The Ontological Crisis of Alzheimer's Disease: Epistemological Challenges of the ATN Framework and the Synaptic Imperative for a Redefinition of the Preclinical Stage

Abstract

The conceptualization of Alzheimer's disease (AD) has undergone a paradigmatic shift over the last decade, transitioning from a clinical-pathological syndrome defined by symptomology and post-mortem verification to a biological construct definable *in vivo* through biomarkers. This transition, formalized in the 2018 National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework and codified in the 2024 Revised Criteria, operationalizes the disease through the ATN classification system (Amyloid, Tau, Neurodegeneration). This doctoral thesis provides a critical, exhaustive examination of this transition, investigating the extent to which the ATN framework challenges the validity of the Amyloid Cascade Hypothesis (ACH) and how emerging synaptic biomarkers necessitate a fundamental redefinition of preclinical AD.

Through a rigorous synthesis of longitudinal cohort data, neuroimaging studies, and fluid biomarker analyses, this research demonstrates that the decoupling of amyloidosis from neurodegeneration within the ATN framework reveals a non-linear disease trajectory that falsifies the deterministic version of the ACH. We identify a pervasive "reification" of risk factors, where the presence of amyloid is conflated with disease presence, creating a population of "patients-in-waiting." Furthermore, we present compelling evidence that emerging synaptic biomarkers—specifically Neurogranin (Ng), Synaptosomal-Associated Protein 25 (SNAP-25), and Synaptic Vesicle Glycoprotein 2A (SV2A)—offer superior prognostic utility compared to traditional markers. The inverse correlation between CSF and plasma exosomal synaptic proteins suggests a distinct pathophysiological mechanism of synaptic failure that precedes gross neurodegeneration. Consequently, this thesis argues for the expansion of the diagnostic framework to AT(S)N, where synaptic dysfunction (S) serves as the obligate marker of active disease, bridging the gap between benign proteinopathy and symptomatic illness.

Chapter 1: Introduction

1.1 The Dissociation of Pathology and Phenotype

For over a century, since Alois Alzheimer's first description of the disease in 1906, Alzheimer's disease (AD) was ontologically anchored in the convergence of clinical symptoms—specifically progressive amnestic dementia—and distinct neuropathological lesions: extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tau tangles.[1] This clinico-pathological dualism served as the gold standard for diagnosis, requiring post-mortem verification to confirm that the clinical syndrome was indeed caused by the suspected pathology. However, the early 21st century has witnessed a radical decoupling of these two distinct entities. Advances in positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarker analysis have allowed clinicians to visualize AD pathology in living individuals, revealing a startling disconnect: a substantial proportion of cognitively unimpaired older adults harbor significant amyloid burdens, while many individuals with clinical dementia syndromes lack the requisite amyloid pathology.[3]

This dissociation precipitated an epistemological crisis. If one can have the pathology without the symptoms, and the symptoms without the pathology, what *is* the disease? In an attempt to resolve this ambiguity, the research community, led by the National Institute on Aging and the Alzheimer's Association (NIA-AA), initiated a profound shift in 2018, proposing that AD be defined purely as a biological construct.[1] Under this framework, AD is no longer a clinical syndrome but a specific aggregate of biological changes, regardless of their phenotypic expression. This definition was further refined and entrenched in the **2024 Revised Criteria for Diagnosis and Staging of Alzheimer's Disease**, which establishes that a diagnosis of AD can be made based solely on the presence of core biomarkers (Amyloid or Tau) in living individuals, essentially rendering the clinical exam secondary to the biological assay.[5]

1.2 The Problem Statement: Reification and the Cascade

This thesis addresses two critical problems arising from this ontological shift. First, the biological redefinition of AD relies heavily on the **Amyloid Cascade Hypothesis (ACH)**, which posits a linear causal sequence from amyloid accumulation to tau pathology, neurodegeneration, and cognitive decline.[3] However, the very biomarkers used to operationalize this definition have generated data that contradicts the linear causality of the cascade. The identification of "Suspected Non-Alzheimer's Pathology" (SNAP)—individuals with neurodegeneration but no amyloid—and "amyloid resilient" individuals challenges the sufficiency and necessity of amyloid as the sole disease initiator.[9] By defining the disease *as* the presence of amyloid (A+), the new framework risks reifying a risk factor into a disease entity, insulating the ACH from falsification by defining non-conforming cases (e.g., dementia without amyloid) out of the disease category entirely.[11]

Second, the current ATN framework (Amyloid, Tau, Neurodegeneration) lacks a specific marker for the primary substrate of cognitive loss: the synapse. Synaptic dysfunction correlates more strongly with cognitive decline than either plaques or tangles.[12] The exclusion

of specific synaptic markers from the core diagnostic criteria limits the ability to stratify risk in the preclinical population, leading to the potential overdiagnosis of "Preclinical AD" in individuals who may never progress to symptomatic illness due to synaptic resilience.

1.3 Research Objectives and Questions

This doctoral thesis aims to critically evaluate the biological redefinition of AD and propose a revised model that integrates synaptic biology. The inquiry is guided by two primary research questions:

1. **To what extent does the transition to the ATN classification framework challenge the validity of the amyloid cascade hypothesis?**
    - *Hypothesis:* The ATN framework, by enabling the in vivo dissection of pathological components, reveals a heterogeneity of disease trajectories (e.g., A+T-N-, A-T+N+) that falsifies the linear, deterministic model of the ACH, suggesting instead a complex system of independent but interacting proteinopathies.
2. **How do emerging synaptic biomarkers necessitate a redefinition of preclinical Alzheimer's disease?**
    - *Hypothesis:* Emerging synaptic biomarkers (Neurogranin, SNAP-25, SV2A) provide a measure of "functional neurodegeneration" that is distinct from and antecedent to gross structural atrophy. Their inclusion allows for the differentiation of "benign" amyloidosis from "malignant" preclinical disease, necessitating a redefinition of the preclinical stage to require evidence of synaptic failure.

1.4 Methodology of Synthesis

This thesis employs a rigorous, multi-dimensional analysis of primary literature, clinical trial data, and biomarker validation studies. We synthesize data from major longitudinal cohorts, including the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Swedish BioFINDER-2 study.[14] The analysis integrates:

- **Quantitative validation studies:** Examining the concordance of ATN profiles with clinical progression.[10]
- **Molecular biology:** Analyzing the mechanisms of synaptic protein release into CSF versus plasma exosomes.[17]
- **Epistemological critique:** Applying concepts from the philosophy of science (specifically Popperian falsification and Kuhnian paradigm shifts) to evaluate the validity of the revised diagnostic criteria.[11]

Chapter 2: The Evolution of Diagnostic Frameworks and the Persistence of the Amyloid Paradigm

To understand the implications of the 2024 Revised Criteria, one must first deconstruct the

historical trajectory of AD diagnostics and the theoretical dominance of the Amyloid Cascade Hypothesis.

2.1 The Amyloid Cascade Hypothesis: A Hegemonic Paradigm

Proposed in 1992 by Hardy and Higgins, the ACH provided a seductive and parsimonious explanation for AD pathogenesis: the deposition of amyloid-beta peptide (Aβ) is the causative agent of Alzheimer's pathology and implies that neurofibrillary tangles, cell loss, vascular damage, and dementia follow as a direct result of this deposition.[3]

2.1.1 The Evidence Base

The hypothesis was built on robust genetic data. Familial Alzheimer's Disease (FAD), caused by autosomal dominant mutations in the *Amyloid Precursor Protein (APP)*, *Presenilin 1 (PSEN1)*, or *Presenilin 2 (PSEN2)* genes, invariably leads to increased production or aggregation of Aβ42 and early-onset dementia.[20] This genetic certainty was extrapolated to sporadic, late-onset AD (LOAD), creating a dogma that Aβ accumulation is the *primum movens* of all AD.[21]

2.1.2 Anomalies and Contradictions

Despite its dominance, the ACH has faced persistent anomalies.

- **Temporal Dissociation:** Aβ deposition often plateaus years or even decades before the onset of cognitive symptoms. Many cognitively normal elderly individuals exhibit substantial amyloid burden at autopsy, indistinguishable from AD patients.[3]
- **Spatial Dissociation:** The spatial distribution of amyloid plaques (often beginning in the neocortex) correlates poorly with the pattern of neurodegeneration and cognitive loss (which typically begins in the medial temporal lobe). Conversely, tau pathology tracks much more closely with atrophy and symptoms.[23]
- **Therapeutic Failure:** Perhaps the most damning evidence against the simple ACH is the recurrent failure of amyloid-centric therapeutics. While recent agents like lecanemab have shown statistical efficacy in clearing plaque, the clinical benefit remains modest, suggesting that amyloid clearance in the symptomatic phase is insufficient to halt the disease process.[19]

2.2 The 2018 NIA-AA Research Framework: The Biological Turn

In 2018, the NIA-AA proposed a radical shift intended to support research into preclinical interventions. Recognizing the poor correlation between clinical symptoms and pathology, they proposed the **AT(N) Framework**.[1]

- **A (Amyloid):** Defined by low CSF Aβ42 or positive Amyloid PET.
- **T (Tau):** Defined by elevated CSF p-tau or positive Tau PET.
- **(N) (Neurodegeneration):** Defined by elevated CSF t-tau, MRI atrophy, or FDG-PET

hypometabolism.

Crucially, the 2018 framework introduced a distinction between **"Alzheimer's Pathologic Change"** (A+T-(N)-) and **"Alzheimer's Disease"** (A+T+(N)-). It explicitly stated that "Alzheimer's disease is defined by its underlying pathologic processes... The diagnosis is not based on the clinical consequences of the disease".[1] This move was explicitly epistemological: it sought to create a "biological construct" to facilitate research, unencumbered by the variability of clinical diagnosis.[26]

2.3 The 2024 Revised Criteria: Codifying the Reification

The 2024 Revised Criteria represent the maturation of this biological definition into clinical practice guidelines. Several key changes in the 2024 criteria hold profound implications for the ACH and the definition of preclinical disease.[5]

2.3.1 The "Core" Distinction

The 2024 criteria categorize biomarkers into "Core 1" and "Core 2":

- **Core 1 (Diagnostic):** Includes biomarkers of Amyloid (A) and soluble phosphorylated tau (T1). Crucially, *either* A+ or T1+ is sufficient to establish a diagnosis of AD.[6]
- **Core 2 (Staging):** Includes biomarkers of aggregated tau (T2), such as Tau PET, used for staging severity but not required for diagnosis.

2.3.2 The Exclusion of Neurodegeneration (N)

In a significant departure from the 2018 framework, the (N) category—markers of non-specific neurodegeneration/neuronal injury like NfL or atrophy—was removed from the specific definition of AD.[7] (N) is now classified alongside inflammatory (I) and vascular (V) markers as "non-specific processes."

- *Implication:* This change implies that neurodegeneration is a *consequence* or a *comorbidity*, but not a defining feature of the disease itself. This reinforces the amyloid-centric view: if you have the protein (A/T), you have the disease, even if your brain is structurally intact and functioning normally.

Chapter 3: The ATN Framework as a Challenge to the Amyloid Cascade Hypothesis

While the ATN framework was designed to operationalize the ACH, its application in large-scale observational studies has generated data that fundamentally challenges the hypothesis's linear validity. By dissecting the pathology into discrete, measurable components, the framework has exposed the heterogeneity of disease pathways.

3.1 Divergent Trajectories: The "Non-Cascaders"

The ACH predicts a specific biological sequence: A-T-N- $\rightarrow$ A+T-N- $\rightarrow$ A+T+N- $\rightarrow$ A+T+N+ $\rightarrow$ Dementia. However, validation studies of the 2024 criteria reveal that this sequence is the exception, not the rule.

A pivotal study by Ferrari-Souza et al. (2024), analyzing the ADNI cohort under the new 2024 criteria, found that only **31% to 36%** of individuals diagnosed with biological AD followed the predicted amyloid cascade trajectory.[10] The remaining majority fell into "resilient" or "copathologic" categories.

- **Resilient Phenotypes (A+T+N- or A+T-N-):** A significant proportion of cognitively unimpaired individuals exhibit A+ or A+T+ profiles without evidence of neurodegeneration (N-) or clinical symptoms. The existence of these individuals—some maintaining this state for over a decade—suggests that A and T accumulation are insufficient to drive neurodegeneration in isolation. This contradicts the deterministic "toxicity" often ascribed to these proteins in the ACH.[10]
- **Non-AD Pathologic Change (SNAP):** The identification of individuals who are A-T+N+ or A-N+ (Suspected Non-Alzheimer's Pathology) is perhaps the most significant challenge. SNAP affects approximately 23-25% of the elderly population.[4] These individuals exhibit the neurodegeneration and cognitive decline of AD without the amyloid "initiator." The prevalence of SNAP demonstrates that the "cascade" of tau and neurodegeneration can be initiated and propagated largely independently of amyloid, falsifying the core tenet that Aβ is the unique upstream trigger for AD-type degeneration.[9]

3.2 The Tautology of the "N" Exclusion

The removal of "N" from the core diagnostic criteria in 2024 [7] can be interpreted as a defensive maneuver to protect the ACH from falsification. By defining AD solely by A and T, the framework ensures that any patient *with* AD has amyloid. Patients with dementia and neurodegeneration but *without* amyloid are simply categorized as "not AD," regardless of how closely their clinical syndrome mimics the disease.

- *Epistemological Critique:* This represents a "No True Scotsman" fallacy in nosology. If a patient has the symptoms (dementia) and the damage (atrophy) but lacks the theoretical cause (amyloid), they are excluded from the disease category. While scientifically precise regarding proteinopathy, this reification obscures the clinical reality that amyloid is often a bystander in the complex pathophysiology of dementia.[11]

3.3 Heterogeneity and Mixed Pathologies

The ATN framework has revealed that "pure" AD is relatively rare in the oldest-old, where mixed pathologies (vascular, synuclein, TDP-43) are the norm.[29] The 2024 criteria attempt to address this by including categories for "V" (Vascular) and "S" (Synuclein - using the

alpha-synuclein seed amplification assay) as co-pathologies.[27] However, treating these as mere "add-ons" to the "core" AD pathology minimizes their potential role as primary drivers. The data suggests that in many cases, Aβ may be acting synergistically with, or even secondarily to, these other pathologies, rather than as the sole hierarchal leader.[20]

3.4 Section Conclusion

The transition to the ATN framework has paradoxically undermined the ACH. By providing the tools to measure A, T, and N independently, the framework has demonstrated that these elements are not locked in an immutable causal chain. The high prevalence of SNAP and amyloid resilience suggests that the link between proteinopathy and neurodegeneration is governed by other, likely permissive, factors—chief among them, synaptic integrity.

Chapter 4: Emerging Synaptic Biomarkers: The Functional Bridge

If amyloid and tau are the "architects" of the disease, synapses are the "structural integrity" of the building. Synaptic loss is the strongest structural correlate of cognitive impairment in AD, yet it remains absent from the core ATN classification. Emerging synaptic biomarkers offer a mechanism to measure this "functional neurodegeneration" directly, potentially resolving the discordance between amyloid positivity and clinical status.

4.1 Fluid Biomarkers: Cerebrospinal Fluid vs. Plasma Exosomes

Recent advancements in mass spectrometry and ultra-sensitive immunoassays (Simoa) have enabled the quantification of synaptic proteins in biofluids. A striking dichotomy has emerged between findings in CSF and plasma exosomes.

4.1.1 Neurogranin (Ng): The Post-Synaptic Sentinel

Neurogranin is a dendritic protein involved in Calmodulin signaling and Long-Term Potentiation (LTP).

- **CSF Findings:** Multiple studies confirm that CSF Ng is significantly elevated in AD, including in the MCI and preclinical stages.[12] This elevation reflects the destruction of dendritic spines and the leakage of postsynaptic proteins into the interstitial fluid.
- **Specificity:** Crucially, Ng appears highly specific to AD. Unlike NfL, which is elevated in almost all neurodegenerative conditions, CSF Ng is not typically elevated in Frontotemporal Dementia (FTD), Parkinson's Disease (PD), or Amyotrophic Lateral Sclerosis (ALS).[31] This specificity suggests that Ng release is mechanistically linked to the Aβ/Tau-mediated synaptotoxicity characteristic of AD, making it a distinct marker from general axonal degeneration.

- **Prognostic Value:** The ratio of Aβ42/Ng has been shown to discriminate AD from FTD with higher accuracy than Ng alone, and baseline Ng levels predict the rate of cognitive decline in A+ individuals.[32]

4.1.2 SNAP-25 and the Exosomal Paradox

SNAP-25 is a presynaptic SNARE complex protein essential for vesicle fusion.

- **CSF Findings:** Like Ng, CSF SNAP-25 is elevated in AD, correlating with tau pathology and cognitive decline.[12]
- **Plasma Exosome Findings:** In a fascinating reversal, studies isolating neuronal-derived exosomes (NDEs) from plasma have found *decreased* levels of synaptic proteins (SNAP-25, Ng, GAP-43, Synaptotagmin-1) in AD patients compared to controls.[17]
- **Mechanistic Interpretation:** This inverse correlation (High CSF / Low Exosome) implies a failure of synaptic maintenance. In healthy neurons, exosomes may be actively secreted to transport synaptic proteins for plasticity or intercellular signaling. In AD, intracellular trafficking mechanisms may fail, or the machinery may be overwhelmed by degeneration, leading to a reduction in regulated exosomal secretion while unregulated leakage into CSF increases.[18]
- **Preclinical Prediction:** A study by Jia et al. (2021) demonstrated that a panel of plasma exosomal synaptic markers (GAP43, Ng, SNAP25, Syt1) could predict the onset of AD **5 to 7 years before cognitive impairment** with an AUC of 0.87-0.89.[25] This suggests that synaptic markers can detect the "tipping point" from resilience to disease well before clinical symptoms manifest.

4.1.3 Plasma SNAP-25

Recent data from 2024-2025 indicates that *total* plasma SNAP-25 (not exosome-specific) is increased in preclinical AD.[38] This finding aligns with the CSF data (leakage into blood) and provides a more accessible screening tool. Plasma SNAP-25 levels increase steeply in A+ individuals experiencing subjective cognitive decline (SCD), effectively flagging those at imminent risk of progression.[38]

4.2 Imaging Biomarkers: Visualizing Synaptic Density with SV2A PET

While fluid biomarkers measure the "debris" of broken synapses, SV2A PET imaging allows for the quantification of the remaining intact synapses.

- **Tracers:** The development of radioligands such as **[11C]UCB-J** and **[18F]SynVesT-1** binds to Synaptic Vesicle Glycoprotein 2A (SV2A), a ubiquitous protein in presynaptic vesicles.[39]
- **Correlation with Fluid Markers:** A 2025 study by Nilsson et al. demonstrated a direct correlation between reduced [11C]UCB-J binding (synaptic loss) and altered CSF levels of synaptic proteins (Ng, SNAP-25).[39] This validates fluid markers as true proxies for physical synaptic density.

- **The Resilience Marker:** Critically, SV2A PET has revealed that some individuals with high amyloid load retain near-normal synaptic density. These individuals tend to remain cognitively unimpaired.[40] This identifies **synaptic maintenance** as the biological substrate of "cognitive resilience." Conversely, significant SV2A loss in the medial temporal lobe is observable in MCI patients often before significant atrophy is detectable on MRI.[42]

4.3 Table 1: Comparative Profile of Core vs. Synaptic Biomarkers

Biomarker Category	Specific Markers	Biological Process Measured	Relationship to Symptoms	Specificity for AD
Core 1 (A)	Amyloid PET, CSF Aβ42, Plasma Aβ42/40	Amyloid Plaque Deposition	Weak / Non-linear (Plateaus early)	High (Defines AD)
Core 1 (T1)	CSF p-tau181/217, Plasma p-tau217	Soluble Tau Response	Moderate (Increases in prodromal)	High
Core 2 (T2)	Tau PET	Neurofibrillary Tangles	Strong (Correlates with decline)	High
Non-Specific (N)	MRI, FDG-PET, NfL	Gross Neurodegeneration	Strong (Late stage)	Low (Seen in all dementias)
Synaptic (S)	**CSF Ng / SNAP-25**	**Active Synaptic Degeneration**	**Very Strong (Predicts future decline)**	**High (Ng is AD-specific)**
Synaptic (S)	**SV2A PET**	**Synaptic Density / Integrity**	**Very Strong (Correlates with function)**	**Moderate**

Synaptic (S)	**Plasma Exosomal Ng/SNAP-25**	**Synaptic Maintenance Failure**	**Predictive (5-7 years prior)**	**High**

Chapter 5: Redefining Preclinical Alzheimer's Disease: The Case for AT(S)N

The current definition of Preclinical AD relies on "A+" or "T+". However, as demonstrated in Chapter 3, many "A+" individuals are resilient non-progressors. Assigning them a disease diagnosis is ethically fraught and clinically imprecise. Synaptic biomarkers provide the necessary granularity to refine this definition.

5.1 The Concept of Synaptic Resilience

The heterogeneity in clinical outcomes among A+ individuals can be largely explained by "Synaptic Resilience"—the capacity of the brain to maintain functional connectivity despite the presence of proteinopathy.[40] Individuals who maintain high SV2A density or normal levels of exosomal synaptic proteins likely possess protective mechanisms (e.g., efficient microglial clearance, lack of inflammation) that prevent the amyloid "trigger" from initiating the synaptic "fire."

5.2 Proposal for a New Staging System: AT(S)N

We propose the integration of Synaptic biomarkers (S) as a distinct category within the diagnostic framework, moving from **ATN** to **AT(S)N**. This addition is crucial for distinguishing between *risk* and *illness*.

Proposed Staging:

1. **Stage 1: Amyloidosis (Risk State)**
    - **Profile:** A+ T- S- N-
    - **Clinical Status:** Asymptomatic.
    - **Interpretation:** The individual has the risk factor (amyloid) but biological homeostasis is maintained. The "cascade" has not activated. This should not be labeled "disease" but "Alzheimer's Pathologic Change" or "At-Risk State."
2. **Stage 2: Preclinical Alzheimer's Disease (Active Illness)**
    - **Profile:** A+ T+ **S+** (Elevated CSF Ng, Reduced Exosomal markers, or focal SV2A loss).
    - **Clinical Status:** Asymptomatic or Subjective Cognitive Decline (SCD).
    - **Interpretation:** Synaptic compensatory mechanisms have failed. The disease is active and progressively dismantling neural networks, even if clinical symptoms are not yet overt on standard testing. *This* is the true target population for aggressive disease-modifying therapy.

3. **Stage 3: Prodromal AD / Dementia**
    - **Profile:** A+ T+ S+ N+ (C+)
    - **Clinical Status:** MCI or Dementia.
    - **Interpretation:** Synaptic loss has crossed the threshold to cause gross atrophy (N) and functional impairment (C).

5.3 Ethical and Clinical Implications

The reification of biomarkers in the 2024 criteria creates "patients-in-waiting"—individuals who live with the psychological burden of a dementia diagnosis without the symptoms.[43] By requiring **S+** for a diagnosis of *active* disease, we align the diagnosis closer to the biological reality of harm.

- **Reduced Overdiagnosis:** A+S- individuals would be spared the "disease" label and monitoring, treating their amyloid status similar to high cholesterol—a risk factor to be managed, not a fatal diagnosis.
- **Trial Enrichment:** Clinical trials for DMTs have often failed because they include mixed populations of progressors and non-progressors. Selecting for **S+** participants ensures that the trial tests the drug in individuals with active neurodegeneration, potentially increasing the signal-to-noise ratio for efficacy.[44]

5.4 Integration with Inflammation (I)

Recent research suggests that synaptic pruning in AD is mediated by neuroinflammation, specifically the complement cascade and microglial activation (TREM2).[46] Synaptic markers often rise in tandem with inflammatory markers (GFAP, YKL-40).[48] An **AT(S)I** framework would provide a mechanistic model: Amyloid (A) + Inflammation (I) $\rightarrow$ Synaptic Loss (S). This tripartite model offers a more robust target for combination therapies (e.g., Anti-Amyloid + Anti-Inflammatory).[48]

Chapter 6: Conclusion

6.1 Synthesis of Findings

The transition to the ATN framework and the 2024 Revised Criteria has been a watershed moment in Alzheimer's research, successfully operationalizing the biological definition of the disease. However, this rigorous biological characterization has inadvertently highlighted the inadequacies of the Amyloid Cascade Hypothesis. The discovery that only a minority of "biological AD" cases follow the linear A$\rightarrow$T$\rightarrow$N trajectory, and the prevalence of amyloid resilience, demonstrates that amyloid is insufficient to define the disease course.

The "reification" of AD as simply "A+" creates an ontological error, confusing a risk factor with

a disease state. This thesis has demonstrated that emerging synaptic biomarkers—specifically Neurogranin, SNAP-25, and SV2A PET—provide the missing link in the diagnostic chain. They possess the specificity to distinguish AD from other dementias and the sensitivity to detect functional failure before structural atrophy.

6.2 The Imperative for Redefinition

We conclude that the exclusion of synaptic markers from the core diagnostic criteria is a significant oversight. To accurately define "Preclinical AD," we must move beyond the static presence of plaques and tangles to the dynamic assessment of synaptic integrity. The **AT(S)N** model proposed herein offers a scientifically robust and ethically superior framework. It respects the heterogeneity of the disease, protects resilient individuals from overdiagnosis, and identifies the biological onset of synaptic failure—the true beginning of the end for cognition.

6.3 Future Outlook

The future of AD diagnostics lies not in the binary classification of amyloid status, but in the multivariate modeling of synaptic health. As plasma exosomal assays for synaptic proteins become standardized and widely available [49], they will likely replace CSF as the primary screening tool for "S" status. This will democratize access to precision diagnostics, allowing for a nuanced, biologically grounded approach to treating one of humanity’s most complex afflictions.

References

1

Jack, C. R., Jr, et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia.

29

Carandini, T., et al. (2019). Testing the 2018 NIA-AA research framework... Alzheimer's Research & Therapy.

25

Jack, C. R., Jr, et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia.

2

NIA-AA. (2017). NIA-AA Draft Framework. Alzheimer's Association.

3

Herrup, K. (2015). The case for rejecting the amyloid cascade hypothesis. Nature Neuroscience.

19

Høilund-Carlsen, P. F., et al. (2024). In 2024, the amyloid-cascade-hypothesis still remains a working hypothesis... Frontiers in Aging Neuroscience.

8

Review of Amyloid Cascade Hypothesis. News-Medical.

20

Use of ADAD to examine amyloid cascade. PMC.

36

Jia, L., et al. (2021). Prediction of Alzheimer's disease using multi-variants from blood... Alzheimer's & Dementia.

12

Sandelius, Å., et al. (2019). CSF GAP-43 as a biomarker of synaptic dysfunction... Alzheimer's & Dementia.

38

Agliardi, C., et al. (2025). Plasma SNAP25 is increased in pre-clinical Alzheimer's disease... Research Square.

51

Review of Aβ and synaptic dysfunction. PMC.

13

Review of synapse loss in AD. Frontiers in Cellular Neuroscience.

9

Neurodegeneration Research on SNAP. JPND.

4

Jack, C. R., Jr, et al. (2016). Suspected non-Alzheimer disease pathophysiology (SNAP)... Nature Reviews Neurology.

43

Ethical challenges of early detection. ScienceDirect.

46

Integrating neuroinflammation into ATN. PubMed.

48

Review of neuroinflammation and ATN(X). ResearchGate.

35

Nilsson, J., et al. (2025). Associations between fluid biomarkers and PET imaging... Alzheimer's & Dementia.

24

Alzheimer's Disease: A New Paradigm... Journal of Health Systems and Policies.

26

Alzheimer's Association Press Release 2018.

52

Prevalence of ATN definitions. JAMA Neurology.

17

Review of exosomes in brain. PMC.

18

Exosomes and Tau transmission. PMC.

10

Ferrari-Souza, J. P., et al. (2024). Validating the Amyloid Cascade Through the Revised Criteria... JAMA Neurology.

16

Validating the Amyloid Cascade... PubMed.

47

Building bridges between Alzheimer's theories. Stanford News.

21

Evidence supporting amyloid cascade. PMC.

19

Frontiers review on Amyloid Cascade. Frontiers.

14

BioFINDER-2 Methods. BioFINDER.se.

5

Jack, C. R., Jr, et al. (2024). Revised criteria for diagnosis and staging... Nature Medicine.

27

Review of 2024 Revised Criteria. IPA Online.

6

Alzheimer's Association Press Release 2024.

7

Commentary on Revised Criteria. PMC.

30

Wang, H., et al. (2024). Neurogranin: A Potential Biomarker... Journal of Integrative Neuroscience.

37

Goetzl, E. J., et al. (2016). Synaptic proteins in exosomes... PMC.

31

Wellington, H., et al. (2018). Neurogranin as a CSF biomarker... Alzheimer's & Dementia.

32

Jurasova, V., et al. (2024). CSF neurogranin levels... PMC.

11

Epistemological limitations of AD research. Frontiers in Aging Neuroscience.

33

Specificity of synaptic markers. DNB.

53

Diagnostic value of SNAP-25 in CJD. PMC.

49

Global Biomarker Standardization Consortium. Alzheimer's Association.

50

Biomarkers for AD: PET to Plasma. GlobalRPH.

27

2024 Revised Criteria Details. IPA Online.

32

Jurasova, V., et al. (2024). CSF neurogranin levels... PMC.

42

Review of SV2A PET. PMC.

39

Nilsson, J., et al. (2025). Associations between fluid biomarkers and PET... ResearchGate.

40

SV2A PET sensitivity analysis. Journal of Nuclear Medicine.

41

Cerebrospinal fluid and brain PET measures of SV2A... *PMC*.

Works cited

1. NIA-AA Research Framework: Toward a biological definition of ..., accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5958625/
2. NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease, accessed December 12, 2025, https://aaic.alz.org/_downloads/nia-aa-draft-9-19-17-updated.pdf
3. The case for rejecting the amyloid cascade hypothesis | Request PDF, accessed December 12, 2025, https://www.researchgate.net/publication/277252553_The_case_for_rejecting_the_amyloid_cascade_hypothesis
4. Suspected non-Alzheimer disease pathophysiology—concept and controversy - PMC - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4784257/
5. Revised criteria for the diagnosis and staging of Alzheimer's disease - Cloudfront.net, accessed December 12, 2025, https://d1xe7tfg0uwul9.cloudfront.net/sbgg.org.br/wp-content/uploads/2024/07/Revised_criteria_for_the_diagnosis_and_staging_of_Alzheimers_disease.pdf
6. Alzheimer's Association Workgroup Publishes Biology-Based Criteria for Diagnosis and Staging of Alzheimer's Disease, accessed December 12, 2025, https://www.alz.org/news/2024/revised-alzheimers-diagnostic-staging-criteria
7. Revised criteria for the diagnosis and staging of Alzheimer's disease - PMC - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11630478/
8. Amyloid Cascade Hypothesis - News-Medical.Net, accessed December 12, 2025, https://www.news-medical.net/life-sciences/Amyloid-Cascade-Hypothesis.aspx
9. Pathophysiology of SNAP in individuals with mild cognitive impairment - JPND Neurodegenerative Disease Research, accessed December 12, 2025,

https://neurodegenerationresearch.eu/survey/pathophysiology-of-snap-in-individuals-with-mild-cognitive-impairment/
10. Validating the Amyloid Cascade Through the Revised Criteria of Alzheimer's Association Workgroup 2024 for Alzheimer Disease | Request PDF - ResearchGate, accessed December 12, 2025, https://www.researchgate.net/publication/391736123_Validating_the_Amyloid_Cascade_Through_the_Revised_Criteria_of_Alzheimer's_Association_Workgroup_2024_for_Alzheimer_Disease
11. Are current etiological theories of Alzheimer's disease falsifiable? An epistemological assessment - Frontiers, accessed December 12, 2025, https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2025.1708234/full
12. CSF GAP-43 as a biomarker of synaptic dysfunction is associated with tau pathology in Alzheimer's disease - PMC - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9576773/
13. Intracellular Trafficking Mechanisms of Synaptic Dysfunction in Alzheimer's Disease, accessed December 12, 2025, https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2020.00072/full
14. Methods - BioFINDER study, accessed December 12, 2025, https://biofinder.se/preclinical-ad/methods/
15. Study Details | NCT03174938 | The Swedish BioFINDER 2 Study - ClinicalTrials.gov, accessed December 12, 2025, https://clinicaltrials.gov/study/NCT03174938
16. Validating the Amyloid Cascade Through the Revised Criteria of Alzheimer's Association Workgroup 2024 for Alzheimer Disease - PubMed, accessed December 12, 2025, https://pubmed.ncbi.nlm.nih.gov/40359457/
17. Physiological and pathological insights into exosomes in the brain - PMC - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7340524/
18. The release and trans-synaptic transmission of Tau via exosomes - PMC - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5237256/
19. In 2024, the amyloid-cascade-hypothesis still remains a working hypothesis, no less but certainly no more - Frontiers, accessed December 12, 2025, https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2024.1459224/full
20. Testing the Amyloid Cascade Hypothesis: Prevention Trials in Autosomal Dominant Alzheimer Disease - PMC - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9399299/
21. Alzheimer's Disease Puzzle: Delving into Pathogenesis Hypotheses - PMC, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10796101/
22. Reassessing the Amyloid Cascade Hypothesis of Alzheimer's Disease - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC2680505/

23. What Are the AT(N) Biomarkers for Alzheimer's Disease? - R&D Systems, accessed December 12, 2025, https://www.rndsystems.com/blog/what-are-atn-biomarkers-alzheimers-disease
24. (PDF) Alzheimer's Disease: A New Paradigm, New Treatments, New Challenges, New Approaches - ResearchGate, accessed December 12, 2025, https://www.researchgate.net/publication/394387945_Alzheimer's_Disease_A_New_Paradigm_New_Treatments_New_Challenges_New_Approaches
25. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease, accessed December 12, 2025, https://pubmed.ncbi.nlm.nih.gov/29653606/
26. Alzheimer's Disease Redefined: New Research Framework Defines ..., accessed December 12, 2025, https://www.alz.org/news/2018/alzheimer-s-disease-redefined-new-research-framework-defines-alzheimer-s-by-brain-changes-not-symp
27. Defining Alzheimer's Disease from a Pure Biological Point of View: The 2024 Revised Criteria by the Alzheimer's Association Workgroup, accessed December 12, 2025, https://www.ipa-online.org/UserFiles/DefiningAlzheimer.pdf
28. Suspected non-Alzheimer disease pathophysiology--concept and controversy - PubMed, accessed December 12, 2025, https://pubmed.ncbi.nlm.nih.gov/26782335/
29. (PDF) Testing the 2018 NIA-AA research framework in a retrospective large cohort of patients with cognitive impairment: From biological biomarkers to clinical syndromes - ResearchGate, accessed December 12, 2025, https://www.researchgate.net/publication/336569540_Testing_the_2018_NIA-AA_research_framework_in_a_retrospective_large_cohort_of_patients_with_cognitive_impairment_From_biological_biomarkers_to_clinical_syndromes
30. The Potential Role of Neurogranin in Alzheimer's Disease - IMR Press, accessed December 12, 2025, https://www.imrpress.com/journal/JIN/24/3/10.31083/JIN25368/htm
31. Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology - PMC - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6096740/
32. CSF neurogranin levels as a biomarker in Alzheimer's disease and frontotemporal lobar degeneration: a cross-sectional analysis - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11378641/
33. The use of synaptic biomarkers in cerebrospinal fluid to differentiate behavioral variant of frontotemporal dementia from primar, accessed December 12, 2025, https://d-nb.info/1326915738/34
34. (PDF) CSF neurogranin levels as a biomarker in Alzheimer's disease and frontotemporal lobar degeneration: a cross-sectional analysis - ResearchGate, accessed December 12, 2025, https://www.researchgate.net/publication/383821723_CSF_neurogranin_levels_as_a_biomarker_in_Alzheimer's_disease_and_frontotemporal_lobar_degeneration_a_cross-sectional_analysis
35. Schematic illustration of the synaptic protein SNAP-25 protein sequence... -

ResearchGate, accessed December 12, 2025, https://www.researchgate.net/figure/Schematic-illustration-of-the-synaptic-protein-SNAP-25-protein-sequence-and-membrane_fig2_361093279
36. Blood neuro-exosomal synaptic proteins predict Alzheimer's ..., accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7984076/
37. Decreased synaptic proteins in neuronal exosomes of frontotemporal dementia and Alzheimer's disease - PMC - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5102122/
38. (PDF) Plasma SNAP25 is increased in pre-clinical Alzheimer's ..., accessed December 12, 2025, https://www.researchgate.net/publication/398540257_Plasma_SNAP25_is_increased_in_pre-clinical_Alzheimer's_disease_and_has_prognostic_value_for_cognitive_decline_and_disease_progression_a_multi-cohort_study
39. Associations between fluid biomarkers and PET imaging ([11C]UCB-J) of synaptic pathology in Alzheimer's disease - ResearchGate, accessed December 12, 2025, https://www.researchgate.net/publication/393588150_Associations_between_fluid_biomarkers_and_PET_imaging_11CUCB-J_of_synaptic_pathology_in_Alzheimer's_disease
40. Imaging Synaptic Density in Aging and Alzheimer Disease with [18 F]SynVesT-1, accessed December 12, 2025, https://jnm.snmjournals.org/content/66/4/620
41. Cerebrospinal fluid and brain positron emission tomography measures of synaptic vesicle glycoprotein 2A: Biomarkers of synaptic density in Alzheimer's disease - PMC - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC12149441/
42. Biomarkers for synaptic dysfunction in Alzheimer's disease - PMC - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC12220704/
43. Ethical challenges associated with the early detection of Alzheimer's disease - DOI, accessed December 12, 2025, https://doi.org/10.1016/B978-0-12-822240-9.00019-3
44. Integration of canonical biomarkers in the diagnosis of preclinical Alzheimer disease - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10342128/
45. Synaptic biomarkers in the cerebrospinal fluid associate differentially with classical neuronal biomarkers in patients with Alzheimer's disease and frontotemporal dementia - PMC - NIH, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10037899/
46. Integrating neuroinflammation biomarkers into the ATN(X) framework: Advances in Alzheimer's pathogenesis, diagnosis, and insights from non-human primate models - PubMed, accessed December 12, 2025, https://pubmed.ncbi.nlm.nih.gov/40801241/
47. Building bridges between Alzheimer's theories - Knight Initiative for Brain Resilience, accessed December 12, 2025, https://brainresilience.stanford.edu/news/building-bridges-between-alzheimers-theories

48. (PDF) Integrating neuroinflammation biomarkers into the ATN(X) framework: Advances in Alzheimer's pathogenesis, diagnosis, and insights from non-human primate models - ResearchGate, accessed December 12, 2025, https://www.researchgate.net/publication/394468470_Integrating_neuroinflammation_biomarkers_into_the_ATNX_framework_Advances_in_Alzheimer's_pathogenesis_diagnosis_and_insights_from_non-human_primate_models
49. Global Biomarker Standardization Consortium (GBSC) - Alzheimer's Association, accessed December 12, 2025, https://www.alz.org/research/for_researchers/partnerships/gbsc
50. Biomarkers for Alzheimer's Disease: PET to Plasma - GlobalRPH, accessed December 12, 2025, https://globalrph.com/2025/09/biomarkers-for-alzheimers-disease-pet-to-plasma/
51. Role of Aβ in Alzheimer's-related synaptic dysfunction - PMC - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9459380/
52. Prevalence of Biologically vs Clinically Defined Alzheimer Spectrum Entities Using the National Institute on Aging–Alzheimer's Association Research Framework - PMC - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6632154/
53. Diagnostic and prognostic value of cerebrospinal fluid SNAP-25 and neurogranin in Creutzfeldt-Jakob disease in a clinical setting cohort of rapidly progressive dementias - PubMed Central, accessed December 12, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10485978/