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Cross-tissue Evaluation of Epigenetic Clocks in Substance Use Disorder

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An accelerated biological aging is a main contributor to adverse outcomes in patients with substance use disorders (SUD). The evaluation of epigenetic clocks (DNA methylation based estimators of biological aging) has been limited to blood in SUD. Consequently, the impact of epigenetic aging in the brain of individuals with SUD remains unknown. We hypothesized that epigenetic aging impacts differently brain and blood tissues. Therefore, epigenetic clocks measures in brain and blood from individuals with SUD will be different. We evaluated the following epigenetic clocks: DNAmAge, DNAmAgeHannum, DNAmAgeSkinBlood, DNAmPhenoAge, DNAmGrimAge, and DNAmTL in postmortem brain (prefrontal cortex) and blood from individuals with SUD (n=42), including alcohol (n=10), opioid (n=19), and stimulant use disorder (n=13), and controls (n=10). For the assessed epigenetic clocks we evaluated: 1) intergroup differences in brain and blood separately; 2) cross-tissue differences, and 3) brain-blood correlations. We found a higher DNAmPhenoAge and lower DNAmTL in blood from individuals with SUD compared to controls. Subgroup analyses showed a lower brain DNAmTL in individuals with alcohol use disorder, compared to those with stimulant use disorder and controls. Cross-tissue analyses indicated a lower blood DNAmTL and a higher blood DNAmGrimAge compared to their respective brain values in the SUD group. This is the first cross-tissue study investigating the relationship between brain and blood epigenetic clocks in SUD. Our results highlight the relevance of tissue specificity in epigenetic aging studies and suggests that peripheral measures of epigenetic clocks in SUD may depend on the type of drug used.