5-HTTLPR and COMTval158met genotype gate amygdala reactivity and habituation

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ABSTRACT

Amygdala reactivity is a heritable trait, potentiated in affective disorders and associated with both the 5-HTTLPR and the COMTval158met polymorphism.

Fifty-four healthy volunteers selected a priori based on gender and 5-HTTLPR/rs25531 and COMTval158met genotypes performed a passive viewing task of angry facial expressions using fMRI. Amygdala reactivity and habituation were investigated using the a priori anatomical region of interest (ROI) approach. Furthermore, salivary cortisol and skin conductance responses were recorded.

We observed an effect of 5-HTTLPR on right amygdala reactivity (s-carrier > l/l) and COMTval158met on left amygdala reactivity (met/met > val-carrier). We provide preliminary evidence that different amygdala habituation curves may partly underlie the differences between 5-HTTLPR and not COMT genotype groups. Further, exploratory analyses find no evidence for additive or interaction effects.

Our results suggest that 5-HTTLPR s-carriers and COMT met/met carriers may be more sensitive to the detection of biologically and socially relevant information and suggest a mechanism behind this for the 5-HTTLPR.

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1. Introduction

Affect and affective disorders are complex phenomena that are influenced by multiple genes, the environment and their interaction. In the causal chain from genes to mental processes and behavior, brain activity is considered an intermediate phenotype.

The amygdala is the core of the brains emotion processing system and increased amygdala reactivity to emotional stimuli has been linked to clinical anxiety (e.g., Etkin and Wager, 2007) and depression (Siegle et al., 2007). Amygdala activation habituates fast with repeated stimulus exposure (Breiter et al., 1996) and less habituation over time is associated with trait anxiety (Hare et al., 2008). Amygdala reactivity has also been shown to be stable and trait-like (Johnstone et al., 2005; Manuck et al., 2007). Thus, to some degree, amygdala reactivity to emotional stimuli is likely to be under genetic control and may be considered an endophenotype (Gottesman and Gould, 2003) for anxiety related behavior.

Research has indeed provided evidence for an association of amygdala reactivity with common genetic polymorphisms in neurotransmitter systems involved in emotion and affective disorders like serotonin (5-HT, Lucki, 1998) and dopamine (DA, Johnson and Lydiard, 1995; Nestler and Carlezon, 2006).

Given that the amygdala is densely innervated by serotonergic fibers and that pharmacological challenge of the 5-HT system affects amygdala activity (Bigos et al., 2008; Del-Ben et al., 2008), genetic variation in the 5-HT system may have the potential to bias amygdala reactivity. Indeed, several neuroimaging studies have reported associations of amygdala reactivity with serotoninergic polymorphisms, e.g., in the serotonin transporter gene (SLC6A4) (for a metaanalysis see Munafò et al., 2008).

The serotonin transporter (5-HTT) mediates the active clearance of 5-HT from the synaptic cleft and thus regulates pre- and postsynaptic 5-HT receptor stimulation. It harbors a functional 43 bp ins/del polymorphism in a 22–23 bp imperfect repeat region in its
promoter, referred to as 5-HTTLPR. The 5-HTTLPR has been shown to affect transcriptional effectiveness and carriers of one or two short (s) alleles have a 40% reduced transcription rate as compared to homozygous for the long (l) allele (Lesch et al., 1996). Recently, an A → G single-nucleotide polymorphism (SNP), rs25531, in close proximity to the 5-HTTLPR has been described (Hu et al., 2006; Kraft et al., 2005). The rs25531 G-allele has also been associated with lower 5-HT mRNA expression and it has become increasingly common to study the 5-HTTLPR/rs25531 mini-haplotype, which is often referred to as tri-allelic, even though it is in fact four-allelic with the Sc allele being extremely rare.

Recent metaanalyses have shown that 5-HTTLPR s-carriers show higher amygdala reactivity to a broad range of emotional and social stimuli (Munafo et al., 2008) and are more prone to anxiety related traits (Sen et al., 2004). Interestingly, the 5-HTTLPR seems to affect amygdala reactivity during both conscious (Lee and Ham, 2008; Smolka et al., 2007) and non-conscious (Damlowsky et al., 2008) processing of emotional stimuli and also affects the allocation of attentional resources when processing emotional stimuli (Beever et al., 2010, 2007, 2009; Fox et al., 2009; Osinsky et al., 2008).

Acute pharmacological challenge of the DA system also affects amygdala reactivity (e.g., Hariri et al., 2002). Furthermore, there is evidence that pharmacologically or pathologically reduced DAergic transmission affects (angry) face recognition (Lawrence et al., 2002, 2007). Thus, also genetic variation in the DA system may have the potential to bias amygdala reactivity to facial stimuli.

Currently, research has focused on the effects of polymorphisms in the Catechol-O-methyltransferase (COMT) gene on emotional processing. COMT mediates the enzymatic degradation of catecholamines which is the main mechanism for degradation of cortical DA. The COMT gene harbors a functional SNP at codon 158, leading to a valine (val) to methionine (met) substitution (COMTval158met). The met-allele leads to a 1/3 decrease in enzyme activity as compared to the val-allele (Lachman et al., 1996) and has been associated with enhanced prefrontal and cognitive functioning, but also with reduced emotional resilience (for a review see e.g., Aleman et al., 2008). Brain imaging studies showed associations of the met-allele with increased amygdala/hippocampus activation to negative emotional pictures (Smolka et al., 2005) as well as hippocampus and vIPFC activation during a face-matching task (Drabant et al., 2006), while the val-allele has been associated with increased amygdala reactivity during affective processing of faces in healthy females (Kempston et al., 2009) and panic patients (Domschke et al., 2008). In summary, the evidence for an effect of the COMTval158met polymorphism on amygdala reactivity is less well studied and more contradictory than for the 5-HTTLPR.

As outlined above, the 5-HTTLPR and COMTval158met polymorphism have both been shown to affect anxiety-related traits as well as amygdala reactivity calling for the need to control for one polymorphism when aiming at studying the other one. In order to avoid unequal group sizes with respect to the genotypes groups of interest (reflecting the population frequencies of the respective alleles), the present study is based on a sample of healthy volunteers that were carefully pre-selected for gender, 5-HTTLPR/rs25531, COMTval158met, and with a low age range (20–31 years). We tested the impact of these genotypes on amygdala reactivity to angry facial expressions in a pure passive viewing task. Our study design allowed us to test the effect of one polymorphism while controlling for the other one and for gender. Furthermore we tested if differences in amygdala reactivity between the genotype groups may be (partly) explained by different habituation slopes. In addition, cortisol levels before and skin conductance responses during the experiment were recorded to investigate possible genotype-effects not only on the neural but also the hormonal and psychophysiological level of emotional reactivity.

**Table 1**

<table>
<thead>
<tr>
<th>COMTval158met</th>
<th>met/met</th>
<th>val-carrier</th>
<th>s-carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>val (13(7))</td>
<td>13(7)</td>
<td>15(8)</td>
<td>28(15)</td>
</tr>
<tr>
<td>met (13(7))</td>
<td>13(7)</td>
<td>26(14)</td>
<td>26(14)</td>
</tr>
<tr>
<td>26(14)</td>
<td>28(15)</td>
<td>N = 54</td>
<td></td>
</tr>
</tbody>
</table>

Note: All participants were non-carriers of the rs25531 G-allele. Based on our prior results (35), participants carrying one or two 5-HTTLPR s-carriers were a priori grouped into one 5HTTLPR s-carrier group and participants carrying one or two COMT158val alleles were a priori grouped into a val-carrier group. The s-carrier group consisted of 12 s/s (8 females) and 6 s/l (7 females) individuals and the COMT val-carrier group consisted of 14 val/val (8 females) and 14 val/met (7 females). 5-HTTLPR genotype groups did not differ in age, while COMT158val-carriers (mean: 23.3, SD: 1.8) were slightly but significantly younger than their met/met counterparts (mean: 25.0, SD: 3.1).
For a subsequent experiment, electrodes for electrotactile stimulation were (for technical reasons) already placed on their right wrist and the intensity of this stimulation was adjusted individually. Participants were explicitly informed that no electro-tactile stimulation would occur during the passive-viewing task. Both faces were presented six times, resulting in 12 presentations of facial stimuli (mean duration 7 s, jittered 6–8 s) and 14 presentations of a fixation cross (mean duration 13 s, jittered 10–16 s).

2.5. Image acquisition

An anatomical scan and fMRI data were obtained using a GE Signa Echo Speed 1.5T scanner and an 8-channel head-coil. Functional whole-brain images were acquired using a gradient echo T2*-weighted echoplanar imaging (EPI) scan, echo time (TE) = 40 ms, repetition time (TR) = 2.5 s, flip angle of 90°, 32 axial slices (thickness = 3.5 mm with 1 mm gap) and a field of view (FOV) = 22 cm × 22 cm. The first scans were defined as dummy scans to allow for longitudinal T1-equilibration and these were not included in the analysis.

2.6. Image preprocessing and analysis

FMRI data were processed using SPM5 (Statistical Parametric Mapping, The Welcome Department of Imaging Neuroscience, Institute of Neuroscience, University College London) running on MatLab2008a (The MathWorks, Natick, MA). Individual Images were realigned to the first volume, corrected for slice timing, spatially normalized to an EPI template and smoothed with an isotropic Gaussian kernel (FWHM of 10 mm). After preprocessing, data were analyzed in the context of the general linear model using fixed-effects (Friston, 1994) at the individual subject level. For main analyses, a model with the two faces as separate events was specified. These were convolved with a canonical hemodynamic response function and a high pass filter with a cut-off frequency of 128 s was applied to remove low-frequency artifacts. The fixation cross served as an implicit baseline. Six movement parameters were included as covariates of no interest. A contrast was defined for faces > fixation cross. These individual contrast images were used in the second level random effects analyses.

Three types of analysis were performed. First, a one-sample t-test for the main effect of task (faces > fixation cross) using a whole brain analysis with 5-HTTLPR and COMTval158met genotype as covariates of no interest. This analysis was performed in order to confirm the involvement of the amygdala as our anatomical a priori region of interest (ROI) in the task. Second, when comparing different genotype groups, a region of interest (ROI) approach based on the central role of the amygdala in emotional processing, and two-sample t-tests were used (see below). Third, for completeness and in order to promote comparability between different studies, explorative whole-brain analyses comparing both 5-HTTLPR and both COMTval158met genotypes groups were performed (see S3 and S4). The anatomical amygdala ROI was created around the amygdala using the Wake Forest University PickAtlas version 2.4 MRI based automatic anatomical labeling (AAL) atlas (Maldjian et al., 2003). As our design allowed us to assess the effect of one polymorphism while controlling for the other one (see Table 1), we conducted two-sample t-tests in the anatomical amygdala ROI for (a) the 5-HTTLPR genotype groups with COMT genotype as covariate and (b) the COMTval158met genotype groups with 5-HTTLPR as covariate. To illustrate the effects, parameter estimates obtained from the two-sample t-tests were extracted from peak activation coordinates that were obtained from the analyses described above using MatLab and plotted using Origin.

For completeness, and in order to exploratory test the 5-HTTLPR × COMTval158met interaction, a full factorial model was performed. If not stated otherwise, the significance threshold was set at p < 0.05 corrected for family-wise error (FWE) at the voxel-level with a minimum extent of 5 voxels. All coordinates reported represent the Montreal Neurological Institute (MNI) space. To test if differences in amygdala Reactivity between the genotype groups may be driven by different habituation slopes, we specified a new first level model where an early and a late phase (first vs. last six faces) were defined as two separate regressors. Three contrasts were defined: (1) face viewing during early > late phase (yielding brain areas habituating over time) (2) faces > fixation cross in the early phase and (3) faces > fixation cross in the late phase. These follow-up analyses were based on the anatomical amygdala ROI and were for contrast (1) restricted to significant ROIs obtained in the two-sample t-tests described above (i.e., the right amygdala for 5-HTTLPR; left amygdala for COMTval158met, both ROIs were anatomical ROIs as described above) and for contrast (2) and (3) based on a bilateral anatomical amygdala ROI. As these analyses were exploratory, a very liberal threshold

1 The individual adjustment was used to reach a level perceived as highly annoying but not painful. The intensity chosen during electro-tactile stimulation adjustment preceding the experiment (needed for a subsequent experiment) did not differ between 5-HTTLPR and COMTval158met genotype groups. Furthermore no significant differences or interactions for the unconditioned SCRs to the electro-tactile stimulation during the intensity adjustment phase were found between the genotype groups, all F(1,50) < 1.

Fig. 1. SCR for 5-HTTLPR and COMTval158met genotype group interactions. Further analysis within 5-HTTLPR and COMTval158met genotype groups revealed that SCRs did not differ between 5-HTTLPR l/l individuals with different COMTval158met genotypes F(1,24) < 1 while 5-HTTLPR s-carriers with the COMT met/met genotype showed significantly higher SCRs than did those carrying the COMT val-allele, F(1,26) = 5.74, p = 0.024, n² = 0.18. Similarly, within COMT val-carriers, those with the 5-HTTLPR l/l genotype showed higher SCR than did 5-HTTLPR s-carriers, F(1,26) = 4.89, p = 0.036, n² = 0.16 while no differences were observed within COMT met/met individuals depending on 5-HTTLPR genotype F(1,24) < 1.1.

3. Results

3.1. Effects of possible covariates

5-HTTLPR (s-carriers vs. l/l) and COMTval158met (val-carriers vs. met/met) genotype groups did not differ in mean STAI state scores, or pre-scan salivary cortisol levels (both when controlling for time of day, menstrual cycle and intake of contraceptive drugs). F(1,49) < 1.3. No interaction effects were observed.

3.2. Skin conductance responses (SCR)

Skin conductance responses (SCR) were acquired with a BIOPAC MP150 digital converter (BIOPAC Systems, Goleta, CA) and fed into AcqKnowledge 4.0 software. SCRs were sampled at 250 Hz, and a 1 Hz low-pass filter was applied during acquisition. An offline filter with a cut-off frequency of 1 Hz and number of coefficients = 200 was applied as well as a 0.05 Hz high-pass filter. SCR responses were scored in AcqKnowledge 4.0 as the largest increase in SCR occurring 0.9–4s post stimulus onset with a minimal amplitude of 0.03 μSiemens. The significance level for all analyses was set at p < 0.05.
3.3. fMRI: main effect of task – whole brain analysis

Viewing of angry faces elicited responses bilaterally in visual areas including the fusiform gyrus, lateral and ventrolateral PFC areas extending into the lateral orbitofrontal cortices, the amygdalae, hippocampi and the thalamus/pulvinar (see S1). Thus, the whole brain analysis has confirmed the involvement of the bilateral amygdalae in the task.

3.4. fMRI: 5-HTTLPR – anatomical ROI analyses

3.4.1. Faces > fixation cross

ROI analysis demonstrated more right amygdala activation during the viewing of angry faces in 5-HTTLPR s-carriers as compared to l/l individuals at \( p < 0.05 \) FWE corrected (Fig. 2A, B and Table 2). No difference in left amygdala activation as a function of 5-HTTLPR genotype was observed at \( p < 0.05 \) (FWE corrected). However, when lowering the

3.4.2. Early faces > late faces (habituation analyses)

For the right amygdala ROI, a two-sample t-test revealed greater amygdala activity for the early as compared to the late phase for individuals with the 5-HTTLPR l/l genotype as compared to s-carriers, significant at \( p < 0.05 \) unc. This indicates slightly stronger amygdala habituation in non-carriers of the 5-HTTLPR s-allele as compared to s-carriers.

Follow-up one-sample t-tests within s-carriers showed no differences in right or left amygdala activation between the early and late phase at \( p < 0.05 \) uncorrected, indicating no amygdala habituation but sustained reactivity over time. Analysis within participants with the l/l genotype in turn, showed significantly higher activation during early as compared to late phases of the experiment in the right amygdala (indicating strong habituation), significant at \( p < 0.05 \) FWE corrected and the left amygdala, significant at \( p < 0.01 \) uncorrected. Separate two-sample t-tests analyzing differences between the 5-HTTLPR genotype groups during the early phase only and the late phase only (faces > fixation cross, contrast 2 and 3 respectively) revealed significantly higher right amygdala activation in s-carriers as compared to those with the l/l genotype, significant at \( p < 0.05 \) FWE corrected for the early phase and at \( p < 0.01 \) uncorrected for the late phase of the experiment. See S5 for a graphical display of the results described here.

3.5. fMRI: COMTval158met – anatomical ROI analyses

3.5.1. Faces > fixation cross

ROI analyses demonstrated significantly more left amygdala activation during the viewing of angry faces in participants with the COMT met/met genotype as compared those carrying a COMT val-allele at \( p < 0.05 \) (Fig. 2D, E and Table 2). No difference in right amygdala activation as a function of COMTval158met genotype was observed at \( p < 0.05 \) (FWE corrected). However, when lowering the
significance threshold to \( p < 0.05 \) uncorrected (min \( k = 5 \)) individuals with the COMT met/met genotype were also found to display higher right amygdala activation than COMT val-carriers (\( x, y, z = 20, 4, -16, k = 35, T = 2.51, Z = 2.43 \)).

3.5.2. Early faces > late faces: (habituation analyses)

For the left amygdala ROI, a two-sample t-test for the early > late contrast revealed no differences between COMTVal158met genotype groups. Separate two-sample t-tests analyzing differences between the COMTVal158met genotype groups during the early phase only and the late phase only (faces > fixation cross, contrast 2 and 3 respectively) revealed significantly higher amygdala activation in participants with the met/met genotype as compared to val-carriers in the early phase (bilateral), significant at \( p < 0.01 \), and in the late phase (in the left amygdala only), significant at \( p < 0.05 \) uncorrected.

3.6. fMRI: exploratory analyses 5-HTTLPR × COMTVal158met – anatomical ROI analyses

3.6.1. Faces > fixation cross

An exploratory full factorial model, performed for means of completeness, revealed the same peak coordinates and basically unchanged statistics for the main effects of 5-HTTLPR and COMTval158met as obtained from the analyses described above. No evidence for a 5-HTTLPR × COMTVal158met interaction was found in the amygdala ROI at 0.05 FWE or at a very liberal threshold of \( p < 0.05 \) uncorrected.

4. Discussion

Our results demonstrate that 5-HTTLPR s-carriers and individuals with the COMT met/met genotype show higher amygdala reactivity to angry faces as compared to individuals with the 5-HTTLPR l/l genotype and those carrying at least one COMT val-allele, respectively. Importantly the effect of one polymorphism was controlled when investigating the other one. While amygdala reactivity differences between the 5-HTTLPR genotype groups seems to be partly driven by a steeper amygdala habituation slope in l/l individuals, no differential habituation was observed between the COMTVal158met genotype groups during the early phase only (faces > fixation cross, contrast 2 and 3 respectively) revealed significantly higher amygdala activation in participants with the met/met genotype as compared to val-carriers in the early phase (bilateral), significant at \( p < 0.01 \), and in the late phase (in the left amygdala only), significant at \( p < 0.05 \) uncorrected.

We observe a right lateralized effect of the 5-HTTLPR polymorphism while the metaanalysis by Munafò et al. (2008) did not find formal evidence for a lateralization effect. However, the effect size for the right amygdala was considerably larger than that for the left amygdala.

Interestingly, also the effect of COMTVal158met on amygdala reactivity was clearly lateralized in our data. Laterality of amygdala activation has been discussed intensively in the emotion literature but a metaanalysis did not find evidence that laterality is significantly related to stimulus type, task instructions, differential habituation rates of the amygdalae or elaborate processing (Baas et al., 2004).

The impact of the COMTVal158met polymorphism on amygdala reactivity has been studied less with less consistent findings than the 5-HTTLPR. While Smolka et al. (2005, 2007) reported enhanced right amygdala activation in individuals with the met/met genotype during passive viewing of negative pictures, higher left amygdala reactivity to faces has been found in females with the val/val genotype (Kempton et al., 2009) and in panic patients carrying the val-allele (Domischke et al., 2008). Yet another study did not observe any effect (Drabant et al., 2006). These divergent findings may be due to task-dependent modulatory inputs of other areas, e.g., prefrontal areas, in particular given low COMT expression levels in the amygdala (Jiang et al., 1998). Indeed, while Drabant et al. (2006) did not find an effect on amygdala reactivity, they observed enhanced functional amygdala – orbitofrontal coupling in participants with the met/met genotype. This stresses that the COMTVal158met polymorphism has only indirect effects on subcortical structures but more direct effects on cortical areas (Bilder et al., 2004).

As amygdala activation habituates very rapidly with repeated stimulus presentations (Breiter et al., 1996), enhanced amygdala reactivity as measured by fMRI may result from higher reactivity or less habituation over time. Our results suggest that, at least for the 5-HTTLPR, differential amygdala habituation may be one of the mechanisms driving differences between the genotype groups. This finding is well in line with recent, yet unpublished results from our group. In a visual search experiment, we observed that
the attentional threat bias disappeared in the second half of the experiment for non-carriers of the 5-HTTLPR s-allele (which can be seen as habituation), while s-carriers maintained this attentional threat bias also during the second half of the experiment. Still, we find higher amygdala reactivity in s-carriers during both the early and late phase of the experiment suggesting that our results of enhanced amygdala reactivity in s-carriers may be explained by both higher reactivity and less habituation, which strikingly resembles the pattern found in anxiety patients (Etkin and Wager, 2007; Lissek et al., 2005).

Even though our study design was aimed at investigating the main effects of both 5-HTTLPR and COMTVal158Met while controlling for the other one, we also performed explorative analyses investigating possible interaction/additive effects. Even though the number of participants in the interaction groups are low (n=13 to n=15) this represents the most reliable evidence from an imaging-genetics study. One fMRI study (Smolka et al., 2007) provided preliminary support for an additive effect on amygdala reactivity to the passive viewing of negative pictures, which stands in contrast to our findings. However this study had not used the prospective genotyping approach and the interaction cell numbers were very unequal (n=2–n=10). Still even our study lacks the adequate power to unequivocally interpret the null finding and results must thus be treated with caution.

No main effect of either polymorphism but a significant interaction was observed for SCRs. We observed a clear dissociation between SCR and amygdala habituation as reported earlier for SCR differentiation and amygdala reactivity during a conditioning task (Tabbert et al., 2006). While 5-HTTLPR s-carriers show less amygdala reactivity in s-carriers during both the early and late phase of the experiment suggesting that our results of enhanced amygdala reactivity in s-carriers may be explained by both higher reactivity and less habituation, which strikingly resembles the pattern found in anxiety patients (Etkin and Wager, 2007; Lissek et al., 2005).

In sum, the present study underscores the importance of accounting for genetic polymorphisms when studying amygdala-dependent processes and suggests that carriers of the 5-HTTLPR s-allele and those with the COMT met/met genotype may have a more reactive neural system to (negative) emotionally salient stimuli and that this may be partly driven by different habituation slopes with respect to 5-HTTLPR but not COMTVal158Met genotype.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.biopsycho.2011.02.014.

References


