The Unthrown Switch

Cholesterol, the membrane raft, and Ari Rappoport's theory of a brain arrested between two stages of memory — a revisitation

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Memory formation runs in two stages, and the gate between them is a physical object — a patch of ordered, cholesterol-rich membrane a neuron must assemble before it can commit to anything it has just proposed. On this account Alzheimer's disease is not a poisoning and not a starvation. It is a brain stuck in the first stage, indefinitely and at low amplitude, and the pathology is the debris of trying again.

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Abstract

Most theories of Alzheimer's disease are theories about a substance. They name a molecule — amyloid-β, tau, a metal ion, a microbe — and account for the disease as that substance's accumulation or its loss. Ari Rappoport's theory is not of that kind. It is a theory about a *transition*: the moment at which a neuron stops making new synaptic candidates and starts choosing between them. On his account the brain runs memory formation as a two-stage process, the gate between the stages is a physical object — a patch of ordered, cholesterol-rich plasma membrane — and Alzheimer's disease is what a brain looks like when that gate will not open. The neuron is not poisoned and not starved. It is stuck in the first stage, indefinitely, at low amplitude, and every recognised feature of the disease follows from that arrest.

The theory has an unusual provenance. Rappoport was a professor of computer science at the Hebrew University of Jerusalem who spent the last fifteen years of his life reading the biomedical literature at industrial scale and writing single-authored theories of eleven brain diseases. He entered the Alzheimer's theory for the 2020 Oskar Fischer Prize; he rewrote it substantially in 2023 and 2024; the final version appeared in the *Annual Review of Biochemistry* in 2025, and in a book published by Elsevier the same year. He died in June 2025. There will be no further revisions, which makes this an unusually clean object of study: a complete theory, fixed in its final form, with a five-year documentary record of how its author changed his mind, and a testable central claim that the literature has since gone looking for without knowing it was looking.

This paper revisits the theory rather than the prize entry. Four findings organise it.

First, the revision between 2020 and 2025 is larger than the shared title suggests, and it runs in the direction of intellectual honesty. The core cause was moved one step downstream, from *cholesterol deficiency* to *raft failure*, which is not a cosmetic change: it converted an assertion about a quantity into an assertion about an assembly. Tau's physiological role was reversed. Long-term potentiation and depression were discarded as theoretical primitives. Short-term memory was promoted to the centre of the argument, giving the theory its sharpest prediction. The locus coeruleus and a sensory prodrome were added. And reelin, which carried substantial load in 2020, was quietly demoted to a background agent and then listed among topics deferred to future work — a retreat made in the same eighteen months in which human genetics delivered the strongest reelin result in the history of the field.

Second, the theory's most specific and most falsifiable claim has since been tested in human material and it held. Rappoport insisted, against the grain of his own supporting literature, that the lesion is in neuronal *uptake* rather than in astrocytic *synthesis*. In 2025 a study of cerebrospinal fluid from Alzheimer's patients reported exactly that dissociation: cholesterol efflux from astrocytes was indistinguishable from control, while lipoprotein-mediated delivery to neurons was significantly reduced, and reconstituted particles carrying APOE4 delivered less cholesterol to neurons than APOE3 particles. That is the theory's load-bearing prediction, stated in 2020,

confirmed in human fluid in 2025.

Third, the theory's central mechanism has also been contradicted, in a well-conducted human stem-cell system, in the opposite direction. APOE4 astrocytes have been shown to *over*-supply cholesterol to neurons, and that over-supply was necessary and sufficient to *expand* neuronal lipid rafts and increase amyloid-β production — with direct imaging of raft-localised amyloid precursor protein confirming it four years later. Rappoport's theory survives this result, because he had already built a two-neuron-type model that accommodates both raft deficiency and cholesterol excess. That survival is the problem. A framework that predicts both signs of its own key measurement has bought its coverage with its falsifiability, and this paper argues that the symmetry is the theory's deepest structural weakness — deeper than any individual error in it.

Fourth, the surrounding field has converged on Rappoport's cell biology from at least four independent directions without converging on his theory. APOE4 has become, in the 2021–2026 literature, a disorder of cholesterol trafficking rather than of amyloid binding. Cholesteryl esters have been shown to drive tau phosphorylation through the proteasome. A non-vesicular cholesterol transporter has been tied to lipid droplets, autophagic failure and phospho-tau in human neurons and in Alzheimer's tissue — answering, in part, the open question Rappoport flagged in his own discussion. And the phosphatase that erases tau turns out to require methylation for its own membrane targeting, in cholesterol-enriched microdomains, which is the single line in his paper with the least supporting text and the most independent corroboration.

The paper states what the theory establishes, what it merely arranges, and what it gets wrong; grades each claim; identifies a factual error about statins with real consequences for the therapeutic reading; and specifies six experiments that would decide the open questions. What survives is not a theory of what starts Alzheimer's disease. It is something rarer and, on the evidence, more useful: a precise, mechanistically committed account of what a neuron must physically accomplish in order to convert an experience into a structure — and of what it looks like when that accomplishment fails.

Note on sources

Rappoport's Alzheimer's theory exists in three public versions with a shared lineage and non-trivial differences: the November 2020 Oskar Fischer Prize submission; the arXiv preprint *A Lipid Rafts Theory of Alzheimer's Disease* (arXiv:2310.20232, version 1 dated 31 October 2023, version 2 dated 19 May 2024); and the peer-reviewed *A Lipid-Raft Theory of Alzheimer's Disease*, *Annual Review of Biochemistry* 94(1):387–416, published June 2025 with online publication on 30 October 2024. It also appears as Chapter 11 of *The Science of the Brain: Function, Dysfunction and Disease* (Elsevier, 2025). Throughout this paper these are cited as **2020**, **2024** and **2025** respectively. Where the argument turns on a difference between versions, both are quoted. The 2024 preprint and the 2025 review

share their abstract and their theoretical architecture; the preprint is quoted where wording is at issue, because it is the openly accessible text of the final theory.

1. A Theory Built by Reading

1.1 The author, and why the provenance matters

Ari Rappoport (1962–2025) was a professor in the Rachel and Selim Benin School of Computer Science and Engineering at the Hebrew University of Jerusalem. His first career was in computational geometry and then in computational linguistics, where he is best known for work on semantic representation and, more publicly, for a sarcasm-detection algorithm that *Time* named among its inventions of 2010. Nothing in that record predicts what followed.

In roughly the last fifteen years of his life he redirected his research entirely, and produced single-authored theories of eleven neurological and psychiatric conditions: autism, anorexia and bulimia, schizophrenia, depression and bipolar disorder, migraine, attention-deficit hyperactivity disorder, obsessive–compulsive disorder, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis with frontotemporal dementia, and Alzheimer's disease. Most were posted as preprints in 2024. All eleven, plus two chapters stating a general theory of brain function and a general architecture of brain control, were collected in *The Science of the Brain* (Elsevier, 2025). He described the method plainly: a systematic pass over the literature at a scale of several hundred thousand articles, of which some tens of thousands were read closely. He worked without a laboratory, without co-authors on the disease theories, and — as far as the public record shows — without ever running an experiment to test any of them.

He was diagnosed with small-cell lung cancer, a non-smoker, and completed several of the disease papers in the weeks after diagnosis. He died on 23 June 2025, a few weeks after the *Annual Review of Biochemistry* version of the Alzheimer's theory appeared in print.

The provenance matters for three reasons, and it is worth naming them before evaluating the content, because each of them cuts.

It explains the theory's shape. Rappoport read the literature as a corpus rather than as a research front. That produces a characteristic kind of theory: broad, tightly cross-referenced, organised around principles rather than around a favourite preparation, and unusually willing to assign physiological roles to molecules that experimentalists study only in their pathological form. Almost nobody with a bench and a grant writes this way, because almost nobody with a bench and a grant has the incentive to. The most valuable thing in his Alzheimer's papers — the account of what tau, amyloid precursor protein and amyloid-β are *for* — is a direct product of that reading posture.

It explains the theory's blind spots. A theory assembled from published claims inherits the publication record's selection effects, including its preference for positive findings and its habit of reporting the direction of an effect without reporting its magnitude. It also inherits a subtler problem: a reader deciding between two contradictory literatures has no experiment available to break the tie, and must break it by judgement. Rappoport broke several such ties, correctly in at least one important case and unfalsifiably in another, and Sections 5, 6 and 8 examine both.

It means the theory cannot answer back. This is the reason the present paper takes the form it does. Ordinarily an evaluation of a research programme is an intervention in a live conversation: the author replies, the theory is revised, the field moves. Here the text is final. What can be done instead is to hold the theory against the record that accumulated while it was being written and after it was finished, and to say precisely which parts of it the record supports.

1.2 What kind of claim this is

Alzheimer's theories are usually adjudicated as theories of **onset** — claims about the first event in a causal chain, tested by temporal priority in human tissue. The amyloid cascade hypothesis is of this kind, and so is most of what competes with it. Theories of onset are notoriously hard to settle, because human tissue offers a single frozen frame of a process that runs for twenty years or more.

Rappoport's theory is partly of that kind and partly not, and separating the two halves is the single most useful thing an evaluation can do for it.

The half that is a theory of onset is the weaker half: the claim that reduced neuronal cholesterol uptake, driven by ageing and pushed past a threshold by APOE4 or infection or insulin resistance, is *the* initiating lesion in sporadic Alzheimer's disease. That claim is exposed to all the usual difficulties, and Rappoport concedes as much in the 2024 text with unusual directness: "Our main theory prediction is that what causes the human disease diagnosed as AD is reduced cholesterol in neural PM LRs during plasticity. This has not been directly shown yet."

The half that is not a theory of onset is the stronger half, and it is what makes the work distinctive. It is a claim about **mechanism-in-health**: that memory formation proceeds in two stages, that the transition between them is gated by the assembly of a specific membrane structure, and that this is why the molecules of Alzheimer pathology exist at all. Claims of that shape are decided by necessity and sufficiency experiments in normal tissue, not by autopsy series. They are the sort of claim a reader without a laboratory can nonetheless get right, because the relevant experiments have mostly already been done for other reasons and are sitting in the literature waiting to be assembled.

The distinction has a practical consequence that recurs throughout this paper. Rappoport's plasticity theory can be substantially right while his disease theory is substantially wrong, and vice versa; they are logically separable even though he presents them as one structure. Readers who

reject the disease theory should not therefore discard the plasticity theory, which is where most of the theory's transferable content lives.

1.3 What this revisitation asks

Four questions organise what follows.

What does the theory actually claim, in its final form? Sections 2 and 3 reconstruct it from the 2024 and 2025 texts. This is necessary because the theory is widely referred to by the 2020 version's slogan — "cholesterol deficiency causes Alzheimer's" — which the final version does not assert.

What did its author change, and what does the pattern of changes reveal? Section 4 sets the versions side by side. The revisions are substantial, they are almost all improvements, and the one significant retreat is instructive.

How has the theory fared against evidence published since it was written? Sections 5 through 7 take the confirmation, the contradiction, and the four independent convergences in turn.

Where is it weakest, and what would settle it? Sections 8 through 10 state the failure modes, grade every load-bearing claim, and specify the experiments.

2. The Plasticity Theory That Carries the Disease Theory

Rappoport's Alzheimer's theory is downstream of a theory of normal plasticity, and cannot be assessed without it. In 2020 he called this the *competition theory of plasticity*; by 2024 it had become *adaptive response plasticity*, abbreviated T*PL. The renaming tracks a real change of emphasis, discussed in Section 4.

2.1 Two stages, and why there must be two

The premise is a piece of engineering logic rather than a piece of biology. When an organism executes a response with any element of novelty and survives, the pathways involved should be made more available in future. But the brain does not know *which* of the many synapses, boutons and branch points active during that response were the ones that mattered. It therefore cannot simply strengthen the correct elements, because it has not identified them.

Rappoport's answer is that biology solves this the way evolution and adaptive immunity solve it: by generating a surplus of candidates and then selecting among them. Plasticity accordingly runs in two stages.

Candidate generation. Neural activity with a novelty component triggers the destabilisation of the existing steady state and the production of an excess of potential modification sites: existing synapses marked for potentiation, new spines, new axonal boutons, new dendritic and axonal branch points, and occasionally new neurons. Destabilisation is not incidental — it is required, because a stable structure cannot generate new geometry. Extracellularly, matrix metalloproteinase-9 digests extracellular matrix and adhesion molecules; tissue plasminogen activator converts pro-neurotrophins to their mature forms; detachment from matrix triggers endocytosis of raft components including caveolin-1. Intracellularly, tau is phosphorylated and inactivated, releasing the microtubule–actin cross-links that hold the existing arrangement in place. Calcium-permeable receptors are inserted into the membrane, so that activity produces large calcium influx. Candidates are generated wherever novelty-related activity is occurring, indiscriminately.

Competition resolution. Winners are enhanced, losers are eliminated, and the whole structure is restabilised. Calcium influx is brought back down in winners *and* losers, because sustained calcium is toxic; calcium-permeable AMPA receptors are replaced by calcium-impermeable ones; GluN2B-containing NMDA receptors are switched to GluN2A.

Winners acquire a stable actin cytoskeleton, cross-linked to microtubules by dephosphorylated tau, and trans-synaptic nanodomains that align the release site with the receptor field. Losers are retracted. A long consolidation phase, much of it during sleep, rebuilds membrane, cytoskeleton, matrix and myelin.

Winner selection is not adjudicated by any central mechanism. It is a race, decided by which candidates sustain high, focused calcium signalling. Rappoport is explicit that competition is "race-like, not direct," with indirect competition over shared cellular resources.

None of the individual components here is novel, and Rappoport does not claim otherwise. Activity-driven spine formation, spine competition, spine elimination, and the receptor-subunit switches are all established. What is novel is the assertion that these constitute one canonical two-stage process with a defined transition between them — and the identification of what throws the switch.

2.2 The gate is a physical object

This is the theory's central and most distinctive claim.

The transition from candidate generation to competition resolution is not triggered by a timer, a counter, or a threshold on activity. It is triggered by the **assembly of plasma membrane lipid rafts**: ordered nanodomains enriched in cholesterol, sphingomyelin and glycolipids, which are the structures through which the membrane connects to the cytoskeleton, to the extracellular matrix, and to the synaptic partner on the other side of the cleft.

The reasoning is that competition resolution requires capabilities that only rafts provide. A winning spine cannot be stabilised without anchoring receptors and scaffolds in position, and stable membrane anchoring of the relevant proteins — postsynaptic density proteins, glutamate receptors and their recycling machinery, steroid receptors, G-protein-coupled receptors, actin regulators — depends on palmitoylation, which targets proteins to rafts. Microtubule-associated proteins, tau chief among them, associate with rafts; disrupting that association produces axonal retraction. Trk receptors and the insulin receptor are anchored and trafficked through caveolin-1-containing rafts. So the neuron cannot begin to consolidate anything until it has built the platform on which consolidation is physically performed.

And then the load-bearing step: **the rate-limiting ingredient in that platform is cholesterol, and neurons do not make their own.** Brain cholesterol does not cross the blood–brain barrier. It is synthesised by astrocytes, packaged into apolipoprotein E particles, released, and taken up by neurons through the LDL receptor and LRP1. Rappoport's argument for why this specific dependency is the vulnerable one is a physical argument rather than a statistical one, and it is the best single paragraph in the theory: unlike glutamine or lactate, the other things astrocytes hand to neurons, cholesterol has a large hydrophobic domain, so it cannot simply diffuse

or ride a small transporter. Its delivery requires "relatively heavy machinery" — a lipoprotein particle, a receptor, an endosome, and a route to the plasma membrane. Any step in that chain can fail, and the chain has no redundancy of the relevant kind, because neuronal cholesterol synthesis, which does exist and does increase under stress, cannot substitute for delivered cholesterol in building plasma membrane rafts.

The claim, then, is that **the switch between the two stages of memory formation is thrown by the arrival of astrocyte-derived cholesterol at the neuronal plasma membrane** — and that this is a design feature, not an accident. Cholesterol arrival is a meaningful signal: it indicates that an astrocyte process is close enough to the new synapse to supply it, and therefore that consolidating a synapse at this location is worth doing. The switch is a supply check.

Whether or not this is true, it is a genuine idea, it is specific, and it is testable. Section 10 says how.

2.3 Double-edged plasticity

The second structural principle is required by the first. If candidates are generated indiscriminately, and if the same diffusing agents reach winners and losers alike, then some mechanism must produce opposite outcomes in the two populations from the same signal.

Rappoport's answer, which he names **double-edged plasticity**, is that a single agent induces opposite effects depending on its amount, its rate, or which cleavage product is present. Amount-dependence works through affinity: an agent binds one receptor at high affinity and another at low affinity, so low concentrations engage only the first and high concentrations engage both. Because chemical signals propagate in a medium, only a spatially focused path enjoys high concentrations — so concentration *is* the spatial code that distinguishes winners from losers.

He offers four instances, of which the first is the important one:

- **Calcium.** High or fast calcium activates calcium/calmodulin-dependent kinase II and marks winners; low calcium activates the phosphatase PP2B (calcineurin) and eliminates losers.
- **Dopamine.** The low-affinity D1-like family supports vigorous activity through Gs and Gq; the high-affinity D2-like family opposes it through Gi/o.
- **Serotonin.** High- and low-affinity receptor families with opposing effects on effortful activity.
- **Cleavage pairs.** Pro-neurotrophins signal through p75 and support loser removal; the mature forms signal through Trk receptors and support winner growth. The amyloid precursor protein behaves the same way, and this is where the principle earns its place in an Alzheimer's theory.

Rappoport notes the resemblance to hormesis and claims that stating double-edged plasticity as a general biological principle is original to him. The individual oppositions — CaMKII against PP2B, Trk against p75 — are of course textbook. What is not textbook is the claim that these are instances of one mechanism doing one job, namely converting a scalar concentration gradient into a binary structural decision.

This principle does a great deal of work later, and it is worth flagging now that it does *too much*. Because a double-edged agent can produce either outcome, a theory built on double-edged agents can accommodate either direction of any measured change. Section 8.1 returns to this.

2.4 Physiological roles for the pathological molecules

The payoff of the plasticity theory, and in my judgement its most durable contribution, is that it assigns each of the major Alzheimer's molecules a job in the healthy brain. This inverts the field's usual posture, in which tau phosphorylation and amyloid-β production are understood primarily as things that go wrong.

Amyloid precursor protein manages cholesterol during plasticity. Its two cleavage routes are mutually exclusive and belong to the two stages. Alpha-secretase cleavage yields soluble APPα, a candidate-generation agent: it is promoted by candidate-generation signals (BDNF, NGF, tissue plasminogen activator, MMP-9, protein kinase C), it occurs in non-raft membrane, it is stimulated by *reduced* membrane cholesterol, and it promotes cholesterol synthesis — the intracellular fragment raises SREBP2 in low-cholesterol cells, and soluble APPα binds and activates the insulin receptor, which drives SREBP2 through PI3K/Akt/mTOR. Soluble APPα also raises surface GluA1, lowers GluA2, and promotes neurite growth, branching and spine density. In other words, APP's alpha route is the neuron requesting cholesterol and building candidates while it waits.

Amyloid-β terminates candidate generation and removes losers. Beta-secretase cleavage begins when cholesterol has arrived and rafts have formed: cholesterol is required for amyloid-β production, and its depletion inhibits β- and γ-secretase additively. Amyloid-β then exerts negative feedback on cholesterol synthesis — the request is cancelled once it has been filled. Its loser-removal function runs through three routes: RhoA, which opposes Rac1; tau phosphorylation via GSK-3β and JNK; and p75, which stops neurite growth, induces apoptosis, and with amyloid-β activates sphingomyelinase to strip sphingomyelin from the membrane of losing candidates. Amyloid-β also opposes candidate-generation signalling broadly — Akt, insulin, nicotinic receptors, NGF and BDNF.

Tau cross-links the cytoskeletons of winners. Phosphorylation inactivates tau; dephosphorylation activates it. During candidate generation tau is phosphorylated everywhere, by PKA, MARK2, CaMKII and ERK at defined sites, in order to release the existing structure. During competition resolution it is dephosphorylated in winners — by PP2A — so that it can

cross-link microtubules to actin and stabilise the growing spine, and it is kept phosphorylated in losers, by GSK-3β and CDK5 with p75, so that they can be dismantled. Tau phosphorylation is therefore a normal, necessary, spatially patterned part of memory formation, not a pathological event.

Whatever one concludes about the disease theory, this triad is a substantive proposal, and it has the property good proposals have of being uncomfortable. It says amyloid-β is *supposed* to remove synapses. It says the field's central pathological marker, phospho-tau, is the default state of tau in any neuron that is currently learning something. And it makes a prediction that has been borne out independently of the theory: interfering with amyloid-β prevents memory consolidation and stabilisation.

2.5 Short-term memory is candidate generation

The final piece is the boldest, it is absent from the 2020 version, and it converts the theory from an account of pathology into an account of cognition.

Candidate generation, Rappoport claims, *is* short-term memory. The destabilised, calcium-permeable, candidate-rich state that follows a novel experience is the physical substrate of holding that experience briefly. Competition resolution is the conversion to long-term memory. Two supporting observations are offered. First, GluA1 — inserted during candidate generation — is required for short-term and working memory but not for spatial reference memory, in knockout animals. Second, sustained calcium/calmodulin binding to PSD-95 reduces its palmitoylation and synaptic localisation and increases AMPA receptor endocytosis within about fifteen minutes, a timescale that "accords with the duration of short-term memory."

The disease consequence is immediate and is the reason the claim matters: if the raft switch fails, short-term memory should be *intact* while its conversion to long-term memory fails. Rappoport states this as one of his three founding clues — "the characteristic symptom of AD, impaired anterograde memory with functioning short-term memory."

This is the most clinically legible prediction in the theory and the one most exposed to falsification. It is also the one place where the theory's phenomenology deserves a harder look than he gives it, because working memory is not in fact well preserved in Alzheimer's disease; deficits in working memory and in attentional control are documented early, and the "isolated anterograde amnesia" picture is closer to the textbook caricature of early Alzheimer's than to the neuropsychological literature. Section 8 treats this as a real liability rather than a quibble: the theory needs *some* short-term retention to survive intact, and the version of that claim which the theory can afford is narrower than the version it asserts.

3. The Disease Theory

3.1 Three clues and one inference

Rappoport builds the disease theory by abduction from three facts, and sets the reasoning out explicitly enough to be audited.

Clue one — APOE4. The strongest genetic risk factor concerns a cholesterol transport protein. This "points to reduced transport, neural uptake, or neural trafficking of cholesterol."

Clue two — the symptom. Impaired anterograde memory with functioning short-term memory "points to a problem in the initiation of Cres or in winner enhancement" — that is, the switch or what follows it.

Clue three — the pathology. Hyper-phosphorylated tau and amyloid-β "point to chronic Cgen or excessive loser removal."

One hypothesis satisfies all three. The main role of cholesterol in plasticity is in rafts; therefore the lesion is raft formation; therefore the switch does not throw; therefore short-term memory is not converted; therefore tau is not dephosphorylated; therefore the neuron is chronically stuck in a low-amplitude generation state, which is a state of chronic loser removal. The conclusion, in his words:

> *AD symptoms and pathology are caused by impaired formation of plasma membrane lipid rafts, which is in turn caused by reduced neural uptake or trafficking of astrocyte-produced cholesterol.*

Note what has happened to the theory's centre of gravity between the two versions. In 2020 the headline lesion was a *quantity* — neural cholesterol deficiency. In 2024 it is an *assembly* — plasma membrane raft formation — with the cholesterol deficit demoted to the most common cause of it. This is the single most consequential revision in the theory's history, and Section 4.2 argues that it is also the most defensible.

3.2 Chronicity does the explanatory work

The mechanism that converts a stalled switch into a disease is *chronicity*, and it is more elegant than it first appears.

If the switch is thrown by raft assembly, and raft assembly is impaired but not abolished, then the neuron neither completes plasticity nor abandons it. Both stages run simultaneously, at lower

agent concentrations than either would use in health, and for far longer. That is the definition of a chronic state.

Three consequences follow, and each maps onto something the field measures.

The staging of agent changes. Early in disease, both generation and resolution agents should be elevated, because both programmes are running. Later, as resources deplete, resolution should rise while generation falls. Rappoport claims this is what the literature shows: tau phosphorylation agents — ERK, p38, JNK, GSK-3, PP2B, CDK5 — chronically increased, PP2A decreased, and, tellingly, protein kinase C and GluA2, which he identifies as the specific hallmarks of successful winner enhancement, *reduced* in Alzheimer's disease, with the largest GluA2 decrease in the most vulnerable hippocampal fields. He draws the inference sharply: PKC is activated by moderate calcium, so chronic calcium should have raised it; that it is reduced instead "indicates a fundamental non-Abeta problem in winner enhancement processes."

Double-edged inversion. Because many plasticity agents are double-edged and chronicity means *lower* concentrations, chronic signalling is tilted towards the resolution edge. Chronic low calcium means chronic loser removal. So the neuron's attempt to compensate — continued candidate generation, which would normally drive cholesterol synthesis and rescue the situation — instead produces degeneration. The compensation is the pathology. This is the theory's best single move: it explains why a partial failure is worse than a complete one.

Receptor desensitisation. Chronic signalling desensitises receptors and pathways through the negative feedback that biological systems rely on, so signalling degrades further. The lesion deepens itself.

3.3 Two kinds of neuron, and one very large concession

The theory's treatment of cholesterol *levels* is where it becomes difficult, and it deserves to be quoted rather than paraphrased.

Rappoport recognises that the literature reports both decreased and increased cholesterol in Alzheimer's brain. He argues that his theory requires neither, because what it requires is reduced cholesterol *in plasma membrane rafts*, which is compatible with elevated cholesterol elsewhere. If raft incorporation fails while synthesis continues — and synthesis will continue precisely because the membrane sensor never registers sufficiency — then the cell accumulates cholesterol it cannot use. Hence: "AD can involve both cholesterol deficiency (in PM LRs) and excess."

He then formalises this into two neuronal populations:

- **Type one.** Chronic cholesterol production eventually succeeds in forming plasma membrane rafts. These neurons form synapses normally and show no tau pathology — but because

cholesterol stimulates amyloid-β production, they over-produce amyloid-β, secrete it, and it aggregates.

- **Type two.** Chronic production does not compensate. These neurons show plasticity failure, tau pathology *and* amyloid pathology.

The pay-off is genuine, and it is the cleanest thing the theory does with the field's most persistent embarrassment. Amyloid plaques are common in cognitively normal older people and correlate weakly with symptoms and with tau — because plaques are the product of *type one* neurons, in which the disease mechanism has been successfully compensated. Plaque is the signature of a solved problem. Tangles are the signature of an unsolved one. "They are neither causal nor essential for the disease."

That is a good explanation. It is also the moment at which the theory stops being falsifiable by any measurement of cholesterol or amyloid in Alzheimer's tissue, and Section 8.1 pursues the consequence.

3.4 Why these regions, and why these senses

The regional argument is one of the theory's strengths, because it is derived rather than fitted.

If the lesion is in plasticity, the most vulnerable regions should be those with the highest plasticity demand. Rappoport identifies the earliest tau-bearing regions as entorhinal cortex, hippocampus and locus coeruleus, and argues that all three are exactly where continuous plasticity is required: entorhinal cortex and hippocampus represent scenes and events, whose richness presents continuous novelty; the locus coeruleus, the brain's principal noradrenergic nucleus, is engaged in every novel situation.

He then does something more discriminating with the hippocampal subfields, which is where the argument earns its keep. CA1 and subiculum are much more vulnerable than dentate gyrus and CA3. His explanation: CA1 and subiculum support *familiar* scenes while dentate gyrus and CA3 encode *new* ones, and most life experience consists of familiar scenes with an element of novelty — the exact condition that triggers candidate generation without triggering wholesale new encoding. Entorhinal cortex serves both, hence its primacy. He notes that the nucleus reuniens, which connects entorhinal cortex, subiculum, CA1 and medial prefrontal cortex, is among the most affected thalamic nuclei.

The sensory argument is newer and sharper. Olfactory, auditory and retinal impairments occur very early in Alzheimer's disease. Rappoport's explanation is that the relevant sensory cells are raft-dependent — and he supports it with a pharmacological triangulation that is characteristic of his method at its best: statin use is associated with sudden hearing loss in a national insurance database; statins are among the drugs that impair olfaction; and cholesterol depletion causes hearing

loss in cats and severe cochlear hair-cell loss in mice. A raft theory predicts a sensory prodrome. The prodrome exists. Cholesterol depletion reproduces it.

3.5 Familial disease as a different disease with the same machinery

Rappoport separates autosomal dominant Alzheimer's disease from the sporadic form and does not attempt to force them into one mechanism — a discipline worth noting, since the field's dominant theory has spent thirty years doing the opposite.

His account: autosomal dominant disease involves loss-of-function mutations in *PSEN1*, encoding a component of γ-secretase, or mutations at the γ-secretase cleavage site of APP. Because those mutations affect both soluble APPα and amyloid-β — a candidate-generation agent and a resolution agent — they damage plasticity from both sides, which explains the early onset. The brain manages until middle age "probably" because of functional redundancy among the many generation and resolution agents.

Two observations. First, the framing of presenilin mutations as *decrease*-of-function rather than as amyloid-increasing is a substantive and contested position in the field, not a neutral description, and the 2024 text adopts it without arguing for it. Second, this is one of the places where the theory's coverage is thinner than its confidence: "probably" and "functional redundancy" are doing a lot of work for a thirty-year latency.

4. What Changed Between 2020 and 2025

The two versions of the Alzheimer's theory share a title, an author and a central molecule, and they are not the same theory. Setting them side by side is the most direct way to see what Rappoport thought was wrong with his own work, and it is the part of this revisitation with no substitute in the secondary literature, because nobody appears to have done it.

	2020 (Prize submission)	**2024 / 2025 (arXiv, *Annual Review*)**
Plasticity theory	Competition theory of plasticity (compPL)	Adaptive response plasticity (T*PL)
Stage names	Positive plasticity / consolidation	Candidate generation / competition resolution
Named core cause	Neural cholesterol deficiency	Impaired plasma membrane lipid raft formation
LTP / LTD	Integrated as theoretical primitives, with a dedicated section	Explicitly discarded: "not used in T*PL"
Tau's role	Supports steady-state stability; membrane–cytoskeleton link	Cross-linker driving dynamic change; activated in winners
Short-term memory	Absent	Central; candidate generation *is* short-term memory
Locus coeruleus	Not mentioned	Among earliest tau regions; explained by novelty demand
Sensory prodrome	Hearing loss as a social-isolation risk factor	Olfaction, hearing, retina as early raft-dependent symptoms
Reelin	Dedicated section; terminates consolidation; suppresses amyloid-β and GSK-3β	Demoted to a candidate-generation agent; listed among deferred topics
Voice	"We present a theory…"	"I present a theory…"
Evidential claim	"We are not aware of any contradicting evidence"	"Supported by very strong evidence"

4.1 The pivot: from a quantity to an assembly

The most important change is the one in the third row, and it is easy to underrate because both versions talk about cholesterol throughout.

The 2020 theory asserts a deficit in a substance. That claim is directly vulnerable to measurement: if brain cholesterol is not reduced in Alzheimer's disease, the theory is in trouble — and brain cholesterol is, on the weight of evidence Rappoport himself assembles, more often reported as *increased*. He was aware of this in 2020 and handled it with an argument that reads, in the earlier text, as a patch: reduced *uptake* rather than reduced *synthesis*, so total cholesterol can rise while neurons starve.

By 2024 that patch has become the architecture. The core cause is no longer a quantity but a structure — raft formation — and cholesterol delivery is one route to failing it among several. This is a genuine improvement in the theory's logical form, because it relocates the claim to the level at which the mechanism actually operates. A raft is either assembled or it is not, and no bulk lipid measurement settles it. It is also what allows the two-neuron-type model, and therefore what creates the falsifiability problem of Section 8.1. The same move that made the theory more accurate made it harder to refute.

4.2 Discarding LTP and LTD

In 2020, long-term potentiation and depression are load-bearing: there is a subsection on them, they are mapped onto the two stages, and a defence is offered of LTD as constructive rather than merely subtractive.

In 2024 they are gone, deliberately and with a stated reason:

> *The notions of long-term potentiation (LTD) and long-term depression (LTD), which are ubiquitously used in relation to plasticity, are not used in T*PL. LTP occurs in both Cgen (all over) and Cres (in winners), and LTD occurs in Cres in both winners and losers. These terms are suitable for describing the local effects of specific experimental conditions, not for the high-level theory.*

(The typographical error in that passage — "long-term potentiation (LTD)" — is his; it survived into the preprint's second version.)

This is a real theoretical decision and, I think, a defensible one. Potentiation and depression are descriptions of what an electrode records under a particular stimulation protocol. If plasticity is a two-stage structural process, then those recordings cut across the stages rather than corresponding to them, and building a theory on them imports a confusion. The cost is significant: discarding the field's standard vocabulary makes the theory harder to test with the field's standard assays, and contributes to the isolation discussed in Section 8.3.

4.3 Tau reversed

In 2020, tau's role "is to support steady state structural stability," and he notes that microtubule stability "is mainly supported by the protein tau, and this is widely viewed as tau's role." His contribution there was to add the membrane: "in our view the role of tau is to support both the cytoskeleton and its membrane/LR interaction."

By 2024 the premise has been withdrawn:

> *Tau binds cytoskeleton MTBs and was initially thought to support MTB stability. However, its detachment from MTBs does not destabilize them or impair axonal transport. It is now viewed as a cross-linker of the MTB and actin cytoskeletons that promotes dynamic changes including axonal elongation, synapse formation, and stabilization of growing neurites.*

This is a straightforward update to the experimental literature, and it improves the theory's internal coherence considerably. A tau whose job is *dynamic cross-linking during growth* fits the two-stage scheme far better than a tau whose job is holding still — and it makes the spatial pattern of tau phosphorylation (dephosphorylated in winners, phosphorylated in losers, at the same moment in the same neuron) into a natural consequence rather than an added assumption. It is the clearest case in the record of Rappoport revising a claim because the evidence moved, at the cost of a position he had published.

4.4 Reelin, demoted

The one significant retreat runs the other way, and its timing is unfortunate.

In 2020, reelin has a dedicated section and carries real load. Its role is "axonal elongation, synapse formation, and consPL termination." It promotes APP and its alpha cleavage. Its receptor ApoER2 is raft-dependent and "crucial to final synaptic adhesion," and suppresses amyloid-β and GSK-3β "to terminate consPL." Reelin's failure is offered as a route to chronic consolidation independent of cholesterol: "defective reelin signaling (e.g., due to impaired LRs) can induce a chronic consPL state." Its expression in entorhinal layer 2 neurons — the earliest-affected population — is used as positive anatomical evidence: "these anatomical impairment data further point to a synapse formation problem (a general one, or specific to reelin)." He cites excess-with-impaired-signalling in Alzheimer's disease, *RELN* variants associated with disease, and reduced reelin with memory deficits in aged monkeys and rats.

In 2024, reelin appears in a single paragraph as a candidate-generation agent promoting alpha cleavage and neurite branching, with the role "to promote integration of new neurons and events into the network." The consolidation-termination function is gone. ApoER2's role in adhesion and amyloid-β suppression is gone. The *RELN* genetics is gone. And reelin appears in the list of "additional topics left to future texts."

Two things make this worth dwelling on rather than noting.

First, it removed the theory's only non-cholesterol route to the central pathology. In 2020 there were two ways to get a chronically stalled switch: cholesterol failure, or reelin-signalling failure. In 2024 there is one. The theory became more parsimonious and simultaneously more fragile — everything now depends on a single supply chain.

Second, the demotion happened across exactly the interval in which reelin produced the strongest human resilience result the field has: the *RELN*-COLBOS variant (H3447R), reported in 2023 in a carrier of the *PSEN1* E280A mutation who remained cognitively intact at 67 and reached only mild dementia at 72, despite very high amyloid burden and with limited entorhinal tau. The variant enhances interaction with ApoER2 and VLDLR and increases downstream DAB1 phosphorylation with suppression of tau phosphorylation. That is: a gain-of-function in the exact receptor system Rappoport had called raft-dependent and crucial, producing exactly the phenotype his theory says matters — amyloid uncoupled from tangles and from dementia, in the entorhinal cortex, in a human being.

The 2024 text does not cite it. I do not think this reflects carelessness so much as the hazard of the method: a solitary reader revising a manuscript makes decisions about what to cut before the field has finished telling him which cuts were wrong, and has no colleague to say *not that one*.

4.5 The register

The last two rows of the table are small and worth recording. The prize submission uses the scientific "we"; the final papers use "I". And the 2020 claim — "All aspects of our AD and plasticity theories are supported by a large corpus of evidence, and we are not aware of any contradicting evidence" — does not survive. The 2024 and 2025 abstracts claim strong support and that the theory "addresses all of the major established facts," which is a different and more defensible assertion. Between 2020 and 2024 Rappoport stopped claiming that nothing contradicted him. Section 8.7 argues he did not go far enough, but the direction is right.

5. The Prediction That Held

Rappoport's theory makes one prediction that is specific, mechanistically committed, contrary to the simpler reading of his own supporting literature, and testable in human material. It concerns the location of the lesion in the cholesterol supply chain.

The chain has three steps: astrocytes synthesise cholesterol; astrocytes package and release it on apolipoprotein E particles; neurons take it up. A theory that merely said "cholesterol is low in Alzheimer's disease" would be agnostic about which step fails. Rappoport was not agnostic. He insisted, in both versions, that the lesion is at **uptake**, not synthesis:

> *Note that chronic cholesterol does not contradict neural cholesterol deficiency and impaired termination of posPL by cholesterol, because the problem in AD is reduced uptake, not reduced synthesis. (2020)*
>
> *The logic and evidence of our theory support a case for impaired neural uptake, not for impaired synthesis. (2020)*

This mattered to him because it was load-bearing in an argument against a rival: he used it to reject brain insulin resistance as the core cause, on the grounds that insulin resistance reduces cholesterol *synthesis*, which is not what his theory claims is wrong.

In 2025, Borràs and colleagues measured precisely this dissociation in human cerebrospinal fluid. Comparing Alzheimer's patients with controls, they reported that **cholesterol efflux from astrocytes to cerebrospinal fluid was similar between the two groups, while cerebrospinal-fluid lipoprotein-mediated neuronal cholesterol uptake was significantly reduced in the Alzheimer's group.** They then tested the isoform question directly with reconstituted particles: synthetic HDL carrying APOE4 delivered less cholesterol to neurons than APOE3-carrying particles.

This is as close to a clean confirmation as an inferential theory is likely to receive. The prediction was published in 2020, restated in 2024, and independently confirmed in human fluid in 2025, in the specific form in which it was made: **supply intact, delivery impaired, APOE4 responsible.** The confirming study makes no reference to Rappoport, which strengthens rather than weakens the point — it was not looking for his theory.

Three qualifications keep this in proportion, and they matter because this is the strongest card the theory holds.

It confirms the step, not the consequence. Impaired neuronal uptake is one link in Rappoport's chain. The chain continues: impaired uptake → impaired plasma membrane raft assembly → failure of the candidate-generation-to-resolution switch → chronic plasticity → tangles and degeneration. Only the first link has been tested. Nothing in Borràs et al. speaks to rafts, to a switch, or to plasticity stages.

Directionality is unresolved. Cerebrospinal-fluid measurements in diagnosed patients cannot distinguish a cause from a consequence. Reduced neuronal uptake in established disease is compatible with reduced uptake having *caused* the disease and with degenerating neurons having reduced their uptake. The rHDL-APOE4 result is stronger on this point, because isoform-dependent delivery in a controlled system is a property of the particle rather than of the patient — but that is a cell-culture claim standing in for a lifetime.

It is a delivery result, not a raft result. Rappoport's theory needs cholesterol to fail to reach a particular destination — the ordered nanodomains of the plasma membrane — and cellular uptake is upstream of that destination. A neuron could take up less cholesterol and still build adequate rafts, or take up normal amounts and fail to build them. Section 6 shows that the second possibility is not hypothetical.

Grade: well-supported. The specific prediction about uptake versus synthesis is confirmed in human material and in a controlled isoform comparison. The inference from it to raft failure remains untested.

6. The Prediction That Came Out Backwards

Set against the confirmation is a contradiction of comparable quality, and the theory's response to it is the most revealing thing about its structure.

In 2021, Lee and colleagues — working in isogenic human induced pluripotent stem cell-derived neurons and astrocytes differing only at the *APOE* locus, with the Tsai laboratory as co-authors — reported the opposite of what Rappoport's mechanism requires at every step. Secreted factors from APOE4 astrocytes raised amyloid precursor protein levels and amyloid-β secretion in neurons. The mediator was cholesterol, and the direction was *up*: **increased cholesterol secretion from APOE4 astrocytes was necessary and sufficient to induce the formation of lipid rafts** in the recipient neurons, providing an expanded platform for APP localisation and processing. The title states the finding without hedging: APOE4 astrocytes *oversupply* cholesterol to promote neuronal lipid raft *expansion*.

The result was not left as an inference from bulk lipid. In 2025 the same group imaged it. Using time-of-flight secondary ion mass spectrometry to visualise rafts at single-cell resolution in human iPSC-derived neurons, Lee et al. showed that astrocytic ApoE4 increases APP localisation *on* lipid rafts, elevating amyloid-β42 production through a clathrin-independent route. The platform was seen, and it was larger.

Every element of Rappoport's mechanism is inverted here. APOE4 astrocytes supply more cholesterol, not less. Neuronal rafts expand, not fail. And the pathological consequence flows *through* successful raft assembly rather than through its absence.

6.1 Why the theory survives, and why that is bad news

Rappoport's framework absorbs this without strain, and it does so because he built the absorber before the result arrived.

Recall the two neuronal types of Section 3.3. Type one is the neuron in which chronic cholesterol production eventually *does* establish plasma membrane rafts: "Such neurons form synapses and do not show tau pathology, but do show excessive Abeta production, causing Abeta secretion and aggregation." That is a precise description of the Lee et al. neuron — cholesterol up, rafts up, amyloid-β up, tau pathology absent from the report. Read through the theory, the 2021 and 2025 results are not a contradiction at all; they are a characterisation of the compensated population, in a dish, in the absence of the ageing that would exhaust it.

This is either an impressive piece of foresight or a symptom, and the honest answer is that it is both, with the second predominating. Consider what the theory now permits:

- Astrocytic cholesterol output reduced → predicted (impaired supply).
- Astrocytic cholesterol output increased → predicted (chronic synthesis without incorporation).
- Neuronal cholesterol reduced → predicted (impaired uptake).
- Neuronal cholesterol increased → predicted (accumulation of unusable cholesterol; type-one compensation).
- Rafts reduced → predicted (the core lesion).
- Rafts expanded → predicted (type-one compensation succeeding).
- Amyloid-β up with tangles → predicted (type two).
- Amyloid-β up without tangles → predicted (type one).

There is no measurement of brain cholesterol, neuronal cholesterol, or raft abundance in Alzheimer's tissue that the theory forbids. Section 8.1 develops this as the theory's central structural weakness. Here the narrower point suffices: the theory's ability to accommodate the Lee results is not evidence in its favour.

6.2 What would actually break the tie

The two literatures are not straightforwardly reconcilable, and the difference between the preparations is where the resolution has to come from.

Borràs et al. measured *delivery to neurons* using cerebrospinal fluid from ageing human beings with the disease. Lee et al. measured *raft formation in neurons* using astrocyte-conditioned medium from young isogenic stem-cell-derived cells with a risk genotype and no disease. Those are different questions asked of different systems at different points in a lifetime, and it is entirely possible that both are right: that APOE4 in a young brain over-supplies cholesterol and expands rafts, which is why APOE4 is associated with better cognition in youth, and that the same allele in an aged brain under-delivers, which is when the disease appears. Rappoport himself argues that APOE4 is efficient early and costly late, and offers "ApoE4 appears to be calibrated such that it can provide the amounts required until middle age, but not later."

That reconciliation is available to the theory, it is consistent with its own commitments, and it converts an apparent contradiction into a prediction — that the direction of the APOE4 effect on neuronal raft cholesterol *reverses with age*. Nobody has tested it. It is the single most decisive experiment the theory implies, and Section 10 specifies it.

Grade: contradicted in a young human cellular system; unresolved in the aged human brain. The theory's accommodation of the contradiction is legitimate but purchased at the cost of falsifiability.

7. The Convergence Nobody Planned

The most interesting thing about the 2021–2026 literature, read against Rappoport's theory, is not any single confirmation or refutation. It is that four independent research programmes, none of them citing him and none in dialogue with each other, moved the field towards his cell biology while leaving his theory untouched.

7.1 APOE4 became a cholesterol-trafficking disease

For thirty years the standard mechanistic account of APOE4 ran through amyloid: differential binding, differential clearance. The literature of the last five years has substantially relocated the mechanism into lipid handling, and specifically into the failure of cholesterol to arrive where it is needed.

The pivotal result is Blanchard et al. (2022). In human cells and in mice, APOE4 produced lipid and cholesterol dysregulation most prominently in *oligodendrocytes*, where cholesterol accumulated intracellularly rather than reaching the myelin sheath — and myelination was impaired as a consequence. Treatment with cyclodextrin reduced the intracellular accumulation, increased trafficking of cholesterol to the sheath, raised myelin basic protein, improved oligodendrocyte maturation and myelination, and produced modest improvements in learning and memory.

The structural analogy to Rappoport's central claim is exact, and it is worth stating carefully because the cell type is wrong. Rappoport's mechanism is: cholesterol is made, cholesterol is not delivered to the membrane structure that needs it, the structure fails, function fails, and the cell accumulates cholesterol it cannot use. Blanchard et al. found that pattern in oligodendrocytes and the structure was myelin. Rappoport claims it in neurons and the structure is the plasma membrane raft. Neither predicts the other, and the oligodendrocyte result is not evidence for the neuronal one. What it establishes is that the *form* of lesion Rappoport posits — synthesis intact, trafficking to a specific membrane destination broken, with intracellular accumulation as the signature — is a real thing that APOE4 does in the human brain.

Around this sit a cluster of findings in the same direction: APOE4 astrocytes accumulating intracellular cholesterol and lipid droplets relative to isogenic APOE3 controls; higher cholesterol synthesis with lower catabolism and efflux predicted transcriptomically across APOE4 glia; APOE4 lysosomal cholesterol accumulation impairing mitochondrial oxidative phosphorylation in human astrocytes. And Fortea et al. (2024) reported that APOE4 homozygotes — 2% of the population, 15% of Alzheimer's patients — show near-universal Alzheimer pathology and elevated biomarkers from age 55, sufficient for the authors to propose APOE4 homozygosity as a distinct genetic form of

the disease rather than a risk factor.

That last result is one Rappoport's theory handles gracefully, and it is worth saying why. If the disease is a failure of a specific delivery step, and APOE4 is a hypomorph for that step, then two copies should behave less like elevated risk and more like a genetic disease with a threshold — which is what the biomarker trajectories show. A theory in which APOE4 acts by modulating amyloid clearance has a harder time explaining why the homozygous state looks like a Mendelian condition with late onset.

7.2 Cholesteryl esters, tau, and the proteasome

The second convergence is the most mechanistically specific, and it arrived before the final version of Rappoport's theory without being incorporated into it.

Van der Kant et al. (2019) screened over 1,600 compounds in iPSC-derived neurons for reduction of phospho-tau and recovered, unexpectedly, statins as among the most potent hits across multiple phospho-epitopes and independent lines. Pursuing the mechanism, they found that it was not free intracellular cholesterol that mattered but **cholesteryl esters** — cholesterol's storage form. Cholesteryl ester accumulation drives abnormal tau phosphorylation by downregulating the ubiquitin–proteasome system, and independently drives amyloid-β secretion through APP's interaction with cholesterol. Reducing cholesteryl esters raised proteasomal subunit levels and overall proteasomal activity, and increased clearance of misfolded tau. They named it the CE–proteasome–pTau axis. Blockade of the esterifying enzyme ACAT1/SOAT1 reproduced the effect, and that pharmacology has been pursued through 2025.

Read against Rappoport, this is a striking near-miss. His theory requires that cholesterol be synthesised and *not usefully incorporated*; esterification is precisely what a cell does with cholesterol it cannot deploy; and he cites the relevant observations — "these neurons show increased sterol esters, which may indicate excessive cholesterol synthesis with impaired incorporation into LRs," and elevated cholesterol esters in entorhinal cortex, and raised esterification enzyme in patient fibroblasts. He had the observation and the interpretation. What he did not have is the mechanism connecting the ester pool to tau, which van der Kant et al. supply and which does not run through rafts at all: it runs through the proteasome.

This is a case where an independent line of work both supports the theory's picture of cholesterol handling and offers a *rival* explanation for its central pathology. Tau hyperphosphorylation can be produced by cholesteryl ester accumulation acting on protein degradation, with no requirement that a raft-gated plasticity switch exists. The theory is not refuted; it is made non-necessary for one of the things it was built to explain.

7.3 GRAMD1B: the transporter that answers his open question

In his discussion, Rappoport named the gap in his own account with precision:

> *Additional research is also needed with respect to LR homeostasis. How precisely does cholesterol get incorporated in PM LRs? One possibility is that it is transported by caveolin1, but the precise mechanisms are still not clear.*

That question has since been partly answered, and by machinery he did not consider. The GRAMD1/Aster family are endoplasmic-reticulum-anchored lipid transfer proteins that sense the *accessible* pool of plasma membrane cholesterol through their GRAM domains and move it non-vesicularly to the endoplasmic reticulum through StART-like domains. They are, in other words, the sensors and movers of exactly the quantity Rappoport's switch is supposed to read.

In 2025, Acosta Ingram et al. reported that GRAMD1B is increased in excitatory neurons of human neural organoids carrying the *MAPT* R406W mutation, and increased in human frontotemporal lobar degeneration and Alzheimer's cases and in PS19 tau mice. Overexpression raised free cholesterol and lipid droplets and impaired autophagic flux; modulating it in iPSC-derived neurons altered PI3K, phospho-AKT, p62, CDK5R1 — and phosphorylated tau.

The significance for Rappoport's theory is twofold. It supplies a molecular answer to the question he flagged, which is to his credit as a diagnostician of his own gaps. And it supplies a second rival route from cholesterol mishandling to phospho-tau — this one through autophagy rather than through the proteasome or through a plasticity switch. The pattern of Section 7.2 repeats: the cell biology he identified is real and consequential, and the specific causal architecture he built on it is not required to explain the outcome.

7.4 PP2A, methylation, and the membrane

The fourth convergence is the one I find most impressive, because it concerns the single sentence in his paper with the least supporting text.

Rappoport's account of tau needs a mechanism by which raft failure specifically impairs tau *dephosphorylation*. He supplies one in eleven words: "Methylated (stronger) PP2A is enriched in LRs and decreases p-tau."

That line turns out to name a substantial independent literature. PP2A's catalytic subunit is methylated by LCMT-1 and demethylated by PME-1, and this modification controls assembly of the Bα-containing holoenzyme that dephosphorylates tau. In Alzheimer's disease and progressive supranuclear palsy the catalytic subunit is hypomethylated, LCMT-1 is markedly reduced, and PME-1 is increased. And the localisation claim is the specific one Rappoport needed: methylated PP2A and LCMT-1 are co-enriched in cholesterol-enriched microdomains, and LCMT-1-dependent methylation controls the targeting of both PP2A *and tau* to the plasma

membrane — such that altered methylation is expected to redistribute both from membrane to cytosol, producing accumulation of cytosolic hyperphosphorylated tau. Work published in 2025 extends the axis functionally, showing that PME-1 and LCMT-1 set sensitivity to injury-related oligomeric tau.

Rappoport's theory predicts that raft failure should strand tau and its phosphatase in the cytosol together. The methylation literature describes a mechanism that does exactly that, from an entirely different starting point — post-translational control of a phosphatase — and reports the loss of that mechanism in Alzheimer's tissue. This is the closest thing in the record to independent corroboration of the theory's *tau* limb, and it deserves more weight than the single sentence he gave it.

7.5 What the convergences mean

Taken together, the four lines establish something narrower and more interesting than "Rappoport was right."

They establish that the cell biology his theory is built from is real, live, and increasingly central: APOE4 acts through cholesterol trafficking; cholesterol that cannot be deployed is esterified and stored, and its storage drives tau pathology; the transporters that move accessible plasma membrane cholesterol are dysregulated in tauopathy; and tau's phosphatase requires a membrane-targeting modification that fails in disease.

They also establish that his particular causal architecture — the two-stage plasticity process with a raft-gated switch — is not required by any of it. Each convergent line reaches tau pathology from cholesterol mishandling by a route that does not pass through his switch. The field arrived at his ingredients and built something else with them.

That is a real result about a theory, and it is not a dismissal. A framework whose ingredients keep turning out to be load-bearing in other people's hands has identified the right level of description. Whether it has identified the right mechanism at that level is a separate question, and Section 10 is about how to answer it.

8. Where the Theory Is Weakest

8.1 The symmetry problem

This is the central charge, and it is not a matter of any particular claim being wrong.

Rappoport's theory is built from two devices that each generate opposite outcomes from the same variable. **Double-edged plasticity** makes high and low concentrations of the same agent produce opposing effects. **Chronicity** makes a partial failure of the switch produce simultaneous activation of both stages at reduced amplitude. Together they mean that for almost any plasticity molecule, either direction of change in Alzheimer's disease is consistent with the theory: an increase because the programme is chronically active, a decrease because the double edge has inverted, or because resources are depleted in later disease.

Rappoport uses this productively. It is how he handles the observation that "virtually all important plasticity agents are dysregulated in AD" — a list including calcium, ERK, p38, JNK, Akt, PKA, PKC, GSK-3β, PP2B, PP1, PTEN, CDK5, BDNF, TrkA, tissue plasminogen activator, MMP-9 and PAI-1. A theory that predicts widespread dysregulation of plasticity machinery is doing better than one that predicts nothing about it. But "dysregulated" is not a direction, and a framework that accommodates both directions for seventeen molecules has explained the *existence* of the dysregulation without constraining its *content*.

The same structure appears in the two-neuron-type model, which as Section 6 showed makes every possible result for cholesterol and raft abundance a confirmation. And it appears in the treatment of risk factors, where nine heterogeneous exposures — ageing, APOE4, viral infection, insulin resistance, vascular damage, brain injury, stress, neuroinflammation, sleep disruption — all converge on raft impairment by mechanisms stated at one sentence each.

The honest formulation is this. Rappoport's framework has very high explanatory coverage and correspondingly low discriminating power. It tells you what kind of thing Alzheimer's disease is; it rarely tells you what to expect from a specific measurement in a way that could come out wrong. The exception — the uptake-not-synthesis prediction of Section 5 — is precisely where the theory earned its most convincing success, which supports rather than undermines the diagnosis: the theory is at its best exactly where it commits.

Grade: structural weakness, not refuted. The symmetry is the price of the coverage, and Rappoport does not acknowledge it as a cost.

8.2 The raft as an operational category

The theory's central object carries an evidential problem the theory does not address.

Rappoport asserts that rafts "were controversial until some time ago due to technical difficulties, but are now fully consensual." The first half is right and the second is too strong for the use he makes of it. The existence of ordered lipid nanodomains in living membranes is well established; what remains contested is whether the entity isolated by the assay that dominates the Alzheimer's raft literature — the detergent-resistant, buoyant membrane fraction recovered from a density gradient — corresponds to a structure that existed in the intact cell, or is partly generated by the detergent.

This matters because much of Rappoport's supporting evidence is of that form. His raft evidence includes reduced cholesterol and sphingomyelin in isolated raft fractions from frontal and entorhinal cortex before tangles appear; lower raft abundance in temporal cortex with the remaining rafts cholesterol-depleted; abnormal flotillin and gangliosides in brain, cerebrospinal fluid and serum; flotillin accumulation in lysosomes of tangle-bearing neurons. These are real findings. They are also, mostly, findings about a biochemical fraction from post-mortem tissue, and the inference from "the detergent-resistant fraction is depleted" to "the neuron could not assemble the platform on which consolidation is performed" is longer than the text acknowledges.

The Lee et al. imaging work of Section 6 is instructive here in a way that cuts against the theory twice: it demonstrates that the raft question *can* be asked with spatial resolution in intact human neurons, and when it was asked that way the answer went in the opposite direction to the theory's requirement.

8.3 One reader, no laboratory

Rappoport's method produced the theory's virtues and it produced one limitation that no amount of reading could remedy: no experiment was ever performed to test it.

The consequence is not that the theory is unsupported — it is extensively supported, by other people's experiments performed for other reasons. The consequence is that the theory has never been *at risk*. Every piece of evidence in it was selected after the fact from a literature the author had already read, which is the epistemic situation in which confirmation is easiest and least informative. The two occasions on which the theory did come under genuine risk are the ones discussed in Sections 5 and 6, and they are both accidents: work done by others, after the theory was fixed, that happened to address it. One confirmed it and one contradicted it.

There is a related and more practical cost. Because the theory discards the field's standard vocabulary (Section 4.2), constructs its own abbreviations, and is single-authored across eleven diseases, it is unusually difficult for a laboratory to engage. A paper in the *Annual Review of Biochemistry*

is read; a theory becomes live when somebody designs an experiment against it. The most valuable thing that could now be done with this body of work is the thing its author could not do.

8.4 The statin claim is wrong, and it matters

In both versions Rappoport asserts that statins do not cross the blood–brain barrier:

> *CVD affects AD via other risk factors, since neither cholesterol nor statins cross the BBB. (2020)*
>
> *They do not cross the blood-brain barrier so should not directly affect AD, but they might reduce risk via the other risk factors. (2024)*

This is incorrect as stated. Lipophilic statins — simvastatin, lovastatin, atorvastatin — do penetrate the central nervous system, by passive diffusion across lipid-rich membranes, and their central effects are measurable: simvastatin lowers cerebrospinal-fluid lathosterol, a marker of brain cholesterol synthesis, and reduces plasma 24S-hydroxycholesterol, the principal brain cholesterol metabolite, within twelve weeks. In a comparative in vitro study of nine statins, simvastatin showed the greatest barrier penetration and the most robust cholesterol-lowering in neuronal cells. The lipophilic statins also account for most of the reported cognitive side effects in the literature. Only the hydrophilic statins, pravastatin and rosuvastatin, approximate the claim.

The error has three consequences, and they are not cosmetic.

It removes a pharmacological probe the theory needed. A brain-penetrant inhibitor of cholesterol synthesis is the most direct available intervention on the theory's central variable. Rappoport dismisses statins from consideration on a factual error, and thereby forgoes his own best natural experiment. His observation that statins are associated with sudden hearing loss and impaired olfaction — which he uses to support the raft-dependence of sensory cells — sits oddly beside the claim that they do not reach the nervous system.

It collides with van der Kant et al. The most potent phospho-tau-lowering hits in an unbiased screen in human neurons were statins, acting through the cholesteryl ester pool. A theory whose central lesion is *insufficient* membrane cholesterol has to say something about why inhibiting cholesterol synthesis reduces tau pathology, and Rappoport's framework can say it — the relevant pool is the unusable esterified one — but only if statins reach neurons, which he denies.

It exposes the symmetry problem in its sharpest form. Under the deficiency reading, statins should worsen the disease. Under the chronic-synthesis reading, statins should improve it. The theory contains both readings and therefore predicts both outcomes. Rappoport's own summary of the clinical record — "Statins do not have a consistent effect in AD" — is accurate, and is exactly what a theory with no directional commitment would expect to find comfortable.

8.5 What the anti-amyloid trials did and did not show

Rappoport's position is that amyloid-β is a normal loser-removal agent, that plaques are "neither causal nor essential," and that the amyloid hypothesis fails for want of an account of amyloid's physiological role. The clinical record of the intervening years bears on this, and it does not resolve cleanly in either direction.

Lecanemab and donanemab both removed amyloid and both slowed decline. The magnitude is contested: time-based analyses put the slowing at roughly five to seven months over the trial periods, with serious adverse events; four-year lecanemab data reported sustained separation, and analyses relating regional amyloid clearance to subsequent tau accumulation reported that greater clearance was associated with less tau. Independent commentators continue to dispute whether the statistical effect is clinically meaningful.

Both a strict amyloid theory and Rappoport's theory can live with this, which is why it settles little. Under his account, removing amyloid-β removes a chronic loser-removal signal, so some benefit is expected — and the ceiling is low, because the upstream lesion is untouched. That is a coherent reading and it fits the data about as well as the cascade reading does. The one place where the record is uncomfortable for him is the amyloid-clearance-to-tau relationship, since his theory treats plaque as the marker of the *compensated* neuron and therefore as roughly orthogonal to tangle formation.

Grade: unresolved, and unresolvable by these trials.

8.6 The short-term memory claim is stated too strongly

Section 2.5 flagged this. The theory's founding clue is "impaired anterograde memory with functioning short-term memory," and the neuropsychological literature does not support the second half in the clean form asserted. Working memory and attentional control deficits are demonstrable in early Alzheimer's disease, and in mild cognitive impairment.

What the theory actually needs is weaker and probably defensible: that the *encoding-to-consolidation transition* fails disproportionately early, relative to immediate retention. That is a real and well-documented dissociation — rapid forgetting over minutes to hours with relatively better immediate span. Restated that way, the claim survives and remains testable. Stated as "functioning short-term memory," it is a liability, and it is characteristic of a recurring stylistic problem: the theory reaches for the version of a clinical fact that is cleanest for the argument.

8.7 "Explains all of the major established facts"

Both versions claim completeness. The 2020 text says the theory "fully explains its etiology, pathology, symptoms and risk factors" and that the author is unaware of contradicting evidence. The final version claims to present "the first complete theory of AD, complete in the sense that it mechanistically explains all of the major AD phenomena."

The retreat between the two is real and was noted in Section 4.5. It did not go far enough. Total explanatory coverage is not a virtue in a theory of a heterogeneous clinical syndrome; it is a warning that the framework's degrees of freedom exceed the constraints available. And there is a specific gap the completeness claim conceals: the theory is a theory of a syndrome defined by memory failure with tangles and plaques, and says almost nothing about the substantial fraction of clinical dementia that presents with mixed pathology, vascular contribution, TDP-43 co-pathology or Lewy pathology. Rappoport is admirably clear that he is theorising sporadic Alzheimer's disease specifically, and that other dementias have other mechanisms. But "explains all major facts about AD" and "AD is a minority of the dementia a clinic sees" are claims that need to be stated together, and in his texts they are not.

8.8 Reelin, again

Section 4.4 covered the demotion. It belongs in the weaknesses list too, because of what it cost the theory structurally rather than because of the missed citation. With reelin carrying load, the theory had two independent routes to a chronically stalled switch and a mechanism tied to the specific neuronal population that fails first. Without it, everything runs through one supply chain, and the theory's account of *why entorhinal layer 2* becomes a general argument about novelty rather than a molecular one. The 2020 version was, on this specific point, the better theory.

9. What Survives: A Graded Ledger

Grades: **Established** — supported by direct evidence in human material or by convergent experimental evidence, and not seriously contested. **Well-supported** — good evidence, some of it indirect or from model systems. **Plausible** — coherent and consistent with evidence, not directly tested. **Unsupported** — asserted without adequate evidence. **Contradicted** — evidence runs the other way.

#	Claim	Grade	Basis
1	Brain cholesterol is astrocyte-produced, ApoE-transported, and neuron-imported; neurons cannot substitute their own for this function	Established	Standard cell biology; not original to the theory
2	Lipid rafts are required for membrane anchoring of the receptors, scaffolds and cytoskeletal links used in synapse stabilisation	Established	Extensive independent literature; palmitoylation dependence
3	Neuronal cholesterol **uptake** is impaired in Alzheimer's disease while astrocytic efflux is preserved, and APOE4 particles deliver less	Well-supported	Borràs et al. 2025, human CSF plus reconstituted-particle comparison
4	APOE4 acts substantially through cholesterol trafficking failure with intracellular accumulation	Well-supported	Blanchard et al. 2022 (oligodendrocytes); APOE4 glial lipid-droplet literature; Fortea et al. 2024
5	Tau phosphorylation is a normal, spatially patterned part of plasticity rather than an intrinsically pathological event	Well-supported	Site-specific kinase literature; tau as dynamic cross-linker
6	Cholesterol mishandling causally drives tau hyperphosphorylation	Well-supported — **by routes other than the theory's**	van der Kant et al. 2019 (cholesteryl esters → proteasome); Acosta Ingram et al. 2025 (GRAMD1B → autophagy)
7	Raft-localised, methylation-dependent PP2A is required for tau dephosphorylation, and its loss strands tau in the cytosol	Well-supported	LCMT-1/PME-1 literature; raft co-enrichment; PSP and AD tissue

#	Claim	Grade	Basis
8	Amyloid precursor protein's alpha and beta routes are mutually exclusive stage-specific agents, with cholesterol as the switch	Plausible	Individual steps documented; the two-stage assignment is the theory's inference
9	Amyloid-β has a physiological loser-removal function and its disruption impairs consolidation	Plausible	Consistent with consolidation-blockade data; not established as *the* function
10	Plasticity runs as one canonical two-stage process — candidate generation then competition resolution	Plausible	Components established; the canonical two-stage architecture is untested as such
11	The generation-to-resolution transition is gated by plasma membrane raft assembly	Plausible, untested	The theory's central claim; no direct test exists
12	Candidate generation *is* short-term memory	Plausible in weak form; **overstated as written**	GluA1/working-memory data supportive; "functioning short-term memory" in AD is not sustained
13	Double-edged plasticity is a general biological principle converting concentration into a binary structural decision	Plausible, and the source of the symmetry problem	Instances are real; the generalisation is the author's
14	Regional vulnerability tracks plasticity demand (entorhinal, CA1/subiculum, locus coeruleus)	Plausible	Correspondence is genuine; explanation is post hoc and not uniquely predicted
15	Early olfactory, auditory and retinal impairment reflects raft dependence in sensory cells	Plausible	Cholesterol-depletion phenocopy is suggestive; not tested in disease
16	Nine heterogeneous risk factors act by converging on raft impairment	Unsupported as stated	One sentence per factor; mechanisms not specified to a testable level
17	Statins do not cross the blood–brain barrier	**Contradicted**	Lipophilic statins penetrate and measurably lower central cholesterol synthesis
18	APOE4 reduces cholesterol supply to neurons, so neuronal rafts are reduced	**Contradicted in young human cellular systems**	Lee et al. 2021, 2025: over-supply, raft expansion, imaged directly
19	Reelin has no significant independent role (final version)	**Contradicted**	RELN-COLBOS resilience via ApoER2/VLDLR with tau suppression, 2023

#	Claim	Grade	Basis
20	The theory explains all major established facts about the disease	Unsupported	Coverage achieved partly through non-directional accommodation

Two observations about the shape of this table.

The strongest rows are the cell biology, and the weakest are the architecture. Rows 1–7 are the theory's foundation and they are in good condition; rows 10–13 are the theory proper and they are collectively untested. That is a coherent position for a theory to be in — it means the thing is *not yet* adjudicated rather than wrong — but it should be stated plainly, and Rappoport's own summaries do not state it.

And row 6 is the most consequential line in the table. Cholesterol mishandling does drive tau pathology; the causal link the theory needs exists. It has been demonstrated by two mechanisms, neither of which requires the raft-gated switch. The theory's central explanandum has been explained without it.

10. Six Experiments

Each of these is technically feasible now and each would move at least one grade in the ledger.

1. Does the APOE4 effect on neuronal raft cholesterol reverse with age? This is the decisive experiment, and Section 6.2 set it up. Take isogenic APOE3 and APOE4 human neurons and astrocytes and measure raft cholesterol and raft-localised APP in neurons using spatially resolved imaging — the ToF-SIMS approach already validated for this question — across a maturation and senescence series, with astrocyte-conditioned medium from donors matched for age. The theory predicts a crossover: APOE4 over-supply and raft expansion in young cells, under-delivery and raft failure in aged cells. A monotonic effect in either direction refutes one half of the theory. Nothing else on this list would tell us as much.

2. Does raft assembly actually gate a plasticity transition? The theory's central mechanism has never been tested as a mechanism. Acutely and locally manipulate raft assembly in a single dendritic segment during a defined plasticity protocol — cholesterol delivery or depletion, or sphingomyelinase, with a control for bulk membrane effects — and ask whether the *timing* of the transition from candidate generation to consolidation shifts accordingly. The readouts the theory specifies are available: the GluN2B-to-GluN2A switch, the calcium-permeable-to-impermeable AMPA receptor switch, spine-population winnowing, and local tau dephosphorylation. If withholding raft cholesterol prolongs the candidate state and restoring it triggers resolution on demand, the theory's core is established. If the transition proceeds on schedule without raft assembly, the theory's core fails.

3. Is tau dephosphorylation in winning synapses raft-dependent and methylation-dependent? This tests row 7 against row 11 and connects the theory's best-corroborated limb to its untested one. In the same single-dendrite preparation, measure PP2A methylation state and localisation alongside raft assembly and spine-specific tau phosphorylation. Manipulate LCMT-1 and PME-1. The theory predicts that winner-specific tau dephosphorylation requires methylated PP2A recruited to a newly assembled raft — a spatially resolvable prediction with three independent handles.

4. Which cholesterol pool drives phospho-tau: unusable ester, or absent raft? Sections 7.2 and 8.4 leave this open, and it is the theory's most therapeutically consequential ambiguity. In human neurons, dissociate the two: reduce cholesteryl esters by ACAT1/SOAT1 blockade while holding raft cholesterol constant, and reduce raft cholesterol while holding esters constant. Measure phospho-tau, proteasomal activity and autophagic flux. If phospho-tau tracks the ester pool independently of raft status, the theory's tau limb is displaced by the CE–proteasome axis.

If it tracks raft status independently of esters, the theory is vindicated where it matters most.

5. Does the switch fail before the pathology in vivo? The theory is a claim about temporal order, and the order has never been checked. In an APOE4 knock-in model, longitudinally quantify raft assembly capacity — ideally by a functional readout, such as the latency of the receptor-subunit switch after a learning episode — against phospho-tau, spine density and behaviour. The theory requires the switch deficit to be first. If tangle-stage pathology precedes measurable switch failure, the causal ordering is wrong.

6. Does the theory's cognitive signature exist in patients? Test the weakened version of row 12 properly, since the strong version is already in trouble. In prodromal Alzheimer's disease stratified by *APOE*, measure immediate span and working memory against consolidation over minutes to hours to days, with a cholesterol-delivery biomarker — the CSF lipoprotein-mediated neuronal uptake assay of Borràs et al. is now available for this. The theory predicts that impaired delivery selectively predicts the consolidation deficit rather than the immediate-retention deficit. This is the only experiment on the list that could be done in human beings within a single study, and it is the one most worth doing first.

11. What the Theory Is For

11.1 A theory of the switch

The most useful thing that can be said about this body of work is that it is not, at bottom, a cholesterol theory. Cholesterol is the mechanism; the subject is a transition.

Rappoport's real proposal is that memory formation contains a discrete, physically implemented decision point — a moment at which a neuron stops proposing and starts committing — and that the implementation is a membrane assembly rather than a signal or a timer. Whether or not that specific implementation is right, the shape of the claim is unusual and valuable, because it identifies a *stage* of the process at which a disease could sit. Alzheimer's disease, on his account, is not too much of something or too little of something. It is a process that will not advance from its first phase to its second, and the pathology is the accumulated debris of a brain trying repeatedly and failing quietly.

That framing has consequences the theory itself draws out and the field has not absorbed. It explains why the compensation is the pathology, since continued generation in the absence of resolution is what produces both hyperphosphorylated tau and chronic loser removal. It explains why partial failure is worse than complete failure. And it predicts that the disease should be visible, before any pathology, as a *timing* abnormality — a lengthened interval between experience and consolidation. That is a testable and unexploited idea about what to measure in people at risk.

11.2 The durable contribution: asking what the pathological molecules are for

If one thing from this work should outlive the framework, it is the methodological commitment of Section 2.4.

Rappoport's operating principle is that you cannot understand a disease molecule until you have an account of its job in health, and that the absence of such an account is why the field's dominant theory has not converged. He states it directly: "without a convincing account of the role of Abeta (and tau phosphorylation) in health, no coherent theory of AD can be articulated."

Whether or not amyloid-β is a loser-removal agent, this is the right demand to make, and it is made too rarely. A field that studies tau phosphorylation almost exclusively as a lesion will find it difficult to notice that phospho-tau is what a learning neuron looks like. A field that studies amyloid-β almost exclusively as a toxin will find it difficult to explain why an organism synthesises the machinery to produce it, conserves that machinery, and impairs memory consolidation when it

is blocked. Rappoport's answers may be wrong in detail. The questions are the correct ones, and asking them is what generated the theory's most valuable content.

11.3 Read as a resilience theory

There is a reading of the theory that its author does not offer and that fits the current evidence better than his own.

Stated as a theory of onset, the account is exposed: the initiating lesion is unproven, the direction of the APOE4 effect is contested, and the risk factors converge by assertion. Stated as a theory of **capacity**, it is much stronger. The claim becomes: the brain's ability to convert experience into structure depends on a supply chain with a single non-redundant step, that step degrades with age, and the clinical syndrome appears when degradation crosses a threshold set by genotype and exposure.

On that reading, the theory's job is not to explain what starts the disease but to explain *what determines who gets it and when* — and the evidence lines up considerably better. Neuronal cholesterol delivery is impaired in patients and by APOE4 particles. APOE4 homozygosity behaves like a threshold condition with near-complete pathological penetrance. Education protects, and Rappoport's explanation for why is the most distinctive thing in either version of the paper: a denser synaptic space needs less new growth per memory, so the cholesterol demand per plasticity episode is lower, and the same supply chain sustains function for longer. That is a mechanistic account of cognitive reserve as a *reduction in demand on the rate-limiting resource* — and unlike most accounts of reserve, it makes a quantitative prediction.

11.4 The most transferable idea

Double-edged plasticity is the part of the theory most likely to be useful outside it, and Section 8.1 has already said why it is also the part most responsible for the theory's weakness. Both are true, and the resolution is a matter of discipline rather than of content.

The idea is that a spatially propagating chemical signal can implement a binary local decision through nothing more than an affinity difference between two receptors — so concentration becomes position, and position becomes fate. That is a genuine and general mechanism, and it makes a prediction the theory does not exploit: for any double-edged agent, the *ratio* of its high- and low-affinity receptors should set the spatial sharpness of the decision, and pathologies of that ratio should produce characteristic failures of selectivity rather than of amplitude. That is a research programme, and it is not about Alzheimer's disease.

Used carelessly, the same principle licenses accommodating any observation. The discipline that makes it a tool rather than an excuse is to specify, in advance and for each agent, the concentration at which the edge flips and the receptor pair that implements it. Rappoport does this

for calcium, dopamine and serotonin. He does not do it for the seventeen dysregulated agents on which his chronicity argument depends, and that is where the principle stops constraining and starts absorbing.

12. Conclusions

The theory in its final form is not the theory it is remembered as. The 2020 submission proposed neural cholesterol deficiency as the cause of Alzheimer's disease. The 2024 and 2025 papers propose failure of plasma membrane lipid raft assembly, with cholesterol delivery as its most common cause. The revision is substantial, it improved the theory's logical form, and it is the reason a summary in terms of "the cholesterol theory" misrepresents what is being claimed.

Its most committed prediction held in human material. Rappoport insisted the lesion was in neuronal uptake rather than astrocytic synthesis, and used that distinction to reject a rival hypothesis. Five years later, human cerebrospinal fluid showed preserved astrocytic efflux with significantly reduced neuronal uptake, and APOE4-bearing particles delivering less cholesterol to neurons than APOE3 particles. That is the best single result in the theory's favour, and it arrived from a group with no interest in the theory.

Its central mechanism has been contradicted in the opposite direction, and the theory's ability to absorb that is its deepest problem. APOE4 astrocytes over-supply cholesterol, expanding neuronal rafts and raising amyloid-β — imaged directly. The two-neuron-type model accommodates this, as it accommodates every possible direction of every cholesterol and raft measurement. A theory built from two devices that each generate opposite outcomes from the same variable has purchased its coverage with its falsifiability, and it does not acknowledge the transaction.

The field has converged on his cell biology without converging on his theory. APOE4 is now a cholesterol-trafficking disorder. Cholesteryl esters drive phospho-tau through the proteasome. A non-vesicular cholesterol transporter drives phospho-tau through autophagy. Tau's phosphatase requires a methylation-dependent membrane targeting that fails in disease. Each of these vindicates the level of description Rappoport chose. None requires the raft-gated switch he built on it. His central explanandum — cholesterol mishandling causing tau pathology — has been explained twice over by routes that bypass his mechanism.

The durable contribution is methodological, and it is the demand that pathological molecules be given jobs in health. The account of amyloid precursor protein as a cholesterol-management protein with two mutually exclusive stage-specific products, of amyloid-β as a loser-removal agent, and of tau phosphorylation as the normal condition of a learning neuron are the most valuable things in these papers, and they were produced by refusing to study disease molecules only as lesions. That refusal is worth borrowing whether or not the answers survive.

Read as a theory of capacity rather than of onset, it is considerably stronger than its author claimed. The version that says *the conversion of experience into structure depends on a supply chain with one non-redundant step, and the syndrome appears when age and genotype push that step past a threshold* is well matched to the evidence, explains the behaviour of APOE4 homozygosity, and yields the most interesting account of cognitive reserve in the literature — reserve as reduced demand on the rate-limiting resource rather than as surplus capacity.

And the specific error to correct is small and consequential. Lipophilic statins do cross the blood–brain barrier. Correcting that returns to the theory the pharmacological probe it needs, forces it to engage with the finding that statins are among the most potent phospho-tau-lowering compounds in human neurons, and exposes the one place where its symmetry becomes untenable: a framework cannot be indifferent to whether lowering brain cholesterol synthesis helps or harms, and then cite the inconsistency of the clinical record as though it were confirmation.

Rappoport wrote that his main prediction "has not been directly shown yet," and named the experiment that would show it, and observed that it would be "a very long and risky process." He was right about that, and he did not get to see it. Six experiments now exist that could be done without a clinical trial. The theory is worth the trouble, not because it is likely to be correct in its architecture — I think it probably is not — but because it is specific enough to be wrong in interesting places, and because it asks the question that the field has spent forty years declining to answer: what, exactly, is a synapse trying to do when it decides to keep itself?

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Appendix A: The Two Versions, Clause by Clause

The following pairs quote the 2020 submission against the 2024 preprint on the points where the theory changed. They are given in full because the difference between the versions is the least-documented aspect of this body of work.

On the core cause.

> *2020: "AD symptoms are due to impaired brain plasticity, specifically, impaired synapse formation. The problem usually results from neural cholesterol deficiency stemming from a combination of genetic susceptibility (e.g., certain ApoE alleles), aging, and risk factors (e.g., viral infections)."*
>
> *2024: "AD symptoms and pathology are caused by impaired formation of plasma membrane lipid rafts, which is in turn caused by reduced neural uptake or trafficking of astrocyte-produced cholesterol."*

On tau's physiological role.

> *2020: "MTB stability is mainly supported by the protein tau, and this is widely viewed as tau's role. However, in addition to binding MTBs, tau also binds membranes via a membrane binding domain… Hence, in our view the role of tau is to support both the cytoskeleton and its membrane/LR interaction."*
>
> *2024: "Tau binds cytoskeleton MTBs and was initially thought to support MTB stability. However, its detachment from MTBs does not destabilize them or impair axonal transport. It is now viewed as a cross-linker of the MTB and actin cytoskeletons that promotes dynamic changes including axonal elongation, synapse formation, and stabilization of growing neurites."*

On potentiation and depression.

> *2020: A dedicated subsection integrating LTP and LTD into the two stages, including a defence of LTD: "LTD may seem to counter plasticity, but it is essential for learning and memory."*
>
> *2024: "The notions of long-term potentiation (LTD) and long-term depression (LTD), which are ubiquitously used in relation to plasticity, are not used in T*PL… These terms are suitable for describing the local effects of specific experimental conditions, not for the high-level theory."*

On reelin.

> *2020: "In compPL, reelin's role is axonal elongation, synapse formation, and consPL termination. It promotes APP, its alpha-cleavage, and axon growth until it meets its destination receptors. ApoER2 signaling, which depends on LRs, is crucial to final synaptic adhesion, and suppresses Abeta & GSK3beta to terminate consPL."*

*2024: "Reelin is a Cgen agent promoting APP alpha cleavage and neurite branching. In T*PL, its role is to promote integration of new neurons and events into the network." And, in the list of deferred topics: "Additional topics are left to future texts, including… prion protein, reelin, AICD…"*

On short-term memory.

2020: No claim.

2024: "Short-term memory (STM). Cgen is what supports STM. In particular, it has been repeatedly shown that GluA1 is essential for STM, with knockout animals showing normal spatial reference memory but markedly impaired spatial working memory and STM."

On the evidential claim.

2020: "All aspects of our AD and plasticity theories are supported by a large corpus of evidence, and we are not aware of any contradicting evidence."

*2024: "T*PL and T*AD address the major established facts known about brain plasticity and AD, methodically identified via a thorough examination of the scientific literature (hundreds of thousands of papers) done over more than ten years. Both theories are supported by very strong evidence."*

Appendix B: The Wider Programme

The Alzheimer's theory is one of eleven, and its structure recurs across them in a way worth recording, because it bears on how much weight the individual theories can carry.

Each of the eleven follows the same template: a single named upstream agent or channel, a chronicity mechanism that converts a physiological process into a pathological one, a claim to explain the condition's symptoms and risk factors completely, and a set of treatment proposals often involving drugs already licensed for other indications.

Condition	Named agent	Venue
Autism spectrum disorder	Corticotropin-releasing hormone (later CRH2–ACTH)	arXiv:2408.06750; book ch. 1
Anorexia and bulimia	CRH2–CRH1	Book ch. 2
Schizophrenia	Polyunsaturated fatty acids	arXiv:2408.06794; book ch. 3
Depression and bipolar disorder	Dynorphin	arXiv:2408.06763; book ch. 4
Migraine	Sympathetic nervous system	arXiv:2408.06780
ADHD	K-ATP channels	Preprints.org 202408.1135
Obsessive–compulsive disorder	CRH–HCN	arXiv:2408.14479
Multiple sclerosis	—	Book
ALS and frontotemporal dementia	Calcium channel α2δ subunit	Book ch. 9
Parkinson's disease	Galactose	Book ch. 10
Alzheimer's disease	Lipid rafts / cholesterol	arXiv:2310.20232; *Annu. Rev. Biochem.* 94:387–416; book ch. 11

Two observations follow, and they pull in opposite directions.

The template's recurrence is a caution. A method that reliably produces a complete, single-agent, chronicity-based theory of whatever condition it is turned on is a method whose output is partly determined by its form. The ASD theory changed its named agent between the 2024 preprint and the 2025 book, which suggests the agent is the most revisable component and the architecture the least.

But the template is also a substantive hypothesis about disease in general, and it deserves to be evaluated as one rather than dismissed as a mannerism. The claim across all eleven is that chronic, low-amplitude, unresolved activation of a normal adaptive process is the general form of brain disease — that these conditions are not

deficits or excesses but *processes that will not terminate*. Applied to Alzheimer's disease, that is the idea developed in Section 11.1, and it is the most interesting thing in the whole body of work. It is also the one claim that no single-disease study can test, and that the eleven theories together were presumably meant to.