

Negative cognitive response to a sad mood induction: Associations with polymorphisms of the serotonin transporter (5-HTTLPR) gene

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Increased negative thinking in response to sad mood states has been identified as a marker of depression risk. The present study examined whether polymorphisms of the serotonin transporter (5-HTTLPR) gene were associated with the tendency to endorse negative cognition after sad or neutral mood inductions in a healthy college student sample. Non-depressed participants were genotyped for the 5-HTTLPR and then viewed films designed to elicit a sad mood ($n = 30$) or a neutral mood ($n = 23$). Analyses indicated that individuals homozygous for the short 5-HTTLPR allele endorsed more negative cognition following a sad mood induction than individuals homozygous for the long 5-HTTLPR allele. Negative cognition did not vary as a function of 5-HTTLPR genetic status in the neutral mood condition. These preliminary results suggest that genetic variation of the serotonin transporter may contribute to depression vulnerability via a tendency to think more negatively in response to events that elicit sad mood.

A number of studies have now documented that increases in negative cognition following a dysphoric mood induction are associated with depression vulnerability (see Scher, Ingram, & Segal, 2005, for a review). Depression-vulnerable people have been shown to exhibit a more negative cognitive response to dysphoric mood inductions across cognitive outcomes,

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including dysfunctional attitudes (Miranda, Gross, Persons, & Hahn, 1998; Segal, Gemar, & Williams, 1999), biased information processing (Ingram & Ritter, 2000; Taylor & Ingram, 1999), and implicit associations between the self and negative traits (Gemar, Segal, Sagrati, & Kennedy, 2001). Further, Segal et al. (2006) documented that increases in dysfunctional thinking following a sad mood induction prospectively predicted depression relapse among a large sample of adults recently treated for depression. This research suggests that cognitive response to sad mood states may play a key role for understanding vulnerability to depression.

Depression vulnerability has also been linked to certain variants of the serotonin transporter gene. Research conducted by Caspi et al. (2003) and others (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005) indicates that polymorphisms of the serotonin transporter (5-HTTLPR) gene appear to moderate the association between life stress and depression onset. Life stress robustly predicts depression onset for individuals with two short 5-HTTLPR alleles. In contrast, life stress correlates weakly with depression onset among individuals homozygous for the long 5-HTTLPR allele. The association between life stress and depression onset fell in between the other two genetic groups for individuals with one short 5-HTTLPR allele and one long 5-HTTLPR allele.

Individuals homozygous for the short 5-HTTLPR allele thus appear to be more sensitive to the effects of life stress, which in turn contributes to depression onset. However, the psychological pathway through which the genetic variants of the 5-HTTLPR operate to influence stress sensitivity and confer depression onset has not been explored. As suggested by Segal et al. (2006), one promising possibility is that genetic variants of the 5-HTTLPR influence cognitive response to sad mood states, which in turn contributes to depression onset.

Although no research that we are aware of has examined links between genetic variants of the 5-HTTLPR and cognitive responses to dysphoric mood states, there is some emerging evidence that serotonin function is involved. Booij and Van der Does (2007) administered a tryptophan depletion procedure to remitted depressed patients and examined whether cognitive reactivity was associated with response to this procedure. Tryptophan depletion has been shown to temporarily lower serotonin function and exacerbate depressive symptoms. Further, individuals with two copies of the short 5-HTTLPR allele have been shown to have the strongest symptomatic response to this procedure (Neumeister et al., 2002). Interestingly, Booij and Van der Does (2007) found that self-reported cognitive reactivity (e.g., endorsing items such as, "When in a sad mood, I become more bothered by perfectionism") was a robust predictor of tryptophan depletion induced depressive symptoms. Other work has also linked the serotonin system to the endorsement of dysfunctional attitudes

among depressed and recovered depressed individuals (Meyer et al., 2003, 2004). Taken together, these data suggest that serotonergic mechanisms may play a role in the aetiology of a negative cognitive response to dysphoric moods.

The current study examined whether genetic variants of the serotonin transporter were associated with a negative cognitive response to a sad mood induction. Non-dysphoric participants were genotyped for the 5-HTTLPR and then randomly assigned to view a film clip designed to elicit a sad mood or a neutral mood. We then measured negative cognition with a modified version of the Automatic Thoughts Questionnaire (ATQ; Hollon & Kendall, 1980). We expected that individuals with two short 5-HTTLPR alleles (i.e., the group that is most sensitive to the effects of life stress) would be more likely to endorse negative cognition than the other 5-HTTLPR allele groups in the sad mood condition. In the neutral mood group, we did not expect any differences between allele groups.

METHOD

Participants

A total of 53 non-depressed undergraduate students (M age = 19.80 years, $SD = 2.30$; 31 female) from a university located in the Midwestern United States participated in partial fulfilment of course requirement. The vast majority of participants self-identified their ethnicity as Caucasian (45/53, 84.9%). Three students were Hispanic (5.7%), one was African American (1.8%), one was Asian (1.8%), one was Native American (1.8%), and two participants did not indicate their ethnicity (3.8%). Genotyping indicated that 15 (28.3%) participants were homozygous for the long 5-HTTLPR allele, 22 (41.5%) had 1 short 5-HTTLPR and 1 long 5-HTTLPR allele, and 16 (30.2%) were homozygous for the short 5-HTTLPR allele. These frequencies are in the expected range for Caucasian samples and therefore do not differ from Hardy Weinberg Equilibrium.

Genotyping

Genomic DNA were isolated from buccal cells using a modification of published methods (Freeman et al., 1997; Lench, Stanier, & Williamson, 1988; Meulenbelt, Droog, Trommelen, Boomsma, & Slagboom, 1995; Spitz et al., 1996). The cheeks and gums were rubbed for 20 s with three sterile, cotton-tipped wooden swabs. The swabs were placed in a 50 ml capped polypropylene tube containing lysis buffer (500 μ l of 1 M Tris-HCl; 200 mM disodium ethylene diaminetetracetic acid (EDTA), pH 8.0; 500 μ l of 10% sodium docecyl sulfate; and 100 μ l of 5 M sodium chloride). The subjects

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then rinsed out their mouths vigorously with 10 ml of distilled water for 20 s, and this was added to the 50 ml tube. The tubes were stored at 4°C until the DNA was extracted.

The 5-HTTLPR gene, which maps to 17q11.1–17q12, contains a 43 bp insertion/deletion in the 5' regulatory region of the gene (Heils et al., 1996). The VNTR in the promoter appears to be associated with variations in transcriptional activity: the long variant (528 bp) has approximately three times the basal activity of the shorter promoter (484 bp) with the deletion (Lesch et al., 1996). The assay is a modification of the method of Lesch and colleagues (Lesch et al., 1996). The primer sequences are: forward, 5'-GGCGTTGCCGCTCTGAATGC-3' (fluorescently labelled), and reverse, 5'-GAGGGACTGAGCTGGACAACCAC-3'. These primer sequences yield products of 484 or 528 bp. Allele sizes are scored by two investigators independently and inconsistencies were reviewed and rerun when necessary.

Questionnaires

AQ1 *Beck Depression Inventory-II (BDI; Beck & Steer, 1993)*. The BDI-II is a widely used self-report questionnaire to assess depression severity in non-clinical student populations (Dozois, Dobson, & Ahnberg, 1998). The BDI-II consists of 21 items and measures the presence and severity of cognitive, motivational, affective, and somatic symptoms of depression. Past reports indicate test-retest reliability is adequate (Beck et al., 1988a). The BDI-II has been found to be valid among non-clinical student samples (Beck et al., 1988a). Internal consistency reliability for this study was adequate ($\alpha = .75$).

AQ1 *Automatic Thoughts Questionnaire, modified (ATQ; Hollon & Kendall, 1980)*. The ATQ is a 30-item self-reported questionnaire that assesses degree of negative thinking about the self. Typically, participants indicate how frequently each statement occurred in the past week across a 5-point scale (1 = *not at all*, 5 = *all the time*). However, for the present study, the instructions were modified such that participants indicated how frequently each statement had occurred in the past week *up to the present moment*. Sample items include, "Why can't I ever succeed" and "My life is a mess". Previous factor analyses of the ATQ indicate that a single factor structure provides a good fit for the data, thus justifying the use of a total score (Hollon & Kendall, 1980; Netemeyer et al., 2002). In the current study, average ATQ total score was 11.51 ($SD = 8.19$; range = 0–32) and Cronbach's alpha was .87.

Sadness rating. Level of sadness was assessed before and after viewing the film stimuli. To quickly assess sad mood, participants responded to a

single item: "How sad or depressed do you feel right now?" Ratings were made on a 5-point scale ranging from 0 = "not at all" to 4 = "extremely". Mood states induced in the laboratory tend to be short in duration, so efficient assessments of mood, such as this one, are often required and used frequently in this type of research (Segal et al., 2006). Burisch has shown that brief measures can provide as much information as longer instruments, particularly when the construct being measured is straightforward (Burisch, 1984).

Film stimuli

Before viewing either film participants were given a few moments to become as relaxed and comfortable as possible. They were then told they were going to view a film and to become as involved with the video as possible. All participants were informed that they would not be tested on material presented in the video. When participants indicated they were ready to view the film, the experimenter started the film and left the testing room.

Sad film. To induce a sad mood, participants viewed an expanded version of a standardised film clip that has been shown to specifically elicit sadness (Gross & Levenson, 1995). The standard film clip is 170 s and is taken from the film, *The Champ*, in which the father of a young boy dies after suffering a severe beating during a boxing match. For the present study, we expanded the film clip so that it was 21 minutes in length. We did this because in pilot testing we did not find that the shorter version reliably induced sad mood states. The expanded version included all of the segments from the briefer version but in addition contained earlier segments from *The Champ* that further established the nature of the relationship between the boy and his father. In pilot testing, with college students, we found that this modified version induced a moderately intense and relatively pure sad mood state.

Neutral film. To induce a neutral mood, participants viewed a 21 minute segment from the first programme of an instructional series on statistics for college and high school classrooms (Consortium for Mathematics and Its Application, 1989). The video consists primarily of on-location footage in which a narrator describes how statistics are being used to help with contemporary and practical problems such as which of two recipes a pizza company should use, the timing of lightening strikes in Colorado, and the relationship between number of home runs hit and salary in major league baseball. In pilot testing, with college students, we found that viewing this video did not induce any changes in either positive or negative mood states.

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Procedure

All procedures were approved by institutional review boards. Depression severity was first assessed during mass pre-screening sessions. Participants with scores in the non-depressed range ($BDI-II \leq 9$) were contacted and invited to participate in a laboratory session. Upon arrival to the laboratory, participants were tested individually. After giving informed consent, participants completed a BDI-II. A score of 9 or below was required in order to participate further in this study ($M = 5.44$, $SD = 2.85$). Eighteen students scored above this threshold and were excluded from participation. The remaining 53 participants provided buccal cells for DNA analysis. Participants then completed a sadness rating and were randomly assigned to view the sad or neutral film. Following completion of the film, participants completed a second mood rating. After this second mood rating, participants completed the ATQ.

RESULTS

Manipulation check

As expected, participants who viewed the sadness-eliciting film reported a significant increase in sadness from before to after the viewing the film ($M = 0.21$, $SD = 0.49$; $M = 1.41$, $SD = 0.91$, respectively), $t(28) = 6.41$, $p < .001$. Change in sadness was not significantly related to 5-HTTLPR status ($ts < 1.5$, ns ; see Table 1), suggesting that a similar sad mood was induced across genetic groups. Mean scores indicated that the film induced participants to feel “a little” to “moderately” sad. In contrast, participants did not report significant change in sadness in the neutral mood condition, $t(22) = 1.00$, ns . Mean scores indicated that participants reported an absence of sadness before and after the neutral film clip ($M = 0.17$, $SD = 0.39$; $M = 0.09$, $SD = 0.28$).

TABLE 1

Mean (standard deviation) sadness rating for each 5-HTTLPR genotype group across mood conditions

	<i>ss</i>		<i>sl</i>		<i>ll</i>	
	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>
Sad film	0.36 (0.67)	1.54 (0.93)	0.15 (0.38)	1.14 (0.86)	0.00 (0.00)	1.80 (0.84)
Neutral film	0.00 (0.00)	0.00 (0.00)	0.12 (0.35)	0.00 (0.00)	0.30 (0.42)	0.20 (0.42)

Main analyses

215 In line with recommendations by Rosnow and Rosenthal (1989, 1995) and
an APA task force (Wilkinson, 1999), analyses focused on a priori
predictions rather than testing all possible main effects and interactions.
This approach is particularly relevant, as the preliminary nature of this study
constrained subject recruitment and resulted in relatively low statistical
220 power. Prior to conducting inferential analyses, standard box-plot analyses
were performed to identify statistical outliers. One outlier was observed for
the ATQ. This outlier was removed and estimated with full information
maximum likelihood methods (Schafer & Graham, 2002). All variables met
criteria for normality, as determined by the Kolmogorov–Smirnov test.

225 In the sad mood condition, we expected participants with two short
5-HTTLPR alleles to have the strongest negative cognitive response. In the
control condition, we did not expect any differences between 5-HTTLPR
allele groups. To test these hypotheses, we compared the mean ATQ score for
groups defined by the number of short alleles (i.e., 0, 1, 2) within each mood
condition. We also used regression analyses to estimate the linear association
230 between number of short 5-HTTLPR alleles and ATQ score within each
mood condition.

In the sad mood condition, individuals homozygous for the short
5-HTTLPR allele reported significantly higher ATQ scores than individuals
homozygous for the long allele, $t(14) = -2.27$, $p = .04$, $d = 1.40$ (see
235 Figure 1). ATQ scores for people with one copy of the short 5-HTTLPR
were in the middle range, as they did not significantly differ from those
with two copies of long, $t(17) = -0.88$, $p = .39$, $d = 0.54$, or short alleles,
 $t(23) = -1.38$, $p = .18$, $d = 0.56$. Regression analyses confirmed a significant
linear association between number of short alleles and negative cognition,
240 $b = 4.22$, $SE = 2.00$, $\beta = .37$, $t(28) = 2.11$, $p = .04$, $d = 0.80$. ATQ scores
increased 4.22 points for every additional short 5-HTTLPR allele (see
Figure 1).

In the neutral mood condition, there were no differences for ATQ score
between any of the 5-HTTLPR allele groups: ll vs. ss, $t(13) = 0.76$, $p = .76$,
245 $d = 0.16$; sl vs. ss, $t(11) = 0.53$, $p = .60$, $d = 0.29$; ll vs. sl, $t(16) = -0.25$,
 $p = .80$, $d = 0.12$. The linear association between number of short alleles
and ATQ score was non-significant, $b = -0.53$, $SE = 2.30$, $\beta = -.05$,
 $t(21) = -0.23$, $p = .82$, $d = 0.10$. Participants in the neutral mood condition
responded similarly to the ATQ regardless of 5-HTTLPR allele status.
250 Finally, we compared the linear association between number of short alleles
and ATQ score across mood-induction conditions. The difference between
groups was a medium effect, but this difference fell short of statistical
significance, $t(49) = 1.56$, $p = .12$, $d = 0.50$.

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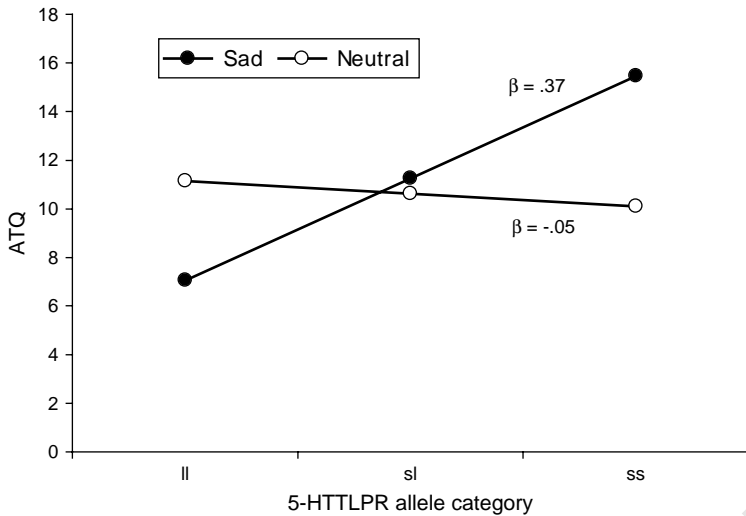


Figure 1. Association between number of short 5-HTTLPR alleles and ATQ score after viewing a sad or neutral film.

DISCUSSION

These preliminary data suggest that polymorphisms of the serotonin transporter gene (5-HTTLPR) are associated with a tendency to endorse negative thoughts following a sad mood induction. More specifically, in the sad mood condition, individuals who were homozygous for the short 5-HTTLPR allele reported significantly more negative cognition than individuals homozygous for the long 5-HTTLPR allele. In the neutral mood condition, all groups reported similar levels of negative cognition regardless of 5-HTTLPR polymorphism status. The linear association between number of short 5-HTTLPR alleles and negative cognition was significant in the negative mood condition but not the neutral condition. The difference between these two parameters was moderate (medium effect size), although it did fall short of statistical significance. Nevertheless, these data are consistent with the position that genetic variants of the 5-HTTLPR contribute to a tendency to think more negatively following a sad affective experience.

These findings point to an interesting possibility that variants of the 5-HTTLPR contribute to mood-linked cognitive reactivity. Interestingly, Segal et al. (2006) found that 33% of their sample displayed a marked decrease in dysfunctional attitudes after a sad mood induction, 37% displayed minimal change, and 29% displayed a marked increase. Those

275 displaying a marked increase were at greatest risk for subsequent relapse.
Based on findings from the current study, we speculate that individuals
homozygous for the long 5-HTTLPR allele might display a marked decrease
in cognitive reactivity and individuals homozygous for the short 5-HTTLPR
280 would report marked increases in cognitive reactivity. As Segal et al. (2006)
suggested, conducting such work might help to identify a potential pathway
via cognitive reactivity that links genetically influenced stress reactivity to
the expression of major depression.

Within the negative mood condition, it is particularly notable that we
observed significant genetic group differences (ss vs. ll) in negative thinking
285 despite no significant group differences in dysphoric mood. This suggests
that the 5-HTTLPR gene may influence how people respond to dysphoric
mood states. Dysphoric moods may more easily trigger negative self-referent
thoughts among short 5-HTTLPR allele carriers whereas dysphoric moods
may actually lead to a slight decrease in negative thoughts about the self in
290 long allele homozygotes. Indeed, several researchers have posited that the
ease with which negative self-referent cognition is activated plays a critical
role in predicting vulnerability to depression (Beevers, 2005; Booij & Van der
Does, 2007; Segal et al., 2006). The 5-HTTLPR gene may therefore make an
important contribution to this type of cognitive vulnerability.

Additional research is needed to determine the generality of the findings
from the current study. That is, it would be important to determine whether
295 the presence of short 5-HTTLPR alleles is also associated with other
cognitive factors thought to confer depression vulnerability, such as the
tendency to ruminate, endorse dysfunctional attitudes, or selectively attend
to negative stimuli. There is preliminary evidence for these cognitive
300 processes to be associated with genetic variants of the 5-HTTLPR (Beevers,
Gibb, McGeary, & Miller, 2007; Canli et al., 2006), but no research has
examined whether these associations are amplified or diminished following a
sad mood induction. Similarly, it would be intriguing to examine cognitive
305 responses to a positive mood induction. This would help to determine the
specificity of the current findings across emotional contexts.

Limitations of this study include small sample size (and attendant low
statistical power), absence of a comprehensive clinical assessment of current
or past psychopathology, and the use of a convenient college sample. Given
310 the encouraging findings from this preliminary study, future work in this
area should consider completing more thorough assessments of current and
lifetime psychopathology within a large sample of healthy controls that vary
in socioeconomic status and age. Interestingly, a recent review suggested that
the association between the 5-HTTLPR and depression may differ across the
315 lifespan (Uher & McGuffin, 2008). Future work should also consider using a
within-subjects design, where negative cognition is measured before and
after a sad mood induction. This approach may provide a more powerful test

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of hypotheses and would also be more consistent with how cognitive reactivity is typically assessed (Segal et al., 2006).

As with any genetic association study, population stratification is a potential concern (Hutchison et al., 2004). Population stratification occurs when cases and controls differ with respect to their ethnic background or another variable that may have led to a pattern of non-random mating. In our study, this confound is unlikely as the vast majority of participants were Caucasian and ethnicity was unrelated to scores on the ATQ. 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 (i.e., one short allele and two versions of the long allele). Future studies should include sufficient power to examine this possibility. Third variable explanations, such as undiagnosed clinical 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, future research should consider examining the effect of multiple genes on cognitive responses to dysphoric mood inductions. This would serve at least two purposes. First, it would determine whether any observed effects are specific to the 5-HTTLPR. We only genotyped the current sample for the 5-HTTLPR, so we were unable to perform such analyses. Further, it is unlikely that a cognitive vulnerability to depression will develop due to variability in a single gene. Promising genes may include variants of the catechol-O-methyltransferase (COMT) and tryptophan hydroxylase-2 (TPH2) genes, both of which have been associated with abnormal neural responses to emotional stimuli and depression (e.g., Eley et al., 2004; Smolka et al., 2005). Further, the brain derived neurotrophic factor (BDNF) genotype has been associated with rumination, a cognitive factor strongly associated with depression (Hilt, Sander, Nolen-Hoeksema, & Simen, 2007). Investigating the unique and combined impact of several genes may ultimately be critical for developing a more comprehensive understanding of the genetic aetiology of cognitive vulnerability to depression.

In conclusion, our findings suggest that polymorphisms of the 5-HTTLPR gene may contribute to a negative cognitive response following a sad mood induction. Incorporating a genetic level of analysis into cognitive vulnerability to depression research may ultimately lead to a more integrated model of depression risk and potentially identify a subset of individuals for whom cognitive models of psychopathology (and by extension cognitive-based treatments) may be particularly relevant. We believe understanding the interplay between biological, cognitive, social, and behavioural risk factors for depression will be critical for developing a

comprehensive understanding of the disorder. This study represents a preliminary step towards that important goal.

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