

Gene by Environment Interaction and Adaptive Functioning in Maltreated and
Nonmaltreated African American Children: A Structural Equation Mixture Model

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Dedication

This thesis is dedicated to the late Herbert Pick Jr., from whom I took my first child psychology course from. Herb always encouraged me to think big and shared with me the pleasure of winter camping.

Abstract

This study used a structural equation mixture model to test for an interaction between genetic variation and child maltreatment experiences predicting profiles of multi-domain adaptive functioning. Children aged 6- to 13- years ($N = 1004$) were recruited to attend a research day camp. Half of the children were recruited based on substantiated maltreatment histories, the other half were non-maltreated but matched on socio-economic status. During the camp, saliva was collected and 12 genetic-variants known to confer *environmental sensitivity* (ES) were genotyped. Measures were of prosocial behavior, antisocial behavior, withdrawn behavior, and depression were also collected. These four indicators of adaptive functioning were used in a latent class analysis (LCA). A 4-class solution was selected as a best-fitting model. The four classes characterized ‘well-adjusted’, ‘externalizing’, ‘internalizing’, and ‘socially-dominant’ groups. The number of maltreatment subtypes experienced significantly predicted this latent class variable controlling for sex and age ($\text{Wald}=35.3, df=3, p<0.000$). The 12 genetic-variants were formed into one formative factor. The interaction of this polygenic formative factor and the maltreatment variable (GxE) also significantly predicted the latent class variable controlling for sex, age, an age-by-maltreatment interaction term, and a sex-by-polygenic factor interaction term ($\text{Wald}=13.5, df=3, p=0.004$). Specifically, significant GxE odds ratios were present in the pairwise comparisons of membership in the externalizing class versus the well-adjusted class as well as the externalizing class versus the socially-dominant class. High genetic factor scores appeared to buffer the effects of maltreatment, thereby contributing to more resilient profiles of adaptive functioning.

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Introduction

Child maltreatment, in the form of abuse and/or neglect perpetrated by a caregiver, is considered one of the most destructive environmental pathogens that a child can experience and is a major public health concern (Cicchetti & Toth, 2005; Vachon, Krueger, Rogosch, & Cicchetti, 2015). Maltreated children are at disproportional risk of developing problems in almost every domain (emotional, cognitive, social, etc.) of psychological health (Cicchetti, 2016). Despite experiencing the trauma of abuse and neglect, not all maltreated children develop along paths of maladaptation. Numerous resources in maltreated children's lives can contribute to resilient functioning (Cicchetti, 2013). These protective and promotive factors exist at multiple-levels-of-analysis, ranging from genetic influences, to personality influences, to family and cultural level influences. A majority of studies that have studied resilience in maltreated children have focused primarily on personality/behavior, family, and cultural level resources (Cicchetti, 2013; MacMillan, 2011). However, recent technological advancements in molecular genetics have afforded researchers the ability to examine particular genetic variants, which may have protective (or vulnerability) effects for maltreated children (Caspi et al., 2002). These types of studies examine what are known as *gene-by-environment interaction* (GxE) effects, wherein the impact of the environment (such as maltreatment) on development depends on genetic variation.

Variation in genes that predict divergent outcomes for maltreated children tend to be genes that are thought to underlie generalized *environmental sensitivity* (ES), which refers to the degree to which individuals perceive, process, and respond to environmental

input (Cicchetti & Rogosch, 2012; Pluess, 2015). Carriers of more ES gene-variants tend to have more sensitive nervous systems and are thus potentially more vulnerable to the harm inflicted by maltreatment. Conversely, individuals who carry less ES gene-variants may be buffered to some degree from the impacts of abuse. Several GxE studies of child abuse have demonstrated these effects; however, the vast majority have investigated only one psychological outcome at a time (i.e., antisocial behavior) (McRory, De Brito, & Viding, 2012). In studies of resilience, examining variation in multiple domains of psychological health is crucial. Manifesting resilience does not simply refer to the absence of any one problem behavior (such as antisocial behavior) but rather suggests competence in several areas of development despite experiencing adversity (Masten, 2001). In fact, to date, only one study (Cicchetti & Rogosch, 2012) has examined how ES gene-variants interact with child maltreatment to influence multiple domains of adaptive functioning.

The current study aims to examine if the effects of child maltreatment on the development of adaptive functioning depend on variation in ES genes. This study will build upon important previous foundational work in several key ways. First, a formative factor will be used to combine the effects of individual ES gene-variants. This method has the advantage of accounting for the fact that some gene-variants may contribute more or less to adaptive functioning than other variants. Second, a structural equation mixture model (SEMM) will be tested. An SEMM combines both *person-centered* and *variable-centered* methodologies, a hybrid approach quickly gaining favor in resilience research (Masten, 2015). Like a traditional structural equation model (SEM), an SEMM combines

both a measurement model/s and structural model. In this study a latent class analysis (LCA) will be preformed on indicators of adaptive functioning (prosocial behavior, antisocial behavior, withdrawn behavior, and depression), thereby modeling groups of children with different profiles of adaptive functioning (i.e., person-centered). The resulting latent class variable will be embedded in a larger structural model wherein class membership will be predicted by maltreatment experiences, a polygenic factor, and their interaction (GxE) (i.e., variable-centered). Using a SEMM to study GxE effects on adaptive functioning in maltreated children is novel. Finally, additional ES genes not originally investigated in Cicchetti and Rogosch (2012) will be included in this study.

Effects of Child Maltreatment on Development

In the year 2014, Child Protective Services in the United States reported that 6.6 million children experienced some form of maltreatment, with a staggering 1,546 fatalities resulting from abuse (U.S DHHS, 2015). Global prevalence rates of self-reported child maltreatment estimate that 18% of girls (7.6% of boys) experience sexual abuse, 22.6% of children experience physical abuse, 36.3% experience emotional abuse, and 16.3% experience physical neglect (Stoltenborgh, Bakermans-Kranenburg, Alink, & IJzendoorn, 2014). The total lifetime U.S. economic burden of child maltreatment, resulting from cases in 2008 alone, was estimated at \$585 billion (Fang, Brown, Florence, & Mercy, 2012). Children with a history of maltreatment often fail to receive the intellectual stimulation, guaranteed safety and nutrition, and social support necessary for healthy development (Cicchetti & Lynch, 1995). Instead, the physical, sexual, emotional, and/or neglectful damage experienced frequently results in severe

abnormalities across multiple domains of psychological and physical health functioning. These traumatic experiences not only affect development in childhood but also often set forth in motion a cascade of deleterious outcomes throughout the entire life-course (Cicchetti, 2016).

In terms of psychopathology, maltreated children tend to exhibit increased rates of depression, bipolar disorder, substance abuse disorders, antisocial personality disorder, and attention deficit hyperactivity disorder, among others (Daruy-Filho, Brietzke, Lafer, & Grassi-Oliveira, 2011; Jaffee, Caspi, Moffitt, & Taylor, 2004; Johnson, Smailes, Cohen, Brown, & Bernstein, 2000; MacMillan et al., 2014; Toth, Manly, & Cicchetti, 1992). In addition to mental illnesses, children who have experienced abuse or neglect display more deficits in cognitive abilities, emotion regulation, pro-social behaviors, interpersonal relationships, and academic functioning as compared to their non-maltreated peers (Crozier & Barth, 2005; Hong, Espelage, Grogan-Kaylor, & Allen-Meares, 2012; Kim & Cicchetti, 2010; Teisl & Cicchetti, 2008). Moreover, maltreated children are at heightened-risk for exhibiting abnormalities in stress biology (Doom, Cicchetti, & Rogosch, 2014), autonomic nervous system reactivity (McLaughlin, Sheridan, Alves, & Mendes, 2014), and brain function/structure (Dannlowski et al., 2012). Finally, child abuse has been associated with cardiovascular disease (Batten, Aslan, Maciejewski, & Mazure, 2004) and obesity (Danese & Tan, 2014) in adulthood.

The specific effects, if any, of particular subtypes of maltreatment (i.e., physical, emotional, sexual, neglect) are largely undetermined and extremely difficult to study. Most maltreated children experience multiple subtypes of abuse, making inferences about

the pure effects of any one subtype challenging to decipher (Manly, Kim, Rogosch, & Cicchetti, 2001). Some studies do try to isolate the effects of particular types of abuse. For example, large epidemiological analyses have revealed that sexual abuse in women is highly predictive of adult substance use (Wilsnack, Vogeltanz, Klassen, & Harris, 1997). Twin and adoption work has supported a causal role between physical abuse and subsequent antisocial behaviors (Jaffee et al., 2004). Despite these findings, Vachon, Krueger, Rogosch, and Cicchetti (2015) investigated widely held notions about the effects of child maltreatment via SEM. Contrary to popular belief, Vachon et al. found that effects from different types of abuse are largely equivalent in terms of affecting broad indices of psychological health. That is, no one type of abuse had a greater affect on development than any other type of abuse. Moreover, cumulative child maltreatment predicted greater problems in externalizing and internalizing domains of functioning generally, but no one specific psychiatric outcome was affected in particular. Thus, it appears that child maltreatment impacts psychological functioning in a non-specific manner (affecting multiple domains) and in an equivalent manner (no one type of abuse particularly damaging).

Resilience and Child Maltreatment

The overwhelming majority of abused and neglect children are affected deleteriously by their traumatic experiences. The failure of caregivers to appropriately provide a safe and nurturing context for normal development is considered one of the most destructive challenges that face some children (Cicchetti & Lynch, 1995). However, developmental processes operate in a *probabilistic-epigenesis* manner, meaning that

bidirectional influences across multiple-levels-of-analysis (from genes to society) give rise to both *equifinality* and *multifinality* (Cicchetti & Rogosch, 1996; Gottlieb, 2007). Of particular relevance to resilience research is the concept of multifinality, which refers to divergent trajectories of development despite similar starting points. Indeed, not all maltreated children follow along paths of maladaptation; instead children have a remarkable capacity to demonstrate resilient functioning (Cicchetti, 2013; Masten, 2001; Masten & Cicchetti, 2012).

The concept of resilience refers to the complex and dynamic capacity of individuals to recover or withstand adversities that have the potential to significantly undermine development (Masten, 2011). Manifesting resilient functioning does not simply refer to an absence of psychopathology, but rather indicates obtaining adaptive levels of developmental competence across multiple domains important for life success. Adaptive functioning in school-aged children with a history of maltreatment is often defined in terms of exhibiting competent levels of prosocial behavior and academic outcomes, as well as showing low levels of aggressive-disruptive behavior, withdrawn behavior, and psychopathology (Cicchetti & Rogosch, 2012; Cicchetti & Rogosch, 1997; Cicchetti, Rogosch, Lynch, & Holt, 1993; Flores, Cicchetti, & Rogosch, 2005; MacMillan, 2011). Non-negligible percentages of maltreated children do in fact demonstrate these across-the-board proficiencies in developmental milestones, thereby exhibiting resilient functioning (Cicchetti & Rogosch, 1997). The goal of resilience research is to, in part, elucidate the manner by which children faced with adversity demonstrate such varied developmental outcomes. Therefore, identifying the protective

and promotive factors in maltreated children's lives, which contribute to resilient functioning is a key step (Cicchetti & Rogosch, 2012; Masten, 2011).

Several of these factors have been identified as particularly important for maltreated children, and moreover, these factors range from individual features (i.e., particular genes and personality traits), to social features (i.e., presence of a supportive adult role model), to community and cultural features (i.e., an active community center) (for reviews see Cicchetti, 2013; MacMillan, 2011). Building resilience starts at the top; safe neighborhoods and high quality education are undeniable influences that help foster resilience in individuals with a history of childhood adversity including abuse and/or neglect (Benzies & Mychasiuk, 2009; Haskett, Nears, Ward, & McPherson, 2006). Consistent personality and behavioral predictors of resilient functioning in maltreated children include having strong *self-regulatory behaviors* and *self-esteem* skills (Baker, 2009; Block & Block, 1980; Cicchetti & Rogosch, 1997; Cicchetti et al., 1993; Flores, Cicchetti, & Rogosch, 2005). On the social level, the presence of supportive peer groups and compassionate non-abusive caregivers or adult role models are incredibly important resources that help maltreated children overcome their challenges (Cicchetti, 2013; MacMillan, 2011).

The preponderance of resilience research in child maltreatment has focused on these crucial personality and social/community mechanisms, with great success (Cicchetti, 2013). Though, with advancements in neuroscience and genetics, resilience researchers have recently pointed to the need to also study biological risk and protective mechanisms (Cicchetti & Curtis, 2007; Cicchetti, 2010; Cicchetti & Rogosch, 2012; Reul

et al., 2015). For example, Curtis and Cicchetti (2007) found that asymmetric electroencephalogram (EEG) activity in maltreated children was an important predictor of resilient functioning. Moreover, Cicchetti and Rogosch (2007) found that high morning levels of the stress hormone cortisol and atypical rises in the hormone dehydroepiandrosterone (DHEA) were both independent predictors of adaptive functioning. Biological influences on adaptive functioning extend beyond the neural and hormonal level to the genetic level. The most commonly used method of studying how genetics may influence psychological resilience is testing for *gene-by-environment interaction* (GxE) effects. When a GxE effect is present, the particular genes and environments being studied act in a multiplicative manner in their contribution to a phenotype (such as behavioral functioning). Namely, the effect of experiencing a particular environment on a phenotype, for a given person, would depend on which genetic variant/s that person carried. Vice versa, a GxE can be interpreted as varying magnitudes of genetic effects depending on the level of exposure to a particular environment. Coincidentally, the first published GxE effect in the behavioral-science literature was from child maltreatment study published by Caspi and colleagues (2002) in the journal *Science*. Caspi et al. demonstrated that the effect of maltreatment on the development of antisocial behaviors depended, in part, on children's genetic make-up (specifically variation in the *MAOA* gene). Since the publication of that landmark study, there has been a boom in the use of GxE techniques to understand divergent outcomes in children with a history of adversity, in particular abusive trauma (Kim-Cohen & Turkewitz, 2012).

Several candidate genes, across a host of biological systems, have been reported as moderators of maltreatment outcomes, with varying success in replication (i.e., Risch et al., 2009; Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014). Initial reports of moderate-to-large GxE effect sizes based on small sample-size studies and improper use of control variables lead to justified criticism of the field as a whole (Duncan & Keller, 2011; Keller, 2014). Nevertheless, large meta-analyses continue to show small (but robust) GxE effects relating to child maltreatment outcomes (Byrd & Manuck, 2014; Sharpley et al., 2014). Evidence for GxE effects extends beyond purely statistical evidence; for example, Klengel et al. (2013) revealed an epigenetic mechanism that explained (mediated) the interaction between a common polymorphism in the FKBP5 gene and child maltreatment with relation to the development of post-traumatic stress disorder (PTSD). In fact, GxE effects are thought to account for over 75% of methylation in variably methylated regions (VMR, an epigenetic biomarker) in the genome (Teh et al., 2014). In other words, it appears as if the multiplicative contribution of common genetic variation and environmental exposures is most important for driving foundational differences in biological activity (i.e., gene expression) and thus potentially explaining resilient functioning (Boyce & Kobor, 2015; Dudley, Li, Kobor, Kippin, & Bredy, 2011).

Review of GxE findings in the maltreatment literature.

One of the most commonly studied genetic variants in the maltreatment literature is the 5-HTT-linked polymorphic region (5-HTTLPR) of the serotonin transporter (*SLC6A4*) gene promoter. This variant is characterized by a 44bp in-del with either a short (deleted) or long (inserted) copy of the repetitive element. Several studies have

demonstrated that maltreated carriers of one or two short alleles of 5-HTTLPR are disproportionately at-risk for developing problems, in particular depression (i.e., Caspi et al., 2003; Cicchetti & Rogosch, 2014; Cutuli, Raby, Cicchetti, Englund, & Egeland, 2013; Kaufman et al., 2004; Li & Lee, 2010). Two large meta-analyses, which specifically examined maltreatment as a stressor, confirmed these findings (Karg, Burmeister, Shedden, & Sen, 2011; Sharpley et al., 2014). It is unclear exactly how 5-HTTLPR interactions operate, although exaggerated amygdala activity in short-allele carriers (Canli & Lesch, 2007) or epigenetic processes are suspected mechanisms (Beach et al., 2014).

The *FKBP5* gene encodes the FK506 binding protein 5, which is known to alter stress system reactivity via control over glucocorticoid receptors (GR) (Binder, 2009). A single nucleotide polymorphism (SNP), rs1360780, in the *FKBP5* gene has been found to interact with child maltreatment to predict a variety of developmental outcomes. In particular, T-allele carriers appear differentially susceptible to the effects of abuse (i.e., Appel et al., 2011; Binder et al., 2008; Cicchetti, Rogosch, Hecht, Crick, & Hetzel, 2014). In a seminal study, the Binder lab found that an epigenetic process of demethylaiton mediated, or explained, the interaction of the T-allele and abuse predicting PTSD (Klengel et al., 2013). Another stress response gene with evidence of maltreatment interactions is the corticotropin-releasing hormone receptor 1 (*CRHR1*). Corticotropin-releasing hormone is a primary mediator of the hypothalamic-pituitary-adrenal axis (HPA), the primary stress system. T-allele carriers of the rs110402 SNP of *CRHR1* have been found to be particularly sensitive to developing maladaptive behaviors when

maltreated (i.e., Bradley et al., 2008; Cicchetti et al., 2011; Cicchetti & Rogosch, 2014). Cortisol dysregulation has been suggested as a possible mediator of *CRHR1*-maltreatment interactions (Cicchetti et al., 2011; Tyrka et al., 2009).

Variation within the oxytocin receptor gene (*OXTR*) has been shown to moderate developmental outcomes for individuals with a history of abuse. Maltreated carriers of the GG genotype of the rs53576 SNP appear to be more likely to develop emotion dysregulation (Bradley et al., 2011), internalizing behaviors (Hostinar, Cicchetti, & Rogosch, 2014; McQuaid, McInnis, Stead, Matheson, & Anisman, 2013) and borderline personality symptoms (Cicchetti et al., 2014). Oxytocin is known to play a crucial role in social behaviors such as attachment, empathy, trust, and social support (Ebstein, Knafo, Mankuta, Chew, & San Lai, 2012; Hostinar et al., 2014). Carriers of the rs53576 G allele are thought to exhibit heightened social awareness, possibly via differential cortisol functioning and/or differences in limbic-hypothalamic structure (Hostinar et al., 2014; Tost et al., 2010). Thus, G allele carriers may be more attuned to the negative social interactions of child abuse and therefore more susceptible to developing problem behaviors. Likewise, the A allele may serve as a protective factor, reducing risk of maladaptation.

A number of variants within genes responsible for the transmission, reception, and reuptake of the neurotransmitter dopamine have been found to interact with maltreatment experiences as well as many other forms of childhood adversity (see Beaver, 2008; Thibodeau et al., 2015). In general, variants, which contribute to less-efficient dopamine functioning are thought to increase sensitivity to environmental input

(Bakermans-Kranenburg & van IJzendoorn, 2011). Perhaps the most well-known such variant is the 7-repeat allele, a variable number tandem repeat (VNTR), of the dopamine receptor D4 gene (*DRD4*). Rather consistent evidence places carriers of the 7-repeat allele at particular risk of maladaptation in contexts of adversity as compared to non-carriers (i.e., Bakermans-Kranenburg & van IJzendoorn, 2011; Ellis et al., 2011; Park, Sher, Todorov, & Heath, 2011). Moreover, another variant in *DRD4*, the TT genotype of the rs1800955 SNP, has been found to predict less resilient functioning in maltreated children (Cicchetti & Rogosch, 2012). Within the dopamine transporter (*DAT1*) gene, the 10-repeat 3'UTR VNTR allele and the C alleles of the SNPs rs40184 and rs27072 are thought to confer heightened susceptibility to harsh environments. Related to the dopamine receptor D2 (*DRD2*) gene, the T(A1) and ‘del’ versions of the SNPs rs1800497 and rs1799732, respectively, have evidence of conferring vulnerability to maltreatment experiences. Finally, carriers of the ‘val’ allele of the catechol-O-methyltransferase (*COMT*) rs4680 SNP appear at most risk of maladaptation in the face of adversity (Davies, Cicchetti, & Hentges, 2015; Groleau et al., 2012; Li & Lee, 2012; Perroud et al., 2010; Thibodeau et al., 2015). A meta-analysis by Bakermans-Kranenburg and van IJzendoorn (2011) found robust evidence that these dopaminergic variants interact with childhood experiences. Inefficient dopaminergic signaling induced by these variants may contribute to reduced reward sensitivity, which in the context of familial adversity may predispose children to impulsive behavior and impaired social learning (Weeland, Overbeek, de Castro, & Matthys, 2015).

The gene variants reviewed here relate to a host of neurobiological systems including neurotransmission, endocrinology, and the HPA axis. A majority of these genes are thought to contribute to *environmental sensitivity* (ES) (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011; Pluess, 2015). ES refers to individual differences in the degree to which individuals perceive, process, and respond to context. Included within the meta-framework of ES are the concepts of *differential susceptibility theory*, *diathesis stress*, *sensory processing sensitivity*, and *vantage sensitivity* (for review see Pluess, 2015). The first three concepts are relevant to studying resilience in child maltreatment outcomes, as those frameworks describe individual variation in response to negative (and positive) environments. Vantage sensitivity research, conversely, only studies interaction effects with regards to positive contexts. A growing number of studies, which composite many of these variants into polygenic indices support the notion of a cumulative genetic ES effects (Beaver, 2008; Beaver, Sak, Vaske, & Nilsson, 2010; Belsky & Beaver, 2011; Bousman, Gunn, Potiriadis, & Everall, 2016; Cicchetti & Rogosch, 2012; Thibodeau et al., 2015). That is, the more ES variants carried, the more likely one is to develop maladaptive behaviors in contexts of trauma such as maltreatment.

While there is some reason to believe that particular ES gene-variants have effects only on specific types of behaviors, such as 5-HTTLPR with depression and *MAOA* with aggression, virtually all ES variants have demonstrated moderation effects across multiple, broad domains of psychological functioning (Moore & Depue, 2016). Given the broad biological roles of the various ES genes (neurotransmitter reuptake, transport, etc.),

the largely non-specific effects on behaviors are perhaps to be expected. Likewise, Belsky and Pluess (2013) argue that ES gene variants likely relate to a domain-general phenotype of plasticity rather than susceptibility to any one specific behavior. Given the likely domain-general nature of the polymorphisms studied under the ES umbrella, cumulative load of these variants should contribute to worse developmental outcomes across multiple domains of functioning in maltreated children. Indeed, Cicchetti and Rogosch (2012) found that maltreated children with multiple forms of abuse who carried three or four ES variants were more likely to score lower on a composite index of resilient functioning (comprised on withdrawn, depressive, antisocial, prosocial, and school functioning).

Characterizing adaptive functioning.

One challenge for resilience researchers deals with how to actually characterize adaptive functioning as a multi-dimensional construct. The most basic definition of resilience requires individuals to have both experienced a significant threat to stability and to have demonstrated competence in important areas of development. The configural nature of this definition is inherently categorical (or focused on groups of individuals); as such, some researchers prefer to study and characterize resilience using *person-centered* statistical approaches (Masten, Gest, Tellegen, Garmezy, & Ramirez, 1999). Person-centered statistical approaches attempt to characterize similarities and differences among individuals based on the assumption that the population is heterogeneous in terms of the relationships between variables (Masyn, 2013). However, more contemporary definitions of resilience (see Masten, 2011; Masten, 2015) put more focus on the dynamic processes

involved in obtaining adaptive functioning in contexts of adversity. Modeling such complex interactions between risk and protective factors is generally best-achieved using *variable-centered* approaches (Masten et al., 1999). Variable-centered, as opposed to person-centered, approaches tend to analyze the relationships among variables (Muthén & Muthén, 2000). However, the person- versus variable-centered nomenclature is slightly misleading. In both cases, variables are being analyzed. The difference is whether the joint distribution of the variables is modeled at the population level, assuming it applies to all individuals (variable-centered), or is modeled at a subgroup level assuming population distribution is the result of a mixing of a finite number of group-specific distributions (person-centered) (Masyn, 2013).

Strictly person-centered approaches used in the resilience literature tend to cluster children in terms of both environment and adaptive functioning (i.e. high adversity + high competence vs. high adversity + low competence) (i.e., Brody et al., 2013; Masten et al., 1999). Strictly variable-centered approaches generally form continuous composites of adaptive functioning and study risk and protective factors as predictors (Daining & DePanfilis, 2007; Luther, 1991). Some researchers use hybrid models, which combine both person- and variable-centered techniques (Cicchetti & Rogosch, 1997; Cicchetti & Rogosch, 2012; Cicchetti et al., 1993; Flores, Cicchetti, & Rogosch, 2005; Masten & Tellegen, 2012). These types of models are appealing and increasingly utilized in the resilience literature (Masten, 2015). The basic definition of resilience includes the categorical notion of *doing well in multiple domains* (Masten, 1999). Thus, it is perhaps valuable, if one wants to make conclusions about resilience, to quantify adaptive

functioning in a person-centered manner using a categorical variable. Moreover, collapsing multiple dimensions of adaptive functioning into a single dimension disregards potential dis-ordinal groups of children high on some variables but low on others. Though, to understand the risk and protective mechanisms, which explain variability in adaptive functioning, a variable-centered technique is also preferred. Hybrid models, therefore, have grown in popularity, in part, because of their ability to incorporate both of these approaches. This study will employ one such type of hybrid model, known as a structural equation mixture model (SEMM). An SEMM involves testing a structural model with one or more categorical latent variables along with one or more continuous factors.

The Current Study

The overall goal of the current study is to examine whether common variation (polymorphisms) in genes thought to confer environmental sensitivity moderates the effects of child maltreatment on multi-domain adaptive functioning. This study will hopefully help elucidate the role of ES genes in either hindering or contributing to more resilient profiles of adaptive functioning in maltreated, and non-maltreated children. Of particular interest to this study is the impact of the number of maltreatment subtypes experienced on adaptive functioning. Based on work by Vachon et al (2015), there is little evidence to suggest that there any specific effects on development from any one type of maltreatment subtype. However, there is substantial evidence that the number of maltreatment subtypes experienced negatively associates with adaptive functioning (i.e., Cicchetti & Rogosch, 2012). That is, children who have experienced 3 or 4 subtypes of

abuse are generally worse off, across multiple domains, than children who have experienced 1 or 2 subtypes or none at all. This study will use an all African-American sample of children for two primary reasons. First, research with African-American children is severely underrepresented in the current behavioral-science literature, especially the genetic literature (Lewis, 2003). Second, genetic analyses are more straightforward when only one ancestral group is studied at a time because common genetic variation can covary with ancestral origin, possibly confounding any genetic results. Moreover, the vast majority of the original sample of maltreated and non-maltreated children is African-American.

Often, when categorizing individuals into classes of adaptive functioning, researcher-employed cut-offs are relied upon such as the ‘75th percentile’, ‘.5 SD above the mean’, or ‘upper-third of group’ (Criss, Pettit, Bates, Dodge, & Lapp, 2002). These “naïve” approaches are potentially problematic for a variety of reasons. Naïve profiling treats all indicators the same, fails to account for measurement error, and fails to account for classification accuracy (Masyn, 2013). One modeling technique that takes into account the shortcomings of naïve profiling is *latent class analysis* (LCA). LCA is an exploratory latent variable modeling technique wherein the latent variable is categorical rather than continuous as with a traditional latent factor. The nature and number of latent classes is derived from a series of step-wise class enumerations (Masyn, 2013). Similar to an exploratory factor analysis, a best-fitting measurement model representing a finite number of component distributions is selected. The few studies to date that have used LCA to characterize multi-domain adaptive functioning, in terms of risk and resilient

profiles, have illustrated meaningful groups. For example, Yates and Grey (2012), using LCA, uncovered a four-class solution of multiform competence in foster care children including subgroups labeled as *resilient*, *maladapted*, *internally resilient*, and *externally resilient*. Brody et al. (2013) reported on unique risk and resilience profiles of children, which varied in terms of whether or not the profiles were more physical or mental health-related. Finally, Lai et al. (2015) found multiform profiles of risk and resilience following hurricane Katrina including individuals with uniquely *internal distressed profiles*, *PTSD profiles*, or *stress-resistant* profiles.

In the current study, a latent class analysis will be formed on four indicators of psychological functioning including prosocial behavior, antisocial behavior, withdrawn behavior, and depression. The resulting latent class variable will model different groups of children with similar profiles of adaptive functioning. This latent class variable will then be imbedded in a structural model with predictor variables. A variable representing the number of maltreatment subtypes experienced will be used to predict membership in each latent class. Furthermore, 12 gene-variants known to confer ES will be examined as potential moderators of any maltreatment-latent class associations. Instead of examining each gene's moderation effects individually, a polygenic factor will be created to test the cumulative effect of genetic variation. Polygenic indices are quickly gaining traction in the GxE literature as a means of testing the cumulative effects of multiple genes (Belsky & Beaver, 2011; Cicchetti & Rogosch, 2012; Thibodeau et al., 2015; Wray et al., 2014). Traditionally, polygenic indices are formed by simply summing the number of gene-variants that a person carries. The resulting polygenic index is then used to predict

outcomes directly or in interaction with another variable (such as maltreatment). The primary limitation of polygenic indices is that most are un-weighted. Un-weighted indices assume that each gene variant contributes equally to the index. In reality, particular gene-variants are likely to have more or less of an individual effect on an outcome than other variants. Such unequal effects should be accounted for through proper weighting.

In some fields of epidemiology, similar indices, termed polygenic risk scores are used to predict disease outcomes. Generally these polygenic risk scores are weighted based on genome-wide association study (GWAS) findings (Dudbridge, 2013). Gene-variants with larger GWAS effect sizes would be weighted higher in the risk score than variants with smaller effect sizes. In other words, these risk scores are considered *fixed-weight composites* because indicator weights are determined *a priori* (Grace & Bollen, 2008). However, polygenic indices used in GxE research are generally constructed based on the use of candidate gene-variants and not variants pulled from GWAS results. The weighting of polygenic indices used in candidate GxE research, therefore, would need to be based on a researcher's sample data. These types of variables are referred to as *unknown weights composites* (Grace & Bollen, 2008).

One method of creating an unknown weights composite is to form a *formative factor*, an approach that has, to date, never been used in GxE research. A formative factor is distinguished from the more traditional latent reflective factor. Conventional reflective factors are unmeasured variables whose variation is conceptualized to cause or explain variation in, and among, their indicators (i.e. arrows pointing from factor to indicators),

thereby necessitating a correlation between indicators (Treiblmaier, Bentler, & Mair, 2011). Conversely, a formative factor is conceptualized as being formed by its indicators (i.e., arrows pointing from indicators to factor), requiring no correlation between indicators (Bollen & Bauldry, 2011). Formative factors come in many forms, including true latent factors with estimated disturbance terms (measurement error accounted for) as well as factors assumed to have no residual variation. The latter type of factor is not latent, but rather is an exact linear combination of weighted indicators, sometimes referred to simply as a weighted composite (Bollen & Bauldry, 2011). The formative indicators are weighted as a function of what the formative factor is predicting, such that the indicator weights represent the indirect effect of each indicator on an outcome via the factor. By themselves, formative factors are not identified, meaning there is no unique solution for the indicator parameters (weights). To identify a formative factor it must be embedded in a model in which it predicts another variable. Indicator weights vary depending on what the factor predicts, which by some is considered a criticism of the formative factor approach to measurement (Grace & Bollen, 2008). However, if a researcher's goal is to form a composite variable, wherein the indicators' contributions to the composite are weighted in terms of their effects on an outcome, then a formative factor approach is quite justified. Formative factors with residual variances set to zero assumes very little measurement error in the indicators (Bollen, 2011). However, genetic variables are generally measured using extremely precise genotyping technologies with very low, if any, measurement error. In summary, a formative factor (weighted composite) will be used to represent the cumulative polygenic effects of the 12 ES genes.

variants used in this study. An interaction between the number of maltreatment subtypes and the polygenic formative factor, predicting latent class membership in adaptive functioning, will be a test of GxE.

Aims

This project has two major aims:

1. Describe heterogeneity in multi-domain, adaptive functioning in African-American maltreated and nonmaltreated children of low socioeconomic background. That is, in an exploratory manner, elucidate the number and nature of a finite number of “adaptive functioning” groups of children.
2. Predict membership in “adaptive functioning” classes based on the number of maltreatment subtypes experienced, a polygenic formative factor comprised of 12 ES gene-variants, and the interaction between them (GxE).

Hypotheses

1. The number of maltreatment subtypes will be significantly associated with latent class membership, thereby distinguishing classes of adaptive functioning.
2. The interaction between the polygenic factor and the number of maltreatment subtypes will also significantly associate with latent class membership.

Methods

Participants

Children aged 6- to 13- years ($N = 1004$; M age = 10.09, $SD = 1.60$) were recruited to participate in a research-based, summer camp developed for low-income youth. Nonmaltreated comparison children ($n = 512$) and maltreated children ($n = 492$) encompassed the complete sample of participants. Among the participants, 495 were girls and 509 were boys. The sample was entirely African-American as indexed by the Add Health system for coding race and ethnicity (<http://www.cpc.unc.edu/projects/addhealth/data/code/race>) (DeYoung, Cicchetti, Rogosch, Gray, Eastman, & Grigorenko, 2011). A single nucleotide polymorphism (SNP) panel of 106 ancestral informative genetic markers (AIMS) was utilized to classify individuals into African, European, and Native American descent (Lai et al., 2009; Yaeger et al., 2008) to verify an accurate degree of homogeneous ancestry. This sample had a mean proportion of African-American ancestry of .93, validating genetic homogeneity.

Recruitment procedures.

Informed consent was obtained from parents of all participants. Furthermore, consent was given for examination of Department of Human Services (DHS) records pertaining to the recruited families. Maltreated children were identified by the county DHS as having experienced child maltreatment and were representative of youth receiving DHS services. To recruit maltreating families, a liaison from DHS contacted a random sample of eligible families and explained the study. Interested parents then signed a release to have

their contact information provided to the project team. Families were free to choose whether or not to participate as well as free to withdraw at any time. Detailed maltreatment information was obtained through comprehensive searches of DHS records and coded using operational criteria from maltreatment nosology specified by the *Maltreatment Classification System* (MCS: Barnett, Manly, & Cicchetti, 1993).

Maltreated children generally resided in socioeconomically disadvantaged backgrounds, a finding consistent with the demographics of maltreating families nationwide (National Incidence Study – NIS-4; Sedlak et al., 2010). Nonmaltreated children from socio-demographically comparable backgrounds were recruited from families receiving Temporary Assistance for Needy Families (TANF). A DHS recruitment liaison reached eligible nonmaltreating families, described the research project, and if parents were interested, their contact information was provided to the project team. Highly trained research assistants interviewed mothers of nonmaltreated children to ensure a lack of any prior maltreatment experiences and prior DHS involvement by administering the *Maternal Maltreatment Classification Interview* (Cicchetti, Toth, & Manly, 2003). Furthermore, DHS records were searched a year following camp attendance to confirm a lack of maltreatment experiences. Only children from families with no history of documented neglect or abuse were retained in the nonmaltreatment comparison sample. Finally, families who received DHS preventive services due to concerns of risk for maltreatment were excluded.

Procedure

Maltreated and nonmaltreated children attended week-long day camps and participated in research assessments. At each camp, children were assigned to groups of eight children of the same age and sex; half of the participants assigned to each group were nonmaltreated. Three trained camp counselors conducted each small group and were blind to maltreatment status of the children as well as study hypotheses. The camp lasted 7hrs/day for five days, providing 35 hours of child-counselor and peer-peer interactions. After assent, and in addition to recreational activities, children participated in a variety of research assessments (see Cicchetti & Manly, 1990, for detailed descriptions of camp procedures) including donating salivary and buccal DNA samples. Additionally, trained research assistants, also blind to study hypotheses and maltreatment status, conducted individual research assessments with children. Clinical consultation and intervention was provided if any concerns over danger to self or others emerged during the camp week.

Measures

The measures described below comprise only a subset of assessments conducted during the research camp. The context of the camp and measurement battery used provided a multi-informant, mult-domain evaluation of child functioning.

Indicators of adaptive functioning.

Peer measures.

Peer behavior ratings. After interacting with their peers during the week of summer camp, children evaluated the characteristics of their camp group peers via a sociometric peer ratings method on the last day of camp (cf., Bukowski, Sippola, Hoza, & Newcomb, 2000; Coie & Dodge, 1983). Counselors guided the sociometric assessment

with individual children. For each peer in the camp group, children were given six behavioral descriptors characterizing different types of social behavior. Children were asked to rate each peer on how characteristic the behavioral descriptor was for that peer on a three-point scale. In the current study, ratings from peers for cooperative behavior, disruptive behavior, shyness, and fighting behavior were used. All ratings from peers on each child for each of the social behavioral descriptors were averaged.

Counselor measures.

Pupil evaluation inventory. At the end of each camp week the Pupil Evaluation Inventory (PEI; Pekarik, Prinz, Liebert, Weintraub, & Neale, 1976) was completed by camp counselors for children in their respective groups. The PEI consists of 35 items yielding three homogeneous and stable social behavior factors, including likeability, aggression, and withdrawn behavior. Interrater reliabilities based intraclass correlations across the years of camp ranged from 0.72 to 0.85 ($M = 0.78$) for likeability, 0.85 to 0.90 ($M = 0.88$) for aggression, and 0.72 to 0.84 ($M = 0.78$) for withdrawal.

Counselor behavior ratings. Camp counselors completed seven-point ratings of children's behavior each day during three separate, 45-minute, observations during structured and unstructured camp activities (e.g., lunch, sports, free play, awards). Counselors rated children on 9 items tapping three domains of interpersonal functioning including aggressive behavior, socially withdrawn behavior, and prosocial behavior. Individual counselor assessments for each of the three scales across the three assessment occasions were averaged to generate individual child scores. Interrater reliabilities based on average intraclass correlations among pairs of raters across the years of assessment

ranged from 0.68 to 0.80 ($M = 0.76$) for prosocial, 0.70 to 0.84 ($M = 0.77$) for aggression, and 0.61 to 0.77 ($M = 0.71$) for withdrawn behavior.

Teacher report form. Counselor rated behaviors were evaluated at the end of each week by counselors' completion of the Teacher Report Form (TRF; Achenbach, 1991). The TRF is a validated, reliable, and widely used assessment of behavioral functioning from the perspective of teachers. This measure was used in the present study because camp counselors are able to observe children in a similar manner as teachers. The TRF, contains 118 items rated for frequency, assesses multiple dimensions of child behavioral symptomatology. In the present study, we examined the rule breaking, aggressive problems, and withdrawn subscales

Self-reported measure.

Children's Depression Inventory. The Children's Depression Inventory (CDI; Kovacs, 1982, 1992) is a widely used, valid, and reliable, self-report questionnaire to assess depressive behaviors in school-aged children. For each item, children chose from among three option statements, depicting increasing levels of depressive symptoms, in order characterize their experiences in the past 2 weeks. Internal consistency for the total scale has ranged from 0.71 to 0.89.

Measures of adaptive functioning.

Because there are multiple indicators of prosocial behavior, antisocial behavior, and withdrawn behavior these indicators were first parceled. Specifically, facet-representative parcels were used (Little, Cunningham, Shahar, & Widaman, 2002). These parcels involve averaging related, facet-specific indicators among individuals. The

resulting averaged composites (parcels) will be used as manifest indicators of the latent class variable. Advantages of using parcels includes estimating fewer parameters, reducing sources of sampling error, lowering indicator-to-subject ratio, and lowering the likelihood of residual covariation (Little et al., 2002). All indicators were z-scored and averaged together to form prosocial behavior, antisocial behavior, and withdrawn behavior parcels. The prosocial parcel included the cooperative behavior, likeability, and leadership subscales of the peer behavior ratings, the likability subscale of the PEI, and the cooperative behavior subscale from the counselor behavior ratings, for a total of five indicators averaged together. The antisocial parcel included the disruptive behavior and fighting behavior subscale of the peer behavior ratings, the aggression subscale of the PEI, the aggressive behavior subscale of the counselor behavior ratings, and the rule breaking and aggressive problems subscales from the TRF for a total of six indicators averaged together. Finally, the withdrawn parcel included the shyness subscale from the peer ratings, and the withdrawn behavior subscales of the PEI, counselor behavior rating, and TRF.

The antisocial, withdrawn, and CDI distributions were highly, positively, skewed. Traditional transformations, such as log-transformations, were unable to normalize these skewed distributions. Generally, continuous indicators would be used in a *latent profile analysis* (LPA); however, class formation is sensitive to within class distributional assumptions. Skewed distributions...

One alternative is to discretize continuous variables, maintaining as much variability as possible along with conserving as much of the original distribution as

possible. These discretized variables can be utilized in a LCA, in which class formation is not sensitive to within class distributional assumptions. The difference between LCA and LPA is that LCA models use categorical/ordinal data whereas LPA models include continuous indicators. Because LCA uses categorical/ordinal data, there is no bias resulting from non-normality. Z-score ranges were used as cut-offs for creating ordinal categories. Criteria for discretizing included maximizing the number of ordinal categories with a minimum of 25 individuals in each category, while maintaining the overall original skew of the continuous parcel. Six categories were eventually derived from each parcel. The z-score range cut-offs for each category of the antisocial, withdrawn, and depression variables is 0= < -.5 SD; 1= >-.5 to 0 SD; 2= >0 to .5 SD; 3= >.5 to 1 SD; 4= >1 to 1.5 SD; 5 = >1.5 SD. The z-score range cut-offs for each category of prosocial variable is 0= < -1.0 SD; 1= >-1.0 to -.5 SD; 2= >-.5 to 0 SD; 3= >0 to .5 SD; 4= >.5 to 1 SD; 5 = >1 SD. Thus, each of the four adaptive functioning indicators is represented as a 6-category ordinal variable. See Table 1 for descriptive statistics for these indicators. Child maltreatment was associated with all variables, individually, except withdrawn behavior.

Predictors of adaptive functioning.

Maltreatment classification. The MCS (Barnett et al., 1993) has been shown to be an extremely reliable and valid measure for classifying child abuse/neglect typology (Bolger, Patterson, & Kupersmidt, 1998; English, Upadhyaya, Litrownik, Marshall, Runyan et al., 2005). The MCS codes all available information from DHS records, making independent determinations of maltreating environments rather than relying on case

dispositions and official designations. The MCS designates all subtypes of experienced child maltreatment (i.e., emotional maltreatment, neglect, physical abuse, sexual abuse) on the basis of operationalized criteria. DHS record coding was conducted by highly trained research assistants, doctoral students, and clinical psychologists. Coders meet strict reliabilities with criterion standards prior to coding any actual records. Coders demonstrated acceptable reliability with the criterion weighted κ 's ranging from .86 to .98. Reliabilities (κ 's) for the presence vs. absence of maltreatment subtypes ranged from .90 to 1.00.

Regarding subtypes of maltreatment, *neglect* refers to a failure to provide for the child's basic physical needs for adequate food, clothing, shelter, and medical treatment. In addition to inadequate attention to physical needs, forms of this subtype include lack of supervision, education neglect, and moral-legal neglect. *Emotional maltreatment* refers to extreme thwarting of children's basic emotional needs for psychological safety, acceptance and self-esteem, and age-appropriate autonomy. Examples of emotional maltreatment include belittling and ridiculing the child, extreme negativity and hostility, exposure to severe marital violence, abandoning the child, and suicidal or homicidal threats. *Physical abuse* pertains to the non-accidental infliction of physical injury on the child (e.g., bruises, welts, burns, choking, broken bones). Injuries range from minor to permanently disfiguring. Finally, *sexual abuse* refers to attempted or actual sexual contact between the child and a caregiver for purposes of the caregiver's sexual satisfaction and/or financial benefit. Events range from exposure to pornography or adult sexual activity, to sexual touching and fondling, to forced intercourse with the child.

Among the maltreated children, 81.7% had experienced neglect, 56.4% had experienced emotional maltreatment, 30.8% had experienced physical abuse, and 7.1% had experienced sexual abuse; 56.6% of the maltreated children had experienced two or more maltreatment subtypes. The number of maltreatment subtypes experienced, ranging from 0 (nonmaltreated) to 4 (having documented experience of all forms of child maltreatment at least once in their childhood) was used as the primary maltreatment variable.

ES genetic variables.

Based on the literature review, 12 genetic variants, thought to confer environmental sensitivity (ES) as well as having shown moderation effects on child maltreatment outcomes, were chosen for inclusion in the polygenic formative factor. For buccal cells, DNA was extracted and prepared for polymerase chain reaction (PCR) amplification using the Epicentre BuccalAmp DNA Extraction Kit (Epicentre, Cat. No. BQ090155C). DNA was first whole-genome amplified using the Repli-g kit (Qiagen, Catalogue No. 150043) per the kit instructions to preserve the availability of data over the long-term for this valuable sample. Then, amplified samples were diluted to a working concentration.

The rs1800955 polymorphism is located in the promote region of *DRD4* gene. This polymorphism was genotyped using a Taq Man SNP assay from Applied Biosystems, Inc. Individual allele determinations were made using Taq Man Genotyping Master Mix (Applied Biosystems, Catalog No. 4371357) with amplification on an ABI 9700 thermal cycler and analyzing the endpoint fluorescence using a Tecan M200 with JMP 8.0 (SAS, Inc., Cary, NC). The call rate was 99.5%. Specifically the ‘C’ allele was

coded as a vulnerability allele. The *DRD4* exon 3 VNTR length was determined by PCR amplifying DNA with primers DRD4 F3 (5'CGGCCTGCAGCGCTGGGA3') and DRD4 R2 D4 (5'CCTGCGGGTCTGCGGTGGAGT3') on a MasterCycler Gradient (Eppendorf, Inc). The Using a CEQ8000 (Beckman Coulter, Inc.), the resulting products were analyzed for length. The ‘7-repeat’ allele was coded as a vulnerability allele.

The *OXTR* rs53576 SNP was genotyped using a TaqMan SNP assay from Applied Biosystems, Inc. Allele determinations were made using Taq Man Genotyping Master Mix (Applied Biosystems, Catalog No. 4371357) with amplification on an ABI 9700 thermal cycler and analyzing the endpoint fluorescence using a Tecan M200 with JMP 8.0 (SAS, Inc.). The ‘G’ allele was coded as a vulnerability allele. *CRHRI* was genotyped using assays for the SNP rs110402 (C2544843, ABI, Bedford, MA). Individual allele discriminations were made with Taq Man Genotyping Master Mix (Applied Biosystems, Catalog No. 4371357) with amplification in an ABI 9700 thermal cycler and analyzing the endpoint fluorescence using a Tecan M200. The ‘T’ allele was coded as a vulnerability allele. The *DAT1*-VNTR was genotyped using the previously reported primers TGTGGTGTAGGGAACGGCCTGAG and CTTCCCTGGAGGTACGGCTCAAGG (Barr et al., 2001); the fragments were then analyzed on a 3130xl Genetic Analyzer (Applied Biosystems). The ‘10-repeat’ allele was coded as a vulnerability allele. DAT1 rs40184 and DAT1 rs27072 were genotyped according to (Davies et al., 2015), and the ‘C’ allele from each SNP was coded as the vulnerability allele.

The 5-HTTLPR samples were genotyped for fragment length polymorphisms of 5-HTTLPR with Hot Star Taq PCR Mix (Qiagen, Catalog no. 203205) with previously described primers (Gelernter, Kranzler, & Cubells, 1997), followed by fragment analysis using a CEQ8000 (Beckman-Colter, Inc., Fullerton, CA). Genotypes with one or two short (S) alleles of the 5-HTTLPR gene are generally associated with lower transcription and function of 5-HTT protein in vitro than genotypes with two long (L) alleles (Bevilacqua and Goldman, 2011). Recently, research identifying a SNP with a A>G substitution upstream from the promoter region has shown that L_G functions more similarly to the S allele than the L_A in its expression and binding potential (Praschak-Rieder et al., 2007). Therefore, an effective triallelic approach was used to categorize genotypes according to their relative efficiency in functioning. Thus either L_G or S alleles were coded as ‘vulnerability’ alleles.

FKBP5 was genotyped using assays for SNPs rs1360780 purchased from Applied Biosystems, Inc. (ABI, Bedford, MA) as C8852038_10. Individual allele discriminations were made using Taq Man Genotyping Master Mix (ABI Catalog No. 4371357) with amplification in an ABI 9700 thermal cycler and analyzing the endpoint fluorescence using a Tecan M200. If a genotype for either gene or SNP could not be determined after the first run, then it was repeated up to four times. The ‘T’ allele was coded as a vulnerability allele. *COMT* Val¹⁵⁸Met (rs4680) SNPs were genotyped using the TaqMan SNP Genotyping C__25746809_50 assay (Applied Biosystems; Grand Isle, New York). The ‘val’/‘G’ allele was coded as the vulnerability allele. Similar genotyping was

preformed on *DRD2* rs1800497 and rs1799732, with the ‘A’ allele and ‘del’ allele coded as the vulnerability alleles.

HWE was tested using the statistical software R version 2.15.2, with package ‘genetics’ version 1.3.8 (R Core Team, 2012; Warnes, 2012). No variants significantly deviated from HWE, except for the *DRD4*-VNTR variant ($\chi^2 (44, N = 995) = 255.28, p = .005$). A departure from HWE is not unusual for the *DRD4*-VNTR nor is it likely to bias the results given strict quality control to prevent genotyping error (DeYoung et al., 2011; Thibodeau et al., 2015; Xu, Turner, Little, Bleeker, & Meyers, 2002). Thus, the *DRD4*-VNTR was not excluded as an indicator of the formative factor.

All 12 genetic variants were coded as additive, dominant, or recessive. An additive coding scheme involved simply counting (0,1, or 2) the number vulnerability alleles in each variant. Dominant coding involves counting one or two vulnerability alleles (1) versus no vulnerability alleles (0), whereas recessive coding involves counting two vulnerability alleles (1) versus one or no vulnerability alleles (0). The literature on GxE is inconsistent regarding which genetic model (additive, dominant, recessive) is most appropriate for each variant, thus model comparisons were conducted using each type of coding scheme.

Data Analytic Approach

Latent class analysis.

Using *Mplus* version 7.4 data analysis software (Muthén & Muthén, 1998-2012), a latent class analysis (LCA) was conducted. LCA is a categorical latent variable modeling approach, which models unobserved population heterogeneity based on

response patterns among a set of observed, categorical indicators (Masyn, 2013). Class-specific item probabilities and class probabilities are the two primary sets of measurement and structural parameters derived from an LCA, respectively. Item probabilities refer to the probability of endorsing a particular item (or category of an indicator) conditional on class membership. Class probabilities correspond to the distribution of the categorical latent variable, reflecting the proportion of the population predicted to belong in each class (Masyn, 2013; Nylund, 2007).

Model building process.

Because there were no a priori assumptions about the number or nature of latent classes in this sample, an exploratory process of determining the best-fitting unconditional LCA was undertaken. Following use of best practices outlined by Masyn (2013), a series of LCA models was fit in an iterative fashion. The LCA procedure involves fitting a series of K -class models beginning with a one-class model and stopping at a K -class model that becomes not well identified (K_{\max}). Models were deemed not well identified if one or more of the following criteria were met: lack of best log likelihood value replication across a set of random start values, lack of model convergence, or an extraction of a class with a small estimated class size, which may indicate over-extraction. For each K -class model a host of statistical heuristics outlined below was recorded and compared across K -class models. The K -class model deemed to have the best combination of absolute fit, relative fit, classification accuracy, and model usefulness was chosen as the final model to be included in the structural component of the structural equation mixture model.

Model estimation.

To estimate latent class analysis parameters, *Mplus* uses the expectation-maximization (EM) algorithm for full information maximum-likelihood (FIML) estimation from incomplete data (Masyn, 2013; Muthén & Muthén, 1998-2012) assuming data is missing at random (MAR) (Little & Rubin, 2002). Random start values were utilized in an attempt to replicate a global maximum of the likelihood function rather than a local solution.

Evaluating model fit.

Unlike traditional factor analysis, no universally agreed upon measures of overall goodness of fit exist for LCA (Nylund et al., 2007). A combination of statistical indicators and substantive interpretation were used to determine the best number of latent classes (Masyn, 2013). The goal is to extract a well-fitting, parsimonious, yet meaningful measurement model. Overall fit was determined using an overall likelihood ratio model chi-square goodness-of-fit test. In terms of relative fit, the likelihood ratio test statistic (LTRS) for nested models was examined. The LTRS compares the fit to the data between two models, one nested in the other (K -class vs. $K + 1$ classes), in terms of the natural log of the likelihood function (LL) values. A p -value less than .05 for an LTRS means the null hypothesis can be rejected favoring a $K + 1$ classes. Another set of relative fit indices, referred to as information-heuristic criteria, was also examined including the Akaike information criterion (AIC), Bayesian information criterion (BIC), consistent Akaike information criterion (CAIC), and the approximate weight of evidence (AWE). Each of these information criteria weighs the fit to the data, in terms of LL values, for each model

by a complexity penalty. The penalty is slightly different for each information criteria and is a function of both sample size n and number of parameters d . Whichever model has a lower information criteria value is considered a better fitting model, however inferential tests of “how much better” do not exist. The approximate Bayes Factor (BF) and the approximate correct model probability (cmP) are comparison approximations derived from Bayesian statistics and are used to get a sense of how much better one model’s fit, in terms of information criteria, is compared to another model’s fit or a set of models (Masyn, 2013; Nagin, 1999). The BF compares two models ($BF_{A,B}$; need not be nested) in terms of the ratio of Model A’s probability of being correct to Model B’s probability of being correct assuming one of the two models is in fact correct. A $BF_{A,B}$ ratio of 1-3, 3-10, and greater than 10 represents weak, moderate, and strong evidence for a given model, respectively (DiCiccio, Kass, Raftery, & Wasserman, 1997). In contrast to $BF_{A,B}$, the cmP approximates the probability of Model A being the correct model in comparison to a set of J models being considered, assuming the true model is in fact one of the models being considered (Masyn, 2013; Nagin, 1999).

In addition to fitting the data well, a good model should contain classes or groups that have a high degree of response homogeneity and are well separated (Masyn, 2013). That is, individual response patterns on the LCA indicators should be largely similar within classes and dissimilar across classes. A variety of diagnostics estimate the degree of homogeneity in response patterns, classification precision, and class separation. These tools are meant to augment the absolute and relative fit diagnostics discussed above when deciding upon a final unconditional measurement model. Most of the classification tools

involve the use of *posterior class probabilities*, which are each individual's probabilities of being in each of the latent classes. These probabilities are based on the maximum likelihood estimates along with the individual's actual responses on the LPA indicator variables.

The first classification diagnostic to be discussed is *relative entropy* (E_K), which summarizes the overall classification precision, based on the posterior class probabilities, for the entire sample across all latent classes. When $E_K = 0$ the posterior classification is no better than chance, when $E_K = 1$ there is perfect classification (Ramasway, DeSarbo, Reibstein, & Robinson, 1993). Evaluation of classification uncertainty for each of the latent classes is computed using the *average posterior class probability* (AvePP). The AvePP is calculated by averaging the posterior class probability for each class, k, for all individuals whose highest posterior class probability is for Class k or their *modal class assignment*. AvePP values higher than .8 are indicative of adequate class separation and precision of classification (Masyn, 2013; Nagin, 2005). A similar summary of class-specific classification accuracy, which uses the AvePP, is the *odds of correct classification ratio* for a given class (OCC_k). The denominator of the OCC_k represents the odds of correct classification based random assignment using the estimated class proportions, and the numerator represents the odds of correct classification using the modal class assignments.

After all model fit and model usefulness tools have been applied, a single unconditional measurement model (the final LCA) will be selected for use in a structural regression model (Nylund & Masyn, 2008).

Structural equation mixture modeling.

The final unconditional LCA model chosen above will be embedded into a larger structural equation mixture model (SEMM). This step is equivalent to the SEM procedure of dropping an unconditional factor measurement model into a larger structural model. However, adding predictors, or outcome variables, into a LCA model may create unintended alterations in the estimated item and class probabilities (Masyn, 2013). One option to avoid this is to hard-classify individuals based on their most likely latent class membership (or model class assignment), which turns the latent class variable into an observed, grouping variable. Doing so fails to account for measurement error, or classification uncertainty. To overcome this shortcoming, an alternative three-step method will be utilized using *Mplus* version 7.4 (Asparouhov & Muthén, 2014). The first step involves saving the model class assignments from the chosen best-fitting unconditional LCA model. In step two, the modal class assignments are formed into a nominal variable and the measurement error rates from the unconditional model are derived by computing the logits of the average latent class probabilities for most likely class membership for each latent class. Finally, in step three, the structural model (with predictors added) is run with the nominal modal class assignment variable used as a single indicator of a latent class variable with the measurement error rates prefixed. Since a latent class variable is an unordered categorical variable, associations are in the form of multinomial logistic regressions.

For Hypothesis 1, the primary predictor will be the number of maltreatment subtypes experienced along with sex and age as control variables. To test hypothesis 2

primary predictors will include the number of maltreatment subtypes experienced as well as the polygenic formative factor, and a polygenic formative factor-by-maltreatment interaction term. To select a coding scheme for the polygenic formative factor indicators, three models (with primary predictors) will be ran with each model containing a formative factor with indicators either coded as additive, dominant, or recessive. The best fitting model in terms of a low BIC and GxE *p*-value, will be selected. Then the control predictors age, sex, and any interaction terms with covariates that associated with either maltreatment or the polygenic formative factor will be added to complete the final structural model (Keller, 2014). The conceptual model for this structural equation mixture model is depicted in Figure 1.

Results

Selecting an Optimal Latent Class Solution

The latent class enumeration results are provided in Table 2. A solution of seven classes was not well identified, thus consideration was only given for a 1- through 6-class solution. As is common in LCA, the fit indices gave somewhat conflicting information. Because of this, making the selection of an optimal solution was not a clear-cut decision. The LMR-LRT indicated no significant improvement in model fit beyond a 3-class solution. Moreover, the lowest BIC and CAIC values were for the 3-class solution. The most parsimonious *K*-class model with a high *BF* ratio, along with the *K*-class solution with a 100% *cmP* was also the 3-class solution. The lowest AWE was for the 2-class solution. The smallest *K*-class solution with a log-likelihood (*LL*) value lower than that of a 1-class model with all indicators allowed to freely co-vary with all other indicators

within its class was the 4-class solution. That is, the 4-class solution was the most parsimonious solution to fit the data better than a fully-saturated mean and variance/covariance model that is an exact fit to the data (in terms of the first- and second-order moments of the data). Finally, examination of a BIC ‘elbow’ plot indicated a downward bend between the 2-class and 4-class solutions.

Because of the ambiguity provided by the results of the fit indices, a decision was made to further interrogate a smaller subset of solutions, specifically the 3- through 5-class solutions, in terms of classification precession, class separation, and class homogeneity. While the 2-class solution seemed to fit the data well, it was not considered further because it masked too much population heterogeneity. Moreover, the LMR-LRT indicated that a 3-class solution fit the data better than the 2-class solution. As seen in Table 3, the 3- through 5-class solutions all had good classification accuracy as indexed by high AvePP, OCC_k , and entropy values. A decision was made to plot the conditional item endorsement probabilities (i.e. profile plots) for each of the three k -class solutions in order to visually examine class homogeneity and separation. There are no standard, objective means of quantifying class homogeneity and separation in latent class analyses with categorical indicators with more than two categories. In terms of identifying good class homogeneity, I looked for classes with indicators that had close to 70% item endorsement probabilities in three or less adjacent categories. In terms of identifying good class separation, I looked for the k -class solutions with the greatest differences in item endorsement probabilities across classes. In all three k -class solutions, the primary driver of class separation appeared to be variation in prosocial and antisocial behavior.

No one k -class solution seemed to stand out has having the best class separation. In all three k -class solutions, the prosocial and antisocial behavior indicators had the best homogeneity (the antisocial indicator frequently had 90% item endorsement probabilities in two adjacent categories). Again, no one k -class solution seemed to have the best-looking class homogeneity with respect to individual indicators.

Because the absolute fit and relative fit to the data was good for each of the three k -class solutions and because the classification precession, class separation, and class homogeneity was unhelpful in narrowing down a final solution, a decision was made to select a final solution based on substantive meaningfulness and interpretability of the classes. The 3-class solution seemed to mask too much population heterogeneity, with two classes with an estimated class size over 36%. Two of the three classes of the 3-class solution were largely interpretable, with one class that seemed to represent well adjustment and another class that was characterized by externalizing behaviors. However, the third class was ambiguous in terms of representing a meaningful class of multi-domain competence. The 4-class solution had much more interpretable and meaningful classes. Again, classes characterized by well adjustment and externalizing behaviors emerged in the 4-class solution. Cross-tabulation of the modal class assignments showed that a majority of children assigned to these classes in the 3-class solution were respectively assigned to those classes in the 4-class solution. Unlike the 3-class solution, a class characterized more by internalizing behaviors and a class characterized by socially dominant behaviors emerged in 4-class solution. Cross-tabulation of the modal class assignments showed that a vast majority of children assigned to the ambiguous class of

the 3-class solution were assigned to either the internalizing, externalizing, or socially dominant classes of the 4-class solution. Thus, the 4-class solution was favored over the 3-class solution because it explains more population heterogeneity (no classes with estimated sizes over 33%), has more interpretable classes, and does not jeopardize classification precision. Moreover, the 4-class but not the 3-class solution fit the data better than the fully-saturated mean and variance/covariance model.

Similar to the 4-class model, in the 5-class model a well-adjusted, externalizing, and internalizing class emerged. However, the 5-class model included two somewhat ambiguous classes characterized by medium-low/medium-high levels of antisocial and prosocial behavior, as well as low levels of depression and withdrawn behavior. These two classes were not well-separated on any of the four competence indicators. Nearly all children modally assigned to the socially dominant class in the 4-class solution were split between these two ambiguous classes in the 5-class solution. Thus, the 5-class solution appears to explain too much population heterogeneity, in turn sacrificing interpretability as well as class separation. The 4-class model was therefore selected as the final unconditional measurement model given its good absolute fit, relative fit, classification precision, and substantive meaningfulness.

Well-adjusted class

The largest model-estimated class (32.5%) from the 4-class solution was given the label of ‘well-adjusted’ and can be visualized in Figure 2A. This class is characterized by high probabilities of endorsing high levels of prosocial behavior (66% chance of endorsing levels of prosocial behavior .5 SD above the mean or greater, or 95% chance of

endorsing levels of prosocial behavior greater than the sample mean). The well-adjusted class is also characterized by a high probability of extremely low antisocial behavior (88% chance of endorsing levels of antisocial behavior less than .5 SD below the mean). Finally, children in this class have high probabilities of endorsing low levels of depression (71% chance of reporting CDI scores below the mean, and 53% chance of endorsing scores 5SD or lower below the mean) and low levels of withdrawn behavior (66% chance of exhibiting withdrawn behaviors below the mean). This class was given the label of ‘well-adjusted’ because the profile of competence characterized by this class (high prosocial, low antisocial, withdrawn, and depression) is similar to profiles considered developmentally adaptive and predictive of positive life-success (Cicchetti & Rogosch, 1993; Masten et al., 1999). The label of ‘well-adjusted’ does not mean to imply competent adaptive functioning across all, important domains of development. For example, academic achievement, an important component of adaptive functioning, (Masten et al., 1999) is absent from this analysis. Rather, this class represents relative positive adjustment in only a few social domains (prosocial, antisocial, and withdrawn) and in only one indicator of psychopathology (depression). Since all children in the sample were from high-risk contexts (i.e. either poverty or poverty with maltreatment), children in this class may be considered to be demonstrating *resilient* functioning.

Socially-dominant class

The next largest model-estimated class (28.8%) was labeled ‘socially-dominant’ and can be visualized in Figure 2B. This class had the lowest levels of withdrawn behavior compared to all other classes (55% probability of exhibiting withdrawn

behavior at or below .5 SD below the mean, and a 80% probability of endorsing withdrawn behavior at or below the sample mean). This class is characterized by medium levels of prosocial behavior (80% chance of endorsing prosocial behaviors in the range of .5 SD below to .5 SD above the sample mean), and medium to medium-high levels of antisocial behavior (50% chance of endorsing antisocial behavior in the range of .5 SD below the mean to the mean, and a 46% chance of endorsing levels from the mean to 1SD above the mean). Finally, this class had a high probability of endorsing low levels of depression (66% chance of reporting levels at or below the sample mean, and a 43% chance of reporting levels at or below .5 SD below the mean). This class was labeled ‘socially-dominant’ because the profile it characterizes matches the literature-defined expression of social dominance, including high social presence (low withdrawn behavior) as well as use of both cooperation (prosocial behavior) and aggression (antisocial behavior) (Hawley, 1999; Teisl, Rogosch, Oshri, & Cicchetti, 2011). Social-dominance refers a pattern of resource acquisition and social control whereby both cooperation and coercion are used (Hawley, 1999). Socially-dominant children are often admired and socially-influential though not necessarily without the use of antisocial behaviors such as bullying to gain such social centrality (Hawley, 1999).

Externalizing class

The third largest class that emerged from the 4-class LCA was termed the ‘externalizing class’ and is plotted in Figure 2C. This class’s most prominent feature was the high probability of endorsing extremely low levels of prosocial behavior (43% chance of exhibiting prosocial behaviors at or below 1 SD below the mean, and 90% probability

of endorsing prosocial behavior at or below .5 SD below the sample mean) and high probability of high levels of antisocial behavior (31% chance of exhibiting antisocial behaviors at or above 1.5 SD above the sample mean, and an 83% chance of exhibiting antisocial behaviors above .5 SD above the mean). Moreover, this class was characterized by relatively low withdrawn behavior (52% probability of endorsing levels of withdrawn behavior at or below the mean). The depression category endorsement probabilities are not as straightforward. While over 50% of children in this class are predicted to have depressive levels at or below the sample mean, 13.5% of children are predicted to endorse the highest category of depression (above 1.5 SD above the mean). Overall, high levels of externalizing behavior, and low levels of prosocial and withdrawn behavior characterized this class. Moreover, this class has mostly low, but some mixed levels of depression. Despite the mixed levels of depression, this class was labeled as an externalizing class for a variety of reasons. For one, high antisocial and low prosocial behavior essentially defines the notion of externalizing behavior (Deater-Deakard, Dodge, Bates, & Pettit, 1998). While children in this class are more likely than not to exhibit low levels of depression, consistent with the dichotomy between internalizing and externalizing spectrums, there is some non-negligible chance of exhibiting high levels of depression. The somewhat mixed endorsement probabilities for depression, in this class, is perhaps to be expected because some children exhibit impulsivity and even agitation as the result of depressive feelings (Ryan et al., 1987). The relatively low levels of withdrawn behavior in this class is consistent with the notion that children characterized by externalizing behaviors are not generally inhibited or reserved, socially. However, this

class still has an estimated 21% of children exhibiting withdrawn behavior greater than .5 SD above the sample mean. This is also not necessarily an unexpected finding nor does it negate the rationale for labeling this class as externalizing. In fact, a subset of children are both aggressive and withdrawn; in these cases antisocial behavior is thought to contribute to social rejection and victimization which may in turn contribute to lonely and reserved behaviors (Ladd & Burgess, 1999). In summary, based on the profile of category endorsement probabilities and consistency with definitions in the literature, this class is considered to represent children who exhibit primarily externalizing symptoms.

Internalizing class

The smallest estimated class (15.5%) is considered the ‘internalizing class’ and is plotted in Figure 2D. This class is characterized by low levels of antisocial behaviors (50% of children in this class are estimated to have antisocial behaviors at levels less than .5 SD below the mean, and 88% of children in this class are predicted to endorse levels of antisocial behavior at or below the mean), and medium levels of prosocial behavior (74% chance of endorsing prosocial behavior between .5 SD below and above the sample mean). This class had relatively high levels of withdrawn behavior (29% chance of endorsing levels of withdrawn behavior greater than 1.5 SD above the mean, and a 68% chance of endorsing levels of withdrawn behavior above .5 SD above the mean). Finally, category endorsement probabilities for depression were mixed. On one hand, this class had the highest probability (16%) of endorsing the highest category of depressed behavior (greater than 1.5 SD above the mean) out of all the classes. Moreover, individuals in this class are estimated to be more likely (54% chance) to have depression

scores above the mean than below the mean. Nevertheless, 25% of individuals in this class are expected to have depression scores below .5 SD below the mean. These mixed endorsement probabilities for difference levels of depression suggest poor item homogeneity. Though, because of low base rates, uncovering a class of children homogeneous for very high levels of depression is unlikely, even in a class characterized by high withdrawn and low antisocial behavior.

Construct validity of latent class labels

It is not straightforward to compare the model-estimated probabilities of endorsing particular levels of each indicator, in a given class, to any literature-based norms. Instead, one method of validating the labels of each latent class is to demonstrate that independent measures reflecting each construct (internalizing, externalizing, well-adjusted, socially-dominant) predict class membership accordingly. Validation was carried out using *California Child Q-Set* criterion sorts and scales (CCQ; Block & Block, 1969/1980). At the end of each camp week, two counselors independently completed the CCQ on the children in their group. The CCQ contains 100 varied items of social, cognitive, and personality characteristics. Counselors rated each child's behavioral profiles by sorting the individual items printed on cards into nine piles with a fixed distribution ranging from least characteristic (scored 1) to most characteristic (scored 9). Scores were averaged across raters to derive one Q-set per child. This Q-set methodology has numerous psychometric strengths including observer-evaluations as opposed to self-reporting, continuous form as opposed to categorical data, and finally, the use of fixed distributions reduces intra- and inter-judge differences (Block, 1961). The CCQ has been

used to derive a number of Q-criterion sorts and scales to assess a wide range of specific psychological constructs. No measure from the CCQ was used as a latent class indicator, thus it is possible to independently validate the construct of each class label.

Using the R3-step method in *Mplus* (Asparouhov & Muthén, 2014), each CCQ measure was added, independently, as a predictor of latent class membership via a multinomial logistic regression. For purposes of validation, the class being validated was used as the reference class. Each association tests the log odds that class membership is k (instead of the reference class), given membership in ether class. To validate the well-adjusted class, the ego-resiliency and social competence q-sorts were examined as predictors. Ego-resiliency refers to the capacity of an individual to modulate their self-control, adaptively, in changing circumstances (Letzring, Block, & Funder, 2005). Social competence is conceptualized as adaptive, prosocial behaviors such as cooperation, likability, and leadership (Waters, Noyes, Vaughn, & Ricks, 1985). Both ego-resiliency and social competence highly negatively associated ($p < .001$) with the internalizing, externalizing, and socially-dominant class, when each of those classes was compared to the well-adjusted class. Thus, with higher levels of ego-resiliency or social competence one is more likely to be in the well-adjusted class, when compared with each other class.

The same method was applied for the internalizing class, externalizing class, and socially-dominant class using the internalizing q-sort, externalizing q-sort, and social dominance q-scale, respectively (Block & Block, 1980; Teisl et al., 2012). In all cases there was a negative association ($p < .001$) between each validating measure and membership in class k versus the class being validated. To summarize, each validating

measure from the CCQ was highly predictive of class membership with respect to the class being validated. These strong associations suggest good construct validity and assurance in the labels used for each class. Finally, 31% of maltreated children were modally assigned to the well-adjusted class. That is, 31% of maltreated children in this sample were exhibiting resilient functioning. These percentages are in line with previous work on the frequency of resilience in children with abusive histories (Cicchetti & Rogosch, 1993).

Structural Equation Mixture Modeling Results

Hypothesis 1.

It was hypothesized that the number of maltreatment subtypes would have a main effect association with the latent class variable. To test this hypothesis, the latent class variable was regressed onto the number of maltreatment subtypes variable, sex, and age. Because the latent class variable is categorical, regression results are based on a multinomial logistic regression, in which simultaneous pairs of logistic regressions are tested. Each logistic regression tests the odds of being in one class versus a reference class assuming membership is in one of the two classes, controlling for all other covariates. Similar to an ANOVA test, an overall global test of association referred to as a Wald statistic can be estimated from an SEMM. In this study the Wald statistic is simply a test for an overall association between a predictor and the latent class variable. To probe a global effect, the pairwise conditional odds estimates from each logistic regression can be examined.

Equality constraints were imposed on the maltreatment effect to test for a global effect, yielding a Wald statistic and corresponding *p*-value. The number of maltreatment subtypes experienced was significantly associated with latent class membership (Wald=35.3, *df*=3, *p*<0.000). To visualize this global effect, an overall probability plot is depicted in Figure 3. The X-axis of the plot corresponding to the number of maltreatment subtypes experienced and the Y-axis corresponding to the *overall* probability of being in a class. Each separate line corresponds to each of the four latent classes. As can be seen, as the number of maltreatment subtypes increases, the probability of being in the externalizing class increases and the probability of being in the well-adjusted class decreases. There are slight declines in the probability of being in both the socially-dominant and internalizing classes as maltreatment increases. The pairwise estimates are not presented for this main effect. Rather pairwise estimates are probed, in more depth, for hypothesis 2.

Hypothesis 2.

For hypothesis 2, it was hypothesized that an interaction of the number of maltreatment subtypes experienced and a polygenic formative factor would also predict latent class membership, controlling for all relevant control variables. The first step in testing this hypothesis was to select a formative factor model with either additive-, dominant-, or recessive-coded variants as indicators. The second step was to add control variables for the final model.

Selecting formative factor model.

Three preliminary, structural equation mixture models, using the alternative-three-step-method (Asparouhov & Muthén, 2014), were run in order to select which formative factor model (additive, dominant, recessive) to carry forward for the final analysis. For each of the three models, the latent class variable was regressed onto the number of maltreatment subtypes experienced, the polygenic formative factor, and a formative factor-by-maltreatment interaction (GxE) term. *DRD4-VNTR* was chosen to have its regression weight set to 1 to scale the formative factors. It was chosen to be the factor anchor because in a non-formative factor model, its individual effect on latent class membership was the strongest. Equality constraints were imposed on the GxE effect, from each model, to test for a global effect, yielding a Wald statistic and corresponding *p*-value. Only the additive model's global GxE effect was significant (Wald=16.8, *df*=3, *p*=0.0008, *p*=0.0024 with bonferroni correction). The BIC values were 2616, 2611, and 2618 for the additive, dominant and recessive models, respectively. Moreover, the log likelihood (*LL*) values were -1229.2, -1226.6, and -1230 for the additive, dominant and recessive models, respectively. While the lowest BIC value was for the dominant model, the *LL* values across the three models were extremely similar. Given that the additive model was the only model with a significant GxE effect, correcting for multiple testing, and because its *LL* was similar to the other models, it was retained as the final model for use with control variables. Moreover, pairwise comparisons in log odds estimates across models were similar. A model with a formative factor predicting an outcome is actually nested within a model with all of the formative indicators individually predicting the outcome. To justify the use of a formative factor model, it should *not* fit the data

significantly worse than a full model with all individual indicator paths. Using a log likelihood chi-square difference test for MLR, the nested formative factor model did not fit the data significantly worse than a model with all individual gene-variants predicting the latent class variable as main effects and in interaction with maltreatment ($\chi^2=28.36$, $df=55$, $p=.99$).

The formative factor indicator weights for the additive model (regression estimates of each variant predicting the factor) were not all positive. Meaning that not all gene-variants contributed to adaptive functioning in the expected way (i.e., vulnerability versus protection). Variants with negative weights were reverse-coded in the final SEMM to make the formative factor results more interpretable. These variants included *DRD4*-rs1800955, *COMT*-rs4680, *DAT1*-rs40184, *DAT1*-rs27072, *DRD2*-rs1800497, and *OXTR*-rs53576. Because of reverse scoring, it is perhaps best to think about factor scores simply as varying degrees of *genetic load* with respect to the specific alleles coded as 1. In the original coding scheme, alleles considered ‘vulnerability alleles’ based on extant literature were coded as 1. For each variant, the number of alleles carried by each child was summed for a total score ranging from 0 to 2 (additive coding). However, six variants were reverse-scored post hoc, meaning that for those six variants the non-vulnerability alleles were instead coded as 1. To derive a *factor score*, each child’s score for each variant is multiplied by the factor weight of that variant. High factor scores correspond to high genetic load, and low factor scores correspond to low genetic load. For example, children with high factor scores may be carrying just a few alleles that have

large effects (large factor weights) or many alleles that have small/moderate effects (small factor weights), or some combination.

With reverse-coding in mind, genetic load, therefore, is in reference to 1.) the 7-repeat allele of *DRD4*-VNTR, 2.) the ‘T’ allele of *DRD4*- rs1800955, 3.) the ‘met/A’ allele of *COMT* Val¹⁵⁸Met (rs4680), 4.) The ‘G’ allele of *DRD2*-rs1800497, 5.) the ‘del’ allele of *DRD2*-rs1799732, 6.) the 10-repeat allele of *DAT1*-VNTR, 7.) the ‘T’ allele of *DAT1*-rs40184, 8.) the ‘T’ allele of *DAT1*-rs27072, 9.) the short allele of 5-HTTLPR, 10.) the ‘G’ allele of *CRHRI*-rs110402, 11.) the ‘A’ allele of *OXTR*-rs53576, and 12.) the ‘T’ allele of *FKBP5*-rs1360780.

Final structural equation mixture model with control variables.

A common oversight in moderated regression analyses conducted in the behavioral sciences is the failure to consider control-variable interaction effects (Yzerbyt, Muller, & Judd, 2004). If a control variable associates with a component of an interaction term, simply adjusting for the main effect of the control variable could result in a biased (inflated) interaction effect. Failure to consider control-variable interaction effects has lead to some scrutiny regarding GxE research (Keller, 2014). Though, this problem is not unique to GxE research. To decide if control-variable interaction terms should be added to the final model, linear associations were tested between the polygenic factor, the number of maltreatment subtypes experienced, sex, and age. There were only significant associations between the polygenic factor and age ($\beta = -0.182, p < 0.001$) and sex and maltreatment ($OR = .93, p = 0.035$). Because of these associations, it is necessary to add sex-by-factor and age-by-maltreatment interaction terms as control variables, in addition

to sex and age as main effects. The final model regressed the latent class variable onto the number of maltreatment subtypes experienced, the polygenic factor, the interaction between maltreatment and the polygenic factor (GxE), age, the interaction between age and maltreatment, sex, and the interaction between sex and the polygenic factor.

Global GxE results. A Wald test for a global GxE effect was significant controlling for all other variables (Wald=13.5, $df=3$, $p=0.004$). That is, the effect of maltreatment on class membership depends on the level of the polygenic factor, or vice versa the effect of the polygenic factor on class membership depends on the number of abuse subtypes experienced. There was no significant association between the polygenic factor and maltreatment, ruling out any possible gene-environment correlation (rGE) (Scarr & McCartney, 1983). The results of the polygenic factor regression weights are presented in Table 4. Factor scores were mean centered with a minimum value of -5.5, a maximum value of 6.3, and a standard deviation of 2.2. All but one gene-variant (*DAT1*-VNTR) significantly contributed to the formative factor. This means that there was virtually no individual impact of *DAT1*-VNTR on latent class membership, and accordingly its factor weight was negligible and non-significant.

Plotting the Global GxE effects. To help visualize the global GxE effects, overall probability curve plots were created (Figure 4A-D). Each plot represents one of the four latent classes with the X-axis corresponding to the number of maltreatment subtypes experienced and the Y-axis corresponding to the *overall* probability of being in that class. There are three probability curves corresponding to different levels of the formative factor (2SD above the mean, the mean, and 2SD below the mean). For the well-adjusted

class, greater genetic load appears to be having a protective effect. For example, children with four subtypes of abuse who have low genetic load (2SD below mean) have essentially 0% chance of being in the well-adjusted class. However, children with high genetic load (2SD above mean) have a 30% chance of being in the well-adjusted class despite experiencing four subtypes of abuse. A similar protective effect was observed in the externalizing class. As genetic load increases, the effect of maltreatment on the probability of class membership attenuates. Interestingly, neither maltreatment nor they polygenic factor have much, if any, relation to the probability of being in the internalizing class. For the socially-dominant class of children, high genetic load appears to increase the effects of maltreatment on the overall probability of class membership.

Multinomial logistic regression results. To further interrogate the global GxE effect, the results of the six pairwise logistic regressions are presented in Table 5. Only two significant pairwise GxE effects emerged controlling for all other variables. One GxE effect corresponds to the comparison between the externalizing class and the well-adjusted class ($OR=.84$, $p=.001$). Specifically, the effect of an increasing number of maltreatment subtypes on the odds of being in the externalizing class versus the well-adjusted class decreases as genetic load increases (i.e., as factor scores increase). To help interpret these interaction effects, the main effects of maltreatment are presented in Table 6 at different levels of the polygenic factor (2SD above the mean, the mean, and 2SD below the mean). For example at factor scores 2SD below the mean, for every additional subtype of maltreatment experienced, the odds of being in the externalizing class versus the well-adjusted class increases by a factor of 3.4, holding all control variables constant

(See Table 6). At mean level factor scores, for every additional subtype of maltreatment experienced, the odds of being in the externalizing class versus the well-adjusted class increases only by a factor of 1.6. At factor scores 2SD above the mean, there is no significant effect of maltreatment.

The other GxE effect corresponds to the comparison between the socially-dominant class and the externalizing class ($OR=1.2$, $p=.005$). Specifically, the effect of an increasing number of maltreatment subtypes on the odds of being in the socially-dominant class versus the externalizing class increase as genetic load increases. At factor scores 2SD below the mean, for every additional subtype of maltreatment experienced, the odds of being in the well-adjusted class versus the externalizing class increases by a factor of 0.37 (decreased odds), holding all control variables constant (See Table 6). At mean level factor scores, for every additional subtype of maltreatment experienced, the well-adjusted class versus the externalizing class increases by a factor of 0.74. At factor scores 2SD above the mean, the odds are increased 1.6 times. Only one pairwise comparison had a significant maltreatment main effect that was not in the context of a GxE. This effect was present when the socially-dominant class was compared to the well adjusted class ($OR=1.3$, $p=.04$). For every additional subtype of maltreatment experienced, the odds of being in the socially-dominant class versus the well-adjusted class increases by a factor of 1.3 holding all covariates constant.

Sensitivity analysis. A variety of sensitivity analyses were conducted to insure the robustness of this model. While not expected, it is possible that there could be configural differences in a 4-class latent variable derived from maltreated kids only versus a 4-class

latent variable derived from non-maltreated kids. This would suggest differential item functioning. To test for this, a 4-class latent class analysis model was run separately for maltreated and non-maltreated children. The configural nature of the two models were essentially the same, meaning very similar-looking classes were derived (i.e., externalizing, internalizing, well-adjusted, and socially-dominant). The only difference were in the estimated class sizes between groups, which is of course to be expected. Thus, there is little evidence for differential item functioning.

Next, because DRD4-VNTR was selected as the factor anchor, it is possible different results would arise with other gene-variants acting as the anchor. A random variant (*DRD4*- rs1800955) was selected to substitute the *DRD4*-variant as the factor anchor. Results of similar direction, magnitude, and significance were obtained (Wald=14.2, $df=3$, $p=0.003$). Moreover, when *DRD4*-VNTR was completely removed the results were nearly identical (Wald=14.2, $df=3$, $p=0.003$). Finally, the interaction results from this study may depend entirely on the use of a formative factor. Because a formative factor has never been used in a GxE study, or any moderation model for that matter, it is important to examine a more traditional composite (un-weighted) as the moderator. An un-weighted (non-formative factor) composite, with the reverse-coded variants, also significantly interacted with maltreatment controlling for all other variables in similar direction and magnitude (Wald=9.8, $df=3$, $p=0.02$). Not surprisingly, the un-weighted composite without reverse-coding did not significantly interacted with maltreatment controlling for all other variables.

Finally, alternative parameterizations of maltreatment were examined in a latent class analysis (i.e. subtype specific and developmental parameters, data no presented). Resulting maltreatment profiles did not provide additional information in terms of latent class membership (adaptive functioning), as compared to the more parsimonious number of maltreatment subtypes variable. This corroborates the findings from Vachon et al. (2015), which indicate that particular subtypes of abuse affect development in a non-specific manner.

Discussion

Study Overview

Child maltreatment in the form of neglect, physical abuse, sexual abuse, and/or emotional abuse places children at high risk of developing problems in multiple domains of psychological functioning (Cicchetti, 2016). While the vast majority of maltreated children suffer consequences of the harm inflicted upon them, numerous influences across multiple-levels-of-analysis (from genetic to community) can contribute to more resilient adaptive functioning (Cicchetti, 2013). This study had two primary aims. The first was to characterize multi-domain, adaptive functioning in maltreated and nonmaltreated, African-American children. The second aim was to predict variation in adaptive functioning based on the number of maltreatment subtypes experienced, a polygenic factor, and their interaction (GxE).

This study also had two primary hypotheses. The first was that an increasing number of maltreatment subtypes experienced would be significantly associated with latent class membership. This hypothesis was confirmed and is expanded upon in

hypothesis 2. The second hypothesis was that an association between the number of maltreatment subtypes experienced and adaptive functioning would be moderated by variation in genes thought to confer differences in *environmental sensitivity* (ES). Indeed, controlling for several variables, an interaction between child maltreatment and a polygenic factor did significantly predict a latent class variable representing profiles of adaptive functioning. Thus, particular variants in ES genes appear to be important vulnerability or protective factors for children with histories of abuse and/or neglect. This study was the first of its kind to combine structural equation mixture modeling (SEMM) with the use of a formative factor to test for gene-by-environment interaction (GxE).

Comment on the Latent Class Analysis

Multi-domain, adaptive functioning was measured in this sample using a variety of peer-reported, camp counselor-reported, and self-reported measures. These measures were used to form parcels (composites) of prosocial behavior, antisocial behavior, withdrawn behavior, and depression. These four constructs are considered a subset of core indicators of competence in children (Cicchetti, & Rogosch, 1997). In order to describe the heterogeneity in childrens' functioning in these indicators, a latent class analysis (LCA) was preformed. An LCA is a model-based, *person-centered*, statistical analysis that characterizes groups (classes) of individuals based on similar response patterns on a set of categorical indicators (Masyn, 2013).

Based on absolute fit, relative fit, classification accuracy, and substantive meaningfulness, a 4-class solution was selected as the final LCA model. With respect to the class-specific item response probabilities, the four classes were labeled as 'well-

adjusted', 'externalizing', 'internalizing', and 'socially-dominant'. The well-adjusted group was characterized by relatively high levels of prosocial behavior along with low levels of antisocial behavior, withdrawn behavior, and depression. The externalizing class was characterized by high levels of antisocial behavior, low levels of prosocial behavior and withdrawn behavior, and moderate levels of depression. The internalizing class was characterized by high levels of withdrawn behavior, low levels of antisocial behavior, and medium levels of prosocial behavior. This class had the highest probability (16%) of endorsing the highest category of depressed behavior (greater than 1.5 SD above the mean) out of all the classes. Moreover, individuals in the internalizing class were estimated to be more likely (54% chance) than not to have depression scores above the mean. Finally, the socially-dominant was characterized by very low levels of withdrawn behavior, medium levels of prosocial and antisocial behavior, and low levels of depression. Associations with independent measures from the California Child Q Set (Block & Block, 1980), including the criterion sorts/scales of social-dominance, social competence, externalizing behaviors, and internalizing behaviors, provided construct validity for each class labels.

In general, profiles of externalizing and internalizing behaviors are considered maladaptive for children's development. For example, children with high levels of these broadband behaviors tend to have more difficulty maintaining friendships, are at heightened risk for abusing substances in adolescence and adulthood, tend to display difficulties in school performance, and tend to be victimized more by their peers (Colder et al., 2013; Masten et al., 2005; Poulin & Chan, 2010; Reijntjes, Kamphuis, Prinzie, & Telch, 2010).

Whether socially-dominant profiles of behavior are maladaptive or not is less clear-cut. Children with high social-dominance tend to express both cooperation and coercion (i.e. both pro and antisocial behavior) and are not withdrawn. However, these behaviors are often utilized in the context of maintaining social power via bullying, especially in more coercive profiles of social-dominance (Olthof, Goossens, Vermande, Aleva, & van der Meulen, 2011; Teisl et al., 2012). Clearly bullying behaviors are neither desirable nor adaptive; however, some reports have found that social-dominance contributes to social-likability, social-centrality, and positive adaptation (Hawley, 2003). It is particularly unclear, in contexts of adversity, how adaptive socially-dominant behaviors are in the long term.

Children in the well-adjusted class may be considered *resilient* regardless of maltreatment histories because all children in this sample came from socio-economically disadvantaged backgrounds. Roughly 33% of the entire sample was predicted to be in the well-adjusted class. Interestingly, this was the largest of the four classes. Moreover, approximately 31% of maltreated children were modally assigned to the well-adjusted class. These proportions resemble those from several other resilience studies on child abuse (i.e., Cicchetti & Rogosch, 2012; Cicchetti & Rogosch, 1997; Flores, Cicchetti, & Rogosch, 2005). It is difficult to say the degree to which the well-adjusted profile in this sample matches notions of well-adjustment in typically developing children. However, the social competence CCQ criterion sort, which was developed with typically developing children, was highly predictive of membership in the well-adjusted class when compared to each other class. This provides some confidence that the well-adjusted

profile observed in this sample really does reflect competent levels of behaviors across these four domains.

It is difficult to compare the results of this LCA to other, similar studies. For one, an LCA, using a similar set of indicators, has never been conducted in a child maltreatment sample. Moreover, the majority of resilience-based research employs latent growth mixture modeling with longitudinal data rather than latent class analysis with cross-sectional data (i.e., Bonanno et al., 2012; Kim, Cicchetti, Rogosch, & Manly, 2009). However, one study by Yates and Grey (2012) did use a latent profile analysis in a similar sample of high-risk children (former foster care youth). The best fitting model from that study was also a 4-class solution with classes described by the authors as *resilient*, *maladapted*, *internally resilient*, and *externally resilient*. The maladapted group was doing poorly across the board, the resilient group was doing well across the board, the externally resilient group showed internalizing problems, and the internalizing group showed externalizing problems. Some similarities can be drawn between the externalizing/internalizing classes from the current study and the internally/externally resilient classes from the Yates and Grey study. However, making direct comparison is challenging. While some competence indicators used by Yates and Grey were similar to those used in present study (relational competence and depression), other indicators were quite different (educational competence, occupational competence, civic engagement, and self-esteem).

Comment on GxE Predictors of Latent Class Membership

Beyond simply describing heterogeneity in adaptive functioning, via an LCA, this study aimed to understand how maltreatment experiences and ES gene-variants relate to adaptive functioning. The first hypothesis was tested by simply predicting variation in each competence indicator individually as a function of the number of maltreatment subtypes experienced. As expected, child maltreatment was significantly associated with worse functioning in each indicator (lower prosocial behavior, higher antisocial behavior, higher withdrawn behavior, and higher depression). These basic associations corroborate findings from several previous studies (i.e., Cicchetti & Rogosch, 2012; Cicchetti, Rogosch, & Thibodeau, 2012; Manly, Cicchetti, & Barnett, 1994; Prino & Peyrot, 1994).

Next, an SEMM was conducted to test the second hypothesis that an interaction between maltreatment and ES-gene variants would significantly predict membership in the four, adaptive functioning latent classes (see Figure 1 for conceptual model). Genetic variation across 12 ES gene-variants was collectively modeled using one formative factor, which is essentially a sample-weighted composite. The interaction between that polygenic factor and the number of maltreatment subtypes experienced, representing a GxE effect, was a significant predictor of the latent class variable. This model controlled for sex, age, an age-by-maltreatment interaction, and a sex-by-polygenic factor interaction (see Keller, 2014).

Because the latent class variable is categorical, there are multiple ways of understanding the overall GxE effect. Perhaps most illustrative are the GxE probability curve plots (Figure 4A-D). These plots represent the *overall* probability of being in a given class as a function of the number of maltreatment subtypes experienced, at different

levels of the polygenic factor. The GxE effects are most striking for the externalizing class, socially-dominant class, and well-adjusted class. For the externalizing class, low polygenic factor scores (i.e., low genetic load) have a vulnerability effect, whereas high polygenic factor scores (i.e., high genetic load) have a protective effect.

In other words, the influence of maltreatment on the probability of being in the externalizing class increases as factor scores decrease. These findings mirror those of the well-adjusted class. As a general trend, as the number of maltreatment subtypes experienced increases, the probability of being in the well-adjusted class decreases. However, that trend is attenuated as polygenic factor scores increase. Thus for both the externalizing and well-adjusted classes, high polygenic scores appear to buffer the negative effects of maltreatment. However, for the socially-dominant class, the opposite is true. Children with high factor scores are more likely to be in the socially-dominant class as the number of subtypes experienced increases.

The overall GxE effect can also be interpreted based on the individual logistic regression results. With four latent classes, a total of 6 pairwise comparisons were estimated. Only two pairwise comparisons had significant GxE effects (externalizing versus well-adjusted, and externalizing versus socially-dominant) (Table 5). Thus, the overall GxE effect estimated by the Wald statistic is primarily the result of these two pairwise GxE effects. In both comparisons, as genetic load increased, the effect of maltreatment on the odds of being in the externalizing class (versus the other class) decreased. There were no main effects or GxE effects with any pairwise comparison involving the internalizing class. There was a main effect of maltreatment, but no GxE

effect, when the socially-dominant class was compared to the well-adjusted class. For every extra subtype of abuse experienced, the odds of being in the socially-dominant class versus the well-adjusted class increases by a factor of 1.3.

These pairwise comparisons help explain what is illustrated in the overall GxE probability plots (Figure 4A-D). In general, low genetic load is a vulnerability factor for maltreated children with respect to membership in the externalizing class, whereas high genetic load appears to have a protective effect. Similarly, maltreated children with high genetic load are more likely to be in the well-adjusted class than maltreated children with low genetic load. Interestingly, a similar pattern is observed for the socially-dominant class. Polygenic scores did not moderate the effects of maltreatment on the odds of being in the socially-dominant class versus the well-adjusted class.

These findings suggest that perhaps one reason for the similar GxE effects for well-adjusted and socially-dominant class is that those classes are not well differentiated from each other by maltreatment, the polygenic factor, or their interaction. That is, while maltreatment and genetic influences are strong predictors of who is or who is not likely to be in the externalizing class (compared to the well-adjusted or socially-dominant classes), they are not great predictors of who is likely to be in the socially dominant class versus the well-adjusted class. These classes are separated primarily by differences in the externalizing and internalizing indicators. The social dominance CCQ q-scale validation results along the small but significant maltreatment main effects do suggest that the well-adjusted and socially-dominant profiles are distinct. Though, the classes do not appear to be distinct enough for GxE effects to distinguish them. Perhaps these findings suggest

that GxE effects are greatest when behavioral profiles are extremely different from each other. This is not unexpected, because GxE effects tend to be small in magnitude. Clearly, more research on GxE and social-dominance is needed to further explore these findings.

As is common in child maltreatment research, the largest maltreatment effects in this study were observed with relation to membership in the externalizing class. The association between abusive histories and behaviors such as aggression, impulsivity, and delinquency are some of the most robust findings in all of psychology (Cicchetti et al., 2012; Jaffee et al., 2004). Furthermore, some of the most consistent data on GxE has come out of studies examining maltreatment-externalizing associations (i.e., Byrd & Manuck, 2014). While maltreatment did associate with the withdrawn and depression indicators directly, there was no main effect of maltreatment or GxE effect predicting membership in the internalizing class. These findings are contradictory and at odds with a large literature suggesting that maltreatment is a risk factor for developing internalizing problems (i.e., Bolger & Patterson, 2001; Cicchetti & Rogosch, 2014; Cicchetti, Rogosch, & Oshri, 2011). The estimated class size was relatively small for the internalizing class (15.5%). Therefore, low power in this study could have contributed to type II error. Moreover, some children with otherwise internalizing struggles (anxiety, depression) may exhibit those behaviors externally through irritability and even aggression (Ryan et al., 1987). This makes distinguishing purely internalizing behaviors from externalizing behaviors difficult, and may have driven down the estimated size of

the internalizing class. Indeed, there was some non-negligible probability of exhibiting moderate levels of withdrawn and depression behavior in the externalizing class.

Interpretation of Genetic Load

A central interpretative question remains: what exactly does genetic load refer to in this study? In most concrete terms, genetic load is in reference to the impact of alleles coded as 1 in the final model. High genetic load means high factor scores; low genetic load means low factor scores. Factor scores were created by multiplying the number of alleles coded as 1 by each variant's factor weight, followed by summing across all variants. Because some variants were reverse coded, the interpretation can get a little tricky. High genetic load protected maltreated children, to some degree, from exhibiting externalizing behaviors. Moreover, maltreated children with high genetic load had a higher probability of being in the well-adjusted class than maltreated children with low genetic load.

Based on the ES literature, one would expect that so-called ‘non-vulnerability’ alleles would contribute to such protective effects. If this were true for the current study, then all variants would have contributed *negatively* to the factor (since high factor scores were protective). However, 5 gene-variants contributed *positively* to the factor, such that the so-called ‘vulnerability’ alleles of those variants had more of a protective effect. This is excluding *DAT1*-VNTR as it was a non-significant contributor to the factor. *DRD4*-VNTR contributed positively to the factor (in opposition to what was expected) when another gene-variant was used as the factor anchor. The alleles that unexpectedly showed more protective effects in this study were 1.) the 7-repeat allele of DRD4, 2.) The ‘del’

allele of *DRD2*-rs1799732, 3.) the short allele of 5-HTTLPR, 4.) the ‘T’ allele of *CRHR1*- rs110402, and 5.) the ‘T’ allele of *FKBP5*-rs1360780. Because it is unclear how maladaptive the socially-dominant class is, terms such as vulnerability or protection are somewhat meaningless. In any case, as with the well-adjusted class, maltreated children with high genetic load had a higher probability of being in the socially-dominant class than maltreated children with low genetic load. Likely, these effects are present because the well-adjusted class and socially-dominant are not well differentiated.

The fact that some alleles contributed to vulnerability/protection in the expected direction and others did not underscores the complexity and capriciousness of candidate GxE research. What is clear is that all variants (save *DAT1*-VNTR) appear to have meaningful moderation impacts. These results corroborate the relative importance of these genetic variants in differentially predicting developmental outcomes in contexts of adversity. Moreover, these results add to a growing number of studies demonstrating polygenic moderation of child maltreatment outcomes (Cicchetti & Rogosch, 2012; Davies et al., 2015; Thibodeau et al., 2015). These results do not, however, support consistency with regards to which alleles tend to confer vulnerability and which variants tend to confer protection.

Such inconsistency is not all that uncommon. A number of reports, for example, have found the short allele as opposed to the long allele of 5-HTTLPR confers protective effects in contexts of abuse (i.e., Banny, Cicchetti, Rogosch, Oshri, & Crick, 2013; Brummett et al., 2008; Cicchetti et al., 2011 Cicchetti & Rogosch, 2014; Laucht et al., 2009; Sharpley et al., 2014; Walsh et al., 2014). Contradictory vulnerability/protection

effects with regards to *FKBP5*-rs1360780 and *CRHR1*- rs110402 have also been reported (Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010; Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014). Based on these inconsistencies, perhaps researchers should not make a priori assumptions about which alleles in ES gene-variants will be associated with plasticity (Cicchetti & Rogosch, 2014). Until more biologically mechanistic studies can be conducted, the reasons for why some of these variants showed more protective versus more vulnerability effects are speculative. Given that all 12 genes play broad roles in neurotransmission, stress biology, and endocrine function, it is not surprising that functional variants within them moderate maltreatment outcomes. What is not clear from this study is exactly why, mechanistically, this is the case. Research into differential epigenetic programming, brain structure/function, endocrine function, and/or use of animal models might elucidate these findings (eg., Bigos & Weinberger, 2010; Meaney, 2010; Klengel et al., 2014).

Comparison to Cicchetti and Rogosch (2012)

What was particularly unique about this project was that profiles of behavior were derived from the examination of adaptive functioning across multiple domains of competence. Only one other study to date, first-of-its-kind work by Cicchetti & Rogosch (2012), examined genetic moderation of maltreatment effects in relation to multi-domain functioning. That study also used a polygenic index of ES gene-variants. The results of this study and Cicchetti and Rogosch's share some similarities and differences. In the Cicchetti and Rogosch study, a continuous composite of adaptive functioning was utilized instead of a categorical latent variable used in the present study. Because of this,

comparisons across studies are not completely straightforward. Several parameters of maltreatment were examined in the Cicchetti and Rogosch study. When just comparing maltreated versus non-maltreated children variation in ES genes played a more differentiating role, in terms of adaptive functioning. These results are at odds with the current results. By examining all of the probability curve plots in Figure 4A-D, there is essentially no differentiation by polygenic score for non-maltreated children. With that said, Cicchetti and Rogosch also examined the number of maltreatment subtypes experienced. Using that variable, there was differentiation due to ES gene variation on both extremes (non-maltreatment and 4 subtypes experienced) in line with differential susceptibility theory (DST; Belsky & Pluess, 2009). These latter findings more closely resemble those in the present study with differentiation occurring for maltreated children as well. By ‘eye-balling’ the plots in Figure 4, they appear to display interactions consistent with diathesis stress (DS; Monroe & Simons, 1991). There are statistical tools to decipher the person-by-environment interaction effects of vantage sensitivity, DST, and DS (Belsky, Pluess, & Widaman, 2013; Roisman et al., 2012). These tools are most effective when a study’s environmental range stretches from positive to negative. The current study has a restricted environmental range with only children from low-income backgrounds sampled. Thus, these tools were not employed. Moreover, there is no clear way of identifying interaction patterns such as those listed when the outcome variable is unordered and categorical.

Study Weaknesses

Despite these strengths, some methodological weaknesses exist as well. With any study of parent behavior-child behavior associations, the directionality of causation can be difficult to infer. Because this study did not employ a twin or adoption design, no definitive conclusions regarding the causality of the impacts of parental abuse/neglect can be made. Moreover, the data were cross-sectional making it difficult to control for child behavior during the time of abuse. Nevertheless, twin and adoption work has suggested a clear and a direct, environmentally-mediated effect of maltreatment on child behavior (Jaffee et al., 2004). The use of a weighted composite to aggregate the effects of multiple gene-variants has its drawbacks. For one, it is difficult to interpret the factor scores. Because the variant effects are weighted, similar factor scores can be derived from children with slightly different genetic profiles.

While statistical interactions were detected, these interactions say little about how the interactions operate biologically at a mechanistic level. Relatedly, Moore and Thoemmes (in-press) demonstrated via statistical simulations that unobserved contextual factors common to both caregiver and child likely inflate GxE estimates contributing to possible type I error. These factors were not controlled for, but are extremely difficult to measure in real-world applications (Moore & Thoemmes, in-press). With regards to the measurement of adaptive functioning, not all important indicators of competence were measured. These include, but are not limited to, psychopathologies other than depression, academic success, and attachment. Finally, the cross-sectional nature of this study limited the ability to truly study the dynamic nature of resilience (Masten, 2011); the latent class

variable represented only a snapshot of adaptive-functioning during a limited period of time.

Study Strengths

This study had a number of notable strengths. First, maltreatment was measured objectively and prospectively via the Maltreatment Classification System (MCS: Barnett, Manly, & Cicchetti, 1993). The vast majority of maltreatment studies rely on self-reported, and prospective measures, which introduce responder bias. Second, to understand resilience properly, adaptive functioning should be examined across multiple domains of competence. This study examined adaptive functioning in four major domains of competence based on measures collected by multiple informants (peers, counselors, self). Moreover, to characterize profiles of adaptive functioning, an exploratory latent class analysis was conducted. This modeling technique accounts for measurement error and classification accuracy, does not treat all indicators the same, and avoids relying on researcher cut-offs (i.e., naïve profiling). Third, rather than focusing on a single candidate gene-variant, 12 variants were examined across 8 genes collectively. Previous studies using polygenic indices in GxE studies have failed to properly weight the indices. This study used a formative factor as a means of creating a sample-weighted composite index of gene-variants. The formative factor allowed gene-variants to have either positive or negative contributions. Because of this, interaction effects were not dependent on the a priori assumptions made about plasticity effects. To the best of my knowledge, this is the first time a formative factor has been used to weight genetic effects; it is also the first time a formative factor has been used in an interaction and the first time that a formative factor

has predicted a latent class variable. A model with a non-weighted composite index of genes, using reverse-coding, also produced a significant GxE with results in the same direction, although the overall estimates were smaller in size. Finally, GxE research is fraught with underpowered studies. This study used a relatively large, ancestrally-homogeneous sample. In accordance with recommendations made by Keller (2014), covariate interaction terms were added, ensuring proper use of control variables.

Concluding remarks

In summary, the following major conclusions are made based on the results of this study. The first is that cumulative child maltreatment is detrimental to four major domains of adaptive functioning, including prosocial behavior, antisocial behavior, withdrawn behavior, and depression when examined individually. The second is that, based on those domains, four unique profiles of adaptive functioning were present in this sample of low-income children. These included ‘externalizing’, ‘internalizing’, ‘socially-dominant’, and ‘well-adjusted’ groups of children. The association between an increasing number of maltreatment subtypes experienced and membership in these classes depended on variation in a set of 12 gene variants known to confer environmental sensitivity. In general, as the number of subtypes of abuse increased, children were more likely to be members in the externalizing class when compared to the well-adjusted or socially-dominant classes. However, these effects were magnified as genetic load decreased. Moreover, the overall probability of being in the externalizing class as a function of cumulative maltreatment increased as genetic load decreased. Conversely, the overall probability of being in the well-adjusted or socially-dominant classes as a function of

cumulative maltreatment increased as genetic load increased. Finally, the number of subtypes experienced was positively associated with the odds of being in the socially-dominant class versus the well-adjusted class and this did not depend on genetic variation.

Given the amount of novel statistical techniques used in this study, caution is warranted regarding the GxE effects. GxE studies are notorious for non-replication (Duncan & Keller, 2011). Despite proper use of control variables and large sample sizes, definitive conclusions regarding the impact of these 12 ES gene-variants on maltreatment multifinality awaits repeated replication. Researchers are encouraged to test the utility of formative factors when conducting GxE research and/or mixture modeling research. In no way do these results suggest that any child is ‘immune’ to the detrimental effects of maltreatment. Child abuse affects all children regardless of genotype; every effort should be made to prevent maltreatment from occurring. If anything, these results suggest that common variation in just a few genes has a small (yet statistically significant) impact on explaining different behaviors observed in maltreated children. At any point in a child’s life, environmental protective factors such as supportive caregivers, strong peer groups, or an influential teacher can dramatically promote resilient functioning no matter what genes are carried. Child abuse is one of the most detrimental environmental exposures that any individual can experience; continued efforts to study the physical and psychological health related outcomes of maltreated children will help develop more effective prevention and treatment tools.

Table 1.

Adaptive Functioning Descriptive Statistics

Variable	Category	Maltreated Freq(%)	Nonmaltreated Freq(%)	Chi- Square Value	<i>df.</i>	<i>p</i> -value
Prosocial	1	72(15%)	32(6%)	48.8	5	<.000
	2	96(20%)	66(13%)			
	3	108(22%)	99(20%)			
	4	124(26%)	139(28%)			
	5	58(12%)	109(22%)			
	6	27(6%)	58(12%)			
Antisocial	1	139(29%)	218(43%)	47.1	5	<.000
	2	102(21%)	132(26%)			
	3	83(17%)	62(12%)			
	4	73(15%)	47(9%)			
	5	35(7%)	23(5%)			
	6	53(11%)	20(4%)			
Withdrawn	1	156(32%)	173(34%)	1.7	5	>.05
	2	129(27%)	134(27%)			
	3	98(20%)	100(20%)			
	4	45(9%)	41(8%)			
	5	31(6%)	25(5%)			
	6	26(5%)	29(6%)			
Depression	1	170(38%)	218(47%)	20.8	5	<.000
	2	95(21%)	83(18%)			
	3	64(14%)	50(11%)			
	4	40(9%)	65(14%)			
	5	28(6%)	16(3%)			
	6	51(11%)	34(7%)			

Note. The z-score range cut-offs for each category of the antisocial, withdrawn, and depression variables is Cat1= < -.5 SD; Cat2= >-.5 to 0 SD; Cat3= >0 to .5 SD; Cat4= >.5 to 1 SD; Cat5= >1 to 1.5 SD; Cat6 = >1.5 SD. The z-score range cut-offs for each category of prosocial variable is Cat1= < -1.0 SD; Cat2= >-1.0 to -.5 SD; Cat3= >-.5 to 0 SD; Cat4= >0 to .5 SD; Cat5= >.5 to 1 SD; Cat6 = >1.

Table 2.
Fit indices for LCA of adaptive functioning

Model	LL	npar	LL χ^2 Test			AIC	BIC	CAIC	AWE	Adj. LMR- LRT			$BF(K,K+1)$	$cmP(K)$
			χ^2	df	p					$\chi^2(df=6)$	p	bootstrapped p		
1-Class	-6269.6	20	1667.5	1275	<.001	12579	12677	12697	12875	542.835	<.001	<.001	0	0
2-Class	-5998.2	41	1103.5	1252	1.00	12078	12279	12320	12685	183.39	<.001	<.001	0	0
3-Class	-5906.5	62	921.2	1231	1.00	11937	12241	12303	12855	108.97	1	<.001	6.4*10⁷	1
4-Class	-5852.0	83	811.6	1210	1.00	11870	12277	12360	13099	58.79	0.374	<.001	$5*10^{18}$	0
5-Class	-5822.6	104	749.8	1188	1.00	11853	12363	12467	13393	52.36	0.897	<.001	$1.3*10^{20}$	0
6-Class	-5796.4	125	721.2	1170	1.00	11843	12455	12580	13693	--	--	--	--	0
Saturated	-5854.5	26	798.2	1267	1.00	11761	11888	11914	12146	--	--	--	--	0

Note. LL = Model log likelihood value; npar = number of free parameters; LL χ^2 Test = log likelihood ratio model chi-square goodness-of-fit test; AIC= Akaike Information Criterion; BIC = Bayesian Information Criterion; CAIC = Consistent Akaike Information Criterion; AWE = Approximate Weight of Evidence Criterion; Adj. LMR-LRT = Adjusted Lo–Mendell–Rubin Likelihood Ratio Test; p = p-value corresponding to the adjusted LMR-LRT χ^2 statistic (df = 6) comparing H_0 : K classes vs. H_1 : K + 1 classes; bootstrapped p= bootstrapped LRT p-value; BF (K, K+1)= Bayes factor ratio of Models K, K+1; cmP(K)=correct model probability; Bolded values correspond to “best” model according to the fit index—columns with no bolded values indicate that the best value for that index was not reached prior to the maximum class extraction supported by the data

Table 3.

Model Classification Diagnostics for the 3- through 5-Class Solutions

<i>K</i> -Class Solution	<i>k</i> -Class	Estimated <i>k</i> -Class Proportion	95% C.I.*	<i>mcaP_k</i>	<i>AvePP_k</i>	<i>OCC_k</i>	Entropy
3-Class	Class 1	.408	(0.348, 0.469)	.382	.977	61.54	.816
	Class 2	.361	(0.299, 0.423)	.392	.858	10.69	
	Class 3	.231	(0.163, 0.298)	.227	.916	36.39	
4-Class	Class 1	.325	(0.251, 0.399)	.318	.913	21.82	.785
	Class 2	.151	(0.074, 0.228)	.119	.853	32.62	
	Class 3	.237	(0.182, 0.291)	.239	.917	35.65	
	Class 4	.288	(0.225, 0.350)	.324	.814	10.84	
5-Class	Class 1	.300	(0.214, 0.377)	.285	.913	25.00	.785
	Class 2	.142	(0.074, 0.210)	.122	.784	21.95	
	Class 3	.191	(0.130, 0.252)	.208	.753	12.88	
	Class 4	.203	(0.132, 0.275)	.222	.808	16.49	
	Class 5	.168	(0.100, 0.236)	.162	.905	47.24	

Note. *Bias-corrected bootstrapped 95% confidence intervals

Table 4.
Polygenic Factor Regression Weights

Gene-Variant	Regression Weight Estimate	Standard Error	Estimate/Standard Error	Two-Tailed P-Value
<i>DRD4</i> -VNTR	1	-	-	-
* <i>DRD4</i> - rs1800955	0.186	0.093	1.992	0.046
* <i>COMT</i> - rs4680	0.714	0.088	8.080	0.000
* <i>DRD2</i> -rs1800497	0.247	0.085	2.918	0.004
<i>DRD2</i> -rs1799732	1.767	0.079	22.308	0.000
<i>DAT1</i> -VNTR	0.092	0.092	0.996	0.319
* <i>DAT1</i> -rs40184	0.256	0.095	2.689	0.007
* <i>DAT1</i> -rs27072	0.809	0.110	7.354	0.000
5-HTTLPR	0.369	0.087	4.258	0.000
<i>CRHR1</i> - rs110402	2.161	0.058	37.425	0.000
* <i>OXTR</i> - rs53576	0.910	0.105	8.677	0.000
<i>FKBP5</i> -rs1360780	0.220	0.084	2.613	0.000

Note. *Refers to a variant reverse-coded. *DRD4*-VNTR estimate was set at 1 to scale the formative factor.

Table 5.
Multinomial Logistic Regression Results

Pairwise Comparison	Predictor	Δ Log Odds(OR) Estimates	Log Odds Standard Error	Log Odds/Standard Error	Two-Tailed P-Value
EX vs. WA	# of Mal Subtypes	0.486(1.6)	0.109	4.478	0.000
	Polygenic Factor	0.062(1.1)	0.062	0.996	0.319
	Mal X Factor	-0.173(.84)	0.054	-3.232	0.001
IN vs. WA	# of Mal Subtypes	0.212(1.2)	0.173	1.225	0.220
	Polygenic Factor	-0.054(.94)	0.094	-0.578	0.563
	Mal X Factor	-0.111(.89)	0.085	-1.303	0.193
SD vs. WA	# of Mal Subtypes	0.235(1.3)	0.115	2.046	0.041
	Polygenic Factor	0.025(1.0)	0.061	0.407	0.684
	Mal X Factor	-0.003(.99)	0.052	-0.048	0.961
IN Vs. EX	# of Mal Subtypes	-0.291(.74)	0.155	-1.879	0.060
	Polygenic Factor	-0.115(.89)	0.099	-1.159	0.246
	Mal X Factor	0.064(1.1)	0.084	0.762	0.446
SD vs. EX	# of Mal Subtypes	-0.293(.74)	0.118	-2.478	0.013
	Polygenic Factor	-0.041(.96)	0.078	-0.519	0.604
	Mal X Factor	0.198(1.2)	0.061	3.236	0.001
SD vs. IN	# of Mal Subtypes	0.050(1.1)	0.179	0.279	0.780
	Polygenic Factor	0.072(1.1)	0.105	0.689	0.491
	Mal X Factor	0.130(1.1)	0.091	1.421	0.155

Note. These estimates are controlling for sex, age, sex-by-factor, and age-by-maltreatment. The polygenic factor, sex, and age were mean centered. SD=socially-dominant; WA=well-adjusted; IN=internalizing; EX=externalizing. OR=Odds ratio.

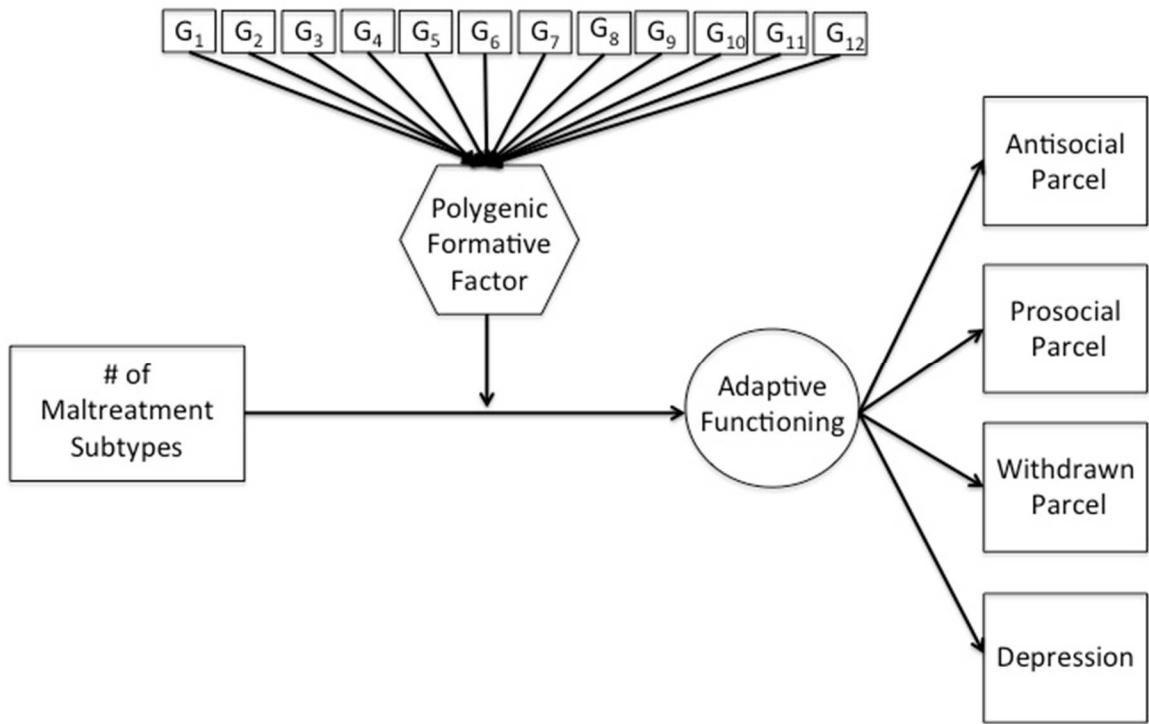
Table 6.

Pairwise comparisons between externalizing class, the well-adjusted, and the socially-dominant class in terms of the effect of the number of maltreatment subtypes experienced on class membership at different levels of the polygenic factor

Pairwise Comparison	Factor Level	# of Mal Subtypes Δlog odds(OR) estimate	Log Odds Standard Error	Log Odds/Standard Error	Two-Tailed P-Value
EX vs. WA	-2SD	1.232(3.4)	0.259	4.756	0.000
	Mean	0.486(1.6)	0.109	4.478	0.000
	2SD	-0.259(.77)	0.251	-1.035	0.301
SD vs. EX	-2SD	-0.987(.37)	0.261	-3.776	0.000
	Mean	-0.293(.74)	0.118	-2.478	0.013
	2SD	0.483(1.6)	0.255	1.894	0.058

Note. These estimates are controlling for sex, age, sex-by-factor, and age-by-maltreatment. SD=socially-dominant; WA=well-adjusted; EX=externalizing. Sex, age, and factor scores were mean-centered. OR=odds ratio.

Figure 1
Conceptual Model

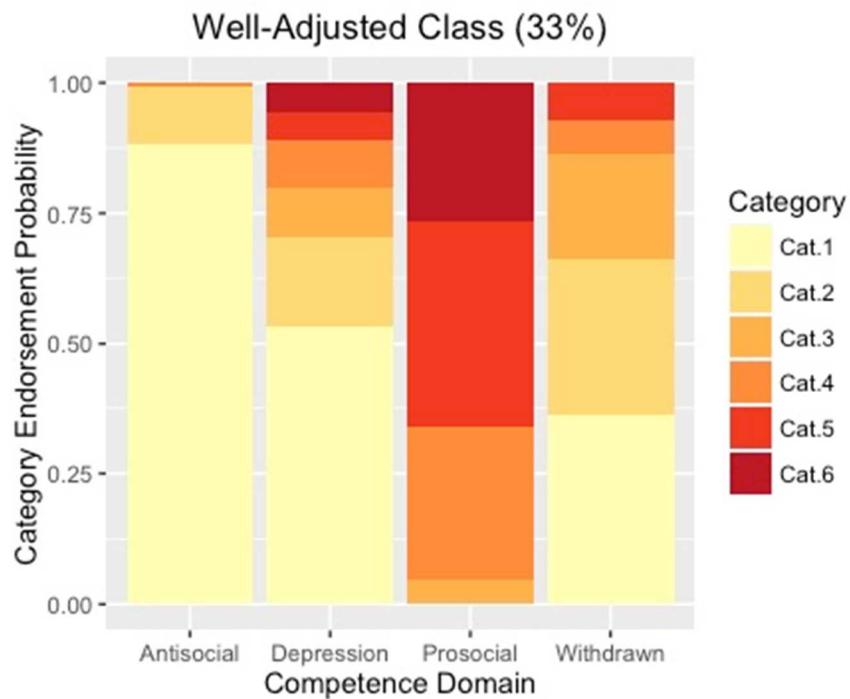


Note. Control variables are not pictured (sex, age, age-by-maltreatment, sex-by-factor). Hexagonal representation of formative factor indicates a composite rather than a latent variable. The 'Adaptive Functioning' variable is a categorical latent class variable.

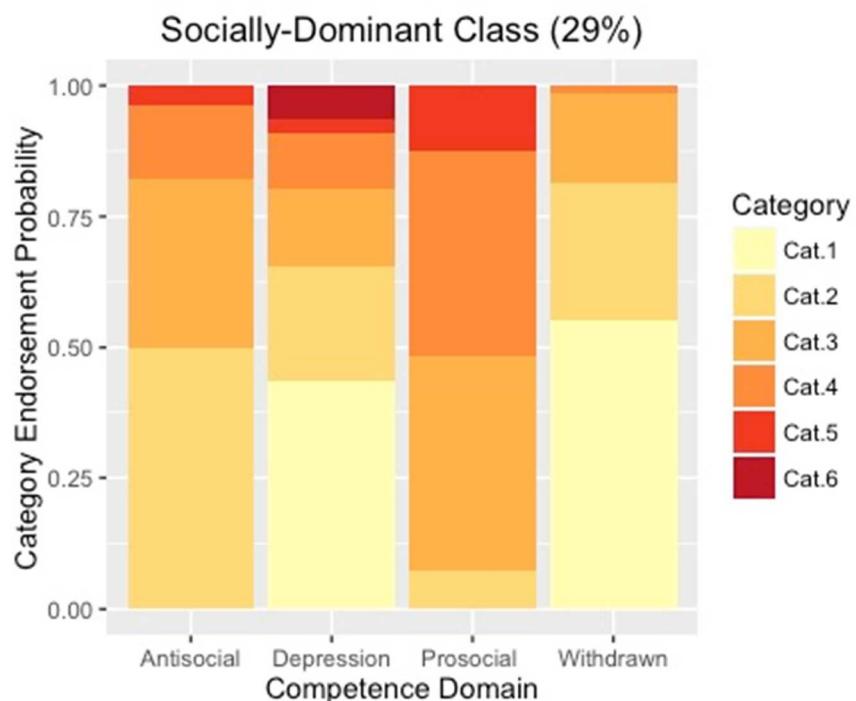
Figure 2.

Profiles of Adaptive Functioning

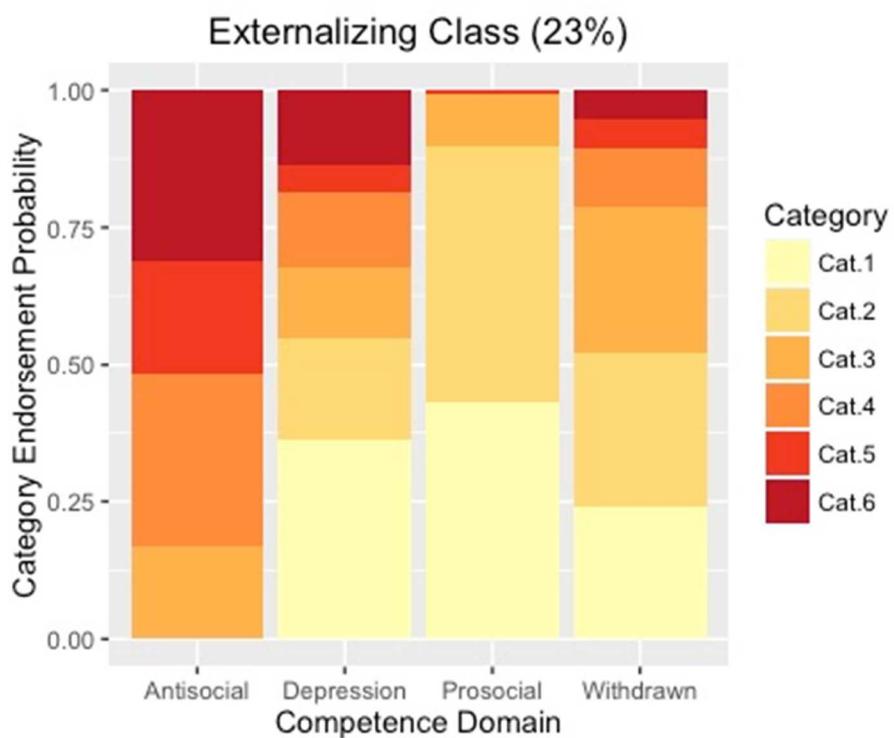
A.



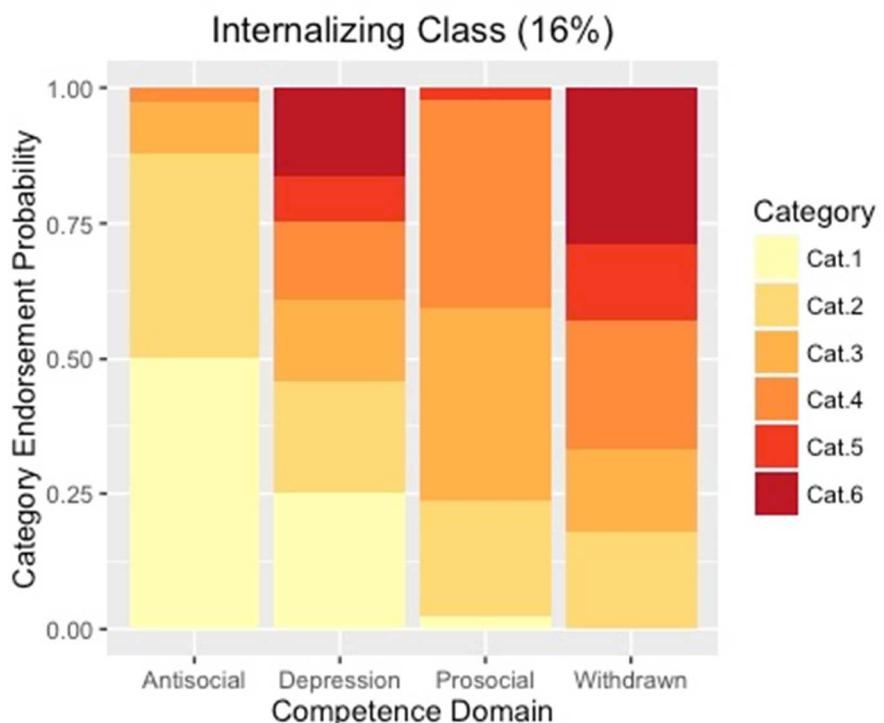
B.



C.

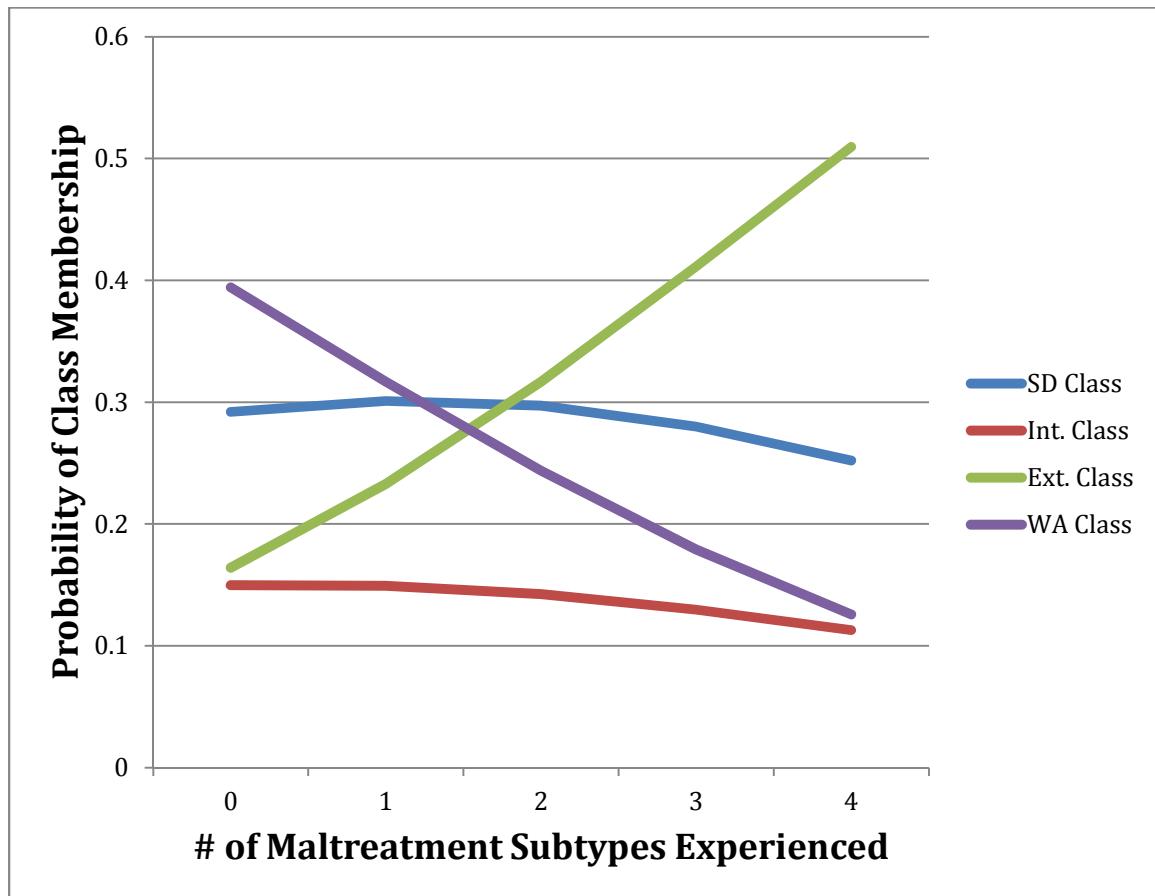


D.



Note. The z-score range cut-offs for each category of the antisocial, withdrawn, and depression variables is Cat1= < -.5 SD; Cat2= >-.5 to 0 SD; Cat3= >0 to .5 SD; Cat4= >.5 to 1 SD; Cat5= >1 to 1.5 SD; Cat6 = >1.5 SD. The z-score range cut-offs for each category of prosocial variable is Cat1= < -1.0 SD; Cat2= >-1.0 to -.5 SD; Cat3= >-.5 to 0 SD; Cat4= >0 to .5 SD; Cat5= >.5 to 1 SD; Cat6 = >1.

Figure 3.
Main Effects of Child Maltreatment Probability Curve Plot



Note. SD=Socially-dominant; Int.=Internalizing; Ext.=Externalizing; WA=Well-adjusted. Controlling for sex and age.

Figure 4.
GxE Probability Curve Plots
A.

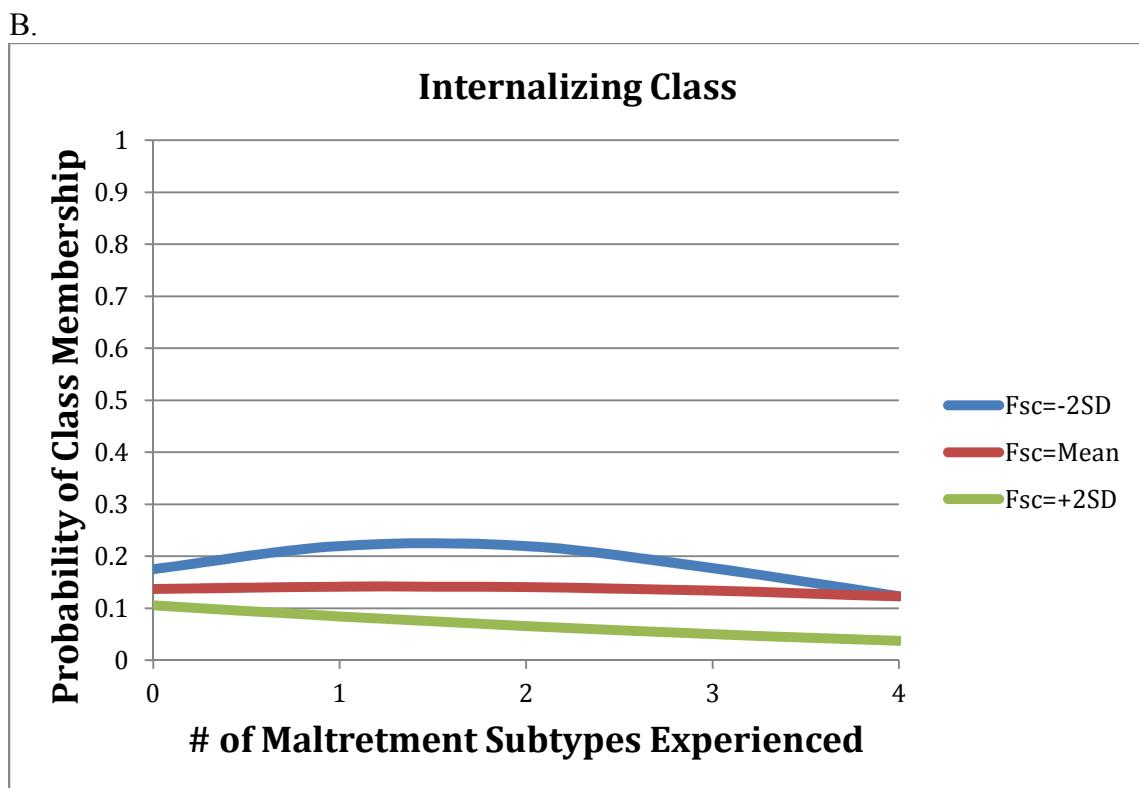
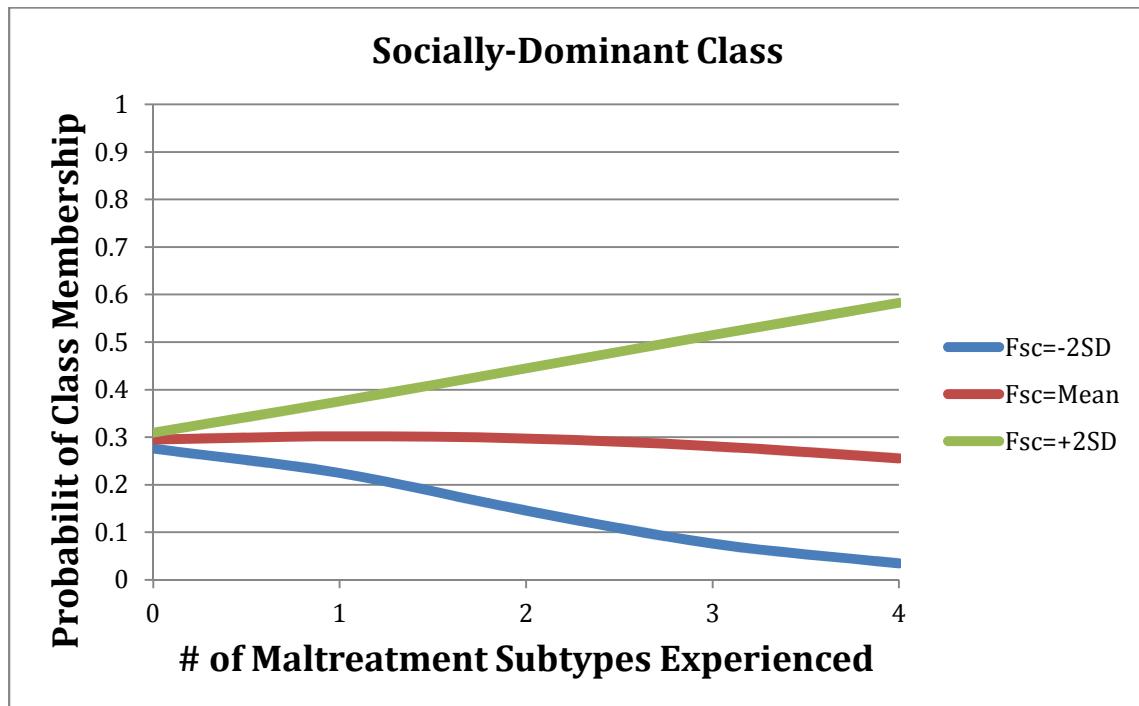
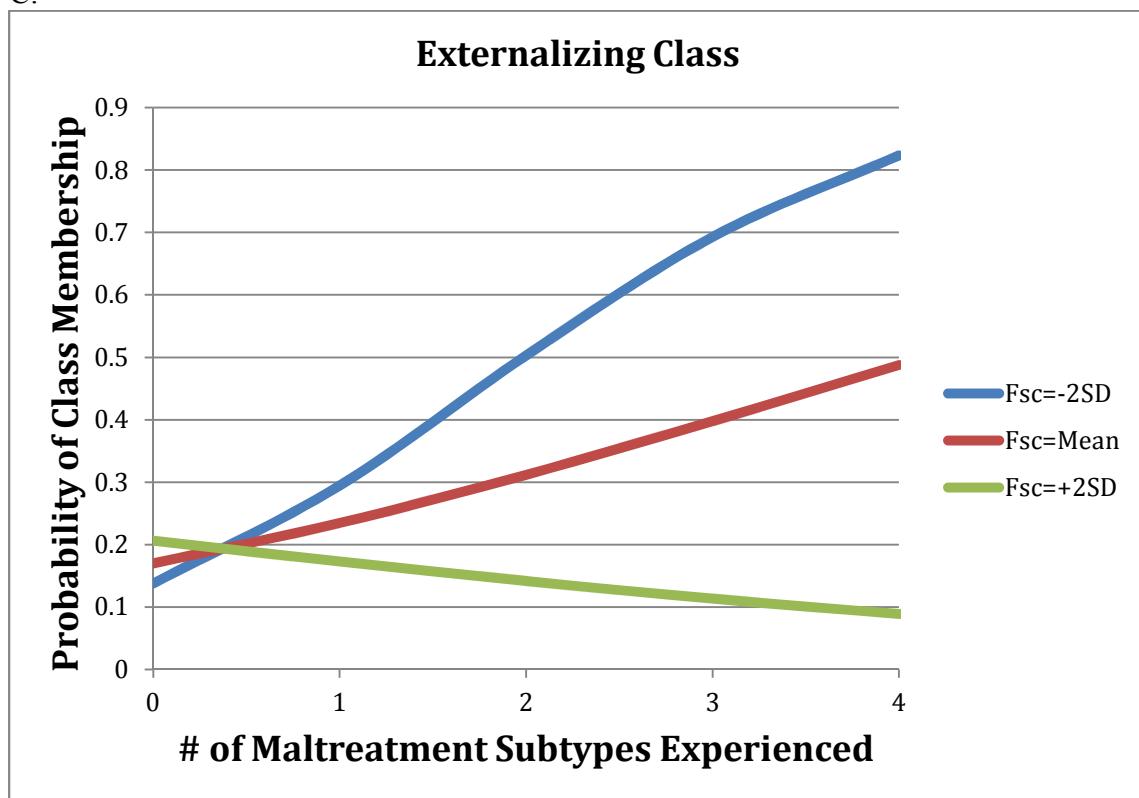
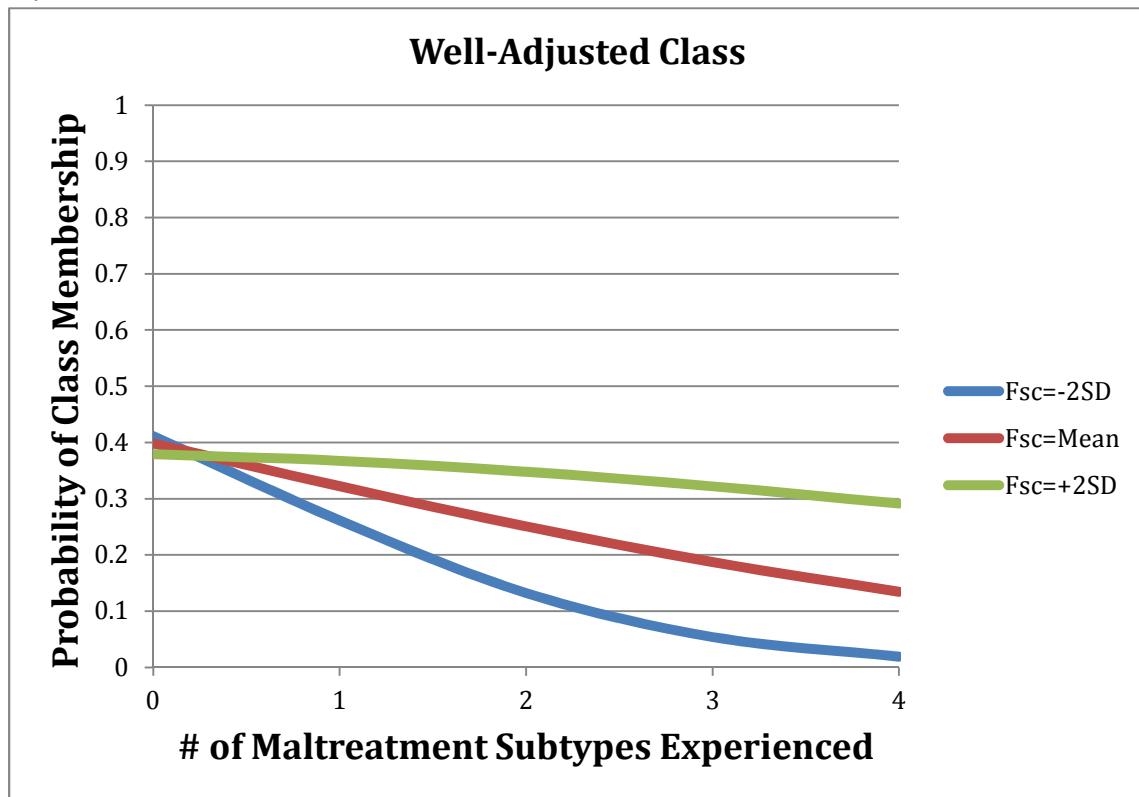


Figure 4. Cont.

C.



D.



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