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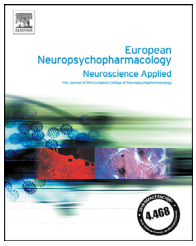

SHORT COMMUNICATION

Differential COMT DNA methylation in patients with Borderline Personality Disorder: Genotype matters

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Abstract
Differential DNA methylation in peripheral tissues has been associated with Borderline Personality Disorder (BPD). Alterations have been found in several genes, among them the Catechol-O-methyltransferase (*COMT*) gene. *COMT* is a known neuropsychiatric candidate gene, which contains a genotype variant (Val$^{108/158}$Met) that affects protein function and has been found associated with several psychiatric disorders. In addition, this variant also affects *COMT* DNA methylation. However, in previous epigenetic studies, the DNA methylation results have not always been controlled for genotype, even though overrepresentation of the Met allele has been frequently reported in cohorts of BPD patients. Therefore, in the present study, we investigated whether alteration of *COMT* DNA methylation in BPD patients is indeed associated with mental health status or merely influenced by a differential distribution of the *COMT* genotype between BPD patients and healthy control individuals. We found significant group differences, as well as a strong effect of genotype on *COMT* DNA methylation. While the direction of effect was different compared to a previous study, our study supports the finding of altered *COMT* DNA methylation in patients with BPD and reinforces the need to include genotype information in future DNA methylation studies of *COMT*.
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1. Introduction

Epigenetic modifications, such as DNA methylation (DNAm), regulate gene expression and have been described as biomarkers for various diseases, among them psychiatric disorders. DNAm within regulatory regions of the genome, such as the gene promoter, is typically associated with decreased gene expression (Jones, 2012). To date, the investigation of DNAm alterations in psychiatric patients has mainly focused on genes of known neuropsychiatric relevance. One of these genes is the Catechol-O-methyltransferase (*COMT*), a catecholamine degrading enzyme that is expressed in various tissues including the brain. COMT exists in two isoforms. The soluble form (S-COMT) is mainly expressed in peripheral tissues, while the membrane-bound form (MB-COMT) is mainly expressed in the central nervous system (Chen et al., 2004). The *COMT* gene contains a common functional single nucleotide polymorphism (SNP) that influences the thermostability of COMT (Chen et al., 2004) and has high relevance for psychiatric disorders (Taylor, 2018). At this locus, substitution of the wild-type guanine (G) allele for an adenosine (A) causes an amino acid exchange from Valine to Methionine (Val$^{108/158}$Met). This exchange leads to structural changes and, ultimately, reduced activity of the COMT protein, which causes disturbances of the dopamine metabolism, especially in prefrontal areas of the brain (Chen et al., 2004). In line with this, the Met allele has been frequently found to be associated with increased levels of prefrontal dopamine as well as with psychiatric disorders (Taylor, 2018). Besides these well-known genotype-dependent differences in COMT activity, altered expression levels of *COMT* may also influence the dopamine metabolism and, therefore, be relevant for psychiatric disorders. Here, *COMT* DNAm may be informative about expression levels, as both in vivo and in cell line experiments report that *COMT* gene expression is correlated with *COMT* DNAm (Swift-Scanlan et al., 2014; Ursini et al., 2011). Indeed, altered *COMT* DNAm has been reported to be associated with risk for psychiatric disorders such as schizophrenia (hypermethylation in exon 1 and promoter of *MB-COMT* (Gao et al., 2017)), bipolar disorder (hypomethylation in *MB-COMT* promoter (Abdolmaleky et al., 2006)) and Borderline Personality Disorder (BPD) (hypermethylation in *S-* and *MB-COMT* promoters (Dammann et al., 2011)).

However, the *COMT* Val$^{108/158}$Met genotype has a strong influence on DNAm such that methylation is higher in Met allele carriers (Schreiner et al., 2011). In several previous epigenetic studies of the *COMT* promoter, most of the observed inter-individual differences in methylation could be accounted for by the underlying variation in Val$^{108/158}$Met genotype (shown in brain (Murphy et al., 2005), buccal (Mill et al., 2006) and blood samples (Schreiner et al., 2011)). The remaining variation is attributed to environmental influences. However, not all previous studies have controlled for genotype when studying *COMT* methylation and the respective findings may have been confounded by group differences in Val$^{108/158}$Met genotype frequencies. We investigated *COMT* DNAm in patients with BPD, which has previously been reported to be altered (Dammann et al., 2011), while controlling for *COMT* Val$^{108/158}$Met genotype. We sought to investigate whether DNAm alterations are truly associated with mental health status or merely influenced by an overrepresentation of the Met allele in cohorts of BPD patients, as has been frequently reported (Liu et al., 2017). Therefore, we chose two CpG sites in the *S-COMT* promoter, whose DNAm levels are known to depend on Val$^{108/158}$Met genotype, but also display a high level of genotype-independent variance (Mill et al., 2006; Murphy et al., 2005).

2. Experimental procedures

2.1. Study population

44 hospitalized BPD patients and 44 healthy control individuals without any history of psychiatric disorders participated in the study. All subjects were of Caucasian origin and groups were matched for age and sex. BPD patients were diagnosed according to the International Personality Disorder Examination (IPDE) and met at least five diagnostic criteria for BPD as defined in DSM-IV. Healthy participants did not have current or past diagnosis of BPD or any other psychiatric disorder. This cohort is the same as investigated in Knoblich et al. (2018) and partially overlaps with the cohort investigated in Thomas et al. (2018). All study participants were further characterized with additional questionnaires as previously described (Thomas et al., 2018), of which the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), as well as nicotine and alcohol consumption (Audit (Saunders et al., 1993) and Fagerstrom-Test (Fagerstrom, 1978)) were included as covariates in this study. Missing nicotine and alcohol consumption data of one BPD patient were imputed from the patients' group mean. The study was approved by the ethics committee of the University of Tuebingen and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

2.2. Sampling and DNA extraction

Venous blood was drawn from all subjects, collected in Ethylenediaminetetraacetic acid (EDTA) tubes and stored at −80 °C until further analysis. DNA extraction was performed using the QIAamp DNA Blood Maxi-Kit (Qiagen, Hilden, Germany).

2.3. DNAm analysis

DNA was bisulfite converted using the EpiTect Fast Bisulfite Conversion Kit (Qiagen) and the region of interest within the *COMT* promoter was amplified using the PyroMark PCR Kit (Qiagen) according to the manufacturer's instructions and with previously published primers (F: 5-GAGTAGGTTGTGGATGGGTTGTA-3, R: 5-Biotin-ACATTTCTAAACCTTACCCCTCTA-3) (Mill et al., 2006). Several PCR runs were performed as technical replicates for each sample (minimum two replications). DNAm at two CpG sites within the *S-COMT* promoter (CpG22:19962541, CpG22:19962532) (hg38) was analyzed and quantified by pyrosequencing of the PCR products using the PyroMark Q24 system, PyroMark GoldReagents, PyroMark Q24 software version 2.0.6 (all from Qiagen) and a previously published sequencing primer (S: 5- GTAATATAGTTGTTAATAGTAGA-3) (Mill et al., 2006). Only samples with standard deviation of $< 3\%$ between technical replicates were included in the analysis. Samples were balanced in all steps of the analysis to avoid batch effects.

Table 1 Overview of patient and control cohorts. Data shown as mean ± standard deviation. P-value is reported from Student's T-test (for group mean comparisons) and Chi-Square-Test (for differences in percentages between groups).

Variable	Controls Mean ± SD	Patients Mean ± SD	p-value
Age	29.7 ± 8.8	29.5 ± 8.4	0.92
Sex (% women)	91.6%	91.6%	1
% Audit total score	3.4 ± 3.2	9.4 ± 8.7	*< 0.001*
% Fagerstrom total score	0.1 ± 0.6	3.3 ± 3.2	*< 0.001*
% under psychopharmacological medication	0%	90.9%	*< 0.001*
CTQ	34.1 ± 8.3	60.5 ± 24.4	*< 0.001*
$Val^{108/158}Met$	Val/Val: 11 Val/Met: 19 Met/Met: 14	Val/Val: 14 Val/Met: 17 Met/Met: 13	0.8

2.4. Genotyping

COMT $Val^{108/158}Met$ (rs4680) was genotyped on a StepOne system using TaqMan® SNP Genotyping Assay C__25746809_50 (Thermo Fisher Scientific, Waltham, U.S.). Accuracy was assessed by duplicating 20% of the original sample, and reproducibility was 100%. The genotype frequencies did not deviate from Hardy-Weinberg equilibrium (HWE; $p = 0.14$ for patients, $p = 0.79$ for controls).

2.5. Statistical analysis

Statistical analysis was performed using R version 3.4.1 (RC Team, 2018). Multiple regression analysis was used to test the effect of group (patients vs. controls) on DNAm, including nicotine consumption (Fagerstrom total score), alcohol consumption (Audit total score), childhood trauma (CTQ total score) and genotype as covariates. Covariates that resulted in a change of estimate (CIE) below 10% were removed from the model. Age and sex were not considered as covariates, as groups were matched for these variables. Group mean comparisons were performed using Student's T-test. Differences in percentages between groups were assessed with Chi-Square-Test.

3. Results

Patient and control cohorts did not differ significantly in *COMT* $Val^{108/158}Met$ genotype frequencies, age and sex. Significant differences were observed for drinking and smoking behavior, intake of psychopharmacological medication, as well as all psychiatric questionnaires (Table 1).

There was a significant effect of group on DNAm at CpG22:19962532 ($\beta = -7.6$, SE = 0.89, 95% CI [−9.371, −5.827], t(85) = −8.53, p-value = 4.86×10^{-13}), but not CpG22:19962541 ($\beta = 0.87$, SE = 0.88, 95% CI [−0.887, 2.631], t(85) = 0.97, p-value = 0.33) (Fig. 1A). In addition, there was a significant effect of genotype on DNAm at both analyzed sites, with carriers of Met alleles showing higher methylation in both groups (CpG22:19962541: $\beta = 4.9$, SE = 0.58, 95% CI [3.752, 6.041], t(85) = −8.51, p-value = 5.42×10^{-13}, CpG22:19962532: $\beta = 5.65$, SE = 0.58, 95% CI [4.493, 6.798], t(85) = 9.74, p-value = 1.74×10^{-15}) (Fig. 1B). Childhood trauma, nicotine and alcohol consumption were not included in the models, as their addition resulted in a CIE of less than 10% for the significant CpG sites (1.8% CIE for group effect, 0.27% and 0.74% CIE for genotype). There was no interaction effect of group and genotype for neither CpG site (CpG22:19962541: $\beta = -0.3$, SE = 1.16, 95% CI [−2.601, 2.007], t(84) = −0.26, p-value = 0.8, CpG22:19962532: $\beta = 0.33$, SE = 1.17, 95% CI [−1.994, 2.648], t(84) = 0.28, p-value = 0.78). Post-hoc sex-specific analysis revealed that the observed effects were present in both male ($N = 14$) and female ($N = 74$) study participants (data not shown).

4. Discussion

We found that patients with BPD display significantly lower DNAm than healthy controls at one of the two analyzed CpG sites in the promoter region of *COMT*, even after controlling for $Val^{108/158}Met$ genotype. This finding of altered *COMT* DNAm is in line with several previous studies reporting differential *COMT* DNAm in patients with BPD (Dammann et al., 2011) and other psychiatric disorders, such as schizophrenia (Abdolmaleky et al., 2006; Gao et al., 2017; Nohesara et al., 2011; Nour El Huda et al., 2018) and bipolar disorder (Abdolmaleky et al., 2006; Zhang et al., 2018), even though different genomic regions of *COMT* were studied. While for BPD, the only previous study reports increased DNAm in patients (Dammann et al., 2011), there are mixed reports for schizophrenia and bipolar disorder, finding both decreased (Abdolmaleky et al., 2006; Nohesara et al., 2011; Nour El Huda et al., 2018), and increased (Dammann et al., 2011; Gao et al., 2017) *COMT* DNAm in patients. However, comparisons between studies are difficult, as they differ not only in cohort characteristics, such as ethnicity, age and sex, but also tissue type, type of DNAm analysis, as well as number and location of analyzed CpG sites. While the majority of *S-COMT* promoter CpG sites analyzed in the previous BPD study showed hypermethylation in BPD patients, no significant difference was found for the two sites analyzed in the present study (Dammann et al., 2011). These varying results may be explained by the effects of genotype frequencies on *COMT* DNAm. We found that carriers of the Met allele display higher DNAm, which is in line with a previous study analyzing DNAm and genotype at the same CpG sites in growth-discordant monozygotic twins and healthy adults (Schreiner et al., 2011). The effect of the $Val^{108/158}Met$ genotype on *COMT* DNAm indicates that the respective SNP is a methylation quantitative trait locus (Smith et al., 2014)

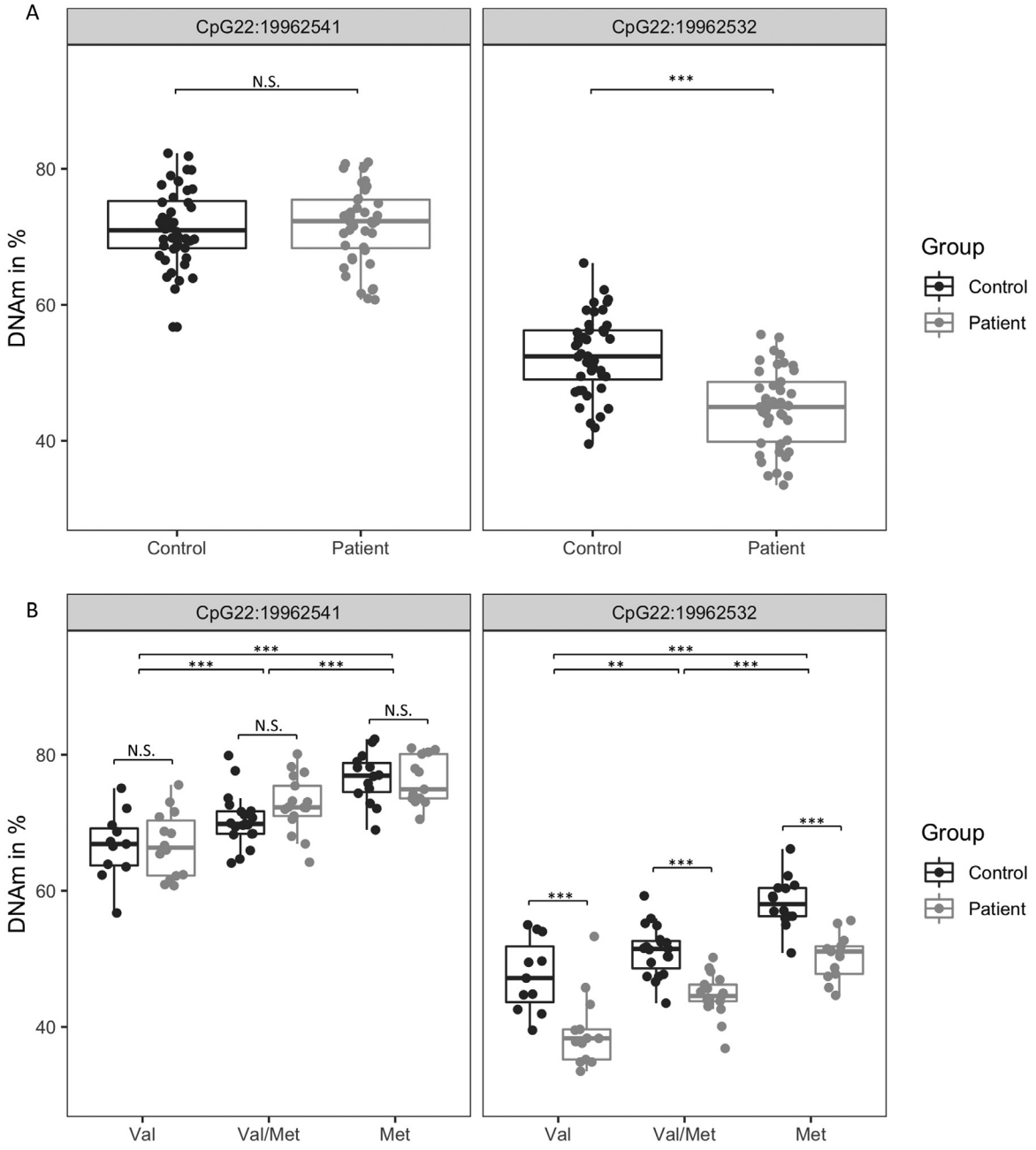

Fig. 1 DNAm at CpG22:19962541 and CpG22:19962532 in BPD patients and controls (A), as well as shown for each Val$^{108/158}$Met genotype Val (G/G), Val/Met (G/A), Met (A/A) (B). Boxplots represent values between 25% and 75% quantile, whiskers extend to most extreme values that are within 1.5x interquartile range (IQR) of boxplot hinges. *** = p-value < 0.001, ** = p-value < 0.01,N.S. = not significant.

or is in linkage with one. Since the Met allele has been reported to be overrepresented in BPD patients, this effect may have confounded previous studies towards higher DNAm in BPD patients. Lastly, we found that the observed alterations in *COMT* DNAm were present in both male and female study participants, even though sex-specific effects of the *COMT* Val$^{108/158}$Met genotype have been frequently reported (Tunbridge and Harrison, 2011). Factors that may have confounded our analysis are lifetime stress and socioeconomic status, as both were found associated with *COMT* DNAm (Swift-Scanlan et al., 2014; Ursini et al., 2011) and were not assessed in our cohort. In addition, comorbid psychiatric or somatic disorders, as well as drug abuse were not assessed and may have influenced our results. Further, we cannot disentangle effects of BPD from effects of psychopharmacological medication, as they were highly correlated with each other. Two other limitations of our study are the use of blood as analysis tissue for the study of psychiatric disorders as well as the lack of evidence for functional relevance of altered *COMT* DNAm. With regards to analysis tissue, previous

studies suggest that peripheral measures of *COMT* DNAm can serve as surrogates for its methylation status in the brain (Murphy et al., 2005; Nohesara et al., 2011; Ursini et al., 2011). In agreement with this, an imaging epigenetics study showed that *COMT* promoter DNAm measured in blood is associated with neural activity in the prefrontal cortex, further supporting the informative value of *COMT* DNAm in blood for the study of psychiatric disorders (Walton et al., 2014). With regards to functional relevance, previous research indicates that *COMT* DNAm is relevant for gene expression (Abdolmaleky et al., 2006; Ursini et al., 2011). Murphy et al. report that the differentially methylated site CpG22:19962532 is embedded in GATA-1, GATA-2 and c-ETS elements and may therefore be involved in the regulation of *S-COMT* expression. Since both sites are located in the *S-COMT* promoter, the predicted consequence of the observed decreased promoter DNAm would be increased *S-COMT* gene expression in BPD patients. In addition, both sites are within the gene body of *MB-COMT* (Tenhunen et al., 1994) and their methylation status may also exert influence on *MB-COMT* expression (Jjingo et al., 2012). A cell culture study showed that higher *COMT* DNAm is associated with decreased expression, however the study did not differentiate between *S-COMT* and *MB-COMT* expression and the methylation assay covered a larger genomic region, including 14 additional CpG sites adjacent to the two sites analyzed in the present study (Swift-Scanlan et al., 2014). Interestingly, increased *COMT* expression is found in brain tissue of depressed suicide victims as compared to healthy controls matched for $Val^{108/158}$Met genotype (Du et al., 2014). This finding supports the relevance of increased *COMT* expression for psychiatric disorders and is in line with our finding of decreased *COMT* DNAm in BPD patients.

Lastly, we did not observe differences in genotype frequencies between healthy controls and BPD patients, even though such differences have previously been reported (Liu et al., 2017). One reason may be that our study was not adequately powered to detect differences in the range of the reported effect sizes. However, one previous large study with sufficient power had also reported no difference in $Val^{108/158}$Met genotype between BPD patients and healthy controls (Rujescu et al., 2003), so that our study may support this finding.

In conclusion, we observed significant alterations of *COMT* DNAm in blood of patients with BPD as compared to healthy controls, even after controlling for genotype. Further studies are necessary to corroborate and extend our findings, but we assume that the observed alterations can be of relevance to the pathophysiology of BPD and its associated symptoms. In addition, we found a strong effect of the $Val^{108/158}$Met polymorphism on *COMT* DNAm in all subjects. Therefore, we recommend including genotype information in future studies of *COMT* DNAm.

CRediT authorship contribution statement

Mara Thomas: Supervision, Writing - original draft. **Annalena Wallisch:** Writing - review & editing. **Katarzyna Glowacz:** Formal analysis. **Julia Becker-Sadzio:** Writing - review & editing. **Vanessa Nieratschker:** Funding acquisition, Supervision, Writing - review & editing.

Role of the funding source

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Conflict of interest

All authors declare that they have no conflict of interest.

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References

Abdolmaleky, H.M., Cheng, K.H., Faraone, S.V., Wilcox, M., Glatt, S.J., Gao, F., Smith, C.L., Shafa, R., Aeali, B., Carnevale, J., Pan, H., Papageorgis, P., Ponte, J.F., Sivaraman, V., Tsuang, M.T., Thiagalingam, S., 2006. Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. Hum. Mol. Genet. 15, 3132–3145.

Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the childhood trauma questionnaire. Child Abuse Negl. 27, 169–190.

Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M., Melhem, S., Kolachana, B.S., Hyde, T.M., Herman, M.M., Apud, J., Egan, M.F., Kleinman, J.E., Weinberger, D.R., 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am. J. Hum. Genet. 75, 807–821.

Dammann, G., Teschler, S., Haag, T., Altmuller, F., Tuczek, F., Dammann, R.H., 2011. Increased dna methylation of neuropsychiatric genes occurs in borderline personality disorder. Epigenetics 6, 1454–1462.

Du, L., Merali, Z., Poulter, M.O., Palkovits, M., Faludi, G., Anisman, H., 2014. Catechol-O-methyltransferase val158met polymorphism and altered COMT gene expression in the prefrontal cortex of suicide brains. Prog. Neuropsychopharmacol. Biol. Psychiatry 50, 178–183.

Fagerstrom, K.O., 1978. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict. Behav. 3, 235–241.

Gao, S., Cheng, J., Li, G., Sun, T., Xu, Y., Wang, Y., Du, X., Xu, G., Duan, S., 2017. Catechol-O-methyltransferase gene promoter methylation as a peripheral biomarker in male schizophrenia. Eur. Psychiatry 44, 39–46.

Jjingo, D., Conley, A.B., Yi, S.V., Lunyak, V.V., Jordan, I.K., 2012. On the presence and role of human gene-body DNA methylation. Oncotarget 3, 462–474.

Jones, P.A., 2012. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat. Rev. Genet. 13, 484–492.

Knoblich, N., Gundel, F., Bruckmann, C., Becker-Sadzio, J., Frischholz, C., Nieratschker, V., 2018. DNA methylation of APBA3

and MCF2 in borderline personality disorder: potential biomarkers for response to psychotherapy. Eur. Neuropsychopharmacol. 28, 252–263.

Liu, J., Nie, G., Guo, W., Gong, J., Xiao, B., Cui, X., He, Y., Meng, T., Shen, Y., Wu, J., 2017. Association between the COMT gene val158met polymorphism and borderline personality disorder: a meta-analysis. Psychiatry Res. 258, 614–615.

Mill, J., Dempster, E., Caspi, A., Williams, B., Moffitt, T., Craig, I., 2006. Evidence for monozygotic twin (MZ) discordance in methylation level at two CPG sites in the promoter region of the catechol-O-methyltransferase (COMT) gene. Am. J. Med. Genet. B Neuropsychiatr. Genet. 141B, 421–425.

Murphy, B.C., O'Reilly, R.L., Singh, S.M., 2005. Site-specific cytosine methylation in s-COMT promoter in 31 brain regions with implications for studies involving schizophrenia. Am. J. Med. Genet. B Neuropsychiatr. Genet. 133B, 37–42.

Nohesara, S., Ghadirivasfi, M., Mostafavi, S., Eskandari, M.R., Ahmadkhaniha, H., Thiagalingam, S., Abdolmaleky, H.M., 2011. DNA hypomethylation of MB-COMT promoter in the DNA derived from saliva in schizophrenia and bipolar disorder. J. Psychiatr. Res. 45, 1432–1438.

Nour El Huda, A.R., Norsidah, K.Z., Nabil Fikri, M.R., Hanisah, M.N., Kartini, A., Norlelawati, A.T., 2018. DNA methylation of membrane-bound catechol-O-methyltransferase in Malaysian schizophrenia patients. Psychiatry Clin. Neurosci. 72, 266–279.

RC Team, 2018. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Rujescu, D., Giegling, I., Gietl, A., Hartmann, A.M., Moller, H.J., 2003. A functional single nucleotide polymorphism (V158M) in the COMT gene is associated with aggressive personality traits. Biol. Psychiatry 54, 34–39.

Saunders, J.B., Aasland, O.G., Babor, T.F., de la Fuente, J.R., Grant, M., 1993. Development of the alcohol use disorders identification test (AUDIT): who collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction 88, 791–804.

Schreiner, F., El-Maarri, O., Gohlke, B., Stutte, S., Nuesgen, N., Mattheisen, M., Fimmers, R., Bartmann, P., Oldenburg, J., Woelfle, J., 2011. Association of COMT genotypes with s-comt promoter methylation in growth-discordant monozygotic twins and healthy adults. BMC Med. Genet. 12, 115.

Smith, A.K., Kilaru, V., Kocak, M., Almli, L.M., Mercer, K.B., Ressler, K.J., Tylavsky, F.A., Conneely, K.N., 2014. Methylation quantitative trait loci (meQTLs) are consistently detected across ancestry, developmental stage, and tissue type. BMC Genom. 15, 145.

Swift-Scanlan, T., Smith, C.T., Bardowell, S.A., Boettiger, C.A., 2014. Comprehensive interrogation of CPG island methylation in the gene encoding COMT, a key estrogen and catecholamine regulator. BMC Med. Genom. 7, 5.

Taylor, S., 2018. Association between COMT val158met and psychiatric disorders: a comprehensive meta-analysis. Am. J. Med. Genet. Part B 177B, 199–210.

Tenhunen, J., Salminen, M., Lundstrom, K., Kiviluoto, T., Savolainen, R., Ulmanen, I., 1994. Genomic organization of the human catechol O-methyltransferase gene and its expression from two distinct promoters. Eur. J. Biochem. 223, 1049–1059.

Thomas, M., Knoblich, N., Wallisch, A., Glowacz, K., Becker-Sadzio, J., Gundel, F., Bruckmann, C., Nieratschker, V., 2018. Increased bdnf methylation in saliva, but not blood, of patients with borderline personality disorder. Clin. Epigenetics 10, 109.

Tunbridge, E.M., Harrison, P.J., 2011. Importance of the COMT gene for sex differences in brain function and predisposition to psychiatric disorders. Curr. Top. Behav. Neurosci. 8, 119–140.

Ursini, G., Bollati, V., Fazio, L., Porcelli, A., Iacovelli, L., Catalani, A., Sinibaldi, L., Gelao, B., Romano, R., Rampino, A., Taurisano, P., Mancini, M., Di Giorgio, A., Popolizio, T., Baccarelli, A., De Blasi, A., Blasi, G., Bertolino, A., 2011. Stress-related methylation of the catechol-O-methyltransferase VAL 158 allele predicts human prefrontal cognition and activity. J. Neurosci. 31, 6692–6698.

Walton, E., Liu, J., Hass, J., White, T., Scholz, M., Roessner, V., Gollub, R., Calhoun, V.D., Ehrlich, S., 2014. MB-COMT promoter DNA methylation is associated with working-memory processing in schizophrenia patients and healthy controls. Epigenetics 9, 1101–1107.

Zhang, H.S., Ke, X.Y., Hu, L.L., Wang, J., Gao, L.S., Xie, J., 2018. Study on the epigenetic methylation modification of bipolar disorder major genes. Eur. Rev. Med. Pharmacol. Sci. 22, 1421–1425.