Commentary

How Three-Pathway Erosion Shapes Distinct Neurodegenerative Diseases

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Neurodegenerative diseases appear distinct, yet growing evidence indicates they arise from patterned stress within the same three biological pathways essential for brain health: mitochondrial capacity, protein and waste management, and neuroimmune regulation. What differs across conditions is not the underlying machinery but the sequence, location, and degree of pathway erosion. This paper proposes that neurodegeneration occurs across a spectrum that reflects how these pathways are taxed over time and across regions. What emerges are the characteristic profiles of Alzheimer's disease, Parkinson's disease, frontotemporal dementia, amyotrophic lateral sclerosis, and mixed dementias. When one pathway becomes seriously eroded, the other two can temporarily stabilize function — until their eventual failure shapes divergent clinical trajectories. This framework offers a unified explanation for why shared mechanisms yield such different outcomes, clarifies the biological basis of mixed dementias, and highlights why some individuals experience rapid decline while others maintain pockets of resilience for years. Viewing neurodegeneration as convergent pathway failure rather than isolated diseases may support earlier detection, more precise risk assessment, and interventions aimed at sustaining pathway resilience across the lifespan. This systems-level perspective also creates a shared conceptual space for researchers working in traditionally separate disease domains, enabling findings in one condition to inform others and helping consolidate research efforts around common mechanisms rather than diagnostic labels.

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Introduction

Neurodegenerative diseases appear diverse in their symptoms and clinical trajectories, yet there is growing evidence that they arise from stress within the same three biological pathways that sustain

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cognitive and motor function. What differs across diseases is not the architecture of vulnerability but the *pattern* of erosion: the sequence in which these pathways start to deteriorate, the brain region initially impacted, and the degree to which compensatory systems can delay collapse across all three systems. While each disease may begin with strain in a single pathway, progression emerges only when compensatory shifts draw the remaining pathways into a self-reinforcing cycle of stress that the system can no longer rebalance. This paper proposes that distinct neurodegenerative diseases emerge from these patterned variations in three-pathway stress, offering a unified explanation for why shared mechanisms yield divergent clinical outcomes. It also clarifies the presence of "mixed dementias" in brain pathology and highlights how specific pathway weaknesses shape different disease expressions.

To briefly summarize the principles set out in the author's hypothesis, "Neurodegeneration as convergent pathway failure: A three-system framework explaining late-life decline," neurodegenerative diseases arise when all three pathways essential for brain health – mitochondrial capacity, protein and waste management (proteostasis), and neuroimmune regulation – together reach the point they can no longer effectively repair erosive damage. While the collective failure of these pathways tends to emerge later in life, they are neither a natural consequence of aging nor do they produce uniform outcomes. Individual differences in genetic makeup, early health, environmental and occupational exposures, habits that impact circadian rhythms and vascular sufficiency together determine who may develop neurodegeneration and what form that may take [1].

Each neurodegenerative disease reveals how different sequences of pathway stress and regional vulnerability give rise to its characteristic patterns of onset, progression, and symptoms. The pattern starts with a single stressed pathway that leads to the other two pathways straining to compensate, until all three pathways are engaged in toxic feedback loops that make it difficult to stabilize.

How Shared Pathways Produce Distinct Symptoms & Trajectories

The two most common neurodegenerative diseases, Alzheimer's and Parkinson's disease, share similar arcs in the genesis of neurodegeneration when a single pathway has become compromised and the other two eventually fail to sufficiently compensate for the initial failure. Amyotrophic lateral sclerosis (ALS), on the other hand, shows what happens when all three pathways fail at the same time – a rare occurrence with little opportunity for recovery, since there is little opportunity for compensatory support when each pathway is already stressed.

Alzheimer's disease: The most common neurodegenerative disease emerges when protein and waste-management stress is the first pathway to fail in the hippocampus and adjacent areas medial temporal lobe regions [2] – the brain areas where cell turnover and the need for prompt clearance is particularly high. Before overt symptoms appear, mitochondrial and neuroimmune systems can compensate for accumulating protein stress, delaying collapse until cognition becomes impaired. When strained mitochondria become dysfunctional, the downstream effects are amplified [3]. This explains the classic Alzheimer's trajectory of early memory loss, gradual spread to association cortices involved in forming new memories, spatial navigation and the ability to link experiences across time [4]. Finally, Alzheimer's leads to late-stage global decline, where language, functional independence and social cognition all start to fail.

Early in this process, mitochondria strive to compensate for rising waste accumulation by increasing energy production and boosting antioxidant defenses, temporarily maintaining synaptic function. Meanwhile, neuroimmune cells intensify efforts to clear debris, prune damaged synapses, and contain inflammation, potentially holding the line for years. But by the time these compensatory systems are fully engaged, a toxic feedback loop is already in motion: impaired clearance accelerates further protein buildup, which increases oxidative stress and inflammation, which further weakens clearance capacity. This self-reinforcing cycle means that simply removing accumulated proteins typically occurs too late to reverse neuronal damage that has already been incurred. Alzheimer's thus reflects slow, regionally anchored erosion of essential protein-clearance capacity, amplified by compensatory responses that delay symptoms while deepening the underlying instability.

Parkinson's disease: In Parkinson's, mitochondrial function is the first system to falter [5], forcing neuroimmune and proteostatic pathways to carry the load. This second most common neurodegenerative disease emerges when mitochondrial stress begins in the substantia nigra, a region with exceptionally high energy demands. This small midbrain structure produces dopamine, which is essential for initiating and maintaining smooth movement. Because substantia nigra neurons carry a high load of the protein α-synuclein, early mitochondrial strain leads to its misfolding and accumulation [6] in an already vulnerable system with high energy needs and little redundancy. When the dopamine supply becomes constrained, movement slows, stiffens, or becomes shaky — and the ability to initiate an intended action may fail entirely, a phenomenon known among people with Parkinson's as "freezing." These misfolded α-synuclein aggregates form Lewy bodies — the same hallmark inclusions seen in Lewy Body Dementia — differing only in where and how early the strain concentrates.

Protein-clearance and neuroimmune systems can compensate for this energy deficit for years, maintaining motor function despite accumulating cellular stress. Protein-clearance mechanisms degrade misfolded α-synuclein and remove damaged mitochondria, helping preserve synaptic function. Meanwhile, neuroimmune cells contain inflammation, support surviving neurons, and prune dysfunctional synapses. But by the time dopamine levels fall enough to cause symptoms, the underlying mitochondrial deficit has already created a toxic feedback loop: mitochondrial stress accelerates α-synuclein misfolding, misfolded α-synuclein further impairs mitochondrial function, and both processes amplify oxidative stress. Their prolonged compensation explains Parkinson's long prodromal phase and why motor symptoms appear only after substantial neuronal loss [7].

Parkinson's thus reflects energy-system-led erosion in a highly specialized, high-demand region, where α-synuclein pathology and dopamine loss are not the root causes but the accelerants and consequences of an upstream mitochondrial collapse. This is why dopamine medication cannot resolve Parkinson's: dopamine loss is downstream of mitochondrial failure. Replacing dopamine restores the signal and improves movement, but it does not repair the energy deficit, interrupt the feedback loop, or rescue neurons already struggling to meet their metabolic demands. As the disease progresses and more substantia nigra terminals are lost, even dopamine replacement becomes less effective because fewer surviving neurons remain to convert Parkinson's medication into dopamine.

ALS: Although ALS research often describes many distinct mechanisms — including protein aggregation, impaired RNA metabolism, defective autophagy, neuroinflammation, oxidative stress, calcium dysregulation, and mitochondrial dysfunction [8] — these processes fall under three broad biological domains: mitochondrial function, protein and waste management, and neuroimmune regulation. In most cases, ALS emerges only when all three systems experience high-degree stress simultaneously. This rare convergence underscores how strong the three-pathway system usually is. Motor neurons are especially vulnerable because of their extreme metabolic demand, extraordinary axonal length, and structural fragility [9]. When each of the three protective pathways is already operating near its limit, there is little reserve to support one another when stress increases, producing the characteristic rapid and relentless progression.

This pattern produces early motor weakness and swift functional decline while cognition remains intact, except in cases where frontotemporal regions are also vulnerable, creating the ALS–FTD overlap [10][11]. In ALS, mitochondrial strain, protein and waste-managment overload, and neuroimmune activation all rise sharply together, leaving almost no opportunity for stabilization or compensatory mechanisms.

ALS illustrates the high-intensity, low-compensation end of the neurodegenerative spectrum: most diseases arise from patterned erosion; ALS arises from simultaneous overload.

Frontotemporal Dementia (FTD): Although FTD encompasses diverse genetic and pathological subtypes, early neuroimmune dysregulation is a consistent feature across variants and provides a unifying explanation for their shared regional vulnerability [12]. FTD emerges when neuroimmune dysregulation is the earliest and most dominant stressor, affecting the frontal and anterior temporal lobes — regions responsible for personality, judgment, language, and social behavior. These areas have unusually dense synaptic networks and high baseline neuroimmune activity, making them especially vulnerable when regulatory stress rises early. Because protein clearance and mitochondrial systems can partially compensate, symptoms may appear abruptly or in unusual forms, contributing to FTD's reputation as the most "mysterious" neurodegenerative disease.

This pattern produces the characteristic FTD variants — behavioral variant FTD, semantic dementia, and non-fluent aphasia. These categories appear different because the first primarily alters behavior and personality, the second erodes word meaning and conceptual knowledge, and the third disrupts fluent, grammatical speech — yet all arise from neuroimmune-led stress affecting slightly different subregions of the same frontal–temporal networks.

FTD's earlier average age of onset reflects that neuroimmune pathway vulnerability can arise long before mitochondrial or proteostatic collapse, evidence that age-related pathway erosion plays a smaller role than in Alzheimer's or Parkinson's disease. This early vulnerability can often be traced to genetic variants — including progranulin, C9orf72, or MAPT — which tilt microglial and synaptic immune signaling starting at a young age [12].

The early loss of insight — a hallmark of FTD — reflects the fact that insight depends on a distributed network linking the anterior cingulate, anterior insula, and orbitofrontal cortex. All three regions must function together for self-monitoring, error detection, and social meaning. Because each of these hubs has high baseline neuroimmune activity and low redundancy, even partial erosion in one node destabilizes the entire network, making insight the first ability to fail [12].

When neuroimmune-led erosion extends into motor regions, the ALS–FTD continuum emerges. Across these presentations, early neuroimmune dysregulation disrupts circuits governing insight, inhibition, emotional regulation, and language long before memory is affected. Unlike Alzheimer's or Parkinson's disease, where long prodromal phases allow years of systemic compensation, FTD offers little

opportunity for modification once neuroimmune dysregulation destabilizes these high-connectivity regions.

Mixed Dementias: Although Alzheimer's is the most common diagnosed neurodegenerative disease, autopsy studies show that mixed pathology is the most common biological finding in late-life dementia, typically combining Alzheimer's, vascular, Lewy body, or frontotemporal features. When vascular systems begin to erode, they amplify stress across all three pathways — impairing mitochondria through reduced perfusion, heightening neuroimmune activation, and increasing protein-clearance burden. These emerge when more than one pathway experiences moderate-to-high stress in different regions at the same time. Instead of a single dominant driver — as in Alzheimer's (protein-clearance), Parkinson's (mitochondrial), or FTD (neuroimmune-led) — mixed dementias reflect converging stresses that exceed compensatory capacity [13] when two or all three pathways experience overlapping erosion of varying degrees.

This pattern produces clinical pictures that blend features of Alzheimer's, vascular issues, Lewy body disease, or frontotemporal involvement. Memory loss may coexist with slower movement, fluctuations in attention, or early behavioral changes, depending on which pathways and regions are stressed first. Because the brain is compensating on several fronts at once, symptoms often appear more variable, more rapidly shifting, or less neatly classifiable than in single-pathway diseases [14].

Mixed dementias are the archetype of convergent pathway erosion. They illustrate how late-life decline often reflects overlapping stressors rather than a single disease process. When protein-clearance, mitochondrial, and neuroimmune systems are all strained — even if none are failing outright — the combined load can exceed the brain's ability to stabilize function, producing blended or rapidly evolving symptoms.

Other Neurodegenerative Diseases

A number of less common neurodegenerative diseases further illustrate how region-specific vulnerability shapes distinct expressions of the same three-pathway architecture. Each reflects early pathway stress in regions with unusual structural demands or limited compensatory capacity. For instance, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) arise when protein-clearance and immune-pathway stress converge in midbrain and frontoparietal circuits that govern balance, gaze control, and executive function [15][16]. In contrast, MSA reflects early, region-concentrated α-synuclein

pathology that burdens protein- and waste-management systems and disrupts energetics in brainstem/cerebellar networks, leading to rapid motor and autonomic decline [17]. Although these diseases appear disparate, each represents a distinct variation on the three themes of pathway stress, regional vulnerability, and compensatory limits. Their existence reinforces the central claim of this model: neurodegenerative diseases are patterned expressions of the same three-pathway architecture, differing not in mechanism but in sequence, location, and degree of erosion.

Discussion

Neurodegenerative diseases have long been treated as distinct entities, each with its own mechanisms, biomarkers, and clinical expectations. Yet the evidence increasingly suggests that these conditions arise from stress within the same three biological pathways that sustain

brain function: mitochondrial capacity, protein and waste management, and neuroimmune regulation. What differs across diseases is not the underlying machinery but the *pattern* of erosion — which pathway is stressed first, which region is most vulnerable, and how effectively the remaining systems can compensate.

This framework helps explain why neurodegenerative diseases can look so different despite sharing core mechanisms. Alzheimer's reflects early protein-clearance stress in the medial temporal lobe. Parkinson's emerges when mitochondrial strain begins in the substantia nigra. FTD arises when neuroimmune-pathway stress targets the frontal and anterior temporal lobes. ALS appears only when all three pathways experience high-degree stress simultaneously — a rare convergence that underscores how robust the system usually is. Mixed dementias, the most common late-life presentation, reflect overlapping stresses that exceed compensatory capacity across two or three pathways at once.

This helps explain why FTD and Alzheimer's present with opposite cognitive signatures. In FTD, early neuroimmune-pathway stress disrupts frontal and anterior temporal circuits responsible for insight, inhibition, and social meaning, while memory systems remain largely intact. Alzheimer's, however, begins with protein-clearance stress in the medial temporal lobe, producing early memory loss even as insight and personality remain preserved for years. These divergent patterns reflect not different mechanisms, but different sequences and locations of pathway erosion.

A look at well-known individuals with a history of neurodegenerative disease offers additional clarity on differences in longevity and progression. A small percentage of people with ALS survive far longer than

expected, and their stories illuminate the variability within even the most severe pathway-collapse pattern. Stephen Hawking is the most widely recognized example: his extraordinary longevity likely reflected a combination of atypical disease biology and exceptionally stable external support that reduced ongoing pathway stress. Highly structured routines, consistent caregiving, circadian regularity, and optimized nutrition may have reduced ongoing pathway load enough for pockets of resilience to persist for years or even decades. In contrast, baseball legend Lou Gehrig — despite exceptional physical health — followed a more typical ALS trajectory, his rapid decline underscoring how unforgiving the disease can be when all three pathways fail early and simultaneously. Together, these cases illustrate the full spectrum of ALS expression — from rapid collapse to rare, prolonged stability — shaped by the degree of pathway damage at onset and the ability to reduce further stress.

Famous cases also illustrate the patterned nature of pathway erosion in other diseases. Ronald Reagan followed the classic Alzheimer's trajectory of early protein-clearance stress in the medial temporal lobe, with years of compensation masking early decline. Muhammad Ali and Pope John Paul II exemplify the slow, energy-system-led erosion of Parkinson's disease, where mitochondrial strain in the substantia nigra produces tremor, rigidity, and slowed movement long before cognition is affected. These public trajectories, like the contrasting courses of Hawking and Gehrig in ALS, highlight how the same three pathways can fail in different sequences and regions, producing distinct but mechanistically related diseases.

A key takeaway is that the three-pathway system is extraordinarily resilient. Most people never develop neurodegeneration, and even among people in their 80s, most do not have Alzheimer's disease. Parkinson's is less common still, and ALS and FTD remain rare. This resilience reflects the system's ability to compensate: when one pathway begins to falter, the remaining two can often sustain function for years or decades. The rarity of ALS is proof of this resilience: only when all three pathways are stressed at once does rapid collapse occur. Even then, a small percentage of individuals defy the typical trajectory, and their extended survival suggests that residual pathway strength may help forestall decline. These cases highlight that even in extreme conditions, the system retains the capacity to respond with resilience.

While clinicians diagnose dementia within established categories, the underlying biology is far more variable: most late-life dementias reveal mixed pathology because the patterns of pathway erosion rarely fall into a single, isolated form.

This framework also clarifies why symptoms often appear to be nonlinear or inconsistent.

High-connectivity regions such as the frontal and temporal lobes do not fail in a stepwise fashion; because they support integrative functions, they unravel in complex ways when immune-pathway stress rises early. Similarly, the long prodromal phases of Alzheimer's and Parkinson's reflect years of compensation by the two intact pathways. Mixed dementias, which blend features of multiple diseases, arise naturally when different pathways or regions experience overlapping stress.

Importantly, this model does not claim to replace diagnostic categories or clinical tools. Rather, it offers a unifying systems-level explanation for why neurodegenerative diseases emerge, why they differ, and why they often overlap. It suggests that future research may benefit from focusing less on disease labels and more on mapping patterns of pathway stress across individuals — a shift that could clarify risk, refine early detection, and guide interventions aimed at supporting pathway resilience whenever possible.

Testable Predictions

Although this paper offers a conceptual framework rather than a mechanistic proof, the model generates several empirically testable predictions that can be evaluated using existing biomarkers, imaging tools, and longitudinal cohorts.

- *Alzheimer's disease — clearance-first temporal ordering*

  If Alzheimer's disease begins with impaired protein and waste clearance, then clearance-related biomarkers — including abnormal Aβ and tau dynamics, glymphatic dysfunction markers, and lysosomal/autophagy indicators — should diverge from baseline before mitochondrial-collapse markers such as mtDNA damage, respiratory chain deficits and ATP decline. Longitudinal cerebrospinal fluid biomarker studies already show early clearance-related abnormalities, but no study has directly compared clearance and mitochondrial markers within the same cohort with explicit temporal ordering. Such designs would allow a clear test of which processes diverge from baseline first.

- *Parkinson's disease — mitochondria-first signatures in substantia nigra circuits*

  If Parkinson's disease is initiated by mitochondrial dysfunction, then mitochondrial biomarkers – such as early changes in energy production, mitochondrial quality-control signals, and oxidative-stress indicators – should diverge from baseline before widespread proteostatic-stress markers (including α-synuclein accumulation and other clearance-stress signals), with the strongest early changes appearing in substantia nigra circuits. Mechanistic work already supports a

mitochondria-first framing, but no longitudinal human study has directly compared mitochondrial and proteostatic biomarkers within the same prodromal cohort. Such studies would provide a decisive empirical test of the primary driver of Parkinson's.

- *Frontotemporal dementia — early neuroimmune activation in high-connectivity hubs*

  If FTD is driven by early neuroimmune dysregulation, then neuroimmune-sensitive imaging -- such as PET scans that detect microglial activation — should show early, focal immune activation in anterior cingulate, anterior insula, or orbitofrontal cortex before major protein-aggregation burden or regional atrophy. This immune-first signature should predict early loss of insight and help distinguish FTD variants based on which subregion shows the earliest immune divergence.

- *Amyotrophic lateral sclerosis — simultaneous multi-pathway stress near symptom onset*

  If ALS reflects high-degree, simultaneous stress across all three pathways, then individuals near symptom onset should show concurrent abnormalities in mitochondrial injury markers, proteostatic breakdown markers, and neuroimmune activation markers. Baseline pathway reserve – the degree to which each pathway is already damaged at symptom onset -- should stratify survival, with individuals showing less severe impairment in any pathway declining more slowly than those with high-degree stress across all three.

- *Mixed dementias — early multi-domain abnormalities* If mixed dementias arise from overlapping pathway stress, then individuals within this catch-all category should exhibit early, moderate abnormalities in two or more pathways across different regions, rather than a single dominant pathway signal. At baseline, this would appear as combined clearance, mitochondrial, and/or immune abnormalities on biomarker panels and imaging, together with multi-domain clinical changes — for example, concurrent memory, gait, and behavioral shifts.

Conclusion

Neurodegeneration is not a collection of unrelated diseases but a set of patterned outcomes arising from stress within three distinct biological pathways. The sequence, location, and extent of this stress determine whether a person develops Alzheimer's, Parkinson's, FTD, ALS, a mixed dementia, or no neurodegenerative disease at all. This framework explains both the diversity of clinical presentations and the deep commonalities observed across pathology, genetics, and aging research. When there is the rare reversal or pause in progression, this is not a miracle but the natural consequence of a system built with redundancy, compensation and repair.

By viewing neurodegeneration as convergent pathway failure rather than isolated disease processes, we gain a clearer understanding of why symptoms emerge where they do, why progression varies, and how compensatory systems can delay collapse for years. This perspective also highlights the remarkable resilience of the three-pathway system — a resilience that can be supported through environments and habits that reduce ongoing pathway stress. Ultimately, this model invites a shift from disease-specific thinking toward a systems-level view of late-life brain health. Such a shift may open new avenues for prevention, early detection, and intervention by focusing on the pathways that sustain cognitive and motor function across the lifespan.

About the Author

Caroline C. Rodgers is an independent science theorist whose peer-reviewed work spans autism, neurodegeneration, and maternal and neonatal health. She explores the potential biological roots of public health issues that are incompletely explained by prevailing theories.

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