Executive Subprocesses in Working Memory

Relationship to Catechol-O-methyltransferase Val158Met Genotype and Schizophrenia

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Background: Cognitive dysfunction in the working memory domain seems to be under genetic control and is a candidate intermediate phenotype in schizophrenia. Genes that affect working memory processing may contribute to risk for schizophrenia.

Methods: Working memory and attentional processing were assessed in a large and unselected sample of schizophrenic patients, their healthy siblings, and controls (N=250). We used the n-back task because it allows parametric analysis over increasing loads and delays and parsing of subcomponents of executive cognition and working memory, including temporal indexing and updating. Participants were genotyped for catechol-O-methyltransferase (COMT) at the Val158Met locus, which has been shown to affect executive cognition and frontal lobe function, likely because of genetically determined variation in prefrontal dopamine signaling.

Results: A significant COMT genotype effect was found: Val/Val individuals had the lowest n-back performance, and Met/Met individuals had the highest performance. Effects were similar in the 1- and 2-back conditions and across all groups, whereas no effect on the Continuous Performance Test was seen, suggesting that genotype was not affecting working memory subprocesses related to attention, load, or delay. Siblings also performed significantly worse than controls on the 1- and 2-back conditions.

Conclusions: A prefrontal cognitive mechanism common to the 1- and 2-back conditions, probably executive processes involved in information updating and temporal indexing, is sensitive to the COMT genotype. Considering that the 3 participant groups were affected more or less linearly by the COMT genotype, an additive genetic model in which the effect of allele load is similar in its effects on prefrontally based working memory irrespective of the genetic or environmental background in which it is expressed is suggested. The findings also provide convergent evidence that an intermediate phenotype related to prefrontal cortical function represents a viable approach to understanding neuropsychiatric disorders with complex genetic etiologies and individual differences in cognition.

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COGNITIVE DYSFUNCTION in the working memory domain is an attractive candidate intermediate phenotype in schizophrenia. Patients with schizophrenia reliably demonstrate working memory impairments using a variety of cognitive tasks, and such impairments are not highly correlated with psychotic symptoms, are stable over time, and are usually unaffected by neuroleptic medications, increasing their potential value as a trait characteristic. Data from a series of family and twin studies suggest that impairment in working memory or cognitive control is also a heritable phenotype related to risk for schizophrenia, suggesting that it is a plausible intermediate phenotype. However, some of these studies involved small sample sizes and included parents and siblings (with possible confounds due to age and generation).

Evidence that working memory deficits are heritable and associated with susceptibility to schizophrenia implicates genes that affect neuronal functions involved in working memory as potential schizophrenia susceptibility genes. Egan et al recently reported that a functional polymorphism in the COMT gene that encodes enzyme variants of differing activity predicted performance on an executive function task, the Wisconsin Card Sorting Test (WCST), presumably via its role in prefrontal dopamine signaling. The allele associated with poorer executive cognition (Val) was also preferentially transmitted by heterozygotic parents to their schizophrenic offspring in family trios, suggesting that the effect of
this polymorphism on prefrontal function increases risk for manifesting schizophrenia. Evidence that the catechol-
O-methyltransferase (COMT) genotype affects executive
cognition has been confirmed by several other re-
search groups,22,23 as has distorted transmission of Val
alleles from heterozygotic parents to their schizo-
phrenic offspring.23 In the present study, we attempted
to further elucidate the relationship of deficits in execu-
tive cognition to the COMT genotype and to genetic risk
for schizophrenia. Because the WCST is a complex prob-
lem-solving test involving many cognitive components
(including information maintenance, abstraction, set shift-
ing, and inhibition of previously rewarded responses),
it is difficult to dissect the specific components of the task
that may have accounted for the elevated relative risk (RR)
of impairment in siblings or that may have been prefer-
tentially sensitive to the effect of the COMT genotype. In
the present study, we sought to parse some of the sub-
processes of executive function by using the n-back task,
which engages the working memory system in maintain-
ing and updating information over short delays. Like the
WCST, this task has been shown to physiologically ac-
tivate the working memory cortical network, which in-
cludes dorsolateral prefrontal and parietal cortices.25-27
However, in contrast to the WCST, the n-back task can
be parametrically varied in terms of increasing set size
or load and in delay, which are imposed over the 0-, 1-, and
2-back conditions. Because it has been suggested that
“slowness” in initiating encoding or decision making ampli-
ifies information maintenance difficulties,28 we also ob-
tained measures of reaction time (RT) during perform-
ance of the n-back task. To address the possibility that
deficits during the n-back task might be manifestations of
attentional impairments, results of the n-back task were
contrasted with those of the Continuous Performance Test
(CPT) of attentional vigilance.

We made several predictions based on evidence that
the COMT genotype has an impact on prefrontal corti-
cal dopamine signaling and on the presumed biological
mechanisms related to information processing during the
n-back task and the CPT: (1) if prefrontal cortical dopa-
mine signaling is critical for attention to a fixed target,
then the 0-back condition or a CPT task should prove
sensitive to COMT effects; (2) if load or delay is critical,
then evidence for a difference in effects of the COMT geno-
type between the 1- and 2-back conditions should be pres-
ent; but (3) if information updating (an aspect of pro-
cessing independent of load and delay) is key and is
reflected in demands for continuous selection and dese-
lection of target items that are common to both levels of
the task, then similarity in effects of the COMT geno-
type on 1- and 2-back conditions should be observed. We
also made predictions about the relationship between ge-
netic risk for schizophrenia and subprocesses of work-
ing memory: (1) if attentional processes in working
memory are related to genetic factors in schizophrenia,
we would expect that siblings would show increased RR
for abnormalities on the 1-back condition and the CPT;
(2) if delay- or load-based processes are related to ge-
netic risk, we would expect greater RR for deficits on the
2-back condition than on the 1-back condition; but (3)
if information-updating processes are reflections of ge-
netic susceptibility factors, we would expect no differ-
ences in RR for deficits on the 1- and 2-back conditions.
We also propose that if COMT genotype effects are equiva-
ient across the large and unselected groups of patients
with schizophrenia, siblings (who were neither psy-
chotic nor had schizophrenia spectrum diagnoses), and
controls, then an additive genetic model is implicated,
whereas if group × genotype interactions are present on
n-back performance, an epistatic model is implicated.

### METHODS

#### PARTICIPANTS

Participants were recruited from local and national sources as
volunteers for the “CBBN/NIMH Sibling Study.” Methods of as-
certainment and potential biasing have been described else-
where.24,25 Briefly, all participants gave written informed
consent to be part of an institutional review board–approved
protocol; families had to have 2 eligible siblings, at least 1 of
whom met DSM-IV criteria30 for schizophrenia or schizoaf-
ductive disorder, depressed type. Participants had to be aged 18 to
60 years and have a premorbid IQ greater than 70. Individuals
with significant medical conditions that might affect central ner-
vous system function, histories of head trauma with loss of con-
sciousness for longer than 5 minutes, or alcohol or other drug
abuse within the past 6 months were excluded.

Thus, each index case had at least 1 full sibling. No twins
were included. Average duration of illness in the index cases
was 12 years. All index cases were receiving neuroleptic medi-
cation. No sibling with a history of schizophrenia, schizoaf-
ductive disorder, or schizophrenia spectrum disorder (schizo-
typal, paranoid, schizoid personality or delusional disorder) was
included in the analyses. All participants, including controls,
underwent a Structured Clinical Interview for Diagnostic and
Statistical Manual of Mental Disorders diagnostic interview.
Demographics of the sample are listed in Table 1. Two hundred
fifty individuals participated in the n-back task, of which 68
were controls, 74 were index cases, and 108 were siblings. Six
percent of the participants were African American; the remain-
der were of European ancestry. Age did not differ significantly
among the groups (ANOVA) (P = .24). Wide Range Achievement Test Reading, an
index of premorbid intelligence,7 did not differ significantly
among the groups (P = .26). Current IQ, however, differed among
the groups significantly. By post hoc t test contrast, index cases
differed from their sibling and controls (P < .001), consistent with earlier studies.

Other demographic variables were examined in a series of χ²
analyses. Sex ratios differed significantly between the
groups: more males were in the index group. Histories of al-

### Table 1. Demographic Characteristics of the Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Index Cases (n = 74)</th>
<th>Siblings (n = 108)</th>
<th>Controls (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>37 (8)</td>
<td>37 (9)</td>
<td>35 (10)</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>59</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>Psychiatric diagnosis, %</td>
<td>NA</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Alcohol or other drug abuse, %</td>
<td>19</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>IQ, mean (SD)</td>
<td>92 (12)</td>
<td>104 (12)</td>
<td>107 (9)</td>
</tr>
<tr>
<td>Wide Range Achievement Test score, mean (SD)</td>
<td>103 (11)</td>
<td>105 (12)</td>
<td>106 (11)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
cohoh or other drug abuse differed among the groups and were higher in index cases and siblings. The proportion of individu-
alms in the sibling group receiving a nonpsychotic psychiatric diagnosis was higher than in the control group. Nearly all non-
psychotic diagnoses, when present, were for major depression (past).

TESTS

N-Back Task

In the present version of the n-back task,27 a number between 1 and 4 was displayed every 1.8 seconds on a computer screen. Stimulus duration was 200 milliseconds. In the 0-back condi-
tion, the participant viewed the number on a screen (ie, 1, 2, 3, or 4) and pressed a corresponding response button. This condition does not involve a memory load per se; it involves at-
tention and stimulus response mapping. In the 1-back condition, in which a working memory load is imposed above and beyond instructional context, the participant views the first stimulus but does not respond; the individual then views the second stimulus and responds by pressing the button corre-
sponding to the first stimulus, and so on. Thus, the individual must continuously recall information that is “1 back” in a se-
quence. In the 2-back condition, the participant must continu-
ously recall the stimulus that was “2 back” and press its cor-
responding button. Thus, compared with the 1-back condition, the 2-back condition involves a longer delay from stimulus pre-
sentation to response and a greater information load to be held in working memory.

N-back performance was scored as the percentage of cor-
rect trials within each condition, followed by an arc sin trans-
formation of the data to normalize the distribution. Partici-
pants received six 28-second trials of each condition (14 stimuli per trial), separated by brief rest periods. In addition, RT data were obtained for each response to the n-back task and aver-
aged for each condition of the n-back (0-, 1-, and 2-back) for each participant. All mean RTs were between 200 and 1800 mil-
seconds and were log transformed to reduce variance. We con-
sidered accuracy to be our primary measure and n-back RT to be a secondary measure given that we wanted to compare n-
back to other accuracy-based tests, that RT and accuracy dur-
be a secondary measure given that we wanted to compare n-

Other Measures

The CPT “1-9 Distractibility Version”30 was used to assess at-
tention and vigilance by requiring that participants view a con-
secutive sequence of digits (presented at the rate of 1 per second) and respond to a fixed target sequence (1 followed by 9). The measure of accuracy that was used was Z as it takes into account both omission and commission errors. IQ was derived from a 4-subtest short form of the Wechsler Adult In-
telligence Scale–Revised31 composed of Similarities, Arith-
matic, Picture Completion, and Digit Symbol. The Wide Range Achievement Test Reading32 standardized score was based on word pronunciation.

COMT Genotyping

Blood samples were collected from all participants, and DNA was extracted. The COMT Val158Met genotype was deter-
mained as a restriction fragment length polymorphism in exon 4 by using the method detailed by Egan et al.19 Twenty-three participants genotyped in this study had not participated in the study by Egan et al.19

DATA ANALYSES

Parametric Statistics

To determine whether COMT genotype and diagnostic group differences were present in phenotypes (n-back and CPT), all participants were included, but family membership was treated as a random factor, and diagnosis and genotype were treated as fixed effects in a mixed model (SAS Mixed-Model ANOVA).34 Such an approach can model and minimize the nonindepen-
dence of multiple members of a family. The dependent mea-
sures were treated as continuous variables. We also examined the relative independence of speed (RT) and accuracy in the n-back task through the use of a mixed-model analysis of co-
variance in which accuracy or RT served as a covariate. Effect sizes were computed to compare COMT genotype and diagno-
sis effects on 1- and 2-back accuracy performances. As neither sex nor age correlated significantly with n-back performance, we did not use these variables as covariates.

Nonparametric Statistics

We computed RR, which compares the frequency of a pheno-
sis in siblings with that in controls,35 by dividing the propor-
tion of “affected” cases in the sibling sample by the proportion of “affected” cases in the control sample. This measure pro-
vides useful parameters for assessing the suitability of a can-
didate phenotype for genetic study. We thus used RR to ad-
dress whether impairment in working memory in siblings can be considered a susceptibility phenotype for schizophrenia. We defined affected status for an individual as 1 or 2 SDs below the mean of the control group for a given cognitive measure. By convention, an RR of less than 2 is considered small, be-
tween 2 and 4 moderate, and greater than 4 large.
vs Met/Met genotype contrast for 1-back performance was 0.41 and for 2-back performance was 0.44.

Diagnostic group means for performance on the 0-, 1-, and 2-back conditions are shown in Figure 2. The index cases and siblings performed more poorly than the controls in the 1- and 2-back conditions. A main effect of diagnostic group was present for each of the n-back conditions as noted previously (Table 2). Post hoc contrasts of adjusted means indicated that index cases differed from their siblings and from controls. Post hoc contrasts of adjusted means indicated that in the crucial comparison between siblings and controls, near significant differences were present on the 1- and 2-back conditions but not on the 0-back condition. The effect sizes of the sibling-control comparison were similar: 0.47 for 1-back and 0.51 for 2-back (Cohen d). Effect sizes for the index case–control contrasts were considerably greater than 1.

N-Back RT and Its Relationship to Accuracy

Next, we analyzed RTs obtained during n-back performance in mixed-model ANOVAs in which diagnosis and genotype were treated as fixed effects and family as a random factor. For the 1- and 2-back conditions, (1) siblings and index cases were slower than controls and

Table 2. Mixed-Model Analyses of Variance for the N-Back Tasks

<table>
<thead>
<tr>
<th>Condition</th>
<th>df or Difference</th>
<th>F or t Test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-Back condition</td>
<td>Diagnosis</td>
<td>2,169†</td>
<td>18.59§</td>
</tr>
<tr>
<td></td>
<td>Genotype</td>
<td>2,169†</td>
<td>2.14§</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × genotype</td>
<td>4,169†</td>
<td>1.59§</td>
</tr>
<tr>
<td></td>
<td>Control vs index</td>
<td>0.21‡</td>
<td>4.76</td>
</tr>
<tr>
<td></td>
<td>Control vs sibling</td>
<td>0.004‡</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Index vs sibling</td>
<td>−0.27‡</td>
<td>5.64</td>
</tr>
<tr>
<td>1-Back condition</td>
<td>Diagnosis</td>
<td>2,173†</td>
<td>30.01§</td>
</tr>
<tr>
<td></td>
<td>Genotype</td>
<td>2,173†</td>
<td>2.77§</td>
</tr>
<tr>
<td></td>
<td>Diagnosis × genotype</td>
<td>4,173†</td>
<td>0.66§</td>
</tr>
<tr>
<td></td>
<td>Control vs index</td>
<td>0.50‡</td>
<td>6.91</td>
</tr>
<tr>
<td></td>
<td>Control vs sibling</td>
<td>0.12‡</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>Index vs sibling</td>
<td>−0.39‡</td>
<td>−6.27</td>
</tr>
<tr>
<td></td>
<td>Val/Val vs Val/Met</td>
<td>0.13‡</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td>Val/Val vs Met/Met</td>
<td>0.15‡</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td>Val/Met vs Met/Met</td>
<td>−0.02‡</td>
<td>−0.32</td>
</tr>
<tr>
<td>2-Back condition</td>
<td>Diagnosis</td>
<td>2,173†</td>
<td>23.13§</td>
</tr>
<tr>
<td></td>
<td>Genotype</td>
<td>2,173†</td>
<td>2.57§</td>
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<tr>
<td></td>
<td>Diagnosis × genotype</td>
<td>4,173†</td>
<td>0.33§</td>
</tr>
<tr>
<td></td>
<td>Control vs index</td>
<td>0.39‡</td>
<td>6.13</td>
</tr>
<tr>
<td></td>
<td>Control vs sibling</td>
<td>0.09‡</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>Index vs sibling</td>
<td>−0.29‡</td>
<td>−5.44</td>
</tr>
<tr>
<td></td>
<td>Val/Val vs Val/Met</td>
<td>0.06‡</td>
<td>1.14</td>
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<tr>
<td></td>
<td>Val/Val vs Met/Met</td>
<td>0.14‡</td>
<td>2.27</td>
</tr>
<tr>
<td></td>
<td>Val/Met vs Met/Met</td>
<td>−0.08‡</td>
<td>−1.36</td>
</tr>
</tbody>
</table>

*Family is treated as a random effect. Post hoc contrasts are reported if main effect is P<.10.
†Degrees of freedom.
‡Difference.
§F statistic.
|| t Test.

Figure 1. Effect of the COMT genotype on participant performances in the 0-back (A), 1-back (B), and 2-back (C) conditions. Error bars represent SEM.

(2) COMT had a near significant effect on RT such that the Val/Val genotype was associated with slower RTs than were Met genotypes. Specifically, in the 0-back condition, although a main effect of diagnosis was present (F_{2,150}=27.58; P<.001), no significant effect of genotype was discerned (F_{2,150}=2.53; P=.11). An interaction between the two was not present (F_{4,150}=0.57; P=.62). Post hoc contrasts of adjusted means were significant by t test
for the Val/Val vs Val/Met contrast. Post hoc contrasts on adjusted means were significant by t test ($P < .03$ for all) such that all diagnostic groups differed from each other in RT. In the 2-back condition, a main effect of diagnosis was present ($F_{2,150} = 11.79; P < .001$), as was a trend effect of genotype ($F_{2,150} = 2.46; P = .09$). An interaction between the two was not present ($F_{4,150} = 0.17; P = .96$). Post hoc contrasts on adjusted means were significant by t test at $P = .03$ for the Val/Val vs Met/Met contrast. Post hoc contrasts on adjusted means were significant by t test such that all diagnostic groups differed from each other in RT at $P < .001$, with the exception of siblings vs controls ($P = .06$).

Correlations between n-back accuracy and RT were consistently negative and significant such that better performance was associated with faster responses in all groups. In controls, correlations between n-back accuracy and RT were –0.67 and –0.68, respectively ($P < .001$); in siblings, the correlations were –0.54 and –0.51 ($P < .001$); and in index cases, the correlations were –0.37 ($P = .002$) and –0.27 ($P = .03$). However, when accuracy served as a covariate in the mixed-model ANOVAs for n-back RTs, the main effects of genotype and diagnosis became nonsignificant in all conditions of the n-back task (for all: $F < 1.25; P > .29$); conversely, when RT served as a covariate for n-back performance accuracy, the main effect of genotype became nonsignificant (for all: $F < 1.96; P > .14$). These results suggest, at the very least, that accuracy and RT monitor overlapping processes during performance of this task.

**Performance and RR**

Because the parametric post hoc analyses suggested at least a trend for differences between controls and siblings, we examined RR, a nonparametric measure of the frequency of impairment in the sibling group. The proportions of affected siblings (and index cases) for accuracy on the 1- and 2-back tasks, defined as performance below –1 or –2 SD of the mean of the control group, are displayed in Figure 3. Thus, the RR for the 1-back condition was 1.9 at –1 SD and 2.8 at –2 SD (both significant by $\chi^2$ at $P = .04$). For the 2-back condition, RR was 1.7 at –1 SD and 3.9 at –2 SD (the latter significant by $\chi^2$ at $P = .04$).

The RR for 1-back RT was 2.0 at –1 SD and 0.52 at –2 SD (nonsignificant by $\chi^2$ at $P = .08$ and $P = .63$, respectively). For the 2-back condition, the RR was 2.4 at –1 SD and 2.6 at –2 SD (the former significant by $\chi^2$ at $P = .03$ and the latter nonsignificant by $\chi^2$ at $P = .36$), owing to small cell sizes. Thus, the significantly elevated frequencies of impairment provided convergent evidence that the 1- and 2-back conditions are susceptibility measures.

**OTHER MEASURES (CPT AND IQ)**

We also used a mixed-model ANOVA to examine the impact of COMT genotype and diagnostic group on CPT performance. In this test, no executive subprocesses involving updating are demanded; instead, attention to a fixed target is required. No effect of genotype was ob-
served (F3,160 = 1.36; P = .26). A main effect of diagnosis was present (F3,160 = 16.94; P < .001); however, post hoc contrasts did not reveal a significant difference between siblings and controls. A genotype × diagnostic group interaction was not present (F3,160 = 0.96; P = .43). The CPT was not subject to ceiling effects, as was the 0-back condition. Genotype did not have a significant effect on IQ (F2,175 = 2.15; P = .12), although diagnostic group effects were present (F2,175 = 30.47; P < .001). No diagnostic group × genotype interaction was present (F2,175 = 0.65; P = .51).

In this study, we sought to clarify the subcomponents of abnormal executive function that are related to the COMT genotype and genetic risk for schizophrenia. Using the n-back task, we examined the different effects of varying load and delay and updating. We assessed whether these various subprocesses are related to genetically controlled variation in COMT. Because dopamine modulation of prefrontal cortical neurons is an important factor in working memory function for learning goal-directed sequences and for cognitive control,36,37 it was reasonable to predict that a genetic polymorphism in the COMT gene that seems to affect the efficiency by which dopamine is inactivated at prefrontal synapses could affect prefrontal-mediated information processing, as in our previous study and several subsequent studies.19,22,23 Evidence for a Val allele load effect was found in the present study: the Val/Val genotype (associated with high enzyme activity and presumably the lowest prefrontal dopamine signaling) was associated with the lowest (and slowest) performance, and the Met/Met allele (associated with a 3- to 4-fold reduction in enzyme activity and presumably more robust prefrontal dopamine signaling) was associated with the highest (and fastest) performance in controls, siblings, and patients. Heterozygotic individuals tended to lie between the two.

Consideration of the finding that no group × genotype interactions were present in the face of a main effect of COMT genotype indicates that the 3 groups (controls, siblings, and index cases) were affected more or less equivalently by COMT. Effect sizes were also similar within each group. These findings are also theoretically consistent with an additive genetic model in which the effect of allele load is similar in its effects on prefrontally based working memory irrespective of the genetic or environmental background in which it is expressed. Presumably, the accumulation of many critical disadvantageous alleles and environmental risk factors shifts an individual beyond some liability threshold.

We also examined whether COMT genotype has an effect on tasks that make fewer demands on the working memory system. First, we examined a CPT of attention and vigilance similar to the 0-back condition in its demand for attention, vigilance, and encoding but with better psychometric characteristics (the problem of ceiling effects was minimized); no COMT effect was observed. However, variants of the CPT can elicit prefrontal activation, although presumably of a different type than that required by the 1- or 2-back conditions.20 Reading is a language-processing task in which maintenance demands are minimal; COMT effects were nonsignificant. IQ is a measure of intellectual efficiency that is composed of subtests, some of which make limited working memory demands; COMT effects were nonsignificant, albeit stronger than the former tests. Thus, it is possible that these tests imposed subtle working memory demands (oculomotor spatial memory or verbal working memory for arithmetic problems in IQ subtests; instructional set) that were subject to COMT effects that were small and could not be measured owing to power issues. The relative specificity for prefrontal cognition is consistent with basic animal research38 showing that although COMT is expressed throughout the brain, its function is especially relevant for prefrontal dopaminergic signaling. These regionally specific effects of COMT may be explained by the relatively low abundance of dopamine transporter expression in prefrontal dopamine synapses, thus increasing the role of COMT in prefrontal dopamine catabolism.39,40

Although we have emphasized the role of COMT in prefrontal cortical processing, it remains possible that COMT will have other important, albeit different, effects on information processing, cognitive or otherwise, depending on the neural system. Moreover, given the relatively small variance in working memory accounted for solely by the COMT genotype and what is known about the complex genetics of schizophrenia,42 other numerous other genes are undoubtedly involved in cognition, executive or otherwise, and genetic susceptibility for schizophrenia.

COMT GENOTYPE AND SUBPROCESSES
IN WORKING MEMORY

By examining some of the processing subcomponents of the n-back task, we could begin to adjudicate among competing cognitive mechanisms associated with sensitivity to genotype and susceptibility for schizophrenia. First, for the 0-back condition, as with the CPT, neither impairments in siblings nor effects of COMT genotype were observed, suggesting that implementation of attentional processes related to fixed targets was neither COMT dependent nor a schizophrenia susceptibility factor. Second, once working memory was more fully engaged in the 1- and 2-back conditions, a significant effect of COMT genotype was observed. The RR for deficits in siblings also became elevated. If, however, crucial parameters in susceptibility and in genetic variation in COMT activity were related to load or delay, we would have expected the 2-back condition to exhibit a greater effect of COMT and more sensitivity to genetic risk for schizophrenia (ie, greater RR). This was not the case. The COMT effects on 1- and 2-back accuracy and RT were similar. The RRs also were similar, as were effect sizes between controls and siblings. (The 1- and 2-back conditions were similar in terms of their discriminatory power based on true score variance [data not shown, but available on request], suggesting that these results were not due to a psychometric artifact and despite prima facie differences in absolute levels of performance, as individuals performed worse in the 2-back condition than in the 1-back condition.)
According to our initial hypotheses, these results favor an account emphasizing information updating and ordering in the face of competing stimuli, cognitive mechanisms common to the 1- and 2-back conditions. Recent data suggest that dopamine may be particularly important in this specific aspect of cognitive control. At the neurophysiologic level, dopamine innervation of prefrontal cortex aids in the reduction of distractibility in subhuman primates, perhaps by enhancing N-methyl-d-aspartate excitation associated with sustained activation (“signal”) and reducing non–N-methyl-d-aspartate excitation associated with “noise.”

The RT data during n-back tasks were consistent with this account in that the more accurately one could process the stimuli, the faster that processing occurred. Given the expected highly significant correlations between speed and accuracy, COMT genotype effects might be conceived to be playing an especially important role in target acquisition, which, by affecting discriminability of target from background, also provides an impetus for rapid decision making (ie, rapidly arriving at a “correct answer”). Indeed, covarying for accuracy in the analysis of the n-back RT data removed the effect of genotype on RT. Although this explanation is parsimonious, it is nevertheless the case that speed and accuracy are intertwined on the n-back task, and it is possible that speed in coming to a decision could be advantageous in the processing of successive stimuli.

Admittedly, this account is speculative, and other interpretations are possible. For example, it has been proposed that updating and manipulation distinguish the 1- and 2-back conditions, with maintenance held in common. We do not think this is likely as there is a frank difference in the maintenance demands between the tasks (1.8 seconds vs 3.6 seconds) and because both tasks require updating in the sense that a target-to-be must be shifted in status to a target before being “dumped” from a computational buffer. We believe that our account fits the range of data in the present study, is parsimonious, and is consistent with other cognitive science and neurobiologic evidence.

This being said, the n-back task is not as simple a test as it first seems. It comprises a variety of subcomponents, including encoding of stimulus features, temporal indexing, updating (which we take to include target selection and deselection in the face of competing stimuli), and information maintenance. The complexity of these operations in the context of the n-back task precluded further task dissection, although some of the subcomponent functions themselves may be mapped to areas of dorsolateral prefrontal cortex, consistent with other studies that have placed a premium on manipulation of representations in memory and functions of dorsolateral prefrontal cortex.

**EXECUTIVE SUBPROCESSES AND RR IN SIBLINGS**

As expected, we found significant differences between siblings and controls and increased RR in siblings for accuracy impairments and for RT on the 1- and 2-back conditions. Our results for the n-back task in the sibling group compare favorably with those of other cognitive phenotypes previously reported in this sample. Egan et al observed significant differences between siblings and controls for WCST perseverative errors, trail-making (form b), and verbal fluency. For these measures, RR in siblings at impairment defined as −1 SD was approximately 2 to 4. Moreover, only these measures, but not those of other cognitive domains (eg, most memory variables and visual-processing variables) yielded significant differences between siblings and controls. These results are also broadly consistent with those of Cannon et al, who argued that “prefrontal-type” cognitive impairments were especially heritable in patients with schizophrenia and their twins.

Also, our results are likely to be conservative because siblings with diagnoses of schizophrenia or schizophrenia spectrum disorders were excluded; that is, our data involved a psychiatrically “purified” sample. Thus, the information we obtained in the parametric and nonparametric RR analyses was not redundant with diagnosis.

**CONCLUSIONS**

Our results are consistent with abundant evidence that prefrontal cortical function is compromised in schizophrenia and more recent evidence that this compromise is also likely to be in part heritable and related to genetic risk for the illness. This study begins to specify the distinct cognitive subprocesses prominently involved (updating an endogenously determined target but not vigilance, load, delay, or speed of processing), their neurobiologic underpinnings, and the strength of the relationship between phenotype and a related genotype. Although the effect of the COMT Val158Met genotype on working memory was small (ie, about 3% in controls, in siblings, and in patients) and in and of itself unlikely to have great impact on behavior, working in concert with other causes of dysfunction (eg, other genes and environmental factors), it would be expected to add to or interact with them to increase risk. Of course, other genes and environmental factors influence working memory performance and risk for schizophrenia. Last, the findings also provide convergent evidence that an intermediate phenotype related to prefrontal cortical malfunction represents a viable approach to understanding neuropsychiatric disorders with complex genetic etiologies and individual differences in cognition.

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