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Does adult ADHD interact with *COMT val^{158}met* genotype to influence working memory performance?

Stefanie C. Biehl[1,2,*], Kathrin M. Gschwendtner[1,3], Anne Guhn[1], Laura D. Müller[1], Susanne Reichert[4], Julia Heupel[1], Andreas Reif[1], Jürgen Deckert[1], Martin J. Herrmann[1], Christian P. Jacob[1]

[1]Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstraße 15, 97080 Würzburg, Germany.

[2]School of Psychology, University of Aberdeen, William Guild Building, Aberdeen AB24 3FX, United Kingdom.

[3]Tumor Biology Center at the University of Freiburg, Germany, Breisacher Straße 117, 79106 Freiburg, Germany.

[4]Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstraße 15, 97080 Würzburg, Germany.

* Corresponding author:

Stefanie C. Biehl

Phone: +44 (0)1224 27-4459
E-mail: s.biehl@abdn.ac.uk

Abstract

Both ADHD and *COMT* genotype have been linked to altered dopaminergic transmission and possible impairment in frontal lobe functioning. This study offers an investigation of a possible interaction between ADHD diagnosis and *COMT* genotype on measures of working memory and executive function. Thirty-five adults with ADHD, who were recruited from the ADHD outpatient clinic at the Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, and thirty-five matched healthy controls completed the *Digit Span* test and the Stroop *Color Word Test*. While there were no main effects of ADHD or *COMT,* the two factors interacted on both *Digit Span* subtests, with the two groups' *met/met* carriers showing significantly different performance on the *Digit Span Forward* subtest and the *val/val* carriers showing significantly different performance on the *Digit Span Backward* subtest. Findings provide preliminary support for a differential impact of *COMT* genotype on working memory measures in adult patients with ADHD compared to healthy controls.

Keywords: adult ADHD; *COMT* genotype; working memory; executive function

Introduction

Attention deficit/hyperactivity disorder (ADHD) is known to impair the regulation of activity, behavioral impulses, and attention as well as various higher order cognitive processes like inhibitory control (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005) and working memory (Barkley, 1997; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Etiological models link ADHD to abnormalities in corticostriatal dopaminergic circuits (Sonuga-Barke, 2005). Neuroimaging findings support these theories by showing altered dopamine turnover in the striatum of ADHD patients, with methylphenidate – a medication known to counteract symptoms of ADHD – acting in the striatum by blocking dopamine re-uptake and thereby increasing synaptic dopamine levels (Krause, Dresel, Krause, Kung, & Tatsch, 2000; Krause, Dresel, Krause, la Fougere, & Ackenheil, 2003).

The gene coding the enzyme catechol-*O*-methyltransferase (COMT), which degrades neurotransmitters such as dopamine (Axelrod, 1957), has previously been studied as a potential candidate gene for ADHD and for possible neuropsychological phenotypes with conflicting results (Caylak, 2012; Kebir & Joober, 2011; Kebir, Tabbane, Sengupta, & Joober, 2009). Due to the low expression of the dopamine transporter in the prefrontal cortex, the COMT enzyme plays a critical role in clearing dopamine from the synaptic cleft in this area (Dickinson & Elvevag, 2009; Lewis et al., 2001; Lewis, Sesack, Levey, & Rosenberg, 1997; Meyer-Lindenberg & Weinberger, 2006; Tunbridge, Bannerman, Sharp, & Harrison, 2004). Furthermore, the activity of COMT has been hypothesized to influence striatal dopamine levels by acting on dopamine that has diffused from the synaptic cleft (Bilder, Volavka, Lachman, & Grace, 2004). Within the *COMT* gene, a functional single nucleotide polymorphism (rs4680) causes a valine (val) to methionine (met) substitution at codon 158 (*val*^{158}*met*) (Lachman et al., 1996), which leads to COMT isoforms that differ greatly in thermolability (Lotta et al., 1995). Two *met* alleles lead to a three to four times lower activity of COMT compared to two *val* alleles, with heterozygosity leading to intermediate COMT activity (Chen et al., 2004; Weinshilboum, Otterness, & Szumlanski, 1999).

According to the tonic-phasic model of subcortical dopaminergic functioning, the sustained tonic release of dopamine can regulate the intensity of the transient phasic dopaminergic response to relevant stimuli (Grace, 1991). In the cortex, the lower COMT activity associated with two *met* alleles has furthermore been hypothesized to lead to increased cortical dopamine concentrations and thus increased stimulation of D1 receptors (Bilder et al., 2004). This might result in increased stability of the neural networks underlying working memory functions in *met/met* carriers. In contrast, the lower concentrations of cortical dopamine caused by two *val* alleles should lead to increased D2 transmission and thus increased flexibility of these networks in *val/val* carriers (Bilder et al., 2004; Levy, 2007).

The influence of the *COMT* polymorphism on higher order cognitive functioning was previously explored in behavioral studies: Healthy *met/met* carriers showed better performance on a letter-number-sequencing test (Bruder et al., 2005), an n-back task (Goldberg et al., 2003), and the Wisconsin Card Sorting Test (Egan et al., 2001) than *val/val* carriers, with *val/met* carriers usually performing in between. A recent meta-analysis showed a positive association of two *met* alleles with IQ score. Associations for n-back performance were less clear, with two *met* alleles being associated with better performance for patient populations but one *val* allele being associated with better performance for non-patient populations (Barnett, Scoriels, & Munafo, 2008). The clinical studies reviewed in this meta-analysis examined the performance of schizophrenic patients. One of these studies found worse performance for all *val/val* carriers irrespective of diagnostic status (Diaz-Asper et al., 2008), while the other study focused on fMRI activation and suspected a left-shift of the inverted-U response curve of schizophrenic patients, leading to less efficient prefrontal functioning (Bertolino et al., 2006).

To our knowledge, only one study examined a sample of adults with ADHD to investigate the influence of *COMT* genotype on various measures of neurocognitive performance. This study found a positive association of the *val/met* genotype and full-scale IQ as assessed with the Wechsler Adult Intelligence Scale (WAIS) (Boonstra et al., 2008). The authors report no main effect of *COMT* genotype on the WAIS subtests *Digit Span Forward* or *Digit Span Backward*

or the Stroop *Color Word Test*. Two similar studies of children with ADHD found no effect of *COMT* genotype on performance on various measures of executive function (Mills et al., 2004; Taerk et al., 2004). However, a third study reports a negative association of *val/val* genotype and a delayed-match-to-sample task in children (Matthews et al., 2012), while a fourth study with children found a negative association of the *met* allele and a measure of sustained attention (Bellgrove et al., 2005). Overall, studies of the impact of *COMT* in ADHD patients show greatly differing results. This heterogeneity of results might either be caused by the different types of working memory measures used in these studies (Matthews et al., 2012), or it might point to an effect of *COMT* on cognition that is less robust than originally assumed. Our review of the literature yielded only one study that examined *COMT* genotype and neurocognitive performance in adult ADHD (aADHD) patients, while four studies investigated children and adolescents. None of the above-mentioned studies investigated a healthy control group.

Our study included carefully diagnosed adult ADHD patients and a healthy control group comparable with regard to age, gender, and years of formal schooling. All participants completed neuropsychological measures of verbal short-term memory, verbal working memory, and inhibitory control. The aim was to preliminarily investigate whether a possible influence of *COMT* genotype on task performance interacted with participants' ADHD diagnosis. The tasks were the same as in a previous study on aADHD and *COMT* (Boonstra et al., 2008). However, contrary to this study we also included a well-matched healthy control group to investigate possible interactive effects of these two factors. As *COMT* might influence performance on cognitive tasks across both patients and healthy controls, our study aimed to investigate whether adult patients with ADHD – a disorder known to affect dopaminergic transmission (Krause et al., 2000) – might be at an additional disadvantage caused by their *COMT* genotype. Furthermore, aADHD patients in our study were medication naïve or without medication for at least three months, meaning that any observed effects would likely not be induced by present stimulant treatment or the short-term discontinuation thereof.

Based on previous studies (Boonstra et al., 2005; Martinussen et al., 2005; Willcutt et al., 2005), we expected aADHD patients to perform worse than healthy controls on all investigated measures of higher order cognitive functioning. Furthermore, according to the tonic-phasic model of dopaminergic functioning (Bilder et al., 2004; Grace, 1991), the *COMT val* allele should be more detrimental to aADHD patients than to healthy controls in a gene-dosage fashion, with *val/val* aADHD patients showing the worst performance.

Methods

Participants

A total of 70 participants (thirty-five patients with ADHD and thirty-five healthy controls) of Caucasian ethnicity took part in a larger study that comprised fMRI measurements and neuropsychological assessments and were included in the analysis. The results of the fMRI measurements will be published elsewhere. Forty-one patients with aADHD were originally recruited from the ADHD outpatient clinic at the Department of Psychiatry, Psychosomatics, and Psychotherapy of the University of Würzburg. Of all recruited aADHD patients, three did not meet full inclusion criteria. Three more patients decided not to proceed with the study after inclusion. Diagnoses were made by an experienced psychiatrist according to DSM-IV-TR (2000). Patients had to be medication naïve or without medication for at least three months prior to testing. Of the investigated sample, 29 % (10 patients) had previously been treated with methylphenidate and/or atomoxetine, and 11 % (4 patients) had previously been treated with an antidepressant or antipsychotic. For 7 patients, no data regarding previous psychopharmacological treatment could be obtained.

To corroborate the initial diagnosis, all patients were administered the Wender-Reimherr-Interview (WRI) (Corbisiero, Buchli-Kammermann, & Stieglitz, 2010), the Conners' Adult ADHD Rating Scales (CAARS) (Conners, Erhardt, & Sparrow, 1999), and the Wender Utah Rating Scale (WURS) (Ward, Wender, & Reimherr, 1993). To assess possible comorbid axis I disorders (an exclusion criterion) and axis II disorders, all patients were assessed with the

Structured Clinical Interview for DSM-IV (SCID-I and SCID-II) (Wittchen, Zaudig, & Fydrich, 1997), the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). Of the investigated sample, 17 % (6 patients) fulfilled diagnostic criteria for an axis II disorder. Unfortunately, no reliable data regarding comorbid axis II disorders could be obtained for 4 of the investigated patients.

Healthy controls without a past or present diagnosis of ADHD were recruited from a previously established sample (see also Biehl et al., 2013; Gschwendtner et al., 2012) as well as through university advertisement. All participants had normal or corrected-to-normal vision, and control participants were free of neurological or psychiatric diseases. A subset of 35 healthy control participants was chosen from all recruited participants to match the patient group most closely in a case-control design ($p > .1$ for age, gender, and years of schooling; see table 1 for sample characteristics). All participants completed the Adult ADHD Self-Report Scale (ASRS) to obtain an estimate of any current ADHD-related symptomatology (Kessler et al., 2005)

Table 1 Means and standard deviations (in parentheses) of the sample characteristics for the groups

	Healthy controls (HC)	*Group with ADHD*
Number of participants (male)	35 (16)	35 (20)
Age	33.6 (9.6)	36.0 (9.9)
School years	11.2 (1.8)	10.6 (1.6)
Raw score Standard Progressive Matrices	49.0 (7.8)	49.1 (6.9)
Inattention[a]	11.5 (4.7)*	23.9 (5.2)*
Hyperactivity/Impulsivity[a]	9.7 (5.8)*	19.1 (6.6)*

Note. [a] Symptoms of inattention and hyperactivity/impulsivity as assessed with the ASRS (Kessler et al., 2005); * denotes significant between-group differences ($p < .001$) in two-tailed t-tests (df = 68)

Procedure

All participants completed the *Digit Span* subtest from the German version of the WAIS (Aster, Neubauer, & Horn, 2006). This test consists of increasingly long strings of 2 to 9 digits

(forward) or 2 to 8 digits (backward), which are read to the participants at a speed of one digit per second. The participant is then asked to repeat these digits back to the examiner, either in the presented order (*Digit Span Forward*) or in backward order (*Digit Span Backward*). If the participant can give the correct answer for at least one of two presented strings, the examiner moves on to the next longer string. The number of correctly repeated strings for each of the two subtests is used as performance measure.

Participants also completed a German version of the Stroop *Color Word Test* (Bäumler, 1985). This test comprises three different subtasks: Naming the color of color blocks, reading color words, and naming the color that was used to print color words (e.g. if the word “blue” is printed in red ink, the participant is required to say “red”). Each subtask is completed three times and the median completion times are used in the analysis. We analyzed the time for naming the color of color blocks as a measure of psychometric speed. The time for naming the color of color words was then divided by the psychometric speed to obtain a measure of inhibitory control.

In addition, the Standard Progressive Matrices (Kratzmeier & Horn, 1988) were administered to obtain an estimate of intellectual functioning. All participants were genotyped for the *COMT val*^{158}*met* polymorphism. Blood was taken and DNA was extracted using a standard de-salting procedure. A standard PCR procedure (slightly modified from the protocol used by Egan et al., 2001) was used to determine *COMT* genotypes, which did not deviate from Hardy-Weinberg equilibrium. Eighteen participants were genotyped as *met/met* (control group: 8; patient group: 10), thirty-five as v*al/met* (control group: 17; patient group: 18), and seventeen as v*al/val* (control group: 10; patient group: 7).

Statistical Analysis

Given the unequal cell sizes caused by the distribution of the *COMT* genotype in the general population, data were analyzed using a non-parametric equivalent of a two-way analysis of variance (ANOVA) that ranks observations for the levels of one factor within the levels of the other factor (Prescott & Shahlaee, 1999; Shirley, 1987). Number of correctly reproduced

strings in *Digit Span Forward*, number of correctly reproduced strings in *Digit Span Backward*, and the median time for naming the color of color words divided by psychometric speed each served as dependent variables. ADHD diagnosis and *COMT* genotype were entered as fixed factors in all analyses. Mann-Whitney-U tests for independent samples were used for post-hoc comparisons and Cohen's *d* is reported to provide a measure of effect size for the post-hoc tests. For all analyses, *p*-values < .05 were considered significant.

Results

For *Digit Span Forward* (verbal short-term memory), we found no significant main effect of ADHD diagnosis ($p = .16$) or *COMT* genotype ($p = .28$). There was, however, a trend level interaction of ADHD diagnosis and *COMT* genotype ($F_{(2,64)} = 2.81$, $p = .07$). Post-hoc tests revealed a significant difference between the two groups for carriers of the *met/met* genotype ($p = .03$, $d = 1.0$), with the group with ADHD performing significantly worse than the healthy control group (see figure 1; see table 2 for all means and standard deviations). There were no comparable differences for carriers of the *val/met* genotype ($p = .25$, $d = 0.4$) or the *val/val* genotype ($p = .54$, $d = 0.3$).

Table 2 Means and standard deviations (in parentheses) of the neuropsychological tests, split by group and *COMT* genotype

		Digit Span: Forward	*Digit Span: Backward*	*Stroop: Inhibitory Control*
HC	*Met/Met* (8)[a]	11.0 (2.6)*****	7.6 (2.9)	1.57 (0.20)
	Val/Met (17)	10.1 (1.4)	6.7 (1.6)	1.60 (0.18)
	Val/Val (10)	10.3 (2.3)	8.9 (2.3)*****	1.58 (0.23)
ADHD	*Met/Met* (10)	8.5 (2.4)*****	6.9 (2.5)	1.67 (0.17)
	Val/Met (18)	10.9 (2.1)	7.7 (2.3)	1.60 (0.18)
	Val/Val (7)	9.6 (2.0)	6.3 (1.8)*****	1.52 (0.06)

Note. [a] Number of participants per group; ***** denotes significant between-group differences ($p < .05$)

For *Digit Span Backward* (verbal working memory), we similarly found no significant main effect of ADHD diagnosis (p = .24) or *COMT* genotype (p = .85). However, there was a significant interaction of ADHD diagnosis and *COMT* genotype ($F_{(2,64)}$ = 3.27, p = .04). Post-hoc tests revealed a significant difference between the two groups for carriers of the v*al/val* genotype (p = .03, d = 1.3), with the group with ADHD performing significantly worse than the healthy control group (see figure 1). There were no comparable differences for carriers of the *met/met* genotype (p = .83, d = 0.3) or the *val/met* genotype (p = .37, d = 0.5)

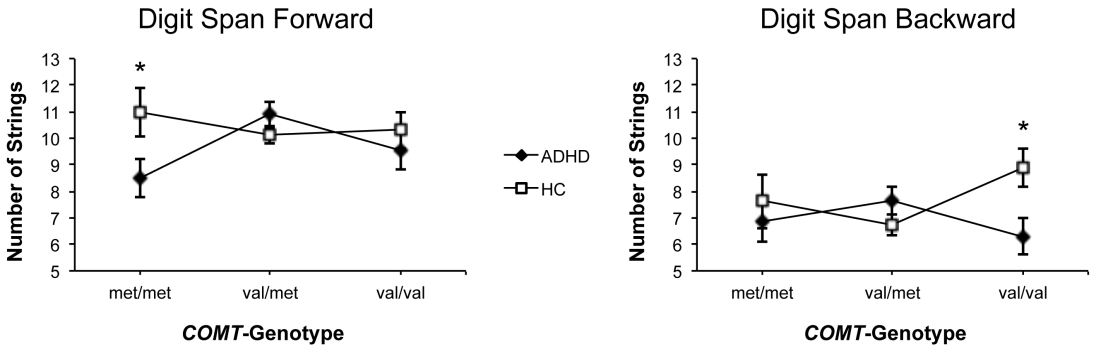

Figure 1 Mean number of correctly reproduced digit strings in the *Digit Span Forward* and in the *Digit Span Backward* subtest, for patients with ADHD and healthy controls and the different *COMT* genotypes. Error bars denote standard error of the mean (SEM). Significant between-group differences (p < .05) are marked by *****

For the Stroop *Color Word Test* (inhibitory control) we found neither a significant main effect of ADHD diagnosis (p = .64) nor *COMT* genotype (p = .37) nor a significant interaction (p = .40).

Discussion

This study aimed to investigate a possible interaction effect of *COMT* genotype and adult ADHD on different measures of working memory and executive function. A possible limitation of this investigation concerns the selection of the patient sample. As inclusion criteria were

rather strict, the obtained results might only apply to a subgroup of aADHD patients, who are still comparably well adjusted.

A further limitation of this study is the small sample size for some of the cells. Caused by the distribution of the *val* and *met* alleles in Caucasian populations (Palmatier, Kang, & Kidd, 1999), we investigated fewer homozygous than heterozygous participants. Especially for the homozygous participants, it is therefore possible that some other factor might have differed between the investigated groups and was not sufficiently counterbalanced, thus affecting the reported results. Although our results can therefore only be regarded as preliminary, we still found interaction effects of genotype and ADHD diagnosis on measures of verbal short-term memory and verbal working memory. Interestingly, the results show substantial effect sizes for a differential impact of *COMT* genotype and ADHD depending on the nature of the task: While *met/met* carriers with ADHD seemed to be at a disadvantage on the measure of verbal short-term memory compared to the other genotypes and healthy controls, *val/val* carriers with ADHD did not seem to profit in the same way as healthy *val/val* carriers on the measure of verbal working memory. There were no significant effects for the Stroop *Color Word Test*.

This pattern of results is more complex than initially hypothesized. Still, our results can be interpreted in terms of the tonic-phasic model of increased stability or flexibility, depending on *COMT* genotype (Barnett et al., 2008; Bilder et al., 2004; Durstewitz & Seamans, 2008; Matthews et al., 2012): The measure of verbal short-term memory (*Digit Span Forward*) required the reproduction on increasingly long strings of numbers. It would therefore seem logical for *met/met* carriers to show better performance, as increased tonic dopamine – and thereby increased representational stability – would be advantageous in this task. However, compared to the healthy control group, the group with ADHD did not show this advantage. This finding is in line with another study that reported worse performance for *met* allele carriers with ADHD on a measure of sustained (i.e. stable) attention (Bellgrove et al., 2005). In contrast, the measure of verbal working memory (*Digit Span Backward*) required retention of lists of numbers as well as internal manipulation of these lists before reproduction. It could therefore be expected to favor *val/val* carriers as this genotype affords increased phasic

dopamine and thereby increased mental flexibility. Compared to healthy controls, patients with ADHD again did not show the expected advantage.

To summarize, although we did not find main effects of *COMT* or ADHD on the investigated measures, two of the three tasks showed interactions of *COMT* genotype and ADHD diagnosis. Our results therefore point to a possible shift in the hypothesized inverted-U response curve of dopaminergic functioning in adults with ADHD compared to healthy controls (Bellgrove et al., 2005; Mattay et al., 2003).

Given our relatively small overall sample size, the achieved power was certainly not sufficient to detect more subtle differences. These results do, however, point to the possibility of differential *COMT* effects in patients with ADHD compared to healthy controls. Given this effect of *COMT* in patients and in non-patients found in our study and also in the general *COMT* literature (Barnett et al., 2008), future patient studies would likely benefit from including healthy control groups.

Ethical Standards

Ethical approval was obtained through the Ethical Review Board of the Medical Faculty of the University of Würzburg; all procedures involved were in accordance with the 2008 Declaration of Helsinki. Participants gave written informed consent after full explanation of procedures.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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