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Neural correlates of polygenic risk for cannabis use and cannabis use disorder

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Genetic liability for Cannabis Use (CU) and Cannabis Use Disorder (CUD) are modestly correlated (rg=0.5), suggesting partially distinct genetic influences. We examined the relation of CU and CUD PRS to substance involvement and brain structure phenotypes (i.e. cortical thickness, subcortical grey matter volume and white matter fractional anisotropy [FA]) in a large cohort of European adolescents (N=1,813) sampled at 14 and 19 years old by the IMAGEN project. It was hypothesized that genetic risk for CU and CUD would exhibit partially unique associations with distinct brain features. CU-PRS was not associated with substance use related measures or brain structure. At age 19, CUD-PRS was associated with five out of nine drug use measures collected as part of the European School Project on Alcohol and Drugs (ESPAD) survey including age of cannabis use onset and an estimate of total lifetime drug exposure although their significance did not survive correction for multiple comparisons. CUD-PRS was not associated with grey matter volume. However, corroborating previous reports, CUD-PRS was associated at age 14 with total average FA (PFDR=0.017) and seven specific white matter tracts including: posterior thalamic radiation (PFDR=0.010), and superior longitudinal fasciculus (PFDR=0.027) which both remained significantly associated with CUD-PRS at age 19. Since it has been independently established that early onset of substance use predicts later problematic use, it is notable that PRS-CUD, but not PRS-CU, is potentially related to cannabis use onset and developing white matter tract integrity in adolescents suggesting a pre-dispositional genetic risk for problematic cannabis use.