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Characterizing the genetic architecture of impulsivity and its overlap with substance use and psychopathology

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Impulsivity is a complex psychological construct with a fundamental role in substance use and psychopathology, but measurement issues hinder our understanding of its etiology. Neuroscientific insights support 'splitting' impulsivity into distinct facets, but factor analytic research has shown that similar traits can be 'lumped' together at multiple levels. Here, we use multivariate methods to advance our understanding of impulsivity by testing the splitting versus lumping hypotheses across biological scales. Using the Genomic SEM framework, we analyzed eight impulsivity facets (*N*s~130k) with two models: an unstructured 'omnibus' model (splitting) and a structured 'common factor' model (lumping). We evaluated these models and their outputs across genomic, transcriptomic, and neuroanatomical levels. We then conducted polygenic score (PGS) analyses in two independent cohorts to characterize links with health and well-being. Results revealed pleiotropy among impulsivity facets (mean r_g=0.43, range=-0.09-0.79) that could be approximated with a common factor model (CFI=0.94, SRMR=0.08). However, subsequent analyses revealed that SNP- and gene-level effects were largely inconsistent with this model of general liability. Many genetic relationships with psychopathology were also facet-specific, such as those with externalizing behavior and substance use disorders (Q_{Trait} *P*s<8.48e-6). PGS results underscored the consequences of erroneous lumping, as 67 associations with medical outcomes were missed with a common factor PGS. Collectively, the results of this study generate new insights into the etiology of impulsivity, implicating novel links to neurodevelopment. Our results support multidimensional approaches as a more informative avenue for studying the heterogeneous biology of impulsive traits and their relationship to addiction and mental health.