GENES BY HOME CHAOS INTERACTIONS PREDICT EXTERNALIZING PROBLEMS IN CHILDHOOD

by

Gregor Horvath

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STATEMENT OF COMMITTEE APPROVAL

Dr. Kristine Marceau, Chair

Department of Human Development and Family Studies

Dr. Valerie Knopik

Department of Human Development and Family Studies

Dr. Sara Schmitt

Department of Human Development and Family Studies

Approved by:

Dr. Melissa Franks

Dedicated to my folks; to Aidan, Amy, and Jonah;
Olivia, Kristine, Emily. All ya'll made this happen

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ABSTRACT

Genetic and home chaos influences in early childhood have been independently associated with externalizing problems, characterized by inattentive, hyperactive, and aggressive behaviors. However, the Behavioral Genetics approach indicates that genetic and environmental influences, although independently effective, interact to produce behavior throughout development. Thus, this thesis uses two samples, the Early Growth and Development study (EGDS), n = 564, and the Avon Longitudinal Study of Parents and Children (ALSPAC), n = 8,952, and two genetically-sensitive approaches, a parent-child adoption approach and a polygenic scoring approach, to examine how genetic influences and home chaos interact in early childhood (age 3-4) to predict externalizing problems later in childhood (age 7). Results indicate that, although home chaos is correlated with later externalizing problems, the effect is reduced in the context of earlier externalizing, possibly suggesting that home chaos is most salient for concurrent, not later, externalizing problems. In addition, genetic influences were not predictive of externalizing problems in either study, nor was the interaction of home chaos and genetic influences. This pattern of results suggests that, although home chaos may be an important factor for concurrent externalizing problems, other factors, e.g., parenting style and prenatal risk, may be more salient than home chaos, especially in interaction with genetic effects. Further, failure to find genetic influence in this thesis suggest that accounting for the broad scope of genetic influences on complex traits like externalizing and the specific genetic risk for individual externalizing phenotypes is important in attempts to find genetic influence and interaction.

CHAPTER 1: INTRODUCTION

Externalizing problems are often categorized into hyperactivity, inattention, and aggressive or oppositional behaviors, with many individuals exhibiting comorbidity (Zahn-Waxler, Klimes Dougan, & Slattery, 2000; Frick & Nigg, 2012). Broadly, externalizing problems are predictive of many maladaptive outcomes, notably violence (Tuvblad, Narusyte, Grann, Sarnecki, & Lichtenstein, 2011), criminality (Leschied, Chiodo, Nowicki, & Rodger, 2008), substance use (King, Iacono, & McGue, 2004), and lower academic achievement (van Lier et al., 2012). In addition, children and adolescents who display higher levels of externalizing problems are also more likely to display higher levels of internalizing problems, particularly anxiety and depression (Chan, Dennis, & Funk, 2008) further highlighting the importance of understanding the etiology of externalizing problems. From these patterns, it is clear that externalizing problems pose a significant and widespread health risk, warranting systemic efforts to reduce them.

However, to curb externalizing problems, one must understand the factors that lead to them, including their genetic and environmental influences. Important to this understanding is the potential for moderation of environmental effects by those from genetic sources, which may represent shifts in biological response to stimuli. There is evidence that genes related to externalizing problems (e.g., 5-HTTLPR) also contribute to neural activity and both affective and physiological reactivity after exposure to negative emotions (Glenn, 2011; Weeland, Overbeek, Orobio de Castro, & Matthys, 2015) and thus genetic influences may both affect externalizing problems directly and moderate environmental influences on externalizing problems by altering an individual's reactivity to their environment. Further, genetically-sensitive investigations of externalizing behaviors that incorporate the early childhood environment allow for the option of offering interventions to individuals who may benefit more from them early in childhood, by fostering a precise and nuanced understanding of the effects of specific environments and their relationships with genetic influence. Intervention in early childhood is important because such interventions most effectively disrupt trajectories of persistent antisocial behavior (Moffitt, 1993; Granic & Patterson, 2006).

One of the strengths of genetically sensitive designs is their ability to contextualize the effects of environments that have been implicated in the development of externalizing problems.

Home chaos, characterized by noise, overcrowding, and a lack of routine within a household is one such environment. In early life, environmental chaos may disrupt the processes involved in young children's cognitive development (Petrill, Pike, Price, & Plomin, 2004) and lead to greater externalizing problems (Coldwell, Pike, and Dunn, 2006). Moreover, parents' reports of home chaos in their households have been indicated as representing an impactful aspect of the home environment, distinct from other well-founded measures of household and family environment (e.g., harsh/inattentive parenting, Dumas et al., 2005; maternal internalizing, Pike, Iervolino, Eley, Price, & Plomin, 2006; and parental positivity, Valiente, Lemery-Chalfant, & Reiser, 2007). Thus, this research assesses the effect of home chaos and inherited risk (i.e., genotypes that increase risk as measured either directly or via birth parent behavior) for externalizing problems to investigate how the effects of genetics and environment influence externalizing problems in children, as well as how the effects of the environment change with greater inherited risk.

This thesis uses two studies to assess both genetics and home chaos as predictors of externalizing problems in young children. These investigations highlight the effects of household chaos in early childhood (e.g., 3 to 4.5 years) on externalizing problems in middle childhood (age 7 years) as well as how the effects of household chaos may be moderated by genetic influences and build upon prior research indicating correlations between concurrent chaos and externalizing and investigate possible persistent effects. In doing so, this research provides a better understanding of how a tumultuous household during a time of preparation for the transition into formalized education (ages 3-4 years) may predict greater externalizing problems later in childhood.

Specifically, this research investigates whether the effect of a chaotic home environment on children decreases as children's inherited risk (i.e., more genetic markers correlated with or birth parents who engaged in more) for externalizing problems increases. Based on prior research on externalizing problems and home chaos (or similar constructs), the basis for the assessment of moderation in this thesis is the vulnerable-stable model. The vulnerable-stable model posits that individuals at risk for externalizing problems will display elevated externalizing, but the effect will be driven by genetic influences if genetic risk is high and will otherwise be driven by environmental influences (Luthar et al., 2000). The vulnerable-stable model of GxE can be traced back to the 'vulnerability model' proposed by Masten et al. (1988), in which children high

in ‘attribute’ (low genetic risk in this thesis) were hypothesized to be more susceptible to stress exposure (chaos), whereas children low in ‘attribute’ were less susceptible to stress exposure but saw worse outcomes regardless due to the direct effect of being low in ‘attribute’. The vulnerable-stable model also bears resemblance to the bioecological model (Bronfenbrenner & Ceci, 1994), in which an environment that carries little risk allows risky genetic influences to be more apparent, although the bioecological model frames the interaction as moderation of genetic influences rather than environmental, which is opposite the direction hypothesized in this thesis. The bioecological model proposes that a more positive environment allows individuals more agency, thereby giving genetic influence more influence over behavior. Thus, children in low chaos environments with low genetic risk would be low on externalizing whereas children high in either predictor would score high in the outcome with little change when scoring high in both as the environment restricts genetic effect. In contrast, the vulnerable-stable model, as noted in the discussion of the ‘vulnerability model’, proposes that genetic risk for a phenotype may both confer risk and reduce the individual’s sensitivity to the environment, overriding positive or low-risk environments and reducing the response to negative environments.

To elaborate on the processes underlying the vulnerable-stable model, Weeland et al. (2015) discuss how genetic influences may reduce reactivity to the environment while directly encouraging externalizing problems by affecting an individual’s physiological reactivity – i.e., because genetic influences govern biological response to external stimuli, genetic influences may moderate environmental effect by altering those biological responses. In terms of the variables in this thesis, genetic risk for externalizing problems would simultaneously increase externalizing problems and decrease the effect of home chaos. Thus, children in high chaos environments would always be high in externalizing but the effect of home chaos would decrease as genetic effect increased, matching exactly with the vulnerable-stable model.

Therefore, I hypothesize that home chaos will positively predict externalizing problems at low and moderate levels of genetic risk, decreasing as genetic risk increases and not predicting externalizing problems at high levels of genetic risk. Each of the two studies included here use a different genetic methodology to assess genetic influences on externalizing problems. By using two separate methods of measuring genetic effect, the results of these studies can be used to triangulate the effects of genetics and home chaos on externalizing behaviors in childhood. The importance of both genetic influences and home chaos independently in predictions of

externalizing problems in childhood has been established (discussed below). This research takes the next steps to identify possible interactions between the two and further elucidate whether chaos and inherited risk during a time of early transition may be related to long-term externalizing trajectories.

Theoretical Basis

A Behavioral Genetics Approach

The theoretical basis for this research stems from the Behavioral Genetics approach, specifically a developmental Behavioral Genetics approach, defined in Plomin (1983) as, "the study of genetic and environmental influences on individual differences in behavioral development." This approach posits that individual characteristics (e.g., genetics) and environments (e.g., household chaos) are linked and bidirectional in their effects on development. More specifically, the Behavioral Genetics approach views the body as a biological factor engaging actively with its socio-cultural and physical surroundings and seeks to explain phenotypic differences, rather than causes. That is not to say that the Behavioral Genetics approach does not consider causation. Researchers using the Behavioral Genetics approach are aware that, with the current methods, there is no way to prove causation, and thus the approach is more concerned with the extent that a genetic factor *may be* causal, rather than proving that it is. The Behavioral Genetics approach provides a framework for addressing the ways in which individual and environmental characteristics interact with and affect each other across the lifespan, seeking to understand genetic, behavioral, and social influences and their interactions.

Moreover, the Behavioral Genetics approach can be used to test developmental theories. For example, dialectical theory states that development is an outcome of interactions between an individual's characteristics (a knower) and their environment (the known; Overton, 2013). Thus, the Behavioral Genetics approach operationalizes "the individual" (i.e., genetics), "the environment", and "the behavior" with quantifiable traits to allow for testing of all three as independent variables. Because the Behavioral Genetics approach takes a holistic view of biology, environment, and behavior, while acknowledging each of the three as independent but intertwined concepts, it is an ideal framework for this research.

Understanding how household chaos and genetic predispositions influence each other and work together to inform behavior is integral in efforts to understand the etiology of externalizing problems in childhood. Thus, this research addresses personal characteristics (genetics), environmental characteristics (home chaos), and their interactions in an effort to gain a more complete and nuanced picture of the factors contributing to behavior (externalizing problems) in childhood.

CHAPTER 2. LITERATURE REVIEW

Household Influences on Externalizing Problems

There is a great deal of research investigating how the home environment predicts children's externalizing problems, but much of the existing literature focuses on measures of parenting. Home chaos is associated with a variety of other household characteristics including parental responsiveness (Evans, Maxwell, & Hart, 1999), maternal depression (Pike, Iervolino, Eley, Price, & Plomin, 2006), parental positivity (Valiente, Lemery-Chalfant, & Reiser, 2007), and discipline (Dumas et al., 2005). However, research that has included home chaos as an environmental factor suggests that home chaos predicts behavior problems uniquely, beyond its associations with these other more-established variables (Coldwell, Pike, & Dunn, 2006).

Home Chaos as a Predictor

Main Effects of Home Chaos

Cross-sectionally, home chaos has been shown to be generally predictive of externalizing problems in the literature. Wang, Deater-Deckard, Petrill & Thompson (2012) found that higher parent-ratings of home chaos at ages 6, 7, and 8 years concurrently predicted parent-rated externalizing problems at each of those ages. Moreover, there were positive zero-order correlations between chaos at time 1 (age 6 years) and externalizing problems at all three ages, but whether these effects persisted with controls was not tested. Pike, Iervolino, Eley, Price, and Plomin (2006) found similar results for younger children (ages 3-4 years), with parent reports of home chaos predicting general behavior problems even after controlling for gender, minority status, socio-economic status (SES), and a variety of maternal measures (e.g., maternal depression, feelings, and discipline). In addition, Vernon-Feagans, Willoughby, & Garrett-Peters (2016) found that more parent-reported household disorganization from ages 0-3 years was correlated with higher teacher ratings on the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001) and ADHD symptoms drawn from the Disruptive Behavior Disorders Scale (Pelham, Evans, Gnagy, & Greenslade, 1992) at age 3 years. However, this association was mediated by parent responsivity and acceptance. The effects of home chaos may also span across cultures, as home chaos has also been shown to predict conduct problems in middle and later

childhood (ages 8-11 years), such that higher parent-rated home chaos predicted more conduct problems in Pakistani school children at these ages (Shamama-tus-Sabah, Gilani, & Wachs, 2011). Thus, the association of home chaos with concurrent behavior problems seems well founded.

This thesis extends these findings by examining the effect of home chaos at ages 3-4.5 years on later externalizing problems. This age is particularly interesting because it represents a period of preparation for the transition into a more structured school day for most children. Therefore, these studies focus on exposure to home chaos in this age range to better understand whether and how home chaos during this transition may lead to persistent increases in externalizing problems.

Longitudinal Effects of Home Chaos

Regarding potentially longitudinal effects of home chaos, there has been some research showing that chaos early in childhood is predictive of later externalizing problems over time. Specifically, Shelleby et al. (2014) found zero-order correlations between home chaos at age 4-5 and conduct problems at age 7.5-8.5, and Hardaway, Wilson, Shaw, & Dishion (2012) found that parent reports of home chaos at 3 years of age indirectly predicted parent reports of externalizing problems at age 5.5 years through children's inhibitory control. These results suggest that home chaos may affect later externalizing problems by disrupting the development of executive function or other predictors of behavior problems. Notably, in both of these studies, the direct paths of chaos to externalizing problems were not significant when other variables were included in the model. However, Jaffee, Hanscombe, Haworth, Davis, and Plomin (2012) found, using a cross-lag design, that child-reported home chaos at age 9 predicted parent-reported conduct problems and hyperactivity at age 12. Similarly, Mills-Koonce et al. (2016) found that household disorganization, a related measure to chaos, in the first 3 years of life predicted increased conduct problems and callousness when the child was in first grade, even when caregiver behavior (i.e., harsh/sensitive parenting) was included in the model.

Although the literature seems to indicate that home chaos in early childhood is an important predictive factor for both concurrent and future externalizing problems, evidence of its direct effect on subsequent externalizing problems when other important environmental variables are controlled is mixed. Specifically, although Shelleby et al. (2014) found zero-order

correlations between home chaos and later externalizing problems, there was no direct effect in the full model, although home chaos did have a direct effect on emotional problems. Indeed, although some researchers have indicated that chaos is more important for externalizing than internalizing problems (Dumas et al., 2005), that relationship seems to be inconsistent, and more work is necessary to fully understand the circumstances under which home chaos may influence the development of externalizing during childhood, particularly using genetically-sensitive designs. That is, including a genetic component for externalizing problems accounts for a source of variance that has largely gone unused in tests of home chaos thus far. Including genetic components not only creates an opportunity to assess the biological underpinnings of externalizing but may also allow for more specific models in which home chaos is more consistently predictive of externalizing problems. This thesis addresses this gap by examining whether and how home chaos predicts later externalizing problems using two separate longitudinal samples, which allows for a more reliable interpretation of how home chaos and genetic influences interact in early childhood to influence behavior.

Ages 3 to 4 Years as a Sensitive Period

Age 3-4 years represents a period of transition for children and parents. Rimm-Kaufman and Pianta (2000) discuss that this age range comes just before the entry into formal education and, as an extension, a shift from interacting primarily with adults to interacting primarily with other children. Moreover, the entry into formal education brings with it an emphasis on behavior regulation, with most teachers (52-88%) rating measures of self-control and attention as 'Very Important' (Lane, Wehby, & Cooley, 2006). A smooth transition into formal education, fostered by a stable home environment, has been shown to predict later beneficial behavioral (Gower, Lingras, Mathieson, Kawabata, & Crick; 2014) and academic (Iruka, Gardner-Neblett, Matthew, & Winn, 2014; Schulting, Malone, & Dodge, 2005) outcomes, and a child's levels of externalizing behavior immediately prior to and upon entering kindergarten seem particularly important for a smooth transition (Gower et al., 2014). This supposition is supported by Blair (2002) where it was found that toddlers with high negative emotionality were at higher risk for poor school readiness, and moreover, that a home environment designed to reduce stress (i.e., an orderly/predictable environment) may benefit children by promoting skills necessary for social and cognitive adaption to the classroom. Although this paper primarily focused on executive

function, the focus on socially acceptable behaviors and self-control could apply equally well to externalizing problems. Thus, this research examines home chaos at ages 3-4.5 years to better understand how home chaos during this time may represent a risk for a difficult transition into schooling, laying the groundwork for future problem behaviors.

Genetic Methodologies

To best contribute to the existing literature, this thesis uses both quantitative and statistical genetic methodologies to assess genetic and environmental effects on externalizing problems. See Table 1 for a brief overview of the genetic methodologies discussed in this thesis.

Quantitative Genetic Approaches

Quantitative genetic studies explore genetic effects as latent, unobserved factors and are vital as they can provide researchers with a better understanding of the relative contributions of genetic and environmental effects on a trait (Knopik, Neiderhiser, DeFries, & Plomin, 2017). Quantitative genetic studies can parse genetic and environmental components by comparing individuals of known genetic relatedness (e.g., twin studies) or assessing individuals in circumstances where genetic contribution is relatively disentangled from the contribution of the environment (e.g., adoption studies).

Models of Heritability and Environment

Quantitative genetic studies often attempt to identify the broad-sense heritability of a trait (h^2) as it varies between specific populations and contexts. Heritability, in its most basic sense, is defined as the proportion of phenotypic differences among individuals that can be attributed to genetic differences within a population (Knopik et al., 2017). One approach to measuring specifically additive, or narrow-sense, heritability (a^2), involves the use of twin studies to fit models of genetic and environmental influence (e.g., AE, ACE/ADE, and ACDE). Whereas h^2 captures the proportion of broad phenotypic variation due to genetic influences and can include effects from dominance (when the effect of an allele masks the contribution of a second allele at the same locus) and epistasis (non-additive interaction between genes at different loci), a^2 strictly captures variation due to additive genetic influences (Wray & Visscher, 2008) - although the

terms are still often used interchangeably (heritability, Knopik et al., 2017) . Notably, heritability is not a measure of genetic effect per se. It is a measure of how likely genetically-related individuals are to express traits similarly – compared to non-genetically-related individuals, or how much of the variance in a population is attributable to genetic influences. The other components of these models are non-shared environment (E), or latent environmental factors that make family members (specifically twins in most studies) different from one another, including measurement error, and shared environment (C) latent factors that make family members more similar to one another, and/or dominance genetic effects (D). Notably, twin models lack the degrees of freedom to test for the ACDE model, and once A and D are included in the model, the model is no longer addressing just narrow-sense heritability but instead broad-sense heritability without epistasis. These models stand out in that they attempt to provide insight into how genetic and environmental effects account for the variance in a trait in proportion to one another. Thus, ACE and ADCE models allow for examinations of how genetic and environmental correlations with a trait may vary from one population to another but are limited in their ability to provide insight into the effects of specific environments. In multivariate extensions of these models, whether specific environments correlate more genetically or environmentally with an outcome can be tested. However, twin studies can only test moderation of genetic influence by environmental variables and thus cannot be used to test the hypotheses of this thesis.

Parent-Child Adoption Models

Parent-child adoption studies can be used to assess the genetic risk for a behavior by evaluating an adopted child's similarity to their biological parent on a trait of interest. Because the child's postnatal environmental influences come entirely from the adopted environment while their biological influences come from their birth parents, any similarities between the adopted child and their adoptive parents can be attributed to an environmental effect, provided that effects of the uterine environment are controlled (Leve et al., 2010; 2013). By isolating the genetic and environmental components by design, researchers can come to a more complete understanding of the influences that predict a trait, as well as how genetic and environmental influences affect one another. Therefore, a key strength of such adoption studies is that they indicate, without genetic confounds, the extent to which a phenotype is environmentally influenced and provide insight into how such environmental influence may change in various

genetic contexts. In parent-child adoption studies, genetic effects can be examined by indexing traits in a birth parent and using those parent-scores to predict the trait in the child. Thus, parent-child adoption studies using scores of inherited risk contribute to the literature's understanding of genetic influences by indicating broad genetic effect in a way that, by design, disentangles genetic and environmental influence. In addition, these studies provide information on environmental influences by controlling for some of the correlation between genetics and environment that stems from biological parents of children also providing their children's environment in non-adoption studies.

Although twin studies provide a more comprehensive indication of genetic influence on a trait, parent-child adoption studies allow researchers to test for moderation of environmental variables by genetic influences – as in this thesis. That is, environmental effects are made more specific through partial disentangling of G and E by examining children not raised by their biological parents, and genetic effects are made more specific through explicit measurement of genetic effect via indices of externalizing problems in parents (as opposed to a completely latent genetic effect if the trait was not specifically measured). Thus, study 1 uses a parent-child adoption design first, to provide a narrower, but more specific measure of genetic influence than a twin study would and second, to allow for clearer environmental effects – ideal for this thesis.

Statistical Genetic Approaches

Statistical genetic studies, in contrast to quantitative genetic studies, assess the effects of identifiable genetic units – e.g., genes, single-nucleotide polymorphisms (SNPs), and genetic loci - in the expression of a trait (e.g., Farbiash, Berger, Atzaba-Poria & Auerbach, 2014; Hohmann et al., 2015). A gene is a sequence of DNA bases (nucleotides) that codes for some output – for example, a protein or an RNA molecule. Genes can vary greatly in the number of forms (alleles) in which they occur, and multiple genes often contribute to a single trait (Knopik et al., 2017). A single gene can also contribute to several traits (pleiotropy, Knopik et al., 2017). Notably, not all DNA is coding DNA and exists between genes on the chromosome.

Genetic variation occurs in a variety of ways including copy number variants, insertion/deletions, and substitutions. However, due in part to technological advances, most research is conducted on common SNPs, variations in single nucleotides that occur in at least 1% of the population (Cavalli-Sforza & Bodmer, 1999). A SNP can be the variation of a nucleotide

inside of a gene, but it does not have to be. Many SNPs occur in non-coding DNA. SNPs within genes are more likely to influence the gene's output, but SNPs in non-coding DNA can still be informative because such a SNP associated with a trait may be nearby to a gene that affects the trait (Eley & Rijsdijk, 2005).

Statistical genetic studies investigate associations between these genetic markers and traits through methods like candidate gene studies, genome-wide association studies (GWAS), and polygenic scoring (Eley & Rijsdijk, 2005). Candidate gene studies are a statistical genetics approach designed to examine associations between individual genes of interest and traits (Knopik et al., 2017). GWAS evaluate the correlations between SNPs and traits more comprehensively by regressing each SNP on the trait of interest in a large sample and adjusting p-value for multiple testing. In this way, GWAS are a powerful method for identifying SNPs of interest regarding a specific trait.

Polygenic Scoring (PGS) Approaches

Polygenic scoring is one method of aggregating influences of small-effect genetic variants into scores indicating broader genetic influence (Maier et al., 2018). PGS approaches aggregate the small effects of individual indicators – often, but not always, SNPs – indicated in GWAS or throughout the literature, to create scores indicating a broader genetic effect. PGS have gained popularity in the field, largely due to the problematic replicability and small effects of candidate gene studies (Maier, Visscher, Robinson, & Wray, 2018). One driving force for this shift is the growing evidence that complex traits are often polygenic – drawing influence from many interconnected genes – and thus they cannot adequately be predicted by single-variant studies (Yang et al., 2012). By aggregating effects across SNPs, PGS results fall between the comprehensiveness of twin and adoption methods and the specificity of candidate gene studies, addressing some of the limitations of each. Although, by design polygenic scoring approaches do not identify specific individual genetic variants associated with an outcome, PGS can be consciously made more interpretable by tailoring the scores towards biologically relevant information (e.g., genes associated with specific hormones, biological systems, or other known functions; see Chhangur et al., 2017). In addition, PGS can be used as a precursor to other approaches, e.g., gene-set analysis, which is used to indicate biological mechanisms by examining whether the SNPs in a PGS are included in functionally related genes (Wang, Jia,

Wolfinger, Chen, & Zhao, 2011) or representative of biological systems (Mi, Muruganujan, Casagrande, & Thomas, 2013).

As statistical genetic methodologies indicate specific genetic markers associated with a trait, they allow researchers to assess biological systems involved in trait expression. However, statistical genetic studies are more limited than quantitative studies in that any influence on a trait stemming from a genetic variant not included in the study cannot be estimated (Gibson, 2012). This is one reason assessments of heritability from specific variants (SNP heritability; h^2_{snp}) are almost always lower than heritabilities estimated with quantitative genetics (Gibson, 2012). Despite this limitation, PGS presents an opportunity to produce reliable and relatively larger effects for complex traits based on measured genetic variants. Therefore, to gain insight into the influence of specific genetic variants, study 2 of this thesis will use a PGS constructed of common SNPs shown in the literature to predict externalizing problems as a measure of genetic influence.

Gene Set Analysis

Gene-set analysis is the process of examining whether certain biological pathways are overrepresented in a specified set of genetic variants (Subramanian et al., 2005). Genetic variants are gathered into a set - in the context of this study, the set of SNPs used to create a PGS would be a set - and then the set is analyzed against a database of gene function, ontologies, and pathways. Using a system like Protein Analysis THrough Evolutionary Relationships (PANTHER), gene families and subfamilies are annotated with ontology terms (GO) and sequences are assigned to PANTHER pathways (Mi et al., 2013). Thus, gene sets, which by their nature obscure the individual biological pathways by which genetics affect behavior, can be more completely analyzed, and those relevant biological pathways statistically revealed. The output of gene-set analyses indicates which biological ontologies are overrepresented in the gene-set and thus by what processes investigated variants may affect behavior.

This thesis uses a parent-child adoption design and a polygenic scoring design interrogated with gene set analysis to assess genetic influences on externalizing problems because of their complementary strengths and weaknesses (See Table 1). That is, study 1 leverages the ability of parent-child adoption studies to disentangle genetic and environmental effect and study 2 leverages the ability of PGS to provide reliable estimates of effects by specific genetic variants.

Table 1. Brief Overview of Genetic Methodologies Discussed in This Thesis

	Theory	Strengths	Weaknesses
Quantitative Genetic Studies			
Twin Studies	Assess differential similarities in a trait between fraternal (DZ) and identical (MZ) twins	Accounts for selection, age, and prenatal environment	Results may not generalize to non-twins, requires access to twin samples, susceptible to passive gene-environment correlation unless combined with an adoption study
Adoption Studies	Assess similarities between child placed at birth and birth parent	Accounts for passive gene-environment correlation	Adoptive parents not representative of all parents, does not control for prenatal environment, does not indicate heritability
Statistical Genetic Studies			
Candidate Gene Studies	Assess correlations of a single gene or genetic variant with a trait	Specific indication of genetic effect	Results often do not replicate, does not represent polygenic effects, small effect size
Genome Wide Association Studies (GWAS)	Assess correlations of many SNPs with a trait using a large sample	Powerful, generally reliable, small effect sizes	Expensive, does not represent polygenic effects
Polygenic Scoring Studies (PGS)	Assess correlation of score created by aggregating GWAS effects with a trait	Better indicator of polygenic effect, moderate effect sizes, more reliable than candidate gene studies	Less specific than candidate gene or GWA studies

Note: This table does not give a comprehensive overview of quantitative or statistical genetic methodologies. For a more comprehensive review, see D'Onofrio, Lahey, Turkheimer, & Lichtenstein (2013) and Leve et al. (2010) for quantitative genetic methodologies and Maier, Visscher, Robinson, & Wray (2018) for statistical genetic methodologies.

Genetic Influences on Externalizing Problems

Quantitative Genetic Studies

Evidence from quantitative genetic studies has indicated that externalizing behaviors are genetically influenced. Saudino, Ronald, and Plomin (2005), using an ACE model and data from the Twins Early Development Study (TEDS) found that 65% of variance in parent-rated conduct problems and 77% of variance in parent-rated hyperactivity were attributable to genetic influences in children age 7 years. Burt, Krueger, McGue, and Iacono (2001), similarly estimated the heritability of three disorders: attention-deficit hyperactivity disorder [ADHD], oppositional defiant disorder [ODD], and conduct disorder [CD]. Their results revealed that, at age 11 years, each disorder showed influence from genetic (~30%) and both shared (~50%) and non-shared environmental factors (~20%). These studies highlight that genetic influences are prominent in different measures of externalizing problems throughout childhood. Additionally, the influence from the shared environment in Burt et al. (2001) is particularly important for this thesis because home chaos is likely to act as a shared environmental influence.

However, results on the influence of shared environment are not consistent. Children in Barnes, Boutwell, Beaver, and Gibson (2013) and Flom and Saudino (2017) both demonstrated lower or negligible contributions from the shared environment on externalizing problems, while heritability was consistently around 70% and non-shared environmental effects were consistently around 30%. Notably, these articles span a range of ages from 0-7 years, better fitting with the age range of this thesis. Barnes et al. (2013) also estimated heritability for parent-reported externalizing problems at age 4, matching with the starting age for this research, around 70%. Additionally, it is notable that different externalizing phenotypes, e.g., rule-breaking and aggression, often have different levels of heritability (Burt, 2013), and heritability will also vary by rater, e.g., teacher and parent reports of conduct problems noted above (Saudino et al., 2005). These indicate that, despite the amount of research on the heritability of externalizing problems, more needs to be done to better understand the interplay between genetic and environmental variables and under what circumstances each are most impactful.

Notably, the heritability of different externalizing phenotypes can vary, but certain externalizing phenotypes (e.g., aggression and attention problems) often show similar levels of heritability. For example, Porsch et al. (2016), using data from the Netherlands Twin Register (NTR) and the TEDS (United Kingdom) indicated that heritability for aggression through

childhood was around 60% for children aged 7 years. Earlier in life (ages 0-5 years), hyperactivity was shown to be heritable at around 66% in a meta-analysis (Nikolas & Burt, 2010). Despite the general consistency in the high levels of heritability for these externalizing phenotypes, the exact levels of heritability for externalizing problems still vary by circumstance. Specifically, heritability is population specific, and thus will vary between populations, and there is evidence to suggest that heritability for externalizing problems increases with age/level of autonomy (Burt, 2009). This stability allows for more certainty comparing phenotypes that seem to be similarly heritable, but variability among phenotypes and populations highlights the importance of taking the specific externalizing measure, age, and other environmental factors into account when examining genetic effect.

Statistical Genetic Studies

Previous candidate gene studies (e.g., Holz et al., 2018) have shown that the combination of early adversity and specific 'risk' genes increases risk for externalizing problems – i.e., one candidate gene study showed that the predictive effect of institutionalized childcare on externalizing behaviors increased in the presence of the 5-HTTLPR genotype (Brett et al., 2015). However, as stated, candidate gene findings are difficult to replicate, and the influence of single genes is typically minuscule, given that genes work in systems (Salvatore et al., 2015).

Salvatore et al. (2015) used PGS – to assess genetic prediction of externalizing disorders and subclinical externalizing behavior in adolescence and early adulthood. They found that even when controlling for parental externalizing-disorder history (a more quantitative genetic and environmental measure of risk), a PGS still positively predicted children's externalizing behaviors. However, Salvatore et al. (2015) examined genetic effects on subclinical externalizing only in adolescents and young adults, not children. Effect sizes were very low for this study (~0.05), but this is not unusual for PGS studies.

Similarly, Groen-Blokhuis et al. (2014) found, using PGS constructed using SNPs and effect sizes pulled from the Netherlands Twin Registry, that PGS predicted teacher and parent ratings of attention problems in preschool and school-aged children – although they did not examine externalizing problems broadly. However, this study and others using similar PGS, do not produce results that easily inform on biological mechanisms because the scores incorporate genetic variants of unknown, unclear, and potentially unrelated biological effect. This limitation

can be slightly ameliorated by selecting variants of known biological effect. As an example, Chhangur et al. (2017), using data from the Observational Randomized Controlled Trial on Childhood Differential Susceptibility (ORCHID), created a PGS consisting of putatively risk-conferring alleles of dopaminergic genes (DRD4, DRD2, DAT1, MAOA, and COMT) to assess a gene-by-intervention interaction between the score and an intervention focused on parenting skills. Results suggested that children ages 4-8 years with more of these risk-conferring alleles were more responsive to an intervention designed to lower externalizing behavior by increasing positive parenting skills in parents. However, because these studies are more limited in the number of genetic variants they include and the inability of single genes to effectively capture broad genetic effect and interactions between genes, effect sizes are often smaller than less restricted PGS (i.e., PGS including more genetic variants, increasing coverage of genetic influences at the expense of biological specificity) and represent little of the full genetic effect on a trait. Regardless of method, research indicates that there are clear and impactful genetic influences on externalizing problems throughout life, and such effects contribute to the pathways of externalizing problems and may cascade over time, resulting in larger effects than are immediately indicated by direct correlations between genetic markers and traits if not intervened upon.

Gene and Environment Interplay

Gene-Environment Correlation

A notable strength of studying genetic effects using the Behavioral Genetic approach is that effective use of the theory necessitates accounting for gene-environment correlation (*r*GE), which is broken into three types, each indicating one manner in which genetic effects are intertwined with environmental effects (Harden, Hill, Turkheimer,& Emery, 2008; Plomin, DeFries, & Loehlin, 1977). Drawing from Knopik et al. (2017), passive *r*GE occurs because parents, who create the home environment, share their genetics with children. Thus, the genetic effect is difficult to disentangle from the effect of the environment because shared genetics potentially influence both factors. As an example, parents who are genetically inclined to read well may be likely to own more books. The child is thus likely to grow up in a household with more opportunity to read and parents who value reading more, correlating the genetic and

environmental effects. Active *r*GE stems from children actively pursuing environments that suit their genetic predisposition. An example of this could be a child who is genetically predisposed to being a good reader (i.e., their genes directly or indirectly ease reading or make them more susceptible to environmental influences that ease reading) actively seeking out more books or spending more time reading because the activity is easier for them. Finally, evocative *r*GE results when a child's genetic predispositions evoke reactions in others that then naturally vary with the child's genetic influences. To continue the reading example, a child who seems interested in books and reads well may be given more - or more reading-level appropriate - books by their parents or teachers, further establishing their environment as one that fosters reading. Accounting for different types of *r*GE allows for more accurate and less entangled measures of independent genetic and environmental effects.

Change in rGE Over Time

Because genetics and environments can correlate in these ways, it can become more difficult to disentangle genetic and environmental effects. Notably, it has been hypothesized that active *r*GE becomes stronger as children age and become more able to influence their environments, whereas passive *r*GE is at its strongest when children are young (Scarr & McCartney, 1983; Lenroot & Giedd, 2011). In support of this hypothesis, Marceau et al. (2016a) found that nonpassive *r*GE (i.e., active or evocative) for positivity between parents and children increased from 10-18 years, and passive *r*GE for positivity between mothers and children decreased, as the children aged. However, it is also noteworthy that, even within this study, these effects were not wholly consistent as there was no change in *r*GE over time for negativity, as opposed to positivity, between parents and children. Thus, studies investigating genetic effects in early childhood benefit from accounting for these different types of *r*GE, and research investigating how the different types of *r*GE vary over time would help the field understand how genetic influences may confound genetically-sensitive results at different developmental periods.

In both adoption studies and statistical genetic studies, researchers can partially account for rGE by examining the effect of the genetic variables in the study on the environmental influence. If the zero-order correlation between the environment (home chaos in this study) and the outcome (externalizing problems) is attenuated when the genetic variable (for example, the PGS) is included, and the genetic variable is correlated with the environment, passive rGE is indicated

(see Marceau et al., 2016b). In addition, under the Behavioral Genetics approach, issues of *r*GE can be partly handled using an adoption framework. That is, one can start to disentangle specific genetic and environmental effects by looking at children raised by individuals who are not genetically related. Because birth parents cannot create their children's environments, passive *r*GE is controlled, but evocative and active *r*GE may still obscure genetic and environmental effects. In both adoption studies and statistical genetic studies, researchers can partially account for rGE by examining the effect of the genetic variables in the study on the environmental influence. If the zero-order correlation between the environment (home chaos in this study) and the outcome (externalizing problems) is attenuated when the genetic variable (for example, the PGS) is included, and the genetic variable is correlated with the environment, passive rGE is indicated (see Marceau et al., 2016b). Using another strategy, Salvatore et al. (2015) also partially addressed *r*GE in their study by regressing their polygenic score onto their environmental variable and vice versa and using the residualized variables to run sensitivity analyses, partialing genetic and environmental effects. Gene-environment correlation can make it difficult to disentangle genetic and environmental effects. However, study designs like the parent-child adoption design, as well as statistical testing and controls, can alleviate some of the uncertainty and allow for more valid and reliable results. The studies in the present thesis attempt to disentangle genetic and environmental effects using these methods.

Gene x Environment Interactions

Gene-by-environment interactions, instances in which genetic effect is strengthened or diminished within an environmental context or vice versa (Duncan & Keller, 2011), are similar to *r*GE in that they help to explain how genetic and environmental influences are intertwined and shape traits. Understanding measures of the environment in discussions of genetic effect is vital, as genetic effects do not exist in isolation. There are several models of GxE that may fit the results of this research: the diathesis-stress model, the differential susceptibility model, and the vulnerable-stable model (see Table 3 for a brief overview of each model). As discussed above, moderation of environmental effects by genetic influences may represent shifts in biological response to stimuli – i.e., genetic influences may make an individual more or less responsive to specific environmental stimuli, strengthening or weakening the effect of that environment. However, explanations also exist for moderation of genetic influences by the environment, either

through increased agency in low-risk/beneficial environments (e.g., the bioecological model, Bronfenbrenner & Ceci, 1994) or environments that trigger genetic/biological responses, as in the diathesis-stress model.

Diathesis-Stress Model

The diathesis-stress or dual-risk model focuses primarily on an individual's vulnerability to negative environmental circumstances (Ingram & Luxton, 2005). The diathesis-stress model of gene-by-environment interaction (Figure 1; see Rende & Plomin, 1992; Rosenthal, 1963) states that an individual may have a predisposition for a trait (diathesis) that is expressed under specific circumstances (stress). Evidence for the diathesis-stress model relies on a pattern wherein the negative impact of genetic risk (e.g., parents with more externalizing problems or high PGS) is triggered in contexts of greater chaos, but has little effect on its own, resulting in main effects of chaos regardless of genetic risk and main effects of genetic risk only in high chaos homes. In the diathesis-stress model, because the effect of home chaos is triggering increased effect of genetic risk, children with both genetic and environmental risk will have the greatest levels of externalizing (Rende & Plomin, 1992; Rosenthal, 1963)

Differential Susceptibility

The differential susceptibility model (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Figure 2) posits that genetic influence moderates individuals' susceptibility to environmental effects - good or bad - simply by increasing the individual's reactivity to their environment. In the case of this research, to find support for the differential susceptibility model, individuals at high genetic risk would be expected to show greater externalizing problems in high-chaos contexts and lower externalizing problems in low-chaos contexts, compared to individuals with low genetic risk. In other words, low genetic risk individuals would be expected to react less to the chaos in their environment. Importantly, patterns of interactions supporting diathesis-stress are functionally indistinguishable from those of differential susceptibility when examining only poorer environments, and thus determining which theory best fits the data requires examining differences (or the lack thereof) in externalizing problems in both low- and high-genetic-risk children in both low- and high-chaos households.

Vulnerable-Stable

The vulnerable-stable model (Figure 3; Luthar et al., 2000) in the literature posits that a problematic outcome like externalizing is typically high when the individual is in a risky environment, but when they are also at high genetic risk, the environmental effect diminishes and the trait is primarily driven by genetic effects (Wang, Pandika, Chassin, Lee, & King, 2016). In this thesis, to find support for the differential susceptibility model, individuals in high chaos environments would be expected to evidence high externalizing problems regardless of their genetic risk, but, as genetic risk increases, the effect of home chaos would decrease without a corresponding decrease in observed externalizing problems. In this model, only children with neither environmental nor genetic risk that predispose them for externalizing problems are expected to exhibit low levels of externalizing problems. Although there is evidence for each of the other models in the literature (e.g., Kochanska, Kim, Barry, & Philibert, 2011), regarding specifically chaos literature, the vulnerable-stable model seems somewhat more common.

However, it is likely that each of these models – differential susceptibility, diathesis-stress, and vulnerable-stable – fits better or worse depending on the level to which a trait is genetically influenced and how susceptible that genetic influence is to environmental effects. Although this thesis specifically hypothesizes that there will be moderation of home chaos effects by genetics most aligning with the vulnerable-stable model, given prior evidence for other models when examining similar traits and environments, it is possible that results will fit a different model.

Table 2. Expected Patterns of Results for Primary Possible Models of GxE

Model	**Expected Pattern of Results**
Diathesis-Stress	At low genetic risk, participants at low and high home chaos will show relatively comparable externalizing problems, allowing for main effects of home chaos. At high genetic risk, the effect of high home chaos will increase, but there will be little change in externalizing for participants in low-chaos homes.
Differential Susceptibility	At low genetic risk, participants at low and high home chaos will show relatively comparable externalizing problems, allowing for main effects of home chaos. At high genetic risk, the effect of home chaos will increase such that participants in high-chaos homes will show greater externalizing problems and individuals in low-chaos homes will show lower externalizing problems.
Vulnerable-Stable	At low genetic risk, individuals in high-chaos households will display high externalizing problems whereas individuals in low-chaos households will display relatively low externalizing problems. At high genetic risk, individuals in both low- and high-chaos households will show high externalizing problems, but the effect will be driven primarily by genetics rather than the environment.

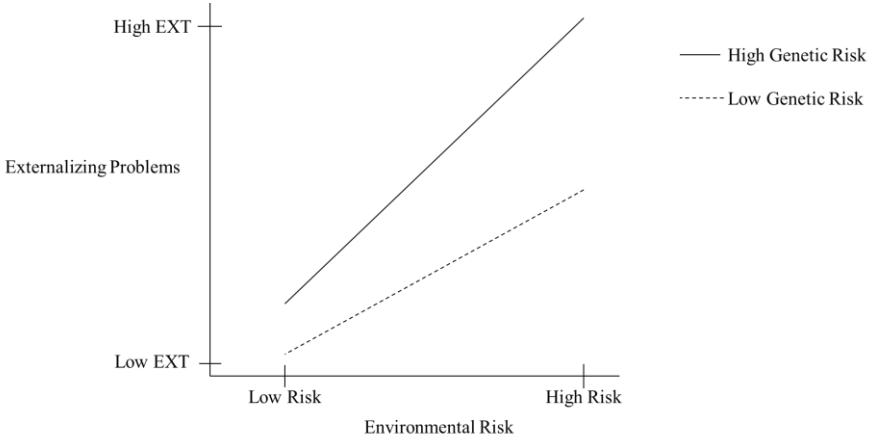

Figure 1. Diathesis-stress model of GxE

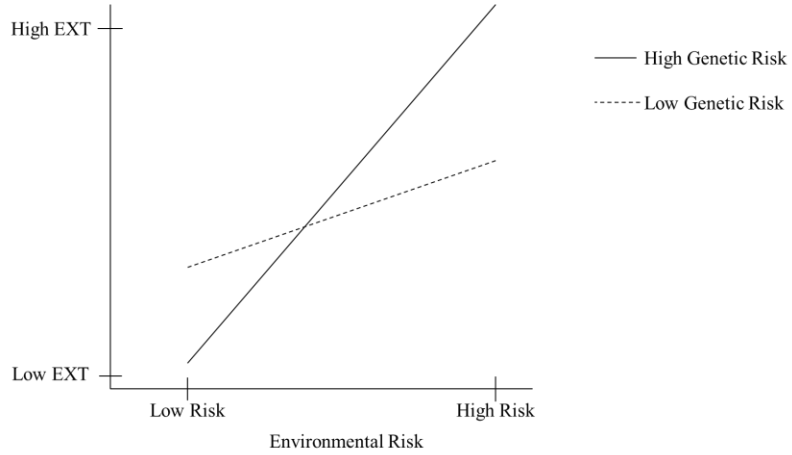

Figure 2. Differential susceptibility model of GxE

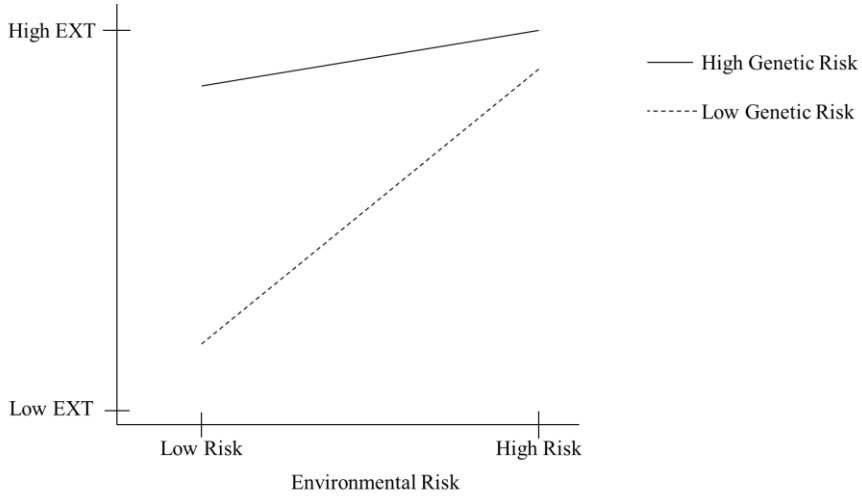

Figure 3. Vulnerable stable model of GxE

Note: Figures shown indicate an extreme example of their respective model and do not represent actual data. Actual interactions will use continuous variables for both genetic and home chaos effect

Home Chaos Interactions

Home Chaos as a Moderator

Most investigations of moderation with home chaos as a variable examine how home chaos may moderate other effects. For example, Coldwell, Pike, and Dunn, (2006) found that household chaos, as rated by parents, moderated the effect of harsh/sensitive parenting on children's problem behavior such that a more chaotic household exacerbated the effect of harsh parenting on problem behaviors for children age 4-8 years. Additionally, home chaos has been shown to moderate genetic effects on externalizing such that genetic influences on externalizing problems were stronger in more chaotic homes (Wang, Deater-Deckard, Petrill, & Thompson, 2012).

Moderation of Home Chaos

However, a case for investigations into the moderation of the effects of home chaos was outlined in Fiese and Winter (2009), wherein it was discussed that the effects of home chaos were not static between high and low SES households and an understanding of how SES and other factors moderated the effects of chaos could be useful for identifying at-risk children. Even so, moderation of the effect of home chaos remains rare as a focus of study. Of note, Shapero and Steinberg (2013) found that the effects of home chaos, as rated by mothers, on total behavior problems (internalizing and externalizing) in adolescence was moderated by the mother's emotional reactivity, such that mothers with greater emotional reactivity saw more of an effect of home chaos on adolescent problem behaviors. However, there are two notable caveats for the results of this study. First, the effect of home chaos on adolescent problems seems to be driven by internalizing, rather than externalizing problems, which is at odds with other research suggesting a closer relationship between home chaos and externalizing than home chaos and internalizing (Dumas et al., 2005). Second, the main effect of home chaos on both externalizing and total problems in adolescence was no longer present when childhood externalizing problems were included in the model.

Although it does not relate perfectly to the key variables in these studies, gender has also been shown to moderate the effects of home chaos on temperament in children age 18 months, with boys specifically showing more emotional negativity if they were from households that

were more disorganized, noisy, or crowded (Matheny & Phillips, 2001). It is unclear whether this moderation would extend to the effects of home chaos on externalizing problems, but there was no moderation by gender on the effects of chaos on externalizing in the sample of Pakistani children mentioned previously (Shamama-tus-Sabah, Gilani, & Wachs, 2011). Thus, there is some evidence for moderation of the effects of home chaos by personal and environmental factors, but despite the probable genetic influences involved in home chaos and externalizing problems, there are few studies of home chaos interactions using genetically-sensitive research methods.

Gene x Home Chaos Interactions in the Literature

Quantitative Genetic Studies

There has been some research investigating gene-by-environment interaction in externalizing problems in childhood, but results for gene x home chaos interactions are far from definitive. Notably, Wang, Deater-Deckard, Petrill, and Thompson (2012) used a twin-design to investigate how household chaos moderated genetic variance and covariance between externalizing problems and attention regulation through childhood (ages 4-7 years in wave 1 and 6.5-10 years in wave 3). They found that, in high chaos households, genetic effects on externalizing decreased, fitting with the standard vulnerable-stable model, but this moderation was only significant in their earliest wave of data. Additionally, genetic variance in externalizing was greater in high chaos homes. Notably for this study, twin studies can only find moderation of genetic influences by the environment and additionally, and the authors did not control for *r*GE. Thus, it is possible that effects were confounded by both chaos and externalizing problems being genetically influenced.

Statistical Genetic Studies – PGS

Although Wang et al. (2012) is, to my knowledge, the only quantitative genetic study investigating the interactions of genetic risk and home chaos for externalizing problems, there has also been some research on this area using statistical genetic techniques. One study (Wang et al., 2016) assessed family disorganization as moderated by a PGS of choice impulsivity to predict adolescent-reported choice impulsivity (e.g., an inability to wait for a larger reward when

offered an immediate smaller reward) and alcohol use in adolescence. Authors relate their findings to transcription of genes coding for D1 and D5 dopamine receptors, which may indicate that the availability of dopamine receptors moderated reactivity to family disorganization, a measure similar to household chaos/disorganization but focusing more on routine and predictability of the caregiver, with less attention to noise and crowding. Their PGS was composed primarily of dopaminergic genes (e.g., DRD2, DRD4, COMT), which have been previously associated with ADHD and aggression (Farbiash et al., 2014; Chen et al., 2005). Their score included 7 total alleles and was not weighted, representing only the total number of putative 'risk' alleles rather than the predicted importance of those risk alleles. The PGS predicted both choice impulsivity and alcohol use, and the authors found a gene-by-environment interaction such that greater family disorganization predicted greater choice impulsivity in adolescents who were at low genetic risk for choice impulsivity and lower family disorganization predicted greater choice impulsivity in adolescents who were at high genetic risk for choice impulsivity. That is, for participants who were not predisposed for choice impulsivity, a disorganized family environment had a greater effect. These results align with a vulnerable-stable model, wherein genetically at-risk individuals are less, not more, responsive to environmental stimuli. However, Salvatore et al. (2015) found an interaction fitting with the diathesis-stress model in their investigation of genetic effect on externalizing problems using parental monitoring and peer substance use instead of home chaos for their environmental effects, and (like Wang et al., 2016) they examined externalizing in adolescents rather than children.

Heritability Over Time

As noted above, heritability of externalizing problems has been found to increase over time. Porsch et al. (2016) found an increase from ~65% to 70% from ages 7-12 for aggression among boys, although notably the pattern was reversed for girls. McGue et al. (2006) similarly demonstrated, using the ACE model, that heritability for adult disinhibitory psychopathology (~75%) was higher than heritability for adolescent problem behaviors (e.g., drug use, police contact, and sexual activity; 21%), with greatly decreased contribution from the shared environment. Increasing heritability by age can likely be partially attributed to the increased difficulty of finding genetic effects in children as children have less control over their own

actions, and thus genetic influences on their behavior tend to be weaker (Burt et al., 2009). However, as noted above, different phenotypes and different raters may influence how the heritability of externalizing problems changes over time. Regardless, the increase in genetic influence with age is important to note for this thesis because this research is working with young children, and thus effect sizes may be small in this sample, especially compared to studies using children in later childhood or adolescence. Conversely, because time moderates the relative variances accounted for by genetic and environmental influences and genetic variance will be minimal at the ages in this study, home chaos, as a shared environmental variable, may be particularly effective.

Marceau et al. (2012), using a twin sample and observational ratings of externalizing problems, rather than self-report, also found that only the sample with older participants (ages 10-18 years), and not participants in middle childhood (ages 6-10 and 7-13 years in two respective samples) showed genetic influences on observed externalizing problems. However, this study also indicated that a large proportion of the variance at all ages was attributable to shared environmental effects and highlighted the importance of the shared environment on externalizing problems. However, Rhee and Waldman (2002) found, in a meta-analysis of twin and adoption studies, that age moderated the genetic effect such that there was a small decrease in the variation captured by genetics from childhood to adolescence and adolescence to adulthood. Notably, this pattern of results differs from that noted above where genetic influence increased over time and the influence of the shared environment decreases. The authors also make note of this discrepancy, suggesting that confounding of moderators may have contributed to these results, which may also be pertinent to this thesis as home chaos may be similarly confounded.

Statistical Genetic Studies – Non-PGS

Farbiash, Berger, Atzaba-Poria, and Auerbach (2014) investigated whether the DRD4 gene moderated the effect of parental levels of ADHD on the child's development of aggression in preschool. Although, results indicated moderate prediction of aggression by the DRD4 gene mediated by home chaos, there was no evidence for moderation of the effects of home chaos by DRD4 risk. Given the low reliability of candidate gene studies, these results are not surprising, but authors propose that a sample low in ADHD/attention problems may have contributed to the

lack of an association. It is also noteworthy that this study was an extension of research indicating moderation of the effect of one environmental influence (inconsistent parenting) by the DRD4 gene on aggression (Martel et al., 2011), rather than on ADHD, and it is possible that interactions of genetic risk and home chaos are more salient for aggression than ADHD/attention problems.

In all, these studies provide evidence that there is interplay between home chaos and genetic influence predicting externalizing behaviors. However, the way in which genetic and environmental effects interact, particularly during childhood, is unclear, and attention to specific phenotypes of externalizing seems to be important for understanding the interplay between chaos and genetic risk. Among studies that test for interactions between home chaos and genetic risk, interactions most consistently fit with the vulnerable-stable model. Thus, this thesis hypothesizes the vulnerable-stable model, but acknowledges a general need to determine the shape of the interaction to understand better whether and how genetic effects moderate the influences of the home environment.

Home Chaos as a Genetically Influenced Variable

Quantitative Genetic Evidence

One confounding factor in these studies is the possibility that home chaos is a genetically-influenced trait – i.e., that any measure of home chaos will be influenced by one's genetic predisposition for traits that may increase home chaos, like externalizing problems and self-regulation. One investigation of home chaos (Hanscombe, Haworth, Davis, Jaffee, & Plomin, 2011) indicated low to moderate additive heritability in later childhood in the TEDS using a twin design (a^2 = 26% for children age 9 and a^2 = 15% for children age 12 years). Butcher and Plomin (2008) also reference a heritability of 50% for home chaos at age 9 years in this same sample but cite unpublished work. Similarly, a separate investigation of the heritability of chaos in earlier childhood Heart (Petrill, Deater-Deckard, & Thompson, 2007) found an additive heritability of 27% among kindergarten through 2nd graders (roughly ages 5-7 years) in the Western Reserve Reading Project.

Statistical Genetic Evidence

Farbiash et al. (2014) did not find an association between DRD4 risk and home chaos, but one should note that this was a candidate gene study with all of the caveats included. Further, one study, to my knowledge, has directly investigated measured genetic influence on home chaos. Butcher and Plomin (2008) conducted a GWA analysis of home chaos as measured using the CHAOS scale (Matheny, Wachs, Ludwig, & Phillips, 1995), assessed via parental report and composited for child's age 3 and 4 years in the Twins Early Development Study. Authors selected 41 SNPs to test for an association with chaos after quality control. Power analyses in this study indicated 99% probability of discovering associations accounting for more than 0.5% of variance, but none of the 41 SNPs was significantly predictive of home chaos. However, the sample for this GWAS was small (3,529), and it is possible that, given the complexity of home chaos as a trait, effect sizes would not have reached $b = 0.005$. Despite the null evidence from interrogations of a few specific genetic variants, it is clear from quantitative genetic studies that home chaos is, itself, a genetically influenced variable, and thus the constructs are intertwined in these studies. By use of the parent-child adoption design and tests for evocative *r*GE, this research seeks to partially disentangle home chaos and genetics and provide more specific analysis of the effects of home chaos and how such effects may be genetically moderated. However, even after such controls, the entangled nature of home chaos and genetic influences represent a limitation for this work.

Triangulation of Study Results

Types of Triangulation

Triangulation of results references the use of multiple methodologies to pinpoint an effect (Jick, 1979). In the social sciences, triangulation stems from the argument that, when attempting to understand the variability of a trait, one must use multiple methods to assess that variability so that the biases of each method can cancel each other out and thus produce more reliable results (Campbell & Fiske, 1959). Following this logic, it stands to reason that one can provide the best argument for the validity of their results by using two (or more) methods to assess an effect and evaluate convergence of results. Triangulation can take two forms: 'between methods' and 'within methods' (Jick, 1979). Between-methods triangulation centers on using two or more distinct methodological approaches to assess a single phenomenon, whereas within-method

triangulation involves the use of multiple techniques within a method (e.g., several scales that assess the same construct) to assess the phenomenon. Triangulation distinguishes itself from the concept of constructive replication in that constructive replication indicates that subsequent studies strengthen the evidence for an effect only if they improve on prior studies (Rutter, 2007). Triangulation of both study designs and variable measures represents a path for generating more reliable conclusions from data and addressing issues of variable convergence when examining a trait like externalizing problems. By utilizing both within- and between-method triangulation in this thesis, this research informs on both quantitative and statistical genetic methodologies, as well as measure of home chaos.

Triangulation Criteria

Lawlor, Tilling, and Smith (2016) note five criteria as the minimum for valid triangulation. First, results must come from at least two different approaches with differing and unrelated key sources of potential biases. Second, the different approaches must address the same underlying causal question. Third, each approach should consider the duration and timing of exposure when comparing results. Fourth, the key sources of bias for each method must be acknowledged when comparing results. Fifth, the expected direction of the effect of the bias must be stated for each method. Thus, each of these criteria must be met to establish a valid attempt at triangulation.

Triangulation in This Thesis

Genetic Effect

This thesis uses both quantitative (parent-child adoption) and statistical (PGS) genetic designs to approach the question of how home chaos and genetics contribute to externalizing problems in childhood, thus the first two criteria for triangulation – the use of two different approaches with unrelated key sources of potential bias attempting to address the same underlying causal question – are met. Note, although the Behavioral Genetics approach does not lend itself to questions of whether a specific influence causes a trait, the use of the specific methods in these studies is not to indicate whether the genetics are causal, but to investigate the shape of the interaction between genetic effects and home chaos and provide the foundation for

later causal work. Thus, although this research does not specifically address causation, it still addresses an underlying causal question.

These studies also make use of longitudinal data (discussed below) to address the timing and duration of effects. Because genetic effects are present throughout the lifespan – although certain genetic effects may be more or less prevalent at different stages of development – I assume that average duration of genetic effect will match across study 1 and study 2 because the ages between the studies are similar. Direction of effect in both studies has been stated, but again, it is expected that individuals who are genetically predisposed for externalizing problems will show higher levels of externalizing problems in both studies and that genetic effect will moderate the association between home chaos and externalizing problems following the vulnerable-stable model. Thus, by comparing results between the two studies, this research provides insight into both genetic effects (and their interaction with home chaos) on externalizing problems and how quantitative and statistical genetic methodologies capture the variance in a trait.

Home Chaos

This thesis uses a different measure of household chaos in each of the two studies. Household chaos is often assessed with a shortened version of the Chaos, Hubbub, and Order (CHAOS) scale (Matheny et al., 1995), which consists of a series of questions gauging the level of noise and crowding within the household, as well as consistency of the child's routine. However, other researchers have examined household chaos in datasets that did not include the CHAOS scale. For example, Vernon-Feagans et al. (2012) used factor analysis of ten features of household chaos indicated in prior literature to derive two factors - disorganization and instability - that were used to assess home chaos. The derived factors have been used in several studies (Berry et al., 2016; Garrett-Peters et al., 2016; Mills-Koonce et al., 2016; Vernon-Feagans et al., 2016). Instability commonly appears in home chaos literature, measuring aspects of family mobility, changes in caregiver, and how often individuals moved into or out of a household (see Vernon-Feagans et al., 2016) but is considered a separate construct from chaos. Similar to the CHAOS scale, Vernon-Feagans' measure of disorganization was built from measures of household noise (e.g., number of hours that the TV is on each day) and crowding (household density: a function of the number of members of a household divided by the number

of rooms in the home). However, the Vernon-Feagans' scale differs in that it does not assess a child's routine and instead evaluates the cleanliness of the home. Vernon-Feagans et al. (2012) explains that routine was left out partially because their study focused on the first three years of life, and sleep and eating schedules are often not set until the child reaches toddlerhood.
This measure of household disorganization has been used previously in the literature to measure the level of discord in a household. Mills-Koonce et al. (2016), as noted in the first section on chaos, used this measure and found that higher scores when a child was 3 years of age predicted increased conduct problems and callousness when the child was in first grade, even when caregiver behavior (i.e., harsh/sensitive parenting) was included in the model. Thus, the measure seems to predict similarly to the CHAOS scale, although, to my knowledge, there has been no direct comparison. This approach is notable because the dataset that is used for study 2 of this thesis does not have a specific indicator for household chaos. Thus, the measure of household chaos for study 2 is indexed by a composite score created from parent-reports of noise, household crowding, and home cleanliness, at child's 3 years, fitting with the measures laid out by Vernon-Feagans (2012). By using this separate measure to assess home chaos, this research is also able to assess triangulation of the main effects of home chaos on childhood externalizing problems or identify differences in patterns of findings by dimensions of home chaos. Biases of these measures will be discussed with results and direction of effect was stated above. Thus, as with the genetic approaches, using these measures of home chaos will both provide insight into the effect of home chaos and how these measures capture chaos as a construct.

Moderation

The attempt to triangulate moderation in these studies is another instance of external triangulation. That is, the designs of the two studies are still varied – as discussed in the triangulation of genetic effect – and thus the attempt to triangulate moderation is, more or less, the same as the attempt to triangulate a genetic effect. Further, the varied measures of home chaos between the studies strengthen this attempt at triangulation because the different measures are more likely to have different measurement error. Thus, this attempt at triangulation meets the first criterion for triangulation by using two different genetic approaches, as well as two different measures of home chaos. Notably, varying both variables in the moderation makes these studies less likely to converge, but this is not a weakness in the attempt at triangulation because,

assuming that the variables still tap the same underlying characteristics, failure to converge should be due to error, and thus the results are still informative (discussed below). This attempt then meets the second criterion for triangulation in that it still attempts to address the same question of genetic/environmental causality. As discussed in the two previous sections, this attempt also meets the third criterion by using variables from the same ages in large samples and can thus assume that these studies account for the duration and timing of exposure to the variables. Finally, as stated previously, it is expected that both higher inherited risk for externalizing problems and greater home chaos will predict greater externalizing problems and that the interaction between the two will fit the pattern of the vulnerable-stable model.

Failure to Converge (in Triangulation)

In cases where the results of attempts to triangulate an effect fail, the biases of each method should be carefully considered to evaluate what further research is needed to establish the effect (Lawlor et al., 2016). Further, although it is unlikely that the triangulating studies will produce the same wrong answer, it is possible for one study to produce one wrong answer, and thus, in addition to the attention given to possible overlapping bias, replication of study results is still important. Overall, effective use of triangulation lends additional credence to the validity and reliability of a study's results. Moreover, attempts at triangulation are not simply attempts to replicate an established effect, and failures of convergence provide as interesting of information as successful convergence by highlighting that the differences in study design or construct measure impact the results enough to change the effect. Such results are informative for the field as they indicate that the designs or measures may either need to be modified to better address the questions and constructs under investigation or that the designs and measures may be tapping into a different source of variance altogether.

However, there is no single study approach – replication, triangulation, or other – that can provide the answer to a complex question of etiology within two studies. Regardless of the results of these studies, additional research will be necessary to pin down whether the findings from this study were true through replication and additional triangulation attempts, or why they were not, through the same process. Triangulation is a tool that lends itself to simultaneous investigation of both constructs and the measurement error of those constructs. Therefore, failure to converge still provides insight into the core aspects of these studies, namely the measure of

genetic influence, home chaos, their interactions, and externalizing problems. However, it should also be noted that it will not be possible, in these studies, to confirm the source of any failure to converge. Rather, sources will be proposed, and future research will need to be conducted to determine the specific cause or causes. Despite this limitation, by following recommendations by Lawlor, Tilling, and Smith (2016), the insight granted by failures to converge can be used to highlight next steps for understanding what about these measures or constructs led to the failure to converge.

The Present Study

To date, the literature on gene-by-chaotic home environment interactions is minimal and in need of further research using both quantitative and statistical genetic methodologies, especially as used to triangulate findings. This thesis investigates how the levels of children's household chaos from age 3 to 4.5 years interact with their genetic risk on externalizing problems in middle childhood (age 7 years), addressing two major objectives. First, this thesis uses a parent-child adoption approach to assess interactions of genetic predisposition for externalizing problems and chaotic home environment from age 3 to 4.5 years in externalizing problems at age 7 years. Second, this thesis assesses the same interactions using a PGS from a longitudinal study including GWAS data. As part of this second objective, this thesis investigates the effectiveness of PGS derived from genetic variants associated with domains of externalizing problems in the wider literature in predicting externalizing problems. Gene set analysis is used to assess whether and how the SNPs used for each PGS relate to specific biological function. Finally, results from the thesis aims are used to triangulate the effects of genetics and home chaos to provide insight into the validity of the results.

This research expands upon the established literature by investigating genetic effects as a context in early childhood, using both quantitative and statistical methodologies, and, further, by using an environment understudied in tests of GxE – home chaos – that has nevertheless been indicated as important in the development of behavior problems. This research also expands on prior use of PGS in predicting externalizing behaviors, as previous efforts, to my knowledge, have not taken additional steps to assess the biological effects of the SNPs used in the PGS. Further, previous PGS created using genes of known effect have not been comprehensive enough to address much of the variance in externalizing problems. Thus, the PGS was designed to be

more comprehensive than those used previously and be used in a large sample to increase the reliability of results. Finally, use of triangulation between the two genetically sensitive approaches provides insight into how these approaches address variance in externalizing problems, and, by using an unrelated sample in each study, provides basic insight into possible generalizability of any significant effects. These contributions are in addition to the replication of genetic measures and home chaos predicting externalizing in two separate samples.

Hypotheses

Fitting with the vulnerable-stable model of gene-by-environment interaction (Luthar, Cicchetti, & Becker, 2000), I hypothesize that both more instability in a child's home environment from age 3 to 4.5 years and genetic risk will be associated with high levels of child externalizing problems at age 7 years in both the quantitative and statistical approaches but that the effect will be primarily genetic when genetic risk is high. Assessments of biological function through gene-set analysis in the second study are exploratory. These studies take a novel approach that integrates quantitative and statistical genetic methods and theories from Behavioral Genetics and Developmental Psychology to investigate GxE mechanisms underlying child externalizing problems.

I use two datasets for this research: The Early Growth and Development Study (EGDS) for study 1 and the Avon Longitudinal Study of Parents and Children (ALSPAC) for study 2. These datasets are well-suited to identifying both latent and specific genetic as well as environmental influences on externalizing behaviors. Although neither dataset is perfect for addressing the aims of this research, used in conjunction, they provide an adequate test for this model. The first study (objective 1) uses data from EGDS, a prospective US-domestic parent-child adoption study of 561 sets of birth parents, adoptive parents, and adopted children to assess the contributions of genetic influences and the home chaos environment in externalizing problems. The second study (objective 2) uses data from ALSPAC, a birth cohort study tracking the health of ~15,000 families in the Bristol area of the United Kingdom that includes GWAS data on 8,952 children, and a polygenic scoring approach to assess the contributions of genetics and the home chaos environment on externalizing problems. Each study is detailed below.

CHAPTER 3. METHOD

Participants

Data for study 1 comes from EGDS. The original EGDS sample consisted of *n* = 567 adoptive mothers and *n* = 552 adoptive fathers, along with *n* = 554 birth mothers and *n* = 208 birth fathers from two cohorts (Leve et al., 2013). Of these families, *n* = 562 had at least partial data on birth parent psychopathology, early home environment from age 3 to 4.5 years, and behavior problems at age 7 years, and of these, *n* = 416 had complete data. All families with partial data, *n* = 561, were included in the sample for hypothesis testing. Adopted children's birth dates ranged from January 2003 to May 2009. Median age at adoption placement was 2 days (M = 6.2, SD 12.45). The sample was 42.8% female and 55.6% Caucasian, 19.3% multiracial, 13% African American, 10.9% Latino, and less than 1% Asian, American Indian, and unknown/not reported (Table 3, Column 2, Row 1-2).

Data for study 2 comes from ALSPAC, a British Cohort Study of 15,247 youth followed longitudinally since birth via 59 questionnaires and 9 clinical assessments (age 7-17 years). ALSPAC was designed to assess how different genotypes and environments interact to affect development. Of the 15,247 youth involved in the study, *n* = 8952 of which have genome-wide genetic data, repeated measures on the home environment from birth through age 4, or behavioral data at age 9 years. The sample consists of youth born to women with expected delivery dates between the 1st of April, 1991 and the 31st of December, 1992 (Boyd, et al. 2013), plus additional children added to bolster the sample when the oldest children in the study were approximately 7 years of age. Attrition from the study was greatest when children were infants and adults. The full sample was 49% female and 96% white, 3% other, and <1% Asian or Black (Table 3, Column 3, Row 1-2; Fraser et al., 2013). Ethical approval for the study was obtained from ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The study website contains details of all available data through a searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). The study and cohort are further described elsewhere (http://www.bristol.ac.uk/alspac/).

Measures

Externalizing Problems

In the EGDS dataset child externalizing problems were measured using adopted mothers' responses to the Child Behavior Checklist (CBCL; Table 3, Column 2, Row 3; Achenbach, Edelbrock, & Howell, 1991). The CBCL was administered as an online survey at child's age 7 years (Mean = 7.04, SD = 0.18). Mothers were asked to respond with 0 (Very true), 1 (Sometimes true), or 2 (not true) to 99 statements that describe their child's behavior in the two months preceding the survey. Of these 99 statements, 35 related to aggressive and rule-breaking behavior and were used to create a measure of general externalizing problems. Each parents' responses were summed separately to create parent-specific indicators of externalizing problems. These parent reports were then averaged to create the measure of externalizing problems for this study. If one parent was missing data, the remaining parent's data was used as the average. Raw scores ranged from 0-70 (mean = 7.06, SD = 5.62). The Child Behavior Checklist has shown to be an accurate and reliable tool for assessing externalizing problems (Hudziak, Copeland, Stanger, & Wadsworth, 2004). Cronbach's $\alpha = 0.89$.

Externalizing problems for children in ALSPAC were measured via parent report of the SDQ in middle childhood (Table 3, Column 3, Row 3; Goodman, 2001). Data for the SDQ was collected as part of a mother-report mail questionnaire when the child was 6 years 8 months of age (Mean = 6.79, SD = 0.11). Mothers responded to questions of whether certain behaviors (e.g., child has been considerate of other people's feelings) applied to their child with 0 (does not apply), 1 (applies somewhat), 2 (certainly applies). Raw scores ranged from 0-33 (mean = 7.29, SD = 4.72 for age 7). As with the Child Behavior Checklist, the SDQ has been used to measure externalizing problems in previous research (Muris, Meesters, & van den Berg, 2003). Scores on the SDQ and CBCL have been shown to be comparable, with correlations of $r = 0.84$ for externalizing/conduct problems (Goodman & Scott, 1999). Cronbach's $\alpha = 0.55$.

Home Chaos

Chaos in the home environment in the EGDS dataset was measured using adoptive parent responses to a shortened version of the Chaos, Hubbub, and Order Scale (CHAOS; Table 3, Column 1, Row 4; Matheny, Wachs, Ludwig, & Phillips, 1995) at child's age 4.5 years, collected

via web survey. Parents responded with 1 (Definitely Untrue), 2 (Somewhat untrue), 3 (Not really true or untrue), 4 (somewhat true), or 5 (definitely true) to six statements describing their home (e.g., It's a real zoo in our home). Three questions were reverse coded such that high scores on this measure represented less chaos/more order. Mothers' and fathers' responses were summed separately to create parent-specific measures of household chaos. The final score for chaos was created by averaging mothers' and fathers' responses. If one parent was missing data, the remaining parent's data was used as the average. Raw scores ranged from 6-30 (mean = 23.21, SD = 3.31) and were all coded such that higher scores indicate lower chaos. Cronbach's $\alpha = 0.60$.

Unlike in EGDS, home chaos was not directly measured in ALSPAC, and thus a composite score was created based on measures collected in ALSPAC that relate to those in the CHAOS scale and the scale used by Vernon-Feagans et al. (2012). Specifically, chaos is measured with primary-caregiver reports of household noise, physical environment (cleanliness), and household crowding, received as part of a survey sent to mothers at child's age 2-4 years (Table 3, Column 3, Row 4; Golding, Pembrey, & Jones, 2001). The measure of household noise consists of responses to the questions, "How much of a problem are the following for you and your family: noise traveling between the rooms of your home, noise from other homes, noise from outside on the street." Responses ranged from 1 (serious problem) to 3 (not a problem). The measure of household crowding was derived from the number of persons in the home divided by the number of rooms in the home. Household cleanliness was measured with two responses to the question: "How would you rate your home in relation to that of other homes with young children?" Parents responded with both a rating of cleanliness from 1 (much cleaner) to 5 (much less clean) and tidiness from 1 (much tidier) to 5 (much less tidy). Each measure was standardized to have a mean of 0 and a standard deviation of 1. Final scores were created by averaging together the scores on each item. Cronbach's $\alpha = 0.51$.

Genetic Effect

Genetic risk in the EGDS sample was measured using a composite score created with principal component analyses (PCA; Table 3, Column 2, Row 5; Marceau et al., 2019). The score included birth mother and father measures of symptoms (symptom count), diagnoses (diagnosis count), and age of onset of conduct disorder and antisocial personality disorder

assessed via the Diagnostic Interview Schedule (DIS; Robins et al., 1981), as well as the proportion of first-degree relatives experiencing externalizing problems. Specifically, the proportion of first degree relatives was calculated on the maximum score the birth parent rated each relative on two items, "ever had a hot temper, been in fights frequently, or been involved in stealing regularly", and "ever come into contact with the legal system because of things s/he has done." These scores are the study-approved most comprehensive scores available for genetic risk for EGDS, and have been found to interact with environmental influences (e.g., prenatal and parenting) to predict conduct problems in middle childhood (Marceau et al., 2019).

Genetic risk in ALSPAC was measured with an empirical PGS (Table 3, Column 2, Row 5). GWAS data in ALSPAC was generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. In total, 9,912 children were genotyped using the Illumina HumanHap550 quad genome-wide SNP genotyping platform. Samples with sex mismatch, call rate <95%, unexpected first-degree relatedness, too much or too little heterozygosity, and non-European ancestry were excluded. Data was imputed to 1000 genomes phase 1 version 3 using the Impute2 software (see ALSPAC documentation for further details). Quality control for SNP data was conducted in Plink (Purcell et al., 2007) and PRSice (Choi & O'Reilly, 2019).

To explore the effectiveness of an empirically based PGS, genetic markers indicated in an independent GWAS (Demontis et al., 2019) as predicting diagnoses of ADHD was used as the discovery sample for this study. A discovery sample is a separate sample independent of the test sample used in the analyses in which weights/effect sizes are derived so that associations between SNP and trait are not being calculated in one sample and then used in a score to predict that trait in the same sample. Although the phenotype in the Demontis et al. (2019) sample chosen for the primary PGS does not match the phenotype of externalizing problems used in this thesis, the Demontis study was the largest study on externalizing problems available that also provided summary statistics, which are necessary to weight the PGS. The greater sample size was deemed more important than a well-matched phenotype, but a PGS with a better matched thesis type was also used (see supplementary analyses).

SNPs identified in the discovery sample that are also measured or imputed in ALSPAC were used to create the test set - the specific genetic markers used in study analyses. Specifically, the PGS for this study was created using the summary statistics from Demontis et al. (2019) and

the –prsice command in PRSice (Choi & O'Reilly, 2019). Notably, avoiding sample non-independence requires that GWAS used for the discovery sample should not include data from ALSPAC, which is addressed by using Demontis et al. (2019) as this paper offers several samples that do not contain ALSPAC. The sample used for the primary analyses in this study was the deCODE sample because it offered the largest sample that did not include ALSPAC (n = 5085 cases of ADHD, and n = 131122 controls). However, an unweighted PGS – i.e., a PGS in which the number of risk alleles was not weighted by the effect of the allele – created using SNPs identified in Tielbeek et al. (2017) was also used for sensitivity analyses. Tielbeek et al. (2017) offers a larger set of SNPs than Demontis with a sizable sample (n = 16,400) and a sub-clinical externalizing phenotype matching that used in ALSPAC – although, notably, ALSPAC was included in the Tielbeek et al. (2017) analyses and thus correlations between SNPs identified in Tielbeek et al. (2017) and externalizing problems are likely inflated. This PGS was unweighted due to an inability to procure association statistics from this GWAS.

The primary PGS for study 2 were created using effect rather than minor alleles because composites of minor alleles can lead to SNPs of different effect directions canceling each other out, creating less informative PGS. By using effect alleles, the PGS represents the total 'risk'. This PGS was incorporated into the model as an exogenous variable. Similarly, as genetic effects in the EGDS sample were assessed directly through the composite score of birth parent risk for psychopathology, they were also included as an exogenous variable. The variables to be used in these studies were constructed and cleaned using R, SAS, PLINK and PRSice.

Covariates

Covariates for both studies include child's sex and ethnicity, caregivers' education, primary caregiver's income, prenatal risk, and earlier externalizing problems (age 4.5 years, using the same measures). Prenatal risk in EGDS was quantified using a Perinatal Risk Index (PRI) – a scale constructed from information provided by birth mothers using data collected on pregnancy risks and complications including weight gain, drug use, labor complications, and other influences found to place the child at greater risk for health and behavior problems. Responses were coded following procedure from McNeil & Sjöström (1995) detailed in Marceau et al. (2016b). Each complication in the score is weighted by the amount of risk it carries to the fetus on a scale from 1-6, where 1 is 'Not harmful or relevant' and 6 is 'Very great harm to or

deviation in offspring'. Prenatal risk in ALSPAC was quantified using the same system to increase comparability, although the actual risks included in the scores differed because of measurement differences across studies. In study 1, openness of the adoption, measured using average reports of adoptive parents' contact with birth parents, was also controlled in order to account for any influences the birth parents may have had on the adopted child's environment (*r*GE). Study 2 controlled for population stratification using PCA, following procedure indicated in Price et al. (2006). Notably, although this method suggests using the 10 principal components with the highest eigenvalues, not all 10 principal components were included in the final analyses of study 2 due to the increased number of variables leading to an unidentified model. Ultimately, only the top eight principal components were included.

Analytic Strategy

After examining the suitability of the data (e.g., missing data patterns, distributions, and violations of assumptions), linear regression analyses were used to investigate how much variance in externalizing problems at age 7 years can be accounted for by chaos in the early home environment and genetic factors. Linear regressions were also used to assess the gene-by-home chaos interaction for child externalizing problems at this age. Analyses were run using R (Lavaan) (Rosseel, 2012) to take advantage of the structural equation modeling (SEM) function's full-information maximum likelihood (FIML) estimation capabilities. Possible sign moderation was also assessed using a Johnson-Neyman plot of the interaction effect.

Finally, in study 2, gene set analysis was performed using the PANTHER Classification System (Mi, et al., 2013) to address whether the SNPs used in the PGS are representative of any specific biological ontology. Specifically, the final gene set used for the creation of the PGS assessed with a Fischer's exact test to determine whether any biological ontologies were overrepresented in the sample.

Table 3. Strengths and Weaknesses, Demographics of ALSPAC and EGDS

	Study 1: EGDS	Study 2: ALSPAC
Study Design	**Parent-child Adoption**	**Birth Cohort with GWAS**
Demographics		
Race/Ethnicity	55.6% Caucasian, 19.3% multiracial, 13% African American, 10.9% Latino, <1% American Indian/unknown/not reported	96.09% White, 3% other, <1% Asian or Black After removing participants who lacked data on all key study variables, sample was 100% White or missing
% female	42.8%	49.69%
Measures		
Home Chaos	Chaos, Hubbub, & Order Scale[1]	Score of household noise, crowding, and cleanliness
Genetic Effect	Computed Risk Scores from Birth Parent Externalizing Problems [2]	Polygenic Risk Scores
Externalizing Problems	Child Behavior Checklist[3]	Strengths & Difficulties Questionnaire[4]
Strengths		
	Ethnically diverse, validated measures, disentangles passive *r*GE , broad indication of genetic effect	Indicates specific genetic markers/biological effect, SDQ is short, less susceptible to population stratification
Weaknesses		
	Does not indicate specific genetic markers/biological effect, susceptible to population stratification, CBCL is long	Ethnically homogeneous, measure of home chaos not validated, entangled passive *r*GE

Note: EGDS: Early Growth and Development Study, ALSPAC: Avon Longitudinal Study of Parents and Children.
[1]Matheny, Wachs, Ludwig, & Phillips, (1995); [2]Marceau et al., 2019; [3]Achenbach, Edelbrock, & Howell, 1991; [4]Goodman,1997

CHAPTER 4. RESULTS

Suitability of Data

Missing Data

The SEM framework allowed for analyses including missing data through full information maximum likelihood (FIML; Enders & Bandalos, 2001). For primary analyses, missing data in the sample were assumed to be missing at random (MAR) as missingness is not expected to vary by any variable not included in the analyses. Additionally, MAR analyses using FIML have been shown to be fairly robust to data that are missing not at random (MNAR; Molenberghs et al., 2004). Although the use of FIML with MNAR data has shown bias, the bias is likely to be less than that for listwise or pairwise deletion or other forms of imputation (Muthén, Kaplan, & Hollis, 1987; Schafer & Graham, 2002). However, patterns of missingness in the data were also assessed and used to contextualize findings. Sources of missingness based on study and demographic variables were assessed using chi-square and Kruskal-Wallis tests.

Specifically, I examined differences in study variables for all participants from both studies across groups where (a) home chaos data were missing versus available or (b) externalizing at age 7 years was missing versus available (to index attrition) using a series of chi-squared tests (for categorical predictors) and Kruskal–Wallis one-way analysis of variance tests (for continuous predictors). The potential predictors of missingness that I investigated included demographic measures used in these studies (parent education and financial difficulties/income), sex, and race, as well as key study variables. Notably, all participants had genetic data in both study 1 and study 2. Significant findings are noted here.

For study 1, Chi-squared tests indicated that participants were less likely to have data on household chaos if their secondary, rather than their primary, caregiver did not progress as far in formal education, suggesting that households in the sample for study 1 were likely slightly more educated than the EGDS sample as a whole. However, there were no other significant predictors of missingness for study 1.

Chi-squared tests indicated that participants in study 2 were less likely to have data on externalizing problems at age 7 if their parents did not have at least a high-school level degree $\chi^2 = 159.62$, $p < 0.0001$, Cramer's V = 0.11, if their household had experienced financial

difficulties $\chi^2 = 94.14$ $p < 0.0001$, Cramer's V = 0.10, and if they were not White, $\chi^2 = 37.03$, $p < .0001$, Cramer's V = 0.07. These same variables were related to missingness for home chaos, $\chi^2 = 133.08$ $p < 0.0001$, Cramer's V = 0.10 for parents' education, $\chi^2 = 232.04$ $p < 0.0001$, Cramer's V = 0.15 for financial difficulties, and $\chi^2 = 29.53$, $p < 0.0001$, Cramer's V = 0.06 for race. Thus, the analytic sample for study 2 is somewhat less disadvantaged than the entire ALSPAC sample. However, sex was not predictive of missingness in this sample. The Kruskal-Wallis indicated that whether participants had data on externalizing at age 7 was also related to two other study variables, externalizing problems at age 3.5 years, $\chi^2 = 22.93$ $p < 0.0001$, and perinatal risk, $\chi^2 = 83.50$, $p < 0.0001$. Perinatal risk was also related to whether participants in study 2 had data on home chaos, $\chi^2 = 15.56$, $p < 0.0001$. That is, participants at greater perinatal risk and participants who had more externalizing problems at age 3.5 were more likely to be missing data at age 7.

Assumptions of Regression

Descriptive statistics for study variables are in Table 4. Additionally, the assumptions of regression, namely linearity of parameters, mean, normality, and homoscedasticity of residuals, autocorrelation of residuals, correlation of variables and residuals, positive variability of variables, and multicollinearity were specifically tested for both studies 1 and 2. It was found that the assumption of homoscedasticity was violated in all models in study 1 except for the first and for models 4, 5, and 6 in study 2. Additionally, all models in study 1 violated the assumption of normality of residuals. To ameliorate these violations, models in both studies 1 and 2 were run using robust standard errors (Robust SE), which do not impose assumptions on the structure of heteroscedasticity and thus addresses the issues of heteroscedasticity. Further, a restricted maximum likelihood (MLR) estimator, which bases estimates on a likelihood function from a transformed dataset rather than the fit of all information so as not to bias estimates, thus addressing issues of non-normality. These adjustments to the model were used in addition to the use of FIML for missing data to minimize bias from imputation or missingness.

Table 4. Descriptive Statistics of Study Variables

	Mean (SD)	N	Min, Max	Skew	Kurtosis
Study 1					
Externalizing Problems (age 7)	7.06 (5.62)	411	0.00, 36.50	1.33	2.34
Home Chaos	6.79 (3.31)	427	0.00, 19.5	0.51	0.26
BP Externalizing Score (Inherited Risk)	0.00 (1.80)	552	-3.74, 4.80	0.08	-0.78
PRI	16.95 (11.84)	562	0.00, 54.00	-0.55	0.50
Externalizing Problems (age 4.5)	12.34 (6.49)	428	0.00, 39.50	1.59	0.39
Parents' Education	0.19 (0.40)	562	0.00, 2.00	2.49	6.50
Household Income	6.15 (3.35)	562	1.00, 12.00	0.17	-1.37
Openness of Adoption	-0.08 (0.90)	421	-2.15, 2.52	-0.10	-0.48
Study 2					
Externalizing Problems (age 7)	1.56 (1.43)	5969	0.00, 10.00	1.01	1.17
Home Chaos	-0.01 (3.15)	6309	-7.34, 16.17	0.63	1.33
PGS	0.01 (0.01)	8804	-0.02, 0.05	0.22	0.27
PRI	9.49 (4.13)	8804	0.00, 30.00	0.66	0.67
Externalizing Problems (age 3.5)	3.62 (2.33)	6843	0.00, 16.00	0.73	0.68
Parents' Education	0.12 (0.33)	7928	0.00, 1.00	2.33	3.44
Household Financial Difficulties	0.10 (0.30)	6671	0.00, 1.00	2.66	5.10

Note: PRI: Perinatal Risk Index, PGS: Polygenic Risk Score, BP: Birth parent, Home chaos was centered for use in the models, Income in study 1 consisted of 12 categories, and parents' education in study 2 was a yes /no question of whether parents had a high-school level degree.

Preliminary Associations

Correlations in study 1 (Table 5 above the diagonal) showed an interesting pattern. First, as expected, home chaos was correlated with more externalizing problems, both concurrently and at age 7. Home chaos was also positively associated with sex, indicating that households in which the child participant was a boy were more chaotic than households in which the child participant was a girl. However, home chaos was not correlated with either household income or adoptive parents' education, indicating that wealthier/higher SES households were not less chaotic as

would have been suspected. Inherited risk (e.g., birth parent externalizing problems) was not correlated with either externalizing problems at age 7 years or home chaos but was correlated with prenatal risk, the other birth-parent variable. Finally, as expected earlier externalizing problems predicted of externalizing problems at age 7 years.

In study 2 (Table 5 below the diagonal), as in study 1, home chaos was positively correlated with externalizing at both ages 7 and 3.5 years, as was the perinatal risk index (PRI). As expected, sex was correlated with externalizing problems such that girls tended to show fewer externalizing problems than boys. Children in households that did not experience financial difficulties also showed fewer externalizing problems than children in households that had experienced financial difficulties. However, unlike study 1, the PGS was not correlated with any variable. Additionally, parents' education was positively correlated with both externalizing problems and household chaos, indicating that households in which parents had at least a high school level degree tended to have children who displayed more externalizing problems and be less stable than households with parents who did not have such a degree.

Table 5. Correlations of Study Variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1.Externalizing problems age 7	-	0.29***	0.06	0.09	0.72***	-0.01	0.04	-0.03	0.00
2. Home Chaos	0.14***	-	-0.02	0.07	0.35***	-0.02	0.01	-0.13**	-0.11*
3. Genetic Risk	0.01	-0.004	-	0.15**	0.08	0.03	0.06	0.02	-0.03
4. PRI	0.10***	-0.03*	0.01	-	0.09	0.02	-0.01	0.08	0.00
5. Earlier externalizing problems	0.40***	0.20***	0.02	0.10***	-	0.03	0.06	-0.06	-0.04
6. Parents' Education	0.06***	0.02	0.02	0.04**	0.03*	-	0.14**	0.07	-0.03
7. Household Financial Difficulties/ Income	0.06***	0.003	0.02	0.09***	0.08***	0.11***	-	0.02	0.01
8. Sex	-0.07***	-0.01	0.00	-0.01	-0.10***	-0.01	0.003	-	0.00
9. Openness of Adoption	-	-	-	-	-	-	-	-	-

*Note: * p < 0.05, ** p < 0.01, *** p < 0.001 PRI: Perinatal Risk Index. Study 1 is above the diagonal, study 2 is below. Because study 1 uses income and study 2 uses financial difficulties, a positive association between this measure in study 1 indicates fewer financial difficulties but in study 2 indicates more.*

Linear Regressions

Hypotheses were tested using a series of five models for both study 1 and study 2. The models were built such that change in R^2 could be used as a measure of effect size, and thus the first model contained only the covariates except earlier externalizing problems predicting externalizing problems at age 7 years. In study 2, principal components identified in PCA to control for population stratification were also included in this model. Model 2 added the key study variables – genetic/inherited risk for externalizing problems and home chaos, as well as *r*GE – correlation between home chaos and genetic risk and correlation between genetic and perinatal risk. Model 3 added the interaction of home chaos and inherited risk. Model 4 added earlier externalizing (4.5 years) as a covariate, and model 5 added another measure of *r*GE – correlations of earlier externalizing problems with the PGS and with home chaos. Notably, in study 1, correlations between earlier externalizing problems and inherited risk and home chaos specifically estimate evocative *r*GE by addressing correlation of inherited influence and home chaos through earlier externalizing problems. However, because passive *r*GE has not been controlled by design in study 2, these paths cannot distinguish between passive and evocative correlation in this study and instead only indicate general *r*GE.

Study 1, Model 1

Covariates in model 1 of study 1 account for roughly 4% of variance in externalizing problems at age 7 years, $R^2 = 0.04$. In this model, only income was associated with externalizing problems.

Study 1, Model 2

Adding the key variables increased the explained variance by 5 percentage points compared to model 1: $R^2 = 0.09$. Home chaos predicted child's externalizing problems at age 7 years such that children in a less chaotic household at age 4 years displayed fewer externalizing problems at age 7 years, $b = 0.40$, SE = 0.10, $p < 0.001$. However, inherited risk did not predict externalizing problems at age 7 years, $b = 0.17$, SE = 0.15, $p = 0.26$, nor was there a correlation of home chaos and inherited risk, $b = 0.42$, SE = 0.30, $p = 0.17$. As anticipated, inherited risk and perinatal risk were correlated, $b = 2.70$, SE = 0.94, $p = 0.004$. Association of covariates was

largely unchanged although primary-caregiver's education was associated with later externalizing problems in this model.

Study 1, Model 3

Adding the interaction between inherited risk and home chaos in model 3 had little effect on the amount of explained variance in externalizing problems at age 7, $R^2 = 0.10$, and the interaction did not predict later externalizing problems, $b = 0.07$, SE = 0.06, $p = 0.22$. Home chaos remained predictive with no change in effect size, $b = 0.40$, SE = 0.11, $p < 0.001$. The effect of inherited risk remained negligible with no change in effect size, $b = 0.17$, SE = 0.15, $p = 0.24$. There was no change in the pattern of correlations or covariates from model 2.

Study 1, Model 4

Introducing earlier externalizing problems into model 4 caused a shift in the pattern of results. The effects of home chaos, $b = 0.02$, SE = 0.07, $p = 0.74$, inherited risk, $b = 0.03$, SE = 0.12, $p = 0.80$, and the interaction, $b = 0.02$, SE = 0.04, $p = 0.59$, on child's externalizing problems at age 7 years were dramatically reduced. In this model, only child's earlier externalizing problems, $b = 0.59$, SE = 0.05, $p < 0.001$ and income, $b = -0.29$, SE = 0.11, $p = 0.01$, predicted later externalizing problems. Thus, it seems that home chaos is associated with later externalizing problems through earlier externalizing problems, contributing to later externalizing problems due to the stability of externalizing over time – although home chaos may also simply be a proxy for earlier externalizing problems. The explained variance for the model increased markedly, $R^2 = 0.49$.

Study 1, Model 5

Inclusion of an estimate of evocative *r*GE in model 5 also had no effect on the pattern of results from model 4. Earlier externalizing problems and income remained predictive of later externalizing problems. Additionally, the main effects of home chaos, $b = 0.03$, SE = 0.07, $p = 0.71$, and inherited risk, $b = 0.02$, SE = 0.12, $p = 0.84$, and their interaction, $b = 0.02$, SE = 0.04, $p = 0.59$, remained non-predictive. The correlation of early externalizing problems and home chaos was present, $b = -7.84$, SE = 1.13, $p < 0.001$, but the correlation between earlier

externalizing problems and inherited risk was not, indicating that evocative *r*GE is unlikely to be mediating the effect of earlier externalizing problems on the pattern of findings. Additionally, the amount of variance explained in this model was functionally unchanged, $R^2 = 0.48$.

Study 2. Model 1

All of the covariates in model 1 of study 2 were associated with externalizing problems at age 7 years, as were the principal components, $R^2 = 0.04$.

Study 2. Model 2

Adding the key variables in model 2 increased the amount of explained variance in the model, $R^2 = 0.05$, and, as with study 1, home chaos predicted later externalizing problems, $b = 0.06$, SE = 0.01, $p < 0.001$, and, genetic risk did not predict later externalizing problems, $b = 1.17$, SE = 2.17, $p = 0.59$. Association of covariates was largely unchanged in this model. Interestingly, unlike in study 1, prenatal risk was not correlated with the PGS for externalizing problems, $b = 0.00$, SE = 0.00, $p = 0.20$.

Study 2. Model 3

Introducing the interaction of the PGS and home chaos in model 3 did not affect the amount of explained variance in this model, $R^2 = 0.06$, although the interaction predicted externalizing problems at age 7 years, $b = 1.51$, SE = 0.75, $p = 0.04$. Plotting the interaction of inherited risk and home chaos (Figure 4) revealed that the effects of home chaos were only predictive of later externalizing problems at high and moderate levels of genetic risk and that the effect of home chaos increased as genetic risk increased, a pattern consistent with the diathesis-stress model. The main effect of the PGS did not change in any meaningful way, $b = 1.14$, SE = 2.16, $p = 0.60$, nor did the main effect of home chaos, $b = 0.06$, SE = 0.01, $p < 0.001$, or covariates.

Study 2. Model 4

In model 4, addition of earlier externalizing problems into the model greatly increased the amount of variance explained, $R^2 = 0.18$, although notably not to the same extent as in study 1.

However, as with study 1, earlier externalizing problems predicted later externalizing problems, $b = 0.23$, SE = 0.01, $p < 0.001$. Although the pattern of results held for most other variables, the interaction of home chaos and genetic risk predicting externalizing problems was no longer predictive of externalizing problems at age 7 in this model, $b = 1.29$, SE = 0.72, $p = 0.07$. This change in results indicates that some of the variance in later externalizing that had been attributed to the interaction in model 3 is better explained by earlier externalizing problems. The effect of home chaos was reduced slightly, $b = 0.03$, SE = 0.01, $p < 0.001$, indicating that it was accounting for variance better attributed to earlier externalizing problems. The effect of the PGS, $b = 0.09$, SE = 2.02, $p = 0.96$, remained negligible.

Study 2. Model 5

Effects in model 5 did not differ from those in model 4. Home chaos, unlike in study 1, still predicted externalizing at age 7, $b = 0.03$, SE = 0.01, $p < 0.001$, and the effects of the PGS, $b = 0.03$, SE = 2.02, $p = 0.99$, and the interaction of genetic risk and home chaos, $b = 1.26$, SE = 0.72, $p = 0.08$, remained negligible. The covariates, except financial difficulties, likewise remained predictive in this model. However, tests of *r*GE had a similar pattern to that in study 1. Specifically, earlier externalizing was correlated with home chaos, $b = 1.26$, SE = 0.11, $p < 0.001$, but not with genetic risk, $b = 0.00$, SE = 0.00, $p = 0.06$, and home chaos and genetic risk were also not correlated, $b = 0.00$, SE = 0.00, $p = 0.89$. Thus, controlling for *r*GE in this model had no impact on the variance explained by increasing the specificity of the key variables and covariates or overall, $R^2 = 0.18$.

Table 6. Results from Study 2 – ALSPAC Cohort with PGS for Inherited Risk

	Model 1	Model 2	Model 3	Model 4	Model 5
Study 1					
Female	-0.85 (0.56)	-0.56 (0.56)	-0.46 (0.55)	-0.12 (0.41)	-0.18 (0.41)
Primary caregiver education	0.46 (0.25)†	0.57 (0.25)*	0.57 (0.25)*	0.35 (0.21)†	0.34 (0.21)†
Secondary caregiver education	-0.02 (0.24)	0.07 (0.77)	-0.07 (0.22)	-0.01 (0.20)	0.01 (0.20)
Income	-0.40 (0.14)**	-0.41 (0.13)**	-0.42 (0.13)**	-0.29 (0.11)**	-0.31 (0.11)**
PRI	0.02 (0.02)	0.01 (0.02)	0.01 (0.02)	0.02 (0.02)	0.02 (0.02)
Openness of Adoption	-0.03 (0.37)	0.10 (0.36)	0.17 (0.37)	0.21 (0.28)	0.19 (0.28)
More than One Race	-0.63 (0.60)	-0.64 (0.58)	-0.58 (0.58)	-0.60 (0.46)	-0.62 (0.45)
Black	0.47 (1.04)	0.50 (1.03)	0.54 (1.02)	0.25 (0.83)	0.24 (0.83)
Hispanic/Latinx	0.30 (1.07)	0.31 (1.07)	0.29 (1.07)	0.88 (0.81)	0.82 (0.81)
Inherited Risk Score		0.17 (0.15)	0.17 (0.15)	0.03 (0.12)	0.02 (0.12)
Home Chaos		0.40 (0.10)***	0.40 (0.11)***	0.02 (0.07)	0.03 (0.07)
Inherited Risk x Home Chaos			-0.07 (0.06)	0.02 (0.04)	0.02 (0.04)
Externalizing (Age 4.5 years)				0.59 (0.05)***	0.59 (0.05)***
Study 2					
Female	-0.18 (0.04)***	-0.18 (0.04)***	-0.19 (0.04)***	-0.08 (0.03)*	-0.08 (0.03)*
Parents' Education	0.27 (0.07)***	0.25 (0.06)***	0.25 (0.06)***	0.22 (0.06)***	0.23 (0.06)***
Financial Difficulties	0.27 (0.07)***	0.17 (0.07)*	0.17 (0.07)*	0.08 (0.07)	0.08 (0.07)
PRI	0.03 (0.01)***	0.03 (0.01)***	0.03 (0.01)***	0.02 (0.00)***	0.02 (0.00)***
PGS		1.17 (2.17)	1.14 (2.16)	0.09 (2.02)	0.03 (2.02)
Home Chaos		0.06 (0.01)***	0.06 (0.01)***	0.03 (0.01)***	0.03 (0.01)***
PGS x Home Chaos			1.51 (0.75)*	1.29 (0.72) †	1.26 (0.72) †
Externalizing (Age 3.5 years)				0.23 (0.01)***	0.23 (0.01)***

*Note: † p <.1, * p < 0.05, ** p < 0.01, p < 0.001. Race variables are dummy coded with White as the reference group.*

Sensitivity Analyses

First, as a test of whether skewed distributions in externalizing problems were influencing findings, externalizing problems were binned to approximate normal distribution and used in a second set of analyses. The binned variable for earlier externalizing was slightly more predictive of later externalizing problems in study 1, but otherwise findings were highly consistent.

Second, the parent-education variable in study 1 was included as two categorical variables indicating the level of education each parent had achieved from high school/GED to upper-level degree. However, the parent education variable in study 2 was entered into the model as a single variable indicating whether parents' education should be factored as an adverse context. It was coded as 1 = adversity present, 0 = no adversity present, and 1 was assigned if neither of the parents had a high-school level degree or better. Thus, to test whether the differences in these variables between the studies was responsible for different findings, the parent-education variables in study 1 were combined and coded to match those in study 2. There was no change in the pattern of results.

Additionally, two variations on the PGS were used as sensitivity analyses in study 2. First, the PGS was residualized on home chaos and vice versa (as in Salvatore et al., 2015) to account for the variance in each attributable to the other, and the residualized versions of these variables were entered into the model in place of the original versions. Second, a different PGS was created using unweighted SNPs identified in Tielbeek et al. (2017), i.e., because beta weights were not available from Tielbeek et al. (2017), the SNPs in that score were purely a measure of the number of risk increasing alleles each participant had, un-weighted for the effect size of the correlation of each SNP with externalizing problems. The pattern of results in both of these sensitivity analyses largely matched those of the primary analyses, except that the interaction between the PGS and home chaos did not predict externalizing problems at age 7 in model 3, indicating either that that result is less reliable than the others in study 2, or that the un-weighted score lacked the precision needed to detect the GxE effect.

Gene Set Analyses

Despite the non-significance of the PGS, gene-set analysis was conducted to address whether there were any over-represented biological ontologies that may have been targets for

sensitivity analyses or future research. Initially, only one SNP in the PGS was associated with a protein-coding gene, and of the other four of the six were located within a gene. No ontologies were overrepresented in this set (Table 7). A second analysis was conducted using the protein-coding genes located closest to the SNPs in the score, but this likewise did not reveal any over represented ontologies.

Table 7. Represented Ontologies in the Study 2 PGS

Pathway	# Genes Associated	P-value
Primary Gene Set		
Unclassified	5	1.00
Nearby Protein-Coding Genes		
Pyrimidine Metabolism	1 (DPYD)	0.0044
Unclassified	6	1.00

Note: Gene set 1 contained only 5 genes; gene set 2 contained 7. The representation of the pyrimidine metabolism group is within the false discovery rate and thus not considered significant.

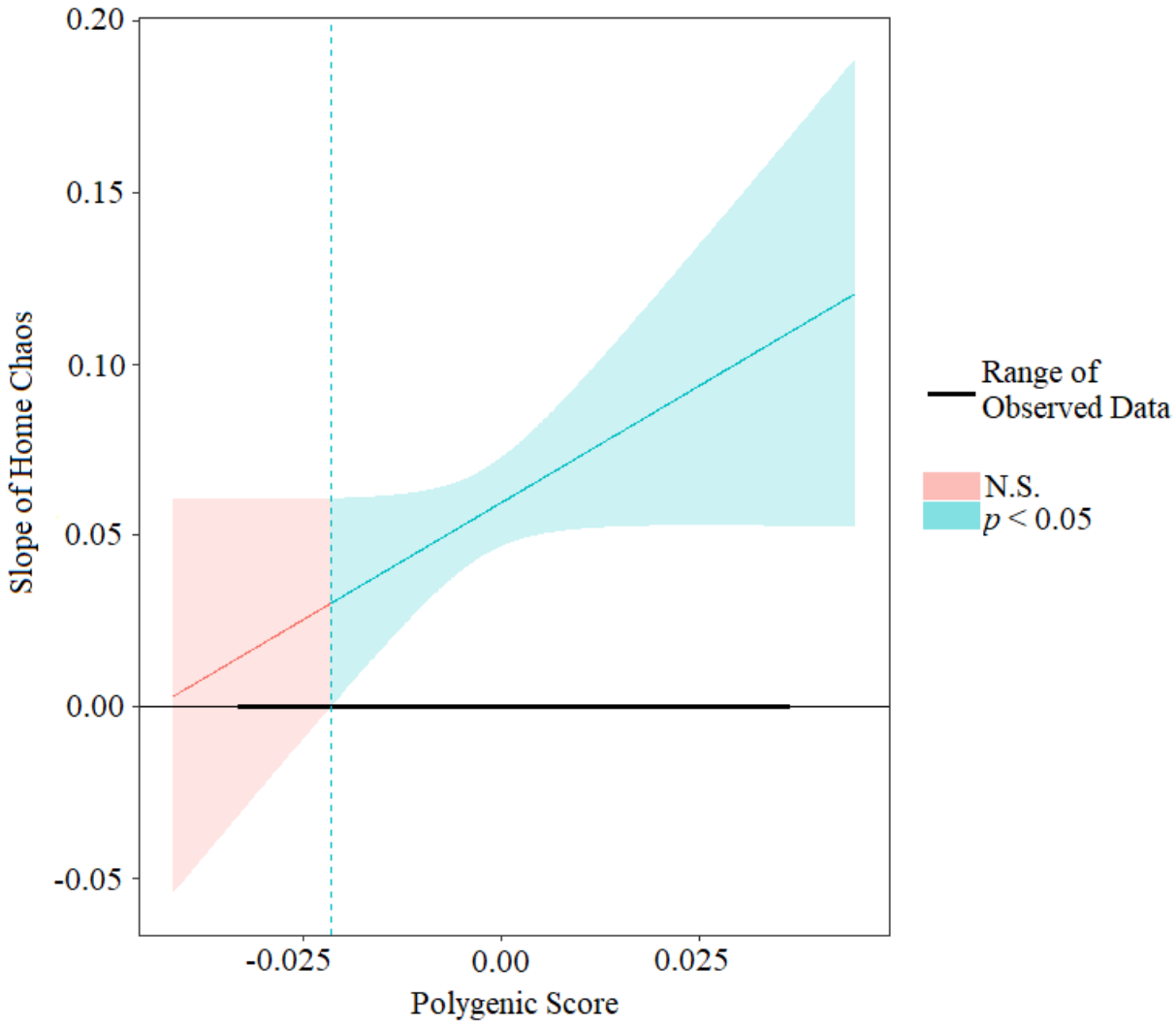

Figure 4. Johnson-Neyman Plot of Genetic Risk (PGS) by Home Chaos Predicting Externalizing Problems

Note: The effect of home chaos is non-significant for participants with PGS below -0.02 when the PGS is mean-centered, n = 102.

CHAPTER 5. DISCUSSION AND CONCLUSION

The studies included in this thesis aimed to assess whether results from two types of genetically-informative designs – an empirically-based PGS and a parent-child adoption study – would produce similar results when used to test effects and interactions of home chaos and genetic risk on externalizing problems in childhood. Results indicated that home chaos was predictive of greater externalizing problems in childhood, but in study 1 this effect did not persist when earlier externalizing problems were included in the model. In the context of this thesis, this result may indicate that effects of home chaos may be time-dependent and that influences of home chaos on later externalizing problems function through effects of home chaos on concurrent or earlier externalizing problems or alternatively, that home chaos is a proxy for concurrent externalizing problems. However, contrary to prior research, measures of genetic risk were not predictive of externalizing problems in either study 1 or 2. There was also no robust interaction between measures of genetic risk and home chaos predicting externalizing problems in either study.

Theoretical Basis

This research used a Behavioral Genetics approach as its foundation because the Behavioral Genetics approach assumes that, although genetic and environmental effects are intertwined, each constitutes an independent effect, allowing for measurable interactions of the two. In the context of this thesis, there was no persistent interaction between genetic risk and externalizing problems in either study 1, which controlled for passive *r*GE by design, or in study 2, wherein inclusion of measures of *r*GE and use of residualized variables for genetic influence and home chaos had no effect on findings. Controls for evocative *r*GE in study 1 also had little effect on the pattern of results. As controls in these studies did little to impact results and the evidence for interactions is tenuous, this thesis does not support the Behavioral Genetic perspective that genetics play an important role independently and in interaction with the environment for childhood externalizing problems. It is possible that the Behavioral Genetics approach is better suited to explaining correlations among different phenotypes, at different ages, or in different samples and should not be discounted based on the results of this thesis.

The loss of the PGS-home chaos interaction (model 3, study 2) when earlier externalizing problems were included in the model indicates that earlier externalizing problems may explain the variance in later externalizing better than the interaction. This result also suggests that the effects of the interaction may be time-limited and affect later externalizing through their influence on concurrent externalizing. This pattern of results suggests a path for disentangling genetic and environmental influences in ALSPAC. Specifically, this thesis highlighted a method introduced by Price & Jaffee (2008) to detect and disentangle passive *r*GE by allowing an environment (home chaos) to correlate with genetic influences while both independently predict the outcome. This method ameliorates misspecification of environmental and genetic main effects by interference stemming from correlations of those influences and allows greater confidence in the independent results of genetic and environmental variables. Further, extrapolating from findings from van der Sluis (2012) in the context of the results of this thesis, by controlling for *r*GE involving earlier externalizing in the final model, we can be more confident in our moderation results. That is, the fact that results did not change when correlations between earlier externalizing and genetic and home chaos influences were included indicates that results were not inflated by uncontrolled *r*GE. Correlations were conceptualized between home chaos and the PGS to correlate with concurrent, rather than subsequent, externalizing problems in this thesis because the effect of the GxE seemed to be active in early, rather than middle, childhood. In theory, adding these controls removed genetic influence shared between the outcome and environment from the covariance model, allowing for cleaner results for the main effects of both the genetic and environmental variables as well as their interaction.

Home Chaos

As noted, home chaos was predictive of externalizing problems in both studies 1 and 2, supporting the hypothesis that home chaos plays a role in externalizing problems in childhood. However, in study 1, the effect of home chaos became negligible when earlier externalizing problems were added into the model. This pattern may suggest that home chaos influences later externalizing problems only through its effects on concurrent externalizing problems and the stability of externalizing behavior, but as this was not specifically tested, this remains an assumption. It is also possible that home chaos is simply a proxy for earlier externalizing problems, but this seems unlikely given that the two variables were only correlated at 0.35,

indicating that they are mostly independent of one another. Notably, in study 2, the effect of home chaos was persistent even when earlier externalizing problems were included in the model, indicating that home chaos has an effect over and above that of earlier externalizing problems. However, the effect size of home chaos still reduced drastically when earlier externalizing was added to the model, providing some additional support for the possibility that the effect of home chaos on later externalizing was occurring through concurrent externalizing. Additionally, the pattern for home chaos in study 2 may be attributable to its higher sample size reducing standard errors and allowing smaller effects to remain under the $p < .05$ threshold.

It is noteworthy here that studies 1 and 2 did not use the same measures of home chaos. Although the computed score from study 2 was designed to tap into chaos in a way similar to the CHAOS scale, several key differences could explain the disparity in results. Specifically, the composite measure of general chaos/unpredictability of the home is based primarily on primary-caregiver reports of tidiness (parent-rated) and crowding (number of individuals living in the home divided by the number of rooms in the home). Whereas, the CHAOS scale uses responses to statements like 'It's a real zoo in our home' and 'There are very few disturbances in our home'. Variance related to tidiness and crowding may be more unique from the child's externalizing problems, whereas externalizing problems may contribute to the parents' responses on measures in the CHAOS scale. The measures of noise in the home differ between studies as well, with the composite score using ratings of noise from other rooms, the street, and neighboring homes, whereas the CHAOS scale uses responses to statements like, 'It's so noisy you can't hear yourself think in our home'. Although these individual measures are hypothesized to represent the same type of environment, the differences in outcome indicate that the less subjective questions regarding noise may be more effective in capturing the noise levels of the household than the mother's general perception of noisiness – although all of this should be weighed against the low internal reliabilities of both scales.

In addition, the CHAOS scale addresses whether the family has a consistent routine, which is not measured in the composite score, and, notably, the composite score focuses more on the cleanliness of the home, which is not addressed in the CHAOS scale. Thus, it is possible that the increase in specificity and the increased distinctiveness of the measures of noise, crowding, and cleanliness may make the composite a more unique predictor of externalizing problems than the more general CHAOS measure. To extend this thought, it is possible that a stable routine may be

related to authoritarian parenting, as well as parenting styles that are less related to externalizing problems. In this case, the correlation of a home chaos measure that includes routine would be somewhat diminished as the effect of routine may be different in an authoritarian vs. an authoritative household. Similarly, cleanliness may be a better indicator of a disruptive household. That is, a less cleanly household may indicate that parents spend less time home or have less energy when they are home, leading to reduced positive interaction with their child and, later, more externalizing problems. Although routine should theoretically tap into that same variance of parents being home less and having fewer interactions, it may be that a less cleanly house is more related to both parents having less time in dual-parent households or is simply indicative of a single parent household. Whereas, a routine could be more easily maintained by one non-working parent or especially diligent working parents in a dual-parent household. Finally, a less cleanly household may indicate more traffic, which was not measured in either study. Although crowding was measured, less cleanly houses may be more commonly frequented by friends or family members who do not live in the household but still contribute to its chaos. Such visitors may have a similar effect to greater crowding without disrupting the household's routine. In these ways, cleanliness may tap better into chaos than routine.

An explanation less focused on the specific measure, however, is the difference in when chaos was measured in study 2 compared to study 1. Chaos in study 2 was measured at ages 2-4, compared to age 4.5 in study 1. Ages 2-4 not only captures the entrance to more formal schooling that is known to be particularly important for predicting behavior problems (Gower et al., 2014) but also the sensitive period of development around ages 2-3 that has also been indicated as important for the development of externalizing problems (McFarland, 2017). Thus, chaos during this time period may be more likely to disrupt vital developmental processes leading to more reliable prediction of externalizing problems later in childhood, explaining how home chaos in study 2 remained predictive after inclusion of earlier externalizing problems while home chaos in study 1 did not.

Interestingly, adoptive households in study 1 did not appear to have a floor effect for chaos, compared to the non-adoptive households in study 2 (see Table 4). Distributions suggest both had means around two standard deviations above the lowest value in the sample and skew slightly above 0.5. The similar distributions suggest that adoptive homes do not seem less chaotic by virtue of the screening parents must pass to be able to adopt when comparing the EGDS and

ALSPAC samples, and differences in levels of home chaos are unlikely to explain the differences in results between studies. However, other sources of order in the child's life could explain the difference in results. Specifically, there is evidence that home chaos affects childrens' externalizing problems through children's self-regulation (Hardaway et al., 2012), which may impact children's ability to make secure attachment relationships with multiple caregivers (Horm et al., 2018). There is also evidence that children can find order in other areas of life, e.g., preschool (Horm et al., 2018), which may mitigate some of the negative influence of having a more chaotic home on self-regulation. Thus, adoptive families, who are more likely to be of higher SES, may be able to afford better preschools which then provide a more orderly environment for children and reduce the long-term effect of home chaos on externalizing problems. Understanding these other possible sources of stability is vital to understanding the influence of home chaos as they may interact with or confound its effects, explaining some of the inconsistency in the literature.

Genetic Influence on Externalizing Problems

Contrary to previous research (e.g., Burt, Krueger, McGue, and Iacono, 2001; Salvatore et al., 2015), genetic influences did not seem to contribute to externalizing problems in either study 1 or study 2. Across the two studies, measures of genetic risk were not statistically significant, and effect sizes were small, especially for the PGS. Thus, the hypothesis that genetic or inherited risk would be predictive of externalizing problems during childhood was not supported, and instead it seems that genetic risk on its own did not predict externalizing problems. Rather, genetic risk needed to interact with an environment to have a noticeable correlation with later externalizing, and even this interaction was not reliable. Explanations for and extensions of these results are discussed in subsections below.

Coverage of Genetic Influences on Externalizing

It is possible that neither the PGS nor the score of parents' externalizing problems captured enough of the genetic variance to contribute meaningfully to externalizing problems in these samples. The low variance in the primary PGS that came about due to the small number of SNPs included – seven – may have stifled results, but this explanation should be weighed against the

sensitivity analysis using ~130 SNPs identified in Tielbeek et al., (2017), which had much greater variance (mean = 62.55 before centering, SD = 3.69). That is, it is likely that the PGS did not predict externalizing problems because of the small number of SNPs it included. However, given that sensitivity analyses of genetic influence in study 2 did not alter results, it is possible that both specificity, in the form of beta-weights, and coverage, in the form of a PGS composed of many SNPs, may be necessary for a PGS to predict externalizing problems in childhood.

Similarly, the PGS was drawn from a GWAS on diagnosis of ADHD, whereas the outcome for this thesis was general externalizing. Evidence in the literature suggests that externalizing problems are not wholly identical in their sources of genetic influence (Burt, 2013), and thus the poorly matched phenotype may have limited how well the identified SNPs could address the variance in the outcome. Additionally, much of the literature (e.g., Burt et al., 2001 and Farbiash et al., 2014) on externalizing problems, including Demontis et al. (2019) from which the data for the PGS was drawn, uses externalizing disorders rather than externalizing problems, as used for the outcomes in this thesis. Thus, evidence for genetic influence in the literature may apply more strictly to clinical externalizing disorders than non-clinical externalizing problems. However, the possibility that results are due to a poor match between the phenotype for the score and the outcome phenotype was tested with a sensitivity PGS using a better matched phenotype without a change in results, and there is evidence in there remains evidence in the literature for genetic prediction of subclinical externalizing problems (e.g., Salvatore et al., 2015; Tielbeek et al., 2017).

It is also notable that neither of the PGS used in study 2 included highly penetrant genetic markers, and there is evidence PGS composed of only a few highly penetrant genes can still predict externalizing problems (e.g., Chhangur et al., 2017). Thus, PGS containing few genetic markers can predict externalizing problems but only if the genetic markers are particularly highly correlated with the outcome. However, even a score created from these genes captures little of the genetic variance in externalizing problems – e.g., the score in Chhangur et al. (2017) was only predictive of externalizing problems in the context of an intervention. Thus, genetic influence on externalizing seems to be broader than scores with small numbers of SNPs can capture, fitting with the rising omnigenic theory of behavior (Boyle, Li, & Pritchard, 2017).

Non-specific Genetic Risk for Externalizing

However, the studies in this thesis may also have failed to find main effects of genetic influence because genetic risk for childhood externalizing problems may work through or overlap with genetic influences on related phenotypes – i.e., the genetic risk for externalizing problems is not specific to externalizing problems. This thesis was based on the assumption that the use of a specific, weighted PGS would allow for interpretable genetic effects, but, if genetic influences on externalizing are diverse and shared with other phenotypes, genetic effects may have been underestimated by focusing too narrowly on genetic influences related specifically to externalizing problems. Externalizing problems have been shown to be comorbid with and share genetic influences with other traits, notably inhibitory control (at age 2 years; Gagne, Saudino, & Asherson, 2011) and internalizing problems (at 7 years Van der Valk, van den Oord, Verhulst, & Boomsma, 2003).

Focusing on the PGS, because genetic influences for externalizing problems are shared between traits, it is possible that a score composed of genetic markers specifically related to externalizing problems will not adequately capture the range of genetic influences that relate to other traits contributing to externalizing behaviors. Thus, an index of genetic influences on externalizing problems may require genetic markers associated with related phenotypes to predict externalizing. Moreover, by not including these other influences, it is impossible to rule out that a child who scores highly on a PGS specifically for externalizing problems does not score low on other genetic influences that may influence their externalizing outcomes.

Further, the gene-set analysis did not find any overrepresented biological ontologies in the PGS, despite there being known biological systems (e.g., cortisol systems; Hawes, Brennan, & Dadds, 2009, and dopamine; Schmidt, Fox, & Hamer, 2007) that contribute to externalizing problems. Thus, scores in this thesis may not have tapped well into biological mechanisms of externalizing problems, failing to capture the heterogeneity in biological pathways to externalizing. That is, some children may have been genetically predisposed to have more cortisol and others less dopamine, but the score contained only one SNP related to each, diminishing the relationship between the PGS and either of their externalizing problems.

Focusing more on the measure of inherited risk, as with the PGS, it is possible that birth-parents' externalizing problems simply did not capture the full scope of genetic risk in externalizing problems well in the EGDS sample. As with the PGS, a score of genetic influence

for externalizing created by indexing specifically parents' externalizing problems may not adequately capture non-specific genetic risk for externalizing. Studies using the EGDS dataset have predicted externalizing problems in children using different measures of genetic influence than were used in study 1 of this thesis. Notably, children whose birth mothers displayed more depressive symptoms were more likely to exhibit externalizing problems at age 6 (Grabow et al., 2017) and children age 6-7 years whose birth mothers processed information more slowly were more likely to experience both externalizing and internalizing symptoms (Roos et al., 2016). Thus, genetic influences on externalizing problems are indicated by inherited risk for related phenotypes and may not be captured by a score using only externalizing problems. Although this thesis was attempting to test for more 'direct' genetic influence for externalizing problems, thorough examination of the different 'routes' of genetic risk for externalizing may help to elucidate reliable phenotypic indications of genetic risk.

However, measures of parents' externalizing problems have also been used to predict externalizing problems in the EGDS sample before – although not decisively. That is, a similar measure predicted externalizing problems in toddlers at age 27 months (Marceau et al., 2013), but so did birth mothers' internalizing disorders, and these effects did not survive when prenatal and postnatal environmental influences were also modeled. Similarly, genetic risk for externalizing behavior as measured by birth-parent reports of their own lifetime drug use, delinquency, and novelty seeking was implicated in a GxE such that infants age 9 months who were at greater genetic risk paid more attention to frustrating events specifically when adoptive mothers also had higher levels of anxious/depressive symptoms (Leve et al., 2010). This example is especially notable as it reinforces how genetic influences may be associated with attention and response to the environment as an explanation of how genetic risk could moderate environmental influences.

Further, a measure of genetic risk composed of birth-parent indicators for externalizing problems and internalizing problems negatively predicted both externalizing and internalizing problems in a model including smoking during pregnancy and had no effect in a model including alcohol use during pregnancy, suggesting that the effect was context dependent and overlapped with the effect of mother's alcohol use (Marceau et al., 2019). Marceau et al. (2015) indexed genetic risk using birth mothers' internalizing and externalizing psychopathology, as well as psychopathology among their first-degree relatives. They found that this measure was not

predictive of externalizing problems at 6 years of age in a model that also contained maternal drug use/internalizing, child cortisol at 4.5 years, and overreactive parenting influences. Thus, the literature seems to indicate that measures of genetic influence using parent externalizing problems are highly contextual and may be confounded by other environmental influences, highlighting the need for research that is highly conscious of both the context of genetic influences and the different sources of genetic risk for externalizing.

Age and Genetic Influences on Externalizing

Further, there is evidence that, in addition to genetic influence increasing over the lifespan, as discussed in the introduction, genetic influences for externalizing problems do not remain stable over the lifespan. That is, evidence suggests that new sources of genetic influence emerge in adolescence and adulthood (Wichers et al., 2013), and thus genetic influences underlying adult externalizing problems, as used in the measure of birth parent externalizing problems, may not match those in early childhood. In this thesis, there is an age disconnect for the measures of genetic risk used in both studies. In study 1, genetic risk is indexed using parent reports of their own externalizing problems, but, given that externalizing problems do not remain static over the lifespan, the genetic influences acting on parents' externalizing problems as adults may predict their children's externalizing problems in childhood. Similarly, the Demontis PGS used results from a deCODE sample, which includes nearly 40% of Iceland's population, and thus, although I was unable to find specific percentages of age groups in this sample, it is reasonable to assume that many adults and adolescents were included. The Tielbeek PGS similarly consisted of both adults and children. Therefore, these PGS may include SNPs, and beta weights in the Demontis score, that are not predictive of children's externalizing problems and exclude SNPs that are. Thus, measures of genetic risk specific to children may be important for finding genetic prediction of behavior in future research.

Gene x Home Chaos Interactions

Although there was no persistent interaction of home chaos and genetic risk, the significant interaction in study 2 model 3 found that home chaos had the greatest positive association with externalizing problems at high levels of genetic risk, a moderate positive association at moderate

levels of genetic risk, and no association at low levels of genetic risk. This result does not fit with the hypothesized vulnerable-stable model but rather with the diathesis-stress model of GxE as the effect of home chaos is increased as genetic risk increases. Notably, the differential susceptibility and diathesis-stress models are indistinguishable in high-risk environments. The measure of chaos in study 2 was purely a reflection of chaos, with low levels on the score indicating less chaotic, not necessarily more orderly, homes. Thus, although the data available suggest the diathesis-stress model in study 2 and assumptions cannot be made, research using broader measures may find a differential susceptibility model. However, it must also be stressed that the result in study 2 does not persist beyond model 3 and was not significant in any of the sensitivity analyses. Thus, there is very little support for an interaction of PGS and home chaos in this thesis.

Other Key Environmental Influences in GxE for Externalizing

There is some evidence that the effect of genetic risk in early childhood interacts with other measures of quality caregiving, but the shape of the interaction is inconsistent across studies. An investigation of G x maternal responsiveness predicting moral internalization (Kochanska et al., 2011) found that children age 4-5.5 years with the risk-increasing allele of the 5-HTTLPR gene who also had responsive mothers had better than average moral internalization and children with unresponsive mothers had worse, fitting with the differential susceptibility model of GxE. Relatedly, Marceau et al. (2019) found that the negative association between genetic risk and externalizing problems for boys in middle-childhood was only significant at low levels of parent-child warmth and decreased as warmth increased, fitting with the diathesis-stress model. Thus, there is evidence for interactions of positive parenting and genetic influence, fitting with models of GxE indicating the genetic influence sensitize individuals to their environment. As other measures of caregiving were not controlled in this thesis, it is possible that they confounded the influences of a chaotic home.

Findings from a similar test of overreactive parenting in EGDS suggest that over-reactive parenting moderated genetic risk for negative affect – indexed through biological mother's negative affect – such that genetic influences predicting negative affect were greatest in the context of low over-reactive parenting in the first two years of life, fitting with the vulnerable-stable model (Lipscomb et al., 2012), and genetic influence on conduct problems has also shown

to be stronger in the context of more directive mothering when the child was between ages 6 and 10, consistent with the vulnerable-stable model in middle childhood (Burt, Klahr, Neale, & Klump, 2013). Thus, there is also evidence for gene-environment interactions with less positive traits, but interestingly these traits seem to follow different patterns of GxE – although several other differences could also contribute to the different patterns of GxE.

Although parenting factors seem to most reliably interact with genetic influence, more less direct influences are still likely to be pertinent. There is evidence for genetic interactions with other parent attributes, e.g., mother's affective state and depressive symptoms, as well as more global measures of the home environment like home chaos. Notably, genetic influences on externalizing problems have been shown to account for more variance in infants' attention to frustrating events in the contexts of adoptive mother's affective state consistent with the diathesis-stress model in infancy (Leve et al., 2010), and Cadoret, Cain, & Crow (1983) found that, for adolescents, the prediction of antisocial behavior by an adverse home environment, operationalized using psychiatric attention for an adoptive parent or sibling and adoptive parents' marital separation/divorce, was increased when the adolescent was also genetically predisposed for externalizing problems, fitting with the diathesis-stress model of GxE. Thus, although parenting factors may be the most prominent in the literature, investigations of these other factors is still important for fully understanding the sources of influence on externalizing problems, although models including both parenting factors mediate and these less direct or more global factors may be most effective for uncovering influence.

Notably, most of the examples above conceptualize the interaction as moderation of genetic influences by the environment, but the opposite, as hypothesized in this thesis, is still worth investigating. One test of GxE predicting externalizing problems (Lipscomb et al., 2014) in EGDS indicated moderation of the effect of attending center-based early care on externalizing in infants such that the effect was stronger only if their birth parents were lower on temperamental regulation, fitting with the diathesis-stress model of GxE. Further, Belsky & Pluess (2013) found an interaction between the DRD4 gene and quality of childcare at age 3-4 years such that the risk increasing allele increased the positive prediction of externalizing problems in kindergarten by low-quality childcare, also fitting with the diathesis-stress model of GxE. The results of Brett et al. (2015), discussed in the introduction, are similar. Notably for these studies, because of the similarity between the patterns of the diathesis-stress and

differential susceptibility models noted above, they may also fit with the differential susceptibility model depending on the true moderator and how the pattern differs when the environment is beneficial.

Looking beyond investigations of the effect of childcare, prenatal variables have also been implicated in gene-environment interactions predicting externalizing. For example, obstetric complications and pregnancy complications were more predictive of having more externalizing problems than internalizing problems at low levels of genetic risk for substance use, and were not associated with symptom type (e.g., a preponderance of externalizing vs. internalizing) at high levels of genetic risk among children age 4.5 years, but importantly because of the way these variables are constructed, it is difficult to apply any of the patterns of GxE indicated in this thesis to these results (Neiderhiser et al., 2016). Given the ubiquity of genetic influence over life and its continuous effects on biological reactivity, hypotheses of moderation of environmental influence by genetics remain important targets of investigation. Thus, although it is common to conceptualize GxE interactions as moderation of genetic influences by the environment, approaching the interaction from the other direction is still worthwhile and may provide additional insight.

The studies mentioned are only a sample of the literature on GxE predicting externalizing problems, and the field may also be served by a thorough overview of the literature - although such a review is out of the scope of this thesis. However, looking broadly and considering the studies discussed in previous paragraphs, there is strong evidence for interaction between genetic influences and different aspects of parenting – particularly warmth, positivity/negativity, and sensitivity – as well as quality of childcare and prenatal factors. There is also evidence, albeit less, for interactions of genetic influence and other environments, e.g,. neighborhood disadvantage. Additionally, parent depressive symptoms in middle childhood (twin study; Clark, Klump, & Burt, 2018), maternal negativity in adolescence (twin/genetic relatedness; Feinberg et al., 2007), peer deviance (twin; Button et al., 2007), restrictive parenting (review; Salvatore & Dick, 2018), and neighborhood advantage in middle childhood (twin; Burt, Klump, Gorman-Smith, & Neiderhiser, 2016) and adolescence (twin; Tuvblad, Grann, & Lichtenstein, 2006) have all also been shown to interact with genetic proclivity for externalizing problems. Likewise, measures of prenatal risk separate from that used in Neiderhiser et al. (2016), notably smoking during pregnancy (candidate gene, Brennan et al., 2011; candidate gene, Kahn et al., 2003), have

also been shown to interact with genetic risk for externalizing. The evidence of gene-environment interactions, especially with aspects of parenting and prenatal risk, is overwhelming. However, the shape and context of these interactions remains unclear.

Triangulation

Several results triangulated across studies, notably the negligible main effects of the genetic risk variables, positive effects of home chaos, reductions of the effect size of home chaos by adding earlier externalizing into the models, and null effects of the interactions between the genetic influences and home chaos in the final models including earlier externalizing. Triangulation across two study designs with different sources of bias allows for more confidence in these results. However, not all effects were perfectly replicated across studies. First, the effect sizes of home chaos differed between studies. Second, the presence of an interaction in model 3 in study 2 but not study 1 was a large deviation in findings. As noted in the introduction, biases between studies must be addressed to make full use of the information gleaned in attempts to triangulate findings. Several of these biases, most notably the differences in the measures of home chaos and genetic risk, have been noted in previous sections of the discussion and thus will not be discussed here.

First, bias in analytic methods should not account for differences in findings across studies because both studies used multivariate regression and accounted for missingness using FIML. In both studies, unmeasured or poorly measured confounders may bias results, as may errors in measurement of key study variables. However, because these issues should bias the studies similarly, they are not useful for determining why results in these studies converged and failed to converge. Additionally, violations of the assumptions of regression analysis were similar between studies, but notably study 1 violated one assumption that study 2 did not – normality of residuals. This violation represents a possible explanation for divergent results, as well as a limitation of this research, but, notably, corrections were applied to mitigate the impact of the violations of assumptions of regression; thus, this issue is less likely to be the source of divergence. It is also noteworthy that, although study 2 violated the assumption of homoscedasticity, it also had a much larger sample than study 1, and studies using large samples tend to be more robust to violated assumptions and was also subject to statistical correction. To fully account for this bias, samples that either did not violate the assumptions of regression or

violated them in the same way and were similar in size would need to be compared, which is not the case for the studies in this thesis. However, given the corrections in place, it is unlikely that violations of regression assumptions were responsible for divergence in this thesis.

The sources of bias most likely to affect the findings were in study design. Due to the design of study 1, adoption becomes a source of bias that is not present in study 2 and passive *r*GE becomes a source of bias in study 2 that is not present in study 1. By not controlling for passive *r*GE in study 2, it is possible that the effects of the PGS were inflated, but it is also notable that these effects were still negligible. However, this increase in effect should be considered regarding the one interaction between home chaos and PGS in model 3 of study 2, which may have been the result of bias.

Future Research

As noted in the chaos section, other sources of order may contribute to a child's externalizing problems, or lack thereof, offsetting the influence of home chaos. Thus, future research into home chaos may consider controlling for other sources of order, and it may be worthwhile to explicitly test whether chaos in school or childcare moderates the influence of home chaos on children's externalizing problems. Similarly, in the case of genetic influences, future research should consider broad sources of genetic influence and be sure that their scores of genetic effect are likely to capture the phenotype they aim to address by matching their training phenotype to their test phenotype, considering the ages at which training and test phenotypes are measured, and considering other sources of genetic influence on the phenotype.

However, future research may be best served by focusing on the environments that have been shown to consistently interact with genetic influences – mostly focusing on caregiving behaviors, and the exact relationships among variables – whether they are best modeled as mediators, moderators, or both. It may also be worth investigating how these environments inform the effect of home chaos on externalizing problems. However, it may be most important to be conscious of how the different models of GxE seem to change for different measures of genetic influence, different environments, and across development.

In that vein, a meta-analysis by Burt (2013) indicated that genetic and environmental influences on different types of externalizing problems (in this instance, rule-breaking and aggression) have a great deal of overlap but remain partially distinct. Thus, different

environments interact with different genetic influences when predicting different types of externalizing behaviors, which, for this thesis, may indicate that only specific externalizing phenotypes are well-predicted by interactions of genetic influences and home chaos. However, context remains an important consideration for these findings, with shared environmental influences being functionally identical for rule-breaking and aggression during childhood and more unique in adolescence. The author extends this reasoning to point out that parental divorce and parent-child conflict, which have been indicated as strong shared-environmental variables predicting externalizing problems, may be differentially related to aggression and rule-breaking in adolescence. The author further expounds upon this possibility in Burt (2015), wherein they review the literature and suggest that the increase in the heritability of externalizing problems in adolescence could be explained by a shift from gene-environment interactions fitting with the bioecological (vulnerable-stable) model in childhood to the diathesis-stress model in adolescence. These shifts across phenotype and development may be especially important for understanding the etiology of externalizing problems.

Three-Way Interactions

Related, a recent review (Gard, Dotterer, & Hyde, 2019) focused on interactions between negative parenting behaviors (e.g., harsh parenting, low parental warmth) and genetic influences predicting antisocial behavior, but primarily cited evidence for single genes, specifically MAOA, DRD4, and 5-HTTLPR. Authors noted that a shift toward biologically informed PGS and gene set analysis for measures of biological influence, and models that accounted for more environmental interactions (specifically tests of GxExE) may be necessary to improve our understanding of the genetic and environmental factors underlying the etiology of externalizing problems.

Tests of GxExE in the literature have helped to shed light on the ways that environmental and genetic influences influence each other in the prediction of externalizing problems. Notably, Marceau et al. (2019) showed that the effect of smoking during pregnancy was predictive of more externalizing problems for children at low genetic risk for externalizing and low hostility, average genetic risk and average hostility, and high genetic risk and high hostility, but not at other combinations of genetic risk and hostility. Thus, at low levels of genetic risk and hostility, the pattern seems to fit the vulnerable-stable model, whereas at high genetic risk and hostility,

the pattern seems to fit the diathesis-stress model. Neiderhiser et al. (2016) found that high genetic risk for externalizing and marital hostility interacted with pregnancy complications to produce the greatest levels of externalizing problems but that, among participants with the same levels of marital hostility but low genetic risk, pregnancy complications instead predicted internalizing problems. This pattern would seem to follow a diathesis-stress model, but the diathesis for internalizing problems is a lack of genetic risk for externalizing problems. Notably, when marital hostility was low, influences of both genetics and smoking during pregnancy were negligible. Studies like these may help to explain why patterns of GxE in the literature are often inconsistent – i.e., unmeasured, variables in the model may be reacting with study variables.

In addition to the findings above, Burt et al. (2013) found that maternal warmth and directiveness jointly moderated genetic influence on externalizing such that genetic influences were strongest in high warmth, high directiveness (authoritative) conditions, and Lipscomb et al. (2014) found results indicating that the effect of overreactive parenting on externalizing problems was greatest among children who attended center-based early care and who were also at greater genetic risk for dysregulation. Both of these results fit the diathesis-stress model of GxE, which may imply that findings of patterns of GxE are more consistent in tests of GxExE, considering the studies mentioned previously. However, the number of studies looking for GxExE predicting externalizing problems is small, and thus it is too early to draw solid conclusions regarding the consistency of results. Regardless, these studies provide greater insight into the nuance of gene-environment interactions and may, with more attention, serve to explain the inconsistent findings in the models of GxE by indicating other environments under which the patterns change. Thus, although the next step from the research presented in this thesis may be a focus on specific high-influence environments, e.g., maternal sensitivity, that may interact more reliably with genetic influences, it is possible that no interaction between genetic influence and one specific environment will effectively capture the genetic and environmental interplay in the etiology of externalizing problems. As larger samples become available for genetically sensitive investigations, tests of GxExE may grow in prominence.

Mechanisms of the Effect of Home Chaos

Finally, in addition to moderation effects, it may be beneficial for future research to consider possible mediators through which home chaos affects externalizing problems as

understanding how such mechanisms contribute to the understanding of why associations between the two are not wholly consistent. Notably, there is evidence for a relationship between home chaos and executive function in the literature that may help to explain the association between home chaos and externalizing. Several recent studies (Brieant et al., 2018; Vrijhof, van der Voort, van IJzendoorn, & Euser, 2018; Lecheile et al., 2020) have established that home chaos in childhood is associated with lower executive function in later childhood and adolescence, but none of these studies extended those results to predictions of behavior. However, Hardaway et al. (2012) found that home chaos was associated with externalizing problems through executive function, and Doan, Fuller-Rowell, & Evans (2012) tested several pathways of cumulative risk, an amalgamation of risk factors including several indicators of home chaos, through maternal responsiveness and self-regulation onto externalizing problems, finding that the best fitting path was cumulative risk on externalizing problems through only self-regulation for children ages 9, 13, and 17 years. Thus, if home chaos affects externalizing problems, it may do so through executive function.

Limitations

Limitations of Both Studies

First, as noted previously, PGS are limited to providing information from SNPs included in their creation, and thus effects of rare variants may not be represented. The PGS used for the primary analyses also contained only 12 SNPs after cleaning and thus has poor coverage of genetic effect. The measure of genetic influence in study 1 was likewise limited in its coverage as birth-parents' externalizing problems may not capture the full scope of externalizing problems as discussed in the section on genetic influence above. It is also possible that measures of chaos used in the presented studies operationalize chaotic/unpredictable home environment in such a way that results from each measure are not addressing the same variance, as discussed in the Home Chaos section. Compounding this possibility, the measures of chaos in both studies had exceptionally low internal reliability, and thus the measures themselves may not tap into a consistent portion of variance.

Additionally, EGDS is more diverse than ALSPAC. Comparing samples that are poorly matched in terms of ethnicity can result in population stratification - a type of confounding in

which between-group differences confound the investigation of biologically relevant within-group effects (Cardon & Palmer, 2003). There are systematic differences in the frequency of genetic variants by ancestry, as well as in risk for externalizing problems (Bouaziz, Ambroise, & Guedj, 2011). Population stratification can occur in racially/ethnically homogeneous samples as well, but it is less common. Given that the entire sample of study 2 was White after removing participants with no data on any key measures, the primary concern is in the comparison of genetic influence between the two studies, which is somewhat less important because study 2 did not measure genetic effect with specific genetic markers. Regardless, population stratification was controlled using the 8 strongest principal components as recommended by Bouaziz et al. (2011).

Further, because the test sample in study 2 is a largely homogenous sample from a relatively small and specific area, it is likely that SNPs that are less common in this population are not represented in the sample. This sample homogeneity will reduce the generalizability of results and may have been smaller than if a more diverse sample had been used. Second, the effect of the PGS may have suffered because the measure of externalizing problems in the GWAS discovery sample does not match the measures of externalizing problems used in ALSPAC. This problem is also apparent in study 1 as 56% of the sample is White, but it is notably less severe than in study 2, which is functionally 100% White.

Finally, both study 1 and study 2 rely heavily on parent report. Although parent report is an efficient way of measuring behavior problems in children, given the impracticality of gathering self-reported data from young children and the costs necessary for observational ratings, this still represents a limitation of this study data because of measurement error and possible differences in child behavior at home, as opposed to at school. This limitation is slightly ameliorated by the use of combined mothers' and fathers' ratings. Additionally, parent-ratings may be subject to social desirability effects, which may reduce the level of externalizing problems, for both parents and children, and home chaos reported, skewing results. It is also possible that parents who are higher in externalizing problems may respond to measures differently than low-externalizing parents and may also be less likely to respond to the questionnaires, further diminishing the level of parent/child externalizing in the sample. Ambroise, & Guedj (2011).

Limitations Specific to Study 1

Notably, the level of behavior problems in EGDS is generally low, and thus effects are likely to be compressed within the sample. This loss in variability was expected given that adoptive parents tend to be of higher education and socio-economic status. For this reason, these results also may not generalize to high-risk samples of children. However, steps were also taken in the analyses to statistically account for limitations regarding failure to satisfy the assumptions of regression analysis.

Limitations Specific to Study 2

One limitation to the approach in study 2 is that it is possible that each SNP included in the PGS interacts with the environment differently, and thus specific SNP x home chaos interactions may be washed out or otherwise not well represented by the polygenic score. This limitation relates to the possibility that the SNPs used in this score do not seem to share biological ontologies. Unfortunately, attempts to ameliorate this possibility would require data from the Psychiatric Genomics Consortium (PGC), and this lab does not have access to PGC data. However, a method of LD score regression analyses was introduced as part of a conference presentation that may allow for direct comparisons with twin GxE methods and some management of SNP x home chaos interactions (Verhulst, Prom-Wormley, Pritikin, & Neale, 2019) in future work. Unfortunately, the paper on this method was not published at the time this thesis was written.

The measure of home chaos in study 2, although based on a validated measure, has not been previously validated. These limitations necessitate replication of both studies with different or better matched measures of both chaos and externalizing behaviors. Additionally, because the PGS in this thesis, like PGS generally, was made using common SNPs, results must be balanced by research that includes effects from rare but highly penetrant variants. Additionally, although the adoption design of study 1 allows passive *r*GE to be disentangled from associations underlying family relationship and child outcomes, passive *r*GE may still be an issue in study 2, although this would likely have inflated the main effect of the PGS, which was negligible in every model.

Conclusion

This thesis found support for the hypothesis that home chaos in early childhood is predictive of externalizing problems in middle childhood but does not support the hypothesis that home chaos and genetic risk will interact following the vulnerable-stable model of GxE. Instead, study 2 provided some support for an interaction following the diathesis-stress model, although the support is weak. Both studies found results for main effects of home chaos on externalizing problems before inclusion of earlier externalizing, as well as null results for genetic influence on externalizing problems, contrary to the general findings of the field. Further, only one of the two studies found evidence for a gene x home environment interaction predicting externalizing. These results indicate that future research may benefit from examining other environmental variables and further highlight the need for novel statistical genetic approaches that better capture the variance of specific genetic markers. This research supports previous findings indicating that home chaos is an important environmental factor in the development of externalizing problems but also indicates that much of its influence is likely through concurrent externalizing problems and may not interact in a noticeable way with genetic risk. Ideally, continuations of this research will identify specific environments that consistently interact with genetic risk to predict externalizing problems, allowing for more effective intervention in early childhood to most-affectively disrupt trajectories of externalizing.

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