Dopaminergic Variants in Siblings at High Risk for Autism: Associations with Joint Attention and Behavior Problems

Devon N. Gangi

University of Miami, devon.gangi@gmail.com

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DOPAMINERGIC VARIANTS IN SIBLINGS AT HIGH RISK FOR AUTISM: ASSOCIATIONS WITH JOINT ATTENTION AND BEHAVIOR PROBLEMS

By

Devon Nicole Gangi

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DOPAMINERGIC VARIANTS IN SIBLINGS AT HIGH RISK FOR AUTISM:
ASSOCIATIONS WITH JOINT ATTENTION AND BEHAVIOR PROBLEMS

Devon Nicole Gangi

Approved:

Daniel S. Messinger, Ph.D.
Professor of Psychology, Pediatrics, Electrical and Computer Engineering, and Music Engineering

Heather A. Henderson, Ph.D.
Adjunct Associate Professor of Psychology

Jennifer C. Britton, Ph.D.
Assistant Professor of Psychology

Eden R. Martin, Ph.D.
Professor of Human Genetics and Public Health Sciences

Michael L. Cuccaro, Ph.D.
Associate Professor of Psychology and Human Genetics

M. Brian Blake, Ph.D.
Dean of the Graduate School
Infant siblings at risk for Autism Spectrum Disorder (ASD; high-risk siblings) exhibit lower levels of joint attention and higher levels of behavior problems than low-risk siblings (siblings with no family history of ASD), but also exhibit high levels of variability in these domains. The neurotransmitter dopamine is linked to brain areas associated with attention, reward, and motivation. Common genetic variants affecting dopamine neurotransmission, \textit{DRD4} and \textit{DRD2}, have been associated with attention difficulties and behavior problems in typically developing children. We examined whether these variants explain variability in ASD-relevant behaviors in high-risk siblings. \textit{DRD4} and \textit{DRD2} genotypes for high-risk and low-risk siblings were coded according to dopaminergic functioning to create a gene score, with higher scores indicating more alleles associated with lower dopaminergic functioning. Initiating joint attention (IJA) was observed in the first year, and parents reported behavior problems at 3 years using the Child Behavior Checklist. Dopamine gene scores indicative of lower dopaminergic functioning were associated with less optimal behavior in the first year (lower levels of IJA) and at 3 years (higher levels of internalizing problems) for high-risk siblings, while the opposite pattern typically emerged in low-risk siblings. Lower dopaminergic function was associated with poorer referential communication and increased behavior problems only in the presence of familial risk for ASD. Findings suggest differential susceptibility—children’s ASD-relevant behaviors were differentially affected by
dopaminergic functioning depending on their familial risk for ASD. Understanding
genes linked to ASD-relevant behavioral difficulties in high-risk siblings will aid in the
very early identification of children at greatest risk for such difficulties, opening the way
for targeted prevention and intervention protocols.
# TABLE OF CONTENTS

| Page |
|---|---|
| LIST OF FIGURES | iv |
| LIST OF TABLES | v |

## Chapter

1. INTRODUCTION
   - Genetics and ASD | 1 |
   - Heterogeneity within ASD | 2 |
   - Dopaminergic Variants and Behavior | 3 |
   - ASD-Relevant Behavior | 4 |
   - Current Study | 6 |

2. METHOD
   - Participants | 8 |
   - Measures | 8 |
   - Analytic Approach | 11 |

3. RESULTS
   - Dopaminergic Genotypes | 12 |
   - Dependent Variables | 13 |
   - Initiating Joint Attention | 13 |
   - CBCL Externalizing Behavior Problems | 14 |
   - CBCL Internalizing Behavior Problems | 15 |
   - Mediation Model | 16 |

4. DISCUSSION | 17 |

REFERENCES | 23 |

FIGURES | 31 |

TABLES | 34 |
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGURE 1</td>
<td>31</td>
</tr>
<tr>
<td>FIGURE 2</td>
<td>32</td>
</tr>
<tr>
<td>FIGURE 3</td>
<td>33</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Page

TABLE 1a .............................................................................................................................................34
TABLE 1b .............................................................................................................................................35
TABLE 2 .............................................................................................................................................36
TABLE 3 .............................................................................................................................................37
TABLE 4 .............................................................................................................................................38
TABLE 5 .............................................................................................................................................39
TABLE 6 .............................................................................................................................................40
CHAPTER ONE

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by a broad range of social and communication impairments and stereotyped patterns of behavior (American Psychiatric Association, 2013) with prevalence estimates of over 1 in 75 children (CDC, 2014). The younger siblings of children with ASD (high-risk siblings) have high rates of ASD diagnosis, with recurrence rates of 4.5-18.7%, and exhibit substantial heterogeneity in behaviors associated with ASD, with an additional one fifth of high-risk siblings exhibiting sub-clinical difficulties (Grønborg, Schendel, & Parner, 2013; Messinger et al., 2013; Ozonoff et al., 2011; Risch et al., 2014), including initiating joint attention and behavior problems. Common genetic variants such as dopaminergic genes \textit{DRD4} and \textit{DRD2} may aid in understanding the variability of phenotypic presentation in high-risk siblings. The current study examined these dopaminergic variants in high-risk siblings and low-risk siblings (siblings with no family history of ASD) to better understand heterogeneity in behavioral phenotypes particularly relevant to ASD, initiating joint attention and behavior problems.

\textit{Genetics and ASD}

Although recent estimates suggest substantial heritability for ASD (Colvert et al., 2015; Hallmayer et al., 2011), specific genes responsible for this heritability are not clear (Geschwind, 2011). Both rare and common variants contribute to understanding genetic susceptibility in ASD. Several rare variants (mutations with a minor allele frequency of less than 1%) associated with ASD have been identified (Betancur, 2011); however, no specific gene accounts for a majority of ASD cases (Abrahams & Geschwind, 2008;
Geschwind, 2011; Muhle, Trentacoste, & Rapin, 2004). Even among siblings both diagnosed with ASD, most do not share the same ASD risk genes, underscoring the genetic heterogeneity of ASD (Yuen et al., 2015) and highlighting the potential difficulty of identifying replicable ASD susceptibility genes. Common variants (polymorphisms that occur in greater than 1-2% of the population) may comprise a substantial portion of the risk heritability of ASD (Gaugler et al., 2014; Klei et al., 2012). However, identified common variants that in combination or alone influence ASD susceptibility have not been well-replicated (Anney et al., 2010; Devlin, Melhem, & Roeder, 2011; Muhle et al., 2004). As genetic underpinnings of ASD are highly heterogeneous and a number of genes likely interact to influence susceptibility (Talkowski, Minikel, & Gusella, 2014), an approach focusing on the genetic basis of behaviors relevant to ASD may be productive in identifying genotypes associated with specific ASD-related traits (Muhle et al., 2004).

**Heterogeneity within ASD**

In addition to ASD’s genetic variability, ASD is phenotypically heterogeneous, encompassing a broad spectrum of impairment. Those diagnosed can exhibit varied combinations of traits and symptoms (Rapin, 1991; Rutter & Schopler, 1987), resulting in a range of later outcomes (Howlin, Goode, Hutton, & Rutter, 2004). ASD-relevant behaviors, which are characteristic of the disorder and its symptomatology, show substantial variability in both children with ASD and in their younger siblings. Even without an ASD diagnosis, high-risk siblings exhibit elevated ASD symptoms, lower levels of developmental functioning, and behavioral difficulties (Gangi, Ibañez, & Messinger, 2014; Georgiades et al., 2013; Messinger et al., 2013).
In low-risk children, common genetic variants have been linked to behavioral phenotypes (e.g., Bakermans-Kranenburg & van IJzendoorn, 2011; Lackner, Sabbagh, Hallinan, Liu, & Holden, 2012; Posner, Rothbart, & Sheese, 2007). Here, we aimed to examine common genetic variants implicated in behavior in the context of risk for ASD, to determine whether these variants may play a role in the heterogeneity seen in behaviors that are relevant to and have implications for ASD. Though individual common genetic variants are unlikely to distinguish children with ASD from case controls, these variants may be related to phenotypic variability in ASD-relevant behaviors (Geschwind, 2011) among high-risk siblings. We examined the role of two common genetic variants (DRD4 and DRD2) in a sample including high-risk siblings to understand phenotypic, behavioral heterogeneity in the context of familial ASD risk.

Dopaminergic Variants and Behavior

While relationships between dopaminergic variants and behavior have been studied in typically-developing children, there has been little examination in children at risk for ASD. Dopamine is a catecholamine that functions as a neurotransmitter in the brain, and it plays a role in several key domains including attention, reward-motivated behavior, and motor control. In the brain, dopamine is produced in areas including the substantia nigra and ventral tegmental area and then is transmitted through several main pathways, some of which are associated with the control of motivation-linked systems relevant to the current study. The mesolimbic and mesocortical pathways begin in the ventral tegmental area and connect to the nucleus accumbens and cerebral cortex, respectively, and they are associated with response to reward and motivation. The
nigrostriatal pathway begins in the substantia nigra and connects to the striatum, and it is associated with motor control.

Several common polymorphisms affect dopamine neurotransmission. The DRD4 gene encodes for dopamine receptor D4, which is expressed in areas including the frontal cortex, hippocampus, amygdala, and hypothalamus (Beaulieu & Gainetdinov, 2011). Variants in a 48-base pair variable number tandem repeat of DRD4 can influence gene expression, and a “long” version (the 7-repeat allele) has been associated with suppressed receptor expression (Schoots & Van Tol, 2003). The 7-repeat allele has been associated with varied attentional and behavioral difficulties in typically developing children and infants (Auerbach, Benjamin, Faroy, Geller, & Ebstein, 2001; Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001; Gizer, Ficks, & Waldman, 2009; Schmidt, Fox, Perez-Edgar, Hu, & Hamer, 2001). Among children with ASD, those with the 7-repeat allele tend to have greater behavior problems than those without the 7-repeat allele (Gadow, DeVincent, Olvet, Pisarevskaya, & Hatchwell, 2010). The DRD2 gene encodes for the dopamine receptor D2, which is expressed in areas including the striatum and nucleus accumbens (Beaulieu & Gainetdinov, 2011), and is associated with the Taq1A polymorphism on ANKK1. The A allele of the polymorphism (hereafter DRD2) is linked to a reduction in D2 receptor expression (Thompson et al., 1997) and is associated with risk for ASD and social interaction and communication difficulties (Hettinger et al., 2012; Salem et al., 2013).

**ASD-Relevant Behavior**

We focused on two ASD-relevant behaviors, initiation of joint attention and behavior problems. Early deficits in initiating joint attention (IJA), a form of referential
communication involving the use of gaze and gesture to coordinate attention between social partners and objects, are a core feature of ASD (Dawson et al., 2004; Mundy, Sigman, Ungerer, & Sherman, 1986). Among high-risk siblings, early IJA is predictive of later ASD symptomatology (Ibañez, Grantz, & Messinger, 2012). While some evidence suggests high-risk siblings tend to display fewer IJA behaviors than low-risk siblings (Cassel et al., 2007; Goldberg et al., 2005; Ibañez et al., 2012; Rozga et al., 2011), other investigations do not report differences (Toth, Dawson, Meltzoff, Greenson, & Fein, 2007; Yirmiya et al., 2006). These mixed findings highlight the necessity for empirical work to explain phenotypic variability among high-risk siblings. High levels of both internalizing and externalizing behavior problems are also reported in children with ASD (Mahan & Matson, 2011; Maskey, Warnell, Parr, Couteur, & McConachie, 2013) and their high-risk siblings (Fisman et al., 1996; Rodrigue, Geffken, & Morgan, 1993; Verté, Roeyers, & Buysse, 2003). Behavior problems are associated with both the severity of ASD symptomatology (Pearson et al., 2006) and parent stress and depression (Davis & Carter, 2008; Ekas & Whitman, 2010).

IJA and behavior problems are particularly relevant to high-risk siblings, as they may be predictive of later symptomatology and family emotional outcomes. Given the role of the dopaminergic system in reward sensitivity and motivation, it may influence whether an infant finds social interaction through joint attention rewarding and is motivated to perform IJA behaviors and whether a child is likely to exhibit externalizing or internalizing behavior problems. In addition, the dopaminergic system’s role in motor control and attention may play a role in infants’ ability to shift attentional focus and execute such behaviors. Despite the relationship between dopaminergic variants and
related functioning in typical development, similar associations have not been examined within children at risk for ASD. Investigating relations between behavioral phenotypes and dopaminergic genotypes in the context of familial risk for ASD may aid in understanding the manifestation of early ASD-relevant behaviors, enabling early identification of behavioral targets for early intervention.

Current Study

The current study examined dopaminergic genotypes \textit{DRD4} and \textit{DRD2} in relation to ASD-relevant behavioral phenotypes (i.e., joint attention and behavior problems) in the context of familial autism risk.

Aim 1. Characterize dopaminergic genotype distributions in high-risk and low-risk siblings. We examined distributions of genotype frequencies (\textit{DRD4}, \textit{DRD2}, and a dopamine gene score comprised of both genes) in high- and low-risk siblings. We did not expect genotype frequencies to differ between groups (i.e., risk alleles would not be overrepresented in high-risk siblings).

Aim 2. Examine the relationship between dopaminergic variants and ASD-relevant behavioral phenotypes in high-risk and low-risk siblings. Regression models tested the effect of dopaminergic genotype, as well as its interaction with risk group status, on ASD-relevant behaviors (i.e., IJA in the first year and behavior problems at three years). We expected lower dopaminergic functioning to be associated with lower levels of IJA and higher levels of problem behaviors.

Aim 3. Determine whether ASD-relevant behavior in the first year (IJA) mediates a relationship between dopaminergic functioning and later ASD symptomatology. A mediation model tested whether dopaminergic functioning (indexed by dopaminergic
genotype composite) is associated with ASD symptomatology at 30 months through its relationship to IJA in the first year.
CHAPTER TWO

METHOD

Participants

Participants were the infant siblings of children diagnosed with Autism Spectrum Disorder (ASD; high-risk siblings, \( n = 55 \)) or the infant siblings of typically developing children with no history of ASD (low-risk siblings, \( n = 38 \)). High-risk siblings have at least one older sibling with a diagnosis of ASD, confirmed upon study enrollment by administration of the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) and clinical diagnosis by a licensed clinical psychologist. Low-risk siblings have older siblings with no evidence of ASD, confirmed by a score lower than 9 on the Social Communication Questionnaire (Berument, Rutter, Lord, Pickles, & Bailey, 1999), a conservative cutoff score, and no family history of ASD.

Measures

Early Social Communication Scales (ESCS). Joint attention was assessed within the ESCS (Mundy et al., 2003) at 8, 10, and 12 months. The ESCS is a semi-structured assessment of infants’ nonverbal communication abilities, during which an examiner (seated across from the infant) presents and activates a series of toys, creating opportunities for the infant to initiate joint attention. After presenting and activating a toy, the examiner remains attentive and responds to the infants’ joint attention bids briefly. The current study focused on initiating joint attention (IJA) bids occurring during the ESCS (e.g., when infant gazed between the examiner and activated toy or showed an object to the examiner). Videotaped assessments were reliably coded by trained coders. Rates per minute of joint attention were calculated for each assessment.
age; a mean was calculated from the standardized values of each assessment age to provide a measure of IJA in the first year for analyses.

*Child Behavior Checklist (CBCL).* Parent-reported behavior problems were assessed within the CBCL (Achenbach, Edelbrock, & Howell, 1987; Achenbach & Rescorla, 2000) at 36 months. The CBCL is a well-validated parent-report measure of children’s behavior problems and yields subscales of Internalizing and Externalizing problems, normed by age and sex.

*ASD Symptomatology.* ASD symptomatology was assessed within the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), a play-based observational measure during with an examiner administers behavioral presses designed to elicit ASD-relevant behaviors. This assessment was administered at 30 months, and children were administered either Module 1 \( (n=39) \) or Module 2 \( (n=41) \) based on language level. Risk groups did not differ in which ADOS Module was administered, \( \chi^2(1)=0.23, p=.63 \).

To capture a continuous measure of ASD symptomatology, overall calibrated severity scores (overall CSS) were calculated for each child based on Gotham, Pickles, and Lord’s (2009) criteria. In addition, Hus, Gotham, and Lord’s (2014) criteria were used to calculate calibrated severity scores for each child in two domains: social affect domain (SA-CSS) and restricted and repetitive behaviors domain (RRB-CSS). Scores for each domain range from 1 to 10 and account for the child’s age and language level.

High-risk siblings \( (M=3.07, SD=.2.17) \) had higher overall CCS than low-risk siblings \( (M=1.51, SD=1.27) \), \( t(78)=-3.76, p<.001 \); high-risk siblings \( (M=3.36, SD=2.27) \) had higher SA-CCS than low-risk siblings \( (M=1.91, SD=1.50) \), \( t(78)=-3.24, p=.002 \); and high-risk siblings \( (M=4.33, SD=2.59) \) had higher RRB-CCS than low-risk siblings.
Ten high-risk siblings had overall CSS at or above the cutoff for ASD (a score of 4 or above), and 7 had scores at or above the cutoff for autism (a score of 6 or above). One low-risk sibling had a score at or above the ASD or autism cutoffs.

Clinical diagnosis was determined at 36 months ($n=85$). The ADOS administered at 30 months, the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Couteur, 1994) administered at 36 months, and the Mullen Scales of Early learning administered at 36 months were used to inform the DSM-IV-based best-estimate diagnosis from a licensed psychologist. Twelve high-risk siblings received a diagnosis of ASD, and no low-risk siblings were diagnosed with ASD.

**Dopamine Genotypes.** Genetic data was collected from saliva samples from participants using Oragene DNA collection kits. Genetic samples were sent for extraction and analysis to the John P. Hussman Institute for Human Genomics (HIHG) at the University of Miami Miller School of Medicine. Genotyping was conducted for DRD4 and DRD2. Genotypes for DRD4 (rs1805186) were grouped according to the presence or absence of the 7-repeat allele (“0” = no 7-repeat, “1” = at least one 7-repeat). For DRD2 (rs1800497), genotypes were grouped according the presence of the A allele (“0” = no A allele, “1” = at least one A allele).

A dopamine gene score was also created by coding DRD4 and DRD2 to reflect dopaminergic functioning. Higher scores indicate more “risk” alleles (indexing lower dopaminergic functioning) and lower scores indicated fewer “risk” alleles (indexing greater dopaminergic functioning). Gene scores serve as an index of cumulative dopaminergic functioning for analyses of outcomes (for similar approaches, see:
Nikolova, Ferrell, Manuck, & Hariri, 2011; Pearson-Fuhrhop et al., 2014; Stice, Yokum, Burger, Epstein, & Smolen, 2012), with participants coded as having 0, 1, or 2 risk genotype sets.

**Analytic Approach**

For Aim 1, initial analyses examined distributions of genotype frequencies, testing whether allelic frequencies were consistent with Hardy-Weinberg equilibrium. Fisher’s exact tests determined whether genotype frequencies differed between high- and low-risk siblings, between high-risk siblings diagnosed with and without an ASD, and between ethnicities. Relations between dependent variables were also examined. For Aim 2, I next determined whether individual genotypes interacted with participants’ risk status to predict behavioral phenotypes. For each dependent variable (IJA, Internalizing, and Externalizing), a 2 (genotype) by 2 (risk group) ANOVA for each of the dopaminergic variants tested for main effects of genotype and risk status, as well as their interaction. This was followed by a regression in which dopamine score, status, and dopamine score*status interaction were entered as predictors to determine the cumulative effect of both dopaminergic genes. Interaction effects were followed up with individual models in which dependent variables were regressed on gene score. For Aim 3, a mediation model was tested to determine whether IJA mediates a relationship between dopamine score and later ASD symptomatology in high-risk siblings.
CHAPTER THREE

RESULTS

Dopaminergic Genotypes

Allelic distributions for DRD4, $\chi^2(1)=0.02$, $p=.85$, and DRD2, $\chi^2(1)=0.00$, $p=.82$, were consistent with Hardy-Weinberg equilibrium (Rodriguez, Gaunt, & Day, 2009).

Allele frequencies for DRD4, $p=.82$, and DRD2, $p=.25$, did not differ between high-risk and low-risk siblings (see Table 1a; all repeat alleles for DRD4 are presented in Table 1b). Within high-risk siblings, allele frequencies for DRD4, $p=1.00$, and DRD2, $p=.47$, did not differ between children diagnosed with and without ASD at 36 months (see Table 2). Allele frequencies for DRD4, $p=.15$, and DRD2, $p=.14$, did not differ by ethnicity (Non-Hispanic White/Caucasian, Hispanic/Latino, and Other; see Table 3).

For analyses, genotypes for DRD4 and DRD2 were grouped according to the presence or absence of any alleles indicating lower dopaminergic functioning (7-repeat or A allele, respectively). Genotype frequencies for DRD4, $p=.48$, and DRD2, $p=.37$, did not differ between high-risk and low-risk siblings (see Table 4). Among high-risk siblings, genotype frequencies for DRD4, $p=1.00$, and DRD2, $p=.32$, did not differ between children diagnosed with and without ASD at 36 months (see Table 5). Genotype frequencies for DRD4, $p=.13$, and DRD2, $p=.14$, did not differ by ethnicity (see Table 6). Dopamine composite scores also did not differ between high-risk and low-risk siblings, $p=.69$, between high-risk siblings diagnosed with and without ASD at 36 months, $p=.51$, or by ethnicity, $p=.23$ (see Tables 4-6).
Dependent Variables

In high-risk siblings, Internalizing Problems was correlated with Externalizing Problems, \( r = .62, p < .001 \). IJA was not correlated with Internalizing Problems, \( r = -.16, p = .36 \), but was correlated with Externalizing Problems, \( r = -.39, p = .02 \). In low-risk siblings, Internalizing Problems was correlated with Externalizing Problems, \( r = .49, p = .007 \). IJA was not correlated with Internalizing Problems, \( r = -.32, p = .09 \), but was correlated with Externalizing Problems, \( r = -.45, p = .02 \).

Initiating Joint Attention

**DRD4.** There was no main effect of genotype, \( F(1, 86) = 0.05, p = .82 \), partial \( \eta^2 = .001 \), power = .66, on IJA. There was a main effect of group status, \( F(1, 86) = 12.08, p = .001 \), partial \( \eta^2 = .12 \), power = .93, with high-risk siblings exhibiting lower levels of IJA than low-risk siblings. This main effect was modified by a genotype*status interaction effect, \( F(1, 86) = 8.80, p = .004 \), partial \( \eta^2 = .09 \), power = .84. Among children without the 7-repeat allele, levels of IJA did not differ between high-risk (\( M = 0.01, SD = 0.84 \)) and low-risk (\( M = 0.11, SD = 0.73 \)) siblings, \( t(62) = 0.48, p = .64 \). Among children with the 7-repeat allele, however, high-risk siblings (\( M = -0.52, SD = 0.75 \)) exhibited lower levels of IJA than low-risk siblings (\( M = 0.73, SD = 1.01 \)), \( t(24) = 3.62, p = .001 \).

**DRD2.** There was no main effect of genotype, \( F(1, 89) = 0.01, p = .91 \), partial \( \eta^2 = .00 \), power = .55, on IJA. There was a main effect of group status, \( F(1, 89) = 6.58, p = .01 \), partial \( \eta^2 = .07 \), power = .72, with high-risk siblings (\( M = -0.13, SD = 0.84 \)) exhibiting lower levels of IJA than low-risk siblings (\( M = 0.29, SD = 0.86 \)). There was no genotype*status interaction effect, \( F(1, 89) = 1.56, p = .22 \), partial \( \eta^2 = .02 \), power = .24.
**Dopamine Score.** A regression model assessed effects of the dopamine score, risk group status, and their interaction on IJA, adjusted $R^2=0.13$, $F(3, 86)=5.31$, $p=.002$, power=.87. There was no main effect of status, $b=0.03$, $t=0.13$, $p=.90$. There was a main effect of dopamine score, $b=0.50$, $t=2.34$, $p=.02$, such that children with higher dopamine scores tended to have higher IJA levels. There was also a dopamine score*status interaction effect, $b=-0.81$, $t=-3.09$, $p=.003$. Regression analyses by risk group indicated that in high-risk siblings, IJA levels decreased as dopamine scores increased, $b=-0.31$, $t=-2.03$, $p=.047$, while in low-risk siblings, IJA levels increased as dopamine scores increased, $b=0.50$, $t=2.35$, $p=.03$ (see Figure 1). Dopamine scores explained a significant proportion of variance in IJA in high-risk siblings, adjusted $R^2=0.06$, $F(1, 52)=4.13$, $p=.047$, power=.45, and in low-risk siblings, adjusted $R^2=0.12$, $F(1, 34)=5.53$, $p=.03$, power=.57.

**CBCL Externalizing Behavior Problems**

**DRD4.** There was no main effect of genotype, $F(1, 57)=0.04$, $p=.84$, partial $\eta^2=.001$, power=.05, on Externalizing Problems. There was a main effect of group status, $F(1, 57)=5.14$, $p=.03$, partial $\eta^2=.08$, power=.61, with high-risk siblings exhibiting higher levels of Externalizing Problems than low-risk siblings. This main effect was modified by a genotype*status interaction effect, $F(1, 57)=4.14$, $p=.047$, partial $\eta^2=.07$, power=.52. Among children without the 7-repeat allele, levels of Externalizing Problems did not differ between high-risk ($M=42.92$, $SD=9.13$) and low-risk ($M=42.28$, $SD=9.13$) siblings, $t(42)=-0.23$, $p=.82$. Among children with the 7-repeat allele, however, low-risk siblings ($M=36.11$, $SD=9.35$) exhibited lower levels of Externalizing Problems than high-risk siblings ($M=48.00$, $SD=12.38$), $t(15)=-2.25$, $p=.04$. 
**DRD2.** There was no main effect of genotype, $F(1, 60) = 0.87, p = .35$, partial $\eta^2 = .01$, power = .15, or group status, $F(1, 60) = 2.77, p = .10$, partial $\eta^2 = .04$, power = .37, on levels of Externalizing Problems, and there was no genotype*status interaction effect, $F(1, 60) = 0.27, p = .61$, partial $\eta^2 = .004$, power = .08.

**Dopamine Score.** A regression model assessed effects of the dopamine score, risk group status, and their interaction on Externalizing Problems, adjusted $R^2 = 0.04$, $F(3, 57) = 1.89, p = .14$, power = .65. There was no main effect of status, $b = 0.03, t = 0.01, p = .99$, or dopamine score, $b = -2.53, t = -0.85, p = .40$. There was no dopamine score*status interaction effect, $b = 6.36, t = 1.65, p = .10$ (see Figure 2).

**CBCL Internalizing Behavior Problems**

**DRD4.** There was no main effect of genotype, $F(1, 57) = 0.01, p = .94$, partial $\eta^2 = .00$, power = .05, on Internalizing Problems. There was a main effect of group status, $F(1, 57) = 4.30, p = .04$, partial $\eta^2 = .07$, power = .53, with high-risk siblings exhibiting higher levels of Internalizing Problems than low-risk siblings. There was no genotype*status interaction effect, $F(1, 57) = 3.39, p = .07$, partial $\eta^2 = .06$, power = .44.

**DRD2.** There was a main effect of genotype, $F(1, 60) = 8.03, p = .01$, partial $\eta^2 = .12$, power = .80, on levels of Internalizing Problems, with children with an A allele ($M = 46.27, SD = 9.37$) exhibiting higher levels of Internalizing Problems than children without an A allele ($M = 38.69, SD = 9.16$). There was no main effect of group status, $F(1, 60) = 1.99, p = .16$, partial $\eta^2 = .03$, power = .28, and there was no genotype*status interaction effect, $F(1, 60) = 3.29, p = .08$, partial $\eta^2 = .05$, power = .43.

**Dopamine Score.** A regression model assessed effects of the dopamine score, risk group status, and their interaction on Internalizing Problems, adjusted $R^2 = 0.13$, $F(3, 57) = 1.89, p = .14$, power = .65. There was no main effect of status, $b = 0.03, t = 0.01, p = .99$, or dopamine score, $b = -2.53, t = -0.85, p = .40$. There was no dopamine score*status interaction effect, $b = 6.36, t = 1.65, p = .10$ (see Figure 2).
There was no main effect of status, $b=-2.84$, $t=-0.90$, $p=.38$, or dopamine score, $b=-2.89$, $t=-1.04$, $p=.30$. There was a dopamine score*status interaction effect, $b=10.42$, $t=2.91$, $p=.005$. Regression analyses by risk group indicated a significant effect of dopamine score for high-risk siblings, $b=7.54$, $t=3.27$, $p=.003$, but not for low-risk siblings, $b=-2.32$, $t=-1.07$, $p=.30$ (see Figure 3). Dopamine scores did not explain a significant proportion of variance in IJA in high-risk siblings, adjusted $R^2=0.04$, $F(1, 32)=2.45$, $p=.13$.

**Mediation Model**

In high-risk siblings who had completed an ADOS assessment at 30 months ($n=44$), dopamine score did not have a direct effect on overall CSS, $b=-0.02$, SE=0.44, $p=.96$. Dopamine score did not predict IJA, $b=-0.19$, SE=0.18, $p=.29$, and IJA did predict overall CSS, $b=-0.81$, SE=0.38, $p=.04$. The indirect effect was tested using a bootstrap estimation approach with 1000 samples (Preacher & Hayes, 2008); the indirect effect was not significant, $b=0.15$, SE=0.16, 95% CI=-0.12, 0.53.

Dopamine score did not have a direct effect on SA-CSS, $b=0.31$, SE=0.47, $p=.52$. Dopamine score did not predict IJA, $b=-0.19$, SE=0.18, $p=.29$, and IJA did predict SA-CSS, $b=-0.92$, SE=0.39, $p=.02$. The indirect effect, tested using a bootstrap estimation approach with 1000 samples, was not significant, $b=0.18$, SE=0.18, 95% CI=-0.15, 0.56.

Dopamine score did not have a direct effect on RRB-CSS, $b=0.26$, SE=0.56, $p=.65$. Dopamine score did not predict IJA, $b=-0.19$, SE=0.18, $p=.29$, and IJA did not predict RRB-CSS, $b=-0.42$, SE=0.48, $p=.39$. The indirect effect, tested using a bootstrap estimation approach with 1000 samples, was not significant, $b=0.08$, SE=0.15, 95% CI=-0.09, 0.56.
CHAPTER FOUR

DISCUSSION

Children at elevated risk for ASD exhibit heterogeneity in symptomatology, other behaviors relevant to ASD, and outcomes. Among high-risk siblings, early behavior often predicts diagnosis, but these patterns of prediction are not clear. We aimed to refine our understanding of heterogeneity in early behavior relevant to ASD by examining the role of common genetic variants. We examined the association between common variants related to dopaminergic functioning and initiating joint attention (IJA) and behavior problems. High-risk siblings with \(DRD4\) and \(DRD2\) genotypes linked to lower dopaminergic functioning exhibited lower levels of IJA and higher levels of internalizing behavior problems than high-risk siblings with variants linked to greater dopaminergic functioning. To our knowledge, this is the first investigation of these genetic variants in relation to attention and behavior problems in siblings at risk for ASD.

For high-risk siblings, lower dopaminergic functioning (indexed by higher dopamine scores) was associated with less optimal behavior both in the first year, with lower levels of IJA, and at three years, with elevated levels of internalizing behavior problems. IJA and behavior problems are both important for the development of high-risk siblings. Referential communication such as IJA is central to later language and social functioning in children at risk for ASD (Gangi et al., 2014; Ibañez et al., 2012; Malesa et al., 2012), and behavior problems have been associated with symptomatology in children with ASD and augment parent stress, with likely effects on the family system (Davis & Carter, 2008; Ekas & Whitman, 2010). Early referential communication difficulties and later behavior problems likely impact social functioning in children at risk.
for ASD, and these behaviors appear to be influenced by dopaminergic genotypes. This link may allow for early identification of high-risk siblings at greatest risk for behavioral difficulties in these areas.

Although higher dopamine scores were associated with less optimal behavior among high-risk siblings, the opposite pattern emerged in low-risk siblings. Low-risk siblings with higher dopamine scores exhibited higher levels of IJA. This pattern suggests differential susceptibility, the hypothesis that children vary in their susceptibility to both adverse and beneficial effects of their environments (Belsky, 2005; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009). Common genetic variants have been identified as potential susceptibility factors that modify individuals’ susceptibility to influences affecting outcomes. The variants in the current study, *DRD4* and *DRD2*, act as susceptibility genes in multiple contexts (e.g., Bakermans-Kranenburg & van IJzendoorn, 2006, 2011; Sheese, Voelker, Rothbart, & Posner, 2007; Van IJzendoorn & Bakermans-Kranenburg, 2006), but have not been examined in the context of familial risk for ASD.

Although the differential susceptibility hypothesis is often conceptualized as susceptibility to rearing, it may also encompass sensitivity to a broader range of influences (Belsky & Pluess, 2009). For example, stronger associations between difficult child temperament and externalizing problems are found in children who have older siblings (Mesman et al., 2009). Endogenous factors have also been conceptualized as internal environments that affect the relationship between genes and outcomes (Schmidt, Fox, Perez-Edgar, & Hamer, 2009). That is, factors within an individual may play a role in moderating the association between genotype and developmental outcomes.
Familial risk for ASD confers increased risk for ASD and related sub-clinical deficits to younger siblings of children diagnosed with ASD. Within a differential susceptibility framework, we conceptualize familial ASD risk as a functional context. Familial ASD risk likely encompasses combinations of genetic and environmental factors to which children may be more or less susceptible. Here, high-risk siblings with alleles linked to lower dopaminergic functioning exhibited lower levels of IJA and higher levels of behavior problems. In siblings with no alleles linked to lower dopaminergic functioning, high- and low-risk siblings exhibited similar levels of IJA. Additional research will be necessary to determine specific genetic and environmental factors responsible for differential susceptibility among high-risk siblings (Hallmayer et al., 2011; Newschaffer et al., 2012; Yuen et al., 2015).

Within high-risk siblings, IJA did not mediate a relationship between dopamine score and later ASD symptomatology. However, this model was also unable to detect the initial association between dopamine score and IJA, likely due to the reduced number of high-risk siblings able to be included in the analysis (44 high-risk siblings who had completed an ADOS at 30 months). Sample size also limited analysis of high-risk siblings with ASD. Twelve high-risk siblings in the study sample were later diagnosed with ASD, a number insufficient for separate analyses. Findings from the current study should also be interpreted with caution until replicated with larger sample sizes. Particularly for analyses of behavior problems, which included fewer participants than IJA analyses, models may have been underpowered to detect interaction effects (power estimates for ANOVAs ranged from .08-.37 and for regressions ranged from .49-.91 for interaction effects). If employing corrections for multiple significance tests, with
division by three for the number of dependent variables tested, the adjusted significance
level would be $p=.02$. All but one significant interaction effect ($DRD4$*status interaction
for Externalizing Problems, $p=.047$) would survive this correction. Future research
aimed at replicating our findings with larger sample sizes would strengthen our findings
of a relationship between dopaminergic genotypes and ASD-relevant behaviors and could
profitably investigate this relationship among high-risk children with ASD outcomes.

In addition to the $DRD4$ and $DRD2$ variants examined in the current study, other
dopaminergic variants might be examined in future investigations of behavioral
characteristics of high-risk siblings and children with autism. For example, a VNTR in
the $DAT1$ gene is associated with expression of the dopamine transporter (Fuke et al.,
2001). Together, these variants might provide a more comprehensive index of
dopaminergic functioning.

Genotypes outside the dopaminergic system may also impact the outcome of
dopaminergic functioning and might further our understanding of dopamine’s role in
behavioral outcomes. For example, catechol-O-methyl transferase (encoded by the
$COMT$ gene) is an enzyme that degrades catecholamines including dopamine, and a
polymorphism in the $COMT$ gene is associated with dopaminergic function (Chen et al.,
2004). Brain-derived neurotrophic factor (BDNF; coded for by the $BDNF$ gene) may
influence dopamine activity as well (Goggi, Pullar, Carney, & Bradford, 2003; Narita,
Aoki, Takagi, Yajima, & Suzuki, 2003; Savitz, Solms, & Ramesar, 2006). Serotonergic
function may also interact with dopaminergic function to influence behavioral outcomes,
particularly internalizing and externalizing behavior problems. Levels of dopaminergic
functioning might influence sensitivity to reward, leading to either high or low
motivation toward rewards. Dopaminergic functioning might then interact with levels of serotonergic functioning influencing effortful control, which could aid in regulation of approach tendencies related to reward sensitivity (Carver, Johnson, & Joormann, 2009). Thus, a combination of high dopaminergic functioning (high reward sensitivity/approach) and low serotonergic functioning (low effortful control) might result in high levels of externalizing behavior.

In the current study, we found that dopaminergic risk alleles were associated with lower levels of IJA and higher levels of behavior problems in high-risk siblings. Given the systems in which dopamine plays a role, dopaminergic functioning could potentially affect children’s social motivation, reward sensitivity, attention coordination, and even motor control. High-risk siblings with lower dopaminergic functioning appear to exhibit less optimal behavior, both in early social interaction and in later levels of behavior problems.

As the search for replicable genes associated with ASD risk is ongoing, an approach investigating genes that may be relevant to specific behaviors important for the development of children at risk for ASD may be a productive avenue of research. Genes that may not be associated with ASD itself may still be linked to particular behaviors. In addition to aiding in identifying high-risk siblings at greatest risk for difficulties, findings may also aid in identifying resilient children. High-risk siblings with fewer genes associated with lower dopaminergic functioning were exhibiting fewer difficulties in ASD-relevant behaviors than high-risk siblings carrying more genotypes associated with lower dopaminergic functioning.
Referential communication and behavior problems are associated with ASD symptoms and outcome. Links between dopaminergic variants and behavioral phenotypes relevant to ASD, such as joint attention and behavior problems, can aid in understanding the developmental heterogeneity of high-risk siblings. Identification of common genetic variants—assessable at birth—that confer increased risk for ASD-relevant behaviors has the potential to aid in assessing risk and informing preventive interventions. If replicated, the current results suggest that genotype screening could aid in identifying siblings at the greatest risk for difficulties in areas relevant to later outcomes, even before the emergence of delays or difficulties. Developmental psychopathology could benefit from utilizing genetic markers with documented roles in healthy and problematic behaviors to assess risk and inform preventive interventions.
REFERENCES


Figure 1

*Mean levels of Initiating Joint Attention (IJA) by group.*

*Note.* Error bars reflect +/- 1 SE. Initiating joint attention reflects a mean of standardized values. In high-risk siblings, 28 had a dopamine score of 0, 18 had a score of 1, and 8 had a score of 2. In low-risk siblings, 19 had a dopamine score of 0, 14 had a score of 1, and 3 had a score of 2.
Figure 2

Mean levels of CBCL Externalizing by group.

Note. Error bars reflect +/- 1 SE. The dopamine score*status interaction effect was not significant for Externalizing Problems. In high-risk siblings, 17 had a dopamine score of 0, 13 had a score of 1, and 4 had a score of 2. In low-risk siblings, 13 had a dopamine score of 0, 12 had a score of 1, and 2 had a score of 2.
Figure 3

Mean levels of CBCL Internalizing by group.

Note. Error bars reflect +/- 1 SE. In high-risk siblings, 17 had a dopamine score of 0, 13 had a score of 1, and 4 had a score of 2. In low-risk siblings, 13 had a dopamine score of 0, 12 had a score of 1, and 2 had a score of 2.
Table 1a. *DRD4 and DRD2 allele frequencies by risk group.*

<table>
<thead>
<tr>
<th>Allele</th>
<th>High-risk Siblings</th>
<th>Low-risk Siblings</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percentage</td>
</tr>
<tr>
<td><strong>DRD4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/-</td>
<td>41</td>
<td>74.5%</td>
</tr>
<tr>
<td>7/7</td>
<td>13</td>
<td>23.6%</td>
</tr>
<tr>
<td><strong>DRD2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>35</td>
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</tr>
<tr>
<td>A/G</td>
<td>19</td>
<td>34.5%</td>
</tr>
<tr>
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<td>1</td>
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</table>
Table 1b. *DRD4* repeat allele frequencies by risk group.

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<td>Frequency</td>
<td>Percentage</td>
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</tr>
<tr>
<td>2/3</td>
<td>1</td>
<td>1.8%</td>
</tr>
<tr>
<td>2/4</td>
<td>8</td>
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<tr>
<td>7/8</td>
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Table 2. *DRD4 and DRD2 allele frequencies of high-risk siblings by ASD diagnosis.*

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<td></td>
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</tr>
<tr>
<td>7/-</td>
<td>3</td>
<td>27.3%</td>
</tr>
<tr>
<td>7/7</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>DRD2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>6</td>
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</tr>
<tr>
<td>A/G</td>
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<td>50.0%</td>
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Table 3. *DRD4* and *DRD2* allele frequencies by ethnicity.

<table>
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<tr>
<th>Allele</th>
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<th>Other</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percentage</td>
<td>Frequency</td>
</tr>
<tr>
<td><strong>DRD4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-/-</td>
<td>34</td>
<td>70.8%</td>
<td>27</td>
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<tr>
<td>7/-</td>
<td>13</td>
<td>27.1%</td>
<td>7</td>
</tr>
<tr>
<td>7/7</td>
<td>1</td>
<td>2.1%</td>
<td>0</td>
</tr>
<tr>
<td><strong>DRD2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>30</td>
<td>58.8%</td>
<td>26</td>
</tr>
<tr>
<td>A/G</td>
<td>20</td>
<td>39.2%</td>
<td>5</td>
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<tr>
<td>A/A</td>
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<td>2</td>
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Table 4. Genotype frequencies by risk group.

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<th>Low-risk Siblings</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percentage</td>
</tr>
<tr>
<td><strong>DRD4</strong></td>
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<td></td>
</tr>
<tr>
<td>7-repeat allele</td>
<td>14</td>
<td>25.5%</td>
</tr>
<tr>
<td>No 7-repeat allele</td>
<td>41</td>
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</tr>
<tr>
<td><strong>DRD2</strong></td>
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<td>36.4%</td>
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<tr>
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<tr>
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Table 5. *Genotype frequencies of high-risk siblings by ASD diagnosis.*

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<td></td>
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<td>Percentage</td>
<td>Frequency</td>
<td>Percentage</td>
</tr>
<tr>
<td><strong>DRD4</strong></td>
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<tr>
<td>7-repeat allele</td>
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<tr>
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<td>73.0%</td>
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Table 6. *Genotype frequencies by ethnicity.*

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<th><strong>Other</strong></th>
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<td>Frequency</td>
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<td>29.2%</td>
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<td>No 7-repeat allele</td>
<td>34</td>
<td>70.8%</td>
<td>27</td>
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<tr>
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<td>41.2%</td>
<td>7</td>
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