Review Article

Neurodegeneration as Convergent Pathway Failure: A Three-System Framework Explaining Late-Life Decline

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Neurodegenerative diseases are not a natural consequence of aging, and understanding their etiology is essential for effective treatment or prevention. This manuscript proposes that neurodegeneration arises from a convergence of stress across three systems that work together to maintain brain health: mitochondrial function, protein and waste management, and neuroimmune regulation. While several environmental and systemic stressors — such as pesticides, sleep disruption, and vascular insufficiency — have been identified as contributing to neurodegeneration, this article examines whether frequent head exposure to low-dose diagnostic radiation may incrementally tax these critical pathways over the years. Medical and dental exposure to ionizing radiation is presented as an illustration of how modern practices may contribute to cognitive decline. This systems-view reframes neurodegenerative risk as measurable beyond genetic contributions and potentially modifiable, opening the door to individualized assessment and targeted mitigation.

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Introduction

Neurodegenerative diseases are not a natural consequence of aging, and understanding their etiology is essential for effective prevention or treatment. Neurodegeneration appears to arise from a convergence of stress across three systems that maintain brain health: mitochondrial function, proteostatic capacity, and neuroimmune regulation. These systems can absorb isolated stressors, but repeated exposures gradually erode repair capacity. As this erosion accumulates, the three pathways become increasingly vulnerable to failing together [1][2] -- a convergence that helps explain why neuropathology can be present without

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significant cognitive impairment, why individuals with similar exposures may have different outcomes, and why no single insult or intervention reliably predicts, prevents, or reverses disease.

The rising global prevalence of neurodegenerative diseases among the elderly – and the concerning trend of early-onset cases – suggest that systems-level stressors associated with modern exposures and habits may be contributing factors [3]. These range from known influences such as disrupted sleep and immune strain to emerging concerns such as diagnostic radiation, a potential contributor that warrants closer scrutiny. Addressing even one of these stressors could enable preventive strategies that reach beyond general lifestyle recommendations, which have failed to ward off cognitive decline in many older adults.

Differences in pathway load and resilience are also evident in populations at the extremes of lifelong protection and risk. Members of the School Sisters of Notre Dame show unusually low rates of cognitive decline despite Alzheimer's-type neuropathology [4], reflecting a lifetime of stable routines and the absence of behaviors or exposures that would undermine these critical pathways. In contrast, individuals with Down syndrome experience early and accelerated vulnerability due to trisomy 21, which increases APP expression, metabolic strain, and chronic immune dysregulation -- stressing all three pathways and producing Alzheimer's neuropathology years earlier than in the general population [5]. These two groups demonstrate how lifelong variation in pathway load shapes late-life outcomes.

While multiple environmental and physiological stressors contribute towards compromised brain function, this paper explores one that has received comparatively little attention: lifelong head exposure to low-dose ionizing radiation [6][7]. As an illustrative example, escalating exposures from dental X-ray technology, chiropractic imaging, and head computed tomography (CT) scans are considered here, each of which may disproportionately affect older adults.

Three core systems critical to brain health

On a systems level, the major pathways to healthy neurological function are:

1. **Mitochondrial capacity:** Synaptic signaling is energy intensive, which is why it is commonly understood that the brain, while representing roughly two percent of body weight, consumes 20 percent of the body's energy. When the energy supply is chronically constrained, neuronal resilience declines, increasing vulnerability to downstream dysfunction when additional stressors are present. Mitochondrial impairment is a consistent feature across virtually all neurodegenerative diseases [8].

2. **Proteostasis:** This is the cell's system for maintaining healthy proteins and clearing damaged or misfolded ones. When these maintenance and clearance pathways are overwhelmed, abnormal proteins accumulate, contributing to neurodegenerative processes such as those seen in Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia, among others [9].
3. **Neuroimmune regulation:** The brain's support cells — particularly microglia and astrocytes — coordinate immune surveillance and tissue repair. When chronically overtaxed, they can shift into a pro-inflammatory state, leading to immune dysregulation and disruption of the blood–brain barrier. Similar patterns are implicated in conditions such as multiple sclerosis and vascular dementia [10].

Neurodegeneration arises when these three core systems experience sustained stress. The outcomes depend not on any single insult, but on the brain's repair and adaptive capacity over time.

Why convergence – not isolated injury – matters

The failure to find a single cause for a neurodegenerative disease – with the exception of diseases that can be traced to a single gene mutation such as Huntington's – is not due to a lack of investment or effort. Many promising leads have been pursued and translated into therapeutic trials, only to deliver limited or no clinical benefit. When a potential cause has been identified, researchers are further baffled when not everyone equally exposed develops a neurodegenerative disease. Even more confounding is the fact that not everyone with brain pathology associated with a neurodegenerative disease -- such as individuals with pronounced amyloid brain plaque accumulation -- demonstrate corresponding cognitive impairment. These apparently conflicting observations can be reconciled by a model of neurodegeneration that depends on the convergence of multiple compromised pathways rather than a single insult.

With this model in mind, variations in outcomes may depend upon individual biological makeup, genetic influences, environmental conditions and health history, each of which shape baseline capacity to buffer stressors as they add up over the years.

Genetics do not equal destiny

Most neurodegenerative diseases are not inherited. Only a small percentage — generally estimated at 5 to 10 percent — can be traced to specific gene mutations. Even then, however, the genes involved do not

introduce new disease mechanisms. Instead, they weaken one or more of the same biological systems that are critical for maintaining brain health. Some of the most commonly known genetic variants reveal the mechanisms at work [11]:

- **Alzheimer's disease**: The best-known genetic risk factor, the *APOE-ε4* variant, influences how the brain manages fats, clears waste proteins such as amyloid, and regulates inflammation, thus impacting two core pathways [11].
- **Parkinson's disease**: Genetic changes in genes such as *LRRK2* and the *PARK* genes are linked to mitochondrial dysfunction and impaired cellular stress responses – also disrupting two pathways [12].
- **ALS:** Mutations involving *SOD1* interfere with the brain's ability to manage oxidative damage. In each case, the gene does not act alone; it erodes systems that normally protect neurons over time, a reminder that some genetic changes can trigger downstream cascades that increasingly erodes compensatory capacity [13].

Seen this way, genetics helps explain why people respond differently to similar exposures or age-related changes. Some individuals begin life with less resilient protective systems, leaving them more vulnerable as stressors add up across decades. Genetic risk, then, does not contradict a convergence model of neurodegeneration — rather it reinforces it, showing how pathways that are weakened to begin with can push the brain past a threshold from compensation to progressive disease.

Environmental exposures associated with neurodegenerative risk

Humans have evolved a number of repair mechanisms that can address mitochondrial injury, protein dysregulation, or immune responses that threaten brain health. However, these defenses developed to address intermittent, naturally occurring stressors and may be less effective when challenged by chronic or novel exposures. Several such exposures have been linked to neurodegeneration, including:

- **Pesticides and herbicides**, such as organophosphates, paraquat, and rotenone, have been linked to higher Parkinson's disease incidence in agricultural workers and in individuals living near golf courses or farmland, where runoff chemicals can enter the water supply. Their effects are understood not as the result of a single exposure, but as chronic, low-level neurotoxic stressors.
- **Heavy metals**, including lead, mercury, manganese, and arsenic, can cause non-acute, cumulative damage to mitochondrial function, promote oxidative stress, and disrupt protein handling and immune regulation – a triple hit.

- **Air pollution:** There is increasing evidence in dementia and Parkinson's research that chronic exposure to pollutants such as fine particulate matter can induce oxidative stress, systemic inflammation, and compromise the blood–brain barrier [2].
- **Age-related iron accumulation:** Often treated as an intrinsic feature of aging, cumulative iron loading is shaped by modern nutritional environments, including widespread iron fortification and supplement use, which have increased lifetime exposure compared with earlier generations. Over decades, excess iron amplifies oxidative strain on mitochondria, promotes protein misfolding and aggregation, and primes microglia toward a pro-inflammatory state [14].

Two other types of exposures that are not unique to modern life also deserve mention, as they are still external stressors that place long-term pressure on the brain's repair systems:

- **Traumatic brain injury (TBI):** Both repetitive TBIs and, in some cases, a single mild injury have been associated with delayed neurodegenerative effects that may emerge years after the initial event.
- **Chronic infections:** Long-lasting infections such as herpesviruses or periodontal disease can act as environmental stressors. They keep the immune system in a low-grade activated state, increasing oxidative load and placing ongoing pressure on all three pathways, gradually eroding the repair capacities that keep these pathways stable [15].

Frequent, life-long head exposure to low-dose ionizing radiation

While the above factors have been the subject of extensive study, one chronic exposure experienced by a majority of people has received comparatively little attention: head exposure to low-dose ionizing radiation accumulated over a lifetime of dental imaging, which may be compounded by other exposures such as chiropractic radiography or head CTs. Within a convergence framework, the significance of low-dose radiation lies not in its immediate effects but in its cumulative demand on systems already taxed by aging.

Low-dose ionizing radiation differs from many established neurotoxic exposures in an important way: it is not typically lethal to cells and rarely produces immediate or observable neurological injury. This has led to the assumption that its long-term effects are negligible, yet the absence of acute harm does not guarantee biological neutrality. At low doses, ionizing radiation acts primarily as a recurrent cellular stressor, repeatedly activating repair, antioxidant, and immune-related processes over time. Because these exposures begin early and recur throughout life — often in clustered sets such as full-mouth series,

panoramic plus bitewings, or multi-stage cone beam computed tomography (CBCT) scans, which produce 3D images — they place cumulative demands on the mechanisms that maintain stability. Here is how each system is affected:

- **Mitochondrial stress:** Although routine dental imaging delivers very low doses, ionizing radiation is known to generate reactive oxygen species (ROS) and transient oxidative stress in directly irradiated cells. Experimental studies using low-dose or low-dose-rate irradiation show mitochondrial changes — including altered membrane potential, disrupted mitophagy, and increased ROS — even when DNA damage is minimal [16]. Repeated exposures over many years may incrementally tax mitochondrial quality-control processes rather than causing acute injury. Over time, even small, recurrent demands on repair and antioxidant systems could narrow the energetic margin available to aging neurons.
- **Proteostasis:** As repair systems become strained, even modest increases in oxidative stress can further burden the machinery responsible for protein repair, refolding, and clearance [9]. When these systems are repeatedly engaged without full recovery, their efficiency may decline, allowing damaged or misfolded proteins to evade clearance. This feedback loop is consistent with the slow accumulation of abnormal proteins observed long before clinical symptoms appear in many neurodegenerative diseases.

- **Neuroimmune activation:** Even in the absence of tissue injury, low-dose radiation can activate immune signaling pathways. Repeated activation may shift neuroimmune cells toward a chronically primed state, increasing baseline inflammation and diverting immune capacity away from neural maintenance and repair [10]. Over time, this may weaken blood–brain barrier integrity and amplify inflammatory signaling in response to otherwise minor insults, creating conditions that favor progressive neurological damage. Recent studies show that older adults who receive recommended vaccines — including influenza, pneumococcus, diphtheria, tetanus, herpes zoster and pertussis (Tdap) — have a significantly lower risk of developing dementia, likely due to reduced infection-related immune activation [15].

What distinguishes low-dose ionizing radiation incurred from routine dental radiation from many other neurotoxic exposures is not the severity of damage caused at any one time, but the frequency with which repair systems must be mobilized. Antioxidant defenses, mitochondrial quality control processes, neuroimmune responses and low-level DNA repair signaling are repeatedly engaged, often without sufficient recovery time. These systems evolved to handle occasional injury, not persistent, sub-threshold

stress sustained across decades. As repair efficiency gradually declines, damage that was once fully reversible may become only partially resolved. This creates a cumulative burden that affects multiple systems simultaneously, increasing the likelihood that compensatory capacity will eventually be exceeded.

Individual differences in repair efficiency — shaped by genetics, early-life health, and cumulative history related to occupations, environments or stress — help explain why similar radiation exposures may result in widely different neurological outcomes. Further, changes in dental technology and practices – especially the widespread adoption of CBCT and in increased use of head CTs -- place senior populations at higher risk because they are more likely to undergo these procedures.

Changes in dental and medical imaging: implications for older adults

Over the past several decades, patterns of head exposure to ionizing radiation have changed in ways that may be particularly relevant to shifting neurodegenerative risk. In dentistry, the transition from film to digital radiography substantially reduced exposure, but the subsequent proliferation of CBCT delivers higher doses than typical intraoral imaging – although actual dose varies across devices, operators and protocols [7]. Since the Food and Drug Administration (FDA) approved CBCT in 2004, its use has expanded from specialist settings into general dental practice. Although CBCT delivers lower radiation doses than conventional medical CT scans, it typically exposes a larger volume of cranial tissue than traditional two-dimensional radiography. Its use in orthodontics, diagnostic evaluations, complex restorative procedures, and implant installation may involve multiple scans -- planning, implementation and follow-up – within a single treatment plan.

In addition to dose considerations, volumetric exposure itself may be biologically relevant. Irradiating a larger region of the head engages immune and glial support cells across a broader territory, increasing the cumulative burden on neuroimmune regulation. Rather than responding to a localized insult, repair and immune systems may be required to address diffuse, low-level stress across multiple regions simultaneously — a demand that may be difficult to meet in aging neural tissue. This may be especially relevant to today's senior population, many of whom were also exposed to higher dental radiation prior to the development of digital X-rays.

Although the American Dental Association (ADA) has long recommended that imaging be ordered only after a clinical evaluation, the expanded availability of CBCT has led to its increasing use for routine screening and treatment planning. The 2026 ADA guidance reiterates that CBCT should be used only when clinically necessary [17], reflecting concern that current practice patterns may not align with long-standing principles of radiation minimization.

Chiropractic care also contributes to cumulative exposure, as many treatment plans include imaging of the skull and cervical spine [18]. Older adults represent a substantial proportion of patients undergoing chiropractic care due to chronic neck and back pain, arthritis, and mobility limitations [19].

Advances in medical imaging since the introduction of head CTs in the 1970s likewise have led to their more frequent use. Older adults are disproportionately affected by conditions that prompt such imaging due to falls, head trauma, stroke evaluation, and altered mental status. As a result, cumulative head exposure to ionizing radiation tends to increase with age, often at a time when mitochondrial efficiency, immune regulation, and repair capacity are already declining.

Within a systems-level framework, these converging trends suggest that imaging-related radiation exposures that are well tolerated earlier in life may place a greater burden on aging neural systems with reduced reserve, potentially accelerating the transition from subclinical dysfunction to overt neurodegenerative disease.

Discussion

This manuscript reframes neurodegeneration as the cumulative failure of three maintenance systems and situates lifelong low-dose radiation as one under-recognized contributor within this broader convergence framework. It also demonstrates that, while neurodegeneration is not a natural consequence of aging, lifetime habits, combined with a declining repair capacity, may progressively weaken these pathways. Within this framework, a wide range of environmental, behavioral, and physiological stressors can be understood as modifiers of pathway load, influencing how quickly or slowly these systems erode over the lifespan.

Known stressors include metabolic strain, immune dysregulation, sleep and circadian disruption, vascular insufficiency, chronic inflammation, traumatic brain injury, environmental exposures and diagnostic radiation – each of which can be intensified by compounding factors. For instance, sleep disruption becomes far more metabolically costly when it occurs against a backdrop of circadian

misalignment — such as irregular bedtimes, late meals, or inconsistent daylight exposure — because the brain must work harder to maintain basic function while its time-sensitive repair programs are weakened. Aging amplifies the impact of all these stressors by narrowing the brain's remaining compensatory capacity.

One reason low-dose diagnostic radiation has received limited attention as a potential contributor to neurodegenerative vulnerability is that its biological impact is often simplified to total dose alone. Comparisons such as "a chest X-ray equals a day in the sun" capture only the amount of exposure but overlook two additional factors that may influence biological response: the rate at which the dose is delivered and the anatomical region exposed. A dose delivered almost instantaneously may induce stress responses that differ markedly from the same dose accumulated over hours or days, and radiation absorbed by head tissues may have different implications than radiation absorbed elsewhere [20]. These distinctions help explain why low-dose diagnostic imaging has long been assumed to have negligible effects and rarely been part of discussions regarding long-term neurological health.

A closer look at the decades-long nun study offers a compelling illustration of how strong compensatory systems can protect cognitive function even in the presence of substantial neuropathology. This study examined early-life autobiographical essays, detailed health records, cognitive assessments, and postmortem brain analyses. Many participants who remained cognitively healthy into advanced age showed extensive amyloid plaques and neurofibrillary tangles at autopsy — levels that, in the general population, are often associated with dementia. Their resilience has been attributed to lifelong habits such as sustained cognitive engagement, stable metabolic patterns, and low levels of chronic inflammation [4]. What is often overlooked is how such well-regulated lives also lacked many of the known stressors. This stability – characteristic of the nuns' metabolic, immune, and behavioral patterns -- preserved the three pathways that sustain brain health. In this light, the fact that neuropathology alone does not determine cognitive outcomes is not confounding, but rather predictable, and demonstrates that lifestyle patterns that maintain metabolic stability, waste clearance, and immune balance can play a decisive role.

In contrast, Down syndrome illustrates how lifelong simultaneous stress across multiple protective systems can accelerate neurodegenerative vulnerability. Triplication of chromosome 21 introduces a third copy of the gene that produces amyloid precursor protein, placing a constant burden on protein management and waste-clearance pathways. Overexpression of genes involved in oxidative stress contributes to chronic mitochondrial strain and reduced energetic resilience. Neuroimmune regulation is

also altered, with heightened immune activity evident from early life. Each of these alterations alone might be manageable, but together they impose continuous strain across all three pathways, leading to the near-universal early-onset development of Alzheimer-type pathology. Clinical symptoms typically appear years earlier than the age at which Alzheimer's is most commonly diagnosed in aging populations [5]. Down syndrome thus reinforces the central premise of this hypothesis: neurodegeneration emerges not from a single cause, but from the convergence of three impaired pathways.

Between these two extremes lies the general population, where individuals differ widely in their baseline resilience and in the cumulative stress experienced over a lifetime. Early-life health, metabolic status, sleep quality, environmental exposures, infections, and lifestyle patterns — many of which have been introduced or become common only in recent decades — all influence the compensatory capacity a person begins with and how quickly it erodes. Although neurodegeneration is not a natural consequence of aging, advancing age increases the likelihood that all three protective pathways will be under strain at the same time. When these systems and their repair mechanisms are compromised together, age emerges as a risk factor not because it causes neurodegeneration directly, but because it marks the point at which compensatory capacity becomes harder to maintain.

Genetic variation also contributes to baseline pathway load by shaping mitochondrial efficiency, proteostatic capacity, and neuroimmune responsiveness from early life. Some individuals inherit variants that confer above-average resilience — such as more efficient mitochondrial function or stronger antioxidant defenses — while others begin life with slightly reduced reserve in one or more pathways. These inherited differences do not determine neurodegenerative outcomes, but they influence how much compensatory capacity a person starts with and how quickly it may erode under cumulative stress. In this framework, genetics functions as part of the initial conditions that interact with lifelong habits, exposures, and repair capacity.

Although longitudinal measures of cumulative pathway load and pathway-specific biomarkers remain limited, this framework provides a coherent structure for interpreting existing findings and identifying priorities for future research.

Taken together, this framework suggests that everyday clinical decisions may influence neurodegenerative vulnerability by altering the cumulative load on these pathways. For example, routine annual checkups in older adults could include brief questions about sleep quality, regularity, and duration, with sleep studies pursued when indicated to identify and treat conditions such as sleep apnea

that can impair nightly waste-clearance. Similarly, ensuring that older adults remain up to date on recommended vaccinations may help reduce their immunological burden by preventing infections that keep neuroimmune pathways activated. And when selecting dental restorations, particularly in seniors, clinicians and patients might weigh not only appearance and durability but also the cumulative radiation burden of imaging modalities such as CBCT, potentially favoring options that minimize repeated cranial exposure.

Conclusion

This framework proposes that neurodegenerative diseases arise when core systems that sustain brain health can no longer compensate for cumulative stress. It raises the possibility that neurodegenerative risk could one day be estimated — and mitigated — by assessing the status of these pathways on an individual basis and developing targeted interventions that restore resilience wherever possible. As tools for measuring mitochondrial efficiency, proteostatic capacity, and neuroimmune regulation continue to advance, a systems-level approach may help identify individuals at heightened risk long before symptoms appear and guide preventive strategies tailored to their specific patterns of vulnerability across these three pathways.

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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