BRIEF REPORTS

Serotonin Transporter Genetic Variation and Biased Attention for Emotional Word Stimuli Among Psychiatric Inpatients

Christopher G. Beevers
University of Texas at Austin

Brandon E. Gibb
Binghamton University

John E. McGeary
Providence Veterans Affairs Medical Center
and Brown University

Ivan W. Miller
Butler Hospital and Brown University

The short allele in a variable repeat sequence of the promoter region of the serotonin transporter gene (5-HTTLPR) has been associated with stronger activation in brain regions critical for processing emotional stimuli. The authors examined whether variants of the 5-HTTLPR promoter polymorphism were also associated with individual differences in attentional biases for emotional stimuli. Words related to anxious and dysphoric emotional states were presented to psychiatric inpatients in a standard dot-probe reaction time task. Compared with participants with two long alleles, carriers of the short 5-HTTLPR allele exhibited a stronger attentional bias for anxious word stimuli. No genetic group difference was observed for dysphoric word stimuli. Findings from this preliminary study highlight the potential for integrating genetic and cognitive models of psychopathology.

Keywords: attentional bias, dot-probe, 5-HTTLPR, genes, cognitive

Cognitive models of psychopathology emphasize that biased attention for emotional stimuli may maintain abnormal mood states (Gotlib & Krasnoperova, 1998; Mogg & Bradley, 2005; Williams, Watts, MacLeod, & Mathews, 1988). The etiology of these biases, however, is not well understood. The purpose of this study was to investigate one potential etiologic factor. Specifically, we examined whether allelic differences in a variable repeat sequence of the promoter region of the serotonin transporter gene (5-HTTLPR) were associated with biased attentional processing of negative emotional information.

The 5-HTTLPR regulates the reuptake of serotonin from the synaptic cleft. A common polymorphism in the promoter region of the 5-HTT gene results in two variants: a short allele and a long allele. The presence of one or two short alleles, rather than two long alleles, is associated with significant decreases (approximately 50%) in serotonin transporter availability (Heinz et al., 2000; Lesch et al., 1996). This, in turn, presumably increases

synaptic concentrations of serotonin. Individuals who carry the short 5-HTTLPR allele should thus have increased levels of extracellular serotonin compared with those with two copies of the long allele.

In part because serotonin has an important role in regulating anxious and depressed mood states (Ressler & Nemeroff, 2000), researchers have examined whether genetic variants of the 5-HTTLPR influence activity in brain regions crucial for processing emotional information. Several studies have examined the relationship of 5-HTTLPR variants with neural responses to emotional stimuli. For instance, Pezawas et al. (2005) reported that among people with no current or past psychiatric condition, people who carried the short allele had significantly more neural activation in limbic circuitries (i.e., amygdala and perigenual cingulate) in response to angry or fearful facial expressions than people homozygous for the long 5-HTTLPR allele (see also Bertolino et al., 2005; Hariri et al., 2005; Hariri, Mattay, et al., 2002). Further, Heinz et al. (2005) reported that healthy carriers of short 5-HTTLPR alleles showed stronger activation of the amygdala and greater coupling between the amygdala and the ventromedial prefrontal cortex in response to aversive images than people homozygous for the long 5-HTTLPR allele (see also Canli et al., 2005).

Given the correspondence between 5-HTTLPR genetic variants and reactivity in the amygdala, a brain region critical for processing emotional information (e.g., Wang, McCarthy, Song, & LaBar, 2005), we hypothesized that carriers of the short 5-HTTLPR allele might also display greater biased attention for emotional stimuli than people homozygous for the long 5-HTTLPR allele. To test this hypothesis, we measured attentional biases with a dot-probe task, an assessment widely used in cognitive psychopathology research (see Mogg & Bradley, 2005). Using this dot-probe task,

we presented masked and unmasked stimuli. Selecting two presentation durations allowed us to measure biased attention at two different time points, a common practice with the dot-probe task (e.g., Mogg, Bradley, & Williams, 1995). We used anxious and dysphoric stimuli to examine whether genetic group effects were specific to one category of emotional stimuli. Relationships between variants of the 5-HTTLPR promoter polymorphism and biased attention for emotional stimuli were then examined.

Method

Participants

Subjects were recruited from a general psychiatric inpatient unit at Butler Hospital, Providence, Rhode Island. The exclusion criteria were an inability to understand English or active psychotic symptoms that would preclude participation. Of the 31 participants who started the study protocol, 27 (87%) completed the genetic and information processing procedures. These 27 individuals were retained for analyses. Gentoyping indicated that 11 participants had two long 5-HTTLPR alleles and 16 participants had at least one short 5-HTTLPR allele ($n = 10$ for one short allele and $n = 6$ for two short alleles). These frequencies do not differ from those expected on the basis of the Hardy–Weinberg equilibrium. See Table 1 for the sample demographics stratified according to 5-HTTLPR status.

All participants were receiving inpatient treatment for a psychiatric condition. Chart diagnoses with sample size (percentage of sample), mean attention bias score (in milliseconds) for anxious stimuli, and standard deviation for anxious stimuli (when $n \geq 2$) for each psychiatric group were as follows: adjustment disorder with depressed mood, $n = 1$ (3.7%), $M = -50.50$; bipolar disorder, $n = 8$ (29.6%), $M = 9.69$, $SD = 57.25$; major depressive disorder (MDD), $n = 13$ (48%), $M = 2.82$, $SD = 36.01$; opioid dependence, $n = 1$ (3.7%), $M = 9.93$; psychosis, not otherwise specified, $n = 1$ (3.7%), $M = 22.08$; schizoaffective disorder, $n = 1$ (3.7%), $M = 8.94$; and substance-induced mood disorder, $n = 2$ (7.4%), $M = 6.91$, $SD = 31.02$. Given that the predominant diagnosis was MDD, we examined whether genetic group was associated with the presence versus the absence of MDD. The probability of having at least one short allele was not significantly associated with MDD, $\chi^2(1, N = 27) = 1.78$, $p = .18$, $r_{\text{effect size}} = .26$.

Assessments

Dot-probe task. A standard dot-probe task (Mogg et al., 1995) was used to assess attentional biases for anxious and dysphoric word stimuli. Each trial began with a 500-ms presentation of a centrally situated fixation cross. This was immediately followed by word stimuli presented simultaneously on a computer screen. The word stimuli were presented one above the other, 3 cm apart. In the masked condition, word pair stimuli were presented for 14 ms and were then followed with a pair of random letter masks (e.g., PLKYWS). Each mask was matched for word length with the stimuli it replaced. The mask was presented for 186 ms, for a total trial length of 200 ms. In the unmasked condition, word stimuli were presented for 750 ms. After stimulus offset in both conditions, a dot immediately replaced one of the words. Participants indicated the location of the dot by pressing a corresponding key on the computer keyboard. Intertrial interval was 1,000 ms. The dependent variable was latency to identify the location of the dot.

Stimuli were taken from lists of emotional words developed specifically for use with this task (John, 1988; Mathews & MacLeod, 1985). Word pairs were matched for frequency in English language and word length. Emotional trials used 28 anxious–neutral word pairs (e.g., scared–deduct) and 28 dysphoric–neutral (e.g., doom–keen) word pairs. In control trials, we used 28 neutral–neutral word pairs. Each of the 84 word pairs was presented as masked and unmasked stimuli for a total of 168 trials. The dot probe had an equal probability of appearing in the upper or lower location for each trial. Participants completed the trials in two blocks: one in which all stimuli were masked and one in which all stimuli were unmasked. Blocks were completed in a randomized order for each participant. Word stimuli within each block were presented in a random order for each participant.

Preferential attention to anxious or dysphoric stimuli is evidenced by a shorter latency to indicate the presence of probes replacing emotional stimuli and a longer latency to indicate the presence of probes replacing neutral stimuli. We used a standard method to compute attentional bias scores (Bradley, Mogg, & Lee, 1997). Specifically, the mean probe detection times for cases in which the probe appeared in the same location as the emotional stimulus was subtracted from the mean probe detection times for cases in which the probe appeared in a location different from the emotional stimulus. Summary attentional bias scores were calculated separately for responses to anxiety- and dysphoric-relevant stimuli. Positive scores indicated a bias toward emotional stimuli, and negative scores reflected a bias away from emotional stimuli. Trials with errors and trials with very fast (<150 ms) or very long ($>1,500$ ms) reaction times were deleted prior to computation of attentional bias scores (cf. Mathews, Ridgeway, & Williamson, 1996). This resulted in the deletion of 4.5% of the trials.

DNA assessment. Participants provided samples of epithelial cells by rubbing swabs along their cheeks and gums and rinsing out their mouth with 10 ml of distilled water. We collected genomic DNA and isolated it from buccal cells using published procedures (Freeman, Powell, Ball, Hill, Graig, & Plomin, 1997; Lench, Stanier, & Williamson, 1988). We used previously reported methods (Pooley, Houston, Hawton, & Harrison, 2003) to assay the 5-HTTLPR. The primer sequences are forward 5′-GCG TTG CCG CTC TGA ATG C-3′ and reverse 5′ GGA CTG AGC TGG ACA ACC AC-3′. Consistent with the protocols of several previous studies (e.g., Hariri et al., 2005), two groups of participants were formed on the basis of their genotyping: individuals homozygous for the long allele and individuals with either 1 or 2 copies of the short allele.

Table 1
Demographics by 5-HTTLPR Genotype

Variable	At least one short allele			Both alleles long		
	M	SD	No.	M	SD	No.
Age (years)	37.31	10.74		33.73	12.92	
Time since admission to hospital (days)	5.44	2.20		7.45	4.96	
Gender (men/women)			8/8			5/6
Ethnicity (White/other)			15/1			9/2
History of psychiatric hospitalization (yes/no)			11/4			9/2

Note. There were no significant group differences for any variable. One short allele carrier did not provide information about her psychiatric hospitalization history. None of the demographic variables were significantly correlated with attentional bias scores.

Procedure

Study procedures were approved by the internal review board at Butler Hospital. Study personnel approached patients about participating in the study. Those who gave informed consent and met inclusion criteria were entered into the study. Participants then provided basic demographic information, completed the dot-probe task, and completed a cheek swab to allow us to obtain genetic material. All of the assessments took place in private, quiet rooms on the inpatient unit at Butler Hospital.

Results

Preliminary Analyses

We first examined attentional bias scores for outliers, skewness, and differential variation across genetic groups, because violations can reduce the statistical power for analyses of variance (ANOVAs; Judd, McClelland, & Culhane, 1995). Each attentional bias score was examined separately. Standard box-plot analyses were performed to identify outlier values. Five outliers were observed across the four bias scores. The presence of an outlier was unrelated to psychiatric diagnosis (MDD, non-MDD), $\chi^2(1, N = 27) = 0.04$, $p = .85$. Outliers were removed from analyses and treated as missing data. We then inputed missing data using expectation-maximization methods. This maximum likelihood approach for estimating missing data is preferred over simple listwise deletion (Schafer & Graham, 2002). Distribution of attentional bias scores with estimated data in place of outliers met criteria for normality, as determined by the Kolmogorov–Smirnov test with the Lilliefors significance correction. Levene's test of equality of error variances indicated that error variability was similar across genetic groups for each attentional bias score.

Genetic Variants and Attentional Biases

A 2 (genetic group: no short 5-HTTLPR alleles, at least one 5-HTTLPR allele) × 2 (stimulus valence: anxious, dysphoric) × 2 (stimulus presentation duration: 14 ms, 750 ms) repeated-measures ANOVA was used to examine whether genetic status was differentially related to selective attention for anxious and dysphoric stimuli across the stimulus duration conditions. Results indicated a significant between-subjects effect for genetic group, $F(1, 25) = 4.24$, $p = .05$, $\eta^2 = .15$. This was qualified by a significant Genetic Group × Stimulus Valence interaction, $F(1, 25) = 6.34$, $p = .02$, $\eta^2 = .20$. None of the other main effects and interactions reached statistical significance: stimulus duration, $F(1, 25) = 0.0$, $p = .99$, $\eta^2 = .00$; Stimulus Duration × Genetic Group, $F(1, 25) = 1.56$, $p = .23$, $\eta^2 = .06$; Valence × Stimulus Duration, $F(1, 25) = 0.62$, $p = .44$, $\eta^2 = .02$; and Valence × Stimulus Duration × Genetic Group, $F(1, 25) = 1.71$, $p = .20$, $\eta^2 = .06$.[1]

To determine the form of the significant Genetic Group × Stimulus Valence interaction, we next examined whether genetic groups differed in response to anxious and dysphoric stimuli collapsing across stimuli duration conditions. For anxious stimuli, carriers of at least one short 5-HTTLPR allele significantly differed from those homozygous for the long 5-HTTLPR allele, $F(1, 25) = 8.85$, $p < .01$, $\eta^2 = .26$. Specifically, carriers of the short allele displayed a significantly greater attentional bias for anxious stimuli than those homozygous for the long allele (see Figure 1). Genetic group accounted for 26% of the variance in attentional bias for anxious stimuli. In contrast, there were

no significant genetic group differences for dysphoric stimuli, $F(1, 25) = 0.26$, $p = .87$, $\eta^2 = .00$.

Allelic Load Effects

Given the significant association between genetic group and biased attention for anxious stimuli, we performed supplemental analyses to examine whether effects were consistent across participants with one or two copies of the short 5-HTTLPR allele. We divided our sample into three groups on the basis of the number of short 5-HTTLPR alleles (i.e., 0, 1, or 2) and tested for attentional bias group differences for anxious stimuli. A significant group effect was observed, $F(2, 24) = 4.25$, $p < .03$, $\eta^2 = .26$. Participants with at least one short 5-HTTLPR allele ($M = 21.47$, $SD = 45.47$) did not significantly differ from those with two short 5-HTTLPR alleles ($M = 21.09$, $SD = 20.08$), $F(1, 14) < 1$, ns, $\eta^2 = .00$. However, participants homozygous for the long allele ($M = -20.26$, $SD = 33.49$) significantly differed from participants with at least one short allele, $F(1, 19) = 5.81$, $p = .03$, $\eta^2 = .23$, and from participants homozygous for the short allele, $F(1, 15) = 7.52$, $p = .02$, $\eta^2 = .33$.

Discussion

We examined associations between genetic variants of the serotonin transporter and biased attention for emotional stimuli as assessed by a standard dot-probe task. Carriers of the short allele in a variable repeat sequence of the promoter region of the serotonin transporter gene (5-HTTLPR) on average displayed a greater attentional bias toward anxious word stimuli than people with two long 5-HTTLPR alleles. This group difference was large (Cohen, 1988): Genetic grouping accounted for 26% of the variance in biased attention for anxious stimuli. This effect did not differ significantly across stimulus presentation duration (14 ms vs. 750 ms). In contrast to the findings for anxious stimuli, a genetic group difference was not observed for dysphoric word stimuli.

To our knowledge, ours is the first study to document an association between genetic variants of the 5-HTTLPR and biased attention (measured with a behavioral reaction time task) among a psychiatric population. Our findings are consistent with research documenting that genetic variants of the 5-HTTLPR are associated with amygdala reactivity in response to unmasked stimuli depicting fearful and angry facial expressions among people without psychiatric disorders (e.g., Hariri et al., 2005; Hariri, Mattay, et al., 2002). Given this previous work, it is possible that short 5-HTTLPR allele-driven amygdala hyperreactivity is associated with the attentional bias effects observed in the present study. Further research incorporating functional magnetic resonance imaging will be needed to confirm this hypothesis.

An intriguing finding was that the 5-HTTLPR genotype effect appeared to be specific to biased attention for anxious word stimuli. This finding is consistent with the possibility that the amygdala is part of a vigilance system used to process potentially threatening information (Whalen, 1998). Carriers of the short 5-HTTLPR allele may thus be especially vigilant for threat-related

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[1] Supplementary analyses indicated that a diagnosis of MDD (present, absent) did not moderate the interaction between genetic group status and stimulus valence, $F(1, 23) = 0.00$, $p = .95$, $\eta^2 = .00$.
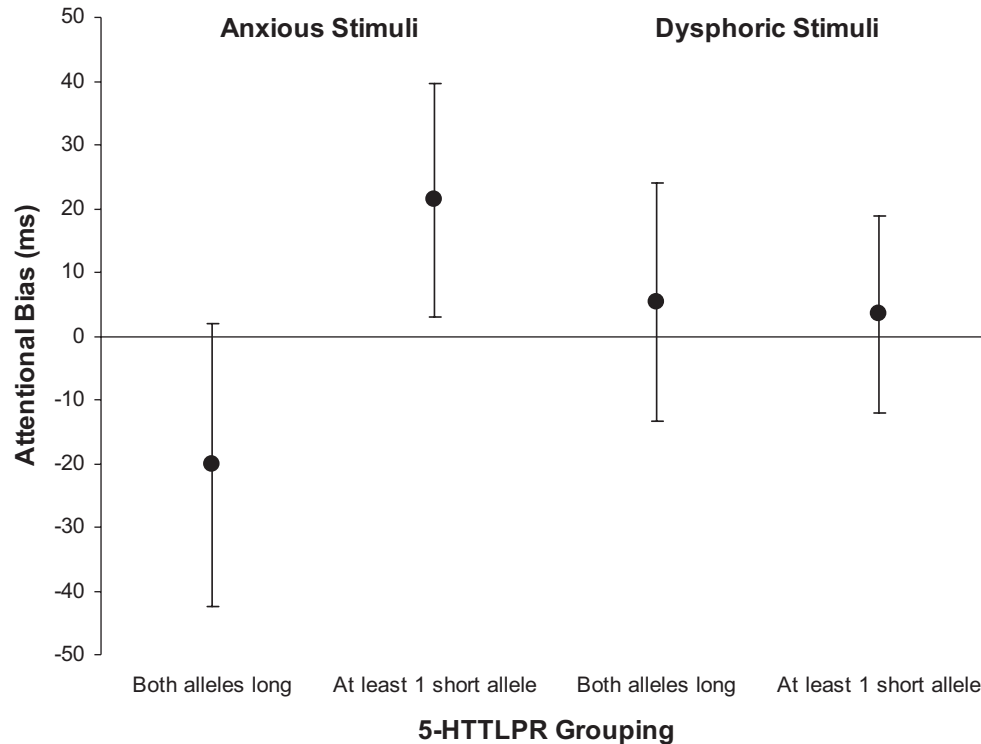
Figure 1. Mean attentional bias scores (in milliseconds) by stimulus valence across genetic groups for the serotonin transporter gene 5-HTTLPR. Error bars indicate 95% confidence intervals.

information. Consistent with this possibility, infant and juvenile monkeys homozygous for the short 5-HTTLPR allele exhibited particularly fearful behavior when exposed to laboratory situations (e.g., human intruder, novel fruit) designed to evoke fearful responses (Bethea et al., 2004). This finding is also consistent with a recent meta-analysis linking 5-HTTLPR genetic variants with anxiety-related personality traits such as neuroticism (Sen, Burmeister, & Ghosh, 2004).

In contrast to the findings for anxious word stimuli, there was no genetic group difference for dysphoric word stimuli. Additional research is needed to determine the generality of this finding. For instance, it will be important to determine whether 5-HTTLPR genetic variants are associated with biased attention for other dysphoric stimuli such as facial expressions. Yang et al. (2002) reported amygdala activation in response to faces depicting a variety of emotional expressions, including happiness and sadness. Other work suggests that faces depicting emotion are particularly effective for generating an amygdala response compared with images depicting other types of emotional information (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). Future work should determine whether 5-HTTLPR groups differ in biased attention for dysphoric and anxious facial expressions, as well as other types of emotional information such as complex affective scenes (Heinz et al., 2005). Doing so will help researchers to determine the scope of the association between 5-HTTLPR genetic variants and biased attention for dysphoric information.

Limitations of this study include the use of a heterogeneous convenience sample of psychiatric inpatients, small sample size, and a lack of standardized clinical interviews. An additional lim-

itation is that we did not assess whether participants were consciously aware of the masked stimuli. Future researchers in this area should consider assessing attentional biases with approaches that afford greater temporal resolution (e.g., evoked response potential or tracking eye movements) than the dot-probe task and should also recruit (and carefully assess) participants with psychopathology in which biases in selective attention are thought to operate. In the present study, we used minimal exclusion and inclusion criteria. As a result, it is unclear whether genetic variants of the serotonin transporter facilitate selective attention in conditions that are characterized by attentional biases, such as anxiety disorders and unipolar depression.

As with any genetic association study, population stratification is a potential concern (Hutchison, Stallings, McGeary, & Bryan, 2004). Population stratification occurs in studies in which the cases and controls differ with respect to their ethnic background or another variable that may have led to a pattern of nonrandom mating. In our study, this confound is unlikely because the vast majority of participants were White, and ethnicity was unrelated to attentional bias scores. An additional concern is that recent research has found evidence of a single nucleotide polymorphism in the long version of the 5-HTTLPR promoter polymorphism (Hu et al., 2005). This finding suggests the possibility of a triallelic system. Future studies should include sufficient power to examine this possibility. Third variable explanations, such as an undiagnosed anxiety disorder or the possibility that the 5-HTTLPR promoter polymorphism is in linkage disequilibrium with another functional genetic marker, should also be considered as explanations for the observed effects. Finally, we should note that there is

debate within the literature regarding which type of dot-probe task (e.g., responding to the location of the probe versus to the type of probe presented) best captures attentional biases. Although one study (Mogg & Bradley, 1999) failed to find substantive differences in the performance of these two versions, researchers should continue to explore how to best assess attentional bias (cf. Fox, Russo, Bowles, & Dutton, 2001).

In conclusion, our findings suggest that the 5-HTTLPR polymorphism should be considered in future attentional bias research. Doing so may enhance the explanatory power of cognitive models of psychopathology. Indeed, genetic information may help to identify a subset of individuals for whom cognitive models of psychopathology may be particularly relevant. Understanding the complex relations among biological, cognitive, social, and behavioral levels of analysis is critical for developing a comprehensive understanding of abnormal behavior. We believe this study represents an exciting preliminary step toward that important goal.

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