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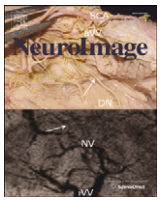

COMT Val158Met polymorphism, verbalizing of emotion and activation of affective brain systems

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ABSTRACT

Genetic variation in the catechol-O-methyltransferase (COMT) Val158Met polymorphism has been shown to influence performance on cognitive and emotional tasks. Specifically, it has been suggested that the Met allele might be less advantageous than the Val allele with respect to emotional processing.

This study addresses the question whether the presence of the Met allele is directly related to both lower emotional verbalizing proficiency and differences in brain activation during emotional processing. Specifically, we investigated whether COMT genotype would be associated with differences in activation in cortical midline structures during valence evaluation of words.

Forty participants ranging from low to high on the verbalizing subscale of the Bermond–Vorst Alexithymia Questionnaire (BVAQ) were genotyped for the COMT Val158Met polymorphism. During fMRI, they evaluated the valence of emotional words.

Met homozygotes reported more difficulties in verbalizing their feelings. In addition, the Met allele was associated with attenuated brain activation in posterior cingulate gyrus and precuneus during valence evaluation.

We conclude that the Met allele modulates neural activation in regions associated with emotional awareness. Our findings may contribute to understanding the neural correlates of susceptibility for affective disorders.

Introduction

Catecholaminergic neurotransmission is central to neural circuits involved in cognitive (Egan et al., 2001; Goldberg et al., 2003) and affective processing (Bishop et al., 2006; Drabant et al., 2006; Heinz and Smolka, 2006; Smolka et al., 2005). Catechol-O-methyltransferase (COMT) is a major enzyme involved in the inactivation of the catecholamine neurotransmitters including dopamine, epinephrine, and norepinephrine. The COMT gene has a functional variant involving the substitution of valine (Val) for methionine (Met) at codon 158 (Val158Met) (Lachman et al., 1996; Mannisto and Kaakkola, 1999). The Met allele is associated with low enzymatic activity resulting in higher levels of prefrontal dopamine. Conversely, the Val allele is associated with high enzymatic activity and lower levels of prefrontal dopamine (Chen et al., 2004; Lachman et al., 1996; Mannisto and Kaakkola, 1999). The Met allele has been associated with several psychiatric disorders such as panic disorder (Domschke et al., 2004; Woo et al., 2007) and bipolar affective disorder (Mynett-Johnson et al., 1998; Papolos et al., 1998). Further, it has been related to increased levels of harm avoidance (Enoch et al., 2003) and to neuroticism in females (Eley et al., 2003).

At first glance, the relationship between COMT Val158Met variation and cognition and emotion does not seem to be clear-cut. On the one hand, a number of studies have suggested that Met carriers perform better on cognitive tasks (Bertolino et al., 2006), accompanied by more efficient processing as deduced from less task-related activation (Egan et al., 2001; Goldberg et al., 2003). On the other hand, Met carriers have been shown to be less proficient compared to Val carriers on emotional processing tasks (Weiss et al., 2007). Zubieta et al. (2003) reported Met homozygotes to show higher sensory and affective ratings of pain and a more negative internal affective state as compared to Val homozygotes. Indeed, these authors implied the Met allele to underlie inter individual differences in less efficient adaptation to pain and other stressful stimuli. Waugh et al. (2009) also hypothesized the Val allele to confer better

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emotion regulation ability and found that Val allele carriers reported greater perceived social acceptance than did Met homozygotes. A recent meta-analysis confirmed the pleiotropic effect of COMT Val158Met variation on cognition with an advantage of the Met allele for cognition and an advantage of the Val allele for emotion, accompanied by increased activation in prefrontal areas for the allele carriers that have reduced ability in the specific domains (Mier et al., 2010). Drabant et al. (2006) reported increased cortico-limbic reactivity in Met carriers and suggested this to underlie emotional dysregulation. In addition, Williams et al. (2010) reported that COMT genotype modulates emotion-related brain activity which was related to a higher negativity bias in Met allele carriers. Furthermore, Montag et al. (2008) demonstrated that Met carriers exhibited a potentiated startle reflex in reaction to aversive stimuli. There is ample evidence implying that reduced emotion regulation ability correlates with a stronger startle reflex (Davidson et al., 2000). Lelli-Chiesa et al. (2010) recently reported that the Met158 allele reduces cortical efficiency in the ventrolateral prefrontal cortex during sad facial affect processing in individuals with affective disorders. Thus, consistent with the assertion by Smolka et al. (2005), these studies also point to an association between COMT genotype and susceptibility for affective disorders.

As COMT genotypes have been associated with difficulties in emotional processing, one may suggest that COMT is related to alexithymia. Alexithymia is a personality trait characterized by difficulties in describing, identifying and analyzing one's own emotions (Nemiah and Sifneos, 1970; Sifneos, 1973) and has been associated with differences in emotional processing (Lane et al., 1996; Luminet et al., 2006; Suslow, 1998; Swart et al., 2009; Vermeulen et al., 2008, 2006) and the use of less healthy emotion regulation strategies (Swart et al., 2009). Alexithymia has been associated with an increased risk for a variety of psychiatric disorders (Taylor et al., 1997) such as somatization (Mattila, 2008), depression (Honkalampi et al., 2000), schizophrenia (van 't Wout et al., 2007) and treatment outcome in anxiety and somatoform disorder (Bach, 1995). A key component of alexithymia is the inability to describe one's feelings with words (emotional verbalizing). Fibromyalgia has been associated with alexithymia (Huber et al., 2009) and a recent study showed the COMT Met/Met genotype to be associated with fibromyalgia and higher sensitivity to pain (Cohen et al., 2009). Another study showed that Met/Met genotype was associated with a reduced ability to regulate affective reactivity to pain in fibromyalgia (Finan et al., 2010). To our knowledge, only one study directly investigated the association between COMT Val158Met variation and alexithymia. In contrast to what would be expected from the literature reviewed above, this study reported that the Val allele was associated with higher alexithymia scores (i.e. indicating emotion regulation problems) on the Toronto Alexithymia Scale-20 (Ham et al., 2005). However, the finding was only marginally statistically significant and did not survive correction for a number of tests conducted. The study also had limited variability in alexithymia scores, as the authors did not select participants for alexithymia. Based on the weight of the evidence regarding emotional proficiency and COMT Val158Met as summarized above, we expected to find an association between the Met allele and alexithymia.

This study focused on the relationship between COMT genotype and both the ability to describe one's feelings and the neural basis underlying valence evaluation of emotional words. During valence evaluation, positive and negative words had to be evaluated on subjectively perceived valence for the participant. This required retrieval of self-related (emotional) information of the word (i.e. what does this word mean to me?). In the control condition, the metrical stress of the same words had to be indicated. This required only retrieval of phonological aspects of the words. By using the same stimuli in both conditions, we were able to examine emotional processing controlled for visual word input and two-choice configuration. By comparing the brain activation underlying valence evaluation versus metrical stress evaluation, we might thus be able to identify regions specific for emotional processing.

Given the evidence that Met carriers may be less proficient in emotional processing (Weiss et al., 2007), they were expected to report more difficulties in describing their feelings, reflecting susceptibility for emotional disorders. In addition, we hypothesized less activation in Met carriers during valence evaluation in cortical midline structures, related to self and emotional processing, including autobiographical memory (Maddock, 1999; Maddock et al., 2003).

Materials and methods

Participants

The study was approved by the medical ethical committee of the University Medical Center Groningen. The verbalizing scale of the BVAQ (Vorst and Bermond, 2001) was administered to screen 493 undergraduate university students in order to include individuals with sufficient variability in emotional verbalizing ability. Participants who scored in the upper or in the lowest quartile of the scale and agreed on participating were randomly invited, with the restriction that half were from the upper quartile and half from the lowest quartile. 40 right-handed participants (26 females and 14 males, mean age = 21.5, SD = 6.2) participated in the experiment. All participants were free from any lifetime neurological disorder or psychiatric disorder during the past 10 years and did not take medication at the time of the experiment. After the MRI session, participants filled in the complete BVAQ, there was no evidence for deviation of normality as tested with the Kolmogorov–Smirnov test ($D(40) = 0.13$, $p = 0.09$) [skewness = 0.54 (0.38); kurtosis = −0.75 (0.74)]. Therefore, we treated alexithymia scores as normally distributed, which matches well with the idea of the degree of alexithymia as a continuum in the general population. The current affective state was measured with the Positive Affect and Negative Affect Schedule (PANAS) (Watson et al., 1988). COMT genotypes did not differ on positive affective state (mean = 32.2, SD = 6.0) nor on negative affective state (mean = 14.8, SD = 3.9). After the MRI session, participants filled in the entire BVAQ. All 40 participants were native Dutch speakers and gave written informed consent. They received €35 for participation.

COMT genotyping

Genotyping of the COMT Val158Met polymorphism (1947G/A; GenBank Z26491; dbSNP: rs4680) was performed with the allelic discrimination technique on an Applied Biosystems 7500 real-time polymerase chain reaction (PCR) system (Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands) according to the protocol supplied by Applied Biosystems. We used primers COMT-GAF (5′-CGAGATCAACCCCGACTGT-3′) and COMT-GAR (5′-CAGGCATGCACACCTTGTC-3′), minor groove-binding probes VIC-5′-TTTCGCTGGCGTGAAG-3′-NFQ (G) and FAM-5′-TCGCTGGCATGAAG-3′-NFQ (A). The reaction was carried out in TaqMan universal PCR master mix (Applied Biosystems).

Bermond–Vorst Alexithymia Questionnaire

The BVAQ is a 40-item self-report scale, which is subdivided into five scales (eight items per scale), comprising the alexithymia features as defined by Nemiah and Sifneos (1970) (Sifneos, 1973), namely verbalizing, analyzing, identifying, emotionalizing and fantasizing. Answers are scored on a 5-point scale (1 = certainly does not apply to me, up to 5 = certainly applies to me). High scores indicate high levels of alexithymia. An example of the verbalizing scale is “I find it difficult to verbally express my feelings”. Previous studies have shown that the BVAQ has good psychometric properties and that the 5-scale structure of the BVAQ is supported by factor-analyses (Berthoz et al., 2000; Berthoz et al., 2007; Vorst and Bermond, 2001; Zech et al., 1999).

fMRI

Valence Evaluation Task (VET)

The Valence Evaluation Task investigated the emotional evaluation of words during fMRI. This paradigm was presented as a block design. Bisyllabic Dutch words, which were rated in a previous study by 33 participants, were presented one at a time in the middle of the screen. Each word was presented for 2 s followed by a fixation cross for 3 s. Participants had to evaluate the valence (positive or negative) of the presented word (e.g. stimulus: "summer"; answer e.g. "positive"). As a control condition, participants had to indicate the syllable that carried the metrical stress (cf. Aleman et al., 2005). An example would be "beauty"; where the correct answer would be 'the 1st syllable' (see supplementary table S3).

In both conditions, participants answered by pressing a button on a response box during the stimulus or just after the stimulus. During baseline, participants were instructed to fixate on the central cross on the screen.

In both conditions, 48 stimuli were randomly selected from a list containing 96 words. Valence (positive/negative) and metrical stress (1st/2nd syllable) were balanced in each condition. The two conditions were alternated in blocks of twelve trials of 60 s. Between the valence evaluation and control blocks, resting blocks of 30 s (baseline) were included. The total duration of the task was about 12 min.

Image acquisition

Scanning was performed using a 3 T Intera Philips scanner equipped with a SENSE head coil. For the VET, 39 slices were acquired with the following parameters using an EPI-sequence (repetition time (TR) 2500 ms; echo time (TE) 30 ms; and α 80° with an in-plane resolution of 64×64 pixels (field of view (FOV) 224 mm)), resulting in an isotropic voxel of 3.5 mm.

For anatomical reference, a T1-weighted image (160 slices; isotropic voxel size of 1 mm; TR 25 ms; TE 4.6 ms; α 30°; and FOV 256 mm) covering the whole brain was acquired.

Data analysis

Genotype data

COMT genotype frequencies were tested for Hardy–Weinberg proportions using the standard one degree of freedom χ^2 test. Age and gender differences in the different genotype groups were analyzed with a Kruskal–Wallis test with genotype as factor and gender and age as dependent variables.

Behavioral data

Group differences were analyzed using SPSS 14 (Norusius, 2002). Genotype effects on accuracy and reaction times on the VET were analyzed using regression analyses with accuracy and reaction times as regressors. Due to technical difficulties, behavioral data were not recorded for two subjects during the VET. Genotype differences on the positive and negative affect scales were analyzed using ANOVA. The subscales of the BVAQ were analyzed with a multivariate analysis of variance (MANOVA). In case of significant differences, a regression analysis was performed to test for a gene-dosage effect.

Imaging data

Data were analyzed with Statistical Parametric Mapping (SPM5; FIL Wellcome Department of Imaging Neuroscience, London, UK). After realignment, the functional images were coregistered to the T1-weighted image. The anatomical image was normalized to a standard T1 MNI (Montreal Neurological Institute) brain and the same transformation was applied to the functional images. The latter were then smoothed with a Gaussian kernel (full width at half maximum 8 mm). For the analyses of the VET, one participant (Val/Val genotype) was excluded because of excessive movement (>3 mm). At the first level, two separate regressors were modeled for valence evaluation blocks and metrical stress blocks with a boxcar function convolving a hemodynamic response function. For each participant, two first level contrasts were defined: 1) to detect genotype dependent effects on emotional evaluation, we defined the contrast: valence evaluation–metrical stress evaluation; and 2) to analyze the effect of genotype on processing of emotional words in general (i.e. across conditions), we made the contrast: valence evaluation+metrical stress evaluation.

First, to detect associations between COMT genotype and valence evaluation compared to metrical stress evaluation, the contrast images (valence evaluation–metrical stress evaluation) of all participants were included in a regression analysis in SPM5. COMT genotype was modeled as the number of Met alleles (0, 1 or 2). The analysis was thresholded at $p<0.001$ with an extent threshold of 20 voxels. Additionally, we controlled for multiple comparisons with a family-wise error (FWE) correction of $p<0.05$ at a cluster level. In a similar way, the contrast images valence evaluation+metrical stress evaluation were included in a regression analysis. For the effect of task, irrespective of genotype, the contrast images were entered into a random effects analysis (RFX).

For further inspection of activation differences between groups, we entered valence evaluation versus rest and metrical stress evaluation versus rest into separate RFX analyses for the Met homozygotes and Val homozygotes.

To control for potential confounding of genotype effects by gender, we performed the same analysis with gender added as a covariate. To control for potential confounding of reaction time differences between genotypes during valence evaluation, we performed the same analysis with individual reaction time during valence evaluation added as a covariate. As genotype and verbalizing are related to each other, it is difficult to control for the possible confounding effect of verbalizing. Therefore, to examine the (possible confounding) effect of verbalizing, we conducted two additional analyses. Firstly, we performed a regression analysis with verbalizing score as a regressor (without genotype). Secondly, we performed a regression analysis with genotype as a regressor and verbalizing score as a covariate. For the additional analyses with a covariate, we used the $p<0.001$ threshold with an extent threshold of 20 voxels to preserve sensitivity due to a reduction in degrees of freedom.

Results

Table 1 presents demographical data and questionnaire scores by genotype.

Genotyping

Out of the 40 participants, twelve participants (30%) (eight women) were homozygous for the Met158 allele and ten (25%) (six

Table 1
Demographic information and questionnaire scores by COMT genotype.

	Met/Met		Val/Met		Val/Val		Statistic
	Mean	SD	Mean	SD	Mean	SD	p
N	10		18		12		
Male/female	4/6		6/12		4/8		0.93
Age (years)	23.50	10.10	21.06	4.04	19.90	0.88	0.77
Overall BVAQ (MANOVA)							0.006
BVAQ verbalizing	26.42	9.89	19.44	8.04	16.70	4.40	0.02
BVAQ fantasizing	18.92	5.07	17.44	6.65	20.00	7.77	0.60
BVAQ identifying	16.83	7.32	14.72	4.16	18.10	4.09	0.25
BVAQ emotionalizing	20.33	6.60	21.06	5.74	17.20	4.49	0.24
BVAQ analyzing	17.58	7.60	13.94	3.84	16.60	5.80	0.21

A MANOVA revealed a significant effect of COMT genotype on the BVAQ ($p=0.006$). Specifically, Met homozygotes were worse in verbalizing ($p=0.02$). BVAQ, Bermond–Vorst Alexithymia Questionnaire; RT, reaction time.

women) were homozygous for the Val158 allele of the COMT gene; eighteen participants (45%) (twelve women) were heterozygous. Allele and genotype frequencies were in Hardy–Weinberg proportions ($\chi^2 = 0.38$, df = 1; p = 0.54). Genotype was not associated with gender ($\chi^2 = 0.14$, df = 2; p = 0.93) nor with age ($\chi^2 = 0.53$, df = 2; p = 0.77).

Questionnaire data

COMT genotype had a significant effect on the subscales of the BVAQ (Pillai's Trace F(10,68) = 2.80, p = 0.006). Between-subjects effects revealed that COMT genotypes differed on the verbalizing subscale (F(2,37) = 4.56, p = 0.02). A post-hoc regression analysis demonstrated that the number of Met alleles was positively correlated with verbalizing score (i.e. more difficulties in emotional verbalizing) ($R^2 = 0.18$, b = 0.43, p = 0.006) (see Fig. 1). No other significant differences were obtained. The distribution of the COMT genotypes in the invited groups of low and high verbalizing score was respectively: (Val/Val, Val/Met, Met/Met): 7/9/4 and 3/9/8.

Behavioral data

With regard to the VET, the number of Met alleles was positively associated with reaction times of valence evaluation ($R^2 = 0.11$, b = 0.33, p = 0.02) (Met/Met: M = 1250.9, SD = 244.4; Val/Met: M = 1192.9, SD = 208.6; Val/Val: M = 1041.3, SD = 172.4). The number of Met alleles was not associated with reaction times of metrical stress evaluation (control condition) (p = 0.90) (Met/Met: M = 1391.7, SD = 269.2; Val/Met: M = 1522.8, SD = 369.9; Val/Val: M = 1387.6, SD = 431.6) nor with accuracy (p = 0.73) (mean percent correct responses Met/Met: 81%; Val/Met: 77%; Val/Val: 79%) (in the valence evaluation condition there are no correct or incorrect answers). Participants assigned to 52% of the words a negative valence and to 48% a positive valence. There were no differences between genotypes in valence assignment (p = 0.13).

Imaging data

Valence Evaluation Task

The contrast valence evaluation versus metrical stress evaluation yielded brain activation in the bilateral precuneus, bilateral dorsomedial prefrontal cortex and right supramarginal gyrus (see Fig. 2 and Table S1 in the supplementary information).

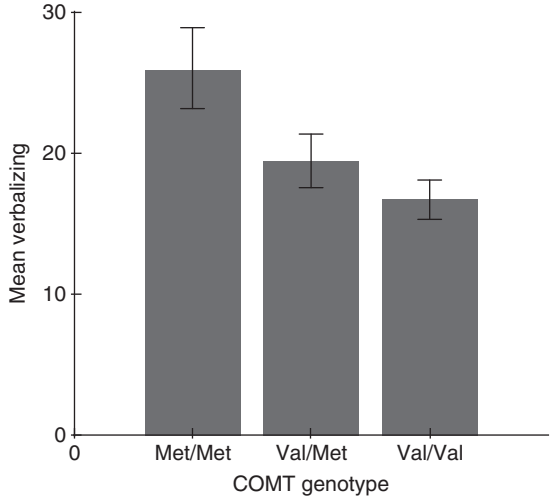

Fig. 1. Mean verbalizing scores per COMT genotype. The number of Met alleles was positively correlated with verbalizing score (i.e. less verbalizing proficiency) (p = 0.02). Error bars represent the standard error of the mean.

COMT Val158Met genotype effect on the Valence Evaluation Task

The regression analysis for the contrast valence evaluation versus metrical stress evaluation demonstrated a significant negative correlation between the number of Met alleles and activation in the left precuneus and bilateral cingulate gyrus (PCC) extending into the precuneus and medial frontal gyrus (MFC) (see Fig. 3 and Table 2).

There was no genotype dependent effect on the processing of emotional words in general as demonstrated by the regression analysis with the contrast valence evaluation+metrical stress evaluation.

An examination of the within group contrasts valence evaluation versus fixation and metrical stress evaluation of the homozygotes revealed that the homozygote groups showed different deactivations during these conditions (p<0.001). The Met/Met genotype showed approximately the same deactivation in PCC during both valence evaluation and metrical stress evaluation. The Val/Val genotype also showed approximately the same deactivation as the Met/Met genotype in response to metrical stress evaluation. However, in response to valence evaluation, the Val/Val genotype had less deactivation in PCC (see supplementary information Fig. S1).

When we controlled for gender, the relation between COMT genotype and activation in PCC extending into precuneus and in MFC remained significant with identical peak activations, indicating that the effect of COMT genotype was independent from gender (see supplementary information Table S2). When we controlled for reaction time during valence evaluation, the same regions remained significant, indicating that there was no confounding effect of this covariate in our findings.

The additional analyses to examine the (confounding) effect of verbalizing demonstrated that an increased verbalizing score was related to decreased activation in MFC (peak maximum (x, y, z): −12, −24, 66). This cluster neighbored and slightly overlapped the cluster in the cingulate cortex related to genotype. The regression analysis with verbalizing score added as a covariate demonstrated that the relation between COMT genotype in both the cingulate cortex and precuneus/cuneus remained significant with the same peak maxima ((x, y, z): 8, −22, 50 and −18, −74, 20, respectively) although the size of the clusters decreased.

We did not find any significant positive correlation between the number of Met alleles and brain activation.

Discussion

The primary finding of our study was that the number of Met alleles was associated with less activation in cortical midline structures (CMS) during valence evaluation of emotional words. In addition, individuals with a higher number of Met alleles reported to have more difficulties in verbalizing their feelings, a core aspect of alexithymia. Our results lend further support to the relevance of CMS for emotional awareness and suggest an involvement of these areas in emotion regulation and disorders thereof.

With regard to self-reported emotion regulation, the Met allele presented a dosage effect on difficulties in emotional verbalizing. This suggests an involvement of the Met allele in alexithymia, which is a novel finding. Previous research has shown that individuals scoring high on alexithymia in general or more specifically on the subscale verbalizing, performed worse on emotion recognition tasks (Lane et al., 1996; Swart et al., 2009). Our finding regarding a role of COMT Met alleles in emotion concurs with a previous behavioral study of emotion processing in Met carriers (Weiss et al., 2007), which showed Met carriers to be less proficient than Val homozygotes in recognition of emotional expressions. A previous study (Ham et al., 2005) in a Korean sample reported that the number of Val alleles was correlated with higher alexithymia scores on the Toronto Alexithymia Scale. As the current study points toward an association of the COMT Met allele alexithymia, replication studies are required to solve this issue. Of note, our finding of a relationship between the Met allele and emotion

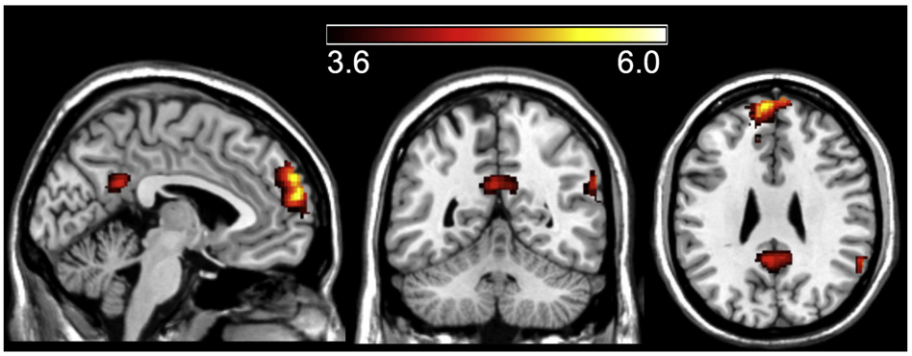

Fig. 2. Brain activation during valence evaluation across groups was in dorsomedial prefrontal cortex and cuneus/precuneus. Contrasted versus metrical stress evaluation (correction for multiple comparison with FWE-correction at cluster level $p<0.05$ with a cluster size of >20 voxels) and superimposed on a single subject T1 image ($x=-4$, $y=-52$, $z=28$).

regulation difficulties is consistent with the evidence of reduced emotional resilience in COMT Met allele carriers (Montag et al., 2008; Smolka et al., 2005; Williams et al., 2010). Thus, based on our results and most other studies into COMT and emotion processing, we suggest that the Met allele is related to emotion regulation difficulties.

During valence evaluation, we found that the bilateral precuneus, posterior cingulate cortex (PCC) and dorsomedial prefrontal cortex were more activated as compared with activation during metrical stress evaluation. In line with our findings, prior imaging studies reported increased activation in the precuneus, medial prefrontal cortex and PCC during valence evaluation of emotional words (Maddock et al., 2003; Posner et al., 2009) and IAPS pictures (Paradiso et al., 1999). Thus, our and other findings suggest that the medial prefrontal cortex, posterior cingulate cortex and precuneus react to the emotionality of the stimulus (Lee and Siegle, 2009; Maddock et al., 2003; Posner et al., 2009) and that this reflects the activation of autobiographical memory (for a meta-analysis see Svoboda et al., 2006). Also, meta-analyses have confirmed that self-referential processing is mediated by cortical midline structures (Northoff et al., 2006; van der Meer et al., 2010). With regard to the COMT genotypes, with increasing the number of Met alleles, activation decreased in the PCC and precuneus during valence evaluation. Met homozygotes have previously been associated with attenuated PCC activation in a sentence completion task in people at high genetic risk for psychosis (McIntosh et al., 2007). In addition, a PET study (Slifstein et al., 2008) found that Met allele carriers showed a decrease in D_1 receptors both in cortical (amongst others: medial prefrontal and parietal cortices) and limbic areas (amygdala and hippocampus). The authors suggested that this polymorphism may also affect the function of these regions (Slifstein et al., 2008).

Our finding of attenuated activation in Met carriers in PCC and precuneus is, as far as we know, the first evidence that COMT modulates activation in cortical midline structures in relation to valence evaluation. As cortical midline structures play a role in self-related processes including emotional awareness (Dimaggio et al., 2009; van der Meer et al., 2010), decreased activation might be related to lower emotional awareness. Additionally, the Met carriers responded more slowly to valence evaluation, which might imply that they had more difficulties performing this task. A possible interpretation of our findings could be that, because Met homozygotes are worse in describing their feelings, and may have lower levels of emotional awareness (cf. Lane et al., 1997), they activate their autobiographical memory to a lesser extent. Thus, areas related to autobiographical memory (and more specifically the PCC) may be less activated. Indeed, Mantani et al. (2005) have observed less PCC activation during imagining future events in individuals with high alexithymia as compared to individuals low in alexithymia.

It is difficult to disentangle the specific effect of COMT or alexithymia on brain activation, as these variables are correlated. Therefore, we examined the effect of COMT genotype on activation with verbalizing score as a covariate and we investigated the effect of verbalizing without genotype. The effect of genotype was stronger than the effect of

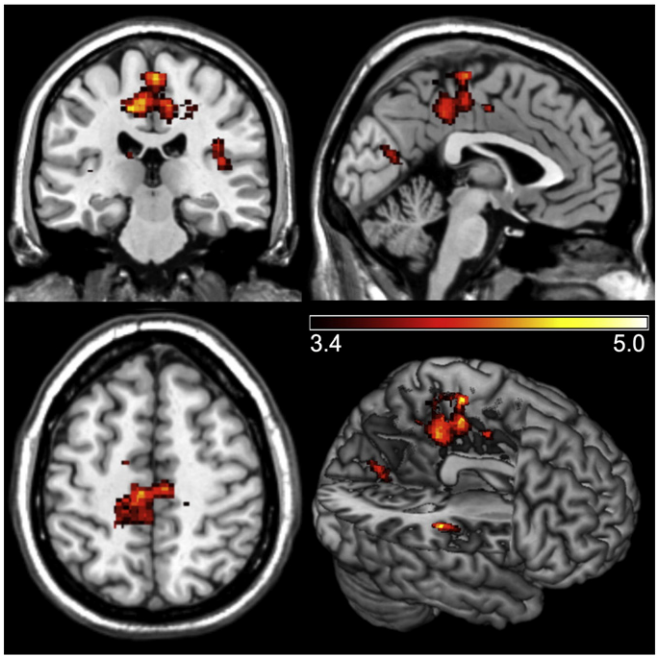

Fig. 3. Effect of COMT genotype on activation during valence evaluation. Met allele load was associated with decreased activation in posterior cingulate gyrus and cuneus/precuneus. Task contrasted against control task and superimposed on a sliced single subject T1 image ($x=-2$, $y=-26$, $z=50$) and on a rendered (below right) image (correction for multiple comparisons with FWE-correction at cluster level $p<0.05$ with a cluster size of >20).

Table 2
Brain areas which were negatively related with the number of Met alleles during valence evaluation.

Area	BA	Side	k	T	Z	Peak maxima (MNI coordinates)		
						x	y	z
Cingulate cortex, precuneus, medial frontal cortex (paracentral lobule)	31, 6	L, R	1687	5.17	4.46	8	−22	50
				4.73	4.16	12	−40	62
				4.6	4.07	−10	−28	46
Supramarginal gyrus, superior temporal gyrus	40	L	198	5.1	4.41	−58	−60	26
				4.02	3.64	−50	−50	34
Rolandic operculum, superior temporal gyrus	13, 41	R	200	4.48	3.98	40	−32	24
				4.31	3.86	44	−28	12
Precuneus, cuneus	31, 18	L	197	4.24	3.8	−18	−74	20
				4.11	3.71	−6	−78	22
				3.95	3.58	−2	−68	16

Correction for multiple comparisons with FWE-correction at cluster level $p<0.05$ with a cluster size of >20 voxels. BA, Brodmann areas; L, left; R, right; k, number of voxels; MNI, Montreal Neurological Institute.

verbalizing on brain activation related to valence evaluation. Additionally, the activation in cingulate cortex was not explained by verbalizing score. Therefore, we suggest that the activation in PCC is mainly explained by COMT genotype.

Interestingly, PCC activation has been associated with self-related processes during rest and self-referential aspects of tasks and with deactivation during non self-related tasks (Dimaggio et al., 2009; Raichle et al., 2001; van der Meer et al., 2010). To examine the PCC activations or deactivations, we compared the valence evaluation condition with rest (visual fixation) and the metrical stress condition with rest in Met and Val homozygotes separately. Both groups deactivated the PCC equally during metrical stress evaluation whereas during valence evaluation the Met homozygotes deactivated the PCC more than the Val homozygotes. The difference in deactivation may also imply that the Met homozygotes recruit autobiographical memory to a lesser extent during valence evaluation.

Only a few imaging studies have investigated COMT polymorphisms in relation to emotional processing, with inconsistent results. More Met alleles have been associated with decreased activation in prefrontal areas during viewing the IAPS pictures used as distracters in a house matching task (Bishop et al., 2006), but also with increased activation in prefrontal areas in response to passively viewing the IAPS pictures (Smolka et al., 2005). In addition, less activation in amygdala and right temporal pole during labeling facial expressions have been shown in Met homozygotes (Kempton et al., 2009) whereas an increased activation have been shown in right hippocampal formation and right VLPFC during matching facial expressions (for a review see Aleman et al., 2008; Drabant et al., 2006). Differences in task design might play a role in these inconsistencies, in addition to regional specificity in cognitive functions of frontal areas. In an attempt at integration, Smolka et al. (2005) have speculated that COMT Met allele carriers might have difficulties to recruit prefrontal regulatory regions under demanding conditions.

It is of importance to note that our results are based on the findings from young and healthy participants with a limited sample size. Methylation of the COMT gene (influenced by aging, nutrition and life events, a.o.) can lead to changes in gene activity, and hence different results may be achieved in older samples due to epigenetic mechanisms (cf. Abdolmaleky, 2006). More research is necessary to further enhance our understanding of the neural differences related to COMT genotype.

The relevance for psychiatric disorders also deserves further elucidation. Although a recent meta-analysis did not find a direct link between COMT and schizophrenia (Okochi, 2009) or depression (Lopez-Leon et al., 2008), they might be indirectly linked via an intermediate phenotype as expressed by neural systems related to emotion processing. Our finding may eventually result in new insights into the complex relationship between COMT genotype and emotional processing underlying both normal variation in affective processing and susceptibility to affective disorders.

In conclusion, we demonstrated that difficulties in emotional verbalizing are positively related to the number of Met alleles. In addition, an increase in the number of Met alleles resulted in a decrease of neural activation in PCC. This might be associated with lower emotional awareness, which in turn may be related to susceptibility for affective disorders.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2010.12.017.

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