Research Article

ASSOCIATION OF THE SEROTONIN TRANSPORTER PROMOTER REGION POLYMORPHISM WITH BIASED ATTENTION FOR NEGATIVE WORD STIMULI

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Background: *Biased attention for emotional stimuli reflects vulnerability or resilience to emotional disorders. The current study examines whether the 5-HTTLPR polymorphism is associated with attentional biases for negative word stimuli.* **Methods:** *Unmedicated, young adults with low current depression and anxiety symptoms (N = 106) were genotyped for the 5-HTTLPR, including the single nucleotide polymorphism (SNP) rs25531 in the long allele of the 5-HTTLPR. Participants then completed a standard dot-probe task that measured attentional bias toward anxiety, dysphoric, and self-esteem words.* **Results:** *The L_AL_A allele group demonstrated an attentional bias away from negative word stimuli. This attentional bias was absent among the S/L_G carriers.* **Conclusions:** *These findings replicate previous work and suggest that 5-HTTLPR L_A homozygotes possess a protective attentional bias that may decrease susceptibility to depression and anxiety. Depression and Anxiety 27:746–751, 2010.*

Key words: *serotonin transporter gene; anxiety; depression; 5-HTTLPR polymorphism; attention*

INTRODUCTION

Cognitive models of depression and anxiety emphasize that biased attention for emotional stimuli can influence vulnerability or resilience to emotional disorders, such as depression and anxiety.[1] Biased attention toward negative information can be detrimental to adaptive self-regulation[2] and is associated with clinical diagnosis of depression[3] and anxiety.[4–6] On the other hand, the absence of a negative bias is associated with enhanced resiliency to stress and lower levels of anxiety.[7] Similarly, longitudinal studies show that biased attention to negative information combines with life stress to predict increases in depressive symptoms, even when controlling for depression history.[8] Indeed, biased processing of negative stimuli is a better predictor of future emotional and cortisol reactivity to laboratory and naturally occurring stressors than neuroticism, trait–anxiety, and extraversion.[9] Even more compelling, experimentally inducing biased attention to negative information can *cause* increased vulnerability to sad and anxious affect.[6,10]

Emerging evidence suggests that genetic variation may foster a negativity bias; specifically, a variable repeat sequence in the promoter region of the serotonin transporter gene 5-HTTLPR; see[11] for a review). The serotonin transporter (5-HTT) refreshes the synaptic cleft by removing serotonin. Consequently, the transporter is responsible for decreasing the amount of serotonin in both the synapse and extracellular space. The function of the serotonin transporter is degraded among carriers of the short 5-HTTLPR allele.[12,13] As a result, carriers of the

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short 5-HTTLPR allele have increased levels of extracellular serotonin and increased serotonin signaling compared with those who have two long alleles. Carriers of short 5-HTTLPR alleles have significantly reduced gray matter volume in the perigenual anterior cingulate (pACC) and the rostral anterior cingulate, both of which are involved in regulating affective information.[14,15] Functional magnetic resonance imaging analyses also suggested that short 5-HTTLPR allele carriers have decreased functional coupling between the pACC and the amygdala. As a result, carriers of the short allele experience heightened reactivity of the amygdala in response to negative emotional stimuli, such as negative pictures,[16] fearful and angry faces,[16–18] and negative words.[19]

To date, few behavioral studies have directly investigated the relationship between the 5-HTTLPR polymorphism and biased attention. The first study to do so[20] sampled 27 psychiatric inpatients and found that carriers of the short 5-HTTLPR allele demonstrated biased attention toward anxiety-related words (e.g., scared and attack) relative to those homozygous for the long allele. More recently, studies have observed attentional bias in healthy populations.[21,22] Beevers et al.[21] found that carriers of the short 5-HTTLPR allele had greater difficulty disengaging from positive and negative stimuli compared to those homozygous for the long alleles. Fox et al.[22] further found that the long 5-HTTLPR allele homozygotes were biased *away* from negative stimuli and *toward* positive stimuli. Finally, Pérez-Edgar et al.[23] found a linear relationship between the number of short 5-HTTLPR alleles and attentional bias for valenced faces in adolescents. The short 5-HTTLPR allele homozygotes were biased toward angry faces, while those homozygous for the long allele were biased toward happy faces.

The current study seeks to replicate and extend earlier findings by manipulating word content rather than valenced pictures or face stimuli (cf. [24]). Using different word conditions allows us to determine whether attentional biases associated with the 5-HTTLPR are specific to certain word categories (e.g., anxiety, self-esteem) or whether attention is biased for negative stimuli in general. Additionally, we also examined the triallelic 5-HTTLPR variation [i.e., deletion polymorphism and rs25531] as only two previous studies in this research area[21,23] have accounted for this variation. Genotyping the rs25531 SNP may provide a more accurate analysis of the association between the 5-HHLPR polymorphism and negativity bias than previous research because the L_G variant of rs25531 and the S 5-HTTLPR allele are similar in function; thus, only the L_A variant is considered high expressing.[25]

METHODS AND MATERIALS

PARTICIPANTS

One hundred and twenty-nine undergraduates from The University of Texas (84 female, 39 male, and 6 unknown) volunteered in the study for partial class credit. Participant age ranged from 17 to 47 years ($M = 19.5$, $SD = 3.10$). After being introduced to a study of personality assessment, participants took part in a dot-probe task, completed questionnaire assessments of depression symptoms,[26] anxiety symptoms,[27] and neuroticism,[28] and provided a saliva sample. Genetic information could not be extracted for three participants. Additionally, the nine participants who reported suspicion about the dot-probe task and 11 dysphoric participants (short form of the BDI (BDI-SF) > 9; [29]) were excluded from the analysis. This left 106 participants in the final analysis. The internal review board at The University of Texas approved all procedures.

MATERIALS

Dot-probe task. Word stimuli were taken from lists of affective words that were pretested and developed for use in dot-probe tasks.[30,31] We matched each word pair for word length as well as frequency of use in the English language. Trials used 20 anxious–neutral (e.g., scared–salad) word pairs, 20 dysphoric–neutral (doom–palm) word pairs, 20 self-esteem-neutral (loser–ladder) word pairs, and 20 neutral–neutral word pairs.

The block of 80 word pairs was presented twice for a total of 160 trials. Each block of 80 word pairs was fully randomized for each participant. Each trial consisted of a white fixation cross on a black background in the middle of the screen for 500 ms, followed by a word pair presented for 500 ms. Word stimuli appeared in the top and bottom halves of the screen. Following the offset of the words, a small white asterisk probe on a black background appeared in the location of one of the words and remained on the screen until the participant responded with a key press on a standard keyboard. The computer recorded the latency and accuracy of each response. Each type of word stimulus (emotional or neutral) and the probe appeared in the top and bottom position with equal frequency.

Participants sat approximately 60 cm from a 15-inch computer monitor. Each stimulus word was approximately 1 cm (0.95° visual angle) high and the word pairs were spaced approximately 3.7 cm (3.5° visual angle) apart. Participants were told that their goal was to locate the position of the asterisk ("top" or "bottom") as quickly and accurately as possible. They used their left index finger to press the "R" key when the asterisk appeared in the location of the top word and their right index finger to press the "N" key when the asterisk appeared in the location of the bottom word. Participants completed 10 practice trials using non-word pairs and repeated the practice until they responded accurately to at least eight of the 10 practice trials.

Genotyping. Genomic DNA were isolated from buccal cells using a modification of published methods.[32–35] The primer sequences are: forward, 5′-GGCGT-TGCCGCTCTGAATGC-3′ (fluorescently labeled), and reverse, 5′-GAGGGACTGAGCTGGACAACCAC-3′. These primer sequences yield products of 484 or 528 bp. Two investigators scored allele sizes independently and inconsistencies were reviewed and rerun when necessary. The frequency of the 5-HTTLPR genotypes (SS, $n = 24$ (22.7%); SL, $n = 47$ (44.3%); LL, $n = 35$ (33.0%)) did not differ from Hardy-Weinberg equilibrium, $\chi^2 = 1.14$, $P = .29$.

To distinguish between the S, L_A, and L_G fragments, the PCR fragment was digested with *Msp*I according to the methods found in Wigg et al.[36] The resulting polymorphic fragments were separated using an ABI 3130XL DNA sequencer (AME Bioscience, Toroed, Norway) (S: 297, 127, and 62 bp; L_A: 340, 127, and 62 bp; and L_G: 174, 166, 127, and 62 bp). Allele frequencies were S: $n = 95$ (44.8%), L_A: $n = 101$ (47.6%), and L_G: $n = 16$ (7.6%). Genotype distribution for the A/G SNP was in Hardy-Weinberg equilibrium, $\chi^2 = 2.40$, $P = .12$. Consistent with previous research, the S and L_G alleles were designated as S′ and the L_A allele was designated as L′. We formed three groups: (a) S′S′ (i.e. SS: $n = 24$ (22.6%); SL_G: $n = 6$ (5.6%); and

L_GL_G: $n = 2$ (1.9%)), (b) S′L′ (i.e. SL_A: $n = 41$ (38.7%), L_GL_A: $n = 6$ (5.7%)), and (c) L′L′ (i.e., L_AL_A: $n = 27$ (25.5%)).

RESULTS

SAMPLE CHARACTERISTICS

Descriptive statistics by 5-HTTLPR genotype group are described in Table 1. There were no significant differences as a function of genotype grouping for age, $F(2,100) = .434$, $P = .65$; gender, $\chi^2(2, N = 102) = 0.440$, $P = .80$; depressive symptoms, $F(2,103) = 1.59$, $P = .21$; anxiety symptoms, $F(2,103) = .647$, $P = .53$; and neuroticism, $F(2,103) = .664$, $P = .52$. Although there was a significant genotype frequency difference as a function race, χ^2 $(2, N = 105) = 9.11$, $P < .05$, the 5-HTTLPR effect on attentional bias for negative stimuli was similar for Caucasians, $F(2,53) = 3.19$, $P = .05$, and non-Caucasians, $F(2,38) = 3.75$, $P = .03$, so we combined groups.

Important to note is that the BDI-SF was used to measure depressive symptoms. The BDI-SF contains 13 items and the scores range from 0 to 39. The BDI-SF score for our sample was marginally significantly lower than that of the general college population ([29]; $t(255.59) = 1.76$, $P = .07$), and our sample scored significantly lower on the BAI than the general college population ([37] $t(167.40) = 3.99$, $P = .00$). Given that we selected participants with low depression symptoms for the current study (because we did not want to confound symptoms with genetic variation), it is not surprising that our sample had lower levels of depression and anxiety than a general student population. Further, this also likely accounts for why 5-HTTLPR allele groups did not significantly differ for anxiety, depression, and neuroticism.

DATA REDUCTION

We analyzed response latencies only from correct responses. Eliminating incorrect responses resulted in a loss of less than 1% of data. In addition, to minimize the influence of outliers, we eliminated response latencies for each participant that were faster than 150 ms or slower than 1,000ms. This resulted in a loss of less than 1% of the data.

BIAS SCORES

Consistent with previous research (e.g. [38]), attentional bias scores were calculated for each participant using the following equation

$$\text{Attentional bias score} = \tfrac{1}{2}[(\text{TpBe} - \text{TpTe}) + (\text{BpTe} - \text{BpBe})] \quad (1)$$

where T = top position, B = bottom position, p = probe, and e = emotional word stimulus. Therefore, TpBe indicates the mean response latency when the probe is in the top position and the emotional word stimulus is in the bottom position, and so on. Positive bias scores indicate a bias toward the emotional stimuli, whereas negative bias scores indicate a bias away from the emotional stimuli.

MAIN RESULTS

A 3 (word type: anxiety, dysphoria, and self-esteem) × 3 (genotype status: S′S′, S′L′, and L′L′) repeated-measures ANOVA examined whether genetic status was differentially related to biased attention for anxious, dysphoric, and self-esteem stimuli. Results indicated a significant between-subjects effect for genetic group, $F(2,95) = 3.75$, $P < .05$, $\eta^2 = .07$. None of the other main effects and interactions reached statistical significance: word type, $F(2,190) = .07$, $P = .93$, $\eta^2 = .00$; and genetic group × word type, $F(4,190) = 1.68$, $P = .16$, $\eta^2 = .03$. A very similar 5-HTTLPR effect was observed when using the bi-allelic classification (i.e. not accounting for the rs25531 SNP in L allele), $F(2,95) = 4.12$, $P < .05$, $\eta^2 = .08$.

To follow-up the significant 5-HTTLPR main effect, we collapsed the dysphoria, anxiety, and self-esteem word scores into a single variable. The S′L′ group ($M = 0.96$, $SD = 10.40$) did not significantly differ from the S′S′ group ($M = 0.78$, $SD = 9.52$) in attentional bias toward negative words, $t(69) = .07$, $P = .94$. Neither the S′S′ group nor the S′L′ group evidenced an attentional bias score significantly different from zero, $t(28) = .44$, $P = .66$, and $t(41) = .60$, $P = .55$, respectively. However, the L′L′ group ($M = -6.11$, $SD = 14.28$) evidenced a significantly greater bias away from negative word stimuli compared

TABLE 1. Demographics presented by 5-HTTLPR genotype[a]

	L′L′ allele ($n = 27$)			S′L′ allele ($n = 47$)			S′S′ allele ($n = 32$)		
Variable	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*
Age (years)	19.70	5.51		19.02	1.42		19.35	1.14	
Gender (men/women)			9/18			16/28			9/22
Race (Caucasian/other)			21/5			22/25			15/17
BDI-SF	2.40	2.10		2.85	2.17		3.40	2.20	
Beck Anxiety Inventory	6.72	6.38		6.13	4.43		7.35	5.76	
Neuroticism	2.40	0.571		2.57	0.652		2.52	0.543	

[a]Gender and race information were missing from four participants.
BDI-SF, short form of the BDI.

to the S′L′ group, $t(43.55) = -2.22$, $P<.05$, and the S′S′ group, $t(44.86) = -2.11$, $P<.05$ (see Fig. 1). Furthermore, the L′L′ group showed a bias away from negative word stimuli that was significantly different from zero, $t(26) = -2.22$, $P<.05$.

DISCUSSION

The current study examined associations between variants of the 5-HTTLPR polymorphism and attentional biases for negative word stimuli. While the bias toward negative words did not achieve significance for those with S/L_G alleles, participants homozygous for the L_A allele demonstrated a significant bias *away* from negative words. This bias was not specific to a particular type of negative stimuli; rather, a similar bias was observed for all three types of negative words (i.e. anxiety, dysphoric, or self-esteem words).

Findings provide an independent replication of Fox et al.[22] who also documented that long 5-HTTLPR allele homozygotes displayed biased attention away from negative images. We believe this replication is significant for several reasons. First, initial behavioral genetic findings are not often replicated.[24] This has been particularly problematic in some areas, including research involving the 5-HTTLPR.[39] Replication is necessary to ensure that initial findings are not due to random or Type-I error (see[40]). Second, it is notable that intermediate phenotypes, such as amygdala reactivity [41] and biased attention for emotion stimuli, appear to have a more consistent association with the 5-HTTLPR polymorphism than clinical outcomes, such as Major Depressive Disorder. Connecting individual differences in intermediate phenotypes to the onset of complex psychiatric conditions represents an important next step for this research. Finally, this study replicates previous findings while accounting for the newly discovered rs25531 SNP in the L 5-HTTLPR allele. Accounting for the L_A/L_G variant may provide a cleaner and more accurate analysis of the relationship between the 5-HTTLPR polymorphism and attentional biases (cf.[22,24]).

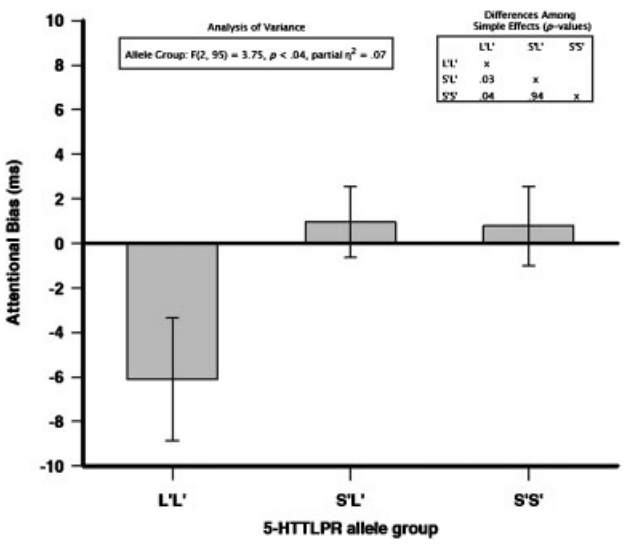

Figure 1. Mean attentional bias scores (in ms) across allele groups for the serotonin transporter promoter region polymorphism (5-HTTLPR). Error bars reflect standard error of the mean.

If indeed the 5-HTTLPR polymorphism is partly responsible for a bias toward or away from negative stimuli, this could inform research and treatment on psychological disorders such as anxiety and depression. Insofar as preferential attention to negative stimuli can trigger and maintain anxiety and depression, the 5-HTTLPR polymorphism may protect some people against psychopathology. Future research should investigate whether the 5-HTTLPR interacts with biased attention to predict severity of depression and anxiety in samples experiencing a wider range of symptoms than in the current study. Further, inducing attentional biases toward aversive information can foster both anxiety and depressive symptoms following a stressful task[6] and training attention away from emotion stimuli leads to symptom improvement.[42–44] Future research should examine whether the 5-HTTLPR moderates the effect of attention training on depression and anxiety symptoms. Doing so may identify which individuals are most likely to benefit from attention training interventions.

Limitations of our study include a limited genetic analysis, as other polymorphisms also likely contribute to biased attention, and unmeasured third variables (e.g., a functional genetic marker in linkage with the 5-HTTLPR promoter polymorphism) could account for our findings. We also did not include positive word stimuli, which would have helped to further document the specificity of biased attention for affective stimuli associated with the 5-HTTLPR. Nevertheless, this study contributes to the growing literature documenting that the 5-HTTLPR polymorphism is associated with biased attention for negative stimuli. By examining risk mechanisms across genetic, cognitive, and behavioral levels of analyses, we hope this study will also facilitate the development of more comprehensive explanatory models of vulnerability to psychopathology.

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