THE CORRUPTION OF THE GARDENER

A Graded Atlas of the Drivers of Microglial Dysfunction in Alzheimer's Disease — Aging, Genetics, Proteinopathy, and the Threshold-Setters, Ranked by Causal Weight

The Substrate · The Switch · The Provocation
The Threshold-Setters · The Ranking

A Graded Reference Atlas Prepared as Field-Companion to the Doctoral Series

Neuroscience · Neuroimmunology · Alzheimer's Disease

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The field-companion to The Coerulean Pincer. That volume isolated a single cause of the microglion's turn from keeper to wrecker — the failure of noradrenergic governance. This atlas places that one cause in its whole field: it surveys the principal drivers of microglial dysfunction — aging, the TREM2–APOE genetic switch, the amyloid/tau proteinopathy and the NLRP3 inflammasome, the lipid axis, and the threshold-setting neuronal, microbial and systemic signals — and grades and ranks them, candid that 'importance' is four questions, not one. The noradrenergic axis sits among them as a moderate-weight threshold-setter, distinguished by being earliest to fail and easiest to reach, not by being the largest.

"The search for a single microglial culprit has cost the field years. The gardener is not corrupted by one hand but by many — aged before the season, switched by its genes, provoked by the proteins, and tuned by a surround of signals that decide the threshold. The honest account is not a suspect but a ranking."

— ONS Methodology Working Notes, 2026

For those who would treat the microglion — and who cannot aim a therapy until they know which of its many corruptions carries the most weight, and which can most readily be reached.

THE MICROGLIAL SERIES A FIELD MAP

Homeostatic Microglial Collapse — *the microglion as an axis of collapse*

The Sensor and the Speck — *the NLRP inflammasome in Alzheimer's disease*

The Coerulean Pincer — *noradrenergic governance, one cause of the microglion's turn*

The Corruption of the Gardener (all the drivers of microglial dysfunction, ranked) — this volume

This atlas answers a question the companion dissertation set aside. *The Coerulean Pincer* had to explain why the microglion — in health the extracellular matrix's keeper — turns into its wrecker, and it isolated one cause: the failure of noradrenergic governance. That isolation was sufficient for that argument but partial, for the microglion is corrupted by many hands. Here the whole crowd of causes is surveyed and ranked. At the foundation sits aging, the substrate that primes and senesces the cell; beside it, of equal weight for disease-specific causation, the genetics of TREM2 and APOE that switch the microglion into its dysfunctional state. Above them ride the major amplifiers — the amyloid and tau proteinopathy that provoke, and the NLRP3 inflammasome that executes and feeds the pathology forward — and the lipid failure at their crossing. Beneath all lie the threshold-setters: the neuronal checkpoints (the noradrenergic axis among them), the microbiome, and systemic inflammation, which decide the trigger and hold most of the modifiable ground. The atlas is candid throughout that 'importance' is four questions, not one — causal attribution, baseline vulnerability, acute execution, and tractability — and that a factor's rank depends on which is asked.

Contents

Abstract

A companion dissertation, *The Coerulean Pincer*, argued that the dysregulated locus coeruleus drives Alzheimer's tauopathy through a two-armed assault, and in doing so it had to explain why the microglion — in health the extracellular matrix's keeper — turns into its wrecker. That explanation isolated a single cause: the failure of noradrenergic governance. The isolation was deliberate and, for that argument, sufficient; but it was also partial, for the microglion is corrupted by many hands, and the noradrenergic one is neither the largest nor the only. This atlas is the reference companion that places the noradrenergic axis in its proper field. It surveys the principal drivers of microglial dysfunction in Alzheimer's disease, grades each by its causal weight, and ranks them — candid throughout that "importance" is not one quantity but four, depending on whether one asks which factor bears the greatest *causal-genetic* attribution, which sets the *baseline vulnerability*, which *executes* the acute damage, or which offers the best *modifiable* point of entry.

The ranking that emerges is layered. At the foundation sits **aging**, the dominant upstream substrate on which every other factor acts: the microglion becomes dystrophic and senescent, loses its homeostatic transcriptional identity, sheds the sensome by which it recognises what to clear, and accumulates lipid — a primed, half-corrupted cell before any disease-specific insult arrives. Beside it, and of comparable weight for *disease-specific causation*, stands **genetics**: the discovery that a large share of Alzheimer's risk genes are expressed in microglia, with *TREM2* and *APOE* foremost, is the strongest evidence that these cells are causal agents rather than bystanders, and the TREM2–APOE axis is the master switch of the disease-associated microglial state. Above these two dominants ride the **major amplifiers** — the amyloid and tau proteinopathy that provokes the primed cell through pattern-recognition and scavenger receptors, and the NLRP3 inflammasome that executes the damage and, through released specks, feeds the pathology forward — and the **intrinsic metabolic failure** of lipid handling that the genetics and the aging both converge upon. Beneath them all lie the **threshold-setters**: the neuronal and systemic signals — purinergic, fractalkine, cholinergic, and the noradrenergic axis of the companion dissertation, together with the microbiome, systemic inflammation, the vasculature, stress, and sleep — that individually are modulatory but collectively decide where the threshold for corruption sits, and that furnish nearly all of the modifiable entry points. The atlas closes on the recognition that these drivers do not compete but converge, and on the placement of the noradrenergic axis within the whole: a moderate-weight threshold-setter distinguished not by the size of its effect but by two properties the corpus has reason to prize — it is among the *earliest* to fail, and it is among the most *reachable*.

I. The Gardener and Its Corruption

In the healthy brain the microglion is a gardener. Its fine, ceaselessly moving processes patrol the parenchyma, sensing with a specialised repertoire of receptors what belongs and what does not; it clears debris and dying cells, prunes synapses with precision, and — held in that disciplined, surveillant, matrix-preserving state by the local microenvironment — does its housekeeping without inflaming the tissue it tends. Alzheimer's disease is, among many other things, the story of this gardener's corruption: the homeostatic cell becomes an activated, inflammatory, poorly-phagocytic one that secretes cytokines and proteases, engulfs the perineuronal net (Crapser and colleagues, 2020), and contributes to the very degeneration it exists to prevent. The companion dissertation, *The Coerulean Pincer*, needed to explain one route to that corruption — the failure of noradrenergic governance — and explained it. This atlas exists to answer the larger question the companion set aside: what *else* corrupts the gardener, and how do the causes rank?

The question matters because microglial dysfunction has become, in the last fifteen years, one of the central facts of Alzheimer's disease rather than a peripheral one. The genetics forced the change: as the risk architecture of the disease was mapped, an unexpectedly large fraction of the risk genes proved to be expressed in microglia and their myeloid kin, which turned the microglion from a suspected bystander into a prime suspect. But the causes of its dysfunction are many and heterogeneous — some intrinsic and some extrinsic, some genetic and some environmental, some initiating and some merely amplifying — and they are too often discussed as rivals, as though the disease had one microglial cause to be discovered. It does not. The corruption is multi-causal and convergent, and the useful task is not to crown a single culprit but to rank the contributors by weight and to say, for each, what *kind* of importance it has.

That last qualification is the burden of the section that follows, because "importance" here is not one quantity. This atlas is organised around it.

II. A Note on "Importance" Four Questions, Four Rankings

Before any factor is weighed, the scale must be named, because a single word — "important" — conceals four distinct questions, and a factor that ranks first on one may rank low on another. Much of the field's apparent disagreement about what drives microglial dysfunction dissolves once it is seen that the disputants are answering different questions.

The causal-genetic question: what factor bears the greatest weight of heritable, disease-specific causation? Here the answer is genetics — *TREM2* and *APOE* above all — because the genetics is what proves microglia are causal in the disease rather than reactive to it. This is the question of *attribution*.

The baseline-vulnerability question: what sets the substrate on which everything else acts? Here the answer is aging, because a primed, senescent, sensome-depleted microglion overreacts to every subsequent insult, and aging is the largest risk factor for the sporadic disease. This is the question of *predisposition*.

The acute-execution question: what actually carries out the damage in the diseased tissue? Here the answer is the proteinopathy that provokes and the inflammasome that executes — amyloid, tau, and NLRP3 — because these are the effectors that convert a primed cell into a frankly destructive one in real time. This is the question of *mechanism-in-the-moment*.

The modifiable-entry question: where can the corruption most readily be interrupted? Here the answer shifts to the threshold-setters — the systemic, microbial, vascular, and neuromodulatory signals, including the noradrenergic axis — because these are the levers that lifestyle and pharmacology can actually move. This is the question of *tractability*.

A factor's rank, then, is always a rank *on one of these axes*. Aging wins the second; genetics the first; proteinopathy and NLRP3 the third; the threshold-setters the fourth. The atlas that follows grades each driver on all four where it can, and the closing ledger states, for each, which kind of importance it chiefly carries. The reader who wants a single ranking is owed one, and will find it — but forewarned that a single ranking is a projection of a four-dimensional quantity onto one line, and loses information in the flattening.

III. Tier I The Substrate: Aging

Aging is the dominant upstream driver, and it earns that place not by any single dramatic lesion but by degrading the microglion along every axis at once, so that the cell which meets the disease-specific insults of Alzheimer's disease is already half-corrupted before they arrive. Four intrinsic changes compose the aged, primed microglion, and each is documented.

The homeostatic identity erodes. The microglion's quiescent, surveillant character is not a default but an actively maintained transcriptional state — a unique, TGF-β-dependent molecular signature that distinguishes microglia from all other macrophages and includes the sensors and

receptors of homeostatic surveillance (Butovsky and colleagues, 2014). This signature is not permanent; it is downregulated with age and in disease, and its loss is the molecular definition of a microglion slipping from its homeostatic identity toward an activated one.

The sensome is remodelled toward defence and away from clearance. The microglion senses its world through a defined cluster of transcripts — the "sensome" — encoding the receptors by which it recognises endogenous ligands and microbes. With aging, the sensome shifts: transcripts for the recognition of *endogenous* ligands, the debris and altered-self signals the gardener is meant to clear, are downregulated, while those for microbe recognition and host defence are upregulated (Hickman and colleagues, 2013). The aged microglion, that is, grows progressively worse at the housekeeping that keeps tissue clean and progressively more tilted toward inflammatory defence — a sensory reorientation that predisposes to dysfunction before any plaque forms.

Lipid accumulates. A striking and recently characterised change is the buildup of lipid droplets within aging microglia. These lipid-droplet-accumulating microglia — LDAM — are frankly dysfunctional: defective in phagocytosis, generating high levels of reactive oxygen species, and secreting proinflammatory cytokines, with a transcriptional profile driven by innate inflammation and distinct from other microglial states (Marschallinger and colleagues, 2020). That several genetic modifiers of lipid-droplet formation are themselves causes of human neurodegeneration — progranulin among them — ties this intrinsic metabolic change directly to disease, and is developed further in Tier II.

The cell becomes dystrophic and senescent. At the far end of the aging trajectory the microglion becomes overtly dystrophic — fragmented, beaded, and shortened in its processes, ferritin-laden, and senescent rather than classically activated. Crucially, these dystrophic (senescent) microglia, and not activated ones, are the cells associated with tau pathology in the human brain, and they appear to *precede* neurodegeneration rather than to follow it (Streit and colleagues, 2009). The implication is pointed: at least one major form of microglial dysfunction in Alzheimer's disease is not over-activation but *exhaustion* — the failure of a senescent cell to do its job — and it is on the timeline early.

Taken together these four changes make aging the substrate of the whole atlas. It does not, by itself, produce Alzheimer's disease; but it produces the primed, sensome-depleted, lipid-laden, senescing microglion that every subsequent driver acts upon, and it is the reason age is the disease's largest risk factor. On the baseline-vulnerability axis, nothing outweighs it.

IV. Tier I The Switch: Genetics

If aging sets the substrate, genetics sets the switch — and it is genetics that carries the greatest weight of *disease-specific causation*, for a reason that is as much epistemic as mechanistic. When the common and rare risk variants of Alzheimer's disease were mapped, an unexpectedly large share of them proved to be expressed selectively or preferentially in microglia and their myeloid lineage. That fact, more than any single experiment, is what moved microglia from the periphery of Alzheimer pathogenesis to its centre: a disease whose risk genes are disproportionately microglial is a disease in which microglia are plausibly causal. Two genes dominate.

TREM2 — the sensor whose loss disables the protective response. Rare heterozygous variants of *TREM2*, the triggering receptor expressed on myeloid cells 2, confer a roughly threefold increase in Alzheimer's risk — an effect size among the largest known for the disease, established simultaneously by two large sequencing studies (Guerreiro and colleagues, 2013; Jonsson and colleagues, 2013). TREM2 is the microglial sensor required to mount the protective response to pathology: it senses lipids and damage-associated ligands, sustains microglial survival and metabolism, licenses phagocytosis, and is indispensable for the transition to the disease-associated state. A TREM2 loss-of-function variant therefore produces a specific, well-mapped form of dysfunction — a microglion that *cannot* respond protectively — and its large effect size makes it the single most informative microglial gene in the disease.

APOE — the largest common risk factor, and the partner of TREM2 at the switch. *APOE4* is the largest common genetic risk factor for sporadic Alzheimer's disease, and much of its effect runs through microglia and lipid biology. The TREM2 and APOE pathways are not parallel but coupled: the TREM2–APOE axis drives the transcriptional conversion of homeostatic microglia into the dysfunctional, disease-associated phenotype, switching *off* the homeostatic signature (the very signature of Butovsky and colleagues, 2014) as the cell is activated by contact with apoptotic neurons and pathology (Krasemann and colleagues, 2017). APOE4 microglia are more inflammatory, worse at clearance, and altered in lipid handling — the same lipid axis that Tier II will show converging from several directions.

The disease-associated state, and its two-step logic. The endpoint of this genetic switch is the disease-associated microglion (DAM), identified by single-cell transcriptomics as a distinct subset found at sites of neurodegeneration, marked by downregulation of homeostatic checkpoints and upregulation of a TREM2-dependent program of lipid and damage sensing (Keren-Shaul and colleagues, 2017). Its activation proceeds in two steps — a TREM2-independent downregulation of the homeostatic checkpoints, followed by a TREM2-dependent activation of the full program — and the state is proposed to be a universal immune sensor of neurodegeneration rather than a disease-specific curiosity (Deczkowska and colleagues, 2018). Two features of the

DAM concept matter for this atlas. First, it is the shared endpoint onto which several of the other drivers converge — the aged microglion, the amyloid-provoked microglion, and the genetically-switched microglion all approach it. Second, it is plausibly, in its own right, an attempt at *protection* — a strain to restrict neurodegeneration (Keren-Shaul and colleagues, 2017) — so that its associated damage is collateral. This double-edge, that the corrupted state is also a defensive one, recurs throughout the atlas and is the single most important nuance in reading it.

On the causal-genetic axis, then, TREM2 and APOE are the heavyweights, and the myeloid enrichment of the risk architecture is the reason microglia are treated as causal at all. On the other three axes their rank is lower — genetics sets no acute mechanism by itself and offers, as yet, few modifiable entry points — but on the axis of attribution nothing outweighs them.

V. Tier II The Provocation: Proteinopathy and the Inflammasome

Aging primes the microglion and genetics sets its switch; the proteinopathy of Alzheimer's disease is what *provokes* the primed, switch-ready cell into frank dysfunction, and the NLRP3 inflammasome is what *executes* the resulting damage and feeds it forward. These are the major amplifiers — enormous in their effect on the disease's course, but, in the causal order, largely reactive: they act upon a cell that aging and genetics have already prepared.

Amyloid provokes through scavenger and pattern-recognition receptors. Aggregated amyloid-β is sensed by the microglion as an altered-self danger signal. A defined receptor logic underlies the provocation: the scavenger receptor CD36 cooperates with a Toll-like-receptor-4–Toll-like-receptor-6 heterodimer to sense amyloid-β (and oxidised lipids), triggering a sterile inflammatory response (Stewart and colleagues, 2010). Chronic engagement of this and related receptors by a plaque that cannot be cleared produces sustained activation, "frustrated phagocytosis," and cytokine release — the provocation that converts a primed microglion into an inflammatory one.

NLRP3 executes, and its activation is causal, not incidental. The convergence point of the inflammatory execution is the NLRP3 inflammasome, the multiprotein platform that activates caspase-1 to release interleukin-1β and interleukin-18. NLRP3 is activated in the Alzheimer brain, and — decisively — its genetic deletion, or that of caspase-1, protects APP/PS1 mice from memory loss, skews microglia toward a protective state, and reduces amyloid deposition (Heneka and colleagues, 2013). The inflammasome is therefore not an epiphenomenon of the

pathology but a causal contributor to it, which makes it one of the more attractive therapeutic nodes in the whole atlas.

The inflammasome feeds the pathology forward — in both proteins. Two findings elevate NLRP3 from an executor to an amplifier that propagates the disease. First, on the amyloid side: microglia release the inflammasome's ASC specks into the extracellular space, where they bind amyloid-β and cross-seed it, spreading amyloid pathology from cell to cell — the microglion becoming a vector of the very aggregate it was meant to clear (Venegas and colleagues, 2017). Second, on the tau side: NLRP3 inflammasome activation drives tau pathology, placing the inflammasome mechanistically *between* amyloid and tau and giving microglial inflammation a direct hand in the tangle (Ising and colleagues, 2019). The proteinopathy provokes the inflammasome; the inflammasome then worsens both proteinopathies. It is a feed-forward loop, and it is why the amplifiers, though reactive in the causal order, are so large in effect.

On the acute-execution axis, this tier ranks first: amyloid, tau, and NLRP3 are what actually carry out microglial damage in the diseased tissue moment to moment. On the causal-genetic and baseline axes they rank lower, because they act on a cell that aging and genetics have already compromised. The distinction between a large *effect* and a primary *cause* is nowhere more important than here.

VI. Tier II Intrinsic Metabolic Failure: The Lipid Axis

A second Tier-II driver deserves separate statement because it is where the intrinsic and the genetic converge, and because it has risen sharply in recognised importance: the failure of microglial lipid handling. The aging microglion accumulates lipid droplets and becomes the dysfunctional LDAM already described (Marschallinger and colleagues, 2020) — but the significance of that finding is amplified by the genetics, for the two dominant Alzheimer microglial genes are themselves lipid genes. APOE is the brain's principal lipid-transport apolipoprotein; TREM2 is a lipid sensor; and the TREM2–APOE axis that drives the dysfunctional state (Krasemann and colleagues, 2017) is, at bottom, a lipid-sensing and lipid-handling axis. The convergence is striking: an intrinsic, age-related lipid pathology (LDAM) and the two strongest genetic risk factors (APOE, TREM2) implicate the same cellular process, and the CRISPR screen that mapped the genetic modifiers of lipid-droplet formation recovered further human neurodegeneration genes, progranulin among them (Marschallinger and colleagues, 2020). Lipid dysfunction thus sits at the intersection of Tier I (aging, genetics) and Tier II (execution), partly downstream of each and partly a driver in its own right. Its rank is genuinely rising, and a fair reading places it as a major axis that the field underweighted for

years.

VII. Tier III The Threshold-Setters

Beneath the dominants and the amplifiers lie the signals that individually are modulatory but collectively decide *where the threshold for corruption sits* — and that, not coincidentally, furnish nearly all of the disease's modifiable entry points. This is the tier in which the companion dissertation's noradrenergic axis lives, as one threshold-setter among several. Grouped, they set the microglial thermostat.

The neuronal "off" signals. Healthy neurons continuously restrain microglia through a set of checkpoint signals, and the loss of any of them disinhibits the cell. The purinergic axis is the surveillance sensor: extracellular ATP, sensed through purinergic receptors, directs the rapid movement of microglial processes toward injury and sustains their baseline motility (Davalos and colleagues, 2005), and the purinergic receptor P2Y12 is a defining marker of the homeostatic microglion (Butovsky and colleagues, 2014) whose loss signals the homeostatic-to-activated shift. The fractalkine axis is a direct neuronal brake: microglia alone in the central nervous system bear the fractalkine receptor CX3CR1, and its deficiency dysregulates microglial responses into frank neurotoxicity across models of endotoxaemia, Parkinson's disease, and amyotrophic lateral sclerosis (Cardona and colleagues, 2006). And the noradrenergic axis — the subject of *The Coerulean Pincer* — is the neuromodulatory governor: the locus coeruleus controls microglial function through norepinephrine (Heneka and colleagues, 2010), noradrenergic tone suppresses microglial surveillance through the microglion's own β-adrenergic receptors (Stowell and colleagues, 2019; Liu and colleagues, 2019), and the failure of that governance is one route by which the gardener turns. These neuronal checkpoints share a logic: they are the means by which the state of the neurons sets the threshold of the microglia, and their loss is a threshold lowered.

The systemic and microbial modulators. The microglion is not governed only from within the brain. The gut microbiota constantly control microglial maturation and function; germ-free animals bear malformed, immature, defective microglia, and the deficit is corrected by microbial products (Erny and colleagues, 2015) — an upstream, environmental, and modifiable determinant of microglial competence. And the primed microglion of the aging or diseased brain is exquisitely sensitive to *systemic* inflammation: microglial priming renders the cell hyper-responsive to a secondary inflammatory stimulus, which in the elderly most often arises from systemic disease, so that a peripheral infection or inflammatory illness can trigger an exaggerated central inflammatory response and accelerate neurodegeneration (Perry and Holmes, 2014). These are the entry points

that lifestyle and the management of systemic disease can actually reach.

The vascular, endocrine, and circadian modulators. Completing the tier are the lower-weight but real modulators the corpus treats elsewhere: breakdown of the blood–brain barrier, which admits peripheral proteins that activate microglia; chronic stress and glucocorticoid exposure, which prime them; and sleep disruption, which impairs their surveillance and clearance. Each is individually contributory rather than dominant, but each is modifiable, and each connects this atlas to a companion volume in the corpus.

The threshold-setters, then, rank low on causal attribution and on baseline vulnerability, and they do not execute the acute damage. But on the fourth axis — tractability — they rank first, because they are where the corruption can most readily be interrupted. The noradrenergic axis is a representative member of this tier, and its distinctive value, developed in the companion dissertation, is temporal: of the threshold-setters, it is among the earliest to fail.

VIII. The Convergence

The gravest error this atlas could invite is to read its tiers as competing hypotheses, as though the reader must choose between aging and genetics and proteinopathy and the threshold-setters. They do not compete; they converge, and the convergence is the actual shape of microglial dysfunction in Alzheimer's disease.

The sequence runs like this. **Aging** primes the microglion — eroding its homeostatic signature, remodelling its sensome away from clearance, loading it with lipid, and pushing it toward senescence — so that the cell is half-corrupted before the disease begins. **Genetics**, chiefly the TREM2–APOE axis, sets the switch that governs the transition to the disease-associated state, and in the risk-carrying brain sets it toward dysfunction. **Proteinopathy** then provokes the primed, switch-ready cell through its scavenger and pattern-recognition receptors, and the **NLRP3 inflammasome** executes the inflammatory damage and, through released specks and its hand on tau, feeds the pathology forward in both proteins. The **lipid axis** sits at the crossing of aging and genetics, an intrinsic metabolic failure that the two dominants both implicate. And beneath all of it the **threshold-setters** — neuronal, microbial, systemic, vascular, endocrine, circadian — decide how easily the whole cascade is triggered and how far it runs, tuning the threshold at which priming becomes provocation.

Several nodes are shared, and the sharing is what makes the picture a network rather than a list. The disease-associated state is the common endpoint of the aged, the switched, and the provoked

microglion. The lipid axis is the common substrate of APOE, TREM2, and LDAM. The homeostatic signature is the common thing that aging erodes, genetics switches off, and the threshold-setters defend. And the double-edge is common throughout: at nearly every tier the "dysfunctional" state is also, in part, a defensive one — the DAM straining to restrict neurodegeneration, the inflammasome executing a response to real danger, the activated cell trying to clear a plaque it cannot digest. The corruption of the gardener is rarely a turn to malice; it is far more often a defence that has become, in a primed and provoked and ungoverned cell, destructive in its effect.

IX. The Ranking A Graded Ledger

The reader is owed a single ranking, with the standing caveat of Section II that it projects a four-dimensional quantity onto one line. The scale is worded: **Dominant** (sets the substrate or bears the greatest causal attribution), **Major** (a large-effect amplifier or executor), **Moderate** (a threshold-setter or convergent axis), **Contributory** (a real but lower-weight modulator). Each entry names the axis of importance on which it chiefly ranks.

Dominant — Aging (the substrate). Erodes the homeostatic signature (Butovsky and colleagues, 2014), remodels the sensome away from clearance (Hickman and colleagues, 2013), accumulates lipid into the dysfunctional LDAM state (Marschallinger and colleagues, 2020), and drives dystrophy and senescence that precede neurodegeneration (Streit and colleagues, 2009). *Chief axis: baseline vulnerability — first, and largest, on that axis.*

Dominant — Genetics: TREM2, APOE, and the myeloid risk architecture. The threefold-risk TREM2 variants (Guerreiro and colleagues, 2013; Jonsson and colleagues, 2013) and the APOE4 common risk factor act through the TREM2–APOE switch that drives the dysfunctional disease-associated state (Krasemann and colleagues, 2017; Keren-Shaul and colleagues, 2017; Deczkowska and colleagues, 2018). *Chief axis: causal-genetic attribution — the reason microglia are treated as causal at all.*

Major — Proteinopathy: amyloid and tau (the provocation). Amyloid provokes the primed cell through CD36–TLR4–TLR6 (Stewart and colleagues, 2010) and related receptors; tau both activates and is spread by microglia. *Chief axis: acute execution — first on that axis, but reactive in the causal order.*

Major — The NLRP3 inflammasome (the executor and amplifier). Causally contributes to pathology (Heneka and colleagues, 2013), cross-seeds amyloid through released ASC

specks (Venegas and colleagues, 2017), and drives tau pathology (Ising and colleagues, 2019). *Chief axis: acute execution; also the most druggable node in the tier.*

Major-to-Moderate — The lipid axis (intrinsic metabolic failure). LDAM (Marschallinger and colleagues, 2020) at the crossing of the two lipid-handling risk genes, APOE and TREM2 (Krasemann and colleagues, 2017). *Chief axis: a convergence of causation and execution; genuinely under-weighted historically, and rising.*

Moderate — The threshold-setters: neuronal checkpoints. Purinergic surveillance and the P2Y12 homeostatic marker (Davalos and colleagues, 2005; Butovsky and colleagues, 2014); the fractalkine brake CX3CR1 (Cardona and colleagues, 2006); the noradrenergic governor (Heneka and colleagues, 2010; Stowell and colleagues, 2019; Liu and colleagues, 2019). *Chief axis: tractability — first on that axis; individually modulatory, collectively decisive of the threshold.*

Moderate — The threshold-setters: microbial and systemic. The microbiota that control microglial maturation (Erny and colleagues, 2015) and the systemic-inflammation priming that turns a primed cell hyper-reactive (Perry and Holmes, 2014). *Chief axis: tractability — the principal lifestyle and systemic-disease entry points.*

Contributory — The vascular, endocrine, and circadian modulators. Blood–brain-barrier breakdown, chronic stress and glucocorticoids, and sleep disruption: individually lower-weight, each modifiable, each a bridge to a companion volume of the corpus.

Where the noradrenergic axis sits. The subject of *The Coerulean Pincer* is, on this ledger, a **Moderate** threshold-setter — not the largest driver of microglial dysfunction, which honesty requires stating plainly: aging and the TREM2–APOE axis outweigh it as causes. Its distinction is not magnitude but two other properties the corpus has reason to prize. It is among the *earliest* threshold-setters to fail, because the locus coeruleus tangles first; and it is among the most *reachable*, because β-adrenergic pharmacology already exists. The companion dissertation leans on exactly those two properties — timing and tractability — and not on any claim that norepinephrine is the biggest cause. This atlas is the check that keeps that claim honest: the noradrenergic axis is one hand among many that corrupt the gardener, distinguished by being first to the work and easiest to stay.

X. Coda The Gardener Corrupted by Many Hands

The companion dissertation watched a single hand close on the microglion — the noradrenergic one — and traced, in detail, how the failure of that one governance turns the gardener into a

wrecker. This atlas has stepped back to show the whole crowd of hands. Aging weakens the gardener before the season begins, wearing away its identity, dulling its senses, weighing it down with lipid, and aging it toward a tired uselessness. Genetics decides how readily it will be switched from tending to tearing, and in the risk-carrying brain sets the switch the wrong way. The proteins of the disease provoke it, and its own inflammasome executes the provocation and carries the ruin outward in both directions at once. Its lipid machinery fails at the crossing-point of its aging and its genes. And a thin surround of neuronal, microbial, systemic, and vascular signals — the noradrenergic one among them — sets the threshold at which all of this is triggered, and decides how far it runs.

No single hand is the culprit, and the search for one has cost the field time. The honest account is a ranking, not a suspect: aging and the TREM2–APOE switch are the dominants; the proteinopathy and the inflammasome are the great amplifiers; the lipid axis is the rising crossing-point; and the threshold-setters, including the noradrenergic governor, are the modulators that decide the trigger and hold most of the modifiable ground. The corpus has now told the microglial story from several of these sides — the homeostatic collapse, the inflammasome, the senescence, the microbiome, the noradrenergic governance — and this atlas is the map that shows how they fit. The gardener is corrupted by many hands. The noradrenergic one is worth its own dissertation not because it is the strongest, but because it moves first and can be stayed — which is exactly the kind of hand a clinician most wants to catch.

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