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Child Dopamine Transporter Genotype and Parenting: Evidence for Evocative Gene-Environment Correlations

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Abstract

The dopamine transporter (*DAT1*) gene is implicated in psychopathology risk. While the processes by which this gene exerts its effects on risk are poorly understood, a small body of research suggests that *DAT1* influences early emerging negative emotionality (NE), a marker of children's psychopathology risk. As child NE evokes negative parenting practices, the *DAT1* may also play a role in gene-environment correlations. To test this model, children (N = 365) were genotyped for *DAT1* and participated in standardized parent-child interaction tasks with their primary caregiver. The *DAT1* 9-repeat variant was associated with child negative affect expressed toward the parent during parent-child interactions, and parents of children with a 9-repeat allele exhibited more hostility and lower guidance/engagement than parents of children without a 9-repeat allele. These gene-environment associations were partially mediated by child negative affect toward the parent. Findings implicate a specific polymorphism in eliciting negative parenting, suggesting that evocative associations play a role in elevating children's risk for emotional trajectories toward psychopathology risk.

Keywords

dopamine transporter; parenting; child negative affect; gene-environment correlation

Dopamine is an important monoamine involved in the regulation of both positive and negative emotions (Bressan & Crippa, 2005). Dopamine availability at the synaptic level is regulated by the dopamine transporter (DAT) protein, which shuttles dopamine from neuronal extracellular space into intracellular compartments (Miller & Madras, 2002). The DAT thus plays a key role in modulating dopamine-mediated behaviors. Expression of the DAT protein is shaped by genetic variation of the *DAT1* gene (*SLC6A3*); located on chromosome 5p15.3, this gene has a 40-base pair variable number of tandem repeat (VNTR)

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polymorphism in the 3'-untranslated region. While this polymorphism has an array of variants in humans, ranging from 3- to 11-repeats, the 9- and 10-repeat polymorphisms are the most common and have been the focus of most research (Ueno, 2003; van Dyck et al., 2007). Although this polymorphism is located in the non-coding region, evidence suggests that it has functional effects; for example, an *in vitro* study using transiently transfected *DAT1* 9- and 10-repeat constructs in human cell lines led to significant differences in DAT protein expression (Miller & Madras, 2002). Another study found that the 9-repeat allele was associated with greater striatal DAT expression in humans (van Dyck et al., 2007), a finding that has been replicated (van de Giessen et al., 2009; although see also Heinz et al., 2000).

Association studies of *DAT1* have linked this gene to various neuropsychiatric disorders, including depression (Dunlop & Nemeroff, 2007) and posttraumatic stress disorder (Segman et al., 2002). The *DAT1* is also linked to childhood disorders, such as attention-deficit hyperactivity disorder (Cook et al., 1995; Durston et al., 2008) and conduct disorder (Lahey et al., 2011). Recently, genetic variants of the *DAT1* have been linked to personality traits, with those with a 9-repeat allele five times more likely to exhibit angry-impulsive traits than those without this variant (Joyce et al., 2009). While research on the role of this gene in temperament and personality is in its infancy, considering these findings as a whole suggests that this gene may increase psychopathology risk by virtue of its influence on early-emerging individual differences in negative emotionality (NE). Although the role of dopamine in positive mood states and reward has received the most attention (Berridge & Robinson, 1998; Spanagel & Weiss, 1999), dopamine may also influence negative emotions and trait negative emotionality. For example, it has been argued that circulating dopamine in the prefrontal cortex predisposes to a heightened attentional focus on negative environmental stimuli (Montag et al., 2008), which may influence individual differences in the capacity to effectively regulate negative emotions. Furthermore, variation in other dopaminergic genes has been linked to heightened levels of negative affect in infants (Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001; Holmboe, Nemoda, Fearon, Sasvari-Szekely, & Johnson, 2011), further suggesting that dopaminergic genetic variation shapes NE. NE shows a substantial degree of heritability (Goldsmith, Buss, & Lemery, 1997), and has been prospectively associated with internalizing and externalizing symptoms and related disorders in children (e.g., Eisenberg et al., 2009), indicating that NE may be an important psychiatric endophenotype (Hasler, Drevets, Manji, & Charney, 2004). Identifying specific genes that influence its development is therefore a key goal for psychiatric genetics.

Research on biological influences on children's emotional development and psychopathology is complicated by the dynamic relationships between children's biological predispositions and the environments in which they are raised (Rutter, 1991; Rutter, 2003). Along these lines, gene-environment interaction (GXE) and gene-environment correlation (rGE) reflect how the interplay between biological and environmental influences may eventuate in psychopathology. Relevant work focused on GXE in childhood, that is, genetic differences in children's susceptibility to particular environments, is accruing rapidly (e.g., Bakermans-Kranenburg & van IJzendoorn, 2006; Hayden et al., 2010; Sheese, Voelker, Rothbart, & Posner, 2007; Smith et al., *in press*), indicating that genetic influences on children's psychopathology risk are moderated by contextual factors. For example, with

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specific regard to *DAT1*, Lahey et al. (2011) found that the influence of parenting on the development of conduct disorder varied as a function of the number of 9-repeat alleles in children. In sharp contrast, there has been much less work on identifying genetic influences on the probability of exposure to particular risk environments (Jaffee & Price, 2007). While the concept of rGEs was described many years ago (see Plomin, DeFries, Loehlin, 1977 for an early synthesis of the concept as pertains to psychology), only relatively recently has it become feasible to obtain the molecular genetic data needed to identify specific genes that may play a role in heightening risk exposure. The first measured rGE was reported by Dick et al. (2006), in which a variant of the gamma-aminobutyric acid (GABA) A receptor, alpha 2 gene (*GABRA2*) was associated with marital status. With respect to psychopathology risk mechanisms, Lucht et al. (2006) reported an association between perceived negative paternal parenting (reported retrospectively by adult offspring) and offspring variants of both *DRD2* and *GABRA6*. Other groups have also reported rGEs involving parenting and *DRD2* (Hayden et al., 2010; Mills-Koonce et al., 2007), although very little is known about the role of other dopaminergic genes, such as *DAT1*, in rGE.

Of the few studies on rGE in psychopathology, most have not examined potential mediators of the rGEs reported (i.e., mechanisms that account for the obtained association between a measured gene and environmental risk). Given that intrinsic (i.e., children's individual differences) and extrinsic (i.e., environmental) risks for psychopathology are often correlated with one another (Rutter, 2009), rGEs represent a means of more clearly delineating how these dual sets of influences become associated with each other during development. The causal mechanisms underlying rGEs are of particular interest, as genetic factors can be related to environmental factors through an array of processes; such associations are thought to be commonly mediated by intermediate behaviors under genetic influence (Rutter, Moffitt, & Caspi, 2006; Rutter, 2007). For example, evocative rGEs refer to the process by which genetically influenced child behavior elicits contextual risk from the child's environment, such as poor parenting practices. Thus, evocative rGE represents a process by which child genetic risk is potentially amplified through its influence on contextual risk, and may therefore have implications for preventative interventions.

In childhood, the quality of parenting children receive is a major source of contextual risk. Supportive parenting has been found to predict lower levels of child behavior problems, greater social skills, and better academic performance (Coplan, Arbeau, & Armer, 2007; Pettit, Bates, & Dodge, 1997; Stormshak, Bierman, McMahon, & Lengua, 2000). In particular, the guidance and support provided by parents to children in the context of skill acquisition and learning, also known as *scaffolding* (Wood, Bruner, & Ross, 1976), is associated with important child outcomes such as intelligence and academic achievement (Englund, Luckner, Whaley, & Egeland, 2004). Conversely, negative parenting practices, such as intrusiveness and hostility, have been consistently associated with child behavioral and emotional problems. For example, Caron, Weiss, Harris, and Catron (2006) found that negative parenting styles (e.g., high behavioral and psychological control) were linked to both externalizing and internalizing child psychopathology. In particular, hostile parenting may have important relevance for negative child outcomes (Sheffield Morris et al., 2002). For example, hostile parenting is strongly linked to depression in older youths (McLeod,

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Weisz, & Wood, 2007) and to disrupted neuroendocrine functioning in the offspring of depressed parents (Gunnar & Vazquez, 2006).

While rGE indicates that parenting behaviors may be linked to children's genetic characteristics, little research has tested this possibility, although it has long been accepted that children are active agents in shaping the environment that parents provide (Deater-Deckard, 2000; Lee et al., 2010). For example, Lengua and Kovacs (2005) found evidence for bidirectionality of the effects of child characteristics and parenting, such that inconsistent discipline increased negative emotionality in children, and child negative emotionality evoked inconsistent discipline by parents. Additionally, maternal control is elicited by child anxiety (Eley, Napolitano, Lau, & Gregory, 2010; Moore, Whaley, & Sigman, 2004), and child disruptive disorders negatively influence parents' ability to engage in appropriate discipline (Burke, Pardini, & Loeber, 2008). Furthermore, Ge et al. (1996) employed an adoption design to illustrate that antisocial behaviors of adopted children evoked negative adoptive parent responses, providing further evidence that passive rGEs (i.e., in the present case, genes that influence parental caregiving behaviors are also inherited by children; Plomin et al., 1977) did not solely account for associations between the heritable and environmental risk present in children at risk for disruptive behavior disorders. Thus, it is clear that child characteristics play a key role in eliciting parenting, and, to the extent that child behavior that elicits adaptive or maladaptive parenting is genetically influenced (e.g., Rhee & Waldman, 2002), evocative rGEs are likely present.

Considering the literature implicating *DAT1* in children's psychopathology risk, this gene may play a role in shaping child behaviors that, in turn, elicit poor parenting. Furthermore, the role of dopamine in bonding and affiliative behavior (Depue & Morrone-Strupinsky, 2005; Lee et al., 2010) further supports the possibility that some of the associations between children's dopaminergic genes and adverse outcomes are mediated by genetic influences on early parent-child relationships. However, very little work has been done to explore this possibility. The current study therefore represents a novel and exploratory attempt to examine associations between the *DAT1* gene and parent-child interactions, and extends our group's efforts to identify rGEs that play a role in emerging psychopathology risk (Hayden et al., 2010). More specifically, we tested whether children with a 9-repeat allele of the *DAT1* exhibited greater negative affectivity directed toward parents during standardized, observational measures of parent-child interaction. We also examined whether the *DAT1* 9-repeat was associated with parenting styles with key implications for adaptive and maladaptive child outcomes: parental hostility and scaffolding. Finally, we planned to attempt to identify the potential mechanism(s) underlying any rGEs by testing whether any associations between children's *DAT1* alleles and parental behavior were mediated by child negative affectivity, thus potentially supporting the presence of an evocative rGE.

Method

Participants were 365 children (197 males) from a larger sample of 567 children and their parents who were participating in a longitudinal study. The mean age of the children at the time of the current study was 72.9 months (SD = 6.0). Eligible children had no significant medical conditions or developmental delays, as well as at least one English-speaking

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biological parent who could also participate. Most participants were from middle-class families, as measured by Hollingshead's Four Factor Index of Social Status (M = 44.4, SD = 10.7) (Hollingshead, 1975). Almost all children came from two-parent homes (88.8%), and were of average cognitive ability as measured by the Peabody Picture Vocabulary Test (M = 103.1, SD = 13.4) (PPVT; Dunn & Dunn, 1997). Children were Caucasian (n = 319; 87.4%), Hispanic (n = 15; 4.1%), or from a variety of other racial and ethnic backgrounds (n = 31; 8.5%).

When children and their parents came to the laboratory to take part in behavioral tasks, we collected buccal cells for genetic analysis by rubbing the inside of each child's cheek with two collection swabs. From the larger sample of 567 children at baseline, 476 had parental consent to provide samples for genetic assessment, and 432 participated in the parent-child interaction tasks. Only those children for whom genetic and parenting data were available were included in the present analyses, yielding a sample size of 365[1]. Children in the current study did not differ from non-participating children on any demographic variables (child sex, socioeconomic status, cognitive ability, number of parents in the home; all ps > .05).

We used the Qiagen DNA MicroKit (Qiagen, Valencia, California, USA) to extract genomic DNA from buccal epithelial cells. Purified genomic DNA was kept at 4 °C while being analyzed and then at −80 °C for long-term storage. Polymerase chain reaction (PCR) was conducted using the Applied Biosystems thermal cycler Gene Amp 9700 (Applied Biosystems, Foster City, California, USA), and PCR products were separated on polyacrylamide gels, stained with ethidium bromide, and visualized and documented by a UV imaging system (BioRad Labs, Mississauga, Ontario, Canada). To insure accuracy of the genetic data, a technician randomly selected and reanalyzed 10% of the genetic samples. In the single case of discrepant results for the *DAT1*, the child's sample was excluded. All research technicians performing genotyping were blind to other study data.

We used the following primers: 5'-TGTGGTGTAGGGAACGGCCTGAG-3' (forward) and 5'-CTTCCTGGAGGTCACGG CTCAAGG-3' (reverse). The PCR conditions were as follows: 5 min initial denaturation at 95 °C and 30 cycles of 30 s initial denaturation at 94 °C, 45 s annealing at 67.5 °C, 45 s extension at 72 °C, followed by 5 min of final extension at 72 °C. The 9-repeat and 10-repeat products yield a 440 bp and 480 bp fragment, respectively. Although genotypes were successfully obtained for 371 children, for the purposes of our analyses, six participants with rare variants of the *DAT1* were excluded. The genotypes of the remaining 365 children were distributed as follows: 177 (48%) children had the 10/10 genotype, 153 (42%) had the 9/10 genotype, and 35 (10%) had the 9/9 genotype. This distribution is in Hardy-Weinberg equilibrium, X^2 = .05, p = .82.

The literature is unclear concerning which *DAT1* allele is associated with negative outcomes (Lee et al., 2007; Rowe et al., 1998), nor whether the repeat variants function in an additive manner. However, most previous findings relevant to child psychopathology risk (Young et al., 2002), as well as functional studies (van Dyck et al., 2005; van de Giessen et al., 2009)

[1]Children for whom DNA and parenting data were available had significantly lower parental hostility than those without DNA, $t(68.38) = 2.54$, $p < .05$. No differences in other study variables were found (all ps >.18).

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have contrasted children with the 9-repeat allele to those without. Furthermore, in analyses not reported in full here, we found no significant differences between children with two copies versus one copy of the 9-repeat on any study variables (all *p*s > .14). Therefore, to conserve space, results are presented based on contrasting children with (*n* = 188) and without (*n* = 177) a 9-repeat allele.

Teaching tasks

All 365 children and a primary caregiver (most often the mother, *n* = 320, 87.7%) participated in a modified version of the Teaching Tasks battery (Egeland et al., 1995). The battery consisted of four standardized parent-child interaction tasks lasting a total of 25 to 30 minutes. The tasks, which occurred in the order listed here, were designed to elicit a variety of parenting styles and child behaviors, and consisted of a guessing game, a marble maze consisting of four different trial types, pictures that had to be arranged to tell a story, and a puzzle with six different designs. We coded parental supportive presence, guidance/engagement (i.e., scaffolding), intrusiveness, and hostility using a global approach to coding, with a single rating given for each parenting behavior for each of the four tasks. Ratings were subsequently averaged across tasks to yield total scores for each parenting dimension. Ratings of parent supportive presence ($\alpha = 0.86$) were based on the parent's provision of emotional support and expression of positive regard. Parent guidance/engagement ($\alpha = 0.76$) was coded based on how well the parent guided the child in completing the tasks, and the parent's degree of engagement in working with the child. Parent intrusiveness ($\alpha = 0.65$) was rated based on the extent to which the parent failed to allow autonomous child behavior. Ratings of parent hostility ($\alpha = 0.75$) were based on anger, annoyance, and rejection of the child displayed by the parent. Interrater ICCs (*n* = 35) for supportive presence, guidance/engagement, intrusiveness, and hostility were 0.84, 0.74, 0.81, and 0.86, respectively.

In addition to parenting, child negative affect toward the parent (child NA toward parent), and overall child positive affect (PA) were coded in each task (the coding system used did not include ratings of child PA directed specifically toward the parent). Child NA toward the parent ($\alpha = 0.68$) was coded based on the degree to which the child displayed anger, dislike, or hostility toward the parent. Ratings of overall child PA ($\alpha = 0.76$) were based on the frequency and intensity of facial, bodily, and vocal indicators of positive emotion during the parent-child interaction tasks. Interrater ICCs (*n* = 35) for child NA toward parent and overall child PA were 0.73 and 0.80 respectively.

Results

Associations between *DAT1* groups (formed based on whether children had a 9-repeat allele) and major study variables can be found in Table 1, and bivariate correlations among all non-genetic study variables are in Table 2. To address the issue of possible population stratification, we initially conducted all analyses with and without non-Caucasian children. Given that results were nearly identical in both cases, and that Caucasian and non-Caucasian children did not differ in terms of the proportion with at least one 9-repeat allele or in terms of child phenotype (i.e., NA directed toward their parents; *p*s > .73), we present findings including children from all ethnicities. Children with and without a 9-repeat allele were not

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significantly different on socioeconomic status or cognitive ability (as indexed by the PPVT). However, there were significantly more boys in the 9-repeat allele group. Child sex was therefore treated as a covariate for all analyses, although mediation analyses yielded a consistent pattern when analyzing boys and girls separately. With respect to behavior during parent-child interactions, the two genotype groups differed in terms of parental hostility, such that parents of children with a 9-repeat allele exhibited more hostility during the parent-child interactions ($p = .05$). The two genotype groups also differed in terms of parent guidance/engagement, such that parents of children with a 9-repeat allele provided less guidance ($p = .01$) The two groups did not differ significantly in parental support or intrusiveness. Children with a 9-repeat allele displayed significantly more NA toward their parent ($p = .04$) during parent-child interactions; there was no significant difference in children's PA expressed while interacting with the parent based on the presence of a 9-repeat allele ($p = .63$); thus, child PA is not considered further as a potential mediator.

Given that the two *DAT1* allelic groups differed in terms of child NA toward the parent, we wanted to test whether child NA mediated the association between children's *DAT1* 9-repeats and parenting. There were significant associations between the hypothesized mediator and the outcome (i.e., child NA toward the parent and parental hostility, $r = .26$, $p = .001$, and parental guidance/engagement, $r = -.22$, $p = .001$). Contemporary theories of mediation assert that associations between the distal predictor or IV and the outcome need not reach significance even when mediation is present (MacKinnon & Fairchild, 2009), although child *DAT1* genotype and parenting were associated in the case of parental hostility and guidance/engagement. The bootstrap sampling procedure and macro developed by Preacher and Hayes (2004, 2008) were used to test mediation. This procedure estimates both mean direct (c) and mean indirect (i.e., mediated, c') effects, as well as confidence intervals (CIs) obtained from multiple samples (set to 5000 for our analyses). The estimated effect is not statistically significant (at $p < .05$) if the estimated CIs obtained by the bootstrapping procedure contain the number zero. This mediation method is similar to more traditional approaches that use multiple regression, but holds many advantages, including greater robustness with regard to small sample sizes and violations of normality (Preacher & Hayes, 2004, 2008).

Two initial models were run using these procedures, the first focusing on parental guidance/engagement and the second focusing on parental hostility (Figure 1). With regard to the former, the bootstrapping procedure yielded a significant estimate of the indirect effect of *DAT1* genotype on parental guidance/engagement after including child NA toward parent in the model ($p < .05$). Given that the effect of *DAT1* genotype on parental guidance/engagement decreased (but did not become zero) with the inclusion of the mediator, it appears that child NA toward the parent partially mediated the relationship between child *DAT1* genotype and parental guidance/engagement (Figure 1). The bootstrapping procedure also yielded a significant estimate of the indirect effect of *DAT1* genotype on parental hostility after including child NA toward parent in the model ($p < .05$). The effect of *DAT1* genotype on parental hostility decreased, becoming nonsignificant with the inclusion of the mediator, indicating that child NA toward parent partially mediated the relationship between child *DAT1* genotype and this parenting dimension (Figure 2).

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We next conducted two supplementary analyses aimed at better establishing temporal associations between children's NA toward their parents and parenting behavior. For these analyses, children's NA during the first part of the parenting battery (i.e., during the guessing game and maze tasks) was examined as a mediator of associations between *DAT1* and parent guidance/engagement and hostility during the second half of the battery (picture story and puzzle), controlling for the equivalent parenting behavior during the first part of the battery and child NA toward the parent during the second half of the battery (i.e., the effects of initial parenting and later child behavior on parenting during the latter half of the parenting assessment were controlled). As these analyses were designed to follow-up significant findings from initial mediation models, one-tailed tests were used. The bootstrap sampling procedure and macro developed by Preacher and Hayes (2004, 2008) were again used to test mediation. In the model predicting parental guidance/engagement, child *DAT1* genotype was not significantly related to child NA during the first part of the battery ($p = .16$), so this analysis is not described further. The model predicting parental hostility is presented in Figure 3. The bootstrapping procedure yielded CIs that did not contain '0' indicating significant mediation.

Discussion

We examined whether there was an association between child *DAT1* genotype and parenting assessed during standardized parent-child interaction tasks, and found that children with a 9-repeat allele received greater parental hostility and lower levels of parental guidance and engagement during parent-child interactions. Tests of mediation indicated that associations between children's *DAT1* genotype and these two parenting dimensions were partially mediated by child NA directed toward the parent during parent-child interactions. Our findings provide preliminary support for the presence of evocative rGEs, whereby the association between children's *DAT1* genotypes and parenting is partially accounted for by the effect of this gene on children's negative affect during parent-child interactions, which may elicit parental hostility and diminished guidance and engagement. Our findings implicate the 9-repeat of the *DAT1* gene in eliciting maladaptive parenting, an important, potentially malleable environmental variable that may possibly compound children's underlying genetic vulnerability, although additional work is needed to test the latter possibility (i.e., the extent to which children at high genetic risk for adverse outcomes are differentially impacted by poor parenting styles, which is addressed later in this section). Child NA toward the parent only partially mediated the relationship between children's *DAT1* genotype and parenting; hence, other mechanisms, such as passive rGEs, may also be operating, or children's *DAT1* variants may influence parenting through its effects on child behaviors not measured in the present study. It is likely that child genetic risk is expressed through an array of pathways (Bakermans-Kranenburg & van IJzendoorn, 2011). In some cases, genetic effects may be relatively direct; that is, genes may influence biochemical processes that increase individual predispositions toward maladaptive emotional and cognitive responses to environmental stimuli (Munafò, Brown, & Hariri, 2008). However, genetic variation may also influence outcomes through relatively indirect processes, such as evocative rGEs.

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We found that children with a 9-repeat allele exhibited greater NA toward parents during parent-child interactions. How genotypic variation at *DAT1* shapes differences in child NA remains unclear, and given the lack of published research on the role of DAT and *DAT1* in child emotional development, our discussion of processes and mechanisms is speculative. It could be that *DAT1* influences child NA by virtue of the role of dopamine in general emotional processing (Badgaiyan, Fischman, & Alpert, 2009). For example, Sevy et al. (2006) found that a decrease in central dopaminergic activity resulted in poor emotion-based decision making, which suggests that variation in *DAT1* may exert its effects at the interface of cognition and emotion. More specifically, dopamine appears to play a role in the regulation of anger and impulsivity; for example, functional imaging findings support the contention that dopamine availability influences anger and impulsivity (Forbes et al., 2009). These findings are supported by a small but generally supportive literature on genetic associations between the *DAT1* and relevant emotional and behavioral phenotypes. Carriers of the 9-repeat allele have been found to have a fivefold increased likelihood of exhibiting angry-impulsive traits (Joyce et al., 2009). Since this allele appears to lead to greater striatal synaptic dopamine (Heinz et al., 2000), this finding is consistent with the notion that efficient reuptake of dopamine from the synaptic cleft, facilitated by the dopamine transporter protein, is key in the effective regulation of anger and impulsivity. In addition, administering a dopamine receptor antagonist has been shown to selectively disrupt the recognition of facial anger (Lawrence, Calder, McGowan, & Grasby, 2002). These findings indicate that dopamine may not only be a biological substrate related to anger and impulsivity, it may also influence the extent to which children are able to process affective and social cues that their behavior is inappropriate or otherwise unacceptable, thus facilitating adaptive modification of such behavior. Considering that dopamine facilitates the development of close interpersonal bonds (Depue & Morrone-Strupinsky, 2005), it is also possible that *DAT1* variants contribute to the extent to which children are impaired in their capacity to develop close bonds with caregivers. A relatively weak dopaminergically-mediated parent-child bond might, over time, result in parent-child interactions characterized by heightened negativity. In summary, there are likely multiple pathways through which genotypic variation at *DAT1* may contributes to childhood externalizing symptoms (Young et al., 2002), although further work is clearly needed.

The children who took part in the current project are part of a larger, ongoing study of childhood risk for psychopathology. These children were previously assessed at age 3, raising the question of whether the obtained rGEs were present in children's earlier interactions with their parents. We did not find evidence for an rGE between *DAT1* and caregiver hostility or guidance/engagement at the earlier assessment using observational measures of parent-child interactions similar to those reported here, nor did we find associations between this gene and child NA. However, children with a copy of the 9-repeat allele had mothers who expressed significantly more negativity and less warmth when discussing their children during an interview. Mothers of children with a 9-repeat allele of the *DAT1* also reported engaging in more negative parenting styles at trend-level. While speculative, we propose that this pattern of findings is suggestive of a transactional process that unfolds over time. More specifically, our findings are consistent with the possibility that there is a genetically-driven process that has fairly weak effects when children are young,

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which is why relatively few genetic associations were obtained with age 3 child behavior. This process may escalate over time, such that by age 6, children with the 9-repeat allele exhibit both greater NA toward their parent, and receive greater hostility and less guidance/engagement from parents. Such a pattern is consistent with a cumulative reciprocity model of parent-child influence (e.g., Rothbaum & Weisz, 1994), whereby negative child behaviors and parents' negative caregiving become increasingly interconnected over time. This process has the potential to strengthen throughout middle childhood, leading to even poorer relationships with parents and greater risk for psychopathology during preadolescence and adolescence. Aside from the development of psychopathology, the nature of parent-child interactions can shape children's relationships with others in negative ways. For example, children who experience exchanges of reciprocal negative affect during interactions with their parents demonstrate low peer competency, are more verbally aggressive, and are less socially skilled overall (Carson & Parke, 1996). Thus, children with a 9-repeat allele of *DAT1* may also be at elevated risk for poor peer relations in later development, another known risk factor for maladaptive outcomes. Determining whether such processes unfold during later childhood and adolescence is an important future step for this research.

Jaffee and Price recently (2007) noted that careful measurement of the environment may play a critical role in the successful identification of rGEs; as observational measures of parenting may show stronger predictive validity for child outcomes (Zaslow et al., 2006), their use is a major strength of our study. There were, however, a number of limitations. First is the issue of population stratification, which may increase the likelihood of false positive associations, although there is debate regarding the extent to which it represents a threat to the validity of association studies (Hutchison, Stallings, McGeary, & Bryan, 2004; Wacholder, Rothman, & Caporaso, 2002). It is possible that the VNTR locus in the *DAT1* gene is in linkage disequilibrium with another sequence or structural variant that is responsible for the obtained associations with child behavior and parenting (Dick et al., 2011). Furthermore, while our sample size is large for one using observational measures, it is relatively small for a genetic association study. In addition, no data were available for parent genotype; not having these data made it impossible for us to examine the role of passive rGEs, which may play a role in driving the associations between child NE and parenting found in this study (Lee et al., 2010). Lastly, the data presented here are cross-sectional, although the interplay between child genetic risk, child behavior, parenting, and negative child outcomes requires longitudinal investigation. However, preliminary tests examining parent-child interaction over the course of our parenting task battery tentatively supported the notion of child-to-parent effects, at least in the case of parental hostility. We are currently collecting additional longitudinal data that will permit more conclusive tests of our larger model of *DAT1* and emerging psychopathology over time.

Future directions for research on rGE and its translation into intervention

The identification of rGEs suggests the possibility of preventative efforts aimed at identifying those at greatest genetic risk for environment precipitants of psychopathology. However, it is clearly implausible that the effects of parent hostility and lower guidance/engagement (scaffolding) on negative child outcomes (Caron et al., 2006; Englund et al., 2004; Sheffield Morris et al., 2002) are driven exclusively by children's NA related to

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having a 9-repeat allele of *DAT1*. An array of factors undoubtedly play a role in shaping positive and negative parenting practices, only some of which are related to child genetic factors. It is therefore unclear whether preventative efforts targeting the parenting of children with a 9-repeat allele would show additional value above and beyond broad interventions focused on improving parenting in the general population, unless it becomes clear that poor parenting has an especially potent impact on these children. This implies the presence of a GXE effect within the context of an rGE, which we did not find in our sample for the *DAT1*. Future work on measured rGE should systematically incorporate tests of GXE toward the long-term goal of determining the feasibility of targeted preventions based on child genetic factors. Additionally, the robustness of rGEs must be determined before it makes sense to apply such findings to preventative efforts. Our group recently provided evidence in support of findings initially published by Propper et al (2008) implicating children's *DRD2* alleles in eliciting supportive parenting; we hope that other research groups will attempt replication of the present findings, as well as other published rGEs in the literature.

A better understanding of the genetic bases of child behaviors that evoke environmental risk may be beneficial if interventions differ in effectiveness as a function of the causal processes involved in shaping the targeted behavior. More specifically, if some forms of child NA are driven primarily by genetic processes, rather than environmental triggers, standard parent-child interventions may be less effective, and interventions focused more exclusively on increasing children's strategies for regulating NA might be indicated. It may also be the case that child behaviors that are strongly genetically influenced might require especially intensive psychosocial interventions, or behavioral interventions augmented with pharmacological treatment. While clearly speculative, this notion is consistent with findings that suggest that psychopathology severity, which is thought to be a marker of greater genetic loading for the disorder, often indicates the need for more intensive intervention strategies or combination therapies (e.g., DeRubeis et al., 2005; Elkin et al., 1989; Khan, Brodhead, Kolts, & Brown, 2005). However, we emphasize that whether research on rGE can be successfully used to develop personalized interventions is an empirical question that has yet to be tested, and is unlikely to be resolved in the immediate future.

It is also important to determine the *magnitude* of the associations of specific genes with environmental risk. Most genes have small effects on disorders and other complex behaviors (e.g., Clarke, Flint, Attwood, & Munafò, 2010; Kendler, 2005), and it stands to reason that associations with environmental variables will likely be weaker still, as these outcomes are even more distal from the biological actions of genes. In the present study, the child *DAT1* 9-repeat allele accounted for a small amount of variance in parenting (i.e., .5–1% of the variance). If it becomes clear that genes with evocative or active effects on the environment are associated with only marginally increased environmental risk, the implications for prevention are limited unless multifactorial models of rGEs can be developed. Such models could potentially account for a greater degree of variance in environmental risk exposure, if, for example, the cumulative effect of genes that influence a common biological pathway implicated in behavior can be modeled. However, the ability to develop such models has been limited by the complexity of epistatic models. Epistasis, the interaction between genes, is likely ubiquitous in shaping complex traits like NA (Moore, 2003), yet the capacity to develop adequate models is hampered by the difficulties inherent to studying how genetic

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processes interact in brain tissue. While an array of approaches have been used to model genetic risk (Chen et al., 2011; Hill, Goddard, & Visscher, 2008; Jones & Szatmari, 2002; Lettre, Lange, & Hirschhorn, 2007), it remains unclear which most accurately captures the nature of genetic interactions in shaping brain systems. Furthermore, developing polygenic models of the complex behaviors involved in rGE necessitates large sample sizes. Unfortunately, sample size tends to be inversely associated with the quality of the measures of phenotypes and environments, which is also critically important for progress to be made in this field (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Jaffee & Price, 2007; Uher & McGuffin, 2010). Optimal strategies for balancing these considerations continue to be a source of debate in the field (e.g., Duncan & Keller, 2011).

Implications for developmental psychopathology

Recent work (e.g., Martel et al., 2010) indicates that personality is a key mediator of the effects of genetic vulnerability on children's psychopathology. While we did not examine psychopathological outcomes specifically, our findings implicate a specific variant in increasing children's NA toward caregivers, a tendency that is almost certainly a marker of children's trait negative emotionality, a known general risk for the development of an array of disorders (Clark, 2005; Eisenberg et al., 2009). However, it has also been proposed that child NA may serve a more complex role as a marker of children's sensitivity to contextual factors, increasing the probability of both positive and negative outcomes in a context-dependent manner (Belsky & Pluess, 2009). While we found some evidence for evocative effects of child NA on negative parenting styles, associations were moderate, indicating that some children who express high levels of NA toward caregivers are not exposed to negative caregiving. Gaining a fuller understanding of parental characteristics that predict a decreased tendency to respond to negative child behavior with negative behavior of their own will help psychopathologists build more comprehensive transactional models of risk and resilience (Belsky & Barends, 2003). Incorporating parental genetic information may contribute toward this goal; such data were unfortunately not available to us at the time of this study.

Consistent with our findings, individual genes are held to have small effects on emotional behavior and personality. However, the context of evocative rGEs provides a means by which the influence of specific genes on negative outcomes may become amplified over time by virtue of eliciting environmental risk. Given that genetic and environmental risks are often correlated (Rutter, 2009), the identification of mediators of rGE clarifies the processes by which these risks become associated. Indeed, such risks may become increasingly interrelated as environmental risk plays a dynamic, regulatory role on gene expression during development via an array of epigenetic mechanisms (Cameron, Parent, Champagne, Fish, Ozaki-Kuroda & Meaney, 2005; Meaney & Szyf, 2005; Mill, 2011). Scientists' understanding of complexity of these mechanisms is continually evolving, and work that delineates such processes in developmental psychopathology is in its infancy. While it is currently unclear how to best incorporate information on epigenetic mechanisms, especially in research on humans, developing appropriate measures of such processes will be an important step toward taking research on GXE and rGE in developmental psychopathology beyond merely demonstrating statistical associations and toward an approach that speaks to biological processes (Mill, 2011).

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In summary, we found evidence for an rGE involving children's *DAT1* 9-repeat allele and parental hostility and guidance/engagement. Our findings are compatible with the larger literature indicating that rGEs are mediated by personality and behavior (see Jaffee & Price, 2007, for a review), in that the association between the 9-repeat allele and parenting was partially mediated by child NA toward parents during parent-child interactions. While further longitudinal work is needed to support the full model we propose, these findings represent an additional contribution to the small but growing literature on the role of rGEs in developmental psychopathology.

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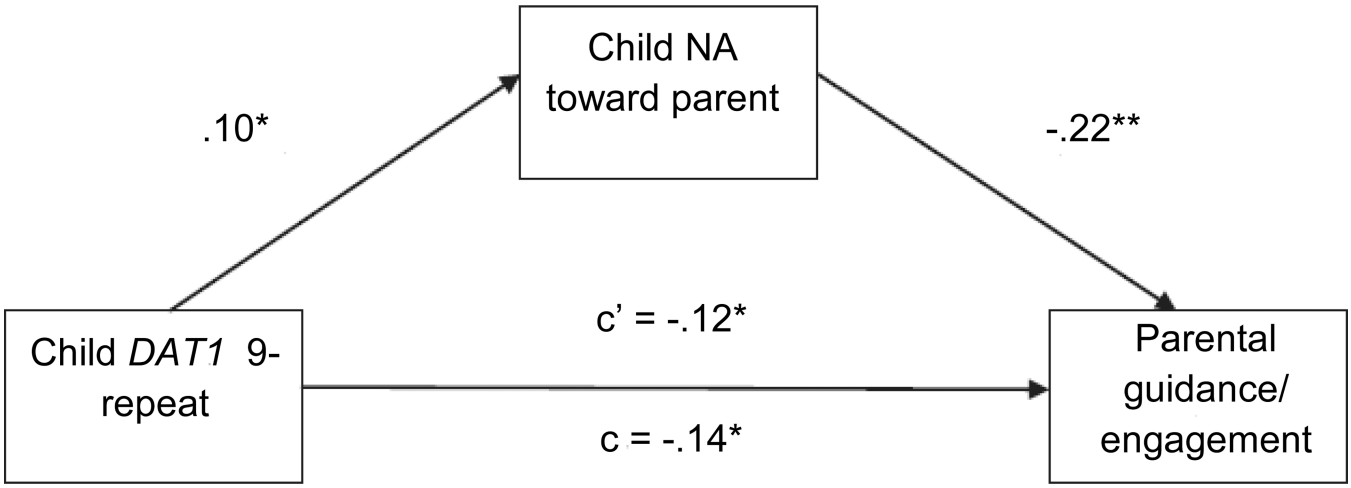

Figure 1. Mediated effect of child dopamine transporter (*DAT1*) genotype on parental guidance/ engagement by child negative affect (NA) toward parent

Note: Child *DAT1* coded as 0 = 10/10 genotype, 1 = 9/9 or 9/10 genotype; parental guidance/engagement coded during parent-child interaction task; c = total effect of child *DAT1* genotype on parental guidance/engagement; c' = effect of child *DAT1* genotype on parental guidance/engagement after including child NA toward parent in the model. *$p < .05$, **$p < .01$.

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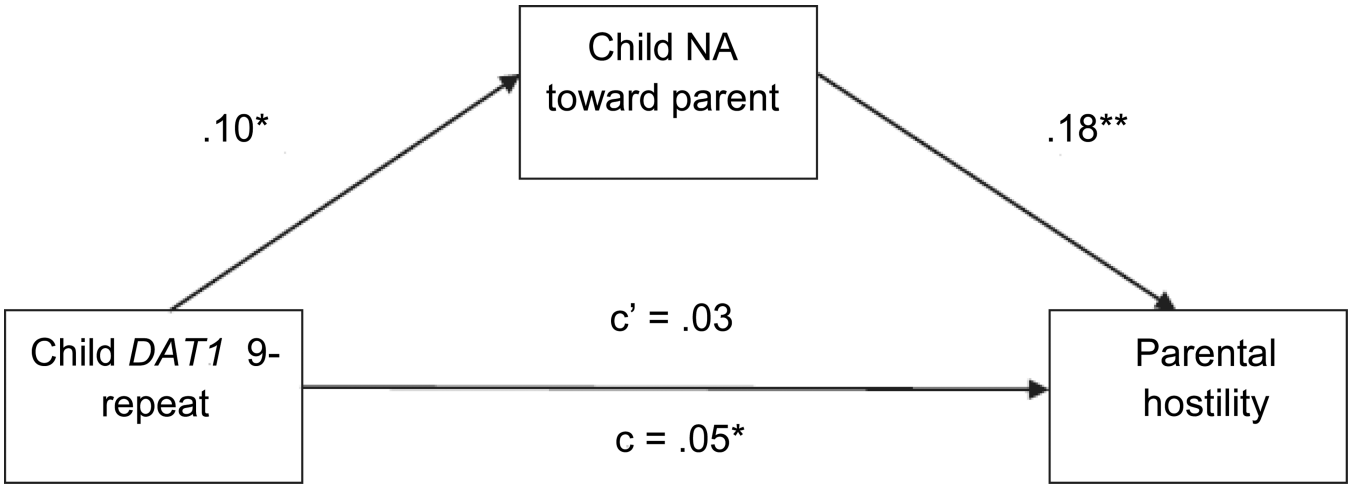

Figure 2. Mediated effect of child dopamine transporter (*DAT1*) genotype on parental hostility by child negative affect (NA) toward parent

Note: Child *DAT1* coded as 0 = 10/10 genotype, 1 = 9/9 or 9/10 genotype; parental hostility coded during parent-child interaction task; c = total effect of child *DAT1* genotype on parental hostility; c' = effect of child *DAT1* genotype on parental hostility after including child NA toward parent in the model. *$p < .05$, **$p < .01$.

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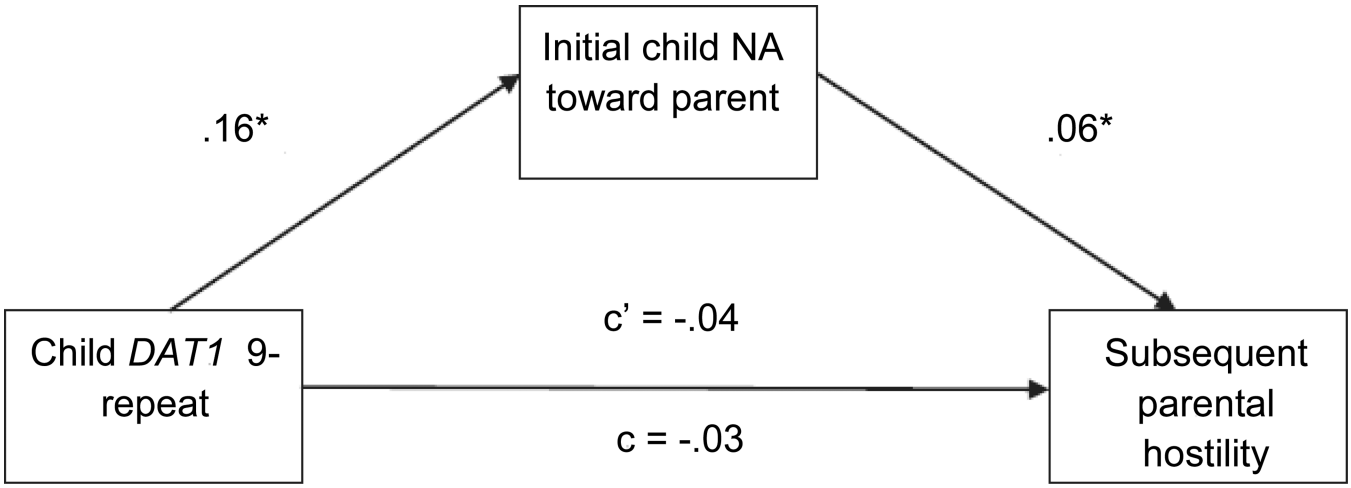

Figure 3. Mediated effect of child dopamine transporter (*DAT1*) genotype on later parental hostility by initial child negative affect (NA)

Note: Child *DAT1* coded as 0 = 10/10 genotype, 1 = 9/9 or 9/10 genotype; parental hostility coded during parent-child interaction task; c = total effect of child *DAT1* genotype on parental hostility; c' = effect of child *DAT1* genotype on parental hostility after including child NA toward parent in the model. Initial levels of parental hostility and subsequent levels of child NA toward the parent were included as covariates. $p < .05$; one-tailed tests used in this model only.

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Table 1

Demographic and study variables by child DAT1 genotype

	Child *DAT1* genotype						
	DAT1 10/10 (*n* = 177)			*DAT1* 9/9 and 9/10 (*n* = 188)			*d*
Variable	***M***	***SD***	***n***	***M***	***SD***	***n***	
Child sex, male *			85 (48%)			112 (60%)	
PPVT	102.58	13.08		103.52	13.80		.07
SES	43.77	10.13		44.88	11.23		.10
PCI support	4.36	0.56		4.27	0.59		.16
PCI guidance *	4.23	0.57		4.08	0.50		.28
PCI hostility *	1.08	0.23		1.14	0.31		.22
PCI intrusiveness	1.62	0.73		1.59	0.68		.04
PCI child PA	2.82	0.62		2.79	0.72		.04
PCI child NA toward parent *	1.21	0.40		1.30	0.47		.21

DAT1, dopamine transporter gene; NA, negative affect; PA, positive affect; PCI, parent-child interaction task; PPVT, Peabody Picture Vocabulary Test; SD, standard deviation; SES, socioeconomic status, as indexed by Hollingshead Four Factor Index of Social Status (Hollingshead, 1975).

* $p \leq .05$.

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Table 2

Bivariate correlations among non-genetic study variables

	r								
Variables	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**
1. Child sex	-	.09	−.08	.01	.06	−.06	−.06	.08	.02
2. PPVT		-	.04	.06	.17**	.02	−.16**	.05	−.08
3. SES			-	.08	.10	−.07	−.06	−.09	.01
4. PCI support				-	.73**	−.47**	−.20**	.08	−.20**
5. PCI guidance/ engagement					-	−.37**	−.46**	.10*	−.19**
6. PCI hostility						-	.23**	−.01	.29**
7. PCI intrusiveness							-	−.14**	.06
8. PCI child PA								-	−.09
9. PCI child NA toward parent									-

Note: Child sex coded as 0 = boys, 1 = girls.

* $p < .05$,

** $p < .01$.