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Polygenic Influences on Alcohol Related Neurophysiological and Neurocognitive Processes across the Lifespan

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Multimodal studies of brain function have identified specific functional and structural deficits in neural circuits in individuals with substance use disorders (SUD) as well as those at risk, pointing to dysfunctional bottom-up reward processing, top-down inhibitory control networks, and interactions between frontal executive networks. Neural biomarkers alongside clinical/behavioral data can be used to further understanding of how recent GWAS findings may lead to aberrant brain functioning and have an important role in addiction. 1,815 multigenerational families (n=12,145 individuals) from the Collaborative Study on the Genetics of Alcoholism (COGA), including those densely affected with SUD, comparison families, and successive generations of these families have been studied extensively across multiple domains: clinical, behavioral, neurophysiological, neurocognitive, and genomic. We examined how polygenic risk scores (PRS) derived from recent GWAS of addiction and related neurocognitive outcomes (e.g., Psychiatric Genomics Consortium's DSM-IV Alcohol Dependence (AD) GWAS, International Cannabis Consortium initiation GWAS, UK Biobank fluid intelligence GWAS) relate to neural connectivity. Preliminary findings indicate that both AD and fluid intelligence PRS predict behavioral and neurocognitive functioning across development. In addition, associations observed among AD PRS and AUD in COGA are partially explained by frontal neural connectivity. From this data, we conclude that neural biomarkers can be used to further understanding of how genetic risk variants from large GWAS may relate to SUD and related behavior. It is now crucial to further understanding of *how* loci identified in GWAS relate to addictive behaviors to push this research closer to molecular understanding and ultimately clinical translation.