NIH Public Access
Author Manuscript
Dev Psychopathol. Author manuscript; available in PMC 2015 August 01.

Published in final edited form as:
Dev Psychopathol. 2014 August ; 26(3): 831–849. doi:10.1017/S095457941400042X.

Moderation of maltreatment effects on childhood borderline personality symptoms by gender and oxytocin receptor and FK506 binding protein 5 genes

Dante Cicchetti[1,2], **Fred A. Rogosch**[2], **Kathryn F. Hecht**[1], **Nicki R Crick**[1], and **Susan Hetzel**[1]

[1]Institute of Child Development, University of Minnesota

[2]Mt. Hope Family Center, University of Rochester

Abstract

In this investigation, gene-environment-gender interaction effects in predicting child borderline personality disorder symptomatology among maltreated and nonmaltreated low-income children (*N* = 1,051) were examined. In the context of a summer research camp, adult-peer-, and self-report assessments of borderline precursor indicators were obtained, as well as child self-report on the *Borderline Personality Features Scale-Children*. Genetic variants of the OXTR genotype and the FKPB5 CATT haplotype were investigated. Children who self-reported high levels of borderline personality symptomatology were differentiated by adults, peers, and additional self-report on indicators of emotional instability, conflictual relationships with peers and adults, preoccupied attachment, and indicators of self-harm and suicidal ideation. Maltreated children also were more likely to evince many of these difficulties relative to nonmaltreated children. In a series of ANCOVAs, controlling for age and ancestrally informative markers, indicated significant maltreatment X gene X gender three-way interactions. Consideration of the maltreatment parameters of subtype, onset, and recency expanded understanding of variation among maltreated children. The three-way interaction effects demonstrated differential patterns among girls and boys. Among girls, the gene-environment interaction was more consistent with a diathesis-stress model, whereas among boys a differential-sensitivity interaction effect was indicated. Moreover, the genetic variants associated with greater risk for higher borderline symptomatology, dependent on maltreatment experiences, were opposite in girls compared to boys. The findings have important implications for understanding variability in early predictors of borderline personality pathology.

Child Maltreatment represents a serious dysfunction in parenting, as well as a substantial disturbance in parent-child relationships that may eventuate in aberrant biological and psychological development and child maladaptation across the life span (Belsky & Jaffee, 2006; Cicchetti & Toth, in press; DeBellis, 2001, 2005). Additionally, experiences of child abuse and neglect may present serious challenges to the species-typical organism-environment “coactions” that play important roles in the emergence and timing of normal developmental processes (Cicchetti & Lynch, 1995; Cicchetti & Valentino, 2006).

Direct correspondence to: Dante Cicchetti, Institute of Child Development, University of Minnesota, 51 East River Road, Minneapolis, MN 55455. cicchett@umn.edu..

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Through scientific investigations of the effects of severe environmental disturbances, such as child maltreatment, researchers may be able to gain insight into processes that normally are so subtle and gradual that they are not observed (Chomsky, 1968). For example, by examining the development of children who have not experienced a benign rearing environment, such as is the case with children who have been abused and/or neglected, researchers may be able to elucidate the impact that caregiving quality can exert on neurobiological structure and function (Belsky & de Haan, 2011; Cicchetti, 1996, 2002a, 2002b; Cowell, Cicchetti, Rogosch, & Toth, in press; McCrory et al., 2010).

Child maltreatment ushers in motion a probabilistic cascade of epigenesis for abused and neglected children that often eventuates in a profile of relatively enduring vulnerability factors that increase the probability of the emergence of maladaptation and psychopathology (Cicchetti & Lynch, 1995; Cicchetti & Toth, in press; Manly et al., 2001; Widom, Dumont, & Cjaza, 2007). Among the personality disorders, borderline personality disorder (BPD) has been examined extensively with regard to the role that adverse childhood experiences play in its etiology, course, and pathogenesis (Fonagy & Luyten, in press; Lenzenweger & Cicchetti, 2005). Given that personality disorders do not emerge de novo at 18 years of age, the cut-off criterion established in the psychiatric nomenclature, some researchers have adapted a developmental psychopathology approach by seeking to identify early precursors, prodromal signs, and processes that confer vulnerability to later personality pathology (Cicchetti, 2014; Cicchetti & Crick, 2009a, 2009b; Tackett, Balsis, Otlmanns, & Krueger, 2009). The discovery of precursors and prodromes that could later coalesce into BPD would contribute to its identification and pave the way for the implementation of early interventions that are developmentally appropriate as well as timed and guided (Fonagy & Luyten, in press; Lenzenweger & Cicchetti, 2005; Toth, Gravener, Guild, & Cicchetti, 2013).

BPD is characterized by features of affective instability and dysregulation, impulsivity, dysfunctional interpersonal relationships with parents and peers, identity problems, and anomalies in self-system processes. (American Psychiatric Association, 2000; Fonagy & Luyten, in press). In general, research conducted with patients with BPD indicates that they report higher rates of maltreatment during their childhoods than is the case with patients who have other personality disorders or Axis I psychiatric disorders (Johnson, Cohen, Brown, Smailes, & Bernstein, 1999; Zanarini, et al., 1997). A major limitation of the research implicating child abuse and neglect in the etiology, course, and sequelae of BPD (as well as in other personality disorders) is that the majority of the work has been retrospective in nature and hence must be interpreted with caution (Lenzenweger & Cicchetti, 2005).

The investigation of maltreated children provides an invaluable opportunity to examine the precursors and pathways to BPD. Abused and/or neglected children manifest functioning deficits in a number of areas that reveal problems associated with BPD. These include maladaptive personality and temperament profiles, relationship disturbances, self-pathology, emotion dysregulation, and increased self-harm and suicidality (Bradley et al., 2011; Cicchetti & Toth, in press; Dube et al., 2001; Evans, Hawton, & Rodham, 2005; Johnson, Cohen, Gould, Kasen, Brown, & Brook, 2002; Rogosch & Cicchetti, 2004).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In efforts to overcome the limitation of extant research on the role that the adverse early experiences of child maltreatment play in the etiology, precursors, and pathways to BPD, prospective research with school-age maltreated and nonmaltreated children has begun to be conducted in our laboratory. Rogosch and Cicchetti (2005) investigated potential precursors to BPD in a sample comprised of 185 maltreated and 175 nonmaltreated children of school-age who had attended a week long research summer day camp. Self-report, peer-report, and counselor-report measures were utilized to assess developmental constructs conceptualized to constitute vulnerability for later emerging BPD. Personality features, representational models of self, parent, and peers, interpersonal relationship difficulties with peers and adults, suicidal/self-harm behavior, and lability/negativity were among the areas included to develop a BPD precursors composite. In addition, the efficiency of three independent attentional networks, alerting, orienting, and conflict, was assessed using a computerized task (Fan, McCandliss, Sommer, Raz, & Posner, 2002; Rueda, Fan, McCandliss, Halparin, Gruber, Lercari, et al., 2004). Maltreated children had higher scores on the BPD precursors composite than did the nonmaltreated comparison children; moreover, children identified as having higher levels of these precursors were more prevalent in the maltreatment group. No differences were found between maltreated and nonmaltreated children for the efficiency of the three attention networks; however, children with high levels of BPD precursors regardless of group status, evinced less efficient processing of the conflict attention network, comparable to findings observed among adult psychiatric patients with BPD. Child maltreatment and efficiency of the conflict attention network independently predicted scores on the BPD precursors composite.

Crick, Murray-Close, and Woods (2005) developed the Borderline Personality Features Scale for Children (BPFS-C), a youth self-report questionnaire that was adapted and modified from the Personality Assessment Inventory (PAI) (Morey, 1991). The PAI is used to assess borderline pathology among adults. Hecht, Cicchetti, Rogosch, & Crick (2014, this issue) administered the BPFS-C to a large sample of maltreated (N=314) and nonmaltreated (N=285) children. Hecht et al (2014, this issue) found that maltreated children reported higher overall borderline feature scores, higher scores on each of the four subscales of the BPFS-C (i.e., affective instability, identity problems, negative relationship, and self-harm), and were more likely to be identified as at high risk for the development of BPD through exhibiting raised scores on each of the four BPFS-C subscales. In addition, maltreatment parameters were examined from coding of Department of Human Services (DHS) records (Manly, 2005). Chronicity, defined as the number of developmental periods during which a child experienced maltreatment, predicted higher overall borderline feature scores on the BPFS-C. In addition, children who experienced early onset and also recent maltreatment were significantly more likely to be included in the high-risk for BPD group.

In this study, we strove to demonstrate how the self-report measure of borderline personality disorder features for children developed by Crick and her colleagues (2005) corresponds to a theoretically and developmentally informed borderline features composite comprised of self-report, parent-report, and counselor-report measures. If it is found that the BPFS-C (Crick et al., 2005) and the composite of borderline features are significantly related, then this would provide further validation of the BPFS-C as a potential self-report measure of childhood borderline pathology.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In addition to the multi-informant composite of borderline personality features and the self-report BPFS-C, we included two candidate genes, the oxytocin receptor gene (OXTR) and the FK506 binding protein 5 (FKBP5) gene, in order to facilitate the understanding of any of the variation in BPD features observed among maltreated children.

The human genotype has a single oxytocin receptor gene that is located on chromosome 3p 25, spanning 17 kb, and containing three introns and four exons (Inoue et al., 1994). The gene encodes a 391-amino acid protein that belongs to the class I G-protein-coupled receptor family. Among their presence in other systems of the body, oxytocin receptors also are present in the central nervous system (Gimpl & Fahrenholz, 2001). These receptors modulate a diversity of behaviors, including stress and anxiety, attachment, affiliation, and aggression.

Variation in OXTR function also is related to social behavior. For example, the distribution of oxytocin receptors across the rodent brain is related to the social organization of a species (Insel & Shapiro, 1992), as well as to natural variations in maternal care behavior that are eliminated by oxytocin receptor antagonists (Champagne, Diorio, Sharma, & Meaney, 2001). In addition to its relation to variation in social behavior, attachment, affiliation, and aggression, the OXTR genotype appears to play differential roles under high and low distress conditions. (Hostinar, Cicchetti, & Rogosch, 2014). Given the relation of these diverse behaviors to borderline personality features, we chose OXTR as one of the candidate genes examined to explain variation in borderline symptoms.

Genes that are implicated in the stress-response system have been targets for research examining the impact of child maltreatment on psychiatric functioning (Dackis, Rogosch, Oshri, & Cicchetti, 2012; Koenen et al., 2005; Koenen et al., 2009). The FK506 binding protein 5 (FKBP5) gene is involved in regulating the sensitivity and binding affinity of the glucocorticoid receptor (GR) and therefore has significant implications within the limbic system. FKBP5 is induced by cortisol and acts within a negative feedback loop to promote the transcription of stress-response target genes, leading to downstream release of adrenocorticotropic hormone (ACTH) and plasma cortisol. Environmental stress is strongly related to differential functioning and regulation of FKBP5 at the GR level. (Dackis et al., 2012). Given that FKBP5 plays a critical role in the pathogenesis of stress-related psychopathology, we included FKBP5 as another candidate gene with the potential of expanding understanding of variation in borderline features.

Finally, gender considerations also were thought to be important determinants of variation in borderline symptoms in BPFS-C. Crick and her colleagues (2005) have found borderline features to be more common in girls. Among 11-year-olds meeting criteria for BPD, girls have been found more likely than boys to have mood reactivity, profound abandonment concerns, and unstable relationships, whereas boys were more likely than girls to engage in physically destructive acts and other forms of impulsivity (Zanarini, Horwood, Wolke, Waylen, Fitzmaurice, & Grant, 2011). It is important to examine both male and female children in interaction with maltreatment status and the candidate genes chosen for inclusion in this study as these genes may contribute differentially to variation in BPFS-C scores for males and females.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Hypotheses

This study is guided by the following hypotheses:

1. Children who exhibit higher mean scores on the BPFS-C will have high levels on adult-, peer-, and self-report indicators of the BPD precursors composite.
2. OXTR genotype variants will interact with child maltreatment status and gender in relation to BPFS-C scores. Females will exhibit a different pattern of gene-environment interaction (GxE) than males.
3. FKBP5 haplotype will interact with child maltreatment status and gender in relation to BPFS-C scores. Males and females will exhibit different patterns of GxE.
4. Separate interactions of OXTR, child maltreatment status, and gender and FKBP5 haplotype, maltreatment status, and gender will contribute independently to BPFS-C scores.

Method

Participants

The participants in this investigation included 1,051 children aged eight to twelve (*M* age = 10.37, *SD* = 1.30) who attended a summer camp research program designed for school-aged low-income children. Assessments were conducted during the summers of 2004-2007 and 2009-2012. The sample included both maltreated children (*n* = 562) and nonmaltreated children (*n* = 489). Among the participants, 50.2 % were girls. The maltreated and nonmaltreated samples were comparable in terms of gender and age. The Add Health system for coding race and ethnicity was used (http://www.cpc.unc.edu/projects/addhealth/data/code/race) (cf. DeYoung, Cicchetti, Rogosch, Gray, Eastman, & Grigorenko, 2011). 61.2.0% of the sample was African American, 10.4.0% was European American, 19.7% was Hispanic, and 8.7% was from other or multi-racial/ethnic groups. The families of the children were low income, with 98.3% of the families having a history of receiving welfare benefits. Single mothers headed 75.5% of the families.

Recruitment and Classification Procedures

Parents of all maltreated and nonmaltreated children provided informed consent for their child's participation, as well as consent for examination of any Department of Human Services (DHS) records pertaining to the family. Children in the maltreated group had been identified by the county DHS as having experienced child abuse and/or neglect, and the sample was representative of the children in families receiving services from the DHS. A recruitment liaison from DHS contacted eligible maltreating families, explained the study, and if parents were interested, then their names were released to the project team for recruitment. Families were free to choose whether or not to participate. Comprehensive searches of DHS records were completed, and maltreatment information was coded utilizing operational criteria from maltreatment nosology specified in the *Maltreatment Classification System* (MCS: Barnett, Manly, & Cicchetti, 1993), as discussed below.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Consistent with national demographic characteristics of maltreating families (National Incidence Study – NIS-4; Sedlak et al., 2010), the maltreated children were predominantly from low socioeconomic status families. Consequently, demographically comparable nonmaltreated children were recruited from families receiving Temporary Assistance for Needy Families (TANF). A DHS recruitment liaison contacted eligible nonmaltreating families, described the project, and if interested, parents signed a release for their names to be given to the project for recruitment. DHS record searches were completed for these families to verify the absence of any record of child maltreatment. Trained research assistants also interviewed mothers of children recruited for the nonmaltreatment group to confirm a lack of DHS involvement and prior maltreatment experiences utilizing the *Maternal Maltreatment Classification Interview* (Cicchetti, Toth, & Manly, 2003). Subsequently, record searches were conducted in the year following camp attendance to verify that all available information had been accessed. Only children from families without any history of documented abuse or neglect were retained in the nonmaltreatment group. In addition, families who had received preventive services through DHS due to concerns over risk for maltreatment were excluded from the sample to reduce the potential for unidentified maltreatment existing within this group.

The MCS is a reliable and valid method for classifying maltreatment (Bolger, Patterson, & Kupersmidt, 1998; English et al., 2005; Manly, 2005) that utilizes DHS records detailing investigations and findings involving maltreatment in identified families over time. Rather than relying on official designations and case dispositions, the MCS codes all available information from DHS records, making independent determinations of maltreatment experiences. Based on operational criteria, the MCS designates all of the subtypes of maltreatment children have experienced (i.e., neglect, emotional maltreatment, physical abuse, sexual abuse). Coding of the DHS records was conducted by trained research assistants, doctoral students, and clinical psychologists. Coders were required to meet acceptable reliability with criterion standards before coding actual records for the study. Coders demonstrated acceptable reliability with the criterion (weighted κ's with the criterion ranging from .86 to .98. Reliabilities (κ's) for the presence vs. absence of maltreatment subtypes ranged from .90 to 1.00.

In terms of the subtypes of maltreatment, *neglect* involves 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, moral-legal neglect, and education neglect. *Emotional maltreatment* involves extreme thwarting of children's basic emotional needs for psychological safety and security, acceptance and self-esteem, and age-appropriate autonomy. Examples of emotional maltreatment of increasing severity 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* involves the non-accidental infliction of physical injury on the child (e.g., bruises, welts, burns, choking, broken bones). Injuries range from minor and temporary to permanently disfiguring. Finally, *sexual abuse* involves attempted or actual sexual contact between the child and caregiver for purposes of the caregiver's sexual satisfaction or financial benefit. Events range from exposure to

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

pornography or adult sexual activity, to sexual touching and fondling, to forced intercourse with the child.

Children in the maltreatment group all had documented histories of abuse and/or neglect. Among the maltreated children, 79.7% had experienced neglect, 58.9% had experienced emotional maltreatment, 29.2% had experienced physical abuse, and 8.7% had experienced sexual abuse. As is typical in maltreated populations (Bolger et al., 1998; Manly et al., 1994; 2001), the majority of children had experienced multiple subtypes of maltreatment. Specifically, 58.7% of the maltreated children had experienced two or more maltreatment subtypes. Among maltreated children, we derived a variable to characterize maltreatment subtype experiences. Given the overlap among subtypes and the relatively lower rates of physical and sexual abuse as compared to neglect and emotional maltreatment, we identified children who had experience neglect and/or emotional maltreatment (PNEM; 63.1%) without physical or sexual abuse versus children who had experience physical and/or sexual abuse (PASA; 36.9%). The PASA group also may have experienced neglect or emotional maltreatment.

The MCS also determines when in the course of development maltreatment events occurred, providing indices of developmental timing. Events were coded as occurring during five developmental periods, including infancy (0-18 months), toddlerhood (19-36 months), preschool (36 to 59 months), early school age (age 5 to 7), and later school age (age 8 to 12). The timing information allows for the determination of whether maltreatment occurred within each of the developmental periods. The developmental periods of *onset* of maltreatment and the *recency* of maltreatment are determined. In the current investigation, we classified maltreated children in terms of onset during infancy (23.3%) vs. post-infancy onset (76.7%), and in terms of recency during school-age (60.7%) vs. recency prior to school-age (39.3%).

Procedure

Children attended a week-long day camp program and participated in research assessments. At the camp, children were assigned to groups of eight to ten same-age and same-sex peers; half of the children assigned to each group were maltreated. Each group was conducted by three trained camp counselors, who were unaware of the maltreatment status of children and the hypotheses of the study. Camp lasted 7 hrs/day for five days, providing 35 hours of interaction between children and counselors. In addition to the recreational activities, after providing assent, children participated in various research assessments (see Cicchetti & Manly, 1990, for detailed descriptions of camp procedures) and provided DNA samples. Trained research assistants, who also were unaware of research hypotheses and maltreatment status, conducted individual research sessions with children, in which questionnaires and other research measures were administered. Clinical consultation and intervention occurred if any concerns over danger to self or others emerged during research sessions. At the end of the week, children in each group completed sociometric ratings of their peers. The counselors, who had been trained extensively for two weeks prior to the camp, also completed assessment measures on individual children, based on their observations and interactions with children in their respective groups.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Measures—The measures described below constitute a subset of assessments conducted during the research camp. The camp context and associated measurement battery provide a multi-informant, multi-perspective view of child adaptive functioning. Measures include child self-report, peer evaluations, and counselor-report assessments of individual children, as well as DNA sample collection. The measures of interest in the current investigation were selected to identify varied aspects of child functioning and relationships that were conceptualized as related to risk for BPD.

Child Self-Report Measures

Borderline Personality Features Scale for Children (BPFS-C, Crick, Murray-Close, & Woods, 2005)—The BPFS-C is a self-report questionnaire used to measure borderline personality features in youth. The scale was developed based on consultation with the author of the *Personality Assessment Inventory* (PAI) (Morey, 1991), a measure used to assess borderline personality pathology among adults. The BPFS-C has demonstrated reliability and validity (Crick et al., 2005). The BPFS-C includes four subscales including affective instability, identity problems, negative relationships, and self-harm. (6 items each) with content comparable to the PAI. Crick and colleagues (2005) adapted the items in order to reflect age-appropriate indicators (e.g., middle childhood and beyond) of borderline personality pathology. *Affective instability* is measured with questions such as, “My feelings are very strong. For instance, when I get mad, I get really really mad. When I get happy, I get really really happy” and “I go back and forth between different feelings, like being mad or sad or happy.” *Identity problems* are assessed by items such as, “I feel that something important is missing about me, but I don’t know what it is” and “I change my mind almost every day about what I should do when I grow up.” *Negative relationship* subscale items include, “I want to let some people know how much they’ve hurt me” and “I’ve picked friends who have treated me badly,” Finally, *self-harm* questions include, “When I get upset, I do things that aren’t good for me” and “I get into trouble because I do things without thinking.” Children rate each statement on a Likert scale based on how true the statement is of themselves, from 1 (*not at all true*) to 5 (*always true*). The Likert scores for these items are averaged (some items are reverse-scored) to generate a composite borderline personality features score, with higher scores indicative of higher levels of borderline traits. For the current sample, internal consistency alpha was .88.

***Perceptions of Peers and Self* (POPS; Rudolph, Hammen, & Burge, 1995)—**The POPS is self-report questionnaire composed of two subscales. The first subscale measures children’s perceptions of their peers and friendships, with feelings of problematic relationships resulting in higher scores. Sample items include: “Other kids will try to put you down or tease you if they have a chance,” “Friends often leave you out when there are other kids to play with,” and “Friends may gossip about you when you’re not around.” The second subscale measures children’s perception of self in the context of relationships. Sample items include: “It’s a waste of other kids’ time to be friends with me,” “When other kids do not want to be around me, it’s probably because there is something wrong with me,” and “I am not very good at getting other kids to let me join their games.” In the current sample, the internal consistencies were as follows: peer scale, $\alpha = .71$, and self scale, $\alpha = .73$. Rudolph et al. (1995) reported 1-month and 5-month test-retest reliablities ranging from .55 to .69.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Negative representations of peers and self have been shown to relate to dysfunctional social behavior and less positive status in the peer group (Rudolph et al., 1995).

Relationship Stance Questionnaire **(RSQ; Finnegan, Hodges, & Perry, 1996)—** The RSQ is a 30-item questionnaire designed to measure features of avoidance and preoccupation in relation to attachment figures. In the current study, the preoccupied scale was of particular interest. Brief vignettes are presented to the child, involving stressful situations, and two response options are provided, one suggesting a preoccupied response, and the other a non-preoccupied response. Children then rate whether their choice is "sort of true" or "really true" for them. The response options describe children who experience a strong need for their mothers in stressful or novel situations, distress over separation, excessive concern over abandonment, emotional distress following reunion, and difficulty functioning adaptively due to strong needs for mother. The internal consistency for the scale in the current study was .75. The preoccupied scale, as an attachment construct, has been found to relate negatively to social functioning in the peer group (Finnegan et al., 1996; Hodges, Finnegan, & Perry, 1999).

Children's Depression Inventory **(CDI; Kovacs, 1982, 1992)—**The CDI is a widely used self-report questionnaire to assess depressive symptomatology in school-age 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 two weeks. Kovacs (1992) reports that internal consistency for the total scale has ranged from .71 to .89, and validity has been well established. In addition to total scores, one critical item involving suicidal ideation was of particular interest in this study.

Counselor Measures

Teacher Report Form **(TRF; Achenbach, 1991)—**Behavioral symptomatology was evaluated at the end of each week by counselors' completion of the TRF. The TRF is a widely used and validated instrument to assess behavioral disturbance from the perspective of teachers, and the measure was used in the present study, because camp counselors are able to observe similar behaviors to that of teachers. The TRF, containing 118 items rated for frequency, assesses two broadband dimensions of child symptomatology, externalizing and internalizing, as well as total behavior problems. Subscales scores are also computed for the following factors: withdrawn, somatic problems, anxiety/depression, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. In the present study, interrater reliability for the internalizing and externalizing scales based on average intraclass correlations among pairs of raters were. .73 and .82, respectively. The counselors' scores for each child were averaged to obtain individual child scores for the broadband dimensions, as well as for the YSR subscales. We also were interested in one critical item, "Deliberately harms self or commits suicide," in order to assess suicidality and self harm behavior in children.

California Child Q-Set **(CCQ; Block & Block, 1969)—**At the end of each week of camp after extensive observation and interaction, two counselors independently completed the CCQ on children in their group. The CCQ consists of 100 diverse items about children's

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

personality, and cognitive and social characteristics. Raters sort the individual items printed on cards into a fixed distribution of piles depicting nine categories, ranging from most to least characteristic of the individual child. Thus, individual profiles of the 100 items are generated for each child. Inter-rater agreement assessed by average intraclass correlations among pairs of raters was. 82.

John and colleagues (1994) utilized the CCQ to develop scales corresponding to the personality dimensions of the Five Factor Model, extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience, based on the placement of specific CCQ items in the overall Q-sort for individual children. In the current study, we were particularly interested in the conscientiousness dimension, which has been linked to effortful control (Posner et al., 2002), and low effortful control has been associated with BPD. Our previous work with similar samples has demonstrated acceptable internal consistency for the conscientiousness dimension, α's ranging from .73 to .78 (Rogosch & Cicchetti, 2004).

Emotion Regulation Checklist **(ERC; Shields & Cicchetti, 1997)—**The ERC is a 24-item rating scale measure completed by adult observers, and camp counselors completed the ERC on children in their group. The ERC contains two factor analytically derived subscales, including *Lability/Negativity* and *Emotion Regulation*. We were particularly interested in the Lability/Negativity scale as in indicator of intense and impulsive negative affect. This subscale is composed of items representing a lack of flexibility, mood lability, and dysregulated negative affect. Sample items include: "Exhibits wide mood swings," and "Is prone to angry outbursts." Inter-rater agreement in terms of the average intraclass correlation among pairs of raters was .82, and counselors' ratings were averaged to obtain scores for individual children. Lability/negativity has been shown to mediate relations between child maltreatment and aggressive behavior (Shields & Cicchetti, 1998).

Student-Teacher Relationship Scale **(STRS, Pianta & Steinberg, 1992)—**The STRS is a 30-item measure assessing the quality of the relationship between a child and teacher, as perceived from the teacher's perspective. Given similarity between the camp and school context, counselors used the STRS to report on the relationship quality they experienced with individual children. Items are rated on a five-point Likert scale. We were particularly interested in the conflicted subscale as an indication of interpersonal antagonism the counselor experienced in trying to relate to the child. Sample items include: "This child and I always seem to be struggling with each other," "This child easily becomes angry with me," "This child feels that I treat her/him unfairly," and "This child's feelings toward me can be unpredictable or can change suddenly." Although individual counselors may have unique relationships with specific children, the ratings of each of the counselors were averaged to derive scores for each child. Internal consistency of the conflicted scale in this study was α = .96. The STRS scales have been shown to predict subsequent adjustment (Pianta & Nimetz, 1992) and resilience in low income children (Flores, Cicchetti, & Rogosch, 2005).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Peer-Report Measure

Peer Sociometric Ratings—After children had interacted with each other during the week of summer camp, children evaluated the characteristics of their peers in their respective camp groups using a peer rating method on the last day of camp (cf., Coie & Dodge, 1983). The peer rating method, as compared to peer nominations, is particularly valuable for assessing peer relations in small groups, and given the combined contributions of multiple raters, peer rating measures provide reliable and valid indicators of children's peer relations (Asher & Dodge, 1986; Bukowski, Sippola, Hoza, & Newcomb, 2000). Counselors conducted the peer rating assessment with individual children. For each peer in the camp group, children were given six brief behavioral descriptors characterizing different types of social behavior and asked to rate each peer on a three-point scale (not true, sort of true, very true). Children also rated how well they liked and disliked each child, using the same scale. Two behavioral descriptors were targeted for this study. These items captured disruptive/upsetting/demanding behavior ("Child name upsets everyone, wants everyone to do things his/her way."), and relational aggression ("Child name, when s/he is mad at someone, refuses to play or talk to the person, will try to get others not to like the person, will spread rumors or talk behind the person's back."). The disliked rating also was used. For each item, all peers' ratings for a specific child were averaged in order to obtain a mean peer rating for each individual child for each respective item.

Derivation of a BPD Precursors Composite

Measures derived from self-, peer-, and counselor-report were used to derive a composite of features indicative of high vulnerability for later BPD. In terms of personality features, the ERC lability/negativity scale was chosen as an indicator of intense negative affect and emotional volatility. Similarly, the Five Factor Model conscientiousness scale has been linked to the temperamental construct of effortful control, and diminished effortful control has been linked to BPD. Interpersonal relationship difficulties with adults and peers also were included. We selected the conflict subscale from the STRS to reflect interpersonal difficulties as experienced by adults in trying to relate to the child. In terms of difficulties in interpersonal relations with agemates, peer ratings of disruptiveness, relational aggression, and dislike were incorporated. Representations of self and other were based on the self and peer scales for the POPS, as well as the Preoccupied scale from the RSQ answered in regard to the child's mother. Finally, any endorsement by the child on the CDI item assessing suicidal thoughts and behaviors was targeted. Similarly, the TRF item evaluating self-harming behaviors and suicidal behavior as observed by counselors also was specifically examined. These 11 scales were transformed to Z-scores and averaged; the means were again restandardized to derive the BPD precursors composite. Cronbach's alpha for the composite was .76.

DNA Collection, Extraction, and Genotyping

Trained research assistants obtained DNA samples from participants by collecting buccal cells using the Epicentre Catch-All Collection Swabs or by collecting saliva using the Oragene DNA Self-Collection kits. DNA was extracted and prepared for polymerase chain reaction (PCR) amplification using the Epicentre BuccalAmp DNA Extraction Kit

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

(Epicentre, Cat. No. BQ090155C). Genotyping was then performed using established protocols. SNP genotyping was conducted using Applied Biosystems Custom Taqman SNP Genotyping Assays. The products of these analyses were then analyzed using endpoint allelic discrimination. Genotypes were identified and sequenced with the Beckman-Coulter CEQ8000 semiautomated florescent sequencing system, which utilizes Fragment Analysis Application and associated software. All samples were genotyped twice for quality control. Human DNA from cell lines were purchased from Coriell Cell Repositories for each genotype and used as control samples using DTCS chemistry on an ABI 3130×l. These cell lines and a no template control were run with study samples representing 9% of the total data output. Samples that were not able to be genotyped to a 95% or greater confidence level were repeated under the same procedures up to four times.

Oxytocin Receptor (OXTR)

The OXTR rs53576 SNP was genotyped. The call rate was 99.8%. Genotype frequencies were as follow: A/A, 7.9% (*n* = 79); A/G, 37.2% (*n* = 390), and G/G, 54.9% (*n* = 576). The genotype distribution was in Hardy-Weinberg equilibrium. For subsequent analyses, minor A allele carrier were combined into an A/G-A/A group and compared to major allele homozygotes (G/G).

FKBP5 -CATT Haplotype

Four FKPB5 SNPs were genotyped: rs3800373, rs9296158, rs1360780, and rs9470080. Table 1 presents the location of each SNP within chromosome 6 and the distribution of genotypes for each SNP within the sample. Haploview software version 4.2 (Barrett, Fry, Maller, & Daly, 2005) was used to determine linkage disequilibrium (LD), Hardy-Weinberg Equilibrium (HWE), and minor allele frequencies within the sample. All four SNPs were in HWE. The call rates for the four SNPs were as follows: rs3800373 = 99.5%; rs9296158 = 99.6%; rs1360780 = 99.4%; rs9470080 = 99.4%.

Arlequin v3.5.1.3 was used to form haplotypes using a pseudo-Bayesian approach to estimate phase (Escoffier & Lischer, 2011). All samples were haplotyped with greater than 98% confidence, with the exception of four samples, which were subsequently excluded from analyses. Over 88% of the sample was represented by either the AGCC or CATT haplotype. Following haplotype assignment, individuals with one or more copies of the CATT haplotype were grouped together and compared to individuals with zero copies of this haplotype. This dichotomous variable was utilized in subsequent analyses.

Ancestral Proportion Determinations

DNA from the study participants was submitted to the BioMedical Genomics Center at the University of Minnesota for quantity and quality testing and subsequent SNP genotyping. Acceptable samples (99.0%, 10 cases were excluded) were subjected to SNP genotyping of the Burchard et al. panel of 106 SNPs (Lai et al., 2009; Yaeger et al., 2008), known to be informative for ancestry from Africa, Europe, and Native America. The SNPs were genotyped using the iPLEX platform from Sequenom Bioscience, Inc which uses the Sequenom MassArray. The SNP genotyping results were then recoded and uploaded into STRUCTURE v2.3.4 which uses algorithms developed by Pritchard et al. (Falush Stephens,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

& Pritchard, 2003, 2007; Hubisz, Falush, Stephens, & Pritchard, 2009). Three SNP tests were excluded based on high allele call rates of the non-DNA containing wells. The data from the remaining 103 loci were uploaded into the software and set to analyze with an Admixture model of ancestry and initialization of the simulation on the GALA cohort. The simulation was set to run with a Burn-in of 10,000, MCMC Reps of 1,000 and assuming 3 populations within the group. The results of the simulations were subsequently identified as percent association to each ancestry group, African, Native American, and European, based on the known ancestry of the GALA cohort.

Results

BPFS-C: Associations with child indicators of potential borderline risk

We examined each of the 11 component indicators of our previously developed borderline precursors composite (Rogosch & Cicchetti, 2005), as detailed above. Based on children's self-report on the BPFS-C, children scoring +1 *SD* were included in a high borderline symptoms group; the remaining children were included in a low borderline symptoms group. More maltreated children (21.7%) than nonmaltreated children (13.7%) were represented in the high borderline symptoms group, $\chi^2(1) = 11.37$, $p < .001$. A MANCOVA was conducted with main effects of high borderline symptom group and maltreatment status, and the 11 indicator variables of borderline precursors composite as dependent variables. Age and gender were included as covariates. For comparability with subsequent analyses involving genetic effects, ancestral proportion scores also were included as covariates. The MANCOVA resulted in significant multivariate main effects for the high BPFS-C symptoms group, Wilks' $\lambda = .87$, $F(11,994)= 12.96$, $p < .001$, and maltreatment status, Wilks' $\lambda = .95$, $F(11,994)= 4.86$, $p < .001$, and the interaction of these main effects, Wilks' $\lambda = .98$, $F(11,994)= 2.05$, $p = .022$. Given these significant multivariate effects, individual univariate effects were examined. The high BPFS-C symptom group obtained significantly higher scores than the low symptom group on all of the 11 borderline indicator component variables (*p*'s ranged from .04 to less than .001). See Table 2. Specifically, compared to the low symptom group, the high BPFS-C group was reported by counselors to have higher lability/negativity, lower conscientiousness, more conflicted relationships with adults, and greater self-harm. Peers rated the high BPFS-C group as higher in disruptive interpersonal behavior, relational aggression, and being disliked. Finally, children in the high BPFS-C group, relative to the low group, self-reported more negative peer experiences, more negative feelings about the self, more preoccupied attachment relationships with mothers, and higher suicidal ideation. In terms of maltreatment status, maltreated children scored significantly higher than nonmaltreated children on all of the adult counselor- and peer-rated borderline indicators (*p*'s ranged from .012 to less than .001). However, significant maltreatment status group differences were not found for the four child-self report variables, i.e., negative peers, negative self, preoccupied attachment, and suicidal ideation. In terms of interaction effects, four significant interactions between the high borderline symptom group and child maltreatment status were observed (*p*'s ranged from .04 to less than .001). In these interactions, maltreated children with high BPFS-C symptoms evinced more extreme scores on lability/negativity, and the peer-rated variables of disruptiveness, relational aggression, and disliked than their nonmaltreated counterparts. Finally, an ANCOVA examining the

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

borderline composite of the 11 component variables indicated strong main effects for the high BPFS-C symptom group, maltreatment status, and their interaction. Children in the high BPFS-C group had substantially higher borderline composite total scores than children in the low group, and maltreated children had higher borderline composite scores than nonmaltreated children. Maltreated children in the high BPFS-C group had higher borderline composite scores than any other group.

Oxytocin Receptor (OXTR)

A series of ANCOVAs was conducted to evaluate the influence of child maltreatment, variation in the OXTR rs53576 SNP, and gender on individual differences in the BPFS-C total scores. Age was included as a covariate. Our initial analyses indicated significant effects of maltreatment status ($p < .001$) and gender ($p = .044$) on BPFS-C scores, as well as a significant 3-way interaction of maltreatment, OXTR genotype, and gender ($p = .009$). Because the sample was racially and ethnically diverse potentially introducing population stratification into the results, we addressed the effects of race/ethnicity with two strategies in order to evaluate whether hypothesized G × E × Gender effects were affected by racial/ethnic variation. In the first approach, we included the child's parent-reported race/ethnic group (Black, White, Hispanic, Other/Multiracial) as a main effect to the ANCOVA model, as well as interactions of maltreatment X race group, gender X race group, and OXTR genotype X race group (cf., Keller, 2014). These main and interactive effects involving race were all nonsignificant (p's > .05), and the main effect of maltreatment status and the three-way interaction of maltreatment status, OXTR genotype, and gender retained significance ($p = .007$).

The second strategy to evaluate race/ethnic effects involved including the ancestral proportion scores for African, Native American, and European groups as covariates in the ANCOVA model. The covariates were not significantly related to the BPFS-C total scores, and the initial main and interactive effects were maintained. Specifically, the main effects of maltreatment status, $F(1,1027) = 29.01$, $p < .001$, and gender, $F(1,1027) = 4.53$, $p = .034$, were significant, whereas the effect of OXTR genotype group was not $F(1,1027) = 1.22$, $p = .27$. No two-way interactions were significant. However, the three-way interaction was significant, $F(1,1027) = 7.14$, $p = .008$. To examine the three-way interaction, we considered the effects of maltreatment status and OXTR genotype separately for girls and for boys, as depicted in Figures 1a and 1b, respectively. Among girls, Bonferroni contrasts indicated that among nonmaltreated girls, there was no effect of genotype. In contrast, among maltreated girls, the effect of OXTR genotype was significant, $p = .016$, with girls in the AG-AA group having higher BPFS-C scores than girls in the GG group. Additionally, among girls with the AG-AA genotypes, maltreated girls had significantly higher BPFS-C scores than nonmaltreated girls, $p < .001$, whereas significant maltreatment status group differences were not observed among girls with the GG genotype. For boys (Figure 1b) in contrast to girls, among those with a GG genotype, maltreated boys had significantly higher BPFS-C scores than nonmaltreated boys, $p < .000$, whereas maltreatment group differences were not significant for boys in the AG-AA genotype group. No other contrasts were significant.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

OXTR genotype and maltreatment subtype groups

The effects of variation in maltreatment experiences were examined by inclusion of a maltreatment subtype variable (Physical and/or sexual abuse, neglect and/or emotional maltreatment without abuse, and nonmaltreated) in place of maltreatment status in the ANCOVA model. Given the comparable results when controlling for race/ethnicity effects using parent-reported group vs. ancestral proportion scores, we present results using ancestral proportion scores as covariates, given the greater genetic specificity of the proportion scores. The ANCOVA, controlling for age and ancestral scores, indicated significant main effects for maltreatment subtype, $F(2,1023) = 14.24$, $p < .001$, and gender, $F(1,1023) = 5.77$, $p = .02$, as well as the three-way interaction of subtype, OXTR genotype, and gender, $F(2,1023) = 4.53$, $p = .01$. The results for girls and for boys are shown in Figures 2a and 2b. For girls, Bonferroni contrasts for genotype group were not significant in the nonmaltreated and PA/SA groups, whereas among girls in the EM/PN group, those with AG-AA OXTR genotypes had significantly higher BPFS-C scores than those in the GG OXTR group, $p = .016$. Additionally, among those with AG-AA genotypes, girls in the EM/PN group had significantly higher BPFS-C scores than nonmaltreated girls, $p < .001$. No subtype group differences were found among girls with GG genotypes. Among boys (Figure 2b), no significant subtype groups differences were observed among boys with AG-AA genotypes. However, among boys in the GG OXTR genotype group, those in both the EM/PN group, $p < .001$, and the PA/SA group, $p = .018$, had significantly higher scores than nonmaltreated boys.

OXTR genotype and maltreatment onset in infancy

The next analyses examined variation in the developmental timing of maltreatment, considering the onset period of maltreatment, with groups comprised of those experiencing onset in infancy, later (post-infancy) onset, and nonmaltreated children. In this ANCOVA, all three main effects were significant, including maltreatment onset group, $F(2,1023) = 13.98$, $p < .001$, OXTR genotype, $F(1,1023) = 4.34$, $p = .037$, and gender, $F(1,1023) = 4.41$, $p = .036$, as well as a gender X genotype interaction, $F(1,1023) = 5.46$, $p = .02$. The effects were further clarified by a three-way interaction of onset, genotype, and gender, $F(2,1023) = 5.063$, $p = .008$. The 3-way interaction was again examined by evaluating Bonferroni contrasts within gender groups (See Figures 3a and 3b). Among girls, those with infancy onset differed significantly based on OXTR genotype, $p = .001$, with girls in the AG-GG genotype group having significantly higher BPFS-C scores than those in the GG genotype group. For girls in the AG-AA genotype group, those with infant onset had significantly higher scores than nonmaltreated girls, $p < .001$, and marginally higher scores than girls with post-infancy onset, $p = .065$. No significant onset group differences were found in the GG genotype group. In contrast for boys, no significant differences in BPFS-C scores were found among boys with the AG-AA genotypes, whereas for boys with GG genotypes, boys in both the infancy onset group, $p < .001$, and the post-infancy group, $p = .02$ had significantly higher scores than nonmaltreated boys.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

OXTR genotype and maltreatment recency in the school-age period

Next, we examined the recency of maltreatment experiences, differentiating children whose most recent maltreatment experiences occurred during the school age years vs. those whose most recent maltreatment occurred prior to school age, and maltreated children. In this ANCOVA, significant main effects were found for recency group, $F(2,1023) = 15.31$, $p < .001$, and gender, $F(1,1023) = 6.15$, $p = .016$, as well as the three-way interaction of recency group, OXTR genotype, and gender, $F(1,1023) = 3.54$, $p = .029$. Examination of interaction effects among girls (See Figure 4a) indicated that for those with AG-GG genotypes, girls with school-age recency had significantly higher BPFS_C scores than nonmaltreated girls. No significant group differences were found among girls with GG genotypes. In contrast among boys (Figures 4b), no significant recency group differences were found for boys with AG-GG genotypes, where as among those boys with GG genotypes, both the school age recency group, $p = .002$, and the prior to school age recency group, $p = .002$, had higher scores than nonmaltreated children.

FKPB5 – CATT Haplotype

To evaluate the influence of the FKBP5- CATT haplotype in conjunction with maltreatment parameters and gender on BPFS-S scores, the same approach as used for OXTR was followed. Initially, an ANCOVA controlling for age resulted in significant main effects for maltreatment status, $p < .001$, and gender, $p = .047$, as well as a significant three way interaction of maltreatment, CATT haplotype group, and gender, $p = .008$. We also applied the two strategies for examining race/ethnicity contributions. In the first analysis, inclusion of race/ethnicity group and its interactions with maltreatment, gender, and haplotype group did not result in significant effects, and the three-way interaction remained significant. Similarly, in using the second strategy to control for race/ethnicity effects, inclusion of the ancestral proportion scores did not alter the three-way interaction effect, and these covariates were not significant in the model. In this ANCOVA, the main effects for maltreatment status, $F(1,1023) = 29.09$, $p < .001$, and gender, $F(1,1023) = 4.30$, $p = .01$, were significant, as was the three-way interaction, $F(1,1023) = 6.66$, $p = .038$. We examined this interaction by investigating effects of maltreatment status and haplotype groups separately among girls and boys. (See Figures 5a and 5b). For girls with 1-2 copies of the CATT haplotype, Bonferroni contrasts indicated that maltreated girls had significantly higher BPFS-C scores than nonmaltreated girls, $p = .003$. No significant differences between maltreated and nonmaltreated girls were observed for those in the 0 copy CATT haplotype group. No other comparisons were significant. In contrast, for boys, significant maltreatment status group differences were found for the 0 CATT copies group, with maltreated boys having significantly higher BPFS-C scores than nonmaltreated boys, $p < .001$, whereas for boys with 1-2 copies of the CATT haplotype, maltreatment status groups did not differ significantly. Additionally, among nonmaltreated boys, those with 1-2 CATT copies had significantly higher scores than those with 0 copies, $p = .04$. Among maltreated boys, the haplotype groups did not significantly differ.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

FKBP5-CATT haplotype and maltreatment subtype groups

The influence of variation in children's maltreatment subtype experiences was examined next in the ANCOVA model, with age and ancestral proportion scores as covariates. Significant main effects emerged for subtype group, $F(2,1023) = 15.36$, $p < .001$, and for gender, $F(1,1023) = 7.92$, $p = .005$, as well as the three-way interaction of subtype, haplotype, and gender, $F(2,1023) = 5.70$, $p = .003$. Figures 6a and 6b illustrate the interaction effects for girls and boys, respectively. Among girls, no significant differences were found based on haplotype group for maltreated girls or for girls in the EMPN group; however, in the PASA group, girls with 1-2 copies of the CATT haplotype had significantly higher BPFS-C scores than girls with 0 copies, $p = .05$. Additionally, among girls with 1-2 copies, those in the EMPN group had significantly higher BPFS-C scores than nonmaltreated girls. No additional contrasts were significant. Among boys, although the haplotype group difference in BPFS-C scores was not significant in the EMPN group, contrasts indicated that in the PASA group, boys with 0 copies of the CATT haplotype had significantly higher scores than boys with 1-2 copies, $p = .02$, whereas among nonmaltreated boys, those with 1-2 copies had significantly higher scores than nonmaltreated boys with 0 copies, $p = .04$. Additionally, although no subtype group differences were significant among boys with 1-2 CATT haplotype copies, among boys with 0 copies, those in the EMPN group, $p = .002$, and in the PASA group, $p < .001$, had significantly higher BPFS-C scores than nonmaltreated boys.

FKBP5-CATT haplotype and maltreatment onset in infancy

When the effects of developmental timing of maltreatment were considered, a similar pattern of results was found based on infancy onset. Specifically, in an ANCOVA examining infancy onset groups (onset in infancy, onset later (post-infancy), and nonmaltreated children), controlling for age and ancestral proportion scores, significant main effects were observed for onset group, $F(2,1019) = 15.03$, $p < .001$, and gender, $F(2,1019) = 4.28$, $p = .039$, as well as the onset group by haplotype group by gender three-way interaction, $F(2,1019) = 3.94$, $p = .02$. Investigation of the three-way interaction proceeded by investigation of the gender groups. (See Figures 7a and 7b). Among girls with 1-2 copies of the CATT haplotype, those with post-infancy onset had significantly higher BPFS-C scores than nonmaltreated girls, $p = .023$; girls with infancy onset had marginally higher scores than nonmaltreated girls, $p = .095$. No significant onset group differences were found among girls with 0 copies of the CATT haplotype. When boys were examined, for those with 0 copies of the CATT haplotype, both boys with infancy onset, $p = .02$, and boys with post-infancy onset, $p < .001$, had significantly higher BPFS-C scores than nonmaltreated boys. Significant onset group differences were not found among boys with 1-2 CATT haplotype copies. Additionally, among boys with post-infancy onset, higher scores were observed among those with 0 copies compared to those with 1-2 copies of the CATT haplotype, $p = .04$, whereas among nonmaltreated boys, the converse was true. Boys with 1-2 CATT copies had higher scores than those with 0 copies, $p = .037$.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

FKBP5-CATT haplotype and maltreatment recency in the school age period

We further examined the recency of maltreatment experiences (school-age, prior to school age, and nonmaltreated children). As in prior analyses, in this ANCOVA, main effects were found for recency group, $F(2,1019) = 16.80$, $p < .001$, and gender, $F(1,1019) = 9.08$, $p = .003$. In addition, a two-way interaction of recency and haplotype group was observed, $F(2,1019) = 5.75$, $p = .003$. However, these effects were clarified by a significant three-way interaction of recency group, haplotype group, and gender, $F(2,1019) = 4.70$, $p = .009$. Investigation of the three-way interaction proceeded by examination of effects within gender groups, as shown in Figures 8a and 8b. Among girls, the nonmaltreated and the school age recency groups did not differ significantly based on haplotype group; however, a marginal difference was observed for recency occurring prior to school age, $p = .056$, with higher scores among girls with 1-2 copies of the CATT haplotype, compared to those with 0 copies. Among girls with 0 copies of the CATT haplotype, those with school age recency had significantly higher BPFS-C scores than those with recency prior to school age, $p = .05$, and nonmaltreated girls, $p = .05$. Among girls with 1-2 copies of the CATT haplotype, girls with school age recency had higher scores than nonmaltreated girls, $p = .007$. When boys were considered, among those with 0 copies of the CATT haplotype, boys with school age recency had higher scores than those with recency prior to school age, $p = .044$, and nonmaltreated boys, $p < .000$. Among boys with 1-2 CATT copies, those with recency prior to school age had higher scores than nonmaltreated boys, $p = .03$; other contrasts among those with 1-2 CATT copies were not significant. Finally, among boys with school age recency, those with 0 copies of the CATT haplotype had significant higher BPFS-C scores than those with 1-2 copies, $p = .002$, whereas among nonmaltreated boys, the converse was true, with those with 1-2 CATT copies having higher scores than those with 0 copies, $p = .037$

Independent contributions of OXTR and FKBP5 - CATT haplotype

In the final analysis, both OXTR and FKBP5 were examined together to determine the extent to which their effects in interaction with maltreatment status and gender were overlapping. Accordingly, an ANCOVA was conducted with main effects of maltreatment status, gender, and both OXTR genotype and FKBP5 haplotype groups. As previously, age and the ancestral proportion scores were used as covariates. In this analysis both of the previously reported three-way interactions conducted separately by gene (maltreatment status, gender, and OXTR; maltreatment status, gender, and FKBP5) remained significant, $F(1,1014) = 5.75$, $p = .017$ and $F(1,1014) = 5.75$, $p = .008$, respectively for the three-way interactions involving OXTR and FKBP5. The pattern of these three-way interactions was consistent with those obtained when the genes were examined separately. Thus, these three-way interaction effects appeared to independently contribute to BPFS-C scores. Further consideration of maltreatment parameter effects was precluded due to cell size restrictions.

Discussion

Consistent with our first hypothesis, children in the high BPFS-C group had significantly higher scores on each of the eleven borderline indicator component variables than the children in the low BPFS-C group. Camp counselors rated the high BPFS-C group as

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

manifesting higher lability/negativity, lower conscientiousness, more conflicted relationships with adults, and greater self-harm than children in the low BPFS-C group. Moreover, the peers in their camp group rated children in the high BPFS-C symptoms group as higher in disruptive interpersonal behavior, relational aggression, and less liked than children in the low symptoms group. Furthermore, children in the high BPFS-C group, relative to the children in the low symptoms group, self-reported more negative experiences with peers, more negative self-feelings, more preoccupied attachment relationships with their mothers, and higher suicidal ideation.

Maltreated children scored significantly higher than nonmaltreated children on each of the adult- and peer-related borderline indicators; however, maltreatment group differences were not obtained for the child self-report borderline indicators. Additionally, the high BPFS-C symptoms maltreatment group evinced significantly higher scores, relative to nonmaltreated children in the high BPFS-C group on lability/negativity, and the peer-related variables of disruptiveness, relational aggression, and disliked. When the overall borderline composite total scores were considered, the high borderline BPFS-C group was substantially higher than the low group on total borderline precursor scores. Maltreated children also were higher than nonmaltreated children on the composite score index. Furthermore, maltreated children with high BPFS-C symptoms evinced more extreme scores on the borderline features composite than nonmaltreated children with high BPFS-C symptoms.

Taken together, these results demonstrating a significant relationship between high scores on the BPFS-C measure and the borderline features composite and its associated indicators provide further validation of the Crick et al. (2005) self-report measure. Moreover, the similarities in the dysfunctional developmental processes displayed by maltreated children and adult patients with BPD provide suggestive evidence for a potential prospective pathway from childhood maltreatment to BPD. Likewise, the striking multiple relations found between maltreatment and higher scores of the BPFS-C and between maltreatment and the borderline composite indicators, conceived as a precursor to borderline personality features, also may portend an earlier emergence of BPD than depicted in the psychiatric literature. (Cicchetti, 2014; Cicchetti & Crick, 2009a, 2009b; Crick, Murray-Close, & Woods, 2005; Fonagy & Luyten, in press; Rogosch & Cicchetti, 2005).

Two candidate genes were chosen to elucidate individual variation obtained among maltreated children. The inclusion of the molecular genetic level also is consistent with one of the principles of developmental psychopathology – namely, that a multiple levels of analysis perspective provides a more comprehensive understanding of normal and abnormal developmental processes than does a single level of analysis (Cicchetti & Dawson, 2002; Cicchetti & Toth, 2009).

Across all of the analyses conducted, the genotype groups for both OXTR and FKBP5 did not demonstrate main effects in predicting BPFS-C scores. In contrast, maltreatment and maltreatment parameters exhibited strong main effects on BPFS-C scores.

Moderation of maltreatment effects by genotypes was discovered for both OXTR and FKBP5; however, these moderation effects occurred differentially for girls and for boys.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Consequently, consistent G × E × gender three-way interactions were observed. In particular, the genotype group typically associated with greater risk for high BPFS-C scores was the opposite in girls and boys.

Specifically, for the maltreatment × OXTR × gender interaction, the highest BPFS-C borderline feature symptoms were found for maltreated girls in the AG-AA group (minor allele A present). These maltreated girls also had significantly higher scores than the nonmaltreated comparison girls who possessed the GG (G is the major, more common allele) genotype.

In contrast, boys exhibited the opposite pattern. The maltreated boys who had the GG genotype had significantly higher BPFS-C scores than the nonmaltreated boys. However, maltreated and nonmaltreated boys did not differ in symptoms if they had the AG-AA genotypes.

Interestingly, the pattern of results for the maltreatment × FKBP5 haplotype group × gender three-way interaction was similar to that found for OXTR. Specifically, the highest BPFS-C symptoms were found for maltreated girls in the 1-2 copies of the FKBP5 haplotype group (indicating that minor alleles are present). These maltreated girls had significantly higher scores than the nonmaltreated girls. However, if the maltreated and nonmaltreated girls had 0 copies of the FKBP5 CATT haplotype, then no differences in BPFS-C symptoms were obtained. As was the case for OXTR, the pattern of findings for the maltreatment × FKBP haplotype group × gender is opposite for boys to that of the results for three-way interaction involving girls. The maltreated boys who possessed 0 copies of the CATT haplotype (and thus primarily major alleles) had significantly higher BPFS-C scores than nonmaltreated boys. However, maltreated and nonmaltreated boys did not differ in symptoms if they possessed 1-2 copies of the CATT haplotype (indicating minor alleles present).

Thus, for both genes maltreated girls appeared to be more at risk for high BPFS-C symptoms when they had minor alleles (i.e., AG or AA of OXTR and 1-2 copies of the FKBP5 CATT haplotype), but not when they possessed major alleles (i.e., GG for OXTR and 0 copies of the FKBP5 CATT haplotype). In contrast, maltreated boys appeared to be at increased risk for higher BPFS-symptoms when they had major alleles (i.e., GG for OXTR and 0 copies of the FKBP5 haplotype). These effects were not obtained for maltreated boys who possessed the minor alleles (i.e., AG or AA for OXTR and 1-2 copies of the FKBP5 CATT haplotype).

What is striking is that the three-way interaction for maltreated girls appears to reflect a “diathesis-stress” model (Falconer, 1965; Gottesman & Shields, 1972), where genotypes of the minor alleles are associated with increased risk for BPFS-C symptoms in the presence of stress. An inspection of the figures illustrating the three-way-interaction findings for girls reveals that the classic cross-over interaction necessary to conform to a differential susceptibility to environmental influences model (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007) are not present. For boys, in contrast, a different picture emerged. Crossover interactions occur frequently and these appear to be quite consistent with a differential susceptibility to environmental influences model. (Belsky et al., 2007; Ellis,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Boyce, Belsky, Bakersman-Kranenburg, & van IJzendoorn, 2011). Further, the "plasticity" genotype (Belsky & Pluess, 2009, 2013) for boys is the opposite of girls as it is comprised of the genotypes of the major alleles.

The consideration of child maltreatment parameters, including subtype, onset, and recency, contributed to further understanding of variation among maltreated children. An examination of maltreatment subtype groups (nonmaltreated, EMPN, and PASA) for OXTR revealed that maltreated girls in the EMPN subtype group who possessed the AG-AA genotype had higher scores on the BPFS-C. Boys with the GG genotype who were either in the EMPN or PASA maltreatment subtype groups had higher BPFS-C scores.

Girls in the EMPN maltreatment subtype group and who possessed 1-2 copies of the FKBP5 CATT haplotype had higher scores than nonmaltreated girls, and for girls in the PASA maltreatment subtype group, those who had 1-2 copies of the FKBP5 CATT haplotype had higher scores on the BPFS-C than girls with 0 copies.

Among boys with 0 copies of the CATT haplotype, both the EMPN and the PASA groups has significantly higher BPFS-C symptoms than nonmaltreated boys; among boys with the 1-2 copies of the haplotype, no subtype group differences were found. Additionally, evidence for a cross-over interactive effect was observed, with boys in the PASA group and 0 copies of the haplotype having higher scores than those with 1-2 copies, whereas among nonmaltreated boys, those with 1-2 copies of the CATT haplotype had higher scores than those with 0 copies.

Analyses of additional maltreatment parameters obtained from MCS coding of DHS records (Barnett et al., 1993) revealed that girls in the infancy onset group with the AG-AA OXTR genotype had higher BPFS-C scores than the nonmaltreated girls. Moreover, the infant onset maltreatment group of girls who possessed the AA-AG genotype had higher symptoms than girls in the GG genotype group. In addition, maltreated girls in the infant onset group with the AA-AG genotype had marginally more BPFS-C scores than girls with the same genotype who experiences maltreatment post-infancy.

In contrast, boys with the GG genotype in the infant maltreated and post-infant onset maltreated groups had higher BPFS-C scores than nonmaltreated boys. No differences were found between the two aforementioned onset groups with AG-AA genotypes and the nonmaltreated boys.

Further, examination of the maltreatment infancy and post infancy onset groups and borderline features was undertaken with FKBP5. The girls who had 1-2 CATT copies of the FKBP5 haplotype and who were maltreated post infancy reported higher BPFS-C scores in comparison to nonmaltreated girls, whereas those girls with infancy onset had marginally higher borderline feature scores than the nonmaltreated girls.

Boys in the infancy and post-infancy onset groups who possessed 0 copies of the FKBP5 CATT haplotype had higher BPFS-C scores than nonmaltreated boys. Furthermore, among boys who were maltreated post infancy, those who had 0 copies of the FKBP5 CATT haplotype had higher borderline feature symptoms than maltreated boys with 1-2 copies of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

the CATT haplotype. Cross-over interaction effects also were found, with post-infancy onset boys with 0 copies of the CATT haplotype having higher BPFS-C scores than those with 1-2 copies of the haplotype, whereas among nonmaltreated boys, the reverse was observed.

An additional inspection of maltreatment parameters was conducted, focusing on maltreatment recency groups (nonmaltreated, prior to school, school age). Maltreated girls in the school age recency group who had the AG-AA OXTR genotypes scored higher on the BPFS-C. No differences were found in the GG group. In contrast, maltreated boys in both the prior to school and the school age recency groups with the GG genotype had greater scores on the BPFS-C than nonmaltreated boys. In contrast, no differences were obtained when maltreated boys possessed the AG-AA genotypes.

Maltreated girls in the school age recency group who had 1-2 copies of the FKBP5 CATT haplotype had higher borderline feature symptoms on the BPFS-C than nonmaltreated comparison girls. However, for maltreated girls who had 0 copies of the CATT haplotype, school age recency is associated with higher BPFS-C symptoms than maltreated girls in the early onset group and nonmaltreated comparison girls.

Maltreated boys who had 0 copies of the FKBP5 CATT haplotype and whose onset of maltreatment was during school age had higher BPFS-C scores than maltreated boys with early onset and nonmaltreated comparison boys. Moreover, borderline feature symptoms were higher in maltreated boys with school age recency who had 0 copies of the CATT haplotype of FKBP5 than maltreated boys who had early onset and nonmaltreated boys. Again, indicative of cross-over interaction effects, among boys with school-age recency, those with 0 copies of the haplotype had higher scores than those with 1-2 copies, whereas nonmaltreated boys with 1-2 copies and higher scores than those with 0 copies.

In summary, consistent with the second hypothesis, OXTR genotype variants interacted with gender and child maltreatment status and associated parameters in relation to BPFS-C scores. The prediction that females would exhibit a different pattern of GxE interaction than males was confirmed. Likewise, congruent with the third hypothesis, the number of copies of the FKBP5 CATT haplotype interacted with child maltreatment status/maltreatment parameters and gender in relation to BPFS-C scores. Additionally, the prediction that males and females would exhibit different patterns of GxE was borne out. The fourth hypothesis that there would be separate interactions of OXTR, child maltreatment status, and gender and FKBP5 CATT haplotype, maltreatment status, and gender that would contribute independently to BPFS-C scores also was confirmed.

Importantly, the results highlight the need to consider gender in G×E studies. Three-way interactions involving candidate molecular genetic and environmental pathogens and gender are rare in gene-environment research. The large sample size included in the present investigation enables the conduct of such three-way interactions as there was sufficient statistical power to consider gender interactive effects.

As was shown with respect to the OXTR genotype and the FKBP5 CATT haplotype copies, girls had different risk and plasticity genotypes than did boys. In fact, the finding regarding genotype × maltreatment upon BPFS-C scores was completely opposite for girls and boys.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

This suggests that the use of vulnerability/risk and plasticity genes that has become common in the literature (Belsky & Pluess, 2009), must realize that a number of factors, including development, race, and gender, in addition to environmental context must be examined before concluding that particular genotypes are considered to be the “risk” or “plasticity” gene.

The inclusion of ancestry-informative markers (AIMs), also known as ancestral proportion scores, in the present investigation enables us to estimate the geographical origins of an individual’s ancestors and to discern the proportion of ancestry that is derived from each geographical region. Because our sample is genetically heterogeneous, unlike many sample utilized in the GxE literature, we were able to obtain a more accurate portrayal of race and racial admixture than self-report of race. The utilization of these Ancestry Informative Markers represents an increase in methodological sophistication and addresses concerns raised by Duncan and Keller (2011) regarding the absence of these AIMs markers in GxE research with genetically heterogeneous samples.

In addition, we controlled for all potential confounders in each of maltreatment status models. Keller (2014) commented on the fact that few GxE investigators had entered all relevant interaction terms in the same model that tests the GxE term. We computed all interactions as Keller (2014) suggested, thus eliminating alternative explanations for our GxE findings. As this study is the first demonstration of a three-way interaction involving genes, maltreatment, and gender, it will be important to replicate these findings in future research. Nonetheless, the current findings have important implications for understanding the differential precursors and pathways to borderline pathology. In order to design efficacious, developmentally appropriate interventions, it will be important to consider the interactions of gene and environment in the context of gender.

Acknowledgments

We greatly appreciate the funding support of this research by the Jacobs Foundation, the National Institute on Drug Abuse (R01- DA17741) and the National Institute of Mental Health (R01-MH83979).

References

Achenbach, TM. Manual for the teacher’s report form and 1991 profile. University of Vermont; Burlington, VT: 1991.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed.. American Psychiatric Association; Washington, DC: 2000.

Asher SR, Dodge KA. Identifying children who are rejected by their peers. Developmental Psychology. 1986; 22:444–449.

Barnett, D.; Manly, JT.; Cicchetti, D. Defining child maltreatment: The interface between policy and research. In: Cicchetti, D.; Toth, SL., editors. Child abuse, child development, and social policy. Ablex; Norwood, NJ: 1993. p. 7-73.

Barrett JC, Fry B, Maller J, Daly MJ. Haploview analysis and visualization of LD and haplotype maps. Bioinformatics. 2005; 21:263–265. [PubMed: 15297300]

Belsky J, Bakermans-Kranenburg MJ, Van IJzendoorn MH. For better and for worse: Differential susceptibility to environmental influences. Current Directions in Psychological Science. 2007; 16:300–304.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Belsky J, de Haan M. Parenting and children's brain development: The end of the beginning. Journal of Child Psychology and Psychiatry. 2011; 52:409–429. [PubMed: 20626527]

Belsky, J.; Jaffee, SR. The multiple determinants of parenting. In: Cicchetti, D.; Cohen, DJ., editors. Developmental psychopathology: Vol. 3. Risk, disorder, and adaptation. 2nd ed.. Wiley; Hoboken, NJ: 2006. p. 38-85.

Belsky J, Pluess M. Beyond diathesis stress: Differential susceptibility to environmental influences. Psychological Bulletin. 2009; 135:885–908. [PubMed: 19883141]

Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. Development and Psychopathology. 2013; 25(4 pt 2):1243–1261. [PubMed: 24342838]

Block, J.; Block, JH. The California child Q-set. University of California Press; Berkeley, CA: 1969.

Bolger KE, Patterson CJ, Kupersmidt JB. Peer relationships and self-esteem among children who have been maltreated. Child Development. 1998; 69:1171–1197. [PubMed: 9768492]

Bradley B, Westen D, Mercer KB, Binder EB, Jovanovic T, Crain D, Heim C. Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: moderation by oxytocin receptor gene. Development and Psychopathology. 2011; 23(2):439–452. [PubMed: 23786688]

Bukowski WM, Sippola LK, Newcomb AF. Variations in patters of attraction of same- and other-sex peers during early adolescence. Developmental Psychology. 2000; 36:147–154. [PubMed: 10749072]

Champagne F, Diorio J, Sharma S, Meaney MJ. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. Proceedings of the National Academy of Sciences of the United States of America. 2001; 90(22): 12736–41. [PubMed: 11606726]

Chomsky, N. Language and Mind. Harcourt Brace Jovanovich; New York, NY: 1968.

Cicchetti D. Child maltreatment: Implications for developmental theory. Human Development. 1996; 39:18–39.

Cicchetti, D. How a child builds a brain: Insights from normality and psychopathology. In: Hartup, W.; Weinberg, R., editors. Minnesota symposia on child psychology: Child psychology in retrospect and prospect. Vol. 32. Lawrence Erlbaum Associates; Mahwah, NJ: 2002a. p. 23-71.

Cicchetti D. The impact of social experience on neurobiological systems: Illustration from a constructivist view of child maltreatment. Cognitive Development. 2002b; 17:1407–1428.

Cicchetti D. Illustrative developmental psychopathology perspectives on precursors and pathways to personality disorder. Journal of Personality Disorders. 2014; 28:172–179. [PubMed: 24344897]

Cicchetti D, Crick NR. Precursors of and diverse pathways to personality disorder in children and adolescents, Part 1. [Special Issue]. Development and Psychopathology. 2009a; 21(3):683–1030. [PubMed: 19583879]

Cicchetti D, Crick NR. Precursors of and diverse pathways to personality disorder in children and adolescents, Part 2. [Special Issue]. Development and Psychopathology. 2009b; 21(4):1031–1381. [PubMed: 19825256]

Cicchetti D, Dawson G. Multiple levels of analysis. Development and Psychopathology. 2002; 14(3): 417–420. [PubMed: 12349866]

Cicchetti, D.; Lynch, M. Failures in the expectable environment and their impact on individual development: The case of child maltreatment. In: Cicchetti, D.; Cohen, DJ., editors. Developmental psychopathology: Vol. 2. Risk, disorder and adaptation. Vol. 2. Wiley; New York: 1995. p. 32-71.

Cicchetti, D.; Manly, JT. A personal perspective on conducting research with maltreating families: Problems and solutions. In: Brody, G.; Sigel, I., editors. Methods of family research: Families at risk. Vol. 2. Lawrence Erlbaum Associates; Hillsdale, NJ: 1990. p. 87-133.

Cicchetti D, Toth SL. The past achievements and future promises of developmental psychopathology: The coming of age of a discipline. Journal of Child Psychology and Psychiatry. 2009; 50:16–25. [PubMed: 19175810]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Cicchetti, D.; Toth, SL. A multilevel perspective on child maltreatment. In: Lamb, M.; Garcia Coll, C., editors. Handbook of psychology and developmental science, 7th ed., Vol. 3: Socioemotional process. Wiley; New York: in press

Cicchetti, D.; Toth, SL.; Manly, JT. Maternal classification maltreatment interview. Mt. Hope Family Center; Rochester, NY: 2003. Unpublished measure

Cicchetti, D.; Valentino, K. An ecological-transactional perspective on child maltreatment: Failure of the average expectable environment and its influence on child development. In: Cicchetti, D.; Cohen, DJ., editors. Developmental Psychopathology: Vol 3. Risk, disorder, and adaptation. 2nd ed. John Wiley & Sons, Inc; Hoboken, NJ: 2006. p. 129-201.

Coie JD, Dodge KA. Continuities and changes in children's social status: A five-year longitudinal study. Merrill-Palmer Quarterly. 1983; 29:261–282.

Cowell RA, Cicchetti D, Rogosch FA, Toth SL. Childhood maltreatment and its effect on neurocognitive functioning: Chronicity and timing matter. Development and Psychopathology. 27 in press.

Crick NR, Murray-Close D, Woods K. Borderline personality features in childhood: A short-term longitudinal study. Development and Psychopathology. 2005; 17(4):1050–1070.

Dackis MN, Rogosch FA, Oshri A, Cicchetti D. The role of limbic system irritability in linking history of childhood maltreatment and psychiatric outcomes in low-income, high-risk women: Moderation by FKBP5. Development and Psychopathology. 2012; 24:1237–1252. [PubMed: 23062294]

DeBellis MD. Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. Development and Psychopathology. 2001; 13:539–564. [PubMed: 11523847]

DeBellis MD. The psychobiology of neglect. Child Maltreatment. 2005; 10:150–172. [PubMed: 15798010]

DeYoung C, Cicchetti D, Rogosch FA, Gray J, Eastman M, Grigorenko E. Sources of cognitive exploration: Genetic variation in the prefrontal dopamine system predicts openness/intellect. Journal of Research in Personality. 2011; 45:364–371. [PubMed: 21804655]

Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: Findings from the Adverse Childhood Experiences Study. Journal of the American Medical Association. 2001; 286:3089, 3096. [PubMed: 11754674]

Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by environment interaction research in psychiatry. American Journal of Psychiatry. 2011; 168:1041–1049. [PubMed: 21890791]

Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. Development and Psychopathology. 2011; 23:7–28. [PubMed: 21262036]

English DJ, Upadhyaya MP, Litrownik AJ, Marshall JM, Runyan DK, Graham JC, Dubowitz H. Maltreatment's wake: The relationship of maltreatment dimensions to child outcomes. Child Abuse & Neglect. 2005; 29(5):594–619.

Escoffier, L.; Lischer, H. *Arlequin* version 3.5. Swiss Institute of Bioinformatics; Bern, Switzerland: 2011.

Evans E, Hawton K, Rodham K. Suicidal phenomena and abuse in adolescents: A review of epidemiological studies. Child Abuse Neglect. 2005; 29:45–58. [PubMed: 15664425]

Falconer DS. The inheritance of liability to diseases, estimated from the incidence among relatives. Annals of Human Genetics. 1965; 29:59–76.

Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: Dominant and null alleles. Molecular Ecology Notes. 2007; 7:574–578. [PubMed: 18784791]

Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: Linked loci and correlated allele frequencies. Genetics. 2003; 164:1567–1587. [PubMed: 12930761]

Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. Journal of Cognitive Neuroscience. 2002; 14(3):340–347. [PubMed: 11970796]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Finnegan RA, Hodges EVE, Perry DG. Preoccupied and avoidant coping during middle childhood. Child Development. 1996; 67:1318–1328.

Flores E, Cicchetti D, Rogosch FA. Predictors of resilience in maltreated and nonmaltreated Latino children. Developmental Psychology. 2005; 41(2):338–351. [PubMed: 15769190]

Fonagy, P.; Luyten, P. A multilevel perspective on the development of borderline personality disorder. In: Cicchetti, D., editor. Developmental Psychopathology. Wiley; New York, NY: in press

Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiological Reviews. 2001; 81(2):629–83. [PubMed: 11274341]

Gottesman, I.; Shields, J. Schizophrenia and genetics: A twin study vantage point. Academic Press; New York, NY: 1972.

Hecht KF, Cicchetti D, Rogosch FA, Crick NR. Borderline Personality Features in Childhood: The Role of Subtype, Developmental Timing and Chronicity of Child Maltreatment. Development and Psychopathology. 2014; 26(3)

Hodges E, Finnegan RA, Perry DG. Skewed autonomy-relatedness in preadolescents' conceptions of their relationships with mother, father and best friend. Developmental Psychology. 1999; 35:737–748. [PubMed: 10380864]

Hostinar CE, Cicchetti D, Rogosch FA. Oxytocin receptor gene (OXTR) polymorphism, perceived social support, and psychological symptoms in maltreated adolescents. Development and Psychopathology. 2014; 26:465–477. [PubMed: 24621832]

Hubisz MJ, Falush D, Stephens M, Pritchard JK. Inferring weak population structure with assistance of sample group information. Molecular Ecology Resources. 2009; 5:1322–1332. [PubMed: 21564903]

Inoue T, Kimura T, Azuma C, Inazawa J, Takemura M, Kikuchi T, Saji F. Structural organization of the human oxytocin receptor gene. Journal of Biological Chemistry. 1994; 269:32451–32456. [PubMed: 7798245]

Insel TR, Shapiro LE. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proceedings of the National Academy of Sciences of the USA. 1992; 89(13): 5981–5985. [PubMed: 1321430]

John OP, Caspi A, Robins RW, Moffitt TE, Stouthamer-Loeber M. The "Little Five": Exploring the nomological network of the Five-Factor Model of personality in adolescent boys. Child Development. 1994; 65:160–178. [PubMed: 8131645]

Johnson JG, Cohen P, Brown J, Smailes EM, Bernstein DP. Childhood maltreatment increases risk for personality disorders during early adulthood. Archives of General Psychiatry. 1999; 56:600–606. [PubMed: 10401504]

Johnson JG, Cohen P, Gould MS, Kasen S, Brown J, Brook JS. Childhood adversities, interpersonal difficulties, and risk for suicide attempts during late adolescence and early adulthood. Archives of General Psychiatry. 2002; 59:741–749. [PubMed: 12150651]

Keller MC. Gene × environment interaction studies have not properly controlled for potential confounders: The problem and the (simple) solution. Biological Psychiatry. 2014; 75:18–24. [PubMed: 24135711]

Koenen KC, Amstadter AB, Nugent NR. Gene-environment interaction in posttraumatic stress disorder: an update. Journal of Traumatic Stress. 2009; 22(5):416–426. [PubMed: 19743189]

Koenen KC, Saxe G, Purcell S, Smoller JW, Bartholomew D, Miller A, et al. Polymorphisms in FKBP5 are associated with peritraumatic dissociation in medically injured children. Molecular Psychiatry. 2005; 10:1058–1059. [PubMed: 16088328]

Kovacs, M. The children's depression inventory: A self-rated depression scale for school-aged youngsters. University of Pittsburgh; Pittsburgh: 1982. Unpublished manuscript

Kovacs, M. Children's Depression Inventory Manual. Multi-health Systems, Inc; North Tonawanda, NY: 1992.

Lai CQ, Tucker KL, Choudhry S, Parnell LD, Mattei J, Garcia-Bailo B, Ordovas JM. Population admixture associated with disease prevalence in the Boston Puerto Rican health study. Human Genetics. 2009; 125:199–205. [PubMed: 19107526]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Lenzenweger MF, Cicchetti D. Toward a developmental psychopathology approach to borderline personality disorder. Development and Psychopathology. 2005; 17(4):893–898. [PubMed: 16613423]

Manly JT. Advances in research definitions of child maltreatment. Child Abuse & Neglect. 2005; 29(5):425–439. [PubMed: 15970318]

Manly JT, Cicchetti D, Barnett D. The impact of subtype, frequency, chronicity, and severity of child maltreatment on social competence and behavior problems. Development and Psychopathology. 1994; 6:121–143.

Manly JT, Kim JE, Rogosch FA, Cicchetti D. Dimensions of child maltreatment and children's adjustment: Contributions of developmental timing and subtype. Development and Psychopathology. 2001; 13:759–782. [PubMed: 11771907]

McCrory E, De Brito SA, Viding E. Research review: The neurobiology and genetics of maltreatment and adversity. The Journal of Child Psychology and Psychiatry. 2010; 51:1079–1095.

Morey, L. Personality Assessment Inventory. Psychological Assessment Resources, Inc.; Odessa, FL: 1991.

Pianta RC, Nimetz SL. Relationships between children and teachers: Associations with classroom and home behavior. Journal of Applied Developmental Psychology. 1991; 12(3):379–393.

Pianta RC, Steinberg M. Teacher-child relationships and the process of adjusting to school. New Directions for Child Development. 1992; 57:61–80.

Posner MI, Rothbart MK, Vizueta N, Thomas KM, Levy KN, Fossella J, Kernberg O. An approach to the psychobiology of personality disorders. Development and Psychopathology. 2003; 15:1093–1106. [PubMed: 14984139]

Rogosch FA, Cicchetti D. Child maltreatment and emergent personality organization: Perspectives from the Five-Factor model. Journal of Abnormal Child Psychology. 2004; 32:123–145. [PubMed: 15164856]

Rogosch FA, Cicchetti D. Child maltreatment, attention networks, and potential precursors to borderline personality disorder. Development and Psychopathology. 2005; 17:1071–1089. [PubMed: 16613431]

Rogosch FA, Cicchetti D, Aber JL. The role of child maltreatment in early deviations in cognitive and affective processing abilities and later peer relationship problems. Development and Psychopathology. 1995; 7:591–609.

Rudolph KD, Hammen C, Burge D. Cognitive representations of self, family, and peers in school-aged children: Links with social competence and sociometric status. Child Development. 1995; 66:1385–1402. [PubMed: 7555222]

Rueda MR, Fan J, McCandliss BD, Halparin JD, Gruber DB, Lercari LP, Posner MI. Development of attentional networks in childhood. Neuropsychologia. 2004; 42(8):1029–1040. [PubMed: 15093142]

Sedlak, AJ.; Mettenburg, J.; Basena, M.; Petta, I.; McPherson, K.; Greene, A., et al. Fourth National Incidence Study of Child Abuse and Neglect (NIS-4): Report to Congress, Executive Summary. U.S. Department of Health and Human Services, Administration for Children and Families; Washington, DC: 2010.

Shields A, Cicchetti D. Emotion regulation among school-age children: The development and validation of a new criterion Q-sort scale. Developmental Psychology. 1997; 33(6):906–916. [PubMed: 9383613]

Shields A, Cicchetti D. Reactive aggression among maltreated children: The contributions of attention and emotion dysregulation. Journal of Clinical Child Psychology. 1998; 27(4):381–395. [PubMed: 9866075]

Tackett JL, Balsis S, Oltmanns TF, Krueger RF. A unifying perspective on personality pathology across the life span: Developmental considerations for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. Development and Psychopathology. 2009; 21(3):687–713. [PubMed: 19583880]

Toth SL, Cicchetti D, Macfie J, Emde RN. Representations of self and other in the narratives of neglected, physically abused, and sexually abused preschoolers. Development and Psychopathology. 1997; 9:781–796. [PubMed: 9449005]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Toth SL, Gravener-Davis JA, Guild DJ, Cicchetti D. Relational interventions for child maltreatment: Past, present, & future perspectives. Development and Psychopathology. 2013; 25(4pt2):1601–1617. [PubMed: 24342858]

Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and co-morbidity in abused and neglected grown up children (grown up). Archives of General Psychiatry. 2007; 64:49–56. [PubMed: 17199054]

Yaeger R, Alvial-Bront A, Abdul K, Nolan PC, Grann VR, Birchette MG, Joe AK. Comparing genetic ancestry and self-described race in African Americans born in the United States and in Africa. Cancer Epidemiology, Biomarkers & Prevention. 2008; 17:1329–1338.

Zanarini MC, Horwood J, Wolke D, Waylen A, Fitzmaurice G, Grant BF. Prevalence of DSM-IV borderline personality disorder in two community samples: 6,330 English 11-year-olds and 34,653 American adults. Journal of Personality Disorders. 2011; 25:607–619. [PubMed: 22023298]

Zanarini MC, Williams AA, Lewis RE, Reich RB, Vera SC, Marino MF, et al. Reported pathological childhood experiences associated with the development of Borderline Personality Disorder. American Journal of Psychiatry. 1997; 154:1101–1106. [PubMed: 9247396]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

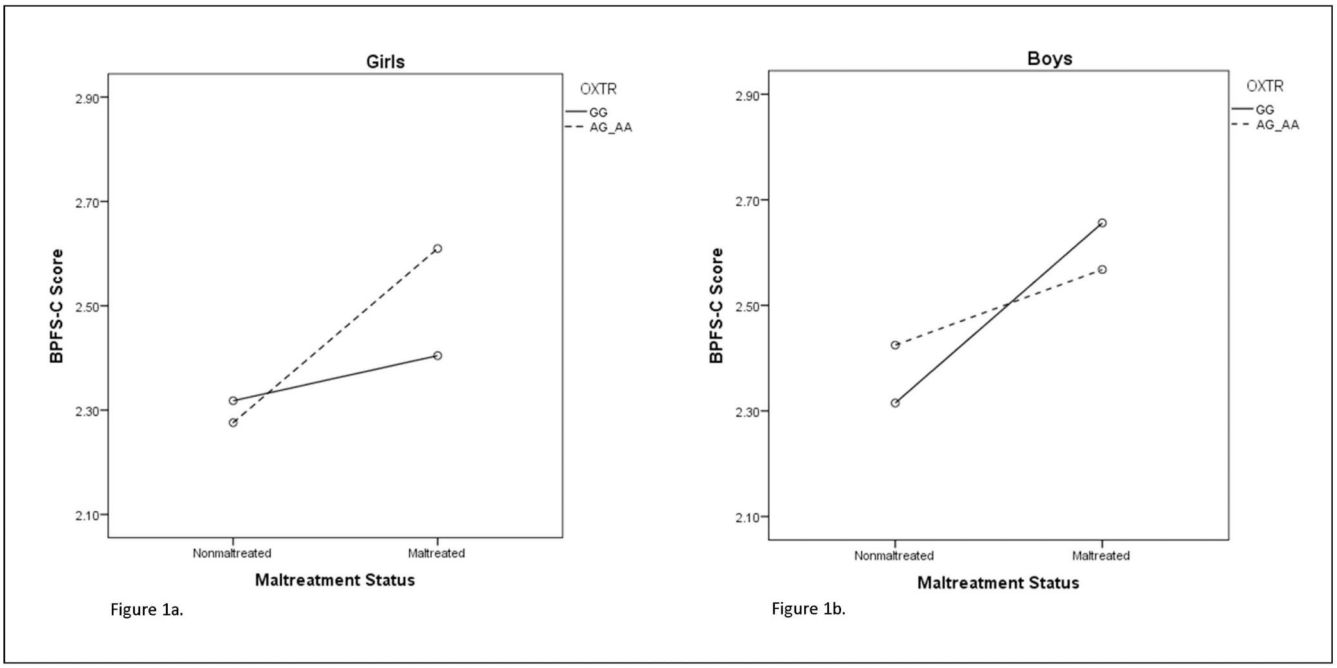

Figure 1.

Interaction of maltreatment status, OXTR genotype, and gender in predicting BPFS-C borderline symptoms.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

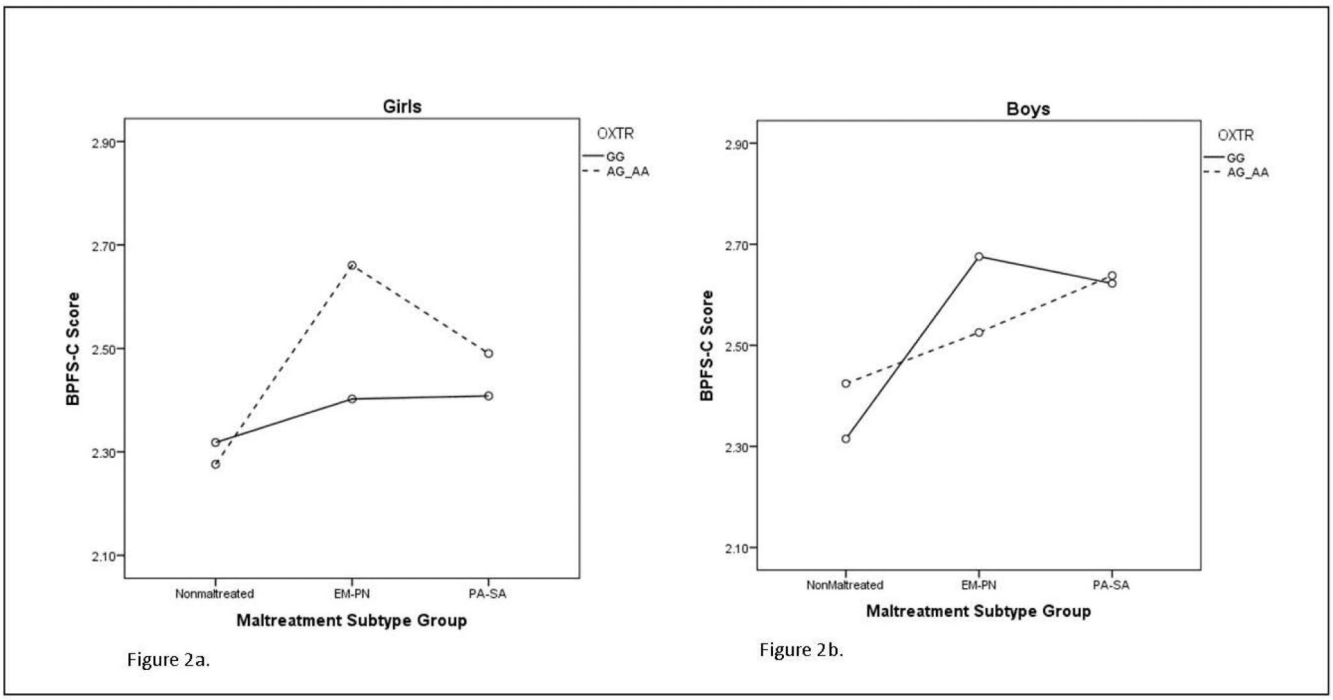

Figure 2.

Interaction of maltreatment subtype group, OXTR genotype, and gender in predicting BPFS-C borderline symptoms.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

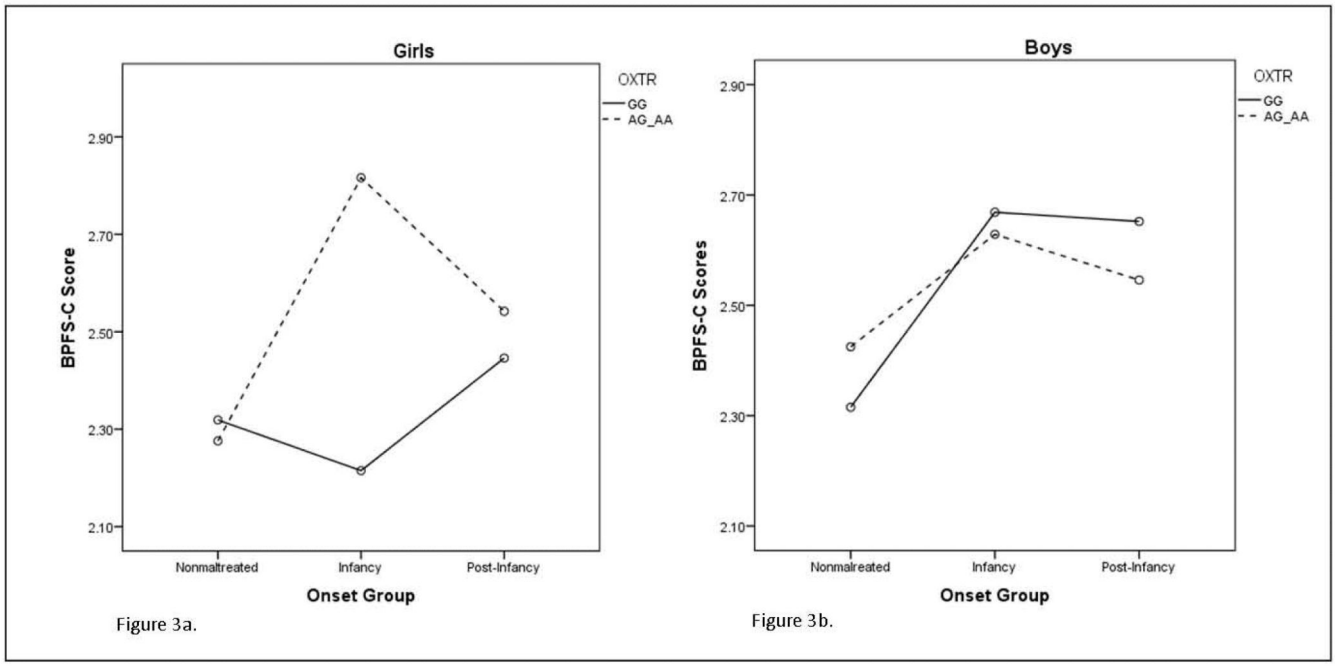

Figure 3.

Interaction of maltreatment onset group, OXTR genotype, and gender in predicting BPFS-C borderline symptoms

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

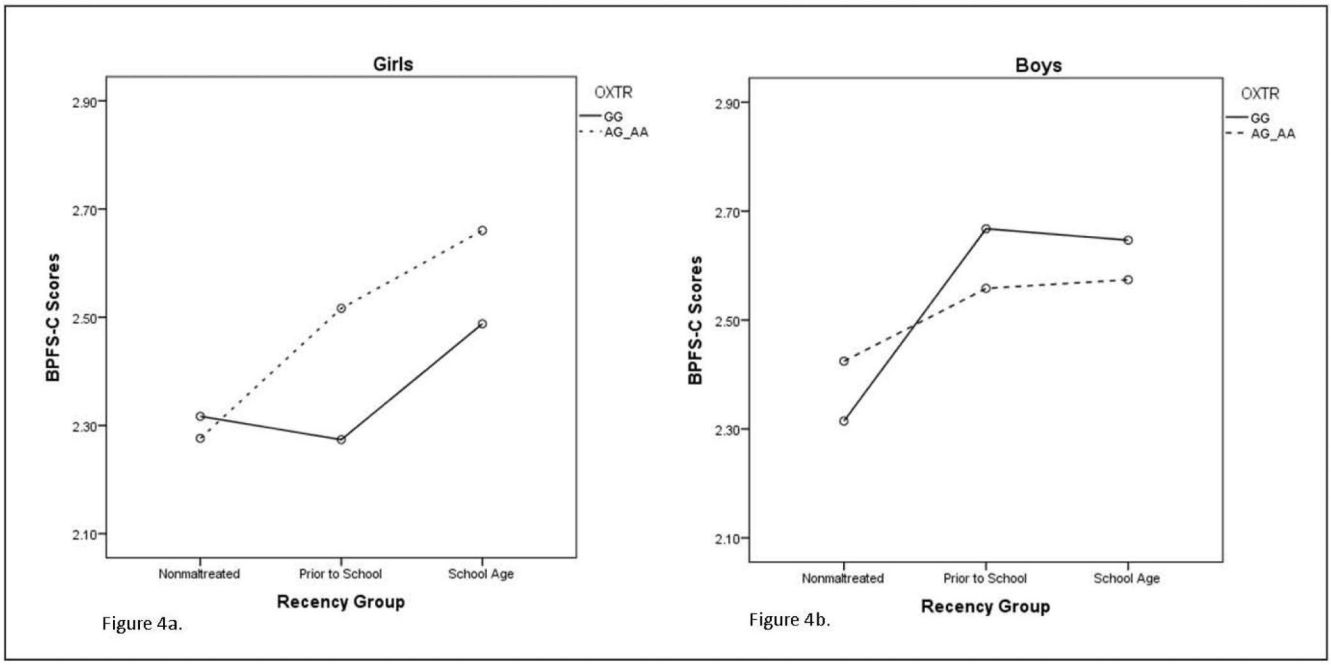

Figure 4.

Interaction of maltreatment recency group, OXTR genotype, and gender in predicting BPFS-C borderline symptoms.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

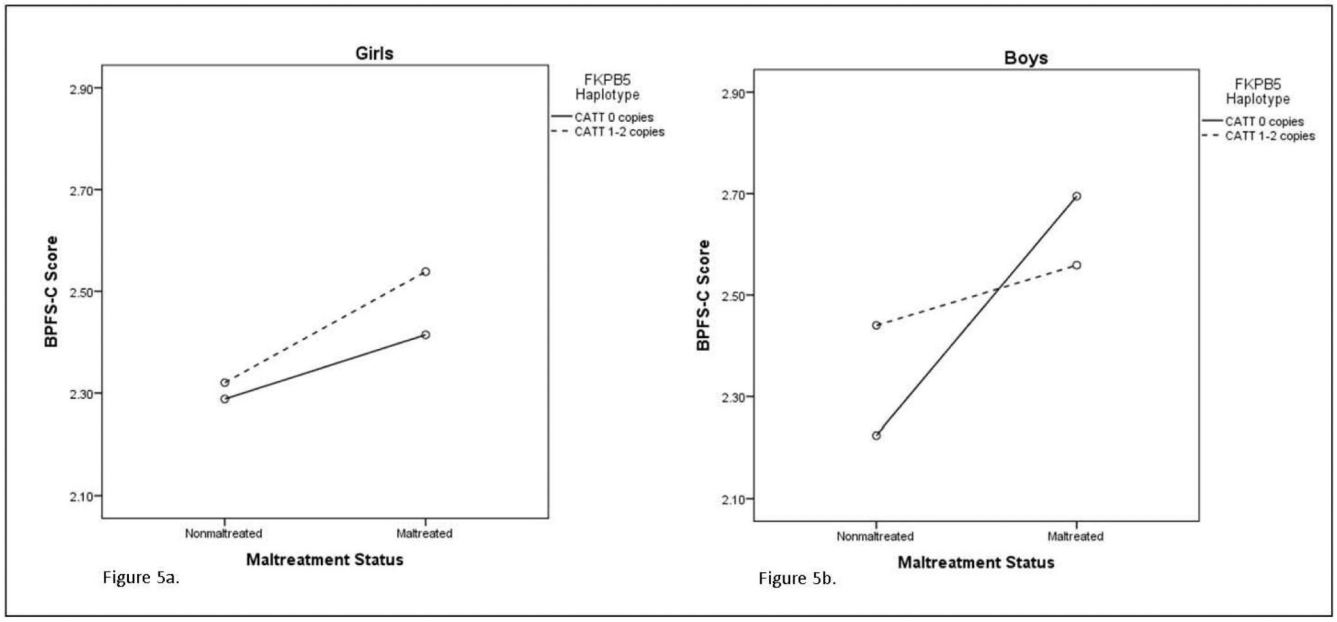

Figure 5.

Interaction of maltreatment status, FKPB5 haplotype, and gender in predicting BPFS-C borderline symptoms.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

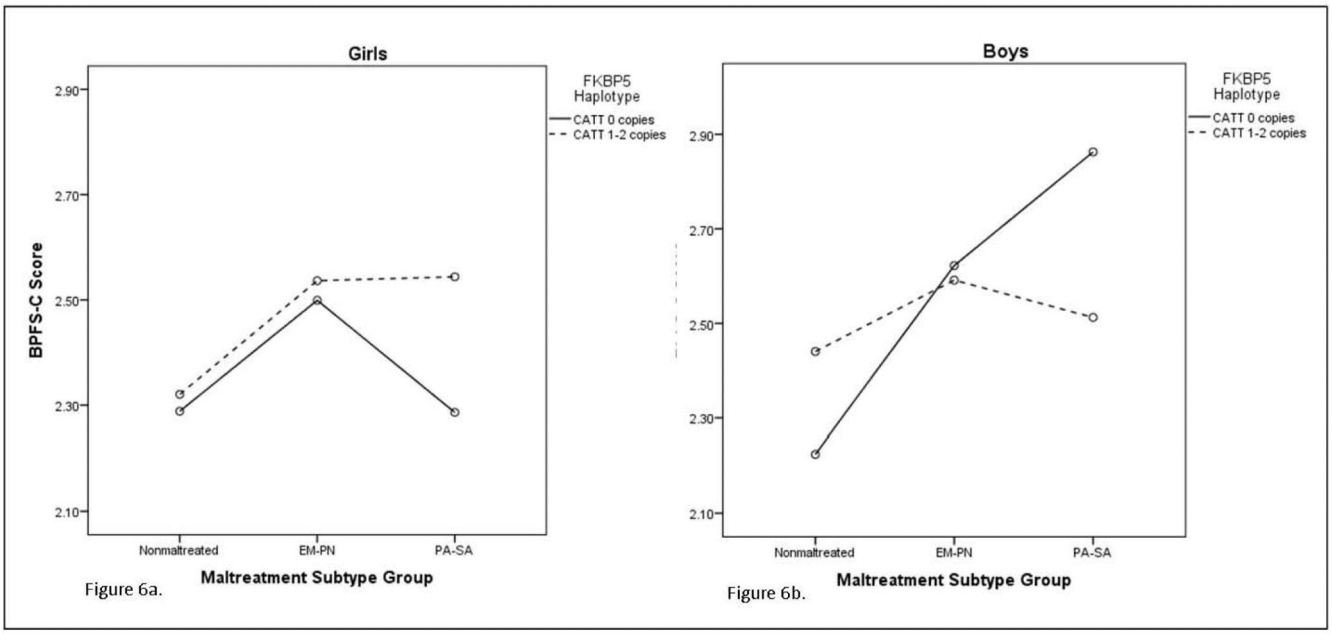

Figure 6.

Interaction of maltreatment subtype group, FKPB5 haplotype, and gender in predicting BPFS-C borderline symptoms.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

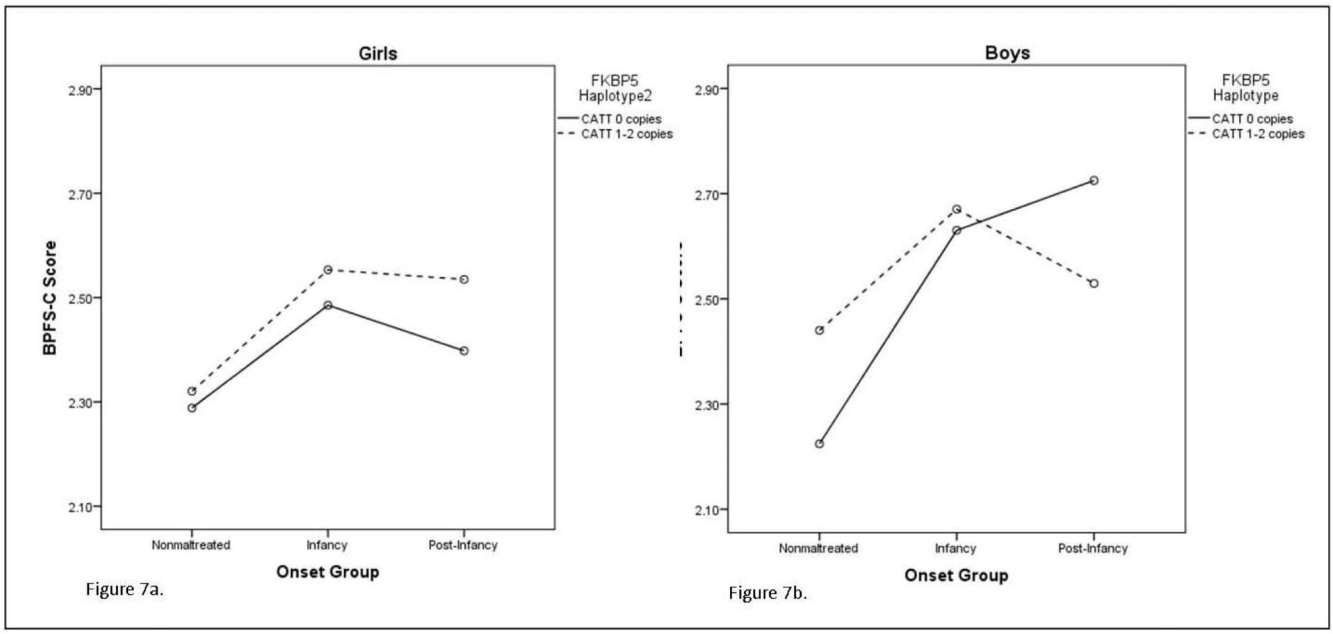

Figure 7.

Interaction of maltreatment onset group, FKPB5 haplotype, and gender in predicting BPFS-C borderline symptoms.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

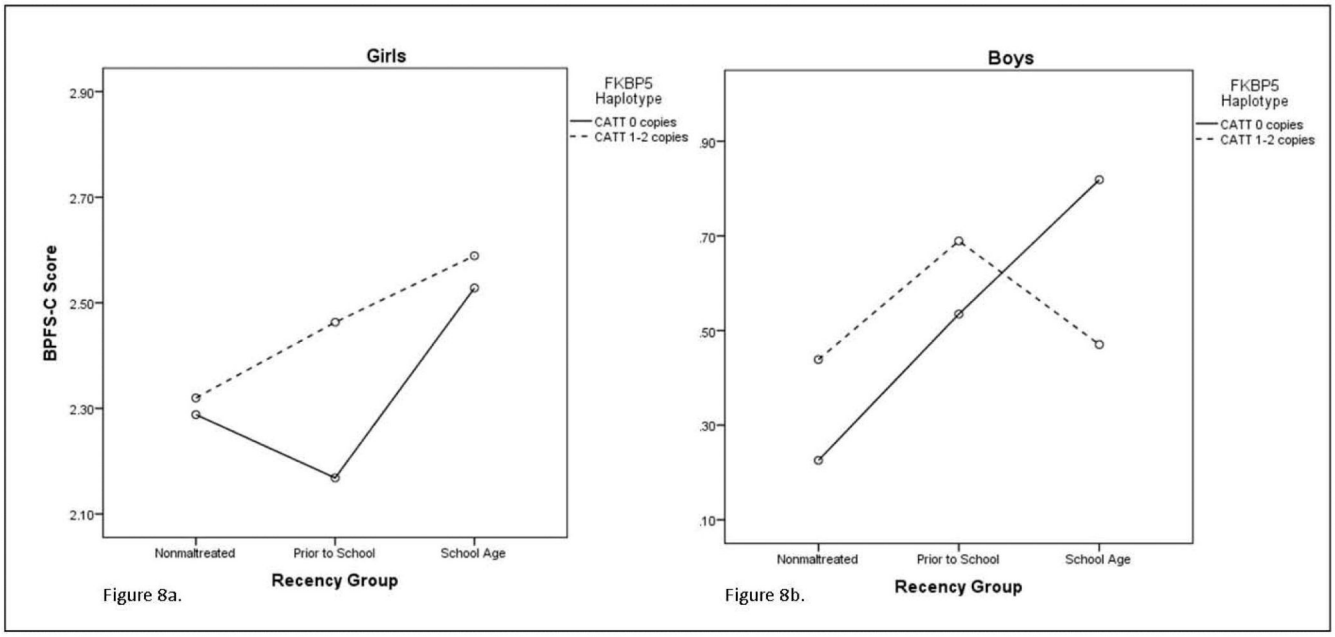

Figure 8.

Interaction of maltreatment recency group, FKPB5 haplotype, and gender in predicting BPFS-C borderline symptoms.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Description of FKPB5 SNPs.

SNP ID	*Distribution*	*MAF*	*Position / Gene*
rs3800373		0.42	35650454 / 3′ UTR
AA	355 (33.9%)		
AC	499 (47.7%)		
CC	192 (18.4%)		
rs9296158		0.46	35675060 / Intron 5
GG	318 (30.3%)		
AG	489 (46.6%)		
AA	240 (22.9%)		
rs1360780		0.41	35715549 / Intron 2
CC	367 (35.1%)		
CT	498 (47.7%)		
TT	180 (17.2%)		
rs9470080		0.45	35754413 / Intron 1
CC	330 (31.6%)		
CT	492 (47.1%)		
TT	223 (21.3%)		
CATT haplotype			
No copies	397 (38.0%)		
1-2 copies	647 (62.0%)		

Note. MAF = minor allele frequency.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Main effects and interaction of high BPFS-C borderline symptoms group and maltreatment status on adult-, peer-, and self-rated borderline precursor indicators.

	High Borderline Symptom Group	Maltreatment Status	Interaction
	F(1,1026)	*F*(1.1026)	*F*(1,1026)
ERC: Lability/Negativity	4.07*	27.26***	4.48*
CCQ: Conscientiousness (reversed)	12.16***	20.47***	.83
STRS: Conflicted Relationship	5.55*	21.11***	2.73+
Peer: Upsets others	9.02**	34.28***	7.64**
Peer: Relational Aggression	9.93**	36.77***	11.48***
Peer: Disliked	8.57**	20.28***	5.62*
POPS: Negative Self	48.52***	3.68+	.56
POPS: Negative Peer	68.27***	.83	.03
RSQ: Preoccupied	21.12***	.15	.10
TRF: Self harm	3.94*	6.33*	3.57+
CDI: Suicidal Ideation	41.10***	.26	3.39+
Borderline Composite	62.07***	39.28***	5.24*

+ $p < .10$,

* $p < .05$,

** $p < .01$,

*** $p < .001$