Brain Structural Evidence of Epistasis between RGS4 & COMT Variations in Schizophrenia

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Abstract

Background: Polymorphisms of the Catechol-O-methyltransferase (COMT) and the Regulator of G protein Signaling 4 (RGS4) genes have independently been implicated in schizophrenia (SZ) genesis. Based on previous findings of statistical and functional evidence of epistatic interactions in the dorsolateral prefrontal cortex (DLPFC), we evaluated our samples for similar associations and, in addition, examined epistatic interactions of RGS4 and COMT polymorphisms on grey matter volumes among SZ and healthy subjects (HS).

Methods: We attempted to replicate the previous findings by examining structural MRI scans from 21 first-episode, antipsychotic-naive schizophrenia or schizoaffective disorder subjects and 19 healthy subjects using both hypothesis free and hypothesis driven tests for interaction using voxel-based morphometry to examine grey matter alterations associated with COMT and RGS4 risk alleles both independently and interactively.

Results: At the whole brain level, we observed RGS4 rs2842018 and COMT rs4818 interactions in the prefrontal, heteromodal association, and temporal regions. The most consistent finding among all interactions was grey matter reductions at the inferior and superior temporal gyri, corresponding to the heteromodal association areas.

Discussion: Our observations suggest that RGS4 and COMT variations are independently and epistatically associated with grey matter reductions at the dorsal components of heteromodal association areas. Previous associations of functional interaction between COMT and RGS4 with altered working memory performance and BOLD responses at the prefrontal cortex in SZ may be mediated by structural changes in the dorsal heteromodal association areas.

Table: Sample Characteristics

<table>
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<tr>
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<th>Schizophrenia (SZ)</th>
<th>Healthy Control Subjects (HS)</th>
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<tbody>
<tr>
<td>Age (in years) mean ± SD</td>
<td>24.16 ± 8.63</td>
<td>24.39 ± 6.29</td>
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<tr>
<td>Gender (%)</td>
<td>Male</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>7</td>
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<tr>
<td>Average SES</td>
<td>41.38 ± 14.66</td>
<td>46.55 ± 11.16</td>
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</table>

Fig 1: rs2842018 (RGS4) & rs4818 (COMT) Interactions

- Significant interactions were observed mainly for the rs2842018 (RGS4) & rs4818 (COMT)
- Individuals homozygous for allele G on both SNPs had significantly higher grey matter volumes on the inferior temporal gyri including the parahippocampal gyrus (red circle), prefrontal region within the Brodmann area 8 (green circle) and the inferior frontal region within the Brodmann area 46/47 (blue circle) and decreased GM volumes at the heteromodal association areas bilaterally (not shown)
- In addition, rs2842018 and rs4818 on COMT; rs2842018 and rs284218 on RGS4 interactions were noted at the middle temporal gyrus
- RGS4 (rs951438) - COMT (rs165559) interactions were noted at the inferior temporal region

Conclusions

Our observations suggest that RGS4 and COMT variations are independently and epistatically associated with grey matter reductions at the prefrontal and dorsal components of heteromodal association areas. Previous associations of functional interaction between COMT and RGS4 with altered working memory performance and BOLD responses at the prefrontal cortex in SZ may be mediated by structural changes in the dorsal heteromodal association areas.

References

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