# Meta-Analysis of the Cognitive Effects of the Catechol-*O*-Methyltransferase Gene Val158/108Met Polymorphism

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**Background:** Cognitive endophenotypes may further our understanding of the genetic basis of psychiatric disorders, and the catechol-*O*-methyltransferase (*COMT*) gene is a promising candidate gene for both cognitive function and disorder. We conducted a meta-analysis of reported associations between the *COMT* Val158/108Met polymorphism and measures of memory and executive function.

**Methods:** The PubMed database was searched for studies relating cognitive functions and the *COMT* Val158/108Met polymorphism. This enabled meta-analyses of six cognitive phenotypes (Trail Making task, verbal recall, verbal fluency, IQ score, n-back task, and Wisconsin Card Sorting Test). Data were extracted by two reviewers and included cognitive scores by *COMT* genotype, publication year, diagnostic status, ancestry, proportion of male participants, and whether genotype frequencies were consistent with Hardy-Weinberg equilibrium.

**Results:** We found no association between *COMT* genotype and the majority of phenotypes. There was evidence of association with IQ score ($d = .06$), which did not differ significantly by ancestry, sex, average sample age, or patient status. For the n-back task, there was no robust evidence for genetic association, but the effect size was significantly larger in patient ($d = .40$) than nonpatient ($d = -.27$) populations, larger in both samples with fewer male subjects, and those of greater average age. There was also evidence of publication bias and decreasing effect sizes with later publication.

**Conclusions:** Despite initially promising results, the *COMT* Val158/108Met polymorphism appears to have little if any association with cognitive function. Publication bias may hamper attempts to understand the genetic basis of psychological functions and psychiatric disorders.

**Key Words:** Catechol-*O*-methyltransferase, cognitive function, *COMT*, endophenotype, genetic association, meta-analysis

Recent studies have suggested several candidates for the multiple genes of small effect that are assumed to underlie genetic risk for neuropsychiatric disorders (1,2), but progress has been hampered by failures to replicate initial findings (2–4). Inadequate sample sizes may result in studies lacking statistical power to detect small effects and increase publication bias through failure to publish null results (5–7). Meta-analytic techniques, which allow synthesis of all available data on a gene-disease association, offer a partial solution to this problem by providing a more accurate estimate of the likely effect size and formally assessing evidence for potential publication bias (6,8). We previously reviewed the advantages and disadvantages of meta-analyses of gene-disease associations (6).

Another reason why psychiatric genetic associations have appeared inconsistent or elusive may be the selection of phenotypes. The use of clinical categorical diagnoses may be less than optimal for genetic studies because they are fallible and probably have complex genetic and environmental etiologies. An alternative is to employ endophenotypes, which are measurable intermediaries on the biological pathway between gene and disease (9,10). Endophenotypes might be better targets for genetic study than categorical diagnoses if they can be more reliably measured or show simpler genetic architecture.

Cognitive dysfunctions related to working memory (11,12) and sustained attention (13) have been suggested as endophenotypes of schizophrenia. They are heritable, cosegregated with illness, present before illness onset (14), and at increased frequency in unaffected relatives (15), meeting Gottesman and Gould's (9) criteria. It nevertheless remains uncertain whether these endophenotypes are more genetically tractable than schizophrenia itself (16). The Val158/108Met single nucleotide polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene has been extensively investigated in relation to schizophrenia (17), as well as other disorders such as major depression (18) and bipolar disorder (19). The evidence of association between *COMT* genotype and schizophrenia is weak (20,21), but it has been argued that this polymorphism influences cognitive function (22) and may thereby influence some aspects of schizophrenia risk or symptom severity. The rationale for investigating *COMT* and cognitive phenotypes has recently been reviewed (17).

We recently made two attempts to synthesize the evidence regarding *COMT* Val158/108Met polymorphism and cognitive function. The first (16), including studies published up to May 2006, examined four putative endophenotypes of schizophrenia, including the n-back working memory task, the Wisconsin Card Sorting Test (WCST), and two electrophysiological measures (P300 amplitude and latency). These analyses showed marginal evidence of association with the WCST and n-back tasks only. The second (23), including studies published up to August 2006, examined the association with WCST more closely in patients with schizophrenia-spectrum disorders and healthy control subjects and found evidence of association only among healthy control subjects and not patients with schizophrenia. Further analyses suggested a moderating influence of ancestry and

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decreasing effect size with later publication date. This latter pattern is common in genetic studies, where the first report of an association often overestimates the true effect size (24).

The present study aimed to further our understanding of the effect of the *COMT* Val158/108Met variant on cognition in both healthy and patient populations. By undertaking a systematic review of the entire *COMT*-cognition literature, we were able to expand the range of cognitive phenotypes available for meta-analysis. We aimed to further assess the impact of sex, age, ethnicity, and patient status and update our meta-analysis of the WCST to include large datasets that have recently become available.

## Methods and Materials

### Search Strategy and Inclusion Criteria

The PubMed database was searched to the end of August 2007 using combinations of the terms "catechol-O-methyltransferase" or "COMT" and "cognitive," "cognition," "IQ," "intelligence," "memory," "executive," "Wisconsin Card Sort*," and "attention." Studies were excluded for the following reasons: no cognitive data reported, sample comprised patients with 22q11 deletion syndrome (who have only one copy of the *COMT* gene), groups matched by cognitive function, studies of a different *COMT* polymorphism, or overlap of reported data between papers.

### Selection of Phenotypes

Cognitive measures were included where results from more than 10 samples had been published, at least 9 of which were from independent samples. Using this criterion, the following phenotypes were selected for meta-analysis: Trail Making task, verbal fluency, verbal recall, IQ score, n-back task accuracy (2-back), and Wisconsin Card Sorting Test perseverative errors.

For each phenotype, only one measure was selected from each sample. For the Trail Making task, the Trails B-A measure was used where available and otherwise Trails B. For verbal fluency, letter versions were taken in preference to category versions. For verbal recall, studies were included if they measured free recall of word lists, sentences, or stories, using list learning in preference to story learning and delayed recall in preference to immediate recall. One study (25) presented a composite score from episodic recall; it was included because most indicators were sentence and word recall under various conditions. For IQ, the more global measure was selected, and adult IQ score was selected over childhood score (26). For the n-back task, verbal versions were selected over spatial versions (27). These hierarchies of measures were established to maximize the uniformity of cognitive measures within each phenotype.

### Data Extraction

Data were independently extracted by two authors and discrepancies were resolved by mutual consent. Where data were reported in a format that did not allow inclusion in the meta-analysis, authors were contacted directly and asked to release data in the appropriate format. For each study, the following were extracted: first author, year of publication, location, reported ethnicity (described as entirely European versus non-European or mixed ethnicity samples), diagnostic status, whether genotype frequencies were reported to be consistent with Hardy-Weinberg equilibrium, number of male and female participants, average age of sample, and mean, standard deviation, and sample size for each cognitive variable by genotype group. Catechol-*O*-methyltransferase genotypes were grouped according to the presence or absence of the Val allele (Val/Val or Val/Met vs. Met/Met). Where more than one study sample (e.g., patients and control subjects) was reported, data were treated independently in the analysis. Where cognitive data were available from more than one occasion, the scores used were from the first assessment only, except in placebo-controlled experiments, where data from the placebo condition were used.

### Statistical Analysis

Data were initially analyzed within a fixed effects framework, and individual study effect sizes (Cohen's *d*) were pooled using inverse variance methods to generate a summary effect size and 95% confidence interval (95% CI). A fixed effects framework assumes that the effect of genotype is constant across studies, and between-study variation is considered to be due to chance or random variation. The assumption was checked using a chi-square test of goodness of fit for homogeneity. The significance of the pooled effect size was determined using a $Z$ test.

Where there was evidence of a significant association between *COMT* genotype and cognitive variables in the presence of significant between-study heterogeneity, a random effects framework was employed, with effects sizes pooled using DerSimonian and Laird methods. A random effects framework assumes that between-study variation is due to both chance or random variation and an individual study effect. Random effects models are more conservative than fixed effects models and generate a wider confidence interval. The significance of the pooled effects size was determined using a $Z$ test.

The effect size of the first published study was compared with the pooled effect size of the remaining studies using a $Z$ test and meta-regression of individual study effect size against year of publication was conducted, as there is evidence for a substantially greater estimate of effect size in the first published study (24).

Stratified analyses by sample ancestry and patient status were conducted to assess the potential moderating effect of these variables, and the difference in pooled effect size was determined using a $Z$ test. Potential moderating effects of sex and age were tested using meta-regression of individual study effect size against the proportion of male participants and average age in individual study samples.

Funnel plots were created to assess potential ascertainment bias by plotting natural logarithm of individual study effect size against the standard error of the natural logarithm of individual study effect size. Ascertainment bias was also assessed using the Egger test (28).

## Results

### Characteristics of Included Studies

The final dataset of 46 studies comprised 67 independent samples published between 2001 and 2007 where cognitive data was reported by *COMT* Val158/108Met genotype. These studies are described in Supplement 1.

### Meta-analysis

Analyses were conducted separately for the following phenotypes: Trail Making task, verbal fluency, verbal recall, IQ score, n-back task accuracy, and Wisconsin Card Sorting Test perseverative errors.

**Trail Making Task.** Six studies, comprising $k = 10$ independent samples (29–34), contributed to the meta-analysis (total $n = 896$). Fixed effects analysis indicated no evidence of association

($d$ = .04, 95% CI −.12 to .19, $Z$ = .44, $p$ = .66), with no evidence of between-study heterogeneity ($\chi^2$ = 6.69, $p$ = .67). Egger's test indicated no evidence of ascertainment bias ($p$ = .22).

The effect size reported in the first published study (29) ($d$ = −.50) was compared with the pooled effect size estimate for the remaining studies ($d$ = .04), and these did not differ significantly ($p$ = .38). Meta-regression indicated no significant association of effect size estimate with year of publication ($p$ = .23).

The pooled effect size estimate for European ($d$ = .08) and non-European ($d$ = −.24) samples did not differ significantly ($p$ = .16). The pooled effect size estimate for patient ($d$ = −.92) and nonpatient ($d$ = .13) samples did not differ significantly ($p$ = .35). Meta-regression indicated no significant association of effect size estimate with proportion of male participants ($p$ = .17) or average age of study sample ($p$ = .80).

Excluding one study that reported genotype frequencies that deviated from Hardy-Weinberg equilibrium (31), which may indicate genotyping error (35), did not alter these results substantially.

**Verbal Fluency.** Nine studies, comprising $k$ = 12 independent samples (25,26,29–31,33,36–38), contributed to the meta-analysis (total $n$ = 1808). Fixed effects analysis indicated no evidence of association ($d$ = −.02, 95% CI −.13 to .09, $Z$ = .37, $p$ = .71), with no evidence of between-study heterogeneity ($\chi^2$ = 11.97, $p$ = .37). Egger's test indicated no evidence of ascertainment bias ($p$ = .94).

The effect size reported in the first published study (29) ($d$ = −.14) was compared with the pooled effect size estimate for the remaining studies ($d$ = −.02), and these did not differ significantly ($p$ = .78). Meta-regression indicated no significant association of effect size estimate with year of publication ($p$ = .35).

The pooled effect size estimate for European ($d$ = −.03) and non-European ($d$ = .00) samples did not differ significantly ($p$ = .84). The pooled effect size estimate for patient ($d$ = .02) and nonpatient ($d$ = −.05) samples did not differ significantly ($p$ = .52). Meta-regression indicated significant positive association of effect size estimate with proportion of male participants (Z = 2.69, $p$ = .007). There was no significant association with average age of study sample ($p$ = .56).

Excluding one study that reported genotype frequencies that deviated from Hardy-Weinberg equilibrium (31) did not alter these results substantially.

**Verbal Recall.** Twelve studies, comprising $k$ = 18 independent samples (25,26,29,30,36–43), contributed to the meta-analysis (total $n$ = 2538). Fixed effects analysis indicated no evidence of association ($d$ = −.04, 95% CI −.13 to .05, $Z$ = .82, $p$ = .41), with evidence of between-study heterogeneity ($\chi^2$ = 28.33, $p$ = .041). Egger's test indicated no evidence of ascertainment bias ($p$ = .95).

The effect size reported in the first published study (29) ($d$ = .70) was compared with the pooled effect size estimate for the remaining studies ($d$ = −.04), and these did not differ significantly ($p$ = .16). Meta-regression indicated no significant association of effect size estimate with year of publication ($p$ = .17).

The pooled effect size estimate for European ($d$ = −.06) and non-European ($d$ = .04) samples did not differ significantly ($p$ = .44). The pooled effect size estimate for patient ($d$ = .03) and nonpatient ($d$ = −.05) samples did not differ significantly ($p$ = .47). Meta-regression indicated significant positive association of effect size estimate with proportion of male participants ($Z$ = 2.69, $p$ = .007). There was no significant association with average age of study sample ($p$ = .72).

**IQ Score.** Sixteen studies, comprising $k$ = 21 independent samples (22,23,25,26,30,43–53), contributed to the meta-analysis (total $n$ = 9115). Fixed effects analysis indicated evidence of association ($d$ = .06, 95% CI .00 to .11, $Z$ = 2.30, $p$ = .021), with higher scores among individuals with two copies of the Met allele. There was no evidence of between-study heterogeneity ($\chi^2$ = 19.61, $p$ = .48). Egger's test indicated no evidence of ascertainment bias ($p$ = .66).

The effect size reported in the first published study (22) ($d$ = .17) was compared with the pooled effect size estimate for the remaining studies ($d$ = .06), and these did not differ significantly ($p$ = .53). Meta-regression indicated no significant association of effect size estimate with year of publication ($p$ = .64).

The pooled effect size estimate for European ($d$ = .05) and non-European ($d$ = .11) samples did not differ significantly ($p$ = .57). The pooled effect size estimate for patient ($d$ = .02) and nonpatient ($d$ = .06) samples did not differ significantly ($p$ = .62). Meta-regression indicated no significant association of effect size estimate with proportion of male participants ($p$ = .54) or average age of study sample ($p$ = .68).

A forest plot of individual study effect sizes and the pooled effect size estimate is presented in Figure 1.

**N-Back Task.** Seven studies, comprising $k$ = 9 independent samples (27,45,46,54–57), contributed to the meta-analysis (total $n$ = 2104). Fixed effects analysis indicated evidence of association ($d$ = −.20, 95% CI −.31 to −.10, $Z$ = 3.74, $p$ < .001), with higher accuracy among individuals with one or more copies of the Val allele. There was evidence of between-study heterogeneity ($\chi^2$ = 100.92, $p$ < .001). Random effects analysis indicated no evidence of association ($d$ = .25, 95% CI −.18 to .68, $Z$ = 1.12, $p$ = .26). Egger's test indicated evidence of ascertainment bias ($t$ = 3.45, $p$ = .011).

The effect size reported in the first published study (55) ($d$ = 1.47) was compared with the pooled effect size estimate for the remaining studies ($d$ = −.22), and these differed significantly ($p$ = .001). Meta-regression indicated significant negative association of effect size estimate with year of publication ($Z$ = 3.56, $p$ < .001).

The pooled effect size estimate for European ($d$ = −.23) and non-European ($d$ = −.04) samples did not differ significantly ($p$ = .18). The pooled effect size estimate for patient ($d$ = .40) and nonpatient ($d$ = −.27) samples differed significantly ($p$ < .001). Meta-regression indicated significant negative association of effect size estimate with proportion of male participants ($Z$ = 7.69, $p$ < .001) and a significant positive association with average age of study sample ($Z$ = 7.79, $p$ < .001).

A forest plot of individual study effect sizes and the pooled effect size estimate, grouped by patient status, are presented in Figure 2.

**Wisconsin Card Sorting Test.** Sixteen studies, comprising $k$ = 25 independent samples (29,32–34,38,39,45,46,51,57–63), contributed to the meta-analysis (total $n$ = 2829). Fixed effects analysis indicated no evidence of association ($d$ = −.04, 95% CI −.13 to .05, $Z$ = .92, $p$ = .36), with evidence of between-study heterogeneity ($\chi^2$ = 39.46, $p$ = .024). Egger's test indicated no evidence of ascertainment bias ($p$ = .26).

The effect size reported in the first published study (29) ($d$ = −.18) was compared with the pooled effect size estimate for the remaining studies ($d$ = −.04), and these did not differ significantly ($p$ = .80). Meta-regression indicated no significant association of effect size estimate with year of publication ($p$ = .12).

The pooled effect size estimate for European ($d$ = .03) and

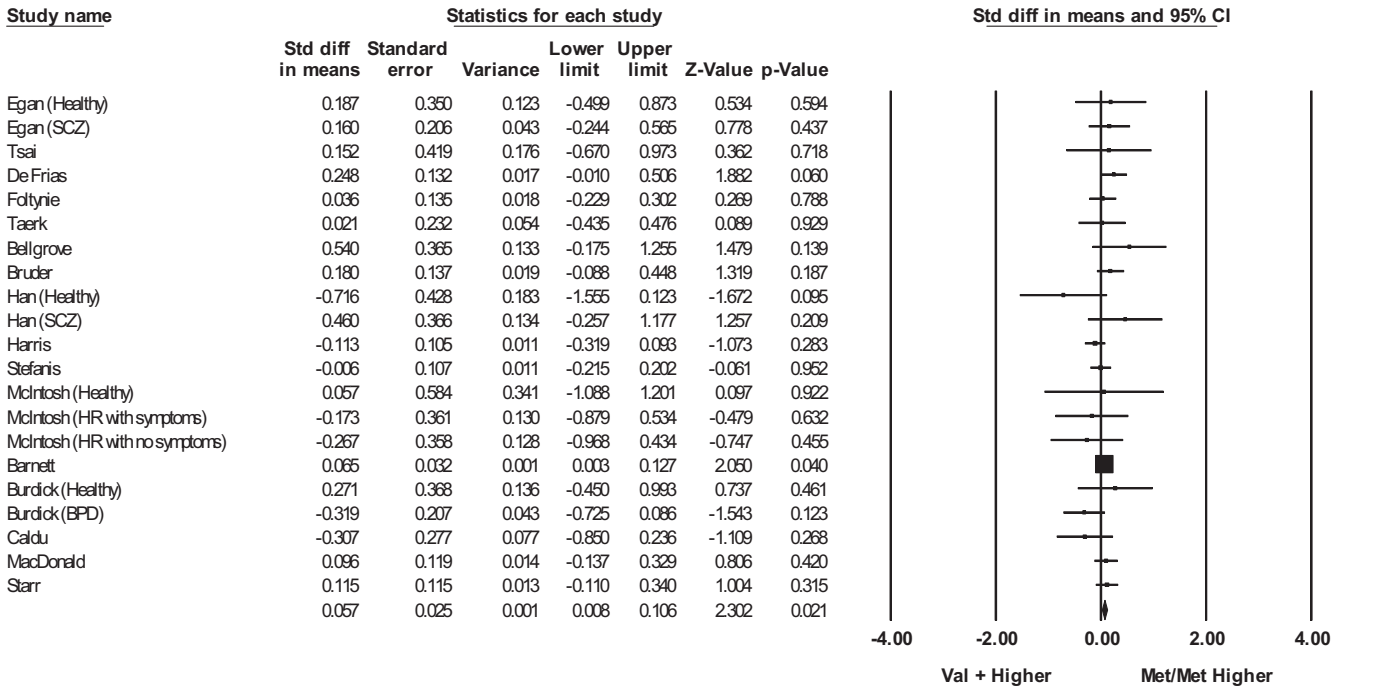


**Figure 1.** Association of the *COMT* Val158/108Met polymorphism with IQ score. Meta-analysis indicates a significant association of the Met/Met genotype with increased IQ score, equivalent to .1% of phenotypic variance. There is no evidence of between-study heterogeneity or moderation by other study characteristics. *COMT*, catechol-*O*-methyltransferase; SCZ, schizophrenia; HR, high risk; BPD, bipolar disorder.

non-European ($d = -.22$) samples differed significantly ($p = .016$). The pooled effect size estimate for patient ($d = -.06$) and nonpatient ($d = -.02$) samples did not differ significantly ($p = .68$). Meta-regression indicated no significant association of effect size estimate with proportion of male participants ($p = .35$) or average age of study sample ($p = .77$).

## Discussion

Meta-analyses showed no association between the *COMT* Val158/108Met variant and indices of memory or executive function, with the exception of a small association between genotype and n-back task performance in the opposite direction from that hypothesized, with evidence of significant between-study heterogeneity. When patient and nonpatient samples were considered separately, these effect sizes differed significantly, although in each case significant between-study heterogeneity remained. There was also a robust, though small, association between genotype and IQ score, which did not differ significantly by sample ancestry, sex distribution, average age of sample, or patient status. These results cannot exclude the

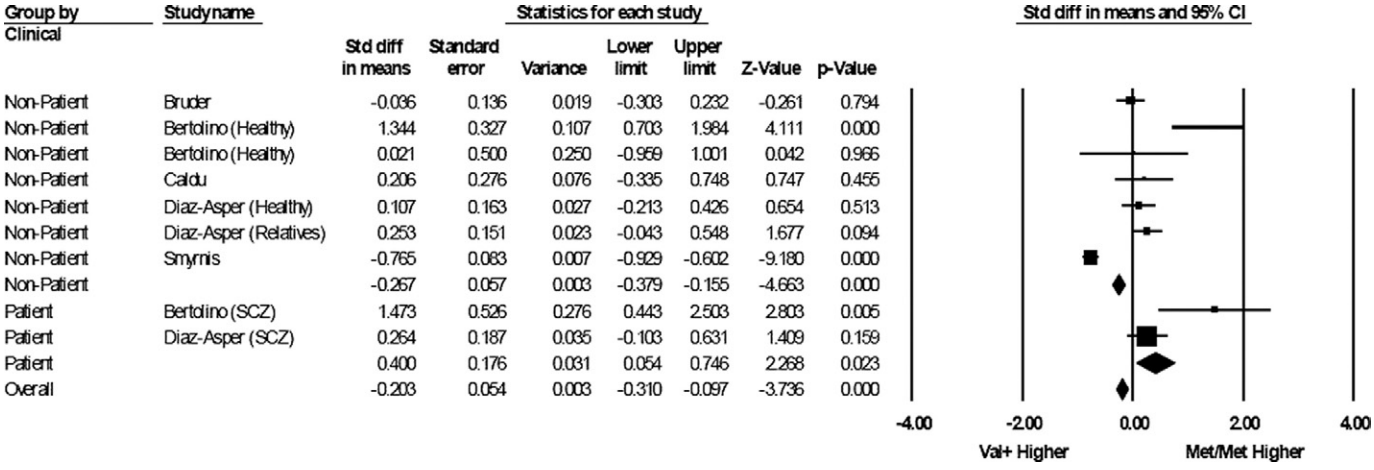


**Figure 2.** Association of the *COMT* Val158/108Met polymorphism with n-back task accuracy. Meta-analysis indicates a significant association of the Val allele with increased n-back task accuracy, equivalent to 4% of phenotypic variance. However, there is evidence of between-study heterogeneity and the association appears to differ in magnitude and direction in patient and nonpatient samples. *COMT*, catechol-*O*-methyltransferase; SCZ, schizophrenia.

possibility that *COMT* genotype is associated with cognitive phenotypes but suggest that any effect, if genuine, may be substantially less than indicated by initial reports. The between-study heterogeneity observed in several analyses also suggests that the strength and nature of any association may differ across populations or as a function of study characteristics we were unable to capture. Future large-scale primary studies will be necessary to test these possibilities.

There are several possible reasons why a genetic association was found for IQ score but not other phenotypes. First, IQ score was the phenotype for which the most data were available and consequently the analysis with the greatest statistical power to detect a small effect. This is a likely explanation since the small effect size ($d = .06$, equivalent to .1% of phenotypic variance) is, in magnitude, similar to the other included phenotypes. Second, IQ score is probably the measure with the best psychometric properties. Third, neuroimaging evidence suggests that the neural basis of general intelligence is not broadly distributed but involves relatively selective areas of lateral frontal cortex (64). Catechol-*O*-methyltransferase is concentrated in prefrontal cortex (65), where it may be particularly important in regulating dopaminergic catabolism (66), for reasons including the relative lack of dopamine transporter there (67). Finally, IQ score was unique among included phenotypes in that it was typically reported only as demographic data and not as an outcome. Publication bias may therefore have been less problematic for the IQ score phenotype than for other phenotypes.

The lack of between-study heterogeneity observed for the association with IQ score is striking and suggests that no individual study is biasing the pooled effect size estimate. This is in contrast with the general picture that emerges from the psychiatric genetics literature, where between-study heterogeneity is common (6). There has been relatively little discussion of IQ score as a cognitive endophenotype for neuropsychiatric disorder and consequently little emphasis on it as a target for genetic associations. As an aggregate measure of highest level cognitive functions, it has the advantage of being well characterized and standardized in measurement. Moreover, IQ score deficits in patients (68) and the presence of a subtle IQ score decrement in children who later develop schizophrenia (14,69,70) are two of the most robust findings with respect to cognition in schizophrenia.

For the n-back task, a fixed effect model found evidence for association in the opposite direction from that hypothesized, with better working memory in Val carriers. In contrast, the more conservative random effects model, used because of significant between-study heterogeneity, found no overall evidence for association. Effect sizes were significantly different and in opposing directions among patient ($d = .40$) and nonpatient ($d = -.27$) populations. One possible explanation for this discrepancy is the "inverted U" hypothesis of prefrontal dopamine, where either hyperdopaminergic function (such as in amphetamine stimulation) or hypodopaminergic function (in schizophrenia) are both detrimental to prefrontal function (71,72). If this explanation were invoked here, it would imply that optimal dopaminergic function was exceeded in healthy Met/Met individuals, since they displayed poorer working memory than Val carriers.

Alternatively, the effect of patient status may be confounded by sex, since men dominated (77%) the two patient samples (55,57) and there was an inverse association between the proportion of male subject and effect size. Functional analyses (73) as well as association studies with psychiatric (74) and cognitive (23) phenotypes add weight to the hypothesis (75) that the functional effects of *COMT* are sexually dimorphic in humans as they are in mice (66). A further source of heterogeneity is ethnicity—we found a greater effect of genotype on the WCST in non-European or mixed ethnicity samples ($d = -.22$) than in European samples ($d = .03$). Although we observed a significant positive association between effect size and average sample age for the n-back task, this effect was not observed for the other phenotypes considered. This general lack of an effect of age is surprising, given evidence that the heritability of cognitive ability changes with age (76).

Meta-analytic techniques have advantages and disadvantages. First, meta-analysis requires combination of comparable data. We attempted to ensure this by analyzing data from distinct cognitive measures separately, but between-study heterogeneity was still common. Increased statistical power from combining studies may be partially offset if substantial heterogeneity is present. Second, we were limited to the published literature. Our results may therefore be based on a selected subset of data that may exist. Such methods may be useful in obtaining more accurate effect size estimates and identifying potential moderating factors but should not be regarded as a substitute for large, adequately powered primary studies (6). Our results suggest these should comprise several thousand individuals (6,77).

The evidence for association with n-back task performance is difficult to interpret. However, the problem may arise from the reporting of results and not study design. Formal analysis suggested evidence of possible publication bias. In addition, reported effect sizes show a pattern of decreasing over time, and removing the initial report significantly reduced the pooled effect size. This is a conservative estimate of the effect, since the true first published report (22) was subsumed in our analyses into a later study (57). These problems are certainly not unique to *COMT* nor to the field of psychiatric genetics (24), but they hamper attempts to understand the true magnitude of genetic associations.

The present analysis was limited to the most common cognitive tests. Effects may be greater in tasks that assess more subtle aspects of cognition. The Met allele may confer increased tonic but decreased phasic dopamine, yielding increased stability but decreased flexibility in neural states (78). The two alleles may therefore be differentially advantageous in cognitive tests, depending on the cognitive operations required (79–81). Given continuing structural (82–84) and functional (85,86) development of the prefrontal cortex during adolescence and the doubling of *COMT* enzyme activity between birth and adulthood (87), the influence of *COMT* on executive functions may alter during this period (23), although we did not observe strong evidence for an effect of age.

The Val158/108Met polymorphism remains a plausible candidate that may contribute to variation in some forms of psychological function (74), given converging evidence for its functional effects. That it does not meet our expectations with respect to cognitive function or schizophrenia (20,21) is disappointing but does not negate the need for scientific rigor in both the analysis and the reporting of results. The widespread acceptance of the hypothesis that *COMT* affects cognitive function appears to have been driven by initial, high-profile, positive reports and by the tendency to emphasize the positive associations within studies at the expense of negative findings. Cognitive endophenotypes for psychiatric disorders have been the subject of much recent debate and a growing body of research (15,16,72,88). We cannot exclude the possibility that *COMT* genotype has a small influence

on cognitive phenotypes, but results presented here suggest that early enthusiasm may not yet be fully warranted.

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*Supplementary material cited in this article is available online.*

1. Straub RE, Weinberger DR (2006): Schizophrenia genes–famine to feast. *Biol Psychiatry* 60:81–83.
2. Harrison PJ, Weinberger DR (2005): Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. *Mol Psychiatry* 10:804.
3. Owen MJ, Williams NM, O'Donovan MC (2004): The molecular genetics of schizophrenia: New findings promise new insights. *Mol Psychiatry* 9:14–27.
4. Owen MJ, Craddock N, O'Donovan MC (2005): Schizophrenia: Genes at last? *Trends Genet* 21:518–525.
5. Colhoun HM, McKeigue PM, Davey Smith G (2003): Problems of reporting genetic associations with complex outcomes. *Lancet* 361:865–872.
6. Munafo MR, Flint J (2004): Meta-analysis of genetic association studies. *Trends Genet* 20:439–444.
7. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR (1991): Publication bias in clinical research. *Lancet* 337:867–872.
8. Salanti G, Sanderson S, Higgins JP (2005): Obstacles and opportunities in meta-analysis of genetic association studies. *Genet Med* 7:13–20.
9. Gottesman, II, Gould TD (2003): The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry* 160:636–645.
10. Gottesman, II, Shields J (1973): Genetic theorizing and schizophrenia. *Br J Psychiatry* 122:15–30.
11. Gasperoni TL, Ekelund J, Huttunen M, Palmer CG, Tuulio-Henriksson A, Lonnqvist J, *et al.* (2003): Genetic linkage and association between chromosome 1q and working memory function in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 116:8–16.
12. Cannon TD, Huttunen MO, Lonnqvist J, Tuulio-Henriksson A, Pirkola T, Glahn D, *et al.* (2000): The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *Am J Hum Genet* 67:369–382.
13. Cornblatt BA, Malhotra AK (2001): Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. *Am J Med Genet* 105:11–15.
14. Jones P, Rodgers B, Murray R, Marmot M (1994): Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 344:1398–1402.
15. Snitz BE, Macdonald AW 3rd, Carter CS (2006): Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophr Bull* 32:179–194.
16. Flint J, Munafo MR (2007): The endophenotype concept in psychiatric genetics. *Psychol Med* 37:163–180.
17. Tunbridge EM, Harrison PJ, Weinberger DR (2006): Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biol Psychiatry* 60:141–151.
18. Funke B, Malhotra AK, Finn CT, Plocik AM, Lake SL, Lencz T, *et al.* (2005): COMT genetic variation confers risk for psychotic and affective disorders: A case control study. *Behav Brain Funct* 1:19.
19. Burdick KE, Funke B, Goldberg JF, Bates JA, Jaeger J, Kucherlapati R, Malhotra AK (2007): COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. *Bipolar Disord* 9:370–376.
20. Munafo MR, Bowes L, Clark TG, Flint J (2005): Lack of association of the COMT (Val158/108 Met) gene and schizophrenia: A meta-analysis of case-control studies. *Mol Psychiatry* 10:765–770.
21. Fan JB, Zhang CS, Gu NF, Li XW, Sun WW, Wang HY, *et al.* (2005): Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: A large-scale association study plus meta-analysis. *Biol Psychiatry* 57:139–144.
22. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, *et al.* (2001): Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A* 98: 6917–6922.
23. Barnett JH, Heron J, Ring SM, Golding J, Goldman D, Xu K, Jones PB (2007): Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children. *Am J Psychiatry* 164:142–149.
24. Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG, Ioannidis JP (2004): Establishment of genetic associations for complex diseases is independent of early study findings. *Eur J Hum Genet* 12:762–769.
25. de Frias CM, Annerbrink K, Westberg L, Eriksson E, Adolfsson R, Nilsson LG (2004): COMT gene polymorphism is associated with declarative memory in adulthood and old age. *Behav Genet* 34:533–539.
26. Harris SE, Wright AF, Hayward C, Starr JM, Whalley LJ, Deary IJ (2005): The functional COMT polymorphism, Val158Met, is associated with logical memory and the personality trait intellect/imagination in a cohort of healthy 79 year olds. *Neurosci Lett* 385:1–6.
27. Smyrnis N, Avramopoulos D, Evdokimidis I, Stefanis CN, Tsekou H, Stefanis NC (2007): Effect of schizotypy on cognitive performance and its tuning by COMT val158 met genotype variations in a large population of young men. *Biol Psychiatry* 61:845–853.
28. Egger M, Davey Smith G, Schneider M, Minder C (1997): Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 315:629–634.
29. Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, *et al.* (2002): Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biol Psychiatry* 52:701–707.
30. Burdick KE, Goldberg TE, Funke B, Bates JA, Lencz T, Kucherlapati R, Malhotra AK (2007): DTNBP1 genotype influences cognitive decline in schizophrenia. *Schizophr Res* 89:169–172.
31. Ehlis AC, Reif A, Herrmann MJ, Lesch KP, Fallgatter AJ (2007): Impact of catechol-O-methyltransferase on prefrontal brain functioning in schizophrenia spectrum disorders. *Neuropsychopharmacology* 32:162–170.
32. Ho BC, Wassink TH, O'Leary DS, Sheffield VC, Andreasen NC (2005): Catechol-O-methyl transferase Val158Met gene polymorphism in schizophrenia: Working memory, frontal lobe MRI morphology and frontal cerebral blood flow. *Mol Psychiatry* 10:229, 287–298.
33. Lipsky RH, Sparling MB, Ryan LM, Xu K, Salazar AM, Goldman D, Warden DL (2005): Association of COMT Val158Met genotype with executive functioning following traumatic brain injury. *J Neuropsychiatry Clin Neurosci* 17:465–471.
34. Szoke A, Schurhoff F, Meary A, Mathieu F, Chevalier F, Trandafir A, *et al.* (2006): Lack of influence of COMT and NET genes variants on executive functions in schizophrenic and bipolar patients, their first-degree relatives and controls. *Am J Med Genet B Neuropsychiatr Genet* 141:504–512.
35. Munafo MR, Clark T, Flint J (2005): Does measurement instrument moderate the association between the serotonin transporter gene and anxiety-related personality traits? A meta-analysis. *Mol Psychiatry* 10:415–419.
36. Golimbet V, Gritsenko I, Alfimova M, Lebedeva I, Lezheiko T, Abramova L, *et al.* (2006): Association study of COMT gene Val158Met polymorphism with auditory P300 and performance on neurocognitive tests in patients with schizophrenia and their relatives. *World J Biol Psychiatry* 7:238–245.
37. Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Sullens A, Yolken RH (2007): The catechol O-methyltransferase Val158Met polymorphism is not associated with broad-based cognitive functioning in schizophrenia. *Schizophr Res* 96:87–92.
38. Woodward ND, Jayathilake K, Meltzer HY (2007): COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia. *Schizophr Res* 90:86–96.
39. Minzenberg MJ, Xu K, Mitropoulou V, Harvey PD, Finch T, Flory JD, *et al.* (2006): Catechol-O-methyltransferase Val158Met genotype variation is associated with prefrontal-dependent task performance in schizotypal personality disorder patients and comparison groups. *Psychiatr Genet* 16:117–124.
40. Strauss J, Barr CL, George CJ, Ryan CM, King N, Shaikh S, *et al.* (2004): BDNF and COMT polymorphisms: Relation to memory phenotypes in

young adults with childhood-onset mood disorder. *Neuromolecular Med* 5:181–192.
41. Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, *et al.* (2006): An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* 31:2748–2757.
42. O'Hara R, Miller E, Liao CP, Way N, Lin X, Hallmayer J (2006): COMT genotype, gender and cognition in community-dwelling, older adults. *Neurosci Lett* 409:205–209.
43. Starr JM, Fox H, Harris SE, Deary IJ, Whalley LJ (2007): COMT genotype and cognitive ability: A longitudinal aging study. *Neurosci Lett* 421: 57–61.
44. Bellgrove MA, Domschke K, Hawi Z, Kirley A, Mullins C, Robertson IH, Gill M (2005): The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. *Exp Brain Res* 163:352–360.
45. Bruder GE, Keilp JG, Xu H, Shikhman M, Schori E, Gorman JM, Gilliam TC (2005): Catechol-O-methyltransferase (COMT) genotypes and working memory: Associations with differing cognitive operations. *Biol Psychiatry* 58:901–907.
46. Caldu X, Vendrell P, Bartres-Faz D, Clemente I, Bargallo N, Jurado MA, *et al.* (2007): Impact of the COMT Val(108/158) Met and DAT genotypes on prefrontal function in healthy subjects. *Neuroimage* 37:1437–1444.
47. Foltynie T, Goldberg TE, Lewis SG, Blackwell AD, Kolachana BS, Weinberger DR, *et al.* (2004): Planning ability in Parkinson's disease is influenced by the COMT val158met polymorphism. *Mov Disord* 19:885–891.
48. McIntosh AM, Baig BJ, Hall J, Job D, Whalley HC, Lymer GK, *et al.* (2006): Relationship of catechol-O-methyltransferase variants to brain structure and function in a population at high risk of psychosis. *Biol Psychiatry* 61:1127–1134.
49. Stefanis NC, Van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Hantoumi I, Stefanis CN (2004): Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: A population study in 543 young men. *Biol Psychiatry* 56:510–515.
50. Taerk E, Grizenko N, Ben Amor L, Lageix P, Mbekou V, Deguzman R, *et al.* (2004): Catechol-O-methyltransferase (COMT) Val108/158 Met polymorphism does not modulate executive function in children with ADHD. *BMC Med Genet* 5:30.
51. Tsai SJ, Yu YW, Chen TJ, Chen JY, Liou YJ, Chen MC, Hong CJ (2003): Association study of a functional catechol-O-methyltransferase-gene polymorphism and cognitive function in healthy females. *Neurosci Lett* 338:123–126.
52. Han DH, Kee BS, Min KJ, Lee YS, Na C, Park DB, Lyoo IK (2006): Effects of catechol-O-methyltransferase Val158Met polymorphism on the cognitive stability and aggression in the first-onset schizophrenic patients. *Neuroreport* 17:95–99.
53. MacDonald AW 3rd, Carter CS, Flory JD, Ferrell RE, Manuck SB (2007): COMT val158Met and executive control: A test of the benefit of specific deficits to translational research. *J Abnorm Psychol* 116:306–312.
54. Bertolino A, Blasi G, Latorre V, Rubino V, Rampino A, Sinibaldi L, *et al.* (2006): Additive effects of genetic variation in dopamine regulating genes on working memory cortical activity in human brain. *J Neurosci* 26:3918–3922.
55. Bertolino A, Caforio G, Blasi G, De Candia M, Latorre V, Petruzzella V, *et al.* (2004): Interaction of COMT (Val(108/158)Met) genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. *Am J Psychiatry* 161:1798–1805.
56. Bertolino A, Caforio G, Petruzzella V, Latorre V, Rubino V, Dimalta S, *et al.* (2006): Prefrontal dysfunction in schizophrenia controlling for COMT Val158Met genotype and working memory performance. *Psychiatry Res* 147:221–226.
57. Diaz-Asper CM, Goldberg TE, Kolachana BS, Straub RE, Egan MF, Weinberger DR (2008): Genetic variation in catechol-O-methyltransferase: Effects on working memory in schizophrenic patients, their siblings, and healthy controls. *Biol Psychiatry* 63:72–79.
58. Galderisi S, Maj M, Kirkpatrick B, Piccardi P, Mucci A, Invernizzi G, *et al.* (2005): Catechol-O-methyltransferase Val158Met polymorphism in schizophrenia: Associations with cognitive and motor impairment. *Neuropsychobiology* 52:83–89.
59. Joober R, Gauthier J, Lal S, Bloom D, Lalonde P, Rouleau G, *et al.* (2002): Catechol-O-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. *Arch Gen Psychiatry* 59:662–663.
60. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D (2002): A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry* 159:652–654.
61. Rosa A, Peralta V, Cuesta MJ, Zarzuela A, Serrano F, Martinez-Larrea A, Fananas L (2004): New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *Am J Psychiatry* 161:1110–1112.
62. Rybakowski JK, Borkowska A, Czerski PM, Dmitrzak-Weglarz M, Skibinska M, Kapelski P, Hauser J (2006): Performance on the Wisconsin Card Sorting Test in schizophrenia and genes of dopaminergic inactivation (COMT, DAT, NET). *Psychiatry Res* 143:13–19.
63. Sjoberg RL, Nilsson KW, Nordquist N, Ohrvik J, Leppert J, Lindstrom L, Oreland L (2006): Development of depression: Sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene. *Int J Neuropsychopharmacol* 9:443–449.
64. Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, Ahmed A, *et al.* (2000): A neural basis for general intelligence. *Science* 289:457–460.
65. Matsumoto M, Weickert CS, Beltaifa S, Kolachana B, Chen J, Hyde TM, *et al.* (2003): Catechol O-methyltransferase (COMT) mRNA expression in the dorsolateral prefrontal cortex of patients with schizophrenia. *Neuropsychopharmacology* 28:1521–1530.
66. Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, Karayiorgou M (1998): Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. *Proc Natl Acad Sci U S A* 95:9991–9996.
67. Lewis DA, Melchitzky DS, Sesack SR, Whitehead RE, Auh S, Sampson A (2001): Dopamine transporter immunoreactivity in monkey cerebral cortex: Regional, laminar, and ultrastructural localization. *J Comp Neurol* 432:119–136.
68. Aylward E, Walker E, Bettes B (1984): Intelligence in schizophrenia: Meta-analysis of the research. *Schizophr Bull* 10:430–459.
69. Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, Poulton R (2002): Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: Results from a longitudinal birth cohort. *Arch Gen Psychiatry* 59:449–456.
70. Seidman LJ, Buka SL, Goldstein JM, Tsuang MT (2006): Intellectual decline in schizophrenia: Evidence from a prospective birth cohort 28 year follow-up study. *J Clin Exp Neuropsychol* 28:225–242.
71. Castner SA, Williams GV, Goldman-Rakic PS (2000): Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science* 287:2020–2022.
72. Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, *et al.* (2003): Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A* 100:6186–6191.
73. Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, *et al.* (2004): Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet* 75:807–821.
74. Pooley EC, Fineberg N, Harrison PJ (2007): The met(158) allele of catechol-O-methyltransferase (COMT) is associated with obsessive-compulsive disorder in men: Case-control study and meta-analysis. *Mol Psychiatry* 12:556–561.
75. Harrison PJ, Tunbridge EM (2007): Catechol-O-methyltransferase (COMT): A gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology* Epub ahead of print: September 5.
76. Finkel D, Pedersen NL, Plomin R, McClearn GE (1998): Longitudinal and cross-sectional twin data on cognitive abilities in adulthood: The Swedish Adoption/Twin Study of Aging. *Dev Psychol* 34:1400–1413.
77. Clayton D, McKeigue PM (2001): Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet* 358:1356–1360.
78. Bilder RM, Volavka J, Lachman HM, Grace AA (2004): The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology* 29:1943–1961.
79. Nolan KA, Bilder RM, Lachman HM, Volavka J (2004): Catechol O-methyltransferase Val158Met polymorphism in schizophrenia: Differential effects of Val and Met *al.*eles on cognitive stability and flexibility. *Am J Psychiatry* 161:359–361.

80. Dreisbach G, Muller J, Goschke T, Strobel A, Schulze K, Lesch KP, Brocke B (2005): Dopamine and cognitive control: The influence of spontaneous eyeblink rate and dopamine gene polymorphisms on perseveration and distractibility. *Behav Neurosci* 119:483–490.
81. Stefanis NC, van Os J, Avramopoulos D, Smyrnis N, Evdokimidis I, Stefanis CN (2005): Effect of COMT Val158Met polymorphism on the Continuous Performance Test, Identical Pairs Version: Tuning rather than improving performance. *Am J Psychiatry* 162:1752–1754.
82. Giedd JN (2004): Structural magnetic resonance imaging of the adolescent brain. *Ann N Y Acad Sci* 1021:77–85.
83. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW (1999): In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat Neurosci* 2:859–861.
84. Reiss AL, Abrams MT, Singer HS, Ross JL, Denckla MB (1996): Brain development, gender and IQ in children. A volumetric imaging study. *Brain* 119(Pt 5):1763–1774.
85. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, *et al.* (2000): Functional frontalisation with age: Mapping neurodevelopmental trajectories with fMRI. *Neurosci Biobehav Rev* 24:13–19.
86. Casey BJ, Giedd JN, Thomas KM (2000): Structural and functional brain development and its relation to cognitive development. *Biol Psychol* 54:241–257.
87. Tunbridge EM, Weickert CS, Kleinman JE, Herman MM, Chen J, Kolachana BS, *et al.* (2007): Catechol-o-methyltransferase enzyme activity and protein expression in human prefrontal cortex across the postnatal lifespan. *Cereb Cortex* 17:1206–1212.
88. Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ (2005): The neuropsychology of obsessive compulsive disorder: The importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci Biobehav Rev* 29:399–419.