

Role of Genetically-Influenced 5-HT Functioning in a Bifactor Model of Psychopathology: Moderation by Fathers' Substance Use Disorder

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Unique etiological factors differentiate disorders lying on internalizing and externalizing spectra of psychopathology, and general risk to develop mental illness (general psychopathology factor). The serotonergic (5-HT) system might contribute to variation in risk for multiple psychiatric conditions, influencing general liability towards psychopathology. Additionally, these associations might be moderated by paternal substance use disorder (SUD). This study examined a polygenic score indexing 5-HT functioning as a predictor of a general psychopathology factor, and of internalizing and externalizing sub-factors, as well as moderation by fathers' SUD in the Center for Education and Drug Abuse Research (CEDAR) project.

CEDAR participants (N=227; 72.7% male) were assessed at three waves (T1: 17-20 years; T2: 20-23 years; T3: 24-26 years). Analyses included non-Hispanic Caucasian offspring (to control for population stratification) whose fathers had SUD (high average risk, HAR; N=112) or no psychiatric disorder (low average risk, LAR; N=115). At T1-T3, psychopathology was assessed using DSM-IV criteria and Achenbach Self-Report Form. The polygenic score was computed using results from an independent genome-wide association study of 5-HIAA concentrations in the cerebrospinal fluid (Luykx et al., 2014). Structural equation modeling tested associations of the polygenic score with a bifactor model that included 3 waves of data.

The bifactor model comprising a general psychopathology (all disorders/symptoms loaded), specific internalizing (all internalizing disorders/symptoms loaded) and specific externalizing (all externalizing disorders/symptoms loaded) fit the data well (RMSEA=0.02, CFI=0.96, WRMR=0.99). For the LAR group only, lower polygenic scores (i.e., lower 5-HT functioning) were associated with higher general psychopathology ($\beta = -0.29$, $p = 0.01$). Polygenic score did not predict any other factor.

Among LAR, 5-HT functioning might increase risk for multiple psychiatric conditions because it influences individuals' general liability towards psychopathology. For HAR, other more potent environmental or genetic risk factors might be more salient in risk for general psychopathology.

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