BMC Psychiatry

BioMed Central

Research article

Open Access

No evidence of association between *Catechol-O-Methyltransferase (COMT) Val*^{158}*Met* genotype and performance on neuropsychological tasks in children with ADHD: A case-control study

Sophie Mills[1], Kate Langley[1], Marianne Van den Bree[1], Eddy Street[2], Darko Turic[1], Michael J Owen[1], Michael C O'Donovan[1] and Anita Thapar*[1]

Address: [1]Department of Psychological Medicine, University of Wales College of Medicine, Cardiff, CF14 4XN, UK and [2]Department of Child Health, University of Wales College of Medicine, Cardiff, CF14 4XN, UK

Email: Sophie Mills - millss1@cf.ac.uk; Kate Langley - langleyk@cf.ac.uk; Marianne Van den Bree - vandenbreemb@cf.ac.uk; Eddy Street - streetec@cf.ac.uk; Darko Turic - turicd1@cf.ac.uk; Michael J Owen - owenmj@cf.ac.uk; Michael C O'Donovan - odonovanmc@cf.ac.uk; Anita Thapar* - thapar@cf.ac.uk

* Corresponding author

Published: 07 June 2004

BMC Psychiatry 2004, **4**:15

Received: 08 January 2004
Accepted: 07 June 2004

This article is available from: http://www.biomedcentral.com/1471-244X/4/15

Abstract

Background: Several studies have suggested an association between the functional *Val*^{158}*Met* polymorphism in the *Catechol-O-Methyltransferase* (*COMT*) gene and neurocognitive performance. Two studies showed that subjects with the low activity *Met* allele performed better on the Wisconsin Card Sorting Test (WCST) and another study found an effect on processing speed and attention.

Methods: We set out to examine the association between the *Val*^{158}*Met* polymorphism and performance on neurocognitive tasks including those tapping working memory, attention and speed, impulsiveness and response inhibition in a sample of 124 children with ADHD. Task performance for each genotypic group was compared using analysis of variance.

Results: There was no evidence of association with performance on any of the neurocognitive tasks.

Conclusions: We conclude *that Val*^{158}*Met COMT* genotype is not associated with neurocognitive performance in our sample.

Background

There has been recent interest in the role of the enzyme *Catechol-O-Methyltransferase (COMT)* and prefrontal cognition. *COMT* together with monoamine oxidase catalyzes degradation of catecholamines [1] with *COMT* being responsible for the majority of dopamine catabolism in the frontal cortex. The *COMT* gene is located on chromosome 22q11 [2]. Most molecular genetic interest in *COMT* has focused on a *Val*^{158}*Met* polymorphism which affects the functional characteristics of the soluble isoform of *COMT*, with the *Met* variant being associated with lower activity and thermostability than the *Val* variant [3]. It is unclear whether the polymorphism affects the function of the membrane form of *COMT*, the major form in brain, in a similar manner.

A study by Egan et al (2001) [4] demonstrated that patients with schizophrenia, unaffected siblings and controls with the *Met* allele (low activity) performed better on the Wisconsin Card Sorting Test (WCST), [5] a neurocognitive test of prefrontal cognition [4]. This effect was more prominent when an individual had two copies of the *Met* allele. These findings have subsequently been replicated in a normal volunteer sample [6] in which fewer perseverative errors on the WCST were made by subjects homozygous for the *Met* allele. In another study of adult volunteers tested using the Attention Network Test (ANT), there was no association of the *COMT* variant with overall reaction time or alerting but there was a trend towards higher executive attention scores in those with the *Met* allele [7]. A more recent study of patients with schizophrenia [8] also reported evidence of association of this *COMT* variant with neurocognitive function, but with a measure of processing speed and attention, rather than executive function. Extending the sample used by Egan et al.,[4] Goldberg et al. (2003)[9] set out to identify which specific neurocognitive components within the WCST were related to *COMT Val*^{158}*Met* differences within Schizophrenic patients, their siblings and controls. Using the n-back task, Goldberg et al. found that genotype differences arose from measures of loading onto working memory rather than general attentional deficits (measured by the Continuous Performance task).

Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable disorder [9] that affects between 2 and 6% of school children.[11] ADHD is characterised by overactivity, impulsivity and inattention and is accompanied by neurocognitive deficits, including those involving executive function [12,13]. Neuropsychological [14] and functional brain imaging studies [15,16] have implicated the involvement of the prefrontal cortex and fronto-striatal pathways in the aetiology of ADHD. Given the importance of the dopaminergic system in ADHD and the associations between the neurocognitive abnormalities and the *Val*^{158}*Met* polymorphism, *COMT* is clearly a compelling candidate gene for ADHD. However, most groups, including our own, have failed to find evidence for association between polymorphisms in this gene and ADHD [17-21]. However, one study [22] has reported an association between the high activity *COMT* allele (*Val*) and a subtype of ADHD; DSM-IV hyperactive-impulsive type.

In this study, we have tested the hypothesis that the *Val*^{158}*Met COMT* polymorphism is associated with specific aspects of the ADHD phenotype, namely neurocognitive function as assessed by tasks that measure attention, response inhibition and, to some extent, working memory in children with ADHD.

Methods

Subjects

Families of children with suspected ADHD were recruited from Child and Adolescent Psychiatry clinics from Greater Manchester and Cheshire and invited to participate in a genetic study. The study was approved by the North West Multicentre Research Ethics Committee and informed written consent and assent was obtained from the families. Families of 124 children meeting ICD-10 criteria for Hyperkinetic Disorder or DSM-III-R/IV criteria for ADHD, who undertook the neurocognitive test battery and who had been genotyped for the *COMT* variant were included in the study. The sample were of British Caucasian origin (including the grandparents of the index child), drug-naïve, aged between 6 and 16 years (mean age 9.2 years, standard deviation 1.8 years). 114 were male and 10 were female. Exclusion criteria included children with an IQ test score below 70, as assessed by the Wechsler Intelligence Scale for Children-Third Edition UK (WISC-III^{UK}), [23] Tourette's syndrome, fragile X syndrome, epilepsy, pervasive developmental disorder, or other major neurological disorders.

Assessment

A research diagnostic interview; the Child and Adolescent Psychiatric Assessment (CAPA) [24] was completed with the parents of the children by trained interviewers all of whom had a degree in Psychology. To determine the diagnostic criterion of pervasiveness of symptoms across situations, the Child ADHD Teacher Telephone Interview (CHATTI) [25] was used to also assess ADHD symptoms and impairment at school. Interviews were audiotaped and tapes were checked for consistency between interviewers. Good inter-rater reliability was found [26]. Diagnoses were then assigned according to ICD-10, DSM-IV and DSM-III-R criteria. Further details of the assessment and diagnostic process and sample characteristics have been published previously [26].

Each child (n = 124) also completed the WISC-III^{UK} to assess IQ and to obtain a measure of working memory derived from the Arithmetic and Digit Span subtests. The forwards and backwards digit span subtest of the WISC III was used as a measure of both attention and working memory. At a second, school based, visit, a battery of neurocognitive tasks were administered, including the Matching Familiar Figures Test (MFFT), [27] the Continuous Performance Test (CPT) [28] and the Stop and Go no Go tasks from the MARS battery (Maudsley Attention and Response Suppression task battery).[14] Data were obtained for 114 children (10 children did not complete the task battery due to administrative difficulties in setting up a second visit at school). The MFFT measures impulse control from reaction time (RT) for correct and incorrect responses, and the number of pictures identified correctly

[27]. The CPT (identical pairs) measures inattention, based on the number of targets missed (omission errors), and sustained attention and impulse control, from the frequency of incorrectly pressing a button (commission errors) [28]. The display duration was 1 second with a inter-stimulus delay of 1.5 seconds. The Stop task and Go no Go task are measures of response inhibition. The number of successful inhibitions and mean reaction times (MRT) were obtained for these tests [14].

Genotyping

DNA was obtained from venous blood or mouthwash samples using standard techniques. Polymerase chain reactions (PCRs) were performed using the primers and conditions described by Norton et al (2002) [29]. The *Val*^{158}*Met* polymorphism was genotyped by single nucleotide primer extension using a template-directed dye-terminator incorporation assay with fluorescence polarization detection [30] based upon AcycloPrime™ reagents (Perkin Elmer Life Science Products, Boston, MA, USA) according to the manufacturers recommendations. Analyses were performed using a LJL Biosystems Analyst™ platform.

Statistics

Children were divided into 3 groups according to genotype (*Val*/*Val*, *Val*/*Met* and *Met*/*Met*) and task performance was compared using one way analyses of variance (ANOVA). A post hoc Bonferroni test was conducted for multiple comparison. All reported p-values have been corrected for multiple testing using Bonferroni statistics.

The groups were compared on all the task measures together using ordinal regression analysis. Power calculations revealed that our sample provides over 80% power to detect an effect size of 0.20 [31].

Results

Data from the WISC-III-R were available for 124 children and the CPT, MFFT and MARS battery were completed on 114 children. The groups did not differ in terms of gender or age. The mean scores on measures for each of the genotypic groups are shown in table 1. The results show no significant difference in attention, working memory or performance on any of the neurocognitive tasks between the three genotypic subgroups. These findings remained when data were analysed for males only (data available from authors). Similarly, where age was significantly associated with neuropsychological measures, this factor was used as a covariate in univariate ANOVAs. Again this did not alter the results (data available from authors). No neurocognitive measure accounted for a significant proportion of the variance in logistic regression analysis.

Discussion

We set out to examine the association between the functional *Val*^{158}*Met* polymorphism in *COMT* and neurocognitive task performance in a sample of children with ADHD. There was no evidence of differences in performance according to the genotypic group. No differences were found between those homozygous for the *Met* allele and those with other genotypes (details available from corresponding author on request). These findings contrast with those of previous studies that have suggested an association between the *COMT* variant and prefrontal cognitive functioning [4,6]. Two studies found an association of *COMT* genotype and performance on the Wisconsin Card Sorting task [4,6] in patients with schizophrenia and in normal adult controls. However in another study of patients with chronic schizophrenia [8], the *COMT* variant was associated with a measure of processing speed and attention and in a different study of adult volunteers, there was a trend toward association with executive atten-

Table 1: Comparison of neuropsychological test scores for each genotype and results of ANOVA

		COMT Genotype							
		Met/Met		*Met/Val*		*Val/Val*		ANOVA	
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	F	P
Working Memory	Freedom from distractability Score	16.65 (4.60)	23	16.51 (4.58)	70	16.55 (5.76)	31	0.007	0.993
MFFT	Mean Reaction Time of Incorrect	607.89 (441.08)	24	659.81 (628.27)	61	661.02 (508.34)	29	0.081	0.922
	Mean Reaction Time of Corrrect	670.17 (498.93)	24	690.30 (669.07)	61	719.86 (578.75)	29	0.045	0.956
	No. of Incorrect	40.29 (38.52)	24	50.57 (42.16)	61	40.28 (40.22)	29	0.896	0.411
CPT	Comission errors	41.92 (43.65)	24	51.15 (42.52)	61	46.41 (40.81)	29	0.437	0.647
	Omission errors	28.50 (41.74)	24	44.34 (47.57)	61	31.62 (42.54)	29	1.42	0.246
Stop Task	% Inhibition	73.45 (25.78)	24	81.95 (23.92)	61	69.32 (32.51)	29	2.456	0.09
	Mean Reaction time (ms)	383.13 (239.67)	24	325.13 (252.60)	61	341.05 (240.64)	29	0.475	0.623
Go No Go Task	% Inhibition	72.86 (24.28)	24	79.61 (22.99)	61	68.52 (29.61)	29	2.075	0.13
	Mean Reaction Time	316.40 (183.10)	24	258.66 (174.35)	61	276.66 (166.51)	29	0.946	0.391

tion scores [7]. Given the postulated link between the *COMT* variant and prefrontal cognition and the findings of Bilder et al, 2002, [8] we had primarily been interested in differences in the measures of response inhibition, attention and working memory.

Our results suggest that in children with ADHD, not only is there no evidence of association of the functional *COMT* variant with ADHD [17-21] but that there is also no association with neurocognitive task performance. Our findings suggest that although ADHD is characterised by neurocognitive deficits, in children with ADHD there are no effects of *COMT* on neurocognitive functioning. However there are alternative explanations for the results.

First, the sample size for which we have neurocognitive data available is small and thus our negative findings could be attributed to a lack of statistical power to detect small effects; in the study by Egan et al, 2001, [4] the *COMT* gentoype explained only 4% of the variance in the frequency of perseverative errors and a larger sample than ours would be needed to detect small effects. Second, previous studies have been based on patients with schizophrenia (and their unaffected siblings) or normal adults. It is plausible that the mechanisms that lead to impaired cognitive functioning are different in ADHD and that important developmental factors lead to contrasting findings in children and adults. Moreover, our sample consists of children who are drug naïve. This is a strength, but again findings could vary depending on exposure to medication. Finally, the Wisconsin Card Sorting Test was not used in this study and some (but not all) of the previously replicated findings were based on performance on this test specifically. It has not yet been resolved how *COMT* may be involved with neurocognitive functioning insofar as a more recent study found no evidence of association with the WCST but rather with processing speed and attention [8]. Nevertheless, it could be argued that our measures did not specifically assess prefrontal cognition in the same way that the Wisconsin Card Sorting Test does. In future studies, it would be advantageous to use the WCST.

Conclusion

We find no evidence of an association between the *COMT* *Val*^{158}*Met* genotype and performance on a variety of neurocognitive tasks in children with ADHD. Family-based studies of the *COMT* gene in this sample may shed further light on any association and are currently underway. Our findings indicate that if the *COMT* gene is involved in ADHD, or a specific phenotypic manifestation of the disorder, as has been suggested, such associations do not lie in differential performance on the neurocognitive tasks undertaken in this study.

Competing interests

None declared.

Authors' contributions

SM was involved in data collection, initial analysis and drafted the manuscript. KL was involved in data collection, participated in statistical analysis and developed the manuscript. MVB was involved in statistical analysis and editing the manuscript. ES provided clinical support during data collection and edited the manuscript. DT performed the genotyping and drafted sections of the manuscript. MO was involved in the study design and edited the manuscript. MO'D was involved in study design, laboratory coordination and editing the manuscript. AT conceived the study, participated in study design and coordination as well as contributing to the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This work has been funded by the Wellcome Trust, Action Research and SPARKS.

Deborah Lawson, Helen Pay, Jane Holmes, Tracey Hever, Richard Harrington, Tony Payton, Jane Worthington and Bill Ollier were involved in the first wave of the study. We thank all the clinicians who supported this work and Dr. Katia Rubia, Professor Eric Taylor and Professor Edmund Sonuga Barke who provided the neurocognitive test measures. Finally, we are especially grateful to all the families who participated in this study.

References

1. Sesack SR, Hawrylak VA, Guido MA, Levey AI: **Cellular and subcellular localization of the dopamine transporter in rat cortex.** *Advances in Pharmacology* 1998, **42:**171-174.
2. Grossman MH, Emanuel BS, Budarf ML: **Chromosomal mapping of the human catechol-o-Methyltransferase gene to 22q11.1-q11.2.** *Genomics* 1992, **12:**822-825.
3. Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilbourn RM: **Human catechol-O-Methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders.** *Pharmacogenetics* 1996, **6:**243-250.
4. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR: **Effect of COMT Val $^{108/158}$ Met genotype on frontal lobe function and risk for schizophrenia.** *Proceedings of the National Academy Sciences USA* 2001, **98:**6917-6922.
5. Heaton RK, Chelune GI, Talley JL, Kay GG, Curtiss G: **Wisconsin Card Sorting Test Manual.** *Odessa, Florida, Psychological Assessment Resources* 1993.
6. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D: **A Functional Polymorphism in the COMT Gene and Performance on a Test of Prefrontal Cognition.** *American Journal of Psychiatry* 2002, **159:**652-654.
7. Fossella J, Sommer T, Fan J, Wu Y, Swanson JM, Pfaff DW, Posner MI: **Assessing the molecular genetics of attention networks.** *BMC Neuroscience* 2002, **3(1):**14.
8. Bilder RM, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, Goldman RS, Hoptman MJ, Sheitman B, Lindenmayer J-P, Citrome L, McEnvoy JP, Kunz M, Chakos M, Cooper TB, Lieberman JA: **Neurocognitive correlates of the COMT Val^{158}Met polymorphism with Schizophrenia.** *Biological Psychiatry* 2002, **52:**701-707.
9. Goldberg TE, Egan MF, Gscheidle T, Coppola R, Weickert T, Kolachana BS, Goldman D, Weinberger DR: **Executive subprocesses in working memory: Relationship to Catelchol-O-Methyltrans-**

ferase Val158Met genotype and Schizophrenia. *Archives of General Psychiatry* 2003, **60:**889-896.
10. Thapar A, Holmes J, Poulton K, Harrington RL: **Genetic basis of attention deficit and hyperactivity.** *British Journal of Psychiatry* 1999, **174:**105-111.
11. Thapar A: **Attention Deficit Hyperactivity Disorder: New genetic findings, new directions.** In *Behavioural genetics in the post-genomic era* Edited by: Plomin R, Defries JC, Craig IW, McGuffin P. Washington DC: American Psychological Association; 2003:445-462.
12. Taylor E: **Syndromes of attention deficit and overactivity.** In *Child and Adolsecent Psychiatry: Modern Approaches* Edited by: Rutter M, Taylor E, Hersov L. Oxford: Blackwell Scientific; 1994:285-307.
13. Barkley RA: **Behavioural inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD.** *Psychological Bulletin* 1997, **121:**65-94.
14. Rubia K, Taylor E, Smith AB, Oksannen H, Overmeyer S, Newman S: **Neuropsychological analyses of impulsiveness in childhood hyperactivity.** *British Journal of Psychiatry* 2001, **179:**138-143.
15. Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, Yolanda CV, Vaituzis AC, Dickstein DP, Safaratti SE, Rapoport JL: **Implication of Right Frontostriatal circuitry in Response Inhibition and Attention-Deficit/Hyperactivity Disorder.** *Journal of the American Academy of Child & Adolescent Psychiatry* 1997, **36(3):**374-383.
16. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SCR, Simmons A, Bullmore ET: **Hypofrontality in Attention Deficit Hyperactivity Disorder During Higher-Order Motor Control: A study with Functional MRI.** *American Journal of Psychiatry* 1999, **156(6):**891-896.
17. Barr CL, Wigg K, Malone M, Schachar R, Tannock R, Roberts W, Kennedy JL: **Linkage Study of Catechol-O-Methyltransferase and Attention-Deficit Hyperactivity Disorder. American Journal of Medical Genetics.** *(Neuropsychiatric Genetics)* 1999, **88:**710-713.
18. Hawi Z, Millar N, Daly G, Fitzgerald M, Gill M: **No Association Between Catechol-O-Methyltransferase (COMT) Gene Polymorphism and Attention Deficit Hyperactivity Disorder (ADHD) in an Irish Sample.** *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 2000, **96:**282-288.
19. Tahir E, Curran S, Yazgan Y, Ozbay F, Cirakoglu B, Asherson PJ: **No Association Between Low-and High-Activity Catecholamine-Methyl-Transferase (COMT) and Attention Deficit Hyperactivity Disorder (ADHD) in a Sample of Turkish Children.** *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 2000, **96:**285-288.
20. Manor I, Ketter M, Sever Y, Eisenberg J, Cohen H, Ebstein RP, Tyano S: **Failure to Replicate an Association Between the Catechol-O-Methyltransferase Polymorphism and Attention Deficit Hyperactivity Disorder in a Second, Independently Recruited Israeli Cohort.** *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 2000, **96:**858-860.
21. Payton A, Holmes J, Barrett JH, Hever T, Fitzpatrick H, Trumper AL, Harrington R, McGuffin P, O'Donovan M, Owen M, Ollier W, Worthington J, Thapar A: **Examining for Association Between Candidate Gene Polymorphisms in the Dopamine Pathway and Attention-Deficit Hyperactivity Disorder: A Family-Based Study.** *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 2001, **105:**464-470.
22. Eisenberg J, Mei-Tal G, Steinberg A, Tartakovsky E, Zohar A, Gritsenko I, Nemanov L, Ebstein RP: **Haplotype relative risk study of Catechol-O-Methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): Association of the high-enzyme activity Val allele with ADHD impulsive-hyperactive phenotype.** *American Journal of Medical Genetics* 1999, **88(5):**497-502.
23. Weschler D: **Weschler Intelligence Scale for Children: UK.** *London:Psychological Corporation* 31992.
24. Angold A, Prendergast M, Cox A, Harrington R, Simonoff E, Rutter M: **The Child and Adolescent Psychiatric Assessment.** *Psychological Medicine* 1995, **25:**739-753.
25. Holmes J, Lawson D, Langley K, Fitzpatrick H, Trumper A, Pay H, Harrington R, Thapar A: **The Child Attention Deficit Hyperactivity Disorder Teacher Telephone Interview (CHATTI): reliability and validity findings.** *British Journal of Psychiatry* 2004, **184:**74-78.
26. Holmes J, Payton A, Barrett JH, Hever T, Fitzpatrick H, Trumper AL, Harrington R, McGuffin P, Owen M, Ollier W, Worthington J, Thapar A: **A family-based and case-control association study of the dopamine D4 receptor gene and dopamine transporter gene in attention deficit hyperactivity disorder.** *Molecular Psychiatry* 2000, **5:**523-530.
27. Sonuga-Barke EJS, Houlberg K, Hall M: **When is impulsiveness not impulsive?: The case of hyperactive children's cognitive style.** *Journal of Child Psychology & Psychiatry* 1994, **35:**1247-1253.
28. Corkum PV, Siegel LS: **Is the Continuous Performance Task a Valuable Research Tool for use with Children with Attention-Deficit-Hyperactivity Disorder?** *Journal of Child Psychology & Psychiatry* 1993, **34(7):**1217-1239.
29. Norton N, Kirov G, Krawczak M, Williams NM, O'Donovan M, Owen M: **Schizophrenia and functional polymorphisms in the MAOA and COMT genes: No evidence for association or epistasis.** *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 2002, **114(5):**491-496.
30. Hsu TM, Chen X, Duan S, Miller RD, Kwok PY: **Universal SNP genotyping assay with fluorescence polarization detection.** *Biotechniques* 2001, **31(3):**560-568.
31. Cohen J: **Statistical power calculations for the behavioural sciences.** *Laurence Erlbaum Associates, Hilldale, New Jersey* 21988.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-244X/4/15/prepub