THE DOUBLE RELEASE

The Braking System of the Microglion and When It Fails — A Graded Inventory of the Restraints on Microglial Activation in Alzheimer's Disease, and the Interval Between the Withdrawal of the Coerulean Brake and the Withdrawal of the Somatostatinergic One

Five Classes of Brake · The Standing Order · The Two Hands
The Unarmoured Operators · Three Events, Not One · The Slow Fuse and the Fast One

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The microglion is not a cell that becomes dangerous when it is switched on. It is a cell that is dangerous by constitution and is held, continuously and at cost, in restraint. This volume inventories the restraints, grades them, and dates the two that are operated by neurons — finding that they are withdrawn not decades apart, as the literature implies, but together.

"Our results demonstrate that CD47–SIRPa signaling prevents excess microglial phagocytosis… and show that molecular brakes can be regulated by activity to protect specific inputs."

— Lehrman and colleagues, *Neuron*, 2018

The sentence is about the developing retina, and it contains the word this dissertation is built on. Synapse elimination in the healthy brain is not merely driven by an eat-me signal; it is held back by a stop signal. What follows asks how many such brakes there are on the microglion of the adult human brain, what retires each of them, and — for the two that are operated by neurons — how close together they fail.

THE MICROGLIAL SERIES THE BRAKING VOLUME

The Corruption of the Gardener (a graded atlas of the drivers of microglial dysfunction, ranked by causal weight)

The Gardener's Restraint (microglial resilience, and the uncoupling of amyloid from dementia)

The Silenced Eraser (the ungoverned microglion and the silencing of tau's phosphatase)

The Coerulean Pincer (the noradrenergic governor, and the two clocks of its failure)

The Unnetted Governor (the somatostatin interneuron: the cell without armour)

The Double Release ← this volume

The five preceding volumes describe what the microglion does once it has turned, and what turns it. None of them asks the question in the other direction: what was holding it, how many hands were on it, and when each let go. This volume asks it. It finds five classes of brake, distinguished not by molecule but by the kind of event that retires each; it names somatostatin as a microglial brake the corpus had not previously recognised; and it dates the two brakes that are operated by neurons — the coerulean and the somatostatinergic — against each other. The interval between their failures turns out to be shorter than the resolution of the instruments used to measure either, which is why no human specimen has ever exhibited the loss of one without the other.

Contents

Abstract

The microglion is not a cell that becomes dangerous when it is switched on. It is a cell that is dangerous by constitution and is held, continuously and at metabolic cost, in a state of restraint. Everything the corpus has previously described as microglial "activation" — the loss of the homeostatic signature, the disease-associated transition, the stripping of the perineuronal net, the silencing of tau's phosphatase, the elimination of the synapse — is better read as the successive lapse of a braking system. This dissertation inventories that system, grades each brake by the strength of the evidence that it exists and the strength of the evidence that it fails in Alzheimer's disease, and then answers a specific chronological question that the corpus has repeatedly raised and never settled: **how close in time is the failure of the noradrenergic brake operated by the locus coeruleus to the failure of the somatostatinergic brake operated by the cortical and hippocampal somatostatin interneuron?**

The inventory yields five classes, distinguished not by molecule but by *what kind of event retires each*. **Class I, the standing order**, is the constitutive instruction that manufactures microglial identity from outside — TGF-β read through SMAD, with IL-34 and CSF1R as the survival term — and it is a subscription, not a settlement, requiring continuous renewal (Butovsky and colleagues, 2014; Zöller and colleagues, 2018; Bohlen and colleagues, 2017). **Class II, the diffuse neuromodulatory brakes**, are volume-transmitted peptides and amines released by distant neurons onto receptors on the microglial surface: norepinephrine acting at the β2-adrenergic receptor, and somatostatin acting at sst2, sst3 and sst4. **Class III, the contact brakes**, are immobilised "self" ligands on the neuronal membrane — CD200, fractalkine, CD47, α2,6-linked sialic acid — read by CD200R, CX3CR1, SIRPα and the inhibitory Siglecs CD22 and CD33. **Class IV, the matrix brake**, is the perineuronal net, which restrains the microglion physically rather than chemically and which this corpus has treated at length. **Class V, the intrinsic ceiling**, is the cell's own transcriptional and phosphatase governor — MEF2C above all, lowered by the type-I interferon milieu of the ageing brain (Deczkowska and colleagues, 2017).

Within Class II the dissertation makes its principal new claim, and grades it carefully. Somatostatin is a microglial brake. Cultured rat microglia transcribe sst2, sst3 and sst4, and somatostatin and octreotide suppress both basal and cytokine-driven microglial proliferation (Feindt and colleagues, 1998). Somatostatin delivered before an inflammatory challenge in the intact rat substantia nigra suppresses microglial activation, reduces TNF-α, IL-1β and prostaglandin E2, lowers inducible nitric oxide synthase and cyclooxygenase-2 through the NF-κB pathway, and prevents the dopaminergic cell loss the challenge would otherwise cause (Bai and colleagues, 2015). Somatostatin raises insulin-degrading enzyme expression and secretion in microglia specifically, and not in astrocytes (Tundo and colleagues, 2012). A selective sst4 agonist increases microglial uptake of Aβ42 under non-inflammatory conditions while suppressing nitrite production and lowering cytosolic calcium under inflammatory ones (Schober

and colleagues, 2021), suppresses TNF-α and IL-6 and raises IL-10 in the same cells (Silwal and colleagues, 2022), and in the 3xTg-AD brain raises neprilysin 9.3-fold and insulin-degrading enzyme 14.8-fold while lowering the inhibitory Siglec CD33 by a quarter and raising the scavenger receptor MSR1 (Sandoval and colleagues, 2019). The brake is therefore double-acting in an unusual way: it damps the inflammatory arm while *releasing* the phagocytic one. It is the only brake in the inventory that does so.

The dissertation is equally explicit about where this brake is weak. A GPCR survey of adult human microglia identifies seventeen robustly transcribed receptors, and *ADRB2* is among them; no somatostatin receptor is reported (Hsiao and colleagues, 2021). The direct microglial evidence is rodent, largely cultured, and in the pharmacological studies the receptor dependence was never tested with an antagonist or a knockout. An indirect route — somatostatin acting on the neuron, and the microglion quieting because the neuron is healthier — is not excluded by any experiment yet performed. The brake is graded accordingly, and the discriminating experiment is named.

The chronological answer occupies the second half of the volume and turns on a methodological correction. A brake has not one datable event but three: **the lesion in the operating neuron**, **the failure of the brake itself**, and **the death of the operator**. The literature dates the first and the third and infers the second, and the three are separated, in the coerulean case, by decades. Dated by first lesion, the locus coeruleus leads by twenty-five to thirty years — pretangle tau in the third decade against a somatostatin cell that never accumulates tangles at all (Braak and Del Tredici, 2011; Ehrenberg and colleagues, 2017; Gabitto and colleagues, 2024). Dated by the death of the operator, the order may actually reverse: somatostatin interneuron loss falls in the early, preclinical phase of the human pseudo-progression, in donors with no cognitive deficit, whereas coerulean somatic loss does not begin until Braak III (Gabitto and colleagues, 2024; Theofilas and colleagues, 2017).

Dated by the event that matters — the moment the microglion stops being restrained — **the two brakes fail together.** The coerulean brake fails not when the locus coeruleus takes its first tau but when its output deranges and, independently, when the microglial receptor is withdrawn: β2-adrenergic receptor message is very low in plaque-associated microglia at every age tested and declines progressively with age in plaque-distal ones, and deleting it before plaque formation worsens amyloid burden and neuritic damage (Le and colleagues, 2025). The somatostatinergic brake fails when the peptide falls, which precedes the loss of the cell that makes it and is therefore earlier still than an already-preclinical event. Both windows fall in the same fifteen-year preclinical band — roughly the sixth and seventh decades in a case reaching dementia at seventy-five. The best estimate of the offset is **zero to ten years, with the coerulean brake probably but not certainly first, and a confidence interval that spans zero.** The correct model is a near-simultaneous double release, not a relay.

Three structural reasons are advanced for why the interval should be short — a common upstream driver in the ageing and early-amyloid milieu, a shared anatomical vulnerability, and a

direct causal arrow from the first failure to the second — and one consequence is drawn that the field has not drawn: because the two brakes fail within the resolution of the instruments used to measure either, **no human tissue has ever been examined during a period of single-brake failure.** Every released microglion yet described in an Alzheimer brain has lost both hands. That is why the two have never been distinguished, and it is the reason the settling experiment has never been done.

The volume closes on an asymmetry with a therapeutic edge. The coerulean brake fails at the *receptor*, while its ligand is present and at times elevated; the somatostatinergic brake fails at the *ligand*, while its receptor is presumably intact. Identical outcome, opposite pharmacology. One cannot restore the first by supplying more transmitter — the corpus has argued at length that more norepinephrine is itself an injury — but one can, in principle, restore the second by supplying an agonist, which is precisely what the selective sst4 compounds are. The prediction that follows is specific and has never been tested: **a β2-adrenergic agonist and an sst4 agonist given together should outperform either alone by more than the sum of their separate effects**, because they re-engage two hands that were released together and have been compensating for nothing ever since.

I. The Wrong Verb — Why Microglia Are Not Activated but Released

The verb the field uses is "activation," and the verb is wrong. It carries the picture of a quiescent cell that receives a signal and does something new — a switch thrown, a programme initiated, a resting state disturbed. Almost every element of that picture is false, and the falsity is not stylistic. It has directed forty years of therapeutic effort at the accelerator and away from the brake.

The microglion is not resting. The word "resting microglia," still in wide use, was retired by the two-photon studies that showed the cell to be the most motile object in the healthy brain, its processes extending and retracting continuously, surveying the entire parenchyma on a timescale of hours. A cell that never stops moving is not at rest. What it is, is *restrained*: doing a great deal, and prohibited from doing certain other things.

The microglion's dangerous capacities are constitutive, not induced. It does not acquire the machinery of phagocytosis, complement opsonisation, cytokine release and proteolysis when it becomes diseased; it possesses that machinery throughout, as a tissue macrophage of the myeloid lineage, and it is descended from a cell that used the machinery freely in the yolk sac. What the healthy brain does is not withhold the machinery but forbid its use. The prohibition is continuous, expensive, and enforced from outside.

Identity is imposed, and it must be renewed. The decisive demonstration is Butovsky's: the microglial homeostatic signature — P2RY12, TMEM119, SALL1, HEXB, OLFML3, the whole badge set — is not an intrinsic property of the lineage but a transcriptional programme installed and sustained by TGF-β signalling from the surrounding tissue, and microglia removed from the brain and placed in culture lose it within hours (Butovsky and colleagues, 2014). Silencing TGF-β signalling in microglia in vivo produces the same result (Zöller and colleagues, 2018). Defined-medium culture confirms the converse: supply TGF-β, cholesterol and IL-34, and the identity can be maintained outside the brain (Bohlen and colleagues, 2017). The microglial character is a subscription. Cancel the payment and the cell reverts — not to a resting state, but to a macrophage.

This changes what a disease mechanism has to explain. If activation were a switch, the question would be what throws it, and the answer would be a ligand: amyloid, tau, an alarmin, a pathogen-associated pattern. The corpus has taken that question seriously and answered it in the atlas of drivers, which found the provocations real but insufficient — proteinopathy provokes an already-ungoverned cell far more effectively than a governed one. If instead restraint is the default

and its lapse the event, the question becomes *which restraints are there, what retires each of them, and in what order do they go.* That is an inventory question and a chronology question, and it is what this dissertation attempts.

A note on why the distinction is not merely semantic. Consider the practical difference. If microglia are activated, the rational therapy is an antagonist — block the receptor, inhibit the kinase, neutralise the cytokine. The field has produced a great many such agents and none has altered the course of the disease. If microglia are released, the rational therapy is an agonist — restore the instruction, re-engage the brake, re-supply the withdrawn ligand. That is a different pharmacology with a different failure mode and a different clinical trial design, and it has barely been attempted. The whole of Section XXIII depends on the distinction.

The two questions this dissertation asks. First: what is the complete braking system, and how is it organised? The answer, in Section II, is that it has five classes, and that the classes are distinguished usefully not by molecule but by the *kind of event that removes them* — which is what determines when in the disease each goes. Second: of the two brakes operated by neurons — the coerulean and the somatostatinergic — how close in time do they fail? That is the question the reader brought, and it is answered, with error bars, in Section XVI.

II. A Taxonomy of Brakes — Five Classes, Distinguished by How Each Is Lost

An inventory organised by molecule is a list. An inventory organised by failure mode is an argument, because the failure mode determines the timing, and the timing determines whether an intervention can reach the brake before it is gone. The five classes below are therefore defined by what retires them.

Class	The brake	How it reaches the microglion	What retires it	Characteristic timing
I. The standing order	TGF-β/SMAD; IL-34–CSF1R; the cholesterol term	Constitutive, from the surrounding parenchyma	Failure of the source tissue; tangle-bearing neurons cannot signal	Gradual, cumulative, late-loading
II. The diffuse brakes	Norepinephrine → β2-AR; somatostatin → sst2/3/4; adenosine; acetylcholine	Volume transmission from a distant or local neuron	Loss of the operating neuron's *output* — not necessarily the neuron	Early; tracks the operator's function, not its survival
III. The contact brakes	CD200 → CD200R; CX3CL1 → CX3CR1; CD47 → SIRPα; α2,6-sialic acid → CD22/CD33	Immobilised ligand read at the membrane on physical apposition	Loss or withdrawal of the ligand from the neuronal surface; or receptor drift	Synapse-local and stepwise; follows the lesion
IV. The matrix brake	The perineuronal net (aggrecan, brevican, hyaluronan)	Steric and biochemical exclusion of the microglial process	Proteolysis of the lattice — MMP-9, ADAMTS aggrecanases	Regional; where the net was never present, absent from the start
V. The intrinsic ceiling	MEF2C; INPP5D/SHIP1; the negative regulators of NF-κB	Cell-autonomous, inside the microglion	The type-I interferon milieu of the ageing brain; genotype	Ageing; the earliest and most diffuse of all

The braking system, classified by failure mode. The rightmost column is the claim; the rest is inventory.

Four features of this table carry the rest of the argument.

First, the classes fail on different schedules, and only two of them fail early enough to matter therapeutically. Class V is the substrate — it declines with age in everyone, and it sets how far the other brakes have to slip before the cell is dangerous. Class I is cumulative and late-loading, because the tissue that issues the standing order has to be substantially sick before the order fails. Class III is synapse-local and follows the lesion rather than preceding it, because a synapse must already be in trouble before its ligands are withdrawn. Class IV, in the two populations that matter most to this dissertation, was never there. **Class II is the class that fails early in the disease and while the operator is still alive** — which is exactly the property one wants in a target.

Second, the classes are not redundant. It is tempting, and wrong, to read a five-class braking system as a five-fold safety margin. It is not, because they do not act at the same point. Class V sets the gain, Class I sets the identity, Class II sets the tone, Class III protects individual synapses, and Class IV excludes the process physically. A cell whose identity is intact but whose tone is gone does something different from a cell whose tone is intact but whose identity has lapsed. They are five different prohibitions, and losing any one of them permits something the others were not forbidding.

Third, the classes interact multiplicatively, which is why the disease looks like a threshold phenomenon. The atlas of microglial dysfunction observed that ageing and genotype dominate the causal ranking while the threshold-setters — the noradrenergic axis among them — rank moderate, and that the ranking is nonetheless misleading, because the threshold-setters are the earliest and the most reachable. The taxonomy explains why both statements are true. Class V lowers the ceiling for everyone; Class II determines whether a given brain reaches it in the eighth decade or not at all.

Fourth, and this is the observation the second half of the volume rests on, two of the brakes are operated by neurons that are themselves among the disease's earliest casualties. The noradrenergic brake is operated by the locus coeruleus. The somatostatinergic brake is operated by the somatostatin interneuron. These are the two cell populations this corpus has spent five volumes establishing as the earliest to fail, and they are the two that lack the Class IV brake themselves. The cells that hold the leash wear no collar. Section XII makes that observation properly.

III. Class I — The Standing Order

The first brake is not a brake on any particular behaviour. It is the instruction that constitutes the cell as the kind of thing that has brakes at all, and it is treated first because everything downstream presupposes it.

The instruction, and how it is read. Transforming growth factor β, present continuously in the healthy brain parenchyma, engages a receptor complex whose type-I subunit phosphorylates SMAD2 and SMAD3; the phosphorylated SMADs partner with SMAD4, enter the nucleus, and operate as transcription factors upon the microglial genome. The output is the homeostatic signature: P2RY12, TMEM119, SALL1, HEXB, OLFML3, GPR34, and the rest of the badge set by which a microglion is recognised as a microglion and not as a monocyte-derived macrophage (Butovsky and colleagues, 2014). Silencing the pathway in vivo impairs homeostasis directly (Zöller and colleagues, 2018), and the developmental and maintenance roles have been reviewed at length (Spittau and colleagues, 2020).

Identity as subscription. The feature that matters is that this is *tonic*. It is not a developmental instruction, given once and thereafter recorded in the cell. It is an instruction that must be re-issued continuously, and the cell reverts within hours of its withdrawal. That is an unusual arrangement in biology and it has an unusual consequence: the microglion's character is only as durable as the health of the tissue around it. A cortex whose neurons are sick is a cortex that issues its microglia a weaker order, and a weaker order is a less-braked cell, which damages more neurons. The loop is obvious once stated and it is the reason Class I is the most self-reinforcing of the five.

The survival term. Alongside TGF-β sit two further constitutive requirements. Colony-stimulating factor 1 receptor signalling, driven in the brain principally by IL-34 rather than CSF1, is required for microglial survival; and defined-medium culture establishes that TGF-β, cholesterol and IL-34 together suffice to maintain the identity outside the brain, which is the cleanest possible demonstration that the instruction is extrinsic (Bohlen and colleagues, 2017). A further and more distant input belongs in this class: the gut microbiota, whose depletion produces globally immature microglia with impaired responses (Erny and colleagues, 2015) — the finding on which the corpus's gut volume was built.

What retires it in Alzheimer's disease. Three lines converge, and none is decisive alone. The type-II TGF-β receptor is reduced in the Alzheimer brain and neuronal TGF-β signalling deficiency promotes neurodegeneration and amyloid pathology (Tesseur and colleagues, 2006). Neurofibrillary tangles appear to interfere with SMAD2/3 signalling in neurons directly,

sequestering the transducer (Chalmers and Love, 2007). And the sheer arithmetic of a cortex losing synapses and neurons reduces the number of sources issuing the order. The corpus's *Silenced Eraser* volume treated this failure as the upstream event of a relay ending at tau's phosphatase, and this dissertation does not repeat that argument; it records the standing order here as Class I and grades its failure as moderate rather than established, because no study has yet measured SMAD-dependent transcriptional output in microglia across the human Braak series.

Why Class I cannot be the answer to the timing question. The standing order fails slowly and diffusely, in proportion to how sick the surrounding tissue already is. It is therefore a late-loading brake, and — this is the important negative — it cannot explain a *regional* or *cell-type-specific* early lesion. Something that fails everywhere in proportion to damage cannot account for a microglion that turns in the entorhinal cortex while the occipital cortex is intact. For that one needs a brake with an address. Classes II, III and IV have addresses. Class I does not.

IV. Class II — The Coerulean Hand

The first of the two diffuse brakes is the one this corpus has treated most fully, and it is summarised here only so far as the comparison requires.

The anatomy of the brake. A single locus coeruleus contains on the order of fifty thousand neurons per side, and their axons reach essentially the whole forebrain — one such neuron has been estimated to accompany some twenty metres of cerebral capillary. Norepinephrine released from these terminals is not confined to synapses; it diffuses, and it reaches every cell in the neighbourhood, microglia included. Microglia express the β2-adrenergic receptor, and *ADRB2* is one of the seventeen GPCRs robustly transcribed by adult human microglia (Hsiao and colleagues, 2021). This is the single most anatomically extensive braking signal in the brain: one nucleus, tonically active in waking, addressing the entire microglial population at once.

What the brake does. Three functions, established separately. It suppresses the inflammatory programme: locus coeruleus lesion in an amyloid model increases microglial inflammatory gene expression, impairs microglial migration and phagocytosis of amyloid, and worsens the pathology, and norepinephrine supplementation reverses it (Heneka and colleagues, 2010). It suppresses process surveillance: in the awake mouse, noradrenergic tone acting at β2 receptors constrains microglial process motility, so that the microglion's housekeeping is dialled down in the waking state and released in sleep and under anaesthesia (Stowell and colleagues, 2019; Liu and colleagues, 2019). And, on the evidence now available, it constrains the disease-associated transition itself: β2 receptor message is markedly low in plaque-associated microglia at every age tested, and declines progressively with age in plaque-distal microglia; deleting the receptor from microglia before plaques form worsens amyloid burden and neuritic damage; and chronic β2 agonism attenuates both (Le and colleagues, 2025).

The paradox this corpus has already met. The two suppressive functions point in opposite directions, and the corpus's *Coerulean Pincer* volume was built on the resulting sign problem. Norepinephrine suppresses inflammation, so its loss should disinhibit the microglion; but norepinephrine also suppresses surveillance, so its *excess* should blind the microglion. Both happen, in sequence, because the coerulean trajectory is biphasic: a long phase of compensatory over-output by surviving neurons, evidenced by rising cerebrospinal-fluid norepinephrine with disease severity (Elrod and colleagues, 1997), raised tyrosine hydroxylase message and axonal sprouting (Szot and colleagues, 2006), and direct recording of increased spontaneous firing in a tauopathy model (Wang and colleagues, 2025); followed by frank depletion. The microglion is first blinded by too much signal and then disinhibited by too little.

The receptor-side lesion, which is newer and more important than it looks. The finding that plaque-associated microglia carry very low β2 receptor message at all ages tested (Le and colleagues, 2025) changes the shape of the coerulean brake's failure. It means the brake can be withdrawn at the microglial end while the coerulean end is still producing transmitter — indeed while it is producing *more* transmitter than normal. This is a receptor-side failure, and it is early, and it is spatially organised around the plaque. Section XIX makes it the pivot of the therapeutic argument, because a receptor that is not there cannot be agonised, and the fact that this receptor is already withdrawn from the microglia nearest the pathology is the strongest reason to doubt that noradrenergic augmentation alone can restore the brake.

A caution about model and species. The receptor-side result is from 5xFAD mice and from mouse microglial transcriptomics. The human evidence for the coerulean brake is inferential: the receptor is present on human microglia; the nucleus degenerates; microglial activation and coerulean loss worsen together in human tissue and in models (Heneka and colleagues, 2010; Cao and colleagues, 2021). No human study has measured microglial *ADRB2* across the Braak series. The ledger grades the brake as established and its human chronology as inferred.

V. Class II, Continued — The Somatostatinergic Hand

The second diffuse brake is the one the corpus has not previously named, and it requires a fuller presentation because the claim is newer and the evidence is thinner.

The receptors. Cultured rat microglia transcribe the messages for sst2, sst3 and sst4, and not those for sst1 and sst5 (Feindt and colleagues, 1998). The BV2 microglial line expresses sst4 (Schober and colleagues, 2021; Silwal and colleagues, 2022). Somatostatin receptors are inhibitory G-protein-coupled receptors of the Gi/Go family; their canonical proximal action is to lower adenylate cyclase activity and cyclic AMP, to open potassium conductances and to close voltage-gated calcium channels — a receptor family built, in every tissue where it has been characterised, to reduce the output of the cell that bears it. If a cell expresses them, they are a brake on that cell; this is not a contested inference.

The functional evidence, in ascending order of how much it establishes. *In culture*, somatostatin and octreotide inhibit both basal and GM-CSF- or IL-3-stimulated microglial proliferation (Feindt and colleagues, 1998). *In a microglial line and in primary microglia*, somatostatin raises the expression and secretion of insulin-degrading enzyme — and does so in microglia and not in astrocytes, which is a specificity control of exactly the right kind (Tundo and colleagues, 2012). *In an sst4-selective pharmacology*, the agonist NNC 26-9100 increases microglial uptake of FITC-tagged Aβ42 under non-inflammatory conditions, reduces lipopolysaccharide-stimulated nitrite production, and lowers cytosolic calcium (Schober and colleagues, 2021); the agonist SM-I-26 lowers TNF-α and IL-6 message and raises IL-10 and catalase in the same cells (Silwal and colleagues, 2022). *In the intact animal*, somatostatin given into the rat substantia nigra one hour before a lipopolysaccharide challenge dramatically reduces the number of activated microglia, reduces TNF-α, IL-1β and prostaglandin E2, lowers inducible nitric oxide synthase and cyclooxygenase-2 and reactive oxygen species through inhibition of the NF-κB pathway, and prevents the loss of tyrosine-hydroxylase-positive neurons that the challenge would otherwise cause (Bai and colleagues, 2015). *In an Alzheimer model*, intracerebroventricular NNC 26-9100 in the 3xTg-AD mouse raises cortical neprilysin 9.3-fold and insulin-degrading enzyme 14.8-fold at twenty-four hours, lowers CD33 by twenty-five per cent and raises the scavenger receptor MSR1 at six hours, and raises catalase 3.6-fold (Sandoval and colleagues, 2019).

The honest limits, stated before the argument is built on them. Four, and each is real.

1. **The human evidence is absent, and its absence is informative.** The most careful available survey of the GPCR repertoire of adult human microglia lists seventeen robustly transcribed receptors — CX3CR1, GPR34, GPR183, P2RY12, P2RY13, ADGRG1, ADORA3, ADRB2, CCR1, C3AR1, C5AR1 among them — and no somatostatin receptor appears in it (Hsiao and colleagues, 2021). This is not the same as a demonstration of absence, since the survey did not set out to test for them and low-abundance GPCRs are notoriously undercounted in single-cell data. But it is a genuine asymmetry with the coerulean brake, where the receptor *is* on the list, and it must be carried through every subsequent claim.

2. **The receptor dependence was not tested.** In neither sst4-agonist study was the effect challenged with a receptor antagonist or a knockout (Schober and colleagues, 2021; Silwal and colleagues, 2022). NNC 26-9100 and SM-I-26 are selective, but selectivity in a binding assay is not the same as receptor dependence in a cell.

3. **The in vivo Alzheimer study did not reproduce the anti-inflammatory effect.** Sandoval and colleagues explicitly report no change in pro-inflammatory cytokines in the 3xTg-AD brain, while finding large changes in the degrading enzymes and the phagocytic mediators. The clearance arm of the brake replicated in vivo; the inflammatory arm did not.

4. **An indirect route is not excluded.** Somatostatin acts on neurons — augmenting the M-current (Moore and colleagues, 1988), licensing neprilysin (Saito and colleagues, 2005; Nilsson and colleagues, 2026), binding the amyloid peptide itself and altering its oligomerisation (Wang and colleagues, 2017; Williams and colleagues, 2023). A microglion in tissue where somatostatin is present may be quieter *because the neurons around it are healthier*, with no microglial receptor involved at all. The Bai result is in vivo and therefore does not distinguish the routes; the Tundo and Schober results are in isolated microglia and therefore do.

The grading. Taken together: that somatostatin restrains microglia in rodent systems is established. That it does so through receptors on the microglion is well-supported for the isolated-cell results and not formally demonstrated. That it does so in the human brain is inference. Section XXII names the experiment.

VI. What the Somatostatin Brake Actually Does — Three Offices of One Peptide

The somatostatin brake is worth a section of its own because it is not one prohibition but three, and because the three are unusual in combination.

Office one: it damps the inflammatory arm. The route is the canonical one for an inhibitory G-protein-coupled receptor arriving upstream of NF-κB. Somatostatin pretreatment lowers TNF-α, IL-1β and prostaglandin E2, and lowers inducible nitric oxide synthase and cyclooxygenase-2, in intact tissue, with NF-κB named as the pathway (Bai and colleagues, 2015); the sst4 agonist reproduces the cytokine result in isolated microglia and adds IL-10 induction (Silwal and colleagues, 2022). Nitrite production falls (Schober and colleagues, 2021). This is a conventional brake and it does what conventional brakes do.

Office two: it releases the clearance arm. This is the unusual part. Every other brake in the inventory suppresses phagocytosis along with inflammation — that is the whole difficulty with the inhibitory Siglecs of Class III, and it is the reason CD22 blockade *improves* clearance in the ageing brain (Pluvinage and colleagues, 2019). The somatostatin brake does the opposite. The sst4 agonist increases microglial uptake of Aβ42 specifically under non-inflammatory conditions (Schober and colleagues, 2021); in the 3xTg-AD brain it lowers CD33 — the inhibitory Siglec that restrains microglial amyloid uptake — and raises the scavenger receptor MSR1 (Sandoval and colleagues, 2019). A brake that lowers an inhibitory receptor is a brake that hands the phagocytic function back while keeping the inflammatory one restrained. That is the therapeutic profile the field has wanted for two decades and has never obtained from an anti-inflammatory agent.

Office three: it licenses enzymatic degradation. Somatostatin raises insulin-degrading enzyme in microglia (Tundo and colleagues, 2012), and the sst4 agonist raises both neprilysin and insulin-degrading enzyme in cortex by an order of magnitude (Sandoval and colleagues, 2019). The neprilysin arm is the one the corpus already knew: somatostatin regulates brain Aβ42 through modulation of proteolytic degradation (Saito and colleagues, 2005), and the receptor dependence has since been resolved to sst1 and sst4 acting on neuronal neprilysin (Nilsson and colleagues, 2026). What the microglial literature adds is a second, parallel enzymatic route in a different cell. The peptide licenses disposal in both compartments.

Why the three offices matter jointly. A single peptide that damps inflammation, releases phagocytosis and licenses proteolysis is not a modulator of one process; it is the permission structure for disposal. Its withdrawal therefore does not produce a simple disinhibition. It produces the

specific combination that the Alzheimer brain actually displays: **a microglion that is inflamed and simultaneously bad at clearing.** That combination has always been slightly puzzling, because activation and phagocytosis usually travel together in myeloid biology, and it is exactly what the loss of this particular brake would predict.

A necessary caution about direction. The peptide's effect on the amyloid peptide itself is not only enzymatic. Somatostatin binds Aβ directly and favours the formation of distinct oligomers (Wang and colleagues, 2017), and slows plaque deposition in aged knock-in mice by blocking aggregation (Williams and colleagues, 2023). Whether the oligomers so favoured are less toxic than those formed without it is not settled, and this dissertation does not assume it. The clearance argument is made on the enzymatic and phagocytic evidence and does not require the aggregation result.

VII. Class III — The Contact Brakes

The diffuse brakes set the tone of the whole population. The contact brakes decide individual cases: this process, this synapse, now. They are immobilised ligands on the neuronal surface, read by inhibitory receptors on the microglial one, and the logic is the logic of an immune "self" signal.

CD200 and CD200R. The founding demonstration is Hoek's: mice lacking CD200 show a myeloid compartment in a constitutively more activated state, with microglia displaying an activated morphology and an accelerated response to injury (Hoek and colleagues, 2000). CD200 is expressed by neurons; CD200R by microglia; the interaction downregulates the myeloid lineage. The Alzheimer evidence is unusually direct for a contact brake: CD200 protein and message are significantly decreased in Alzheimer hippocampus and inferior temporal gyrus, and not in cerebellum, and CD200R message is decreased in the same two regions and not the third (Walker and colleagues, 2009). That regional pattern — affected regions yes, spared region no — is precisely what a lesion-following brake should show, and it is the reason Class III is placed after the lesion rather than before it.

CX3CL1 and CX3CR1. Fractalkine is a chemokine that is unusual in being membrane-tethered on the neuron, so that its signal is delivered by contact rather than by diffusion; CX3CR1 is one of the core homeostatic microglial receptors, and one of the badges lost in the disease-associated transition. Mice lacking the receptor show microglial neurotoxicity in three separate models of neurodegeneration (Cardona and colleagues, 2006). The brake's failure in Alzheimer's disease is therefore over-determined: the ligand is lost with the neuron and the receptor is shed with the homeostatic signature. It is worth noting the complication honestly — CX3CR1 deficiency reduces amyloid burden in some models while worsening tau pathology in others, so the brake is not uniformly protective, and the corpus's own reading is that this is another instance of the same context-dependence that afflicts TREM2.

CD47 and SIRPα. The cleanest demonstration that microglial pruning is held back by a molecular stop signal comes from development. CD47 is expressed by neurons, SIRPα by microglia; their expression tracks the peak of retinogeniculate pruning; and mice lacking either show increased microglial engulfment of retinogeniculate inputs and fewer synapses in the dorsal lateral geniculate nucleus (Lehrman and colleagues, 2018). The authors' own summary is the epigraph of this volume: molecular brakes can be regulated by activity to protect specific inputs. The direct Alzheimer evidence is thinner than for CD200, and this dissertation does not overstate it; what the developmental result establishes is the *architecture* — that synapse elimination in the healthy brain is limited by a stop signal and not only driven by an eat-me signal — and that architecture is what the

complement literature has largely omitted.

The sialic-acid Siglecs, and the brake that should be released. The neuronal glycocalyx carries α2,6-linked sialic acid, which is read as self by the inhibitory Siglecs. Two matter here. CD22 is upregulated on aged microglia, mediates the anti-phagocytic effect of α2,6-sialic acid, and its blockade promotes clearance of myelin debris, amyloid-β oligomers and α-synuclein fibrils in vivo, reprogramming microglia toward a homeostatic transcriptional state and improving cognition in aged mice (Pluvinage and colleagues, 2019). CD33 is an Alzheimer risk gene whose product inhibits microglial uptake of amyloid. These are brakes that grow *stronger* with age, not weaker — and they are the reason "restore the brakes" is not a slogan that can be applied uniformly. Section XXIII takes this up as the inventory's principal internal contradiction.

What retires the contact brakes, and why they are late. All four require the neuronal surface to be present and correctly decorated. A synapse that is already sick has already lost or altered its ligands; a neuron that is dead has none. The contact brakes therefore fail *downstream* of the lesion, and they are best read as the mechanism by which a lesion propagates locally rather than as a cause of the lesion. They are indispensable to the pathology and useless as an early target.

VIII. Class IV — The Matrix Brake

The fourth brake is the corpus's own, treated across three prior volumes, and it is included here for completeness and for one specific purpose that becomes central in Section XII.

The lattice. The perineuronal net is a condensed extracellular matrix of hyaluronan, lecticans — aggrecan and brevican chief among them — link proteins and tenascin-R, assembled around the soma and proximal dendrites of a defined subset of neurons. It is not a diffuse ground substance but a structure, with holes at synaptic contacts, and it does several things at once: it stabilises synapses, buffers cations, closes critical periods, and — the office relevant here — physically restricts access to the neuronal surface.

The brake, and the evidence for it. Neurons bearing aggrecan-based nets are protected against tau pathology in the subcortical regions of the Alzheimer brain (Morawski and colleagues, 2010), and resilience to Alzheimer's disease associates with alterations in perineuronal nets in human tissue (de Vries and colleagues, 2024). The microglial half of the relation is direct: microglia facilitate the loss of perineuronal nets in the Alzheimer brain, and depleting microglia preserves the nets (Crapser and colleagues, 2020). The relationship is therefore adversarial and reciprocal — the net excludes the microglion, and the microglion degrades the net — which makes it the only brake in the inventory that its target actively attacks.

How it fails. By proteolysis. The corpus's *Coerulean Shears* volume named the protease and the hand: matrix metalloproteinase-9, called up by norepinephrine acting at β-adrenergic receptors, degrading the lecticans and the heparan-sulfate proteoglycans of the same surface; the ADAMTS aggrecanases, several of which are encoded on chromosome 21, supply a parallel route that the Down syndrome volume treated. What is distinctive about Class IV is that its failure is not a withdrawal but a demolition, and that the demolisher is the cell the brake restrains.

The observation that matters for this volume. A brake that must be present in order to fail is a brake whose *absence* is a permanent, constitutional exposure. Parvalbumin-expressing interneurons wear dense nets. Somatostatin-expressing interneurons largely do not. The locus coeruleus does not. Those two facts, taken with the taxonomy, produce the observation of Section XII, and it is the structural heart of this dissertation: **the two neurons that operate the diffuse brakes on the microglion are themselves the two neurons that lack the matrix brake.** The system's two long-range governors are its two least-protected cells.

IX. Class V — The Intrinsic Ceiling

The last class is not imposed from outside at all. It is the microglion's own governor on the amplitude of its response, and it is the brake that fails in everybody.

MEF2C. The myocyte-specific enhancer factor 2C is a transcription factor that functions, in microglia, as an off-switch — conferring resistance to the inflammatory conditions that prevail in the aged brain. Deczkowska and colleagues established the chain: the aged brain milieu contains chronic type-I interferon; interferon-β overexpression in the adult wild-type central nervous system induces an ageing-like microglial transcriptional signature and impairs cognition; the interferon milieu downregulates microglial *Mef2C*; and mice lacking Mef2C in microglia mount an exaggerated response to immune challenge with adverse behavioural consequences (Deczkowska and colleagues, 2017). The finding has since been extended mechanistically, with MEF2C restraining microglial overactivation through inhibition of the kinase CDK2. *MEF2C* is, additionally, an Alzheimer's disease risk locus, which places the same molecule in the genetics and the ageing biology at once.

Why this is the ceiling and not merely another brake. MEF2C does not tell the microglion what to do; it determines how far the cell travels when something else tells it. That is the definition of a gain control, and it explains the epidemiology of the whole system. Age is the dominant risk factor for Alzheimer's disease, and the atlas of microglial dysfunction ranked it dominant among the drivers. What ageing does to this system, on the MEF2C evidence, is lower the ceiling — so that provocations which a young brain absorbs without incident, and brake failures which a young brain compensates, produce in an old brain a response that exceeds the tissue's tolerance.

INPP5D and the genotype term. The inositol polyphosphate-5-phosphatase encoded by *INPP5D*, whose product SHIP1 opposes phosphoinositide-3-kinase signalling downstream of the immunoreceptor tyrosine-based activation motifs that TREM2 and other receptors use, is an Alzheimer's disease risk gene expressed in microglia and induced in plaque-associated microglia. It belongs in Class V as a genotype-set element of the ceiling: a negative regulator of the activating pathway, whose variants shift where the ceiling sits before any disease process begins. The corpus's protective-genome volume treated the general form of this argument.

What retires the ceiling. Time, and the interferon milieu that accumulates with it. There is no acute event and no address. This is why Class V cannot explain regional specificity and why it nonetheless dominates any ranking by attributable risk: it is the reason the disease is a disease of the old, and it is the reason the other four brakes have to fail against a background that is already less

forgiving than it was.

A consequence for the timing question. Because Class V declines continuously from midlife in everyone, the *same* Class II failure has different consequences at different ages. A withdrawal of the somatostatinergic brake at fifty in a brain with a high ceiling may produce no observable microglial change; the identical withdrawal at seventy may produce a great deal. This is not a complication to be noted and set aside. It means the timing question of Section XVI cannot be answered by dating the brakes alone — the answer must be relative to a ceiling that is itself falling.

X. The Order of Failure — A Consolidated Ledger of Brakes

The inventory can now be set out in one place, with each brake graded on two axes that are usually conflated: how well established the brake is in health, and how well established its failure is in Alzheimer's disease. The two are not the same, and several brakes are strong on the first axis and weak on the second.

Brake	Established as a brake?	Failure in AD established?	What the failure looks like	Where in the disease
TGF-β/SMAD standing order	Yes — direct, definitional	Moderate — receptor loss, tangle interference, no human staging series	Loss of the homeostatic signature; reversion toward macrophage	Cumulative; late-loading
IL-34/CSF1R; cholesterol; microbiota	Yes	Weak in AD specifically	Impaired maturation; reduced survival	Background
Norepinephrine → β2-AR	Yes — lesion, rescue, receptor deletion	Strong in model; inferred in human	Receptor withdrawn early at the plaque; transmitter deranged then lost	Preclinical, biphasic
Somatostatin → sst2/3/4	Rodent yes; human not demonstrated	Ligand loss strong; microglial route inferred	Peptide withdrawn; clearance licence lapses with it	Preclinical
CD200 → CD200R	Yes	Yes — regionally specific human data	Both ligand and receptor down in affected regions only	Follows the lesion
CX3CL1 → CX3CR1	Yes	Yes — but direction context-dependent	Ligand lost with neuron; receptor shed with signature	Follows the lesion
CD47 → SIRPα	Yes — developmental	Weak in AD	Loss of the synaptic stop signal	Inferred, synapse-local

Brake	Established as a brake?	Failure in AD established?	What the failure looks like	Where in the disease
α2,6-sialic acid → CD22/CD33	Yes	Yes — but the brake *strengthens*	Over-braking of phagocytosis; clearance falls	Ageing; strengthens with age
Perineuronal net	Yes	Yes	Proteolytic demolition by the cell it restrains	Regional; absent from the start in the unnetted
MEF2C ceiling	Yes	Yes — via the interferon milieu	Gain control lowered; every other failure amplified	From midlife, in everyone

The braking system, graded. Note that two entries fail by strengthening rather than by lapsing.

Three readings of the table.

The first is that "restore the brakes" is not a coherent programme. Two entries — CD22 and CD33 — are brakes whose *increase* is part of the pathology, and the demonstrated intervention on both is blockade, not agonism (Pluvinage and colleagues, 2019). Any therapeutic slogan that treats microglial restraint as uniformly good is refuted by its own inventory. What the disease presents is not a uniform release but a *dissociation*: the inflammatory arm released, the clearance arm over-braked. The correct programme is therefore selective, and Section VI has already identified the one signal in the inventory that produces that selectivity on its own.

The second is that the brakes with addresses are the diffuse ones and the matrix one. Class I and Class V fail everywhere; Class III fails wherever the lesion already is. Only Class II and Class IV can explain why the entorhinal cortex turns while the occipital cortex does not — Class IV because the net's distribution is regional, Class II because the operating neurons project regionally. This is the structural reason the volume's second half is about Class II.

The third is that only two brakes fail while their operator is still alive and treatable. This is the criterion that matters for intervention and it eliminates most of the table. The standing order fails because the tissue is sick. The contact brakes fail because the synapse is sick. The matrix brake fails because it has been demolished. The ceiling fails because the patient is old. But the coerulean and somatostatinergic brakes fail *by loss of output from neurons that are still there* — the locus coeruleus loses no cells until Braak III, and the somatostatin cell's peptide falls before the cell does. In both cases there is an interval in which the brake is gone and the operator is alive. That interval is the therapeutic window, and locating it is the business of the rest of this dissertation.

XI. The Two Hands — Why the Coerulean and Somatostatinergic Brakes Are One Kind of Object

Before the two can be compared in time they must be shown to be comparable in kind, and the case is stronger than it first appears.

Both are volume-transmitted. Neither signal is confined to a synaptic cleft. Norepinephrine escapes the varicosity and diffuses through the neuropil; somatostatin is released from dense-core vesicles, characteristically at extrasynaptic sites and on sustained rather than single-spike activity, and diffuses likewise. A microglion has no synapse and cannot be addressed by a point-to-point signal. Volume transmission is the only modality by which a neuron can speak to a microglion at all, and these are the two neuronal populations that use it at scale in the cortical and hippocampal territory the disease attacks.

Both act through inhibitory G-protein-coupled receptors of the same broad family. β2 is a Gs-coupled receptor and the somatostatin receptors are Gi/Go-coupled, so the proximal second messengers differ in sign; but the functional consequence in the myeloid cell converges, because the microglial inflammatory programme is suppressed by cyclic-AMP elevation through protein kinase A and by the pathways the somatostatin receptors engage alike, and both terminate on NF-κB. The convergence has been demonstrated separately on each arm (Heneka and colleagues, 2010; Bai and colleagues, 2015) and never in the same preparation. That is a gap and it is named in the predictions.

Both are tonic, and both are activity-coupled. This is the property that makes them brakes rather than signals. The locus coeruleus fires tonically in waking at one to three hertz, so norepinephrine is continuously present and its level reports the arousal state. Somatostatin release is activity-dependent and is sustained rather than phasic, so peptide tone reports the recent activity of the local inhibitory network. In both cases the microglion is not being told to do something; it is being continuously told not to, and the instruction's strength tracks the state of the circuit. A brake whose force reports circuit activity is exactly what a tissue needs if its resident macrophage is to be permitted more licence when the circuit is quiet or damaged and less when it is working.

Both operate on the same two arms — inflammation and clearance — and in the same direction on the first. Norepinephrine suppresses inflammatory transcription and improves amyloid phagocytosis and migration (Heneka and colleagues, 2010). Somatostatin

suppresses inflammatory transcription and improves amyloid uptake and degradation (Bai and colleagues, 2015; Schober and colleagues, 2021; Sandoval and colleagues, 2019). The functional overlap is close to complete, and that overlap is itself the reason the two have never been separated in a human tissue study: they do the same job, so their joint absence looks like one lesion.

Where the two differ, and it is the difference that matters. The coerulean brake is delivered by a nucleus of some hundred thousand cells to the entire forebrain; the somatostatinergic brake is delivered by a distributed population of local interneurons to their own laminae. One is a global tone, the other a local one. This means that the coerulean brake's failure should be diffuse and near-simultaneous everywhere, while the somatostatinergic brake's failure should follow the disease's regional trajectory — entorhinal cortex, CA1, prefrontal cortex, in that order, as the corpus's somatostatin volume established. **The prediction that falls out of this is testable and, so far as this dissertation can determine, has never been tested: in early disease there should exist regions with the coerulean brake gone and the somatostatinergic brake intact, and these should be the regions the disease has not yet reached.** If so, the single-brake state — the state Section XVI argues has never been observed — should be findable, but only outside the affected zone.

XII. The Operators Wear No Armour

The two diffuse brakes are operated by two neuronal populations, and this section records what those two populations have in common. The observation is simple, and once made it is difficult to regard as coincidence.

The locus coeruleus has no perineuronal net. The nucleus is among the structures where net-bearing neurons are sparse or absent, and the corpus's *First Ember* and *Coerulean Shears* volumes built on that fact: the coerulean neuron has no lattice to stage the reelin signal that brakes its tau kinase, and no lattice to exclude the microglial process. It is constitutionally unarmoured, and it is the first neuron in the human brain to accumulate abnormal tau.

The somatostatin interneuron largely has no perineuronal net either. This is the point on which the corpus's *Unnetted Governor* volume turned, and it is the cleanest available contrast in cortical cell biology, because the somatostatin interneuron's sibling — the parvalbumin-expressing basket cell — is the canonical net-bearing neuron (Härtig and colleagues, 1992). Two inhibitory interneuron classes, born of the same medial ganglionic eminence, occupying the same cortical territory, differing in this: one wears the lattice and one does not. And in the human Alzheimer brain, the somatostatin cell is lost in the early, preclinical phase while the parvalbumin cell is lost in the late one (Gabitto and colleagues, 2024), and cell-count studies find somatostatin interneurons reduced in temporal cortex where parvalbumin cells are not (Waller and colleagues, 2020).

The observation. The two long-range chemical brakes on the microglion are operated by the two neuronal populations that lack the physical brake on the microglion. Stated as an aphorism: **the cells that hold the leash wear no collar.** Stated as a mechanism: the operators are exposed to the very cell they restrain, and the restraint is therefore self-undermining, because a microglion released even slightly attacks preferentially the neurons that were doing the restraining.

Why this is not merely rhetorical. It converts what would otherwise be two independent early lesions into a structural prediction about their *order and their coupling*. If the operators were armoured, the loss of one brake would be a discrete event with no particular consequence for the other. Because they are not, the loss of either brake accelerates the loss of the other, and the corpus has documented one direction of that arrow already: the somatostatin cell is stripped of its synapses from outside by microglia, and the microglion that strips it is the one the coerulean brake was restraining. This dissertation adds the return arrow — that the stripped somatostatin cell withdraws its own peptide brake from the same microglion — and Section XX treats the resulting loop.

A caution, and a distinction the corpus has drawn before. The net explains *exposure*; it does not dictate the assailant. The somatostatin volume made this point precisely: two cells, both unnetted, both early, injured by different agents — the coerulean neuron by its own tau, the somatostatin neuron by amyloid, microglia and excitatory load, since somatostatin cells are not known to accumulate tangles and their loss precedes tangle deposition in the same tissue (Gabitto and colleagues, 2024). The shared absence of armour explains why both are reachable. It does not explain why each fails, and it must not be asked to.

XIII. Dating a Brake — Three Events, Not One

The question "when does the brake fail?" has produced confused answers in this literature because it is three questions wearing one sentence. Any brake operated by a neuron has three separately datable events, and they can be decades apart.

Event one: the lesion in the operating neuron. The first moment at which the neuron that operates the brake is abnormal by any measure. For the locus coeruleus this is exquisitely well dated: pretangle tau appears in the third decade of life and is present in a substantial minority of coerulean neurons before any cortical tangle exists at all (Braak and Del Tredici, 2011; Ehrenberg and colleagues, 2017).

Event two: the failure of the brake. The moment the microglion stops receiving the restraint. This is the event that matters and it is the one nobody measures, because it requires a measurement in the *microglion* — receptor occupancy, or downstream signalling, or the transcriptional state that the brake maintains — rather than in the neuron. It has two sub-events which can occur in either order: **ligand-side failure**, when the neuron stops supplying the signal, and **receptor-side failure**, when the microglion stops reading it.

Event three: the death of the operator. The moment the neuron is lost and countable as lost. This is the event the classical neuropathology dated, because it is the event a stain can see.

The three are not interchangeable, and the error of substituting one for another is not small. In the coerulean case the corpus's chronology volume established that events one and three are separated by a quarter of a century — tau in the third decade, somatic loss beginning at Braak III — and that a fourth event, the removal of the axon, falls between them and is complete in a target field while every cell body is still present and countable (Theofilas and colleagues, 2017; Meyer and colleagues, 2025). A field that dates the coerulean contribution by event one concludes the locus coeruleus is a preclinical structure with a thirty-year lead. A field that dates it by event three concludes the locus coeruleus is a late structure that degenerates alongside the cortex. Both conclusions have been published. Both are answers to questions nobody asked.

Which event governs the microglion. Event two, and specifically its earlier sub-event. The corpus's *Coerulean Pincer* volume made this argument for norepinephrine and it generalises: the microglion is governed by *output*, not by the health of the neuron producing it, so a tau-bearing but tonically firing locus coeruleus keeps its microglia homeostatic for as long as the discipline holds.

The long latent decades of coerulean tau are not the microglion's concern. Equally, a somatostatin interneuron that has stopped releasing peptide has withdrawn its brake whether or not it is still alive and countable — and the somatostatin literature is unusually clear that peptide output falls before cells are lost (Davies and colleagues, 1980; Beal and colleagues, 1986; Sandoval and Witt, 2024).

The methodological consequence, stated plainly. Any comparison of two brakes must compare event two with event two. Comparing the coerulean event one with the somatostatinergic event three — which is what the available literature invites, because those are the two best-measured quantities — produces a spurious separation of two to three decades. Comparing like with like produces a very different answer, and Section XVI gives it.

XIV. The Coerulean Brake, Dated

Event one is the best-dated event in the natural history of Alzheimer's disease. Pretangle tau appears in locus coeruleus neurons in the second and third decades of life, before any cortical pathology exists (Braak and Del Tredici, 2011). By Braak stage 0 — brains with no cortical tangles whatsoever — 7.9% of coerulean neurons already bear hyperphosphorylated tau inclusions (Ehrenberg and colleagues, 2017). Neurofibrillary degeneration in the nucleus is documented across ageing, mild cognitive impairment and early disease (Grudzien and colleagues, 2007). This is a lesion of the third decade of life.

Event three is nearly as well dated, and it is far later. Unbiased stereology across the full staging series finds coerulean neuronal number essentially preserved through Braak stages 0–II and falling only from stage III, with roughly 30% of neurons already lost at amnestic mild cognitive impairment and a cumulative end-stage figure of 63–83% (Theofilas and colleagues, 2017; Zarow and colleagues, 2003; Kelly and colleagues, 2017). In calendar terms for a sporadic case reaching dementia in the eighth decade, event three begins around the seventh.

Event two must be placed between them, and there are four independent handholds.

The first is the axon. Noradrenergic fibre degeneration in a coerulean target field is pronounced at Braak stage I–II and does not further decline afterwards, while cell counts are normal (Meyer and colleagues, 2025). A target field that has lost its innervation is a field whose microglia have lost their tone, whatever the cell bodies are doing. This places a functional withdrawal of the brake, in at least some territories, around Braak I–II.

The second is the derangement of output. Cerebrospinal-fluid norepinephrine rises with disease severity (Elrod and colleagues, 1997); surviving neurons show raised tyrosine hydroxylase message and dendritic and axonal sprouting (Szot and colleagues, 2006); and coerulean neurons in a tauopathy model show increased spontaneous firing (Wang and colleagues, 2025). Excess is not the absence of a brake, but it is the beginning of the brake's failure, because sustained agonist exposure desensitises a β-adrenergic receptor, and because the surveillance-suppressing arm of the brake is engaged maximally at exactly the moment the inflammatory-suppressing arm is being habituated away.

The third, and the most direct, is the receptor. β2-adrenergic receptor message is very low in plaque-associated microglia at every age tested, and declines progressively with age in plaque-distal microglia; genetic deletion of microglial β2 before plaque formation significantly worsens amyloid burden and neuritic damage; chronic β2 agonism attenuates both (Le and colleagues, 2025). This is

a receptor-side failure of the brake, it is spatially organised around the earliest pathology, and it is early. If it transfers to the human brain — which is not established — then the coerulean brake begins to fail at the microglial end as soon as plaques begin to form, which in human calendar terms is roughly two decades before symptoms.

The fourth is the microglial phenotype itself. Microglial activation is detectable in human Alzheimer's disease at the prodromal and possibly the preclinical stage, and at that early stage is protective, patients bearing more of it declining more slowly (Hamelin and colleagues, 2016). An early microglial change is evidence that an early brake has slipped.

The dating, stated with its uncertainty. Event two for the coerulean brake falls in the window between the first appearance of amyloid plaques and the onset of amnestic mild cognitive impairment — Braak I to Braak III, roughly ages fifty-five to seventy in a case demented at seventy-five. Its earlier bound is set by the receptor-side result and is model-derived; its later bound is set by the human axonal and output data. **It is not the third decade.** The coerulean brake does not fail when the coerulean neuron first sickens; it fails some twenty-five years later, and the interval between them is the corpus's central chronological finding.

XV. The Somatostatinergic Brake, Dated

Event one is poorly dated and is not a tau lesion. Somatostatin interneurons are not known to accumulate neurofibrillary tangles, and their loss precedes tangle deposition in the same tissue (Gabitto and colleagues, 2024). Whatever injures the somatostatin cell first is therefore not its own tau, and the candidates the corpus assembled are amyloid acting on the cell directly, microglial elimination of its synapses, and the excitatory load its own dysfunction generates. None of these has an age of onset in the human brain. The honest statement is that event one for the somatostatin cell cannot be dated at present, except by the constraint that it cannot precede the first appearance of amyloid.

Event three is well dated and is early. This is the finding on which the whole comparison turns. Pseudoprogression analysis of the middle temporal gyrus across eighty-four donors resolves an early phase — slow accumulation of pathology, inflammatory microglia, reactive astrocytes, loss of somatostatin-positive inhibitory neurons — from a late phase of exponentially increasing pathology with loss of excitatory neurons and of parvalbumin and VIP interneurons; and the donors in the early phase have no cognitive deficits, which the authors read as a preclinical stage (Gabitto and colleagues, 2024). Cell-count work in temporal cortex confirms the selectivity: somatostatin interneurons reduced, parvalbumin cells not (Waller and colleagues, 2020). **The death of the operator is a preclinical event.**

Event two must therefore be earlier still. Peptide output falls before the cell is lost, and the evidence for the fall is the oldest in this entire literature: reduced somatostatin-like immunoreactivity in Alzheimer cortex (Davies and colleagues, 1980), widespread reduction across cortex with the temporal lobe worst (Beal and colleagues, 1986), and across the assembled modern literature a frontal reduction of the order of seventy per cent (Sandoval and Witt, 2024). Functionally, the cell is documented as dysfunctional before it is lost: its synaptic connectivity fails to remodel with learning, through reduced cholinergic drive (Schmid and colleagues, 2016); its somatic activity becomes abnormal, and specifically so near plaques (Algamal and colleagues, 2022). A cell that is not remodelling and is firing abnormally is a cell whose peptide tone has changed, and peptide release is activity-dependent and sustained-firing-dependent, so abnormal firing is a direct route to abnormal peptide tone.

The complications, recorded rather than smoothed. Three.

The regional gradient is unresolved. The frontal reduction is the largest reported and the temporal-worst gradient is what the classical immunoreactivity work and the cell-count work found (Beal and colleagues, 1986; Waller and colleagues, 2020; Sandoval and Witt, 2024). Different

cohorts, assays and stages; a peptide measure that cannot distinguish depletion from cell loss. The corpus's somatostatin volume noted this tension and did not resolve it, and neither does this one.

The cerebrospinal-fluid measure does not behave as a simple depletion marker. In a cohort of forty-three elderly participants with mild cognitive impairment, cerebrospinal-fluid somatostatin correlated *positively* with Aβ42 and remained independently associated with it in multivariate analysis, with no healthy control group for direct comparison (Duron and colleagues, 2018). A positive correlation with the biomarker that falls in Alzheimer's disease is consistent with somatostatin falling too, but the study cannot establish the level relative to normal, and this dissertation does not cite it as showing that somatostatin is reduced at the mild-cognitive-impairment stage. It is cited as showing that the peptide is already coupled to amyloid at that stage.

There is a negative study. At least one older report found the cortical somatostatinergic system unaffected in Alzheimer's and Parkinson's diseases. The weight of evidence is overwhelmingly on the other side, and the modern single-nucleus data are decisive on cell loss; but a literature in which every study agrees is a literature that has not been read carefully, and the disagreement is recorded here.

The dating, stated with its uncertainty. Event two for the somatostatinergic brake falls before event three, and event three is preclinical. In calendar terms for the same sporadic case reaching dementia at seventy-five, that places the peptide withdrawal in the preclinical band of roughly ages fifty-five to seventy, with the cell loss at its later end. The uncertainty is larger than for the coerulean brake, because the somatostatin literature has no equivalent of the coerulean staging series — nobody has counted somatostatin interneurons across the Braak stages the way Theofilas counted coerulean ones.

XVI. The Interval — How Close in Time?

This is the section the question demands, and it is set out in three parts: the table, the number, and the caveat that limits the number.

Datable event	Coerulean brake	Somatostatin brake	Offset	Basis
E1 — lesion in the operating neuron	Pretangle tau, 2nd–3rd decade; 7.9% of neurons at Braak 0	Not a tau lesion; loss precedes tangles in the same tissue; onset undated	**LC leads by 25–30 yr**	Braak & Del Tredici 2011; Ehrenberg 2017; Gabitto 2024
E2a — receptor-side brake failure	β2-AR message very low in plaque-associated microglia at all ages; falls with age in plaque-distal	Not measured; no human microglial sst receptor data exists	LC measurable, SST not	Le 2025; Hsiao 2021
E2b — ligand-side brake failure	Output deranged upward (CSF NE rises, sprouting, hyperexcitability); target-field fibre loss at Braak I–II	Peptide output falls before cell loss; cell loss is preclinical, so peptide loss is earlier	**0–10 yr, LC probably first; CI spans zero**	Meyer 2025; Elrod 1997; Szot 2006; Davies 1980; Beal 1986; Gabitto 2024
E3 — death of the operator	Somatic loss begins Braak III; ~30% gone at amnestic MCI	Loss falls in the early, preclinical pseudo-progression phase	**SST may lead**	Theofilas 2017; Gabitto 2024

The two brakes on four datable events. The row that answers the question is E2b; the rows above and below it are the two answers the literature gives by accident.

The number. Dated by the event that governs the microglion — the moment the restraint stops arriving — **the two brakes fail within the same fifteen-year preclinical window, and the best estimate of the offset between them is zero to ten years, with the coerulean brake probably though not certainly first.** In calendar terms for a sporadic case reaching dementia at seventy-five, both failures fall between roughly age fifty-five and age seventy. The correct description is a **near-simultaneous double release**, not a relay.

Why the answer is not the obvious one. The obvious answer, and the one the literature invites, is that the locus coeruleus leads by decades, because the coerulean tau lesion is famously the earliest event in the disease. That answer is true of E1 and irrelevant to the microglion. The locus coeruleus is a **slow fuse**: it is lit in the third decade and burns for twenty-five years before it reaches anything the microglion can feel. The somatostatin interneuron is a **fast fuse**: it is lit late — it cannot precede amyloid — and it burns quickly, from injury to peptide withdrawal to cell loss inside the preclinical phase. Lit decades apart, they reach the charge together. That coincidence is the finding.

The inversion at E3, which is worth stating separately. If one dates by the death of the operating neuron rather than by the failure of the brake, the order may reverse: somatostatin interneuron loss is placed in the early, preclinical phase of the human pseudo-progression, while coerulean somatic loss does not begin until Braak III and is only about thirty per cent complete at amnestic mild cognitive impairment. On the currently available human data it is entirely possible that **the somatostatin cell dies before the coerulean cell does**, notwithstanding that the coerulean cell sickened twenty-five years earlier. Three different orderings, all defensible, all answers to different questions — which is precisely why Section XIII insisted on separating the events before comparing them.

The caveat that limits the number, and it is a large one. No study has measured both brakes in the same brains. The coerulean chronology comes from stereology and tau immunohistochemistry in one set of cohorts; the somatostatin chronology from single-nucleus transcriptomics and peptide immunoassay in another; the receptor-side coerulean result from mice. The offset stated above is a synthesis across cohorts, species and instruments, and the measurement error on each component is plausibly of the same order as the offset itself. **The honest formulation is that the interval between the two brake failures is smaller than the resolution of the instruments used to measure either.** That is a real result and not merely a disclaimer — it is what licenses the phrase "double release" rather than "sequence" — but it must not be quoted as though the offset had been observed.

A consequence nobody appears to have drawn. If the two brakes fail within a decade of each other, and both fail in the preclinical phase, then **every microglion ever examined in an Alzheimer brain has lost both hands.** Human tissue arrives at the microscope after death, which in this disease means after a decade or more of dementia, which is fifteen to thirty years past both failures. There has never been a specimen of the single-brake state. The two brakes have not been distinguished in human tissue because they cannot be, on any specimen the field has ever held. This explains a methodological absence that would otherwise be puzzling, and it identifies exactly where the single-brake state must be sought instead: in a model, longitudinally; or in the living human brain, by imaging; or — per Section XI — in the regions the disease has not yet reached, where the global coerulean brake should already be gone and the local somatostatinergic one still

intact.

XVII. Three Reasons the Interval Is Short

A coincidence of this size in two processes with different mechanisms and different onset times should not be accepted as chance. Three structural reasons are advanced, in increasing order of how much they claim.

The first is a common upstream driver. Both brakes fail in a milieu of ageing plus early amyloid, and both are sensitive to it. The receptor-side coerulean failure is spatially organised around plaques — the lowest β2 message is in plaque-associated microglia (Le and colleagues, 2025). The somatostatin cell's dysfunction is likewise plaque-associated, with abnormal somatic activity specifically near plaques (Algamal and colleagues, 2022), and somatostatin is found in neuritic plaques (Morrison and colleagues, 1985). Meanwhile Class V is falling in both cases, since the interferon milieu that lowers MEF2C is systemic (Deczkowska and colleagues, 2017). Two brakes with a shared driver will fail at similar times for no other reason than that the driver arrives at both at once. This reason is the weakest of the three in explanatory content and the strongest in evidential support.

The second is a shared anatomical vulnerability. Both operating populations lack the perineuronal net (Section XII). Both have extensive, thin, energetically expensive axonal arbors relative to their somata. Both are peptidergic or aminergic cells whose signalling requires sustained firing and dense-core or varicose release, which is metabolically more demanding than fast synaptic transmission. Cells built alike fail alike, and cells that lack the same protection lose it at the same point. This reason explains why the two are both early without needing them to be causally linked at all.

The third, and the strongest claim, is a direct causal arrow with a return path. The coerulean brake's failure releases microglia. Released microglia strip synapses, and the somatostatin interneuron is a documented target of that stripping — the corpus's somatostatin volume devoted a section to the cell stripped from outside, and complement-dependent inhibitory synapse elimination by microglia is established in Alzheimer models (Dejanovic and colleagues, 2022). A somatostatin cell losing its synapses is a somatostatin cell firing abnormally, and a somatostatin cell firing abnormally withdraws its peptide. So the first brake's failure *causes* the second's, with a lag that is the lag of synaptic stripping — months in a mouse, plausibly a few years in a human, which is precisely the size of the offset estimated in Section XVI. And the return path closes the loop: the withdrawn somatostatin brake further releases the same microglion that is doing the stripping.

Which reason the dissertation prefers, and why it matters. All three are probably operating, and they are not exclusive. But they make different predictions, and the difference is testable. If the first reason dominates, the two failures are correlated but not causally linked, and preventing one will not prevent the other. If the third dominates, they are serially linked, and **arresting the coerulean failure should prevent or delay the somatostatinergic one** — which is a far stronger therapeutic claim and the one Section XXII proposes to test. The corpus's position, graded as inference, is that the third reason is real and partial: it explains the coupling but not the whole of the timing, because the somatostatin cell has injuries the coerulean brake's failure does not supply.

XVIII. The Case for the Opposite Order

The estimate of Section XVI put the coerulean brake first with a confidence interval spanning zero. This section states, as strongly as it can be stated, the case that the order is the other way round, because an argument that cannot state its own refutation has not been tested.

First: the somatostatin lesion is the earliest thing the best human instrument can resolve. The single-nucleus atlas of the Alzheimer brain does not merely find somatostatin interneuron loss early; it finds it in the *earliest resolvable phase*, alongside the first inflammatory microglia and the first reactive astrocytes, in donors with no cognitive deficit (Gabitto and colleagues, 2024). Nothing in that dataset is earlier. If one asks what the best-powered modern human study identifies as the first cellular event in the cortex, the answer includes the somatostatin cell, and does not include the locus coeruleus — which was not sampled.

Second: the coerulean brake requires a long and uncertain chain before it fails. For norepinephrine to stop restraining microglia, the coerulean neuron must first bear tau for twenty-five years, then lose excitability control, then derange its output, then desensitise the receptor, or else lose enough terminals to matter. Every link in that chain is supported and no link is certain, and the chain's total duration is the sum of five uncertainties. The somatostatinergic chain is shorter: injure the cell, and the peptide falls. A shorter chain with fewer links will generally complete sooner even if it starts later, and this dissertation has already conceded that the somatostatin cell's injury cannot be dated.

Third: the receptor-side coerulean evidence is mouse, and 5xFAD mice are not a chronology. The finding that plaque-associated microglia have very low β2 message is the single strongest reason to date the coerulean brake failure early, and it comes from an aggressive amyloid model in which plaques appear within months and the natural history is compressed beyond recognition (Le and colleagues, 2025). Reading a human decade off a 5xFAD month is not a permissible operation, and the dissertation has performed a version of it. If that result does not transfer, the coerulean brake's early bound moves substantially later, and the somatostatinergic brake fails first.

Fourth: the somatostatin brake has an amplification the coerulean one lacks. Somatostatin does not merely restrain the microglion; it licenses the enzymatic disposal of amyloid, in neurons through neprilysin (Saito and colleagues, 2005; Nilsson and colleagues, 2026) and in microglia through insulin-degrading enzyme (Tundo and colleagues, 2012). Its withdrawal therefore raises the local amyloid load, and the raised amyloid load is what withdraws the coerulean brake at the receptor, since the lowest β2 message is in plaque-associated microglia. On this reading the

arrow of Section XVII reverses: **the somatostatinergic failure causes the coerulean one**, by way of the plaque.

What this dissertation concludes. The fourth argument is the serious one, and it is not answerable on present evidence. The dissertation's position is therefore weaker than its section headings suggest and should be stated plainly: **the two brakes fail close together; which fails first is not established; and there is a defensible mechanism running in each direction.** What survives regardless of the ordering is the finding that matters — that they fail close enough together that no observed human specimen has ever separated them, and that any therapy addressing one alone is addressing half a lesion.

XIX. The Asymmetry of Failure — Receptor Versus Ligand

The two brakes fail at nearly the same time and by opposite mechanisms, and the opposition is the most therapeutically consequential fact in this volume.

The coerulean brake fails at the receptor, in the presence of its ligand. This is the shape of the evidence. Norepinephrine is not absent during the critical window; cerebrospinal-fluid norepinephrine *rises* with disease severity (Elrod and colleagues, 1997), surviving neurons upregulate tyrosine hydroxylase and sprout (Szot and colleagues, 2006), and coerulean neurons in tauopathy fire faster (Wang and colleagues, 2025). Meanwhile the microglial receptor is being withdrawn, earliest and most completely in the microglia nearest the pathology (Le and colleagues, 2025). A ligand that is present and rising, addressing a receptor that is disappearing: the brake fails despite the signal, not for want of it.

The somatostatinergic brake fails at the ligand, with its receptor presumably intact. Here the shape is inverted. The peptide falls — this is the single most consistently reproduced neurochemical finding in the entire Alzheimer literature, dating to 1980 — and the cell that makes it is lost. There is no evidence of somatostatin receptor downregulation on microglia, though it must be said at once that there is also no evidence of somatostatin receptors on human microglia at all, so the absence of evidence here is unusually thin. What can be said is that the microglial receptors, wherever they are demonstrated, remain pharmacologically responsive in the diseased brain: an sst4 agonist administered to a 3xTg-AD mouse produces large effects on exactly the microglial and enzymatic readouts the brake governs (Sandoval and colleagues, 2019). A receptor that answers a drug is a receptor that is there.

Why the asymmetry decides the therapy. A brake that has failed at the ligand can be re-engaged by supplying a ligand. A brake that has failed at the receptor cannot, and worse, the attempt may be actively harmful. The corpus has argued this at length on independent grounds: raising noradrenergic tone drives β-adrenergic matrix metalloproteinase-9 against the sulfated surface that stages reelin's brake on tau, and floors glycogen-synthase-kinase-3β from inside. More norepinephrine is not a restored brake; it is a second injury delivered to a receptor that is no longer listening. Whereas more somatostatinergic tone, delivered by a selective sst4 agonist, addresses a receptor that is present, has no endocrine liability at that subtype, and produces the one combination the disease actually needs — inflammation down, clearance up.

The three consequences, in order of confidence.

1. **Noradrenergic augmentation should be expected to fail as a monotherapy, and the reason is receptor-side.** This is consistent with what the clinical literature on noradrenergic agents in Alzheimer's disease has generally found, and it predicts that any success such agents have will be in early disease, before the receptor is withdrawn, and in the territories furthest from plaques.

2. **Somatostatinergic augmentation is the more tractable of the two brakes**, and its tractability is not a matter of the peptide being more important — it is not; the coerulean brake is anatomically larger and better evidenced — but of the failure mode being the recoverable one.

3. **The combination should be superadditive**, and this is the specific prediction Section XXII states. Two brakes released together, neither compensating for the other for a decade or more, should respond to joint restoration by more than the sum of the separate restorations — because the pathology that each alone must overcome is the pathology the other's absence has been generating.

XX. The Compounding — Why Two Brakes Failing Together Is Worse Than Twice One

A system with two brakes that fail independently is a system with a safety margin. A system with two brakes that fail together has none, and the difference is not arithmetic.

The first compounding is the loss of compensation. Each brake, alone, has a compensatory reserve. A microglion with the coerulean brake gone but the somatostatinergic brake intact is a partly restrained cell: its inflammatory transcription is still opposed, its clearance licence is still issued, and the peptide is still raising neprilysin and insulin-degrading enzyme in its neighbourhood. It is more dangerous than a fully braked cell and much less dangerous than an unbraked one. Because the two failures are near-simultaneous, that intermediate state is brief or absent, and the reserve is never drawn on.

The second compounding is the dissociation of the two arms. This is the more interesting one. Recall from Section X that the disease presents not a uniform release but a dissociation: the inflammatory arm released and the clearance arm over-braked, the latter by the age-strengthening inhibitory Siglecs. Now note which brake, uniquely, opposes both halves of that dissociation. The somatostatinergic brake damps inflammation *and* releases clearance — it is the one signal in the inventory that lowers CD33 (Sandoval and colleagues, 2019). Its withdrawal therefore does not merely remove a restraint; it removes the only counterweight to the Siglec over-braking that ageing installs. Losing this brake makes the microglion inflamed and simultaneously worse at clearing, which is exactly the phenotype, and no other single brake in the inventory would produce that combination on its own.

The third compounding is the feed-forward loop, and it has now been closed on both sides. The corpus previously established one arm: the released microglion strips the somatostatin cell's synapses from outside. This dissertation adds the other: the stripped somatostatin cell withdraws its peptide brake from the same microglion. Set them together and the loop is complete — release the microglion, and it removes the cell whose peptide was restraining it, which releases it further. The coerulean brake's failure is what starts the loop; but once started, the loop does not require the locus coeruleus, which is the standard property of a feed-forward mechanism and the standard reason that treating the initiator late does nothing.

The fourth compounding is that both brakes governed the same two arms. Norepinephrine and somatostatin both suppress inflammatory transcription and both improve amyloid handling (Section XI). Redundancy of function with simultaneity of failure is the worst possible combination: it means the system looked robust — two independent signals doing the same protective job — and was not, because the robustness was never tested by a single failure. A design that has two brakes on the same drum, operated by the two most fragile cells in the machine, is a design whose margin exists only on paper.

What this predicts about the shape of the decline. A system losing brakes serially declines in steps. A system losing two brakes together, against a ceiling that ageing has already lowered, crosses a threshold. The Alzheimer trajectory is famously not linear — a long silent phase, then an inflection, then a rapid course, which the pseudo-progression analysis resolved as an early slow phase and a late exponential one (Gabitto and colleagues, 2024). The double release is a candidate account of the inflection: it is the point at which the microglion's remaining restraints are Class I, Class III and Class V, none of which has an address and none of which can be strengthened by the tissue on demand.

XXI. The Validity Ledger

The claims of this dissertation are of unequal strength and are separated here. The tiers are the corpus's standard three.

Tier I — Established

The microglial homeostatic character is imposed and continuously renewed by TGF-β read through SMAD. Directly demonstrated by signature loss on removal from the brain, by in vivo silencing, and by reconstitution in defined medium (Butovsky and colleagues, 2014; Zöller and colleagues, 2018; Bohlen and colleagues, 2017).

Norepinephrine restrains the microglion at the β2-adrenergic receptor, and the restraint is lost in Alzheimer models. Lesion, rescue and receptor deletion have all been performed (Heneka and colleagues, 2010; Stowell and colleagues, 2019; Liu and colleagues, 2019; Le and colleagues, 2025). *ADRB2* is among the seventeen GPCRs robustly transcribed by adult human microglia (Hsiao and colleagues, 2021).

Somatostatin restrains microglia in rodent systems. Receptor message in cultured microglia; proliferation suppressed; in vivo suppression of microglial activation, cytokines, iNOS, COX-2 and ROS through NF-κB, with neuroprotection (Feindt and colleagues, 1998; Bai and colleagues, 2015).

CD200/CD200R and CX3CL1/CX3CR1 are microglial brakes, and both are reduced in the affected regions of the Alzheimer brain. (Hoek and colleagues, 2000; Cardona and colleagues, 2006; Walker and colleagues, 2009.)

Inhibitory Siglec signalling suppresses microglial phagocytosis and strengthens with age, and its blockade restores clearance. (Pluvinage and colleagues, 2019.)

The locus coeruleus bears tau from the third decade and loses neurons only from Braak III. (Braak and Del Tredici, 2011; Ehrenberg and colleagues, 2017; Theofilas and colleagues, 2017.)

Somatostatin interneuron loss falls in the early, preclinical phase of the human disease, before parvalbumin and VIP interneuron loss and before excitatory neuron loss. (Gabitto and colleagues, 2024; Waller and colleagues, 2020.)

Tier II — Well-supported inference

Somatostatin acts as a brake through receptors on the microglion itself, and not only indirectly through healthier neurons. Supported by two isolated-microglia results in which no neuron is present — the insulin-degrading-enzyme induction with astrocyte specificity control (Tundo and colleagues, 2012) and the sst4-agonist phagocytosis, nitrite and calcium results in BV2 cells (Schober and colleagues, 2021). Weakened by the absence of any antagonist or knockout control in the agonist studies and by the absence of human microglial receptor data.

The coerulean brake fails at the microglial receptor early and in a plaque-organised distribution. Directly measured in 5xFAD mice with a supporting deletion and agonist experiment (Le and colleagues, 2025). Transfer to the human natural history is inference, and 5xFAD chronology does not scale to human decades.

The somatostatinergic brake's ligand-side failure precedes the death of the somatostatin cell. Supported by the peptide literature (Davies and colleagues, 1980; Beal and colleagues, 1986; Sandoval and Witt, 2024) and by the documented functional dysfunction of the cell before its loss (Schmid and colleagues, 2016; Algamal and colleagues, 2022). Not measured directly as peptide tone across stages.

The two operating populations are both unnetted, and this shared exposure contributes to their shared earliness. Established for the individual facts (Härtig and colleagues, 1992; Morawski and colleagues, 2010; de Vries and colleagues, 2024; Crapser and colleagues, 2020); the causal contribution is inference.

The released microglion strips somatostatin interneuron synapses, closing a feed-forward loop with the peptide's withdrawal. The stripping arm is supported (Dejanovic and colleagues, 2022); the return arm is this dissertation's synthesis.

Tier III — Synthesis, and graded as such

The two brake failures fall within zero to ten years of each other, in the same preclinical window. This is the volume's central quantitative claim and it is a synthesis across cohorts, species and instruments that were never co-registered. The offset is smaller than the measurement error on either component. It should be quoted as a hypothesis with a stated interval, never as an observation.

The coerulean brake fails first. Preferred by this dissertation and not established. Section XVIII states a serious case for the reverse, resting on the somatostatin brake's amyloid-clearance licence and the plaque-organised distribution of the coerulean receptor loss.

No human specimen has ever exhibited the single-brake state. An inference from the timing plus the nature of post-mortem sampling, not an observation. It would be refuted by any

human dataset showing regionally dissociated brake failure — which Section XI argues should be sought outside the affected zone.

Joint restoration of the two brakes will be superadditive. A prediction with a mechanistic rationale and no data. It has, so far as this dissertation can determine, never been tested in any preparation.

Not established, and not required

A direct molecular interaction between the noradrenergic and somatostatinergic signalling pathways within the microglion. The argument requires only that both terminate on the same inflammatory transcriptional programme, which is separately supported for each. Convergence at NF-κB is plausible and unmeasured in the same preparation.

That somatostatin receptors are present on human microglia. Not demonstrated. Their absence from the most careful available human microglial GPCR survey (Hsiao and colleagues, 2021) is the single largest weakness in this volume and is named as such.

XXII. Predictions and Falsification

Each prediction below would, if it failed, damage a stated claim; the claim damaged is named.

On the existence of the somatostatinergic brake in humans. Single-nucleus or single-cell transcriptomics of human microglia, interrogated specifically for *SSTR1–5* with adequate depth for low-abundance G-protein-coupled receptors, will detect *SSTR2* and/or *SSTR4* above background in at least a subpopulation. *If no somatostatin receptor is detectable in human microglia at adequate depth, the direct microglial arm of the brake is refuted in humans and the argument reduces to the indirect route through the neuron — which would leave the timing analysis intact but change the therapeutic reading substantially.*

On receptor dependence. The anti-inflammatory and pro-phagocytic effects of NNC 26-9100 and SM-I-26 in microglia will be abolished by an sst4 antagonist and in *Sstr4*-null microglia. *If the effects survive receptor deletion, the compounds are acting off-target and the pharmacological arm of the evidence collapses.*

On the two clocks, co-registered. In a single longitudinal cohort or model, microglial homeostatic-signature loss will onset with the withdrawal of noradrenergic and somatostatinergic tone in close temporal proximity, rather than with the first coerulean tau. *If microglial ungoverning tracks coerulean tau rather than coerulean output, the whole event-two framework of Section XIII is wrong.*

On the order. In a model permitting both manipulations, arresting the coerulean brake's failure — by preventing β2 receptor loss, or by normalising coerulean output — will delay the somatostatinergic brake's failure. *If the somatostatinergic failure proceeds on an unchanged schedule, the causal arrow of Section XVII is refuted and the shared-driver account of the coincidence is left standing alone.*

On the single-brake state, and where to find it. In early human disease, regions not yet reached by the pathology will show evidence of coerulean brake withdrawal — reduced noradrenergic innervation, reduced microglial *ADRB2* — with somatostatin interneurons and peptide intact. *If no such regional dissociation exists at any stage, the claim that the brakes are anatomically distinct in their failure — global versus local — is wrong.*

On the dissociation. Microglia in tissue with somatostatin depletion will show elevated CD33 and reduced amyloid uptake relative to microglia in tissue with preserved somatostatin, at matched amyloid burden. *If CD33 is unrelated to somatostatinergic tone in tissue, the claim that this brake uniquely opposes the clearance dissociation is refuted.*

On superadditivity, which is the practical test. In an amyloid or tauopathy model, a β2-adrenergic agonist and an sst4 agonist given together will reduce plaque load, neuritic dystrophy

and microglial inflammatory transcription by more than the sum of their separate effects. *If the combination is merely additive, the double-release model still stands but its therapeutic corollary is downgraded to a convenience. If the combination is sub-additive, the two brakes are more redundant than this dissertation claims.*

On the ledger's internal contradiction. Combined sst4 agonism and CD22 blockade will outperform either alone on clearance. *If sst4 agonism and Siglec blockade are redundant, the claim that the somatostatinergic brake acts partly through CD33 is supported rather than refuted — the two predictions are deliberately opposed and the experiment distinguishes them.*

XXIII. Therapeutic Corollaries

The inventory generates a therapeutic logic that differs from the field's in three respects, and one internal contradiction that must be handled before any of it is usable.

The contradiction first: not all brakes should be restored. Two entries in the ledger of Section X are brakes whose failure mode is *strengthening*. The inhibitory Siglecs CD22 and CD33 over-brake phagocytosis in the ageing brain, and the demonstrated intervention is blockade, which restores clearance of myelin debris, amyloid oligomers and α-synuclein fibrils and reprograms microglia toward a homeostatic state (Pluvinage and colleagues, 2019). Any programme built on "restore microglial restraint" must therefore specify *which* restraint, and a non-selective one would make the clearance deficit worse. The disease is not a release; it is a **dissociation** — the inflammatory arm released, the clearance arm over-braked — and the therapeutic target is the dissociation, not the release.

The first corollary: the somatostatinergic brake is the one signal that addresses the dissociation directly. It is the only entry in the inventory that damps inflammation and *releases* clearance at once — lowering CD33 and raising MSR1 while raising neprilysin and insulin-degrading enzyme by an order of magnitude, and reducing nitrite and TNF-α and IL-6 while raising IL-10 (Sandoval and colleagues, 2019; Schober and colleagues, 2021; Silwal and colleagues, 2022). This is not a claim that it is the most important brake — it is not; the coerulean brake is anatomically larger and far better evidenced — but a claim that it is the best-shaped one. And the sst4 subtype is the right handle for a further reason the pain literature established long before the Alzheimer field took an interest: sst4 mediates anti-inflammatory and analgesic effects without the endocrine actions that make somatostatin analogues difficult, and selective agonists of nanomolar affinity and several-hundred-fold subtype selectivity exist.

The second corollary: the coerulean brake should not be approached by supplying more transmitter. This follows from Section XIX and from the corpus's prior volumes. The failure is receptor-side and the ligand is already elevated; raising it further recruits the matrix-degrading arm of β-adrenergic signalling and the intracellular kinase arm, both of which are injuries. The rational coerulean intervention is not augmentation but *stabilisation* — quieting the deranged output, preserving the receptor, and doing so in the excess phase rather than the depleted one. The corpus's *Coerulean Pincer* volume dated that window; this volume adds the receptor as its object.

The third corollary, and the one that is genuinely new: the two should be given together. If the brakes failed together and neither has been compensating for the other since, then

restoring one leaves the microglion with the other still absent and a decade of accumulated pathology from both. The prediction of superadditivity is stated in Section XXII and the experiment is inexpensive: a β2 agonist and an sst4 agonist, alone and in combination, in a model, against plaque load, neuritic dystrophy and microglial transcriptional state. So far as this dissertation can determine, the two literatures have never cited one another, and the combination has never been given.

On timing, which governs everything above. All of it is preclinical. Both brakes fail in the sixth and seventh decades in a case reaching dementia at seventy-five; the microglion has been released for fifteen to twenty years by the time a patient presents. The corollaries above are prevention or very-early-intervention corollaries, and to state them as treatments for established dementia would be to repeat the error that has consumed the amyloid programme. What they require is a way to detect brake failure in the living brain — which, for the coerulean arm, neuromelanin-sensitive imaging of locus coeruleus integrity now partly provides, and for the somatostatinergic arm, does not yet exist. A cerebrospinal-fluid or imaging measure of somatostatinergic tone is the enabling technology this whole argument waits on.

What this does not claim. It does not claim that restoring the brakes would arrest Alzheimer's disease. The braking system is one of the levels at which this disease operates and the corpus has described several others. What the argument supports is narrower and firmer: that the microglial contribution to the disease is a release rather than an activation, that the release is double and preclinical, and that one half of it is pharmacologically re-engageable while the other is not.

XXIV. Coda — The Released Hand

There is a picture of Alzheimer's disease in which the microglion is the villain — a cell that turns, that becomes inflamed, that begins eating what it should have protected. The picture is not wrong about what the cell does. It is wrong about the grammar. The microglion does not turn. It is let go.

Two hands were on it. One belonged to a nucleus the size of a grain of rice in the floor of the fourth ventricle, whose axons reach every cortical territory and whose transmitter, released tonically through the waking day, tells every microglion in the forebrain to stay quiet and keep still. The other belonged to a scattered population of small inhibitory cells in the cortex and the hippocampus, whose peptide, released where they work, tells the microglia around them to stay quiet and keep clearing. Neither hand is armoured. Neither cell wears the lattice that protects its neighbours from the very cell it is restraining. They are the least protected cells in the system and they are the ones holding it.

The first hand is lit early — in the third decade, in a person who will not be diagnosed for fifty years — and it burns slowly, so slowly that for twenty-five years the nucleus is sick and the grip does not loosen. The second is lit late and burns fast. And so, having started decades apart, the two hands open at nearly the same moment, somewhere in the sixth or seventh decade, in a person with no symptoms and no diagnosis and nothing to be measured except by an instrument nobody has yet built.

What follows is not an activation. It is fifteen years of an unrestrained macrophage in a tissue that cannot replace what it removes, and by the time the tissue's distress is visible as forgetting, both hands have been off for a decade and a half and everything the cell has done in that interval has become the disease.

The corpus has spent many volumes on the mechanisms downstream of that release — the protease, the kinase, the inflammasome, the silenced phosphatase, the stripped net. This volume is about the hands. Its finding is that there are two of them, that they open together, that they open long before anyone is watching, and that one of the two can still be closed by a drug — because it failed for want of a signal rather than for want of a receiver.

A Note on Provenance and Verification

The claims in this volume that are new to the corpus — the somatostatin–microglia literature in its entirety, the microglial β2-adrenergic receptor result, the contact-brake set, and the MEF2C ceiling

— were located and verified against primary sources during the preparation of this document, and citation details including journal, volume, pages and identifiers were checked against the publisher or PubMed Central record rather than reconstructed. Two corrections to the framing that prompted this volume arose from that check and are recorded rather than absorbed silently: the receptor subtypes transcribed by cultured microglia are sst2, sst3 and sst4, not sst2 and sst4 (Feindt and colleagues, 1998); and the receptor subtypes governing neuronal neprilysin are sst1 and sst4, not sst2 and sst4 (Nilsson and colleagues, 2026).

Claims imported from prior volumes of this corpus — the coerulean chronology, the somatostatin interneuron's trajectory, the perineuronal-net axis, the TGF-β standing order — carry citations verified in the preparation of those volumes and are reproduced here in the form in which they were verified there.

Two limitations of the present session are recorded for the reader's benefit. The PubMed connector was not available, so verification proceeded through publisher and PubMed Central records retrieved directly; where a preprint and a journal version both exist, the journal version is cited. And no claim in this volume rests on a source that was not opened during its preparation, with the single exception of the negative report on the cortical somatostatinergic system noted in Section XV, which is cited from its title and abstract listing alone and is flagged there.

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