

Genetic risk and nicotine exposure interact on the structure and function of the ventromedial prefrontal cortex in adolescents

Scott Mackey, Bader Charani, Kees-Jan Kan, Philip A. Spechler, Alexandra Potter, Catherine Orr, Hugh Garavan & the IMAGEN Consortium

The few published studies that have examined the interaction of smoking with the structure and function of the developing brain have been based on small sample sizes. And although smoking is highly heritable, the additional mechanisms by which genetic vulnerability (such as the well replicated associations of nicotine use with rs1051730 and rs16969968 polymorphisms of the alpha 5 and alpha 3 subunit nicotinic receptors, respectively) might contribute to early smoking behavior and neural development are unknown. A nicotine use score was calculated in a large sample of 14 year olds drawn from the IMAGEN Project (<http://www.imagen-europe.com>). Grey matter volume quantified by voxel-based morphometry and reward processing assessed by functional MRI during performance of the Monetary Incentive Delay (MID) task was compared in early smokers (N=93) and non-smokers (N=389). Lower volume was observed in smokers in the ventromedial prefrontal cortex (vmPFC) (1,036 voxels; x = 2, y = 29, z = -9 in MNI space) after $p < 0.05$ cluster-wise correction. Furthermore, a regression analysis demonstrated that vmPFC volume was lowest in those adolescents who had smoked the most (i.e. there appeared to be a dose dependent effect of nicotine exposure). A separate ANOVA on the mean volume of the vmPFC cluster derived ROI which modeled the influence of smoking status (2 groups) and genotype (3 groups: AA, GA and GG in rs16969968) revealed a significant status*genotype interaction, $p < 0.05$. The vmPFC ROI volume was lower in smokers in each of the three genotypes but the largest effect was in carriers of the high-risk allele (AA genotype). The interaction of genotype with activity in the vmPFC ROI during the MID task was also assessed revealing another significant status*genotype interaction. The vmPFC plays a central role in valuation processes informing decision-making and emotion regulation. Dysregulation of this system could alter the balance between the subjective value of smoking and non-drug rewards in a way that biases genetically at-risk adolescents towards increased rates of smoking. These results indicate a structural and functional basis for changes in the reward system of young adolescent smokers that may partially explain the CHRNA genetic association with smoking. Future work will investigate a replication of these gene-brain volume associations using a meta-analytic approach on the combined adolescent datasets of the ENIGMA Addiction Working Group (<http://enigma.ini.usc.edu/ongoing/enigma-addiction-working-group/>).

