Journal of Abnormal Psychology
2011, Vol. 120, No. 1, 187–197

0021-843X/11/$12.00 DOI: 10.1037/a0022125

Associations Between Serotonin Transporter Gene Promoter Region (5-HTTLPR) Polymorphism and Gaze Bias for Emotional Information

Christopher G. Beevers and C. Nathan Marti
University of Texas at Austin

Han-Joo Lee
University of Wisconsin—Milwaukee

Deborah L. Stote
University of Texas at Austin

Robert E. Ferrell
University of Pittsburgh

Ahmad R. Hariri
Duke University

Michael J. Telch
University of Texas at Austin

The serotonin transporter promoter region polymorphism (5-HTTLPR) is associated with neural response to negative images in brain regions involved in the experience of emotion. However, the behavioral implications of this sensitivity have been studied far less extensively. The current study used eye-tracking methodology to examine how individuals genotyped for the 5-HTTLPR, including the single nucleotide polymorphism (SNP) rs25531, allocated attention during prolonged (30-s) exposure to face stimuli depicting positive and negative emotion. Short 5-HTTLPR allele carriers and carriers of the long allele with guanine at the sixth nucleotide (S/L_G) displayed a stronger gaze bias (total fixation time, number of fixations, mean fixation length) for positive than for sad, threat, or neutral stimuli. In contrast, those homozygous for the long 5-HTTLPR allele with adenine at the sixth nucleotide (L_A) viewed the emotion stimuli in an unbiased fashion. Time course analyses indicated no initial 5-HTTLPR group differences; however, S/L_G 5-HTTLPR allele carriers were more likely than L_A 5-HTTLPR homozygotes to direct gaze toward happy than toward sad stimuli over time. This bias toward positive stimuli during the later stages of information processing likely reflects a strategic effort to downregulate heightened reactivity to negative stimuli among 5-HTTLPR S/L_G allele carriers.

Keywords: eye tracking, emotion processing, cognitive bias, polymorphism, serotonin

Individual differences in the regulation of emotional information are thought to have important consequences for a range of affective states, such as depression and anxiety (Gross & Munoz, 1995). In particular, the ability to allocate attention to emotion cues in the environment is a crucial element of effective self-regulation (Posner & Rothbart, 2000). Although it is adaptive to attend to salient stimuli, successful regulation requires flexibility and cognitive control over emotional information. This includes strategic filtering of stimuli, timely disengagement from stimuli, and being appropriately vigilant for meaningful emotional cues. In line with this conclusion, Hasler, Drevets, Manji, and Charney (2004) argued that biased processing of emotional stimuli is a plausible putative intermediate phenotype. Further, they specifically identified the serotonin transporter linked polymorphic region (5-HTTLPR) polymorphism as a promising candidate gene that may be associated with biased processing of emotional information (see Figure 1 of Hasler et al., 2004, p. 1766).

The serotonin transporter (5-HTT) plays an important role in the regulation of emotion-related behavior by mediating the active clearance of extracellular serotonin and thereby influencing the duration and intensity of serotonin signaling via pre- and postsynaptic receptors located on target neurons of an affective corticolimbic circuitry (for a review, see Hariri & Holmes, 2006). The efficiency with which the 5-HTT returns serotonin to the presynaptic neuron appears to be influenced by a common variable number tandem repeat polymorphism in the proximal gene promoter (i.e., the 5-HTT linked polymorphic region, or 5-HTTLPR). The 5-HTTLPR is most commonly represented by two variants: a

This article was published Online First January 10, 2011.

Christopher G. Beevers, Deborah L. Stote, and Michael J. Telch, Department of Psychology, University of Texas at Austin; C. Nathan Marti, Division of Statistics and Scientific Computation, University of Texas at Austin; Han-Joo Lee, Department of Psychology, University of Wisconsin—Milwaukee; Robert E. Ferrell, Department of Human Genetics, University of Pittsburgh; Ahmad R. Hariri, Department of Psychology and Neuroscience, Duke University.

This research was supported by the U.S. Army Research, Development & Engineering Command Acquisition Center, Natick Contracting Division, and U.S. Defense Advanced Research Projects Agency under Contract No. W911QY-07-C-0002 awarded to Michael J. Telch. We thank Brian Baldwin, the research assistants, and the soldier volunteers for their invaluable contributions to this project.

The views expressed in this publication are those of the authors and may not necessarily be endorsed by the U.S. Army.

Correspondence concerning this article should be addressed to Christopher G. Beevers, Department of Psychology, University of Texas at Austin, 1 University Station, A8000, Austin, TX 78712. E-mail: beevers@psy.utexas.edu

short (S) allele and a long (L) allele. The presence of one or two S alleles, rather than two copies of the L allele, may be associated with reduced transcriptional efficiency that putatively results in significant decreases (approximately 50%) in serotonin reuptake (Heinz et al., 2000; Lesch et al., 1996). Further, it has recently been suggested that 5-HTTLPR gene expression may be modulated by an additional single-nucleotide polymorphism (SNP), namely, rs25531, which is composed of an adenine to guanine change at the sixth nucleotide in the first of two extra 20- to 23-base-pair repeats of the L allele (Wendland, Martin, Kruse, Lesch, & Murphy, 2006). It is important to note that the L allele with guanine at the sixth nucleotide (L_G) and the S allele are similar in terms of transcriptional activity; therefore, only the L allele with adenine at the sixth nucleotide (L_A) is associated with relatively increased transcriptional activity (Hu et al., 2005).

Consistent with the modulatory effects of 5-HT on emotional responses, the 5-HTTLPR appears to influence a corticolimbic circuit that is critical for regulating emotional arousal. For instance, among healthy participants, studies have consistently shown that S/L_G 5-HTTLPR carriers have greater amygdala reactivity to negative stimuli, such as angry or fearful facial expressions, compared with individuals homozygous for the L_A allele (for a meta-analysis, see Munafò, Brown, & Hariri, 2008). In addition, S/L_G allele carriers exhibit altered functional coupling between the amygdala and regions of the medial prefrontal cortex involved in the integration and regulation of amygdala mediated arousal (Heinz et al., 2005; Pezawas et al., 2005). Thus, altered corticolimbic function may partly account for the greater amygdala reactivity to negative stimuli observed in S/L_G allele carriers (see also Pacheco et al., 2009).

This evidence indicates that S/L_G 5-HTTLPR allele carriers are more sensitive to negative emotion cues at a neural level than are L_A allele homozygotes. This finding is also consistent with a recent review suggesting that low serotonergic function, which is putatively associated with the S/L_G 5-HTTLPR allele, disinhibits reactivity to the environment—particularly for emotional cues (Carver, Johnson, & Joormann, 2008). Increased reactivity to negative emotion cues may therefore influence how S/L_G 5-HTTLPR allele carriers process negative stimuli compared with homozygous L_A 5-HTTLPR individuals.

Consistent with this possibility, S 5-HTTLPR allele carriers display biased attention for anxious-relevant words when paired with neutral words (for 14 ms or 750 ms) compared with those homozygous for the L allele (Beevers, Gibb, McGeary, & Miller, 2007). Similarly, S allele carriers displayed biased attention toward images of phylogenetic fear-relevant stimuli (i.e., spiders) presented for 2,000 ms in comparison with L allele homozygotes (Osinsky et al., 2008). Individuals homozygous for the S/L_G 5-HTTLPR allele also experience more difficulty disengaging attention from negative and positive stimuli than do individuals homozygous for the L_A 5-HTTLPR allele (Beevers, Wells, Ellis, & McGeary, 2009). Number of S/L_G 5-HTTLPR alleles has been positively associated with biased attention for angry faces and inversely associated with biased attention for happy faces among adolescents (Pérez-Edgar et al., 2010). Similarly, S 5-HTTLPR allele carriers may lack an attentional bias for positive information presented for 500 ms that is found in individuals homozygous for the L allele (Fox, Ridgewell, & Ashwin, 2009). In general, these studies are consistent with the idea that S/L_G 5-HTTLPR allele carriers are more biologically sensitive to negative stimuli and therefore display biased attention for such stimuli at early stages (e.g., $<$2,000 ms) of attentional processing.

Although these results are very intriguing, this prior work provides a somewhat incomplete picture of how emotional stimuli are processed over time. Current cognitive models emphasize two modes of processing (Beevers, 2005; Carver et al., 2008). The first, a more primitive mode, is an automatic (or associative) mode of processing where individuals quickly process information, require few limited-capacity cognitive resources, and can initiate action under time pressure. This mode of processing is closely linked to reactivity to stimuli. The second mode is more deliberative (or reflective), occurs over a longer time course, and requires more limited-capacity cognitive resources to implement strategic or rule-based processing. This mode of processing is more closely linked with effortful regulation of stimuli.

There are several examples of how these dual modes may contribute to biased processing of negative stimuli (e.g., Hermans, Vansteenwegen, & Eelen, 1999). For instance, individuals with spider phobia initially attend to images of spiders and then subsequently shift attention away from such stimuli (Rinck & Becker, 2006). This likely reflects an automatic bias to initially react to and then strategically avoid phobia-relevant stimuli. In contrast, depressed individuals do not automatically orient to dysphoric stimuli but instead display gaze biases toward sad stimuli and away from positive stimuli in later stages of processing (Kellough, Beevers, Ellis, & Wells, 2008). This may reflect the deficient deliberative or effortful processing often associated with depression (Hartlage, Alloy, Vázquez, & Dykman, 1993).

Despite this distinction between automatic and effortful processing, most behavioral studies of biased attention and the 5-HTTLPR polymorphism have studied relatively automatic processing of negative stimuli. One prior study has examined associations between the 5-HTTLPR polymorphism and biased processing of emotion stimuli in a paradigm that allows for strategic processing. This small study of healthy control participants, which tracked eye movements to obtain a relatively continuous index of information processing (cf. Hermans et al., 1999; Isaacowitz, 2006), presented a 2 $\times$ 2 matrix of positive and negative images simultaneously for 30 s (Beevers, Ellis, Wells, & McGeary, 2010). S 5-HTTLPR allele homozygotes selectively attended to positive emotion scenes to a greater extent than to threatening, neutral, or dysphoric images. This bias was not evident in the first 5 s but instead emerged in the later stages of processing (i.e., at 5–20 s). Thus, this pattern likely reflects biased strategic processing of emotion stimuli—S 5-HTTLPR allele homozygotes (with no current psychopathology) in which such individuals may initially view all emotional content and then strategically shift attention toward positive stimuli in an effort to regulate heightened reactivity to negative stimuli. Consistent with this possibility, young adults who were instructed to regulate emotions while viewing similar stimuli viewed negative stimuli less often than did participants in a control condition (Xing & Isaacowitz, 2006).

Although this initial study of the 5-HTTLPR polymorphism and prolonged processing of emotion cues is intriguing, it has impor-

tant limitations. First, Beevers et al. (2010) only examined associations between time course and biased attention for positive stimuli. It is important to determine whether S 5-HTTLPR allele carriers selectively attend to positive stimuli compared with other stimuli over time. Doing so would demonstrate the specificity of this bias. In the absence of such a test, it remains possible that S 5-HTTLPR allele homozygotes display a similar gaze bias over time for all emotion stimuli. To address this alternative explanation, we used a multinomial linear growth curve model to directly assess whether 5-HTTLPR status is associated with greater probability of viewing positive stimuli relative to other stimuli over time.

A second important limitation is that although it is well accepted that 5-HTTLPR allele frequencies differ across races (Gelernter, Kranzler, & Cubells, 1997), there is emerging evidence indicating that the 5-HTTLPR polymorphism may function differently across racial groups. For instance, amygdala response to angry faces is greater in L 5-HTTLPR allele carriers than in S allele homozygotes among Korean women (Lee & Ham, 2008); the reverse pattern is typically observed in Caucasian samples (Munafò, Brown, & Hariri, 2008). Among African Americans, S 5-HTTLPR allele carriers reported lower neuroticism than did L 5-HTTLPR allele homozygotes, but the opposite pattern was observed among Caucasians (Gelernter, Kranzler, Coccaro, Siever, & New, 1998). Other research reports that associations among the 5-HTTLPR polymorphism, depression, and anxiety differ across cultures (Chiao & Blizinsky, 2010). Thus, it is important to examine whether race/ethnicity moderates the association between the 5-HTTLPR polymorphism and emotion processing. Beevers et al. (2010) did not perform this analysis; thus, it is possible that effects within one race/ethnicity are primarily responsible for observed associations. The absence of this analysis could contribute to the development of an overgeneralized model of 5-HTTLPR and emotion processing (cf. Greenwald, Pratkanis, Leippe, & Baumgardner, 1986).

Finally, conceptual replication is critically important for genetic association studies, as nonreplication of initial genetic associations is often observed (Ioannidis, Ntzani, Trikalinos, & Contopoulos-Ioannidis, 2001; Munafò, Durrant, Lewis, & Flint, 2008). Further, in the current study, stimuli are more tightly controlled (i.e., emotional facial expressions from the same actor vs. a variety of emotional scenes), data analyses are more comprehensive, and sample size is much larger compared with Beevers et al. (2010). Consistent results across studies would suggest that significant associations between 5-HTTLPR and processing of emotion stimuli are not attributable to a particular set of stimuli, participant population, or data-analytic approach. More importantly, observing similar effects across independent samples heightens confidence that results represent reliable effects.

The current study presented emotional stimuli (i.e., a 2 × 2 matrix of faces depicting sad, frightened, happy, and neutral emotional expressions) for 30 s while line of visual gaze was measured. Participants were instructed to look freely at the images with no constraints, as if they were watching television or viewing images in a photo album. These instructions encouraged naturalistic information processing, as in other eye-tracking studies (Isaacowitz, 2006). Consistent with previous research (Beevers et al., 2010), we expected that S/L_G 5-HTTLPR carriers would strategically view positive stimuli to a greater extent than would L_A homozygotes in an effort to decrease heightened negative affect elicited by the negative stimuli. Thus, we expected S/L_G 5-HTTLPR carriers, in comparison with LA 5-HTTLPR homozygotes, to have more fixations and more total fixation time directed toward positive images. Further, we hypothesized that a gaze bias for positive compared with negative stimuli would become stronger over time for S/L_G 5-HTTLPR carriers in comparison with L_A 5-HTTLPR allele homozygotes.

Method

Participants

Participants were selected from a pool of 178 soldiers with no prior exposure to a war zone environment scheduled for deployment to Iraq from Fort Hood. They were all unpaid volunteers from a larger, longitudinal study examining risk factors for combat-related posttraumatic stress disorder. Twenty participants were excluded because they were currently experiencing one of the following psychiatric disorders listed in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [*DSM–IV*]; American Psychiatric Association, 1994): major depressive disorder, generalized anxiety disorder, social phobia, obsessive–compulsive disorder, dysthymic disorder, or adjustment disorder with anxiety. Participants were required to complete at least seven of the eight eye-tracking trials with adequate eye-tracking data (i.e., 60% or more data points available); 18 (10%) participants were excluded because of difficulty obtaining eye-tracking data (e.g., excessive blinking, droopy eyelids that obscured the pupil, ocular abnormalities that interfered with eye tracking), which is typical for eye-tracking studies.

The 140 participants that remained after exclusions produced the following race/ethnicity distribution: 25 Hispanic (17.9%); 12 African American or Black (8.6%); six American Indian or Alaska Native (4.3%); four Asian, Native Hawaiian, or other Pacific Islander (2.9%); three other (2.1%); and 90 Caucasian (64.3%). As indicated above, it is important to determine whether race moderates the association between 5-HTTLPR and gaze bias before determining the final sample. Analyses indicated that race/ethnicity indeed moderated the 5-HTTLPR Genotype × Stimulus category interaction for predicting total fixation time, $F(3, 4217) = 3.60$, $p < .001$. As reported below, the interaction between 5-HTTLPR and stimulus emotion category for predicting total fixation time was significant among Caucasian participants ($p < .001$). In contrast, this same interaction was not significant for non-Caucasian participants ($p > .25$).

In light of this interaction, the strong possibility that the 5-HTTLPR might function differently within each race group, and an insufficient number of minority group participants within each allele group (e.g., among Hispanic participants, the largest minority group in this sample, three individuals had the L_AL_A genotype), we decided to analyze only Caucasian participants. Thus, the final sample consisted of Caucasian participants ($N = 90$). Most participants were male (94%) with a high school education (48%) or greater (34% some college, 7% college degree) and a mean age of 23.15 years ($SD = 5.6$). It is

important to note that results from the current study should not be generalized to non-Caucasians.

Diagnostic Assessment

Axis I *DSM–IV* psychiatric disorders were assessed with the Structured Clinical Interview for the *DSM–IV* Diagnoses—Patient Edition (SCID–I/P; First, Spitzer, Gibbon, & Williams, 1998). Assessors were advanced doctoral students in clinical psychology who participated in 15 hr of training, wherein they practiced interview skills, reviewed diagnostic criteria for relevant disorders in the *DSM–IV*, observed mock interviews, and role played interviews. At the time of each SCID–I/P interview, a senior investigator with extensive experience (Michael J. Telch) in using the SCID–I/P interview was available to consult with interviewers. Any uncertainty concerning a diagnosis was discussed immediately following the SCID–I/P interview, and a consensus diagnosis was determined on a case-by-case basis. The SCID–I/P interview was used to determine participants' current and past psychiatric history.

DNA Collection

Saliva was collected with the Oragene DNA self-collection kit following the manufacturer's instructions (DNA Genotek, 2004b, 2006). Participants were instructed to rub their tongues around the inside of their mouth for about 15 s and to then deposit approximately 2 ml of saliva into the collection cup. Once saliva reached the 2-ml guides on the inside of the cup, participants secured the cap firmly by screwing the cap clockwise until snug. The vial is designed so that once it is securely fastened, solution from the lower compartment is released and mixes with the saliva. This starts the initial phase of DNA isolation and stabilizes the saliva sample for long-term storage at room temperature (Rogers, Cole, Lan, & Crossa, 2007). Saliva samples were stored at room temperature and shipped to the University of Pittsburgh for DNA extraction.

Genotyping

A triplex polymerase chain reaction (PCR) protocol followed by double restriction endonuclease digestion was used to identify the 5-HTTLPR and rs25531 variants: S, L_A, and L_G (Wendland et al., 2006). In a total volume of 20 μl, 25 ng of genomic DNA were amplified in 1 × Multiplex master mix (Qiagen, Valencia, CA) primers at final concentrations of 200 nM. The primer sequences were the following: forward, 5′-TCCTCCGCTTTGGCGCCTCTTCC-3′, and reverse, 5′-TGGGGGTTGCAGGGGAGATCCTG-3′ (T = thymine; C = cytosine; G = guanine; A = adenine). Thermal cycling involved 15 min of initial denaturation at 95 °C followed by 35 cycles at 94 °C for 30 s, 62 °C for 90 s, and 72 °C for 60 s. This was followed by thermal cycling at 72 °C for 10 min. To distinguish the A/G SNP of the rs25531, we extracted 7 μl of the PCR product for digestion by 5 U *Hpa*II (an isoschizomer of *Msp*I) or 10 U *Msp*I, for a total reaction of 17 μl. These were loaded side by side on 2.5%–3.0% agarose gel.

These methods produced allele frequencies of S, $n = 59$ (41.7%); L_A, $n = 92$ (54.6%); and L_G, $n = 4$ (3.5%), and a genotype distribution of SS, $n = 8$ (8.8%); SL_G, $n = 2$ (2.2%); L_GL_G, $n = 0$ (0%); SL_A, $n = 46$ (51.1%); L_GL_A, $n = 2$ (2.2%); and L_AL_A, $n = 32$ (35.5%). Genotype distribution was in Hardy–Weinberg equilibrium, $\chi^2(3, N = 90) = 0.67$, $p = .85$. Consistent with previous research (Hu et al., 2005; Zalsman et al., 2006), the S and L_G alleles were treated as equivalent for purposes of analysis. For total time spent viewing happy faces, comparisons revealed no differences between SS and SL_G groups, $t(8) = 0.65$, $p = .26$, partial $\eta^2 = .00$, or between SL_A and L_GL_A groups, $t(46) = 0.75$, $p = .77$, partial $\eta^2 = .00$, suggesting that it is appropriate to treat the S and L_G allele groups as equivalent.

Eye-Tracking Paradigm

The task for the eye-tracking paradigm involved simultaneous presentation of four images selected from the Pictures of Facial Affect photo set developed by Ekman and Friesen (1976). Stimuli were photographs of faces from 12 different actors split evenly by gender. These photo stimuli are standardized and have been used extensively for this purpose. For the current task, four facial expressions from the same actor were presented simultaneously in each quadrant of visual field (for an example, see Figure 1). Happy, sad, fearful, and neutral facial expressions were randomly assigned for each participant to each quadrant with the constraint that facial expressions from each emotion category be presented in each quadrant with equal frequency.

Eight critical trials were presented with happy, sad, fearful, and neutral facial expressions in a new random order for each participant. Four filler trials were also included to obscure the critical trials from participants. Each filler trial contained four facial expressions: three from previously unseen emotion categories (disgust, surprise, anger) and one from a previously seen emotion category (happy, sad, fearful, neutral). In each trial, filler stimuli were randomly assigned to screen quadrants without constraint. Order of filler and critical trials was randomly determined for each participant.

Each trial began with a centrally presented fixation cross, followed by presentation of face stimuli for 30 s. The experimenter initiated each trial after determining that participant's fixation was within 1° of visual angle of the fixation cross. If fixation was not within 1° of visual angle of the fixation cross, small adjustments to calibration were made. Given that this paradigm was brief, calibration adjustments were typically unnecessary.

Line of visual gaze was assessed with a remote optics eye-tracking system, Model R6 from Applied Science Laboratories (Bedford, MA). Head location was fixed with a chin rest and a forehead bar. The direction of gaze, measured with *x* and *y* coordinates, was sampled every 16.7 ms (60 Hz). This resulted in 1,796 gaze location measurements for each 30-s trial. Eye movements that were stable for more than 100 ms within 1° of visual angle were classified as a fixation. Areas of interest were also identified for each trial and corresponded with the total area for each of the four images. Thus, it was possible to determine total time spent viewing each of the four images during each trial, how viewing patterns changed over time, and location of first fixation. We used E-Prime software (Psychology Software Tools; Pittsburgh, PA) to present stimuli and to automate the recording of eye location with the eye tracker software.

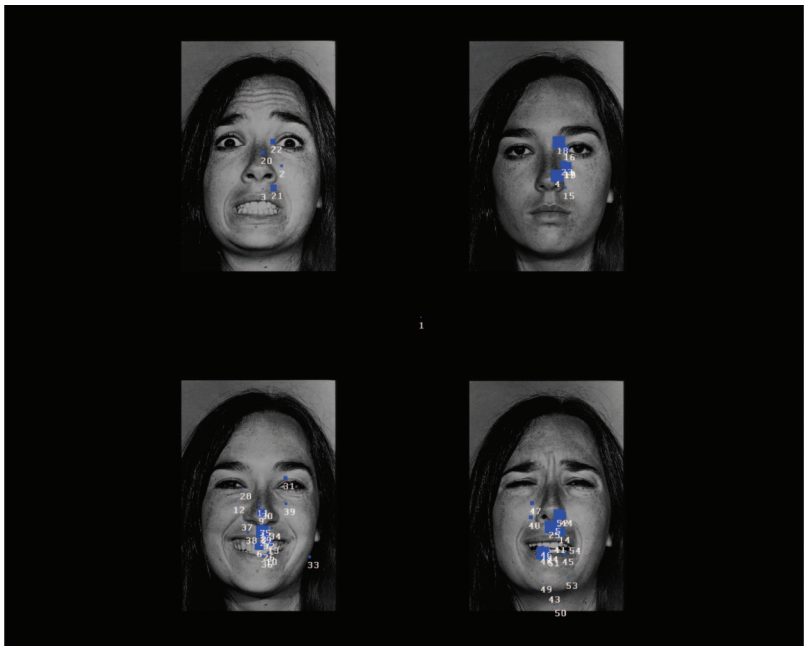

Figure 1. Example of stimuli used in this study. Participants' fixations from this trial are superimposed on the image. Larger diameter of fixations indicates longer fixation duration. Numbers next to each fixation indicate the sequence in which fixations occurred. Facial images are from the Pictures of Facial Affect database. Copyright 1976 by the Paul Ekman Group LLC. Reproduced with permission.

Procedure

After completing informed consent, participants completed a demographics form, the SCID–I/P, and provided buccal cells for genotyping. Each participant was then escorted to the eye-tracking room and seated in a height-adjustable chair so that the participant's chin fit comfortably in the chin rest. The chin rest was positioned so that the participant's eyes were level with the middle of the 17-in. (43.2-cm) monitor on which the stimuli were presented. This ensured that all participants' eyes were in the same location relative to the camera and the monitor. After the eye tracker was adjusted to best capture each participant's right eye, a 9-point calibration was completed. Once calibration was complete, the experimenter confirmed that the eye tracker was recording line of visual gaze within 1° of visual angle for each calibration point. Calibration was repeated until this criterion was met.

Once calibration was successful, participants were informed that the task would begin shortly and that all instructions would be presented on the computer screen. Participants were instructed to view images naturally, as if they were watching television or viewing photos in a photo album. They were also instructed to view whatever seemed interesting. The only constraint was that they were to view images at all times during each trial. They were also instructed to look at the fixation cross prior to each trial in order to standardize location of participants' gaze. The experimenter (located in the same room but outside of the participant's visual field) monitored stimulus presentation and eye tracking throughout the experiment.

Analytic Plan

Our analyses focused on five outcomes: (a) total fixation time for each stimulus category, (b) average number of fixations per category, (c) average fixation duration per category, (d) location of first fixation, and (e) change in probability of viewing each stimulus category over time. We used SAS PROC MIXED for analyses of fixation time for each stimulus category, average number of fixations per category, and average fixation duration per category, which implements restricted maximum likelihood and allows for uneven observations across participants, thus allowing us to use all available data. All models contained a genotype factor, a stimulus category factor, and a genotype by stimulus category interaction; trials were nested within participants, and intercepts were treated as random effects. Total fixation time was examined by summing duration of all fixations for each stimulus category within each trial. Average number of fixations per category was examined by computing total number of fixations for each stimulus category within each trial. Average fixation duration was examined by computing average duration of all fixations for each stimulus category within each trial.

We analyzed location of first fixation using multinomial mixed models implemented with the SAS procedure PROC GLIMMIX, which accommodates correlated data for nonnormally distributed outcomes. The procedure produces F tests for fixed factors and regression parameters, which were useful for evaluating variables with multiple levels. Multinomial outcomes represent preferences of response category relative to a reference response category.

To model change in probability of viewing stimuli from each category over time, we implemented a generalized linear mixed

model with the SAS procedure PROC GLIMMIX. Location of fixation at a given point in time was modeled with a multinomial distribution with a generalized logit link function. Multinomial outcomes represent preferences of response category relative to a reference category. We selected the happy expression as the reference category because preferences relative to the happy expression were involved in all of our hypotheses.

We first conducted a preliminary analysis examining whether we could collapse theoretically similar genetic groups (i.e., form an S/L_G carrier group). Thus, we compared whether individuals with two of the S/L_G 5-HTTLPR variants had similar results to those with one S/L_G allele. Groups were collapsed only when no statistically significant differences were observed between groups.

Results

Collapsing Across 5-HTTLPR Groups

We evaluated the possibility of collapsing the group of individuals having two S/L_G 5-HTTLPR alleles with the group of individuals having one S/L_G 5-HTTLPR allele in a model limited to these two groups where total fixation time per stimulus category was the outcome and 5-HTTLPR allele group, stimulus category, and the interaction between 5-HTTLPR genotype and stimulus category were independent variables. The interactions were the critical terms of interest, and these were used to determine whether there was sufficient similarity between allele groups. The stimulus category by 5-HTTLPR allele group interaction term was not significant, $F(3, 1744) = 0.33$, $p = .80$; thus, we treated the S/L_G 5-HTTLPR carriers as a single category in subsequent models and compared them with individuals homozygous for L_A 5-HTTLPR.

Total Fixation Time

Analyses indicated significant stimulus category, $F(3, 2738) = 40.12$, $p < .001$, and 5-HTTLPR Genotype × Stimulus Category effects, $F(3, 2738) = 9.30$, $p < .001$, but no main effect for 5-HTTLPR genotype, $F(2, 2738) = 2.72$, $p = .099$. Descriptive statistics are presented in Table 1. To ensure that the interaction captured effects of theoretical interest, we constructed a contrast between happy stimuli and all other facial expressions within each allele group. For S/L_G 5-HTTLPR carriers, the contrast represented significantly longer total fixation times for happy faces compared with all others, $t(2738) = 10.45$, $p < .001$. However, this contrast was not significant among the L_AL_A 5-HTTLPR allele homozygotes, $t(2738) = 1.53$, $p = .12$. Follow-up analyses also revealed that S/L_G 5-HTTLPR carriers had significantly fewer fixations relative to L_AL_A 5-HTTLPR homozygotes, for fearful, $t(2738) = 3.04$, $p = .002$; neutral, $t(2738) = 4.36$, $p < .001$; and sad, $t(2738) = 4.77$, $p < .001$ expressions relative to happy expressions (see Table 1). These analyses indicate that S/L_G 5-HTTLPR carriers display a clear bias for happy facial expressions relative to L_A 5-HTTLPR homozygotes.

Number of Fixations Per Stimulus Category

Results indicated significant stimulus category, $F(3, 2738) = 26.34$, $p < .001$, and 5-HTTLPR Genotype × Stimulus Category effects, $F(3, 2738) = 5.32$, $p < .001$, but no main effect for 5-HTTLPR genotype, $F(3, 2738) = 0.77$, $p = .38$. Descriptive statistics are presented in Table 1. Contrasts comparing happy versus all other facial expressions within each allele group indicated that S/L_G 5-HTTLPR carriers had significantly more fixations for the happy faces, $t(2738) = 8.12$, $p < .001$. However, this contrast was not significant among the L_A 5-HTTLPR homozygotes, $t(2738) = 1.49$, $p = .13$. Further, follow-up analyses also revealed that S/L_G 5-HTTLPR carriers had significantly fewer fixations relative to L_A 5-HTTLPR homozygotes, for fearful, $t(2738) = 1.97$, $p = .049$; neutral, $t(2738) = 3.36$, $p < .001$; and sad, $t(2738) = 4.52$, $p < .001$, expressions relative to happy expressions (see Table 1). These analyses indicate that S/L_G 5-HTTLPR carriers compared with L_A 5-HTTLPR homozygotes had significantly more fixations for happy facial expressions.

Average Fixation Duration

Results indicated that there were significant stimulus category, $F(3, 2738) = 19.85$, $p < .001$, and 5-HTTLPR Genotype × Stimulus Category, $F(3, 2738) = 4.26$, $p = .005$, effects but no significant main effect for 5-HTTLPR genotype, $F(3, 2738) = 3.61$, $p = .058$. Descriptive statistics are presented in Table 1. Contrasts comparing happy versus all other facial expressions within each allele group indicated that the S/L_G 5-HTTLPR carriers exhibited significantly longer fixation durations for happy expressions relative to other facial expressions, $t(2738) = 7.41$, $p < .001$. However, this contrast was not significant among the L_A 5-HTTLPR homozygotes, $t(2738) = 1.22$, $p = .22$. Follow-up analyses also revealed that S/L_G 5-HTTLPR carriers had signifi-

Table 1
Means (and Standard Deviations) for Total Fixation Time, Average Number of Fixations, Glance Duration, and Percentage of First Fixation for Each Stimulus Category Presented by 5-HTTLPR Polymorphism

Stimulus category	Fixation time (s)		Fixations (count)		Fixation duration (s)		First fixation (% of total)	
	S/L_G	L_AL_A	S/L_G	L_AL_A	S/L_G	L_AL_A	S/L_G	L_AL_A
Happy	7.63 (5.75)	5.89 (4.23)	14.13 (7.47)	13.05 (7.52)	0.55 (0.36)	0.45 (0.20)	25%	27%
Neutral	5.33 (4.04)	5.60 (3.89)	11.16 (6.44)	12.44 (6.21)	0.47 (0.22)	0.45 (0.19)	24%	25%
Sad	4.80 (3.16)	5.27 (3.75)	10.71 (6.19)	12.10 (6.33)	0.44 (0.17)	0.43 (0.18)	26%	22%
Fear	5.72 (3.98)	5.38 (3.87)	12.20 (6.81)	12.53 (6.96)	0.47 (0.21)	0.43 (0.18)	26%	26%

Note. S = short allele; L_G = long allele with guanine at the sixth nucleotide; L_A = long allele with adenine at the sixth nucleotide.

cantly shorter fixation duration times, relative to L_A 5-HTTLPR homozygotes, for fearful, $t(2738) = 2.17$, $p = .030$; neutral, $t(2738) = 2.97$, $p = .003$; and sad, $t(2738) = 3.21$, $p = .001$, expressions relative to happy expressions (see Table 1). These analyses indicate that S/L_G 5-HTTLPR carriers, relative to L_A 5-HTTLPR homozygotes, had significantly longer fixations when viewing happy facial expressions.

Location of First Fixation

Given that stimulus category served as the dependent variable in this analysis and that there was no time effect (i.e., we were only interested in the first fixation), we examined whether 5-HTTLPR genotype predicted location of first fixation. The 5-HTTLPR genotype was not associated with location of first fixation, $F(4, 443) = .30$, $p = .914$. Descriptive statistics are presented in Table 1.

Change in Probability of Viewing an Emotion Category Over Time

In this phase of analysis, our goal was to understand change across time and to fit a model that represented that change. We evaluated change in fixation location for each emotion expression as a function of time in an unconditional growth model that consisted of linear and quadratic terms. The purpose of this analysis was to evaluate nonlinearity in fixations across time so that we could account for nonlinearity in the model should it be present. The time terms provided evidence for a quadratic relationship between time of fixation and participants' preference for a putative facial expression: The linear term was a significant predictor of expression preference, $F(3, 49894) = 6.35$, $p < .001$, as was the quadratic term, $F(3, 49894) = 3.16$, $p = .024$.

Because our principal analysis involved interactions between time and genotype, it was critical that time terms be independently interpretable. Thus, we considered a piecewise model. To determine the point at which the relationship between the slope and the dependent variable changed, we graphed predicted values from quadratic models. After visual inspection, we interpreted the pattern to consist of rapid initial change, which likely represents a familiarization phase, followed by steady increasing preferences for particular stimuli. Thus, we constructed a piecewise model that allowed for separating rates of change for distinct time periods in the model. This method facilitates modeling interactions between time and person-level variables (such as genotype), as slope coefficients represent a linear relationship between outcome and time within each time period.

We thus fit a piecewise model that treated time as two pieces: The first piece represented a linear term in the first 5 s of the trial, and the second represented the linear term in the last 25 s of the trial. We then confirmed that the two linear slopes in the piecewise model accounted for the overall quadratic effect. Quadratic effects are characterized by a single curve; by modeling time as two distinct pieces, the first piece represented change prior to the curvature and the second piece represented change subsequent to the curvature. We confirmed that the two time periods were linear by fitting linear and quadratic models to each time period individually. For the initial piece, neither the linear term, $F(3, 7996) = 0.55$, $p = .648$, nor the quadratic term, $F(3, 7996) = 1.13$, $p = .283$, was a significant predictor of expression preference in the quadratic model; however, the linear term alone was a significant predictor in a linear time model, $F(3, 7999) = 3.05$, $p = .026$. For the second piece, neither the linear term, $F(3, 38592) = 0.70$, $p = .550$, nor the quadratic term, $F(3, 38592) = 0.47$, $p = .702$, was a significant predictor of expression preference in the quadratic model; however, the linear term was a significant predictor in a linear time model, $F(3, 38595) = 10.01$, $p < .001$. As there was no evidence of nonlinearity within each time period and the linear models were significant for each time period, we determined that the overall quadratic effect was adequately captured by a linear parameter in each time period. On the basis of this sequence, we treated time in all subsequent models as piecewise, in which Time Piece 1 consisted of the first 5 s of each trial and Time Piece 2 consisted of the last 25 s of each trial.

Significant effects were observed for Time Piece 1, $F(3, 32473) = 4.24$, $p = .005$; Time Piece 2, $F(3, 32473) = 4.38$, $p = .004$; and the interaction between Time Piece 2 and the 5-HTTLPR genotype, $F(3, 32473) = 3.23$, $p = .02$. No significant effects were observed for 5-HTTLPR, $F(2, 32473) = .93$, $p = .45$, or for the interaction between Time Piece 1 and 5-HTTLPR, $F(3, 32473) = 1.72$, $p = .16$. To follow up the main effect for Time Piece 1, we performed regression parameters contrasting fixations for happy stimuli with each of the other emotion categories. Analyses indicated that participants were significantly less likely to view fearful expressions relative to happy expressions across the first 5 s of each trial, $t(32473) = 2.50$, $p = .01$. Follow up of the significant interaction between 5-HTTLPR allele groups and Time Piece 2 indicated that S/L_G 5-HTTLPR carriers, relative to L_A 5-HTTLPR homozygotes, exhibited an increasing preference for happy expressions relative to sad expressions across time, $t(32473) = 3.01$, $p = .003$. There were no significant genotype differences for preferences for threat or neutral faces relative to happy faces across time (see Figure 2).

Discussion

The current study examined whether the 5-HTTLPR polymorphism was associated with biased processing of emotional stimuli by assessing line of visual gaze with eye-tracking methodology. 5-HTTLPR S/L_G allele carriers were significantly more likely than L_A homozygotes to view stimuli depicting positive facial expressions. This pattern was evident in total fixation time, number of fixations, and average fixation duration. Further, S/L_G allele carriers were more likely to view happy than sad facial expressions over time compared with L_A homozygotes. Thus, visual gaze of S/L_G allele carriers was measurably responsive to the emotional content of the stimuli, whereas L_A homozygotes did not differ in time spent viewing positive versus all other stimuli.

Although previous research indicates that S/L_G 5-HTTLPR allele carriers show a bias toward negative stimuli (Beevers et al., 2007; Osinsky et al., 2008; Pérez-Edgar et al., 2010) and may lack a bias toward positive stimuli (Fox et al., 2009), this previous research has examined biases in the early stages of information processing. Consistent with this behavioral work, there is also substantial evidence that faces depicting negative expressions produce greater neural reactivity in brain regions involved in the experience of emotion among S/L_G 5-HTTLPR allele carriers (for a review, see Hariri & Holmes, 2006; Hariri et al., 2002). Thus, the

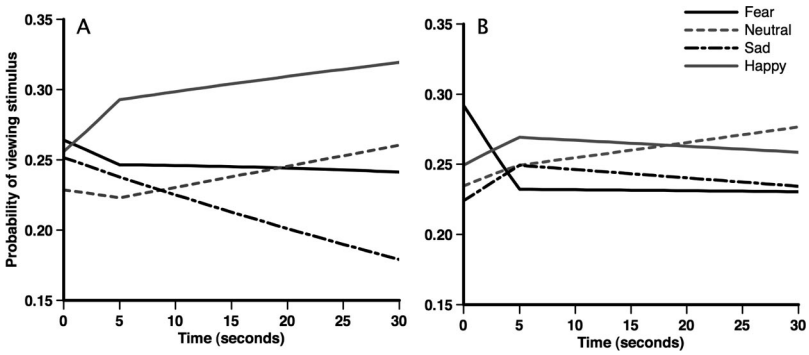

Figure 2. Mean probability of fixation occurring within each stimulus category over time presented by serotonin transporter gene promoter region (5-HTTLPR) polymorphism groups: (A) results for S/L_G (short allele/long allele with guanine at the sixth nucleotide) 5-HTTLPR carriers; (B) results for L_A (long allele with adenine at the sixth nucleotide) 5-HTTLPR homozygotes.

observed bias toward positive stimuli during the later stages of information processing likely reflects a strategic effort to down-regulate heightened reactivity to negative stimuli among 5-HTTLPR S/L_G allele carriers. L_A 5-HTTLPR allele homozygotes, in contrast, may be less reactive to emotional stimuli and therefore less compelled to regulate visual attention by subsequently attending to positive stimuli.

Consistent with this possibility, analyses revealed two distinct patterns of information processing during the course of a 30-s trial. A piecewise model that treated the first 5 s as distinct from the subsequent 25 s provided a good fit for the data. This piecewise model likely reflects visual scanning of stimuli during the first 5 s followed by a period of attention regulation. That is, individuals likely scanned all images initially, with a general tendency to avoid faces depicting fear. This initial tendency to avoid fearful faces is likely driven by the amygdala (Thomas et al., 2001); thus, we might have expected an exaggerated response in S/L_G carriers (cf. Osinsky et al., 2008). However, 5 s may be too long a period within which to observe an attentional bias for fear stimuli that is associated with 5-HTTLPR status, as most previous work observed biases 500 to 2000 ms after stimulus onset (Fox et al., 2009; Osinsky et al., 2008). Further, our eye gaze assessment only measured overt shifts of attention. It may be that early biases for aversive stimuli are best captured by methodologies that capture covert shifts of attention (Bradley, Mogg, & Millar, 2000).

Nevertheless, 5-HTTLPR genotype effects did emerge in the latter stages of information processing, which likely reflects effortful regulation of attention by prefrontal brain regions. During this period (i.e., 5–30 s), S/L_G 5-HTTLPR carriers preferentially viewed happy images relative to dysphoric images. There was no such difference among L_A 5-HTTLPR homozygotes. This pattern parallels what occurs when people are specifically instructed to regulate their emotions—they view negative images less often and positive images more often (Xing & Isaacowitz, 2006).

It is also noteworthy that S/L_G 5-HTTLPR carriers viewed neutral stimuli in a similar fashion to their viewing of sad and fearful facial expressions. This suggests that S/L_G 5-HTTLPR carriers directed their attention toward happy facial expressions rather than simply avoiding negative stimuli. However, it is possible that the S/L_G 5-HTTLPR carriers viewed neutral faces as negative or threatening, which would be consistent with biases observed among people with high trait and state anxiety (cf. Yoon & Zinbarg, 2007, 2008). Future work should examine whether S/L_G 5-HTTLPR carriers view neutral facial expressions as more threatening than do L_A homozygotes.

A possible alternative explanation of the results from the current study is that S/L_G 5-HTTLPR allele carriers attended to positive stimuli not because of valence but because positive stimuli were substantively different (i.e., an oddball) compared with the other stimuli. Results from previous research may mitigate this concern. Specifically, in prior research (Beevers et al., 2010), the 5-HTTLPR genotype was also associated with late-stage biased processing of positive stimuli. In that study, most neutral stimuli depicted inanimate objects (e.g., vases, candlesticks, fire hydrants), whereas valenced stimuli consisted of mainly animate objects (e.g., people interacting, snakes attacking). Although the use of both animate and inanimate objects in the previous study is a limitation (internal validity is stronger when stimuli vary on only a single characteristic, such as valence in the current study), we believe it is informative for addressing the oddball hypothesis. Specifically, in the previous study, the perceptual oddball was the inanimate object (e.g., a candlestick in the context of several pictures of people interacting). If S 5-HTTLPR allele carriers were sensitive to the uniqueness of the stimuli, rather than to valence, S 5-HTTLPR allele carriers should have viewed neutral stimuli more often than all others. However, this was not the case. S 5-HTTLPR homozygotes spent more time viewing positive stimuli (in the later stages of processing) than all other stimuli. Given the consistency of findings across studies despite different stimuli, we believe that the oddball hypothesis does not fully account for the current study findings.

The current study also found that race/ethnicity moderated the 5-HTTLPR Genotype $\times$ Stimulus Category interaction for predicting total fixation time. This finding suggests that the association between the 5-HTTLPR polymorphism and processing of emotion stimuli differs across race/ethnicity groups. This may be an important finding, as other evidence suggests that associations between the 5-HTTLPR polymorphism and emotion-related outcomes differ across race (Gelernter et al., 1998; Lee & Ham, 2008). Because of an insufficient number of racial minority par-

ticipants within each allele group in the current study (e.g., Hispanics, the largest minority group in this sample, were represented by 3 individuals with the L_AL_A genotype), we could not assess linkages between 5-HTTLPR and processing of emotion stimuli within non-Caucasians. Nevertheless, until additional research is performed with large samples of individuals with diverse racial/ethnic backgrounds, the current findings should be constrained to Caucasian participants and not generalized to individuals from other races. This will be an important direction for future research.

Finally, the finding that the 5-HTTLPR genotype is associated with selective attention for positive stimuli is consistent with a developing literature on biological sensitivity to context (Ellis & Boyce, 2008). This model, which is rooted in evolutionary–developmental biology, suggests that selection pressures favor adaptive phenotypic plasticity—the capacity for a genotype to flexibly influence behavior depending on environmental context (Boyce & Ellis, 2005). The 5-HTTLPR polymorphism appears to fit this pattern (Belsky & Pluess, 2009). Studies have shown that the 5-HTTLPR influences neural and information-processing responses to negative and positive stimuli (Canli et al., 2005). Further, mood states are positively influenced by social support (Kaufman et al., 2004) and negatively impacted by adversity (Caspi et al., 2003), more so for S/L_G 5-HTTLPR carriers than for L_A homozygotes. Thus, the 5-HTTLPR genotype may not only confer vulnerability to negative health outcomes during adversity but also contribute to positive outcomes under conditions of support. This possibility should also be explored in future research.

Several limitations of this study should be noted. Relatively small sample size is an important limitation, as effects observed in small samples are less likely to be replicated than effects initially observed in large samples (Maxwell, 2004). We also considered genetic variability associated with 5-HTT only. Future work with larger sample sizes should consider examining interactions between the 5-HTTLPR and polymorphisms impacting signaling mechanisms known to interact with 5-HT (e.g., other monoamines, brain-derived neurotrophic factor) so that additive (Canli, Congdon, Todd Constable, & Lesch, 2008) and interactive (Pezawas et al., 2008) effects among genetic polymorphisms can be explored. Our eye-tracking paradigm involved relatively few trials, which may have limited our ability to identify 5-HTTLPR genotype effects for location of first fixation. Finally, as with any genetic association study, population stratification is a potential concern. Population stratification is the existence of a systematic difference in allele frequencies among subpopulations, perhaps due to different ancestry. This confound is unlikely as participants retained for analyses were Caucasian, but formal testing of potential population stratification is preferred.

Despite these limitations, we believe this study makes an important and interesting contribution to understanding how the 5-HTTLPR genotype contributes to biased processing of emotional stimuli. Individuals who inherit S/L_G 5-HTTLPR alleles may be more sensitive to negative information in the environment than L_A homozygotes (cf. Osinsky et al., 2008; Pérez-Edgar et al., 2010). In an effort to regulate heightened reactivity to negative stimuli, S/L_G 5-HTTLPR allele carriers turn attention toward positive stimuli during the later stages of information processing. As a result, when processing is not constrained in any fashion, they subsequently selectively attend to positive stimuli. This type of regulation may be possible under the benign conditions of a laboratory experiment. However, when information is overwhelmingly negative, or when the ability to turn attention away from negative stimuli is compromised, this sensitivity to negative stimuli may contribute to the expression of certain forms of psychopathology, such as major depression or anxiety.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Beevers, C. G. (2005). Cognitive vulnerability to depression: A dual process model. *Clinical Psychology Review, 25,* 975–1002. doi:10.1016/j.cpr.2005.03.003

Beevers, C. G., Ellis, A. J., Wells, T. T., & McGeary, J. E. (2010). Serotonin transporter gene promoter region polymorphism and selective processing of emotional images. *Biological Psychology, 83,* 260–265. doi:10.1016/j.biopsycho.2009.08.007

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,* 208–212. doi:10.1037/0021-843X.116.1.208

Beevers, C. G., Wells, 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,* 670–681. doi:10.1037/a0016198

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin, 135,* 885–908. doi:10.1037/a0017376

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary–developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17,* 271–301.

Bradley, B. P., Mogg, K., & Millar, N. H. (2000). Covert and overt orienting of attention to emotional faces in anxiety. *Cognition and Emotion, 14,* 789–808. doi:10.1080/026999300501566636

Canli, T., Congdon, E., Todd Constable, R., & Lesch, K. P. (2008). Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on neural correlates of affective processing. *Biological Psychology, 79,* 118–125. doi:10.1016/j.biopsycho.2008.01.004

Canli, T., Omura, K., Haas, B. W., Fallgatter, A., Constable, R. T., & Lesch, K. P. (2005). Beyond affect: A role for genetic variation of the serotonin transporter in neural activation during a cognitive attention task. *Proceedings of the National Academy of Sciences of the United States of America, 102,* 12224–12229. doi:10.1073/pnas.0503880102

Carver, C. S., Johnson, S. L., & Joormann, J. (2008). Serotonergic function, two-mode models of self-regulation, and vulnerability to depression: What depression has in common with impulsive aggression. *Psychological Bulletin, 134,* 912–943. doi:10.1037/a0013740

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301,* 386–389. doi:10.1126/science.1083968

Chiao, J. Y., & Blizinsky, K. D. (2010). Culture–gene coevolution of individualism–collectivism and the serotonin transporter gene. *Proceedings of the Royal Society B: Biological Sciences, 277,* 529–537. doi:10.1098/rspb.2009.1650

Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect.* Palo Alto, CA: Consulting Psychologists Press.

Ellis, B. J., & Boyce, W. T. (2008). Biological sensitivity to context. *Current Directions in Psychological Science, 17,* 183–187. doi:10.1111/j.1467-8721.2008.00571.x

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1998). *Structured Clinical Interview for DSM–IV Axis I Disorders: Patient Edition* (SCID I/P, Version 2.0, 8/98 revision). New York, NY: New York State Psychiatric Institute, Biometrics Research Department.

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

Gelernter, J., Kranzler, H., Coccaro, E. F., Siever, L. J., & New, A. S. (1998). Serotonin transporter protein gene polymorphism and personality measures in African American and European American subjects. *American Journal of Psychiatry, 155,* 1332–1338.

Gelernter, J., Kranzler, H., & Cubells, J. F. (1997). Serotonin transporter protein (SLC6A4) allele and haplotype frequencies and linkage disequilibria in African- and European-American and Japanese populations and in alcohol-dependent subjects. *Human Genetics, 101,* 243–246. doi:10.1007/s004390050624

Greenwald, A. G., Pratkanis, A. R., Leippe, M. R., & Baumgardner, M. H. (1986). Under what conditions does theory obstruct research progress? *Psychological Review, 93,* 216–229. doi:10.1037/0033-295X.93.2.216

Gross, J. J., & Munoz, R. F. (1995). Emotion regulation and mental health. *Clinical Psychology: Science and Practice, 2,* 151–164. doi:10.1111/j.1468-2850.1995.tb00036.x

Hariri, A. R., & Holmes, A. (2006). Genetics of emotional regulation: The role of the serotonin transporter in neural function. *Trends in Cognitive Sciences, 10,* 182–191. doi:10.1016/j.tics.2006.02.011

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., . . . Weinberger, D. R. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297,* 400–403. doi:10.1126/science.1071829

Hartlage, S., Alloy, L. B., Vázquez, C., & Dykman, B. (1993). Automatic and effortful processing in depression. *Psychological Bulletin, 113,* 247–278. doi:10.1037/0033-2909.113.2.247

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology, 29,* 1765–1781. doi:10.1038/sj.npp.1300506

Heinz, A., Braus, D. F., Smolka, M. N., Wrase, J., Puls, I., Hermann, D., . . . Büchel, C. (2005). Amygdala–prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nature Neuroscience, 8,* 20–21. doi:10.1038/nn1366

Heinz, A., Jones, D. W., Mazzanti, C., Goldman, D., Ragan, P., Hommer, D., . . . Weinberger, D. R. (2000). A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity. *Biological Psychiatry, 47,* 643–649. doi:10.1016/S0006-3223(99)00171-7

Hermans, D., Vansteenwegen, D., & Eelen, P. (1999). Eye movement registration as a continuous index of attention deployment: Data from a group of spider anxious students. *Cognition & Emotion, 13,* 419–434. doi:10.1080/026999399379249

Hu, X., Oroszi, G., Chun, J., Smith, T. L., Goldman, D., & Schuckit, M. A. (2005). An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. *Alcoholism: Clinical and Experimental Research, 29,* 8–16. doi:10.1097/01.ALC.0000150008.68473.62

Ioannidis, J. P. A., Ntzani, E. E., Trikalinos, T. A., & Contopoulos-Ioannidis, D. G. (2001). Replication validity of genetic association studies. *Nature Genetics, 29,* 306–309. doi:10.1038/ng749

Isaacowitz, D. M. (2006). Motivated gaze: The view from the gazer. *Current Directions in Psychological Science, 15,* 68–72. doi:10.1111/j.0963-7214.2006.00409.x

Kaufman, J., Yang, B.-Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., et al. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the United States of America, 101,* 17316–17321. doi:10.1073/pnas.0404376101

Kellough, J. L., Beevers, C. G., Ellis, A. J., & Wells, T. T. (2008). Time course of selective attention in clinically depressed young adults: An eye tracking study. *Behaviour Research and Therapy, 46,* 1238–1243.

Lee, B. T., & Ham, B. J. (2008). Serotonergic genes and amygdala activity in response to negative affective facial stimuli in Korean women. *Genes, Brain, and Behavior, 7,* 899–905. doi:10.1111/j.1601-183X.2008.00429.x

Lesch, K.-P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., . . . Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274,* 1527–1531. doi:10.1126/science.274.5292.1527

Maxwell, S. E. (2004). The persistence of underpowered studies in psychological research: Causes, consequences, and remedies. *Psychological Methods, 9,* 147–163. doi:10.1037/1082-989X.9.2.147

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

Munafò, M. R., Durrant, C., Lewis, G., & Flint, J. (2008). Gene × environment interactions at the serotonin transporter locus. *Biological Psychiatry, 65,* 211–219.

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, 8,* 584–588. doi:10.1037/a0012826

Pacheco, J., Beevers, C. G., Benavides, C., McGeary, J., Stice, E., & Schnyer, D. M. (2009). Frontal-limbic white matter pathway associations with the serotonin transporter gene promoter region (5-HTTLPR) polymorphism. *Journal of Neuroscience, 29,* 6229–6233. doi:10.1523/JNEUROSCI.0896-09.2009

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,* 269–271. doi:10.1016/j.biopsycho.2009.08.009

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., . . . Weinberger, D. R. (2005). 5-HTTLPR polymorphism impacts human cingulated–amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience, 8,* 828–834. doi:10.1038/nn1463

Pezawas, L., Meyer-Lindenberg, A., Goldman, A. L., Verchinski, B. A., Chen, G., Kolachana, B. S., . . . Weinberger, D. R. (2008). Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. *Molecular Psychiatry, 13,* 709–716. doi:10.1038/mp.2008.32

Posner, M. I., & Rothbart, M. K. (2000). Developing mechanisms of self-regulation. *Development and Psychopathology, 12,* 427–441. doi:10.1017/S0954579400003096

Rinck, M., & Becker, E. S. (2006). Spider fearful individuals attend to threat, then quickly avoid it: Evidence from eye movements. *Journal of Abnormal Psychology, 115,* 231–238. doi:10.1037/0021-843X.115.2.231

Rogers, N. L., Cole, S. A., Lan, H. C., & Crossa, A. (2007). New saliva DNA collection method compared to buccal cell collection techniques for epidemiological studies. *American Journal of Human Biology, 19,* 319–326. doi:10.1002/ajhb.20586

Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., . . . Casey, B. J. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry, 58,* 1057–1063. doi:10.1001/archpsyc.58.11.1057

Wendland, J. R., Martin, B. J., Kruse, M. R., Lesch, K. P., & Murphy, D. L. (2006). Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. *Molecular Psychiatry, 11,* 224–226. doi:10.1038/sj.mp.4001789

Xing, C., & Isaacowitz, D. M. (2006). Aiming at happiness: How motivation affects attention to and memory for emotional images. *Motivation and Emotion, 30,* 243–250. doi:10.1007/s11031-006-9032-y

Yoon, K. L., & Zinbarg, R. E. (2007). Threat is in the eye of the beholder: Social anxiety and the interpretation of ambiguous facial expressions.

Behaviour Research and Therapy, 45, 839–847. doi:10.1016/j.brat.2006.05.004

Yoon, K. L., & Zinbarg, R. E. (2008). Interpreting neutral faces as threatening is a default mode for socially anxious individuals. *Journal of Abnormal Psychology, 117,* 680–685. doi:10.1037/0021-843X.117.3.680

Zalsman, G., Huang, Y., Oquendo, M. A., Burke, A. K., Hu, X., Brent, D. A., . . . Mann, J. J. (2006). Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. *American Journal of Psychiatry, 163,* 1588–1593. doi:10.1176/appi.ajp.163.9.1588

Received September 11, 2009
Revision received October 8, 2010
Accepted October 11, 2010 ■