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Examining Gene-Environment Interactions in Comorbid Depressive and Disruptive Behavior Disorders using a Bayesian Approach

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Abstract

Objective—The objective of this study was to apply a Bayesian statistical analytic approach that minimizes multiple testing problems to explore the combined effects of chronic low familial support and variants in 12 candidate genes on risk for a common and debilitating childhood mental health condition.

Method—Bayesian mixture modeling was used to examine gene by environment interactions among genetic variants and environmental factors (family support) associated in previous studies with the occurrence of comorbid depression and disruptive behavior disorders youth, using a sample of 255 children.

Results—One main effects, variants in the oxytocin receptor (*OXTR*, *rs53576*) was associated with increased risk for comorbid disorders. Two significant gene x environment and one significant gene x gene interaction emerged. Variants in the nicotinic acetylcholine receptor $\alpha 5$ subunit (*CHRNA5*, *rs16969968*) and in the glucocorticoid receptor chaperone protein FK506 binding protein 5 (*FKBP5*, *rs4713902*) interacted with chronic low family support in association with child mental health status. One gene x gene interaction, 5-HTTLPR variant of the serotonin transporter (*SERT/SLC6A4*) in combination with μ opioid receptor (*OPRM1*, *rs1799971*) was associated with comorbid depression and conduct problems.

Conclusions—Results indicate that Bayesian modeling is a feasible strategy for conducting behavioral genetics research. This approach, combined with an optimized genetic selection strategy (Vrieze, Iacono, & McGue, 2012), revealed genetic variants involved in stress regulation

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(*FKBP5*, *SERTxOPMR*), social bonding (*OXTR*), and nicotine responsivity (*CHRNA5*) in predicting comorbid status.

Keywords

Bayesian mixture modeling; Markov chain Monte Carlo; depression; disruptive behavior; comorbidity

1. Introduction

There is overwhelming evidence that depression and disruptive behavior disorders co-occur more frequently than by chance alone (Angold, Costello, & Erkanli, 1999). Despite the differences in presentation, a high proportion (22.7-83.3%) of children and adolescents with a diagnosis of depression have comorbid disruptive behavior disorders (conduct disorder, and/or oppositional-defiant disorder), and a high proportion (8.5-45.4%) of those with disruptive behavior disorders meet criteria for co-morbid depression (Angold et al., 1999) (Wolff & Ollendick, 2006). Comorbid depression and disruptive behavior disorders are associated with increased impairment, school failure and suicidal behaviors (Wolff & Ollendick, 2006). The high prevalence and associated impairment have garnered research attention for this heterotypic comorbid condition. Researchers have suggested that the common occurrence of comorbidity across externalizing and internalizing dimensions is evidence for a broad construct of emotional distress that underlies different forms of psychopathology. Examination of the structure of comorbid depression and disruptive behavior disorders indicates that classes of conditions are differentiated by number of symptoms as opposed to symptom type (Mezulis, Stoep, Stone, & McCauley, 2011). Krueger (2002) suggests that the co-occurrence of depression, anxiety, disordered conduct and substance dependence stems from the common vulnerability factors associated with both conditions (Krueger, 2002). In this context, co-morbid depression and disruptive behavior disorders could represent a particularly severe phenotype of emotional distress in youth.

1.1 Diathesis-Stress Framework

The diathesis-stress framework is the predominate model driving gene by environment interaction (GxE) research. Core to diathesis stress model is the view that some individuals are vulnerable due to biological underpinnings and disproportionately likely to be affected adversely by environmental stress. Despite focused attention in the identification of GxE in association studies, identification of critical variants has been difficult to replicate. In a seminal GxE study by Caspi and colleagues *5-HTTLPR* was found to interact with a measure of stressful life events to predict adult depression (Caspi et al., 2003). A decade after the 2003 study, experts disagree about the nature of these interactions, and meta-analyses efforts to summarize findings support very different conclusions (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Caspi et al., 2003; Karg K, 2011; Risch et al., 2009). The state of the literature has prompted researchers to evaluate the limitations of existing GxE research findings and methods and to recommend new strategies for selecting genetic variants (Vrieze et al., 2012). A recommended strategy that may optimize analysis for GxE interactions capitalizes on both genome wide association studies (GWAS) and candidate

gene approaches by filtering the set of single nucleotide polymorphisms (SNPs) that have indicated promise in past empirical work (Vrieze et al., 2012). Using genetic variants that have been identified in the literature, rather than those based on hypothesized biological mechanisms, may open additional avenues of exploration unconstrained by knowledge of the putative mechanism of action.

1.2 Etiology of Comorbid Depression and Disruptive Behavior Disorders

The underlying premises that drove phenotype select for this study are 1) adolescent depression and conduct disorders tap a common biological substrate, and 2) children who meet diagnostic criteria for both depression and conduct disorders are particularly vulnerable to damage due to this underlying substrate and constitute an uncontroversially affected group. Research probing possible mechanisms responsible for the phenotype of comorbid depression and disruptive behavior disorders has highlighted a common vulnerability model (Fergusson, Lynskey, & Horwood, 1996). Previous examination of etiological factors contributing to comorbid depressive and disruptive behavior disorders included in this study are identified in the following three sections: environmental factors, genetic factors, and GxE factors.

The role of environmental influences in developmental trajectories of depressive and disruptive behavior disorders has been widely supported in research examining human and animal development, with studies indicating as much as two thirds of the variance accounted for by shared environmental risk factors (Fergusson et al., 1996). In particular, weak parent-child attachments and low family support lead to deficits in coping and self-regulatory behaviors (Repetti, Taylor, & Seeman, 2002). Further, there is evidence that chronic exposure to unsupportive family environments increases risk for adolescent and later psychiatric illness in part through biobehavioral pathways, including detrimental impacts to developing neuroendocrine systems (Repetti et al., 2002). The association between chronic lack of family support and child psychopathology has been highlighted both concurrently and prospectively for comorbid depressive and disruptive behavior disorders (Repetti et al., 2002). Previous studies indicate that families characterized by lack of support are more likely to have children with internalizing and externalizing problems, whereas higher quality parent-child relationships also predict lower symptoms in both domains (Galambos, Barker, & Alameida, 2003). Although family environmental influences have a robust literature connecting to depression and disruptive behavior disorders, most study designs focused solely on environmental factors and thus were not sensitive to genetic or GxE as mechanisms of risk.

1.3 Genetic Vulnerability for Depressive and Conduct Disorder Phenotypes

Variants important for the downregulation of emotional arousal and stress responses have driven a large portion of the gxe studies, including the 43bp insertion/deletion polymorphism (5-*HTTLPR*) in the promoter region of the serotonin transporter (SERT) gene, which influences the available amount of SERT protein with resultant effects on brain development (Jedema et al., 2010). This variant has been widely associated with emotional reactivity, stress response and depression occurring as a result of childhood abuse or neglect (Karg K, 2011). The coding val66met (*rs6265*) variant of the brain derived neurotrophic

factor (*BDNF*) affects stress resilience, either alone, (Taliaz et al., 2011) or in combination with the *5-HTTLPR* variant of SERT (Martinowich K, 2008). The coding val159met polymorphism of the catechol-O-methyltransferase (*COMT*, *rs4680*) gene has been associated with stress reactivity (Papaleo et al., 2008) and psychopathology both alone (DeYoung et al., 2010; Waugh, Dearing, Joormann, & Gotlib, 2009) and in combination with *5-HTTLPR* (Conway, Hammen, Brennan, Lind, & Najman, 2010). Oxytocin is a neuropeptide with a strong role in human attachment and social function (Macdonald & Macdonald, 2010). A variant in its receptor (*OXTR*, *rs53576*) has been associated with stress reactivity and depression (Saphire-Bernstein S, 2011). Similar to the *SERT*, *BDNF*, and *COMT* genes described above, there is also evidence for interaction of *OXTR* variants with the *5-HTTLPR* polymorphism of SERT (Montag, Fiebach, Kirsch, & Reuter, 2011). We included the coding asn40asp variant of the μ opioid receptor (*OPRM1*, *rs1799971*) on the basis of a prior study showing its influence on parent-child relations. (Copeland et al., 2011) The coding variant asp398asn of the nicotinic acetylcholine receptor $\alpha 5$ subunit (*CHRNA5*, *rs16969968*) is associated with externalizing and reward-driven behaviors. (Stephens et al., 2012) Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been tied to an abnormal stress response and broad deficits in emotional reactivity and regulation (Ehlert, Gaab, & Heinrichs, 2001). Consequently a number of common variants in genes which form part of the HPA axis are associated with depression and stress sensitivity in adolescents. The glucocorticoid receptor (*GCCR*) *rs6198* variant has been linked to glucocorticoid sensitivity, depression in the presence of childhood adversity, and externalizing behaviors in children. (Bet PM, 2009) The chaperone protein FK506 binding protein 5 (*FKBP5*) alters glucocorticoid receptor function. Variants in this gene, among them SNP *rs4713902*, have been associated with cortisol reactivity, stress vulnerability, and depression in children and adults (Luijk MP, 2010; Menke A, 2013). Likewise, variants in the corticotropin-releasing hormone receptor 1 (*CRHR1*, *rs1876831*) and corticotropin releasing hormone binding protein (*CRHBP*, *rs10055255*) have been associated with cortisol reactivity in children. (Sheikh HI, 2013) Finally, the variants *rs2251219* in polybromo-1 (*PBRM1*) and *rs1170169* in diacylglycerol kinase eta were included because they were among the few SNPs which have previously shown robust associations with affective disorders in genome-wide association studies (Weber H, 2011).

1.4 Analytic Approach for Examining Multiple Candidate Genes

GxE research is a rapidly expanding research paradigms within behavioral science (Dick, 2011). In our current understanding of psychopathology, multiple genetic and environmental factors interact in a complex way, with each individual factor expected to contribute only a small effect. Comprehensive models require that a large number of genes and environmental factors are included in the analyses, exhausting computation model space, thus providing limited utility for probing multiple gene-environment interactions. These computational problems have no doubt contributed to lack of clarity in understanding how genetic contributions together with environment context affect typical and atypical development. Bayesian methods provide a computational framework for variable selection and model estimation based on induction (Wakefield, De Vocht, & Hung, 2010). Bayesian approaches utilize a rational method based on probability to combine prior beliefs in combination with the sampling model to provide the posterior distribution. This approach makes an

improvement on model selection because model comparison does not depend on the parameters used by each model, but instead considers the probability of the model considering all possible parameter values (Wakefield, 2013). Similar to the likelihood ratio test, but without maximization of the likelihood, Bayesian methods average all of the parameter estimates.

1.5 This Study: The Interplay of Genetic and Environmental Mechanisms

As multiple lines of evidence support polygenetic variations and familial experiences as important factors in predicting the development of depression and disruptive behavior disorders, research has turned to interactive models of genetic and environmental influences to best capture the unique and moderated conditions that promote the emergence of psychopathology. Individual characteristics, including genetic variability, are associated with variations in responsiveness to environmental influences. Environmental influences, including experiences of familial adversity, are not expected to uniformly influence development, but rather the nature and magnitude of effects will vary based on genetic vulnerability. Using a Bayesian mixed modeling approach, we examined the direct and interactive effect of 12 polymorphisms in genes associated with affect regulation and stress response (SLC6A4, BDNF, COMT, OXTR, OPRM1, CHRNA5, GCCR, FKBP5, CRHR1, CRHBP, PBRM1, and DGKH) with the environmental stressor of chronic low family support to examine the role of genetic vulnerability for depression and disruptive behavior disorders in adolescents.

2. Methods

2.1 Sample

This is a sub-study of a larger investigation, the Developmental Pathway Project (DPP), a community-based 7-wave longitudinal study focused on the antecedents, phenomenology, and outcomes of co-morbid depressive and conduct problems. DPP was carried out in an urban community in the Pacific Northwest. Four cohorts were recruited in 4 consecutive years (2001-2005) from a universal emotional health screening program in the 6th grade. The study has been described in detail elsewhere (McCarty et al., 2013; Vander Stoep et al., 2005).

2.1.1 Study eligibility—The sampling frame for DPP was the population of middle school students who were screened for depressive symptoms and conduct problems using the Moods and Feelings Questionnaire (Angold & Costello, 1987) and the externalizing scale of the YSR (Achenbach, 1991), respectively. Youth were categorized into depressive, conduct, or comorbid problems based on a screening score of .5 *SD* above the sampling mean on the aforementioned measures. To enhance the likelihood of observing psychopathology and related outcomes, children whose screening scores were high on either or both depressive or conduct problem dimensions were over-sampled for participation in the longitudinal study. A target number of children randomly selected from the four cells in a ratio of approximately 1 CM : 1 DP : 1 CP : 2 NE were recruited. Since in the general school population, the ratio is close to 1 CM: 1 DP : 1 CP: 6 NE, this sample selection approach yielded an over-representation of children in the CM, DP, and CP groups relative

to their representation in the general population (for details see (Vander Stoep et al., 2005)). Two-component sampling weights were applied to make the longitudinal sample comparable to the screened population on depression/disruption status as well as gender, race/ethnicity, and educational program. Assessments occurred at: Baseline/Late sixth grade (T1), early seventh grade (T2), late seventh grade (T3), early eighth grade (T4), late eighth grade (T5), early ninth grade (T6) and 12th grade (T7).

2.1.2 Study participants—The DPP sample was comprised of 249 (47.8%) girls and 272 (52.2%) boys. With regard to race/ethnicity, 148 (28.4%) were African American, 97 (18.6%) were Asian American, 21 (4.0%) were Native American, and 255 (48.9%) were European American. Within the sample, 10.2% was of Hispanic ethnic origin. The mean age of participants at the baseline interview was 12.02 years ($SD=.43$). Participating families gave income and employment information that was then aggregate via Hollingshead recommendations to obtain an estimate of socioeconomic status (SES; (Hollingshead, 1975) SES spanned a range of lower and middle income levels, with 26.7% of families having a total household annual income of under \$25,000, and 31.1% of families having a household income of over \$75,000. Among study participants, 31.5% had at least one immigrant parent.

Of the 521 young adolescents enrolled in the study, 472 (90.5%) completed the T7 assessment. Every attempt was made to contact and assess enrolled participants at each assessment; 91.3% were retained for four or more of the seven assessments. 400 (76.7%) youth elected to participate in the genotyping. Attrition analyses verified that participants who were missing data at follow-up periods did not differ significantly on the variables examined, suggesting that the attrition did not introduce bias. Table 1 presents the demographic characteristics of the subsample used for analysis. Ethical approval for the study was obtained from the University of Washington's Institutional Review Board. All participants provided informed consent.

2.2 Measures

2.2.1 Comorbid depressive and disruptive behavior disorders—The lay interviewer administered computerized Diagnostic Interview Schedule for Children (DISC-IV; (Columbia University DISC Development Group, 1998) was administered to the child and parent/caregiver at baseline and annually for three years (T1, T3, T5, and T6) and then three years later (T7) to determine the presence of major depressive disorder (MDD), oppositional defiant disorder (ODD) and conduct disorder (CD), as specified in the DSM-IV in the past 12 months. Interviewers were trained by author (EM), who was certified by the Columbia University DISC Development Group. Test-retest reliability of the C-DISC-IV modules have been assessed in a clinical sample, with intraclass kappas for past year, combined parent and youth diagnoses are adequate in the analyses.(Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) Positive diagnoses were assigned by combining child and caregiver reports at the criterion level using the either/or rule (Piacentini, Cohen, & Cohen, 1992) and defined as present at any of the four assessments. Child and parent C-DISC-IV interviews were available for 400 study participants. Outcome group assignment was missing at one or more assessment in 143 of 2000 potential instances (~8%). Using this

method, there were 194 with no disorder, 80 with disruptive behavior diagnosis, 65 with depressive diagnosis, and 61 who were classified as comorbid. For the purposes of this study, only those classified as no diagnosis and comorbid were included

2.2.2 Chronic low family support—Family support was assessed using the Multidimensional Scale of Perceived Social Support (MSPSS), a self-report measure designed to assess the amount of support one feels one has from one's friends, family and a significant other (Zimet, Powell, Farley, Werkman, & Berkoff, 1990). Participants responded to 12 items rated on a 5-point Likert scale (0= Not True, 4= Very True). The family support subscale was used for this study. The MSPSS has been widely used and has adequate psychometrics, with Cronbach's coefficient alpha ranging from .81-.98 (Zimet et al., 1990). Participants completed the PSS at each of the seven assessments, and scores were standardized at each time point. Youth who had total scores that were one standard deviation below the mean were considered to have chronic low family support.

2.2.3 Genotyping—Subjects donated a saliva sample for genetic testing, using Oragene DNA OG-250 format mail-in collection kits (DNA Genotek Inc., Ontario, Canada); DNA was extracted according to the manufacturer's protocol and checked for quality and concentration on a Nanodrop 1000 Spectrophotometer (Thermo Scientific, DE, USA). Genotyping was done on a StepOnePlus Real-Time PCR System (Applied Biosystems, CA, USA). The 5'-*HTTLPR* variant of SERT was genotyped in 10µl PCR reactions containing 50-100ng genomic DNA from each subject, 0.5µM flanking oligonucleotide primers (forward: 5'- CCAGCAACTCCCTGTACCC -3' and reverse: 5'- ATGCTGGAAGGGCTGCA -3') as well as 5µl HotStar Taq Master Mix (Qiagen, CA), and 2.5µl Betaine (Sigma-Aldrich, MO). PCR cycling parameters were: 15-minute incubation at 95°C, followed by 33 cycles of 94 °C for 1 min, 60 °C for 1 min, and 72 °C for 2 min, followed by a 10-minute final extension step of 72 °C for 10 minutes. PCR products were size fractionated on a 5% TBE-urea gel allowing for the distinction of the s-allele, yielding a 117bp fragment, and the l-allele, resulting in a 160bp fragment. All other variants (SNPs) were genotyped using TaqMan SNP Genotyping Assays (Applied Biosystems, CA, USA), and following the manufacturer's instructions. Investigators performing DNA extraction and genotyping were blind to any subject information. For quality control, 10% of samples were genotyped in duplicate. Genotypes were checked for deviation from Hardy-Weinberg equilibrium (HWE). No significant deviations were found except for the *GCCR* SNP, where allele frequencies were in violation of HWE with $p=0.038$. We observed a two-fold greater number of rare C/C homozygotes than expected (observed 9, expected 4.9). Given this violation of HWE, we removed *GCCR* SNP from analyses.

2.3.4 Covariates—Socioeconomic status, (Hollingshead, 1975) and race/ethnicity were used as covariates in the current analyses.

2.4 Analyses

Bayesian hierarchical modeling provides a flexible framework with straightforward probabilistic interpretations to model multiple gene and environment effects and their interactions. Bayesian variable selection methods offer a solution to the multiple-testing

problem, are computationally feasible, and may yield fewer false positives and more robust inferences. (Wakefield et al., 2010) Using a Bayesian mixture modeling approach we explored multiple gene-environment interactions in the development of co-morbid depressive and disruptive behavior disorders, our hierarchical model consists of three levels. The first stage model posits an additive logistic regression model on comorbid depression and disruptive behavior disorders (yes/no) with main gene variant effects, main environment effects and gene-environment interactions as covariates. The second stage assumes two-component mixture priors on the first stage regression coefficients (e.g., log odds ratios). One of the two components captures the prior belief that the main effects or interaction effects are null, while the other component represents the non-null effects. The coefficient is assumed to follow one of the two component distributions with Bernoulli probability. The third stage completes the specification with priors on all other parameters in the model. Parameter estimation and inference can then be made based on the resultant posterior distribution. Consistent with recommendations, for computation we used Markov chain Monte Carlo (MCMC) techniques. (Richey, 2010) Calculations were implemented using OpenBUGS, a popular program for implementing Bayesian hierarchical models.

Three additional potential confounders were included in every model: sex, SES and a categorical ethnicity variable. The set of models considered ranges over all combinations of the genetic and environmental variables and their interactions. These included twelve genetic variants, an indicator for low family support, and twelve interactions between the genetic variants and family support, giving a total of 25 variables. An additive genetic model was used, so genetic variants were treated as allele dosages of 0, 1, or 2. The prior probability for a non-null effect was 0.2. The prior variance for non-null effect distribution was 0.31 and for distribution of null effect was 1.45×10^{-5} (see (Wakefield et al., 2010) for details). We ran three Markov chains simultaneously for 5×10^6 iterations, and kept sampled parameter values at every 500th iteration for analysis so the final sample consisted of 10,000 values for each coefficient. We checked convergence of the MCMC using ('a' or 'the') Rubin-Gelman diagnostic test. Posterior means and posterior 90% credible intervals (CI) were then constructed for each coefficient using MCMC samples. When credible intervals did not include zero, we concluded that the result was significant. A final logistic regression model was run using only the significant main effects and interactions. We strengthened our analytic approach by applying simulation modeling to investigate potential power limitations. Finally, we employed logistical regression to compare of the two analytic methods.

3. Results

3.1 Bayesian Modeling Results

We applied a Bayesian method to identify genexgene and GxE interactions for co-morbid depressive and conduct disorders. First, we conducted MCMM on all 11 genetic variants considering only main effects without interaction effects and calculated the estimated marginal posterior probabilities for all of the potential genetic variants by using OpenBUGS. We then calculated the estimated marginal probabilities for the selected genetic variants interacting with low family support using the same method. Finally, we calculated the

estimated marginal probabilities for the selected 10 SNPs interacting with SERT using the same method. Table 3 summarized the results of the main and interactive effects based on our calculated marginal posterior probabilities and 90% credible interval (CI).

3.1.1 Main effects—The main effect of *OXT-R* ($\beta = .40$, 90% CI=.02-.78) indicated the G allele was associated with increased risk for co-morbid disorders.

3.1.2 Gene x environment effects—For the 12 interactions, values of the estimated marginal posterior probabilities lay between $-.28$ and $.73$. Two GxE interactions were associated with co-morbid disorders. The T allele of *FKBP5*, in the context of low family support was associated with increased risk for co-morbid disorders ($\beta = .70$, 90% CI=.05-1.26). In addition, the G allele of *CRHNA5*, in the context of low family support, was associated with increased risk for co-morbid disorders ($\beta = .73$ 90% CI=.13-1.26).

3.1.3 Gene x gene effects—With regards to gene x gene interactions, S allele of SERT interacted with the G allele of *OPRM1* and was associated with decreased risk of comorbid conduct disorders ($\beta = -.47$, 90% CI= $-.03$ — $-.96$). Table 3 presents the posterior estimates with 90% credible coverage interval for all main and interactive effects.

3.2 Simulation Study

To understand how well powered the analysis was, we conducted a pair of simulations with artificial trait values. The artificial trait value was set at a weak but detectable effect of 1.3 log odds for each additional allele. The simulated intercept was chosen to approximately match the observed trait penetrance. In all other respects the original study data was used. The same MCMC method was applied to both datasets.

Simulated data indicated adequate power to detect main effects, suggesting that none of the main effects of comparable magnitude (i.e., OR 1.3) were overlooked. However, the simulated interaction effect was above zero less than 80% of the time, a level comparable to what we observed in our results, indicating power may have affected the ability to detect interactive effects. This is not surprising given the general difficulty in detecting interaction effects in psychological research due to limited sample sizes, small effect sizes, and measurement factors (Vrieze et al., 2012). Interaction effects for *CRHNA5* and *FKBP5* were sampled above zero at rates similar to the simulation study. Consequently, the simulation results for these two genetic variants interacting with family support were suggestive of significant effects.

3.3 Logistic Regression Results

As a point of comparison, we performed a standard frequentist logistic regression on *CRHNA5* and *FKBP5*. In the Bayesian analysis, both in our data and with simulated data, these genetic variants were significant in the context of low family support, and acted to increase risk for co-morbid disorders. Variables included in the regression were age, SES, and ethnicity, genetic variant (*CRHNA5* or *FKBP5*, modeled separately), family environment, and the interaction of the genetic variant with family environment.

The results appear in Table 4. They indicate that the frequentist analysis do not converge with the Bayesian analysis. The main effect of *CRHNA5* has a negative coefficient, with a p-value of 0.018, and the interaction coefficient is positive but not close to significant. Results were not significant for the *FKBP5* main or interactive effect. The Bayesian approach revealed several promising gene by environment interactions that were not detected with single model estimates.

4. Discussion

The goal of this study was to examine gene-gene and GxE associated with co-morbid depressive and disruptive behavior disorders with Bayesian mixed modeling. This approach has previously been employed to examine genetic risk factors in other disorders (Lin & Hsu, 2009) (Wang et al., 2013), but this is the first application to psychiatric gxe. We believe the approach is both feasible and practical for exploring multiple gene-gene and gene-environment interactions, as the models were stable and had good performance when compared to simulated and multiple single frequentist models.

One main effect emerged to implicate *OXTR* in the development of comorbid depression and disruptive behavior disorders. The *rs53576* SNP of *OXTR* results indicated an addition of each G allele was associated with increased risk for comorbid depressive and DBDs. Our work converges with research conducted with maltreated adolescents in which the G allele carries more risk for psychological problems following negative social experiences. Specifically, maltreated youth with G/G genotype of the *rs53576 OXTR* reported higher levels of internalizing symptoms despite similar levels of maltreatment (Hostinar, Cicchetti, & Rogosch, 2014).

Findings from the Bayesian approach implicate the HPA axis in portending risk for depressive and conduct disorders. Dysregulation of the HPA axis is implicated in the common vulnerability hypothesis explaining the development of depressive and conduct disorders (Ehlert et al., 2001). Common genetic variants have been associated with changes in HPA axis reactivity and consequently differences in an individual's stress response. The effect of *FKBP5* was modified by family support, as our results indicate that individuals with the T allele are at higher risk for comorbid depressive and disruptive behavior disorders in the context of low family support. Previous studies have identified that the T allele is associated with higher risk for bipolar disorder in adults. (Willour et al., 2009) Given the developmental differences in the samples, future research should examine if this comorbid presentation is predictive of future bipolar disorder. Alternatively, dysregulation of the HPA axis may be a transdiagnostic risk factor for mood and behavior problems across the lifespan.

The results from the Bayesian analyses indicated the effect of *CHRNA5* SNP may be modified by the contextual factors such that individuals with A-allele are at higher risk for co-morbid depressive and disruptive behavior disorders in the context of low familial support. The A allele of *CHRNA5* has been linked to risk for externalizing behaviors in previous studies and point to inheritance of genetic vulnerability to generalized disinhibitory psychopathology (Stephens et al., 2012).

SNP x SERT interactions were examined. This area has been unexplored with relationship to psychopathology, likely due to computational limitations. One significant finding emerged, linking the interaction of SERT and *OPRM1* such that the S allele of SERT in the context of G allele from *OPRM1* was associated with decreased risk for comorbid problems. *OPRM1* encodes the mu opioid receptor, and is linked to stress responsivity, and serum levels of pro-inflammatory cytokines.

Finally, we compared the Bayesian analyses with frequentist analyses for significant interactions. These two sets of results did not converge. This non-convergence of findings are likely due to either the logistic regression analyses being underpowered, or the findings from the Bayesian models being false positives. Replications of our results are needed to determine what accounts for the discrepant findings.

4.1 Limitations

Several limitations need to be acknowledged. First, Bayesian analyses rely upon an appropriate specification of the prior probability distribution. Our selection of the prior was based on extant literature but is still an assumption that if misspecified could affect our results. For exploration of the influence of the prior on our results, we ran a wide range of priors, which did not significantly alter the estimates of the main effects and interactions. Therefore, we decided to stick with the prior that was most consistent with the extant literature and are assured that it is not providing undue influence on our results. Second, our measure of parental support utilized self-report of the adolescent over several time points. This is different from an acute event occurring once (e.g., indicator of abuse or life event). Notably, of the existing studies a broad array of adverse environmental factors has been examined as potential moderators of genetic vulnerability for psychopathology and adjustment problems. Such factors have included negative life events and childhood maltreatment, which are broad experiences reflecting an array of adverse developmental contexts. The operationalization of the environment is a critical factors and differences in this operationalization of the environment may contribute to lack of reproducibility across GxE studies. Additionally, though this study incorporated longitudinal aspect of the data, it is limited in that it did not identify specific time-relevant mechanisms in the unfolding of this mental health condition. We hope future work will address timing of environmental changes in the context of genetic vulnerabilities. This study was also limited with respect to the number of genetic variants that were examined. It is certainly possible that our selection, while guided by extant literature, did not include significant contributors to this phenotype. Finally, phenotypic selection is of critical importance. We selected co-morbid depression and disruptive behavior disorders because this presentation occurs commonly, is associated with severe impairment and poor prognosis reflecting non-transient difficulties (Wolff & Ollendick, 2006).

In summary, through the use of Bayesian modeling, this study illuminated three genes associated with higher risk of comorbid depressive and disruptive behavior disorders. Given current evidence for polygenetic influences, genes associated with arousal regulation, negative emotionality, and social bonding appear critical in determining vulnerability to risk for psychopathology. Results support further investigation of multiple genetic variants

underlying stress responses and social bonding in the context of low chronic family support and highlight the feasibility and utility of the Bayesian approach for exploring simultaneous multiple genetic variants in the context of suggested environmental moderators. Integrating our results with the broader literature then suggests a general principle of gene-environment interplay such that environments that are structured, warm, supportive and less stressful may suppress genetic risk, whereas environments characterized by lack of parental support and more stress amplify genetic risk for the co-occurrence of internalizing and externalizing behaviors.

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Highlights

- We employed Bayesian, simulated, and frequentist approaches for psychiatric genetic analyses.
- Bayesian mixed modeling to explore gene-gene and GxE associated with co-morbid depressive and disruptive behavior disorders is feasible way to accommodate many interactions.
- Variants involved in oxytocin receptivity, HPA axis, and nicotinic regulation important for this phenotype.

Table 1

Demographic Characteristics of the Sample

Variable	Whole DPP Sample (N=521)	Subsample (N=255)
Female sex	249 (48.3)	124 (48.6%)
Race/ethnicity		
White, non-Hispanic	232 (39.5)	121 (47.5)
White, Hispanic	53 (10.1)	24 (9.4)
Black	143 (24.9)	60 (23.5)
Asian/Pacific Islander	88 (24.1)	47 (18.4)
Native American	5 (1.4)	3 (1.2)
Age at Baseline	12 (.36)	12.1 (.37)
Hollingshead Household SES score	39.0 (14.2)	39.9 (13.9)

Table 2

Genotype by Phenotype Descriptives

#	Gene Symbol	Full Gene Name	Variant/RS#	Previous Literature Support	Reported MAF in Caucasians	No Diagnosis (N=194)	CoMorbidity Depressive and Conduct Diagnoses (N=61)
1	<i>BDNF</i>	Brain derived neurotrophic factor	val66met rs6265 C/C C/T T/T	Mood disorders in interaction with SERT (Pezawas et al., 2008; Wichers et al., 2008)	0.20	67.5 29.4 3.1	70.5 24.6 4.9
2	<i>CHRNA5</i>	Cholinergic receptor, neuronal nicotinic, alpha polypeptide 5	asp398asn rs16969968 A/A A/G G/G	Smoking (Hong et al., 2011) Substance use (Wang et al., 2009)	0.39	6.2 29.4 63.4	8.2 39.3 54.5
3	<i>COMT</i>	Catechol-o-methyltransferase	val158met rs4680 A/A A/G G/G	Conduct disorder (DeYoung et al., 2010) Mood disorders in interaction with SERT (Conway et al., 2010) PTSD (Kolassa et al., 2010)	0.48	18.6 45.9 35.1	13.1 54.1 32.8
4	<i>CRH-BP</i>	Corticotrophin releasing hormone binding protein	rs10055255 A/A A/T T/T	PTSD (Mehta & Binder, 2012) Substance use (Ray, 2011)	0.40	25.7 49.5 23.7	32.8 47.5 19.7
5	<i>CRHR1</i>	Corticotrophin-releasing hormone receptor	rs1876831 C/C C/T T/T	Mood disorders (Bradley et al., 2008)	0.22	71.6 24.7 3.1	72.1 26.2 1.6

#	Gene Symbol	Full Gene Name	Variant/RS#	Previous Literature Support	Reported MAF in Caucasians	No Diagnosis (N=194)	CoMorbidity Depressive and Conduct Diagnoses (N=61)
6	<i>DGKH</i>	Diacylglycerol kinase eta	rs1170169 C/C C/G G/G	Mood disorders (Weber et al., 2011) Conduct disorders (Weber et al., 2011)	0.31	44.8 38.7 12.9	45.9 41.0 11.5
7	<i>FKBP5</i>	FK506 binding protein 5 (glucocorticoid receptor chaperone protein)	rs4713902 C/C C/T T/T	PTSD (Binder, 2009) Conduct disorders (Bevilacqua et al., 2012)	0.25	4.6 34.0 59.3	6.6 24.6 68.8
8	<i>GCCR (NR3C1)</i>	Glucocorticoid receptor	rs6198 C/C C/T T/T	Mood disorders (Bet et al., 2009)	0.20	2.1 14.9 81.4	3.3 26.2 70.5
9	<i>OPRM1</i>	μ opioid receptor	asn40asp rs1799971 A/A A/G G/G	Substance use (Bond et al., 1998) Mood disorders (Dowlati et al., 2010)	0.16	73.7 21.6 4.6	78.7 19.7 1.6
10	<i>OXTR</i>	Oxytocin receptor	rs53576 A/A A/G G/G	Mood disorders (Thompson et al., 2014) Negative emotionality in interaction with SERT (Montag, et al 2011)	0.26	15.5 45.4 38.7	6.6 42.6 50.8
11	<i>PBRM1</i>	Polybromo-1	rs2251219 C/C C/T	Mood disorders (McMahon et al.,	0.34	13.9 39.7	11.5 44.3

#	Gene Symbol	Full Gene Name	Variant/RS#	Previous Literature Support	Reported MAF in Caucasians	No Diagnosis (N=194)	CoMorbid Depressive and Conduct Diagnoses (N=61)
			T/T			46.4	44.3
12	<i>SLC6A4</i>	Serotonin transporter (SERT)	5-HTTLPR L/L S/L S/S	Mood disorders (Karg et al., 2011) Conduct disorders (Oquendo & Mann, 2000)	.43	40.2 41.2 18.6	44.2 47.5 8.2

Note. Individual study outcomes were collapsed into diagnostic groups for succinct presentation. Abbreviations. PTSD=Post traumatic stress disorder.

Table 3

Posterior Estimates of Genetic and Environmental Effects and Their Interactions

	<u>Main effects</u>			<u>Interaction effects w/ environment</u>			<u>Interaction effects w/SERT</u>		
	5%	Median	95%	5%	Median	95%	5%	Median	95%
<i>BDNF</i>	-0.52	-0.08	0.35	-0.47	0.21	0.89	-0.82	-.35	0.09
<i>CRHNA5</i>	-0.83	-0.44	-0.05	0.13	0.73	1.26	-0.63	-0.26	0.04
<i>COMT</i>	-0.27	0.09	0.46	-0.42	0.22	0.88	-0.43	-0.12	0.24
<i>CRHBP</i>	-0.56	-0.19	0.18	-0.18	0.53	1.22	-0.46	-0.11	0.22
<i>CRHRI</i>	-0.55	-0.09	0.34	-0.31	0.44	1.16	-0.45	-0.01	0.40
<i>DGKH</i>	-0.53	-0.15	0.21	-0.93	-0.30	0.30	-0.35	-0.03	0.31
<i>FKBP5</i>	-0.19	0.22	0.64	0.05	0.70	1.26	-0.18	0.15	0.58
<i>OPRM</i>	-0.82	-0.34	0.13	-1.05	-0.28	0.49	-0.97	-0.49	-0.05
<i>OXTR</i>	0.03	0.40	0.78	-0.47	0.26	1.01	-0.10	0.25	0.62
<i>PBRM1</i>	-0.32	0.03	0.40	-0.57	0.07	0.70	-0.49	-0.16	0.16
<i>SERT</i>	-0.61	-0.26	0.09	-0.51	0.14	0.81			

Note. *BDNF*= Brain derived neurotrophic factor, *CRHNA5*= Cholinergic receptor, neuronal nicotinic, alpha polypeptide 5, *COMT*= Catechol-o-methyltransferase, *CRHBP*= Corticotrophin releasing hormone binding protein, *CRHRI*= Corticotrophin-releasing hormone receptor, *DGKH*= Diacylglycerol kinase eta, *FKBP5*= FK506 binding protein 5, *GCCR*= Glucocorticoid receptor, *OPRM*= μ opioid receptor, *OXTR*= Oxytocin receptor, *PBRM1*= Polybromo-1, *SERT*= Serotonin transporter.

Table 4

Point Estimates and P-values from Standard Logistic Regression Using the Covariates, Family Environment, Genetic variants and Interaction

	Estimate	P-value
Sex	−0.04	0.89
SES	0.00	0.70
Ethnicity	0.04	0.80
Family environment	0.12	0.94
<i>CRHNA5</i>	−0.60	0.02
Fam. × <i>CRHNA5</i>	1.02	0.28

	Estimate	P-value
Sex	−0.06	0.86
SES	−0.00	0.66
Ethnicity	0.15	0.36
Family environment	1.21	0.28
<i>FKBP5</i>	0.28	0.38
Fam. × <i>FKBP5</i>	0.38	0.58

	Estimate	P-value
Sex	−0.05	0.86
SES	−0.01	0.65
Ethnicity	0.15	0.36
SERT	.24	0.40
<i>OPRM</i>	−.01	0.80
SERT× <i>OPRM</i>		