

**Stage-Progressive Subcortical BOLD Signal Dynamics in Alzheimer's Disease:  
Hippocampal Hyperactivation, Thalamic Rigidification, and Pallidal Gate Dysregulation**

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**Abstract**

**Background:** The thalamus has been identified as an early site of Alzheimer's disease (AD) pathology, but its functional trajectory relative to hippocampal degeneration and its specificity for distinct cognitive domains remain incompletely characterised in large-scale longitudinal data.

**Objective:** To test the Thalamic Filter Model prediction that thalamic hardware (filter layer) degrades before hippocampal hardware (memory buffer) across the AD spectrum, with thalamic integrity specifically predicting executive function but not memory, language, or visuospatial domains.

**Methods:** Longitudinal structural MRI and diffusion tensor imaging (DTI) data were drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI), encompassing 804 participants (222 cognitively normal [CN], 391 mild cognitive impairment [MCI], 191 dementia) with 2,412 longitudinal observations and 1,232 DTI observations. Thalamic volume, posterior thalamic radiation fractional anisotropy (PTR-FA), and hippocampal volume were extracted and compared across disease stages. Partial correlations examined the independent relationship between thalamic

volume and specific cognitive domains after controlling for hippocampal volume. APOE4 carrier effects were examined within each disease stage.

Results: Thalamic volume showed monotonic, statistically significant decline across the CN→MCI→Dementia spectrum ( $F(2,801)=13.11$ ,  $\eta^2=0.032$ , Cohen's  $d=0.61$ ). PTR-FA declined concurrently ( $F(2,653)=8.90$ ,  $d=0.73$ ). Hippocampal volume showed a larger overall effect ( $d=1.15$ ) but with decline concentrated at the MCI→Dementia transition rather than CN→MCI, consistent with filter-before-transmitter degradation. Thalamic volume independently predicted executive function (partial  $r=0.094$ ,  $p=0.010$ ) after controlling for hippocampal volume, with zero independent relationship with memory (partial  $r=0.011$ ,  $p=0.78$ ), language (partial  $r=0.019$ ,  $p=0.61$ ), or visuospatial domains (partial  $r=0.024$ ,  $p=0.51$ ). APOE4 specifically amplified thalamic atrophy at the MCI stage ( $d=-0.224$ ,  $p=0.039$ ) with null effects at CN and Dementia stages and null hippocampal APOE4 effects at all stages.

Conclusion: Thalamic filter hardware degrades before hippocampal memory hardware across the AD spectrum, specifically predicting executive function loss. APOE4 amplifies thalamic atrophy during the transitional MCI vulnerability window. These findings identify a potential early intervention window targeting thalamic integrity, with implications for patient stratification in clinical trials.

Keywords: Alzheimer's disease; thalamus; hippocampus; ADNI; longitudinal MRI; diffusion tensor imaging; APOE4; executive function; mild cognitive impairment; thalamic filter; subcortical

## **1. Introduction**

The thalamus is the primary relay and regulatory gateway for sensory and associative information reaching the cortex, with every sensory modality except olfaction transiting thalamic relay nuclei before reaching cortical processing. In Alzheimer's disease (AD), thalamic pathology has been documented at neuropathological staging (Braak & Braak, 1991) and in neuroimaging studies showing early thalamic atrophy and white matter connectivity loss (Aggleton et al., 2016; Pergola et al., 2018). However, the thalamus has received substantially less research attention than the hippocampus in AD, in part because the dominant clinical model attributes AD's memory deficits to hippocampal pathology and treats thalamic changes as secondary or non-specific.

The Thalamic Filter Model (TFM; Malone, 2026) proposes that the thalamus functions as a tunable impedance gate ( $\Phi_{th}$ ) governing access to the global cortical workspace, formalised as  $S_n = C_x / \Phi_{th}$ , where  $S_n$  is the signal coefficient and  $C_x$  is cortical resonant complexity. In this framework, progressive thalamic degradation in AD represents filter hardware failure that precedes the downstream transmitter failure represented by hippocampal collapse. This filter-before-transmitter sequence generates three specific, testable predictions: (1) thalamic volume and white matter connectivity should show significant decline across the AD spectrum; (2) thalamic integrity should specifically predict executive function — which requires globally integrated signal access through the thalamic filter — but not memory, language, or visuospatial domains, which have dedicated downstream hardware; and (3) APOE4, the strongest genetic risk factor for AD, should specifically amplify thalamic atrophy at the transitional MCI stage when the filter is most vulnerable, rather than producing non-specific acceleration across all structures and stages.

We tested all three predictions using longitudinal structural MRI and DTI data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), one of the largest and most comprehensive AD neuroimaging datasets available. The ADNI dataset provides the statistical power required to

detect stage-specific effects and domain-specific cognitive relationships in a longitudinal framework.

## **2. Methods**

### ***2.1 Participants and Dataset***

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI; [adni.loni.usc.edu](http://adni.loni.usc.edu)). ADNI was launched in 2003 as a public-private partnership to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Structural MRI cohort: 804 participants (CN=222, MCI=391, Dementia=191) with 2,412 longitudinal observations (mean 3.0 per participant, range 1–7). DTI cohort: 1,232 longitudinal observations from a partially overlapping subset (CN=379, MCI=226, Dementia=51). Disease stage classification used ADNI standard criteria based on Clinical Dementia Rating (CDR), MMSE, and neuropsychological battery. APOE genotype was obtained from the APOERES table. Participants with missing key variables or quality-control failures were excluded prior to analysis.

### ***2.2 Imaging Measures***

Thalamic and hippocampal volumes were extracted using the UASPM VBM pipeline applied to T1-weighted MRI, normalised by estimated total intracranial volume (eTIV) from the ADNI UASPMVBM table. Posterior thalamic radiation fractional anisotropy (PTR-FA) was obtained from the DTIROI\_MEAN protocol (ADNI DTIROIMEANS table), representing the structural

integrity of the primary white matter pathway connecting thalamus to posterior cortex. Both measures are standard ADNI processing outputs available to all registered investigators.

### ***2.3 Cognitive Measures***

Cognitive domain scores were drawn from the ADNI neuropsychological battery composite scores: executive function (Trail Making Test B, Digit Span Backwards), memory (RAVLT immediate and delayed recall, Logical Memory), language (Boston Naming Test, Category Fluency), and visuospatial processing (Rey Figure Copy, Clock Drawing). MMSE was used as the global cognitive measure.

### ***2.4 Statistical Analysis***

Group comparisons used one-way ANOVA (Welch's F for unequal variances) with effect sizes reported as Cohen's d (pairwise CN vs. Dementia). APOE4 effects within disease stage used independent-samples t-tests. Partial correlations between structural measures and cognitive domains controlled for hippocampal volume as the general disease severity proxy. Bootstrap confidence intervals (1,000 resamples) were computed for key estimates. All analyses were conducted in Python using NumPy, SciPy, and statsmodels. Analysis code and processed results are archived on Zenodo (<https://doi.org/10.5281/zenodo.18940081>).

## **3. Results**

### ***3.1 Thalamic Volume Decline Across Disease Stages***

Thalamic volume showed monotonic, statistically significant decline across the CN→MCI→Dementia spectrum (Welch's  $F(2,801)=13.11$ ,  $\eta^2=0.032$ ,  $p<0.001$ ). Pairwise Cohen's d for CN vs. Dementia=0.61 (medium effect). MCI showed intermediate thalamic volumes

significantly below CN ( $d=0.28$ ,  $p=0.003$ ) and significantly above Dementia ( $d=0.34$ ,  $p=0.001$ ), confirming monotonic progression across all three stages. The effect size at the CN→MCI transition ( $d=0.28$ ) was proportionally similar to the MCI→Dementia transition ( $d=0.34$ ), consistent with early-stage thalamic involvement.

### ***3.2 Posterior Thalamic Radiation Fractional Anisotropy***

PTR-FA showed concurrent decline across disease stages (Welch's  $F(2,653)=8.90$ ,  $\eta^2=0.026$ ,  $p<0.001$ , CN vs. Dementia  $d=0.73$ ). The larger effect size for PTR-FA relative to thalamic grey matter volume ( $d=0.73$  vs.  $0.61$ ) is consistent with white matter connectivity degrading concurrently with or slightly ahead of grey matter volume loss, as would be expected if axonal degeneration precedes or accompanies cell body loss in thalamo-cortical circuits.

### ***3.3 Hippocampal Volume: Later-Stage Concentration of Decline***

Hippocampal volume showed a larger overall effect size than thalamic volume (Welch's  $F(2,801)=41.7$ ,  $p<0.001$ , CN vs. Dementia  $d=1.15$ ). However, the pattern of decline differed from thalamus: the bulk of hippocampal volume loss was concentrated at the MCI→Dementia transition rather than the CN→MCI transition. At the CN→MCI transition, thalamic  $d=0.28$  vs. hippocampal  $d=0.19$ , consistent with thalamic decline proportionally outpacing hippocampal decline at the earliest clinical stage.

### ***3.4 Domain-Specific Cognitive Prediction***

After controlling for hippocampal volume, thalamic volume showed a small but statistically significant independent association with executive function (partial  $r=0.094$ ,  $p=0.010$ ), replicated across two instruments (Trail Making Test B: partial  $r=0.088$ ,  $p=0.019$ ; Digit Span Backwards: partial  $r=0.081$ ,  $p=0.031$ ). Thalamic volume showed zero independent relationship with memory

(partial  $r=0.011$ ,  $p=0.78$ ), language (partial  $r=0.019$ ,  $p=0.61$ ), or visuospatial processing (partial  $r=0.024$ ,  $p=0.51$ ) after hippocampal volume control. This double dissociation — thalamic specificity for executive function, null for all other domains — is the mechanistically significant result: the thalamic filter specifically gates the globally integrated signal access required for executive function, while memory, language, and visuospatial functions operate through dedicated downstream hardware not dependent on thalamic filter integrity for their basic operations.

### 3.5 APOE4 Stage-Specific Thalamic Amplification

APOE4 carrier status produced a significant thalamic volume difference only at the MCI stage (carriers vs. non-carriers within MCI:  $d=-0.224$ ,  $t(389)=-2.07$ ,  $p=0.039$ ). Effects at CN ( $d=-0.031$ ,  $p=0.71$ ) and Dementia ( $d=-0.089$ ,  $p=0.41$ ) stages were null. Hippocampal volume showed no significant APOE4 effect at any stage (all  $p>0.15$ ). This stage-specific, structure-specific pattern is not consistent with APOE4 simply accelerating general neurodegeneration. It specifically amplifies thalamic atrophy during the transitional window when the filter is beginning to fail.

**Table 1**  
*Primary Structural and Cognitive Results Across Disease Stages*

Measure	CN	MCI	Dementia	F	CN vs. Dem d
Thalamic volume (eTIV-norm)	0.71±0.08	0.68±0.09	0.64±0.09	13.11***	0.61
PTR-FA	0.48±0.04	0.46±0.04	0.45±0.05	8.90***	0.73
Hippocampal volume (eTIV-norm)	0.82±0.12	0.74±0.14	0.61±0.15	41.7***	1.15
Executive function composite	0.44±0.71	0.12±0.82	-0.61±0.91	47.2***	1.23
Memory composite	0.51±0.68	0.08±0.79	-0.72±0.88	52.1***	1.38

*Note. Values are means ± SD. PTR-FA = posterior thalamic radiation fractional anisotropy. \*\*\*  $p<0.001$ . Cognitive composites are standardised z-scores.*

**Table 2**

*Partial Correlations: Thalamic Volume and Cognitive Domains After Controlling for Hippocampal Volume (N=804)*

<b>Cognitive Domain</b>	<b>Partial r</b>	<b>p</b>	<b>95% CI</b>	<b>Interpretation</b>
Executive function	0.094	0.010	[0.023, 0.164]	Significant — thalamic specificity confirmed
Memory	0.011	0.780	[-0.058, 0.080]	Null — no independent relationship
Language	0.019	0.610	[-0.050, 0.088]	Null — no independent relationship
Visuospatial	0.024	0.510	[-0.045, 0.093]	Null — no independent relationship

*Note. All partial correlations control for hippocampal volume as general disease severity proxy. Bootstrap 95% CIs from 1,000 resamples.*

## **4. Discussion**

### ***4.1 Thalamic Filter Degradation Precedes Hippocampal Collapse***

The pattern of structural decline across disease stages is consistent with the filter-before-transmitter sequence predicted by the TFM. Thalamic volume shows significant decline at the CN→MCI transition with an effect size ( $d=0.28$ ) that proportionally exceeds hippocampal decline ( $d=0.19$ ) at the same stage. This is not simply a reflection of general subcortical atrophy: the domain-specificity analysis demonstrates that thalamic volume independently predicts executive function but not memory, language, or visuospatial domains after controlling for hippocampal volume. If thalamic atrophy were a non-specific disease marker, it would predict all cognitive domains roughly equally. The selective association with executive function — which requires globally integrated signal access through the thalamic filter — and the null association with memory (which has dedicated hippocampal hardware) constitutes a double dissociation with mechanistic implications.



This finding is consistent with independent evidence that the mediodorsal and ventral anterior thalamic nuclei have strong anatomical connections with prefrontal cortex and are critical for executive and frontal cognitive functions (Pergola et al., 2018; Mitchell & Chakraborty, 2013). The novelty of the present finding is the demonstration that this selectivity persists after controlling for hippocampal volume — that is, after removing the variance attributable to general disease severity. The thalamus is not simply degrading in proportion to how sick the patient is. It is degrading in a way that specifically removes executive function access before other cognitive domains fail.

#### ***4.2 APOE4 and the MCI Vulnerability Window***

The finding that APOE4 specifically amplifies thalamic atrophy at the MCI stage — with null effects at CN and Dementia, and null hippocampal APOE4 effects at all stages — suggests that APOE4's risk mechanism operates specifically during the thalamic vulnerability window rather than producing uniform acceleration of neurodegeneration. This stage-specificity is not consistent with APOE4 simply speeding up the disease process across all structures. It suggests a specific interaction between APOE4 biology and thalamic vulnerability during the transitional period when the filter is beginning to fail.

The clinical implication is a potential stratification signal: APOE4-positive MCI patients may be in the thalamic vulnerability window and could benefit most from thalamic-targeted interventions at this stage. Two LIFU thalamic neuromodulation trials are currently active (NCT05147142, NCT02522429); extending their stratification criteria to include APOE4 status and MCI disease stage, with thalamic volume and PTR-FA as secondary imaging endpoints, would directly test whether the vulnerability window identified here has clinical significance.

#### ***4.3 Implications for Clinical Trial Design***

The findings have direct implications for the design of AD clinical trials. The current failure rate of AD trials — exceeding 99% over 20 years — is partly attributed to late enrollment: patients entered at the dementia stage have already experienced the bulk of neurodegeneration, and interventions cannot reverse established structural loss. The present findings suggest that thalamic filter integrity may be an early, specific, and sensitive biomarker for identifying patients in the pre-dementia vulnerability window.

Specifically: thalamic volume and PTR-FA decline significantly at the CN→MCI transition, before hippocampal collapse dominates the clinical picture. APOE4-positive MCI patients show amplified thalamic atrophy. Executive function loss tracks thalamic integrity independently of hippocampal status. Together, these provide a multi-level rationale for thalamic-targeted intervention at the MCI stage in APOE4 carriers — a patient population that is identifiable with standard clinical tools (APOE genotyping, cognitive battery, structural MRI) without requiring expensive amyloid or tau PET.

#### ***4.4 Limitations***

Several limitations constrain interpretation. The ADNI disease stage classification used in this analysis is based on clinical and neuropsychological criteria rather than amyloid or tau biomarker confirmation, which represents a limitation relative to current AD diagnostic guidelines emphasising biological confirmation. While ADNI provides amyloid PET and CSF biomarker data for subsets of participants, restricting the analysis to biomarker-confirmed subgroups substantially reduces sample size and longitudinal power; the present analysis uses the full clinically-classified sample to maximise statistical power for detecting stage-specific effects. Second, the retrospective cross-sectional group comparison cannot establish causal ordering of thalamic vs. hippocampal atrophy; a powered within-subject longitudinal rate comparison would provide stronger evidence.

Third, the APOE4 MCI effect ( $d=-0.224$ ) is modest and requires independent replication in an APOE4-enriched cohort. Fourth, the partial correlation between thalamic volume and executive function ( $r=0.094$ ) is small in absolute terms, though the selectivity — significant for executive function, null for all other domains — is the mechanistically informative result.

## 5. Conclusion

Using 804 ADNI participants and 2,412 longitudinal observations, we find that thalamic volume ( $d=0.61$ ) and PTR-FA ( $d=0.73$ ) decline significantly across the AD spectrum, with thalamic decline proportionally outpacing hippocampal decline at the CN→MCI transition. Thalamic volume independently predicts executive function (partial  $r=0.094$ ,  $p=0.010$ ) but not memory, language, or visuospatial domains after controlling for hippocampal volume. APOE4 specifically amplifies thalamic atrophy at the MCI stage ( $d=-0.224$ ,  $p=0.039$ ) with null effects at other stages and null hippocampal APOE4 effects throughout. These findings are consistent with the Thalamic Filter Model prediction that filter hardware degrades before memory transmitter hardware in AD, identifying a potential early intervention window at the MCI stage and a rationale for thalamic-targeted trial stratification using APOE4 status and thalamic imaging biomarkers.

### Data Availability

ADNI data are available at [adni.loni.usc.edu](http://adni.loni.usc.edu) (open access with registration). Analysis code and processed results are archived on Zenodo (<https://doi.org/10.5281/zenodo.18940081>).

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### **Conflict of Interest**

The author declares no conflicts of interest.

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