

Epigenetic Drift Does Not Dictate Cognitive Fate: Reframing Biological Aging Through Cognitive Reserve

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BACKGROUND

Epigenetic age acceleration has emerged as one of the most robust biomarkers of biological aging and is increasingly interpreted as a proxy for cognitive vulnerability and neurodegenerative risk. However, this interpretation implicitly assumes a deterministic link between epigenetic drift and cognitive decline. Whether epigenetic aging uniformly translates into cognitive deterioration, or instead represents a modifiable biological pressure whose phenotypic expression depends on cognitive reserve, remains unresolved.

METHODS

We conducted a conceptual scoping review of human studies examining epigenetic aging in relation to cognitive performance, brain network integrity, and resilience-related modifiers. Twelve studies published between 2016 and 2025 were included, spanning population-based longitudinal cohorts, digital cognitive phenotyping, functional neuroimaging, and molecular analyses of epigenetic regulation. Epigenetic measures included first- and second-generation DNA methylation clocks (Horvath, Hannum, PhenoAge, GrimAge, DunedinPACE), alongside mechanistic markers of epigenetic drift.

RESULTS

Across studies, second-generation epigenetic clocks—particularly GrimAge and DunedinPACE—were consistently associated with accelerated cognitive decline, impaired processing efficiency, and altered functional brain connectivity, predominantly affecting medial temporal and limbic networks. Crucially, epigenetic aging was more strongly linked to subtle cognitive inefficiency—manifested as increased response latency, variability, and reduced network efficiency—than to overt cognitive impairment. Multiple lines of evidence demonstrated marked effect modification: individuals with preserved functional connectivity, higher cognitive reserve, active social engagement, volunteering, or stronger psychosocial purpose showed attenuated or absent cognitive consequences despite advanced epigenetic aging. Mechanistic data further supported this dissociation, identifying preserved FOXO3a signaling and adaptive epigenetic regulation as features of successful aging phenotypes.

CONCLUSIONS

Epigenetic drift reflects biological pressure, not cognitive destiny. Cognitive reserve—spanning neural network efficiency, behavioral engagement, and psychosocial resilience—critically determines whether epigenetic aging translates into cognitive decline. These findings challenge deterministic interpretations of epigenetic age acceleration and reposition it as a context-dependent vulnerability signal rather than an inevitable marker of cognitive failure. Integrating epigenetic biomarkers with measures of cognitive reserve may refine risk stratification and reveal novel targets to preserve cognitive function despite biological aging.