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Limited evidence for a general dimension of impulsivity across genomic, transcriptomic, and neuroanatomical levels of analysis

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Impulsivity is a psychological construct with clear connections to substance use disorders and related behaviors. Despite this, there remains no clear consensus on how it should be conceptualized, measured, and studied. One key area of debate concerns whether impulsivity should be considered a unitary versus multidimensional construct. Here, we used the Genomic Structural Equation Modeling framework to study the genetic bases of eight impulsivity phenotypes (*N*s~125k) across genomic, transcriptomic, and neuroanatomical levels of analysis. Specifically, we investigated the joint genetic architecture of these complex traits, and evaluated the validity of a general dimension of impulsivity. Genetic factor analysis indicated that a parsimonious common factor model could be fit to the data, with comparable fit to more complex models (CFI=0.946, SRMR=0.078). Our subsequent multivariate GWAS and TWAS implicated novel genes (e.g., *MAPT*, *MADD*, *CLN3*) and pathways (e.g., voltage-gated calcium channel signaling, perinatal development) in the genetic etiology of impulsivity. However, these analyses also revealed substantial heterogeneity across traits. We found little-to-no signal that was consistent with a general dimension of impulsivity; instead, most genetic associations were driven by one to three phenotypes. This pattern was observed for individual SNPs and genes, as well as genetic correlations with brain structure, where we found that impulsivity traits were differentially related to alterations in the cortex. Collectively, our results suggest that a multidimensional approach is likely to be vastly more informative when studying the biology of impulsivity.