.3 Scope and Limitations

This volume is a bridge, and its scope is bounded accordingly. It does **not** re-derive the five-axis substrate model of *The Depression Continuum*, the reversibility gradient, or the case for depression-and-dementia identity; those are the work of that thesis and are here taken as its established framework and cited as such. It does **not** re-derive the microbial ecology, the barrier, the two routes out of the gut, the neuropod synapse, or the medullary relay; those are the work of *The Microbial Prologue* and its companions and are similarly taken as given. The present contribution is the weld: the demonstration that the upstream end of the one and the downstream end of the other are the same structure, and the consequences that follow when the two are treated as one.

The limitations of the evidence recur throughout and are stated once here. The human data linking the gut microbiome to depression are, as in the neurodegenerative case, overwhelmingly cross-sectional and associative, and they carry a reverse-causation hazard that is, if anything, sharper at the mood end than at the cognitive end: depression alters appetite, diet, sleep, and gut motility, each of which alters the microbiome, so that a dysbiotic signature in a depressed patient may be a consequence of the depression rather than a cause. The causal weight of the argument does not rest on those cross-sectional data. It rests, exactly as in the parent volume, on the manipulation experiments — germ-free rearing, antibiotic

perturbation, and above all faecal transplantation — in which the microbiome is *moved* and the behavioural phenotype moves with it. The reader should therefore hold the human association evidence to the standard of a reproducible direction, the animal transfer evidence to the standard of demonstrated sufficiency in a clean system, and the integrated double-first claim to the standard of a hypothesis with a defined set of falsifying experiments, which Chapter VII supplies. The bridge is a claim about the *coincidence and leverage* of two firsts; it is not a claim that the gut is the sole cause of either phenotype, and Chapter VIII is explicit about the brain-intrinsic vulnerabilities the gut does not create and the depressive subtypes the gut-origin reading fits least well.

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2. Literature Review

2.1 The First Parent: The Depression Continuum

The Depression Continuum built its case on six convergent lines: that the rapid-antidepressant cascade (NMDA blockade on parvalbumin interneurons ☐ disinhibition ☐ glutamate surge ☐ BDNF ☐ TrkB ☐ mTOR ☐ synaptogenesis) is molecularly identical to the extrinsic-pole death pathway of Alzheimer's disease, differing only in the reversibility of the substrate; that the inflammation hypothesis of depression invokes precisely the NLRP3/IL-1β/kynurenine machinery that the microglial-collapse account of Alzheimer's disease identifies; that the metabolic-psychiatry framework of Picard, Sarnyai, and Sethi and the bioenergetic account of Alzheimer's disease describe one mitochondrial substrate; that the perineuronal net gates both the sustained antidepressant effect and neurodegenerative resilience; that the locus coeruleus provides the anatomical bridge between the depressive and dementing phenotypes; and that adult hippocampal neurogenesis is the shared cellular substrate of antidepressant action and cognitive reserve. From these it drew the reversibility gradient and the clinical claim that depression is the most treatable window of a single disease.

What that thesis did not resolve was the question of what sets the substrate in motion. It named chronic stress and chronic inflammation as upstream, but it did not identify the specific, modifiable source of the chronic inflammatory and metabolic tone that its inflammatory and bioenergetic axes require as input. It

flagged this openly: among the ten phenomena its framework "does not yet explain" it listed early-life exposure and, in its discussion of suicide, the gut-microbiome alterations reported in its most severe patients. The present volume reads those two acknowledgements as the same gap, and fills it.

2.2 The Second Parent: The Microbial Prologue

The Microbial Prologue established that the gut microbiome is a late-recognised organ with a degenerative as well as a developmental trajectory; that the Alzheimer and Parkinson gut carries a reproducible pro-inflammatory dysbiotic signature (loss of fibre-fermenting, butyrate-producing taxa; relative expansion of endotoxin-bearing Proteobacteria); that the microbial metabolome is a chemistry of neurodegeneration, in which the loss of butyrate withdraws support from an anti-amyloid cathelicidin checkpoint while the gain of lipopolysaccharide, trimethylamine N-oxide, and altered bile acids raises the injurious afferent load; that in its strongest form the gut is a seeding compartment where bacterial amyloid may template proteinopathy; that the gut's exports leave through a failing barrier by a humoral and a neural route that converge on the brainstem; and that all of it lands on the locus coeruleus, closing a gut–coerulean spiral whose most upstream segment runs through an ecology we can change.

What that thesis did not pursue was the psychiatric read-out of its own cascade. Its clinical horizon was the neurodegenerative diseases, and depression appeared in it only as a downstream neuropsychiatric symptom of locus-coeruleus decline. It did not ask whether the earliest clinical manifestation of the cascade it described might be a mood rather than a memory disorder — a question that becomes unavoidable only once *The Depression Continuum*'s identity claim is granted.

2.3 The Microbiota-Gut-Brain Axis in Psychiatry

Between the two parent literatures sits a third, which neither parent fully drew upon and which the bridge requires: the mature body of work establishing that the gut microbiome shapes mood, stress physiology, and the serotonergic and neurotrophic systems on which antidepressant action depends. Its foundations are causal and experimental, not merely correlative. Germ-free rearing programmes an exaggerated hypothalamic-pituitary-adrenal stress response and lowers hippocampal brain-derived neurotrophic factor, a phenotype partly corrected by early — but not late — bacterial reconstitution (Sudo et al., 2004); germ-free status alters brain development and reduces anxiety-like behaviour together with the expression of synaptic genes (Diaz Heijtz et al., 2011); and the microbiome regulates the hippocampal serotonergic system, elevating central serotonin and its precursor tryptophan in the germ-free animal in a manner resistant to later normalisation (Clarke et al., 2013). The gut is upstream even of peripheral serotonin synthesis itself: indigenous spore-forming bacteria drive serotonin production from colonic enterochromaffin cells, supplying the mucosa, lumen, and circulating platelets (Yano et al., 2015). A defined Lactobacillus strain alters emotional behaviour and central GABA-receptor expression through the vagus nerve, an effect abolished by vagotomy (Bravo et al., 2011). And the human association literature is now large and directional: fewer butyrate-producing Faecalibacterium and Coprococcus in depression and lower quality of life at population scale (Valles-Colomer et al., 2019); altered faecal community composition with depleted Faecalibacterium in major depressive disorder (Jiang et al., 2015); and reviews that place the microbiota-gut-brain axis at the centre of anxiety and depression (Foster & McVey Neufeld, 2013; Cryan et al., 2019) and that implicate the same axis, through microbiota-immune-nervous interactions, in both depression and Alzheimer's disease within a single frame (Fung et al., 2017).

The two experiments that convert this literature from suggestive to load-bearing are the transfer experiments. Faecal microbiota transplantation of a "depression microbiota" from patients with major depressive disorder into germ-free mice induces depression-like behaviours, in a pathway mediated through host carbohydrate and amino-acid metabolism, that colonisation with a healthy-donor microbiota does not (Zheng et al., 2016); and transplantation of a depressed-patient microbiota into microbiota-depleted rats induces the behavioural and physiological features of depression, including anhedonia and altered tryptophan metabolism, in

the recipient animals (Kelly et al., 2016). These are, for the mood phenotype, precisely the class of demonstration that the gut-to-brain α-synuclein propagation experiments are for the neurodegenerative phenotype: a defined ecology, moved into a naïve host, that carries its brain phenotype with it.

2.4 The Unbuilt Bridge

Three literatures, then, run in parallel and rarely meet. The microbiome-psychiatry literature demonstrates, causally, that the gut shapes mood — but terminates at "depression," with the neurodegenerative endpoint and the locus coeruleus unmentioned. The microbiome-neurodegeneration literature, consolidated by *The Microbial Prologue*, demonstrates that the gut shapes the earliest brain lesion of dementia — but terminates at "Alzheimer's," with the depressive prodrome unmentioned. And *The Depression Continuum* demonstrates that depression and dementia are one disease — but leaves the upstream cause of that disease generic, and does not reach for the gut. No account has yet placed the specific ecology of the dysbiotic gut at the upstream end of the specific depression-to-dementia continuum, such that the earliest reading of an ecological drift is a reversible mood disorder and its latest reading is an irreversible cognitive one. Supplying that account — connecting a named ecological cause to a named continuum through a named conduit and a shared nucleus — is the gap this dissertation exists to fill.

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3. Methodology

This dissertation is a work of mechanistic synthesis conducted under the Organic Network Synthesis (ONS) methodology of AdultCognitiveDisease.com. It is not experimental; it is integrative, and its integrative act here is specifically that of a *bridge* or *weld* volume: it takes two prior syntheses as fixed structures and argues that a terminus of the one is identical to a terminus of the other, constructing the mechanistic adjacencies that make the identity precise and grading, at each link, what is demonstrated against what is inferred.

The method imposes three disciplines that structure the chapters. First, **the two firsts must be argued as one, not merely juxtaposed**: it is not enough to observe that the gut is early and depression is early; the volume must show that they are the same early, through shared mediators (the inflammatory tone, the tryptophan

fork, the vagal conduit, the coerulean receiver) that operate in both accounts. Second, **each weld must be graded**: the volume maps the gut onto each of the five axes of *The Depression Continuum*, and states for each whether the link is demonstrated (as for the inflammatory and tryptophan axes), plausible-and-partially-demonstrated (as for the bioenergetic and synaptic axes), or inferential (as for the perineuronal axis), rather than asserting a uniform strength it does not have. Third, **the synthesis must be falsifiable at the join**: a bridge whose failure no experiment could reveal is, by the methodology's standard, decorative, and Chapter VII therefore states the predictions whose failure would sever specific spans of the bridge while leaving others standing.

The volume's evidentiary posture is inherited from both parents and is correspondingly explicit. Its strongest claims are those for which the faecal-transplant and gnotobiotic experiments supply causal closure in the mood direction, exactly paralleling the vagotomy and propagation experiments that supply it in the neurodegenerative direction. Its weakest, flagged as such, are those that rest on the conjunction of two cross-sectional human associations — a dysbiotic signature in depression and a dysbiotic signature in dementia — without a longitudinal human demonstration that the one becomes the other. The double-first is offered as the field's next experiment, not as a settled result.

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4. Chapter I — The Double-First: Origin and Prodrome as One Event

4.1 Two Claims About Primacy

The bridge begins from a formal observation about the two parent theses. Each contains a claim of the form "X is the first Y," and each uses that claim to locate the point of maximum therapeutic leverage.

The Microbial Prologue's claim is causal-temporal: the ecological drift of the gut is the *first cause* — the most upstream node on the chain microbial ecology ☐ chemistry and seed ☐ barrier ☐ afferent ☐ brainstem relay ☐ locus coeruleus — and it is therefore where correction prevents the most downstream harm. *The Depression Continuum*'s claim is clinical-temporal: the depressive phenotype is the *first window* — the earliest and most reversible clinical presentation of the multi-axis substrate —

and it is therefore when correction is most effective. The first is a claim about *where* on the causal chain to act; the second is a claim about *when* on the clinical trajectory to act.

4.2 The Coincidence

These two claims have been treated as belonging to separate problems. This chapter's contention is that they refer to the same segment of the same process, because the cause the first names and the window the second names are contemporaneous.

Consider the trajectory laid out in the unified case history of *The Depression Continuum*: a first moderate depressive episode in the mid-thirties, against a background of chronic stress and mildly elevated systemic inflammatory markers, with a substrate that is dysregulated but reversible at all five axes. Now ask what, mechanistically, is producing the mildly elevated systemic inflammatory markers and the substrate dysregulation at that age. The answer *The Microbial Prologue* supplies is a gut that has begun its ecological drift — a loss of butyrate producers, a weakening of the barrier, a low-grade metabolic endotoxemia — the very drift that thesis placed at the head of the neurodegenerative cascade. The drift and the first depressive episode are not sequential; they are simultaneous, because the drift is one of the proximate producers of the episode. The person is dysbiotic *while* they are first depressed, and partly *because* they are dysbiotic.

The double-first is this simultaneity, stated as a thesis: **the earliest cause of the disease (the ecological drift) and the earliest clinical reading of the disease (the depressive prodrome) occupy the same window of the same trajectory.** The origin and the prodrome coincide.

4.3 What the Coincidence Buys

The coincidence is not merely tidy; it is load-bearing, because it makes two independently derived claims about leverage apply to the same act.

The Depression Continuum established that the depressive window is the moment of maximum *biological reversibility*: the parvalbumin interneurons are stressed but viable, the microglia are reactive but not fully transitioned, the mitochondrial substrate is impaired but its biogenic capacity is preserved, the tryptophan partition is shifted but not chronically fixed, and the perineuronal matrix

is attenuated but restorable. *The Microbial Prologue* established that the gut is the point of maximum *ecological modifiability*: it is reachable through the lumen, it turns over on a timescale of weeks, and it responds to fibre, to the bacteria that ferment it, to the barrier that contains it, and in the limit to wholesale replacement. The double-first places these two maxima at the same point in time. The depressive window is when the downstream substrate is most restorable *and* when the upstream cause is most correctable — and, because the cause is upstream of the substrate, correcting it in that window relieves the substrate at the moment the substrate can still recover.

The therapeutic corollary is the sharpest single sentence of this volume: the highest-leverage intervention on the depression-to-dementia continuum is the correction of the gut ecology during the depressive window, because it is the only move that is simultaneously the most upstream in the causal chain and the most reversible on the clinical trajectory. *The Microbial Prologue*'s "the prologue can be rewritten" and *The Depression Continuum*'s "the most treatable window" become one instruction: **rewrite the prologue while the substrate is still reversible.**

4.4 What the Coincidence Does Not Assert

The claim is disciplined, and three things it does not assert must be stated at once, because the remainder of the volume depends on them.

It does not assert that the gut is the sole cause of depression, or of dementia. The trajectory is genuinely multiplex; the brain carries intrinsic vulnerabilities — the bioenergetic marginality of the locus coeruleus, the intrinsic fragility of fast-spiking parvalbumin interneurons, the apolipoprotein-E genotype — that the gut does not create, and depression has genuine primary-psychological and genetic determinants that no ecology fully explains. The double-first is a claim about the coincidence and leverage of *one* important upstream cause with *one* important early window, not a claim of ecological monocausality.

It does not assert that every depression is a fermented prodrome. The gut-origin reading fits most cleanly the inflammatory and kynurenine-shifted subtypes that both parent frameworks identify as the ones their mechanisms explain best; the melancholic, atypical, and psychotic subtypes, and reactive depressions with a predominantly psychological aetiology, may weight the gut very differently, and Chapter VIII returns to this.

And it does not assert temporal strict precedence at every measurement. It asserts contemporaneity of a cause and a reading, not that the ecological signal always precedes the mood signal by a measurable interval — though it does predict, testably (Chapter VII), that in serial longitudinal sampling the ecological drift is detectable at or before the first depressive episode in those who progress.

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5. Chapter II — The Gut Writes the Five Axes

5.1 The Logic of the Mapping

The Depression Continuum organised its argument around five axes, each examined for its depressive-state and its dementia-state manifestation and for the mechanism connecting them. It did not, however, ask what sets each axis's dysregulation in motion. This chapter answers that question uniformly: the gut microbiome is upstream of every one of the five axes, and its drift is a coherent single perturbation that pushes all five in the pathological direction at once. The mapping is graded — the welds differ in strength — and the grading is stated for each.

5.2 The Microglial-Inflammatory Axis — Demonstrated

This is the strongest weld, and it is the one both parents converge on from opposite sides. *The Depression Continuum* made the NLRP3 inflammasome and its IL-1β output the load-bearing node of its inflammatory axis, and identified microglial state transition as the cellular substrate common to the sickness behaviour of depression and the homeostatic collapse of Alzheimer's disease. *The Microbial Prologue* identified the gut as the source of the inflammatory afferent load: dysbiotic loss of butyrate weakens the barrier, barrier failure produces the low-grade metabolic endotoxemia of circulating lipopolysaccharide (Cani et al., 2007), and lipopolysaccharide is the prototypical Toll-like-receptor-4 agonist that primes the inflammasome.

The weld is not merely that both cite inflammation; it is that the gut is upstream of the specific cell type both theses make central. Erny and colleagues (2015) demonstrated that the host microbiota continuously control the maturation and function of microglia, that germ-free microglia are malformed and defective, and that short-chain fatty acids restore them — placing the microbiome upstream of the very

microglia whose state transition *The Depression Continuum* invokes for depression and whose homeostatic collapse *The Microbial Prologue* invokes for dementia. Fung and colleagues (2017) drew the microbiota-immune-nervous interactions of this axis explicitly across both depression and Alzheimer's disease. The single ecological perturbation — dysbiotic loss of the anti-inflammatory, HDAC-inhibiting butyrate signal together with the gain of pro-inflammatory endotoxin — therefore drives the inflammatory subtype of depression at low cumulative exposure and the microglial collapse of dementia at high cumulative exposure. One inflammatory source; two temporally separated readings.

5.3 The Tryptophan-Partition Axis — Demonstrated

The tryptophan fork is the keystone weld, and because it carries so much of the bridge's weight, Chapter IV is devoted to it in full. In brief here: *The Depression Continuum*'s sixth axis is the indoleamine-2,3-dioxygenase-driven shift of tryptophan from the serotonergic to the kynurenine branch, which produces substrate-limited serotonin (depression) acutely and neurogenic loss with excitotoxic kynurenine burden (dementia) chronically. *The Microbial Prologue* identified the gut microbiome as the ecological controller of that very partition. The two theses describe one fork from two ends, and the gut sits at the controlling end (O'Mahony et al., 2015). This is a demonstrated weld, and its detail is the subject of the next chapter.

5.4 The Bioenergetic Axis — Plausible and Partially Demonstrated

The Depression Continuum adopted the metabolic-psychiatry framework in which mitochondria are the organelle on which chronic stress, inflammation, and metabolic burden converge, and it proposed a mitochondrial allostatic load index integrating peripheral and central measures of mitochondrial competence. The gut is upstream of this index in a way the index's own construction implies but did not name. Butyrate is not only the colonocyte's fuel and the barrier's signal; it is a systemic energetic and epigenetic modulator whose withdrawal removes a mitochondria-supportive, histone-deacetylase-inhibiting influence, and whose fibre-fermentation origin ties the index to diet through the microbiome. The population-scale depletion of butyrate producers in depression (Valles-Colomer et al., 2019) is, on this reading, a depletion of a bioenergetic support signal; and the gain of trimethylamine N-oxide and the shift in secondary bile acids that *The Microbial Prologue* catalogued are systemic metabolic signals with central correlates. The weld is plausible and partially demonstrated — the butyrate and endotoxin ends are experimentally grounded, but a direct demonstration that a defined dysbiosis lowers a validated central mitochondrial-load measure has not, to my knowledge, been performed, and the chapter does not overstate it.

5.5 The Synaptic Axis — Plausible and Partially Demonstrated

The Depression Continuum's synaptic axis is the BDNF/TrkB/mTOR synaptogenic cascade and its cellular correlate in adult hippocampal neurogenesis, driven by serotonergic and noradrenergic trophic input. The gut is upstream of the trophic substrate this axis acts on, though not of the acute pharmacology that acts on it. Germ-free rearing lowers hippocampal BDNF and disturbs the serotonergic system (Sudo et al., 2004; Clarke et al., 2013); the microbiome regulates host serotonin biosynthesis at the enterochromaffin cell (Yano et al., 2015); and normal colonisation shapes the expression of synaptic-plasticity genes (Diaz Heijtz et al., 2011). The microbiome therefore sets the level of the neurotrophic and serotonergic tone on which the antidepressant synaptogenic cascade operates — a dysbiotic gut is a low-BDNF, low-serotonergic-tone gut, and the cascade has less substrate to work with. The extension of this weld to the specific parvalbumin-interneuron and perineuronal vulnerabilities that *The Depression Continuum* makes central at the synaptic death-pole is inferential and is not claimed as demonstrated.

5.6 The Perineuronal Axis — Inferential

This is the weakest weld and is graded as such. *The Depression Continuum*'s fifth axis is the perineuronal net, degraded in both depression and dementia by microglial matrix-metalloproteinase and cathepsin activity under chronic stress and inflammation. The gut connects to this axis only indirectly: its inflammatory export is one upstream driver of the microglial proteolytic pressure that degrades the net, and stress — which reduces perineuronal coverage — is itself bidirectionally coupled to the microbiome through the hypothalamic-pituitary-adrenal axis (Sudo et al., 2004). But there is no direct experiment demonstrating that a defined dysbiosis degrades perineuronal nets, and the chapter does not pretend otherwise. The perineuronal weld is offered as a plausible extension of the demonstrated inflammatory weld — the same microglial pressure, one step further downstream — and is flagged in Chapter VII as one of the bridge's spans most in need of a direct test.

5.7 The Coherence of the Single Perturbation

The value of the mapping is not that the gut touches each axis separately but that a single ecological drift pushes all five in the same direction at once, exactly as *The Microbial Prologue* argued the drift "fails as a system, and the failures compound." The loss of butyrate simultaneously withdraws an anti-inflammatory signal (microglial axis), a bioenergetic support (bioenergetic axis), a serotonergic-trophic influence (synaptic axis), and a barrier fuel whose loss raises the endotoxin that drives all of the above; the gain of endotoxin simultaneously primes the inflammasome, diverts tryptophan by inducing indoleamine 2,3-dioxygenase (tryptophan axis), and sustains the microglial pressure on the matrix (perineuronal axis). The five axes of *The Depression Continuum* are not five independent things the gut happens to affect; they are five downstream faces of one upstream ecological perturbation. That coherence is why the gut is a credible *origin* of the whole substrate rather than a contributor to one corner of it.

6. Chapter III — Sickness Behaviour: The Acute Prototype of the Depressive Prodrome

6.1 Sickness Behaviour as the Bridge's Rosetta Stone

The single phenomenon in which the three literatures — microbiome, psychiatry, and neuroimmunology — already speak one language is *sickness behaviour*: the coordinated behavioural response to peripheral immune activation comprising anhedonia, fatigue, hypersomnia or insomnia, appetite change, social withdrawal, psychomotor slowing, and cognitive impairment. *The Depression Continuum* invoked Dantzer's account of sickness behaviour as the canonical demonstration that peripheral inflammation produces a depressive phenotype centrally; *The Microbial Prologue* invoked the same peripheral inflammatory load, from the gut, as the injurious afferent signal to the brainstem. Sickness behaviour is where the two accounts already touch, and this chapter argues that it is the acute, experimentally inducible prototype of the depressive prodrome: what a bolus of endotoxin produces in hours, a lifelong dysbiotic drift produces in decades, and the phenomenology is continuous between them.

The overlap is not analogical but mechanistic. Dantzer's canonical pathway — peripheral inflammation elevates circulating cytokines, which signal to the brain through cytokine transport, vagal afferents, perivascular cells, and the leaky circumventricular regions, producing both the behavioural syndrome and a downstream indoleamine-2,3-dioxygenase-driven kynurenine shift — is, route for route, the pathway *The Microbial Prologue* mapped for the gut's inflammatory export. The cytokines of sickness behaviour and the cytokines of the gut's afferent load are the same cytokines; the vagal afferents that carry the sickness signal are the same afferents that carry the dysbiotic signal; and the kynurenine shift that sickness behaviour induces is the same shift that the tryptophan axis of the next chapter makes central. Sickness behaviour is the depressive prodrome run fast.

6.2 The Vagal Conduit Is the Same Conduit

The Microbial Prologue anatomised, in detail it declined to repeat and this volume also takes as given, the neural route by which the gut speaks to the brainstem: the enteroendocrine neuropod cell that forms a genuine glutamatergic synapse with a vagal afferent (Kaelberer et al., 2018), placing a luminal sensor a single fast synapse from the nerve; the vagal afferent's central terminus at the nucleus tractus solitarius; and the dominantly indirect medullary relay from the solitary nucleus to the locus coeruleus. That this conduit is the operative route for behaviour, and not merely an available one, is established by the vagotomy-sensitive behavioural experiments: a defined Lactobacillus alters emotional behaviour and central GABA-receptor expression through the vagus, an effect abolished by vagotomy (Bravo et al., 2011). The mood-relevant signal and the dementia-relevant signal travel the same cable, because there is only one cable, and the sickness-behaviour literature and the microbiome-behaviour literature are describing its traffic from two windows.

6.3 The Transfer Experiments: The Mood-Side Twin of the Propagation Experiments

The strongest evidence in *The Microbial Prologue* was the gut-to-brain propagation experiment: pathological α-synuclein injected into the mouse gut ascends the vagus to the brain, reproduces the caudo-rostral spread, and is blocked by truncal vagotomy — a defined seed, a defined route, a defined brain pathology, and a defined interruption. This chapter's contention is that the depression literature contains the exact structural twin of that experiment, in the mood direction, and that the two together are the empirical heart of the double-first.

The twin is the faecal-transplant experiment. Transplantation of a "depression microbiota" from patients with major depressive disorder into germ-free mice induces depression-like behaviours that a healthy-donor microbiota does not, through a pathway mediated by host carbohydrate and amino-acid metabolism (Zheng et al., 2016); and transplantation of a depressed-patient microbiota into microbiota-depleted rats induces the behavioural and physiological features of depression — anhedonia, anxiety-like behaviour, and altered tryptophan metabolism — in the recipients (Kelly et al., 2016). The logical structure is identical to the propagation experiment: a defined ecology, moved into a naïve host, that carries its brain phenotype with it. Where Kim and colleagues moved a proteinopathy and got a

movement disorder, Zheng and Kelly moved an ecology and got a mood disorder.

The juxtaposition is the chapter's central image. The gut can transmit, by transplantation, *both* a proteinopathy (the neurodegenerative reading) *and* a mood (the depressive reading) — two phenotypes of one continuum, both carried by the same organ, both demonstrated in the cleanest available causal system. That a single compartment is sufficient to transfer the reversible-early phenotype and, in its proteinopathic form, the irreversible-late phenotype is exactly what the double-first predicts, and it is the observation that most directly unifies the two parent volumes. The transfer experiments do not yet close the full loop — no experiment has transplanted a depressed-patient microbiome and measured a locus-coeruleus or tau-adjacent read-out, which is precisely the experiment Chapter VII proposes — but they establish, on each side separately, the sufficiency the bridge requires.

6.4 The Landing on the Locus Coeruleus

Sickness behaviour and the depressive prodrome share not only a source and a conduit but a receiver. The vagal and humoral routes that carry the gut's inflammatory export converge, through the medullary relay, on the locus coeruleus — the nucleus that *The Coerulean Interface* and *The Microbial Prologue* identified as the first to fail, the anti-inflammatory brake whose loss disinhibits the very inflammation the gut is driving, and a structure too bioenergetically marginal to sustain a chronic afferent load. *The Depression Continuum* independently identified the locus coeruleus as the anatomical bridge between the depressive and dementing phenotypes, because its early noradrenergic dysfunction produces the emotional-regulation, arousal, and sleep disturbances of midlife depression long before its loss produces cognitive decline. The two theses arrived at the same nucleus from opposite ends, and Chapter VI takes up its role as the shared hinge. For the present chapter it is enough to note that the acute prototype and the chronic prodrome land in the same place: the gut's signal, whether delivered as a bolus that produces sickness behaviour in an afternoon or as a drift that produces depression over a decade, terminates on the structure whose failure the whole programme has placed at the beginning of dementia.

7. Chapter IV — The Tryptophan Fork as the Keystone Weld

7.1 Why the Fork Bears the Most Weight

Of the five welds of Chapter II, one is exact rather than merely convergent, and it is the one on which the bridge's identity claim rests most securely. The tryptophan partition is the single molecular node at which the same mechanism — not a shared class of mechanism, but the same reaction on the same substrate — produces the depressive phenotype acutely and the dementing phenotype chronically, and at which the gut sits demonstrably at the controlling end. This chapter develops it in full because it is the place where the double-first is not an inference from coincidence but a mechanism read forward and backward through one branch point.

7.2 The Fork, Stated Once

Tryptophan, the sole substrate for serotonin synthesis and a major substrate for nicotinamide-adenine-dinucleotide synthesis, is partitioned among three fates: hydroxylation by tryptophan hydroxylase 2 toward serotonin; oxidation by indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase toward the kynurenine pathway; and direct microbial conversion to indole and its derivatives. Under inflammatory conditions — chronic elevation of interferon-γ, tumour necrosis factor-α, and interleukin-1β — indoleamine 2,3-dioxygenase is transcriptionally induced and the partition shifts toward kynurenine. *The Depression Continuum*'s sixth axis is exactly this shift: the depressive reading is substrate-limited serotonin (tryptophan availability falls below the Michaelis constant of tryptophan hydroxylase 2, so that reuptake inhibition cannot rescue a neurotransmitter the brain can no longer adequately synthesise), and the dementing reading is the accumulation of the excitotoxic and pro-oxidant kynurenines and the withdrawal of serotonergic trophic support from adult neurogenesis. One shift; two temporally separated outputs. This is the depression thesis's clearest single mechanism, and it is the sharpest expression of its identity claim.

7.3 The Gut Controls the Fork Three Ways

The Microbial Prologue placed the gut at the controlling end of this partition, and the microbiome-psychiatry literature makes the control specific. The gut regulates the fork by three distinct mechanisms, and the depressive and dementing consequences follow from each.

First, **direct substrate consumption.** The gut microbiota metabolise dietary tryptophan directly into indole and its derivatives — ligands of the aryl hydrocarbon receptor that shape mucosal immunity and barrier function — and in doing so remove tryptophan from the pool available for host serotonin synthesis. A microbiome shifted toward indole-producing metabolism lowers the serotonergic substrate at source.

Second, **inflammatory induction of the diverting enzyme.** The dysbiotic gut's endotoxin export and its loss of anti-inflammatory butyrate raise the systemic cytokine tone that transcriptionally induces indoleamine 2,3-dioxygenase — so that the gut drives the kynurenine shift not only by consuming substrate but by inducing the enzyme that diverts it. O'Mahony and colleagues (2015) state the consequence exactly: the gut microbiota control host tryptophan metabolism along the kynurenine pathway, "thereby simultaneously reducing the fraction available for serotonin synthesis and increasing the production of neuroactive metabolites." That single sentence is, read one way, the mechanism of *The Depression Continuum*'s sixth axis, and read the other way, the ecological control of it; the gut is the subject of the verb.

Third, **demonstrated transfer of the altered partition.** The faecal-transplant experiment of Kelly and colleagues (2016) did not merely transfer a depressive behavioural phenotype; it transferred *altered tryptophan metabolism* along with it. The dysregulated fork travelled with the ecology into the naïve host. This is the causal closure the cross-sectional data cannot supply: the gut is sufficient, when moved, to move the partition.

7.4 One Fork, One Controller, Two Readings

The keystone weld can now be stated as a single mechanism read through one branch point. The gut microbiome is the ecological controller of the tryptophan fork; the tryptophan fork is the molecular node at which one shift produces substrate-limited serotonin (the reversible, depressive reading) acutely and kynurenine excitotoxicity with neurogenic withdrawal (the irreversible, dementing reading) chronically. Therefore the gut, through this one node, is upstream of both readings of the continuum, and the depressive and dementing phenotypes are, at this node, literally the same reaction observed at two times and two cumulative doses. The tryptophan fork is where the double-first stops being a coincidence of two theses and becomes a demonstrable feature of one biochemical pathway: the ecological cause, the reversible mood reading, and the irreversible cognitive reading are three points on one branch of one metabolic tree, and the gut holds the branch.

7.5 The Therapeutic Reading of the Keystone

The fork's therapeutic implications are correspondingly unified and are developed in Chapter VII, but the principle belongs here. *The Depression Continuum* predicted that antidepressant response should vary inversely with the kynurenine-to-tryptophan ratio, because reuptake inhibition cannot rescue substrate-limited synthesis; and it predicted that partition-rebalancing interventions should benefit both the depressive and the dementing phenotypes. The bridge adds the most upstream partition-rebalancing intervention of all: correcting the ecology that controls the fork. Restoring butyrate producers lowers the inflammatory induction of indoleamine 2,3-dioxygenase; shifting the microbial metabolism of tryptophan away from indefinite indole diversion preserves the serotonergic substrate; and doing either in the depressive window acts on the fork while the downstream neurogenic and excitotoxic consequences are still reversible. The keystone weld is thus also the keystone intervention: the fork is both where the two diseases are most clearly one and where the gut-directed correction of the double-first is most mechanistically legible.

8. Chapter V — The Reversibility Gradient Acquires an Ecological Floor

8.1 The Gradient as Given

The Depression Continuum defined a reversibility gradient across each of its five brain-intrinsic axes: parvalbumin interneurons recover if viable but not if dead; microglia revert from reactive states but not from a fully consolidated disease-associated program; mitochondrial populations restore if their biogenic capacity is preserved but not if it is lost; the tryptophan partition normalises if the induction is recent but not if it is chronically fixed; and the perineuronal matrix is remade if the neurons it enclosed survive but not once they are gone. Depression occupies the reversible end of the gradient at most axes for most patients; dementia occupies the irreversible end; and the therapeutic implication was stage-matched intervention, deployed while the substrate can still recover.

8.2 The Missing Floor

The gradient, as drawn, begins at the brain's own substrate — at the first of the five axes. But the substrate has an upstream, and the upstream has a reversibility of its own. This chapter's contribution is to extend the gradient one segment further, below the synaptic axis, to the ecology that sets the tone of all five: the gut microbiome. The claim is that the gut is not merely upstream of the gradient's five axes (Chapter II) but is itself the *most reversible segment of the entire structure* — an ecological floor beneath the brain-intrinsic gradient.

The gut is the most reversible node for reasons *The Microbial Prologue* established: it turns over on a timescale of weeks rather than decades; it is reachable through the lumen rather than across the blood-brain barrier; and it responds to interventions — fibre, prebiotic substrate, butyrate-producing consortia, barrier repair, and in the limit faecal transplantation — that act on the ecology directly rather than on its distant consequences. Where the brain-intrinsic axes become progressively harder to reverse as damage accumulates in cells that may ultimately die, the ecology can be re-seeded at any point, because bacteria are replaceable in a way neurons are not. The floor of the gradient is more reversible than any point above it.

8.3 The Two Reversibility Maxima Coincide

The ecological floor and the depressive window are the same location on the gradient, and this is the double-first restated in the gradient's own terms. The depressive window is the point at which the five brain-intrinsic axes are at their most reversible (the claim of *The Depression Continuum*); the ecological floor is the point at which the upstream cause is at its most reversible (the claim of *The Microbial Prologue*); and because the ecology is what sets the axes, the two maxima are contemporaneous. At the depressive window, one is standing at the most reversible point of the brain-intrinsic gradient *and* at the most reversible point of the ecological floor beneath it — and the ecological floor, being upstream, is the lever by which the whole structure above it can be relieved.

This is why the gut-directed intervention in the depressive window is not one option among the stage-matched interventions but the foundational one. Stage-matched intervention, as *The Depression Continuum* framed it, meant deploying the intervention appropriate to the substrate's state across the five axes. The bridge adds a sixth, most-upstream, most-reversible tier — the ecology — and argues that it should be corrected first and always, because its correction relieves all five axes at once and because it is the tier that remains reversible longest. The gradient does not begin at the synapse; it begins at the ferment, and the ferment is where restoration is cheapest.

8.4 The Threshold Question, Extended

The Depression Continuum raised, without answering, the question of whether the transition from reversible to irreversible occurs at the same threshold on each axis, and concluded that the axis-specific thresholds are the true staging variables. The ecological floor extends this question downward. It predicts that the ecology has the *latest* threshold of all — that a dysbiotic gut can be re-seeded even after several of the brain-intrinsic axes have crossed their thresholds, so that gut correction retains some leverage even in the dementing phase, though far less than in the depressive one, because the downstream substrate it would relieve has by then partly lost the capacity to recover. The gut's late-crossing threshold is the mechanistic basis for the modest but real benefit that *The Depression Continuum* and *The Microbial Prologue* both anticipated from gut- and metabolism-directed interventions even in established disease: the cause remains correctable after the substrate no longer fully responds. The leverage falls not because the ecology becomes irreversible but because what lies above it does.

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9. Chapter VI — The Gut–Coerulean–Mood Spiral

9.1 The Spiral Inherited

The Microbial Prologue closed on a synthesis it named the gut–coerulean spiral: dysbiosis lowers butyrate and weakens the barrier; the weakened barrier exports endotoxin and raises the inflammatory afferent load; the chronic load drives and bioenergetically stresses the locus coeruleus; coerulean noradrenaline falls; the falling noradrenaline disinhibits central microglia and, through reduced anti-inflammatory autonomic tone, the periphery — including the gut barrier itself — which worsens the dysbiosis that began the loop. The spiral's distinction was that it closed outside the brain, making the whole cascade interruptible at its ecological origin.

9.2 The Mood Arm

This chapter adds an arm to that spiral, drawn from the second parent. The same falling coerulean noradrenaline that disinhibits microglia and the peripheral barrier also produces, directly, the mood and arousal disturbances that *The Depression Continuum* attributed to early locus-coeruleus dysfunction: impaired top-down regulation of the amygdala, elevated hypothalamic-pituitary-adrenal tone, disturbed sleep architecture, and the anhedonic, hyperaroused, emotionally dysregulated phenotype of midlife depression. The locus coeruleus is therefore not only the receiver on which the gut's exports come to matter (the parent's claim) but the emitter of the earliest mood reading of the cascade — and the mood reading feeds back into the spiral, because depression degrades sleep, diet, and stress physiology, each of which worsens the gut ecology.

The result is a gut–coerulean–mood spiral with three coupled arms: the ecological arm (dysbiosis ☐ barrier failure ☐ endotoxin), the coerulean arm (afferent load ☐ noradrenergic failure ☐ microglial and peripheral disinhibition), and the mood arm (noradrenergic failure ☐ depressive phenotype ☐ degraded sleep, diet, and stress physiology ☐ worse dysbiosis). Each arm drives the next; the loop closes through the body twice — once through the autonomic periphery, as the parent described, and once through behaviour, as the depressive phenotype feeds back onto the gut. The mood arm is what makes the spiral clinically visible early: the depression is the first arm a patient reports, decades before the coerulean arm produces cognitive decline.

9.3 The Locus Coeruleus as the Shared Hinge

The chapter's deeper point is that both parent frameworks placed the locus coeruleus at the centre of their accounts, from opposite directions, and the bridge is the recognition that it is the same centre. *The Microbial Prologue* made it the receiver of the gut's exports and the arsonist that operates the sprinkler — the brake whose loss releases the inflammation the gut is driving. *The Depression Continuum* made it the anatomical bridge between the depressive and dementing phenotypes — the nucleus whose early noradrenergic loss produces depression and whose later loss produces dementia. Read together, the locus coeruleus is the single structure at which the gut's ecological drift, the depressive prodrome, and the dementing endpoint all converge: the drift loads it, its early failure reads as depression, and its late failure reads as dementia. It is the hinge on which the whole continuum turns, and it is the point at which the two parent theses were, without knowing it, describing the same nucleus. The bridge is, in one sense, nothing more than the observation that the locus coeruleus of the origin volume and the locus coeruleus of the continuum volume are one nucleus — and that everything upstream of it (the gut) and everything it emits early (the mood) therefore belong to one account.

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10. Chapter VII — Therapeutic Implications and Falsifiable Predictions

10.1 The Convergent Program, With an Ecological Tier

The Depression Continuum proposed an axis-stratified, multi-modal intervention program — synaptic, microglial, bioenergetic, tryptophan, and perineuronal interventions deployed according to biomarker-identified substrate state. *The Microbial Prologue* proposed an ordered, most-upstream-first gut program — restore the fermentation, repair the barrier, subtract the noxious organisms and seeds, replace the ecology, and defend the receiver. The bridge unifies these: the gut program is the most upstream tier of the depression continuum's own convergent program, and it should be deployed first and always, because it relieves all five axes at once and occupies the most reversible node of the gradient.

The clinical reframing is that the interventions long siloed in "gut-brain psychiatry" — dietary fibre, psychobiotics, butyrate restoration, and, in the research

setting, faecal transplantation for depression — are, on the double-first, simultaneously antidepressant therapy and dementia prevention, deployed at the point of maximum leverage. The psychiatrist prescribing a fibre-rich anti-inflammatory diet and a butyrate-restoring regimen to a patient with a first inflammatory depression is not treating depression and incidentally reducing later dementia risk; they are correcting the ecological origin of a single disease during its most reversible window. The neurologist's gut-directed prevention and the psychiatrist's gut-directed treatment are the same act on the same continuum, thirty years apart.

10.2 The Predictions Only the Bridge Can Make

Each parent volume closed with falsifiable predictions internal to its own frame. The bridge's predictions are those that require both frames at once — that could not be stated, and whose failure could not be interpreted, without the double-first. Their failure would sever specific spans of the bridge while leaving others standing, as noted for each.

Prediction 1 (Transfer of both readings). Faecal microbiota transplantation from patients with inflammatory- or kynurenine-subtype treatment-resistant depression into gnotobiotic rodents will transfer *both* a depressive behavioural phenotype *and* a neurodegeneration-relevant substrate signature — elevated kynurenine-to-tryptophan ratio, microglial priming, and, in a proteinopathy-sensitised host or over sufficient time, an accelerated locus-coeruleus or tau-adjacent vulnerability. This is the experiment that closes the loop the transfer experiments have so far left open on each side. *Falsification:* the depressed-patient microbiome transfers mood but leaves every neurodegeneration-relevant read-out unmoved — which would sever the core identity span while leaving the depression-side welds intact.

Prediction 2 (The dysbiosis of treatment-resistant depression). Treatment-resistant depression — which *The Depression Continuum* interprets as depression whose pathology has shifted from the synaptic axis toward the inflammatory, kynurenine, and bioenergetic axes, closer to the Alzheimer configuration — will carry a gut signature closer to the Alzheimer dysbiotic signature than treatment-responsive depression does: greater loss of butyrate-producing Faecalibacterium and Coprococcus, greater relative expansion of endotoxin-bearing

Enterobacteriaceae, and a higher kynurenine-to-tryptophan ratio. *Falsification:* treatment-resistant and treatment-responsive depression carry indistinguishable gut signatures — which would sever the claim that the axis-shift of treatment resistance is ecologically grounded.

Prediction 3 (Conduit-dependent continuity). A midlife dysbiotic signature together with an elevated kynurenine-to-tryptophan ratio will jointly predict both depression incidence over the subsequent decade and dementia incidence over the subsequent three decades, with overlapping predictive populations; and the gut-to-outcome association will be attenuated in vagotomised individuals, in whom the neural route is severed. This weld joins the conduit-dependence prediction of *The Microbial Prologue* to the biomarker-continuity prediction of *The Depression Continuum*. *Falsification:* the signature predicts one phenotype but not the other, or severing the conduit does not weaken the association — which would sever the shared-conduit span.

Prediction 4 (Upstream-dominance in the depressive window). A gut-directed intervention (fibre and butyrate restoration, barrier repair, or ecological replacement) begun in the depressive window will alter the long-term cognitive trajectory more than an equally timed, equally intensive brain-directed antidepressant that does not touch the ecology. This is the core testable claim of the double-first — that the most upstream and most reversible move outperforms an equally early but more downstream one. *Falsification:* gut-directed and brain-directed interventions of equal timing produce equal long-term cognitive effect — which would sever the leverage claim while leaving the identity claim intact.

Prediction 5 (Butyrate, mood, and amyloid on one axis). In inflammatory-subtype depression, restoration of butyrate (through fibre, prebiotic, or postbiotic) will produce an antidepressant response whose magnitude scales with the restoration of the cathelicidin (LL-37) checkpoint and the fall in circulating endotoxin, and the same intervention on long-term follow-up will lower dementia incidence in proportion to the same biomarkers. This welds *The Microbial Prologue*'s butyrate–cathelicidin causality prediction to *The Depression Continuum*'s anti-inflammatory disease-modification prediction. *Falsification:* butyrate's antidepressant effect is unrelated to the cathelicidin/endotoxin axis, or its mood and dementia effects dissociate — which would sever the specific butyrate span while leaving the broader inflammatory weld standing.

10.3 What Would and Would Not Survive

The bridge states, as both parents did, which of its spans are load-bearing and which are expendable. The tryptophan-fork weld (Chapter IV) is the best supported and would survive nearly any negative result elsewhere, because it rests on a demonstrated mechanism read through a single branch point with the gut at the controlling end. The inflammatory weld (Chapter II) is nearly as strong, resting on the demonstrated microbial control of microglia. The transfer-experiment argument (Chapter III) is strong on each side separately and awaits the single experiment (Prediction 1) that would join them. The bioenergetic and synaptic welds are plausible and partially demonstrated; the perineuronal weld is inferential and is the span most in need of a direct test. The double-first itself — the coincidence-and-leverage claim — rests on Predictions 1 and 4; their joint failure would refute the bridge as a therapeutic thesis even if the individual mechanistic welds survived as an account of shared biology. The bridge is offered, in the methodology's spirit, as a structure built to be tested at named joints, not as a settled span.

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11. Chapter VIII — What the Bridge Does Not Yet Explain

This section is required by the ONS methodology. The bridge is comprehensive at the level of shared mechanism but incomplete at several levels, and the incompletenesses are stated plainly.

- **The reverse-causation hazard is sharper at the mood end.** Depression alters appetite, diet, sleep, motility, and medication, each of which alters the gut, so that a dysbiotic signature in a depressed patient may be a consequence rather than a cause of the depression. The bridge rests its causal weight on the faecal-transplant and gnotobiotic experiments, but those are rodent, and the human direction remains, as in the parent volume, associative. The double-first is a hypothesis with defined tests, not a demonstrated human result.
- **No end-to-end human chain.** The chain gut ecology ☐ vagal and humoral afferent ☐ locus coeruleus ☐ depressive phenotype ☐ later cognitive decline is assembled from links each evidenced separately; no single human study has traversed it whole. The bridge is an argument that the links compose, not a demonstration that they have been observed to.

• **The tau extension is inherited as inferential.** The bridge's neurodegenerative endpoint depends, for Alzheimer's disease specifically, on *The Microbial Prologue*'s honestly flagged inference that the bacterial-amyloid cross-seeding and gut-origin logic demonstrated for α-synuclein extends to tau. Where that inference fails, the bridge's Parkinson-side and inflammatory-side spans survive but its Alzheimer-specific proteinopathic span does not.

• **Depression is heterogeneous, and the gut-origin reading fits one part of it.** The fermented prodrome is cleanest for the inflammatory and kynurenine-shifted subtypes. The melancholic subtype (with its cortisol non-suppression), the atypical subtype, the psychotic subtype, bipolar depression, and reactive depressions with a predominantly psychological aetiology may weight the gut very differently or scarcely at all. The bridge does not claim that all depression is a fermented prodrome; it claims that the subtype both parent frameworks explain best is the subtype the gut originates.

• **The brain-intrinsic vulnerabilities are real and are not gut-created.** The bioenergetic marginality of the locus coeruleus, the intrinsic fragility of parvalbumin interneurons, the apolipoprotein-E genotype, and the other constitutional risk factors set the substrate's baseline vulnerability, and the gut acts upon a substrate whose susceptibility it did not create. The double-first is a claim about one upstream cause and one early window, not a claim of ecological monocausality.

• **The phasic and reward dimensions are unaddressed.** Like its depression parent, the bridge is a tonic-dysregulation account. It does not address manic and mixed states, rapid cycling, or the mesolimbic dopaminergic substrate of anhedonia — though it notes that the microbiome has documented effects on dopaminergic metabolites (Valles-Colomer et al., 2019) that a future extension might develop.

• **The strength of the leverage claim is unquantified.** The double-first asserts that gut correction in the depressive window is the highest-leverage act, but it does not quantify how much of the continuum's variance the gut tier accounts for relative to the brain-intrinsic tiers. Prediction 4 would begin to quantify it; until then, "highest-leverage" is an argued ranking, not a measured effect size.

• **The threshold values remain unspecified.** The ecological floor is asserted to have the latest reversibility threshold of the gradient, but neither its value nor the values of the five axis-specific thresholds above it are specified, and their determination is a research program the bridge implies but does not execute.

Synthesis and Conclusion — The Mood Before the Memory

Two prior volumes of this programme reached for a claim about what comes first. *The Microbial Prologue* argued that before the tangle there is the drift — that the earliest cause of a brain disease may be neither neuronal nor proteinaceous but ecological, a shift in which organisms ferment our food. *The Depression Continuum* argued that before the dementia there is the depression — that the earliest clinical reading of the same disease is a reversible disturbance of mood, observed in midlife, in a substrate that can still recover. This dissertation observed that the two firsts are one: the drift that begins the disease and the depression that first makes it legible occupy the same window of the same trajectory, because the drift is one of the things that is making the person depressed.

From that coincidence — the double-first — the bridge drew a synthesis that neither parent could reach alone. It supplied *The Depression Continuum* with the concrete, modifiable, upstream ecological variable it had left generic, and mapped the gut onto each of that thesis's five axes, grading the welds from the demonstrated inflammatory and tryptophan spans to the inferential perineuronal one. It supplied *The Microbial Prologue* with its earliest human read-out, showing that the first clinical manifestation of the gut-origin cascade is a mood disorder, not a memory disorder. It read sickness behaviour as the acute prototype of the depressive prodrome and the faecal-transplant experiment as the mood-side twin of the gut-to-brain propagation experiment — one organ sufficient, when moved, to transfer both a mood and, in its proteinopathic form, a pathology. It isolated the tryptophan fork as the keystone, where one reaction on one substrate, controlled by the gut, produces the reversible reading acutely and the irreversible reading chronically. It extended the reversibility gradient downward to an ecological floor, the most reversible tier of all, and showed that the floor and the depressive window are the same location — so that the moment of maximum biological reversibility and the moment of maximum ecological modifiability coincide. And it extended the gut–coerulean spiral into a gut–coerulean–mood spiral, locating the locus coeruleus as the single hinge on which the drift, the mood, and the memory all turn.

The conclusion is a reordering of clinical hope. Three figures have appeared throughout this volume: the dysbiotic gut, drifting quietly for decades; the patient in

the psychiatrist's office with a first inflammatory depression; and the patient in the neurologist's office thirty years later with early cognitive decline. The conventional taxonomy assigns them to a gastroenterologist, a psychiatrist, and a neurologist, and supposes them to be three problems. The double-first says they are three views of one process, seen at three distances — and it says that the most hopeful of the three is the first, because the gut is the most upstream cause and the depressive window is the most reversible time, and they are the same point. The tangle cannot be untangled and the tangle's memory cannot be restored; but a prologue written in an organ we ferment our food with, read out first as a mood we already know how to treat, can — while it is still only a mood — be rewritten.

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A bridge volume welding The Microbial Prologue *(the gut microbiome as the ecological origin of the vagal–coerulean cascade) to* The Depression Continuum *(major depressive disorder as the reversible-state phenotype of the multi-axis collapse that sustains as Alzheimer's disease). Prepared under the Organic Network Synthesis methodology, AdultCognitiveDisease.com, July 2026. Its central claim —*

the double-first — is that the earliest cause of the disease (the gut's ecological drift) and its earliest clinical reading (the depressive prodrome) are the same event, so that correcting the gut ecology during the depressive window is simultaneously the most upstream and the most reversible intervention on the entire depression-to-dementia continuum.