Gene Effects and G x E Interactions in the Differential Prediction of Three Aspects of Impulsiveness

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What is This?
Gene Effects and G × E Interactions in the Differential Prediction of Three Aspects of Impulsiveness

Charles S. Carver¹, Joelle LeMoult², Sheri L. Johnson³, and Jutta Joormann⁴

Abstract
Several polymorphisms relevant to dopamine and serotonin have been identified as potential contributors to individual differences in impulsivity versus self-control. Because impulsivity is a multifaceted construct, a need remains to examine more closely how various genes relate to different aspects of impulsivity. We examined four dopamine-related polymorphisms and the serotonin transporter as predictors of three aspects of impulsivity, two bearing on impulsive reactions to emotions and one on difficulty in completing intended actions. Early adversity was also examined as a potentiator of genetic effects. Undergraduates completed measures of impulsivity and early adversity and were genotyped. COMT, BDNF, DRD4, and 5HTTLPR (the latter two in interaction with early adversity) made independent contributions to prediction of Pervasive Influence of Feelings. BDNF made a contribution to Lack of Follow-Through. ANKK1 and 5HTTLPR (both in interaction with early adversity) made independent contributions to Feelings Trigger Action. Thus, five polymorphisms contributed to predicting impulsivity, but different polymorphisms related to different aspects.

Keywords
impulsiveness, DRD4, BDNF, COMT, ANKK1, 5HTTLPR

Impulsivity versus self-control is an important trait dimension, which also has robust relations to diverse psychopathologies (Johnson, Carver, & Joormann, 2013). The construct is very broad, however, with multiple distinguishable facets that are not strongly correlated (Sharma, Markon, & Clark, 2014; Smith et al., 2007; Whiteside & Lynam, 2001). Thus, impulsive qualities are reflected in a wide range of measures, including measures of sensation seeking, difficulty overcoming prepotent responses, distractibility, difficulty delaying gratification, reactivity to emotions, and more.

Impulsiveness is widely viewed as reflecting strong approach tendencies, driven at least partly by the dopaminergic system. Dopamine is implicated in “wanting” (Berridge, 2007) and in effort in the pursuit of goals (Kurniawan, Guitart-Masip, & Dolan, 2011; Salamone & Correa, 2002), and has been linked to hyperactivity, reward seeking, extraversion, and novelty seeking (Buckholtz et al., 2010; Comings & Blum, 2000; Neter, 2006). Genes affecting the dopaminergic system thus are likely candidates to underlie impulsivity-related personality traits and disorders. The following sections describe four dopamine-related polymorphisms that have been linked to aspects of impulsiveness.

Dopamine-Related Genes

DRD4. DRD4 (rs1805186) refers to a variable number of tandem repeats (VNTR) in exon 3 of a gene related to dopaminergic function. Research typically focuses on the presence versus absence of the seven-repeat (long) allele (generally operationalized as 7 or higher vs. all less than 7). This allele is believed to lessen D4 receptor responsiveness and reduce dopamine-binding efficiency (Asghari et al., 1995; Cravchik & Goldman, 2000). This is thought to result in elevated approach or approach-related impulsiveness among carriers of the long allele.

Consistent with this, the longer allele has been linked to lower conscientiousness (Benjamin et al., 1996), riskier task decisions (Carpenter, Garcia, & Lum, 2011; Roussos, Giakoumaki, & Bitsios, 2009), and psychopathologies that involve impulsivity, such as attention-deficit hyperactivity disorder (ADHD; Faraone, Doyle, Mick, & Biederman, 2001; Li, Sham, Owen, & He, 2006; Wu, Xiao, Sun, Zou, & Zhu, 2012), drug use (McGeary, 2009), and problem alcohol use (Ray et al., 2008).
The long allele has also been associated with greater novelty seeking (Benjamin et al., 1996), though questions have been raised about that link (Schinka, Letsch, & Crawford, 2002). Instead of main effects, some studies have found interactions between DRD4 and early adversity (which may potentiate the genetic effect) in predicting sensation seeking (Sheese, Voelker, Rothbart, & Posner, 2007), delay discounting (Sweitzer et al., 2013), and externalizing problems (Bakermans-Kranenburg, & van Ijzendoorn, 2006).

ANKK1. ANKK1 (rs1800497), formerly known as DRD2 Taq1a, is also linked to dopaminergic function. Taq1a is actually not located within the DRD2 gene, as previously believed, but within the neighboring ANKK1 gene (Neville, Johnstone, & Walton, 2004). Carriers of the A1 allele have fewer D2 receptors than those without the A1 (Ritchie & Noble, 2003).

The A1 allele has been linked to greater reward responsiveness (Lee, Ham, Cho, Lee, & Shim, 2007) and extraversion (Smillie, Cooper, & Pickering, 2011), and to impulsivity on a card sorting task (White, Morris, Lawford, & Young, 2008) and a delay discounting task (Eisenberg et al., 2007). Some have also found a link between the A1 allele and Novelty seeking or sensation seeking (Biederman et al., 2008; Ratsma, Stelt, Schoffelmeer, Westerveld, & Boudewijn Gunning, 2001). This allele has also been linked to ADHD (Bobb, Castellanos, Addington, & Rapoport, 2006; Sery et al., 2006) and substance abuse (Munafò, Matheson, & Flint, 2007; Noble, 2003).

COMT. The enzyme catechol-O-methyltransferase (COMT) is involved in degradation of several catecholamines, including dopamine. The most commonly studied polymorphism in the COMT gene (rs4680) is characterized by a methionine (met) to valine (val) substitution at codon 158. The met allele results in higher levels of extracellular dopamine, particularly in the prefrontal cortex (Chen et al., 2004). The met allele has been linked to larger task switching costs, whereas the val predicts greater cognitive flexibility (Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010). This has been interpreted as indicating that dopamine facilitates maintaining cognitive representations when confronting distractors, whereas low dopamine facilitates change in cognitive representation (Mier, Kirsch, & Meyer-Lindenberg, 2010).

The met allele of this polymorphism has been associated with novelty seeking (Golimbet, Alfimova, Gritsenko, & Ebstein, 2007) and alcohol dependence in the context of childhood adversity (Schellekens et al., 2013). The met allele has also been linked to greater expression of anger (Rujescu, Giegling, Gietl, Hartmann, & Möller, 2003) and to higher levels of corticolimbic reactivity to negative emotional stimuli (Drabant et al., 2006; Smolka et al., 2005), which has been interpreted as a predisposition toward inflexible processing of affective stimuli (Waugh, Dearing, Joormann, & Gotlib, 2009).

BDNF. Brain-derived neurotrophic factor (BDNF) is involved in neuroplasticity and protection against stress-induced neural damage. BDNF also plays a role in the mesolimbic dopamine pathway, where it increases the release of dopamine (Neal, Cunningham, Lever, Pezet, & Malcangio, 2003). BDNF also controls the expression of the dopamine D3 receptor via a mechanism involving stimulation of the dopamine D1 receptor (Guillin et al., 2001).

The genetic marker for BDNF that is most studied is often referred to as C667T (rs6265), the met allele being associated with lower BDNF activity (Chen, Bath, McEwen, Hempstead, & Lee, 2008). The met allele has been linked to elevations in alcohol problems (Colzato et al., 2011; Shin et al., 2010), drug use (Cheng et al., 2005), eating disorders (Gralcak et al., 2007), and increased risk of suicide in depressed persons (Sarchiapone et al., 2008). Other studies have linked the met allele in interaction with life adversity to depression or depressive symptoms (Aguilera et al., 2009; Carver, Johnson, Joormann, LeMoult, & Cuccaro, 2011). The met allele has also been associated with elevations in the tendency to ruminate (Beever, Wells, & McGee, 2009) and elevations in Harm Avoidance (Montag, Basten, Stelzel, Fiebach, & Reuter, 2010). On the other hand, there are some inconsistencies in the literature, with the val allele being linked in some studies to bipolar disorder (Neves-Pereira et al., 2002; Sklar et al., 2002), although these findings have not been consistently replicated (Kanazawa, Glatt, Kla-Keating, Yoneda, & Tsuang, 2007).

Serotonin

Another neurotransmitter implicated in impulsiveness is serotonin (Carver, Johnson, & Joormann, 2008). Serotonergic function is thought to constrain excitatory amygdala activity (Hariri & Holmes, 2006; Hariri & Weinberger, 2003). Serotonergic influence on impulsiveness thus is sometimes characterized as constraining impulses (Carver, Johnson, Joormann, Kim, & Nam, 2011; Depue, 1995; Nigg, 2006; Spoont, 1992). The gene most often examined in this context is the serotonin transporter (5HTTLPR). Carriers of the short allele appear to show less inhibitory regulation of the amygdala than those with the long allele (Heinz et al., 2005).

Serotonergic function may be particularly relevant to constraining impulsive responses to emotions. Evidence of this comes from several sources, but particularly salient is work linking impulsive reactions to anger to low serotonergic function (reviewed by Carver et al., 2008). The short allele of 5HTTLPR has also been related independently to self-reports of impulsive reactions to diverse emotions, including positive emotions (Carver, Johnson, Joormann, Kim, et al., 2011).

Present Research

Much research on involvement of these various genes in impulsiveness examines one gene at a time. Here we examined all of these five genes in the same study. Since some genetic effects are potentiated by exposure to early adversity (Boulle et al., 2012; Champagne, 2010), yielding gene by environment (G × E) interactions, we also assessed early life adversity.
It is also the case that research examining genes and impulsivity has used measures that vary considerably in how impulsiveness is manifested, and generally one measure at a time. In contrast, the study reported here examined three self-report aspects of impulsivity, which were derived previously from an array of measures (Carver, Johnson, Joormann, Kim, et al., 2011; described in Method section; see also Supplemental Materials found at http://spps.sagepub.com supplemental). Two latent variables from that prior analysis concern aspects of impulsive reactions to emotions. One focuses mostly on impulsive cognitive reactions to (mostly negative) emotions, such that the arousal of an emotion reflexively colors the person’s view of the world. Another focuses on the impulsive triggering of actions by emotions (including positive emotions). A final factor does not contain content bearing on reactions to emotions, but instead captures tendencies to be easily distracted away from intended actions by other things.

The two factors concerning impulsive reactions to emotions have been related to a range of psychopathological tendencies, including mania vulnerability, anxiety, depression, suicidality, alcohol problems, aggressive tendencies, and borderline personality traits (Carver, Johnson, & Joormann, 2013; Johnson, Carver, & Joormann, 2013; Johnson, Carver, Mulé, & Joormann, 2013). In contrast, the factor bearing on completing intended actions had a unique relation only to alcohol problems. The differential validity of these aspects of impulsivity with respect to these outcomes suggests the importance of investigating differences in their origins.

Method

Procedures were approved by the University of Miami institutional review board. Some of the self-reports were collected in undergraduate classes at the start of the semester. A description of the project was then posted on a website, where interested persons signed up for sessions (groups of 20), in which they gave blood for genotyping and completed additional self-reports, plus tasks unrelated to this article. The analyses reported here used only participants who had complete data on all measures (N = 298, 191 female). Mean age was 18.81 years (standard deviation [SD] = 1.95); the sample self-identified as 54% Caucasian, 23% Hispanic, 8% Asian, and the rest divided among African American, Caribbean, and “other.” For purposes of data analysis, the sample was divided into non-Hispanic white versus all others.

Genotyping was performed by the laboratories of the Hussman Institute of Human Genomics, University of Miami Miller School of Medicine. Genotyping was done for the GrA (valinermethionine) variation at position 758 of the BDNF coding sequence (rs6265); for the single nucleotide protein located on exon 8 of the ANKK1 gene (rs1800497); and for the met to val substitution at codon 158 of the COMT gene, all using Taqman allelic discrimination. Custom analyses, conforming to established protocols, were used for DRD4 and 5HTTLPR.

BDNF frequencies were val/val 66%, val/met 28%, met/met 7%, which was not in Hardy–Weinberg equilibrium, with more val/met and fewer val/met than expected. As in previous studies, carriers of one or more met alleles were combined and compared against val/met. ANKK1 frequencies were GG 64%, AG 31%, AA 5%, in Hardy–Weinberg equilibrium. As in previous studies, carriers of one or more A alleles were combined and compared against GG. COMT frequencies were met/met 19%, val/met 52%, val/val 29%, in Hardy–Weinberg equilibrium. Given this distribution, COMT was treated as three groups. DRD4 frequencies were short/short 68%, short/long 28%, long/long 5%, in Hardy–Weinberg equilibrium. Consistent with previous studies, carriers of one or more long allele were combined and compared against those homozygous for the short allele. 5HTTLPR frequencies were 30% LL, 50% SL, and 20% SS, in Hardy–Weinberg equilibrium. Analyses treated the three as distinct groups.

Impulsiveness Measures

Several measures bearing on impulsiveness were administered, some preexisting, others developed for this project (Carver, Johnson, Joormann, Kim, et al., 2011). Given response burden (sessions included many measures), some scales were slightly abbreviated by selecting highest loading items from the originals. Items were reverse-coded as needed, so that higher values indicate greater impulsivity. Unless indicated otherwise, responses were on a 1–5 scale of agreement and responses were averaged (all items of each scale are in Supplemental Materials found at http://spps.sagepub.com supplemental).

Negative generalization. Negative Generalization is a 4-item subscale from a measure of depressogenic cognitive tendencies (Carver, La Voie, Kuhl, & Ganellen, 1988). Items reflect reflexively generalizing from a single negative event to the broader sense of self-worth (e.g., “When even one thing goes wrong I begin to wonder if I can do well at anything at all”; \( M = 2.99, \text{SD} = .95, \kappa = .78 \)).

Urgency and lack of perseverance. The UPPS Impulsive Behavior scale (Whiteside & Lynam, 2001) assesses impulse tendencies within the five-factor personality model. Subscales reflect distinct processes that might lead people to act without regard for potential consequences. Two subscales were used. Urgency is the tendency to experience strong impulses (\( M = 2.78, \text{SD} = .88, \kappa = .88 \)); some items indicate that the impulses either follow from or lead to negative affect (e.g., “When I am upset I often act without thinking”), the rest do not specify negative valence (e.g., “It is hard for me to resist acting on my feelings”). Lack of Perseverance assesses inability to stay focused on difficult or tedious tasks (e.g., “I am a productive person who always gets the job done” [reversed]; \( M = 1.98, \text{SD} = .69, \kappa = .87 \)).

Positive urgency. The Positive Urgency Measure (Cyders et al., 2007) assesses the tendency to act recklessly or inappropriately when experiencing positive emotions (Cyders & Smith, 2008; e.g., “I tend to act without thinking when I am really excited”);
Laziness. The Behavioral Indicators of Conscientiousness (Jackson et al., 2010) is an inventory of behaviors related to conscientiousness (self-control). It asks how often respondents (e.g., “I am able to work effectively toward long-term goals”; \( M = 2.63, SD = .70, \alpha = .83 \)).

Self-control. The Self-Control scale (Tangney, Baumeister, & Boone, 2004) is a measure of self-control tendencies versus impulsiveness (we used the 13-item Brief version). It predicts grade point average, adjustment, alcohol abuse, and interpersonal skills. Items tend to focus on persistence in completing activities (e.g., “I am able to work effectively toward long-term goals”; \( M = 2.29, SD = .81, \alpha = .81 \)). It has predicted risky behaviors such as vandalism (Cyders et al., 2007) and high alcohol consumption per sitting.

Laziness. The Behavioral Indicators of Conscientiousness (Jackson et al., 2010) is an inventory of behaviors related to conscientiousness (self-control). It asks how often respondents engage in specific behaviors, from 1 (never) to 5 (very often). We administered the Laziness scale (low conscientiousness), reflecting lack of carry-through (e.g., “Watch TV instead of taking care of responsibilities”; \( M = 2.71, SD = .58, \alpha = .80 \)).

Project-specific scales. Items intended to target very specific reflections of reactivity versus control were written for the larger project from which this study is drawn; the formation of separate scales was determined by principal components analysis (Carver, Johnson, Joormann, Kim, et al., 2011). Sadness Paralysis is reacting reflexively to sad feelings with inaction (e.g., “I respond to feeling sad by just stopping moving,” \( M = 2.30, SD = .96, \alpha = .77 \)). Inability to Overcome Lethargy is a more general inability to get moving despite having things to do—reflexive inaction, in response to feelings of fatigue (e.g., “It’s hard to get myself moving, even when I know what I want to do,” \( M = 2.44, SD = .89, \alpha = .87 \)). Emotions Color Worldview reflects the experience of having an emotion lead reflexively to biased perceptions of the world (e.g., “When I have emotional experiences, they strongly influence how I look at life,” \( M = 3.60, SD = .94, \alpha = .77 \)). Reflexive Reaction to Feelings reports the tendency to act reflexively and quickly when experiencing emotions (e.g., “I react impulsively to my feelings,” \( M = 2.89, SD = .83, \alpha = .86 \)). Distractibility is the tendency to be drawn off-task readily (e.g., “I am easily distracted by stray thoughts,” \( M = 3.08, SD = .95, \alpha = .90 \)).

Reduction of Impulsiveness Measures

The measures of impulsiveness described above have been previously reduced to three latent variables (Carver, Johnson, Joormann, Kim, et al., 2011) using a combination of exploratory and confirmatory analyses (for loadings of the individual scales on the three factors, see Supplementary Materials found at http://ssps.sagepub.com/supplemental). Factor 1 (Pervasive Influence of Feelings) reflects a tendency for emotions to reflexively shape the person’s mental orientation to the world. Its main contributors are Negative generalization, Sadness paralysis, Emotions color worldview, Inability to overcome lethargy, and Urgency. Factor 2 (Lack of Follow-Through) centers on the tendency to complete tasks versus being distracted away. Its main contributors are Lack of perseverance, Self-control (reverse-scored), Laziness, and Distractibility. Factor 3 (Feelings Trigger Action) centers explicitly on impulsive behavioral reactivity to emotions, including positive emotions. Its main contributors are Reflexive reactions to feelings, Positive urgency, and Urgency. The cross-loading of the Urgency scale on Factors 1 and 3 appears to reflect the fact that some Urgency items specify responses to negative affect and others more neutrally specify responses to “feelings.”

Three factor scores for each participant were created from the factor analysis, yielding standardized values across the sample for each factor. The factor scores correlated positively but not strongly with one another (.36 to .16). The factor scores were the dependent measures in the analyses reported here. Results are reported such that higher values on the factor reflect greater impulsiveness.

Early Adversity

Early adversity was assessed by a self-report called Risky Families, which has been validated against clinical interviews (Taylor, Lerner, Sage, Lehman, & Seeman, 2004). One study found that reports on this scale interacted with 5-HTTLPR in predicting depression symptoms (Taylor et al., 2006); another study found a similar interaction in predicting diagnosis of major depression (Carver, Johnson, Joormann, LeMoult, et al., 2011). Respondents rate 13 aspects of their early family environment on 5-point scales. Items assess whether the respondent, for example, had felt loved and cared for; was insulted, sworn at, or made to feel threatened; was shown physical affection; was pushed, grabbed, shoved, or slapped; was verbally or physically abused; observed violence or aggression between family members; lived with a substance abuser. Responses were averaged (\( M = 1.80, SD = .55, \alpha = .82 \)), with higher values representing more adverse early environments.

Results

All analyses included gender and ethnicity (non-Hispanic white vs. all others) as covariates and used an alpha of .05. Risk was centered to reduce multicollinearity. Genotypes were dummy coded (0, 1) except for COMT and 5HTTLPR, which were coded −1, 0, and 1. Gene by Risk interaction terms were created by multiplying centered Risk by the coding of each gene. Each impulsiveness factor score was analyzed separately, by hierarchical multiple regression. Each analysis entered sex, ethnicity, and risk on the first step, all five gene main effects on a second step, and all five gene by risk interactions on a third step.¹

Impulsiveness Factors

Table 1 displays the cumulative variance accounted for after each step in the model for Pervasive Influence of Feelings, along with the final βs, t values, and p values for each predictor variable in the analysis. As can be seen there, significant independent main effects emerged for gender (women higher than
Table 1. Hierarchical Multiple Regression Analysis of Impulsivity Factor 1, Pervasive Influence of Feelings, From Risk, Sex, Ethnicity, Five Polymorphisms, and Interactions Between Polymorphisms and Risk.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Final β</th>
<th>t(284)</th>
<th>p</th>
<th>Cumulative $r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>.08</td>
<td>.90</td>
<td>.37</td>
<td>.052</td>
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<tr>
<td>Sex</td>
<td>-.18</td>
<td>3.14</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>.02</td>
<td>.39</td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4</td>
<td>-.03</td>
<td>-.51</td>
<td>.61</td>
<td>.085</td>
</tr>
<tr>
<td>BDNF</td>
<td>.13</td>
<td>2.38</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>COMT</td>
<td>-.13</td>
<td>2.28</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>ANKK1</td>
<td>-.02</td>
<td>-.41</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>5HTTLPR</td>
<td>-.05</td>
<td>-.95</td>
<td>.35</td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4 × Risk</td>
<td>.17</td>
<td>2.27</td>
<td>.03</td>
<td>.132</td>
</tr>
<tr>
<td>BDNF × Risk</td>
<td>-.03</td>
<td>-.37</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>COMT × Risk</td>
<td>.01</td>
<td>.16</td>
<td>.87</td>
<td></td>
</tr>
<tr>
<td>ANKK1 × Risk</td>
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<td>-.26</td>
<td>.80</td>
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<tr>
<td>5HTTLPR × Risk</td>
<td>.17</td>
<td>2.93</td>
<td>.004</td>
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Final model $F(13, 284) = 3.31, p < .001.$

Table 2. Hierarchical Multiple Regression Analysis of Impulsivity Factor 2, Lack of Follow-Through, From Risk, Sex, Ethnicity, Five Polymorphisms, and Interactions Between Polymorphisms and Risk.

<table>
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<tr>
<th>Predictor</th>
<th>Final β</th>
<th>t(284)</th>
<th>p</th>
<th>Cumulative $r^2$</th>
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<tr>
<td>Step 1</td>
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<tr>
<td>Risk</td>
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<td>.41</td>
<td>.049</td>
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<td>Sex</td>
<td>.10</td>
<td>1.72</td>
<td>.09</td>
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<td>Ethnicity</td>
<td>.09</td>
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<td>.14</td>
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<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4</td>
<td>-.04</td>
<td>.64</td>
<td>.52</td>
<td>.073</td>
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<tr>
<td>BDNF</td>
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<td>2.09</td>
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</tr>
<tr>
<td>COMT</td>
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</tr>
<tr>
<td>ANKK1</td>
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<td>.08</td>
<td>.94</td>
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</tr>
<tr>
<td>5HTTLPR</td>
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<td>.92</td>
<td>.36</td>
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<tr>
<td>Step 3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DRD4 × Risk</td>
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<td>BDNF × Risk</td>
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<td>COMT × Risk</td>
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<td>ANKK1 × Risk</td>
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<td>.69</td>
<td>.49</td>
<td></td>
</tr>
<tr>
<td>5HTTLPR × Risk</td>
<td>.04</td>
<td>.62</td>
<td>.54</td>
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Final model $F(13, 284) = 2.38, p < .005.$

Table 3. Hierarchical Multiple Regression Analysis of Impulsivity Factor 3, Feelings Trigger Action, From Risk, Sex, Ethnicity, Five Polymorphisms, and Interactions Between Polymorphisms and Risk.

<table>
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<th>Predictor</th>
<th>Final β</th>
<th>t(284)</th>
<th>p</th>
<th>Cumulative $r^2$</th>
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</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
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<td>Sex</td>
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<td>.48</td>
<td>.63</td>
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<td>Ethnicity</td>
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<td>-.15</td>
<td>.88</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
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<td></td>
<td></td>
</tr>
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<td>DRD4</td>
<td>-.06</td>
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<td>.037</td>
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<td>COMT</td>
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</tr>
<tr>
<td>ANKK1</td>
<td>-.06</td>
<td>1.09</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>5HTTLPR</td>
<td>.04</td>
<td>.66</td>
<td>.51</td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4 × Risk</td>
<td>-.07</td>
<td>.96</td>
<td>.34</td>
<td>.084</td>
</tr>
<tr>
<td>BDNF × Risk</td>
<td>-.02</td>
<td>.34</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>COMT × Risk</td>
<td>.03</td>
<td>.56</td>
<td>.57</td>
<td></td>
</tr>
<tr>
<td>ANKK1 × Risk</td>
<td>.21</td>
<td>2.45</td>
<td>.015</td>
<td></td>
</tr>
<tr>
<td>5HTTLPR × Risk</td>
<td>.15</td>
<td>2.46</td>
<td>.015</td>
<td></td>
</tr>
</tbody>
</table>

Final model $F(13, 284) = 2.01, p < .02.$

Table 3 displays the cumulative variance accounted for after each step in the model for Feelings Trigger Action, along with final βs, t values, and $p$ values for each predictor variable in the analysis. As can be seen there, no predictor had a significant main-effect relation to this factor, but two gene by risk interactions emerged, one involving ANKK1 and the other involving 5HTTLPR (the latter had been reported in Carver, Johnson, Joormann, Kim, et al., 2011). The form of the interaction involving ANKK1 (Figure 2) was such that carriers of the A allele had higher scores on Feelings Trigger Action as a function of exposure to greater childhood adversity (risk effect $p = .001$), whereas adversity had no effect for those not carrying the A allele ($p = .46$).
The largest number of associations were with the impulsivity factor Pervasive Influence of Feelings. All dopamine genes but \textit{ANKK1} were linked to this factor, either as main effects or in interaction with adversity. This diversity of associations may reflect the fact that this factor is in some respects the broadest of those of any of the dopamine-related genes we examined. To the extent that serotonin and dopamine have separable functions, then, the results seem to support a view in which at least two functions are involved in at least some sorts of impulsivity.

**Discussion**

This study examined the separate contributions of four dopamine-related genes (and one previously examined serotonergic gene) to three aspects of impulsivity. We examined both main effects and interactions with early adversity and some of each emerged. Additive (independent) contributions to prediction (as main effects or interactions) emerged on two of the factors related to impulsivity, and the different factors of impulsivity were linked to different sets of genes.

The only polymorphism that related to Lack of Follow-Through was \textit{BDNF}, which was also related to the first factor. The involvement of \textit{BDNF} in these two factors may reflect the fact that Lack of Follow-Through is one natural consequence of lethargy and paralysis, both contributors to Pervasive Influence of Feelings. The fact that \textit{BDNF} (but no other gene) bridged across these two factors suggests the possibility that \textit{BDNF}'s involvement in impulsiveness is largely expressed in variation in how distractible people are away from intended pursuits into inaction and rumination (cf. Beevers et al., 2009). In contrast to the other dopamine-related genes, \textit{ANKK1} had no relation to either of the first two factors, but was the only dopamine-related gene to relate to Feelings Trigger Action. This suggests that \textit{ANKK1}'s role in impulsiveness may pertain more directly to jumping into motion when incentives are available, consistent with previous findings relating \textit{ANKK1} to reward responsiveness (Lee et al., 2007) and novelty and sensation seeking (Biederman et al., 2008; Ratsma et al., 2001).

As noted in the Introduction, dopamine is not the only neurotransmitter proposed to be relevant to impulsiveness. It can be argued that impulsiveness is a resultant, influenced both by reflexive processes and by effortful control that can overcome those reflexive processes (Carver et al., 2008, 2013). Serotonergic function has been proposed by some as involved in effortful control over emotional reactions (Carver et al., 2008; Depue, 1995; Spoont, 1992). The results reported here show clearly that the contributions of \textit{5HTTLPR} to Pervasive Influence of Feelings and Feelings Trigger Action are independent of those of any of the dopamine-related genes we examined. To the extent that serotonin and dopamine have separable functions, then, the results seem to support a view in which at least two functions are involved in at least some sorts of impulsivity.

**Limitations and Conclusions**

The study has a number of limitations, of course. All of the measures of impulsivity were self-reports, and it would certainly be desirable to have behavioral measures. The data came from an unrestricted sample of undergraduates; thus, generalizability is an issue. We did not employ a correction for multiple tests, given that this was an exploratory investigation.

Despite limitations, the study yields several conclusions. The fact that different genes related to different facets of impulsiveness indicates the importance of differentiating more carefully among aspects of impulsiveness. Particularly important may be the distinction between impulsive reactions that are emotion-driven and those with other sources. Also suggested by the results is the importance of continuing to examine the role of early experiences that may dispose the vulnerable individual to poorer emotional control. Third, the fact that from one to four genes were involved in various aspects of impulsivity demonstrates how multiple genes may simultaneously underlie many kinds of behavior; a candidate gene approach need not imply looking at only one polymorphism for a given outcome. Finally, the results provide support for the involvement of both dopaminergic and serotonergic genes in emotion-related impulsivity.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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*Image: Figure 2.* Interaction of Childhood Risk with ANKK1 as predictors of impulsivity factor feelings trigger action. Note: Risk was centered for all analyses to reduce multicollinearity, but is displayed here uncentered.
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Note

1. Some researchers have analyzed multilocus genetic composites when several genes are hypothesized to relate to the same broad function (e.g., Nikolova, Ferrell, Manuck, & Hariri, 2011; Stice, Yokum, Burger, Epstein, & Smolen, 2012). The gain from this approach is that it merges genetic contributions that individually are too small to account for significant variance, so that an overall effect can emerge. The loss is that it does not examine effects of the individual genes. For this reason, we focus on the analyses reported in the body. Supplemental analysis substituting a dopamine composite for the individual variables yielded a similar, though less differentiated, picture.

Supplemental Material

The online data supplements are available at http://spp.sagepub.com/supplemental.

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