# COMT × DRD2 epistasis modulates a putative emotional connectomic intermediate phenotype for schizophrenia

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Our prior work using graph theory based method, presented at the 43rd Annual Meeting of Society for Neuroscience, has identified a disrupted visual-limbic subnetwork in unaffected first-degree relatives of schizophrenia during emotion processing, and validated this connectomic finding as a robust and task-specific intermediate phenotype (presented at the 20th Annual Meeting of Organization for Human Brain Mapping). Here, to further investigate the utility of this potential phenotype in imaging genetics, we examined the main effects and interaction of two dopaminergic risk variants on this identified subnetwork: a candidate variant for emotion dysregulation (COMT val158met) [1] and a genome-wide supported schizophrenia risk variant in DRD2 (rs2514218) [2].
Our sample consisted of 289 healthy individuals of European ancestry without a first-degree relative with mental illness (mean age 33.73±9.78 years, 155 females). The subjects were recruited from the communities in Mannheim, Bonn and Berlin. For each individual, the COMT val158met polymorphism was directly genotyped by the DNA arrays while DRD2 rs2514218 genotype was imputed with Impute2 using reference haplotypes derived from the 1000 Genomes Project [3]. Following the procedures of the previous studies, the carriers of the presumed protective alleles were combined into one group (COMT: val/val + val/met; DRD2: risk C allele number <1.5). The observed genotype distributions did not deviate from Hardy-Weinberg equilibrium (COMT: 207 Val-carriers, 82 Met/Met, P=0.79; DRD2: 174 T-carriers, 115 CC, P=0.36). The four genotype groups for both variants did not show significant differences in demographic, psychological and fMRI performance data (all P values >0.10).
All the subjects underwent a well-established emotional face-matching task. The image preprocessing followed the standard procedures implemented in SPM8. The mean time series were extracted from each of the 90 anatomical regions defined by AAL template and corrected for noises. Whole-brain connectivity matrices were subsequently computed by the pairwise correlations between the corrected time series of each of the 90 nodes. Here, the averaged connectivity measures of the same subnetwork reported in our previous studies were extracted and entered as the dependent variable into an ANCOVA model with genotypes
(COMT and DRD2) as variables of interest and age, sex and site as covariates of non-interest. Significance was measured at P<0.05.
No significant main effects for both COMT and DRD2 genes on this phenotype measures were found (COMT: P=0.95, DRD2: P=0.15). However, the epistatic study demonstrated a strong COMT × DRD2 interaction (p=0.01). Specifically, in the group of COMT met/met homozygotes, there was a significant decrease of the phenotype in DRD2 CC homozygotes compared to T carriers (p=0.01). In contrast, no significant difference was found between DRD2 genotypes in the group of COMT val carriers (p=0.36), indicating that COMT val158met is epistatic to DRD2 rs2514218 on the identified phenotype.
This study showed that genetic epistasis between COMT val158met and DRD2 rs2514218 could modulate the identified emotional connectomic phenotype for schizophrenia and highlighted the utility of this potential phenotype in imaging genetics.

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**References**

[1] Mier, D., Kirsch, P., Meyer-Lindenberg, A., 2010. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. Molecular Psychiatry 15(9), 918-927.
[2] Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510), 421-427.

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