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RGS4 and *COMT* risk variants are associated with brain structural alterations

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Dear Editors,

We hypothesized that *RGS4* and *COMT* polymorphisms interact to affect brain structure among schizophrenia (SZ) and healthy control (HC) subjects using voxel-based

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Contributors

Drs. Marc Lener, Vishwajit Nimgaonkar and Konasale Prasad conceived the idea, and designed and executed the study. Mr. Steven Goodnow and Dr. Marc Lener conducted the analysis under Dr. Prasad's supervision. Drs. Nimgaonkar and Keshavan reviewed the manuscript, suggested further analyses and interpreted the results along with other authors. Drs. Prasad and Chowdari conducted the genetic assays, conducted quality assurance and selected the tag SNPs in consultation with Dr. Nimgaonkar. Dr. Chowdari and Mr. Wood conducted the LD analysis. All authors took part in going through the manuscript carefully.

Conflict of interest

None of the authors have any conflict of interest to declare that would impinge on the design, execution, analysis or reporting and discussion of the results.

morphometry (VBM) based on evidence of statistical, genetic, and functional epistasis between these risk gene variants (Lipska et al., 2006; Buckholtz et al., 2007; Nicodemus et al., 2007).

This sample was derived from our prior study of Caucasian subjects (Prasad et al., 2005) (n = 50; 26 first-episode, antipsychotic-naïve SZ; 24 HC). MRI scans were obtained on GE 1.5T whole-body scanner using previously described methods (Prasad et al., 2011). The dorsolateral prefrontal cortex (DLPFC) mask (Brodmann areas 9 and 46) was created using the WFU PickAtlas (Maldjian et al., 2003). Based on 10,000 Monte Carlo simulations using AlphaSim, a cluster of 60 voxels at voxelwise $p < 0.001$ provided a corrected alpha <0.05 for the DLPFC mask. For whole-brain comparisons, cluster of 652 voxels at voxelwise $p < 0.00004$ provided corrected alpha <0.05. We extracted volumes of significant gray matter clusters from the native spaces of all scans in that particular contrast using the MarsBar (Brett et al., 2002) for analysis using SPSS 20 (SPSS, 2011). *COMT* rs4818, *COMT* rs6269 and *RGS4* rs2842018 were selected as we had adequate n in each cell. Genotypes were grouped as GG and AG on *RGS4* rs2842018, and GG and C carriers on *COMT* rs4818. No subjects were homozygous for A allele on *RGS4* rs2842018.

Groups did not differ in age (SZ, 25.08 ± 9.11 years; HC, 24.72 ± 6.62 years; $t = 0.16$, $p = 0.88$), sex (SZ M/F = 21/5; HC M/F = 10/14, $\chi^2 = 2.99$, df 1, $p = 0.084$) or genotype distribution (rs2842018 AG/GG, SCZ 5/21, HC 2/22; rs4818 C carriers/GG, SZ 15/11, SZ 11/13). There was no main effect of diagnosis on the prefrontal volumes. The DLPFC mask showed the main effect of *COMT* rs4818 but not of *RGS4* rs2844018. C carriers on *COMT* rs4818 had smaller cluster volumes (0.44 ± 0.006 cm^3) than those homozygous on G allele (0.48 ± 0.005 cm^3). Whole-brain analysis revealed main effects of *RGS4* rs2842018 on the right fusiform gyrus. Main effect of *COMT* rs4818 was also noted in bilateral fusiform gyri, right inferior frontal gyrus (BA 47), and left medial frontal gyrus (Table 1).

Within the DLPFC mask, significant interaction between *COMT* rs4818 and *RGS4* rs2844018 suggested that *COMT* rs4818 C carriers showed the greatest reduction (≈25%) in the DLPFC cluster volume (0.24 ± 0.01 cm^3) than those homozygous on G allele of *COMT* rs4818 (0.32 ± 0.04 cm^3) when these subjects were heterozygous AG carriers on *RGS4* rs2842018. Against the background of homozygous G allele on *RGS4* rs2842018, *COMT* rs4818 C carriers (0.29 ± 0.04 cm^3) and those homozygous on G allele of COMT rs4818 (0.30 ± 0.03 cm^3) did not differ in the DLPFC cluster volumes ($t = 1.51$, $p = 0.14$). Using a full-factorial model for whole-brain analysis, we noted interactions between AG/GG on *RGS4* rs2842018 and C carriers/GG on *COMT* rs4818 at bilateral fusiform gyri, right inferior frontal gyrus, and left medial frontal gyrus. Again, *COMT* rs4818 C carriers showed the most volume reduction in these regions when they also were heterozygous AG carriers on *RGS4* rs2842018. Genotypes AA on *RGS4* rs2842018 and CC on *COMT* rs9265 were excluded (n = 3) due to inadequate cell size. *COMT* rs6269 was in tight linkage disequilibrium ($r^2 = 1$), had similar distribution as rs4818, and the results were identical to that of rs4818. Within-diagnostic group analysis of the main and interaction effects was not conducted because of small n's in each cell.

Although it is unclear how *RGS4* and *COMT* interactions lead to volumetric reductions, interactions may affect neurotrophic or neurotoxic activities via synaptic dopamine signaling. Therefore, schizophrenia vulnerability at the level of gene–gene interactions may confer risk via maintenance of regulated synaptic transmission and neuronal integrity.

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Table 1

Epistatic interaction: *RGS4* rs2842018 and *COMT* rs4818.[a]

Test of hypothesis	Brain region (Brodmann areas)	SPM statistics						Extracted volume statistics		
		MNI coordinates			k_e	t	p[b]	Main effect		Interaction effect
		x	y	z				*RGS4*	*COMT*	
Prefrontal region	R. inferior frontal gyrus (BA 46)	44	38	16	59	2.54	0.007	F(5,49) = 1.09, p = 0.30	F(5,49) = 10.57, p = 0.002	F(5,49) = 4.52, p = 0.039
Whole brain	R. fusiform gyrus (BA 20)	42	−18	−28	915	4.77	0.00001	F(5,49) = 5.16, p = 0.028	F(5,49) = 10.04, p = 0.003	F(5,49) = 9.74, p = 0.003
	R. inferior frontal gyrus (BA 47)	24	10	−14	656	3.30	0.0005	F(5,49) = 3.89, p = 0.055	F(5,49) = 14.13, p < 0.001	F(5,49) = 4.31, p = 0.043
	L. medial frontal gyrus (BA 6, 8)	−8	14	52	1252	3.24	0.0006	F(5,49) = 0.343, p = 0.56	F(5,49) = 8.12, p = 0.007	F(5,49) = 6.71, p = 0.013
	L. fusiform gyrus (BA 20)	−42	−24	−16	1405	3.11	0.0009	F(5,49) = 1.65, p = 0.22	F(5,49) = 5.37, p = 0.025	F(5,49) = 5.32, p = 0.026

[a] Results for rs6269 are the same as those for rs4818 because subject distributions between rs6269 and rs4818 were identical.

[b] p-Values are corrected for a combined intensity and spatial threshold using AlphaSim simulations.