Sex effects for the interaction of dopamine related genetic variants for COMT and BDNF on declarative memory performance

Sandra Van der Auwera1,2 | Jan Terock3 | Alexander Teumer4 | Georg Schomerus5 | Georg Homuth6 | Hans J. Grabe1,2

1Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany
2German Centre of Neurodegenerative Diseases (DZNE), Greifswald, Germany
3Department of Psychiatry and Psychotherapy, University Medicine Greifswald, HELIOS Hanseklinikum Stralsund, Stralsund, Germany
4Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany
5Department of Psychiatry and Psychotherapy, University of Leipzig Medical Center, Leipzig, Germany
6Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany

Correspondence
Sandra Van der Auwera, Department of Psychiatry, University Medicine Greifswald, Ellenholzstraße 1-2, 17489 Greifswald, Germany.
Email: auweras@uni-greifswald.de

Funding information
Federal State of Mecklenburg-West Pomerania; Siemens; Ministry of Cultural Affairs and the Social Ministry of the Federal State of Mecklenburg-West Pomerania; Federal Ministry of Education and Research, Grant/Award Numbers: 01ZX1614E, 03ZIK012, 01ZZ0403, 01ZZ0103, 01ZZ9603

Abstract
Genetic factors are assumed to contribute to memory performance, especially genes affecting the dopaminergic neurotransmission. We aimed to evaluate leading functional genetic variants of the dopamine system, Catechol-O-methyltransferase (COMT) SNP rs4680 and Brain-derived neurotropic factor (BDNF) SNP rs6265, previously found to be associated with memory performance. In two independent general population cohorts (total N = 5937) we investigated direct and interaction effects between COMT and BDNF SNPs on declarative memory performance. We found significant two-way interactions for COMT and BDNF in both cohorts but no direct genetic effects. Sensitivity analyses revealed that an interaction between COMT and BDNF was mainly carried by females. While direct associations of COMT and BDNF on memory have been reported previously, we could demonstrate that the interaction of COMT and BDNF is sex-dependent and more complex and needs further investigation. Our results could be demonstrated in two independent cohorts of valuable size.

KEYWORDS
BDNF, COMT, delayed memory, gene–gene interaction, sex effect

INTRODUCTION
Neurocognitive performance comprises a wide range of cognitive tasks including reading and mathematics performance, visual and verbal memory, problem solving, or learning.1 This neurocognitive performance generally declines with age2 and is also associated to a wide range of psychiatric and neurological disorders like schizophrenia, depression,3,4 Alzheimer’s, or Parkinson’s disease.5 The individual cognitive decline is likely attributed to a wide range of causes including environmental and genetic influences. On the genetic side evidence suggests that the neurotransmitter dopamine plays an important but complex role in several cognitive processes.6 A major candidate gene...
for cognition and especially memory function is Catechol-O methyltransferase (COMT), an enzyme that catabolizes dopamine. Within the COMT gene the single nucleotide polymorphism rs4680 (COMT Val158Met) is of major interest. The exchange of valine and methionine at codon 158 leads to a common variant that reduces COMT activity and by that increases dopamine availability. Studies report that carriers of the Val-allele show reduced performance in several cognitive tasks compared to Met/Met homozygotes but meta-analyses yielded inconclusive results for the role of COMT Val158Met on cognitive performance. Another possible candidate is the rs6265 (Val66Met) polymorphism in the BDNF gene (brain-derived neurotrophic factor), a gene which is important for the growth of neurons and highly expressed in regions that are vital to learning and memory. The Met-allele of rs6265 was found to increase the activity dependent secretion of BDNF by altering the intracellular trafficking and was associated with lower hippocampal N-acetyl-aspartate levels and with impaired episodic memory. Nevertheless, meta-analyses could not confirm the role of BDNF Val66Met on cognitive performance or memory. Importantly, there are many lines of experimental evidence that demonstrate a functional interconnection between the serotonin system and BDNF, especially in neurogenesis and synaptic plasticity. Both polymorphisms, COMT rs4680 and BDNF rs6265, are involved in the dopamine system, modulate stress reaction and cognitive function and are associated with several psychiatric disorders. These findings indicate a possible genetic epistasis between COMT Val158Met and BDNF Val66Met polymorphisms (further referred to as COMT and BDNF). This principle of genetic interaction between COMT and BDNF has indeed been shown in previous studies for cognition related traits. Witte et al. reported an interaction of BDNF Val-allele homozygotes and COMT Met-allele homozygotes on better performance on implicit grammar learning in a small sample of females (N = 32). Whereas, Das et al. found a positive effect of the interaction between BDNF Met-allele carriers and COMT Met-allele carriers on cognitive performance in a sample of N = 400 older adults. Similar Han et al. report higher scores in word reading tests for BDNF Met homozygotes and COMT Met homozygotes in schizophrenia (N = 96) and Konishi et al. found a three-way-interaction between panic disorder*BDNF*COMT on extraversion (N = 928). Another three-way interaction is reported by Sapkota et al. between COMT*BDNF*APOE-4 on executive function performance in N = 634 older adults. Using fMRI resting state Chen et al. found an effect of BDNF*COMT interaction on working-memory related brain areas (N = 298). However, these still inconsistent results regarding the effect allele cannot provide a full picture of the BDNF*COMT interaction on cognition. Moreover, sample size varied between N = 32 and N = 928 which is still far too small for genetic interaction analyses, especially in three-way analyses. Another influencing factor is the putative sex-dependency of the dopaminergic system, especially in association with substance use disorders.

We aim to explore the interaction between COMT rs4680 and BDNF rs6265 in two independent samples with overall sample size N = 5937 to analyze the still inconclusive findings. We hypothesize that the COMT and BDNF genetic polymorphisms as well as their combination have an impact on memory function in the general population. We further hypothesize that effects are sex-dependent.

2 | MATERIAL AND METHODS

2.1 | Study sample and phenotypes

We analyzed data from the Study of Health in Pomerania (SHIP) comprising adult German residents in northeastern Germany. A two-stage stratified cluster sample of adults aged 20–79 years was randomly drawn from local registries. 4308 Caucasian subjects participated at baseline (1997–2001). As part of the SHIP baseline study 2400 subjects were included in the “Life-Events and Gene-Environment Interaction in Depression (LEGEND)” sample, a sub-sample with extended examination of various psychosocial, clinical and metabolic factors. Among others, subjects were administered the auditory Verbal Learning and Memory Test (VLMT), a German adaptation of the widely used Rey Auditory Verbal Learning Test. The VLMT was used to assess short-term learning as well as delayed retrieval. Subjects were asked to remember neutral semantically unrelated nouns from an orally presented list in three consecutive encoding runs. Participants have 120 s after each encoding run for immediate retrieval. A sum score of the correctly remembered terms of the three encoding runs was formed to measure short-term learning. Late retrieval was tested 20 min after the first encoding trial. The number of correctly remembered words reflected long-term retrieval.

In 2008 a new independent sample called SHIP-TREND (N = 4420) from the same area was drawn, encompassing similar examinations like SHIP-LEGEND. However, instead of the VLMT, the word list of the Nuremberg Age Inventory (NAI) was used as a measure for immediate- and delayed memory performance. The NAI is a German test developed to measure the cognitive abilities during brain aging. It consists among others subtests of a list of eight neutral words. Eight words are read to the participant, who is asked to recall as many words as possible immediately. After 20 min the participant is asked to retrieve the eight words previously learned from a list containing eight additional distractor words in a passive recall. The number of correctly identified words is summarized to a sum score minus the number of identified distractor words.

The investigations in both studies were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. The survey and study methods were approved by the institutional review boards of the University of Greifswald.

2.2 | Genetic data

The SHIP sample was genotyped using the Illumina HumanSNP Array 6.0. The overall genotyping efficiency was 98.55%. Genotyping of a subset of the SHIP-TREND subjects (N = 986) was performed using the Illumina HumanOmni 2.5-Quad. The final sample call rate was 99.51%. The remaining SHIP-TREND sample (N = 3133) was genotyped using the Illumina GSA-24. Arrays with a genotyping call rate < 94% were removed. For further details see.
Imputation of genotypes was performed using the HRCv1.1 reference panel and the Eagle and minimac3 software implemented in the Michigan Imputation Server for pre-phasing and imputation, respectively. SNPs with a Hardy–Weinberg-Equilibrium p-value <0.0001, a call rate < 0.95, and a MAF <1% were removed before imputation.

After exclusion of subjects due to missing data, at least 2098 subjects from SHIP LEGEND and 3839 subjects from SHIP-TREND were included in our analyses.

2.3 | Statistical analyses

In both samples, linear regression analyses assuming an additive effects of the SNPs were applied in order to calculate predictive effects of the genetic variants of COMT and BDNF on early as well as delayed recall of neutral words. Additional gene–gene-interaction analyses were performed. To account for the nonnormal distribution of the outcome variables from VLMT and NAI, confidence intervals, and p-values were assessed through bootstrap with 1000 replicates. To ease comparison of effects, the word recall scores have been z-transformed prior to analyses. As two genetic variants were tested for their effects on verbal memory in two independent cohorts, significance p-value was set to p < 0.0125. Analyses were performed using STATA/MP software, version 13 (StataCorp LP, College Station, TX).

3  | RESULTS

Demographic results and allele frequencies for BDNF and COMT.

There were no significant group differences between SHIP-LEGEND and SHIP-TREND for COMT or BDNF frequencies (Chi²-test: p = 0.12 and p = 0.44). Both SNPs were in Hardy–Weinberg equilibrium in both samples (all p > 0.1). The minor allele frequencies were 14% and 19% for BDNF and 47% and 46% for COMT in SHIP-LEGEND and SHIP-TREND, respectively. A detailed demographic characteristic is given in Table 1. In general, females performed significantly better than males in all verbal memory tests, age was highly associated with lower verbal memory score (p < 0.001) as well as higher education level.

3.1 | Direct effects of COMT and BDNF

In SHIP-LEGEND there was a positive nominal significant association between the Val-allele of COMT and delayed recall of words

### TABLE 1 Demographic characteristic for LEGEND and TREND VLMT/NAI scores

|                      | LEGEND (N = 2098) | TREND (N = 3839) | p       |
|----------------------|------------------|-----------------|---------|
| Age in years         | 55.3 ± 13.8 [29–89 years] | 51.6 ± 15.3 [20–83 years] | <0.001a |
| Sex                  |                  |                 | P = 0.36b |
| Females              | 1102 (53%)       | 1967 (51%)      |         |
| Males                | 996 (47%)        | 1872 (49%)      |         |
| BDNF (rs6265)        |                  |                 | P = 0.44b |
| Met/Met (T/T)        | 70 (3.3%)        | 151 (3.9%)      |         |
| Val/Met (C/T)        | 626 (29.8%)      | 1165 (30.3%)    |         |
| Val/Val (C/C)        | 1402 (66.9%)     | 2523 (65.8%)    |         |
| COMT (rs4680)        |                  |                 | P = 0.12b |
| Met/Met (A/A)        | 604 (28.8%)      | 1078 (28.1%)    |         |
| Val/Met (G/A)        | 1017 (48.5%)     | 1960 (51.1%)    |         |
| Val/Val (G/G)        | 477 (22.7%)      | 801 (20.8%)     |         |
| VLMT (only LEGEND)   |                  |                 |         |
| Immediate recall     | 24.6 ± 6.3, range: 1–45 | NA             |         |
| Late recall          | 7.9 ± 3.1, range: 0–15 | NA             |         |
| NAI (only TREND)     |                  |                 |         |
| Early recall         | NA               | 5.2 ± 1.3, range: 0–8 |         |
| Delayed recall       | NA               | 5.7 ± 1.7, range: 0–8 |         |
| Education            |                  |                 | P < 0.001b |
| <10 years            | 565 (26.9%)      | 844 (22%)       |         |
| 10 years             | 1115 (53.1%)     | 2011 (52.4%)    |         |
| >10 years            | 418 (20%)        | 984 (25.6%)     |         |

*p-value from t-test.

b p-value from chi² test.
(β = 0.06, p = 0.021) but missed significance for immediate recall (p = 0.054). A direct association could not be replicated in SHIP-TREND. BDNF exhibited no direct effect on recall of words neither in SHIP-LEGEND nor in SHIP-TREND (see Table 2).

### 3.2 | Gene–gene interaction (COMT*BDNF)

We observed nominal significant gene–gene interactions only for delayed recall in both samples (SHIP-LEGEND: β = 0.1, p = 0.032; SHIP-TREND: β = 0.07, p = 0.049) with higher scores in word recall when carrying the Val-alleles for COMT rs4680 and BDNF rs6265. The size of the gene–gene interaction subgroups was between 12 and 670 individuals in SHIP-LEGEND and between 33 and 1281 in SHIP-TREND. All results remained significant even after additional adjustment for current depressive symptoms measured with the Beck Depression Inventory II (see ref. (25)).

### 3.3 | Sex-separated sensitivity analyses

As previous studies have found sex differences in dopamine neurobiology, we additionally analyzed sex differences regarding the association with verbal memory. In sex-separated analyses we could see that this specific effect was only influenced by the female sample (SHIP-LEGEND: β = 0.18, p = 0.0074; SHIP-TREND: β = 0.16, p = 0.0029) while in men there was no gene–gene interaction (Table 3, Figure 1).

These analyses exceeded the corrected p-value of p < 0.0125 for multiple testing. Because the minor allele frequencies for BDNF was very low (SHIP-LEGEND MAF = 14%, SHIP-TREND MAF = 19%), we ran sensitivity analyses for the sex separated two-way interaction BDNF*COMT by dichotomizing only BDNF genotype (Met-allele carriers vs. Val-allele homozygotes). The gene–gene interaction in females remained significant in both samples (SHIP-LEGEND p = 0.0084, SHIP-TREND p = 0.0096).

Based on this dichotomization we analyzed the effect of COMT in BDNF Met-allele carriers and BDNF Val-allele homozygotes separately. Within the BDNF Val-allele homozygotes group, COMT was significantly associated with delayed recall independent of sex (SHIP-LEGEND N = 1402, β = 0.1, p = 0.001; SHIP-TREND N = 2523, β = 0.016, p = 0.07) as depicted in Figure 1 with the Val-allele for COMT associated with higher verbal memory score.

### 4 | DISCUSSION

Our results showed that the interaction of COMT rs4680 and BDNF rs6265 genotype has an influence on memory performance in the general population especially with regard to sex. These results could be supported in two independent samples of valuable size (each sample N > 2000).

It is well known that genetic polymorphisms are associated with memory function as episodic memory is a heritable and polygenic trait. Both genes, COMT and BDNF are well established candidate

| TABLE 2 | Direct genetic effects of COMT and BDNF on recall of words in each sample as well as sex-separated |

|                | LEGEND (N = 2098) | TREND (N = 3839) |
|----------------|------------------|-----------------|
| **Immediate recall** |                  |                  |
| COMT           | β = 0.05, CI = -0.001, 0.10, p = 0.054 | β = 0.02, CI = -0.03, 0.06, p = 0.46 |
| BDNF           | β = -0.02, CI = -0.08, 0.05, p = 0.56  | β = 0.02, CI = -0.03, 0.07, p = 0.48 |
| **Delayed recall** |                  |                  |
| COMT           | β = 0.06, CI = 0.01, 0.11, p = 0.021, | β = 0.03, CI = -0.01, 0.07, p = 0.17 |
| BDNF           | β = -0.02, CI = -0.09, 0.05, p = 0.62, | β = -0.01, CI = -0.06, 0.04, p = 0.65 |
| **Females only** | N = 1102 | N = 1967 |
| **Immediate recall** |                  |                  |
| COMT           | β = 0.03, CI = -0.04, 0.11, p = 0.35, | β = -0.002, CI = -0.05, 0.05, p = 0.93 |
| BDNF           | β = -0.02, CI = -0.11, 0.07, p = 0.70, | β = 0.03, CI = -0.04, 0.10, p = 0.36 |
| **Delayed recall** |                  |                  |
| COMT           | β = 0.05, CI = -0.02, 0.13, p = 0.16, | β = 0.004, CI = -0.05, 0.06, p = 0.89 |
| BDNF           | β = -0.02, CI = -0.12, 0.07, p = 0.65, | β = 0.03, CI = -0.04, 0.10, p = 0.40 |
| **Males only** | N = 996 | N = 1872 |
| **Immediate recall** |                  |                  |
| COMT           | β = 0.06, CI = -0.01, 0.13, p = 0.092, | β = 0.03, CI = -0.02, 0.09, p = 0.26 |
| BDNF           | β = -0.02, CI = -0.12, 0.07, p = 0.61, | β = 0.004, CI = -0.07, 0.08, p = 0.91 |
| **Delayed recall** |                  |                  |
| COMT           | β = 0.07, CI = -0.002, 0.14, p = 0.057, | β = 0.06, CI = -0.01, 0.12, p = 0.07 |
| BDNF           | β = -0.01, CI = -0.11, 0.09, p = 0.79, | β = -0.06, CI = -0.14, 0.02, p = 0.15 |

Note: CI: 95% confidence-interval; Adjusted for age, sex, age*sex and education.
genes with a huge amount of literature confirming the effects. However, contrasting previous findings, our results did not provide support for direct effects of either of the two investigated polymorphisms. Still, finding interactive effects between these polymorphisms may help to integrate the currently inconclusive body of research. In our samples COMT Val-allele was associated with better cognitive performance in verbal memory tasks especially in the BDNF Val-allele homozygotes. This is somehow counterintuitive as most findings demonstrate that better cognitive performance was associated with the COMT Met-allele which is associated with higher dopamine levels in cognition relevant brain areas. For BDNF most of the literature suggests that the Met-allele was associated with less BDNF and dopamine availability and impaired cognitive performance.

In our gene–gene interactions we observed that in the female sample the effect of COMT Val/Met polymorphism on memory function changed depending on the BDNF allele. When carrying the Met/Met genotype for COMT, females showed the highest scores for delayed recall of words when also being Met-allele carriers for BDNF. When being Val homozygous for COMT, being Val homozygous for BDNF was associated with higher scores (see Figure 1). In the combined sample of both sexes we observed a linear association between COMT polymorphism and delayed memory only in carriers of BDNF Val-allele homozygotes (see Figure 1) with higher verbal memory scores when carrying one or two Val-alleles of COMT.

Previous results showed that the COMT Met-allele and the BDNF Val-allele were associated with higher dopamine levels than their respective counterparts. By that, the combination of COMT Met-allele and BDNF Val-allele would lead to the highest levels of dopamine while COMT Val-allele and BDNF Met-allele would lead to the lowest. The other two combinations would lead to intermediate levels of dopamine. Previous results indicate that dopamine and cognition follow a U-shaped association where both excessively high and low dopamine levels are associated with impairment.

In our results, genetic variant combinations leading to intermediate levels of dopamine were associated with better cognitive performance. In the sex combined sample we found an effect of COMT and BDNF on cognitive function could be demonstrated in the female population only. It is known that dopamine related psychiatric disorders such as ADHD or substance use disorders exhibit an increased prevalence in males compared to females. This could be based on sex differences in developmental dopamine receptor expression.
dopamine which is longer available in the synaptic cleft which is associated with higher cognitive function. But COMT gene-expression is decreased by estrogen which leads to lower COMT activity in females compared to males. As a result, females show higher baseline dopamine levels than males. This is why males benefit more from increased dopamine levels when carrying the rs4680 Met-allele. Females in our cohorts showed the highest cognitive performance in verbal memory tests when carrying variants that lead to an intermediate level of dopamine. We can argue that because females already show a higher level of dopamine in the brain than males and the association between cognition and dopamine is U-shaped, females only benefit from variants that keep dopamine levels within a physiological window where it can exhibit its effect.

Such sex differences in cognitive performance or related phenotypes have been reported previously. Konishi et al. found a significant interaction of sex, BDNF rs6265 and COMT rs4680 on personality traits extraversion and neuroticism in subjects with panic disorder. Males carrying only Val-alleles or only Met-alleles for both COMT and BDNF showed the highest scores for extraversion. In females no interaction was observable. In a study about cognitive decline in older age from Hupfeld et al. males showed the highest scores in a number of cognitive and motor measures when carrying the genetic variant for COMT associated with more effective dopamine transmission. In females such a beneficial effect of genetic variants could not be seen.

Finally, we can say that the interaction between COMT rs4680 and BDNF rs6265 has an impact on verbal memory performance. But this interaction is complex and also depending on sex differences in dopamine levels. This could be observed in two large independent samples (in total ≈ 6000 individuals) drawn from the same source population. Our findings of no direct, but interactive effects between these polymorphisms may contribute to explain the heterogeneous findings from previous studies.

ACKNOWLEDGMENT
SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ1003, and 01IZ0403), the Ministry of Cultural Affairs and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Genome-wide SNP typing in SHIP have been supported by a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg-West Pomerania. Generation of genome-wide SNP typing in SHIP-TREND-0 was supported by the Federal Ministry of Education and Research (grant no. 03ZIK012). SV was funded by the German Federal Ministry of Education and Research (BMBF) within the framework of the eMed research and funding concept (Integrament; grant no. 01ZX1614E). Open access funding enabled and organized by Projekt DEAL.

CONFLICTS OF INTEREST
All authors declare that no competing interest exist. The interpretation of the data was not influenced by any funding.

DATA AVAILABILITY STATEMENT
The data used in this study are freely available after data application and a data transfer agreement on the study website (https://www.fvcm.med.uni-greifswald.de/dd_service/data_use_intro.php).

ORCID
Sandra Van der Auwera https://orcid.org/0000-0002-1757-7768

REFERENCES
1. Bellis MD, Hooper SR, Spratt EG, Woolley DP. Neuropsychological findings in childhood neglect and their relationships to pediatric PTSD. J Int Neuropsychol Soc JINS. 2009;15:868-878.
2. Gard T, Hölzel BK, Lazar SW. The potential effects of meditation on age-related cognitive decline: a systematic review. Ann N Y Acad Sci. 2014;1307:89-103.
3. Gómez J, Jesús Marín-Méndez J, Molero P, Atakan Z, Ortuño F. Time perception networks and cognition in schizophrenia: a review and a proposal. Psychiatry Res. 2014;220:737-744.
4. McClintock SM, Husain MM, Greer TL, Cullum CM. Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. Neuropsychology. 2010; 24:9-34.
5. Lv Q, Du A, Wei W, Li Y, Liu G, Wang XP. Deep brain stimulation: a potential treatment for dementia in Alzheimer’s disease (AD) and Parkinson’s disease dementia (PDD). Front Neurosci. 2018;12:360.
6. Lövdén M, Karalija N, Andersson M, et al. Latent-profile analysis reveals behavioral and brain correlates of dopamine-cognition associations. Cerebral Cortex (New York, N.Y.; 1991). 2018;28:3894-3907.
7. Stuart K, Summers MJ, Valenzuela MJ, Vickers JC. BDNF and COMT polymorphisms have a limited association with episodic memory performance or engagement in complex cognitive activity in healthy older adults. Neurobiol Learn Mem. 2014;110:1-7.
8. Barnett JH, Scoriliis L, Munafò MR. Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. Biol Psychiatry. 2008;64:137-144.
9. Toh YL, Ng T, Tan M, Tan A, Chan A. Impact of brain-derived neurotrophic factor genetic polymorphism on cognition: a systematic review. Brain Behav. 2018;8:e01009.
10. Grabe HJ, Schwahn C, Mahler J, et al. Genetic epistasis between the brain-derived neurotrophic factor Val66Met polymorphism and the 5-HTT promoter polymorphism moderates the susceptibility to depressive disorders after childhood abuse. Prog Neuropsychopharmacol Biol Psychiatry. 2012;36:264-270.
11. Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology. 2008;33:73-83.
12. Li W, Liu B, Xu J, Jiang T, Yu C. Interaction of COMT rs4680 and BDNF rs6265 polymorphisms on functional connectivity density of the left frontal eye field in healthy young adults. Hum Brain Mapp. 2016;37:2468-2478.
13. Witte AV, Kürten J, Jansen S, et al. Interaction of BDNF and COMT polymorphisms on paired-associative stimulation-induced cortical plasticity. J Neurosci. 2012;32:4553-4561.
14. Das D, Tan X, Bielak AAM, Cherbuin N, Eastal S, Anstey KJ. Cognitive ability, intraindividual variability, and common genetic variants of catechol-O-methyltransferase and brain-derived neurotrophic factor: a longitudinal study in a population-based sample of older adults. Psychol Aging. 2014;29:393-403.
15. Han DH, Park DB, Choi TY, et al. Effects of brain-derived neurotrophic factor-catecholamine-O-methyltransferase gene interaction on schizophrenic symptoms. Neurorport. 2008;19:1155-1158.
16. Konishi Y, Tanii H, Otowa T, et al. Gene × gender interaction of BDNF and COMT genotypes associated with panic disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2014;51:119-125.
17. Sapkota S, Bäckman L, Dixon RA. Executive function performance and change in aging is predicted by apolipoprotein E, intensified by catechol-O-methyltransferase and brain-derived neurotrophic factor, and moderated by age and lifestyle. *Neurobiol Aging*. 2017;52:81-89.

18. Chen W, Chen C, Xia M, et al. Interaction effects of BDNF and COMT genes on resting-state brain activity and working memory. *Front Hum Neurosci*. 2016;10:540.

19. Woodcock EA, Zakiaez Y, Morris ED, Cosgrove KP. Sex and the dopaminergic system: insights from addiction studies. *Handb Clin Neurol*. 2020;175:141-165.

20. Zachry JE, Nolan SO, Brady LJ, Kelly SJ, Siciliano CA, Calipari ES. Sex differences in dopamine release regulation in the striatum. *Neuropsychopharmacology*. 2021;46:491-499.

21. Volzke H, Alte D, Schmidt CO, et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol*. 2011;40:294-307.

22. Schulz A, Schmidt CO, Appel K, et al. Psychometric functioning, socio-demographic variability of childhood maltreatment in the general population and its effects of depression. *Int J Methods Psychiatr Res*. 2014;23:387-400.

23. Helmstaedter C, Durwen HF. VLMT: Verbaler Lern- und Merkfähigkeitstest. Ein praktikables und differenziertes Instrumentarium zur Prüfung der verbalen Gedächtnisleistungen. *Schweiz Arch Neurol Psychiatr* (Zurich, Switzerland: 1985). 1990;141:21-30.

24. Oswald WD. 1999. Nürnberger-Alters-Inventar (NAI): NAI-Testmanual und-Textband.

25. van der Auwera S, Janowitz D, Schulz A, et al. Interaction among childhood trauma and functional polymorphisms in the serotonin pathway moderate the risk of depressive disorders. *Eur Arch Psychiatry Clin Neurosci*. 2014;264(Suppl 1):S45-S54.

26. McClearn GE, Johansson B, Berg S, et al. Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science* (New York, N.Y.). 1997;276:1560-1563.

27. Papassotiropoulos A, de Quervain DJ-F. Genetics of human episodic memory: dealing with complexity. *Trends Cogn Sci*. 2011;15:381-387.

28. Perkovic MN, Strac DS, Tudor L, Konjevod M, Erjavec GN, Pivac N. Catechol-O-methyltransferase, cognition and Alzheimer’s disease. *Curr Alzheimer Res*. 2018;15:408-419.

29. Hupfeld KE, Vaillancourt DE, Seidler RD. Genetic markers of dopaminergic transmission predict performance for older males but not females. *Neurobiol Aging*. 2018;66:180.e11-180.e21.

30. Schacht JP. COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review. *Pharmacogenomics J*. 2016;16:430-438.

31. Sinclair D, Purves-Tyson TD, Allen KM, Weickert CS. Impacts of stress and sex hormones on dopamine neurotransmission in the adolescent brain. *Psychopharmacology (Berl)*. 2014;231:1581-1599.

32. Woods JS, Heyer NJ, Russo JE, et al. Genetic polymorphisms of catechol-O-methyltransferase modify the neurobehavioral effects of mercury in children. *J Toxicol Environ Health Part A*. 2014;77:293-312.

33. Harrison PJ, Tunbridge EM. Catechol-O-methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology*. 2008;33:3037-3045.

---

**How to cite this article:** Van der Auwera S, Terock J, Teumer A, Schomerus G, Homuth G, Grabe HJ. Sex effects for the interaction of dopamine related genetic variants for COMT and BDNF on declarative memory performance. *Genes, Brain and Behavior*. 2021;20:e12737. [https://doi.org/10.1111/gbb.12737](https://doi.org/10.1111/gbb.12737)