A Multi-Gene by Environment Perspective of ADHD Symptomatology in Young Children

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A Multi-Gene by Environment Perspective of ADHD Symptomatology in Young Children

A Dissertation

Submitted to the Graduate Faculty of the
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Doctorate of Philosophy
In
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Amber Allison
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Abstract

Attention deficit hyperactivity disorder (ADHD) is a heritable disorder, which has detrimental effects on childhood development and is associated with maladaptive functioning in adulthood. Despite this, we are far from an understanding of the etiology and possible trajectories of ADHD, possibly due to investigations focusing on the contribution of single genes. In fact, single genes are likely not influential enough to alter behavior, but the additive effect of many genes may predispose an individual toward certain behaviors. Further, environmental input can activate or suppress genetic expression, thereby leading to vast individual differences in both normative behavior and psychopathological illness, including ADHD. This study investigated the effect of cumulative genetic sensitivity across three dopaminergic polymorphisms (DRD2 A1, DRD4 7R, and DAT1 10R) on ADHD symptomatology in very young children. In addition, we were interested in the G x E associations with ADHD symptomatology. Findings provide novel evidence regarding the effects of dopamine polymorphisms on inattention, and thus ADHD, symptomatology in very young children. Specifically, the findings suggest that the cumulative effect of genetic sensitivity across several dopamine polymorphisms predicts severity of symptomatology, particularly in males. In addition, a robust G x E interaction emerged, whereby a specific genetic predisposition moderated the effect of family context on behavior. This finding, lending support to the BSC model and the differential susceptibility hypothesis, suggests that genetic sensitivity can moderate environmental influence, for better and for worse.

Keywords: dopamine, ADHD, family environment, gene x environment
A Multi-Gene by Environment Perspective of ADHD Symptomatology in Young Children

Looking through the latest version of the Diagnostic and Statistical Manual (DSM-5), one would likely notice that the field of psychology is better capable of identifying and describing mental illness than explaining the etiology or risk factors for developing it. In fact, the etiology of most mental illnesses is largely unknown. There are numerous factors contributing to complex behaviors, such as mental illness, and the associations between factors are complex. Genetic variation can explain some of the individual differences in prevalence and expression of mental health outcomes (Goldsmith, Gottesman, & Lemery, 1997; Moffitt, Caspi, & Rutter, 2005), and environmental input can activate or suppress genetic expression to further shape an individual’s mental health trajectory (Rutter, 2006). For example, identical twins reared separately may be quite different as adults because of differential environments and experiences.

The mechanisms whereby genes and environments interact to produce complex behavior are not yet completely understood. Initial investigations suggest, however, that single genes are likely not influential enough to alter behavior in detectable ways; rather, the additive effect of many genes may cumulatively predispose an individual toward certain behaviors. Specifically with regard to psychopathology, predispositions across many genes may modify an individual’s sensitivity to behaviorally relevant environmental stimuli. Building on this, the purpose of the current research endeavor is to enhance the current literature by testing a model in which genetic predispositions cumulatively interact with environmental factors to influence mental health in childhood
(see Figure 1). This information would aid in efforts to identify those most at risk, as well as efforts to develop interventions for children with these genetic predispositions, such as assisting them in avoiding environmental input that would lead to maladaptive behavior (i.e., psychopathology) and, simultaneously, directing them toward environments that would lead to the most favorable and advantageous outcomes.

Figure 1. Theoretical model of GxE predicting ADHD symptomatology

GENES AND BEHAVIOR

The two dominant procedures for analyzing the importance of genes are behavioral genetics and molecular genetics. In pure behavioral genetics, three principles dominate: (1) all behavioral traits are inherited; (2) the effect of being raised in the same family is less than the effect of genes; and (3) a substantial portion of the variation seen in complex human behavioral traits is not accounted for by genes or families (Turkheimer, 2000). Based on these principles, most research in behavioral genetics involves twin or adoption studies. In twin studies, the similarity between monozygotic twins is attributed to genes and dissimilarity is attributed to non-shared environment. In adoption studies, the similarity between the birth parent(s) and the adopted child that is not shared by the adoptive parent is considered genetic.
In molecular genetics, on the other hand, specific genes are targeted based on theories and evidence linking those genes to certain behaviors. The Human Genome Project revealed that humans have somewhere between 20,000 and 25,000 genes on 23 pairs of chromosomes, and each gene may have numerous polymorphic sites with several possible variations. These variant forms arise through mutations in germ cells, such as insertions, deletions or repeats. Although we are a long way from understanding how each of these genes and mutations influence mental and physical health, several genes have been extensively researched and found to influence risk or resistance to disease. For example, Huntington’s Disease is a neurodegenerative disorder caused by a mutation on chromosome four that leads to an abnormally increased number of the nucleotide sequence CAG in the coding region of the gene. Other physical diseases that can be traced to genetic abnormalities include cystic fibrosis and sickle cell anemia.

With regard to mental health, it is almost impossible to trace disorders to one particular gene. Nevertheless, twin, adoption, and molecular genetics studies indicate a strong influence of heredity in some mental illnesses. For example, schizophrenia, autism, major depressive disorder, and panic disorder have a substantial hereditary component (Insel & Wang, 2010; Uher, 2009). A commonality between these heritable mental illnesses is that symptoms are often identifiable in childhood. This is not surprising considering that heritability suggests a genetic or otherwise biological etiological component of the disorder, which might lead to earlier onset than disorders that are mostly, if not completely, a result of environmental experiences or exposure. Understanding the genetic predispositions that underlie disorders with childhood onset is
crucial for developing and utilizing strategies to mitigate both the immediate and the long-term consequences of these disorders.

**Attention Deficit Hyperactivity Disorder**

Attention deficit hyperactivity disorder (ADHD) is a particularly important childhood disorder to investigate due to its heritability, detrimental effects on childhood development, and association with maladaptive functioning in adulthood. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), ADHD is the most commonly diagnosed childhood disorder, with between 3-7% of school-aged children receiving diagnoses, and even higher estimated rates in community samples. In school-aged children, elevated levels of inattention and hyperactivity associated with ADHD interfere with academic functioning and social development. For example, children with ADHD are five to six times more likely to be identified as having significant deficits in social skills (Merrell & Wolfe, 1998; Spira & Fischel, 2005) and are at increased risk for grade retention (Biederman, 2003).

Additionally, there is substantial developmental stability in ADHD from preschool to adolescence, with the inattentive component of the disorder evidencing more stability than hyperactivity (August, Braswell, & Thuras, 1998; B. Lahey, Pelham, Loney, Lee, & Willcutt, 2005). The latest version of the DSM (DSM-5) was amended to reflect that, although ADHD begins in childhood, it is a pervasive developmental disorder that can negatively affect functioning throughout the lifespan. In fact, at least 60% of children with ADHD retain symptoms in adulthood (Ingram, Hechtman, & Morgenstern, 1999; Ramsay, 2010). In adults, the impairment associated with ADHD often interferes
with professional and, indirectly, personal functioning (Barkley & Murphy, 2006). For example, adults with ADHD may have difficulty following instruction, concentrating, organizing information and completing tasks, making it substantially more difficult to obtain and maintain a demanding and high-earning job. Possibly as a direct result of these difficulties, adults with ADHD are more likely to have less job satisfaction and fewer professional accomplishments, higher incidence of divorce, and increased rates of substance-abuse disorders.

**Dopaminergic Polymorphisms**

Existing literature suggests that activity within the dopaminergic system may contribute substantially to ADHD symptomatology (LaHoste et al., 1996), though the association between dopamine polymorphisms and the disorder are inherently complicated (M. Bakermans-Kranenburg & van Ijzendoorn, 2006). Dopamine (DA) transmission involves a mesostriatal pathway and mesocorticolimbic pathway. In the mesostriatal pathway, dopaminergic axon terminals originating in the midbrain directly innervate the striatum, which primarily provides input to the basal ganglia. Glutamatergic axons originating in the cortex also converge on the striatum, enabling DA to strongly modulate the effects of cortical input and striatal output. There are three parts to the striatum: the caudate nucleus, the putamen, and the nucleus accumbens (NAc). The mesocorticolimbic pathway involves midbrain DA axons originating in the ventral tegmental area (VTA) that innervate the frontal cortex, the limbic system, and the reward system. Together, these pathways control areas that are pivotal for behavior, emotion and
cognition; thus, dopamine (DA) has emerged as an essential neurotransmitter influencing mental health.

The effects of DA are mediated by its interaction with five different receptor subtypes, which can be subsumed under an earlier classification of DA receptor types based on the intracellular effects that they mediate. D1-like receptors increase levels of the intracellular messenger cAMP; D2-like receptors reduce or have no effect on cAMP (Sibley & Monsama, 1992). Further, D1-like and D2-like receptors can be divided into genetically distinct receptor subtypes. DRD1 and DRD5 genes encode for D1-like receptors. The DRD2, DRD3 and DRD4 genes, on the other hand, encode for D2-like receptors.

The D2-like receptors were first linked to mental health when it was discovered that there was a high positive correlation between the binding ability of antipsychotic drugs to the D2-like receptors and the clinical efficacy of those receptors (Sunahara, Seeman, Van Tol, & Niznik, 1993). Like most genes, each gene that encodes for a D2-like receptor exists in various forms, due to polymorphisms. Variations in the primary structure of the DNA nucleotide sequence can modify the degree of expression of a gene or the amino acid structure in the coded protein, depending on where the polymorphism is located. Specifically, there are two general types of polymorphisms: (1) those that occur within the coding region of the gene, which alter the amino acid sequence, and therefore function, of the protein, as in the case of the DRD4 VNTR polymorphism (described in detail below); and (2) those that occur in the non-coding region, which alter the level of expression but not the protein structure, as in the case of the DRD2 TaqA1 and DAT1 polymorphisms (described in detail below). Despite their differential
molecular mechanisms, each of these polymorphisms influences the quantity of DA synaptic levels, which can confer variability in the susceptibility of various diseases or conditions. This, in combination with the areas of the brain where DA transmission occurs, renders the DRD2, DRD4, and DAT1 genes and their polymorphisms likely candidates for influencing susceptibility for inattention and hyperactivity, the two hallmark features of ADHD.

**DRD2.** TaqA1, a DRD2 polymorphism, involves chromosome 11q23 and a Thymine to Cytosine (T to C) switch in the 3’ un-translated coding region of the gene. The possible resulting genotypes are homozygous for the A1 allele (A1/A1), homozygous for the A2 allele (A2/A2), and heterozygous (A1/A2), with the majority of individuals being homozygous A2 or heterozygous (see Table 1).

*Table 1. Genotypic Distribution of TaqA1 Polymorphism*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Lawford et al., 1999</th>
<th>Noble et al., 1994</th>
<th>Cerasa et al., 2009</th>
<th>Marino et al., 2004</th>
<th>Vijayan et al., 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1/A1 (T/T)</td>
<td>1 (1)</td>
<td>6 (8)</td>
<td>0 (0)</td>
<td>4 (3)</td>
<td>46 (11)</td>
</tr>
<tr>
<td>A1/A2 (T/C)</td>
<td>37 (39)</td>
<td>27 (37)</td>
<td>15 (21)</td>
<td>32 (27)</td>
<td>170 (42)</td>
</tr>
<tr>
<td>A2/A2 (C/C)</td>
<td>57 (60)</td>
<td>40 (55)</td>
<td>55 (79)</td>
<td>84 (70)</td>
<td>190 (47)</td>
</tr>
</tbody>
</table>

The receptors that DRD2 genes code for are most commonly found on the GABAergic interneurons of the prefrontal cortex (PFC) and striatal regions (Kotecha et al., 2002), particularly the NAc. These areas are highly associated with hyperactive behavior (Giedd, Blumenthal, Molloy, & Castellanos, 2001). The significance of the DRD2 polymorphism is substantial, such that individuals carrying either one or two A1 alleles (i.e., those hetero- or homozygotic for the TaqA1 allelic variant) have
approximately 30% fewer D2 receptors in the putamen/caudate area (Jonsson, Nothen, & Grunhage, 1999; Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997; Ritchie & Noble, 2003). This decrease in D2 receptor density is associated with less DA binding and, thus, less efficacious DA transmission in these areas of the brain (Thompson et al., 1997).

Research regarding the effects of the DRD2 polymorphism suggests a strong association between the A1 allele and psychopathology. For example, individuals with A1/A1 genotype, regardless of ethnicity, were found to be more susceptible to mood disorders in comparison to individuals with A1/A2 and A2/A2 genotypes (Zou et al., 2012). The literature is mixed, however, regarding the association between the A1 allele and ADHD, with some studies suggesting possessing the A1 allele increases the risk of ADHD (Sery et al., 2006) and other research indicating no association (Huang, Lin, Wu, Chao, & Chen, 2003). Incongruent findings may be due to differences in methodology (i.e., looking at both sexes versus just males) or lack of consideration of the interplay of environmental variables in activating the polymorphisms effect.

Although the evidence supporting a direct association between the A1 allele and ADHD is mixed, the A1 allele has been associated with other conditions and behaviors that are more prevalent among adults with ADHD, including substance use (Uhl, Blum, Noble, & Smith, 1993) and obesity (Cortese et al., 2008). The guiding theory regarding these associations is that individuals with the A1 allele compensate for the inherent deficiency of their dopaminergic system by the use of alcohol, food, and other reinforcing substances known to increase brain dopamine levels (Noble, 1996). For example, the A1 allele was present in 67% of obese/overweight subjects compared to 3.3% of controls (A. Chen et al., 2012). Interestingly, the association with obesity may be linked to substance-
use disorders; the DRD2 A1 allele was present in 73.9% of obese individuals with comorbid substance use, compared to 23.5% of obese individuals without comorbid substance use (Blum et al., 1996). As such, the A1 allele may increase risk for developing addictive behaviors (i.e., food addiction, substance use, or both). However, not every individual with the A1 allele develops an addiction, indicating that other factors are required to activate this genetic predisposition.

**DRD4.** There is a wealth of literature pertaining to the DRD4 gene and its polymorphisms, possibly because DRD4 receptors are well represented in the frontal cortex, amygdala and mesencephalic portions of the brain (Tarazi & Baldessarini, 1999). The dopamine receptor DRD4 has a 48 base pair (48-bp) Variable Number of Tandem Repeats (VNTR) polymorphism that alters the length of the receptor. The VNTR resides in the third intracellular loop of the protein and displays a high degree of variability, such that several nucleotide repeat combinations are possible. The 2-, 4-, and 7-repeats (2R, 4R and 7R, respectively) are the most frequent alleles (D'Souza et al., 2004), though often there are substantial differences in allelic distribution across ethnicities. Commonly in research, individuals with and without a 7R allele are compared, as the 7R allelic version is associated with blunted intracellular response to DA and suppressed expression of DRD4, compared to 2R and 4R allelic versions (Forbes et al., 2007); in fact, in vitro studies indicate that the sensitivity of the 7R allele receptor is half that of 2R and 4R variants (Van Tol, 1992). When dichotomized this way, most individuals do not have a 7R allele, though 7R group is often large enough for meaningful comparison (see Table 2).
Table 2. Genotypic Distribution of DRD4 VNTR Polymorphism

<table>
<thead>
<tr>
<th>DRD4</th>
<th>Frequency N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Das et al., 2011</td>
</tr>
<tr>
<td>7R allele</td>
<td>676 (59)</td>
</tr>
<tr>
<td>No 7R</td>
<td>472 (41)</td>
</tr>
</tbody>
</table>

Interestingly, the 7R allele does not appear to be solely a risk or protective allele, but rather confers behavioral tendencies that can be beneficial or detrimental, depending on the environment in which they are expressed. For example, the 7R allele is associated with tendency toward novelty and thrill seeking (Kluger, Siegfried, & Ebstein, 2002; Savitz & Ramesar, 2004), which could be unfavorable for a child required to sit in a classroom for eight hours per day but, from an evolutionary perspective, could be beneficial in a context where seeking new environments could lead to new mating and agricultural opportunities. In support of this, the 7R allele exists in higher frequencies in populations that have migrated geographically farther in the last 1,000 to 30,000 years (C. Chen, Burton, Greenberger, & Dmitrieva, 1999). Additionally, the 7R allele, while being associated with thrill and novelty seeking, is not associated with delinquency or short temper, which further supports the notion that the 7R allele is not inherently a “bad” or “risk” allele (Dmitrieva, Chen, Greenberger, Ogunseitan, & Ding, 2011).

Relatively, building on research suggesting that D4 receptors are expressed in brain regions known to be crucial for attention (Petersen & Posner, 2012), LaHoste and colleagues (1996) discovered that the 7R allele is more prevalent in children with ADHD, which, as was mentioned previously, has behavioral expression similar to novelty.
seeking. This finding has been consistently replicated, confirming that the 7R allele is associated with higher risk for ADHD (see Gizer, Ficks & Waldeman (2009) for meta-analysis). Further, the 7R allele appears to moderate behavioral outcomes depending on the environment; for example, children with the 7R allele were most likely to exhibit externalizing behaviors but were also most likely to experience the largest decrease in externalizing behavior when parents used positive discipline (M. Bakermans-Kranenburg, van Ijzendoorn, Pijlman, Mesman, & Juffer, 2008).

Dopamine Transporter (DAT). The dopamine transporter (DAT) gene, in comparison to the post-synaptic DRD2 and DRD4 genes, is a presynaptic channel that regulates DA levels in the intra- and extracellular space. Specifically, DAT plays a crucial role in the regulation of DA by mediating the active reuptake of dopamine from the synapse into the presynaptic terminal (Giros & Caron, 1993). DAT1 is a polymorphism located in the non-coding region of the gene coding for DAT; thus, the effect of this polymorphism involves a change in the concentration of the transporter on the presynaptic membrane. The DAT1 polymorphism is a VNTR consisting of a 40 base pair (40-bp) sequence in the 3’ un-translated region that repeats between three and eleven times. The most common alleles are the nine (9R) and ten (10R) repeats, with most individuals being homozygous for the 10R allele (see Table 3).

Table 3. Genotypic Distribution of DAT1 Polymorphism

<table>
<thead>
<tr>
<th>DAT</th>
<th>Frequency N(%)</th>
<th>Kirov et al., 1999</th>
<th>Biehl et al., 2011</th>
<th>Bidwell et al., 2009</th>
<th>van den Hoofdakker et al., 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/9</td>
<td>25 (7)</td>
<td>62 (39)</td>
<td>139 (50)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>9/10</td>
<td>131 (38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/10</td>
<td>193 (55)</td>
<td>98 (61)*</td>
<td>141 (50)*</td>
<td>27 (54)</td>
<td></td>
</tr>
</tbody>
</table>

*These studies combined the 9R/9R and 9R/10R individuals into one group for statistical comparison
In vitro, the 9R allele is associated with an increased transcription rate, compared to the 10R allele (Michelhaugh, Fiskerstrand, Lovejoy, Bannon, & Quinn, 2001). However, findings regarding the in vivo effects of the DAT1 polymorphism are mixed; some studies report increased DAT binding in individuals homozygous for the 10R allele (Heinz et al., 2000), some report homozygous 10R individuals have significantly reduced DA transporter binding in the striatum (Jacobsen et al., 2000), and others report no differences among individuals with different DAT1 allelic variations (Martinez et al., 2001).

Importantly, DAT is the principle site of action of methylphenidate (MPH), which is a common pharmacological treatment for ADHD, and individuals homozygous for the 10R allele are at increased risk for combined type ADHD (Turic, Swanson, & Sonuga-Barke, 2010). Children with ADHD who are homozygous for the 10R allele performed worse on tests of sustained attention, compared to children with ADHD who do not carry a 10R allele, suggesting the DAT1 10R allele may mediate the neurological impairment characteristic of ADHD (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005). Further, a recent preliminary study found genetic moderation of differences in the effectiveness of treatment for ADHD; individuals with the 10/10 genotype exhibited no difference between treatment groups (Routine clinical care, RCC, versus behavioral parent training, BPT), but individuals with none or one 10R allele improved the most with a combined (BPT+RCC) treatment paradigm (van den Hoofdakker et al., 2012). This finding suggests that the 10R allele may increase sensitivity to contingencies and, thus, sensitivity to treatments targeted at shaping environmental context at the family level.
ENVIRONMENTAL FACTORS

The diathesis stress model suggests that some individuals, due to an inherent vulnerability (i.e., temperament, physiology, or genetic predisposition), are more likely to be negatively affected by environmental adversity or undesirable experiences (Monroe & Simons, 1991). While this theory is useful in explaining risk, it does not attempt to explain receptiveness to advantageous environments and narrowly views predispositions as indicators of risk. Biological forces may indicate who is the most vulnerable to the detrimental effects of adversity and conflict and who is most likely to benefit from a supportive and nurturing environment. In line with this, the polymorphisms previously discussed do not independently influence cognition, emotion, or behavior. That is, an individual possessing the A1 allele is not guaranteed to develop ADHD, alcoholism, or a mood disorder. Rather, biological factors, with genetic polymorphisms being the micro-level and fundamental biological factors, appear to interact with environmental input to produce individual variation in outcomes.

Boyce and Ellis (2005) proposed a theory of biological sensitivity to context (BSC), suggesting that reactivity to environmental stressors or situations may underlie susceptibility toward or protection from psychopathology. The BSC theory postulates that individuals who are highly reactive (‘orchid children’) are more likely to be negatively affected by high stress environments but also more likely to flourish in low stress or protective environments. Low reactive individuals (‘dandelion children’), on the other hand, are expected to develop relatively similarly across a range of environments, appearing buffered from deleterious consequences of stress in challenging contexts but also appearing relatively resistant to some positive aspects of supportive environments as
well. Following the BSC theory, one would predict that those children who are easily shaped by their environment are also the children who are biologically reactive and sensitive to environmental cues (Boyce, 2007). Empirical research has confirmed that BSC is a viable explanation of the variation and individual differences in the development and expression of mental illness (Boyce et al., 2006; B. J. Ellis, Essex, & Boyce, 2005; Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010).

In a parallel manner, the differential susceptibility hypothesis stipulates that certain individuals, particularly due to their genetic predisposition(s), are more sensitive to both negative and positive contextual input. Individual differences in environmental susceptibility are considered evolutionarily adaptive, in that this variation has been maintained over time due to the fitness advantages offered by the range of environments humans encounter. For example, in environments characterized by stress and conflict, it may be advantageous for a child to develop aggressive and/or hyperactive behaviors that would aid in dealing with or getting away from such an environment. On the other hand, in an environment that provides support and stability, it would be advantageous for a child to be capable of utilizing those resources by developing attentiveness and focus (Boyce & Ellis, 2005; B. Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011).

In order to accurately and validly test the differential susceptibility model empirically, it is ideal to compare outcomes in individuals with a specific genetic predisposition who are exposed to negative environmental input with those exposed to positive environmental input. That is, it is best to have a range of environmental exposure rather than to treat the absence of adversity as a viable comparison to the
presence of adversity. This allows for investigation of positive effects of a gene by environment interaction, rather than referring to protective effects. Further, when considering environmental influences on children, environment can be conceptualized as a general or macrocosm influence, as in socioeconomic status or cultural group, or as a more proximal or contextual influence, as in family dynamic and family adversity. With regard to the development of psychopathology, proximal influences, particularly family climate, are most salient and typically best at predicting best- and worst-case behavioral outcomes. The adversity experienced by a family may influence parenting stress, parental mood and the specific parenting practices used, which may be interpreted and internalized by the child and, thus, have a direct influence on that child’s behavioral and cognitive functioning.

DA polymorphisms play a role in differential susceptibility in ADHD symptomatology in children, perhaps via moderation of environmental influence. For example, infants with the DRD4 7R allele who were exposed to maternal insensitivity expressed a six-fold increase in externalizing behavior (i.e., oppositional, aggressive), compared to non-carriers exposed to maternal insensitivity, while 7R carriers exhibited the least externalizing when mothers were highly sensitive (M. Bakermans-Kranenburg & van Ijzendoorn, 2006). Similarly, Laucht and colleagues (2007) found that adolescents with the 10R allele of the DAT1 polymorphism demonstrated both the highest and lowest levels of inattention when experiencing high and low levels of psychosocial adversity, respectively. Further, support for differential susceptibility is found in research regarding the A1 allele; infants exposed to high and low maternal sensitivity had the most and least
affective problems as toddlers, respectively, but this was only true for carriers of the A1 allele (Mills-Koonce et al., 2007).

MULTI-GENE X ENVIRONMENT PERSPECTIVE

Previous research examining complex behavioral phenotypes has revealed that genetic effects on these complex phenotypes tend to be stronger and more consistent when multiple polymorphisms are combined to create a genetic predisposition or profile (Beaver, Wright, DeLisi, & Vaughn, 2008; Belsky & Beaver, 2011). With regard to ADHD symptomatology, decreased DA efficacy, as is seen with the DRD2 A1, the DRD4 7R, and the DAT 10R alleles, is associated with decreased attention and reward mechanisms (Robbins & Everitt, 1999) and stronger preference toward immediate reinforcers (Tripp & Wickens, 2008), but, as reviewed above, the valence of these associations appears to depend on the environment. Thus, these polymorphisms may act in a cumulative manner in their interaction with the environment to predict with the severity of ADHD symptomatology.

Individuals carrying sensitivity alleles are more likely to be affected by their environments “for better and worse,” with their functioning being disproportionally impaired or enhanced by adverse versus supportive environments, respectively (Belsky & Pluess, 2009). In one of the first studies utilizing a multi-gene by environment perspective, Belsky and colleagues (2011) found that adolescents with more so-called “plasticity” alleles (10R DAT, A1 DRD2, 7R DRD4, short 5HT, 2R/3R MAOA) exhibited more and less self-regulation when exposed to supportive and unsupportive maternal parenting, respectively. Importantly, this finding was limited to males, perhaps
indicating that genetic moderation of environmental influences, or at least maternal parenting, is gender-specific.

**THE PRESENT STUDY**

The present study utilized a multi-gene by environment approach in order to predict ADHD symptomatology in young children. We focused on kindergarten aged children because this is an important developmental milestone as the child enters a formal school setting, and behavior during this time sets the stage for future academic successes or failures.

Specifically, we looked at DRD2, DRD4, and DAT polymorphisms, a range of family contextual variables, and ADHD symptomatology in kindergarten and first grade. We predicted that possessing one or more of the dopamine “sensitivity” alleles will be associated with ADHD in some children. Further, we speculated that a cumulative effect will emerge, in that the more sensitivity alleles present, the more severe ADHD symptomatology will be and the more likely it will remain stable longitudinally (i.e., into first grade). Last, we predicted that, across the three genes of interest, the more sensitivity alleles an individual has (i.e., zero, one, two or three), the more sensitive that individual will be to both positive and negative family environments.

Though we do not have direct measures of positive family functioning (i.e., warmth, positive parenting techniques), as would be ideal for these analyses, we conceptualize that having low adversity scores indicates at least a degree of positive contextual influence. As such, we predicted that more sensitive children will develop the least and most ADHD symptoms, depending on levels of adversity in their environment,
as would be predicted by the differential susceptibility theory. Figure two demonstrates the hypothesized associations between variables.

**Hypotheses:**

1. **GENETIC MAIN EFFECTS**
   a. Children with one or more dopamine sensitivity alleles will be more likely to exhibit ADHD symptomatology in kindergarten.

2. **ADDITIVE GENETIC EFFECT**
   a. The dopamine sensitivity allelic variations will additively predict ADHD symptomatology both concurrently and longitudinally (from kindergarten to first grade).

3. **GENE x ENVIRONMENT EFFECT**
   a. Children carrying sensitivity alleles who experience high levels of family adversity will exhibit the most ADHD symptomatology and will be more likely to remain symptomatic into first grade, while children with sensitivity alleles exposed to positive family environments will exhibit the lowest levels of ADHD symptomatology.
METHODS

Participants

Participants were recruited in three waves from 29 kindergarten classrooms within six public schools in the San Francisco Bay Area during the falls of 2003 to 2005. Schools were selected to represent a variety of socio-demographic and ethnic characteristics of the metropolitan area. Families were recruited through presentations at kindergarten parent welcome nights and in-person recruitment during drop-off and pick-up (see (Obradović et al., 2010) for detailed description of study). Genetic data was
collected on a sample of 192 (93 male) children. The sample was ethnically diverse, with 11.2% African American, 8.6% Asian, 54% Caucasian, 3.2% Latino, 19.2% multiethnic, and 2.1% other. At kindergarten entrance, children averaged 5.34 years of age (SD = 0.31, range 4.75-6.24). Average household income ranged from less than $10,000 to more than $400,000 (M= $60,000–79,000). Highest level of educational attainment ranged from less than high school degree (2.7%) to advanced degrees (54%), with 78% of sample having at least a college degree. SES was calculated using a composite of standardized income and highest education (M= 0.21, SD= 0.80).

**Procedures**

*Genetic Information.* With parental consent, children’s genetic information was collected in 2010, when children were nine to 11 years old. DNA was collected using the Oragene OG-500 DNA all-in-one system for the collection, stabilization, transportation and purification of DNA from saliva. Children were asked to spit into a small vial and samples were immediately mixed with stabilizing solution and stored at room temperature until assay. The target SNP (rs53576) was assayed using the Taqman assay platform with 7900HT instrument (Applied Biosystems). The DNA sample was mixed with the Taqman assay mix and Master Mix containing the amplification primers and target locus probes, and the reaction was run on the instrument and analyzed with SDS software (all from Applied Biosystems). The resulting data plot provided genotype calls for the samples.

The distribution of the DRD2, DRD4, and DAT polymorphisms are each in Hardy Weinberg equilibrium. The genotypic frequency of each gene is presented in Table four.
Table 4. Dopaminergic Polymorphisms Frequency Distribution

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>DRD2</td>
<td>A1/A1</td>
<td>10 (5)</td>
</tr>
<tr>
<td></td>
<td>A1/A2</td>
<td>58 (30)</td>
</tr>
<tr>
<td></td>
<td>A2/A2</td>
<td>124 (65)</td>
</tr>
<tr>
<td>DRD4</td>
<td>No 7R alleles</td>
<td>132 (69)</td>
</tr>
<tr>
<td></td>
<td>One 7R allele</td>
<td>53 (28)</td>
</tr>
<tr>
<td></td>
<td>Homozygous 7R</td>
<td>7 (3)</td>
</tr>
<tr>
<td>DAT</td>
<td>No 10R alleles</td>
<td>12 (6)</td>
</tr>
<tr>
<td></td>
<td>One 10R allele</td>
<td>74 (38)</td>
</tr>
<tr>
<td></td>
<td>Homozygous 10R</td>
<td>105 (56)</td>
</tr>
</tbody>
</table>

Environmental Variables. In the present study, children were exposed to a range of contextual influences, with some children experiencing adversity and others experiencing very little or no adversity, and, thus, presumably relatively positive environments. Specifically, the Peers and Wellness Study (PAWS) data contains six indices of family context: parenting overload, marital conflict, negative anger expression, maternal depression, financial stress, and harsh/restrictive parenting (see Table 5). Information on family context was collected via parental self-report when the children were in kindergarten.
Table 5. Family Adversity Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Derived From</th>
<th># of Items</th>
<th>What is Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial Stress</td>
<td>Essex, Klein, Cho, and Kalin (2002)</td>
<td>4</td>
<td>Parents’ thoughts about finances, difficulty paying bills, and perceived limited opportunities due to lack of finances ($\alpha = .81$)</td>
</tr>
<tr>
<td>Parenting Overload</td>
<td>Essex et al. (2002)</td>
<td>5</td>
<td>Feeling overwhelmed with parenting responsibilities, including lack of personal time due to obligations to children ($\alpha = .79$)</td>
</tr>
<tr>
<td>Marital Conflict</td>
<td>O’Leary-Porter Overt Hostility Scale (Johnson &amp; O’Leary, 1987; Porter &amp; O’Leary, 1980)</td>
<td>10</td>
<td>How often parents argue, express hostility, and criticize one another in the presence of the child ($\alpha = .72$)</td>
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<tr>
<td>Negative/Anger Expression</td>
<td>Family Expressiveness Questionnaire (FAQ; (Halberstadt, 1986) and Anger Expression Inventory (AEI; (Spielberger, 1988)</td>
<td>FAQ = two 10 item subscales AEI = three 8 item subscales</td>
<td>FAQ: Overt anger, contempt and hostility within the family ($\alpha = .83$), as well as the frequency of passive sulking, crying and disappointment ($\alpha = .75$) AEI: Tendency to express anger overtly ($\alpha = .69$), keep anger in ($\alpha = .68$), and control anger expression ($\alpha = .74$)</td>
</tr>
<tr>
<td>Maternal Depression</td>
<td>Center for Epidemiological Studies Depression Scale (CES-D; (Radloff, 1977)</td>
<td>20</td>
<td>Maternal feelings of depression ($\alpha = .81$)</td>
</tr>
<tr>
<td>Harsh/Restrictive Parenting</td>
<td>Questionnaire version of Child-Rearing Practice Report (CRPR; (Deković,</td>
<td>18</td>
<td>Supportive versus harsh parenting styles ($\alpha = .83$)</td>
</tr>
</tbody>
</table>
Behavioral Outcomes. The MacArthur Health and Behavior Questionnaire (HBQ; Armstrong, Goldstein, & the MacArthur Working Group on Outcome Assessment, 2003) was administered to assess ADHD symptomatology in children. Both parents and teachers completed the HBQ in Fall and Spring of kindergarten and in first grade. In kindergarten, children also reported on their own behavior via the Berkeley Puppet Interview (BPI), which is designed to elicit responses to inquiries that parallel the HBQ questionnaires given to parents and teachers. For the purposes of this study, we focused on the inattention and impulsivity HBQ subscales, in addition to the composite ADHD scale. The items included in the inattention and impulsivity subscales are summarized in Table six.

Table 6. Behavioral Outcome Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description of Item</th>
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<tbody>
<tr>
<td><strong>Inattention</strong></td>
<td>Is distractible.</td>
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<td></td>
<td>Has difficulty following directions.</td>
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<td></td>
<td>Can’t concentrate.</td>
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<tr>
<td></td>
<td>Jumps from activity to activity.</td>
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<tr>
<td></td>
<td>Does not listen.</td>
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<tr>
<td></td>
<td>Loses things.</td>
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<tr>
<td><strong>Impulsivity</strong></td>
<td>Fidgets.</td>
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<tr>
<td></td>
<td>Is impulsive.</td>
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<tr>
<td></td>
<td>Has difficulty awaiting turn.</td>
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<tr>
<td></td>
<td>Interrupts, blurs out answers to questions too soon.</td>
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<tr>
<td></td>
<td>Has difficulty playing quietly.</td>
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<tr>
<td></td>
<td>Talks excessively.</td>
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<tr>
<td></td>
<td>Butts in on others.</td>
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<tr>
<td></td>
<td>Does dangerous things.</td>
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<tr>
<td></td>
<td>Doesn’t stay seated when required to do so.</td>
</tr>
<tr>
<td><strong>ADHD</strong></td>
<td>Sum of Inattention and Impulsivity Subscales</td>
</tr>
</tbody>
</table>
Data Preparation

As is consistent with previous literature, dichotomized variables were created in order to compare individuals with and without the “sensitivity” alleles. For the DRD2 TaqA1 and DRD4 VNTR polymorphisms, variables were created to compare individuals with (1) and without (0) the A1 allele and with (1) and without (0) the 7R allele. For the DAT1 polymorphism, a variable was created to compare individuals with (1) and without (0) the 10/10 genotype. Because of the inconsistency in the literature pertaining to which DAT genotype is most associated with mental health outcomes, another variable was created with the reverse coding, thus comparing individuals who are not homozygous 10/10 (1) to those who are homozygous 10/10 (0). Then, adding the number of sensitivity alleles for each individual created two cumulative dopamine sensitivity variables; “sensitivity1” includes A1, 7R, and 10/10 while “sensitivity2” includes A1, 7R, and no10/10. Gender was dichotomized as male (0) and female (1). Ethnicity was dichotomized as Caucasian (0) and minority (1).

Gender, age at first day of kindergarten, and ethnicity differences in frequency of dopamine categories were tested. Minority children were more likely to have the 10/10 DAT1 polymorphism (t(183) = -2.012, p = .046). As such, minority children were slightly less likely to have zero sensitivity alleles when 10/10 genotype was included as a sensitivity (χ²= 7.353, p = .061) but more likely to have three sensitivity alleles when not having 10/10 was included as sensitivity (χ²= 7.001, p = .072). This information is presented in Table seven.
Table 7. Demographic Characteristics of Sample by Dopamine Category Frequency

<table>
<thead>
<tr>
<th>Gene</th>
<th>Categorical Variable (N)</th>
<th>Males N (%)</th>
<th>Age in Years M (SD)</th>
<th>Caucasian N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD2</td>
<td>A1 carrier (68)</td>
<td>32 (47)</td>
<td>5.35 (.32)</td>
<td>36 (53)</td>
</tr>
<tr>
<td></td>
<td>Non-carrier (124)</td>
<td>64 (52)</td>
<td>5.34 (.31)</td>
<td>66 (53)</td>
</tr>
<tr>
<td>DRD4</td>
<td>7R carrier (60)</td>
<td>31 (52)</td>
<td>5.38 (.33)</td>
<td>35 (58)</td>
</tr>
<tr>
<td></td>
<td>Non-carrier (132)</td>
<td>65 (49)</td>
<td>5.32 (.30)</td>
<td>67 (51)</td>
</tr>
<tr>
<td>DAT1</td>
<td>10/10 genotype (105)</td>
<td>54 (51)</td>
<td>5.34 (.31)</td>
<td>53 (61)</td>
</tr>
<tr>
<td></td>
<td>Non-10/10 (87)</td>
<td>42 (48)</td>
<td>5.35 (.32)</td>
<td>49 (46)</td>
</tr>
<tr>
<td>Sensitivity1</td>
<td>0 (35)</td>
<td>17 (48)</td>
<td>5.34 (.30)</td>
<td>25 (71)</td>
</tr>
<tr>
<td></td>
<td>1 (93)</td>
<td>48 (52)</td>
<td>5.33 (.31)</td>
<td>41 (44)</td>
</tr>
<tr>
<td></td>
<td>2 (52)</td>
<td>24 (46)</td>
<td>5.31 (.31)</td>
<td>29 (56)</td>
</tr>
<tr>
<td></td>
<td>3 (12)</td>
<td>7 (58)</td>
<td>5.52 (.28)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Sensitivity2</td>
<td>0 (52)</td>
<td>27 (52)</td>
<td>5.30 (.29)</td>
<td>22 (42)</td>
</tr>
<tr>
<td></td>
<td>1 (76)</td>
<td>37 (49)</td>
<td>5.34 (.31)</td>
<td>45 (59)</td>
</tr>
<tr>
<td></td>
<td>2 (53)</td>
<td>28 (53)</td>
<td>5.41 (.33)</td>
<td>26 (49)</td>
</tr>
<tr>
<td></td>
<td>3 (11)</td>
<td>4 (36)</td>
<td>5.23 (.31)</td>
<td>9 (82)</td>
</tr>
</tbody>
</table>

Given that there were so few individuals with all three sensitivity alleles, this variable was collapsed to compare individuals with zero, one, and two/three sensitivity alleles. This was supported by preliminary analyses that suggested a “threshold effect” of sensitivity, such that the effect of sensitivity was not heightened in the individuals with three sensitivity alleles, compared to those with two sensitivity alleles.

Next, standardized variables were created for each of the six indices of family context. As we were primarily interested in capturing the effect of overall exposure to family context and adversity, these standardized scores were composited into an adversity
composite variable for each individual. The ranges, means, and standard deviations for these variables are presented in Table eight.

Table 8. Descriptive Statistics for the Adversity Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial Stress</td>
<td>-1.42</td>
<td>2.67</td>
<td>-0.06 (.99)</td>
</tr>
<tr>
<td>Parenting Overload</td>
<td>-2.69</td>
<td>2.59</td>
<td>0.124 (1.03)</td>
</tr>
<tr>
<td>Marital Conflict</td>
<td>-1.76</td>
<td>3.27</td>
<td>0.03 (1.01)</td>
</tr>
<tr>
<td>Negative/Anger Expression</td>
<td>-2.25</td>
<td>2.96</td>
<td>0.05 (1.03)</td>
</tr>
<tr>
<td>Maternal Depression</td>
<td>-1.18</td>
<td>4.85</td>
<td>0.11 (1.03)</td>
</tr>
<tr>
<td>Harsh/Restrictive Parenting</td>
<td>-2.39</td>
<td>3.78</td>
<td>-0.013 (.93)</td>
</tr>
<tr>
<td>Adversity</td>
<td>-2.19</td>
<td>3.20</td>
<td>0.04 (.96)</td>
</tr>
</tbody>
</table>

For kindergarten outcomes, each child’s functioning was determined via parent, teacher and self-report. Core scores for Fall and Spring inattention, impulsivity, and ADHD symptoms were created by standardizing and averaging across the three informants to represent the trait dimension (i.e., individual differences in adaptation and functioning) of behavior. Standardizing and averaging across parent and teacher report created the first grade core scores. Descriptive statistics for these variables are presented in Table nine.

Table 9. Descriptive Statistics for Inattention, Impulsivity and ADHD Symptomatology

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>-1.59</td>
<td>3.54</td>
<td>-0.10 (.96)</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>-1.66</td>
<td>3.11</td>
<td>-0.07 (.92)</td>
</tr>
<tr>
<td>ADHD</td>
<td>-1.62</td>
<td>3.38</td>
<td>-0.08 (.95)</td>
</tr>
<tr>
<td><strong>Spring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>-1.66</td>
<td>3.07</td>
<td>-0.07 (1.02)</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>-1.64</td>
<td>2.69</td>
<td>-0.06 (.94)</td>
</tr>
<tr>
<td>ADHD</td>
<td>-1.70</td>
<td>2.98</td>
<td>-0.06 (.97)</td>
</tr>
</tbody>
</table>
Missing data for the adversity components and the BPI and HBQ scales were handled using the recommended maximum-likelihood estimation procedure for missing data. Percentages of missing data were as follows, Fall Inattention (1.6%), Fall Impulsivity (1.6%), Fall ADHD (1%), Spring Inattention (1%), Spring Impulsivity (1%), Spring ADHD (1%), 1st Grade Inattention (2.1%), 1st Grade Impulsivity (2.1%) 1st Grade ADHD (2.1%) and Fall Kindergarten Adversity Composite (2.6%).

The purpose of the regression analyses was to investigate main effects and interaction effects of dopaminergic polymorphisms and adversity on ADHD symptomatology in kindergarten and in first grade. As such, two sets of regression models were tested to predict (1) kindergarten levels of inattention, impulsivity and ADHD symptomatology, and (2) change in levels of inattention, impulsivity and ADHD symptomatology from kindergarten to first grade. To create change scores, core levels of symptomatology for Fall and Spring of kindergarten were averaged and then subtracted from the first grade core score for each subscale.

Two-way interaction effects were tested following the procedure outlined by Baron and Kenny (1986). Significant interactions were further investigated using the technique proposed by Aiken and West (1991), whereby we compared children with and without sensitivity alleles residing in families with high (i.e., 1 SD above the mean) and low (i.e., 1 SD below the mean) family adversity. In addition, given the documented

<table>
<thead>
<tr>
<th>1st Grade</th>
<th>Inattention</th>
<th>3.04</th>
<th>0.03 (.84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>-0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impulsivity</td>
<td>-1.21</td>
<td>2.94</td>
<td>0.01 (.86)</td>
</tr>
<tr>
<td>ADHD</td>
<td>-1.18</td>
<td>2.65</td>
<td>0.02 (.85)</td>
</tr>
</tbody>
</table>
gender differences in ADHD symptomatology, gender was included in all regression analyses, including any gender interactions with the genetic variables and with adversity. Any significant gender main effects or gender interactions were further investigated by using split-file analyses to compare significant models in males versus females. Finally, three-way interactions among genetics, gender and adversity were also tested.

For each regression model, stepwise regression analyses investigated the main effects of genetics, adversity, and gender (step one), all possible two-way interactions (step two), and the three-way interaction (step three). See regression equations below, where “$Y_1$” is kindergarten levels of symptomatology, “$Y_2$” is change in levels of symptomatology from kindergarten to first grade, “a” is adversity, “b” is genetic polymorphism/sensitivity, and “c” is gender. Backward elimination technique was then used to capture the model with the best predictive ability.

$$Y_1 = a + b + c + (a*b) + (a*c) + (a*b) + (a*b*c)$$

$$Y_2 = a + b + c + (a*b) + (a*c) + (a*b) + (a*b*c)$$

RESULTS

Preliminary Analyses

Bivariate correlations among key variables included in this study are presented in Table ten. Age at kindergarten entry was not related to dopamine allelic distribution frequency, adversity levels or any of the behavioral outcomes; thus, age was not included in further analyses. SES was related to inattention, impulsivity and ADHD symptomatology; thus, all regression analyses controlled for the effects of SES. Also, as
previously mentioned, since ethnicity was related to the DAT1 polymorphism frequency distribution, ethnicity was controlled when the DAT1 variable was included in analyses.
Table 10. Bivariate Correlations Across Variables of Interest

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Eth</th>
<th>Gen</th>
<th>SES</th>
<th>ADV</th>
<th>A1</th>
<th>7R</th>
<th>10</th>
<th>Sen</th>
<th>Ina</th>
<th>Im</th>
<th>A</th>
<th>Ina</th>
<th>Im</th>
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<th>A</th>
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<th>A</th>
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<tbody>
<tr>
<td><strong>FALL</strong></td>
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<td><strong>1ST GRADE</strong></td>
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<td>Gen</td>
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<tr>
<td>SES</td>
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<td>-.42*</td>
<td>.07</td>
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<td>Adv</td>
<td>.02</td>
<td>.08</td>
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<td>-.22*</td>
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* indicates significance at p<.01; Eth = ethnicity; Gen = Gender; Adv = Adversity; Sens = Sensitivity collapsed across three categories; F = Fall; S = Spring; 1 = First Grade; Ina = Inattention; Im = Impulsivity; A = ADHD.
**Predicting Kindergarten Levels of ADHD Symptomatology**

*Genetic Main Effects.* After controlling for effects of SES and ethnicity (when necessary), there were no independent main effects of DRD2 A1, DRD4 7R or DAT1 polymorphisms on kindergarten Fall or Spring levels of inattention, impulsivity, or ADHD. There were, however, trend level main effects of cumulative dopamine sensitivity on kindergarten Spring Inattention ($B(184) = .131, p = .057$) and kindergarten Spring ADHD ($B(184) = .115, p = .084$). Only the “sensitivity2” variable was significant, meaning individuals were more sensitivity if they possessed the DRD2 A1 and DRD4 7R alleles and/or were NOT homozygous 10R for DAT1. Individuals with increased sensitivity, when defined this way, had increased levels of inattention (see Figure 3) and ADHD.

*Figure 3. Dopamine Sensitivity Predicting Spring Inattention*

There were also main effects of gender ($B(184) = -.284, p < .0001$) and adversity ($B(184) = .154, p = .035$) in predicting levels of inattention, such that boys had more
reported levels of inattention, as did children in higher adversity families. Similarly, gender ($B(184) = -.298, p < .0001$), adversity ($B(184) = .148, p = .036$) and SES ($B(184) = -.126, p = .094$) were associated with ADHD symptomatology, such that being male, experiencing higher adversity, and being from a lower SES family were associated with increased ADHD symptomatology. Together, these variables explained 14.4% of the variance in levels of Spring Inattention and 16.4% of the variance in Spring ADHD symptomatology.

Though there were no significant interaction effects between gender and genetic sensitivity, given the main effect of gender, post-hoc analyses compared this model in males and females. The effect of sensitivity was only significant in predicting levels of inattention ($B(93) = .241, p = .023$) and ADHD ($B(91) = .202, p = .047$) in males (see Figures 4 and 5).

*Figure 4. Dopamine Sensitivity Predicting Levels of Spring Inattention in Males and Females*
GxE Effects. After controlling for ethnicity, SES and gender, there was a significant interaction effect between the DAT1 polymorphism and adversity in the prediction of Spring Inattention ($B(184) = .207, p = .004$) and Spring ADHD ($B(184) = .161, p = .018$) symptomatology. Not being homozygous 10/10 was associated with increased inattention and ADHD symptomatology, but only for children in families characterized by high adversity. Conversely, this same genotype was associated with lowest levels of inattention and ADHD in children in families with low adversity (see Figure 6). Only the slope of the non-10/10 group was significant ($p = .034$), suggesting that only children not homozygous 10R evidenced significant genetic moderation of the effect of environment on their symptomatology, whereas behavioral outcomes in homozygous 10R children were not significantly influenced by their genotype. These
models explained 18.8% of the variance in levels of Spring Inattention symptomatology and 21% of the variance in levels of Spring ADHD symptomatology.

Post-hoc analyses were used to investigate which, if any, of the adversity variables were primarily driving this GxE effect. These analyses revealed that the “harsh and restrictive parenting” variable produced the strongest interaction effect, of the independent indices of adversity. The interaction between harsh and restrictive parenting and DAT1 polymorphism explained 15.4% of the variance in levels of Spring Inattention ($B(181) = .156, p = .066$) and 19.4% of the variance in levels of Spring ADHD ($B(181) = .149, p = .065$).

There were no significant gender interactions, nor were there any significant three-way interaction (GxADVxGender) effects on any of the Fall or Spring behavioral outcomes.
Predicting Change in ADHD from Kindergarten to First Grade

After controlling for SES, gender, and ethnicity (when necessary), there were no main effects of independent dopamine polymorphisms on change in inattention, impulsivity or ADHD symptomatology from kindergarten to first grade. There was, however, a significant interaction between cumulative dopamine sensitivity and gender when predicting the change in inattention ($B(182) = .129, p = .040$), such that males with little to no genetic sensitivity actually experienced a large increase in inattentiveness from kindergarten to first grade, while more sensitive males evidenced decreases in inattentiveness (see Figures 7 and 8). In females, on the other hand, change in levels of inattention was not related to their genetic sensitivity.

Figure 7. Dopamine Sensitivity and Mean Levels of Inattention in Kindergarten and First Grade in Males and Females
There was also an effect of adversity (\(B(182) = -.132, p = .047\)), such that more adversity was associated with less change (though still an increase) in inattention from kindergarten to first grade. Together, these variables explained 6% of the variance in the change in inattentiveness from kindergarten to first grade.

There were no other significant two-way interactions, nor were there any significant three-way interactions when predicting change in symptomatology from kindergarten and first grade.

**DISCUSSION**

The main purpose of this investigation was to test for genetic main effects and interaction effects of dopaminergic polymorphisms and adversity on ADHD...
symptomatology in kindergarten and first grade children. Regarding genetic main effects, while none of the genes of interest independently predicted behavior, cumulative dopamine genetic sensitivity across three dopaminergic genes predicted increased levels of inattention and ADHD symptomatology in kindergarten. Cumulative genetic sensitivity was increased in this case if an individual possessed the DRD2 A1 allele, the DRD4 7R allele, and/or was not homozygous 10R for the DAT1. Interestingly, this association between cumulative genetic sensitivity and symptomatology was specific to males, such that females’ levels of reported symptomatology was not related to their cumulative genetic sensitivity profile. This may be due to fewer number of ADHD symptoms reported for females in this study, but it is also consistent with literature suggesting that the association between the dopamine system and behavior is stronger in males (Andersen & Teicher, 2000). Regardless, the fact that the cumulative genetic sensitivity in males contributed to inattention and ADHD symptomatology highlights the need to consider genetic effects additively as opposed to independently, particularly in smaller samples where independent genetic effects are often not found (Payton et al., 2001).

In line with this, when predicting the change in symptomatology from kindergarten to first grade, there was an effect of genetic sensitivity, but again only in males. Specifically, males with more sensitivity evidenced a decrease in inattentiveness; conversely, less sensitive males actually experienced an increase in levels of inattentiveness. It should be noted that, when looking at the actual levels of inattention from kindergarten to first grade, this increase in attentiveness evidenced by less sensitive males and decrease in inattentiveness evidenced by the most sensitive males actually
resulted in equal levels of inattentiveness in first grade across the two groups of males. However, since we were primarily interested in the genetic effect on the change in levels of inattention, this finding is important to interpret. While it may at first seem counterintuitive, it could be the case that more genetically sensitive males were able to acclimate to the stability and dynamics of the school environment (i.e., routine schedule, enriching learning opportunities, social contact), such that by first grade, they exhibited significantly less inattentiveness compared to their less sensitive male peers. While the current study does not contain indices of positive school environment to test this, it follows from the differential susceptible hypothesis that males with increased genetic sensitivity would benefit from an enriching and stable school environment to produce the most favorable outcomes, in this case a decrease in inattentiveness from kindergarten to first grade. If this were in fact the case, one would expect that levels of inattention would continue to decrease in genetically sensitive males throughout their school experience, as they continued to reap the benefits of their environment. This would be consistent with previous research indicating that genetic sensitivity can moderate the effect of positive environmental influence on behavior in males (Belsky & Beaver, 2011).

With regard to gene by environment interactions, there was an interaction between the DAT1 polymorphism and adversity in predicting levels of inattention and ADHD in kindergarten. Specifically, children who were not homozygous for the 10-repeat allele exhibited the highest levels of inattention, but only if they were in environments characterized by high adversity. Conversely, this same genotype was associated with lowest levels of inattention in lower adversity environments. Children homozygous for the 10-repeat allele seemed relatively unaffected by the level of family
adversity, similar to dandelion children described by Boyce and Ellis (2005). As such, this finding supports the BSC theory and differential susceptibility hypothesis, rather than the diathesis stress model, in that genetic sensitivity moderated the effect of environmental context on children’s behavior for better and worse.

In line with the evolutionary perspective of the BSC theory, it is conceivable that high levels of inattention in a classroom may be the result of an adaptive behavioral phenotype characterized by the ability to disengage or distract oneself from an uncomfortable situation. On the other hand, this same genotype may enable a child from a positive and supportive environment to actively engage with his or her environment in order to reap the intellectual and social benefits of such engagement, which would appear phenotypically quite different from the inattentive child.

The current finding that the DAT1 polymorphism moderated the influence of family adversity is consistent with previous literature suggesting an interaction between the 9-repeat allele (and, thus, not in individuals homozygous 10R) and maternal emotion (E. J. Sonuga-Barke et al., 2009) as well as negative parenting (B. B. Lahey et al., 2011) on both concurrent and longitudinal behavioral outcomes in children. Sonuga-Barke and colleagues (2009) found that, in a sample of 251 males, 9/9 and 9/10 individuals showed sensitivity to the effects of positive maternal expressed emotion (PMEE) with regard to the development of conduct problems (CP) and emotional problem (EE), though 10/10 individuals did not. Specifically, 9/9 and 9/10 males who experienced high PMEE showed the lowest levels of CP and EE, while the same genotypes accounted for the highest levels of CP and EE in individuals who experienced low levels of PMEE. Similarly, Lahey and colleagues (2011) reported an inverse association between positive
and negative parenting (at four to six years of age) and future conduct disorder symptoms (five to eight years later), but only in children with two copies of the 9R allele. The mechanism whereby environmental influence, including parenting, interacts with the DAT1 gene requires further research. However, it should be noted that one animal study found that early maternal deprivation resulted in decreased expression of the DAT protein (Zhu et al., 2010), suggesting a direct link between parental influence and gene expression.

The limited interaction findings (i.e., only the DAT1 polymorphism exhibited interaction effects) in this study are not entirely surprising given that previous literature with dopamine polymorphisms has not consistently found G x E effects, specifically when predicting ADHD outcomes. In fact, even a genome wide association scan study looking at genetic moderation of parental expressed emotion on clinical levels of ADHD failed to find any significant G x E effects (E. J. S. Sonuga-Barke et al., 2008). Given that most children in this particular sample did not experience high levels of adversity (i.e., the number of children in the higher range of adversity was small), it may be that the influence of daily family-based stressors was not salient enough to interact with independent genetic predispositions. Conceptualizing SES as the environmental context variable interacting with genetic status may yield a more fruitful prediction, given that SES is a relatively stable and comprehensive marker of hardship, and previous literature has found main effects of SES on ADHD (Pineda et al., 1999) as well as gene x SES interaction effects (Lasky-Su et al., 2007).

In addition, there is a plausible explanation for why the genetic main effects and G x E effects only occurred for Spring (as opposed to Fall) levels of kindergarten
symptomatology. The beginning of kindergarten presumably represents a chaotic and unsettling transition for many children, as it is their first experience with a full day of structure and obligatory learning, even if children have attended preschool (Magnuson, Ruhm, & Waldfogel, 2007). As such, much of the behavior interpreted as symptomatology by parents and teachers during this time may actually be artifacts of the transition and would not, therefore, be likely to have the same genetic underpinnings as more trait-driven behaviors. In support of this, levels of reported symptomatology decreased, though not significantly, between Fall and Spring, potentially as some children initially labeled as inattentive adapted to the school environment, while those children with true inattentive symptoms remained symptomatic. This would then allow for genetic associations with true inattentiveness to emerge in the Spring.

Finally, it is important to point out that both the main genetic effects on ADHD and the G x E associations with ADHD were driven by the inattentive subscale. In fact, there were no significant findings with the impulsivity subscale. Previous research has also found differential genetic effects for different ADHD phenotypes (McCracken et al., 2000; Rowe et al., 2001; Waldman et al., 1998), though the specific genes underlying different phenotypic profiles is still debated. However, it has been proposed that identifying the separate ADHD behavioral phenotypes is crucial for interpreting previous genetic effects and for designing future genetic studies (Stevenson et al., 2005).

**Strengths, Limitations, and Future Directions**

This study presented several unique strengths, as well as important limitations that can inform trajectories for future research. A relatively large, ethnically diverse sample
of kindergarten children with very little missing data allowed for examination of both genetic main effects on and G x E associations with parent, teacher and self-reported behavior in very young children. As has been stated previously, these analyses would have been improved if there were an actual continuum of positive to negative environmental context, such that we could have investigated true positive effects of an environment, rather than referring to protective effects. However, that we were able to identify genetic main effects and a strong G x E effect in a low-risk community sample characterized by fairly low levels of adversity and moderately high average SES suggests that these effects may be amplified in higher-risk samples with clinical levels of symptomatology. Thus, this study stands to provide a “normative springboard” for future research with access to more extreme samples.

In addition, within this sample, it would be interesting to investigate the contribution of other genetic polymorphisms to our cumulative genetic sensitivity construct. For example, the PAWS data includes serotonin and COMT polymorphisms, both of which have previously identified sensitivity allelic variations associated with ADHD (Hawi & Gill, 2002; Nobile et al., 2010). It conceptually stands to reason that if these allelic variations were included in our sensitivity variable, we may be able to further identify the cumulative effect of genetic sensitivity across various systems. It would also be interesting to replicate these analyses to predict internalizing symptomatology, given that previous research has linked depression to diminished dopamine transmission (Dunlop & Nemeroff, 2007). Under this assumption, the same genetic sensitivity that was found to predict ADHD symptomatology in males may predict susceptibility for internalizing disorders in females. If this is true, cumulative
dopamine sensitivity may signify a general biological predisposition for mental illness, though the expression would be gender-specific.

**Conclusions**

This study provides novel evidence regarding the effects of dopamine polymorphisms on inattention and ADHD symptomatology in very young children. Specifically, the findings suggest that the cumulative effect of genetic sensitivity across several dopamine polymorphisms predicts severity of symptomatology, but only in males. As such, the study highlights the need to consider genetic effects cumulatively and separately in males and females. In addition, a significant G x E interaction emerged, whereby a specific genetic predisposition moderated the effect of family context on behavior. The DAT1 polymorphism, which codes for the dopamine transporter, was found to moderate the influence of levels of family adversity to predict levels of inattention and ADHD symptomatology in kindergarten. This finding lends support to the BSC theory and the differential susceptibility hypothesis and suggests that genetic sensitivity can moderate environmental influence, for better and for worse.

Both clinical and sub-clinical levels of ADHD are detrimental to childhood development and adult functioning. As such, identifying risk factors for the development of ADHD is imperative. We know there is a broad range of environmental contributors to ADHD and we know that ADHD is a heritable disorder; however, there is not a complete understanding of how biological predispositions (i.e., genetics) independently contribute to and interact with environmental contingencies to influence the development of ADHD. This study provides important insight into the genetic predispositions...
underlying susceptibility for ADHD symptomatology, particularly that the genetic contribution may be cumulative, more prominent in males, more linked to the inattention component, and may be partially dependent on contextual variables, especially parenting. Upon replication of the current findings, particularly with a higher-risk sample with clinical levels of ADHD, there will be a better understanding of how genetic predispositions contribute to this detrimental childhood disorder. With that knowledge in hand, it may become feasible to design and implement intervention studies targeting the family environment of genetically sensitivity children in order to minimize the risk for developing ADHD symptomatology and, rather, to maximize the potential of these sensitive children.
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Vita

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