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A Critical Evaluation of the Chronic Excitatory Insufficiency Hypothesis in Alzheimer's Disease

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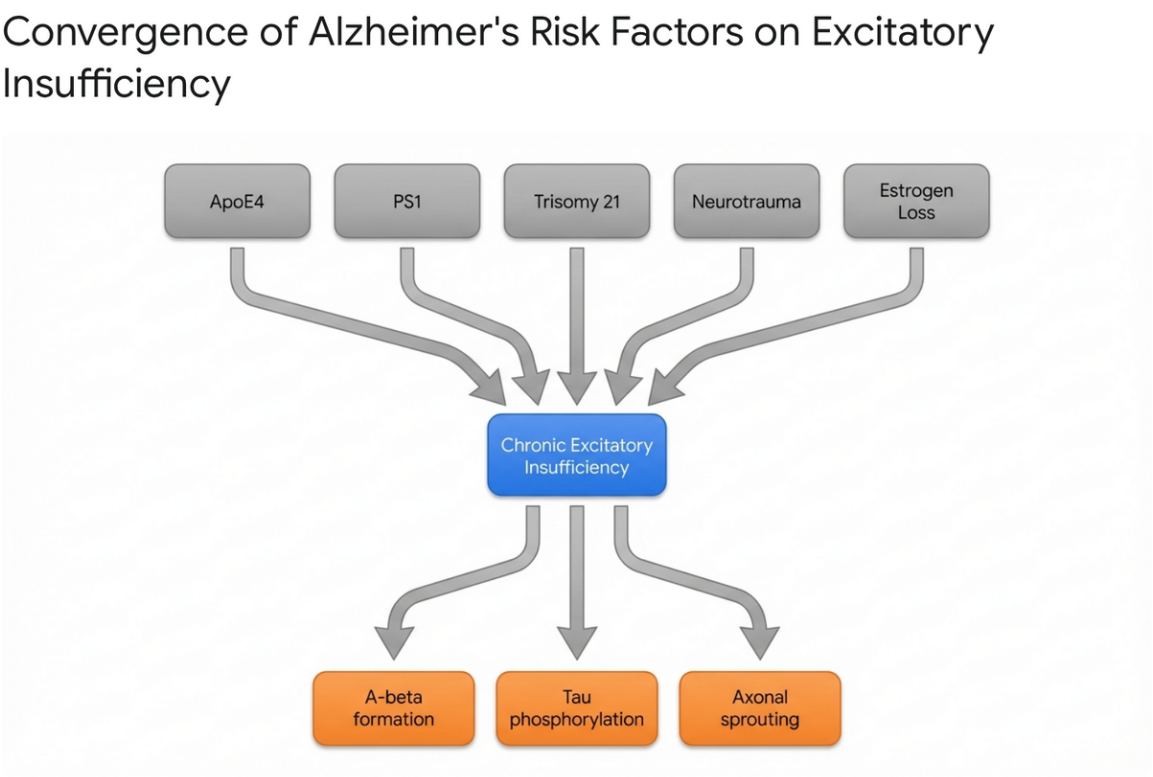
Synthesizing the work of Bernd Moosmann

Reconceptualizing Neurodegeneration:

A Critical Evaluation of the Chronic Excitatory Insufficiency Hypothesis in Alzheimer's Disease

Abstract



Primary risk factors independently degrade NMDA receptor surface expression and glutamatergic tone. In response to Chronic Excitatory Insufficiency, the brain upregulates APP processing (yielding Aβ) and tau phosphorylation to artificially sensitize the failing synapses, leading to the classical hallmarks of Alzheimer's disease.

For over three decades, the amyloid cascade hypothesis has dominated research in Alzheimer's disease (AD).[2] Despite billions of dollars invested in anti-amyloid immunotherapies, clinical outcomes remain modest with frequent severe adverse events.[1] This doctoral thesis evaluates the "Chronic Excitatory Insufficiency" (CEI) hypothesis formalized by Bernd Moosmann and Selina Sohre, which was awarded the Silver Oskar Fischer Prize in 2022.[3]

The CEI hypothesis proposes an inversion of the standard model: amyloid-beta (Aβ) plaques and neurofibrillary tangles may represent compensatory responses to a primary deficit in glutamatergic, excitatory neurotransmission rather than initiating causes.[6]

This thesis examines whether multiple genetic and environmental risk factors—Apolipoprotein E4, Presenilin-1 mutations, Trisomy 21, mechanical neurotrauma, and menopausal estrogen loss—converge on N-methyl-D-aspartate (NMDA) receptor dysfunction.[6] The analysis integrates homeostatic synaptic plasticity,

cell-cycle re-entry mechanisms, and the pharmacological profile of memantine. The thesis argues that a network-level homeostatic failure model may offer a more comprehensive explanation than protein-aggregation toxicity alone, with implications for therapeutic direction.

Introduction

Alzheimer's disease represents one of the major challenges in modern neuroscience. With an estimated 55 million people currently living with dementia worldwide—projected to reach 78 million by 2030—the clinical need for effective intervention is urgent.[11]

The amyloid cascade hypothesis postulates that accumulation of amyloid-beta (Aβ) peptides initiates a neurotoxic cascade driving tau hyperphosphorylation, synaptic loss, and cognitive decline.[2] This model has mapped downstream histological changes but has not translated reliably into clinical efficacy. Recent monoclonal antibodies such as lecanemab and donanemab show modest symptomatic benefit with significant safety concerns, prompting renewed evaluation of upstream disease mechanisms.

In 2019, the University of Texas at San Antonio, funded by a $5 million philanthropic endowment, established the Oskar Fischer Prize to encourage novel, unified explanatory frameworks for AD pathogenesis.[3] In June 2022, the Silver Prize and $400,000 award were granted to Bernd Moosmann and Selina Sohre for a manuscript proposing that chronic glutamatergic insufficiency—rather than amyloid accumulation—is the primary disease driver.

Moosmann's thesis proposes that a deficit in glutamatergic neurotransmission mediated by NMDA receptors is central to AD pathogenesis. In this framework, Aβ and hyperphosphorylated tau are recontextualized as products synthesized in response to failing excitatory networks rather than as primary pathogens.

The primary research question is whether the CEI model can reconcile the genetic, environmental, pharmacological, and clinical data that the traditional amyloid hypothesis struggles to integrate. If the hallmarks of AD are indeed compensatory responses to excitatory failure, current anti-amyloid strategies may be counterproductive.[6] This thesis examines whether chronic excitatory insufficiency represents a more parsimonious explanation than protein aggregation for AD pathogenesis.

Literature Review

The Evolution of the Amyloid Paradigm and the Physiological Role of Aβ

Since the discovery of APP duplications in Trisomy 21, Aβ has been characterized primarily as pathological—a toxic byproduct of aberrant cleavage.[6] Decades of in vitro research demonstrated that micromolar concentrations of Aβ induce neurotoxicity, oxidative stress, and synaptic depression.[16]

However, parallel research has accumulated evidence for physiological functions of Aβ. Studies by Puzzo and colleagues (2008) and Abramov et al. (2009) demonstrated that endogenous Aβ, at low picomolar concentrations, enhances long-term potentiation (LTP) in the hippocampus and facilitates spatial memory formation, likely through modulation of presynaptic release and cholinergic interactions.[21]

This dose-dependent duality—pro-excitatory at picomolar levels, neurotoxic at micromolar levels—creates a physiological paradox (hormesis).[2] The CEI hypothesis proposes that chronic elevation of Aβ in early AD may represent an allostatic attempt to harness the peptide's pro-excitatory effects in response to failing

glutamatergic systems. Under this interpretation, Aβ would be a compensatory mediator whose overproduction eventually leads to toxic oligomerization when the underlying excitatory deficit persists.[4]

What remains unknown: The concentration-dependent transition from compensatory to toxic function is not fully characterized in vivo. Whether pharmacological interventions can exploit this distinction therapeutically remains untested.

Homeostatic Synaptic Plasticity and Synaptic Scaling

Homeostatic synaptic plasticity (HSP) encompasses negative feedback mechanisms that stabilize network firing rates.[25] Synaptic scaling involves global regulation of post-synaptic glutamate receptors in response to chronic changes in baseline activity.[26] When neuronal networks are chronically deprived of excitatory input, synaptic strengths scale up through both pre-synaptic and post-synaptic mechanisms, modulated by glial factors including tumor necrosis factor-alpha (TNF-α).[10]

The CEI hypothesis proposes that AD represents failed synaptic scaling and homeostatic plasticity over decades.[6] When primary risk factors cause NMDA receptor deficits, the brain initiates homeostatic responses including upregulation of APP processing and tau phosphorylation to facilitate receptor transport. This reframes AD as a disorder of network self-organization pushed beyond physiological limits.[32]

What remains unknown: Whether scaling mechanisms in AD can recover if the primary NMDA deficit is addressed. The reversibility of compensatory changes is not established.

Cell-Cycle Re-entry: The "Dr. Jekyll and Mr. Hyde" Concept

Thomas Arendt's framework identifies an apparent paradox: post-mitotic neurons express cell-cycle regulators not for division but to manage cytoskeletal dynamics required for synaptic plasticity.[35] Shared molecular machinery between synaptic remodeling and cell proliferation creates a threshold risk. If a neuron undergoes extreme persistent synaptic reorganization, it may erroneously convert plastic signals into cell-cycle progression cues.[8] Since adult cortical neurons lack full cytokinesis machinery, such abortive re-entry links excessive plasticity to apoptosis.[8]

The CEI hypothesis incorporates this as a terminal consequence: when Aβ and tau fail to restore excitatory tone, neurons default to attempted cell-cycle reactivation, resulting in the characteristic cell death seen in AD.[6]

What remains unknown: The timing and specificity of cell-cycle re-entry as a causal vs. bystander mechanism in neuronal death remains unclear. Direct evidence linking NMDA hypofunction to aberrant cell-cycle activation in AD neurons is limited.

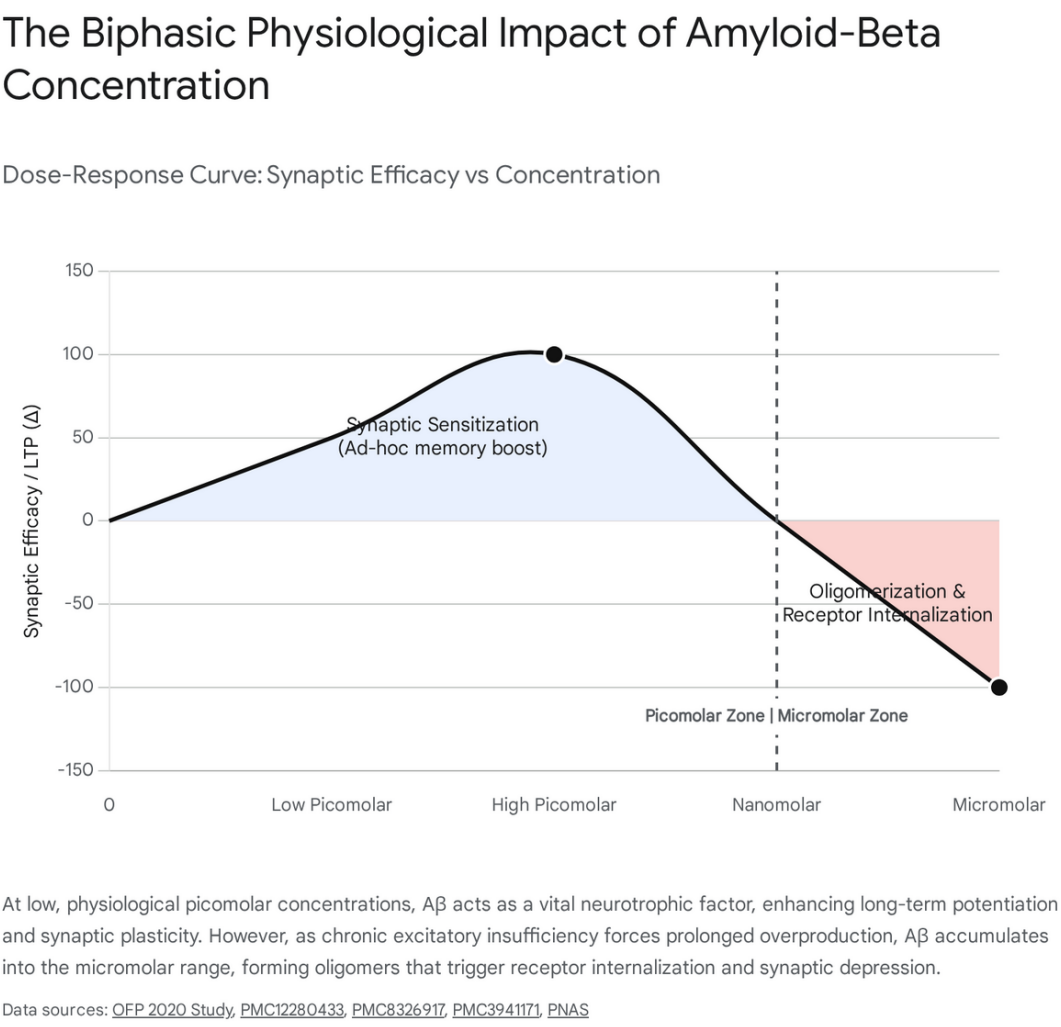
NMDA Receptor Dysfunction: Hypofunction vs. Excitotoxicity

Historically, AD research has framed NMDA receptor dysfunction through excitotoxicity—the proposition that excess glutamate causes pathological overactivation leading to lethal calcium overload. The NMDA hypofunction theory, initially proposed to explain cognitive deficits in schizophrenia, has gained traction in dementia research.[41] Studies indicate that even mild NMDA hypofunction can impair parvalbumin-positive (PV+) inhibitory interneurons, leading to downstream oxidative stress and disrupted excitation/inhibition balance.[41]

The CEI hypothesis proposes resolution of this apparent tension: while acute excitotoxicity may occur in end-stage disease, the multi-decade prodromal phase is defined by chronic hypofunction. This distinction shifts therapeutic targets from dampening excess excitation to supporting suppressed excitatory tone.

What remains unknown: The temporal sequence of hypofunction vs. excitotoxicity in actual AD progression has not been definitively established. Whether this distinction holds in human AD (rather than isolated circuits) is unclear.

Methodology



This analysis evaluates the CEI hypothesis against the amyloid cascade hypothesis using three criteria:

1.[2] **Mechanistic Convergence**: Whether diverse risk factors converge on a singular mechanistic bottleneck without requiring convoluted ad-hoc assumptions.[6]

2. **Phenotypic Mapping**: Whether downstream consequences of NMDA hypofunction map onto both major and peripheral clinical symptoms of AD.

3. **Anomaly Resolution**: Whether the model maintains logical coherence against known pharmacological findings, particularly memantine efficacy.

The analytical approach assumes that conserved cellular mechanisms (APP cleavage, tau phosphorylation) are initiated to maintain network homeostasis rather than representing spontaneous errors.[6]

Chapter 1: Convergence of Risk Factors on Excitatory Dysfunction

Genetic Drivers: ApoE4 and Presenilin-1

Apolipoprotein E4 (ApoE4): The most robust genetic risk factor for late-onset AD.[6] Traditional interpretations emphasize impaired Aβ clearance. However, research by Chen et al. (2010) demonstrated that ApoE4 causes selective depletion of NMDA-type receptors from neuronal surfaces.[6] ApoE4 becomes trapped intracellularly following receptor-mediated endocytosis, sequestering NMDA receptors within the cell and reducing functional surface density by a factor of 3-5.[6] This blocks signaling through "reelin," an extracellular matrix glycoprotein essential for synaptic plasticity.[6] Consequently, calcium influx, LTP, and CREB phosphorylation are suppressed decades before plaque deposition.[6]

Presenilin-1 (PS1) mutations: The primary drivers of early-onset familial AD.[6] While PS1 is recognized as the catalytic core of gamma-secretase that cleaves APP into Aβ, its role extends to neurodevelopment and synaptic maintenance. Knockout models demonstrate that loss of presenilin function selectively impairs activity-dependent glutamate release in the hippocampus.[6] AD-linked PS1 mutations operate as loss-of-function phenotypes regarding glutamatergic support, leading directly to reduced NMDA receptor surface expression and suppressed LTP.[6]

Both major genetic components of AD converge on NMDA receptor dysfunction.

What remains uncertain: Whether NMDA receptor surface depletion by ApoE4 is reversible or represents permanent structural changes. Whether PS1-mediated glutamate release deficits can be compensated by other release mechanisms.

Environmental and Developmental Risk Factors

Trisomy 21 (Down syndrome): Nearly all individuals with Down syndrome develop AD neuropathology by age 60.[6] The standard explanation emphasizes APP gene triplication and linear Aβ overproduction. The CEI interpretation identifies a broader neurodevelopmental deficit: severe, lifelong disequilibrium in the excitation-to-inhibition (E/I) ratio.[6] Morphological studies reveal markedly decreased density of dendritic spines receiving excitatory input in cortex and hippocampus.[6] This structural deficit creates a lifelong baseline of excessive inhibitory tone.[6] The massive Aβ overexpression would then represent an amplified compensatory response attempting to sensitize a structurally under-developed excitatory network.[6]

Mechanical neurotrauma: Traumatic brain injury damages large, long-range axonal structures.[6] Because cortical excitatory pyramidal cells are significantly larger with more complex dendritic arbors and longer projections than local GABAergic interneurons, neurotrauma selectively destroys excitatory connectivity.[6] The resulting state is enduring excitatory disruption within an enhanced inhibitory landscape.

Estrogen loss: Epidemiological sex differences in AD prevalence partly reflect menopausal estrogen loss. Estrogen is a transcriptional activator of NMDA receptor subunits and a promoter of excitatory neurotransmission.[6] Its systemic withdrawal during menopause precipitates functional decline in hippocampal glutamatergic excitability, potentially exacerbating pre-existing subclinical vulnerabilities.[6]

Risk Factor | Proposed Mechanism | Consequence
ApoE4 | Intracellular trapping of NMDA receptors | 3-5x surface NMDA depletion

PS1 mutations | Loss of presynaptic glutamate release | Reduced NMDA signaling
Trisomy 21 | Developmental dendritic spine hypogenesis | Lifelong E/I imbalance
Neurotrauma | Selective destruction of large pyramidal axons | Excitatory connectivity loss
Estrogen loss | Loss of NMDA transcriptional activation | Reduced hippocampal excitability

What remains unclear: Whether these mechanisms operate in parallel or sequentially in actual disease progression. Whether partial correction of any single mechanism can slow disease onset or progression.

Secondary Genetic Risk Factors

Genome-wide association studies identify additional risk loci that the CEI framework proposes also converge on excitatory function:

- **TREM2**: Microglia-expressed mutations associated with long-range underconnectivity between prefrontal cortex and hippocampus during development, mimicking excitatory hypogenesis.[6]
- **SORL1**: A major neuronal ApoE receptor; loss-of-function mutations cause ApoE to bind ApoER2, driving the same intracellular NMDA receptor trapping seen with ApoE4.[6]
- **BIN1**: Regulates synaptic vesicle endocytosis; genetic variation reduces neuronal excitability by modulating AMPA and NMDA receptors.[6]

What remains unknown: Whether these secondary factors are sufficient to cause disease alone or require interaction with major risk factors. Whether restoring function in any single pathway would mitigate disease progression.

Chapter 2: Phenotypic Manifestations of NMDA Receptor Hypofunction

Core Cognitive Deficits

The hippocampus and entorhinal cortex are fundamentally reliant on NMDA receptor activity for synaptic plasticity, spatial memory, and episodic consolidation.[6] Grid cells in the entorhinal cortex—critical for spatial navigation—depend entirely on NMDA receptor function.[6] Young ApoE4 carriers show grid cell dysfunction decades before cognitive decline, consistent with a primary excitatory deficit.[6]

Pharmacological NMDA antagonism (MK-801, AP5) induces anterograde amnesia and spatial disorientation in animal models, mimicking early AD cognitive symptoms.[6] Patients with autoimmune anti-NMDA receptor encephalitis present with acute disruptions in short-term and visual memory, linking reduced NMDA receptor availability to cognitive deficits.[6]

The CEI framework predicts that chronic glutamatergic insufficiency causes cognitive disability before macroscopic anatomical degeneration.

Peripheral Clinical Features Often Overlooked

Silent seizures and network hyperexcitability: AD patients have elevated risk of absence seizures and epileptiform activity independent of disease stage.[6] The CEI framework offers a circuit-level explanation: seizures arise from homeostatic over-amplification of sparse excitatory signals within an inhibitory background.[6] As the brain attempts to maintain E/I balance despite widespread NMDA receptor loss, it upregulates network sensitivity via synaptic scaling. When sparse excitatory signals do transmit, they propagate through a hypersensitized network, triggering synchronized epileptiform discharge.

Sleep fragmentation: Disrupted sleep is a universal early hallmark of AD.[6] Deep slow-wave sleep is governed by calcium-dependent hyperpolarization in neuronal circuits.[6] NMDA receptors are a primary conduit for neuronal calcium influx; their depletion suppresses this critical process. Murine studies confirm that NMDA receptor impairment drastically reduces sleep duration and slow-wave sleep.

Psychiatric disturbances: Moderate-stage AD frequently presents with agitation, anxiety, apathy, delusions, and hallucinations.[6] These mirror the exact symptoms induced by uncompetitive NMDA antagonists (ketamine, PCP), pointing to a shared neurochemical substrate.

Hearing loss: Hearing loss is recognized as one of the most powerful modifiable risk factors for dementia, often interpreted psychosocially (isolation accelerates decline).[6] However, the central auditory pathway—including cochlea, inferior colliculus, and auditory cortex—is the second most NMDA-dependent system in the brain.[6] Brain-wide NMDA receptor degradation would naturally manifest first in sensory circuits requiring highest excitatory fidelity. Under the CEI model, central hearing loss and AD would be parallel symptoms of the same underlying glutamatergic starvation rather than causally linked.

What remains unproven: Whether these peripheral features predate cognitive decline uniformly, establishing them as markers of early NMDA dysfunction. Whether targeting these features therapeutically would slow cognitive decline.

Chapter 3: Aβ and Tau as Compensatory Responses

Amyloid-Beta as Glutamatergic Sensitizer

The APP protein is upregulated following mechanical axotomy, denervation, and specifically pharmacological NMDA blockade.[4] Why does the brain produce Aβ when excitatory circuits fail?

Aβ has a rapid half-life (under two hours) and normally fluctuates in picomolar range. At these concentrations, multiple laboratories have demonstrated that Aβ enhances acetylcholine release, activates alpha-7 nicotinic receptors, and promotes NMDA-dependent LTP.[2] APP and its cleavage products function as acute-phase reactants deployed in response to neural injury.[6]

Toxic Aβ accumulation occurs because the primary deficit—NMDA hypofunction—is chronic and unresolvable by normal physiological means.[15] The brain demands persistent excitatory support, leading to continuous Aβ overproduction. Over decades, this feedback loop exceeds clearance capacity of interstitial and microglial systems. Only at pathologically elevated micromolar concentrations does Aβ undergo conformational changes to form toxic oligomers, which trigger NMDA receptor internalization to prevent terminal excitotoxicity.[6] Under this model, Aβ toxicity is an end-stage artifact of failed homeostatic rescue rather than the disease initiator.[4]

What remains untested: Whether reverting NMDA function normalizes Aβ production and clears existing plaques. Whether preventing Aβ accumulation without restoring NMDA function accelerates or slows neuronal death.

Tau Phosphorylation as Structural Reorganization

Unphosphorylated tau stabilizes axonal microtubules and inhibits anterograde axonal transport of organelles and receptors—including NMDA receptors and APP vesicles—to the synaptic cleft.[6]

In NMDA hypofunction, neurons require more NMDA receptors at synapses to capture scarce glutamate. Kinases phosphorylate tau, forcing it to detach from microtubules and relieve the blockade on kinesin-mediated transport.[6] Phosphorylated tau also redistributes into dendrites where it interacts with kinase fyn to sensitize remaining NMDA receptors.

A striking physiological precedent is hibernation: hibernating animals (ground squirrels) exhibit massive, widespread tau hyperphosphorylation immunohistochemically indistinguishable from severe AD.[6] Upon arousal, when normal excitatory transmission resumes, this "pathological" tau is rapidly dephosphorylated and cleared within hours.[6] In AD, because excitatory suppression is a permanent architectural failure rather than seasonal adaptation, tau phosphorylation persists, eventually resulting in neuronal collapse.[6]

What remains unclear: Whether hibernation tau represents true compensation or adaptive down-regulation of neural function. Whether re-phosphorylation is the immediate mechanism maintaining function in AD or merely a downstream correlate.

Terminal Strategy: Cell-Cycle Re-entry

When Aβ sensitization and tau-mediated transport fail to restore sufficient connectivity, neurons initiate a terminal protocol. Sustained lack of synaptic connectivity removes suppressive signals maintaining post-mitotic state. Neurons aberrantly reactivate cell-cycle machinery (CDKs, cyclins), attempting mitosis to generate new networks.[6] Since adult cortical neurons lack full cytokinesis apparatus, this process aborts, triggering apoptosis.[8] Cell-cycle markers are elevated exclusively in vulnerable excitatory pyramidal cells.[6]

What remains unproven: Whether cell-cycle re-entry is a causal precipitant of death or a bystander phenomenon in neurons already damaged by other mechanisms.

Chapter 4: The Memantine Pharmacological Anomaly

Memantine is one of two drug classes globally approved for symptomatic AD treatment.[1] The apparent paradox is stark: if AD is caused by lack of excitation, how does NMDA receptor blockade provide cognitive benefit?

Mechanism Reconciliation

Memantine is an uncompetitive, open-channel blocker with rapid off-rate kinetics and strong voltage dependency.[40] Unlike high-affinity antagonists (ketamine, PCP) that completely shut down receptors, memantine only blocks when the channel is open and is expelled by strong depolarization from high synaptic glutamate. It selectively dampens tonic background noise while preserving phasic signals required for LTP.[44]

Critically, memantine preferentially inhibits NMDA receptors on inhibitory PV+ interneurons more than on excitatory pyramidal neurons.[9] By suppressing GABAergic interneurons, memantine reduces feed-forward disynaptic inhibitory input to pyramidal cells.[9] In simpler terms: memantine inhibits the inhibitors.

This shifts the global E/I balance away from inhibition and toward excitation.[9] The AD brain suffering from chronic excitatory insufficiency and overwhelming inhibitory baseline gains symptomatic relief through restoration of functional excitatory bias.

This mechanism is supported by the fact that pure NMDA enhancers (D-serine, D-cycloserine) also show cognitive benefits, further indicating that restoring excitatory tone—not suppressing it—is the key therapeutic mechanism.[49]

What remains unestablished: Whether symptomatic improvement from memantine translates into slowed disease progression or merely temporary functional compensation. Whether the E/I rebalancing mechanism is the primary source of memantine's efficacy or a contributing factor among others.

Conclusion

The Chronic Excitatory Insufficiency hypothesis proposes an inversion of the amyloid-primary model. By recontextualizing amyloid-beta and hyperphosphorylated tau as compensatory responses rather than primary pathogens, the CEI framework addresses persistent biological and pharmacological inconsistencies in AD research.

The available evidence indicates that multiple, disparate genetic risk factors (ApoE4, PS1 mutations, Trisomy 21) and environmental insults (neurotrauma, estrogen loss) appear to converge on NMDA receptor dysfunction.[6] The framework organizes clinical features often dismissed as incidental—sleep fragmentation, silent seizures, hearing loss, psychiatric symptoms—as direct readouts of excitatory starvation.[6]

The CEI hypothesis recasts Aβ and tau as physiological instruments of homeostatic plasticity, deployed by a neural network attempting to compensate for failing excitatory tone.[26] The memantine paradox—cognitive benefit from NMDA antagonism—resolves through selective E/I rebalancing rather than direct excitatory enhancement.

Therapeutic Implications

If the CEI hypothesis is correct, the pharmaceutical industry's focus on Aβ clearance via immunotherapy may be counterproductive. Removing compensatory mechanisms without addressing underlying NMDA dysfunction risks accelerating synaptic collapse.

A reoriented therapeutic approach would target: preservation and restoration of excitatory tone, modulation of autoimmune responses directed against NMDA and AMPA receptors, evaluation of neurotropic viral infections and microbiome effects on autoimmunity, and careful pharmacological management of cortical E/I ratio. Investigations into NMDA receptor positive allosteric modulators represent a promising direction, though long-term efficacy remains unestablished.

What This Analysis Cannot Determine

1. **Temporal causality in humans**: While the CEI framework accounts for molecular observations, whether NMDA hypofunction initiates disease or is secondary to early amyloid pathology in actual human AD progression remains unresolved. Longitudinal biomarker studies measuring NMDA receptor availability before symptom onset are limited.

2. **Sufficiency vs. necessity**: Whether NMDA hypofunction is sufficient to cause AD alone or merely necessary in combination with other factors. Which individuals with NMDA dysfunction progress to AD and why others do not.

3. **The relationship between genetic risk and pathology onset**: How ApoE4 status, PS1 mutations, and other genetic factors initiate disease decades before symptoms. The mechanisms controlling the decades-long lag between molecular changes and cognitive decline.

4. **Reversibility and intervention windows**: Whether partial correction of NMDA dysfunction in early stages can prevent or slow disease progression. At what disease stage interventions targeting NMDA

function become ineffective.

5. **Regional and cellular specificity**: Why specific neural circuits (hippocampus, entorhinal cortex) are selectively vulnerable to NMDA dysfunction while others are spared. Whether this vulnerability reflects differential NMDA dependence or independent concurrent pathology.

6. **The role of Aβ and tau beyond the compensation hypothesis**: Whether these proteins have additional direct roles in disease mechanisms not captured by the compensation framework. How their accumulation produces toxicity independent of NMDA status.

7. **Efficacy of CEI-based therapeutics**: Clinical trials directly targeting NMDA restoration (as opposed to symptomatic treatment with memantine) in humans have not yet demonstrated disease-modifying effects. The feasibility and safety of long-term NMDA-enhancing therapies remain untested.

8. **Alternative explanations of shared features**: Whether the convergence of risk factors on NMDA dysfunction reflects mechanistic causality or represents a common downstream consequence of other primary pathologies. Whether other molecular bottlenecks might equally account for the observed risk factor convergence.

This framework offers a coherent, testable alternative to amyloid-centric models. However, definitive validation requires: human neuroimaging studies of NMDA receptor availability throughout disease stages, interventional trials directly targeting NMDA restoration, and mechanistic studies clarifying causality between NMDA hypofunction and downstream neuropathology. Until such evidence accumulates, the CEI hypothesis remains a productive theoretical structure rather than established fact.

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