## Functional Connectivity Signatures of Polygenic Depression Risk in Youth

Authors: Louise Moles, Steve Riley, Sarah D. Lichenstein, Marzieh Babaeianjelodar, Robert Kohler, Annie Cheng, Corey Horien Abigail Greene, Wenjing Luo, Jonathan Ahern, Bohan Xu, Yize Zhao, Chun Chieh Fan, R. Todd Constable, Sarah W. Yip Abstract: Background: Risks for depression are myriad and include both genetic and brain-based factors. However, relationships between these systems are poorly understood, limiting understanding of disease etiology, particularly at the developmental level. Methods: We use a data-driven machine learning approach connectome-based predictive modeling (CPM) to identify functional connectivity signatures associated with polygenic risk scores for depression (DEP-PRS) among youth from the Adolescent Brain and Cognitive Development (ABCD) study across diverse brain states, i.e., during resting state, during affective working memory, during response inhibition, during reward processing. Results: Using 10-fold cross-validation with 100 iterations and permutation testing, CPM identified connectivity signatures of DEP-PRS across all examined brain states (rho's=0.20-0.27, p's<.001). Across brain states, DEP-PRS was positively predicted by increased connectivity between frontoparietal and salience networks, increased motor-sensory network connectivity, decreased salience to subcortical connectivity, and decreased subcortical to motor-sensory connectivity. Subsampling analyses demonstrated that model accuracies were robust across random subsamples of N's=1,000, N's=500, and N's=250 but became unstable at N's=100. Conclusions: These data, for the first time, identify neural networks of polygenic depression risk in a large sample of youth before the onset of significant clinical impairment. Identified networks may be considered potential treatment targets or vulnerability markers for depression risk.

Keywords: genetics, functional connectivity, pre-adolescents, depression

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