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Catechol-*O*-methyltransferase Val^{158}Met genotype affects neural correlates of aversive stimuli processing

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It was previously shown that variation of the catechol-*O*-methyltransferase (COMT) gene modulates brain activity during the processing of stimuli with negative valence, but not for pleasant stimuli. Here, we tested whether the COMT genotype also modulates the electrophysiological correlates of emotional processing and explored whether the environmental factor of life stress influences this effect. Using the early posterior negativity (EPN) paradigm, event-related brain potentials were measured in 81 healthy individuals during the processing of pictures that evoked emotions of positive and negative valence. As was hypothesized, the COMT genotype affected the EPN amplitudes for unpleasant stimuli, but not for pleasant ones. Specifically, Met/Met carriers respond more sensitively to unpleasant stimuli, as compared with Val/Val carriers. We did not find evidence that life stress moderates the effect of the COMT genotype on emotional stimuli processing.

Catechol-*O*-methyltransferase (COMT), which degrades the catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine, has recently gained increasing interest with respect to emotional and cognitive brain functions. A common single nucleotide polymorphism exists in the COMT gene, causing a Val-to-Met substitution at amino acid position 158, which is commonly designated as Val^{158}Met. The Met variant corresponds to the so-called *thermo-labile* enzyme, displaying lower enzymatic activity. This results in increased synaptic dopamine and strengthened (prefrontal) dopaminergic tone. Met/Met homozygotes exhibit approximately 25% COMT activity of Val/Val homozygotes, with heterozygotes in between (Lotta et al., 1995). The Val variant is associated with an impaired cognitive performance (the first positive results of impaired cognitive performance were not confirmed by a recent meta-analysis [Barnett, Scoriels, & Munafò, 2008]) but seems to provide increased emotional resilience against negative mood states and various psychiatric disorders (Heinz & Smolka, 2006).

Investigation of the effects of COMT Val^{158}Met variation on functional brain activity during emotional stimuli processing, using functional magnetic resonance imaging (fMRI), revealed a positive association between the gene dose coding for Met variants and the functional brain activity in the amygdala for unpleasant stimuli, but not for pleasant ones (Smolka et al., 2007; Smolka et al., 2005). Consistent with these fMRI results, a recent study showed that the COMT genotype significantly affected startle reflex modulation by aversive stimuli, which can be considered a psychophysiological measure of emotion processing (Montag et al., 2008). In this study, subjects homozygous for the Met allele exhibited a potentiated startle reflex, as compared with Val allele carriers. Similar effects of the COMT genotype were found for the activity of the ventral striatum during reward processing. In this area of the brain, stronger responses to loss incentives were described with an increasing number of Met alleles (Schmack et al., 2008), without any significant effect of the COMT genotype on ventral striatum activation during reward incentives (Forbes et al., 2009; Schmack et al., 2008). Since COMT has been found to be expressed not only within the prefrontal cortex, but also in the human amygdala and striatum (Hong, Shu-Leong, Tao, & Lap-Ping, 1998), it might well be that elevated dopamine in Met^{158} homozygotes in the ventral striatum and amygdala enhances the salience of environmental threat cues. This would be in line with a recent positron emission tomography study (Kie-

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nast et al., 2008) showing that dopamine storage capacity in the human amygdala was positively correlated with fMRI blood-oxygen-level-dependent signal changes in the amygdala that were evoked by aversive stimuli.

Alternatively, the model of tonic and phasic dopamine signaling (Bilder, Volavka, Lachman, & Grace, 2004) suggests that elevated dopamine in the prefrontal cortex could result in an inflexible attentional focus on aversive stimuli. According to this model, the COMT Met allele (associated with low enzyme activity) results in increased levels of tonic dopamine and reciprocal reductions in phasic dopamine in subcortical regions. The authors hypothesized that such a pattern could lead to increased stability but decreased flexibility of the neural network states underlying working memory and executive functioning. A diminished capacity to update and shift attentional focus may, therefore, lead to an impaired disengagement of attentional resources from perceived sources of threat. This notion has been supported by Bishop, Cohen, Fossella, Casey, and Farah (2006), who found that the COMT Met allele correlated negatively with activity in control and task-related regions during performance under emotional distraction.

In addition, an initial study demonstrated that the COMT Val^{158}Met genotype (with Met as a risk variant) was associated with depression following exposure to stressors (Mandelli et al., 2007). These findings suggest that COMT and life stress may interact on the neural correlates of emotional processing, as has been shown for 5-HTTLPR (Canli et al., 2006). A possible mechanism accounting for the hypothesized COMT $\times$ life stress interaction might be a moderating effect of the genotype on the individual responsiveness to stress. Therefore, one would expect that stressful life events lead to increased negative emotional reactions, especially in Met allele carriers. Alternatively, positive stimuli might be devaluated by life stress, especially in Met allele carriers.

In the present study, we wanted to investigate whether COMT also modulates the neural correlates of emotional processing, measured with the event-related brain potential (ERP). One major component of the ERP for emotional processing is the early posterior negativity (EPN) potential, which can be detected over the occipital cortex between 170 and 300 msec after stimulus presentation (Junghöfer, Bradley, Elbert, & Lang, 2001; Schupp, Junghöfer, Weike, & Hamm, 2003; Wieser, Mühlberger, Kenntner-Mabiala, & Pauli, 2006). Schupp et al. (2003) argued that this EPN reflects facilitated sensory encoding of affective stimuli by naturally occurring selective attention. The electroencephalograph (EEG) recording offers an excellent tool for the investigation of emotion discrimination in humans with a high temporal resolution (within milliseconds). This early emotional tagging reflected in the EPN can be differentiated from later conscious processing by using an ERP paradigm, which has previously been found to be associated with the 5-HTTLPR and the tryptophan hydroxylase (TPH2) genotype (Herrmann et al., 2007). Therefore, the measurement of the EPN allowed us to test the hypothesis (Bishop et al., 2006) that Met allele carriers show a different allocation of attentional resources to threat stimuli.

On the basis of previous studies (Bishop et al., 2006; Forbes et al., 2009; Schmack et al., 2008; Smolka et al., 2007; Smolka et al., 2005), we hypothesized that individuals with the Met/Met genotype would show increased EPN amplitudes to negative stimuli, as compared with individuals with the Val/Val genotype. In addition, we investigated the effect of life stress on the association between COMT and the neural correlates of emotional processing.

METHOD

Subjects

Eighty-one healthy, right-handed adults participated in this study. We began with a larger sample of 178 normal volunteers and, on the basis of the genotype with the lowest frequency (Val/Val), selected 27 subjects (17 female and 10 male) for each possible COMT Val^{158}Met genotype group (Val/Val, mean age = 23.9 years, *SD* = 5.3; Val/Met, mean age = 23.8 years, *SD* = 5.1; Met/Met, mean age = 23.7 years, *SD* = 3.2). Exclusion criteria were a history of psychiatric disorder, current use of mood-altering medication, and history of severe head trauma, neurosurgery, or another neurological condition. The study was performed in accordance with the latest version of the Declaration of Helsinki and was approved by the local Institutional Review Board. All the subjects were informed about the nature of the experiment in detail before providing written informed consent.

EEG Measurement and Analyses

EEG was recorded from 21 electrodes according to the extended International 10–20 System (Fp1, Fp2, F3, F4, F7, F8, T3, T4, C3, C4, T5, T6, P3, P4, O1, O2, Fpz, Fz, Cz, Pz, and Oz). Three additional electrodes were placed at the outer canthi of both eyes and below the right eye to register horizontal and vertical eye movements. The recording reference was placed at FCz and the ground electrode at AFz. Electrode impedances were kept below 5 kΩ. EEG was sampled continuously at a rate of 1000 Hz, with a band-pass filter from 0.1 to 70 Hz.

During EEG measurement, the subjects passively viewed two presentations of a 120 picture set from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1999). The pictures were presented for 1,000 msec, with a variable interstimulus interval of between 1,000 and 2,000 msec in a randomized order. The sample of IAPS pictures used in this study consisted of 40 pleasant (mean arousal = 5.6, mean valence = 7.1), 40 unpleasant (arousal = 6.3, valence = 2.3), and 40 neutral (arousal = 2.8, valence = 4.9) pictures, based on norm ratings (Lang et al., 1999) of arousal and valence (values ranging between 1 and 9; in the arousal dimension, 1 = *low arousal*; in the valence dimension, 1 = *negative*).

Time epochs lasting from -200 msec before to 1,000 msec after stimulus presentation were extracted and analyzed for artifacts ($\pm 100\ \mu$V) after average reference recalculation. All the subjects had a sufficient number of trials (at least 20 artifact free), of which the ERPs were averaged. Baseline was corrected using the -200 msec before stimulus presentation. The ERPs were filtered using a band-pass filter from 0.5 to 20 Hz. In the time curves of the difference waves over all subjects, we see two distinct negative components with a clear distribution over occipital brain areas. The first component peaks at 139 msec; the second at 265 msec over Oz (see Figure 1). Since Schupp and colleagues analyzed the EPN between 200 and 300 msec (Schupp et al., 2004; Schupp et al., 2007; Schupp et al., 2008), we also named the second component EPN (mean amplitudes between 230 and 300 msec) but additionally analyzed the first peak (mean amplitudes between 120 and 160 msec). The time windows were based on the time curves of the difference waves (around the peaks for Oz at 139 and 265 msec, respectively). To analyze the individual values of the two components, we calculated the mean amplitudes within the defined time windows, instead of peak detection.

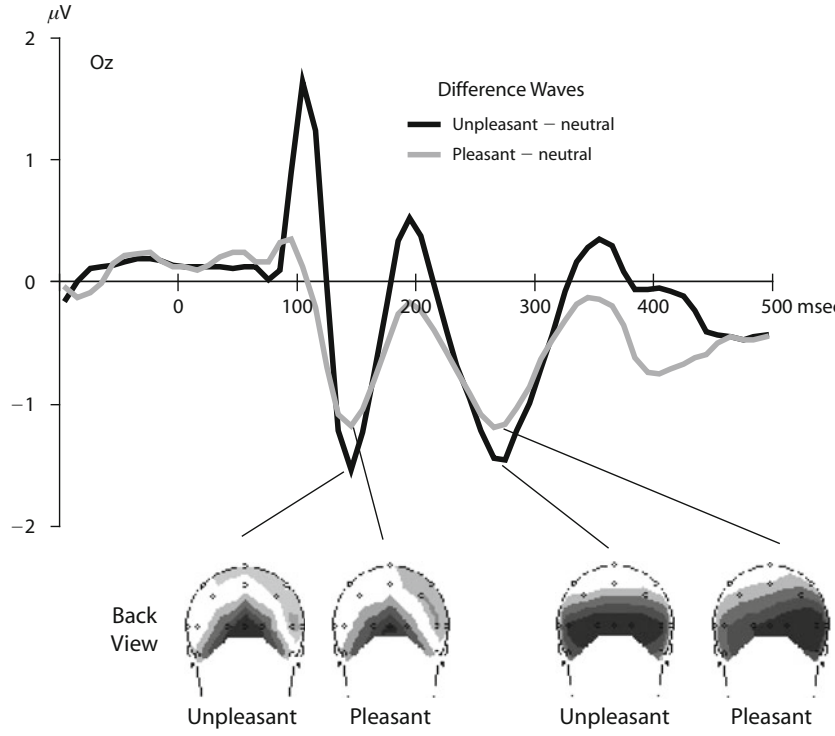

Figure 1. Grand mean event-related potentials (for all subjects) over electrode position Oz for the differences between pleasant minus neutral and unpleasant minus neutral stimuli. In addition, the distribution of the difference waves over the scalp is displayed in a back view for both negative components.

Life Stress Assessment

Life stress history was based on a self-report questionnaire (Canli et al., 2006) developed from items in the life history calendar. It contained 28 items related to work, financial, and legal problems, death and serious illness, family and relationships, and other stressful life events. The subjects indicated for each item whether they had experienced a particular event and at which age. For the analysis of this study, life stress was quantified as the number of items that were endorsed by each subject (Canli et al., 2006). The number of reported stressful life events ranged from 1 to 14 in our sample, with $M = 5.1$ ($SD = 2.5$, median = 5).

Genotyping

DNA was extracted from whole blood. Genotyping of the COMT Val^{158}Met variation was accomplished using standard polymerase chain reaction (PCR) procedures modified from a previously published protocol (Egan et al., 2001); primers were 5′-GGG GCC TAC TGT GGC TAC TC-3′ (forward) and 5′-TTT TTC CAG GTC TGA CAA CG-3′ (reverse). PCR reactions were performed in a reaction volume of 25 μl and included approximately 50 ng of template genomic DNA, 10 pmol of each primer, 2.5 mM of each dNTP, 0.75 mM $MgCl_2$, and 1 U of Taq DNA polymerase. Annealing temperature was 58ºC (35 cycles). PCR products were digested with *Nla*III (3 h at 37ºC; fragment sizes: G1947 variant, 114 bp; 1947A variant, 96 and 13 bp) and subsequently were visualized on a 4% agarose gel. G1947 corresponds to the high-activity Val variant; 1947A codes for the low-activity Met variant.

Statistical Analyses

To analyze the COMT genotype effect on neural correlates of emotional processing, we calculated an ANCOVA with condition (pleasant, unpleasant) and electrode position (O1, Oz, O2) as within-subjects factors and COMT genotype (Val/Val, Met/Val, Met/Met) as a between-subjects factor. Number of life events was entered as a continuous covariate.

RESULTS

The difference waves between emotional and neutral stimuli revealed negative deflections over the occipital cortex for two separate time frames (see Figure 1). Testing these negative deflections against zero revealed significant effects in the first time frame for both stimuli categories over electrode positions O1 [unpleasant condition, $t(80) = -2.3, p = .03$; pleasant condition, $t(80) = -3.1, p = .003$] and Oz [unpleasant condition, $t(80) = -5.1, p = .001$; pleasant condition, $t(80) = -5.1, p = .001$], but not for electrode positions Pz [unpleasant condition, $t(80) = 0.66$, $p = .51$; pleasant condition, $t(80) = 1.2, p = .22$] or Cz [unpleasant condition, $t(80) = 1.68, p = .10$; pleasant condition, $t(80) = 0.55, p = .59$]. In the second time frame, we found a significant negative deflection for electrode positions O1, Oz, and O2 [$t(80) > -5.1, p < .001$], but not for electrode positions Pz [unpleasant condition, $t(80) = -0.49$, $p = .63$; pleasant condition, $t(80) = -1.86$, $p = .07$] or Cz [unpleasant condition, $t(80) = -1.68, p = .10$; pleasant condition, $t(80) = 0.55, p = .59$]. Therefore, we further analyzed the COMT effect for electrode position Oz for the first time frame and the three electrode positions O1, Oz, and O2 for the second time frame.

COMT and Life Stress Modulation on Emotional Processing

Our analysis confirmed that COMT modulates the neural correlates of emotional processing for the second

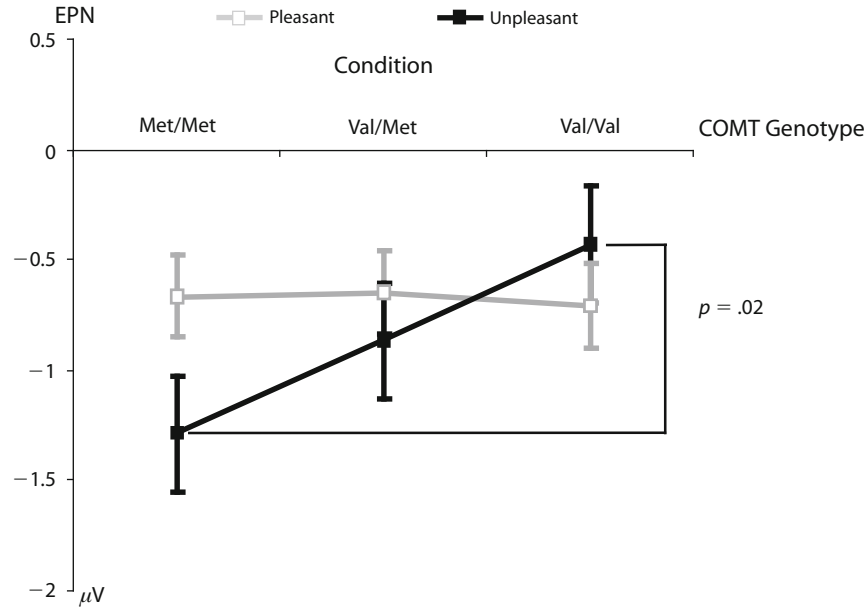

Figure 2. Interaction of COMT genotype (Met/Met, Val/Met, Val/Val) and category (pleasant and unpleasant stimuli) for the EPN (more negative, more activity), with mean values and standard errors of the means over the three electrode positions: O1, Oz, and O2.

time frame (EPN). We found a significant COMT × category interaction (see Figure 2) for the amplitudes of the EPN [$F(2,75) = 3.22$, $p = .046$] and a significant category × electrode position interaction [$F(2,150) = 8.45$, $p = .001$], with only a tendency for main effects of category [$F(1,75) = 3.13$, $p = .08$] and electrode position [$F(2,150) = 2.67$, $p = .07$]. The main effects of COMT [$F(2,75) = 0.80$, $p = .45$] and life events [$F(1,75) = 0.76$, $p = .39$] did not reach significance. In addition, we could not find a three-way category × COMT × life events interaction [$F(2,75) = 1.34$, $p = .27$].

Post hoc *t* tests for the unpleasant condition showed that individuals with the Met/Met variant had significantly increased negative EPN amplitudes, as compared with subjects with the Val/Val variant [$t(52) = -2.44$, $p = .02$].

The category × electrode position interaction can be explained by more negative EPN values over the right hemisphere (O2, $M = -0.81$, $SD = 1.01$) than over the left hemisphere (O1, $M = -0.57$, $SD = 1.00$) [$t(80) = 4.35$, $p = .001$] for the pleasant condition, but not for the unpleasant condition [O2, $M = -0.86$, $SD = 1.43$; O1, $M = -0.88$, $SD = 1.51$; $t(80) = -0.28$, $p = .78$].

For the first time frame, we found no significant effect for category [$F(1,75) = 1.69$, $p = .20$] or COMT genotype [$F(2,78) = 0.22$, $p = .80$] and no significant category × genotype interaction [$F(2,75) = 0.14$, $p = .87$].

DISCUSSION

The electrophysiological detection of an interaction effect between the COMT genotype and the neural correlates of emotional processing as measured by the EPN is the primary finding of this study. As was expected from previous fMRI literature (Smolka et al., 2007; Smolka et al., 2005), we confirmed a positive association between the number of Met variants and the functional brain activity for the unpleasant stimuli, but not for the pleasant ones. More specifically, we found that subjects with the genotype encoding Met/Met had significantly increased EPN amplitudes, as compared with subjects homozygous for Val, but only for the processing of unpleasant stimuli.

This finding could be interpreted as an impaired disengagement of attentional resources from negative stimuli, as hypothesized by a recent fMRI study on emotional distraction (Bishop et al., 2006). However, alternatively, our finding could be interpreted as an increased engagement of attentional resources with negative stimuli. The question as to which of the two possible interpretations is more accurate cannot be answered on the basis of our EEG approach. Further studies are needed that directly investigate this issue, and the recording of eye movements might be one way to distinguish these different processes. One previous eyetracking study, for example, showed that subjects show a disengagement of attentional resources from negative stimuli, but not from positive ones (Kellough, Beevers, Ellis, & Wells, 2008) in a free-viewing task. The tendency to disengage one's attentional resources from negative stimuli, but not from positive ones, might also explain why the COMT genotype affects only the processing of negative stimuli. Further studies should test the hypothesis that Met allele carriers also show impaired disengagement of attentional resources from neutral and positive stimuli, if this disengagement is stipulated by the task instructions. Measuring eye movements together with ERPs might help to elucidate the effect of the COMT genotype on attentional processes and neural correlates of emotional pro-

cessing. Even though our results are not unambiguous, we would argue that the present findings support the model of tonic and phasic dopamine signaling (Bilder et al., 2004).

Furthermore, in our study, we analyzed the effect of life stress on the interaction between the COMT genotype and emotional processing. In contrast to previous studies showing that life stress interacts with the 5-HTTLPR (Canli et al., 2006), we could not find any interaction between life stress and COMT on the neural correlates of emotional processing. It might be that the questionnaire we used to assess life stress did not reflect the kind of stressors that have been shown to be relevant for the development of depression in interaction with the COMT Val^{158}Met genotype (Mandelli et al., 2007). In addition, it might be that we would have to include patients with psychiatric disorders to analyze the interaction effect of COMT and life stress. It might be that our subjects with a high level of life stress who had not developed a psychiatric disorder reflected a special selection of subjects (perhaps based on additional factors—e.g., a high level of social support). Further studies will be necessary to clarify this possible COMT × life stress interaction.

One limitation of our study was the small number of at least 20 artifact-free EEG trials for which the ERPs for each subject and condition were averaged. This small number might have increased the proportion of noise signal in the ERPs.

In conclusion, Met/Met carriers tend to respond more sensitively toward unpleasant stimuli, which is reflected by increased EPN values, and therefore show an attentional bias toward unpleasant experiences.

AUTHOR NOTE

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