Serotonin Transporter Genotype (5-HTTLPR) and Electro cortical Responses Indicating the Sensitivity to Negative Emotional Cues

Ilona Papousek, Eva M. Reiser, Günter Schulter, and Andreas Fink
University of Graz

Harald Niederstätter, Simone Nagl, and Walther Parson
Innsbruck Medical University

Emily A. Holmes
University of Cambridge

Elisabeth M. Weiss
University of Graz

Growing literature indicates that emotional reactivity and regulation are strongly linked to genetic modulation of serotonergic neurotransmission. However, until now, most studies have focused on the relationship between genotypic markers, in particular the serotonin transporter-linked polymorphic region (5-HTTLPR), and neural structures using MRI. The current study aimed to bridge the gap between the relevant MRI literature on the effects of the 5-HTTLPR genotype and the research tradition focusing on transient lateralized changes of electrocortical activity in the prefrontal cortex using electroencephalography (EEG). Lateral shifts of EEG alpha asymmetry in response to an aversive film consisting of scenes of real injury and death were assessed in healthy participants (n = 165). To evaluate the specificity of the 5-HTTLPR effect, participants were also tested for the COMT Val158Met polymorphism which is linked to dopamine inactivation. While viewing the film, individuals homozygous for the 5-HTTLPR short allele displayed a clear lateral shift of dorsolateral frontal activity to the right, which was virtually absent in participants carrying the long allele. The heightened electrocortical response to the aversive stimulation and its direction indicates a greater propensity of s/s homozygotes to experience withdrawal oriented affect in response to negative emotion cues in the environment. Moreover, together with previous research the findings support the notion of a link between the serotonergic system and self-regulation related to avoidance motivation, and a link between the dopaminergic system and self-regulation related to approach motivation.

Keywords: EEG asymmetry, genetic polymorphisms, emotional reactivity, withdrawal motivation

Emotional reactivity and regulation is strongly linked to serotonergic neuromodulation. A key regulator of serotonin (5-HT) function is the serotonin transporter (5-HTT), which facilitates the reuptake of 5-HT from the synaptic cleft. One common polymorphic variant of the serotonin transporter linked promoter region (5-HTTLPR), located on chromosome 17q11.1-q12, results in two prevalent alleles: the short allele (s-allele) and the long allele (l-allele). The s-allele is associated with lower 5-HTT expression and function compared with the l-allele (Caspi et al., 2003; Hu et al., 2005). A growing body of literature has associated the s-allele with increased negative emotionality (Beever et al., 2011; Carver, Johnson, & Joormann, 2008; Munafò, Brown, & Hariri, 2008) including anxiety-related personality traits (for meta-analysis see Minelli, Bonvincini, Scassellati, Sartori, & Gennarelli, 2011) as well as an attention bias for negative emotional information (for meta-analysis see Pergamin-Hight, Bakemans-Kranenburg, van Izendoom, & Bar-Haim, 2012). Furthermore, considerable attention has focused on the 5-HTTLPR as a putative moderator of the stress-depression relationship (for a recent meta-analysis see Karg, Burmeister, Shedden, & Sen, 2011).

Besides the numerous association studies between 5-HTTLPR and common psychological disorders like affective disorders, post-traumatic stress disorder, and personality disorders (e.g., Blom et al., 2011; Hankin et al., 2011; Wang et al., 2011; Xie, Kranzler, Farrer, & Gelernter, 2012), the strategy to elucidate relationships
between genotypic markers and neural structures or processes has gained revealed interest in this context. Previous functional MRI studies have demonstrated heightened amygdala activation in response to negative emotional stimuli in s-allele carriers compared to l-allele carriers (for a review see Scharinger, Rabi, Sitte, & Pezawas, 2010; for meta-analysis see Murphy et al., 2012), which may lead to enhanced susceptibility for affective disorders (Hariri et al., 2002). However, until now no study has related the 5-HTTLPR genotype to transient lateralized electrocortical responses in the prefrontal cortex in response to averse emotional information with traumatic content. Therefore, the purpose of the present study was to bridge the gap between the relevant research on the effects of the 5-HTTLPR genotype that has largely focused on the amygdala using MRI and the research tradition focusing on transient lateralized changes of electrocortical activity in the prefrontal cortex using electroencephalography (EEG).

The amygdala and the dorsolateral prefrontal cortex are functionally interlinked. According to a model proposed by Johnstone and colleagues, the ventrolateral prefrontal cortex modulates the activity of the amygdala in the context of affective processing via a relay station in the ventromedial prefrontal cortex (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007). This relay station is not only linked to the amygdala, but is also directly linked to the dorsolateral prefrontal cortex (Barbas, 1995; Ongur & Price, 2000). Moreover, there is evidence of an emotion-related information-processing path between the amygdala and the dorsolateral prefrontal cortex via the orbitofrontal cortex that may be involved in the generation of emotional states (Phillips, Drevets, Rauch, & Lane, 2003; Phillips, Ladouceur, & Drevets, 2008).

Transient changes of dorsolateral prefrontal EEG alpha asymmetry are considered to represent an objective correlate of the relative activation of two motivational systems: an approach system, associated with the left prefrontal cortex, and a withdrawal system, associated with the right prefrontal cortex (Davidson, 1998; Harmon-Jones, Gable, & Peterson, 2010). The approach–withdrawal model is conceptually closely related to the dichotomy of self-regulatory systems in motivational theories such as the Reinforcement Sensitivity Theory (Demaree, Everhart, Youngstrom, & Filmore, 2005). In the revised version of Gray’s (1994) theory, the Fight-Flight-Freeze System (FFFS) is posited to be a motivational system responsible for mediating reactions to aversive stimuli. Its activation is associated with avoidance and escape behaviors and negative hedonic experience. The Behavioral Approach system (or Behavioral Activation System, BAS) is assumed to be sensitive to signals of reward and to mediate reactions to appetitive stimuli. Activation of the BAS is associated with approach behaviors and mostly positive emotions (Gray & McNaughton, 2000). A lateral shift toward relatively greater activity in the right prefrontal cortex (indexed by attenuated EEG alpha band activity, which is inversely related to cortical activity) is posited to indicate a withdrawal-oriented and more negative affective state. A lateral shift to the left is thought to indicate a more approach oriented affective state (Davidson, 1998; Harmon-Jones et al., 2010). Consequently, environmental stimuli that encourage withdrawal responses and, therefore, activate the withdrawal system of FFFS should result in increased right versus left prefrontal activation.

Empirical studies have confirmed these associations between the response of the motivational systems and transient changes of prefrontal EEG asymmetry. These associations have been demonstrated in studies directly manipulating reward and punishment contingencies or using conditioned aversive stimuli to produce withdrawal or approach oriented motivational states (Flo et al., 2011; Shankman, Klein, Tenke, & Bruder, 2007; Shankman, Sarapas, & Klein, 2011; Sobotka, Davidson, & Senulis, 1992). Additionally, studies have used various methods such as emotional films, voluntary facial expressions, social-evaluative stress, or anger provocation to induce withdrawal-oriented emotional states such as disgust, fear or sadness, and approach-oriented emotional states such as joy or anger (e.g., Coan & Allen, 2004; Coan, Allen, & Harmon-Jones, 2001; Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Davidson, Marshall, Tomarken, & Henriques, 2000; Ekman & Davidson, 1993; Harmon-Jones & Sigelman, 2001; Peterson, Gravens, & Harmon-Jones, 2011; Verona, Sadeh, & Curtin, 2009). The most common site of these effects is the dorsolateral prefrontal cortex in the region of the EEG electrode positions F3 and F4. Importantly, in this general context, the relative difference between the hemispheres is more important than the absolute level of independent left or right hemisphere activity per se. Consequently, relationships often have not been observed if only the absolute activity at individual sites was examined and data of the left and the right hemisphere were not related to each other, for instance, using appropriate laterality coefficients (e.g., Blackhart & Kline, 2005; Cole, Zapp, Nelson, & Perez-Edgar, 2012; Harmon-Jones, 2006; Papousek & Schulte, 2004; Papousek, Schulte, & Lang, 2000; Shankman et al., 2011).

Moreover, it has been suggested that interindividual differences in lateral shifts of prefrontal EEG alpha asymmetry can be used to assess the proneness or capability for approach- versus withdrawal-tendencies dominated responses during emotionally salient events (e.g., Coan, Allen, & McKnight, 2006). In line with this proposition, stronger lateral shifts to the left or to the right relevant stimuli were observed in individuals characterized by a predisposition or capability for more pronounced approach- or withdrawal-oriented responses respectively: for instance, individuals with greater social anxiety, better emotion perception skills, greater liking ratings of objects, and relevant neurophysiological traits (Cole et al., 2012; Davidson et al., 2000; Gable & Harmon-Jones, 2008; Harmon-Jones & Gable, 2009; Papousek, Freudenthaler, & Schulte, 2011; Papousek, Reiser, Weber, Freudenthaler, & Schulte, 2012). Taken together, the evidence indicates that interindividual differences in prefrontal EEG alpha asymmetry responses reflect an individual’s sensitivity to environmental triggers of withdrawal or approach oriented affect (see also Cole et al., 2012).

Research has suggested that the 5-HTTLPR short allele is specifically associated with the strength of avoidance-oriented motivation but not of the BAS. This was shown using a self-report questionnaire assessing the strength of Gray’s motivational systems as a trait characteristic (Whisnant, Richardson, & Smolen, 2011). In line with this, the 5-HTTLPR short allele was specifically associated with heightened amygdala responses to sad but not happy faces, suggesting that the 5-HTTLPR genotype impacts the processing of negative environmental cues but not emotionally salient stimuli in general (Dannlowski et al., 2010). In contrast, there is evidence that the strength of the BAS is associated with another genetic polymorphism: the Val158Met single nucleotide polymorphism (rs4680) of the gene coding for the catechol-O-
methyltransferase (COMT) enzyme that inactivates extraneuronal dopamine. Homozygotes for the high-activity Val allele, who are expected to have lower prefrontal dopamine levels but at the same time higher striatal dopamine levels, showed higher trait BAS scores than carriers of the low-activity Met allele (Wacker, Mueller, Hennig, & Stemmler, 2012). In an EEG study in which participants were exposed to an approach motivational context, individuals homozygous for the Val allele showed greater relative activation of the left over the right dorsolateral prefrontal cortex than carriers of the Met allele (Wacker, Mueller, Pizzagalli, Hennig, & Stemmler, 2013). To our knowledge, the emerging evidence for an effect of the dopamine-related COMT Val158Met polymorphism on approach-related electrocortical responses is not complemented by studies addressing a potential relationship between the serotonin-related 5-HTTLPR polymorphism and electrocortical responses indicating the sensitivity to environmentally triggered affect in withdrawal-related contexts. There has been some sparse research on potential effects of the 5-HTTLPR genotype on prefrontal EEG measures in resting conditions, but this does not allow clear conclusions (Bismark et al., 2010; Lee et al., 2011).

Healthy participants were confronted with an aversive film consisting of scenes of real injury and death, to activate withdrawal motivation. The size of the response to the aversive film in terms of lateral shifts of EEG alpha asymmetry was assessed as an objective indicator of an individuals’ proneness for withdrawal motivation dominated affect. No regulation instructions were given, in order to study characteristic and predominantly automatic responses (e.g., Jackson et al., 2003). According to theoretical approaches, approach and avoidance emotions are relatively reflexive, that is, they are involuntary tendencies to approach incentives and avoid threats. The automatic response tendencies may be moderated by effortful (deliberate) control, which is not thought to be specific to the motivational systems (Carver et al., 2008). Studying automatic response tendencies, therefore, fits in with the theoretical framework of the present study and the examination of lateralized EEG responses in the prefrontal cortex. To evaluate the specificity of the 5-HTTLPR effect, the participants were also tested for the COMT Val158Met polymorphism. Participants homozygous for the 5-HTTLPR short allele were expected to show a more pronounced electrocortical response indicating withdrawal motivation dominated affect compared with participants carrying the long allele.

### Method

#### Participants

The sample comprised 165 right-handed female Caucasian university students aged between 18 to 59 years (M = 22.5, SD = 4.8). They were drawn from a larger screening sample on the basis of their 5-HTTLPR genotype. Buccal swabs were taken to genotype all participants for the 5-HTTLPR and COMT Met158Val polymorphism. No other polymorphisms were examined. Table 1 shows the distribution of genotypes. Individuals who reported having a neuropsychiatric disease or using psychoactive medication and individuals who reported traumatic experiences related to car crashes, surgery or death of a close person within the past 12 months were excluded from the study (n = 6). In addition, only participants who had at least 30 s of artifact free EEG data in each of the experimental conditions were included in the final sample (n = 165). A female only sample was chosen, because previous research showed sex differences moderating the association between 5-HTTLPR and emotion-related phenotypes (Cannon et al., 2013; Mizuno et al., 2006) and the neural mechanisms underlying emotional processes (Whittle, Yücel, Yap, & Allen, 2011). Handedness was assessed by a standardized hand performance test (Hand Dominance Test; Papousek & Schultler, 1999; Steingrüber & Lienert, 1971). Participants were requested to refrain from alcohol for 12 hours and from coffee and other stimulating beverages for 2 hours prior to their lab appointment, and to come to the session well rested. The study was performed in accordance with the American Psychological Association’s Ethics Code and the 1964 Declaration of Helsinki and was approved by the local ethics committee. Participants gave their written consent to participate in the study.

#### Genotyping

**DNA Extraction.** DNA was extracted from individual saliva swabs using a modified Chelex (Biorad, Hercules, CA) method (Berger et al., 2013).

**Genotyping of 5-HTTLPR.** Polymerase chain reaction (PCR) followed the protocol published by Hu et al. (2006) with modifications. The amplification cocktails had a volume of 10 μl containing 5 μl TaqMan Universal PCR Master Mix (Life Technologies, Paisley, United Kingdom), 2.5 μg nonacylated bovine serum albumin (Sigma-Aldrich, St. Louis, MO), 4% (vol/vol) dimethyl sulfoxide, 100 nM primer HTTLPR_F: FAM-GCAACCTCCCCACGCAACTCCTGGTA, 100 nM primer HTTLPR_R: GAGGTGCAGGGGATGCTGGAA, and 2 μl sample DNA. The thermal cycling conditions were set according to Hu et al. (2006). Genotypes were determined by capillary electrophoretic separation of the PCR products on an ABI Prism 3100 Genetic Analyzer (Life Technologies).

**Genotyping of COMT Val158Met (rs4680).** For the determination of the COMT Val158Met genotypes high resolution melting (HRM) curve profiles of short PCR amplicons were used. PCR and subsequent HRM analysis were conducted on a Rotor-Gene Q real-time PCR cycler (Qiagen, Hilden, Germany). The amplification cocktail had a total volume of 20 μl and consisted of 1x Type-it HRM PCR master mix (Qiagen), 250 nM primer COMT-F_44 and COMT-R_27 (both Oberacher et al., 2005), 5 μg nonacylated bovine serum albumin, and 2 μl DNA extract. The thermal cycling conditions were set according to Oberacher et al. (2006). Following amplification, the PCR products were subjected to HRM analysis. For the automated COMT Val158Met genotype calling the Rotor-Gene Screen-Clust HRM software (v 1.10.1.2,

### Table 1

| Genotype | COMT         | 5-HTTLPR | Met/Met | Val/Met | Val/Val |
|----------|--------------|----------|---------|---------|---------|
|          | Row total    |          |         |         |         |
| s/s      |              | 11       | 23      | 16      | 50      |
| s/l      |              | 12       | 25      | 20      | 57      |
| l/l      |              | 12       | 26      | 20      | 58      |
| Col. total|              | 35       | 74      | 56      | 165     |
Qigien; Reja et al., 2010) was run in the supervised analysis mode. In initial Experiments 99.5% concordant genotype inferences were obtained for a set of 189 samples with known rs4680 genotype. Due to an additional sequence variant (C > T at chr22:19,951,246, GRCh37/hg19) in the ampiclon, in the initial concordance study a single sample was attributed erroneously the A/A (Met/Met) instead of the actual G/A (Val/Met) genotype.

**Stimulus Material**

The aversive film (approx. 10 min in length) contained 11 clips that have been used in previous studies as an experimental analogue of psychological trauma. In stressful film studies, affect reliably deteriorates over film viewing (Holmes & Bourne, 2008). For instance, in the studies of Holmes, James, Coode-Bate, and Deeprose (2009) and Holmes, James, Kilford, and Deeprose (2010), which used the same film as the current study, negative mood was measured using a composite score comprising of sadness, hopelessness, and depression. These studies demonstrated a significant increase in negative affect from pre- to postfilm. Results extended with an adapted version of the film used in the current study (Deeprose, Zhang, Dejong, Dalgleish, & Holmes, 2012). Indeed, recent work combining data from 16 studies has shown that withdrawal-oriented negative affective states are reliably induced from the trauma film paradigm (Clark, Mackay, & Holmes, 2013). Effects of the film were generally found to be higher on scales representing depressed than fearful affect. The EEG was recorded during the last 5 minutes of the film during which there were five clips depicting several car accidents and a rampaging elephant injuring people at a circus. These clips included graphic scenes of severely injured, dying, and mourning people. The film was displayed on a 21” computer monitor viewed at 100 cm and was presented without sound, so that the stimulation people. The film was displayed on a 21” computer monitor viewed at 100 cm and was presented without sound, so that the stimulation

**EEG Recording and Quantification**

The EEG was recorded from 19 channels according to the international 10–20 system, using a Brainvision BrainAmp Research Amplifier (Brain Products) and a stretchable electrode cap, and was referenced to a mathematically averaged ears reference (Hagemann, 2004). Impedance was kept below 5 kΩ for all electrodes. Horizontal and vertical EOG measures were obtained for identification of ocular artifacts. According to the research question, the dorsolateral frontal positions F3 and F4 were used for the analyses. All data were inspected visually, in order to eliminate intervals in which ocular or muscle artifacts occurred. Power spectra (epoch length 1 s, overlapping 50%, Hanning window) were averaged across all artifact-free intervals for an individual. (The mean numbers of artifact-free epochs were $M = 150.0, SD = 46.7$ for the initial recording at rest, and $M = 121.1, SD = 43.7$, $M = 224.1, SD = 10.05, and M = 129.3, SD = 43.9$ for the baseline, film, and postfilm recordings, respectively). Following a common approach in the field, power within the alpha frequency band (8 Hz–12 Hz) was used for the analyses. EEG laterality coefficients (LC) were computed as follows: $LC = [(R - L)/(R + L)] \times 100$. Positive values indicate higher alpha activity in the right than in the left hemisphere (i.e., greater left hemisphere cortical activity). The calculation of LC has a long tradition in laterality research, because it separates the variance in asymmetry from the variance in general magnitude (e.g., Porac & Coren, 1981). In EEG studies, this asymmetry ratio is equivalent to another common metric (lnL – lnR), with which it is virtually perfectly correlated (Davidson, 1988; Papousek & Schulter, 2002). However, LC allows easier comparison of data from different studies, different frequency bands, and locations (Pivik et al., 1993).

**Self-Report Measures**

A composite mood score was calculated by summing participants’ ratings on three 10 cm horizontal visual analogue scales for feeling “sad,” “depressed,” and “hopeless” (Deeprose et al., 2012; Holmes et al., 2009, 2010). The responses were scored in millimeters from 0 (not at all) to 100 (extremely). Depressive affect was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D, German version by Hautzinger & Bailer, 1993). It is comprised of 20 items referring to mood and attributions over the past week (internal consistency reliability in the present sample $\alpha = .87$), designed for measuring subclinical depressive experiences in the general population (Wood, Taylor, & Joseph, 2010). In addition, the trait form of the Stait-Trait Anxiety Inventory was administered (STAI, German version by Laux, Glanzmann, Schaffner, & Spielberger, 1981; 20 items; $\alpha = .91$).

**Procedure**

After completing the handedness test and the CES-D, participants were seated in an acoustically and electrically shielded examination chamber, electrodes were attached, and participants completed the mood rating scales using the computer mouse. The EEG was recorded in an initial two minutes rest period with closed eyes. Participants were then instructed that they would see a film to which they should direct their whole attention. They were asked to view the film as if they were really there, like a bystander at the scene of the events and to not close their eyes or look away. The film was immediately preceded and followed by recording periods in which the participants were exposed to the neutral visual display (2 min each; baseline and postfilm recording). Participants were instructed to watch the green circle. The experimenter was positioned outside the examination chamber, and participants were monitored using a camera. After the last recording period, the participants completed the rating scales again.

**Statistical Analysis**

The general impact of the aversive stimulation on dorsolateral frontal EEG asymmetry (LC) was assessed using a one-way repeated-measures analysis of variance, with recording period (baseline, aversive film, postfilm recording) as the independent variable. A paired $t$ test comparing the composite mood scores obtained before and after the EEG recordings was used to test the film’s effect on subjective withdrawal-related affect.

To evaluate the specific hypothesis of the main research question, that is, the impact of the 5-HTTLPR genotype on the size of
withdrawal-related EEG responses to the aversive stimulation, a planned comparison was performed. This comparison tested the specific a priori contrast s/s versus s/L, l/L in a 3 × 3 analysis of variance, with the 5-HTTLPR genotype (s/s, s/L, l/L) and the COMT genotype (Met/Met, Met/Val, Val/Val) as the between-subjects factors, and EEG reactivity (LC film minus LC baseline) as the dependent variable. Results of the omnibus F tests are also reported. The two genotypes were simultaneously entered in the analysis to test the effect of the 5-HTTLPR genotype independently of the COMT Val158Met genotype (using the regression approach to the analysis of variance, which also controls for unequal cell sizes).

An analysis analogous to that of the EEG changes was conducted using the composite mood score (rating at the end of the experiment minus rating at the beginning) as the dependent variable. In addition, potential effects of genotype on interindividual differences in dorsolateral prefrontal EEG asymmetry at rest (first recording period, closed eyes) were tested (analysis of variance with 5-HTTLPR and COMT as the independent variables). Two supplementary analyses tested whether the genotype groups differed in their trait depression or anxiety scores. Estimates of effect size are reported using partial eta-squared ($\eta^2_p$). The sphericity assumption was not violated. A significance level of $p < .05$ was used for all analyses.

Results are reported in terms of cortical activation: a relative change of asymmetry “to the right” indicates an increase of right versus left sided cortical activity (i.e., a decrease of right vs. left sided EEG alpha values, because alpha power is inversely related to cortical activity).

**Results**

Watching the aversive film provoked the expected transient shift of dorsolateral prefrontal EEG asymmetry to the right ($F_{3,328} = 3.4, p < .05, \eta^2_p = 0.021$). Figure 1 shows the average changes across the baseline, aversive film, and postfilm recordings (baseline vs. film $t_{164} = 2.0, p < .05$; film vs. postfilm recording $t_{164} = 2.5, p < .05$). The composite mood rating indicated significant mood deterioration in terms of sadness, depression, and hopelessness following the film ($t_{164} = 14.7, p < .001$; $M = 19.1$, $SD = 37.6$ and $M = 87.4$, $SD = 58.9$).

The main analysis tested the effect of the 5-HTTLPR genotype on individual differences in the EEG responses to the stimulation. The hypothesis-driven a priori contrast ($t_{156} = 2.44, p < .05$) indicated that compared with the other 5-HTTLPR genotype groups, participants homozygous for the short allele (s/s) showed the most pronounced EEG response to the film, that is, a clear lateral shift of dorsolateral frontal asymmetry to the right from baseline to viewing the aversive film. The other two groups did not display a comparable response (see Figure 2). The $F$ test for the main effect of 5-HTTLPR in the omnibus analysis of variance was also significant ($F_{2,156} = 3.1, p < .05, \eta^2_p = 0.039$). There was no significant main effect of COMT ($F_{2,156} = 1.0$, ns.) or 5-HTTLPR by COMT interaction ($F_{2,156} = 1.4$, ns.). Baseline asymmetry scores of the three HTTLPR genotype groups were s/s: $M = 1.78$ ($SD = 7.64$), s/L: $M = -0.07$ ($SD = 5.46$), l/L: $M = 0.05$ ($SD = 6.10$; $F_{2,162} = 1.4$, ns.).

In the analysis using the participants’ mood changes from the beginning to the end of the experiment as the dependent variable, none of the effects were significant ($t_{156} = 0.3$, ns.; 5-HTTLPR $F_{2,156} = 0.1$, ns.; COMT $F_{2,156} = 1.3$, ns.; 5-HTTLPR by COMT $F_{2,156} = 0.7$, ns.). No relationship between genotype and dorsolateral prefrontal resting asymmetry in the first baseline recording was observed (5-HTTLPR $F_{2,156} = 1.1$, ns.; COMT $F_{2,156} = 0.9$, ns.; 5-HTTLPR by COMT $F_{2,156} = 1.1$, ns.).

The genotype groups did not differ in their trait depression scores (5-HTTLPR $F_{2,164} = 0.6$, ns.; COMT $F_{2,164} = 1.8$, ns.; 5-HTTLPR by COMT $F_{4,164} = 0.5$, ns.), nor in their trait anxiety scores (5-HTTLPR $F_{2,164} = 0.1$, ns.; COMT $F_{2,164} = 0.2$, ns.; 5-HTTLPR by COMT $F_{4,164} = 0.5$, ns.)

**Discussion**

The results showed that individuals homozygous for the 5-HTTLPR s-allele displayed a clear lateral shift of dorsolateral frontal activity to the right while viewing a film containing traumatic content, which was virtually absent in participants carrying the long allele. According to the relevant literature, the heightened electrocortical response to the aversive stimulation and its direction indicates a greater propensity of s/s homozygotes to experience withdrawal-oriented affect in response to negative emotion cues in the environment (Coan et al., 2006; Cole et al., 2012; Harmon-Jones et al., 2010). Although observed in the context of a different research tradition, this novel finding is in line with the association of the 5-HTTLPR s-allele to heightened amygdala responsiveness to negative emotional stimulation (e.g., Domshche et al., 2012; Munho et al., 2008; von dem Hagen, Passamonti, Nutland, Sambrook, & Calder, 2011), with which activity changes in the dorsolateral prefrontal cortex are interlinked (Johnstone et al., 2007; Phillips et al., 2003, 2008; see introduction). Lateralized prefrontal changes as a function of the 5-HTTLPR genotype have not been evident in functional MRI (fMRI) studies, because fMRI.

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1 Exploratory analyses showed that EEG responsiveness at other electrode positions than those for which the theoretical and empirical context of the study had suggested an effect did not vary as a function of genotypes.
It should be noted in this context that the application of the electrodes in the EEG laboratory can be an aversive situation for some people, accompanied by respective changes in prefrontal EEG asymmetry (Blachar, Kline, Donohue, LaRowe, & Joiner, 2002). Another study exploring the potential effect of the 5-HTTLPR genotype on the EEG in resting conditions found no differences between s/s homozygotes and carriers of the l-allele in the absolute EEG power in various frequency bands and electrode positions including the alpha band power at prefrontal sites (Lee et al., 2011). The relative left to right hemisphere EEG activity was not examined in the study of Lee et al. Analogous to the present study, associations between the COMT Val158Met polymorphism and dorsolateral prefrontal EEG alpha asymmetry were only detectable in a situation in which approach motivation was highly salient, indicating that associations between genetic polymorphisms and brain indicators of individual traits may only become apparent in situational contexts relevant to the traits of interest (Wacker et al., 2013). Both the present findings and the findings of Wacker, Mueller, Pizzagalli, Hennig, and Stemmler (2013) support the notion that transient changes in prefrontal EEG asymmetry are produced by the interaction between the emotional or motivational demands of a specific situation and the capability of the individual’s nervous system to produce (appropriate) and inhibit (inappropriate or unfavorable) responses in that context (Coan et al., 2006; Papousek et al., 2011, 2012).

Moreover, the pattern of findings of the present study and of Wacker et al. (2013) are consistent with the proposed links between the serotoninergic system and self-regulation related to avoidance motivation, and between the dopaminergic system and self-regulation related to approach motivation. In addition to correlations of the 5-HTTLPR s-allele with self-report measures of the strength of avoidance-oriented motivation (but not the BAS; Whisman et al., 2011) and of the COMT Val-allele with self-report measures of the strength of the BAS (but not avoidance motivation; Wacker et al., 2012), there is also evidence from animal studies suggesting that avoidance-motivated behavior is largely controlled by serotoninergic pathways, whereas approach-motivated behavior is mediated by mostly dopaminergic pathways (Demaree et al., 2005). The present study and the study of Wacker et al. (2013) add to this evidence by demonstrating corresponding links with electrocortical measures indicating the sensitivity to withdrawal or approach-oriented affect.

In contrast to the electrocortical measure of withdrawal motivation dominated responses during viewing the aversive film, the 5-HTTLPR polymorphism had no effect on a subjective measure of mood. Several explanations may account for this finding. The self-report measure obtained at the end of the experiment may provide a less precise measure than the EEG measure that was obtained directly during the stimulation. Further, the EEG response may be dominated by the expression of motivational direction; Wacker et al. (2013) are consistent with the proposed links between the serotoninergic system and self-regulation related to approach motivation; Wacker et al., 2012), there is also evidence from animal studies suggesting that avoidance-motivated behavior is largely controlled by serotoninergic pathways, whereas approach-motivated behavior is mediated by mostly dopaminergic pathways (Demaree et al., 2005). The present study and the study of Wacker et al. (2013) add to this evidence by demonstrating corresponding links with electrocortical measures indicating the sensitivity to withdrawal or approach-oriented affect.

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It is of note that differences between the 5-HTTLPR genotype groups were only observed in the transient electrocortical responses to the triggers of withdrawal oriented affect (i.e., in the changes within individuals, provoked by the stimulation from the aversive scenes). The genotype groups did not differ in their EEG alpha asymmetry during the first stimulation-free baseline recording. Related to this, it was found that tryptophan depletion generally does not affect mood per se, but may exaggerate mood change in response to a stressor (Carver et al., 2008). However, Bisnark et al. (2010) observed a small effect of the 5-HTTLPR s-allele on prefrontal EEG alpha asymmetry in resting conditions, which was qualified by an interaction with lifetime major depression disorder.

studies are typically not specifically concerned with differences between the activity in the two hemispheres, but only focus on whether an active area meets a particular statistical threshold in one hemisphere as well as the other (Davidson, 1998; Herrington et al., 2005). In the context of individual differences in responses to emotional cues, the relative difference in activation between the hemispheres seems to be more important than the absolute level of independent left or right hemisphere activation. That is, no effect of increased left-hemisphere activation on approach and avoidance motivation may be expected if the right hemisphere is also more activated (Davidson, Chapman, Chapman, & Henriques, 1990; Harmon-Jones, 2006; Heller, Nitschke, Etienne, & Miller, 1997). The easier implementation of appropriate methods to relate left and right hemisphere data to one another may be one reason why EEG has had a predominance in research on lateralized brain activation during avoidance versus approach actions has also be demonstrated using MRI methods (Berkman & Lieberman, 2010).

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& Coan, 2011). This effect might have been amplified by introducing some temporal distance between the film and the ratings through the study design.

A limitation of the study may be that, following the tradition of MRI research that has almost exclusively been concerned with negative stimuli, an appetitive condition was not included, preventing direct comparison. However, it seems highly implausible that the s/s genotype might also be related to greater responsiveness to appetitive stimuli. In fact, it was directly demonstrated in a MRI study that the 5-HTTLPR impacts the amygdala responsiveness to negative environmental cues specifically, but not to emotionally salient stimuli in general (Damldowski et al., 2010). A further limitation may be that the present study did not directly verify the sensitivity of the EEG measure. However, the study is based on a well-founded theoretical background according to which transient changes of prefrontal EEG asymmetry to the left and to the right indicate activation of the approach and the withdrawal motivational system, respectively. Therefore, the study was not designed to reconfirm this link, which has been demonstrated in a large number of empirical studies (e.g., Coan & Allen, 2004; Coan et al., 2001; Davidson, Ekman, et al., 1990; Davidson et al., 2000; Ekman & Davidson, 1993; Flo et al., 2011; Harmon-Jones & Sigelman, 2001; Papousek et al., 2012; Peterson et al., 2011; Sobotka et al., 1992; Shankman et al., 2007, 2011; Verona et al., 2009).

In conclusion, the present findings provide a novel addition to the literature documenting associations between the serotonin related 5-HTTLPR genotype and heightened sensitivity to emotional cues, which to date had primarily been based on amygdala responses in MRI studies. Linking this evidence with the research tradition focusing on transient lateralized changes of activity in the prefrontal cortex using electroencephalography, the current study demonstrated that the 5-HTTLPR short allele is associated with responses in the dorsolateral prefrontal cortex indicating a heightened sensitivity to environmentally triggered withdrawal-oriented affect.

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