Risk and Resilience Predictors of Teenage Drug Use.

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Identifying risk factors for addiction is important for both allocating clinical resources and for furthering our theoretical understanding of probable causal mechanisms underlying addiction. I will present data from the IMAGEN project, a longitudinal study of 2,000 teens assessed at ages 14, 16 and 19 (http://www.imagen-europe.com). All participants completed extensive phenotypic batteries including structural and functional neuroimaging assessing inhibitory control, reward and face processing and provided blood samples for genetic analyses.

I describe two approaches to identifying risk factors. The first takes advantage of the wealth of information in this large dataset by employing a machine-learning discovery approach. We explore thousands of measures at age 14 (neuroimaging, genetic, phenotypic) and develop elastic net regression models that predict drug use at age 16 and we guard against false positive findings by quantifying the predictive accuracy of these models using internal cross-validation. Separate analyses investigate the predictors of cigarette, alcohol and cannabis use and highlight the predictive value of family history of use, stressful life events, personality, and individual differences in brain function and structure.

The second approach is a hypothesis-driven investigation of specific risk mechanisms. An example of this approach is the role that genetic variation in the alpha 5 nicotinic receptor system may have in the effects of cigarette use on brain function. We find that fourteen year old (relatively light) smokers show reduced grey matter volume in the vmPFC compared to non-smokers. A significant negative linear relationship between volume and smoking levels suggests effects at even very low levels of cigarette exposure. We confirm the genetic association between smoking and the alpha 5 nicotinic receptor SNP (rs16969968) and show a gene x exposure interaction in the vmPFC with the greatest volume reduction in those smokers possessing the high-risk allele. Finally, reward processing on the Monetary Incentive Delay task shows a similar interaction effect in this brain region. Examination of the patterns of reward-related activation across gene and exposure groups suggests a causal mechanism whereby activation differences related to genotype confer vulnerability to the reinforcing effects of cigarette use. Subsequent smoking exposure appears to affect the structure and function of this vmPFC region which is thought to be central to reward/value related decision making.

A final analysis focuses specifically on resilience. We identify the neurobiological characteristics of resilient teens who, despite lifetime adversity, have good academic, mental health and behavioral outcomes. These teens are characterized by increased right prefrontal grey matter volumes.

In summary, these analyses show that identifying risk factors for teenage drug use is possible. Importantly, they also show evidence of a neurobiology of resilience. Future directions include the replication and extension of these findings, animal models to confirm causal mechanisms and, ultimately, the application of interventions for those most at risk.