

Peer Review

Review of: "The Future of Longevity Medicine: Repairing the Parts or Preserving the Whole? Holmes' Carriage as a Metaphor for Two Fundamentally Different Models of Aging"

Mounir El Maï¹

1. Institute for Research on Cancer and Aging, Nice, Nice, France

This manuscript presents an interesting conceptual distinction between **"fragmented aging"** and **"coherent aging"**, using Holmes' carriage as a metaphor for two different modes of biological ageing. The central idea - that ageing should be viewed not only as an accumulation of molecular damage but also as a progressive loss of organismal coordination - is intellectually appealing and resonates with contemporary systems biology.

However, in its current form, the manuscript remains largely **philosophical rather than scientific**. Many central statements are presented as factual despite lacking supporting evidence, important concepts remain undefined, and the discussion frequently contrasts "modern medicine" with "traditional populations" in a way that oversimplifies demographic and epidemiological realities.

The paper has the potential to become a valuable commentary article, but it requires substantial revision before publication.

Major comments:

1-The entire paper revolves around the notion of **systemic coherence**, yet this concept remains descriptive rather than operational. For example, the manuscript repeatedly states "loss of systemic coherence" without explaining what coherence actually means, how it differs from resilience, whether it represents network robustness, physiological reserve, or biological complexity. From the perspective of

ageing biology, this is a critical weakness. The authors should propose at least a preliminary biological definition.

2-The manuscript ignores much of the existing ageing literature. The authors repeatedly suggest that modern ageing research focuses exclusively on repairing damage. This is simply inaccurate. Numerous fields already investigate organism-level coordination. As written, the paper unintentionally gives the impression that the authors are proposing something entirely novel when, in reality, there is substantial conceptual overlap with existing literature. The manuscript should clearly position itself relative to current theories.

3-No mechanistic framework is proposed. The article repeatedly asks “What maintains coherence?” but never proposes plausible mechanisms. A commentary article should provide hypotheses. Possible candidates include, for instance: inter-organ communication, endocrine synchronization, autonomic nervous system, immune surveillance, extracellular vesicles, circadian regulation, inflammaging, cellular senescence, proteostasis networks, etc...

Without such discussion, the article remains philosophical.

4-The discussion of longevity interventions is not balanced. The manuscript implies that gene therapy, epigenetic reprogramming, and regeneration may actually increase systemic incoherence. This is entirely speculative with no evidence presented. Some interventions may indeed improve coordination. For example, partial reprogramming improves multiple hallmarks simultaneously in animal models. Senolytics improve systemic function across organs. Rapamycin affects numerous ageing pathways simultaneously. The discussion should distinguish speculation from established evidence.

5- The comparison with Blue Zones is oversimplified. The manuscript repeatedly argues that traditional populations exhibit coherent ageing because they maintain functionality despite less advanced medicine. This is problematic. Blue Zone research remains controversial. Many studies have highlighted age-reporting errors, survivor bias, migration effects, socioeconomic confounding, and incomplete birth records. Moreover, healthy ageing in these populations is associated with diet, physical activity, social integration, lower smoking rates, and reduced obesity, rather than evidence of a distinct biological ageing mechanism. The manuscript should present this as a hypothesis rather than implying causality.

Minor comments:

1- The bibliography is surprisingly limited. The first reference cannot be found online.

Declarations

Potential competing interests: No potential competing interests to declare.