We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

11

Childhood Maltreatment and County-Level Deprivation Jointly Modify the Effect of Serotonin Transporter Promoter Genotype on Depressive Symptoms in Adolescent Girls

Monica Uddin[1], Erin Bakshis[2] and Regina de los Santos[2]
[1]*Center for Molecular Medicine and Genetics and Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI*
[2]*Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI*
USA

1. Introduction

Depression is a commonly occurring mood disorder defined by the presence of persistent sad feelings, low energy, loss of interest in activities that were once pleasurable, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration, among other symptoms (American Psychiatric Association, 1994). Among adults 18 and older in the United States, the prevalence of major depressive disorder (MDD) is higher than that of any other commonly occurring DSM-IV mental disorder in the U.S., with a lifetime prevalence of 16.6%, and 12-month prevalence estimated at 6.7% (Kessler & Wang, 2008). The World Health Organization estimates that depression will rank second among the leading contributors of disease burden by the year 2020 (WHO, 2009). MDD is associated with enormous costs to both the individual and society, with the economic burden of depression estimated to be $83 billion per year as of 2000 (Greenberg et al., 2003), and the impairment in proper role functioning due to MDD known to be significantly worse when compared to a number of commonly occurring chronic medical disorders (Druss et al., 2009). The large public health burden of MDD is due, at least in part, to its onset relatively early in life: at least 25% of lifetime MDD cases start before age 19 (Kessler et al., 2005).

Despite substantial research, our understanding of the factors that contribute to the etiology of depression remain incomplete. Genetic factors account for an estimated 35-45 percent of the variance in risk for depressive symptoms (Shih et al., 2004). In addition, meta-analysis supports an association between polymorphisms in six different candidate genes and MDD (Lopez-Leon et al., 2008). Nevertheless, there is growing recognition that genetic influences on depression may only be evident under certain environmental conditions—i.e. that there may be gene X environment (G X E) interactions, such that individuals of the same genotype may express different phenotypes depending on their environmental contexts (Moffitt et al., 2005). In particular, a growing body of work indicates that genetic variation, in combination with adverse experiences early in life, shape risk for mental illness.

Seminal work by Caspi et al (Caspi et al., 2003) was the first to demonstrate that genetic variation at the promoter (*5-HTTLPR*) region of the serotonin transporter (*SCL6A4)* locus interacted with the experience of childhood maltreatment, including physical and sexual abuse, such that childhood maltreatment predicted adult depression only among individuals carrying an *s* allele but not among l/l homozygotes (Caspi et al., 2003). These findings were replicated by subsequent studies (Scheid et al., 2007), and detected not only in adults but also adolescents and children (Eley et al., 2004; Kaufman et al., 2004; Sjoberg et al., 2006). Nevertheless, some studies have either failed to detect any significant findings with respect to *5-HTTLPR* x maltreatment interactions in depression (Chipman et al., 2007; Surtees et al., 2006) or have detected significant interactions, but for other *5-HTTLPR* genotypes/alleles (Laucht et al., 2009). In addition, two recent meta-analyses have called into question the weight of evidence of G x E associations reported for the *5-HTTLPR* locus (Munafo et al., 2009; Risch et al., 2009). These meta-analyses, however, have been criticized on a variety of levels, including (but not limited to) the heterogeneity in measurement of both environment and outcome (Lotrich & Lenze, 2009), the use of a dichotomized outcome for studies that were originally assessed with dimensional outcomes (Schwahn & Grabe, 2009), and a failure to consider the biological plausibility of G x E interactions at the *5-HTTLPR* locus in light of animal and clinical data (Koenen & Galea, 2009; Rutter et al., 2009). Furthermore, an additional, more recent meta-analysis, including a greater number of studies, confirmed previous findings of an association between increased risk of depression under stressful conditions among carriers of the *s* allele (Karg et al., 2011); notably, this association was particularly pronounced when analyses were restricted to studies that assessed childhood maltreatment as the stressor of interest (Karg et al., 2011).

Importantly for the present study, we have also suggested that an additional consideration is the failure of the current literature to consider measurement of relevant social environmental variables that may interact with underlying genetic variability and vulnerability to produce increased risk for, or resilience to, mental illness. (Koenen & Galea, 2009; Koenen et al., 2010) Recent work suggests that macrosocial contextual influences, in conjunction with genetic variation at the *5-HTTLPR* locus, contribute to risk of mental illness (Koenen et al., 2009; Uddin et al., 2010); and as outlined above, there is clear evidence that genetic variation moderates the effect of childhood maltreatment on risk of depression. Nevertheless, there has, to date, been little consideration of the joint and/or interacting effects of how these risk factors, operating at multiple levels, shape risk for mental illness. To address this gap in the literature, here we assess whether *5-HTTLPR* genetic variation, childhood maltreatment, and macrosocial context interact to shape risk for depressive symptoms in a U.S. adolescent population. Consistent with recent recommendations regarding G X E studies involving the *5-HTTLPR* locus (Uher & McGuffin, 2008), and depression more generally (Lupien et al., 2009), we conducted this investigation separately for males and females, and report results separately for each genotype.

2. Methods

2.1 Sample

The data source for our analysis is drawn from the National Longitudinal Study of Adolescent Health (AddHealth), a nationally representative, school-based sample of over 90,000 adolescents in grades 7 – 12, initially sampled in 1994 – 1995 in the United States and followed for three subsequent waves. A subsample (N=20,745) of participants from the in-

school portion of the study was selected to participate in an additional, 90-minute in-home interview during Wave I, which provided the primary data source for the analyses reported here. In 2002, during Wave III, DNA samples were collected from a subsample of siblings (n=2,574) who had participated in the in-home interview portion of the study. The in-home and genetic data are part of the restricted use/contractual AddHealth dataset (Harris, 2008) and IRB approval to work with this dataset was secured prior to undertaking any of the below-described analyses. More detail regarding the design and data availability for the genetic component of AddHealth is available elsewhere (Harris et al., 2006).

The sample for our primary analysis is comprised of 1,097 individuals from the sibling subsample who provided DNA, belonged to a same sex sibling cluster, and for whom there was a complete set of data available for each sibling in the cluster for each of the measures included in our models. The analytic sample did not differ from the excluded sample with respect to genotype, childhood maltreatment, county-level deprivation or depressive symptoms, i.e. the main variables in the study.

2.2 Measures

2.2.1 Individual- and family-level health indicators

Depressive symptom scores were obtained using a shortened, 17-item version of the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977), based on the CES-D questions that were posed in the AddHealth *Feelings Scale* during the in-home interviews conducted during Wave I (Apr. – Dec. 1995) and II (Apr. – Aug. 1996). Responses to the 17 questions were ordinal, ranging from 0 (never or rarely) to 3 (most or all of the time) and were summed for use as the outcome variable in all analyses, with higher scores indicative of more depressive symptoms. Respondents were required to answer all 17 questions in Waves I and II in order to be included in our analyzed sample. The final current depression index was standardized to the mean in order to facilitate model interpretation. Shortened versions of the CES-D have previously been found to have very high sensitivity and specificity for detecting depressive symptoms (Kohout et al., 1993).

Siblings were classified as monozygotic twins (MZ), dizygotic twins (DZ), full siblings (FS), half siblings (HS), or cousins (CO), as indicated in the AddHealth data files.

Genotype: The *5-HTTLPR* locus is characterized by a variable number of tandem repeat (VNTR) polymorphism with two predominant alleles: the long (*l*) allele with 16 repeats and the short (*s*) allele with 14 repeats, the latter of which corresponds to a ~44bp deletion in reference to the long allele (Heils et al., 1996). Respondents were assigned one of three possible *5-HTTLPR* genotypes: homozygote long (*ll*; referent category), homozygote short (*ss*), and heterozygote (*sl*).

Age and race/ethnicity: Age was calculated using date of birth and date of interview and left as a continuous variable in the model. Race/ethnicity was self-reported using the following categories: White (reference), African-American, Hispanic, Asian, and other race.

Family structure assessed the number of household resident parent(s) and categorized respondents as belonging to a two-biological parent family (referent category), a one-biological parent family (i.e. single biological parent or one biological parent and a stepparent) or "other family structure."

Family-level socioeconomic position (SEP) was assessed via whether at least one resident parent was receiving public assistance (PA).

Social support was measured by averaging the responses to eight questions that represent respondents' perceived value and support from family members, friends and teachers;

responses ranged from 1 (not at all) to 5 (very much). If respondents missed one or more of the 8 questions, the average was determined from the remaining, answered questions.
Childhood maltreatment was assessed retrospectively in Wave III of the AddHealth study, conducted in August 2001 to April 2002, when participants were between 18 and 26 years old. Participants were asked "By the time you started sixth grade, how often had your parents or other adult care-givers slapped, hit, or kicked you?" and "how often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?" These questions thus assessed participants' exposure to maltreatment by an age that captured the youngest age of AddHealth participants at Wave I. Although additional measures assessing the occurrence of supervision neglect and physical neglect were also available in the AddHealth dataset, we focused on exposure to physical and/or sexual maltreatment due to its more robust association with depression (Brown et al., 1999). Exposure to maltreatment was coded 1 if a participant had been exposed one or more times to physical and/or sexual abuse, and 0 otherwise. If a participant was missing data for either physical or sexual maltreatment (or both), they were excluded from analyses.

2.2.2 County-level health indicator

Consistent with previous work (Robert, 1998), county-level public assistance (PA) was selected as a measure of exposure to poor social environments, i.e. a proxy for county-level deprivation. The proportion of households receiving PA income in each county for each respondent was assessed using U.S. Census data from 1990, geocoded to respondents' interview data via the AddHealth contextual database. We calculated the median proportion of PA based on the counties represented by respondents in our dataset and a dummy variable was then created indicating 1 if the value was greater than the median and 0 otherwise. Individuals who relocated to a different county between Waves I and II were removed from the dataset.

2.3 Statistical analysis

2.3.1 Hardy Weinberg Equilibrium

Genotype frequencies were assessed for Hardy-Weinberg Equilibrium (HWE) using Rodriguez et al.'s (Rodriguez et al., 2009) online HWE Chi Square calculator by randomly sampling one sibling per family cluster. Calculations were performed separately for each gender.

2.3.2 Analytic models

A repeated multi-level modeling approach using mixed models was employed in our study. Mixed models have proven to be useful when dealing with nested and clustered data (Searle et al., 1992). In our analysis, level 1 refers to the repeated measurements of individuals' depressive symptom scores, level 2 refers to the individual respondent, and level 3 refers to the family cluster to which the respondent belongs. Equation one (Eqn1) below describes the basic mixed model used in our analysis:

$$\begin{aligned} \text{CESD}_{ij(s)} = {} & \beta_0' X_{ij} + \beta_1' \text{5-}HTTLPR_{ij} + \beta_2' \text{family structure}_{ij} + \beta_3' \text{SEP}_{ij} + \beta_4 \text{support}_{ij} + \\ & \beta_5 \text{maltreatment}_{ij} + \beta_6 \text{ county level predictor}_{ij} + u_{j(s)} + v_{ij} + e_{ij(s)} \end{aligned} \quad (1)$$

where *i*, *j* and *s* indicate individual and sibling cluster, respectively. Each beta represents a single coefficient or a vector of coefficients for each predictor component in the model; X

represents age and race, *5-HTTLPR* represents the serotonin transporter promoter genotype, family structure represents the variants in resident parents, SEP refers to parent receipt of PA, support refers to social support, maltreatment refers to childhood maltreatment, and county-level predictor represents PA. The random effect of the family cluster is represented by $u_{j(s)}$, v_{ij} is the random effect of the repeated observations on the same individual, and $e_{ij(s)}$, is the error term. This model allows the random effect of family cluster and the error term to vary by sibling type (Guo & Wang, 2002), denoted by *s (s = mz, dz, fs, hs, co)*. All predictors were set at Wave I values and the outcome variable (depressive symptom score) was assessed across Waves I and II. Interactions among *5-HTTLPR* genotype, childhood maltreatment, and county-level deprivation were explored in models with interaction terms included in which the *ll* genotype, low PA, and no maltreatment were the referent categories and all other covariates were maintained. All models were stratified by gender, and all analyses were conducted using SAS v. 9.2

3. Results

Table 1 presents the descriptive statistics of the sociodemographic variables included in our final model. The average age in both our male (*n*=512) and female (*n*=585) samples was

	Males (n=512)		Females (n=585)		Test
	n /mean	% / std	n /mean	% / std	p
Genotype					
SS	112	21.88	109	18.63	0.18
SL	239	46.68	277	47.35	0.82
LL	161	31.45	199	34.02	0.37
Demographics					
Age	16.08	1.66	16.0	1.69	0.43
White	288	56.25	368	62.91	**0.02**
Black	70	13.67	76	12.99	0.74
Hispanic	80	15.63	69	11.79	0.06
Asian	38	7.42	30	5.13	0.12
Other	36	7.03	42	7.18	0.92
Family structure					
Two biological parents	340	66.41	373	63.76	0.36
One biological parents	144	28.13	167	28.55	0.88
Other family structure	28	5.47	45	7.69	0.14
Support and maltreatment					
Social support	4.0	0.54	4.03	0.59	0.88
Exposure to physical or sexual abuse	163	31.84	166	28.38	0.21
Family-level SEP					
Parent receives public assistance	39	7.62	54	9.23	0.34
County-level SEP					
High deprivation	268	52.34	278	47.52	0.11
17-CESD					
Depressive symptom score	9.3	6.04	11.0	7.27	**<0.0001**

Table 1. Sociodemographic characteristics of AddHealth participants included in the present study, stratified by gender.

approximately 16 years (range in males: 12-19; range in females: 12-20). Genotype frequencies for the *5-HTTLPR* locus were in Hardy-Weinberg Equilibrium for both males (χ^2 =0.16, df=1 p=0.69) and females (χ^2 =0.59, df=1 p=0.44). Approximately one-third of adolescents of both genders had been exposed to one or more incidents of physical and/or sexual abuse by an adult caregiver, and approximately half of the male and female samples resided in high deprivation counties. The main predictors of interest (childhood maltreatment, *5-HTTLPR* genotype, and county-level deprivation) did not differ significantly between males and females; however, the average depressive symptom score was significantly higher in female (11.0) vs. male (9.3) adolescents (p<0.001).

A number of predictor variables also showed gender differences in the unadjusted models (Table 2). Notable to this study, however, was the detection in females of a significant

	Male				**Female**			
	b	**p**	**95% CI**		***b***	**p**	**95% CI**	
Genotype								
SS	0.08	0.43	-0.12	0.28	**0.25**	**0.04**	**0.02**	**0.49**
SL	-0.13	0.11	-0.29	0.03	**-0.19**	**0.03**	**-0.37**	**-0.02**
LL	0.09	0.30	-0.08	0.27	0.06	0.56	-0.13	0.25
Demographics								
Age in years	0.04	0.15	-0.01	0.08	0.05	0.06	0.00	0.10
White	**-0.31**	**<0.001**	**-0.48**	**-0.14**	**-0.27**	**0.01**	**-0.48**	**-0.07**
Black/African-American	**0.26**	**0.04**	**0.01**	**0.51**	-0.06	0.70	-0.35	0.23
Hispanic/Latino	0.02	0.84	-0.22	0.27	0.13	0.40	-0.18	0.43
Asian	**0.43**	**0.01**	**0.10**	**0.75**	**0.67**	**<0.01**	**0.22**	**1.13**
Other race	0.21	0.23	-0.13	0.55	**0.44**	**0.02**	**0.06**	**0.81**
Family Structure								
Two biological parents	**-0.25**	**0.01**	**-0.43**	**-0.06**	**-0.37**	**<0.001**	**-0.57**	**-0.18**
One-biological parent	**0.24**	**0.01**	**0.05**	**0.44**	**0.32**	**<0.01**	**0.11**	**0.54**
Other family structure	0.10	0.63	-0.29	0.49	0.29	0.13	-0.08	0.66
Support and maltreatment								
Social Support	**-0.67**	**<0.0001**	**-0.80**	**-0.54**	**-0.82**	**<0.0001**	**-0.95**	**-0.69**
Exposure to physical or sexual abuse	0.04	0.64	-0.13	0.20	**0.30**	**<0.01**	**0.11**	**0.49**
Family-level SEP								
Parent receives public assistance	**0.50**	**<0.01**	**0.18**	**0.82**	0.30	0.08	-0.04	0.64
County-level SEP								
High Deprivation	0.16	0.08	-0.02	0.33	0.01	0.93	-0.19	0.21

Table 2. Unadjusted associations predicting standardized depressive symptom score, stratified by gender.

protective effect of the *sl* genotype (b=-0.19, 95% CI: -0.37, -0.02; p=0.03), and a corresponding risk-enhancing effect of the *ss* genotype (b=0.25 95% CI: 0.02, 0.49; p=0.04), with respect to depressive symptom scores. Exposure to maltreatment was also significantly and positively associated with depressive symptom scores in females (b=0.30, 95% CI: 0.11, 0.49; p<0.01); however, for the remaining main predictor of interest, county-level deprivation, no significant association was observed in females (b=0.01, 95% CI: -0.19, 0.21; p=0.93). In contrast, male AddHealth participants showed no significant associations between genotype and depressive symptom scores, or maltreatment and depressive symptom scores (Table 2); however, the association between residing in a high deprivation county and depressive symptom score was marginally significant (b=0.16, 95% CI: -0.02, 0.33; p=0.08).

Table 3 presents the results of our multivariable, multi-level main effects model. Females with the *sl* genotype continued to show significantly decreased depressive symptom scores in this fully adjusted main effects model (b=-0.21, 95% CI: -0.39, -0.03; p=0.02); however, the previously observed positive association between the *ss* genotype and depressive symptom scores in females was attenuated to non-significance (b=-0.03, 95% CI: -0.26, 0.21; p=0.82). The previously observed positive association between maltreatment and depressive

	Male				**Female**			
	b	**p**	**95% CI**		***b***	**p**	**95% CI**	
Genotype								
SS	-0.01	0.95	-0.21	0.20	-0.03	0.82	-0.26	0.21
SL	-0.05	0.53	-0.22	0.12	**-0.21**	**0.02**	**-0.39**	**-0.03**
Demographics								
Age in years	0.01	0.63	-0.03	0.05	0.01	0.75	-0.04	0.05
Black/African-American	**0.34**	**0.01**	**0.08**	**0.59**	-0.02	0.89	-0.29	0.25
Hispanic/Latino	0.11	0.31	-0.11	0.34	0.13	0.33	-0.13	0.40
Asian	**0.51**	**<0.001**	**0.21**	**0.82**	**0.72**	**<0.001**	**0.33**	**1.12**
Other race	0.17	0.27	-0.13	0.48	0.20	0.23	-0.12	0.52
Family structure								
One-biological parent	0.09	0.33	-0.09	0.27	**0.31**	**<0.01**	**0.12**	**0.50**
Other family structure	0.00	0.99	-0.35	0.35	0.27	0.11	-0.06	0.61
Support and maltreatment								
Social Support	**-0.67**	**<0.0001**	**-0.80**	**-0.54**	**-0.78**	**<0.0001**	**-0.91**	**-0.65**
Exposure to physical or sexual abuse	-0.06	0.40	-0.21	0.08	0.16	0.07	-0.01	0.33
Family-level SEP								
Parent receives public assistance	**0.45**	**<0.01**	**0.17**	**0.74**	0.04	0.81	-0.27	0.35
County-level SEP								
High deprivation	0.03	0.77	-0.14	0.19	-0.08	0.38	-0.25	0.10

Table 3. Adjusted main effects model predicted standardized depressive symptom score, stratified by gender.

symptom scores in females was also attenuated in these adjusted main effects models; however, results for this variable remained marginally significant (b=0.16, 95% CI: -0.01, 0.33; p=0.07). As in the unadjusted models, the fully adjusted model revealed no significant associations between genotype and depressive symptom scores, or maltreatment and depressive symptom scores in males (Table 3); and, the previously observed, marginally significant positive association between county-level deprivation and depressive symptom score was markedly attenuated (b=0.03, 95% CI: -0.14, 0.19; p=0.77).

Table 4 presents results from the multi-level, multivariable models with the three-way interaction terms included. Among females, the three-way interaction terms for *5-HTTLPR*

	Male				**Female**			
	b	**p**	**95% CI**		***b***	**p**	**95% CI**	
Genotype								
SS	0.10	0.58	-0.27	0.48	0.07	0.72	-0.34	0.49
SL	0.10	0.49	-0.19	0.39	-0.07	0.61	-0.35	0.20
Demographics								
Age in years	0.01	0.72	-0.04	0.05	0.00	0.93	-0.04	0.05
Black/African-American	**0.32**	**0.02**	**0.06**	**0.57**	-0.05	0.75	-0.32	0.23
Hispanic/Latino	0.11	0.32	-0.11	0.33	0.13	0.36	-0.14	0.40
Asian	**0.52**	**<0.01**	**0.21**	**0.83**	**0.74**	**<0.001**	**0.34**	**1.15**
Other race	0.17	0.29	-0.14	0.47	0.17	0.31	-0.16	0.50
Family structure								
One-biological parent	0.08	0.38	-0.10	0.26	**0.32**	**<0.01**	**0.13**	**0.52**
Other family structure	-0.02	0.93	-0.37	0.34	0.30	0.08	-0.04	0.64
Support and maltreatment								
Social Support	**-0.68**	**<0.0001**	**-0.81**	**-0.54**	**-0.79**	**<0.0001**	**-0.92**	**-0.65**
Exposure to physical or sexual abuse	-0.01	0.95	-0.44	0.41	**0.47**	**0.03**	**0.04**	**0.89**
Family-level SEP								
Parent receives public assistance	**0.45**	**<0.01**	**0.16**	**0.74**	-0.01	0.96	-0.32	0.30
County-level SEP								
High deprivation	0.24	0.16	-0.09	0.58	0.17	0.30	-0.16	0.50
Maltreatment* Genotype*County-level SEP								
Maltreatment* S|S * High Deprivation	0.10	0.82	-0.75	0.94	**0.97**	**0.04**	**0.05**	**1.89**
Maltreatment*S|L* High Deprivation	0.10	0.79	-0.60	0.79	**0.86**	**0.03**	**0.09**	**1.63**

Table 4. Adjusted interaction model predicted standardized depressive symptom score.

genotype, maltreatment, and county-level deprivation were significant: in the context of both exposure to maltreatment and high deprivation at the county-level, females with the *sl* genotype showed significantly higher depressive symptom scores (b=0.86, 95% CI: 0.09, 1.63; p=0.03), as did females with the *ss* genotype (b=0.97, 95% CI: 0.05, 1.89; p=0.04). In contrast, no significant three-way interaction terms were observed among males.

4. Discussion

The goal of this study was to investigate the joint and interacting effects of genetic variation at the *5-HTTLPR* locus, childhood maltreatment, and macrosocial context in shaping risk for, or resilience to, depressive symptoms in a U.S. adolescent population, controlling for a number of factors previously associated with depression in this population. Results showed that, among females, the *sl* genotype conferred a protective main effect against higher depressive symptom scores; however, interaction models revealed that, among females who were both exposed to childhood maltreatment and resided in high deprivation counties, the *sl* genotype conferred increased risk of higher depressive symptom scores. An additional, risk-enhancing three-way interaction was observed among females carrying the *ss* genotype. In contrast, among males, no significant associations were observed between our predictors of interest and depressive symptom scores in either main effects or interaction models. These findings demonstrate that factors operating at multiple levels—biologic, social, and macrosocial—combine to shape risk for mental illness, and confirm that these factors can differ by gender, particularly in adolescent populations.

Our results confirm and extend previous findings regarding the link between childhood maltreatment and depression. A large body of work has established that exposure to maltreatment during childhood is a potent risk factor for depression (eg (Maniglio, 2010; Powers et al., 2009) and other mental illnesses (Afifi et al., 2008; Molnar et al., 2001; Molnar et al., 2001a; Schilling et al., 2007), with many of these studies identifying gender differences in the effect size associating maltreatment and psychopathology. Nevertheless, the vast majority of these studies has focused on childhood maltreatment as a risk factor for later depression during adulthood. In contrast, there is a paucity of studies examining the relation between childhood maltreatment and adolescent depression. Findings from these studies are mixed, with some studies finding a main effect maltreatment-depression association (e.g. (Åslund et al., 2009; Sesar et al., 2011)) while others fail to find such an association (Brown et al., 1999; Cicchetti, et al., 2007). However, when interaction between genetic variation at the *5-HTTLR* locus and childhood maltreatment is assessed, specific genotypes are implicated in increased risk of depression , particularly among adolescent females (Åslund et al., 2009; Cicchetti et al., 2007), in the subset of individuals who have experience maltreatment. This heterogeneity of effect by genotype suggests that the impact of child maltreatment on adolescent depression is particularly acute among carriers of the *ss* genotype.

Although three-way interactions incorporating genetic, social (i.e. maltreatment) and macrosocial variables have not, to our knowledge, previously been reported, some parallels can be drawn to earlier findings from our own group based on the same cohort. Specifically, earlier work using the AddHealth cohort found that adolescent boys are more susceptible to macro- (i.e, county) level contextual effects on depressive symptoms than their female counterparts, who showed stronger genetic effects on their risk for depression (Uddin et al., 2010). Results of the present study confirm the findings of a main genetic effect on risk of

depressive symptoms for adolescent females, and two-way interaction models also showed a marginally significant (p=0.09) interaction whereby adolescent male carriers of the *sl* genotype, showed lower depressive symptom scores when residing in counties with high deprivation (data not shown) consistent with our earlier work (Uddin et al., 2010). More importantly, the present study augments the earlier work by including an important factor known to contribute to subsequent depression, namely childhood maltreatment. Remarkably, the inclusion of this variable in the models presented here effectively negated the protective main effect of the *sl* genotype observed in females in this study and our earlier work. We have previously noted the high levels of genetic variation surrounding the *5-HTTLPR* locus in different human populations, and have suggested that different alleles and/or genotypes in this region may confer selective advantages in different environments (Uddin et al., 2010), in much the same way as the well-known sickle-cell anemia example. Results of the current study lend support to this hypothesis by demonstrating how the same genotype can, on average, reduce risk of depressive symptoms in females while at the same time increase risk among the subset of females exposed to both childhood maltreatment and adverse county-level social environments.

Findings from this work should be interpreted in light of a number of limitations. The primary limitation of this study is the possibility of information bias. Reports of childhood maltreatment were collected retrospectively and may thus be under reported due to recall difficulties. However, the AddHealth study was specifically designed to collect this potentially sensitive information during adulthood, at a time when most participants would no longer be subject to the care of the potential perpetrator of the maltreatment; this limitation was thus unavoidable. In addition, longitudinal research suggests that adult recall of physical and sexual abuse during childhood may actually underestimate the prevalence of childhood maltreatment (Widom & Kuhns, 1996; Widom et al., 1999). Furthermore, and again because of our reliance on secondary data analysis, we were unable to assess the role of an additional common genetic variation at the *5-HTTLPR* locus in which a single nucleotide polymorphism renders the *l* allele more functionally similar to the *s* allele (Uddin et al., 2010). Our reliance on the two *5-HTTLPR* alleles genotyped by AddHealth, however, would likely have biased our results toward the null.

Strengths of our study include the use of a dataset that allowed an assessment of "E" at multiple levels (i.e. adverse experiences and county-level social environment) and that also provided genetic data, allowing us to test three-way interactions defined at multiple levels. An additional strength was the longitudinal design of our investigation, which assessed depressive symptoms across a one-year time frame and excluded individuals who relocated to different counties during this time frame. This approach enhances our ability to make causal inferences regarding the influence of genetic variation, maltreatment, and county level social environment on depressive symptoms in this study population. Furthermore, our study controlled for the family-level analog (parental receipt of public assistance) of our macrosocial predictor of interest, county-level public assistance/deprivation. Our findings are thus less likely to be attributable to confounding by factors more proximal to the individual. Finally, by conducting our analyses stratified by gender, our study was able to detect important differences in the factors influencing depressive symptoms in adolescent females vs. males that may have been otherwise missed. These sex-specific effects render plausible that different triggers, or stressors, may be salient to depression in adolescent males and females and have implications for interventions designed to reduce risk of depressive symptoms following adverse exposures early in life.

5. Conclusion

In conclusion, we have shown that exposure to childhood maltreatment and adverse county-level social environments jointly moderate the effect of genetic variation at the *5-HTTLPR* locus on depressive symptoms in female adolescents. Female adolescents exposed to both childhood maltreatment and county-level deprivation are at significantly increased risk of higher depressive symptom scores if they possess the *sl* or *ss* genotypes at the *5-HTTLPR* locus. Future work should aim to replicate these findings in additional adolescent cohorts, and to understand how factors operating at multiple levels—biologic, social, and macrosocial—interact to shape risk for mental illness in ways that may differ between genders.

6. Acknowledgements

This research uses data from Add Health, a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill, and funded by grant P01-HD31921 from the Eunice Kennedy Shriver NICHD with cooperative funding from 23 other federal agencies and foundations. Special acknowledgment is due Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Information on how to obtain the Add Health data files is available on the Add Health website (http://www.cpc.unc.edu/addhealth). No direct support was received from grant P01-HD31921 for this analysis. The authors would like to thank Drs. Sandro Galea and Karestan Koenen for helpful comments and discussions regarding this work. This work was supported by NIH grants DA022720, DA022720-S1 and RC1 MH088283-01.

7. References

Afifi, T.O., Enns, M.W., Cox, B.J., Asmundson, G.J., Stein, M.B & Sareen, J. (2008). Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. *American Journal of Public Health*, Vol.98, (May 2008), pp. 946-952, ISSN 1541-0048

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders DSM-IV-TR Fourth Edition (Text Revision)*, ISBN-10: 0890420254 Washington, DC

Åslund, C., Leppert, J., Comasco, E., Nordquist, N., Oreland, L. & Nilsson, K. (2009). Impact of the Interaction Between the 5HTTLPR Polymorphism and Maltreatment on Adolescent Depression. A Population-Based Study. *Behavior genetics,* Vol.39, No.5, (July 2009), pp. 524-531, ISSN 1573-3297

Brown, J., Cohen, P., Johnson, J.G. & Smailes, E.M. (1999). Childhood abuse and neglect: specificity of effects on adolescent and young adult depression and suicidality. *Journal of the American Academy of Child & Adolescent Psychiatry*, Vol.38, No.12, (December 1999), pp. 1490-1496, ISSN 1527-5418

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A & Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*, Vol.301, No. 5631, (July 2003), pp. 386-389, ISSN 0036-8075

Chipman, P., Jorm, A.F., Prior, M., Sanson, A., Smart, D., Tan, X & Easteal, S. (2007). No interaction between the serotonin transporter polymorphism (5-HTTLPR) and childhood adversity or recent stressful life events on symptoms of depression: results from two community surveys. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, Vol.144B, No.4, (June 2007), pp. 561-565, ISSN: 1552-4841

Cicchetti, D., Rogosch, F.A. & Sturge-Apple, M.L. (2007). Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: depressive symptomatology among adolescents from low socioeconomic status backgrounds. *Development and Psychopathology*, Vol.19, No.19, (2007), pp. 1161-1180, ISSN 0954-5794

Druss, B.G., Hwang, I., Petukhova, M., Sampson, N.A., Wang, P.S & Kessler, R.C. (2009). Impairment in role functioning in mental and chronic medical disorders in the United States: results from the National Comorbidity Survey Replication. *Molecular Psychiatry,* Vol.14, (Febuary 2008), pp. 728-737, ISSN 1359-4184

Eley, T.C., Sugden, K., Corsico, A., Gregory, A.M., Sham, P., McGuffin, P., Plomin, R & Craig, I.W. (2004). Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry,* Vol.9, (July 2004), pp. 908-915, ISSN 1359-4184

Greenberg, P.E., Kessler, R.C., Birnbaum, H.G., Leong, S.A., Lowe, S.W., Berglund, P.A & Corey-Lisle, P.K. (2003). The economic burden of depression in the United States: how did it change between 1990 and 2000? *The Journal of clinical psychiatry,* Vol.64, No.12, (December 2003), pp. 1465-1475, ISSN 0160-6689

Guo, G. & Wang, J. (2002). The mixed or multilevel model for behavior genetic analysis. *Behavior genetics,* Vol.32, No.3, (August 2001), pp.37-49, ISSN 1573-3297

Harris, K.M., Halpern, C.T., Smolen, A & Haberstick, B.C. (2006). The National Longitudinal Study of Adolescent Health (Add Health) twin data. *Twin research and human genetics: the official journal of the International Society for Twin Studies,* Vol.9, No.6, (December 2006), pp. 988-997, ISSN 1832-4274

Harris, K.M. (2008). The National Longitudinal Study of Adolescent Health (Add Health), Waves I & II, 1994–1996, Wave III, 2001–2002 [machine-readable data file and documentation], in. Edited by. Chapell Hill, NC, Carolina Population Center, University of North Carolina at Chapel Hill., 2008.

Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D & Lesch, K.P. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry*, Vol.66, No.6, (June 1996), pp. 2621-2624, ISSN 1471-4159

Karg, K., Burmeister, M., Shedden, K & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Archives of General Psychiatry*, Vol.68, (May 2011), pp. 444-454, ISSN 0003-990x

Kaufman, J., Yang, B.Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J.H & Gelernter, J. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.10, No.49, (December 2004), pp. 17316-17321, ISSN 0027-8424

Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R & Walters, E.E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry,* Vol.62, No.6, (June 2005), pp. 617-627, ISSN 0003-990X

Kessler, R.C & Wang, P.S. (2008). The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annual Review of Public Health* Vol.29, (April 2008), pp. 115-129, ISSN 0163-7525

Koenen, K.C., Aiello, A.E., Bakshis, E., Amstadter, A.B., Ruggiero, K.J., Acierno, R., Kilpatrick, D.G., Gelernter, J & Galea, S. (2009). Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. *American Journal of Epidemiology*, Vol.169, (Febuary 2009), pp. 704-711, ISSN 0002-9262

Koenen, K.C. & Galea, S. (2009). Gene-Environment Interactions and Depression. *JAMA: The Journal of the American Medical Association*, Vol.302, No.5, (August 2011), pp. 1859-1862, ISSN 0098-7484

Koenen, K.C., Uddin, M., Amstadter, A.B & Galea, S. (2010). Incorporating the social environment in genotype environment interaction studies of mental disorders. *International journal of clinical practice*,Vol.64, No.11, (October 2010), pp. 1489–1492, ISSN 1368-5031

Kohout, F.J., Berkman, L.F., Evans, D.A & Cornoni-Huntley, J. (1993). Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *Journal of Aging & Health*, Vol.5, No.2, (May 1993), pp. 179-193, ISSN 0898-2643

Laucht, M., Treutlein, J., Blomeyer, D., Buchmann, A.F., Schmid, B., Becker, K., Zimmermann, U.S., Schmidt, M.H., Esser, G., Rietschel, M & Banaschewski, T. (2009). Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: evidence from a high-risk community sample of young adults. *The international journal of neuropsychopharmacology*, Vol.12, (January 2009), pp. 737-747, ISSN 1461-1457

Lopez-Leon, S., Janssens, A.C., Gonzalez-Zuloeta Ladd, A.M., Del-Favero, J., Claes, S.J., Oostra, B.A & van Duijn, C.M. (2008). Meta-analyses of genetic studies on major depressive disorder. *Molecular psychiatry,* Vol.13, (October 2007), pp. 772-785, ISSN 1476-5578

Lotrich, F.E & Lenze, E. (2009). Gene-Environment Interactions and Depression. *JAMA: The Journal of the American Medical Association,* Vol.302, (2009), pp. 1859a-1862, ISSN 1368-5031

Lupien, S.J., McEwen, B.S., Gunnar, M.R & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, Vol.10, (June 2009), pp. 434-445, ISSN 1471-0048

Maniglio, R. (2010). Child sexual abuse in the etiology of depression: A systematic review of reviews. *Depression and anxiety*, Vol.27, (2010), pp. 631-642, ISSN 1091-4269

Moffitt, T.E., Caspi, A & Rutter, M. (2005). Strategy for investigating interactiosn between measured genes and measured environments. *Archives of general psychiatry,* Vol.62, (2005), pp. 473-481, ISSN 1538-3636

Molnar, B.E., Berkman, L.F & Buka, S.L. Psychopathology, childhood sexual abuse and other childhood adversities: relative links to subsequent suicidal behaviour in the US. *Psychological Medicine*, Vol.31, (2001), pp. 965-977, ISSN 0033-2917

Molnar, B.E., Buka, S.L & Kessler, R.C. (2001). Child sexual abuse and subsequent psychopathology: results from the National Comorbidity Survey. *American Journal of Public Health*, Vol.91, (2001), pp. 753-760, ISSN 0090-0036

Munafo, M.R., Durrant, C., Lewis, G & Flint, J. (2009). Gene X environment interactions at the serotonin transporter locus. *Biological Psychiatry,* Vol.65, (2009), pp. 211-219, ISSN 0006-3223

Powers, A., Ressler, K.J & Bradley, R.G. (2009). The protective role of friendship on the effects of childhood abuse and depression. *Depression and Anxiety*, Vol.26, (2009), pp. 46-53, ISSN 1091-4269

Radloff, L. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied psychological measurement*, Vol.1, (1977), pp. 385-401, ISSN 0146-6216

Risch, N., Herrell, R., Lehner, T., Liang, K.Y., Eaves, L., Hoh, J., Griem, A., Kovacs, M., Ott, J. & Merikangas, K.R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *The Journal of the American Medical Association*, Vol.301, (2009), pp. 2462-2471, ISSN 0098-7484

Robert, S.A. (1998). Community-level socioeconomic status effects on adult health. *Journal of health and social behavior,* Vol.39, (1998), pp. 18-37, ISSN 0022-1465

Rodriguez, S., Gaunt, TR & Day, IN. (2009). Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. *American Journal of Epidemiology*, Vol.169, No.4, (January 2009), pp. 505-514, ISSN 0002-9262

Rutter, M., Thapar, A. & Pickles, A. (2009). Gene-Environment Interactions: Biologically Valid Pathway or Artifact? *Archives of general psychiatry,* Vol.66, (2009), pp. 1287-1289, ISSN 0003-990X

Scheid, J.M., Holzman, C.B., Jones, N., Friderici, K.H., Nummy, K.A., Symonds, L.L., Sikorskii, A., Regier, M.K & Fisher, R. (2007). Depressive symptoms in mid-pregnancy, lifetime stressors and the 5-HTTLPR genotype. *Genes, Brain, and Behavior*, Vol.6, (2007), pp. 453-464, ISSN 1601-1848

Schilling, E.A,. Aseltine, R.H. Jr., & Gore S (2007). Adverse childhood experiences and mental health in young adults: a longitudinal survey. *BMC Public Health*, Vol.7, No.30, (March 2007), ISSN 1471-2458

Schwahn, C. & Grabe, H.J. (2009). Gene-Environment Interactions and Depression. *The Journal of the American Medical Association,* Vol.302, (2009), pp.1859-b-1862, ISSN 0098-7484

Searle, S.R., Casella, G & McCulloch, C.E. (1992). *Variance components: Wiley series in probability and mathematical statistics. Applied probability and statistics*. ISBN 0471621625, Wiley, New York

Sesar, K., Simic, N & Barisic, M. (2011). Multi-type childhood abuse, strategies of coping, and psychological adaptations in young adults. *Croatian medical journal*, Vol.51, (2011), pp. 406-416, ISSN 0353-9504

Shih, R.A., Belmonte, P.L. & Zandi, P.P. (2004). A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *International review of psychiatry*, Vol.16, (2004), pp. 260-283, ISSN 1048-0021

Sjoberg, R.L., Nilsson, K.W., Nordquist, N., Ohrvik, J., Leppert, J., Lindstrom, L. & Oreland, L. (2006). Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene. *The international journal of neuropsychopharmacology,* Vol.9, (2006), pp. 443-449, ISSN 1461-1457

Surtees, P.G., Wainwright, N.W., Willis-Owen, S.A., Luben, R., Day, N.E & Flint, J. (2006). Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. *Biological Psychiatry,* Vol.59, (2006), pp. 224-229, ISSN 0006-3223

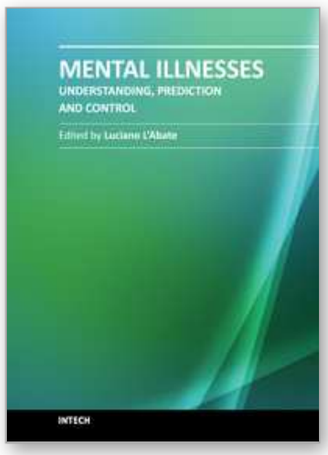
Uddin, M., Koenen, K.C., de Los Santos, R., Bakshis, E., Aiello, A.E & Galea, S. (2010). Gender differences in the genetic and environmental determinants of adolescent depression. *Depression Anxiety*, Vol.27, No.7, (July 2010), pp. 658-666, ISSN 1091-4269

Uher, R. & McGuffin, P. (2008). The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Molecular psychiatry,* Vol.13, (2008), pp. 131-146, ISSN 1359-4184

WHO. (2009). *Depression*, Available from: <http://www.who.int/mental_health/management/depression/definition/en/>

Widom, C.S. & Kuhns, J.B. (1996). Childhood victimization and subsequent risk for promiscuity, prostitution, and teenage pregnancy: A prospective study. *American Journal of Public Health*, Vol.86, (1996), pp. 1607-1612, ISSN 1541-0048

Widom, C.S., Weiler, B.L & Cottler, L.B. (1999). Childhood victimization and drug abuse: A comparison of prospective and retrospective findings. *Journal of Consulting and Clinical Psychology,* Vol.67, (1999), pp. 867-880, ISSN 0095-8891



Mental Illnesses - Understanding, Prediction and Control

Edited by Prof. Luciano LAbate

ISBN 978-953-307-662-1
Hard cover, 458 pages
Publisher InTech
Published online 05, January, 2012
Published in print edition January, 2012

In the book "Mental Illnesses - Understanding, Prediction and Control" attention is devoted to the many background factors that are present in understanding public attitudes, immigration, stigma, and competencies surrounding mental illness. Various etiological and pathogenic factors, starting with adhesion molecules at one level and ending with abuse and maltreatment in childhood and youth at another level that are related to mental illness, include personality disorders that sit between mental health and illness. If we really understand the nature of mental illness then we should be able to not only predict but perhaps even to control it irrespective of the type of mental illness in question but also the degree of severity of the illness in order to allow us to predict their long-term outcome and begin to reduce its influence and costs to society. How can we integrate theory, research evidence, and specific ways to deal with mental illness? An attempt will be made in the last conclusive chapter of this volume.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Monica Uddin, Erin Bakshis and Regina de los Santos (2012). Childhood Maltreatment and County-Level Deprivation Jointly Modify the Effect of Serotonin Transporter Promoter Genotype on Depressive Symptoms in Adolescent Girls, Mental Illnesses - Understanding, Prediction and Control, Prof. Luciano LAbate (Ed.), ISBN: 978-953-307-662-1, InTech, Available from: http://www.intechopen.com/books/mental-illnesses-understanding-prediction-and-control/childhood-maltreatment-and-county-level-deprivation-jointly-modify-the-effect-of-serotonin-transport

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen