Cogn Affect Behav Neurosci (2014) 14:354–363
DOI 10.3758/s13415-013-0200-8

Attention biases and habituation of attention biases are associated with *5-HTT*LPR and *COMT*val158met

Tina B. Lonsdorf · Pernilla Juth · Christin Rohde · Martin Schalling · Arne Öhman

Published online: 13 August 2013

Abstract Fundamental biases in affective information processing are modulated by individual differences in the emotional response to environmental stimuli that may be partly based on the individual's genetic make-up. To extend prior dot probe studies on attention genetics, we used a visual-search paradigm (VSP) with pictures of angry and happy faces of both sexes as targets, neutral faces as distractors, and a varying set size. Participants were selected a priori depending on their *5-HTT*LPR (s/s, s/l, l/l; on a constant rs25531 A-allele background) and *COMT*val158met (val/val, valmet, met/met) genotypes and were matched for sex and age. We demonstrate a bias towards angry male faces (as opposed to happy male faces) irrespective of *5-HTT*LPR genotype in the first experimental block that was maintained during the second experimental block only in carriers of the s-allele, which implies differential habituation processes. While a bias towards angry male faces was observed irrespective of *COMT*val158met genotype, only individuals with the val/val genotype exhibited a bias towards a happy female face (as opposed to an angry female face). In sum, our results both replicate and extend prior findings in the field of attention genetics and add important pieces of information to the research on attentional biases in emotion processing.

Keywords Anxiety · Attention · Serotonin · Emotion · Dopamine · Amygdala

Electronic supplementary material The online version of this article (doi:10.3758/s13415-013-0200-8) contains supplementary material, which is available to authorized users.

T. B. Lonsdorf · P. Juth · C. Rohde · A. Öhman
Department of Clinical Neuroscience, Karolinska Institutet, Psychology Section, Stockholm, Sweden

T. B. Lonsdorf (✉)
Institute of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany
e-mail: t.lonsdorf@uke.de

T. B. Lonsdorf · A. Öhman
Stockholm Brain Institutet, Stockholm, Germany

T. B. Lonsdorf · M. Schalling
Center for Molecular Medicine and Surgery, Karolinska Institutet, Neurogenetics Unit, Stockholm, Sweden

T. B. Lonsdorf · M. Schalling
Center for Molecular Medicine (CMM), Karolinska University Hospital, Stockholm, Sweden

Attentional processes help to select relevant environmental information for further processing, thus assisting sensory systems in overcoming their limited capacity. Enhanced attentional sensitivity to threat-related stimuli is characteristic of patients suffering from anxiety disorders (e.g., Mogg & Bradley, 1999; for a meta-analysis, see Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007) and manifests as enhanced shifting and attentional engagement towards fear stimuli (e.g., Ohman, Flykt, & Esteves, 2001), as well as impeded disengagement from these stimuli (e.g., Rinck, Reinecke, Ellwart, Heuer, & Becker, 2005). This attentional bias is not only symptomatic of anxiety but may, in fact, be causally involved in both development and maintenance of anxiety (Bar-Haim et al., 2007; Yiend, 2010). The spatial attention capture by visual threat signals has often been studied using the dot probe paradigm (DPP) and the visual search paradigm (VSP).

Dot probe paradigm versus visual search paradigm

In the DPP, two stimuli (e.g., pictures) are presented on the right and left sides of a fixation cross. Subsequently, one of the stimuli is replaced by a probe (e.g., :) that participants are instructed to detect and react to as quickly as possible. Enhanced reaction times (RTs) to probes appearing in the location previously occupied by threatening pictures (facilitated threat detection), as opposed to neutral pictures, are taken to reflect difficulty in "disengaging" (Posner, 1980; selection and

processing of a stimulus is withdrawn) from threat. The dot probe task, however, cannot discriminate between disengagement and engagement (Posner, 1980; selection and facilitation of processing of a stimulus) processes (Bar-Haim et al., 2007). The VSP, in turn, measures the latency of detecting an emotionally evocative target stimulus among an array of distractor stimuli and primarily assesses attentional shifts in orienting (Posner, 1980; spatial relocation of attention across the visual field). When using neutral or homogenous distractors (as in the present study), the VSP represents processes of clean attentional engagement that is not confounded by disengagement processes and, thus, is considered superior to the DPP or cuing studies (Yiend, 2010). Using a potentially threatening target stimulus and neutral faces as distractors, several studies have reported faster detection of angry than of happy target faces (Öhman, Lundqvist, & Esteves, 2001; Pinkham, Griffin, Baron, Sasson, & Gur, 2010), particularly among anxious individuals (Gilboa-Schechtman, Foa, & Amir, 1999; Juth, Lundqvist, Karlsson, & Öhman, 2005). However, this finding is controversial, some studies even reporting faster detection of happy than of angry faces, particularly if the faces are female (Calvo & Nummenmaa, 2008; Juth et al., 2005; Öhman, Juth, & Lundqvist, 2010).

The serotonin transporter-linked polymorphic region

Biases in affective information processing are modulated by individual differences that partly reflect the individual's genetic make-up. Two genetic polymorphisms have commonly been associated with individual differences in attention processes and/or emotional reactivity: the *5-HTT*LPR/rs25531 and the *COMT*val158met polymorphisms (see below). The *5-HTT*LPR represents a 43-bp ins/del in the serotonin transporter promoter. The minor s-allele (as compared with the long l-allele) is associated with reduced 5-HTT expression in vitro (Heils et al., 1995), but results from in vivo and postmortem studies are inconsistent (Uher & McGuffin, 2008). Recent studies suggest that (early) neurodevelopmental effects may underlie these functional associations (Gaspar, Cases, & Maroteaux, 2003; Jedema et al., 2010). The minor G-allele of a single-nucleotide polymorphism (SNP), rs25531, in close proximity to the *5-HTT*LPR, reduces 5-HTT expression levels in *5-HTT*LPR l-allele carriers to an expression level similar to s-carriers (Hu et al., 2006). Since the combination of *5-HTT*LPR and rs25531 ("triallelic *5-HTT*LPR") is thought to better capture the functionality of the *5-HTT* promoter region, their combination has become the standard procedure.

The *5-HTT*LPR s-allele is associated with enhanced neuroticism (for a review, see, e.g., Sen, Burmeister, & Ghosh, 2004), increased amygdala reactivity (Munafò et al., 2008), and less amygdala habituation (Lonsdorf et al., 2011), as well as facilitated fear acquisition (Lonsdorf et al., 2009). Studies that assessed the effect of the *5-HTT*LPR on human attention (Beevers, Gibb, McGeary, & Miller, 2007; Carlson, Mujica-Parodi, Harmon-Jones, & Hajcak, 2012; Fox, Ridgewell, & Ashwin, 2009; Fox, Zougkou, Ridgewell, & Garner, 2011; Kwang, Wells, McGeary, Swann, & Beevers, 2010; Osinsky et al., 2008; Pérez-Edgar et al., 2010) primarily used the dot probe task (MacLeod, Mathews, & Tata, 1986) or, in some cases, the spatial cuing paradigm introduced by Posner (1980; Beevers, Pacheco, Clasen, McGeary, & Schnyer, 2010; Beevers, Wells, Ellis, & McGeary, 2009).

The results of these studies show that participants who were homozygous for the *5-HTT*LPR l-allele showed vigilance for positive information by demonstrating shorter RTs to probes that followed positive rather than negative pictures. In addition, avoidance of negative pictures was demonstrated by shorter choice RTs when the probe followed a neutral picture paired with a negative rather than a positive stimulus (Fox et al., 2009; Kwang et al., 2010; Pérez-Edgar et al., 2010; for a review, see Pergamin-Hight et al., 2012). Participants homozygous for the s-allele display a bias toward negative stimuli (for a meta-analysis, see Pergamin-Hight et al., 2012; but see Fox et al., 2009). This pattern of orienting spatial attention to fearful faces in s-carriers and directing attention away from fearful faces was also observed using backward-masked fearful faces and, thus, under restricted processing conditions (Carlson et al., 2012). In addition, a recent fMRI study in adolescents reports greater attention bias only to subliminally, but not supraliminary, presented fear stimuli (Thomason et al., 2010). In sum, these studies on *5-HTT*LPR reveal a rather consistent picture, suggesting a bias for negative material in s-carriers and a bias for positive material in homozygous l-carriers, which line up with results from the fields of emotion and anxiety (for a review, see Homberg & Lesch, 2011).

The *COMT*val158met polymorphism

A common SNP in the gene coding for the catecholamine degrading enzyme catechol-o-methyltransferase (COMT), *COMT*val158met, leads to the substitution of the amino acid valine by methionine at codon 158. The met-allele, which is associated with a four times reduced enzymatic activity (Weinshilboum, Otterness, & Szumlanski, 1999), has also been associated with the processing of emotional stimuli (Heinz & Smolka, 2006), slow extinction of conditioned fear responses (Lonsdorf et al., 2009), and heightened amygdala reactivity (Lonsdorf et al., 2011; Rasch et al., 2010; Smolka et al., 2007; but see Domschke et al., 2012). Amygdala activation in met-carriers has also been shown to be increased during the processing of facial fear expressions and to be decreased during processing of happy facial expressions (Williams et al., 2010). Together, studies in the field of emotion suggest a modulatory role for this polymorphism in the

processing of and attention to emotional material, with the met-allele being associated with heightened reactivity to negative material. However, studies directly addressing the role of *COMT*val158met in attention processes are largely lacking to date. A single study reported a positive correlation between val-allele load and activity in control- and task-related regions during attention allocation performance under emotional distraction (Bishop, Cohen, Fossella, Casey, & Farah, 2006).

The present study

The present study was planned to broaden the database for the roles of the *5-HTT*LPR and *COMT*val158met polymorphism in the emotional guidance of attention. Rather than the frequently used (with respect to attention genetics studies) DPP, we used a VSP to discriminate between engage and disengage components of attention allocation. In this VSP, participants looked for single angry or happy photographically depicted target faces in a "crowd" of neutral faces. In a previous study (Öhman et al., 2010), we showed that the VSP, depending on context and target gender, can result either in an angry advantage (faster detection of angry than of happy faces) or in a happy advantage (faster detection of happy than of angry faces).

In addition, cognitive load was manipulated by using arrays of different set sizes (4, 8, 12, or 16 pictures). According to influential theory (Treisman, 2006; Treisman & Gelade, 1980; Wolfe, 1994), assessing the effect of cognitive load allows differentiation between automatic and cognitively controlled attention. Thus, minimal effect of increasing set size with a particular target–distractor combination suggests automatic target detection, whereas a reliable effect of set size is taken as evidence of controlled serial search. For exploratory purposes, effect size was thus manipulated in our study. On the basis of previous studies in the fields of emotion and attention, we predicted an association between the *5-HTT*LPR l/l-genotype, as well the *COMT* val/val genotype, and a happy VSP advantage. Furthermore, we expected an association of the *5HTT*LPR s-allele genotype, as well the *COMT* met-allele, with an angry VSP advantage.

Method

Participants

Participants were recruited from a large pool (~600) of genotyped individuals. They were selected on the basis of their *5-HTT*LPR/rs25531 and *COMT*val158met genotypes (rs4680) and were matched for gender and age. This created genotype groups for each polymorphism that differed neither with respect to the genotype distribution of the other polymorphism nor in age and gender. Exclusion criteria were selfreported lifetime psychiatric disorders, psychopharmacological treatment, or non-Caucasian ancestry. In total, 52 participants (27 females) participated in the experiment, of which 3 (2 females) had to be excluded from data analyses due to technical problems, which left 49 individuals (26 females) for analyses. Age of the participants ranged between 19 and 32 years, with a mean of 24.4 years (SD = 3.0). All participants had normal or corrected—to-normal vision and received two cinema ticket vouchers for their participation. The gender and genotype distributions of the participants are displayed in Table 1.

Genotyping

Genetic material was collected as either 20-ml whole blood samples (stored at −20°C until DNA extraction) or as saliva samples (stored at room temperature) using the Orangene® DNA self-extraction kit (DNA Genotek Inc., Kanata, Canada). DNA extraction was performed using the protocol and reagents supplied by Orangene (saliva samples) or was performed robotized by the local Biobank (KI Biobank, Karolinska Institutet, Stockholm) using standard methods (Autopure LS system, Gentra Systems, Minneapolis, MN). All DNA samples were genotyped as described earlier in detail for *5-HTT*LPR/rs25531 (Lonsdorf et al., 2010; see also the correction) and *COMT*val158met (Lonsdorf et al., 2009).

Stimuli

Stimuli were taken from the *Karolinska Directed Emotional Faces* (KDEF), which is an extensive set of faces incorporating 70 actors of Caucasian origin (Lundqvist, Flykt, & Öhman, 1998). A pool of 12 actors was selected (females no. 01, 07, 16, 21, 29, 35; and males no. 03, 10, 17, 28, 30, 31); each displayed three different facial expressions (neutral, happy, and angry) on separate pictures. During the experiment, participants were exposed to a subset of six randomly selected individual faces from this pool of 12 actors (3 female and 3 male). Different KDEF stimuli were used for the

Table 1 Genotype distributions (number of females is given in parentheses)

		*5-HTT*LPR Genotype*			
		Long/Long	Short/Long	Short/Short	
*COMT*val158met genotype	Met/met	6 (3)	6 (3)	6 (4)	18 (10)
	Val/met	5 (2)	6 (2)	6 (3)	17 (7)
	Val/val	5 (2)	5 (3)	4 (1)	14 (6)
		16 (7)	17 (8)	16 (8)	49 (26)

* All participants were selected on a constant rs25531 A-allele background (in other words, all participants carrying a rs25531 G-allele were a priori not included).

practice session, and these were not included in the experimental tasks. A computer with an AMD Athlon™ 1.67-GHz and 1.00-GB RAM processor, with a 20-in. 85Hz Sony GDM-F520 CRT monitor, was programmed in Macromedia Director MX software (Macromedia, Inc) to present visual displays and to measure RTs and accuracy. The resolution of the screen was 2,560 × 1,600, and the size of the presented stimuli was 120 × 160 pixels.

Maximally, 48 stimuli were shown placed in a virtual matrix, since this matrix was maximally 8 stimuli in width and 6 stimuli in height. The set size varied between 4, 8, 12, and 16 positions within these possible 48 positions, which were randomly selected. Placement within the matrix was (on average) spaced by 200 pixels in both the *x* and the *y* directions (with a deviation of 40 and 30 pixels, respectively). Any given stimulus was presented on the given position with a deviation of ±20 on the *x*-axis and ±15 on the *y*-axis. On the screen, the distance from the center of the display to the center of each face was 11 cm (9° in visual angle). Each face was 7.2 × 5.3 cm (approximately 6° × 4° in visual angles), and the size of the whole display was 27.3 × 26.1 cm (approximately 22° × 21° in visual angles). Participants were seated at a distance of approximately 70 cm from the screen. Trials were initiated by the appearance of the fixation cross (0.4 cm) at the center of the screen. It remained on for 1 s, when it was replaced by the face array, which remained on until terminated by the response or when 10 s had elapsed. The intertrial intervals were 3 s.

Experimental paradigm

The participants were tested individually and received self-paced computerized instructions of the visual search task, with demonstrations and practice sessions immediately before the task. On half of the trials, the display showed only neutral faces (no-target trials), and on the other half (target trials), one of the neutral faces was exchanged for an emotional target face depicting an angry or happy facial expression. Half of the target trials showed a male, and the other half showed a female target face. Distractor pictures always displayed individuals with a neutral facial expression. Target position was randomized, with the constraint that it appeared with equal probability at all possible locations. The size of the array (i.e., the set size) varied between 4, 8, 12, and 16 faces across trials, with one emotional target face and the remaining positions occupied by neutral distractor faces on target trials and only neutral distractor faces on no-target trials. The task included a total of 192 trials, balancing target presence (2), target emotion (2), target position (6; each face served as a target 6 times), set size (4), and block (2). The participants' task was to use two designated keys on the computer keyboard to indicate whether a discrepant emotional face was present in the display or not as quickly and accurately as possible,

Statistical analyses

RTs were analyzed using separate mixed model ANOVAs (target gender [2] × target emotion [2] × set size [4] × block [2]), with genotype (*5HTT*LPR or *COMT*val158met, respectively) as the between-subjects variable and RT and accuracy, respectively, as the dependent measure. Outlier data points (±3 *SD*s from the individual's mean) were replaced by the individual's mean (±3 *SD*s). RTs were log-transformed in order to rectify the positively skewed distributions. Back-transformed values are given in tables and figures. All statistical analyses were performed using PASW (Version 18, SPSS Inc., Chicago, IL); $p < .05$ was considered significant, and Greenhouse–Geisser corrected degrees of freedom were used when appropriate.

Results

Descriptive analyses

Neither *5-HTT*LPR nor *COMT*val158met genotype groups differed significantly in gender distribution, as was indicated by nonsignificant χ^2 tests (both *p*s > .65). Furthermore, a nonsignificant χ^2 test confirmed that within *5-HTT*LPR genotype groups, the *COMT*val158met genotype groups were equally distributed, $p = 1$ (see also Table 2) and, thereby, confirmed successful participant matching despite some drop-outs (see above). Genotype groups did not differ in age, all *F*s < 1.

Reaction times

Main effects of task were found to replicate prior results (see, e.g., Juth et al., 2005; Öhman et al., 2010) of shorter RTs for angry versus happy targets (angry bias) and an effect of set size (shorter RTs for smaller set sizes), as well as an interaction between target gender and target valence (happy bias for female targets and angry bias for male targets). Detailed results can be found in the Supplementary material.

5HTTLPR

A mixed-model ANOVA (target gender [2] × valence [2] × set size [4] × block [2]) on RTs, with *5-HTT*LPR genotype (l/l, s/l, s/s) as a between-subjects variable, revealed a four-way target gender × target valence × block × *5-HTT*LPR interaction, $p = .011$ (see Table 2A for statistical details and Fig. 1), representing a modulation of the main effect of task (target gender × target valence) by *5-HTT*LPR genotype and time. In the case of a male target, participants displayed a bias toward angry faces in the first block of the experiment irrespective of *5-HTT*LPR genotype [s/s, $F(1, 15) = 5.05$, $p = .04$, $\eta^2 = .25$; s/l, $F(1, 16) = 5.11$, $p = .038$, $\eta^2 = .24$; l/l, $F(1, 15) = 10.11$, $p < .001$,

Table 2 Statistical results for the analyses including *5-HTT*LPR (**A**) or *COMT*val158met genotypes (**B**) as factors

(A) 5-HTTLPR Genotype Effects	*df*	*F*	*p*	η^2	Direction of the Effect (RT)
Set size × block × 5-HTTLPR	6,135	3.24	.007	.13	Small arrays (4, 8):
					l/l, 2nd block > 1st block; s/s and s/l, 2nd block = 1st block
					Large arrays (12, 16):
					l/l, 2nd block = 1st block; s/l, 2nd block >1st block; s/s, 2nd block > 1st block for 16 items, but 2nd block = 1st block for 12 items
Target valence × target gender × block × 5-HTTLPR	2,45	5.01	.011	.18	Male target:
					1st block: angry > happy for all 5-HTTLPR genotypes
					2nd block: angry > happy for s/l and s/l but not l/l
					Female target:
					1st block: happy > angry for l/l but not s/l or s/s
					2nd block: happy = angry for all 5-HTTLPR genotypes
(B) COMTval158met genotype effects					
Target valence × target gender × COMTval158met	2,45	3.52	.038	.14	Female target:
					Angry > happy only for val/val but not val/met or met/met
					Male target:
					happy > angry for all COMTval158met genotypes

η^2 = .57]. In the second block, carriers of one or two s-alleles (s/l and s/s) both still displayed this bias [s/s, $F(1, 15) = 4.77$, $p = .045$, $\eta^2 = .24$; s/l, $F(1, 16) = 16.28$, $p = .001$, $\eta^2 = .50$], while individuals with the l/l genotype did not show an attentional bias toward a male face with an angry expression, $F(1, 15) < 1$, $p = .54$.

To the contrary, in the case of female targets, carriers of one or two s-alleles did not show any attentional bias during the first half [s/s, $F(1, 15) = 1.23$, $p = .29$; s/l, $F(1, 16) < 1$, $p = .86$]. Individuals with the l/l genotype, in turn, displayed a bias toward happy female faces in the first block of the experiment [happy bias: $F(1, 15) = 6.23$, $p = .025$, $\eta^2 = .29$]. During the second block, no attentional bias to a female target was observed in either genotype group, all Fs ≤ 1. In addition, a three-way set size × block × *5-HTT*LPR interaction ($p = .007$; see Table 2A for statistical details) was observed that was,

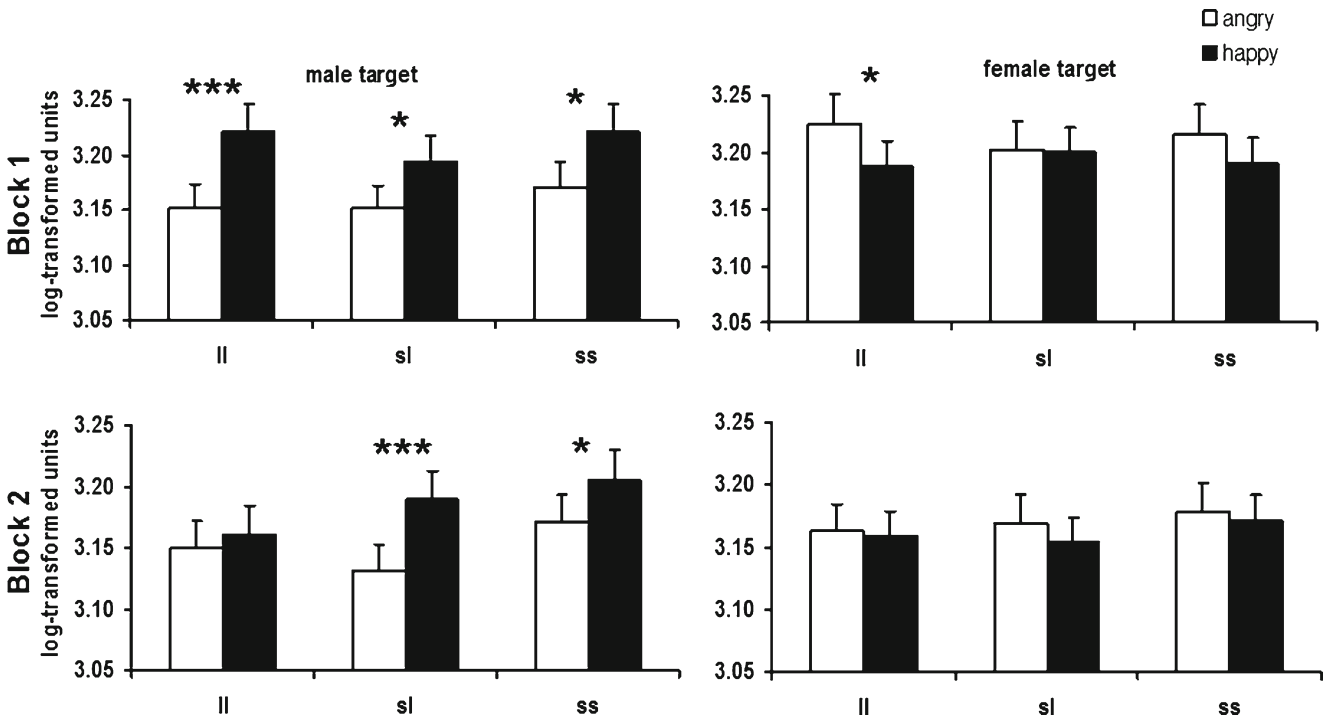

Fig. 1 Graphical display of the target gender × target valence × block × *5-HTT*LPR interaction. *$p < .05$; **$p < .01$; ***$p < .001$

however, not of interest to our main hypotheses (thus, we refer the interested reader to the Supplementary materials).

COMTval158met

A mixed-model ANOVA (target gender [2] × valence [2] × set size [4] × block [2]) on RTs, with *COMT*val158met genotype (val/val, val/met, met/met) as the between-subjects variable, revealed a target valence × target gender × *COMT*val158met genotype interaction, $p = .038$ (see Table 2B for statistical details and Fig. 2). In the case of a male target, all *COMT*val158met genotype groups showed significantly shorter RTs toward angry, as compared with happy, faces [met/met, $F(1, 17) = 9.35$, $p = .007$, $\eta^2 = .36$; val/met, $F(1, 16) = 8.79$, $p = .009$, $\eta^2 = .36$; l/l, $F(1, 13) = 27.87$, $p < .001$, $\eta^2 = .68$]. In cases of a female target, however, only individuals with the val/val genotype showed shorter RTs to happy than to angry faces, $F(1, 13) = 8.98$, $p = .010$, $\eta^2 = .41$. Carriers of one or two met-alleles, however, did not react faster to angry or happy female faces [met/met, $F(1, 16) = 3.04$, $p = .10$; val/met, $F(1, 16) < 1$, $p = .53$].

Accuracy and post hoc power calculations

Detection accuracy was better in smaller set sizes (vs. bigger ones) and for female targets (vs. male targets). Furthermore, in the case of a female target, a happy face was detected more accurately, while in the case of a male target, an angry face was detected more accurately (see the Supplementary material for statistical details). No main effect or interaction effect involving *5-HTT*LPR or *COMT*val158met genotype yielded statistically significant results.

Post hoc power calculations were performed using the program GPower (Faul, Erdfelder, Lang, & Buchner, 2007). On the basis of the partial η^2 of our major finding (target valence × target gender × block × 5-HTTLPR), a large effect ($f = .47$) was calculated by the program. On the basis of this effect size, the sample size of 49, three different groups, and an α-level of .05, G-Power calculated a power ($1 - \beta$ − probability error) of .99 for our study. Thus, we can conclude that our study did not suffer from power issues. Assuming a medium small effect size of $f = .25$ and a lower correlation between the measurements (e.g., as for the explorative target valence × target gender × block × set size interaction, where the number of trials per condition would only be 3), our study would have only had a power of .74 to detect an effect.

Discussion

Our results replicate prior results from VSP studies, as well as attention genetics studies, and add important new pieces of information to this field. We replicate prior findings from VSP experiments using photographically depicted real faces, showing that the interplay between target gender and target valence affects detection biases. Specifically, the detection of an angry facial expression is facilitated in the case of a male target, while the detection of a happy facial expression is facilitated in the case of a female target (Becker et al., 2007; Öhman et al., 2010). With respect to attention genetics, the present study extends these prior findings by demonstrating that this target gender × target valence interaction effect is further modulated by *COMT*val158met and *5-HTT*LPR genotypes (and time) and, thereby, provides important new information beyond previous results based on dot probe studies.

First, in line with our hypotheses, these results show a more pronounced time-stable threat-superiority effect in *5-HTT*LPR s-carriers. In addition, as was expected, a happy-superiority effect was found only in individuals homozygous for the *5-HTT*LPR l-allele. Our results thus replicate findings on *5-HTT*LPR and attention biases originating from the DPP (where the emotional valence of the picture is task irrelevant) using a different methodology (VSP, where the emotional valence of the target is task relevant, since a deviant picture has to be detected) and thus suggest that the engagement component, which is captured by both tasks, might be related to this genotype, rather than disengagement components, which are captured by the DPP but not the VSP. This means that attentional selectivity with respect to the 5-HTTLPR

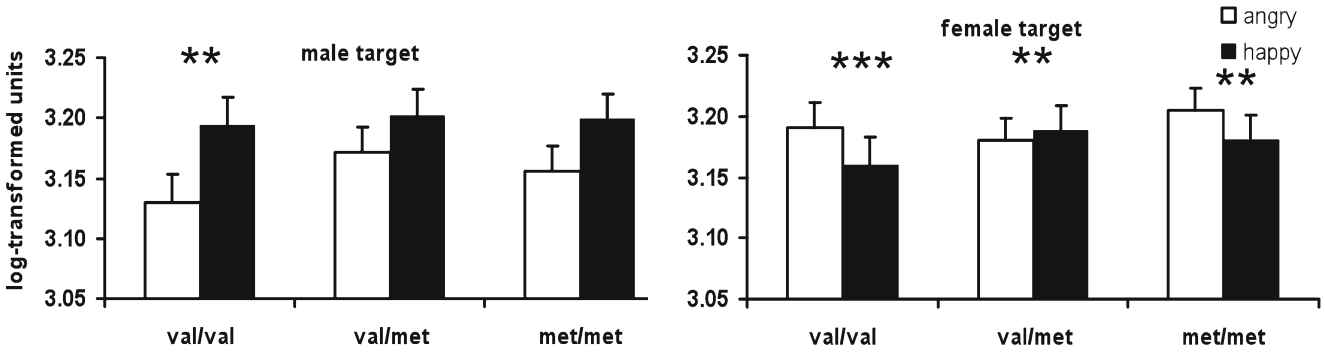

Fig. 2 Graphical display of the target valence × target gender × *COMT*val158met interaction. *$p < .05$; **$p < .01$; ***$p < .001$

might result from preferential attention engagement with emotionally threatening stimuli, rather than from selective difficulty in disengaging attention from such information. However, it has to be noted that research using clinical or anxious populations has generally suggested difficulties in disengaging attention from threat in these populations (for a review, see, e.g., Cisler & Koster, 2010). Furthermore, in visual search tasks, longer response latencies are attributed to interference, but it has not been unequivocally shown whether such interference is the result of biased attentional engagement with or biased attentional disengagement from threatening material (for a review, see, e.g., Cisler & Koster, 2010).

While s-carriers have consistently shown a bias toward negative stimuli in DPP studies (Beevers et al., 2007; Carlson et al., 2012; Kwang et al., 2010; Osinsky et al., 2008; Pérez-Edgar et al., 2010), a bias toward positive stimuli or away from negative stimuli was observed in individuals with the l/l genotype only (Carlson et al., 2012; Fox et al., 2009; Kwang et al., 2010; Pérez-Edgar et al., 2010). These findings have recently been confirmed by a meta-analysis (Pergamin-Hight et al., 2012) and have been extended by Fox and colleagues, who used an attention bias modification technique (Colin MacLeod, & Mathews, 2012) to demonstrate that s-carriers/low 5-HTT expressing individuals develop stronger biases for both negative and positive stimuli (Fox et al., 2011). This finding, as well as a generally more pronounced attentional threat-bias in *5-HTT*LPR s-carriers, relates to facilitated fear conditioning in this genotype group (Lonsdorf et al., 2009), since attentional threat biases are primarily acquired through fear learning (Beaver, Mogg, & Bradley, 2005; Pischek-Simpson, Boschen, Neumann, & Waters, 2009). Despite these associations with negative emotionality, the *5-HTT*LPR has been discussed lately rather in the framework of a plasticity-inducing (for better and for worse; Belsky et al., 2009) polymorphism, and in line with this, Fox et al. (2011) found s-carriers to be more responsive to the induction of both negative and positive attention biases in an attention bias modification task using the DPP. This finding may be taken to suggest that this genotype group may profit more from (cognitive) psychological treatment interventions. However, therapy genetics studies have not revealed a consistent picture (for a review, see Lester & Eley, 2013). The data in Fox et al. (2011) may, however, suggest that s-carriers may be particularly sensitive for cognitive, as opposed to exposure-based, treatments. That is, the cognitive aspects of CBT aim at changing the biased information processing (i.e., cognitive modification; e.g., Clark & Beck, 2010) that is central to anxiety disorders. In support of this hypothesis, no effects on fear extinction processes are observed in humans (Lonsdorf et al., 2009).

The second new piece of information with respect to attention genetics supports our previous findings of different amygdala habituation slopes in the processing of angry faces (Lonsdorf et al., 2011). Here, we find additional evidence for a steeper habituation curve in homozygous l-carriers, as compared with *5-HTT*LPR s-carriers: While we observed a bias toward angry male faces (vs. happy male faces) irrespective of *5-HTT*LPR genotype in the first block of the experiment, this bias was maintained during the second block in *5-HTT*LPR s-allele carriers only. Similarly, while a happy superiority effect was absent in s-carriers throughout the experiment, this bias was present in homozygous l-carriers in the first block but disappeared in the second block, again suggesting habituation. Thus, while *5-HTT*LPR s-carriers maintained their attentional biases (or their absence) during both blocks of the experiment, noncarriers exhibited no specific biases during the second block of the experiment. These results may represent a behavioral correlate of our recent report of different amygdala habituation slopes during face processing (Lonsdorf et al., 2011).

The third new piece of information provided by our results is the happy superiority effect that was observed in the COMTval158met val/val genotype group only (happy vs. angry female face), while a negativity bias (angry vs. happy male face) was present irrespective of COMTval158met genotype. It is interesting to note that the happy superiority effect was observed only for individuals who were either noncarriers of the *5-HTT*LPR s-allele (l/l) or noncarriers of the *COMT*val158met met-allele (val/val). Both the *5-HTT*LPR s-allele and the *COMT*val158met met-allele have previously been associated with negative emotionality and anxiety-related traits, as well as clinical anxiety disorders. Thus, it is interesting that the homozygous carriers of the so-called "nonrisk" or "protective" alleles for both polymorphisms displayed a happy advantage, while "risk-allele" carriers did not. This suggests that these individuals, in fact, may be emotionally resilient against negative life events and stress (for *5-HTT*LPR: Kuepper et al., 2012), due to their perceptual bias, which may contribute to mental health and well-being (Fox, 1993).

Selective attention to threatening or negative emotional stimuli has been suggested as a main risk factor in the aetiology, as well as the maintenance, of affective disorders (Bar-Haim et al., 2007), and it has even been suggested to be causally involved in this vulnerability (Yiend & Mathews, 2004). In particular, the absence of a protective bias (here, toward happy female faces) in combination with a persistent vulnerability factor in terms of an angry bias observed in carriers of the *5-HTT*LPR s-allele or the *COMT*val158met met/met genotype may enhance their vulnerability to developing negative emotionality. In fact, heightened neuroticism scores have been associated with the *5-HTT*LPR s-allele (Sen et al., 2004), and the *COMT*val18met met/met genotype has also been associated with resistance to extinction (Lonsdorf et al., 2009), resistance to profiting from exposure-based CBT (Lonsdorf et al., 2010), and enhanced activation in limbic areas during the processing of unpleasant stimuli as measured

by fMRI (Lonsdorf et al., 2011; Rasch et al., 2010; Smolka et al., 2007; but see Domschke et al., 2012) and EEG (Herrmann et al., 2009).

We have demonstrated an association of attentional biases with both the *5-HTT*LPR and the *COMT*val158met polymorphisms. Even though these results are interesting, it should be pointed out clearly that no single polymorphism or single gene *causes* attentional biases. Furthermore, our study employed an association study approach that does not allow causal inferences. Genes and their polymorphisms do not code for behavior or attentional biases, but they affect the neurochemical environment of the developing and adult brain and, thus, may bias and shape neural networks and neural connectivity involved in attentional and emotional processes. Thus, the mechanisms underlying these associations remain to be elucidated.

While our study has several major strengths (e.g., the prospective genotyping approach, a well-studied experimental design), some limitations should also be mentioned here. Our experimental sample was highly selected in multiple ways, since individuals were selected on the basis of genotype, age, and gender from a large pool of genotyped individuals. Thus, inferences on the general population may not be adequate. In addition, our sample was rather small for a genetic association study. The findings involving the explorative highest order target valence × target sex × block × set size interaction were nonsignificant, since, given our sample size, statistical power was not satisfactory.

Despite these limitations, we believe that our study extends prior findings in the field of attention genetics, adds important pieces of information to the research on attentional biases in emotion processing, and makes a contribution to their understanding. The present results may be of relevance for personalized treatment of affective disorders: If individuals with a certain genetic make-up are more prone do display attention biases that may enhance or maintain vulnerability for these disorders, it may be assumed that these individuals not only may be more prone for these disorders, but also may suffer from more severe symptoms (Lonsdorf et al., 2010). Furthermore, these attentional biases may represent an appropriate and promising intervention point for personalized cognitive-behavioral treatments (e.g.. attention bias modification therapy; MacLeod & Mathews, 2012)—in particular, for individuals with a specific genetic profile (Fox et al., 2011).

Acknowledgements We are thankful to Daniel Lundqvist for help with experiment programming and providing technical equipment. We report no conflict of interest.

References

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin, 133*(1), 1–24. doi:10.1037/0033-2909.133.1.1

Beaver, J. D., Mogg, K., & Bradley, B. P. (2005). Emotional conditioning to masked stimuli and modulation of visuospatial attention. *Emotion (Washington, D.C.), 5*(1), 67–79. doi:10.1037/1528-3542.5.1.67

Becker, D. V., Kenrick, D. T., Neuberg, S. L., Blackwell, K. C., & Smith, D. M. (2007). The confounded nature of angry men and happy women. *Journal of Personality and Social Psychology, 92*(2), 179–190. doi:10.1037/0022-3514.92.2.179

Beevers, C. G., Gibb, B. E., McGeary, J. E., & Miller, I. W. (2007). Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. *Journal of Abnormal Psychology, 116*(1), 208–212. doi:10.1037/0021-843X.116.1.208

Beevers, C. G., Pacheco, J., Clasen, P., McGeary, J. E., & Schnyer, D. (2010). Prefrontal morphology, 5-HTTLPR polymorphism and biased attention for emotional stimuli. *Genes, brain, and behavior, 9*(2), 224–233. doi:10.1111/j.1601-183X.2009.00550.x

Beevers, C. G., Wells, T. T., Ellis, A. J., & McGeary, J. E. (2009). Association of the serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. *Journal of Abnormal Psychology, 118*(3), 670–681. doi:10.1037/a0016198

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry, 14*(8), 746–754. doi:10.1038/mp.2009.44

Bishop, S. J., Cohen, J. D., Fossella, J., Casey, B. J., & Farah, M. J. (2006). COMT genotype influences prefrontal response to emotional distraction. *Cognitive, Affective, & Behavioral Neuroscience, 6*(1), 62–70.

Calvo, M. G., & Nummenmaa, L. (2008). Detection of emotional faces: Salient physical features guide effective visual search. *Journal of Experimental Psychology: General, 137*(3), 471–494. doi:10.1037/a0012771

Carlson, J. M., Mujica-Parodi, L. R., Harmon-Jones, E., & Hajcak, G. (2012). The orienting of spatial attention to backward masked fearful faces is associated with variation in the serotonin transporter gene. *Emotion (Washington, D.C.), 12*(2), 203–207. doi:10.1037/a0025170

Cisler, J. M., & Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical psychology review, 30*(2), 203–216. doi:10.1016/j.cpr.2009.11.003

Clark, D. A., & Beck, A. T. (2010). Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. *Trends in cognitive sciences, 14*(9), 418–424. doi:10.1016/j.tics.2010.06.007

Domschke, K., Baune, B. T., Havlik, L., Stuhrmann, A., Suslow, T., Kugel, H., & Dannlowski, U. (2012). Catechol-O-methyltransferase gene variation: Impact on amygdala response to aversive stimuli. *NeuroImage, 60*(4), 2222–2229. doi:10.1016/j.neuroimage.2012.02.039

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods, 39*(2), 175–191.

Fox, E. (1993). Attentional bias in anxiety: selective or not? *Behaviour Research and Therapy, 31*(5), 487–493.

Fox, E., Ridgewell, A., & Ashwin, C. (2009). Looking on the bright side: biased attention and the human serotonin transporter gene. *Proceedings. Biological Sciences / The Royal Society, 276*(1663), 1747–1751. doi:10.1098/rspb.2008.1788

Fox, E., Zougkou, K., Ridgewell, A., & Garner, K. (2011). The serotonin transporter gene alters sensitivity to attention bias modification: evidence for a plasticity gene. *Biological Psychiatry, 70*(11), 1049–1054. doi:10.1016/j.biopsych.2011.07.004

Gaspar, P., Cases, O., & Maroteaux, L. (2003). The developmental role of serotonin: news from mouse molecular genetics. *Nature Reviews. Neuroscience, 4*(12), 1002–1012. doi:10.1038/nrn1256

Gilboa-Schechtman, E., Foa, E. B., & Amir, N. (1999). Attentional Biases for Facial Expressions in Social Phobia: The Face-in-the-Crowd Paradigm. *Cognition & Emotion, 13*(3), 305–318. doi:10.1080/026999399379294

Heils, A., Teufel, A., Petri, S., Seemann, M., Bengel, D., Balling, U., & Lesch, K. (1995). Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. *Journal of Neural Transmission-General Section, 102*(3), 247–254.

Heinz, A., & Smolka, M. N. (2006). The effects of catechol O-methyltransferase genotype on brain activation elicited by affective stimuli and cognitive tasks. *Reviews in the Neurosciences, 17*(3), 359–367.

Herrmann, M. J., Würflein, H., Schreppel, T., Koehler, S., Mühlberger, A., Reif, A., & Fallgatter, A. J. (2009). Catechol-O-methyltransferase Val158Met genotype affects neural correlates of aversive stimuli processing. *Cognitive, Affective & Behavioral Neuroscience, 9*(2), 168–172. doi:10.3758/CABN.9.2.168

Homberg, J. R., & Lesch, K.-P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological psychiatry, 69*(6), 513–519. doi:10.1016/j.biopsych.2010.09.024

Hu, X., Lipsky, R., Zhu, G., Akhtar, L., Taubman, J., Greenberg, B., & Goldman, D. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American journal of human genetics, 78*(5), 815–826.

Jedema, H. P., Gianaros, P. J., Greer, P. J., Kerr, D. D., Liu, S., Higley, J. D., & Bradberry, C. W. (2010). Cognitive impact of genetic variation of the serotonin transporter in primates is associated with differences in brain morphology rather than serotonin neurotransmission. *Molecular Psychiatry, 15*(5), 512–522, 446. doi:10.1038/mp.2009.90

Juth, P., Lundqvist, D., Karlsson, A., & Öhman, A. (2005). Looking for Foes and Friends: Perceptual and Emotional Factors When Finding a Face in the Crowd. *Emotion, 5*(4), 379–395. doi:10.1037/1528-3542.5.4.379

Kuepper, Y., Wielpuetz, C., Alexander, N., Mueller, E., Grant, P., & Hennig, J. (2012). 5-HTTLPR S-allele: a genetic plasticity factor regarding the effects of life events on personality? *Genes, brain, and behavior, 11*(6), 643–650. doi:10.1111/j.1601-183X.2012.00783.x

Kwang, T., Wells, T. T., McGeary, J. E., Swann, W. B., & Beevers, C. G. (2010). Association of the serotonin transporter promoter region polymorphism with biased attention for negative word stimuli. *Depression and Anxiety, 27*(8), 746–751. doi:10.1002/da.20708

Lester, K. J., & Eley, T. C. (2013). Therapygenetics: Using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biology of mood & anxiety disorders, 3*(1), 4. doi:10.1186/2045-5380-3-4

Lonsdorf, T. B., Golkar, A., Lindstöm, K., Fransson, P., Schalling, M., Ohman, A., & Ingvar, M. (2011). 5-HTTLPR and COMTval158met genotype gate amygdala reactivity and habituation. *Biological Psychology.* doi:10.1016/j.biopsycho.2011.02.014

Lonsdorf, T. B., Rück, C., Bergström, J., Andersson, G., Ohman, A., Lindefors, N., & Schalling, M. (2010). The COMTval158met polymorphism is associated with symptom relief during exposure-based cognitive-behavioral treatment in panic disorder. *BMC Psychiatry, 10,* 99. doi:10.1186/1471-244X-10-99

Lonsdorf, T., Weike, A., Nikamo, P., Schalling, M., Hamm, A., & Ohman, A. (2009). Genetic Gating of Human Fear Learning and Extinction: Possible Implications for Gene-Environment Interaction in Anxiety Disorder. *Psychological science, 20*(2), 198–206. doi:10.1111/j.1467-9280.2009.02280.x

Lundqvist, D., Flykt, A., & Öhman, A. (1998). The Karolinska Directed Emotional Faces - KDEF, CD ROM from Department of Clinical Neuroscience, Psychology section, Karolinska Institutet, ISBN 91-630-7164-9.

MacLeod, C., & Mathews, A. (2012). Cognitive Bias Modification Approaches to Anxiety. *Annual Review of Clinical Psychology, 8*(1), 189–217. doi:10.1146/annurev-clinpsy-032511-143052

MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology, 95*(1), 15–20.

Mogg, K., & Bradley, B. P. (1999). Some methodological issues in assessing attentional biases for threatening faces in anxiety: a replication study using a modified version of the probe detection task. *Behaviour Research and Therapy, 37*(6), 595–604.

Munafò, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological Psychiatry, 63*(9), 852–857. doi:10.1016/j.biopsych.2007.08.016

Ohman, A., Flykt, A., & Esteves, F. (2001). Emotion drives attention: detecting the snake in the grass. *Journal of experimental psychology. General, 130*(3), 466–478.

Öhman, A., Juth, P., & Lundqvist, D. (2010). Finding the face in a crowd: Relationships between distractor redundancy, target emotion, and target gender. *Cognition & Emotion, 24*(7), 1216. doi:10.1080/02699930903166882

Öhman, A., Lundqvist, D., & Esteves, F. (2001). The face in the crowd revisited: A threat advantage with schematic stimuli. *Journal of Personality and Social Psychology, 80*(3), 381–396. doi:10.1037//0022-3514.80.3.381

Osinsky, R., Reuter, M., Küpper, Y., Schmitz, A., Kozyra, E., Alexander, N., & Hennig, J. (2008). Variation in the serotonin transporter gene modulates selective attention to threat. *Emotion (Washington, D.C.), 8*(4), 584–588. doi:10.1037/a0012826

Pérez-Edgar, K., Bar-Haim, Y., McDermott, J. M., Gorodetsky, E., Hodgkinson, C. A., Goldman, D., & Fox, N. A. (2010). Variations in the serotonin-transporter gene are associated with attention bias patterns to positive and negative emotion faces. *Biological Psychology, 83*(3), 269–271. doi:10.1016/j.biopsycho.2009.08.009

Pergamin-Hight, L., Bakermans-Kranenburg, M. J., Van IJzendoorn, M. H., & Bar-Haim, Y. (2012). Variations in the Promoter Region of the Serotonin Transporter Gene and Biased Attention for Emotional Information: A Meta-Analysis. *Biological Psychiatry, 71*(4), 373–379. doi:10.1016/j.biopsych.2011.10.030

Pinkham, A. E., Griffin, M., Baron, R., Sasson, N. J., & Gur, R. C. (2010). The face in the crowd effect: Anger superiority when using real faces and multiple identities. *Emotion, 10*(1), 141–146. doi:10.1037/a0017387

Pischek-Simpson, L. K., Boschen, M. J., Neumann, D. L., & Waters, A. M. (2009). The development of an attentional bias for angry faces following Pavlovian fear conditioning. *Behaviour Research and Therapy, 47*(4), 322–330. doi:10.1016/j.brat.2009.01.007

Posner, M. I. (1980). Orienting of attention. *The Quarterly journal of experimental psychology, 32*(1), 3–25.

Rasch, B., Spalek, K., Buholzer, S., Luechinger, R., Boesiger, P., De Quervain, D. J.-F., & Papassotiropoulos, A. (2010). Aversive stimuli lead to differential amygdala activation and connectivity patterns depending on catechol-O-methyltransferase Val158Met genotype. *NeuroImage, 52*(4), 1712–1719. doi:10.1016/j.neuroimage.2010.05.054

Rinck, M., Reinecke, A., Ellwart, T., Heuer, K., & Becker, E. S. (2005). Speeded detection and increased distraction in fear of spiders: evidence from eye movements. *Journal of abnormal psychology, 114*(2), 235–248. doi:10.1037/0021-843X.114.2.235

Sen, S., Burmeister, M., & Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American Journal of Medical Genetics, 127B*(1), 85–89. doi:10.1002/ajmg.b.20158

Smolka, M. N., Bühler, M., Schumann, G., Klein, S., Hu, X.-Z., Moayer, M., & Heinz, A. (2007). Gene–gene effects on central processing of aversive stimuli. *Molecular Psychiatry.* doi:10.1038/sj.mp.4001946

Thomason, M. E., Henry, M. L., Paul Hamilton, J., Joormann, J., Pine, D. S., Ernst, M., & Gotlib, I. H. (2010). Neural and behavioral

responses to threatening emotion faces in children as a function of the short allele of the serotonin transporter gene. *Biological Psychology, 85*(1), 38–44. doi:10.1016/j.biopsycho.2010.04.009

Treisman, A. (2006). How the deployment of attention determines what we see. *Visual Cognition, 14*(4–8), 411–443. doi:10.1080/13506280500195250

Treisman, A. M., & Gelade, G. (1980). A feature-integration theory of attention. *Cognitive Psychology, 12*(1), 97–136. doi:10.1016/0010-0285(80)90005-5

Uher, R., & McGuffin, P. (2008). The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Molecular Psychiatry, 13*(2), 131–146. doi:10.1038/sj.mp.4002067

Weinshilboum, R. M., Otterness, D. M., & Szumlanski, C. L. (1999). Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annual Review of Pharmacology and Toxicology, 39,* 19–52. doi:10.1146/annurev.pharmtox.39.1.19

Williams, L. M., Gatt, J. M., Grieve, S. M., Dobson-Stone, C., Paul, R. H., Gordon, E., & Schofield, P. R. (2010). COMT Val(108/158)Met polymorphism effects on emotional brain function and negativity bias. *NeuroImage, 53*(3), 918–925. doi:10.1016/j.neuroimage.2010.01.084

Wolfe, J. M. (1994). Guided Search 2.0 A revised model of visual search. *Psychonomic Bulletin & Review, 1*(2), 202–238. doi:10.3758/BF03200774

Yiend, J. (2010). The effects of emotion on attention: A review of attentional processing of emotional information. *Cognition & Emotion, 24*(1), 3. doi:10.1080/02699930903205698

Yiend, J., & Mathews, A. M. (2004). *Cognition, emotion, and psychopathology: theoretical, empirical, and clinical directions*. Cambridge University Press.