HHS Public Access

Author manuscript

World J Biol Psychiatry. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

World J Biol Psychiatry. 2017 April ; 18(3): 247–254. doi:10.1080/15622975.2016.1208844.

Manic symptom severity correlates with COMT activity in the striatum: a post-mortem study

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Abstract

Objectives—The enzyme catechol-O-methyl transferase (COMT), which catalyzes the degradation of dopamine and norepinephrine, is posited to participate in the pathophysiology of bipolar disorder (BD) and schizophrenia. In support of this notion, rich evidence has documented that the severity of various BD and schizophrenia symptoms is moderated by *rs4680*, a single nucleotide polymorphism of the *COMT* gene featuring a valine (Val)-to-methionine (Met) substitution that results in lower catalytic activity. Nevertheless, the specific relevance of COMT enzymatic activity in the pathophysiology of BD and schizophrenia dimensions remains elusive.

Methods—We measured COMT catalytic activity in post-mortem prefrontal cortices, striata and cerebella of schizophrenia and BD patients, as well as non-affected controls. These values were then correlated with *rs4680* genotypes and psychopathology scores in the last week of life.

Results—No direct correlation between COMT activity and *rs4680* genotypes was found; however, the severity of manic symptoms was highly correlated with COMT activity in the striatum, irrespective of the diagnostic group.

Conclusions—These results suggest that COMT striatal activity, but not *rs4680* genotype, may serve as a biomarker for manic symptoms. Future studies are warranted to confirm these findings and assess the neurobiological links between COMT striatal activity and manic symptoms.

Keywords

Catechol-O-methyltransferase; schizophrenia; bipolar disorder; manic symptoms; single nucleotide polymorphism

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Conflict of interest: None to declare.

INTRODUCTION

The catecholamine neurotransmitters dopamine (DA) and norepinephrine (NE) have been extensively implicated in the pathophysiology of schizophrenia and bipolar disorder (BD) (Axelrod and Tomchik, 1958; van Kammen et al., 1991; Manji et al., 2003; Yamamoto and Hornykiewicz, 2004; Cousins et al., 2009; Howes and Kapur, 2009). In line with this idea, several lines of research have investigated the link between these psychiatric disorders and the enzyme catechol-*O*-methyltransferase (COMT), which catalyzes the degradation of DA and NE into 3-methoxytyramine and normetanephrine, respectively (Lachman et al., 1995; Männistö and Kaakkola, 1999).

To date, most research on the role of COMT in behavioral regulation and psychopathology has focused on *rs4680*, a single nucleotide polymorphism (SNP) of the *COMT* gene featuring a substitution of a guanine to adenine at codon 148. The resulting mutation is a valine (*Val*)-to-methionine (*Met*) transition, which leads to a significant reduction of catalytic activity *in vitro* (Moskovitz et al., 2015). We recently showed that the functional deficits in *Met* variants may be partially contributed by the sulfoxidation of this amino acid mediated by oxidative stress (Egan et al., 2001).

Several studies have suggested that the *Met* allele may confer slightly lower risk for schizophrenia (Kirov et al., 1998), but greater risk for mania (Goghari and Sponheim, 2008; Zhang et al., 2009). In parallel with this evidence, several reports have documented that, while the severity of manic symptoms in BD is typically higher in carriers of the *Met* allele (Bilder et al., 2002; Benedetti et al., 2010, 2011; Lelli-Chiesa et al., 2011; Soeiro-de-Souza et al., 2012), this allele is generally predictive of lower intensity of cognitive deficits and negative symptoms in schizophrenia (Malhotra et al., 2002; Bray et al., 2003; Gallinat et al., 2003; Tunbridge et al., 2006; Ehlis et al., 2007). In line with these findings, the *Met* allele has also been associated with alterations in behavioral functions in healthy subjects, including a decreased vulnerability for cognitive impairments (Strous et al., 1997; Goldberg et al., 2003; Blasi et al., 2005; Smolka et al., 2005), as well as higher predisposition for aggression in vulnerable individuals (Jones et al., 2001; Strous et al., 2003; Albaugh et al., 2010; but see also Chen et al., 2004, for conflicting results).

These results suggest that, irrespective of the specific diagnosis, *COMT* genotypes may modulate the severity of selected symptoms by influencing COMT activity and catecholaminergic neurotransmission. However, in contrast with evidence *in vitro*, the three *COMT rs4680* genotypes were found to be associated with only modest differences in brain-regional COMT catalytic activity (Tunbridge, 2010), possibly reflecting the influence of environmental and sex-related factors on enzymatic function (Tunbridge, 2010; Godar and Bortolato, 2014). COMT activity may also be affected by its redox status; for example, we showed that COMT activity may be robustly predicted by the activity of methionine sulfoxide reductase, which regulates the degree of oxidation of *Met* residues in proteins (Moskovitz, 2014).

Based on this background, the present study was designed to study whether, in human post-mortem tissue, brain-regional COMT catalytic activity may be correlated with the severity of different psychopathology symptoms in BD and schizophrenia, as compared with non-affected controls. Furthermore, we verified whether these relationships may be paralleled by associations between *COMT* genotypes and symptom severity.

MATERIALS AND METHODS

Human Subjects

The present study was conducted on the same postmortem brain tissues used in a previous study (Moskovitz et al., 2015). All demographic and clinical characteristics of the individuals are described in Table 1. Briefly, the subjects were ten schizophrenia/schizoaffective disorder patients, thirteen BD patients, and nine control subjects. The three groups did not significantly differ by age [$F(2,29)=1.94$, NS] (Table 1). Samples were obtained from the Southwest Brain Bank, Department of Psychiatry, University of Texas Health Science Center at San Antonio, with consent from the next-of-kin.

The Southwest Brain Bank collection of postmortem tissues for research is conducted under the jurisdiction of the State of Texas Anatomical Review Board and the UTHSCSA Institutional Review Board regulates the interviews with the next-of-kin (Thompson et al., 2013). Trained clinicians interview the next-of-kin about the donor and conduct a DSM-IV-based Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Diagnoses were determined by expert diagnostician group consensus (MINI inter-rater reliability for schizophrenia = 0.8) after review of the interview materials and available medical records.

To assess mood state, psychiatric symptoms, during the last of week of life, and lifetime impulse-control characteristics the following scales were administered to the next-of-kin: Bipolar Inventory of Symptoms Scale (BISS) (Bowden et al., 2007; Thompson et al., 2010); Barratt impulsiveness scale-11 (BIS-11) (Patton et al., 1995), 31-item Hamilton Rating Scale for Depression (HRSD-31) (Hamilton, 1967; Williams, 2001); Brief Psychiatric Rating Scale (BPRS) (Williams, 2001, Overall, 1962); and Young Mania Rating Scale (YMRS) (Young et al., 1978).

Subjects with a major neurological condition, e.g., Alzheimer's disease, Parkinson's disease, brain tumors, etc. were excluded from the study. Postmortem intervals (PMI) ranged between 20 and 45 h, and did not differ significantly across the three subject groups (Table 1). The pH values of brain tissues were also equivalent across groups (Table 1).

Intact fresh brains were transported to the Southwest Brain Bank, and the cerebrum was hemisected. Each hemisphere was cut into 1-cm thick coronal blocks and immediately frozen in 2-methylbutane (Fisher Scientific Co, Fair Lawn, NJ), and stored at −80°C. All tissue samples were analyzed by a neuropathologist, and found to be free of any confounding gross and microscopic neuropathology. The following brain regions were dissected from the right hemisphere: prefrontal cortex (PFC; corresponding to Brodmann

area 9); dorsal striatum (rostral caudate); and cerebellum (lateral cerebellar cortex) (Thompson et al., 2013).

The selected brain regions were homogenized in the presence of 25mM Tris-HCl, pH, 7.4 and protease inhibitors cocktail (Roche) at 4°C. Following centrifugation at 10,000 x g for 20 minutes, the supernatants were collected and stored at −80°C for future analyses.

COMT rs4680 genotyping

Genomic DNA was extracted from brain tissue and COMT rs4680 genotyping was performed as previously indicated (Moskovitz et al, 2015).

Enzymatic activity assay for COMT

Postmortem human brain sections were homogenized as described above and their COMT activity was monitored as previously indicated in Moskovitz et al (2015).

Statistical analyses

Normality and homoscedasticity of data distribution were verified using Kolmogorov-Smirnov and Bartlett's tests. Comparisons between diagnostic groups and genotypes were performed by ANOVAs, followed by Tukey's test with Spjøtvoll-Stoline corrections for *post-hoc* comparisons. Multiple correlations between brain-regional COMT activity levels and symptom severity scores were assessed by Pearson's coefficients. Relations between genotypes and COMT activities were tested by multiple regression, using dummy codes for *rs4680* genotypes (0 for *Met/Met*, 1 for *Met/Val* and 2 for *Val/Val*), and compared across diagnostic groups by ANCOVAs. Significance threshold was set at 0.05. Bonferroni corrections for multiple testing were applied throughout the study, as appropriate. However, in consideration of the objections to the conceptual limits of Bonferroni adjustments (Perneger, 1998), uncorrected significant values were also reported. All statistical analyses were performed by STATISTICA 9 (Statsoft, Tulsa, OK).

RESULTS

Differences in brain-regional COMT catalytic activities across diagnostic groups and genotypes

We first assessed the differences in brain-regional COMT activities between controls, schizophrenia and BD subjects, across the three *rs4680* genotypes. All values are reported in Table 2. No significant differences in COMT activity among diagnostic groups were found in any of the tested regions [PFC: $F(2,28)=0.72$, NS; striatum: $F(2,29)=1.19$, NS; cerebellum: $F(2,28)=1.47$, NS]. Logistic regression found no significant associations between COMT activity and *rs4680* genotype [PFC: $F(1,29)=1.30$, NS; striatum: $F(1,30)=1.43$, NS; cerebellum: $F(1,29)=0.97$, NS]. No differences in brain-regional COMT activities were found among *rs4680* genotypes [PFC: $F(2,28)=0.63$, NS; striatum: $F(2,29)=0.89$, NS; cerebellum: $F(2,28)=2.02$, NS].

Correlations of behavioral scores and brain-regional COMT activity

The behavioral scores for all subjects are reported in Table 3. The relationships between brain-regional COMT activities and behavioral scores were first analyzed irrespective of diagnostic groups and genotypes (Table 4). Significant correlations were identified between COMT activity in the striatum and both BISS Mania (R= 0.95) and YMRS (R=0.70) scores (P<0.005). Uncorrected significant correlations (P<0.05) were found also for the same scores and COMT activity in the prefrontal cortex; furthermore, correlations were found between BISS Total and BISS Anxiety scores with COMT in both PFC and striatum (Table 4). ANCOVA revealed that the relation between brain-regional COMT activity and symptom severity was not affected by diagnosis. Finally, no correlation was found between brain-regional COMT activities and age (Table 4).

Relation between COMT genotypes and symptom scores

As shown in Table 5, multiple regression analyses revealed corrected significant associations (P<0.005) between *rs4680* genotype and BISS-Depression, BISS-Anxiety, BISS-Total, and BPRS scores. In addition, uncorrected significant associations (P<0.05) were found with BISS-Irritability, HDRS-31 and YMRS scores. The comparison of severity across different genotypes revealed that *Met* homozygous carriers exhibited higher BISS Total and BISS Anxiety scores in comparison with *Val* homozygous carriers (P<0.005, ANOVAs); uncorrected significant differences were also found between *Met/Met* and *Val/Val* genotypes with respect to HDRS-31, BPRS, YMRS scores and BISS Depression, Irritability and Psychosis sub-scores (P<0.05, ANOVAs). ANCOVA revealed that the relation between *rs4680* genotypes and symptom severity was not affected by diagnosis. No significant differences between genotypes were found with respect to BISS Mania and BIS-11 scores (Table 6).

DISCUSSION

The results of this study showed a robust correlation between COMT activity in the striatum and manic symptom severity, as defined by both BISS Mania and YMRS scores. Neither association, however, was specific for any diagnostic category. These findings are quite surprising, given that manic symptoms have been typically associated with hyperactivity of DA and NE neurotransmission in the striatum (Manji et al., 2003); a possible interpretation, however, may be that the observed increase in COMT activity in this region is likely secondary to high levels of catecholamine efflux. This compensatory mechanism may be enacted physiologically in the striatum, as a way to curb the negative consequences of oxidative stress induced by DA auto-oxidation (Liu and Mori, 1993). In agreement with this interpretation, preliminary evidence has shown that COMT activity is up-regulated in response to treatment with levodopa, the precursor of DA and NE (Zhao et al., 2001) that augments DAergic neurotransmission and increases the propensity for manic symptoms in BD and non-affected patients (Beaulieu-Boire and Lang, 2015). Notably, preclinical studies suggest that COMT does not serve a physiological role in the metabolism of striatal DA (Gogos et al., 1998), but may play a key role in the degradation of this monoamine in case of excess synthesis/release or deficient reuptake/deamination metabolism (Kaakola and Wurtman, 1992; Huotari et al., 2002). In line with this concept, Chang et al. (2010)

documented a reduction of DA transporter in the caudate of BD patients (but see Anand et al., 2011 for contrasting results). Given that our analyses could not include the measurement of brain-regional DA and NE levels, future studies will be needed to validate this intriguing hypothesis.

Our analyses could not confirm the impact of the *rs4680* genotype on COMT activity, likely due to our relatively low number of subjects. Nevertheless, our analyses showed that, irrespective of the diagnostic group, *Met/Met* carriers displayed increases in BISS Anxiety and BISS Total scores, as compared with their *Val/Val* counterparts. In addition, uncorrected significant associations were found for other severity scores, such as the BPRS, HDRS and YMRS scores. These results are in substantial agreement with previous findings on the association of the *Met* allele with greater risk for psychopathology as measured by the BPRS scores (Herken and Erdal, 2001; van Winkel et al., 2008). In addition, a number of reports have shown that the *Met* allele may predispose to affective disturbances in specific groups of vulnerable individuals (Hoth et al., 2006; Åberg et al., 2011). These preliminary findings collectively suggest that the *COMT Met* variant may be a risk factor for greater severity of several behavioral traits related to anxiety and other dimensions of emotional dysregulation. Although both *Val* and *Met* alleles appear to have influences on psychopathology, the moderating effects of these variants may signify distinct contributions to the ontogeny of mental disorders, possibly in relation with other genetic or environmental interactive factors (Vrijsen et al., 2014).

The lack of differences in BIS-11 lifetime impulsivity total scores across different *rs4680* genotypes is in agreement with previous findings (Forbes et al., 2009; Paloyelis et al., 2010). Although this result suggests that COMT may not play a direct role in the organization of impulsive behavior, it is worth noting that the *Met/Met* genotype has been recently associated with worse performance in the Iowa Gambling Task (IGT) (Malloy-Diniz et al., 2013), one of the best-validated tasks to assess decision-making alterations in impulsive individuals (Bechara et al., 1994). This apparent discrepancy may reflect the poor association between BIS-11 scores and IGT performance (Kjome et al., 2010), which is posited to signify the high complexity and multifactorial nature of the clinical construct of impulsivity.

In substantial agreement with prior evidence (Daniels et al., 1996; Gutiérrez et al., 1997; Kunugi et al., 1997; Lachman et al., 1997; Karayiorgou et al., 1998; Strous et al., 2006), neither schizophrenia nor BD were associated with differences in either *COMT* alleles or brain-regional COMT catalytic activity. This result, together with the finding that the association between COMT and symptom severity was not specific to any disease, suggests that a phenotype-based approach may be better suited than current diagnostic criteria to study the biological bases of neuropsychiatric disturbances. This idea is in keeping with the framework established by the Research Domain Criteria of the National Institute of Mental Health, which has underscored the importance of a novel dimensional perspective in the search for diagnostic biomarkers that may assist in the management of mental disorders (Morris and Cuthbert, 2012).

Several limitations should be acknowledged in this study. First, due to the small sample size, the present study is underpowered to identify potential diagnostic differences, as well as significant relationships between diagnoses, COMT activity and *rs4680* genotype; furthermore, the same limitation does not allow for the analysis of complex interactions between genotype and gender across different diagnostic groups, or for the evaluation of potential effects of individual medications on COMT activity, which may have interfered with some of the observed correlations. This type of analysis can best be completed using animal models. Second, type I errors may have resulted from potential treatments and/or substance abuse, which may not have known by their next-of-kin. Third, our analyses of COMT activity were based on its shorter, soluble form (S-COMT) expressed in the cytosol, rather than the membrane-bound allozyme (MB-COMT), which features a *N*-terminal sequence of 50 extra hydrophobic amino acids (Bertocci et al., 1991; Tenhunen et al., 1994; Ulmanen et al., 1997) and is more abundant in the brain (Tenhunen et al., 1994; Tunbridge, 2010). Nevertheless, it is likely that the results obtained on S-COMT can be generalized to MB-COMT, given their similar catalytic activity (Lachman et al., 1996).

These limitations notwithstanding, the present study provides potentially critical contributions to our understanding of the role of COMT in behavioral regulation, and opens to the possibility that striatal elevations in its activity may prove valuable as a potential biological index for the severity of manic symptoms. Future post-mortem investigations and neuroimaging studies with radiolabeled COMT inhibitors are warranted to confirm these results and determine the potential value of COMT striatal activity as a diagnostic index to help monitor the severity of manic symptoms.

Acknowledgments

Funding Sources

This research was supported by NIH grants R01MH104603 (to MB), K01MH077777 (to CWB), R24MH076039 (to PMT), as well as the Hedwig Miller Fund for Aging Research and by an Institutional Development Award (IDeA) from the NIGMS grant P30 GM1110761 (to JM). None of the institutions had any further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The authors wish to thank Dr. Dianne Cruz for her technical support, as well as the Southwest Brain Bank at UTHSCSA for providing tissue for this project and to the donor families that make this research possible.

Abbreviations

COMT	Catechol-O-methyltransferase
BD	bipolar disorder
DA	dopamine
NE	norepinephrine
PFC	prefrontal cortex

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Table 1

Characteristics of subjects.

	Controls	Schizophrenia	Bipolar disorder
Number	**9**	**10**	**13**
Mean death age ± SEM	51.56 ± 5.08	54.3 ± 1.81	45.77 ± 2.70
Median death age	54	53	45
Range	20–67	49–64	25–62
% Suicides	0.00%	20.00%	69.23%
% Smokers	30.00%	70.00%	80.00%
Race/ethnicity			
Caucasians	77.78%	60.00%	84.61%
Hispanics	22.22%	40.00%	15.39%
Gender			
Males	66.67%	70.00%	61.54%
Females	33.33%	30.00%	38.46%
Other characteristics			
pH	6.48 ± 0.05	6.23 ± 0.14	6.56 ± 0.04
PMI	26.06 ± 1.11	29.98 ± 2.21	28.22 ± 1.78
BMI	27.93 ± 2.24	29.73 ± 1.23	26.34 ± 1.92

Table 2

Brain-regional COMT activities in diagnostic groups and *COMT* genotypes.

		Prefrontal cortex	Striatum	Cerebellum	N
Controls	*Met/Met*	12.19	11.44	33.15	1
	Met/Val	19.29 ± 3.02	18.6 ± 2.72	34.39 ± 1.77	4
	Val/Val	20.55 ± 6.3	17.8 ± 1.17	39.96 ± 21.19	4
Schizophrenia	*Met/Met*	14.73 ± 3.19	13.12 ± 3.28	29.06 ± 1.98	4
	Met/Val	19.56 ± 1.63	18.78 ± 2.01	32.07 ± 2.31	4
	Val/Val	21.26 ± 2.16	18.11 ± 2.23	39.98 ± 5.85	2
Bipolar disorder	*Met/Met*	26.93 ± 4.89	19.79 ± 5.58	65.02 ± 1.14	2
	Met/Val	22.47 ± 3.18	31.54 ± 10.72	40.55 ± 6.01	9
	Val/Val	20.55 ± 6.3	17.8 ± 1.17	39.96 ± 21.19	2

All values are expressed in pmol HMBA/mg protein/min. Data are represented as means ± SEM.; PFC, prefrontal cortex; STR, striatum, CER, cerebellum.

Table 3

Psychometric characteristics of subjects.

	Controls	Schizophrenia	Bipolar Disorder	P	η^2
Number	**9**	**10**	**13**		
BISS Mania	1.17 ± 0.98	4.5 ± 2.01	5.64 ± 3.12	0.53	0.05
BISS Depression	*2 ± 1.26*	*22.13 ± 4.63**	*15.27 ± 3.84*	*0.01*	*0.33*
BISS Irritability	0	4.63 ± 1.46	2.73 ± 1.18	0.07	0.21
BISS Anxiety	0.5 ± 0.34	5.5 ± 1.28	5 ± 1.86	0.12	0.18
BISS Psychosis	***0***	***5.75 ± 1.76 *****	***1.09 ± 0.45***	***0.002***	***0.42***
BISS Total	*3.67 ± 1.67*	*42.5 ± 8.78 **	*29.73 ± 8.29*	*0.01*	*0.32*
BIS-11	71.86 ± 9.09	51.5 ± 5.5	68.56 ± 3.79	0.12	0.37
HRSD-31	*0.33 ± 0.33*	*36 ± 18.23 ***	*17.55 ± 5.59*	*0.01*	*0.80*
BPRS	***20.10 ± 2.63***	***48.13 ± 6.42 ******	***30.45 ± 3.64***	***0.0003***	***0.49***
YMRS	*1.39 ± 0.64*	*10.38 ± 3.02 ***	*5.82 ± 1.45*	*0.006*	*0.86*

Uncorrected significant correlations (P<0.05) are reported in italics and highlighted in grey. Uncorrected significant differences (P<0.05) are reported in italics and highlighted in grey. Corrected significant correlations (P<0.005; Bonferroni correction for multiple testing) are marked in bold. The values indicated in the table are the mean activities ± SEM, as well as the *P* values of the comparisons (ANOVA).

* p<0.05;

** p<0.01,

*** p<0.001 in comparison with non-affected controls (Tukey's test with Spjøtvoll-Stoline correction for unequal n).

Table 4

Correlations of behavioral scores with brain-regional COMT activities.

	Age	COMT		
		PFC	Striatum	Cerebellum
BISS Mania	−0.61	*0.63*	***0.95***	*0.55*
BISS Depression	−0.15	0.33	0.32	0.22
BISS Irritability	−0.09	0.34	0.40	0.32
BISS Anxiety	−0.33	*0.48*	*0.60*	0.45
BISS Psychosis	0.11	0.21	0.06	−0.01
BISS Total	−0.34	*0.52*	*0.64*	0.42
BIS-11	−0.40	−0.03	0.13	0.30
HRSD-31	−0.11	0.40	0.47	0.38
BPRS	−0.07	0.09	0.26	0.15
YMRS	−0.48	*0.51*	***0.70***	0.47

Uncorrected significant correlations (P<0.05) are reported in italics and highlighted in grey. Corrected significant correlations (P<0.0005; Bonferroni correction for multiple testing) are marked in bold. The values indicated in the table are Pearson's r coefficients for each correlation. PFC, prefrontal cortex

Table 5

Associations between COMT genotype and symptom severity scores, as revealed by logistic regression.

	Adjusted R^2	P
BISS Mania	−0.02	0.50
BISS Depression	***0.28***	***0.004***
BISS Irritability	*0.21*	*0.01*
BISS Anxiety	***0.36***	***0.001***
BISS Psychosis	*0.18*	*0.02*
BISS Total	***0.31***	***0.002***
BIS-11 Total	0.06	0.17
HRSD-31	*0.23*	*0.006*
BPRS	***0.27***	***0.003***
YMRS	*0.23*	*0.007*

Uncorrected significant differences (P<0.05) are reported in italics and highlighted in grey.

Table 6

Differences in behavioral scores across COMT genotypes.

	***COMT* genotype**			**P**	**η^2**
	***Met/Met* (n=7)**	***Met/Val* (n=17)**	***Val/Val* (n=8)**		
BISS Mania	5.6 ± 3.09	4.54 ± 2.67	2.57 ± 1.29	0.79	0.02
BISS Depression	*29.6 ± 4.76*	*12.15 ± 2.84*	*7.29 ± 4.85**	*0.006*	*0.37*
BISS Irritability	*6.2 ± 2.46*	*2.38 ± 0.9*	*0.71 ± 0.47**	*0.04*	*0.26*
BISS Anxiety	***9.6 ± 2.62***	***3.77 ± 1.12***	***0.71 ± 0.57*****	***0.003***	***0.40***
BISS Psychosis	*6.4 ± 2.58*	*1.46 ± 0.73*	*1 ± 0.65**	*0.02*	*0.31*
BISS Total	***57.4 ± 11.64***	***24.31 ± 6.58***	***11.25 ± 5.33*****	***0.004***	***0.38***
BIS-11 Total	63 ± 1	65.23 ± 3.44	83 ± 20.6	0.28	0.16
HRSD-31	*33.67 ± 9.43*	*11.85 ± 4.14*	*6.5 ± 3.69**	*0.01*	*0.31*
BPRS	*49 ± 10.05*	*30.08 ± 3*	*22.88 ± 2.84**	*0.008*	*0.33*
YMRS	*12 ± 4.11*	*4.54 ± 1.2*	*2.38 ± 1.16**	*0.01*	*0.30*

Uncorrected significant differences (P<0.05) are reported in italics and highlighted in grey. Corrected significant correlations (P<0.005; Bonferroni correction for multiple testing) are marked in bold. The values indicated in the table are the mean activities ± SEM, as well as the *P* values of the comparisons (ANOVA).

* p<0.05;

** p<0.01 in comparison with *Met/Met* genotype (Tukey's test with Spjøtvoll-Stoline correction for unequal n).