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Genetic correlate of cognitive training response in schizophrenia

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ABSTRACT

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 (Bosia 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, intelligency quotient; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MDS, multidimensional scaling vectors; SNP, single nucleotide polymorphism.

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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 ClinicalTrial.gov: one for adults with persistent schizophrenia (NCT ID: NCT00312 962) and one for young adults within 5 years of schizophrenia onset (NCT ID: NCT00694 889). 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 cognitive training or a computer games control condition (50 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 spectrotemporal 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.

Table 1
Study subjects.

Measure	Value
Age, mean (S.D.)	33.6 (13.1)
Gender, % male	70.8
Ethnicity (%)	
Caucasian	52.1
African-Americans	12.5
Asian	22.9
Other	12.5
IQ, mean (S.D.)	102.3 (14.3)
Years of illness, mean (range)	12.9 (0.2–42)
Z-Score change in global cognition, mean (S.D.)	0.32 (0.44)
PANSS total score, mean (S.D.)	64.4 (17.7)
PANSS positive, mean (S.D.)	15.8 (5.7)
PANSS negative, mean (S.D.)	16.3 (6.4)
Dose of antipsychotic medication, mean (S.D.) of chlorpromazine-equivalents (mg/day)	317.3 (420.9)
Serum anticholinergic burden (Minzenberg et al., 2004), mean (S.D.) of atropine-equivalents (pmol/ml)	4.2 (11.5)

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 for analysis to correct the *COMT* gene SNP data by genetic ancestry. A total of 329,192 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, African-American, 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, $p < 0.01$), rs5993891 (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 2
Association between training-induced change in cognition and SNPs in *COMT* gene.

SNP	BP	BETA	*p*
rs165599	19,956,781	−0.29	0.004
rs9265	19,957,631	−0.27	0.006
rs5993891	19,959,746	−0.33	0.021
rs758373	19,960,394	−0.33	0.021
rs2239395	19,962,203	−0.33	0.021
rs2240713	19,961,101	−0.36	0.027
rs739368	19,939,096	0.66	0.040
rs1544325	19,931,668	0.19	0.043

The table lists the SNP ID (SNP), its position on the chromosome (BP), the association beta (BETA), and the *p*-value (*p*). *p*-values <0.05 are shown.

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 $Y \sim b0 + b1.A + b2.B + b3.AB + e$, 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 improvement in cognition of 0.53 (S.D. = 0.52), comparing to −0.04 (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.

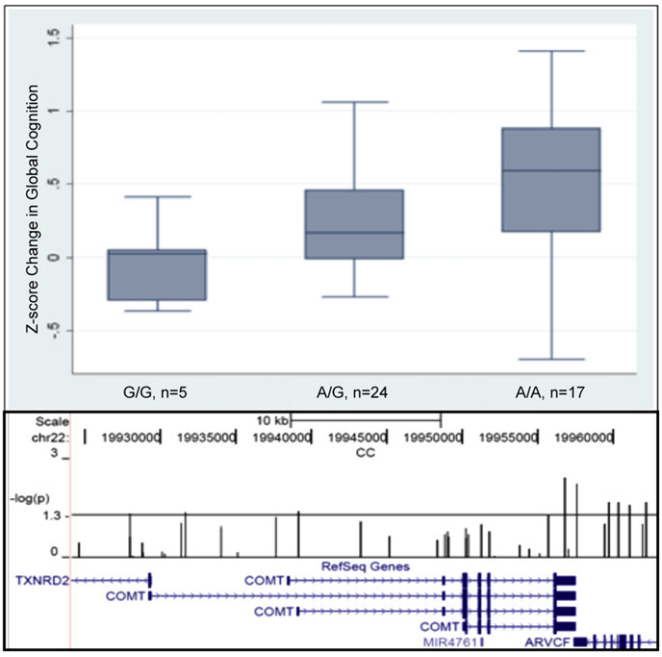

Fig. 1. Variants in *COMT* gene are associated with training-induced change in cognition in schizophrenia. *Upper panel*, genetic association between *COMT* SNP rs165599 and phenotype defined by "Z-score change in global cognition" ($p = 0.004$). The graph represents changes in cognition with relation to the three SNP genotypes, with sample size for each genotype. *Lower panel*, regional associations plot showing SNPs in *COMT* ±5 kb, with the −($\log_{10}$ *p*-value) for the logistic regression for the change in cognition. Genes are depicted on UCSC genome build hg19, showing predicted alternative *COMT* splicing variants.

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.

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