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# A Kernel Machine Method for Detecting Higher Order Interactions in Multimodal Datasets: Application to Schizophrenia

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## Abstract

**Background:** Technological advances are enabling us to collect multimodal datasets at an increasing depth and resolution while with decreasing labors. Understanding complex interactions among multimodal datasets, however, is challenging.

**New Method:** In this study, we tested the interaction effect of multimodal datasets using a novel method called the kernel machine for detecting higher order interactions among biologically relevant multimodal data. Using a semiparametric method on a reproducing kernel Hilbert space, we formulated the proposed method as a standard mixed-effects linear model and derived a score-based variance component statistic to test higher order interactions between multimodal datasets.

**Results:** The method was evaluated using extensive numerical simulation and real data from the Mind Clinical Imaging Consortium with both schizophrenia patients and healthy controls. Our method identified 13-triplets that included 6 gene-derived SNPs, 10 ROIs, and 6 gene-specific DNA methylations that are correlated with the changes in hippocampal volume, suggesting that these triplets may be important for explaining schizophrenia-related neurodegeneration.

**Comparison with Existing Method(s):** The performance of the proposed method is compared with the following methods: test based on only first and first few principal components followed by multiple regression, and full principal component analysis regression, and the sequence kernel association test.

**Conclusions:** With strong evidence ($p$-value $\leq 0.000001$), the triplet (**MAGI2, CRBLCrus1.L, FBXO28**) is a significant biomarker for schizophrenia patients. This novel method can be appli-

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