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A Critical Evaluation of Compensatory Models from the Oskar Fischer Prize to the Lipid-Raft Hypothesis

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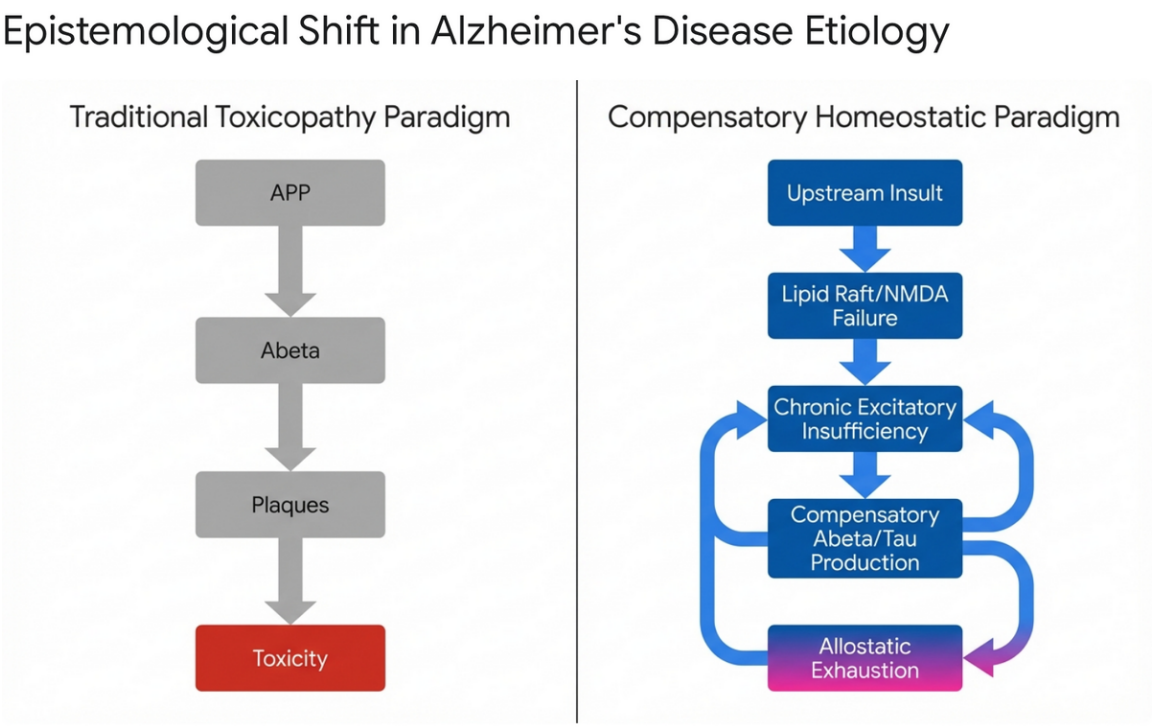
Synthesizing the work of Ari Rappoport

Reconceptualization of Alzheimer's Disease Etiology: A Critical Evaluation of Compensatory Models

Abstract



The traditional Amyloid Cascade Hypothesis assumes a linear path from toxic protein aggregation to neurodegeneration. Conversely, modern systemic models reframe Aβ and p-tau as physiological sensitizers induced by upstream structural (Lipid-Raft) and functional (NMDA) deficits.

For three decades, the Amyloid Cascade Hypothesis has dominated Alzheimer's disease research, proposing that amyloid-beta accumulation drives neurodegeneration[2].

Despite substantial investment, anti-amyloid therapies have failed to meaningfully reverse cognitive decline, suggesting the hypothesis may not capture the disease's primary drivers[6].

This thesis evaluates two alternative frameworks: the "Chronic Excitatory Insufficiency" model proposed by Moosmann (2022 Oskar Fischer Prize silver winner) and the "Lipid-Raft and Adaptive Response" theory articulated by Rappoport (2025)[119].

The first posits that NMDA receptor hypofunction, triggered by diverse genetic and environmental factors, initiates compensatory responses[9].

The second proposes that lipid raft degradation in neuronal membranes directly precipitates receptor dysfunction[11].

This analysis argues that both models are compatible in scope.

By reframing amyloid-beta and phosphorylated tau as compensatory molecules rather than primary toxins, the disease may be understood as homeostatic exhaustion—the brain's unsuccessful attempt to maintain function through decades of metabolic strain.

This reframing suggests therapeutic targets fundamentally different from current ablative approaches: membrane stabilization and excitatory tone restoration rather than protein clearance[116].

Introduction

The Research Problem

Alzheimer's disease affects an estimated 50 million individuals globally[1].

The Amyloid Cascade Hypothesis, dominant since the early 1990s, posits a linear pathway from amyloid-beta aggregation to tau hyperphosphorylation, neuroinflammation, synaptic uncoupling, and neuronal death[225].

However, clinical trials demonstrate a critical disconnect: anti-amyloid immunotherapies effectively clear plaques from the brain but frequently fail to halt cognitive decline and occasionally accelerate it.

This biomarker-outcome disconnect suggests the hypothesis may misidentify a consequence of disease as its primary cause.

Historical Context: The Oskar Fischer Prize Initiative

In 2019, the Oskar Fischer Prize was established to challenge the research establishment and synthesize fragmented literature into comprehensive disease models.

Notably, this prize resurrects Oskar Fischer's work from 1907, which independently documented amyloid plaques and neurofibrillary tangles.

Fischer's erasure from the medical canon reflects geopolitical rather than scientific factors—his contributions were overshadowed by Emil Kraepelin's promotion of Alois Alzheimer's narrative and compounded by the historical marginalization of Jewish scientists under the Third Reich.

Two significant theoretical frameworks have emerged: Moosmann's "Chronic Excitatory Insufficiency" model and Rappoport's "Lipid-Raft/Adaptive Response" theory[119].

This thesis evaluates their explanatory power and complementarity.

Research Questions

To what extent do these models explain the genetic, clinical, and molecular phenotypes of Alzheimer's disease where the traditional amyloid cascade hypothesis falls short[2]? ## Literature Review

The Physiological Turn: Re-evaluating Aβ and Tau

Recent literature challenges the toxicopathy model through evidence of physiological roles for implicated molecules.

Amyloid-beta at picomolar concentrations (physiological levels) acts as a modulator of synaptic function, enhancing NMDA receptor-dependent long-term potentiation and facilitating neuronal growth[2].

At these concentrations, it behaves as an endogenous neuropeptide released upon neuronal stimulation[2].

Amyloid-beta fragments possess neuroprotective properties, including protection against oxidative stress[15].

Similarly, tau hyperphosphorylation is reframed not solely as pathological collapse but as a regulatory mechanism facilitating axonal transport of organelles under cellular stress and sensitizing NMDA receptors[1125].

These observations provide a basis for interpreting these molecules as compensatory rather than primary pathogenic agents.

NMDA Receptor Hypofunction

The NMDA receptor hypofunction hypothesis emerged in psychiatric neuroscience to explain schizophrenia, noting that dissociative anesthetics (NMDA antagonists) reproduce psychotic and cognitive symptoms in healthy subjects[16179].

Researchers subsequently identified overlaps between schizophrenia, aging-related cognitive decline, and early Alzheimer's disease in spatial-temporal memory disruption, psychiatric disturbance, and glutamatergic dysfunction[16].

Despite these observations, the Alzheimer's research establishment long treated NMDA dysfunction as a downstream consequence of amyloid toxicity rather than a primary cause.

Recent work reassesses this relationship.

Chapter 1: The Oskar Fischer Paradigm—Chronic Excitatory Insufficiency

Overview

Moosmann's model proposes that chronic suppression of NMDA receptor-mediated excitation underlies Alzheimer's disease[9].

The model integrates disparate risk factors—genetic, environmental, and age-related—as different pathways converging on a single functional endpoint: reduced glutamatergic signaling.

Five Upstream Mechanisms

The model identifies mechanisms by which major Alzheimer's risk factors reduce NMDA receptor function:

ApoE4: The ApoE4 isoform causes prolonged intracellular trapping of NMDA receptors compared to ApoE2/ApoE3, reducing surface expression by 3-5 fold and suppressing calcium influx and long-term potentiation[1129]. **Presenilin 1 mutations**: These mutations reduce presynaptic glutamate release and NMDA receptor surface expression, effects that are loss-of-function rather than primarily related to gamma-secretase activity[9]. **Trisomy 21**: Down syndrome brains exhibit a developmental excess of GABAergic inhibition relative to excitatory input, reducing dendritic spine density for excitatory synapses[9].

Compensation requires sustained amplification of excitatory tone. **Traumatic brain injury**: Mechanical forces selectively damage large pyramidal neurons with long axonal projections more than small inhibitory interneurons, permanently reducing excitatory connectivity[9]. **Menopausal estrogen loss**: Estrogen acts as a transcriptional activator of NMDA receptor expression in the hippocampus[9].

Its acute withdrawal creates sudden excitatory deficit.

Clinical Phenotypes

If NMDA hypofunction drives Alzheimer's disease, clinical features should mirror other states of glutamatergic blockade:

- **Sleep disruption**: Impaired NMDA receptor function reduces calcium-dependent neuronal hyperpolarization, shortening sleep duration[9]. - **Hearing loss**: The auditory system is highly dependent on glutamatergic plasticity; NMDA hypofunction directly compromises auditory processing[10]. - **Seizures**: The brain's attempted compensation through excessive amplification of failing excitatory signals can trigger seizures, consistent with observations in Trisomy 21 and temporal lobe epilepsy[9]. - **Psychiatric symptoms**: Agitation, delusions, hallucinations, and apathy parallel behavioral effects of NMDA antagonists such as ketamine[179].

These associations require prospective validation but are consistent with the model's predictions.

What Remains Unknown

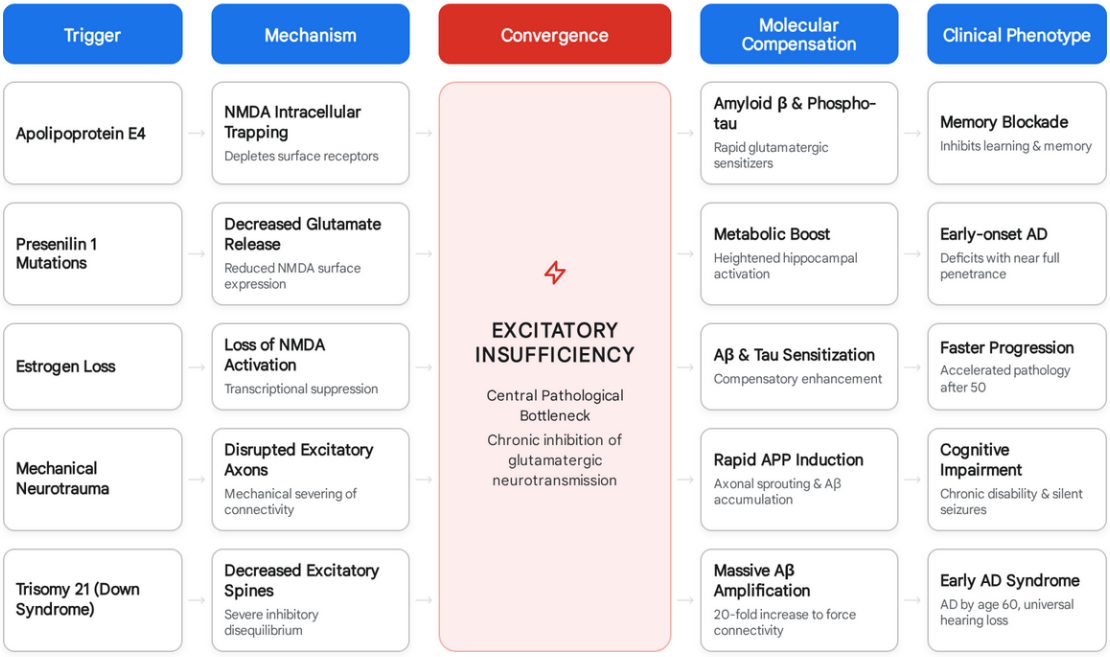
The model does not establish causation definitively.

Whether NMDA hypofunction causes the observed pathology or represents an early consequence of membrane damage (as the lipid-raft hypothesis suggests) requires further investigation.

The relative contribution of different upstream triggers in individual patients cannot yet be determined.

Chapter 2: The Physiological Sensitizers—Amyloid-Beta and Tau

Convergence of Disparate Triggers in the Excitatory Insufficiency Paradigm



The Chronic Excitatory Insufficiency model uniquely reconciles diverse genetic, developmental, and environmental risk factors, demonstrating their shared mechanical consequence: the suppression of glutamatergic signaling and the subsequent induction of compensatory sensitizers.

Data sources: Moosmann (2020)

Reframing Pathological Molecules

Under excitatory insufficiency, the brain faces a biological imperative: restore function despite chronic undersupply of excitatory drive[9].

The proposed compensatory response involves deployment of amyloid-beta and tau phosphorylation[25].

Amyloid-Beta as a Compensatory Molecule

Within the Moosmann framework, APP induction and amyloid-beta generation are interpreted as adaptive responses to excitatory blockade[29].

NMDA antagonists, mechanical injury, and axonal damage all induce rapid Aβ secretion[17].

At physiological (picomolar) concentrations, amyloid-beta enhances NMDA-dependent long-term potentiation and facilitates learning and memory[2].

The toxicity observed in older in-vitro studies occurred at supra-physiological (micromolar) concentrations over prolonged periods—conditions that trigger neuronal defensive responses misinterpreted as Aβ toxicity.

Under this interpretation, amyloid-beta functions as an acute excitatory sensitizer, deployed to maintain synaptic function when baseline glutamatergic signaling is suppressed.

The APP molecule can be understood holistically: sAPP-alpha provides synaptic growth support, Aβ acts as an acute sensitizer, and the AICD fragment supports metabolic glutamate provisioning.

Tau Hyperphosphorylation as Compensatory

Hyperphosphorylation of tau is reframed as facilitating emergency axonal transport[25].

Normally, tau stabilizes microtubules, but this stability impedes rapid cargo transport[25].

Under conditions of severe excitatory deficit, the neuron must rapidly transport synaptic components (APP vesicles, NMDA receptors) from soma to dendrites[11].

Tau phosphorylation reduces its microtubule affinity, clearing transport pathways[25].

Additionally, phosphorylated tau redistributes to somatodendritic compartments where it interacts with kinase fyn to sensitize NMDA receptors[11].

A physiological analog supports this interpretation: hibernating mammals reversibly develop tau pathology indistinguishable from advanced Alzheimer's brains, serving to maintain connectivity under extreme metabolic suppression.

This pathology disappears within hours of arousal.

Allostatic Load and Terminal Collapse

The model proposes that while these compensatory mechanisms are remarkably successful for decades—visible as hypermetabolic activation in asymptomatic young carriers of genetic risk—eventually they fail.

After 30-40 years of sustained metabolic strain, protein clearance mechanisms are overwhelmed[6].

Amyloid-beta aggregates into extracellular plaques, tau collapses into intracellular tangles, and the biological system exhausts its capacity for self-regulation.

What Remains Unknown

This interpretation requires evidence distinguishing early-phase compensatory amyloid production from later pathological aggregation.

Mechanisms by which exactly the brain determines when to activate these responses versus when clearance begins to fail are not specified.

The model does not address why some individuals with substantial amyloid pathology remain cognitively intact while others decline rapidly.

Chapter 3: Rappoport's Lipid-Raft and Adaptive Response Theory

Structural Foundations

Rappoport's framework shifts focus from protein aggregates to neuronal membrane architecture[11].

Lipid rafts are specialized membrane microdomains enriched in cholesterol, sphingomyelin, and gangliosides[1131].

Contemporary neurobiology recognizes them not as inert scaffolding but as essential signaling platforms.

Critical molecular machinery—NMDA receptors, AMPA receptors, and APP—requires lipid raft integrity for proper spatial organization, trafficking, and signal transduction[11].

The Role of Lipid Raft Degradation

The model proposes that lipid raft degradation is a primary structural vulnerability initiating Alzheimer's pathology[11].

The aging brain experiences systemic changes in lipid metabolism and cholesterol biosynthesis[31].

ApoE4, a cholesterol transporter, is less efficient than ApoE3 at delivering cholesterol from astrocytes to neurons for membrane repair[319].

Consequently, ApoE4 carriers experience chronic deficits in lipid raft maintenance[119].

When lipid rafts destabilize, embedded proteins lose functional anchoring[11].

For APP, altered spatial relationships with membrane-bound secretases shift enzymatic processing away from the neurotrophic alpha-secretase pathway toward the amyloidogenic beta/gamma-secretase pathway.

For NMDA receptors, raft degradation leads directly to desensitization and endocytic internalization[11].

This mechanism directly links structural membrane degradation to NMDA receptor hypofunction, bridging the two theoretical frameworks[9].

The ARAR Architecture

Rappoport embeds lipid-raft theory within a broader framework termed ARAR (Allow, Restrain, Amplify, Respond)[11].

The healthy brain maintains dynamic balance between excitatory signals (Allow/Amplify) and GABAergic restraint (Restrain) to produce adaptive output (Respond). "Double-edged plasticity" describes the inherent trade-off: mechanisms enabling learning and adaptation (LTP, LTD) are metabolically expensive and structurally fragile[11].

When lipid raft degradation cripples the Amplify capacity, the brain faces an impossible choice: allow cognitive output to collapse or aggressively upregulate compensatory plasticity mechanisms[11].

The aggressive response generates excessive amyloid-beta to lower synaptic activation thresholds and hyperphosphorylated tau to force transport.

This Amplification is initially successful but ultimately unsustainable—aligning precisely with allostatic load theory.

What Remains Unknown

The model does not specify the relative timing of lipid raft degradation versus NMDA receptor dysfunction[11].

Whether raft degradation is primary or secondary to other processes remains unclear.

The mechanisms by which aging and ApoE4 specifically degrade lipid rafts versus other potential causes require further characterization[119].

The proposed link between cholesterol delivery and raft maintenance is plausible but not definitively proven at the scale of whole brain function[31].

Chapter 4: Synthesis and Complementarity

Proposed Temporal Sequence

The two models align on a logical sequence:

1. **Upstream structural insult**: Genetic liabilities (ApoE4, TREM2 mutations) or environmental factors (aging, traumatic injury, metabolic syndrome) impair cholesterol delivery and basal membrane maintenance[11319]. 2. **Lipid raft disintegration**: Ordered membrane scaffolding physically degrades. 3. **NMDA receptor dysfunction**: Without raft anchoring, receptors fail to cluster at synapses; endocytosis traps them intracellularly[11]. 4. **Chronic excitatory insufficiency**: Limbic and cortical circuits experience sustained reduction in glutamatergic signaling[9]. 5. **Compensatory allostasis**: The ARAR architecture upregulates adaptive response plasticity[11].

APP shifts toward amyloidogenic processing; tau is hyperphosphorylated. 6. **Pathological exhaustion**: Decades of sustained hypermetabolism, mitochondrial strain, and unchecked sensitizer production lead to aggregation, oxidative stress, and terminal collapse of vulnerable networks.

Integration of Secondary Genetic Risk Factors

This framework integrates secondary genetic associations more coherently than amyloid-centric models.

SORL1, BIN1, and PICALM are implicated in endocytosis, vesicle recycling, and ApoE receptor dynamics[11].

Dysfunctions in these genes exacerbate both lipid raft destabilization and intracellular NMDA receptor trapping, driving further excitatory insufficiency[9].

Integration of Immune and Infectious Mechanisms

The framework accommodates emerging evidence for autoimmunity and chronic viral infection[15].

Lifelong micro-damage and innate immune activation may trigger autoantibodies against excitatory structures.

The well-documented condition anti-NMDA receptor encephalitis—where patient antibodies cause acute memory and psychiatric deficits through NMDA receptor internalization—demonstrates this mechanism is biologically feasible[22].

In Alzheimer's disease, chronic autoimmune degradation of NMDA receptors, masked for decades by compensatory amyloid and tau elevation, could drive the proposed excitatory insufficiency[11229].

Limitations of the Synthesis

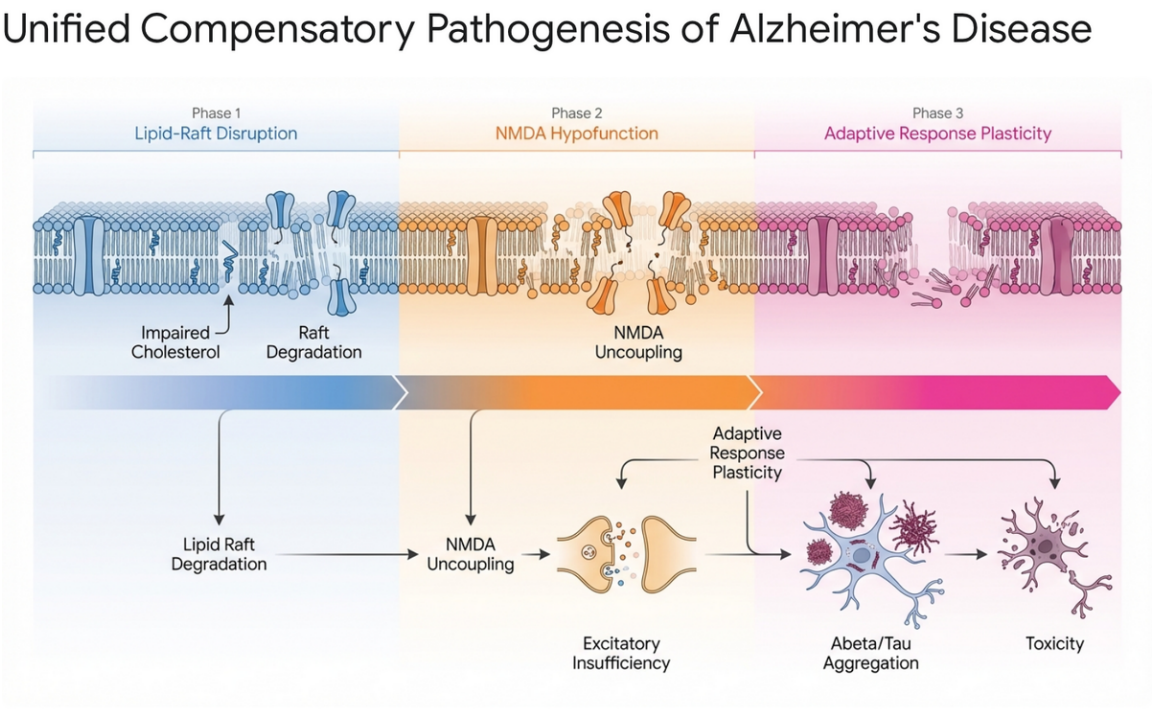
The two models, while compatible in their propositions, do not fully explain each other.

Lipid raft theory does not uniquely predict NMDA hypofunction (other consequences are possible); NMDA hypofunction does not uniquely require lipid raft degradation (other upstream causes exist)[11].

The temporal relationship between these processes in individual patients remains unspecified.

The synthesis is thematic rather than strictly mechanistic.

Critical Gaps and Uncertainties



A synthesis of contemporary theoretical models. Upstream insults degrade lipid raft integrity (Rappoport), uncoupling NMDA receptors. The resulting excitatory insufficiency (Moosmann) triggers massive compensatory upregulation of Aβ and p-tau, culminating in allostatic exhaustion.

What This Analysis Cannot Determine

Causation versus consequence: Does NMDA hypofunction cause amyloid and tau pathology, or do these molecular changes cause hypofunction? The proposed compensatory interpretation requires prospective data distinguishing early adaptive responses from pathological accumulation. **Individual variability**: Why do some asymptomatic individuals develop extensive amyloid and tau pathology while remaining cognitively intact? Why do others decline rapidly with minimal pathology? The models do not account for compensatory reserve or protective factors. **Therapeutic thresholds**: At what point does compensatory response transition to pathological exhaustion? Current models cannot predict when intervention would be beneficial versus when it might disrupt necessary adaptive mechanisms. **Tissue specificity**: The models address hippocampal and cortical pathology but not the selective vulnerability of specific neuronal populations.

Why does the basal forebrain cholinergic system collapse while other populations persist? **Role of inflammation and proteostasis**: While mentioned, the models do not fully integrate microglial senescence, proteasomal and autophagy dysfunction, or the interaction between these systems and proposed primary mechanisms. **Convergent mechanisms versus parallel pathways**: In polygenic disease like sporadic Alzheimer's, multiple risk factors act simultaneously.

The models assume convergence on NMDA hypofunction but do not clarify whether non-convergent pathways also operate.

Required Evidence

Definitive evaluation requires:

- Prospective studies dissecting temporal relationships between lipid raft degradation, NMDA receptor clustering, early amyloid/tau production, and cognitive decline
- Single-cell and subcellular imaging demonstrating proposed membrane and transport mechanisms in human tissue
- Therapeutic trials targeting membrane stability and excitatory tone restoration, with careful monitoring of unintended compensatory disruption
- Clinical stratification identifying which patients exhibit which upstream drivers and which compensatory mechanisms predominate

Implications for Therapeutic Strategy

If these models are substantially correct, current anti-amyloid and anti-tau strategies may be counterproductive, disrupting compensatory mechanisms without addressing upstream causes[11].

Rational alternatives would focus on:

- Membrane stabilization: Lipid raft preservation, cholesterol homeostasis support
- Excitatory restoration: Targeted NMDA receptor enhancement or upstream glutamatergic augmentation
- Precision intervention: Timing treatment to support rather than disrupt compensatory plasticity

However, without resolution of the uncertainties outlined above, such strategies remain speculative[1131].

Conclusion

The Amyloid Cascade Hypothesis has demonstrably failed to explain clinical trial outcomes or guide effective therapeutics[2].

The two frameworks evaluated here—Moosmann's Chronic Excitatory Insufficiency and Rappoport's Lipid-Raft/Adaptive Response theory—offer plausible alternative accounts of disease mechanisms[119].

Both models propose that amyloid-beta and hyperphosphorylated tau represent compensatory responses to upstream deficits in membrane structure and excitatory signaling, rather than primary neurotoxins.

By reframing the disease as homeostatic exhaustion—the terminal failure of decades-long compensatory effort—they suggest therapeutic strategies fundamentally different from current approaches[27].

Importantly, these models remain partially speculative.

While they integrate existing evidence more coherently than amyloid-centric accounts, they require substantial prospective validation.

The field would benefit from recognition of what remains genuinely uncertain rather than from overconfident claims of paradigm-shifting synthesis.

The future of Alzheimer's research depends less on the victory of any single model than on rigorous experimental evaluation of competing mechanistic proposals and willingness to discard failed approaches in favor of evidence-based alternatives.

Works Cited

translational failure in the history of modern biomedical science. This staggering failure stems not from a lack of empirical data, technological prowess, or financial investment, but from a profound rigidity of thought—a dogmatic adherence to a fundamentally flawed epistemological paradigm. By myopically viewing amyloid-beta and phosphorylated tau solely as rogue, primary pathological agents, the global biomedical community has spent billions of dollars and decades of research attempting to violently strip the aging brain of its own endogenous, highly sophisticated compensatory sensitizers. The theoretical models analyzed in this thesis provide a necessary, revolutionary corrective to this scientific impasse. The "Chronic Excitatory Insufficiency" model, elegantly articulated by Moosmann in the 2022 Oskar Fischer Prize initiative, and subsequently expanded upon architecturally by Rappoport's 2025 "Lipid-Raft/Adaptive Response" theory, successfully and comprehensively integrate the disease's genetics, epidemiology, and histopathology. Synthesized, these frameworks effortlessly explain the catastrophic failure of amyloid clearance therapies, accurately account for historically marginalized clinical phenotypes such as profound hearing loss and silent epileptic seizures, and beautifully reconcile the vital physiological roles of amyloid and tau with their tragic, pathological end-states. In these advanced compensatory frameworks, Alzheimer's disease is revealed to be fundamentally a disorder of homeostatic allostasis. The aging or genetically vulnerable human brain, facing relentless structural membrane decay and a plummeting excitatory baseline, fights back with the only molecular tools evolution has provided it: extreme hyper-metabolism, dynamic amyloid-beta production, and emergency tau phosphorylation. Recognizing Alzheimer's disease not as a passive death by toxic proteins, but as the terminal exhaustion of this heroic, decades-long physiological effort opens entirely novel, rational avenues for future therapeutics. Rather than blindly attacking the biochemical smoke, modern pharmacological research must now pivot to extinguishing the underlying fire. The future of Alzheimer's treatment must focus on preserving lipid-raft integrity and cholesterol homeostasis to stabilize the neuronal membrane, directly modulating NMDA receptor availability to restore excitatory tone, and aggressively silencing the autoimmune and viral mechanisms that continuously degrade the glutamatergic synapse. Only by respecting the brain's profound capacity for adaptive compensation can we hope to finally arrest the devastation of this disease. Works cited

1. UTSA Opens Call for Entries for $4 Million Oskar Fischer Prize to Expand Understanding and Explanation of Alzheimer's Disease - PR Newswire, accessed March 23, 2026, https://www.prnewswire.com/news-releases/utsa-opens-call-for-entries-for-4-million-oskar-fischer-prize-to-expand-understanding-and-explanation-of-alzhei mers-disease-300974079.html
2. From synaptic guardian to neurodegenerative culprit: rewiring the amyloid-β feedback loop in Alzheimer's disease - JCI, accessed March 23, 2026, https://www.jci.org/articles/view/200393
3. Peripheral Pathways to Neurovascular Unit Dysfunction, Cognitive Impairment, and Alzheimer's Disease - Frontiers, accessed March 23, 2026, https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.20 22.858429/full
4. NMDA receptors in neurodegenerative diseases: mechanisms and emerging therapeutic strategies - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12328396/
5. Entwined processes in Alzheimer's disease: Brain cellular senescence and Alzheimer's disease pathology - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12538649/
6. Alzheimer disease: Amyloid peptide controversies and challenges of anti-Aβ immunotherapy - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12489360/
7. Solving the Alzheimer's puzzle: Q&A; with creator of Oskar Fischer Prize - UT San Antonio Today, accessed March 23, 2026, https://news.utsa.edu/2020/10/solving-the-alzheimers-puzzle-qa-with-creator-of -oskar-fischer-prize/
8. The Oskar Fischer Lecture Series | Dell Medical School, accessed March 23, 2026, https://dellmed.utexas.edu/units/mulva-clinic-for-the-neurosciences/oskar-fische r-lecture-series
9. OFP_2020_paper_145 (1).pdf
10. The pathological hallmarks of Alzheimer's disease derive from compensatory responses to NMDA receptor insufficiency | bioRxiv, accessed March 23, 2026, https://www.biorxiv.org/content/10.1101/418566v1.full-text
11. The Science of the - Brain, accessed March 23, 2026, https://urn.ub.unibe.ch/urn:ch:slsp:zbz:9780443450082:ihv:pdf
12. The Science of the Brain Function, Dysfunction and Disease - Perivolaropoulou, accessed March 23, 2026, https://www.perivolaropoulou.gr/the-science-of-the-brain-function-dysfunction- and-disease-el
13. The Science of the Brain - 1st Edition | Elsevier Shop, accessed March 23, 2026, https://shop.elsevier.com/books/the-science-of-the-brain/rappoport/978-0-443- 45008-2
14. A Physiological Role for Amyloid-beta Protein: Enhancement of Learning and Memory, accessed March 23, 2026, https://www.researchgate.net/publication/26807608_A_Physiological_Role_for_A myloid-beta_Protein_Enhancement_of_Learning_and_Memory
15. Amyloid, tau, pathogen infection and antimicrobial protection in Alzheimer's disease –conformist, nonconformist, and realistic prospects for AD pathogenesis - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC6306008/
16. Prefrontal Cortex-Mediated Impairments in a Genetic Model of NMDA Receptor Hypofunction Are Reversed by the Novel M 1 PAM VU6004256 - ACS Publications, accessed March 23, 2026, https://pubs.acs.org/doi/10.1021/acschemneuro.6b00230
17. The NMDA Receptor and Schizophrenia: From Pathophysiology to Treatment - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC5518924/
18. N-methyl-D-aspartate receptor hypofunction as a potential contributor to the progression and manifestation of many neurological disorders - Frontiers, accessed March 23, 2026, https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnm ol.2023.1174738/full
19. Aging-Associated Cognitive Decline is Reversed by D-Serine Supplementation - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC9186414/

20. NMDA receptor function, memory, and brain aging - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC3181613/
21. mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing | Brain | Oxford Academic, accessed March 23, 2026, https://academic.oup.com/brain/article/134/12/3435/259493
22. Compensatory hallucinogenesis across three neuropsychiatric disorders: a Bayesian account - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12835829/
23. NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC3608949/
24. Full article: NMDA receptor function, memory, and brain aging - Taylor & Francis, accessed March 23, 2026, https://www.tandfonline.com/doi/full/10.31887/DCNS.2000.2.3/jnewcomer
25. (PDF) The pathological hallmarks of Alzheimer's disease derive from, accessed March 23, 2026, https://www.researchgate.net/publication/327723058_The_pathological_hallmarks_of_Alzheimer's_disease_derive_from_compensatory_responses_to_NMDA_rece ptor_insufficiency
26. γ-secretase targeting in Alzheimer's disease - PMC - NIH, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12188074/
27. Therapeutic and preventive strategies based on the maladaptive plasticity hypothesis for Alzheimer's disease - PMC, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12864465/
28. Amyloid-β and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice | PNAS, accessed March 23, 2026, https://www.pnas.org/doi/10.1073/pnas.0905529106
29. The brain's adaptive response process: function and anatomy - ResearchGate, accessed March 23, 2026, https://www.researchgate.net/publication/392887635_The_brain's_adaptive_respo nse_process_function_and_anatomy
30. Donald Weaver awarded Oskar Fischer Prize for Alzheimer's research - Department of Chemistry | University of Toronto, accessed March 23, 2026, https://www.chemistry.utoronto.ca/news/donald-weaver-awarded-oskar-fischer- prize-alzheimers-research
31. ABCA1■Mediated Cholesterol Efflux Capacity to Cerebrospinal Fluid Is Reduced in Patients With Mild Cognitive Impairment and Alzheimer's Disease | Journal of the American Heart Association, accessed March 23, 2026, https://www.ahajournals.org/doi/10.1161/JAHA.115.002886
32. Alzheimer's researchers awarded $4M in Oskar Fischer Prizes from UTSA, accessed March 23, 2026, https://news.utsa.edu/2022/06/alzheimers-researchers-awarded-4m-in-oskar-fis cher-prizes-from-utsa/
33. Exzitatorische Insuffizienz als Auslöser von Morbus Alzheimer - Gutenberg Open Science, accessed March 23, 2026, https://openscience.ub.uni-mainz.de/bitstreams/f1eb7c8c-e589-4a83-929d-9dd5 3e4c6a66/download
34. Ari Rappoport - The Hebrew University of Jerusalem, accessed March 23, 2026, https://cris.huji.ac.il/en/persons/ari-rappoport/
35. A lipid-raft theory of Alzheimer's disease - ResearchGate, accessed March 23, 2026, https://www.researchgate.net/publication/392876272_A_lipid-raft_theory_of_Alzh eimer's_disease
36. Mitochondrial Dysfunction in Alzheimer's disease: Focus on Dynamics and Electron Transport Chain, accessed March 23, 2026, https://www.aginganddisease.org/EN/10.14336/AD.2025.1046
37. The origin of NMDA receptor hypofunction in schizophrenia - PMC - NIH, accessed March 23, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC6981256/