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Environmental, Genetic, and Neural Correlates of Adolescent Polysubstance Use: Insights from the ABCD Study

Polysubstance use (PSU) among adolescents, involving alcohol, cannabis, and nicotine, is an escalating public health concern linked to compounded risks for brain development, cognitive impairment, and progression to substance use disorders (SUDs). Despite its severe implications, PSU remains understudied, with most research focusing on single substances.

In this study, we leveraged data from the Adolescent Brain Cognitive Development (ABCD) study ($n = 11,868$, release 5.1) to investigate environmental, genetic, and neurobiological factors contributing to PSU and its impact on adolescent brain connectivity. Participants were categorized into no substance use (NSU), single substance use (SSU), and PSU groups. We examined environmental exposures—including parental monitoring, maternal substance use, and life events—and polygenic scores (PGS) for general SUD risk using mixed-effect models. Resting-state and subcortical-cortical functional connectivity analyses were conducted to explore brain pathways associated with substance use.

Our findings reveal that low parental monitoring is the most significant environmental factor differentiating PSU from SSU ($p < 0.05$). Critically, gene-environment interaction analyses indicate that parental mental health issues amplify genetic susceptibility to PSU in adolescents with high genetic risk ($F = 12.44$, $p = 4.2 \times 10^{-4}$). Adolescents engaged in SSU and PSU exhibit decreased connectivity between the dorsal attention and retrosplenial temporal networks and weakened subcortical-cortical connectivity in regions such as the cingulo-parietal network and accumbens area (all $p < 0.05$).

This study identifies parental mental health and monitoring as critical targets for PSU prevention in youth, while neural connectivity patterns offer potential early detection biomarkers. These findings advocate for family-centered interventions and underscore the need for longitudinal research to understand SSU to PSU progression. Our results support integrated approaches combining family support, mental health services, and biomarker monitoring to promote healthier youth development and reduce substance use burden.