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## **Associations of polygenic risk scores with neurocognitive and psychiatric phenotypes in Bulgarian substance users**

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Genetic association studies of addiction tend to focus on substance use phenotypes, with limited integration of neurobehavioral and psychiatric phenotypes of potentially mechanistic significance. The current study is based on a small (N=383) but extensively phenotyped sample of Bulgarian substance dependent individuals in protracted abstinence, characterized by predominantly mono-dependent patterns of opiate and stimulant use. Participants were genotyped with the Smokescreen array and deeply phenotyped with a comprehensive assessment battery, including seven neurocognitive tasks of decisional/'choice' and motor/'action' impulsivity, and personality and psychiatric measures of externalizing and internalizing phenotypes, commonly comorbid with addictions. We calculated a series of polygenic risk scores (PRS) based on several large-scale GWAS of phenotypes relevant to substance use outcomes (e.g. risk tolerance/risky behavior, cannabis use, alcohol dependence, depression, educational attainment) that included SNPs meeting increasingly stringent  $p$ -value thresholds in the discovery GWAS. The PRS were then used to predict neurocognitive, psychiatric, and substance use phenotypes in the Bulgarian sample. The strongest PRS predictor was based on the first PC of the GWAS 'risky behavior' phenotype, which explained 4.3% of the variance in the antisocial/impulsive factor of the Psychopathy Checklist: Screening Version in our Bulgarian sample, previously shown to be the strongest and only common predictor of dependence on 5 different classes of drugs (Vassileva et al., 2019). The 'risky behavior' PRS was also associated with heroin/opioid dependence. Additional associations emerged between educational attainment, sensation seeking, and ability to inhibit prepotent motor responses. Notably, none of the PRS were associated with amphetamine/stimulant dependence in our sample.