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Genetic Variation in COMT: Effects on Working Memory in Schizophrenic Patients, Their Siblings, & Healthy Controls

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Abstract

Background—COMT val$^{108/158}$met (*rs4680*) is thought to affect dopamine regulated prefrontal cortical activity during working memory (WM) tasks, and to weakly increase risk for developing schizophrenia. Recently, other single nucleotide polymorphisms (SNPs) across the gene have emerged as additional risk factors for schizophrenia: namely *rs737865*, *rs165599*, and *rs2097603*. In a large sample, we examined whether these SNPs affect WM.

Method—Schizophrenic probands (n=325), their nonpsychotic siblings (n=359), and normal control subjects (n=330) completed tests of WM function. Data were analyzed with a series of mixed model ANOVAs.

Results—Val homozygotes performed most poorly on all conditions of the N-BACK, irrespective of diagnosis. Additionally, there was a trend towards a disease-only val$^{108/158}$met effect on a test of attentional set-shifting; val homozygote probands performed most poorly. Significant or near-significant effects of *rs737865* were found on all conditions of the N-BACK, with G homozygotes performing worst. There also was a disease-only COMT *rs737865* effect on the 0-BACK. None of the other SNPs showed main effects by themselves. A haplotype constructed from promoter and val$^{108/158}$met SNPs showed main effects on WM parameters, consistent with inverted U models of dopamine signaling.

Conclusions—We extended earlier findings of a val$^{108/158}$met effect on WM function, and suggest that combinations of alleles within COMT may modulate the val$^{108/158}$met effect in a nonlinear manner.

Keywords

Schizophrenia; Catechol-O-Methyltransferase; COMT; Working Memory; Attention; Prefrontal Cognition

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INTRODUCTION

Cognitive dysfunction is widely accepted as a cardinal feature of schizophrenia, with deficits in attention, working memory and executive function commonly reported [1, 2]. One gene that affects neuronal functions involved in working memory, and may be a potential susceptibility gene to develop the disorder, is catechol-o-omethyltransferase (COMT), a methylation enzyme that converts dopamine to inactive 3-methoxytyramine [3–5]. The COMT gene, mapped to chromosome 22q11, contains a functional polymorphism, val$^{108/158}$met (*rs4680*) that results in two common variants of the enzyme (val and met), and exerts a significant effect on enzyme activity (val being associated with higher activity). This polymorphism appears to affect dopamine regulated prefrontal cortical activity during working memory tasks [6–13]. For example, we have previously reported that COMT val$^{108/158}$met genotype predicts performance on two different tests of working memory/ executive function (the Wisconsin Card Sorting Test (WCST) and N-BACK), with the high activity val allele, which presumably allows less dopamine to become available at the synapse, being associated with poorest performance [7, 9]. These effects were observed independent of psychiatric diagnosis.

The relationship between COMT genotype and prefrontal cognitive function, together with demonstrated prefrontal functional abnormalities in schizophrenia [14, 15], implicates COMT genotype as a plausible risk factor to develop the disorder. In fact, inheritance of one or two val alleles may slightly elevate the risk of developing schizophrenia [3, 7, 16–21]. Recently, other single nucleotide polymorphisms (SNPs) across the COMT gene have emerged as possible alleles that increase risk for schizophrenia, including *rs737865* (located in intron 1), *rs165599* (located in the 3' flanking region), and *rs2097603* (in the P2 promoter region) [19, 22–24].

The aim of the present study was to re-examine the previously reported relationship between the COMT val$^{108/158}$met genotype and working memory function in an expanded test battery, and also to explore potential cognitive effects of three other COMT SNPs. Based on our previous work, we predicted that carriers of the COMT val allele would perform more poorly than met allele carriers on tests of working memory/executive function, notably updating [9] and distraction control [25]. We further predicted that COMT val$^{108/158}$met genotype would affect basic attention or target detection functions on the Continuous Performance Test (CPT) in this larger sample, based on several lines of evidence, including animal research ([26–28], ADHD [29], and cognitive enhancement [30].

Shifman and colleagues reported that the G–G genotype at *rs737865* and at *rs165599* were most strongly associated with risk to develop schizophrenia in their large Ashkenazi Jewish sample, (with slightly different effects based on gender) [19]. Therefore, we sought similar findings with *rs737865* and *rs165599* as with val$^{108/158}$met; namely that the "risk" alleles of the two COMT SNPs (i.e., G–G) would be associated with deficits on tests sensitive to updating and attentional function. No clear risk allele has emerged for the P2 promoter (*rs2097603*), although Li and colleagues reported a nonsignificant preferential transmission of the A allele in 198 Chinese schizophrenic family trios [31]. This finding is consistent with evidence in lymphocytes and in brain that the A allele is associated with greater COMT activity, an effect analogous to the val allele [16]. We therefore predicted that the A allele would be most strongly associated with poor working memory function in our sample.

Finally, based on recent data from our group that haplotypic combinations of functional loci within the COMT gene can result in non-linear effects on prefrontal function, consistent with other evidence of an inverted U shaped dopamine-response function within prefrontal

cortex [12, 32, 33], we examined the impact of COMT P2 promoter/val$^{108/158}$met diplotypes on prefrontal cognitive function.

METHOD

Subjects

1014 subjects participated in this study, recruited from local and national sources as volunteers for the Clinical Brain Disorders Branch/NIMH sibling study, as has been previously described [7, 34]. In brief, all participants provided written informed consent of an IRB-approved protocol. Most families had two eligible full siblings (at least one of whom met DSM-IV criteria for schizophrenia or schizoaffective disorder, depressed type). All subjects were between 18 and 60 years of age, had a premorbid IQ above 70, and were able to provide informed consent. Subjects with significant medical problems, history of head trauma with loss of consciousness for longer than 5 minutes, or alcohol or drug abuse within the last 6 months were excluded. Given that COMT allele frequencies differ across some ethnic groups [24, 35], only Caucasian subjects were included in these analyses. Of the 1014 subjects, 250 were included in a previous study of COMT effects on cognition [9].

Each schizophrenic proband had at least one full sibling included in the study. No twins were included. Siblings with a history of schizophrenia, schizoaffective disorder, or schizophrenia spectrum disorder were excluded. All subjects were medically screened and interviewed by a research psychiatrist using the Structured Clinical Interview [36]. Demographic information for the sample is presented in Table 1. Diagnosis for schizophrenia was confirmed by a second board-certified psychiatrist. All schizophrenic patients were clinically stable and receiving antipsychotic medications (predominantly second generation) at the time of testing.

Procedure

Subjects were tested on a wide range of neuropsychological tests assessing various cognitive functions, including attention and concentration, language and visuospatial function, working memory and executive function, and semantic and episodic memory. Here, we report only the results of tests of intellectual function (WAIS-R) and select tests assessing attention and working memory/executive function (Table 2). Since our previous reports of a relationship between COMT val$^{108/158}$met and working memory function [7, 9], we have included an additional test of executive function in our test battery (ID/ED), specific stages of which have been shown to be mediated by prefrontal dopaminergic function [27] [37] (Table 2).

COMT genotyping—Blood samples were collected from all subjects, and DNA was extracted using standard methods. COMT val$^{108/158}$met genotype was determined using the Taqman allelic discrimination assay, as previously described [38]. In addition to the COMT val$^{108/158}$met polymorphism, SNPs *rs737865* and *rs165599* [19] and the promoter SNP *rs2097603* [22] were genotyped using the same technique. All SNPs were in Hardy-Weinberg Equilibrium for each group. D', a measure of linkage disequilibrium, was >.93 for *rs2097603* and *rs737865* for all groups; was between .44 and .49 for *rs737865* and *rs4680* for all groups; was between .47 and .53 for *rs2097603* and *rs4680* for all groups; and was between .65 and .79 for *rs4680* and *rs16559* for all groups.

Data Analyses

Parametric statistical analyses were conducted to determine if COMT genotype and diagnostic group differences were present in our working memory/executive function phenotypes (N-BACK, CPT, WCST, ID/ED). All subjects were included in the analyses, but

family membership was treated as a random factor, and diagnosis, genotype, and gender were treated as fixed effects in a mixed model (SAS Mixed-Model ANOVA [39]). The dependent measures were treated as continuous variables. Although some studies have reported linkage disequilibrium between COMT val$^{108/158}$met and *rs737865* and *rs165599*, we did not find evidence of this in our sample, so chose to examine these SNPs independent of val$^{108/158}$met.

We also conducted a series of similar mixed model analyses to assess the effects of a COMT haplotype on prefrontal cognition. In our sample, (and earlier reports, e.g. [23]) the *rs737865* SNP is in strong linkage disequilibrium with the P2 promoter, *rs2097603*. We chose to examine the P2 promoter/val$^{108/158}$met haplotype, which encompasses this linkage disequilibrium, based on evidence that *rs209760* and val$^{108/158}$met are functional variants in the gene (Bray 2003). To minimize phase uncertainty in diplotype assignment, we excluded all individuals who were heterozygous at both loci and then examined genotype interactions with ANOVAs. Haplotypes were determined using SNPHAP. Based on the putative inverted U-shaped curve model [12, 32], we predicted a G-G/val-val diplotype would result in superior prefrontal cognitive test performance compared with an A-A/val-val diplotype, presumably due to underavailability of dopamine at the synapse in the latter group, and an A-A/met-met diplotype would result in superior test performance compared with a G-G/met-met diplotype, as here overavailability of dopamine might impair information processing in the latter group.

For the ID/ED task, we analyzed subjects' performance "non-conditionally," which assigns subjects who failed a stage the maximal error score for all subsequent stages. Mean errors at three stages of the task were analyzed; the C_D stage, the intradimensional (IDS) shifting stage, and the extradimensional (EDS) stage (see Table 2).

To control for multiple comparisons within our data, we adopted a stringent Bonferroni corrected *p*-value of .001, based on 11 comparisons across 4 SNPs for a COMT main effect. (The haplotype analyses were exploratory so excluded from this calculation). We chose to report all alpha values between the uncorrected, conventional level of .05 and our corrected value of .001, as trends.

RESULTS

As shown in Table 1, age, gender ratios, and performance on estimates of both premorbid and current intellectual function differed significantly among the groups.

Table 3 summarizes all significant and trend-level COMT main effects and interactions for the four SNPs.

COMT val$^{108/158}$met (*rs4680*)

N-BACK—In a series of mixed-model ANOVAs in which diagnostic group, COMT genotype, and gender served as main effects, COMT val$^{108/158}$met genotype had a significant effect on 1-BACK accuracy, and a near significant effect on 0-BACK and 2-BACK accuracy. The val-val group performed more poorly than the val-met and met-met groups, who did not differ from each other. This pattern was present irrespective of diagnostic group (proband, sibling, or control). The effect sizes (Cohen d) of the val-val, met-met genotype contrasts across all N-BACK conditions were at the low end of the moderate range: 0.20 for the 0-BACK, 0.31 for the 1-BACK and 0.29 for the 2-BACK. Across all N-BACK conditions, there was a significant or near-significant main effect of diagnosis and of COMT genotype, but no interaction between the two (see Table 3). Planned contrasts revealed that the probands performed significantly (or near significantly) more

poorly than their siblings and the healthy controls, who performed better than the other groups.

When we restricted our analyses to those individuals who did not participate in our prior study (Goldberg 2003), we found that the results remained significant, and demonstrated that COMT genotype had a significant impact on both 1-BACK and 2-BACK performances ($F(2,491)=6.76$, $p=.001$ and $F(2,490)=6.74$, $p=.001$ respectively), suggesting a positive replication.

WCST—There was no significant main effect of COMT $val^{108/158}$met genotype on perseverative errors (t-score) or categories achieved on the WCST. However, there was a main effect of diagnostic group, with probands performing significantly more poorly than siblings and controls, who did not differ from each other.

CPT—There was no significant main effect of COMT $val^{108/158}$met genotype on Vigilance or Distractibility performance on the CPT. However, there was a significant main effect of diagnostic group for both variables, with probands performing significantly more poorly than their siblings and the healthy controls, who did not differ from each other. There also was a trend towards a COMT/gender interaction for the Vigilance portion ($F(2,817)=3.04$, $p=.048$), with males with two copies of the val allele performing more poorly overall. A near significant interaction between COMT $val^{108/156}$met genotype and diagnosis on Distractibility performance also was observed ($F(4,812)=3.36$, $p=.010$). Probands with two copies of the val allele performed most poorly overall.

ID/ED—There was no significant main effect of COMT $val^{108/158}$met genotype on any of the three conditions of the ID/ED task (C_D errors, IDS errors, and EDS errors). However, across all conditions, there was a main effect of diagnosis, and a near significant interaction between diagnosis and genotype for C_D ($F(4,149)=2.86$, $p=.026$) and IDS errors ($F(4,149)=2.46$, $p=.048$). Probands with two copies of the val allele performed most poorly, at both the IDS and C_D stages. The lack of a main effect of COMT $val^{108/158}$met genotype may have been due to ceiling effects in the sibling and control groups. Planned contrasts revealed that the probands committed significantly more errors than the healthy controls, and near-significantly more than their siblings. Siblings and controls did not differ from each other.

IQ—There was no significant main effect of COMT $val^{108/158}$met genotype on estimated IQ, as measured by the WAIS-R. However, unsurprisingly, there was a main effect of diagnostic group, with probands performing significantly more poorly than siblings and controls, and a trend towards siblings performing more poorly than controls.

Other COMT SNPs

Main effects of diagnosis and gender will not be further discussed in the SNPs listed below, as results differed only trivially due to small fluctuations in sample size. Evidence of strong linkage disequilibrium between *rs4680* and two of the other COMT SNPs (*rs737865* and *rs165599*) was not present in our sample. Therefore, the following analyses were not conditioned against $val^{108/158}$met homozygote backgrounds.

COMT *rs737865* (5' region)

As shown in Table 3, significant and near-significant main effects and COMT/diagnosis interactions for *rs737865* were restricted to the N-BACK and CPT. Specifically, there was a significant main effect of COMT on the 0-BACK, with the G-G genotype group performing more poorly than both the A–A and A–G genotype groups, who did not differ from each

other. A similar pattern was seen at the trend level for a main effect of COMT on the 1-BACK and 2-BACK, with the G–G genotype group performing most poorly overall. The effect sizes (Cohen d) of the A–A, G–G contrasts across all N-BACK conditions were at the low end of the moderate range: 0.38 for the 0-BACK, 0.25 for the 1-BACK and 0.27 for the 2-BACK. The significant COMT/diagnosis interaction on the 0-BACK was characterized by G–G probands performing most poorly overall. There were no main effects of COMT seen on the CPT, but near significant COMT/diagnosis interactions were found for both Vigilance ($F(4,643)=3.41$, $p=.009$) and Distractibility ($F(4,637)=3.76$, $p=.0049$). Both interactions were characterized by G–G probands performing most poorly overall. Of note, this SNP also is in tight linkage disequilibrium with *rs2097603*, which shows asymmetric allele sharing across these loci [23, 38]. Thus, we cannot disambiguate in our sample the possible effects of linkage disequilibrium across these loci.

COMT *rs165599* (3' region)

There were no significant main effects of *rs165599* on any of the measures, although there was a trend towards a COMT/diagnosis interaction on the Distractibility portion of the CPT ($F(4,628)=2.55$, $p=.039$). This interaction was characterized by G–G probands performing most poorly overall, and G–G controls performing the best.

COMT *rs2097603* (P2 promoter region)

Rs2097603 showed no significant main effects on any of the measures, but trends towards COMT/diagnosis interactions on both the Vigilance ($F(4,792)=2.95$, $p=.019$) and Distractibility ($F(4,789)=3.12$, $p=.015$) portions of the CPT were seen. Both of these interactions were characterized by A–A probands performing most poorly overall.

Diplotype Analyses—We next examined the effects of COMT P2 promoter/val$^{108/158}$met diplotypes on cognition. (G-G/val-val individuals (n=1 in the probands, n=5 in the whole sample) were excluded because of the very small cell size. (All other cell sizes were greater than 22)). A significant three-way interaction between diplotypes and diagnosis on CPT Vigilance was observed ($F(8,704)=3.30$, $p=.001$), with G-G/met-met homozygotes and A-A/val-val homozygotes performing more poorly than other diplotypes, most strikingly in the schizophrenic group. There were no significant interaction effects (i.e., diplotype effects) across the whole sample for all other tasks, though a near significant three-way interaction between diplotypes and diagnosis on the 1-BACK task ($F(6,361)=2.39$, $p=.03$) similar to that noted above, was seen. Thus, the significant P2 promoter/val$^{108/158}$met/diagnosis interaction was characterized by both low COMT expression met homozygotes (putatively related to very high dopaminergic tone) and high expression val homozygotes (putatively related to very low dopaminergic tone) performing most poorly overall, with the profile most evident in the probands. (However, we note the presence of ceiling effects in the control and sibling groups on these tasks).

DISCUSSION

COMT val$^{108/158}$met (*rs4680*)

Our current findings support and extend our earlier report of a COMT val$^{108/158}$met genotype effect on working memory function [9]. Consistent with our prediction, individuals with two copies of the val allele performed most poorly on the N-BACK, irrespective of psychiatric diagnosis. Met homozygotes demonstrated the best performance on the task, and heterozygotes performed intermediate between the other two groups. Once again, we failed to see a COMT/diagnosis interaction on any condition of the N-BACK, in the face of a significant COMT effect, which suggests that normal controls, siblings, and probands were more or less equally affected by val$^{108/158}$met. The fact that the three diagnostic groups were

affected in a near linear fashion in this, and our earlier studies [7, 9], supports the notion of an additive genetic model in which allele loading influences working memory in a similar fashion, irrespective of an individual's specific clinical background.

In contrast with our previous findings, we found a near-significant val$^{108/158}$met genotype effect on 0-BACK performance in the current study. Additionally, as predicted, we found a near significant COMT/diagnosis interaction on performance on the Distractibility portion of the CPT, which we did not find previously with our smaller sample [9]. Both the 0-BACK and the CPT make demands on attention, vigilance and encoding in the service of target detection. In a related study of a novel attentional control task dependent primarily on cingulate cortex function, Blasi et al [25] recently showed an effect of COMT val$^{108/158}$met genotype on task performance and on cingulate activation, broadly consistent with our results here. Certainly, there is evidence supporting a role for dopamine in attention and target detection tasks (e.g. [29]). Interestingly, Bilder et al [6] suggested something similar when they examined COMT val$^{108/158}$met genotype effects on cognition in schizophrenia, reporting that met homozygotes outperformed heterozygotes and val homozygotes on a composite measure of attention and processing speed. Furthermore, Crofts et al. [27] reported increased susceptibility to distraction from task-irrelevant stimuli in marmosets with catecholamine-depleted frontal lobes, supporting the contention that COMT val$^{108/158}$met genotype could influence performance on the CPT, and Eisenberg and colleagues [40] reported that the val allele was strongly associated with false alarms on a version of the CPT.

We also found a near-significant COMT/diagnosis interaction on two of the three ID/ED attentional set shifting measures examined. Probands with two copies of the high activity val allele committed substantially more errors at the C_D stage than probands with one or no copies of the allele. Distracting and irrelevant stimuli are introduced at the C_D stage, and subjects must ignore stimuli from the novel dimension and continue to respond to the previously-rewarded stimulus. Our results are consistent with both the animal literature [27] and work from our group [41]. There also was a trend towards a COMT/diagnosis interaction at the IDS stage, which suggests probands with two copies of the val allele were significantly less able to discern the conceptual category within which they were responding. A deficit in ID shifting represents an impairment in the ability to generalize a discrimination learned for a particular set of exemplars to another set from the same category in the face of newly salient distractors. These results raise the more general possibility that val$^{108/158}$met genotype affects both updating or rule learning during interference laden contexts (ID/ED, N-BACK) and attentional control (CPT, 0-BACK). We suspect that the failure to find an overall effect of genotype relates to ceiling effects in the performance of the control subjects on this task.

Although we found a significant group effect at the EDS stage of the ID/ED task, we failed to see a COMT/diagnosis interaction, which was unexpected, given that ED shifting is the core component of the WCST, and is the basis for achieving novel sorting categories [41]. We, and others, have previously reported a significant COMT val$^{108/158}$met effect on WCST performance [7, 11] (but also see [42]), so we expected to replicate this result in the current study. However, we failed to see a significant COMT effect on the WCST in our sample, nor for EDS, the stage from the ID/ED most comparable to the WCST. These findings, using a substantially larger sample than in our previous study, argue that the WCST may not be the ideal task to examine COMT effects on working memory function. Other studies have also reported negative findings for COMT and the WCST [42, 43], suggesting that the N-BACK and other attentional control tasks (e.g., CPT, C_D, IDS) may be more sensitive measures to detect the specific cognitive operations influenced by val$^{108/158}$met genotype. Significant

findings from previous studies might have more to do with the characteristics of their smaller, less representative samples, than to an effect of COMT per se.

As we predicted, and consistent with our previous work [9], we failed to see a val$^{108/158}$met genotype effect on intelligence, as assessed by the four-subtest version of the WAIS-R. This result speaks again to a continuing argument in the genetics of cognition literature, whether specific cognitive processes can be parsed genetically independent of their correlation with "g." While our findings support the contention that COMT val$^{108/158}$met genotype influences prefrontally-mediated working memory/executive function, with inheritance of two copies of the val allele most detrimental to performance, results from other studies have not been uniformly positive (e.g., [42–44]. However, there are a number of methodological differences between these and the current study that may, at least in part, explain some of the discrepancies, including cohort differences, and differences in test design and cognitive manipulation requirements. Evidence from the N-BACK, and to a lesser extent, the ID/ED task, lead us to favor the hypothesis that COMT genotype affects cognitive updating, yet we recognize that other explanations could be supported by these data, including cognitive control hypotheses pertaining to interference suppression, and working memory load.

rs737865 (5' region)

Overall, findings from this SNP bore similarity to those for val$^{108/158}$met. For example, significant or near-significant effects of *rs737865* genotype were seen across all load levels of the N-BACK, with the G–G genotype group performing most poorly overall. Furthermore, an interaction between *rs737865* and diagnosis was seen on both subtests of the CPT, with G–G probands performing most poorly overall. Of note, the observed effects for all of these updating and attentional control tests were in the predicted direction, with probands homozygous for the presumed risk G allele performing most poorly overall.

rs165599 (3' region) and *rs2097603* (P2 promoter region)

Overall, the results from these two SNPs were far less compelling than those for val$^{108/158}$met and *rs737865*. Specifically, we failed to see any significant COMT main effects on working memory/executive function for either the *rs165599* or *rs2097603* SNPs alone. However, there was a near significant interaction between *rs165599* and diagnosis for the Distractibility portion of the CPT, with G–G probands performing most poorly overall (similar to that reported by Chan and colleagues [45]).

We also found an interaction effect of *rs2097603* and diagnosis on both subtests of the CPT, with the A–A genotype appearing most disadvantageous for probands. Interestingly, the A allele was reported in one study to be (non-significantly) preferentially transmitted in schizophrenia [31], and has a weak effect on COMT enzyme activity in cultured lymphocytes, but less clearly in brain [16].

***rs2097603/rs4680* Diplotypes—**The complex nature of the findings with the SNPs other than val$^{108/158}$met may in part be explained by the possibility that combinations of alleles at these various loci modulate the val$^{108/158}$met effect. This is suggested by the functional analyses in tissue [16, 22] and by an fMRI study of haplotypes in COMT [33]. Because allele frequencies at all these loci in COMT show considerable population variation [23], discrepancies in the literature involving associations with COMT and cognition and psychosis may also be related to some of this haplotypic variation in COMT population genetics [46]. Consistent with models that predict performance on the basis of an inverted u-shaped curve [12, 32, 47], the two diplotypes putatively related to highest and lowest levels of dopaminergic tone also performed worse overall on select tests of attentional control (CPT Vigilance) and, to a lesser extent, cognitive updating (1-BACK). This was especially

pronounced in the schizophrenic group, perhaps because they had the least ability to compensate for these more “extremes” of prefrontal physiology. (However, ceiling effects in the performance of the sibling and control groups suggests circumspection regarding this interpretation. Furthermore, different aspects of dopamine transmission at high and low levels of COMT enzyme activity (e.g., tonic versus phasic [48]) may have contributed to these findings). These results add to evidence that COMT genotype per se, even at the $val^{108/158}$met locus, does not capture the complex biology of interacting functional loci within the gene.

As a final caveat, we note that, despite numerous near significant results, ultimately only two significant main effects of COMT genotype survived our strict Bonferroni correction, and both involved the N-BACK test. Furthermore, medication effects in the schizophrenic group may have influenced our findings. We did not assess these due to the variety of medication regimens, but we note that medication may have produced main effects in some instances. However, the consistency of results across the unmedicated healthy control group somewhat mitigates this.

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Table 1

Demographic Characteristics of the Groups

Characteristic	Probands (n=325)	Siblings (n=359)	Controls (n=330)
Age (years)[1]	36.43 (9.21)	37.02 (9.81)	34.29 (10.35)
Sex (% male)[2]	77	40	47
Current IQ[3,4]	93.05 (12.06)	106.15 (10.42)	108.23 (8.99)
Premorbid IQ[5,6]	102.54 (11.31)	107.45 (9.93)	108.96 (8.67)

[1] Control subjects were significantly younger than probands and siblings, who did not differ from each other

[2] Significantly more males comprised the proband group

[3] As measured by a 4-subtest short-form of the Wechsler Adult Intelligence Scale, Revised

[4] Probands' current IQ was significantly lower than siblings and controls. There was a trend towards siblings' IQ being lower than controls

[5] As measured by the Wide Range Achievement Test-Revised, Reading subtest, standard score

[6] Probands' premorbid IQ was significantly lower than siblings, whose IQ was lower than controls

Table 2

Tests Used in the Current Study

Test	Description	Dependent Variable
N-BACK	A number between 1 and 4 is presented every 1.8 seconds for a 200 msec duration, at set locations at the points of a diamond-shaped box. Subjects are instructed to recall the stimulus seen "N" previously. In the 0-BACK condition, subjects press the corresponding number onscreen (i.e., no memory load per se). In the 1-BACK condition, subjects do not respond to the first number that appears, but when the second number appears, press the first number, and so on. Subjects complete six trials each of the 0, 1, and 2-BACK conditions.	Mean percent correct per condition
	The total *N* available for the N-BACK was 620.	
WCST[1]	In this computerized task, subjects view four key cards at the top of the screen and must match a card at the bottom of the screen to one of those above. Each card contains stimuli that are characterized by three different stimulus dimensions. The subject is told to match each new card to one of the four key cards, and is given feedback by the computer as to whether each sort is correct or incorrect. After 10 consecutive correct sorts, the sorting rule changes without the subject's knowledge. The task ends when all cards have been sorted, or when all categories are attained. The maximum number of cards is 128.	Percent perseverative errors (*t*-score), and number of categories achieved
	The total *N* available for the WCST was 880.	
CPT[2]	In the Vigilance portion of the test, subjects view a continuous sequence of single digits (presented at the rate of one per second) on a screen and must respond to an infrequently occurring target sequence (1 followed by 9). The Distractibility portion is similar, except that other digits appear simultaneously flanking the stimuli that the subject is told to pay attention to. Each portion of the test lasts six minutes.	d` (takes into account both omission and commission errors) for Vigilance and Distractibility.
	The total *N* available for the CPT was 877.	
WAIS-R[3]	All subjects completed a short form of the Wechsler Adult Intelligence Scale-Revised (WAIS-R;(Wechsler 1981)), consisting of Arithmetic, Similarities, Picture Completion, and Digit Symbol subtests.	IQ
	The total *N* available for the WAIS-R was 896.	
ID/ED[4]	Subjects learn a series of discriminations in which one stimulus dimension (e.g., line contour) is relevant and the other (e.g., object shape) is not. On each trial, the two test stimuli appear randomly in two of four squares positioned towards the perimeter of the screen. The subject must determine which is the correct stimulus by touching one of the two patterns. After indicating their choice, subjects receive visual and auditory feedback. The test comprises 9 stages (subtests of increasing difficulty), presented in a fixed order. For each subtest, continuation to the next trial is dependant on a criterion of 6 consecutive correct discriminations being reached. If the criterion is not reach at the 50^{th} trial of a subtest, the test is discontinued. Three stages were examined in the current study: At the third (compound discrimination, C_D) stage, additional stimuli are superimposed on the original two line drawings presented, (i.e., a second (and irrelevant) stimulus	Number of errors at stages 3 (C_D), 6 (IDS), and 8 (EDS)

Test	Description	Dependent Variable
	dimension is introduced). Correct feedback is contingent upon responding to the originally-correct "line" stimulus. The sixth (intradimensional shift, IDS) stage comprises new exemplars of "line" and "shape." Correct feedback is contingent upon continuing to respond to the "line" stimuli. At the eighth (extradimensional shift, EDS) stage, new exemplars from each dimension are again introduced, but correct feedback relies on selecting one of the two "shape" stimuli.	
	The total *N* available for ID/ED was 171.	

[1] Wisconsin Card Sorting Test [49]

[2] Continuous Performance Test [50]

[3] Wechsler Adult Intelligence Scale-Revised [51]

[4] Intradimensional-Extradimensional set shifting [52]

Table 3

Significant and Near-Significant (Italics) Results for a COMT Effect* on Working Memory/Executive Function, by COMT Genotype

Genotype	Test Name	Diagnosis Main Effect	COMT Main Effect	Gender Main Effect	COMT/Diagnosis Interaction	COMT/Gender Interaction	3-Way Interaction
COMT val^{158}met (*rs4680*)	**0-BACK**	*F(2,573)=5.94 p=.003*	*F(2,573)=3.60 p=.028*	--	--	--	--
	1-BACK	F(2,574)=41.38, p<.0001	F(2,574)=6.93, p=.001	--	--	--	--
	2-BACK	F(2,573)=63.84, p<0001	*F(2,573)=5.93 p=.003*	*F(1,573)=5.31 p=.022*	--	--	--
	CPT Vigilance	F(2,817)=65.56, p<.0001	--	--	--	*F(2,817)=3.04 p=.048*	--
	CPT Distractibility	F(2,812)=100.46, p<.0001	--	--	*F(4,812)=3.36 p=.010*	--	--
	WCST Perseverative Errors	F(2,819)=39.13, p<0001	--	--	--	F(2,819)=6.90, p=.001	--
	WCST Categories	F(2,827)=101.45, p<.0001	--	--	--	*F(2,827)=3.90, p=.021*	--
	IDED C_D	F(2,149)=8.38, p=.0004	--	--	*F(4,149)=2.86 p=.026*	--	--
	IDED IDS	F(2,149)=7.17, p=.001	--	--	*F(4,149)=2.46 p=.048*	--	--
	WAIS-R IQ	F(2,835)=113.94, p<.0001		--	--	*F(2,835)=3.75 p=.024* --	--
rs737865	**0-BACK**	F(2,432)=26.83, p<0001	F(2,432)=8.01, p=0004	--	F(4,432)=5.80, p<0001		--
	1-BACK	F(2,432)=36.21, p<.0001	*F(2,432)=4.19 p=.0158*	--	--	--	--
	2-BACK	F(2,432)=40.93, p<0001	*F(2,432)=4.13 p=.0167*	--	--	--	--
	CPT Vigilance	F(2,643)=61.27, p<.0001	--	--	*F(4,643)=3.41, p=.009*	--	--
	CPT Distractibility	F(2,637)=75.67, p<.0001	--	*F(1,637)=4.31 p=.0384*	*F(4,637)=3.76 p=.0049*	--	*F(6,637)=3.25 p=.0038*
rs165599	**CPT Distractibility**	F(2,628)=62.47, p<.0001	--	*F(1,628)=4.84, p=.0281*	*F(4,628)=2.55, p=.0385*	--	--
rs2097603	**CPT Vigilance**	F(2,792)=50.10, p<.0001	--	--	*F(4,792)=2.95, p=.019*	--	--
	CPT Distractibility	F(2,789)=76.62, p<0001	--	--	*F(4,789)=3.12, p=.015*	--	--

* Main effects of diagnosis only, while present for numerous other tests for *rs737865*, *rs165599*, and *rs2097603* are not reported here.