

Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene

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Abstract

Previous research has demonstrated that a polymorphism in the serotonin transporter gene (5-HTTLPR) and adverse psychosocial circumstances interact to predict depression. The purpose of the present study was to explore the extent to which sex modulates these effects. Eighty-one boys and 119 girls (16–19 years old) were interviewed about psychosocial background variables and genotyped for the 5-HTT promoter polymorphism. There were two main results. First, boys and girls carrying the short 5-HTTLPR allele react to different kinds of environmental factors. Whereas males were affected by living in public housing rather than in own owned homes and by living with separated parents, females were affected by traumatic conflicts within the family. Second, the responses of males and females carrying the short 5-HTTLPR allele to environmental stress factors go in opposite directions. Thus, whereas females tend to develop depressive symptoms, males seem to be protected from depression. The results suggest that both the molecular and the psychosocial mechanisms underlying depression may differ between boys and girls.

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Introduction

Adolescent and adult males and females differ in the extent to which they develop depression. One possible explanation for this pattern would be that a certain genotype will increase the risk for female depression but has either no or an opposite effect in males. This explanation would be in line with the suggestion that psychosocial stress confers different effects on the tendency of men and women to develop psychiatric diseases (Rutter et al., 2003). Sex differences in the tendency of an individual to develop depression in response to a dangerous and hostile environment would make sense, since different reproductive strategies are likely to be effective in men and women respectively, under such conditions (Buss and Schmitt, 1993; Buss and Shackelford, 1997).

Polymorphisms of the serotonin transporter (5-HTT) gene have, in several studies, been associated with personality and affective disorders. At least two 5-HTT polymorphisms have been identified; an insertion/deletion polymorphism in the upstream regulatory region (5-HTTLPR) (Lesch et al., 1996), and a variable number of tandem repeats (VNTR) polymorphism in the second intron (Lesch et al., 1994; Ogilvie et al., 1996). Functionality studies have shown that 5-HTT gene transcription is differentially modulated by the long and short variants of the 5-HTTLPR, where the short variant is associated with lower expression of 5-HTT and lower 5-HT re-uptake activity (Collier et al., 1996). The 5-HTTLPR polymorphism has been studied extensively in relation to personality and psychiatric disorders and a number of studies have indicated that the genotype of the 5-HTTLPR allele is associated with anxiety-related personality traits, such as neuroticism and affective disorders (Collier et al., 1996; Lesch et al., 1996; Mazzanti et al., 1998). Although not undisputed, the existence of such

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associations were recently supported by results from an overview (Van Gestel and Van Broeckhoven, 2003) and a meta-analysis (Schinka et al., 2004).

Also studies on an association between the 5-HTTLPR genotype and depressive disorders have yielded conflicting results (Lesch, 2004). Neumeister and colleagues demonstrated a higher susceptibility to depressive reactions during tryptophan depletion in women being homozygous with regard to the short 5-HTTLPR allele (Neumeister et al., 2002), and it has also been demonstrated on a sample of more than 1000 men and women that the 5-HTTLPR polymorphism interacts with psychosocial stress to predict depression (Caspi et al., 2003). However, in a modified study of this interaction on a smaller sample of adolescents, clear effects were only found when males were removed from the sample. Although the authors did not elaborate on this finding in their report, one possible explanation might be that the effect of 5-HTTLPR genotype interaction with the environment in males goes in the opposite direction in comparison with females (Eley et al., 2004). This would weaken multivariate analyses when parametrical statistics are used. Another fact, which seems to support this hypothesis, is that the result in the study by Eley et al. (2004) where 219 females were analysed, was also significant, despite a smaller sample size than in the study by Caspi et al. (2003).

Interestingly, the same polymorphism (5-HTTLPR) has also been shown to interact with suboptimal rearing conditions to predict aggressiveness and conduct disorder among adopted children, although in different directions in boys and girls. Thus, whereas the short allele seemed to be associated with more severe symptoms among boys, it showed the opposite effect among girls (Cadoret et al., 2003). It has also been shown that an orthologous polymorphism (rh5-HTTLPR) interacts with adversity among rhesus macaques in the form of peer rearing to influence adrenocorticotrophic hormone (ACTH) response to stress and, further, that this interaction is sexually dichotomous (Barr et al., 2004a).

The purpose of the present study was to explore the possibility that interactions between the 5-HTTLPR polymorphism and environmental stress go in opposite directions in males and females when depressive scores were used as phenotypic expression.

Material and methods

Subjects

All students in the ninth grade in primary school and third grade in secondary school in Västmanland, a

medium-sized county of Sweden, i.e. 2987 ninth graders and 2186 third graders, comprised the target population. The students were asked to complete the questionnaire in their classroom during a 1-h session under the supervision of a specially trained research assistant. In total there were 2611 (mean age 16.0 years) and 1649 (mean age 19.2 years) students, 87% and 75% respectively, who completed the questionnaire. All students had the opportunity to give their informed consent to participate in an in-depth interview and agree to the donation of a blood sample, by including their full personal code number on the form's front page. Informed consent was received from 785 students who could be traced with valid names. All students were classified with a risk index, depending on their risk behaviours reported in the questionnaire, and divided into four groups according to their respective risk index. Randomized samples of 400 students, matched for age, sex and risk behaviour were drawn from the volunteers. Eighty-one of the boys and 119 of the girls agreed to give blood samples and to take part in an interview when asked for informed consent a second time (in line with recommendations from the human ethical committee of the medical faculty at Uppsala University, which approved the study). The risk index showed no significant differences between the group interviewed and those responding to the initial questionnaire.

5-HTT gene analysis

Venous blood was drawn from all interviewed students for molecular genetic analyses. Two students were excluded due to hepatitis infection. DNA was extracted from venous blood and 5-HTTLPR genotyping performed essentially according to the protocol by Collier et al. (1996). In order to confirm that the correct regions the 5-HTT gene were amplified, PCR products representing all genotypes were sequenced using BigDye[®] Terminator chemistry (Applied Biosystems, Foster City, CA, USA) and analysed by an automated ABI PRISM[™] (PerkinElmer, Foster City, CA, USA). The DNA fragments were analysed using the Sequencer[™] 3.1.1 software (PerkinElmer).

Psychosocial measures

The psychosocial variables were measured by the questions: 'What type of house do you live in?'; 'How do you live, how do you like your neighbourhood?'; 'Could you describe your family?'; 'What is good with your family, your mother/father and siblings?'; 'What is not so good with your family?'; 'How was it

Table 1. Distribution of the independent variables for boys and girls with percentages for each sex and variable presented separately

	Sex	
	Boys	Girls
5-HTTLPR		
SS	19 (24%)	27 (23%)
LS	30 (38%)	60 (51%)
LL	31 (39%)	31 (26%)
Family constellation		
Nuclear family	51 (64%)	70 (59%)
Separated family	29 (36%)	49 (41%)
Type of residence		
Multi-family house	21 (28%)	30 (26%)
Owned own home	55 (72%)	87 (74%)
Family relationship		
No conflicts	48 (59%)	64 (54%)
Traumatic conflict	33 (41%)	55 (46%)
Psychosocial index		
Factors < median	44 (55%)	68 (57%)
Factors > median	36 (45%)	51 (43%)

in your family when you were seven, and thirteen?'; 'Have there ever been any tough or hard periods within your family'? All interviews were audio-taped and these tapes were used to code psychosocial variables. The responses of the participants to these questions of psychosocial variables were then combined and transformed from a 'qualitative' to a 'quantitative' dichotomous measure, comprising the psychosocial variables 'type of residence' (owned own homes/multi-family houses), 'separated families' (nuclear family/separated parents), 'traumatic conflicts within the family' (yes/no). Furthermore, open questions of socioeconomic measures were asked and coded as dichotomies; parental education (<10 years/ \geq 10 years), parental occupation (both employed/one or both unemployed) and family economy (good/stretched). The dichotomous psychosocial variables (fathers' and mothers' education, parental occupation, family economy, quality of family relationships and traumatic conflicts within the family were merged into an index and then dichotomized to psychosocial risk (no and one risk/ two or more risks).

Depression symptoms and depression

Three years after the initial questionnaire and interviews an additional questionnaire was mailed to the

participants. Of the initial study population 66 out of 81 boys and 114 out of 119 girls answered, at that time being 19 and 22 years of age. A self-rating scale [Depression Self-Rating Scale (DSRS)] of the DSM-IV (A-criterion) for major depression was used. A sensitivity of 96.1% and a specificity of 59.4% for major depression have been reported using this scale (Svanborg and Ekselius, 2003). The depressive symptom index was calculated as a summation of symptoms reported in the scale. One symptom was only counted once. Thus, for example on the third criterion of significant weight loss or gain, the participants could only score once even if they had experienced both weight loss and weight gain during the latest 2 wk.

Statistical analysis

Because of the skewed distribution of the dependent variable depressive symptoms, a non-parametric test for interactions, based on aligned ranks (program written in FORTRAN) was applied. Briefly, this test is based on the joint ranking of all observations after removing the effect of the factors 5-HTTLPR gene and other independent variables (Type of residence, Separated family, Traumatic conflicts and Psychosocial risk index – dichotomized) in each model. Suitably normalized, the weighted sum of squared differences between the subcategories mean rank (each combination of 5-HTTLPR gene and psychosocial variables) and the total mean rank will be approximately *F* distributed (Öhrvik, 2002). To describe the gene and psychosocial effects we used the Hodges–Lehmann (H–L) estimator, which is the median of the pairwise means of the observations. It is known to have very good robustness properties (see Hampel, 1974).

Results

The genotype frequencies for males were 19 (24%) (short/short), 30 (37%) (short/long) and 31 (39%) (long/long) and for females 27 (23%) (short/short), 60 (51%) (short/long) and 31 (26%) (long/long). The genotype frequencies showed no significant difference to Hardy–Weinberg distribution. However, there was a trend ($p < 0.2$) for a skewed distribution among males between observed and expected frequencies, therefore, results with males should be regarded with some caution. One boy and one girl were excluded from the genotype analysis due to hepatitis infection. (See Table 1 for a further description of the distribution of the measurements.)

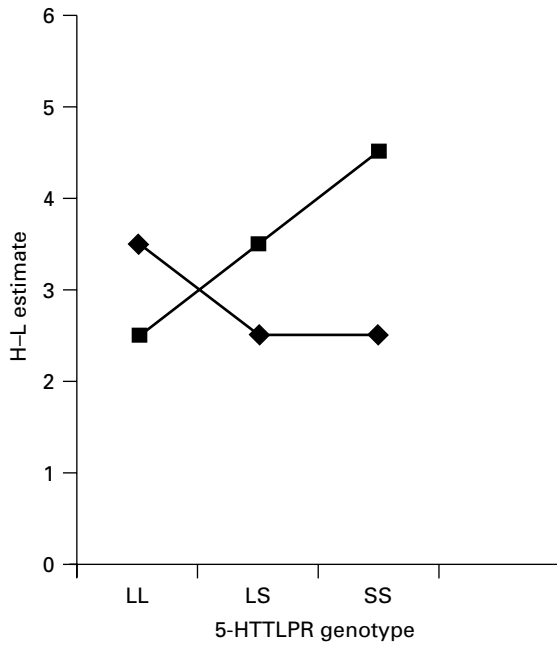


Figure 1. Effects of 5-HTTLPR genotype and conflicts within the family on depressive symptoms for girls ($p=0.019$) based on Hodges–Lehmann (H–L) estimates. –■–, Conflict; –◆–, no conflict.

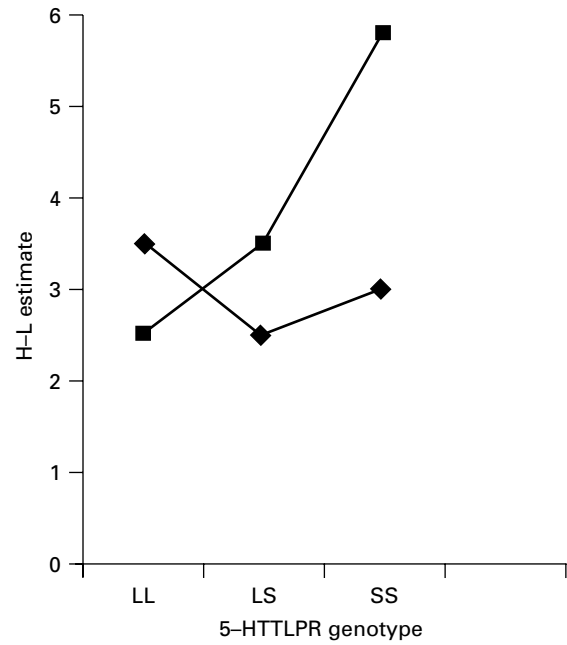


Figure 2. Effects of 5-HTTLPR genotype and psychosocial risk on depressive symptoms for girls ($p=0.018$) based on Hodges–Lehmann (H–L) estimates. –■–, Risk; –◆–, no risk.

Table 2. Results from non-parametric test of interaction in relation to depressive symptoms

Interaction effect		Depression (DSRS) p value
Boys and girls		
Sex	Psychosocial index*	0.004
Sex	5-HTT	0.0003
5-HTT	Type of residence	0.106
5-HTT	Separated families	0.106
5-HTT	Traumatic conflicts	0.019
5-HTT	Psychosocial index	0.004
Boys		
5-HTT	Type of residence	0.0016
5-HTT	Separated families	0.0016
5-HTT	Traumatic conflicts	0.211
5-HTT	Psychosocial index*	0.032
Girls		
5-HTT	Type of residence	0.265
5-HTT	Separated families	0.121
5-HTT	Traumatic conflicts	0.002
5-HTT	Psychosocial index*	0.018

DSRS, Depression Self-Rating Scale.

* Replication of index from Caspi et al. (2003) and Eley et al. (2004).

Probability values from the non-parametric test of interactions are presented in Table 2. H–L estimates (describing the central tendencies of each subgroup included in the non-parametric test) are found in Table 3. Figures 1–4 are based on the H–L estimates.

We found that there was a significant gene–sex interaction in relation to depression. We also found a significant interaction effect of sex and the dichotomized psychosocial risk index. Similarly, the 5-HTTLPR genotype interacted significantly with traumatic conflicts within the family and the dichotomized psychosocial risk index in relation to depressive symptoms, when the boys and girls were analysed in the same model.

Among boys, the psychosocial variables type of residence and separated families interacted significantly with the 5-HTTLPR genotype in relation to depressive symptoms, whereas traumatic conflicts within the family and the dichotomized psychosocial risk index showed no such relationship. Among girls, there was no significant interaction between 5-HTTLPR genotype and type of residence or separated families in relation to depressive symptoms, whereas traumatic conflicts within the family and the dichotomized psychosocial risk index showed such an interaction.

Table 3. Hodges–Lehmann estimates of depressive symptoms of each subgroup included in the non-parametric test of interaction in Table 2

	Social index		
	No risk	Risk	
Sex			
Boys	1.5	2.5	
Girls	3.0	3.0	
	5-HTTLPR		
	LL	LS	SS
Sex			
Boys	2.5	2.0	1.0
Girls	3.5	3.0	3.0
Residence			
Own home	2.5	2.5	2.5
Multi-family	3.5	3.0	3.0
Family 1			
Nuclear	2.5	2.0	2.5
Separated	3.0	3.5	2.5
Family 2			
No conflicts	3.0	2.0	2.0
Conflicts	2.5	3.0	3.5
Social index			
No risk	2.5	2.0	2.0
Risk	3.0	3.0	3.0
Boys			
Own home	2.0	2.0	0.8
Multi-family	4.0	2.0	2.5
Family 1			
Nuclear	2.0	1.5	1.0
Separated	3.5	3.0	1.0
Family 2			
No conflicts	2.5	1.8	1.0
Conflicts	2.0	2.5	0.8
Social index			
No risk	2.5	2.0	1.0
Risk	3.0	3.0	1.5
Girls			
Own home	3.0	3.0	3.5
Multi-family	3.0	3.0	3.0
Family 1			
Nuclear	3.5	2.5	3.0
Separated	3.0	3.5	3.5
Family 2			
No conflicts	3.5	2.5	2.5
Conflicts	2.5	3.5	4.5
Social index			
No risk	3.0	2.5	3.0
Risk	2.5	3.5	5.8

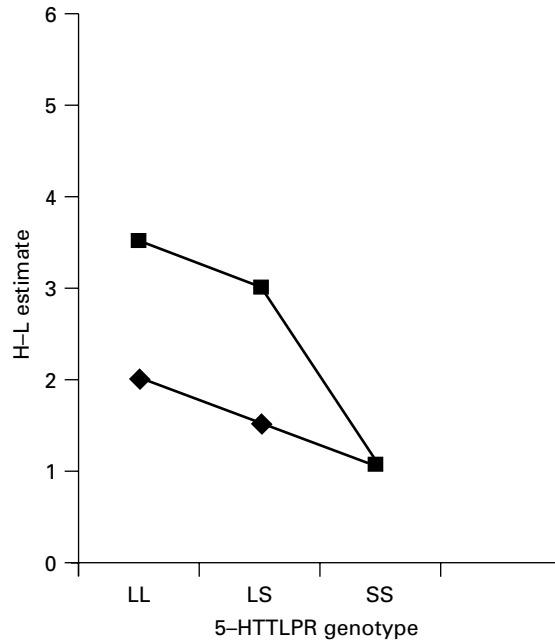


Figure 3. Effects of 5-HTTLPR genotype and parental separation on depressive symptoms for boys ($p=0.0016$) based on Hodges–Lehmann (H–L) estimates. –■–, Separation; –◆–, no separation.

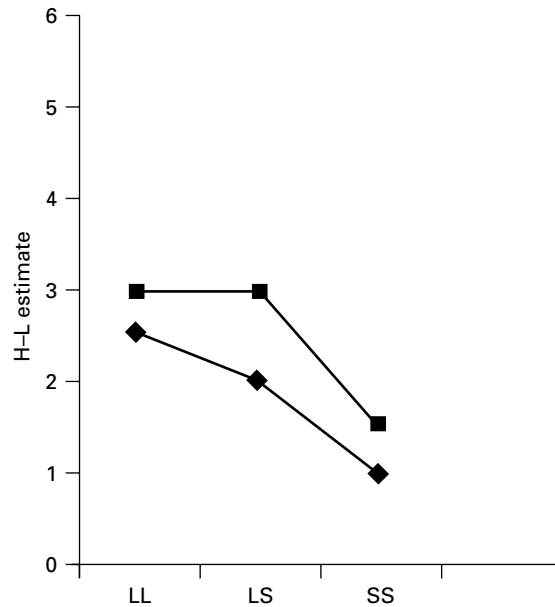


Figure 4. Effects of 5-HTTLPR genotype and psychosocial risk on depressive symptoms for boys ($p=0.032$) based on Hodges–Lehmann (H–L) estimates. –■–, Risk; –◆–, no risk.

To describe the gene and psychosocial effects we used the H–L estimator. The results of the H–L estimator calculations are shown in Table 2 and Figures 1–4. As is exemplified in Figure 1, girls with

presence of the short 5-HTTLPR allele displayed a significant increase in depressive symptoms if conflict within the family were at hand. In contrast, among boys, presence of the long 5-HTTLPR allele interacted with parental separation (Figure 3) and psychosocial risk (Figure 4) with significantly higher scores on depression.

Discussion

In the present study we investigated whether previously studied interactions between the short variant of a functional polymorphism in the serotonin transporter gene promoter region (5-HTTLPR) (Collier et al., 1996) and psychosocial risk have similar effects on depression in males and females.

The two main findings were:

- (1) Males and females carrying the short 5-HTTLPR allele respond to different environmental factors. Whereas males were negatively affected, on a significant level, by living in public housing rather than in their own owned homes and by living with separated parents, females were affected by traumatic conflicts within the family. A number of possible explanations to this finding are feasible. One possibility would be that the variables that affect males are associated with social status, while those affecting females are more associated with human relationships.
- (2) The responses of males and females carrying the short 5-HTTLPR allele to environmental stress factors go in opposite directions. Thus, whereas females tended to develop depressive symptoms, males seemed to be protected from depression. One possible explanation for this finding is that adolescent males develop other kinds of pathological behaviours, which might be regarded as a male variant of depression, but which produces inverted scores on the depression scale used. However, the results probably reflect a true difference between sex, which in turn might reflect a difference in the interaction between the 5-HTTLPR polymorphism and for example gonadal and/or adrenocortical hormones. This explanation would be consistent with previous observations that these hormones are likely to interact with both sex and depression (Brooks-Gunn and Warren, 1989; Heim et al., 2000). It is also supported by recent results obtained in a study on non-human primates, where the interaction between a 5-HTT promoter polymorphism, almost identical to that

in humans, and early adversity (mother or peer rearing) was studied in relation to ACTH and cortisol response to stress (Barr et al., 2004b). The results indicated that in particular peer-reared female animals, carrying the short 5-HTTLPR allele, exhibited increased stress-induced release of ACTH and decreased total cortisol levels. By extension, Barr et al. (2004b) suggested that human females, carrying the short 5-HTTLPR allele, could be more vulnerable to the effect of early adversity, which might underlie the increased incidence of certain stress-related disorders in women.

One important limitation of our study is that it relies primarily on self-reports. Reports regarding potentially ambiguous circumstances, such as the presence or absence of traumatic conflicts within the family, which are likely to be subject to subjective retrospective interpretations and reconstructions, should be interpreted with caution (Offer et al., 2000; Sjöberg and Lindblad, 2002; Widom et al., 1999). Thus, there is a possibility that traumatic conflicts are not significantly contributing to the development of depression in girls carrying the short allele of the 5-HTTLPR polymorphism, but rather that these girls have a greater vulnerability to become depressed and, as a consequence of the depression, report differently.

Another limitation is the small sample size which leads to a low power and ability to detect both significant differences and similarities.

Various explanations to the difference between sex with regard to incidence of depression are possible (see Introduction). Thus, males and females may react differently to similar life experiences, but there may also be different genetic and molecular mechanisms behind female and male psychopathology (Rutter et al., 2003; Silberg et al., 1999). In sum, however, the results of the present study suggest that sex is of great importance for the effects of gene–environment interactions on depression as phenotypic expression, at least when the 5-HTT genotype is taken into account.

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Statement of Interest

None.

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