ORIGINAL ARTICLE

Genotype Link With Extreme Antisocial Behavior

The Contribution of Cognitive Pathways

Kate Langley, PhD; Jon Heron, PhD; Michael C. O'Donovan, FRCPsych, PhD; Michael J. Owen, FRCPsych, FMedSci, PhD; Anita Thapar, FRCPsych, PhD

Context: As genes associated with common disorders are increasingly identified, we need to progress from observing associations to identifying risk pathways. The high-activity *COMT* genotype, in the presence of attention-deficit/hyperactivity disorder (ADHD), has previously been shown to be associated with extreme antisocial behavior. The same genotype has also been implicated in affecting cognitive function in healthy individuals. Impaired cognitive function might therefore lie on the risk pathway from genotype to clinical outcome.

Objectives: To replicate the association between *COMT* genotype and antisocial behavior in ADHD and to then test whether (1) impaired executive control or (2) impaired social understanding act as intermediate phenotypes for this association and lie on the risk pathway between *COMT* genotype and antisocial behavior.

Design: Prospective epidemiological cohort sample.

Setting: The Avon Longitudinal Study of Parents and Children.

Participants: Four thousand three hundred sixty-five children with data on *COMT* Val[158]Met genotype, ADHD symptoms and diagnoses, and measures of social cognition/understanding and executive control.

Main Outcome Measures: Antisocial behavior at age 7.5 years assessed using *DSM-IV* conduct disorder symptoms.

Results: We replicated the association of the high-activity *COMT* genotype, in the presence of ADHD, with extreme antisocial behavior (odds ratio, 2.82; 95% confidence interval, 2.02-3.94; $P<.001$ for the most severe antisocial behavior). The high-activity *COMT* genotype was associated with both executive control and impaired social understanding. The strength of the association between genotype and antisocial behavior was unchanged by including executive control in the model but dropped when impaired social understanding was included (odds ratio, 1.87; 95% confidence interval, 1.26-2.76; $P=.002$).

Conclusions: The high-activity *COMT* genotype in ADHD is associated with antisocial behavior in part via impaired social understanding. Impaired executive control was also associated with the high-activity *COMT* genotype but may not lie on the risk pathway to antisocial behavior. The findings demonstrate the importance of testing links between genotype, intermediate phenotype, and clinical outcome in the same sample to identify potential risk pathways.

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Author Affiliations: Department of Psychological Medicine and Neurology, School of Medicine (Drs Langley, O'Donovan, Owen, and Thapar), and MRC Centre for Neuropsychiatric Genetics and Genomics (Drs Langley, O'Donovan, Owen, and Thapar), Cardiff University, Cardiff, Wales; and Avon Longitudinal Study of Parents and Children, School of Social and Community Medicine, University of Bristol, Bristol, England (Dr Heron).

SEVERE ANTISOCIAL BEHAVIOR IS of tremendous societal and clinical concern.[1] The most severe and persistent subtype of antisocial behavior has its onset in childhood and is accompanied by attention-deficit hyperactivity disorder (ADHD),[2] a disorder characterized by impulsivity, hyperactivity, and inattention. This subtype of antisocial behavior has strong biological and genetic origins[3] and is a critical path into adult criminality and violence.[1,2,4] Three independent studies[5,6] report that this extreme antisocial behavior subtype is associated with the high-activity *COMT* (catechol *O*-methyltransferase) valine/valine (Val/Val) genotype. Having identified a robust genetic risk factor, a key step is to elucidate the specific brain mechanisms and pathways that underlie the genetic association.

It has been proposed that a powerful way of identifying mechanisms through which specific genetic risk factors influence disorder is to identify intermediate phenotypes,[7,8] which are internal phenotypes that are assumed to lie on the pathway between genes and disease. A problem with this approach is that the observation that a risk genotype is associated with both a putative intermediate phenotype and a clinical outcome does not prove a causal relationship between the 2 phenotypes.[9] Statistical approaches to this problem have been developed,[10] but to date, studies of psychiatric and behavioral phenotypes have not been appropriately designed or sufficiently powered to apply them. Thus, the burgeoning

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Table 1. List of Items Included in Antisocial Behavior and Social Cognitive Function Measures

DAWBA-Derived *DSM-IV* Conduct Disorder Items[a]	Social Cognitive Dysfunction Items[b]
Instructions to parents: How has your study child been over the past 12 months? Answer how he or she is usually, not just on the occasional "off days."	How much do the following descriptions apply to your study child?
Has he or she told lies to get things or favors from others or to get out of things he or she was supposed to do?	Not aware of others' feelings
Has he or she often started fights (other than with brothers and sisters)?	Does not realize when others are upset or angry
Has he or she bullied or threatened people?	Does not notice the effect of his or her behavior on other members of the family
Has he or she stayed out much later than he or she was supposed to?	Does not realize he or she offends people with his or her behavior
Has he or she stolen things from the house or other people's houses or shops or school?	
Has he or she run away from home or ever stayed away all night without your permission?	
Has he or she often played truant (bunked off) from school?	

Abbreviation: DAWBA, Development and Well-being Assessment.[28]
[a] Not all *DSM-IV* conduct disorder symptoms were assessed.
[b] Selected items from the Skuse Social Cognition Scale.[29]

literature reporting intermediate brain phenotypes such as performance on cognitive tasks that are associated with candidate genes[11-13] might simply be identifying phenotypes that share genetic risk with psychiatric outcomes (pleiotropy) rather than illuminating disease mechanisms. Large longitudinal cohort studies in which multiple behavioral and cognitive measures have been made offer a potentially powerful means to address these issues because each link in the hypothesized risk pathway can be tested in turn in the same sample. The present study provides a proof of principle of this approach.

On the basis of previous findings, we hypothesized 2 putative intermediate phenotypes for a risk pathway between the high-activity *COMT* Val/Val genotype in the presence of ADHD and antisocial behavior: impaired executive control and social cognitive dysfunction. These are plausible intermediate phenotypes because both executive control (eg, planning, suppressing inappropriate responses) and social cognition (processing social information) are stable, inherited characteristics that are precursors or risk factors for subsequent severe antisocial behavior (eg, fighting, stealing).[14,15]

Both these intermediate phenotypes have also been linked to the *COMT* Val[158]Met variant.[12-18] The *COMT* Val[158]Met genotype has been most extensively studied in relation to executive control performance. Although evidence is mixed,[16,17] many research groups have found better function in Met carriers and that the high-activity *COMT* Val/Val carriers perform more poorly on different executive control tasks.[16,18-21] The same *COMT* genotype has also been associated with social cognitive dysfunction, lower emotional responsiveness,[21] and higher pain sensitivity.[21,22] In a clinical study of children with ADHD, those with the high-activity genotype were rated as having lower social cognitive function.[23] Imaging studies in both adults[24] and children[21,25] suggest Val/Val carriers are less responsive to emotional (fearful faces) or unpleasant stimuli. These findings suggest those with the high-activity *COMT* genotype may have less understanding of others' feelings or be less emotionally and socially responsive to the feelings and behavior of others.[23]

We set out to (1) replicate the previously observed association of *COMT* Val[158]Met genotype with the extreme antisocial behavior subtype and then (2) test the hypothesis that either poor executive control and/or social cognitive dysfunction act as intermediate phenotypes for this association or, alternatively, are independent pleiotropic effects of the *COMT* Val[158]Met genotype.

METHODS

We tested these hypotheses in a representative[26] population cohort of UK children, the Avon Longitudinal Study of Parents and Children (ALSPAC).[26] ALSPAC originally recruited 14 541 pregnant women resident in Avon, England, with expected delivery dates of April 1, 1991, to December 31, 1992, and an additional 548 children at 7 years old who would have been eligible but whose mothers did not enroll during pregnancy. We used data from families who participated in questionnaire and clinic-based cognitive assessments when the children were aged 7.5 and 8 years, respectively.[27] Data for both points were available for 5726 individuals of European origin. Additionally, we excluded those with low IQ or pervasive developmental disorder (n=49). Genotyping data were unavailable for others (n=1161). Also accounting for those with missing data for individual items (n=151), a sample of 4365 children (51% male) was available for analyses.

Ethical approval for all aspects of the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. Parents provided written consent and their children assent at each assessment. The control of ALSPAC data ensures hypotheses are registered and only access to relevant specific data given, demonstrating the a priori nature of our putative intermediate phenotypes.

ADHD DIAGNOSES AND ANTISOCIAL BEHAVIOR SCORES

The Development and Well-being Assessment (DAWBA)[28] was administered to parents when their children were aged 91 months (7.5 years; mean [SD]=91.74 [1.56] months). The DAWBA assesses the presence of *DSM-IV* symptoms of psychiatric disorders as well as qualifying information regarding severity, longevity, and impact on functioning and well-being. Diagnoses of *DSM-IV* ADHD and conduct disorder were generated by the clinician authors of the DAWBA.[28] Individuals who met diagnostic criteria for a pervasive developmental disorder (n=7) or intellectual disability (full-scale IQ [FSIQ] <70) were excluded from analyses (n=42).

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The 7 DAWBA-derived *DSM-IV* conduct disorder items were rated by parents as having not, perhaps, or definitely occurred over the past 12 months (**Table 1**). Each reply scored 0, 1, and 2, respectively, and scores were summed to give an antisocial behavior score (mean [SD] = 0.51 [0.96]). As recommended by the ALSPAC statistical team, the prorated score, imputing individual missing items, was used. To account for the positive skew of our antisocial behavior outcome variable, as expected in a general population sample of children of this age, antisocial behavior was grouped into 5 categories of increasing severity based on scores of 0, 1, 2, 3 to 4, and 5 and higher that best resulted in more equally sized groups. Because our sample was aged 7.5 years, all antisocial behavior symptoms were of childhood onset,[30] thought to represent a persistent, more severe type of antisocial behavior.[1,2]

EXECUTIVE CONTROL TASKS

From the Test of Everyday Attention for Children battery[31] administered at age 8 years (mean [SD] score = 103.07 [2.67]), we selected the 2 measures considered to most closely tap executive control, the Sky search selective attention task and Opposite Worlds task.

The Sky search selective attention task assesses the time taken to identify identical pairs of spaceships within a group of mismatched pairs and loads with the Stroop Task in factor analysis (a measure of executive function).[31] The Opposite Worlds trial is a measure of executive control assessed using response inhibition. Participants had to inhibit a prepotent verbal response when reading a string of the numbers by saying 2 when presented with a 1 and vice versa. A Same Worlds score, reading the numbers as they appear, was subtracted from the Opposite Worlds score to account for differences in reading ability. The task has been described as tapping executive control[31] and is thought to most closely tap the same prefrontal cortex pathways as tasks such as the Wisconsin Card Sorting Test. Following previous analysis in this sample,[16] these measures were normalized using log 10 (Sky search selective attention task) and 1/square root (Opposite Worlds task) transformations.

SOCIAL COGNITIVE DYSFUNCTION

The measure of social cognition/social understanding was obtained using items tapping this construct from the parent-reported Skuse Social Cognition Scale at age 7.5 years[29] that most closely resembled the social dysfunction items in our previous study of *COMT*.[23] Four items (Table 1) rated on a Likert scale of not true, quite/sometimes true, and very/often true were summed to give a score between 4 and 12.

GENOTYPING

Genotyping was undertaken by KBioscience. Details of the assay design are available from their Web site (http://www.kbioscience.co.uk [select Lab Services, SNP Genotyping, and Chemistry Choice from the drop-down menu]). Only data from white participants of European origin were analyzed because of known ethnic differences in allele frequencies for this variant.

Allele frequencies were 0.51 for the Met allele and 0.49 for the Val allele; there was no deviation from Hardy-Weinberg equilibrium ($\chi^2_1 = 0.98$; $P > .10$) calculated using the χ^2 test. DNA was not available or was not of sufficient quality for genotyping for a number of families (n = 1013). Genotyping failed in 3.3% of the sample (n = 148). There were no significant differences on any measures for those for whom genotyping was unavailable or for whom genotyping failed. As in previous studies, we divided the sample into those with the high-activity Val/Val genotype (n = 1046; 24%) and those with 1 or more Met alleles (n = 3319; 76%).

STATISTICAL ANALYSIS

Replicating Association Between *COMT* Val[158]Met Genotype in the Presence of ADHD and Antisocial Behavior

To replicate the previously observed association, our outcome variable of antisocial behavior was regressed onto a 3-level predictor variable of *COMT* × ADHD. This was the product term of *COMT* Val/Val genotype (vs possession of ≥1 Met alleles) × ADHD (present/absent).

Testing Intermediate Phenotypes

A series of regression analyses were used. First, association between *COMT* genotype in the presence of ADHD and the putative intermediate phenotype was tested. Second, the relationship between the intermediate phenotype and antisocial behavior was examined. Where both associations were significant, the association between *COMT* genotype in the presence of ADHD and the antisocial behavior outcome variable was tested in the presence of the intermediate variable. Where the association between *COMT* × ADHD and antisocial behavior is reduced in the presence of the (significant) intermediate phenotype, this indicates that the intermediate phenotype is likely to be on the risk pathway.

We used cumulative logit models for ordinal data in our main analyses. We selected this method for ease of interpretation of results (odds ratios [ORs]) and to allow for the nonnormality of data. For these models, an OR was obtained for the transition between each group and its adjacent group (providing an OR for the transition between group 0 and group 1, an OR for the transition between group 1 and group 2, and so on). This enabled us to gain insights into the change in influence of a variable at differing levels of outcome severity.

Undertaken using the GOLOGIT2 commands in Stata version 10,[32] these models enable testing of the parallel lines assumption (that the effect of the independent variable is equal across each transition). Following this test, variables can then be constrained (resulting in a single OR across transitions) or unconstrained (different ORs across transitions) as required.

All analyses were performed on untransformed outcome and social cognitive dysfunction data (presented) and then repeated using transformed data. No differences in the findings were observed.

Sex was included in all analyses as a covariate but did not act as a moderator of our findings. Age was also investigated but because all individuals were assessed at similar ages, no significant effect was observed and so this covariate was dropped.

RESULTS

REPLICATING ASSOCIATION BETWEEN *COMT* Val[158]Met GENOTYPE IN THE PRESENCE OF ADHD AND ANTISOCIAL BEHAVIOR

We found strong evidence for association between the *COMT* Val[158]Met genotype, in the presence of ADHD, and antisocial behavior (**Figure 1**). The strength of association increased with higher levels of antisocial behavior (OR, 2.82; 95% confidence interval [CI], 2.02-3.94; $P < .001$ for >4 conduct disorder symptoms) (**Table 2**).

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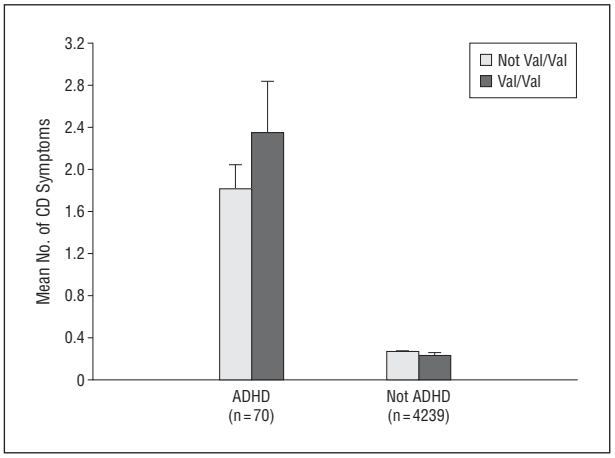

Figure 1. Association between *COMT* genotype and antisocial behavior. Val/Val genotype in the presence of attention-deficit/hyperactivity disorder (ADHD) increases antisocial behavior (*DSM-IV* conduct disorder [CD] symptoms).

As in the previous studies and as originally hypothesized,[5] the *COMT* Val[158]Met genotype was only associated with this extreme antisocial behavior subtype, not with antisocial behavior in those without ADHD ($\beta < 0.001$; $t = 0.02$; $P = .93$) or ADHD alone ($P > .20$).

Similar results, supporting our findings, were observed when FSIQ was added as a potential covariate (OR at most severe level of antisocial behavior, 2.75; 95% CI, 1.97-3.84; $P < .001$), the outcome measure was a diagnosis of conduct disorder (odds ratio, 3.37; 95% CI, 1.79-6.34; $P < .001$), there were teacher reports of antisocial behavior (OR, 1.47; 95% CI, 1.14-1.90; $P = .003$), and a dimensional measure of ADHD (parent-reported symptoms) was used (OR at most severe level of antisocial behavior, 1.68; 95% CI, 1.13-1.20; $P < .001$).

TESTING POTENTIAL INTERMEDIATE PHENOTYPES

The Val/Val genotype in the presence of ADHD was associated with both of the executive control measures (Sky search selective attention: $\beta = -0.05$; $t = -3.06$; $P = .002$; Opposite Worlds verbal inhibition score: $\beta = -0.07$; $t = -4.54$; $P = 6 \times 10^{-6}$) and social cognitive dysfunction ($\beta = 0.09$; $t = 5.87$; $P < 10^{-7}$).

We then tested the relationship between these putative intermediate phenotypes and extreme antisocial behavior. As was necessary to test for statistical purposes, social cognitive dysfunction scores and 1 of the 2 executive control tasks (Opposite Worlds) were significantly associated with antisocial behavior (OR at most severe level of antisocial behavior, 2.15; 95% CI, 1.84-2.50; $P < .001$ and OR, 0.02; 95% CI, 0.001-0.24; $P = .002$, respectively). Because the Sky search selective attention measure was not significantly associated with antisocial behavior, it was not taken forward for further analysis. We finally determined whether executive control and/or social cognitive dysfunction contributed to the association between the Val/Val genotype in those with ADHD and antisocial behavior.

Table 2 and **Figure 2** show these results. The magnitude of the genotype in the presence of ADHD association with antisocial behavior remained the same when the executive control measure was included in our model (Table 2 and Figure 2). When social cognitive dysfunction was entered into the model, the strength of the association between genotype in the presence of ADHD and antisocial behavior dropped both in the level of significance and the magnitude of the ORs (2.82 to only 1.87 for those with the most severe antisocial behavior) (Table 2 and Figure 2).

As some have suggested, FSIQ might be the cognitive measure most significantly associated with *COMT* genotype[33]; we also tested this. Although FSIQ was associated with *COMT* genotype in the presence of ADHD and antisocial behavior, it did not serve as an intermediate phenotype because no change to the strength of the genotype-outcome association was observed when FSIQ was added to the model (*COMT* × ADHD association at most severe level of antisocial behavior: OR, 2.75; 95% CI, 1.97-3.84; $P < .001$ with FSIQ in the model).

To ensure our findings were not due to mothers rating both clinical outcome and social cognitive dysfunction, we repeated the analysis using teacher ratings of antisocial behavior (parent-teacher correlation in antisocial behavior scores: $r^2 = 0.24$; $P < .01$; *COMT* × ADHD association with teacher reports of antisocial behavior, including social cognitive dysfunction: OR, 1.37; 95% CI, 1.04-1.80; $P = .02$).

Finally, we further tested the role of our putative intermediate phenotypes using structural equation modeling. Structural equation modeling analyses replicated our findings. When the effects of the 2 putative intermediate phenotypes were compared, significantly more of the *COMT* association with antisocial behavior in the presence of ADHD was explained by the social cognitive dysfunction pathway than through executive control (results available on request).

COMMENT

In the context of previous reports, our study now provides compelling evidence for association between extreme antisocial behavior in children and the *COMT* Val/Val genotype in people with ADHD. We next tested 2 candidate pathways that might link genotype to the antisocial phenotype, one related to executive control and the other to social cognitive dysfunction. Despite evidence for association between the *COMT* Val[158]Met variant and executive control, our findings suggest that *COMT* genotype in the presence of ADHD confers independent effects on executive control and antisocial behavior and that our measure of executive control may not act as a link between this genetic variant and antisocial behavior (**Figure 3**A). Our data more strongly support social cognitive dysfunction as an intermediate phenotype. Thus, the inclusion of social cognitive dysfunction in the model led to a drop in the magnitude of the genotype–antisocial behavior association (Figure 3B). While it accounted for a large proportion of the genotype–antisocial behavior association, our measure of social cognitive dysfunction does not explain all of it. This implies either that there are additional intermediate pathways or that our measure did not capture all the relevant variation in social cognitive dysfunction.

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Table 2. *COMT* Genotype in ADHD and Antisocial Behavior With and Without Putative Intermediate Phenotypes[a]

Predictor Variable	OR (95% CI)	*P* Value	Comparison of β, *t*, and *P* Values (Degree of Association) for *COMT* With and Without Intermediate Phenotypes
COMT × ADHD with no intermediate phenotypes	2.82 (2.02-3.94)	<.001	
COMT × ADHD with executive control as intermediate phenotype			
TEACH Opposite Worlds verbal inhibition score	0.02 (0.001-0.21)	.002	No change in OR
COMT × ADHD	2.77 (1.98-3.87)	<.001	
COMT × ADHD with social cognitive dysfunction as intermediate phenotype			
Social cognitive dysfunction score	2.03 (1.73-2.39)	<.001	Drop of 35% in OR
COMT × ADHD	1.87 (1.26-2.76)	.002	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio; TEACH, Test of Everyday Attention for Children.[31]
[a] Cumulative logit model for ordinal data analysis testing for association between the *COMT* high-risk genotype in the presence of ADHD and antisocial behavior without (model 1) and with (models 2 and 3) intermediate variables. Most severe levels of antisocial behavior are tabulated. Where an intermediate variable is included and the magnitude of the *COMT* association with antisocial behavior is reduced when compared with model 1, this indicates a significant intermediate phenotype variable.

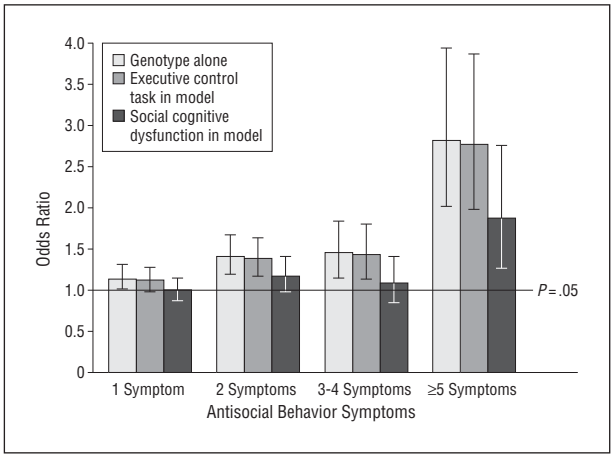

Figure 2. Association of *COMT* genotype in the presence of attention-deficit/hyperactivity disorder with antisocial behavior.

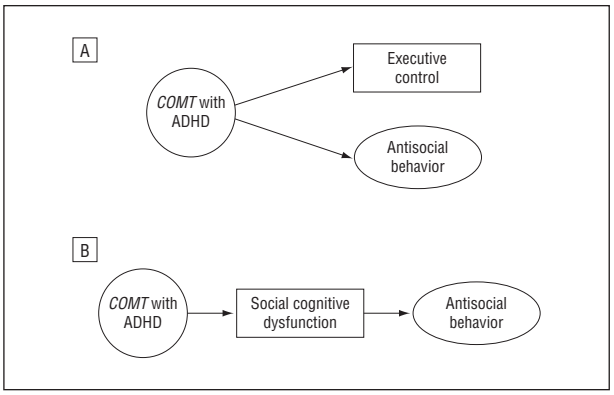

Figure 3. Associations between *COMT* genotype with attention-deficit/hyperactivity disorder (ADHD), putative intermediate phenotypes, and antisocial behavior. A, Association between *COMT* Val[158]Met genotype in the presence of ADHD and antisocial behavior with putative intermediate phenotype of executive control functioning, demonstrating possible independent effects. B, Association between *COMT* Val[158]Met genotype in the presence of ADHD and antisocial behavior with putative intermediate phenotype of social cognitive dysfunction; it is on the risk pathway for the association.

Our findings underline the fact that caution should be exercised before concluding that a putative intermediate phenotype lies on a pathway between genotype and behavioral and psychiatric outcomes, as has increasingly become practice in recent years.[34,35] Given that it is essential to identify causal links if treatments for a disorder that target putative intermediate phenotypes are to be successful, it will be important for the relationship between putative intermediate pathways and clinical outcomes to be evaluated more widely using similar approaches to those we report herein.

As we observe herein, the majority of studies, including meta-analyses, investigating the *COMT* Val[158]Met variant as a possible risk factor for ADHD do not report a significant association,[6,36,37] a finding replicated in this investigation. Our results and those from 2 previous epidemiological studies[6] also show no association between the *COMT* Val[158]Met variant and antisocial behavior alone. Instead, the association appears to be specific to antisocial behavior in those with ADHD. Twin and family studies[3,38] have previously demonstrated that antisocial behavior in ADHD indexes increased familial loading and heritability and some distinct (including genetic) etiological factors when compared with ADHD alone. It may be that the *COMT* Val[158]Met variant is one of the genetic risk factors within this specific group.

We chose to focus a priori on 1 variant, Val[158]Met, in the *COMT* gene for this analysis. That is because it is this specific variant that has previously been found to be associated with antisocial behavior in those with ADHD. To date, other *COMT* variants studied have not shown association.[6] It is also the variant that has been most widely investigated in relation to putative intermediate phenotypes. However, future studies could also investigate other variants that capture *COMT* gene variation.

Our findings may have potentially important implications for the treatment and prevention of the myriad negative consequences of early and extreme antisocial behaviors. First, this is the fourth independent demonstration that *COMT* genotype influences antisocial behavior in those with ADHD. This variant, like other associated genetic risk factors for complex disorders, is not a deterministic predictor of behavior. The ORs observed, while

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large in relation to other common risk alleles conferring risk to common disorders, are still only modest. However, these findings do provide clues about potential biological and cognitive mechanisms that underlie an important clinical problem. For example, given that current medication used to treat ADHD appears to have limited long-term benefits on associated antisocial behavior,[39] *COMT* inhibitors might be considered for evaluation in the treatment of this specific group with comorbid ADHD and antisocial behavior. Second, the finding that social cognitive dysfunction is on the risk pathway between *COMT* genotype with antisocial behavior in those with ADHD suggests that targeting social cognitive skills might prevent the development of antisocial behavior in this specific high-risk group of children with ADHD. Further investigation is needed to test these possibilities.

There are some limitations to our study. Although a large comprehensive cohort sample was used, not all individuals had sufficient data for inclusion in this study and only 1 measure of executive control was used. In such a large sample with a wealth of data, it would not be possible to have administered tests to assess all aspects of executive control; it is possible that other tasks may better index an intermediate phenotype on the risk pathway between genotype and disorder. This should be studied in more detail in more focused experimental studies including more detailed testing because we do not exclude the possibility that executive control is a contributor.

Our parent-rated measure of social cognitive dysfunction may not fully capture the necessary concept. However, because our measure did appear to be on the risk pathway, it is worthy of further investigation through more detailed and focused assessments. Any cohort or observational study, no matter how large, is insufficient on its own to prove causality, and designs, such as randomized controlled trials, are needed to confirm causal hypotheses.[40] Furthermore, although replicated using regression and structural equation modeling analyses, we cannot rule out the possibility of unmeasured confounding factors influencing our putative intermediate phenotypes.

CONCLUSIONS

Using a large cohort sample, we confirm the association between the high-activity *COMT* genotype and a severe subtype of antisocial behavior. For the first time, to our knowledge, we were also able to simultaneously test for links between genotype to putative intermediate phenotype and behavioral outcome in the same sample. The link between the high-activity *COMT* genotype, executive control, and antisocial behavior may represent independent pleiotropic effects of genotype rather than the presence of a causal pathway, whereas social cognitive dysfunction does appear to lie on the pathway between risk genotype and antisocial behavior.

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Correspondence: Kate Langley, PhD, Department of Psychological Medicine and Neurology, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, Wales (langleyk@cardiff.ac.uk).
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