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Large-scale mediation analysis to identify gene-brain network-nicotine addiction pathways using imaging-genetics data

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Nicotine addiction is a complex biopsychosocial disorder influenced by both genetic and environmental factors. A key challenge in nicotine addiction genetics research is to understand how multiple genetic variants interactively influence nicotine addiction traits through impacting the central nervous system. We propose a large-scale mediation analysis framework to integrate the genetics and neuroimaging data and identify gene – brain circuitry – addiction pathways. Because both genetic variants and brain imaging features (mediators) are high-dimensional with complex and organized correlation patterns, the statistical modeling and inference procedures are inherently challenging. We develop and apply network topology oriented statistical learning methods to recognize the complex and organized interaction structures between the imaging-genetics data and thus can perform multivariate statistical inference with higher efficiency. In addition, the statistical inference of gene – brain circuitry – addiction pathways in the mediation model includes three steps, and a pathway is selected only if all steps are statistically significant. Therefore, the overall false positive rates of the pathway can better controlled than conventional multivariate phenotype-genotype analysis.

We perform extensive simulation analyses, and the results show that the proposed large-scale mediation framework can simultaneously increase statistical power and reduce false positive rates for gene – brain circuitry – addiction pathway detection. We also apply this approach to the imaging-genetics data of 400 subjects for nicotine addiction research. We first focus on genetic variants based on previously reported nicotine addiction related genomic regions and identify integrated gene – brain circuitry – nicotine addiction pathway candidates.