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Polygenic Risk Scores for Commonly Used Substances Predict Brain Structural differences in Drug Naïve Children

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Substance use and use disorders have been reliably linked to individual differences in brain structure. Whether these correlations reflect consequences of drug exposure, predisposing liability, or non-etiological correlates remains unknown. Here, we leveraged data from the Adolescent Brain and Cognitive Development (ABCD) study to test whether polygenic risk scores (PRS) for alcohol use (i.e., drinks/week), alcohol use disorder (AUD), and tobacco smoking (i.e., cigarettes/day) are associated with brain morphology (i.e., white matter integrity, cortical thickness, etc.). We restricted our ABCD dataset to children of genomically-confirmed European ancestry (for PRS applicability) who reported no alcohol, tobacco or other illicit substance use ($n=3,282$; age: 9.93 ± 0.76 ; 48% female). Covariates included age, sex, measures of SES, 20 ancestry PCs and random effects for scanner and family. FDR correction was applied across each brain map and then an additional spectral decomposition to the FDR corrected p-values across the PRS thresholds. Effects were largely observed in higher order brain areas, indicating behavioral mechanisms. After multiple testing correction, AUD PRS were related to greater white matter integrity in the cingulum bundle ($r^2=.0025$, corrected $P=.011$) and less gray matter thickness in the suborbital sulci ($r^2=.0045$, corrected $P=.0179$). Drinks per week PRS related to more volume in the Wernicke's area ($r^2=.0044$, corrected $P=.0126$). No findings were made for cigarettes per day. MRI anatomical patterns (and particularly structural connectivity) will likely be a fruitful phenotype in contextualizing results from major substance use GWAS and may assist in distinguishing stage specific genetic effects in substance use development in the future.