

# An Integrative Network-Based Mediation Model (NMM) to Estimate Multiple Genetic Effects on Outcomes Mediated by Functional Connectivity

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Functional connectivity of the brain, characterized by interconnected neural circuits across functional networks, is a cutting-edge feature in neuroimaging. It has the potential to mediate the effect of genetic variants on behavioral outcomes or diseases. Existing mediation analysis methods can evaluate the impact of genetics and brain structure function on cognitive behavior or disorders, but they tend to be limited to single genetic variants or univariate mediators, without considering cumulative genetic effects and the complex matrix and group and network structures of functional connectivity. To address this gap, the paper presents an integrative network-based mediation model (NMM) that estimates the effect of multiple genetic variants on behavioral outcomes or diseases mediated by functional connectivity. The model incorporates group information of inter-regions at broad network level and imposes low-rank and sparse assumptions to reflect the complex structures of functional connectivity and selecting network mediators simultaneously. We adopt block coordinate descent algorithm to implement a fast and efficient solution to our model. Simulation results indicate the efficacy of the model in selecting active mediators and reducing bias in effect estimation. With application to the Human Connectome Project Youth Adult (HCP-YA) study of 493 young adults, two genetic variants (rs769448 and rs769449) on the APOE4 gene are identified that lead to deficits in functional connectivity within visual networks and fluid intelligence. This is a joint work with Wei Dai.

**Thursday, March 21, 2024, 3:30-4:30PM Eastern**

**133 Rosenau Hall**

**Zoom Link:**

<https://unc.zoom.us/j/98423779288?pwd=b0tqYThCQTaxeDdTQ0FRY3RnazdwQT09>

**Meeting ID: 984 2377 9288**

**Passcode: 631794**