NEUROSCIENCE · NEW HYPOTHESIS · SUMMARY

Decoherence via Demyelination

A Hypothesized Mechanism of Cognitive Decline

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> *What if cognitive aging isn't about losing brain cells, but losing the right timing?*

THE THEORY

Cognitive aging as decoherence

Brain operations depend on the synchronized activation of neuronal assemblies across distributed regions. That synchronization requires precise inter-regional timing: signals must arrive at target circuits aligned to the correct phase of their local oscillations. Myelin—the fatty insulation around axons— is what makes that timing precise, narrowing the variance of action potential arrival times to milliseconds.

The **Decoherence via Demyelination Hypothesis (DDH)** proposes that heterogeneous, age-related demyelination of long-range white matter projections disrupts conduction timing, degrades the inter-regional neuronal communication coherence required for distributed cognition, and produces the cognitive deficits characteristic of normal aging.

> **CORE CLAIM**
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> Heterogeneous, age-related demyelination of long-range white matter projections disrupts conduction timing, degrades inter-regional neuronal communication coherence, and produces the cognitive deficits characteristic of normal aging.

THE MECHANISM

Multi-area communication requires fine-tuned timing

Convergent inputs from distinct projection sources (a, b, c) onto a common receiving area (d) only produce coherent representations when their conduction times are tuned by selective myelination. Activity-dependent oligodendrocyte plasticity provides this tuning across development and learning.

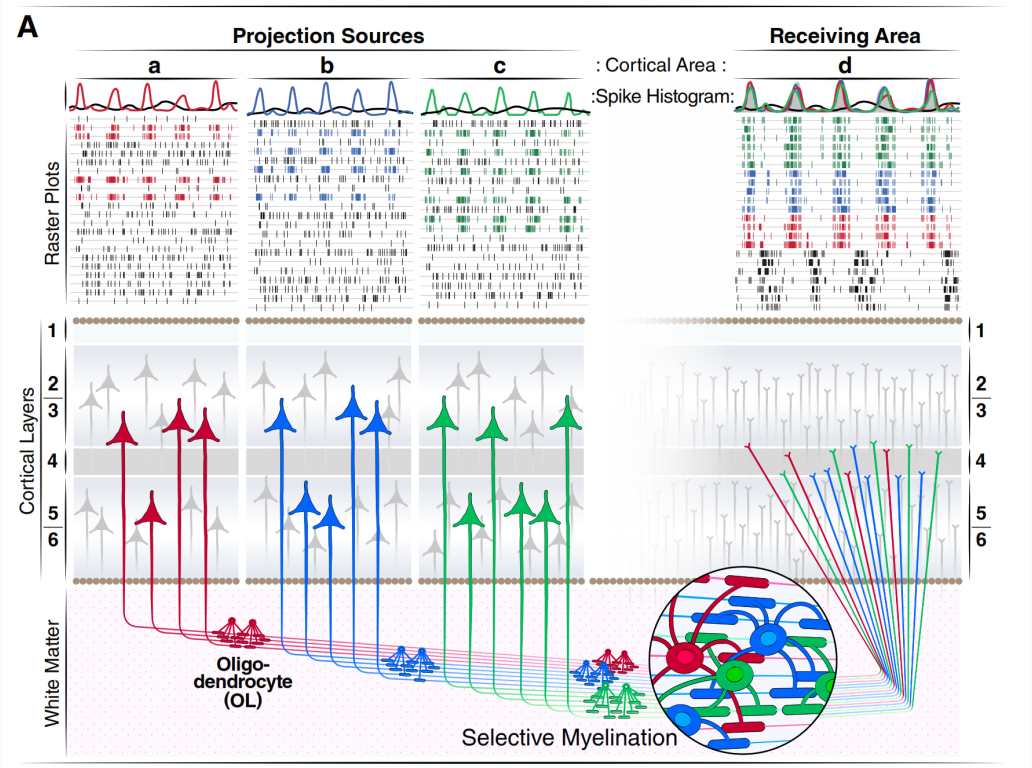


Figure 1A. *Projection sources, oligodendrocyte selective myelination, and convergence at the receiving area.*

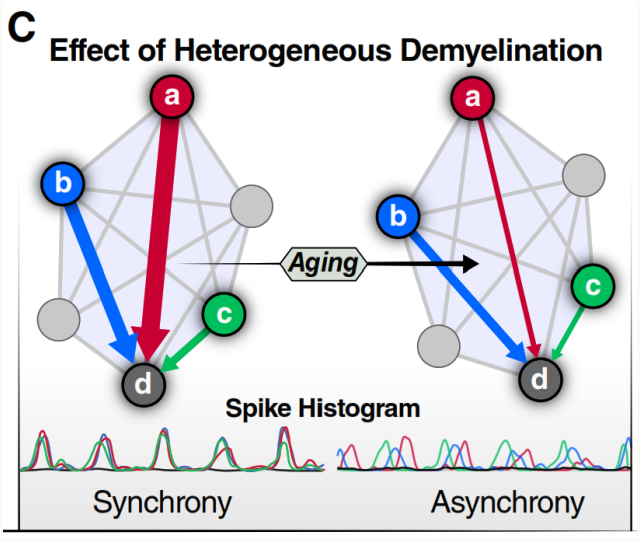


Figure 1C. *Effect of heterogeneous demyelination. With intact myelin (left) the same input pattern produces a coordinated, synchronous response. With age-related uneven demyelination (right) the once-coherent assembly becomes asynchronous.*

STRUCTURAL EVIDENCE

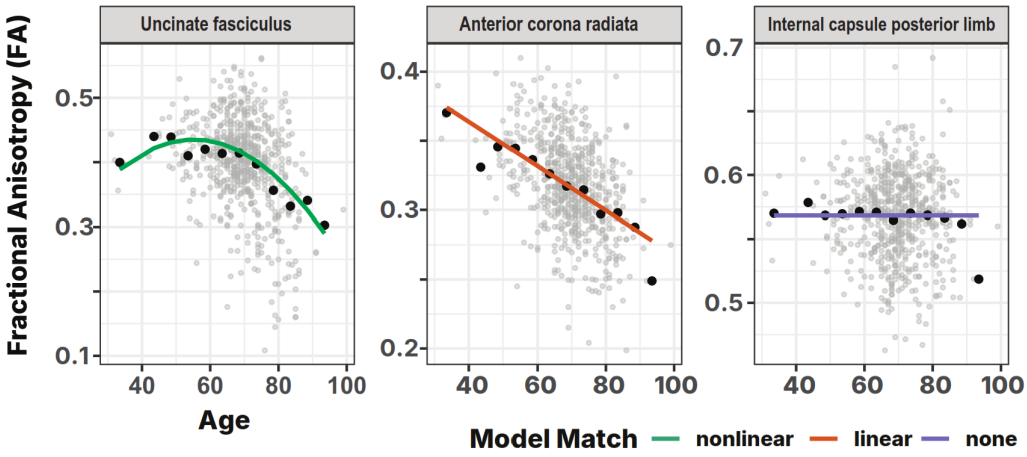
Three predictions, tested in sequence

If the DDH is correct, the human aging brain should show three specific structural signatures. The paper tests each, in order, using diffusion-weighted MRI in 638 adults aged 40–99 years from the UCSF Hillblom Aging Network.

PREDICTION 1

Heterogeneous, tract-specific decline in higher-order pathways. White matter integrity should decline unevenly with age, with accelerated loss in association tracts.

Evidence:15 of 28 tracts show non-linear decline accelerating after ≈60 years. The strongest effects are in the uncinate fasciculus, fornix, and anterior limb of the internal capsule—pathways serving memory, language, and executive function. Sensory and motor tracts are largely spared.



Tract	Model choice	N obs	P-val linear	P-val nonlinear	ΔAIC	ω nonlinear
Internal capsule anterior limb	nonlinear	638	**0.0000**	**0.0000**	**-26.88**	**1.00**
Uncinate fasciculus	nonlinear	638	**0.0000**	**0.0000**	**-26.65**	**1.00**
Splenum of corpus callosum	nonlinear	638	**0.0000**	**0.0000**	**-26.08**	**1.00**
Thalamic radiation posterior	nonlinear	638	**0.0000**	**0.0000**	**-15.93**	**1.00**
Superior fronto-occipital fasciculus	nonlinear	638	**0.0000**	**0.0001**	**-14.47**	**1.00**
Global FA	nonlinear	638	**0.0000**	**0.0001**	**-14.25**	**1.00**
Superior cerebellar peduncle	nonlinear	638	**0.0003**	**0.0020**	**-7.58**	**0.98**
Sagittal stratum	nonlinear	638	**0.0000**	**0.0034**	**-6.65**	**0.97**
Column and body of fornix	nonlinear	638	**0.0000**	**0.0050**	**-5.94**	**0.95**
Body of corpus callosum	nonlinear	638	**0.0000**	**0.0081**	**-5.07**	**0.93**
Fornix	nonlinear	638	**0.0000**	**0.0082**	**-5.04**	**0.93**
Retrolenticular part of internal capsule	nonlinear	638	**0.0300**	**0.0239**	**-3.14**	**0.83**
Inferior cerebellar peduncle	nonlinear	638	**0.0003**	**0.0279**	**-2.87**	**0.81**
Cortico-spinal tract	nonlinear	638	**0.0232**	**0.0322**	**-2.62**	**0.79**
Medial lemniscus	nonlinear	638	**0.0007**	**0.0358**	**-2.44**	**0.77**
Anterior corona radiata	linear	638	**0.0000**	0.2695	0.77	0.40
Genu of corpus callosum	linear	638	**0.0000**	0.0792	-1.10	0.63
Cingulum cingulate gyrus	linear	638	**0.0000**	0.0643	-1.45	0.67
External capsule	linear	638	**0.0000**	0.2287	0.54	0.43
Superior longitudinal fasciculus	linear	638	**0.0000**	0.0564	-1.67	0.70
Cingulum hippocampus	linear	638	**0.0001**	0.6400	1.78	0.29
Cerebral peduncle	linear	638	**0.0263**	0.3815	1.23	0.35
Middle cerebellar peduncle	linear	638	**0.0320**	0.1836	0.22	0.47
Inferior fronto-occipital fasciculus	none	638	0.8601	0.4920	1.52	0.32
MCP pontine crossing tract	none	638	0.1949	0.9068	1.99	0.27
Posterior corona radiata	none	638	0.2705	**0.044***	**-2.07***	**0.74***
Internal capsule posterior limb	none	638	0.1913	0.5658	1.67	0.30
Superior corona radiata	none	638	0.3316	0.9126	1.99	0.27

Figure 2. *Age-related FA trajectories with model selection. Green = non-linear (quadratic), orange = linear, purple = no detectable age effect. ΔAIC and Akaike weight (ω) for each tract shown in table.*

PREDICTION 2

Microstructure consistent with myelin loss, not axonal loss. NODDI parameters should show changes in the cellular environment around axons, not in the orientation of axons themselves.

Evidence:Across 34 cortical white matter cushions, age is negatively associated with intracellular volume (ficv ↓) and positively associated with isotropic free water (fiso ↑). Orientation dispersion (odi) is largely age-invariant. The fiber architecture is preserved; the supporting cellular environment—consistent with oligodendrocyte and myelin loss—degrades.

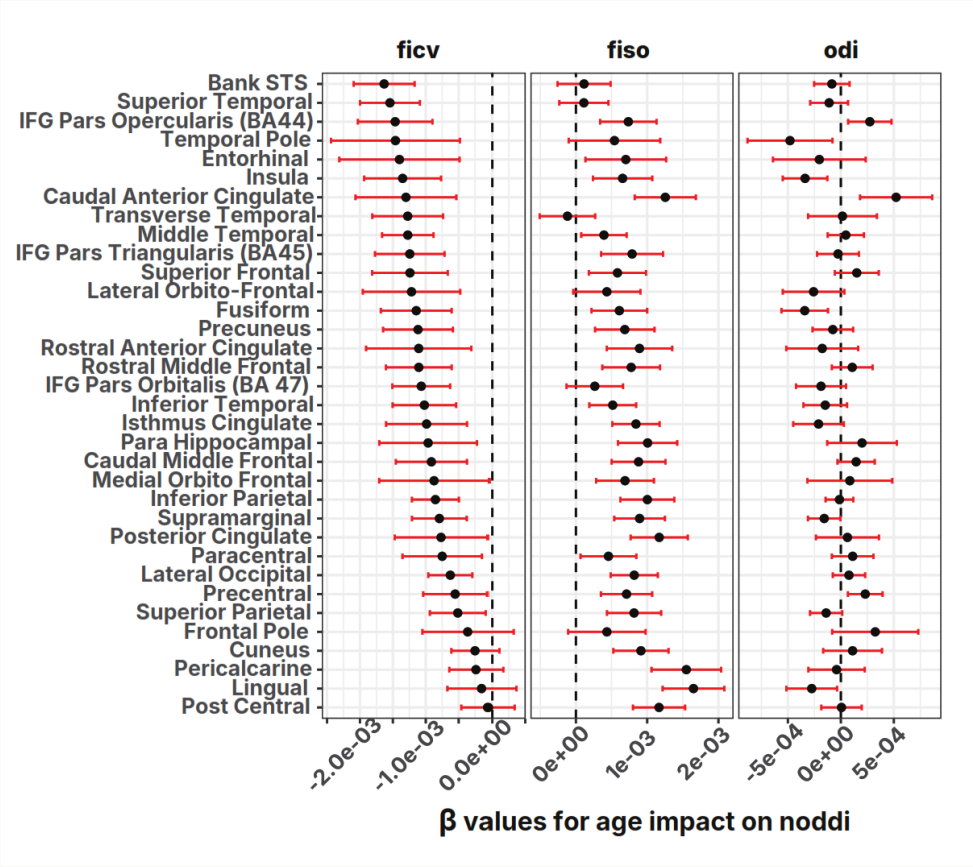


Figure 3. *Age β estimates for NODDI parameters across 34 cortical parcels. ficv (left) and fiso (middle) show robust mirror-image effects; odi (right) clusters near zero.*

PREDICTION 3

A single dominant age axis links structure to cognition. Multivariate analysis should reveal one shared dimension where microstructural damage and cognitive decline co-vary, primarily explained by age.

Evidence:Canonical Correlation Analysis between NODDI metrics (102 imaging variables) and 7 cognitive assessments yields a dominant axis with $R = 0.72$ ($p < 2.2 \times 10^{-16}$), explaining 52% of shared variance. Imaging contributors are dominated by fiso in association cortex; cognitive contributors are led by processing speed (reaction times) and executive function. Age accounts for the majority of variance in both variates.

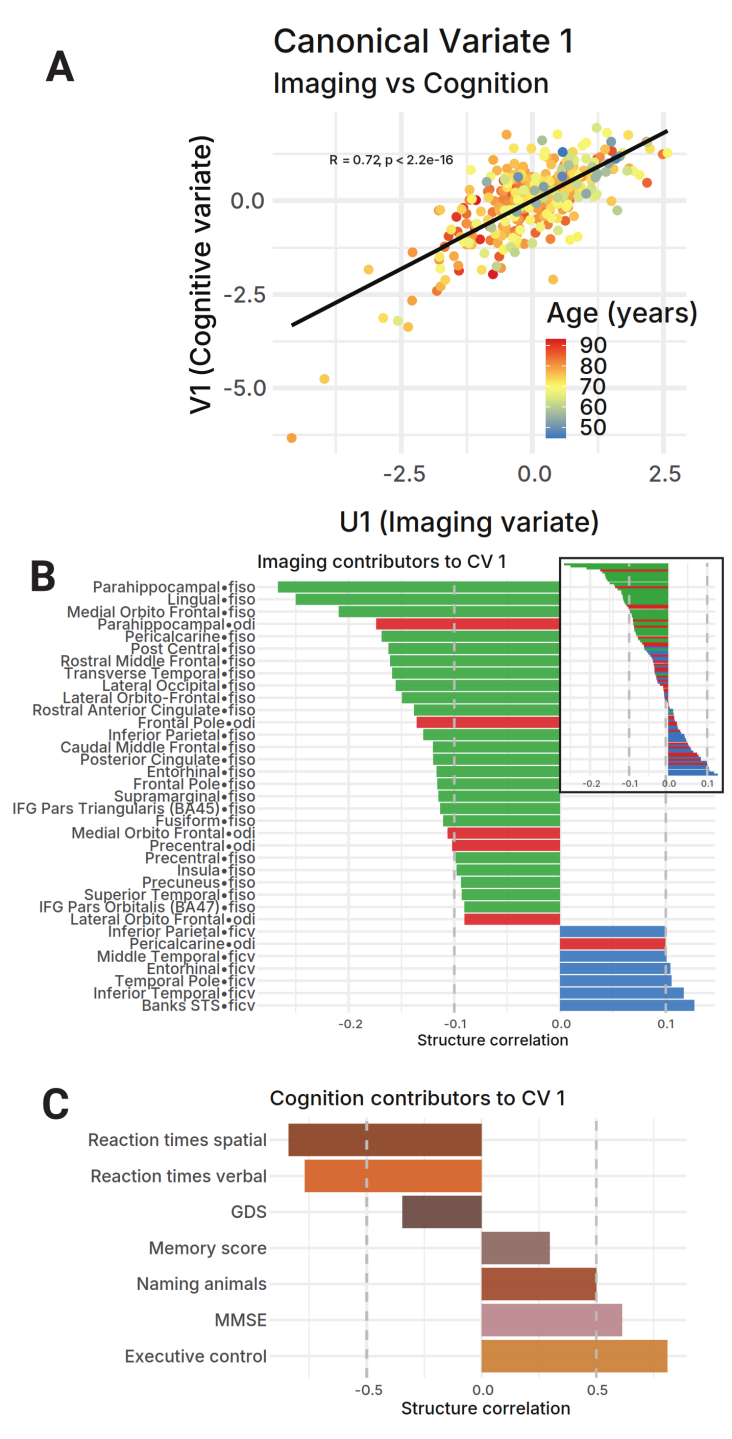


Figure 4. *CCA results. (A) CV1 scatter colored by age; (B) top imaging contributors; (C) cognitive contributors.*

WHY THIS MATTERS

A different therapeutic target

Prevailing models of cognitive aging emphasize neuronal death and synaptic degradation. The DDH proposes a different primary driver: **loss of inter-regional timing precision** caused by heterogeneous myelin degradation across white matter pathways.

This reframes the therapeutic target. Rather than trying to keep individual neurons alive, interventions can aim to preserve or restore the connective infrastructure: the myelin that synchronizes distributed brain networks.

> WHY MOST AGING BRAINS STILL WORK PRETTY WELL
>
> For most people, age-related cognitive deficits are mild despite substantial white matter changes. The likely explanation is compensation: the aging brain recruits additional functional connectivity to preserve performance. Because demyelination is heterogeneous, however, it produces asymmetric damage that can eventually outpace this compensation—which helps explain the late-life acceleration. Cognitive engagement, novel learning, exercise, and sleep all support the activity-dependent feedback loops that maintain myelin.

THERAPEUTIC AVENUES

- Promoting oligodendrocyte precursor cell (OPC) proliferation and differentiation
- Targeting the immune drivers of myelin damage: microglial activation, complement-mediated (C1q/C3) attack on damaged myelin, and chronic systemic inflammation (measurable via inflammatory aging clocks such as iAge)
- Activity-dependent interventions that drive remyelination
- Tract-specific myelin biomarkers for early detection
- Targeted pharmacological support for myelin maintenance

RELATIONSHIP TO OTHER THEORIES

Where DDH fits in the landscape

vs. Amyloid Cascade / Tau Pathology. DDH proposes a different primary driver of cognitive aging than protein-aggregation models. The two are not mutually exclusive: DDH may describe a continuous structural process operating across the entire aging population, of which advanced amyloid or tau pathology is one possible downstream complication.

And Communication Through Coherence (Fries 2005, 2015). Independent theories that converge. Pascal Fries' CTC framework arrived at the centrality of timing through electrophysiology in primate visual cortex; DDH arrived at the same conviction through cognitive aging biology and human white-matter MRI. Neither theory is derived from the other. Both treat timing as the substrate of cognition, but describe different chapters of that story — CTC at the cellular scale of cortical communication, DDH at the population scale of lifespan structural change. The convergence strengthens both without subordinating either.

CITE

Gershteyn IM, Markov NT, Kramer J, Casaletto K, Olzinski M, Ellerby LM, Furman D. Decoherence via Demyelination (DDH): A Hypothesized Mechanism of Cognitive Decline. *bioRxiv* preprint, 2026. https://ddh-theory.com

For the full preprint, interactive explanation at three levels of complexity, data figures, and a complete glossary, visit **ddh-theory.com**.