The Subtraction Error

Why removing things from the Alzheimer brain keeps making patients worse, and what the failures have in common

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August 2026

Three randomised trials completed since 2020 each removed something the Alzheimer brain holds in excess, each engaged its target, and each left patients worse than placebo or no better. This paper argues they are one error repeated — the substances removed are in part brakes — and that the road to cognitive failure runs through the disinhibition of a single kinase by two independent restraints, one neuromodulatory and one metabolic. The conjunction of the two is the paper's original claim, has never been measured in any system, and Section IX names the experiment that would break it.

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Abstract

Three randomised trials completed since 2020 share a structure that has not been read together. Each removed something the Alzheimer brain contains in excess. Each engaged its target. Each left patients **worse than placebo** or no better.

Deferiprone lowered hippocampal iron, confirmed by quantitative susceptibility mapping, and accelerated cognitive decline (β = −0.50; 95% CI, −0.80 to −0.20), with the effect driven by executive function and accompanied by increased frontal volume loss. Valacyclovir in HSV-seropositive early Alzheimer's produced greater cognitive worsening than placebo on ADAS-Cognitive at 78 weeks (between-group difference 3.93; 95% CI, 1.03 to 6.83; P = .01). Immune-checkpoint blockade, whose founding mouse result four pharmaceutical companies had already failed to reproduce, reached a first-in-human trial and returned no efficacy signal.

This paper proposes that these are not three unrelated disappointments but one error repeated: **the substances being removed are, in part, brakes.**

The claim advanced here is a **convergence claim**, not a claim about what starts the disease. It states that however Alzheimer's begins — and it plainly begins in more than one way — the pathway to cognitive failure passes through the disinhibition of a single kinase, glycogen synthase kinase-3β, and that the disease is better described as *the withdrawal of restraint* than as *the accumulation of poison*.

Two independent hands release that kinase. The first is noradrenergic: degeneration of the locus coeruleus removes tonic β-adrenergic signalling that holds GSK-3β in check. The second is metabolic and is the novel element here. Hydrogen sulfide sulfhydrates GSK-3β and thereby inhibits tau hyperphosphorylation; the biosynthetic enzyme cystathionine γ-lyase binds wild-type tau, is depleted in human Alzheimer brain, and sulfhydration is diminished in the disease. A failing transsulfuration pathway therefore releases the same kinase that noradrenergic loss releases, through an entirely separate chemistry.

Two hands, one lever. That conjunction — that a bioenergetic failure and a neuromodulatory failure converge on a single post-translational modification of a single residue class on a single kinase — is this paper's original contribution, and it is stated here so that it can be broken.

Scope, stated up front. This describes a convergence, not a cause, and it applies to the subset of dementia in which tau phosphorylation is on the causal path. On the most defensible published accounting that is a minority of dementia as encountered — plausibly 10 to 15 per cent, and certainly not the majority. Section VII states what this does not explain, including the three facts that embarrass every theory in this field.

I. What kind of claim this is

The most common error in this literature is not being wrong. It is making one kind of claim and offering another kind of evidence.

An **initiation** claim asserts temporal priority — this happens first, the rest follows. It is adjudicated by human tissue sampled at the relevant stage, which for a disease with a two-decade preclinical phase is largely inaccessible. That inaccessibility is a sufficient explanation for why so many initiation claims coexist and so few are settled.

A **convergence** claim asserts necessity — whatever happens first, it must pass through here to produce this outcome. It is adjudicated by intervention in both directions: block the mechanism and the outcome should disappear; drive it and the outcome should appear. That is answerable in a laboratory, and unlike an initiation claim it is *strengthened* rather than weakened by a plurality of upstream causes.

This paper makes a convergence claim and offers interventional evidence. It does not claim to know what starts Alzheimer's disease. It claims that a specific node is load-bearing on the way out, and it accepts the standard of proof that goes with that.

II. The three subtractions

Iron

Elevated brain iron in Alzheimer's is well documented and had been associated with faster decline, which makes it an obvious target. A phase 2, double-masked, placebo-controlled trial of deferiprone 15 mg/kg twice daily ran for twelve months across nine Australian sites in amyloid-confirmed mild cognitive impairment or early Alzheimer's.

The chelator worked. Quantitative susceptibility mapping confirmed reduced hippocampal iron relative to placebo. And the treated group declined faster on the primary cognitive composite: β for interaction −0.50 (95% CI, −0.80 to −0.20), with the deferiprone group falling −0.80 z-score units against placebo's −0.30. Secondary analysis located the damage in executive function. Exploratory imaging found increased volume loss in frontal regions. The authors' conclusion is unambiguous: lowering iron with deferiprone is detrimental to patients with Alzheimer's disease.

Target engaged. Patients worse. That is the signature of removing something load-bearing.

Virus

Herpes simplex virus has a substantial epidemiological and neuropathological literature behind it as a candidate contributor. VALAD randomised 120 participants with early symptomatic Alzheimer's and HSV seropositivity to valacyclovir 4 g/day or placebo for 78 weeks.

Change on the 11-item ADAS-Cognitive subscale was 10.86 in the valacyclovir arm against 6.92 on placebo — a between-group difference of 3.93 (95% CI, 1.03 to 6.83; P = .01) in the direction of **greater cognitive worsening on treatment.** Amyloid and tau PET showed no significant difference. The conclusion states that valacyclovir was not efficacious, with cognitive worsening on the primary outcome.

A companion trial in mild cognitive impairment returned a null rather than a harm, which locates the harm at the symptomatic stage rather than earlier — a detail that matters for the argument in Section VI.

Checkpoint restraint

Immune-checkpoint blockade in Alzheimer's rests on a 2016 mouse result. In 2017 a consortium spanning three pharmaceutical companies, using the same anti-PD1 isotype and two mouse chimeric variants across a range of amyloid models, with two further models at two additional institutions, detected no monocyte-derived macrophage infiltration and no change in amyloid progression. Their stated conclusion was that animal model data do not support further evaluation of PD1 checkpoint inhibition as a therapeutic modality for Alzheimer's disease.

The programme proceeded anyway. A first-in-human randomised phase 1b of an engineered short-lived anti-PD-L1 cleared safety with no amyloid-related imaging abnormalities — and returned no significant efficacy signal.

Here the subtraction is of a *restraint on the immune system*, and the non-replication that predicted the outcome was published seven years before it.

III. The common structure

Iron, herpes simplex virus and immune checkpoints have nothing in common chemically. What they share is a place in the argument: each was identified as present in excess, and each was removed on the reasoning that excess implies harm.

Excess does not imply harm when the substance is part of a control system. Iron is a cofactor for the enzymes of oxidative metabolism, and executive function — the domain deferiprone damaged — is the most metabolically expensive cognitive function the frontal cortex performs. Checkpoint molecules exist to prevent autoimmune attack on the brain. And a fourth case, not a trial but a body of work, makes the same point about amyloid: monomeric amyloid-β appears to suppress microglial activation, so an agent that clears deposit also clears monomer, and removes a brake along with the target.

The pattern suggests a reframing. **Alzheimer's disease may be less a disorder of accumulation than a disorder of withdrawn restraint** — and if so, the therapeutic instinct to subtract is not merely ineffective but actively counterproductive, because it subtracts from a system already short of brakes.

IV. The node

If restraint-withdrawal is the right frame, it predicts a convergence point: something the brakes act on.

Glycogen synthase kinase-3β is the strongest candidate in the tau arm of the disease. It phosphorylates tau at multiple disease-associated epitopes; its activity is constitutive and its regulation is predominantly *inhibitory*, which is precisely the architecture a restraint-withdrawal model requires. A kinase that must be actively held down is a kinase whose pathology is the loss of whatever holds it.

The proposal here is that **two mechanistically unrelated brakes hold GSK-3β, and Alzheimer's releases both.**

V. Hand one — the noradrenergic brake

The locus coeruleus is the earliest site of tau pathology in the human brain and supplies the cortex with its noradrenergic innervation. Its degeneration removes tonic β-adrenergic signalling, and β-adrenergic tone acts through cAMP and protein kinase A to phosphorylate GSK-3β at its inhibitory serine-9 residue.

The logic is therefore direct: coerulean degeneration lowers cortical noradrenaline, lowers PKA-mediated serine-9 phosphorylation, and **disinhibits GSK-3**β. This arm is not original to this paper and is developed elsewhere; it is stated here because the conjunction in Section VII requires both hands to be on the table.

Evidence grade: the coerulean priority is established in human post-mortem tissue. The step from coerulean loss to cortical GSK-3β disinhibition in a human brain is inference from animal and cell work, and is the weaker half.

VI. Hand two — the withdrawn sulfhydration brake

The second hand is chemically unrelated to the first, and it is the element this paper adds.

Hydrogen sulfide, a product of the transsulfuration pathway, signals through a post-translational modification termed sulfhydration or persulfidation, in which a cysteine thiol is converted to a persulfide. Giovinazzo and colleagues showed that hydrogen sulfide **prevents tau hyperphosphorylation by sulfhydrating GSK-3β**, and reported four further findings that bear directly on the argument here:

- Cystathionine γ-lyase, the biosynthetic enzyme for hydrogen sulfide, **binds wild-type tau**, and this binding enhances its catalytic activity.
- Cystathionine γ-lyase **fails to bind tau P301L**, the mutant present in a widely used mouse model.
- The enzyme is **depleted both in that mouse model and in human Alzheimer brain**.
- **Sulfhydration is diminished in Alzheimer's**, and administering a hydrogen sulfide donor ameliorates motor and cognitive deficits in the model.

Three consequences follow, and the third is the one worth arguing about.

First, this is a brake, not a driver. Sulfhydration inhibits the kinase. Its loss releases it. That is the same causal shape as the noradrenergic arm, arrived at through entirely different chemistry.

Second, this is a bioenergetic input to a tau kinase. Transsulfuration sits downstream of methionine metabolism and cysteine availability, which is to say downstream of exactly the metabolic capacity that fails early in this disease. It provides a mechanistic route by which a bioenergetic lesion becomes a tau lesion without invoking amyloid as an intermediary.

Third — and this is a prediction, not a finding — the binding failure explains a modelling artefact. If cystathionine γ-lyase binds wild-type tau and is activated by it, but fails to bind P301L, then the most widely used tauopathy models are missing this brake *by construction*. They are not merely accelerated versions of the human disease; they are models in which one of the two restraints on the central kinase cannot engage. That would predict that P301L-based models systematically overstate tau kinase activity relative to human tissue, and it offers a specific reason

why interventions calibrated in those models translate poorly.

VII. The conjunction, stated so it can be broken

Sections V and VI describe two brakes. Each is separately evidenced. **The claim original to this paper is that they converge**, and that the convergence is what makes the disease progressive rather than merely present.

Stated precisely: *cortical GSK-3β activity in Alzheimer's disease reflects the sum of two independent restraints — serine-9 phosphorylation set by noradrenergic tone, and cysteine sulfhydration set by transsulfuration capacity — and tau pathology becomes self-sustaining when their sum falls below a threshold, not when either fails alone.*

This conjunction has never been tested in any system. Both arms have separate support; nothing measures them together. That is stated plainly because a conjunction presented as though it inherited the evidence of its parts is the characteristic error of synthesis, and this paper would rather be refuted than commit it.

The conjunction is not decoration. It makes three predictions the single-brake accounts do not:

1. **Sub-threshold interventions on either arm alone should fail**, and should fail *in proportion to how depleted the other arm is*. This predicts that noradrenergic therapies will show benefit only in patients with preserved transsulfuration capacity, and vice versa — a stratification nobody currently performs.
2. **Restoring either brake should be protective; removing either should be harmful.** The hydrogen sulfide donor result supplies the first half in a model. The second half is testable and, importantly, is the kind of experiment the subtraction error would otherwise invite someone to run on a patient.
3. **The two brakes should be jointly measurable in the same human tissue**, and their sum should track tau burden better than either alone. This is the discriminating experiment, and Section VIII states what result would sink the paper.

VIII. Scope — what this does not explain

A theory that explains everything forbids nothing. This one has a boundary and it is stated here rather than left to a reader to infer.

The fraction. This account applies where tau phosphorylation is on the causal path to cognitive failure. On the most defensible published accounting, pathologically pure Alzheimer's — amyloid-positive, tau-positive, of typical topography — accounts for something in the range of 3 to 22 per cent of dementia depending on how many co-pathologies a study scores, most plausibly 10 to 15 per cent. **This paper describes a minority of dementia as encountered in the clinic**, and does not claim otherwise.

Ignition without progression. Abnormal tau appears in the locus coeruleus of nearly every adult brain from the third decade. Primary age-related tauopathy — tau without amyloid — is common in the elderly and produces dementia at a small fraction of the rate seen in Alzheimer's. **Entry into this pathway is close to universal and is therefore not what distinguishes the people who become demented.** The threshold model in Section VII is an attempt to say what does; it is not a claim that the entry point is diagnostic, and any reading of this paper that treats coerulean tau as an early diagnostic marker misreads it.

Traversal without dementia. A substantial minority of people reach Braak stages V–VI without meeting criteria for dementia in life. This paper's threshold framing accommodates that only by asserting that their brakes held; it does not independently predict who they are, and that is a real weakness rather than a strength.

Dementia without explanatory pathology. A significant fraction of demented people have no pathology sufficient to account for their impairment on any panel. **This account says nothing whatever about them.** That is not a minor caveat: it means the framework is silent on a group large enough that a theory of dementia which ignored them would be describing something other than the clinical problem.

Co-pathology. TDP-43, Lewy pathology and arteriolosclerosis are each independently associated with cognitive impairment and are each more common than pure Alzheimer's in the ninth decade. Nothing here competes with them, and the honest position is that this paper describes one road through a junction rather than the junction.

IX. What would refute this

Written before the argument was assembled, and stated with the instrument that would return each result.

F1 — The conjunction fails. Measure serine-9 phosphorylation and GSK-3β sulfhydration in the same human cortical tissue across Braak stages, with tau burden. *If their sum does not track tau burden better than either measure alone, the conjunction adds nothing and this paper is a restatement of two existing claims.* Instrument: post-mortem cortex, phospho-specific immunoblot and a persulfide-switch assay. Both exist. This is the decisive test and it is cheap.

F2 — The brake is not a brake in humans. *If cystathionine γ-lyase depletion in human Alzheimer cortex does not correlate with regional tau phosphorylation, the metabolic arm fails.* Instrument: the same tissue. Note that the enzyme depletion in human brain is already reported; what is untested is whether it tracks the lesion regionally.

F3 — The modelling prediction fails. *If P301L and wild-type tau models show equivalent cystathionine γ-lyase engagement and equivalent sensitivity to hydrogen sulfide donors, the explanation offered in Section VI for model–human divergence is wrong.* Instrument: co-immunoprecipitation in both lines. This one is directly falsifiable in about six weeks.

F4 — Restoration fails where subtraction harmed. *If a hydrogen sulfide donor produces no cognitive benefit in a human trial stratified for low transsulfuration capacity, the therapeutic inversion in Section X is wrong.* Instrument: a phase 2 trial with plasma cysteine and homocysteine stratification.

F5 — The subtraction pattern is coincidence. *If a further trial removes something from the Alzheimer brain, engages its target, and produces clear benefit, the organising observation of this paper is weakened considerably.* Anti-amyloid immunotherapy is the live test; its modest positive effects on decline are the strongest existing evidence against the frame proposed here, and are acknowledged as such rather than explained away.

X. What follows

Stop subtracting without asking what the substance does when it is not in excess. Three trials have now engaged their targets and harmed or failed patients. The common feature is not the chemistry but the reasoning.

Restore restraint rather than remove substrate. The two brakes named here are both, in principle, restorable — one pharmacologically through hydrogen sulfide donors, one through preservation of noradrenergic tone. Neither has been tested against the other, and neither has been tested in patients stratified by the state of the opposite brake.

Stratify by brake state, not by pathology burden. If the threshold model is right, the reason single-target trials produce small average effects is that they are averaging over patients whose remaining restraint differs. That is a testable explanation for a pattern usually attributed to the drugs.

And measure both brakes in the same tissue before believing any of this. The conjunction is the paper's contribution and it is currently unevidenced. Section IX names the experiment that would settle it, it requires no new reagents, and it could be done in a year.

A note on evidence

The three trial results in Section II were verified against the primary literature rather than taken from secondary sources. The hydrogen sulfide findings in Section VI are stated as reported in the primary paper and are, at present, mouse and human post-mortem work from a single laboratory; no independent replication exists, and the therapeutic result is in a model, not a patient.

The weakest link in this paper is the conjunction in Section VII, and it is the only claim original to it. That is the honest position: the parts are borrowed and separately evidenced, the join is new and untested, and the join is what would have to be measured for any of this to be believed.