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Author
Vinogradov, Sophia

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Genetic correlate of cognitive training response in schizophrenia

Rogerio Panizzuttia, Steven P. Hamiltonb,c, Sophia Vinogradovc,d,*

a Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, 21941-590, Brazil
b Institute for Human Genetics, University of California, San Francisco, CA 94143-0794, USA
c Department of Psychiatry, University of California, San Francisco, CA 94143-0984, USA
d Department of Veterans Affairs Medical Center, San Francisco, CA 94121, USA

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Intensive computerized auditory training results in improved cognition for schizophrenia patients, but participants show variation in their cognitive gains and the biological factors that affect the response to training are unknown. Single nucleotide polymorphisms (SNPs) in the catechol-O-methyltransferase (COMT) gene have been related to cognitive function. Here we asked if functional variation in this gene has an impact on the response of schizophrenia patients to cognitive training. We genotyped 48 schizophrenia patients who completed 50 h of computerized cognitive training and analyzed the association between DNA variants in the COMT gene and the improvement in global cognition. Although conventional analyses did not reveal any significant associations, a set-based analysis examining the aggregate effect of common variation in the COMT gene (42 SNPs) suggested association with improvement in global cognition. Eight SNPs, mostly located in the 3′ end of the COMT gene, were nominally associated with improvement in cognition. These data suggest that genotype influences the response to intensive cognitive training in schizophrenia, and may indicate that cognitive training regimens need to be personalized to the underlying biosignatures of each individual patient.

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1. Introduction

In a randomized controlled clinical trial, we found that 50 h of a neuroscience-informed computerized cognitive training program resulted in significant improvements in global cognition in clinically stable outpatients with schizophrenia (Fisher et al., 2009). Of interest, participants in the active training condition showed a large amount of variation in their degree of cognitive improvement, ranging from no change in cognition to improvements of 1.25 SD on a standardized global cognition summary score.

It is likely that multiple neurobiological factors influence the ability to engage in training-induced enhancements in cognition, including genotype. Indeed, one study in 50 schizophrenia patients found that patients with the catechol-O-methyltransferase (COMT) Met allele (rs4680) made greater gains in cognitive flexibility after computerized cognitive training than patients without the Met allele (Rosia et al., 2007). However, a second study of 87 subjects engaged in therapist-guided (non-computerized) cognitive remediation, found instead no relationship between COMT genotype and treatment outcome (Greenwood et al., 2011). Functional SNPs in the COMT gene predispose to impaired performance in working memory in healthy subjects and to significant improvement in working memory following treatment with antipsychotic medication in patients with schizophrenia (Egan et al., 2001; Bertolino et al., 2004; Meyer-Lindenberg et al., 2006). Given previous findings of an association between the COMT gene and cognitive functioning in healthy subjects and in patients with schizophrenia, we hypothesized that variation in this gene would have an impact on the response of schizophrenia patients to neuroplasticity-based computerized cognitive training. Thus we genotyped 48 schizophrenia outpatients who had participated in our cognitive training studies and analyzed the association between DNA variants in the COMT gene and training-induced improvement in global cognition, assessed as a standardized summary score.

Abbreviations: COMT, catechol-O-methyltransferase; IQ, intelligence quotient; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MDS, multidimensional scaling vectors; SNP, single nucleotide polymorphism.

* Corresponding author. Department of Psychiatry, UCSF/SFVAMC, 116A, 4150 Clement Street, San Francisco, CA 94121, USA. Tel.: +1 415 221 4810x3106; fax: +1 415 379 5574.
E-mail address: Sophia.Vinogradov@ucsf.edu (S. Vinogradov).
2. Methods

2.1. Subject sample and study procedure

All subjects from our two randomized controlled trials of cognitive training in schizophrenia, for whom we had access to DNA, were included in this study. The trials were registered on ClinicalTrials.gov: one for adults with persistent schizophrenia (NCT ID: NCT00312962) and one for young adults within 5 years of schizophrenia onset (NCT ID: NCT00669488). Inclusion criteria were: Axis I diagnosis of schizophrenia (determined by the DSM-IV-SCID); no substance dependence or current substance abuse; good general physical health; and English as first language. Subjects were clinically stable outpatients who were stratified by age, education, gender, and symptom severity, and randomly assigned to either active computerized training or a computer games control condition (90 h/10 weeks for the persistently ill adults; 40 h/8 weeks for the recent-onset subjects). Here we report results from 48 subjects who completed the cognitive training and on whom we also collected venous blood samples and extracted DNA from whole blood using standard procedures. All subjects underwent cognitive and clinical testing before and after cognitive training. All subjects provided written informed consent for study participation, and received nominal payment for each successful day and week of participation that was contingent on attendance only. Sample demographics are listed in Table 1.

2.2. Cognitive assessments

Cognition was assessed via MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) recommended measures (Nuechterlein et al., 2008). Raw cognitive scores were converted to Z-scores using published normative data, and cognitive change was computed as the difference post-training minus baseline scores. A Global Cognition composite score was computed as the mean of the 6 MATRICS-defined cognitive domains: Speed of Processing, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, and Problem Solving.

2.3. Neuroplasticity-based cognitive training

The neuroplasticity-based computerized cognitive training exercises were provided free of charge by Posit Science Inc. and have been described in detail elsewhere (Fisher et al., 2009). In brief, subjects were driven to make progressively more accurate distinctions about the spectrtemporal fine structure of auditory stimuli and speech under conditions of increasing working memory load and to incorporate and generalize those improvements into language comprehension and verbal working memory.

2.4. Definition of phenotype of interest

We assessed cognitive improvement as measured by the change from baseline to post-training in Global Cognition, a composite score previously used by us which showed a significant effect of neuroplasticity-based computerized cognitive training (Fisher et al., 2009). The schizophrenia patients sampled in this study showed a mean Z-score improvement in Global Cognition of 0.32 (S.D. = 0.44) which is very similar to the mean Z-score improvement of 0.36 previously reported by us (Fisher et al., 2009). Improvement in Global Cognition after training was mainly driven by effects on verbal learning and memory and verbal working memory. Training had no significant effect on measures of visual processing, indicating the targeted nature of the training approach.

2.5. Genotyping

Samples were genotyped using Illumina OmniExpress SNP arrays, which contain 731,442 SNPs. We found very high sample and SNP call rates in the genotyped samples. There were no gender misidentifications. SNPs chosen for analysis had minor allele frequencies \( > 0.01 \) and call rates \( > 0.95 \). All individuals had \( > 0.95 \) completeness rates (i.e., \( > 95\% \) of SNPs were called). A total of 2822 SNPs failed missingness test \( (> 0.05) \) and 30,103 SNPs failed frequency test (minor allele frequencies \( < 0.01 \)). Due to the heterogeneous nature of sample and small sample size, Hardy-Weinberg Equilibrium violations were not used for filtering.

A pruning procedure was used to obtain SNPs for clustering analysis to correct the COMT gene SNP data by genetic ancestry. A total of 129,192 SNPs were used to generate an identity-by-state matrix, and multidimensional scaling vectors (MDS) were calculated. Samples clustered as expected, based on self-reported ancestry.

We extracted SNPs found on Illumina OmniExpress SNP arrays that were within the COMT gene boundaries and up to 5000 base pairs (5 kb) from the gene. The size of the region covered was 38,233 base pairs, and included 56 SNPs.

2.6. Analysis

We sought to determine which variables were associated with improvement in Global Cognition. We tested demographic variables and IQ as well as 10 MDS vectors. Ethnicity was reduced to three variables, Caucasian, Asian, and Asian. No variable was associated with Global Cognition improvement.

We followed an approach that describes the gene as the basis of each test, rather than the individual SNP (Neale and Sham, 2004). This approach was implemented in PLINK (Purcell et al., 2007), and relies on permutation to derive empirical \( p \)-values that are adjusted for the 42 SNPs within the COMT gene by taking account of the linkage disequilibrium between these SNPs. The resulting set-based test is thought to provide enhanced power to detect associations than tests of individual SNPs, particularly when a number of SNPs within a gene are correlated with the trait (Ott and Hoh, 2003). We determined the interaction test statistic for each SNP, followed by an averaging of test statistics for top-ranked SNPs within the gene set. We used the following thresholds for analysis, \( r^2 = 0.5 \), SNP number for subsetting = 5, and \( p \)-value threshold for subsetting = 0.05. Permutation of the dataset 10,000 times was then used to approximate the significance for the set statistics. This accounts for SNP and test correlation, and provides an empirical measure of significance at the gene (set) level (Perlis et al., 2008). We also analyzed individually the 42 SNPs for Global Cognition improvement and reported the association beta (BETA), and the \( p \)-value (p).

3. Results and discussion

First, we tested the association of improvement in Global Cognition and demographics, IQ, and genetic ancestry as approximated with 10 multidimensional scaling vectors derived from genome-wide SNP data. No variable was nominally associated with improvement in Global Cognition.

Gene-based analyses examined the aggregate effect of common variation in COMT gene (42 SNPs) on Global Cognition improvement. We found a significant empirical \( p \)-value of 0.02 after 10,000 permutations, suggesting that the aggregate effect of variation in the COMT gene is associated with cognitive improvement after computerized training.

At the single SNP level, cognition improvement was nominally associated with the SNPs: rs165599 (BETA = -0.29, \( p < 0.01 \)), rs9265 (BETA = -0.27, \( p < 0.01 \)), rs9939891 (BETA = -0.33, \( p < 0.05 \)), rs758373 (BETA = -0.33, \( p < 0.05 \)), rs2239395 (BETA = -0.33, \( p < 0.05 \)), rs2240713 (BETA = -0.36, \( p < 0.05 \)), rs739368 (BETA = 0.66, \( p < 0.05 \)) and rs1544325 (BETA = 0.19, \( p < 0.05 \)) (Table 2). None of the SNPs met the single SNP significance threshold after Bonferroni adjustment for 42 tests of \( p = 0.0012 \). Additionally, given the impact of medications with anticholinergic activity on the response to cognitive training (Vinogradov et al., 2009), we examined the associations adjusting for anticholinergic burden, and observed no change in the results (data not shown).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (S.D.)</td>
<td>33.6 (13.1)</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>70.8</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>52.1</td>
</tr>
<tr>
<td>Caucasian</td>
<td>12.5</td>
</tr>
<tr>
<td>Asian</td>
<td>22.9</td>
</tr>
<tr>
<td>Other</td>
<td>12.5</td>
</tr>
<tr>
<td>IQ, mean (S.D.)</td>
<td>102.3 (14.3)</td>
</tr>
<tr>
<td>Years of illness, mean (range)</td>
<td>12.9 (2.0-42)</td>
</tr>
<tr>
<td>Z-Score change in global cognition, mean (S.D.)</td>
<td>0.32 (0.44)</td>
</tr>
<tr>
<td>PANS total score, mean (S.D.)</td>
<td>64.4 (17.7)</td>
</tr>
<tr>
<td>PANS positive, mean (S.D.)</td>
<td>15.8 (5.7)</td>
</tr>
<tr>
<td>PANS negative, mean (S.D.)</td>
<td>16.3 (6.4)</td>
</tr>
<tr>
<td>Dose of antipsychotic medication, mean (S.D.) of chlorpromazine-equivalents (mg/day)</td>
<td>317.3 (420.9)</td>
</tr>
<tr>
<td>Serum anticholinergic burden (Minzenberg et al., 2004), mean (S.D.) of atropine-equivalents (pmol/ml)</td>
<td>4.2 (11.5)</td>
</tr>
</tbody>
</table>
The COMT variant rs165599 interacts with the COMT Met allele (rs4680) in predicting inefficient prefrontal working memory response (Meyer-Lindenberg et al., 2006). In a post hoc analysis, we did not observe a significant epistatic interaction between rs4680 and rs165599 (\(BETA = 0.04, p = 0.78\)) using the linear model \(Y = b_0 + b_1A + b_2B + b_3AB + e\), where A and B represent each SNP, and the interaction test is based on coefficient b3. Fig. 1 show the relationship between rs165599 and the improvement in Global Cognition. Individuals with the A/A genotype showed a mean Z-score change in global cognition of 0.53 (S.D. 0.31) in those with the G/G genotype. In a post hoc analysis, this improvement was significantly different between A/A homozygotes and G/G homozygotes (\(p < 0.05\)). Overall, the most associated SNPs, presumably driving much of the statistical signal, lie at the 3’ end of the COMT gene (Fig. 1).

We do not know if the findings we report here are specific to schizophrenia subjects, or if they would also be seen in healthy subjects. In addition, we cannot say whether the observed associations are found only in the kind of neuroplasticity-based computerized auditory training studied here, or whether they would also be found in other successful cognitive, behavioral, or pharmacological interventions. Finally, we cannot rule out that our results may reflect some complex interaction between COMT genotype and medication regimen used in our participants with schizophrenia. Moreover, the analysis method derived from Ott and Hoh (2003) has not been widely used in genetic association studies, and thus the current study must be regarded only as hypothesis-generating work. It is noteworthy that the use of permutation provides a means for reducing type I error.

In sum, our preliminary data suggest the possibility that a functional variant in the COMT gene may influence the response to intensive “neuroplasticity-based” computerized cognitive training in patients with schizophrenia. Indeed, a z-score change of 0.5 S.D. in global cognition may be clinically meaningful, as seen in individuals with the A/A genotype; this is in contrast to individuals with the G/G phenotype, who showed no change in global cognition after the intervention. Further research must determine if this finding is replicated in larger samples, and if it is observed in other clinical populations who undergo cognitive training. If yes, “cognitive genotype” may represent an important predictor for treatment response in patients undergoing cognitive neurotherapeutics, and may indicate fruitful research pathways for novel agents that can enhance clinical outcomes.

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### Conflict of interest

Dr. Vinogradov is a consultant to Brain Plasticity Institute, Inc., a company with a financial interest in computerized cognitive training software. She is also a consultant to Genentech, Amgen, and Hoffman LaRoche. Drs. Panizzutti and Hamilton declare no conflicts of interest.

### References


