gp.genomicpress.com

Genomic Psychiatry

OPEN

EDITORIAL

The forgotten clockwork of the brain: Untangling accelerated aging in substance use disorders

Genomic Psychiatry; https://doi.org/10.61373/gp025d.0035

When the scaffolding of biology is hurried by pathology, we are forced to confront time, not as chronology but as degeneration. The elegant study by Kluwe-Schiavon et al. plunges into precisely this conceptual breach: where substance use disorders (SUDs) hijack the natural rhythm of aging, pushing the clock forward with biochemical violence and neuroepigenetic insistence (1). The new article buils on a body of work in this area (2–4). This is not just a question of whether drugs kill. We already know they do. The deeper question, provocative and new, thanks to this anatomically grounded work, is whether drugs age the brain (5). And if so, how (see Fig. 1). There is also a quieter dimension here: one that lives outside the elegant research presented in this article. In this same issue of *Genomic Psychiatry*, a personal interview with Dr. Consuelo Walss-Bass sheds light on the emotional and intellectual backdrop to this research (6).

With rigor and restraint, the authors dissect the transcriptomic and epigenetic landscapes of the dorsolateral prefrontal cortex (DLPFC)—a brain region central to decision-making and executive control, but also particularly vulnerable to the long shadows cast by addiction. Using post-mortem brain tissue from individuals with alcohol, opioid, and stimulant use disorders, the authors deploy not one but three specialized epigenetic clocks calibrated for cortical tissues. These include DNAmClock-Cortical, CerebralCortexClockcommon, and PCBrainAge; each of them represents a fine-grained chronometer that ticks not with seconds, but with methylation.

The central insight of the study is unsettling in its clarity: individuals with SUDs exhibit signs of accelerated biological aging, and this aging is neither cosmetic nor metaphorical. It is cellular. It is molecular. And it is coded into the methylated terrain of the genome (7, 8). That these effects were observed specifically in the brain—rather than peripheral tissues—deepens their clinical gravity. We are not speaking here of graying hair or stiffening joints, but of the cognitive architectures that underlie judgment, memory, and behavioral restraint.

What the Data Whispered

The authors' analytical choreography is both sophisticated and honest. Samples were stratified into those with and without accelerated aging (AA), allowing for within-cohort comparisons that illuminate rather than blur. The transcriptomic profiles revealed overlapping and unique gene expression changes across SUD subtypes. These alterations were not vague or diffuse. They were concentrated in specific biological pathways: mitochondrial function, cellular metabolism, immune modulation, and neuroinflammation (9).

Of particular interest is the mitochondrial signature that emerges across all SUDs, suggesting a shared mechanism of neuroenergetic decay (10). If mitochondria are indeed the powerhouses of the cell, then substance use seems to be the arsonist. The implication is grim: that addiction robs the brain of its metabolic youth.

Equally fascinating is the differential enrichment across substance types. For instance, alcohol and stimulants shared vascular and oxygen transport system disruptions, while opioids and stimulants converged on inflammatory pathways. Alcohol and opioids, in contrast, intersected within cellular signaling and neurodevelopmental tracks. These divergences underscore a point that psychiatry often ignores in its pharmacological zeal: that not all addictions are created equal at the molecular level. There is no "one SUD to rule them all"—only overlapping morbidities traversing unique biological corridors.

Figure 1. The biological clock of addiction. This conceptual image illustrates the central theme of accelerated biological aging in substance use disorders. A human brain model positioned alongside an analog clock and substance residue (cocaine) visually represents how substance use disorders can accelerate the biological aging process of neural tissue, highlighting the "ticking clock" metaphor discussed throughout the editorial. Image generated by Grok (xAI, 2025) with active author input.

Bravery in Limitation

The authors, commendably, resist the temptation of over-interpretation. They acknowledge the limitations inherent to cross-sectional post-mortem studies. They admit the absence of causality, the specter of confounding, the constraints of nominal significance thresholds. Most notably, they point out that no differentially expressed genes (DEGs) survived false discovery rate (FDR) correction, a humbling reminder of the statistical rigor demanded by genomic inquiry.

Yet, science often advances not through definitive answers, but through the elegance of an intelligent question. And this study asks many—quietly but insistently. Why do some brains crumble faster than others under the same pharmacological siege? Could there be predisposing genomic signatures: either genetic susceptibilities or epigenetic scars left by early-life adversity, that make some individuals biologically fragile to the insult of drugs? What role might immune priming,

Received: 21 April 2025. Accepted: 24 April 2025.
Published online: 29 April 2025.

neurovascular shifts, or hormonal derangements play in this neurobiological acceleration?

The Policy Reverberations

It would be a mistake to leave this study in the quietude of the laboratory. Its implications are vast, reaching into public health, addiction medicine, criminal justice, and even education policy. If substance use induces premature biological aging, then we must treat it not merely as a moral lapse or behavioral choice, but as an accelerant of neurodegeneration. What we call relapse may sometimes be the cognitive exhaustion of a prematurely aged cortex. What we term non-adherence might instead be mitochondrial collapse.

In an era that fetishizes longevity and "healthspan," it is almost tragicomic that we ignore entire populations whose biological age far outpaces their years. Youth, in the statistical sense, is no shield when the brain is decades older than the body it inhabits.

A Call Forward

This study opens the door to a field that remains embryonic but urgent: the psychiatry of aging in young people. It calls for longitudinal investigations that follow individuals through abstinence, relapse, remission, and decay. It demands integrative biomarker panels that combine methylation, gene expression, and neuroimaging. It proposes, albeit implicitly, a new taxonomy for SUD, not just based on behavior or drug class, but on biological decay signatures.

If one is to be optimistic, and one must be, even in the face of molecular entropy, then perhaps these findings mark the beginning of a therapeutic redirection. Anti-aging interventions, long the obsession of cosmetic medicine and Silicon Valley biohackers, might soon find their most ethically urgent application in addiction psychiatry.

Julio Licinio[1]

[1] *Editor-in-Chief,* Genomic Psychiatry*, Genomic Press, New York, NY 10036, USA*
✉ *e-mail: julio.licinio@genomicpress.com*

References

1. Kluwe-Schiavon B, Stertz L, Barichello T, Meyer TD, Fries GR, Walss-Bass C. Deciphering the molecular basis of accelerated biological aging in substance use disorder: integrative transcriptomic analysis. Genomic Psychiatry. 2025. DOI: 10.61373/gp025a.0029.
2. Zillich L, Cetin M, Hummel EM, Poisel E, Fries GR, Frank J, et al. Biological aging markers in blood and brain tissue indicate age acceleration in alcohol use disorder. Alcohol Clin Exp Res (Hoboken). 2024;48(2):250–9. DOI: 10.1111/acer.15241. PMID: 38276909; PMCID: PMC10922212
3. Cabrera-Mendoza B, Stertz L, Najera K, Selvaraj S, Teixeira AL, Meyer TD, et al. Within subject cross-tissue analyzes of epigenetic clocks in substance use disorder postmortem brain and blood. Am J Med Genet B Neuropsychiatr Genet. 2023;192(1-2):13–27. DOI: 10.1002/ajmg.b.32920. PMID: 36056652; PMCID: PMC9742183
4. Bachi K, Sierra S, Volkow ND, Goldstein RZ, Alia-Klein N. Is biological aging accelerated in drug addiction? Curr Opin Behav Sci. 2017;13:34–9. DOI: 10.1016/j.cobeha.2016.09.007. PMID: 27774503; PMCID: PMC5068223
5. Ersche KD, Jones PS, Williams GB, Robbins TW, Bullmore ET. Cocaine dependence: a fast-track for brain ageing? Mol Psychiatry. 2013;18(2):134–5. DOI: 10.1038/mp.2012.31. PMID: 22525488; PMCID: PMC3664785
6. Walss-Bass C. Consuelo Walss-Bass: why does my sister have schizophrenia and I do not? Understanding how a person's unique genetic makeup interacts with their environment to shape behavior is one of the final frontiers in medicine. Genomic Psychiatry. 2025:1–4. DOI: 10.61373/gp025k.0014
7. Clark SL, McGinnis EW, Zhao M, Xie L, Marks GT, Aberg KA, et al. The impact of childhood mental health and substance use on methylation aging into adulthood. J Am Acad Child Adolesc Psychiatry. 2024;63(8):825–34. DOI: 10.1016/j.jaac.2023.10.014. PMID: 38157979; PMCID: PMC11745081
8. Onisiforou A, Zanos P, Georgiou P. Molecular signatures of premature aging in Major depression and Substance Use disorders. Sci Data. 2024;11(1):698. DOI: 10.1038/s41597-024-03538-z. PMID: 38926475; PMCID: PMC11208564
9. Li X, Ramos-Rolón AP, Kass G, Pereira-Rufino LS, Shifman N, Shi Z, et al. Imaging neuroinflammation in individuals with substance use disorders. J Clin Invest. 2024;134(11). DOI: 10.1172/JCI172884. PMID: 38828729; PMCID: PMC11142750
10. Reece AS. Evidence of accelerated ageing in clinical drug addiction from immune, hepatic and metabolic biomarkers. Immun Ageing. 2007;4:6. DOI: 10.1186/1742-4933-4-6. PMID: 17892544; PMCID: PMC2041948