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Neural Correlates of Polygenic Risk Scores for Problematic Substance Use in Adolescents

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A potentially useful strategy in imaging genetics involves generation of polygenic risks scores (PRS) to exploit the power of large GWAS. PRS for cannabis use disorder (CUD), cigarettes per day (CPD) and problematic alcohol use (PAU) were examined in relation to substance use behavior and structural brain features in three large adolescent datasets: IMAGEN (1813 adolescents sampled at ages 14 and 19), Philadelphia Neurodevelopmental Cohort (PNC) (323 adolescents sampled at age 14) and ABCD (4589 children sampled at age 11). In IMAGEN, all three PRS were associated with early cigarette, alcohol and cannabis use as well as total drug exposure at age 14 and 19. There was insufficient substance use in the PNC and ABCD samples to assess this association. In IMAGEN, the medial orbitofrontal cortex was associated with CPD PRS (P_{14y}=0.001 and P_{19y}=0.031), PAU PRS (P_{14y}=0.004 and P_{19y}=0.019) and CUD PRS (P_{14y}=0.049) at age 14 and 19. Each association explained approximately 10% of the variance. In PNC, CPD PRS was also associated (p=0.022) with the medial orbitofrontal cortex thickness. No associations with this brain region was observed in the younger ABCD sample. The medial orbitofrontal cortex's processing of the subjective value of anticipated outcomes has been implicated in addiction. The appearance of a neural phenotype associated with the disorder at 14 years old (IMAGEN, PNC) but not 9-10 years old (ABCD) suggests a developmental critical period in the etiology of problematic substance use. Confirmation will be assessed in other participating ENIGMA Addiction sites including PING and the Michigan Longitudinal Study.