

Peer Review

Review of: "Neurodegeneration: A Convergence Hypothesis Linking Chronic Low-Dose Diagnostic Radiation to Accelerated Decline"

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This preprint proposes a convergence framework for neurodegeneration centered on three maintenance domains—mitochondrial capacity, proteostasis (protein and waste management), and neuroimmune regulation—and hypothesizes that repeated, low-dose diagnostic radiation to the head/neck could represent an under-examined, incremental stressor that may accelerate decline over decades. The systems framing is coherent and hypothesis-generating, but the manuscript requires clearer operationalization and stronger epidemiologic framing to be testable.

1. Define exposure in measurable terms. Please specify what “chronic low-dose diagnostic radiation” means for empirical work: anatomy scope (cranial/cervical vs non-cranial), exposure unit(s) (counts, time-windowed cumulative indices), and an operational definition of “rapid succession” exposures.
2. Align language with evidence level. The argument is largely based on biological plausibility; statements implying a “significant contributor” should be softened (e.g., “plausible, under-examined contributor”) unless supported by quantitative data.
3. Higher cranial imaging often reflects greater healthcare use and underlying risks, raising confounding and reverse-causation concerns. Please add a limitations paragraph and propose lagging exposures, adjusting for healthcare use, propensity methods, and non-cranial negative controls.
4. Provide falsifiable predictions. Add 3–5 testable predictions (e.g., stronger association for cranial vs non-cranial imaging; age interaction; attenuation with pre-diagnosis lag exclusions; correlation with intermediate markers aligned to the three domains).

5. Clarify exposure definitions. Please briefly operationalize what is meant by “chronic low-dose” and “repeated/rapid-succession” imaging (e.g., cranial/cervical vs non-cranial scope; counts or time-windowed cumulative indices).

6. Add a short limitations note on confounding/reverse causation. Higher cranial imaging frequency may correlate with healthcare utilization and baseline risks (vascular disease, falls/trauma, frailty, prodromal symptoms). A brief paragraph describing mitigation strategies—lagged exposure windows (e.g., excluding imaging within 2–5 years before diagnosis), adjustment for healthcare-use metrics, propensity approaches, and non-cranial negative controls—would strengthen interpretation.

7. Provide 2–3 testable predictions. A concise list of falsifiable expectations would improve scientific utility and guide future studies.

8. Contextualize dental CBCT statements. If possible, add a sentence clarifying key comparators and conditions (protocol/FOV) to avoid misinterpretation.

Overall, the manuscript is promising; these minor clarifications would improve rigor and readability.

Recommendation

Major revision. The conceptual framework is interesting, but clearer exposure definitions, bias handling, and explicit testable predictions are needed for a robust hypothesis paper.

Declarations

Potential competing interests: No potential competing interests to declare.