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Multivariate Mediation Analysis of Genetic Variants, Brain Connectome and Nicotine Addiction

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Background and significance: Nicotine addiction (NA) is a multifaceted disorder, characterized by the brain's reward system, genetics, and environmental factors that lead to compulsive tobacco use despite harmful health effects. Differential expression of brain functional connectivity (FC) characterizes the functional brain subnetwork related to NA. Recent studies have suggested a link between genetic profile (e.g., SNPs) and the development of NA, making it essential to investigate the SNP-FC-NA pathways to establish mediation pathways among genetics, brain functioning, and nicotine addiction.

Hypothesis and methods: Our study hypothesized that a pathway exists from SNPs to FC to NA. To validate this hypothesis, we utilized 38762 participants from the UK Biobank with smoking status and nicotine intake data and FC data. We then utilized a novel mediation analysis model for multivariate causal variables and connectome network mediators to extract the NA-related FC subnetwork from the subjects' resting-state fMRI data. Optimization was conducted to investigate the SNR-FC-NA pathways, with SNPs as the multivariate causal variables, NA as the outcome, and FC as the multivariate network mediator.

Results and discussion: We identified a significant mediation pattern ($p<0.001$) consisting 271 genetic variants and 130 FC edges. The 271 genetic variants were all from the CHRNA5-CHRNA3-CHRNB4 gene cluster. The 130 FC edges formed a bipartite network linking between the bilateral frontal lobes including insula cortices and basal ganglia regions (e.g., nucleus accumbens). Our study highlights the importance of the SNP-FC-NA pathway in understanding the complex mechanisms of nicotine addiction and provides valuable insights into the regulatory mechanisms of nicotine addiction and its dependence in the brain. These findings have significant implications for developing effective treatments and interventions.