Serotonin Transporter Polymorphism Interacts With Childhood Adversity to Predict Aspects of Impulsivity
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A polymorphism in the promoter region of the serotonin transporter gene, 5HTTLPR, is linked to psychiatric diagnoses (e.g., Beitchman et al., 2003; Caspi et al., 2003), qualities of personality (e.g., Lesch et al., 1996), and overt and covert aspects of behavior (Munafò, Brown, & Hariri, 2008), often in Gene × Environment interactions (Caspì, Hariri, Holmes, Uher, & Moffitt, 2010). A common view is that this polymorphism underlies anxiety traits (Lesch et al., 1996; Lesch & Canli, 2006), with the S (short) allele being a marker for higher anxiety.

An alternative view, based partly on the fact that 5HTTLPR relates to several other traits, including agreeableness, conscientiousness, sensation seeking, and aggression (see Carver, Johnson, & Joormann, 2008), is that serotonergic function relates to a dimension of impulsive reactivity versus constraint (Depue, 1995; Depue & Spoopt, 1986; Spoopt, 1992), particularly impulsive reactivity to strong emotions. Most people think of impulsiveness in terms of rash actions (e.g., sensation seeking), but this view focuses instead on the reflexive versus deliberative nature of the response. In this view, inaction can be impulsive, if it is a reflexive response. Put differently, reactions to emotions diverge sharply by emotion. An impulsive response to anger is aggression. An impulsive response to desire is grabbing. Sadness, however, is a deactivating emotion—a call for passivity, for giving up (Frijda, 1986). An impulsive response to sadness is inaction.

The idea that impulsive reactivity can yield both active and passive behavioral responses would account for the fact that serotonergic function, and the 5HTTLPR polymorphism, have been related both to behaviors that are easily recognized as impulsive (e.g., impulsive aggression; Manuck, Kaplan, & Lotrich, 2006) and to behaviors that appear at first glance to be the antithesis of impulsive (e.g., the passive lethargy common in depression; Uher & McGuffin, 2010). We regard both behaviors as impulsive because both are reflexive; both reflect a lack of cognitive and behavioral control over responses to the respective emotions (i.e., anger and sadness).

Of course, not all impulsivity is about emotion. Impulsivity also reflects a lack of planfulness and a lack of perseveration (Whiteside & Lynam, 2001). The diversity of properties that are termed “impulsive” suggests that multiple mechanisms may...
underlie them, and that these mechanisms may have different underpinnings. Drawing on our earlier review (Carver et al., 2008), we hypothesized that 5HTTLPR is linked to impulsive reactivity to emotions. We had no prediction regarding other aspects of impulsivity.

To test this hypothesis, we gathered diverse measures of impulsiveness and related constructs. We included measures of impulsive reactions to negative emotions, to positive emotions, and to emotions in general. We also included measures that appear to have little to do with emotions and more to do with the ability to maintain one’s focus to complete tasks.

The 5HTTLPR polymorphism appears to have its effect most clearly under relatively extreme environmental conditions (Caspi et al., 2010; Uher & McGuffin, 2010), though the mechanism underlying this effect is far from clear (see Cole, 2009, on how context affects gene expression). Accordingly, we also examined childhood adversity and the interaction between genes and the environment.

Method

The final sample comprised 303 University of Miami undergraduates (195 females and 108 males; mean age = 18.81 years, SD = 1.94) with data on all measures. The sample was approximately half non-Hispanic Whites (n = 157) and a quarter Hispanics (n = 65), with the remainder relatively evenly divided among African Americans (n = 14), Caribbean islanders (n = 13), Asians (n = 23), self-identified “others” (n = 15), and 16 participants who did not report their ethnicity. Although chi-square analyses revealed no ethnic difference in allele distribution, ethnicity (dichotomized as non-Hispanic Whites vs. all other participants) was used as a control variable throughout the analysis.

Self-report measures were completed in group sessions early in the semester. A departmental Web site then listed opportunities for students to sign up to participate in further group sessions 1 to 3 weeks later. In those sessions, blood was drawn for genotyping, and more self-reports were completed along with other tasks.

Impulsiveness

Several measures bearing on impulsiveness were administered. These measures included some preexisting scales as well as item sets developed expressly for this study. Given the response burden (the sessions included many other measures), some scales were slightly abbreviated by selecting high-loading items from the originals. Responses to the items on each scale or subscale were made on 5-point scales (from 1, I agree a lot, to 5, I disagree a lot) and averaged to create a composite score for each measure of impulsiveness (except for one scale noted later).

Negative Generalization. Negative Generalization is a four-item subscale from a measure of potentially depressogenic cognitive tendencies (Carver, La Voie, Kuhl, & Ganellen, 1988). Items reflect the tendency to reflexively generalize from a single negative event to one’s broader sense of self-worth (Table 1). The mean, standard deviation, and alpha for this and other impulsiveness measures are in Table 1.

Urgency and Lack of Perseverance. The UPPS Impulsive Behavior Scale (Whiteside & Lynam, 2001) assesses impulsive tendencies within the five-factor personality model. The UPPS factors reflect distinct processes that might lead people to act without regard for potential adverse consequences. Two of the four UPPS subscales were administered—Urgency and Lack of Perseverance. Urgency is the tendency to experience strong impulses; about half the items on this subscale refer to impulses following from negative affect; the rest do not. Lack of Perseverance assesses the inability to stay focused on difficult or tedious tasks. We used 12 items from the Urgency subscale and 10 items from the Lack of Perseverance subscale.

Positive Urgency. The Positive Urgency Measure (Cyders et al., 2007) assesses the tendency of respondents to act recklessly or inappropriately when in positive moods. This measure predicts diverse risky behaviors (Cyders et al., 2007). We used seven items from this measure.

Self-Control. The Self-Control scale (Tangney, Baumeister, & Boone, 2004) is a measure of general self-control tendencies (we used the 13-item Brief scale). Self-control predicts grade point average, adjustment, alcohol abuse, and interpersonal skills (Tangney et al., 2004). Items on the Self-Control scale tend to focus on persistence in completing activities. To orient all scales used in the study in the same direction, we computed scores on this measure as lack of self-control (i.e., we reverse-scored this scale).

Laziness. The Behavioral Indicators of Conscientiousness (Jackson et al., 2010) is an inventory of behaviors related to conscientiousness. It asks respondents how often they engage in specific behaviors. Ratings are made on a scale from 1 (never) to 5 (very often) and averaged. We administered the Laziness scale, which reflects low conscientiousness.

Study-specific scales. A number of items that target very specific aspects of impulsiveness were written expressly for this study. The separation of these items into scales was verified by a principal component analysis.1 Sadness Paralysis (two items) is the tendency to react reflexively to sad feelings with inaction. Inability to Overcome Lethargy (seven items) is a more general inability to get moving despite having things to do (i.e., reflexive inaction). Emotions Color Worldview (three items) refers to having an emotional state bias perceptions of the world. Reflexive Reaction to Feelings (seven items) is responding reflexively and quickly when experiencing emotions. Distractibility (nine items) is the tendency for one’s attention to be drawn off task.
Genotyping

Genotyping was performed at the Hussman Institute of Human Genomics, University of Miami School of Medicine, using standard techniques derived from the method described in Lesch et al. (1996). Three nanograms of genomic DNA that was extracted from each blood sample were used in the amplification reaction. Cycling was performed on GeneAmp PCR Systems 9700 thermocyclers (Foster City, CA). End-point fluorescence was measured on the Applied Biosystems 7900 HT system (Foster City, CA). Genotype discrimination of results was then conducted using Applied Biosystems’ 7900 HT Sequence Detection Systems (Version 2.3) analysis software. To ensure genotyping accuracy, we included 32 quality-control samples of known genotype on the 384-sample plate.

The LL 5HTTLPR genotype was found in 31% of the participants, the SL genotype in 50%, and the SS genotype in 19%. This distribution was in Hardy-Weinberg equilibrium. Analyses treated participants with the three genotypes as distinct groups. Assays were also conducted for a more recently used triallelic categorization, in which one variant of the L (long) allele (Lg) functions as an S allele and another variant (La) functions as an L allele (Neumeister et al., 2006). Categorizing genotypes separating the L allele variants that way (i.e., LaLa: 23%; SLa/LgLg: 50%; SS/SLg/LgLg: 28%) also revealed a distribution in Hardy-Weinberg equilibrium.

Childhood adversity

Childhood adversity (hereafter, adversity) was assessed by a self-report measure that has been validated against clinical interviews (Taylor, Lerner, Sage, Lehman, & Seeman, 2004) and has been shown to interact with 5HTTLPR genotype in predicting depressive symptoms (Taylor et al., 2006) and diagnosis of depression (Carver, Johnson, Joormann, LeMoult, & Cuccaro, in press). Respondents rated 13 aspects of their early environment on a scale from 1 (not at all) to 5 (very often or very much). Items included whether the respondent felt cared...
for, was insulted or made to feel threatened, was abused, or observed violence between family members. Positively framed items were reverse-coded, and responses were averaged ($\alpha = .87$; range = 1.00–4.23, $M = 1.80$, $SD = 0.55$); higher values indicate a more adverse early environment.

**Results**

We began our analysis by reducing the impulsiveness-related measures to a smaller number of underlying variables, using both exploratory and confirmatory techniques. Exploratory analysis yielded three factors with eigenvalues greater than 1. A parallel analysis suggested that the third factor might represent overextraction. We used confirmatory analyses to test the three-factor model (with Urgency specified as loading on two of the factors, as occurred in the exploratory analysis) against a two-factor model combining two of the three factors (from an exploratory analysis forcing two factors). The three-factor model fit the data significantly better than the two-factor model. The three-factor model (with Urgency specified as loading on two factors, as occurred in the exploratory analysis) against a two-factor model combining two of the three factors (from an exploratory analysis forcing two factors). The three-factor model fit the data significantly better than the two-factor model, $\chi^2(3) = 39.75$, $p < .001$. Subsequent analyses used factor scores from the three-factor exploratory model as the outcome measures.

The pattern matrix is in Table 2. The substantive content of Factor 1 (Pervasive Influence of Feelings) reflects the tendency for emotions to strongly shape one’s orientation to the world. People with high levels of this factor have their worldview affected by temporary feelings, generalize reflexively from negative events, and react to sadness with inaction. Factor 2 (Follow-Through) centers on the tendency to carry tasks to their conclusion versus letting things go; this factor has no obvious involvement of reactions to emotion. The cross-loading of the Inability to Overcome Lethargy scale on Factors 1 and 2 reflects the fact that items on that measure reflect both a strong influence of feelings of fatigue and a failure to follow through. Factor 3 (Feelings Trigger Action) centers on impulsive behavioral reactivity to emotions, including positive emotions. The cross-loading of the Urgency scale on Factors 1 and 3 reflects the fact that some Urgency items specify responses to negative affect, and others more neutrally specify responses to “feelings.” The correlations between the three factors were as follows—Factors 1 and 2: $r = .36$; Factors 1 and 3: $r = .34$; and Factors 2 and 3: $r = .16$. The fact that these correlations were positive confirms that all three factors reflect impulsiveness; the relatively low magnitude of the correlations is consistent with the differences in their item content.

Having identified three aspects of impulsiveness, we tested for genetic effects using regression analysis. The main effect of adversity (centered), the main effect of genotype (LL, SL, or SS), and the control variables sex and ethnicity were entered as one block. The interaction between genotype and adversity was entered as a second step. Factor scores from the factor analysis were the outcomes.

The first block of predictors was significantly associated with Pervasive Influence of Feelings, $R^2 = .06$, $F(4, 298) = 4.66$, $p < .002$; unique effects were found for adversity, $t(298) = 2.41$, $p = .02$, and sex (females were higher on Factor 1 impulsiveness than males), $t(298) = 3.21$, $p = .002$. Entering the interaction between genotype and adversity increased the variance accounted for by the model, $\Delta R^2(1, 297) = 8.39$, $p < .005$, overall $R^2 = .09$. The interaction made a significant unique contribution, $\beta = 0.41$ ($SE = 0.14$), $t(297) = 2.90$, $p < .005$, $\Delta R^2 = .03$. Simple-slopes analysis determined that greater adversity was associated with greater impulsiveness among people with the SS genotype, $t(297) = 3.75$, $p < .001$, and those with the SL genotype, $t(297) = 2.90$, $p < .001$ (Fig. 1a). Among people with the LL genotype, there was a nonsignificant tendency for greater adversity to be associated with lower impulsiveness, $t(297) = 0.70$, $p = .48$.

The first block of predictors was significantly associated with Follow-Through, $R^2 = .05$, $F(4, 298) = 3.58$, $p < .01$; a unique effect was found for adversity, $t(298) = 2.83$, $p < .01$. Entering the interaction between genotype and adversity did not significantly increase the variance accounted for by the model.

**Table 2. Factor Loadings of Impulsiveness-Related Measures After an Oblimin Rotation**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Factor 1: Pervasive Influence of Feelings</th>
<th>Factor 2: Follow-Through</th>
<th>Factor 3: Feelings Trigger Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Generalization</td>
<td>.85</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sadness Paralysis</td>
<td>.80</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Emotions Color Worldview</td>
<td>.71</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Inability to Overcome Lethargy</td>
<td>.54</td>
<td>.39</td>
<td>—</td>
</tr>
<tr>
<td>Lack of Perseverance</td>
<td>—</td>
<td>.88</td>
<td>—</td>
</tr>
<tr>
<td>[Lack of] Self-Control</td>
<td>—</td>
<td>.79</td>
<td>—</td>
</tr>
<tr>
<td>Laziness</td>
<td>.38</td>
<td>.61</td>
<td>—</td>
</tr>
<tr>
<td>Distractibility</td>
<td>.38</td>
<td>—</td>
<td>.56</td>
</tr>
<tr>
<td>Reflexive Reaction to Feelings</td>
<td>—</td>
<td>—</td>
<td>.83</td>
</tr>
<tr>
<td>Positive Urgency Measure</td>
<td>—</td>
<td>.30</td>
<td>.69</td>
</tr>
<tr>
<td>Urgency</td>
<td>.42</td>
<td>—</td>
<td>.44</td>
</tr>
</tbody>
</table>

Note: Loadings below .3 are omitted from this table.
The first block of predictors was not significantly associated with Feelings Trigger Action, $R^2 = .01, F(4, 298) = 1.05, p = .38$. Entering the interaction between genotype and adversity significantly increased the variance accounted for by the model, $\Delta F(1, 297) = 7.09, p < .01$, overall $R^2 = .04$; the interaction made a significant contribution to the model, $\beta = 0.39 (SE = 0.15), t(297) = 2.66, p < .01, \Delta R^2 = .023$. Simple-slopes analysis determined that greater adversity was associated with greater impulsiveness among people with the SS genotype, $t(297) = 3.75, p = .001$, and those with the SL genotype, $t(297) = 2.90, p = .005$ (Fig. 1b); among people with the LL genotype, there was a nonsignificant tendency for greater adversity to be related to lower impulsiveness, $t(297) = 0.70, p = .48$.

Reanalysis using the triallelic categorization scheme (i.e., treating Lg alleles as S alleles) yielded similar results (Fig. 2). The interaction between genotype and adversity made a significant unique contribution to the model predicting Pervasive Influence of Feelings, $\beta = 0.30 (SE = 0.15), t(287) = 2.04, p < .05, \Delta R^2 = .02$. Greater adversity related to greater impulsiveness among people with the SS/SLg/LgLg genotype, $t(287) = 3.13$, $p = .001$; among people with the LL genotype, $t(287) = 0.80, p = .42$.
Among people with the SS/Lg/LgLg genotype, $t(287) = 2.51, p = .002$, and those with the SLa/LgLa genotype, $t(287) = 2.51, p = .03$. The interaction between genotype and adversity also made a significant unique contribution to the model predicting Feelings Trigger Action, $\beta = 0.34$ (SE = 0.15), $t(287) = 2.26, p < .01, \Delta R^2 = .02$. Greater adversity predicted greater impulsiveness among people with the SS/SLg/LgLg genotype, $t(287) = 2.86, p = .005$, but not among people with the SLa/LgLa genotype, $t(287) = 1.73, p = .085$, or the LaLa genotype (Fig. 2).

Discussion

Our results indicate that impulsive reactions to emotions are distinguishable from impulsive tendencies to be drawn off task in ways that do not involve emotions. The S allele in combination with childhood adversity predicted higher endorsement of both kinds of emotion-related impulsivity—the triggering of impulsive actions by emotions (including positive emotions; Factor 3) and the tendency to let emotions pervade and color one’s orientation to the world (Factor 1). This interaction did not emerge for endorsement of being drawn off task in ways that do not involve emotion (Factor 2). Although the data suggest tendencies toward crossover interactions (i.e., S carriers with very low adversity reported the lowest levels of impulsiveness), the extent of crossover was very slight, thus only hinting at, rather than strongly supporting, the argument that the S allele confers plasticity of reactions (Belsky & Pluess, 2009).

Several aspects of this study may limit its generalizability. The sample was well educated and young, and had had relatively low exposure to childhood adversity. The measures of childhood adversity and impulsivity, being self-reports, may have been biased. The scales we used to measure impulsiveness do not cover all aspects of impulsiveness. As is true of most genetic effects, and particularly interactions, the effects were small. Despite these limitations, the study has potentially important implications.

The first implication concerns the role of 5HTTLPR in human experience. As noted in the introduction, it is widely believed that 5HTTLPR marks anxiety-related traits. That view does not fully fit our results. It would be consistent with the finding for Factor 1, which reflects a kind of contagion from (largely negative) emotions to the person’s life space. It does not, however, fit the finding for Factor 3, which reflects the triggering of impulsive actions by emotions in general, including positive emotions. The finding for Factor 3 does, however, fit a view in which 5HTTLPR is a marker for impulsiveness (vs. control) in reacting to emotions (Carver et al., 2008; Depue, 1995; Depue & Spoont, 1986; Spoont, 1992).

Second, in supporting the link between 5HTTLPR and impulsive reaction to emotions, the findings shed light on why 5HTTLPR relates to a bewildering diversity of psychopathology, ranging from depression and anxiety to violent aggression and attention-deficit disorder. That is, 5HTTLPR relates to deficits in the ability to regulate cognition and behavior in responding to emotion. Different emotions evoke different responses to be controlled and regulated. Thus, the form of psychopathology (or of personality) expressed by S allele carriers depends partly on tendencies other than impulsiveness, such as propensity toward certain emotions (Depue & Lenzeweger, 2005), including positive ones. To fully explore this idea, research must examine effects of 5HTTLPR in combination with diverse emotional tendencies.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Note

1. This analysis is available from the first author.

References


