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

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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:

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

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

7. References

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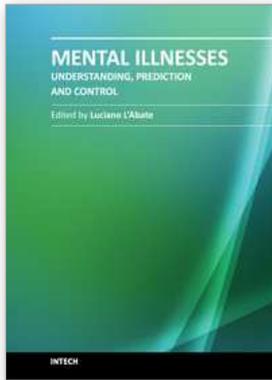
Mental Illnesses - Understanding, Prediction and Control

Edited by Prof. Luciano LAbate

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.

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