# THE TIDE-GATE

*The Choroid Plexus as Source, Sieve, and Sentinel of the Cerebrospinal Fluid — and Its Failure in Alzheimer's Disease*

*The Blood–CSF Barrier · The Vanishing Tide · The Lost Chaperone*
*The Transduced Periphery · The Growing Ruin*

*A Dissertation Submitted in Partial Fulfillment of the Requirements for the*

*Degree of Doctor of Philosophy in Neuroscience*

Prepared under the Organic Network Synthesis methodology

**AdultCognitiveDisease.com**

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July 2026

*A border-organ interface companion to The Temporal Architecture of Collapse — turning from the clearance routes the fluid travels to the organ that makes the fluid: the choroid plexus, source of the tide, guardian of the blood–CSF border, and the tap upstream of every drain the field has studied.*

*"The brain has no lymphatic vessels; it has, instead, a tide — half a litre a day, secreted against the grain of every gradient by a few grams of tissue the textbooks dismissed as plumbing. Study the drain all you like. The flood begins at the tap."*

— ONS Methodology Working Notes, 2026

*For the anatomists who mistook a gland for a pipe — and for the physiologists who spent their careers insisting the choroid plexus was neither passive nor unimportant.*

# THE COLLAPSE TRILOGY  INTERFACE COMPANION

*I. Convergent Synaptic Collapse*

*II. Homeostatic Microglial Collapse*

*III. Bioenergetic Collapse*

*— The Temporal Architecture of Collapse —*

*Interfaces: The Vagal Interface · The Coerulean Interface · The Pineal Interface*

*The Microbial Prologue · The Glymphatic Collapse · The Clearance Collapse*

**The Tide-Gate  this volume**

This volume is the border-organ interface the clearance theses presuppose but never name. Where *The Glymphatic Collapse* follows the cerebrospinal fluid *after* it enters the brain, and *The Clearance Collapse* follows the intracellular machinery that disposes of waste, the present volume turns to the organ that makes the fluid in the first place — the choroid plexus: source of the tide, sieve of the blood–CSF barrier, and sentinel of the brain's fluid border. It traces the organ through three failing offices and grades, connection by connection, how much of the failure we can honestly claim to see.

# Contents

# Abstract

Every account of Alzheimer's disease that speaks of *clearance* — of amyloid that fails to leave, of interstitial fluid that no longer flushes, of a brain drowning in its own metabolic waste — silently presupposes a fluid to do the clearing. That fluid is the cerebrospinal fluid, and roughly four-fifths of it is manufactured, actively and against gradients, by a single organ that most theories of the disease never name: the choroid plexus. This dissertation is an argument that the organ deserves naming. The choroid plexus is not one clearance route among many; it is the source of the tide the clearance routes depend upon, the sieve that guards what crosses between blood and brain, and the sentinel through which the body's inflammatory and metabolic state first reaches the cerebrospinal compartment. Its failure, if it fails, would be felt at the head of every downstream mechanism the disease is built from.

We trace the organ through three offices and ask, of each, both *how it fails* and *how well the failure is evidenced*. As **Source**, the plexus secretes cerebrospinal fluid at a prodigious rate through the coordinated action of ion transporters and aquaporins on a cuboidal epithelium; in Alzheimer's disease that epithelium atrophies, its basement membrane thickens, its transporter and mitochondrial genes fall, and measured CSF production drops — halving, in one direct human study, the rate that flushes the brain. As **Sieve**, the plexus is the brain's principal manufacturer of transthyretin, a protein that binds amyloid-β, blocks its aggregation, and helps ferry it from brain to blood; transthyretin declines with age and disease, and mouse genetics show, bidirectionally, that more of it protects and less of it worsens — the single strongest causal thread in the whole account. As **Sentinel**, the plexus is the gateway through which peripheral immune signals are transduced into the brain, by an aging-induced type I interferon program and by the release of inflammatory extracellular vesicles into the fluid — a gateway whose therapeutic manipulation has produced both striking mouse results and sobering replication difficulties.

We do not overstate. A central section of this dissertation is a validity ledger that grades each connection honestly and names, for each, the experiment that would settle it. The gravest hazard here is reverse causation: nearly all human evidence is cross-sectional or post-mortem, and a plexus that looks diseased in an Alzheimer brain may be the disease's victim rather than its author. The most-cited imaging finding — that the plexus paradoxically *enlarges* as the disease advances — is a correlation whose mechanism (inflammation? lipid infiltration? not, it now seems, mere calcification) is unresolved, and whose apolipoprotein-E dependence hints at cause without proving it. And a respected minority holds, on direct measurement of cerebrospinal fluid composition, that the plexus does *not* fail in the aged and the demented at all. We give that dissent its full weight, because a paper that cannot state the strongest case against itself has not earned the case for itself. What survives the grading is a defensible middle claim: the choroid plexus is best supported not as the initiator of Alzheimer's disease but as an early, permissive, and treatable *amplifier* — a border organ whose slow insufficiency removes a chaperone,

weakens a tide, and opens a gate, and whose one genuinely upstream function, the manufacture and defence of the fluid the whole brain is bathed in, makes it worth naming at the head of the clearance story rather than leaving it, as the field has, unspoken beneath it.

## I. The Organ the Clearance Story Forgot

Alzheimer's research has, over the past fifteen years, rediscovered clearance. After a generation spent on the production and aggregation of amyloid-β — how it is cut from its precursor, how it oligomerizes, how it seeds — the field turned to the other side of the ledger and asked why the peptide, produced in every human brain across a lifetime, accumulates catastrophically in only some. The answer that emerged was one of failed removal: of a glymphatic system whose sleep-gated perivascular flushing decays with age; of receptor-mediated efflux across the blood–brain barrier that slows; of intracellular autophagy and lysosomal degradation that clog. Each of these is a real and load-bearing mechanism, and each has its own literature. But each is a mechanism of *removal*, and removal is only half of a hydraulic system. The other half is supply. A drainage network is only as good as the fluid that runs through it, and the fluid that runs through the brain's drainage network — the cerebrospinal fluid that fills the ventricles, cushions the cortex, and, on the glymphatic account, is drawn down along penetrating arteries to exchange with the interstitium — has a maker. It does not well up from nowhere. It is secreted, litre upon litre across a life, by the choroid plexus.

This dissertation takes the choroid plexus as its subject and makes a single organizing claim: that the organ sits *upstream* of the clearance mechanisms the field has learned to care about, and that its slow failure — if the failure is real — would be felt at the head of all of them. The companion volumes in this series have each traced a clearance route to its collapse. *The Glymphatic Collapse* follows the cerebrospinal fluid *after* it enters the brain, along the perivascular influx routes, through the astrocytic aquaporin-4 exchange, out the perivenous drains; it assumes the fluid as an input and traces its fate. *The Clearance Collapse* follows the intracellular machinery — mitophagy, macroautophagy, the lysosome — by which each neuron disposes of its own damaged contents. Neither examines where the fluid comes from, nor the barrier that governs what enters it from the blood. That is the gap this volume fills. The choroid plexus is the production side of a production-and-clearance economy that the disease may unbalance from either end, and a theory that models only removal has modelled a bathtub by studying the drain and ignoring the tap.

There is a reason the organ was forgotten, and it is worth stating, because it is the same reason it was long underestimated in physiology generally. The choroid plexus does not look like a brain structure. It is a frond of tissue, dark red with blood, hanging into the ventricular cerebrospinal fluid like seaweed into a tide pool; under the microscope it is not neurons but a single sheet of cuboidal

epithelium wrapped around a fenestrated vascular core. For most of the twentieth century it was regarded as plumbing — a passive filter that dribbled plasma ultrafiltrate into the ventricles. We now know it to be nothing of the kind. It is a secretory gland of extraordinary metabolic intensity, an immunological organ, an endocrine tissue, and one of the two great barriers between the blood and the central nervous system. The task of this dissertation is to bring that revised understanding to bear on Alzheimer's disease, and to do so with the discipline the subject demands — because the same features that make the plexus fascinating make it easy to over-read, and the literature connecting it to Alzheimer's disease is a literature in which enthusiasm has sometimes outrun evidence.

## II. What the Choroid Plexus Is

### An epithelium turned inside out

The choroid plexus is found in all four cerebral ventricles — a pair in the lateral ventricles, one each in the third and fourth — and together they weigh only a few grams, yet they manufacture the majority of the roughly half-litre of cerebrospinal fluid a human produces each day. The structure is deceptively simple and, once seen clearly, deeply informative. A core of fenestrated, leaky capillaries — vessels that, unlike those elsewhere in the brain, freely admit the contents of plasma — is wrapped in a thin stroma and then sealed within a continuous monolayer of epithelial cells derived, embryologically, from the ependyma. It is this epithelium, not the vasculature, that constitutes the barrier. The capillaries of the choroid plexus are open; the epithelial cells that surround them are joined at their apical margins by tight junctions, and it is across this epithelial sheet, and only across it, that the passage from blood to cerebrospinal fluid is controlled.

This is the crucial architectural fact, and it inverts the logic of the blood–brain barrier. At the blood–brain barrier proper, the seal is *endothelial*: the capillary walls themselves are tight, and the barrier is the vessel. At the choroid plexus the vessel is deliberately porous and the seal is thrown up one layer out, at the epithelium, forming the *blood–cerebrospinal-fluid barrier*. The distinction matters because it defines the organ's function. By admitting plasma into the stromal core and then interposing a metabolically active, transporter-studded epithelium between that core and the ventricle, the plexus is built not to exclude but to *select* and to *secrete* — to take the raw material of blood and, against concentration gradients and at great energetic cost, manufacture from it a fluid of exquisitely controlled composition. The epithelial cell is polarized for the task: its basolateral surface faces the blood-filled stroma, its apical surface, crowned with a dense brush border of

microvilli and a population of cilia, faces the cerebrospinal fluid. Between the two, an armamentarium of ion channels, cotransporters, exchangers, and the sodium–potassium ATPase — sited, unusually, on the apical rather than the basolateral membrane — drives the vectorial movement of sodium, chloride, and bicarbonate that osmotically pulls water, through aquaporin-1, into the ventricle.

### Four offices in one sheet of cells

From this single architecture flow the plexus's functions, and it is useful to name them at the outset as four offices held by one epithelium, because the argument of this dissertation is that Alzheimer's disease compromises each in turn.

The first office is **secretion**: the manufacture of cerebrospinal fluid itself, the bulk fluid that fills and flushes the neuraxis. The second is **synthesis**: beyond water and ions, the plexus secretes a nutritive and protective cocktail of proteins into the fluid — most consequentially transthyretin, but also insulin-like growth factor II, transferrin, gelsolin, and a suite of others — making it a genuine secretory gland with an endocrine reach over the brain it bathes. The third is **barrier and clearance**: the blood–CSF barrier is not merely a wall but a two-way transport interface, expressing efflux transporters and receptor systems that pull metabolites, drugs, and — importantly for our purposes — amyloid-β out of the cerebrospinal fluid and back toward the blood. The fourth is **immune surveillance**: the plexus is one of the principal gateways through which immune cells traffic into the central nervous system, a tissue that constitutively expresses adhesion molecules and chemokines, houses its own resident population of border macrophages, and functions as a sensory organ reporting the inflammatory state of the body to the brain.

Four offices, one epithelium, and a single vulnerability running through all of them: they are all *energetically expensive*, all *age-sensitive*, and all dependent on the structural integrity of a cell layer that this dissertation will argue is quietly compromised in Alzheimer's disease. The remainder of the argument traces three of these offices — the source, the sieve, and the sentinel — through their failure, and grades, at each step, how much of the failure we can actually see.

## III. The Plexus in Brief

Before defending it in detail, the argument is worth seeing whole. Read as a border organ standing between the blood and the brain's fluid, the choroid plexus contributes to Alzheimer's disease through three functional failures, each with a characteristic mechanism, a characteristic downstream consequence, and — this is the discipline the subject requires — a characteristic

strength of evidence.

**The Source fails — the vanishing tide.** *The secretory office.* The epithelium atrophies and its basement membrane thickens; the genes for ion transport, carbonic anhydrase, and mitochondrial ATP synthesis fall; and cerebrospinal fluid production and turnover decline. A brain flushed less often is a brain in which amyloid-β and other solutes dwell longer, and the glymphatic system downstream is starved of the very tide it circulates. *Evidential grade: moderate. Human production data exist but are small and confounded by global metabolic decline, and a serious minority disputes the failure entirely.*

**The Sieve fails — the lost chaperone.** *The synthetic and clearance office.* The plexus is the brain's chief source of transthyretin, which binds amyloid-β, prevents its aggregation, and assists its efflux from brain to blood; transthyretin falls with age and in disease, and the barrier's efflux transporters weaken while its tight junctions loosen. *Evidential grade: strong for the transthyretin thread — the only place in this account where bidirectional mouse genetics establish causation — and moderate for the barrier and transporter failures.*

**The Sentinel fails — the transduced periphery.** *The immune office.* An aging-induced type I interferon program at the plexus suppresses its reparative type II interferon activity, and the epithelium transmits peripheral inflammation into the cerebrospinal fluid through the release of vesicle-borne inflammatory signals. *Evidential grade: mixed — mechanistically vivid and elegantly demonstrated in models, but the therapeutic corollary has met replication trouble, and the AD-specific case leans on extrapolation from other inflammatory states.*

**The visible sign — the growing ruin.** Beneath and across these functional failures runs one clinical observation: on magnetic resonance imaging the choroid plexus does not shrink as it fails but *enlarges*, and the enlargement tracks neurodegeneration, apolipoprotein-E4 genotype, and blood markers of Alzheimer pathology. *Grade: the correlation is robust and replicated; its cause and its direction are not.*

The map has one property worth stating in advance, because it governs everything that follows. The choroid plexus is a *border* organ — it stands, by anatomy and by function, at the interface between the periphery and the brain — and a border organ can fail in two directions at once. It can fail to *supply and protect* (losing the tide, losing the chaperone) and it can fail to *guard* (opening the gate to peripheral inflammation). The disease, on this reading, is served by both failures simultaneously, which is precisely why an organ so easily dismissed as plumbing deserves a place at the head of the account.

# IV. The Source Fails  The Vanishing Tide

## A secretory gland of the first rank

To appreciate what its failure would cost, one must first appreciate what the choroid plexus does when it works. The secretion of cerebrospinal fluid is not filtration; it is active, energy-consuming, transcellular transport, and it proceeds at a rate that, per gram of tissue, exceeds the secretory output of almost any other epithelium in the body. The physiology, worked out over decades and synthesized in its modern form as a coordinated model of ion and water movement, runs as follows: carbonic anhydrase within the epithelial cell generates protons and bicarbonate from carbon dioxide and water; basolateral exchangers import chloride and sodium; the apical sodium–potassium ATPase — sited, against the usual epithelial arrangement, on the cerebrospinal-fluid-facing membrane — extrudes sodium into the ventricle; and the resulting ionic gradient draws water osmotically through apical aquaporin-1. The whole apparatus turns over the brain's entire cerebrospinal fluid volume several times a day, generating a slow but relentless tide that carries metabolites away from the brain and toward the sites of drainage.

The consequence of that tide is a *sink*. Because cerebrospinal fluid is continually produced and continually drained, the brain sits perpetually upstream of a concentration gradient that pulls solutes — including soluble amyloid-β — from the interstitial fluid into the cerebrospinal fluid and away. This is the sense in which the choroid plexus is upstream of the glymphatic system rather than parallel to it. The paravascular clearance route demonstrated by Iliff and colleagues, in which cerebrospinal fluid enters the parenchyma along penetrating arteries, exchanges with interstitial fluid, and carries amyloid-β out along perivenous drains, requires a supply of cerebrospinal fluid at the arterial end and a sink at the venous end. The choroid plexus provides both the fluid and, through continuous turnover, the sink. A plexus that secretes less does not merely make less fluid; it lowers the head of pressure driving the entire downstream clearance system and lengthens the time any given molecule of amyloid-β lingers before removal. Turnover, not volume, is the variable that matters, and turnover is the plexus's to set.

## The evidence that it declines — and the honest caveats

Three lines of evidence bear on whether this secretory office fails in Alzheimer's disease, and they are of unequal strength.

The first is *morphological*. Post-mortem morphometric study of the Alzheimer choroid plexus, most cleanly by Serot and colleagues, finds a stereotyped picture: the epithelial cells, cuboidal and tall in youth, become flattened and atrophic; the basement membrane on which they sit thickens; the stroma becomes fibrotic and accumulates calcified concretions and Biondi ring tangles.

Critically, these changes occur in normal aging too, but are *significantly accentuated* in Alzheimer's disease beyond what age alone predicts — an epithelial atrophy and basement-membrane thickening that the authors read, reasonably, as a structural substrate for impaired secretion and filtration. The picture is corroborated at the level of gene expression: transcriptomic analysis of Alzheimer choroid plexus by Kant, Stopa, and colleagues finds coordinated decreases in exactly the machinery the secretory model predicts — ion transporters such as the sodium-bicarbonate cotransporter, carbonic anhydrase, aquaporins, and mitochondrial ATP-synthase subunits — alongside decreased expression of the tight-junction protein claudin-5 and increased pro-inflammatory transcripts. The molecular portrait is of an epithelium losing both the pumps that make fluid and the seals that hold the barrier.

The second line is *functional and direct*, and it is the most striking single datum in this section. Silverberg and colleagues measured cerebrospinal fluid production rate directly, by a ventricular infusion technique, in living patients, and reported that the rate in Alzheimer's disease was roughly half that of comparison patients — on the order of 0.2 millilitres per minute against 0.4. If taken at face value, this is a halving of the tide, and it would be difficult to overstate its downstream significance. But it must not be taken uncritically. The study was small — a handful of Alzheimer patients — the comparison group were patients with Parkinson's disease rather than healthy controls, and the measurement is invasive and difficult. It is a real and important finding, but it is a single small study, and the honest reader holds it as strong suggestion rather than settled fact.

The third line is *inferential*, running from the well-documented decline in cerebrospinal fluid turnover with age to the proposition that reduced turnover impairs clearance. This is coherent and probably correct, but it is inference, not demonstration, and it shares the confound that dogs the entire section: cerebrospinal fluid production tracks brain metabolic rate, and brain metabolic rate falls in Alzheimer's disease for reasons that have nothing to do with the plexus. A plexus secreting less might be a plexus responding appropriately to a less demanding brain, not a plexus failing. Disentangling the plexus as *cause* of reduced clearance from the plexus as *passive reporter* of reduced demand is the central difficulty, and it is not yet resolved.

### The dissent that must be answered

No section on the failing plexus is honest without confronting its most serious opposition, and here it is unusually pointed. Spector and Johanson, authorities on choroid plexus physiology, have argued directly against the concept of "choroid plexus failure" in aging and Alzheimer's disease. Their case rests on direct measurements of cerebrospinal fluid *composition*: the concentrations of ascorbate and folate, actively transported into the fluid by the plexus; the secretion of transthyretin; the maintenance of acid–base balance and electrolyte concentration. On these measures, they contend, the aged and even the Alzheimer plexus performs within normal limits, and the morphological changes so often cited are, on their reading, either overinterpreted or functionally compensated. This is not a fringe position; it is a serious argument from people who know the organ intimately, and it cuts at the heart of the secretory claim. The resolution, such as it is, may lie in the distinction between *composition* and *flow*: a plexus can maintain the concentrations of the solutes it actively transports while still producing a reduced *volume* of fluid at a reduced *rate*, and it is flow and turnover, not composition, that the clearance argument depends upon. But this is a reconciliation offered, not proven, and the reader should note that the very existence of the failure this section describes is contested by qualified dissent — a fact that fixes the secretory office at a grade of *moderate*, not strong.

## V. The Sieve Fails  The Lost Chaperone

### Transthyretin: the plexus's answer to amyloid

If the secretory office is the plexus's contested contribution, the synthetic office contains its strongest. Among the proteins the choroid plexus manufactures and secretes into the cerebrospinal fluid, one stands out both for its abundance and for its relevance: transthyretin. Long known as a carrier of thyroxine and, in complex with retinol-binding protein, of vitamin A, transthyretin is synthesized in the brain almost exclusively by the choroid plexus, which pours it into the cerebrospinal fluid in quantities that make it one of the dominant locally-produced CSF proteins. Its second career, discovered later, is the one that concerns us: transthyretin is an amyloid-β binding protein and a natural inhibitor of amyloid aggregation.

The founding observation, by Schwarzman and colleagues, was elegant and direct. When amyloid-β was added to human cerebrospinal fluid, it was rapidly sequestered into stable complexes — and the sequestering protein was transthyretin, not apolipoprotein E. Purified transthyretin prevented amyloid formation in vitro. The interpretation the authors drew has aged well:

cerebrospinal fluid normally contains a chaperone that binds amyloid-β and keeps it soluble, and failure of that sequestration would permit the aggregation that defines the disease. Transthyretin, on this view, is a constitutive brain defence against amyloid — and it is a defence manufactured by the choroid plexus.

What lifts this from an interesting in-vitro finding to the strongest causal claim in the entire dissertation is the mouse genetics, and specifically its *bidirectionality*. Buxbaum and colleagues showed that overexpressing a human transthyretin transgene in an Alzheimer mouse model ameliorated the behavioural and neuropathological phenotype, while silencing the endogenous transthyretin gene *accelerated* it. Protection scaled with the protein in both directions: more transthyretin, less disease; less transthyretin, more disease. This is the logical structure that observational human data can never supply — a manipulation in both directions with the predicted opposite effects — and it is the reason the transthyretin thread earns a grade of *strong* while the rest of the account earns lower marks. A mechanism, later work by Alemi and colleagues suggested, extends beyond simple sequestration: transthyretin appears to assist the *efflux* of amyloid-β across the blood–brain barrier from brain toward blood, acting through the low-density-lipoprotein-receptor-related protein LRP1, and to move directionally from brain to blood itself. Transthyretin is thus not only a chaperone that keeps amyloid soluble but a carrier that helps carry it out — a two-fold contribution to clearance, both arms of it traceable to the protein the choroid plexus makes.

The disease-relevant fact is that transthyretin declines. Cerebrospinal fluid transthyretin is reduced in Alzheimer's disease and in mild cognitive impairment, and it falls with age. If the choroid plexus is the factory and transthyretin the product, then plexus insufficiency — the epithelial atrophy of the preceding section — is a plausible upstream cause of the chaperone's disappearance, and the disappearance of the chaperone is a mechanistically specified, causally supported contributor to amyloid aggregation and impaired efflux. This is the cleanest line the choroid plexus offers to the disease, and it runs directly through the organ's synthetic office.

## The barrier as a two-way sieve, and its leak

Transthyretin is the plexus's secreted defence; the epithelial barrier is its structural one, and the barrier is not a wall but a sieve — a selectively permeable interface studded with transporters that move solutes in both directions. On its apical, cerebrospinal-fluid-facing surface the epithelium expresses megalin (LRP2), a large endocytic receptor that internalizes amyloid-β complexed with carrier proteins such as clusterin, and it expresses efflux pumps of the ATP-binding-cassette family that export xenobiotics and metabolites. The barrier's job, in the clearance economy, is to pull amyloid-β and other waste out of the cerebrospinal fluid and hand it back toward the blood, and to do so while maintaining the tight-junctional seal that keeps the blood's contents — proteins, immune cells, pathogens — out of the fluid.

Both halves of that job appear to weaken in Alzheimer's disease, though the evidence is more circumstantial than for transthyretin. The transcriptomic decline in claudin-5 and other junctional proteins, noted above, implies a loosening seal; clinical measures of barrier permeability, most simply the ratio of albumin in cerebrospinal fluid to albumin in serum, are elevated in a subset of dementia patients, indicating a blood–CSF barrier that has become leakier. A leaky barrier is a double liability: it admits into the fluid what should be excluded — inflammatory mediators, and on some accounts pathogens and peripheral proteins — while its degraded transport machinery removes less of what should be cleared. The sieve, in other words, fails simultaneously as a filter and as a pump. This is a coherent and probably correct picture, but its evidential base in Alzheimer's disease specifically is thinner than the transthyretin story's, and it earns a grade of *moderate*: the transporters and junctions are real, their decline is documented in aggregate, but the causal weight of that decline in the human disease is inferred rather than proven.

## VI. The Sentinel Fails  The Transduced Periphery

### The interferon gate

The third office is the one that has generated the most excitement and the most difficulty. The choroid plexus is an immunological organ — a constitutive gateway for the trafficking of immune cells into the central nervous system, expressing the adhesion molecules and chemokines that permit leukocytes to cross from blood to cerebrospinal fluid, and housing its own resident border macrophages. This gateway is not static; it is regulated, and its regulation changes with age in a way that a landmark study by Baruch and colleagues placed at the centre of brain aging.

Their finding, from genome-wide analysis across organs, was that the aged choroid plexus develops a *type I interferon* signature — the gene-expression program normally mounted against viral infection, marked by interferon regulatory factor 7 and interferon-β — and that this program is induced not by a pathogen but by signals arriving from the aging brain itself, carried in the cerebrospinal fluid. The chronic type I interferon response, in turn, suppresses the plexus's *type II interferon* (interferon-γ)-dependent activity, the program that supports its reparative and trafficking functions. The balance between the two interferons, on this account, governs whether the plexus operates as a healthy gateway or a dysfunctional one, and aging tips it the wrong way. Strikingly, blocking type I interferon signalling in the aged mouse brain partially restored cognitive function and hippocampal neurogenesis — a causal manipulation suggesting the interferon gate is not merely a marker of aging but a contributor to its cognitive cost. The same type I interferon signature was

detectable in aged human brain, lending the mouse finding cross-species support.

The second mechanism by which the sentinel transmits the periphery is more concrete and, in its original context, cleanly demonstrated. Balusu and colleagues showed that the choroid plexus epithelium responds to systemic inflammation by releasing *extracellular vesicles* — exosomes and microvesicles — into the cerebrospinal fluid, laden with pro-inflammatory microRNAs such as miR-146a and miR-155. These vesicles enter the brain parenchyma, are taken up by astrocytes and microglia, and there repress their microRNA targets and up-regulate inflammatory genes; blocking vesicle release reduced the brain's inflammatory response. Here the plexus is caught in the act of *transducing* a peripheral inflammatory state into a central one — sensing the body's inflammation and re-broadcasting it, in molecular packets, to the brain's glia. In a disease increasingly understood to involve systemic inflammation, infection, and a gut–brain inflammatory axis, a border organ that converts peripheral inflammatory tone into central glial activation is a mechanism of obvious relevance, and it connects the choroid plexus to the microglial phase of the disease as directly as transthyretin connects it to the amyloid phase.

## The therapy that would not replicate

The immunological office is also where this dissertation must be most careful, because it is where the gap between striking result and reliable knowledge is widest. The Schwartz laboratory extended the interferon-gateway concept into a therapeutic program with two prominent papers. In the first, transient depletion of regulatory T cells was shown to open the choroid-plexus gateway, recruit immunoregulatory monocyte-derived macrophages to sites of amyloid pathology, clear plaques, and improve cognition in an Alzheimer mouse model. In the second, and more consequentially, blockade of the PD-1 immune checkpoint was reported to evoke an interferon-γ-dependent systemic immune response, drive macrophage recruitment through the gateway, clear cerebral amyloid, and improve memory. The mechanistic arc was beautiful: rejuvenate exhausted peripheral T cells, re-open the border, let reparative immunity in.

It did not hold up cleanly. Independent attempts to replicate the anti-PD-1 benefit in Alzheimer models were, at best, mixed and, in a notable multi-laboratory effort, negative — a cautionary episode in a field with a long history of mouse results that failed to translate. The honest lesson is not that the interferon-gateway concept is wrong; the aging type I interferon signature and the vesicle-transduction mechanism rest on their own, separately demonstrated foundations. The lesson is that the *therapeutic* manipulation of the sentinel is far less secure than its *description*, and that the leap from "the plexus is an immune gateway that changes with age" to "opening the gateway treats Alzheimer's disease" is a leap the data have not underwritten. The sentinel's office therefore earns a split grade: *moderate-to-strong* for the existence of an age- and inflammation-regulated immune gateway, and *speculative* for the proposition that manipulating it is therapeutic in the human disease.

## VII. The Growing Ruin The Imaging Paradox

There is one sign of the failing plexus that can be seen in the living human brain, and it presents a paradox worth dwelling on. One might expect an atrophic, failing secretory organ to *shrink*. On magnetic resonance imaging, the Alzheimer choroid plexus does the opposite: it *enlarges*. Across multiple cohorts, choroid plexus volume is increased in Alzheimer's disease and mild cognitive impairment relative to controls, and the enlargement correlates with cognitive decline, with markers of neuroinflammation, and — in recent, careful work — with blood-based biomarkers of the disease. Bouhrara and colleagues, using advanced quantitative imaging across a wide age range, found that reduced choroid-plexus microstructural and macrostructural integrity was associated with plasma markers of Alzheimer pathology, neurodegeneration, and neuroinflammation — pTau181, neurofilament light, and glial fibrillary acidic protein — and, importantly, that these associations were present *before* clinically detectable cognitive impairment, suggesting the plexus degrades early enough to serve as a marker of preclinical disease.

Why would a failing organ grow? The naïve hypothesis — calcification, the calcified concretions long known to accumulate in the aging plexus — has recently been tested and largely rejected as the driver. Ozsahin and colleagues, combining structural MRI, calcium-sensitive CT, and amyloid PET, found that choroid-plexus enlargement was associated with reduced hippocampal volume, particularly in apolipoprotein-E4 carriers, but that calcium deposition was *not* the independent driver of the pathological enlargement. Their inference, by exclusion, points to other space-occupying processes: inflammatory-cell infiltration and lipid accumulation, both of which are known to occur in the plexus and both of which are regulated by apolipoprotein E. The paradox thus resolves, tentatively, into a picture of the plexus enlarging not by hypertrophy of function but by infiltration and inflammation — swelling as it fails, the way an inflamed tissue swells, its growth a sign of pathology rather than of capacity.

Two features of this imaging literature deserve emphasis, one encouraging and one cautionary. The encouraging feature is the apolipoprotein-E4 dependence. That the strongest single genetic risk factor for late-onset Alzheimer's disease modulates the plexus's structural pathology is a genuine convergence: it places the choroid plexus on the apolipoprotein-E axis, hints that some of apolipoprotein-E4's risk may be transacted at this border organ through its known roles in lipid handling and inflammation, and raises the possibility that the plexus is one site where a well-established genetic cause does its work. The cautionary feature is the one this dissertation has raised at every turn: these are *cross-sectional correlations*. That the plexus is enlarged in disease, tracks its severity, and does so more in high-risk genotypes is entirely consistent with the plexus being a

*cause* — and equally consistent with its being a *victim*, swelling in reaction to a pathology driven from elsewhere. Imaging tells us the plexus is involved; it cannot, by itself, tell us whether it is upstream or downstream.

## VIII. Where the Plexus Sits Cause, Victim, or Amplifier

This is the question on which the value of the entire account turns, and it must be answered without flinching. Is the choroid plexus a *cause* of Alzheimer's disease, a *consequence* of it, or something in between? The temptation, having assembled the preceding mechanisms, is to crown the plexus as an initiator — the failing spring from which the whole flood follows. The evidence does not support that crown, and claiming it would repeat exactly the error this dissertation was written to avoid.

Consider what would be required for the plexus to be a genuine *initiator*. Its failure would have to precede the earliest disease pathology, and its failure would have to be sufficient, or nearly so, to set the disease in motion. Neither is established. The earliest identifiable pathology in Alzheimer's disease — pretangle tau in the locus coeruleus, decades before symptoms — arises in a brainstem nucleus with no obvious primary dependence on the choroid plexus, and no evidence places plexus failure temporally ahead of it. Nor is there any human or animal demonstration that a primary lesion of the choroid plexus, in isolation, produces Alzheimer's disease. The initiator hypothesis is unsupported and should be set aside.

Consider, at the other extreme, the plexus as *pure victim* — an organ that atrophies and inflames downstream of a disease it plays no causal role in, its every abnormality a reaction. This, too, is inconsistent with the evidence, and the inconsistency is located precisely in the transthyretin thread. The bidirectional mouse genetics — protection with more transthyretin, acceleration with less — establish that a plexus-derived product *causally modulates* the disease. A pure victim does not, by its secretions, change the trajectory of the pathology that afflicts it; transthyretin does. So the plexus cannot be merely a victim either.

What remains is the defensible middle, and it is the position this dissertation adopts: the choroid plexus is an *amplifier and a permissive node* — not the match that lights the disease, but a set of failing safeguards whose loss accelerates and worsens a process driven from elsewhere. This verdict has a specific structure. The plexus contributes at least one function that is *genuinely upstream and causally supported* — the manufacture of transthyretin, whose decline removes an amyloid chaperone and an efflux carrier before and during the disease. It contributes several functions that are *permissive and probably contributory but confounded* — the secretory decline that weakens clearance, the barrier leak, the

immune-gateway shift — real failures whose causal weight is entangled with the general metabolic and vascular decline of the aging brain. And it contributes an *early, visible sign* — the imaging changes — whose value is as a biomarker regardless of whether the underlying process is cause or effect. The plexus, in short, sits where a border organ sits: not at the origin of the disease, but athwart several of the routes by which the disease advances, failing in ways that let those routes run faster. This is a more modest claim than the mechanisms, taken breathlessly, might invite — and it is the claim the evidence will bear.

## IX. The Validity Ledger

The preceding sections have graded their claims in passing; this section gathers the grading into one place, because the honesty of the whole enterprise depends on its being auditable. Two failure modes threaten every connection drawn in this dissertation, and each entry in the ledger is a judgement about how far a given claim escapes them. The first failure mode is *confounding by aging*: nearly every feature of the choroid plexus that changes in Alzheimer's disease also changes in normal aging, and separating disease-specific failure from the tissue's ordinary senescence is genuinely difficult. The second, and graver, is *reverse causation*: the overwhelming majority of the human evidence is cross-sectional or post-mortem, a photograph of the plexus in the presence of established disease, incapable by its nature of distinguishing an organ that helped cause the disease from one the disease damaged.

**Strong — transthyretin as amyloid chaperone and efflux carrier.** This is the ledger's one entry that escapes both failure modes, and it does so for one reason: bidirectional genetic manipulation in animals. Overexpression protects, silencing accelerates; the effect is causal, dose-dependent, and directional, and it is corroborated by an in-vitro sequestration mechanism and a plausible LRP1-mediated efflux route. *Settling experiment (largely done): the bidirectional transgenic series exists; what remains is human confirmation that plexus-derived transthyretin decline precedes and predicts amyloid accumulation longitudinally.*

**Moderate — cerebrospinal fluid production and turnover decline.** The morphology is consistent, the transcriptomics are consistent, and one direct human measurement shows a halving of production rate. But the human production study is small and its comparison group imperfect, the confound with brain metabolic demand is unresolved, and a qualified minority disputes the failure outright on compositional grounds. *Settling experiment: longitudinal measurement of CSF production or turnover in preclinical individuals, correlated with subsequent amyloid accumulation, in numbers large enough to adjust for metabolic rate.*

**Moderate — blood–CSF barrier leak and transporter decline.** Junctional-gene decline, elevated albumin ratios in a subset, and known efflux-transporter biology make a coherent case, but the AD-specific causal weight is inferred. *Settling experiment: quantify plexus-specific amyloid-β efflux capacity in vivo and test whether its decline is Alzheimer-specific or a general feature of the aging barrier.*

**Moderate-to-strong (description) / speculative (therapy) — the immune gateway.** The aging type I interferon signature and the vesicle-transduction mechanism are well demonstrated in their own right; the therapeutic corollary, that opening the gateway treats the disease, met replication trouble and must be held as unproven. *Settling experiment: independent, pre-registered, multi-site replication of gateway-opening immunotherapy, and demonstration that the interferon shift occurs in human Alzheimer plexus specifically, not aging generally.*

**Robust correlation / uncertain direction — the imaging enlargement.** That the plexus enlarges, tracks severity, tracks neuroinflammatory and Alzheimer blood markers, and does so more in apolipoprotein-E4 carriers is replicated and probably real. Whether the enlargement is cause, consequence, or bystander is unresolved, and calcification has been largely excluded as its driver. *Settling experiment: longitudinal imaging showing whether plexus change precedes or follows amyloid and tau accumulation, and whether baseline plexus integrity predicts conversion independent of amyloid.*

**Unsupported — the plexus as initiator.** No evidence places plexus failure temporally ahead of the earliest disease pathology or shows that isolated plexus injury produces the disease. This claim is not made in this dissertation and should not be made from it.

The ledger's shape is its message. One strong causal thread, several moderate and confounded contributions, one vivid but therapeutically unreliable immune mechanism, one robust correlation of uncertain direction, and one hypothesis firmly rejected. This is the profile not of a primary cause but of a genuine, gradeable, partially-upstream amplifier — which is exactly what the previous section concluded, arrived at here from the direction of the evidence rather than the mechanism.

## X. Therapeutic Corollaries

An amplifier is worth treating precisely because it is not the origin: intervening on it will not cure the disease, but it may slow a process it accelerates, and it may do so through targets that are unusually accessible. The choroid plexus sits at a fluid interface, bathed in cerebrospinal fluid on one side and freely-perfused blood on the other, which makes it more pharmacologically reachable than most of the brain. Four therapeutic directions follow from the account, each inheriting the grade of the mechanism it targets.

The first, and best-grounded, is **augmenting or defending transthyretin**. Because the transthyretin thread is the account's one causally established mechanism, raising the availability of functional transthyretin — or preventing its decline — is the most rational plexus-directed strategy. But it comes with a warning that echoes this series' work on molecules that read in two directions: transthyretin is *itself* an amyloidogenic protein, whose destabilized tetramers cause the systemic and hereditary transthyretin amyloidoses. Simply "more transthyretin" is therefore not unambiguously safe; the protective species is the stable, native tetramer, and the therapeutic goal is a *stabilized* tetramer, not merely an abundant one. Tetramer-stabilizing drugs already exist for transthyretin amyloidosis, which makes this an unusually translatable idea — but the possibility that stabilizing the tetramer alters its amyloid-β-binding behaviour, or that raising brain transthyretin trades an amyloid-β benefit for a transthyretin-aggregation risk, must be tested, not assumed. The inversion warning is explicit: the plexus's chaperone is a double agent, protective in one conformation and pathogenic in another.

The second is **preserving the tide** — supporting cerebrospinal fluid production and turnover rather than suppressing it. This direction is more a principle than a drug: it counsels caution with interventions that reduce choroid plexus secretion (carbonic-anhydrase inhibitors such as acetazolamide, for instance, directly suppress the plexus's secretory machinery), and it motivates the search for ways to sustain turnover in the aging brain. Its grade is *moderate*, inheriting the contested status of the secretory-failure claim; one does not aggressively support a function whose failure is disputed by serious authorities.

The third is **modulating the sentinel with restraint**. The interferon-gateway and vesicle-transduction mechanisms suggest targets — dampening the aging type I interferon program, or blocking pathological extracellular-vesicle release from the epithelium — but the replication difficulties of gateway-opening immunotherapy counsel humility. This is a direction for careful, mechanism-first investigation, not for clinical enthusiasm, and its grade is frankly *speculative*.

The fourth is not a treatment but a use: **the plexus as biomarker**. Of everything in this dissertation, the imaging finding is the nearest to clinical utility, and it is useful regardless of the cause-or-victim question. If choroid plexus volume and microstructural integrity change early — before cognitive symptoms, in proportion to Alzheimer blood markers, and more in high-risk genotypes — then the plexus is a candidate window onto preclinical disease, measurable non-invasively on standard MRI, and potentially valuable for enrichment of prevention trials and for monitoring. A biomarker does not need to be a cause; it needs only to be an early and reliable index, and the growing-ruin literature suggests the plexus may be exactly that.

## XI. Predictions and Falsification

A frame earns its keep by the predictions it makes and the observations that would sink it. The amplifier account of the choroid plexus commits to the following, each stated so that its failure would count against the frame.

It predicts that **baseline choroid-plexus integrity predicts conversion**: among cognitively normal individuals, those with more degraded plexus structure or lower cerebrospinal fluid turnover at baseline should convert to Alzheimer's disease at higher rates, and — the strong form — should do so partly *independent* of baseline amyloid burden, reflecting the plexus's own contribution. If plexus status adds nothing to amyloid in predicting conversion, the upstream claim weakens.

It predicts an **apolipoprotein-E4 interaction that is mechanistic, not incidental**: because plexus pathology is more pronounced in E4 carriers, plexus-directed interventions — transthyretin defence above all — should benefit E4 carriers disproportionately. A flat response across genotypes would argue the E4–plexus association is a bystander correlation.

It predicts **directionality of the transthyretin effect in humans**: raising functional, stabilized transthyretin should shift the brain-to-blood gradient of amyloid-β toward efflux, measurable as increased peripheral clearance. Absence of any such shift would undercut the efflux arm of the account.

It predicts that **the secretory failure, if real, is separable from metabolic demand**: a study powered to adjust cerebrospinal fluid production for brain metabolic rate should still find a plexus-specific deficit in Alzheimer's disease. If the deficit vanishes on adjustment, Spector and Johanson are vindicated and the secretory office falls to *weak*.

And it predicts, as its clearest falsifier, that **the plexus changes early**. If longitudinal imaging shows plexus enlargement and degradation arising *only after* amyloid and tau are well established, the organ is relegated to victim, the biomarker value survives but the amplifier claim does not, and the account is substantially wrong. The frame is built to be broken on this point, which is the mark of a claim worth making.

## XII. Coda Naming the Tap

The history of the choroid plexus in neuroscience is a history of underestimation. Called plumbing when it was a gland, called passive when it was among the most metabolically active epithelia in the body, it has been the organ the field looks past on its way to the neurons. Alzheimer's research has repeated the pattern in its own idiom: it has built an elaborate and largely correct science of clearance — of the fluid that must flush the brain and the machinery that must remove the waste — while leaving unnamed the organ that makes the fluid in the first place. This dissertation has tried to supply the name, and to supply it with discipline.

The disciplined version of the claim is not that the choroid plexus causes Alzheimer's disease. It is that the plexus is a *border organ that fails in both directions* — losing the tide that flushes the brain and the chaperone that guards it against amyloid, while opening the gate through which the periphery's inflammation is transduced inward — and that these failures, though driven partly by a disease originating elsewhere, are not merely passive: at least one of them, the loss of transthyretin, causally worsens the disease, and several others plausibly accelerate it. The plexus is the amplifier at the head of the clearance story, the tap upstream of the drain the field has studied so well. To model the bathtub honestly, one must model the tap as well as the drain — and the tap, it turns out, is a gland, a sieve, and a sentinel, all three of them quietly failing, and all three of them, at last, worth naming.

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