# An Imaging Gene by Environment Interaction (IG×E) Approach to Understanding Youth Antisocial Behavior

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## Abstract

An examination of the complex interplay of genes, environmental experience, and the brain is critical to understanding psychopathology, violence, and aggression. This essay reviews the gene–environment (G×E) interaction and imaging genetics literature relating to the development of youth antisocial behavior (AB). A model is proposed that bridges these approaches within an imaging gene×environment (IG×E) interaction framework. The potential application of an IG×E framework to youth AB is outlined and ongoing research challenges are discussed.

## INTRODUCTION

Using an imaging gene×environment framework, this essay outlines an approach that builds on traditional gene×environment interactions using neuroimaging to examine how the brain may be the mechanism linking the interaction of biology and experience to behavior. We use youth antisocial behavior (AB) as an example to illustrate how gene×environment interactions can be examined in the context of neuroimaging studies and build a model for understanding the conditional mechanisms that underlie the development of psychopathology.

## FOUNDATIONAL RESEARCH

### Definitions of Youth Antisocial Behavior

AB refers to a range of behaviors that cause harm and are costly to individuals, communities, and society as a whole. A variety of definitions for youth AB and violence exist across disciplines, including diagnoses in psychology

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and psychiatry [e.g., conduct disorder (CD)] and legal terms (e.g., delinquency); however, in general, these behaviors include rule-breaking, aggression, and other dangerous behaviors, such as early drug use. One of the most consistent predictors of adult antisocial and criminal behavior is a history of disruptive behavior problems starting in childhood (e.g., Campbell, Shaw, & Gilliom, 2000). Beyond later AB outcomes, children with these early-starting behavior problems are also at risk of developing a wide range of other adverse mental health problems in adulthood, including substance use and depression (Odgers *et al*., 2008). As such, a large body of literature has examined risk factors that are associated with the development of youth AB. A better understanding of how different risk factors interact is of particular importance as such research has the potential to inform how, when, and for whom we should intervene (Olds *et al*., 1998) and is thus instrumental in designing more effective treatment and prevention programs.

### Role of "E"—Environment

Etiological models of AB have benefited from adopting an ecological perspective, which emphasizes an examination of risk across levels (e.g., from communities to schools to parents to children), considering how these levels interact over time (Bronfenbrenner, 1986; Shaw & Gross, 2008). While individual factors, such as low intelligence, difficult temperament, and poor executive functioning, have been identified as risks for AB (Loeber & Farrington, 2000), environmental factors have also been robustly related to the development of AB. In particular, strong evidence supports links between the development of youth AB and parenting practices (e.g., lack of supervision or involvement and harsh parenting; Loeber, Farrington, Stouthamer-Loeber, & Van Kammen, 1998), child maltreatment (e.g., abuse and neglect; Widom, 1989), parental criminality (Loeber *et al*., 1998), socioeconomic status (Sadeh *et al*., 2010), neighborhood dangerousness (Barnes & Jacobs, 2013), and deviant peer affiliation (Dishion & Patterson, 2006). However, as is the case for many psychological phenomena, although these findings are robust, a majority of children who are exposed to these specific environmental risk factors do not experience poor behavioral outcomes (Kim-Cohen *et al*., 2006). It appears that various factors render some individuals more or less susceptible to the *same* experiences, making it difficult to define single, causal, or overwhelming "risk environments" (Ellis & Boyce, 2011; Pluess & Belsky, 2013). Thus, recently researchers have begun to focus their attention on identifying reasons why some individuals are more or less susceptible to harsh or risky environments.

### Role of "G"—Genetics

Genetic variation is a key factor that may play a role in differences in susceptibility and put certain individuals at greater risk of developing AB. Some portion of individual genetic risk stems from *common genetic polymorphisms*, which are regions of the genome for which there exist two or more different versions (i.e., alleles). Functional genetic polymorphisms can reflect changes in a single (or multiple) base pairs of DNA that affect transcription of a gene and/or the structure of the resulting translated protein. These changes may then lead to differential protein function, which can in turn affect neurotransmitters key to brain function and subsequent behavior (Hyde, Swartz, Waller, & Hariri, 2014; Meaney, 2010). Many candidate genes for AB are polymorphisms that have been directly linked to youth AB or related constructs in behavioral studies (e.g., impulsivity, low fear, and aggression) or are polymorphisms that have been shown to affect neurotransmitter systems that influence key brain structures or functioning linked to aggression, violence, and AB.

For example, the enzyme monoamine oxidase A (MAOA) supports the breakdown of monoamine neurotransmitters, including serotonin and norepinephrine. In a seminal paper, researchers identified a rare mutation in this *MAOA* gene that created an *MAOA* protein deficiency and was related to high rates of aggressive, violent, and criminal behavior in a Dutch kindred (Brunner, Nelen, Breakefield, Ropers, & Van Oost, 1993). Later studies have built on this finding and reliably linked a more common polymorphism in *MAOA* (a "low activity allele") to AB, particularly among males and in the context of maltreatment (e.g., Byrd & Manuck, 2013; Caspi *et al*., 2002; see next section).

In more recent years, studies investigating the genetic basis of child and adolescent AB have continued to focus on gene variants related to neurotransmitter pathways involving dopamine and serotonin. This focus stems from the fact that these neurotransmitters and their neural targets are implicated in a variety of behaviors including emotion, reward, and learning, which are all areas that are recognized as being disrupted in AB (Hyde, Shaw, & Hariri, 2013). In particular, research has explored *DRD4*, *DRD2*, 5-HTTLPR, *TPH*, and *COMT* genes in relation to AB (Belksy & Pluess, 2009). At the same time, it is important to note that direct gene-behavior studies have not yielded consistent answers (Viding & Frith, 2006), emphasizing that it is unlikely that we will find specific "AB genes" that are invariant across environments.

## The Interaction Between an Individual's Genes and Their Environment (G×E Interactions)

*Background to G×E Interactions.* To address weak and inconsistent findings in gene-behavior links, including a lack of replication across studies and the failure of genome-wide approaches to yield genetic variants that explain the expected amount of "heritability" from twin studies (Maher, 2008), some research has shifted to an examination of gene×environment (G×E) interactions. Specifically, G×E interaction research demonstrates that the effect an environmental experience has an outcome (e.g., youth AB) is conditional on genetic background (i.e., genotype). Similarly, G×E interaction research also supports the idea that the effect of genotype on behavior is contingent on experience (Moffitt, Caspi, & Rutter, 2005, 2006).

*Examples of G×E Studies.* In one of the earliest examples of a G×E interaction, the low activity allele of the *MAOA* gene was found to predict AB in boys, but only in the context of childhood maltreatment (Caspi *et al*., 2002). Since this novel finding, many studies have replicated and extended research examining whether variation in genotype moderates the relationship between environmental risk and AB. Table 1 provides a summary of 45 studies to date that have examined interactions between genes and experiences of environmental adversity in predicting youth AB. The majority of these studies (27 of 45) have investigated *MAOA* allelic variants, while the remainder has examined other candidate genes previously linked to AB, including those linked to dopamine and/or serotonin neurotransmission.

The most consistent evidence of G×E interactions has been found with *MAOA*. Specifically, the low activity allele of *MAOA (MAOA-L)* appears to be related to increased risk for AB, but only in the context of childhood adversity and typically more strongly in samples of boys/men (Byrd & Manuck, 2013). In addition, genes affecting the dopamine (e.g., *DRD4* and *DRD2*) and serotonin (e.g., 5-HTTLPR) neurotransmitter systems appear to interact with environmental context (particularly parenting and prenatal risk) to predict youth AB (e.g., Kieling *et al*., 2013; Zohsel *et al*., 2014). Finally, in addition to genetic effects being stronger in the context of harsh environments, a majority of studies have found that experience has a direct main effect on AB. That is, harsh environments are robust predictors of youth AB, whereas specific genetic variants do not consistently have a main effect on AB. However, taken together, the findings from these 45 studies imply that genes affecting relevant brain systems can help identify individuals more sensitive to the environmental effects on AB.

**Table 1**
G×E Studies of Youth Antisocial Behavior

| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Choe *et al*. (in press) | 189 (0%) | 1.5–20[a] | *MAOA-L* | Punitive discipline[b] | Violent attitude; juvenile arrests; ASB | Yes | **Choe, D.E., Shaw, D.S., Hyde, L.W., & Forbes, E.E. (2014). Interactions between MAOA and Punitive Discipline in African American and Caucasian Men's Antisocial Behavior** Clinical Psychological Science, 2, 591–601**.** |
| Zohsel *et al*. (2014) | 308 (51) | 8, 11, 15 | *DRD4-L* | Prenatal stress[b] | CD, ODD | Yes | **Zohsel, K., Buchmann, A.F., Blomeyer, D., Hohm, E., Schmidt, M.H., Esser, G., Brandeis, D., Banaschewski, T., Laucht, M. (2014). Mothers' prenatal stress and their children's antisocial outcomes- a moderating role for the dopamine receptor D4 (DRD4) gene. *Journal of Child Psychology and Psychiatry, 55,* 69–76.** |
| Haberstick *et al*. (2014) | 4316 (0) | 12–18<br>13–20<br>24–34 | *MAOA* | Childhood maltreat-ment | AB; CP; violent convictions; disposition toward violence | No | Haberstick, B.C., Lessem, J.M., Hewitt, J.K., Smolen, A., Hopfer, C.J., Halpern, C.T., … Harris, K.M. (2014). MAOA genotype, childhood maltreatment, and their Interaction in the etiology of adult antisocial behaviors. *Biological Psychiatry, 75,* 25–30. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Willoughby *et al*. (2013) | 171 (0) | 6 mo, 1, 2, 3 | *BDNF-met* | Harsh parenting[b] | CU, ODD | Yes | Willoughby, M.T., Mills-Koonce, R., Propper, C.B., Waschbusch, D.A. (2013). Observed parenting behaviors interact with a polymorphism of the brain-derived neurotrophic factor gene to predict the emergence of oppositional defiant and callous–unemotional behaviors at age 3 years. *Development and Psychopathology, 25,* 903–917. |
| Kieling *et al*. (2013) | 4101 (51) | 0, 11, 15 | *DAT1* & *MAOA* | Prenatal smoking[b], Maltreat-ment | CP | No | **Kieling, C., Hutz, M.H., Genro, J.P., Polanczyk, G.V., Anselmi, L., Camey, S., *et al*. (2013). Gene–environment interaction in externalizing problems among adolescents: evidence from the Pelotas 1993 Birth Cohort Study. *Journal of Child Psychology and Psychiatry, 54,* 298–304** |
| Barnes and Jacobs (2013) | 1078 (0) | 12–18 | *DAT1-10R, DRD2-A1, DRD2, DRD4-L* | Neighborhood disadvantage[b], Crime[b] | Violent behavior | Yes | **Barnes, J.C. & Jacobs, B.A. (2013). Genetic risk for violent behavior and environmental exposure to disadvantage and violent crime: The case for gene-environment interaction. *Journal of Interpersonal Violence, 18,* 92–120** |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Cicchetti *et al*. (2012) | 62 (50) | 10–12 | *MAOA-L,* 5-HTTLPR-*S; TPH-T* | Maltreatment[b] | AB | Yes | Cicchetti, D., Rogosch, F., Thibodeau, E.L. (2012). The effects of child maltreatment on early signs of antisocial behavior: Genetic moderation by tryptophan hydroxylase, serotonin transporter and monoamine oxidase A genes. *Development and Psychopathology,* 24, 907–928. |
| Nederhoff *et al*. (2012) | 1134 (52) | 10–11 15–16 | *DRD2-L, DRD4, COMT-A* | Parental separation[b] | Ext behavior | Yes; DRD2 - no | Nederhoff, E., Belsky, J., Ormel, J., Oldehinkel, A.J. (2012). Effects of divorce on Dutch boys' and girls' externalizing behavior in Gene-Environment perspective: Diathesis stress or differential susceptibility in the Dutch Tracking Adolescents' Individual Lives Survey study? *Development and Psychopathology, 24,* 929–939. |
| McDermott *et al*. (2012) | 2665 (0) | 12–26 | *MAOA-L* | Traumatic life events | Weapon use, Public fighting | Yes | McDermott, R., Dawes, C., Prom-Wormley, E., Eaves, L., Haterni, P.K. (2012). MAOA and Aggression: A Gene–Environment Interaction in Two Populations. *Journal of Conflict Resolution, 57,* 1043–1064. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Conway *et al*. (2012) | 381 (61) | 15, 20 | 5-HTTLPR-*S* | Chronic life stress | Aggression | Yes | Conway, C., Keenan-Miller, D., Hammen, C., Lind, P., Najman, J., & Brennan, P. (2012). Coaction of stress and serotonin transporter genotype in predicting aggression at the transition to adulthood. *Journal of Clinical Child & Adolescent Psychology, 41*, 53–63. |
| Fergusson *et al*. (2012) | 351 (0) | 15–30[a] | *MAOA-L* | Maltreatment[b], Prenatal smoking[b], Deprivation[b], Leaving school | Property offenses; violent offenses; CP; hostility | Yes | Fergusson, D.M., Boden, J.M., Horwood, L.J., Miller, A., Kennedy, M.A. (2012). Moderating role of the MAOA genotype in antisocial behaviour. *British Journal of Psychiatry, 200,* 116–123. |
| Lahey *et al*. (2011) | 162 (40) | 4–6 9–11 | *DAT1-10R* | Negative and positive parenting[b] | CD | Yes | Lahey, B.B., Rathouz, P.J., Lee, S.S., Chronis-Tuscano, A., Pelham, W.E., Waldman, I.D., Cook, E.H. (2011). Interactions between early parenting and a polymorphism of the child's dopamine transporter gene in predicting future child conduct disorder symptoms. *Journal of Abnormal Psychology, 120,* 33–45. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Dick *et al*. (2011) | 374 (50) | 10–17[a] | *CHRM2* | Low parental monitoring[b] | Ext behavior | Yes | Dick, D.M., Meyers, J.L., Latendresse, S.J., Creemers, H.E., Lansford, J.E., Pettit, G.S., … & Huizink, A.C. (2011). CHRM2, Parental Monitoring, and Adolescent Externalizing Behavior Evidence for Gene-Environment Interaction. *Psychological Science, 22,* 481–489. |
| Latendresse *et al*. (2011) | 452 (52) | 12–22[a] | *CHRM2* | Deviant peer affiliation[b] | Ext behavior | Yes | Latendresse, S.J., Bates, J.E., Goodnight, J.A., Lansford, J.E., Budde, J. P., Goate, A., … & Dick, D. M. (2011). Differential susceptibility to adolescent externalizing trajectories: Examining the interplay between CHRM2 and peer group antisocial behavior. *Child Development, 82*, 1797–1814. |
| Beaver *et al*. (2011a) | 2574 (0) | 12–18<br>13–20<br>18–28 | *DRD2, DRD4-L* | Neighborhood disadvantage[b] | Adolescent victimization; delinquent peers; violent delinquency | Yes | Beaver, K.M., Gibson, C.L., Delisi, M., Vaughn, M.G., Wright, J.P. (2011a). The interaction between neighborhood disadvantage and genetic factors in the prediction of antisocial outcomes. *Youth Violence and Juvenile Justice, 10,* 25–40. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Lee (2011) | 672 (0) | 12–18<br>13–20<br>20–24 | *MAOA-H* | Deviant peer behavior[b] | Covert and overt AB | Yes | Lee, S.S. (2011). Deviant peer affiliation and antisocial behavior: Interaction with monoamine oxidase a (MAOA) genotype. *Journal of Abnormal Child Psychology, 39,* 321–332. |
| Beaver *et al*. (2011b) | 913 (54) | 12–18<br>28–34 | *MAOA-L* | Protective risk factor index[b] | Incarceration; anger; hostility | Yes | Beaver, K.M., Nedelec, J.L., Wilde, M., Lippoff, C., Jackson, D. (2011b). Examining the association between MAOA genotype and incarceration, anger and hostility: The moderating influences of risk and protective factors. *Journal of Research in Personality, 45,* 279–284. |
| Fergusson *et al*. (2011) | 398 (0) | 16–30[a] | *MAOA-L* | Physical and sexual abuse, Inter-parental violence | Property offenses; violent offenses; CP; hostility | Yes | Fergusson, D.M., Boden, J.M., Horwood, J.L., Miller, A.L., Kennedy, M.A. (2011). MAOA, abuse exposure and antisocial behavior: 30-year longitudinal study. *British Journal of Psychiatry, 198,* 457–463. |
| Enoch *et al*. (2010) | 7158 (56) | 0, 0–1, 2–3, 3–4, 7 | *MAOA-L* | Family adversity[b], Stressful events[b] | CP | Yes | Enoch, M.A., Steer, C.D., Newman, T.K., Gibson, N., Goldman, D. (2010). Early life stress, MAOA, and gene-environment interactions predict behavioral disinhibition in children. *Genes, Brain, & Behavior, 9,* 65–74. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Wakschlag *et al*. (2010) | 177 (56) | 0, 15 | *MAOA-L* | Prenatal smoking[b] | CD; hostile attribution bias | Yes | **Wakschlag, L.S., Kistner, E.O., Pine, D.S., Biesecker, G., Pickett, K.E., Skol, A.D., *et al*. (2010). Interaction of prenatal exposure to cigarettes and MAOA genotype in pathways to youth antisocial behavior. *Molecular Psychiatry, 15,* 928–937.** |
| Edwards *et al*. (2010) | 186 (0) | 5–22[a] | *MAOA-L* | Physical discipline[b] | Delinquency | Yes | Edwards, A.C., Dodge, K.A., Latendresse, S.J., Lansford, J.E., Bates, J.E., Pettit, G.S., *et al*. (2010). MAOA-uVNTR and early physical discipline interact to influence delinquent behavior. *Journal of Child Psychology and Psychiatry, 51,* 679–687. |
| Sadeh *et al*. (2010) | 118 (58) | 12–16 | 5-HTTLPR-*L* | Socioeconomic status[b] | APSD, CU | Some | **Sadeh, N., Javdani, S., Jackson, J.J., Reynolds, E.K., Potenza, M.N., Gelernter, J., Lejuez, C.W. (2010). Serotonin Transporter Gene Associations With Psychopathic Traits in Youth Vary as a Function of Socioeconomic Resources. *Journal of Abnormal Psychology, 11,* 604–609.** |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Derringer *et al*. (2010) | 841 (29) | 11, 14, 15, 17, 21, 25 | *MAOA-L* | Harsh discipline, Sexual abuse | Substance problems; AB; CD | Yes | Derringer, J., Krueger, R.F., Irons, D.E., Iacono, W.G. (2010). Harsh discipline, childhood sexual assault, and MAOA genotype: an investigation of main and interactive effects on diverse clinical externalizing outcomes. *Behavior Genetics, 40,* 639–648. |
| Li & Lee (2010) | 2488 (52) | 12–18 18–26 | 5-HTTLPR-*S* | Maltreatment | AB | Yes | Li, J.J. & Lee, S.S. (2010). Latent Class Analysis of Antisocial Behavior: Interaction of Serotonin Transporter Genotype and Maltreatment. *Journal of Abnormal Child Psychology, 38,* 789–801. |
| Weder *et al*. (2009) | 114 (34) | 5–15 | *MAOA-L* | Maltreatment[b] | Aggression | Yes | Weder, N., Yang, B., Douglas-Palumberi, H., Massey, J., Krystal, J.H., Gelernter, J., Kaufman, J. (2009). MAOA genotype, maltreatment, and aggressive behavior: The changing impact of genotype at varying levels of trauma. *Biological Psychiatry, 65,* 417–424. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Sonuga-Barke, *et al*. (2009) | 708 (0) | 5–17 | *DAT1-10R*, 5-HTTLPR-*S* | Maternal expressed positive emotion[b] | CP | Yes | Sonuga-Barke, E.J.S., Oades, R.D., Psychogiou, L., Chen, W., Franke, B., Buitelaar, J., & Faraone, S.V. (2009). Dopamine and serotonin transporter genotypes moderate sensitivity to maternal expressed emotion: The case of conduct and emotional problems in attention deficit/ hyperactivity disorder. *Journal of Child Psychology and Psychiatry, 50,* 1052–1063. |
| Prom-Wormley *et al*. (2009) | 721 (100) | 8–17 | *MAOA-H* | Maltreatment[b] | CD | Yes[d] | Prom-Wormley, E.C., Eaves, L.J., Foley, D.L., Gardner, C.O., Archer, K.J., Wormley, B.K., *et al*. (2009). Monoamine oxidase A and childhood adversity as risk factors for conduct disorder in females. *Psychological Medicine, 39,* 579–590. |
| van der Vegt *et al*. (2009) | 239 (0) | 10–15 | *MAOA-L* | Maltreatment[b] | Ext behavior | No | Van der Vegt, E.J.M., Oostra, B.A., Arias-Vásquez, A., van der Ende, J., Verhulst, F.C., Tiemeier, H. (2009). High activity of monoamine oxidase A is associated with externalizing behavior in maltreated and non-maltreated adoptees. *Psychiatric Genetics, 19,* 209–211. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Hart & Marmorstein (2009) | 672 (100) | 11–23 | *MAOA-L* | High % of children in neighborhood[b] | Aggression | Yes | Hart, D. & Marmorstein, N.R., (2009). Neighborhoods and genes and everything in between: Understanding adolescent aggression in social and biological contexts. *Development and Psychopathology, 21,* 961–973. |
| Beaver & Holtfreter (2009) | 818 (0) | 12–18<br>13–20<br>18–28 | *MAOA-H* | Delinquent peers[b]<br>Family risk[b],<br>Parental incarceration[b] | Fraudulent behavior | Yes[d] | Beaver, K.M., & Holtfreter, K. (2009). Biosocial influences on fraudulent behaviors. *The Journal of Genetic Psychology, 170,* 101–114. |
| DeLisi *et al*. (2009) | 232 (100) | 12–18<br>13–20 | *DRD2* | Parental incarceration[b] | Delinquency; violent delin-quency; police contact | Yes | DeLisi, M., Beaver, K.M., Vaughn, M.G., Wright, J.P. (2009). All in the family: Gene×environment interaction between DRD2 and criminal father is associated with five antisocial phenotypes. *Criminal Justice and Behavior, 36,* 1187–1197. |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Bakermans-Kranenburg *et al*. (2008) | 157 (45) | 13mo-2<br>1–3<br>2–4<br>4–5 | *DRD4* | Positive parenting[b] | Ext and oppositional behavior | Yes | Bakermans-Kranenburg, M.J., Van IJzendoorn, M.H., Pijlman, F.T.A., Mesman, J., & Juffer, F. (2008). Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized control trial. *Developmental Psychology, 44,* 293–300. |
| Langley *et al*. (2008) | 266 (nr) | 7–11 | *DRD5-5R, DAT1-10R* | Prenatal smoking[b], Low birth weight[b] | ODD; CD | Yes | Langley, K., Turic, D., Rice, F., Holmans, P., van den Bree, M.B.M., Craddock, N., *et al*. (2008). Testing for gene×environment interaction effects in Attention-Deficit Hyperactivity Disorder and associated antisocial behavior. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics), 147B,* 49–53. |
| Propper *et al*. (2007) | 72 (50) | 6 mo, 1, 1.5, 2, 2.5 | *DRD4-L* | Negative & positive parenting[b] | Ext behavior | Yes[d] | **Propper, C., Willoughby, M., Halpern, C.T., Cox, M., & Carbone, M.A. (2007). Parenting quality, DRD4, and the prediction of externalizing and internalizing behaviors in early childhood. *Developmental Psychobiology, 49,* 619–632.** |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Sjoberg *et al*. (2007) | 117 (100) | 16–19 | *MAOA-L* | Maltreatment[b], Type of residence[b] | Criminal activity | Yes | Sjoberg, R.L., Nilsson, K.W., Wargelius, H.L., Leppert, J., Lindstrom, L., & Oreland, L. (2007). Adolescent girls and criminal activity: Role of MAOA-LPR genotype and psychosocial factors. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144B,* 159–164. |
| Bakermans-Kranenburg *et al*. (2006) | 47 (51) | 10 mo, 2, 3 | *DRD4-S* | Maternal insensitivity[b] | Ext behavior | Yes | Bakermans-Kranenburg, M.J. & Van IJzendoorn, M.H. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48,* 406–409. |
| Kim-Cohen *et al*. (2006) | 975 (0) | 5, 7 | *MAOA-L* | Maltreatment[b], Intimate partner violence[b] | Emotional problems, ADHD | Yes | **Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I.W, Moffitt, T.E. (2006). MAOA, maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry, 11,* 903–913.** |

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| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Young *et al*. (2006) | 247 (0) | 12–18 | *MAOA* | Maltreatment | CD | No | Young, S.E., Smolen, A., Hewitt, J.K., Haberstick, B.C., Stallings, M.C., Corley, R.P., Crowley, T.J. (2006). Interaction between MAO-A genotype and maltreatment in the risk for conduct disorder: Failure to confirm in adolescent patients. *American Journal of Psychiatry, 163,* 1019–1025. |
| Huizinga *et al*. (2006) | 277 (0) | 11–15<br>14–17<br>24–28 | *MAOA* | Maltreatment[b] | CD; violent offense arrest; disposition toward violence, APSD | No | Huizinga, D., Haberstick, B.C., Smolen, A., Menard, S., Young, S.E., Corley, R.P., *et al*. (2006). Childhood maltreatment, subsequent antisocial behavior, and the role of monoamine oxidase A genotype. *Biological Psychiatry, 60*, 677–683. |
| Widom & Brzustowicz (2006) | 631 (48) | 0–11<br>31–35 41 | *MAOA-L* | Maltreatment[b] | AB | Yes | Widom, C.S., Brzustowicz, L.M. (2006). MAOA and the "Cycle of Violence": Childhood abuse and neglect, MAOA genotype, and risk for violent and antisocial behavior. *Biological Psychiatry, 60,* 684–689. |

(*continued overleaf*)

**Table 1**
(*Continued*)

| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Nilsson *et al*. (2006) | 79 (0) | 16–19 | *MAOA-L* | Maltreatment, Type of residence | Criminal activity | Yes | Nilsson, K.W., Sjoberg, R.L., Damberg, M., Leppert, J., Ohrvik, J., Alm, P.O., *et al*. (2006). Role of monoamine oxidase A genotype and psychosocial factors in male adolescent criminal activity. *Biological Psychiatry, 59,* 121–127. |
| Haberstick *et al*. (2005) | 772 (0) | 12–18<br>13–30<br>18–28 | *MAOA* | Maltreatment, Adolescent victimization[b] | CP; violent conviction | No | Haberstick, B.C., Lessem, J.M., Hopfer, C.J., Smolen, A., Ehringer, MA., Timberlake, D., Hewitt, J.K. (2005). Monoamine oxidase A (MAOA) and antisocial behaviors in the presence of childhood and adolescent maltreatment. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 135,* 59–64. |
| Foley *et al*. (2004) | 514 (0) | 8–17 | *MAOA-L* | Maltreatment | CD | Yes | Foley, D.L., Eaves, L.J., Wormley, B., Silberg, J.L., Maes, H.H., Kuhn, J., Riley, B. (2004). Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. *Archives of General Psychiatry, 61,* 738–744. |

(*continued overleaf*)

**Table 1**
(*Continued*)

| References | *N* (% female) | Age range[a] | Allele | Environment[b] | Measure of youth AB | G×E (sig?) | Citation[c] |
|---|---|---|---|---|---|---|---|
| Kahn *et al*. (2003) | 161 (52) | 6 mo, 1, 1.5, 2, 3, 4, 5 | *DAT1* | Prenatal smoking[b] | Hyperactive, inattentive, oppositional | No | Kahn, R.S., Khoury, J., Nichols, W.C., & Lanphear, B.P. (2003). Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive–impulsive, inattentive, and oppositional behaviors. *Journal of Pediatrics, 143,* 104–110. |
| Caspi *et al*. (2002) | 671 (34) | 3–11 26 | *MAOA-L* | Maltreatment[b] | CD; violent conviction; APSD; violence disposition | Yes | **Caspi, A., McClay, J., Moffitt, T.E., Mill, J., Martin, J., Craig, I.W., Taylor, A., Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*, 851–854.** |

*Note*:
[a]Annual assessment.
[b]Prospective assessment of environment.
[c]**Bold citations** = references that appear in the text and are thus listed in the references section. All other citations only appear in this table.
[d]Interaction significant but association with *lower* AB.
CD, conduct disorder; ODD, oppositional defiance disorder; CP, conduct problems; APSD, antisocial personality disorder; CU, callous unemotional traits; AB, antisocial behavior; Ext, externalizing behavior.

## CUTTING-EDGE RESEARCH

### Imaging Genetics

Although G×E interaction research has increased the complexity of our understanding of how experience and the genome interact in the development of AB, G×E interaction research alone cannot reveal *specific biological mechanisms* linking genes and experience to behavior. These variables must ultimately affect brain structure and function if they are to affect behavior and increase risk for AB (Hyde *et al*., 2014). In mapping pathways from genes to behavior, we first need to understand how genetic polymorphisms affect brain structure and function, particularly since many candidate genes for youth AB (and psychopathology more broadly) are genes that affect neurotransmitter systems.

Several highly connected brain areas have been identified within neuroimaging studies as regions of interest in relation to youth AB. Among neuroimaging studies that have used magnetic resonance imaging (MRI) to assess the function and structure of brain areas related to youth AB, research has clearly identified robust links with the amygdala. Emerging studies have also begun to implicate other areas, including the orbitofrontal cortex (and the broader ventralmedial prefrontal cortex), dorsolateral and dorsomedial prefrontal cortex, anterior cingulate cortex, and insula. These areas are broadly implicated in the development of AB likely owing to their collective roles in affective processing, responsivity to reward/punishment, learning, integration of sensory information, monitoring of internal states and motivation, execution of planned behavior, and working memory (for a review, see Hyde *et al*., 2013). However, questions remain as to how and why these individual differences in neural structure and function arise.

In order to address questions relating to the origins and mechanisms through which differences in brain structure and function emerge and develop, we adopt an imaging genetics approach that links common genetic polymorphisms to individual differences in brain structure and function (Hariri, Drabant, & Weinberger, 2006). An imaging genetics approach has several advantages when used in studies to understand the development of psychopathology. First, by connecting genetic variation to biological phenotypes in the brain, a *mechanism* is provided through which genes can affect behavior. Second, by focusing on neural and genetic variables, imaging genetics enables greater synergy with animal models and other neuroscience approaches, which can, in concert, advance our understanding of the molecular and cellular pathways linking genetic variation to differences in brain structure and function, and ultimately to differences in behavior (e.g., Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). Third, the

dimensional and relatively objective intermediate phenotypes within imaging genetics (e.g., brain activation) are advantageous relative to other forms of psychopathology research that can be hindered by broad nosological definitions. In particular, diagnostic criteria have typically been plagued by heterogeneity within diagnosis and comorbidity across diagnoses (Burt, 2012; Frick, Ray, Thornton, & Kahn, 2014; Moffitt, 1993; also see Key Issues for Future Research), and using the brain as an outcome may lead to more precise, homogenous, and dimensional phenotypes.

Thus, imaging genetics has proven to be a fruitful approach for understanding how differences in genotype lead to individual differences in brain structure and function, which can, in turn, be linked to differences in behaviors. However, despite the fact that imaging genetics holds much promise for understanding the development of youth AB, little work has applied imaging genetics to this outcome and no research to date has examined how G×E interactions may fit into this pathway.

### The Integration of Imaging Genetics and G×E: IG×E

A cutting edge approach to examine how genetic and environmental variables interact to "*get under the skin*" involves integrating a G×E interaction approach with an imaging genetics approach. This recent strategy of examining the brain as a mediator between G×E interactions has been termed "*imaging gene–environment interactions*" (IG×E; Hyde, Bogdan, & Hariri, 2011) and fits within a broader neurogenetics approach that seeks to understand pathways through which genes, environments, and the brain interact to predict behavior and risk for psychopathology (Bogdan, Hyde, & Hariri, 2012). In particular, we believe that linking these pieces together (i.e., G×E interactions predicting brain function) helps to test the inherent complexity in models of youth AB (see Figure 1; Hyde *et al*., 2011). In an IG×E interaction model, genes have an effect on the brain, as demonstrated in imaging genetics studies (see pathway b, Figure 1), and the environment interacts with these genes to predict behavior, as demonstrated by G×E interaction studies (pathway a). In combining these approaches, IG×E models emphasize that the environment interacts with genetic variability to predict brain function and structure, and ultimately behavior (see pathways b–e), specifying conditional mechanisms among genes, context, the brain, and behavior.

### Application of IG×E to Youth AB

IG×E interaction studies are exciting, but they remain at the cutting edge of empirical research as the approach has been recently proposed and few empirical studies exist to test the full model (i.e., G×E interactions that predict

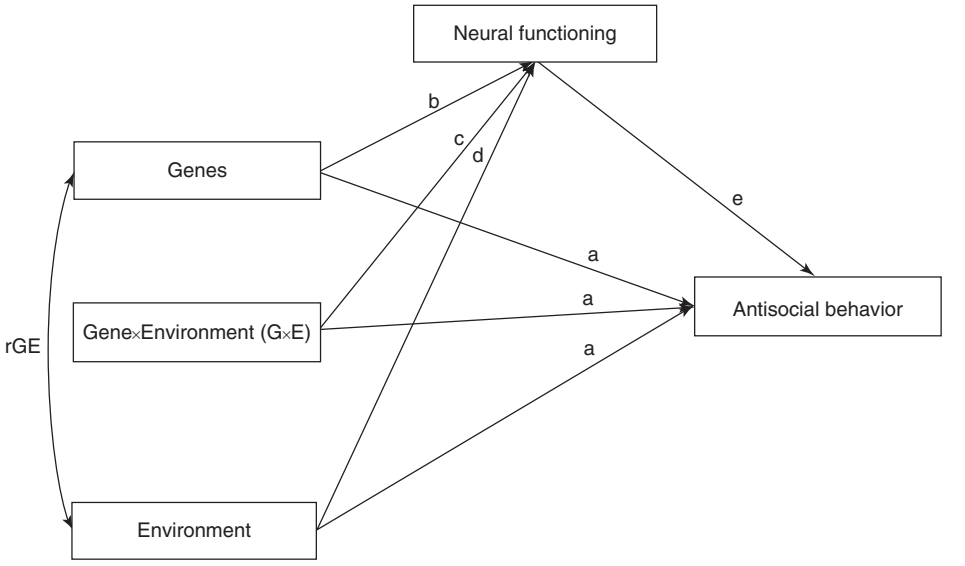


**Figure 1** Theoretical Model of IG×E. A theoretical model of IG×E highlighting how IG×E can be modeled conceptually and statistically. Relationships of the variables are shown for more traditional G×E and imaging genetics paths, as well as new paths possible in IG×E. The "a" paths model typical G×E relationships; "b & e" paths model traditional imaging genetics links; "d" paths show direct effects of the environment on neural functioning; "c & e" paths model gene–environment interactions predicting behavior via neural functioning. Within this model, the covariance between a genetic variant and an environment is modeled and reflects the correlation (rGE) between specific genetic variant and specific environment.

behavior via their effect on the brain). However, several studies have published results in which G×E interactions predict *brain function*, a critical first step in this emerging field. For example, in a study testing portions of an IG×E interaction model, Canli and colleagues (2006) found that that variability in a gene affecting the serotonin system (5-HTTLPR) interacted with life stress to predict amygdala reactivity during a resting period in the MRI scanner. More recently, Bogdan, Williamson, & Hariri (2012) showed that variation a gene affecting HPA axis functioning (key to stress-reactivity) predicted amygdala reactivity but only in the context of previous emotional neglect. These studies support the notion that genetic effects on the brain are likely to be contingent on experience and that modeling IG×E pathways may lead to a better understanding of the development of neural circuits, key to understanding psychopathology. However, studies to date have focused primarily on the brain, and are yet to examine an outcome of broader psychopathology. Thus, IG×E studies of youth AB are needed that link G×E interaction results to behavior through their effect on the brain. These studies are likely to focus

on G×E interactions involving genetic polymorphisms related to serotonin and dopaminergic neurotransmitter systems that can be reliably linked to alterations in the functioning of key regions of the brain relevant to youth AB.

Figure 2 presents a summary of these potentially important variables and how they could interact based on evidence to date, providing a testable

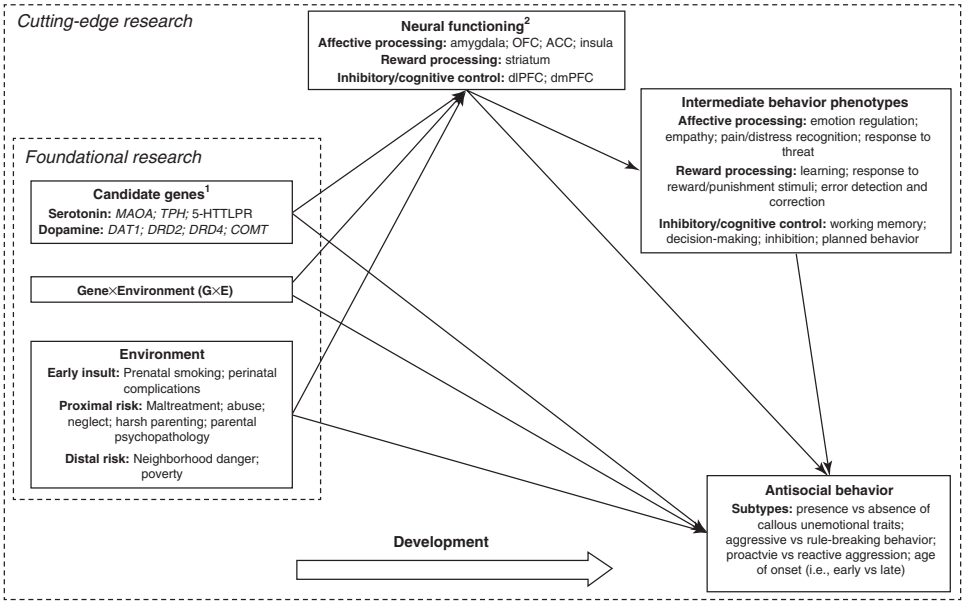


**Figure 2** Summary of potential IG×E targets toward understanding youth antisocial behavior. A preliminary hypothetical model outlining potential targets for future IG×E studies examining AB development among youth. The model emphasizes the interaction between the environment and biology (genes and neural reactivity) as these variables predict antisocial phenotypes or AB. Consistent with other works in this series, we differentiate between *foundational research*, including traditional G×E paths, and *cutting-edge* research, comprising newly proposed paths specific to IG×E models (Hyde *et al*., 2014). *Note*. [1]We highlight gene variants that have seen the bulk of research to date. For simplicity we have separate these genes according to their influence on serotonin versus dopamingeric systems. However, several genes presented have multiple and complex effects on multiple neurotransmitter systems (e.g., MAOA affects all monoamines, not just serotonin). [2]We highlight regions of interest in relation to youth AB that have received the most research focus to date. The brain areas listed are involved in multiple dimensions and thus could be listed in more than one way (e.g., the ACC is involved both affective and error processing). The complex inter-connectivity between these different regions should therefore not be overlooked (Hyde *et al*., 2013). Finally, we have not modeled the moderating effects of the environment and genes on paths from neural functioning to intermediate behavioral phenotypes or from intermediate behavior phenotypes to antisocial behavior, but again, the potential for this additional complexity should be noted.

framework of multiple possible IG×E interaction pathways. Previous studies have hinted at these effects. For example, in one study male carriers of the *MAOA-L* allele, which has been linked in G×E interaction studies to greater risk for aggressive behavior, showed greater amygdala activation to emotionally arousing stimuli and reduced activity in regulatory prefrontal regions compared to individuals with the high expressing allele (Meyer-Lindenberg *et al*., 2006). The same neural profile has been linked to AB in youth and adults (Hyde *et al*., 2013). The results of this imaging genetics study, taken in conjunction with findings from G×E interaction studies linking *MAOA-L* to increased risk for AB following maltreatment or other environmental adversity, suggests a potential IG×E pathway from gene to brain to youth AB (Buckholtz & Meyer-Lindenberg, 2008). Specifically, *MAOA-L*, in the context of maltreatment, appears to lead to greater amygdala reactivity, which may lead to risk for AB, particularly impulsive and reactive aggression (Viding & Frith, 2006). Nevertheless, it should be emphasized that *MAOA* cannot be considered an "AB gene," but rather as one of many allelic variants that confers risk for specific vulnerability in neural processing, which could lead to the development of AB given the "right" (or wrong) environmental context.

## KEY ISSUES FOR FUTURE RESEARCH

While IG×E interaction studies hold much promise, no empirical studies have tested full IG×E interaction models pertaining to youth AB and future research in this field faces a number of theoretical and methodological challenges.

### Definition of Environment?

First, controversy remains surrounding the use and definition of "environment." Typically, environment refers to both experiential phenomena (e.g., harsh parenting) and exposure to physical forces (e.g., natural disasters). However, these potential influences differ in how much an individual's genotype could contribute to their own experience. Factors such as natural disasters are less likely to be correlated with genotype, whereas experiences such as parenting received by a child may be influenced, at least to some extent, by a child's genotype (and the genes shared with parents). A wealth of research suggests that many "experiences" appear to be correlated with genotype such that it is difficult to determine their "causal" nature (Jaffee, 2011). For example, children with difficult temperaments have been shown to "evoke" harsher parenting. However, these youth also share their parents' genes, which may influence their difficult temperament, their parent's

harshness, and/or their (or their parent's) subsequent AB. This scenario demonstrates both passive (sharing genes) and evocative ("evoking" or eliciting a different environment) gene–environment correlations (*r*GE). G×E and IG×E interaction studies may thus be biased by *r*GE because many "experiences" are correlated with genotype meaning that G×E interactions could actually be reflecting *G×G interactions* (Jaffee, 2011). Studies can minimize biases from *r*GE using genetically informed approaches (i.e., twin or adoption studies), examining the effects of natural disasters/experiments, or using randomized controlled trial designs (Hyde *et al*., 2011).

### G×E×E and G×G×E

Second, although G×E interaction research has the potential to increase the complexity of our understanding of risk factors for AB, even greater complexity likely exists in the form of G×E×E and G×G×E interactions (Rutter & Dodge, 2011). For example, in an interesting G×E×E study, a well replicated G×E interaction finding that 5-HTTLPR genotype interacts with maltreatment to influence depression risk (Caspi *et al*., 2003) was found to be *further* moderated by social support. Specifically, only those with the "risk allele" in the 5-HTTLPR with both a history of childhood maltreatment *and* low social support showed increased depressive symptoms (Kaufman *et al*., 2004). This finding emphasizes the complex and multifaceted nature of the relationship among genes, experiences, and behavior, in which some environments exacerbate risk (e.g., maltreatment), while others appear to be protective (e.g., high social support). Moreover, this study illustrates the complex interactions that multiple experiences and genetic polymorphisms likely have in shaping behavior across development.

### Measurement

Third, measurement approaches and methods differ substantially across G×E interaction studies (Table 1). For example, across the 45 reviewed G×E interaction studies of youth AB, complex environments such as harsh parenting and child maltreatment were captured via single item questions and general questionnaire items, with only a few studies using observations of experience. These methodological differences make it difficult to compare findings. In addition, many studies relied on self-report questionnaires to assess both risk and outcome, which can bias the results. Further, many G×E interaction studies of youth AB measured childhood maltreatment employed retrospective assessment of the environment. Research has shown that the incidence of childhood traumatic events varies depending on informant, point of assessment, and developmental stage (Shaffer, Huston, & Egeland, 2008). Reliance on self-reported, retrospective data may thus result

in the magnitude of associations being underestimated (i.e., difficulties recalling) or overestimated (i.e., negative bias affecting reporting of current behavior and past events). Future G×E and IG×E studies are needed that adopt prospective longitudinal designs to examine environmental risk factors and behavioral outcomes as they occur, develop, and interact, using a variety of assessment methods (e.g., Choe *et al*., 2014).

### Sample Size and Composition

Fourth, IG×E interaction models require especially large samples to gain acceptable levels of power. Models that test whether the effects of gene on behavior via the brain are further moderated by environment require large sample sizes. Specifically, 500–1000 subjects is likely the minimum sample size range required in order to examine expected small to moderate effects of individual variables modeled in a moderated mediation framework (Preacher, Rucker, & Hayes, 2007). Future IG×E studies need to adopt creative strategies to increase sample size and power, including piecing together smaller convenience samples (e.g., Yan, Craddock, Zuo, Zang, & Milham, 2013), using consortium models (e.g., Thyreau *et al*., 2012), or conducting neuroimaging meta-analysis (e.g., Jahanshad *et al*., 2013). Furthermore, many studies utilize samples of convenience, such as college students in subject pools or community volunteers who respond to a flier. These kinds of samples are likely to vary in a number of important dimensions that could affect the consistency and replicability of findings and distort the relationship between individual differences in brain and behavior. Thus, future IG×E studies must be thoughtful about sampling and *who* the study will generalize to, with representative samples offering particular advantages (Falk *et al*., 2013).

### Demographic Factors

Fifth, demographic variables including age (Lenroot & Giedd, 2011), gender (Wakschlag *et al*., 2010), race/ethnicity (Propper *et al*., 2007), and genetic substructure (Cardon & Palmer, 2003) are likely to influence findings, and require careful control and examination as additional moderators in future studies of youth AB.

### Developmental Stage

Sixth, development is likely to play an important role in the unfolding of gene–environment–brain–behavior relationships. Many genetic variants relevant to AB (e.g., *MAOA* and 5-HTTLPR) are likely to have influences

on neural functioning *in utero* or very early in development. Environmental experiences also likely differ in their impact depending on developmental stage (Sroufe & Rutter, 1984) and during particular "sensitive periods" of development (Meaney, 2010). For example, in relation to IG×E interactions and youth AB, harsh parenting may only moderate the effect of certain genotypes when harsh parenting is measured in early childhood and when AB is measured in adolescence. In contrast, interactions between genotype and deviant peer experiences may only relate to AB when both peer experiences and AB are measured in adolescence. Studies that test IG×E interactions longitudinally across multiple developmental periods are likely to help uncover these more complex interactions (i.e., IG×E×development – "IG×E×D"; Hyde *et al*., 2014).

### Subtypes of AB

Finally, thoughtfulness about phenotype is critical to the study of youth AB adopting an IG×E interaction framework, as a high level of precision is needed to find smaller or complex effects. Converging evidence across multiple methods suggests that antisocial youth are not a homogenous group, but rather may include several subgroups with different etiologies. For example, AB that begins early (before age 10) is associated with greater early risk, including neurocognitive deficits, harsher parenting, more difficult temperament, and higher comorbidity (Moffitt *et al*., 2002; Patterson, Reid, & Dishion, 1992); a more chronic and escalating trajectory of behavior (Shaw & Gross, 2008); and worse outcomes in adulthood (Moffitt *et al*., 2002). In contrast, AB that starts in adolescence has been linked to deviant peer affiliation (Dishion, Patterson, Stoolmiller, & Skinner, 1991), fewer proximal family risks, and a less elevated and less chronic trajectory of AB with fewer problematic outcomes during adulthood (Moffitt, Caspi, Dickson, Silva, & Stanton, 1996). Thus, we may expect these subgroups to have very different neural and genetic correlates, though few studies have addressed this question.

In addition, research has examined callous-unemotional (CU) traits among a subgroup of antisocial youth, characterized by diminished displays of empathy toward others. Empirical studies using this subtyping approach demonstrate that youth with high levels of CU traits and AB display more severe, chronic, and highly heritable forms of AB (Frick *et al*., 2014). Moreover, this research has emphasized that subgroups differ in their neurocognitive vulnerability: youth with AB and *high* levels of CU traits have *less* amygdala reactivity to threat, whereas those with AB but with *low* levels CU traits have been shown to have *greater* amygdala reactivity to threat. In sum, an examination of both age of onset and/or the presence of CU traits

may help to uncover important subgroups of antisocial youth who differ in genetic risk profile, contingent experiential risk, and developmental course.

## CONCLUSION

G×E interaction studies emphasize that genotype interacts with environment across development to influence risk for psychopathology, particularly youth AB. IG×E interaction studies can ultimately elucidate conditional mechanisms by which genes (e.g., *MAOA*) and experience (e.g., maltreatment) interact to affect neural structure and function (e.g., amygdala reactivity), and resulting psychopathology (e.g., youth AB). Recent research suggests that several genes, experiences, and behaviors are most promising for understanding the development of AB and adopting these variables into an IG×E approach may help us better understand the complex development of these costly and dangerous behaviors.

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