The Hands That Let Go

The brakes that hold microglia in check: what makes a microglion different from a macrophage, and which restraints fail in Alzheimer's disease

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The second of the short papers on the model's three stacked phases. The brain's immune cell is not switched on by disease; it is let go. This paper inventories the eight restraints that hold it, asks what retires each one, and follows the order in which they fail.

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Abstract

The first paper in this series described the base of the stack: the brainstem and basal forebrain neurons whose supplies begin to fade in the third decade of life. Two of those supplies, noradrenaline and acetylcholine, do not act on other neurons alone. They act on the brain's immune cell, the microglion, and they hold it in check. This paper is about what happens when that holding fails.

The field's usual verb is wrong. Microglia are not *activated*, as though a switch were thrown on a cell at rest. They are *released*. The microglion possesses the full destructive equipment of a tissue macrophage — phagocytosis, protease release, complement tagging, cytokine production — at all times, and it is prevented from using that equipment by a braking system that must be renewed continuously and at metabolic cost. What makes a microglion different from an ordinary macrophage is not its machinery. It is the restraint.

This paper inventories that braking system. Nine brakes are described, grouped by what retires each one:

- **The standing order.** A continuous instruction from the surrounding tissue, carried by TGF-β, that manufactures microglial identity itself. Remove it and the cell reverts to a macrophage within hours.
- **The two diffuse brakes.** Noradrenaline from the locus coeruleus and somatostatin from cortical interneurons, both withdrawn in the first step of the stack.
- **The four contact brakes.** Signals held on the neuronal surface and read on touch: CD200, **fractalkine (CX3CL1, read by the microglial receptor CX3CR1)**, CD47 and the sugar coat read by the inhibitory Siglecs. The fractalkine brake is the one this paper gives its own treatment, because it fails twice over — the neuron that displays the ligand is sick, and the receptor is among the first badges the microglion sheds.
- **The matrix brake.** The protective lattice around certain neurons, which keeps the microglion physically away from the cell surface.
- **The ceiling.** The microglion's own gain control, lowered by ageing.

Three conclusions follow. First, the brakes fail in a particular order, and the order explains the shape of the second step: the diffuse brakes go early, with their operating neurons; the contact brakes follow the lesion rather than causing it; and the ceiling falls in everyone with age, which is why this is a disease of the old. Second, one brake grows *stronger* with age rather than weaker, which means "restore the brakes" cannot be applied uniformly. Third, the two neurons that operate the diffuse brakes are the two that lack the matrix brake themselves — the system's long-range governors are among its least protected cells.

A section on amyloid runs beside the inventory. The first step has already been retarding amyloid for thirty years by three separate routes — serotonin brakes its production, somatostatin licenses its disposal, noradrenaline enables both its cellular clearance and its nightly drainage — so the deposit that names the disease is what accumulates when those brakes have gone and the microglion then stops clearing. The paper closes with the step's exit: a released microglion assembles its inflammasome, which suppresses clearance, seeds more amyloid, and licenses the enzymes that digest the protective lattice. That is the transition into the third step and the subject of the next paper.

How to read this paper

This is the second of the short papers on the model's three stacked steps. It follows *What the Brainstem Stops Sending* and assumes its conclusions, which are summarised in Section 1 for a reader starting here. Each section below condenses a longer volume in the corpus; those volumes carry the full argument and their own ledgers.

The grades are the corpus's four. **Established** means replicated in human material by more than one group. **Probable** means good evidence with a gap — a single cohort, or an animal result not yet confirmed in people. **Inference** means a conclusion drawn here, or in the corpus, from evidence gathered for another purpose. **Speculative** means coherent and untested.

One caution governs the whole paper. Most of what is known about microglial brakes comes from mice, and mouse microglia are not human microglia. Where a brake rests only on rodent work, the text says so, and the ledger in Section 11 grades it accordingly.

1. Where the First Paper Left Off

The first paper described five populations of neurons at the base of the stack and asked what each supplies. Four of its findings carry into this one.

Function goes before the cell. The locus coeruleus accumulates abnormal tau from the second and third decades of life, loses its axons across the following decades, and does not lose neurons in number until the disease is half over (Braak and Del Tredici, 2011; Theofilas and colleagues, 2017; Meyer and colleagues, 2025). The nucleus basalis stops displaying its growth-factor receptor long before it stops making acetylcholine, and stops making acetylcholine long before it dies (Mufson and colleagues, 2000; Gilmor and colleagues, 1999). A brake operated by such a neuron therefore fails when the neuron's *output* fails, which is decades before the neuron's death.

The step does not end. Phase I keeps worsening underneath Phase II and Phase III. The brainstem is still failing in the eighth decade.

Two of the withdrawn supplies are brakes on this cell. Noradrenaline holds microglia at rest (Heneka and colleagues, 2010). So, on the evidence assembled in the corpus, does somatostatin. Both fall in the first step.

The first step loosens, it does not trigger. Nothing in the first paper claims that the brainstem *causes* the microglial turn. It removes restraints. What follows is the subject of this paper.

The model's name for the second step is the **Microglial Bridgehead**, placed in the sixth and seventh decades and centred on the hippocampus. The name is apt in one way and misleading in another. It is apt because this is where the disease establishes itself in the structures that make memory. It is misleading if it suggests an invasion. Nothing invades. A cell that was always present, and always capable of this, stops being held back.

2. The Cell, and Why It Is Not a Macrophage

Every tissue in the body has resident macrophages: cells of the myeloid lineage that eat debris, digest it, call for help and clear up afterwards. The microglion is the brain's. It arrives early — microglia derive from primitive macrophages of the yolk sac, not from blood monocytes (Ginhoux and colleagues, 2010) — and thereafter it is largely self-renewing and very long-lived.

What distinguishes it is not what it can do. It is what it is forbidden to do, and the forbidding is extrinsic.

The microglion is not resting. The phrase "resting microglia" survives in textbooks and should not. In the healthy brain the cell is the most motile object there is, its fine processes extending and retracting continuously, surveying the whole of the tissue on a timescale of hours. A cell that never stops moving is not at rest. It is restrained: doing a great deal, and prohibited from certain other things.

Its identity is a subscription, not a settlement. The decisive experiment is Butovsky's. The molecular badge set by which a microglion is recognised — P2RY12, TMEM119, SALL1, HEXB, OLFML3, CX3CR1 and the rest — is not an intrinsic property of the lineage. It is a transcriptional programme installed and maintained from outside by TGF-β signalling, and microglia removed from the brain and put in culture lose it within hours (Butovsky and colleagues, 2014). Silencing the pathway in the living animal does the same (Zöller and colleagues, 2018). Conversely, supply TGF-β, cholesterol and IL-34 in a defined medium and the identity can be held outside the brain (Bohlen and colleagues, 2017). **Established.**

That is an unusual arrangement, and it has a consequence the rest of this paper depends on. The microglion's character is only as durable as the health of the tissue around it. A cortex whose neurons are sick issues its microglia a weaker order, and a less-braked microglion damages more neurons. The loop closes on itself.

What a disease mechanism now has to explain. If activation were a switch, the question would be what throws it, and the candidates would be amyloid, tau or an infection. The corpus has taken that question seriously and found the provocations real but insufficient: proteinopathy provokes an ungoverned cell far more effectively than a governed one (*The Corruption of the Gardener*). If restraint is instead the default and its lapse the event, the questions become which restraints exist, what retires each, and in what order they go. That is an inventory, and Sections 3 to 9 are it.

The practical difference is not semantic. If microglia are activated, the rational drug is an antagonist: block the receptor, inhibit the kinase, neutralise the cytokine. The field has produced many such agents and none has altered the course of the disease. If microglia are released, the rational drug is an agonist: restore the instruction, re-engage the brake. That is a different pharmacology, and it has barely been tried. **Inference**, and the corpus's own argument (*The Double Release*).

3. The Standing Order

The first brake is not a brake on any particular behaviour. It is the instruction that makes the cell the kind of thing that has brakes at all.

What it is. Transforming growth factor β is present continuously in healthy brain tissue. It engages a receptor on the microglion whose inner part phosphorylates the proteins SMAD2 and SMAD3; these enter the nucleus and switch on the homeostatic badge set (Butovsky and colleagues, 2014; reviewed by Spittau and colleagues, 2020). The signal comes from the surrounding neurons and astrocytes. It must be re-issued continuously.

How it fails 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 impairing neuronal TGF-β signalling promotes both neurodegeneration and amyloid pathology (Tesseur and colleagues, 2006). Neurofibrillary tangles appear to interfere with SMAD2/3 signalling inside neurons, sequestering the transducer (Chalmers and Love, 2007). And a cortex losing synapses and neurons simply has fewer sources issuing the order. **Probable.** No study has yet measured SMAD-driven transcription in microglia across the human

Braak series, which is the measurement this brake most needs.

Why it cannot be the whole answer. The standing order fails slowly and everywhere, in proportion to how sick the tissue already is. It cannot explain why a microglion turns in the entorhinal cortex while the occipital cortex is intact. For that you need a brake with an address, and the next six have one.

4. The Two Diffuse Brakes

These are the brakes the first paper's neurons operate. They reach the microglion by diffusion from a distant cell, so they govern tone across a whole territory rather than deciding individual cases.

Noradrenaline, from the locus coeruleus

The anatomy makes this the most extensive braking signal in the brain. One nucleus of a few tens of thousands of neurons, tonically active through the waking day, addresses the entire microglial population at once. Microglia carry the β2-adrenergic receptor, and it is among the seventeen rhodopsin- and adhesion-family receptors found to be reliably transcribed by human microglia (Hsiao and colleagues, 2021). **Established.**

What it does. Three functions, each established separately. It suppresses the inflammatory programme: lesioning the locus coeruleus in an amyloid-bearing mouse raises microglial inflammatory gene expression, impairs the migration and phagocytosis of amyloid, and worsens the pathology, while supplying the missing transmitter reverses it (Heneka and colleagues, 2010). It constrains surveillance: in the awake mouse, noradrenaline acting at the β2 receptor dials down microglial process motility, which is released again in sleep (Stowell and colleagues, 2019; Liu and colleagues, 2019). And it constrains the disease-associated transition itself: β2 receptor message is very low in microglia near plaques at every age tested and falls with age in those further away; deleting the receptor from microglia before plaques form worsens amyloid burden and neuritic damage (Le and colleagues, 2025). **Probable**, in models.

The complication, and it matters for therapy. The brake can be withdrawn at the microglial end while the brainstem end is still producing

transmitter — indeed while it is producing more than normal, since surviving coerulean neurons compensate before they fail. A receptor that is no longer there cannot be agonised. This is the strongest reason to doubt that simply raising noradrenaline would restore the brake (*The Double Release*). **Inference.**

Somatostatin, from cortical and hippocampal interneurons

The first paper introduced the somatostatin interneuron as the neighbour that fails early, and described its licence over neprilysin, the enzyme that clears amyloid. The corpus makes a further claim: the same peptide is a microglial brake.

The evidence. Cultured microglia transcribe somatostatin receptors, and somatostatin suppresses their proliferation (Feindt and colleagues, 1998). Somatostatin given before an inflammatory challenge in the intact rat brain suppresses microglial activation, lowers inflammatory mediators, and prevents the neuronal loss the challenge would otherwise cause (Bai and colleagues, 2015). A selective agonist at the fourth somatostatin receptor increases microglial uptake of amyloid-β while suppressing inflammatory output (Schober and colleagues, 2021), and in a mouse model raises neprilysin 9.3-fold and insulin-degrading enzyme 14.8-fold (Sandoval and colleagues, 2019). This brake is unusual in damping the inflammatory arm while *releasing* the clearing arm. **Probable**, in rodents.

Where it is weak, stated plainly. The same survey lists seventeen such receptors in human microglia and no somatostatin receptor among them (Hsiao and colleagues, 2021). That is not a demonstration of absence — the survey did not set out to test for them, and scarce receptors are easily missed — but it is a real asymmetry with the noradrenergic brake, whose receptor *is* on the list. An indirect route, in which somatostatin acts on the neuron and the microglion quiets because its neighbour is healthier, has not been excluded by any experiment yet performed. **The corpus grades its own claim here as the weakest in the inventory, and so does this paper.**

How close in time do the two fail?

The Double Release puts the question carefully and answers it with error bars. Dated by first lesion, the locus coeruleus leads by twenty-five to thirty years. Dated by the death of the operating neuron, the order may reverse, because somatostatin interneurons are lost in the early preclinical phase while coerulean neurons are not lost until Braak III (Gabitto and colleagues, 2024; Theofilas and colleagues, 2017). Dated by the event that actually matters — the moment the microglion stops being restrained — the two fall within the same fifteen-year preclinical band, and the best estimate of the offset is zero to ten years with a confidence interval spanning zero. The correct picture is a near-simultaneous double release rather than a relay. **Inference**, and the volume's central claim.

One consequence deserves stating. Because the two fail within the resolution of any instrument 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.

5. The Contact Brakes, and the One That Was Missed

The diffuse brakes set the tone of a whole territory. The contact brakes decide individual cases: this process, this synapse, now. Each is a molecule held on the neuronal surface and read by a receptor on the microglial one. The logic is the immune system's logic of a "self" signal: *do not eat me, I am one of yours*.

Fractalkine and CX3CR1

This is the brake Jim Ray raised, and the corpus mentions it in a dozen places without ever giving it a section of its own. It deserves one, for three reasons.

It is unusual in its physics. Fractalkine (CX3CL1) is a chemokine, but unlike other chemokines it is not released to diffuse. It is tethered to the neuron's membrane, so its signal is delivered only on contact. The neuron is therefore not broadcasting a general request for calm; it is saying, to one microglial process at one point of touch, *not here*. A brake with that geometry

can protect one synapse while leaving its neighbour unprotected.

It is both a brake and a badge. CX3CR1, the receptor that reads fractalkine, is one of the core markers of the homeostatic microglion — part of the same badge set that the standing order of Section 3 maintains. This is what makes it structurally different from the other contact brakes, and it is the point the corpus has not emphasised. The fractalkine brake fails twice over, by two independent routes. The *ligand* is lost as the neuron that displays it sickens and dies. The *receptor* is shed as the microglion leaves its homeostatic state, and that shedding is among the earliest and most reliable events in the transition — in single-cell studies of the disease-associated microglion, the loss of P2RY12, TMEM119 and CX3CR1 is the most consistent feature of the change, more consistent than anything the cell switches on (Keren-Shaul and colleagues, 2017; Krasemann and colleagues, 2017). So the brake can be released from the microglial side before the neuron it protects has lost anything at all.

What its loss does. Mice lacking the receptor show dysregulated, neurotoxic microglia in three separate experiments in living animals: an inflammatory challenge, a toxic model of Parkinson's disease, and a model of motor neuron disease (Cardona and colleagues, 2006). **Probable.**

The complication, stated rather than smoothed. The brake is not uniformly protective. Losing CX3CR1 *reduces* amyloid burden in some models while worsening tau pathology in others. The corpus reads this as another instance of the context-dependence that afflicts TREM2, where the same receptor helps at one stage and harms at another. Any therapy aimed here would have to specify which pathology, in which decade. **Established** that the direction is context-dependent; **inference** as to why.

Why it belongs with the sick neuron rather than the healthy one. This brake, like the other three below, requires a neuronal surface that is present and correctly decorated. It therefore fails *downstream* of the lesion. It is best read as the mechanism by which a lesion spreads locally, not as a cause of the lesion — which makes it indispensable to the pathology and a poor early target.

CD200 and CD200R

The founding demonstration: mice lacking CD200 carry a myeloid compartment in a permanently more activated state, their microglia showing an activated shape and a faster response to injury (Hoek and colleagues, 2000). The Alzheimer evidence is unusually direct for a contact brake. Both CD200 and its receptor are significantly reduced in the Alzheimer hippocampus and inferior temporal gyrus, and not in the cerebellum (Walker and colleagues, 2009). Affected regions yes, spared region no — exactly the pattern a lesion-following brake should show. **Established.**

CD47 and SIRPα

The cleanest proof that microglial pruning is held back by a stop signal comes from development rather than disease. CD47 sits on neurons, SIRPα on microglia; their levels track the peak of synaptic refinement in the visual system; and mice lacking either show increased microglial engulfment of inputs and fewer synapses (Lehrman and colleagues, 2018). What this 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. The complement literature has largely omitted that half. The direct Alzheimer evidence is thinner, and this paper does not overstate it. **Established** in development; **speculative** in the disease.

The sugar coat, and the brake that should be released

The neuronal surface carries a coat of sialic acid, read as "self" by inhibitory receptors called Siglecs. Two matter. CD22 rises on aged microglia and blocks their phagocytosis; blocking CD22 in turn restores the clearance of debris, amyloid oligomers and α-synuclein in living mice, shifts microglia back toward a homeostatic state, and improves cognition in aged animals (Pluvinage and colleagues, 2019). CD33 is an Alzheimer risk gene whose product inhibits microglial uptake of amyloid (Griciuc and colleagues, 2013). **Established** in models; the human genetics for CD33 is **established**.

These are brakes that grow *stronger* with age, not weaker. They are the reason "restore the brakes" cannot be a slogan applied uniformly, and Section 11 returns to the contradiction.

6. The Matrix Brake

The sixth brake is not chemical. It is a structure.

Certain neurons wear a dense lattice of extracellular matrix around the cell body and the nearest dendrites — the perineuronal net, built of hyaluronan, aggrecan, brevican, link proteins and tenascin-R, with holes left at synaptic contacts. Among other jobs, it keeps the microglion physically away from the neuronal surface.

The evidence that it is a brake. Neurons wearing aggrecan-based nets are protected against tau pathology in subcortical regions of the Alzheimer brain (Morawski and colleagues, 2010). Resilience to Alzheimer's disease is associated with alterations in these nets in human tissue (de Vries and colleagues, 2025). And the microglial half of the relation is direct: microglia facilitate the loss of perineuronal nets in the Alzheimer brain, and depleting microglia preserves them (Crapser and colleagues, 2020). **Established.**

The relationship is therefore adversarial and reciprocal. The net excludes the microglion; the microglion digests the net. It is the only brake in the inventory that its own target attacks.

The observation that organises this paper. Parvalbumin interneurons wear dense nets. Somatostatin interneurons largely do not. The locus coeruleus does not. So the two neurons that operate the diffuse brakes of Section 4 are themselves the two that lack the matrix brake. The system's two long-range governors are among its least protected cells, and that is why the first step of the stack falls where it does. **Inference**, and the structural heart of *The Double Release*.

7. The Ceiling

The last brake is not imposed from outside at all. It is the microglion's own limit on how far it will travel when something provokes it — a gain control rather than an instruction.

MEF2C. This transcription factor acts in microglia as a restraint on the inflammatory response. Deczkowska and colleagues established the chain: the aged brain carries chronic type-I interferon; interferon-β in the adult brain induces an ageing-like microglial signature and impairs cognition; the interferon milieu lowers microglial *Mef2C*; and mice lacking it in microglia mount an exaggerated response to challenge, with behavioural consequences (Deczkowska and colleagues, 2017). *MEF2C* is additionally an Alzheimer risk gene, which places the same molecule in the genetics and the ageing biology at once. **Probable.**

Why this is the ceiling and not another brake. MEF2C does not tell the microglion what to do. It determines how far the cell goes when something else does. That is what makes it the system's gain control, and it explains the epidemiology: age is the dominant risk factor for this disease, and what ageing does to this system is lower the ceiling, so that provocations a young brain absorbs produce in an old brain a response the tissue cannot tolerate.

A consequence for timing. Because the ceiling falls continuously from midlife in everyone, the *same* brake failure has different consequences at different ages. Withdrawing the somatostatin brake at fifty in a brain with a high ceiling may produce nothing observable; the identical withdrawal at seventy may produce a great deal. The brakes cannot be dated in isolation — they must be read against a ceiling that is itself falling.

8. The Order of Failure

Table 1 gathers the nine brakes.

Table 1. The braking system, grouped by what retires each brake. "When" is relative to the lesion in the tissue, not to a calendar age.

Brake	How it reaches the microglion	What retires it	When
The standing order (TGF-β/SMAD)	Continuously, from surrounding tissue	Sickness of the source tissue; tangles sequester the transducer	Gradual, late-loading

Brake	How it reaches the microglion	What retires it	When
Noradrenaline → β2 receptor	Diffusion from the brainstem	Loss of coerulean output; and loss of the receptor itself	Early
Somatostatin → its receptors	Diffusion from local interneurons	Loss of the peptide, before the cell that makes it	Early
Fractalkine → CX3CR1	Contact with the neuronal membrane	Ligand lost with the neuron; receptor shed with the badge set	Both early and late
CD200 → CD200R	Contact	Withdrawal of the ligand from the sick neuron	Follows the lesion
CD47 → SIRPα	Contact	Loss of the stop signal at the synapse	Follows the lesion
Sialic acid → CD22, CD33	Contact	Nothing: this brake *strengthens* with age	Inverted
The perineuronal net	Physically, by excluding the cell	Digestion by the microglion it restrains	Late; the exit into the third step
The ceiling (MEF2C)	Internal to the cell	Ageing, through chronic interferon	Continuous from midlife

Read down the table, three patterns emerge.

The diffuse brakes go first, and they go together. They are the only two whose failure precedes the local lesion, because they depend on the output of a distant neuron rather than on the health of the neuron next door. They are therefore the only two that could in principle be targeted before the damage they permit.

The contact brakes follow the lesion. All four require a neuronal surface that is present and properly decorated. They matter enormously to how the damage spreads, and they are poor candidates for early intervention.

The system has no single point of failure, which is why it fails slowly. When the noradrenergic brake is withdrawn, the others continue to operate and are sufficient to hold a homeostatic-like state for a time. That is why the second step does not follow immediately on the first. But the released brake

raises the demand on those remaining, and the cumulative demand eventually exceeds what an ageing supply can meet (*The Locus Coeruleus Bridge*). **Inference.**

9. What the Released Microglion Does

A microglion that has lost its restraints does not do one new thing. It does several, and the corpus's reading is that the various named states in the literature — disease-associated, lipid-droplet-accumulating, dystrophic — are variants of one event rather than distinct programmes. The most reliable feature of all of them is not what the cell switches on, which varies between datasets, but what it switches off: the homeostatic badge set, including the fractalkine receptor (Keren-Shaul and colleagues, 2017; Krasemann and colleagues, 2017; Marschallinger and colleagues, 2020). **Probable**, and the corpus's own synthesis.

Four outputs matter for what follows.

It tags and eats synapses. The classical complement cascade — C1q marks a synapse, C3 is cleaved, and the microglial receptor CR3 engulfs what has been marked — is the mechanism of normal developmental pruning, and it is reactivated in the Alzheimer brain to eliminate synapses that should not be eliminated, before plaques form (Hong and colleagues, 2016). This is the clearest single mechanism linking a released microglion to the loss of connections the model measures throughout. **Established** in models.

It digests the matrix. Released microglia secrete matrix-degrading enzymes, MMP-9 among them, which break down the perineuronal net; depleting microglia preserves the nets (Crapser and colleagues, 2020). Section 10 follows that arm to the exit from this step.

It stops finishing its work. A cell under metabolic strain does not go quiet; it stops clearing and starts broadcasting. Andreasson's programme traces that inversion to a lipid switch acting through the EP2 receptor, and removing the receptor from myeloid cells restores a youthful cytokine profile and rescues memory in old mice (*The Starving Housekeeper*). **Probable**, in rodents; every causal result in that programme is murine.

And it compacts plaques, which is protective. The disciplined microglion wraps a deposit and compacts it into an inert core, insulating the surrounding neurites. TREM2 is central to that barrier (Wang and colleagues, 2016; Ulland and colleagues, 2017), which is why TREM2 variants raise risk (Guerreiro and colleagues, 2013; Jonsson and colleagues, 2013). This is the strongest reason to resist reading the released microglion as simply harmful: the same cell, restrained, is doing work the brain cannot do without (*The Gardener's Restraint*).

10. What Happens to Amyloid

The disease is named for a deposit, and so far this paper has mentioned it only in passing. That is deliberate: the brakes come first, and amyloid is best understood as something the braking system handles. But the handling is where the second step does its most consequential work, and it is also where the first step turns out to have been acting all along.

Amyloid is made continuously, and disposal is the variable. A healthy brain produces amyloid-β throughout life. What changes with age and disease is not chiefly how much is made but how much is taken away, and there are three routes of removal.

- **Enzymatic.** Neprilysin is the rate-limiting enzyme for the aggregation-prone form of the peptide: tracing labelled amyloid-β injected into the rat brain showed it degraded through this enzyme, and inhibiting the enzyme produced deposition of the animal's own peptide (Iwata and colleagues, 2000). **Established.**
- **Cellular.** Microglia take the peptide up and digest it in their lysosomes, and a restrained microglion also compacts a deposit into an inert core (Section 9).
- **Drainage.** The peptide is washed out of the tissue during sleep, by a flow that noradrenaline oscillations drive (Hauglund and colleagues, 2025).

The first step already retards amyloid, by three different routes. This is the point Dr. Truchard's note makes, and it deserves stating plainly, because it changes what the second step inherits. The populations of paper one are not

merely upstream of the amyloid problem; each of them is holding part of it back.

- **Serotonin brakes production.** The raphe's tonic signal drives the harmless cleavage of the amyloid precursor, and a single course of a serotonergic drug slowed amyloid production in healthy people by 37 per cent (Sheline and colleagues, 2014; Cirrito and colleagues, 2011).
- **Somatostatin licenses enzymatic disposal.** The peptide from the cortical interneuron raises neprilysin activity, through a defined receptor pathway (Saito and colleagues, 2005; Nilsson and colleagues, 2026).
- **Noradrenaline enables cellular clearance and nightly drainage.** Lesioning the locus coeruleus impairs microglial migration and phagocytosis of amyloid, and supplying the missing transmitter restores both (Heneka and colleagues, 2010); the same nucleus's slow oscillations drive the sleeping brain's clearance (Hauglund and colleagues, 2025).

Read together, these say something the three-phase picture can obscure. **By the time the microglion is released, the brain has already lost one brake on amyloid production and two on its removal.** The deposit that defines the disease is not simply the product of the second step. It is what accumulates when the first step has been failing for thirty years and the second step then stops clearing.

When does the microglion lose its ability to clear? Not at a single moment, and not by one mechanism. Four measurable changes remove the capacity, and they are separable in principle.

- **The inhibitory receptors rise.** CD33 inhibits microglial uptake of amyloid and is raised in microglia in the Alzheimer brain (Griciuc and colleagues, 2013); CD22 rises on aged microglia, and blocking it restores clearance (Pluvinage and colleagues, 2019). These are the Siglec brakes of Section 5, strengthening when they should not.
- **The cell fills with fat.** Lipid-droplet-accumulating microglia, which build up with age in mouse and human brain, are defective in phagocytosis, produce high levels of reactive oxygen species, and secrete inflammatory cytokines (Marschallinger and colleagues, 2020).
- **The barrier apparatus fails.** The TREM2-built barrier that compacts a plaque is what stands between a diffuse, neurotoxic deposit and an inert

one (Wang and colleagues, 2016; Ulland and colleagues, 2017).

- **The inflammasome shuts clearance down.** This is the most direct answer to the question, and it is taken up next.

The inflammasome, and the toxins it licenses

The NLRP3 inflammasome is a sensor assembled inside the microglion. Its activation is the event that converts a cell that has stopped clearing into a cell that is actively doing harm, and the sequence is unusually well characterised.

Amyloid activates it, by being eaten. The microglion takes up fibrillar amyloid, the peptide damages the lysosome, cathepsin B is released into the cytoplasm, and the sensor assembles (Halle and colleagues, 2008). **Established.** The cell is set off by the very material it was trying to dispose of.

It is activated in the human disease, and removing it protects animals. Active caspase-1 is strongly raised in human mild cognitive impairment and Alzheimer brain. Mice carrying familial Alzheimer mutations and lacking either NLRP3 or caspase-1 were largely protected from the loss of spatial memory, showed reduced inflammasome activity, **enhanced clearance of amyloid**, and less deposition (Heneka and colleagues, 2013). **Established** in models; the human finding is a measurement of activation, not of causation.

Activation suppresses clearance, which closes a loop. A systemic inflammatory challenge reduced microglial clearance of amyloid in amyloid-bearing mice, and deleting NLRP3 blocked that reduction (Tejera and colleagues, 2019). Inhibiting the sensor pharmacologically does the converse: it stimulates uptake of the peptide, reduces its accumulation, and improves cognition in the same model (Dempsey and colleagues, 2017). So the amyloid that activates the inflammasome causes the cell to clear less amyloid. **Probable**, and the clearest self-amplifying loop in the second step.

It seeds more amyloid directly. The activated sensor builds a particle called an ASC speck, which the microglion releases. Released specks bind amyloid-β rapidly and increase its aggregation, and injecting them into amyloid-bearing mice spread the pathology, while the spread failed in mice lacking the speck protein and was blocked by an antibody against it (Venegas and colleagues, 2017). **Probable**: a striking result from one programme, not yet independently replicated in human tissue.

And it licenses the enzymes that destroy the protective lattice. The cytokine the inflammasome exists to mature, interleukin-1β, is the principal inducer of the aggrecan-degrading proteases — the ADAMTS aggrecanases and matrix metalloproteinases — that cleave the core of the perineuronal net. This is the best-characterised route from a cytokine to a protease in all of matrix biology. But it was characterised in cartilage, and the corpus grades it honestly: **established** in the joint, **conjecture** in the brain, where the intermediate steps have not been measured (*One Sensor, Two Collapses*). The net itself is also directly vulnerable, because it protects the cell it wraps against oxidative stress and is itself degraded by that stress (Cabungcal and colleagues, 2013).

That last arm is the exit from this step. A microglion that has lost its restraints, stopped clearing, and assembled its inflammasome is a cell that secretes the enzymes which digest the matrix brake — the last brake in the inventory, and the one whose loss defines the third step.

A step underneath all of this, treated in the fourth paper. Every route described in this section ends in digestion, and digestion happens in the lysosome. A microglion with all nine brakes intact but a failed lysosome takes material in and does not break it down; *The Long Way Back* gives the evidence that this disposal step fails in the same cell, in the direction that makes matters worse.

One concession, which the corpus states and this paper repeats. The inflammasome is an amplifier, not the initiator. It is activated by a pathology that began upstream of it, in a brain whose brakes were already going. Nothing in this section claims that the microglion starts the disease.

11. Two Contradictions the Inventory Must Carry

An honest inventory has to state where it argues against itself.

Not every brake should be restored. Seven of the nine brakes weaken. The Siglec brakes strengthen, and strengthening is the problem: an aged microglion that cannot phagocytose is not a safe microglion but a useless one,

and blocking CD22 improves clearance and cognition in aged mice (Pluvinage and colleagues, 2019). So the therapeutic instruction is not "restore restraint" but "restore the *right* restraints" — damp the inflammatory arm, release the clearing arm. The somatostatin brake is the only one in the inventory that does both at once, which is the strongest argument for pursuing it and the reason its weak human evidence matters so much.

Context-dependence is not a detail. CX3CR1 and TREM2 both change sign depending on model, stage and which pathology is measured. A brake that protects against tau while permitting amyloid, or that helps early and harms late, cannot be targeted without specifying the decade. The corpus's position is that this is a genuine property of the system rather than noise in the literature, and that it is the main reason single-target immune therapies have failed. **Inference.**

12. Graded Ledger

Table 2. Each claim in this paper, with its grade and the evidence it rests on.

#	Claim	Grade	Basis
1	Microglia derive from yolk-sac macrophages, not blood monocytes	Established	Ginhoux et al. 2010
2	Microglial identity is installed and maintained extrinsically by TGF-β	Established	Butovsky et al. 2014; Zöller et al. 2018; Bohlen et al. 2017
3	The standing order is impaired in Alzheimer's disease	Probable	Tesseur et al. 2006; Chalmers and Love 2007
4	Noradrenaline restrains microglial inflammation and surveillance	Established (models)	Heneka et al. 2010; Stowell et al. 2019; Liu et al. 2019
5	The β2 receptor is lost from plaque-associated microglia	Probable	Le et al. 2025 (mouse)

#	Claim	Grade	Basis
6	Somatostatin is a microglial brake	Probable (rodent); weakest in the inventory	Feindt et al. 1998; Bai et al. 2015; Schober et al. 2021; Sandoval et al. 2019
7	No somatostatin receptor appears in the human microglial GPCR survey	Established	Hsiao et al. 2021
8	The two diffuse brakes fail within the same preclinical band	Inference	*The Double Release*; Gabitto et al. 2024; Theofilas et al. 2017
9	Fractalkine is a contact brake whose loss causes microglial neurotoxicity	Probable	Cardona et al. 2006
10	CX3CR1 is shed early as part of the homeostatic badge set	Established	Keren-Shaul et al. 2017; Krasemann et al. 2017
11	The fractalkine brake therefore fails by two independent routes	Inference	This paper, from rows 9 and 10
12	CD200 and its receptor are reduced in affected regions and not in spared ones	Established	Walker et al. 2009; Hoek et al. 2000
13	CD47–SIRPα limits synaptic pruning	Established (development); speculative (AD)	Lehrman et al. 2018
14	The Siglec brakes strengthen with age and should be released	Established (models)	Pluvinage et al. 2019; Griciuc et al. 2013
15	The perineuronal net is a physical brake, and microglia digest it	Established	Morawski et al. 2010; Crapser et al. 2020; de Vries et al. 2025
16	The operators of the diffuse brakes are themselves unnetted	Inference	*The Double Release*
17	MEF2C sets a ceiling that ageing lowers through interferon	Probable	Deczkowska et al. 2017

#	Claim	Grade	Basis
18	Loss of the homeostatic signature is the common event behind every named microglial state	Probable	Keren-Shaul et al. 2017; Krasemann et al. 2017; Marschallinger et al. 2020
19	Complement-tagged synapses are eaten before plaques form	Established (models)	Hong et al. 2016
20	Restrained microglia compact plaques, and TREM2 builds that barrier	Established	Wang et al. 2016; Ulland et al. 2017; Guerreiro et al. 2013; Jonsson et al. 2013
21	Neprilysin is the rate-limiting enzyme for amyloid-β disposal	Established	Iwata et al. 2000
22	The first step retards amyloid by three routes: production, enzymatic disposal, clearance and drainage	Inference, from established parts	Sheline et al. 2014; Saito et al. 2005; Heneka et al. 2010; Hauglund et al. 2025
23	Amyloid activates the NLRP3 inflammasome through lysosomal damage	Established	Halle et al. 2008
24	The inflammasome is activated in human AD; its deletion protects animals and enhances clearance	Established (models); activation measured in humans	Heneka et al. 2013
25	Inflammasome activation suppresses microglial amyloid clearance	Probable	Tejera et al. 2019; Dempsey et al. 2017
26	Released ASC specks cross-seed amyloid	Probable; one programme	Venegas et al. 2017
27	Interleukin-1β induces the proteases that strip the perineuronal net	Established in cartilage; conjecture in brain	*One Sensor, Two Collapses*

13. What Would Change This Account

- A measurement of SMAD-driven transcription in human microglia across the Braak series showing the standing order intact. The first brake would leave the inventory.
- Human microglia shown to carry no functional somatostatin receptor, with the rodent effect traced to an action on neurons instead. The second diffuse brake would become an indirect one, and the near-simultaneous double release would lose half its substance.
- A human series showing CX3CR1 lost only after the neurons that supply its ligand have died. The two-route failure of Section 5 would collapse into one.
- Evidence that the homeostatic badge set is shed *after*, not before, the destructive programme begins. The whole framing of release rather than activation would need rewriting.
- A single-target immune therapy that works across stages. The context-dependence of Section 11 would be noise after all.
- A measurement in brain showing that interleukin-1β does not induce the aggrecan-degrading proteases there. The exit into the third step would need another mechanism.

The next paper takes up the third step: the digestion of the protective lattice, the failure of inhibition, and the loss of connections that makes the illness visible.

Corpus papers drawn on

The Double Release: The Brakes on Microglial Activation in Alzheimer's Disease — A Graded Inventory. *The Corruption of the Gardener*: The Drivers of Microglial Dysfunction, Ranked by Causal Weight. *The Gardener's Restraint*: Microglial Restraint as Resilience. *The Second Brake*: Amyloid-β Restrains Microglia Twice. *Homeostatic Microglial Collapse*. *The Locus Coeruleus Bridge*: The Locus Coeruleus as Phase Bridge. *The DAM Trajectory*: Deczkowska's Programme and the Matrix-Degrading Arm. *The Complement-Pruning Substrate*: Beth Stevens's Programme. *The Starving Housekeeper*: Andreasson's EP2, IDO1 and TREM1 Programme. *The Silenced Eraser*. *What the Brainstem Stops Sending* (paper one of this series). All are available in full at AdultCognitiveDisease.com.

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