A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: Interaction with adverse childhood environment

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Abstract

Although attention-deficit/hyperactivity disorder (ADHD) is highly heritable, environmental conditions play an important role in its manifestation during childhood development. Here, we report the results of an investigation on the interaction of adverse childhood environment with a functional polymorphism of the serotonin transporter promoter gene (5-HTTLPR) and its impact on ADHD psychopathology in young adult delinquents. Standardized instruments were used to assess childhood and current ADHD and adverse childhood environment in 184 male delinquents. Each subject was genotyped for 5-HTTLPR long (L) and small (S) alleles. Logistic regression analysis revealed independent effects of high childhood environmental adversity and the 5-HTTLPR LL-genotype on self-reported childhood ADHD and on persistent ADHD. In addition, a significant gene by environment interaction was found, indicating that carriers of at least one 5-HTTLPR short allele are more sensitive to childhood environment adversity than carriers of the LL-genotype. The results support prior findings of association between ADHD and 5-HTTLPR LL-genotype and adverse childhood environment, and they underline the need for further investigation of gene by environment interaction with respect to ADHD.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable, chronic condition with onset in childhood. Genetic epidemiological studies indicate heritability of about 80% (Thapar et al., 1999). Up to now, only a few genome-wide linkage studies have been performed, indicating the relevance of genetic variants from several chromosomal regions for development of ADHD (Smalley et al., 2002; Bakker et al., 2003; Ogdie et al., 2003; Hebebrand et al., 2006). In contrast, a large number of association studies have been carried out, inspired by evidence of monoaminergic dysfunction in ADHD (Pliszka et al., 1996). A recent meta-analysis, reporting pooled odds ratios of the respective association studies, confirmed an association of ADHD with
the dopamine D4 and D5 receptor genes and the dopamine DAT1 transporter gene (Faraone et al., 2005).

In addition, there is a mounting body of evidence suggesting an association of ADHD with genes involved in the regulation of serotonergic neurotransmission. Associations have been reported regarding the serotonin-1B receptor gene (Hawi et al., 2002) and the tryptophan hydroxylase 2 gene (Sheehan et al., 2005; Walitza et al., 2005). Independent replicated associations have been reported regarding ADHD and the long allele of the serotonin transporter (5-HTT) gene, which was confirmed by a recent meta-analysis (Faraone et al., 2005).

The human 5-HTT gene is located on chromosome 17q11.2. A 44-bp insertion/deletion polymorphism in the promoter of the 5-HTT gene (5-HTTLPR) has been identified that modifies the transcription rate of the gene (Lesch et al., 1996; Greenberg et al., 1999). The short allelic variant has been shown to result in diminished 5-HT levels and reduced serotonin (5-HT) reuptake into human platelets. Association of the long (L) 5-HTTLPR allele and the long/long (LL)-genotype with ADHD has been demonstrated by different groups in population- and family-based case-control studies (Manor et al., 2001; Seeger et al., 2001; Zoroglu et al., 2002; Beitchman et al., 2003) and quantitative trait loci approaches (Retz et al., 2002; Curran et al., 2005). Kent et al. (2002) found a small but significant association when they analysed pooled data from three recent studies, but not in their own study. Other studies similarly did not replicate the association of ADHD with the 5-HTTLPR long allelic variant (Johann et al., 2003; Langley et al., 2003).

Besides genetic risk factors, twin studies on ADHD additionally suggest some influence of shared and non-shared environmental risk factors in ADHD (Thapar et al., 1999, 2001). Several longitudinal epidemiologic studies assessed psychosocial environmental factors including family conflict, child maltreatment, social class, family size, maternal psychopathology, and paternal criminality as risk factors for child psychopathology (Blanz et al., 1991; Fergusson et al., 1996; Rutter, 1999). Recent studies confirmed these risk factors, particularly for ADHD (Biederman et al., 1995). Furthermore, differential effects of these environmental risk factors were found in boys and girls. Boys were more vulnerable to environmental adversity than girls (Biederman et al., 2002).

Regarding the interaction of genetic and environmental risk factors in psychiatric disorders, recent studies suggest that the association of 5-HTTLPR with behavioral phenotypes and certain disease states may depend on environmental influences and individual life-history experiences (Barr et al., 2003; Caspi et al., 2003; Fox et al., 2005; Sjöberg et al., 2006). They also indicate that genetic regulation of serotonergic neurotransmission may be sensitive to environmental influences (Bennett et al., 2002; Manuck et al., 2004).

Based on the findings of previous studies, the present study aimed to confirm the link between allelic 5-HTTLPR variations and ADHD psychopathology in childhood and persistent ADHD in adulthood. In addition, we hypothesized that developmental influences of an adverse psychosocial environment would modulate the association between 5-HTTLPR and ADHD in childhood and persistent ADHD.

2. Method

2.1. Subjects

A sample of 184 unrelated males (age 34.1 years, S.D. 11.7 years), consecutively referred for psychiatric examination to the Institute of Forensic Psychiatry of the Saarland University, entered the study after providing written informed consent and explanation of the aims of the study. Non-Caucasians and non-German-speaking subjects were not included. The study was approved by the local Ethical Committee.

2.2. Instruments

All subjects underwent a semi-structured psychiatric interview by well-trained psychiatrists and a neurological examination. Psychiatric comorbidity was assessed according to ICD-10 criteria, using modified, standardized checklists (Hiller et al., 1990) by well-trained psychiatrists. Subjects with a diagnosis of current substance dependence, acute schizophrenia, major depression/bipolar disorder, or any other severe Axis-I diagnosis according to DSM-IV as well as subjects with the diagnosis of mental retardation (IQ<70) were excluded from the study.

Childhood ADHD symptomatology was assessed by the German version of the Wender Utah Rating Scale (WURS-k). This self-report instrument consists of 25 items reporting symptoms associated with childhood ADHD (Retz-Junginger et al., 2002). A cut-off score of 30 points has been shown to differentiate male individuals with ADHD from controls with a sensitivity of 85% and specificity of 76% (Retz-Junginger et al., 2003). Current ADHD was assessed by the ADHD-DC, which is a standardized instrument for the clinical rating of current ADHD symptoms (Rösler et al., 2004). Individuals with persistent ADHD had to have WURS-k scores ≥30 and had to meet DSM-IV criteria for current ADHD.
Childhood environmental risk factors were rated by an independent investigator (D.W.), who was unaware of diagnostic status and genotype. The following childhood risk factors were assessed for each individual with regard to his first 10 years of life: social status of the family (financial problems, unemployment, social welfare), family structure (institutional care, changing caregivers, frequent separation from family), emotional family climate (experiences of violence, delinquency, chronic conflicts), social integration (no friends, hanging around, no stable interests/clubs) and school education (suspensions, no qualifications, dropouts). The items were graded with 0–2 points, with higher ratings indicating worse environmental conditions. A mean score of adverse childhood environment was calculated for each subject, giving a total adverse environment index of 0 (optimal childhood environment) to 2 (most adverse childhood environment). The index was not calculated when more than two items could not be rated due to lacking or unreliable information.

2.3. Genotyping

Polymorphisms in the promoter region of the 5-HT transporter gene were determined after extraction of genomic DNA from venous blood samples following standard procedures. DNA amplification was performed using a well-established polymerase chain reaction procedure (PCR) as described elsewhere in detail (Lesch et al., 1996). For PCR, two oligonucleotide primers flanking the polymorphic gene region were used (5′-GGC GTT GCC GCT CTG AAT GC-3′ and 5′-GAG GGA CTG AGC TGG ACA ACC A-3′). The PCR process consisted of a 5-min denaturation step at 94 °C, 40 cycles of 30-s denaturation at 94 °C, 30-s annealing at 63 °C and 60-s extension at 72 °C and a final 10-min extension step at 72 °C. PCR products were separated by electrophoresis in a 3% agarose gel stained with ethidium bromide and visualised by UV transillumination. The different bands for the long and the short allele were defined by specific bands.

2.4. Statistics

Descriptive data of the subjects with WURS-k scores <30 and ≥30 were compared by independent sample t-tests and $\chi^2$-tests. Similarly, the rate of persistent ADHD in individuals with high (≥0.4) and low (<0.4) childhood adverse environment index (CAEI) scores by genotype were compared by $\chi^2$-tests.

To analyse the impact of the 5-HTTLPR and childhood environmental risk factors on ADHD in childhood, the dependent measure of interest (childhood ADHD symptoms rated by WURS-k) was dichotomised into ADHD present (WURS-k ≥30) and ADHD not present (WURS-k <30). WURS-k scores were only analysed in this dichotomised version and not as a continuous outcome measure because they were not normally distributed in this sample. Persistent ADHD as the second outcome measure of interest was defined as mentioned above. Based on the assessment of the differential functional effects of the 5-HTTLPR short allele in vitro and in vivo, the SS- and SL-genotypes were combined and compared with the LL-genotype (Lesch et al., 1996; Bennett et al., 2002). Logistic regression analyses with childhood ADHD and persistent ADHD as dependent variables and the following independent measures of interest were performed: the dichotomised 5-HTTLPR, the childhood adverse environmental index (CAEI) and an interaction term of both predictive variables. Age differences were adjusted for by adding age (in years) as independent covariate to the model.

As CAEI values of 10 individuals (8 with WURS-k ≥30) were missing, the results of the analysis in the 174 individuals without missing data were compared with analyses in all 184 individuals, with three different methods of implementation of the missing CAEI values: (1) the CAEI was set to 0.0; (2) the CAEI was set to 0.4 (median); (3) the CAEI was set to the mean of 0.79 for individuals with WURS-k ≥30 and to the mean of 0.37 for individuals with WURS-k <30.

Statistical analyses were performed by the SAS statistical package (SAS/STAT, version 8.2, SAS Institute Inc., Cary, NC, 1999). The Hardy-Weinberg equilibrium of the 5-HTTLPR was assessed by the program FINETTI (TF Wienker, personal communication).

3. Results

3.1. Description of the sample

The mean age of the entire study population was 34.1 years (S.D. 11.7 years). Demographic data show typical features of a delinquent sample with poor school education (no regular school education: 12.9%; ≤9 years of education: 70.6%; >9 years of education: 16.6%), low rate of vocational training (49.5%) and low marital status (single: 56.1%; divorced: 23.8%; married: 20.1%). The rate of prior convictions was 49.7%. Criminal offenses comprised a wide spectrum: The most frequent (>5%) were sexual offenses (15.8%), physical injury (15.2%), property offenses (13.0%), robbery (9.2%), homicide (8.2%), fraud (6.0%), and drug offenses (5.4%). Further descriptive data of the 184 male subjects are found in
The 105 subjects with a WURS-k score below 30, indicating no history of ADHD in childhood, are compared with the 79 subjects with a WURS-k score ≥30, indicating a history of ADHD in childhood. As expected, current and childhood ADHD symptoms were highly prevalent in this forensic study population. The mean WURS-k score of the entire group was 27.1 (S.D. 12.5), respectively. No difference was found for history of any substance use disorders and personality disorders were present in 27.2%, personality disorders were present in 27.2%, personality disorders of clusters A and C in 7.6% of the sample. Cluster B personality disorders were the most prevalent psychiatric lifetime diagnoses according to DSM-IV criteria in this forensic sample. Cluster B personality disorders were present in 27.2%, personality disorders of clusters A and C in 7.6% of the sample. Other psychiatric lifetime diagnoses were less frequent and comprised a history of psychotic disorder (8.2%), paraphilia (4.5%), affective disorder (2.2%), neurotic disorder and disorder of impulse control (3.8%). Childhood environmental risk factors were far more prevalent in the subjects with childhood ADHD than in the subjects without childhood ADHD (t-test, t = −4.7, df = 120, P < 0.0001). No difference was found for history of any personality disorder, history of antisocial personality disorder in particular or for history of substance abuse disorder. Individuals with childhood ADHD were younger than individuals without (t-test, t = 4.2, DF = 181, P < 0.0001); therefore, age was controlled for in further analyses.

The 5-HTTLPR genotypes were in Hardy–Weinberg equilibrium. Genotype frequencies of the entire study population were as follows: LL: N = 61 (33.2%), SL: N = 90 (48.9%) and SS: N = 33 (17.9%). Allele frequencies were 156/368 (42.4%) for the S-allele and 212/368 (57.6%) for the L-allele.

### Risk factor analysis

Risk factor analysis for childhood ADHD was first performed in the 174 subjects with complete data. In the final model 5-HTTLPR (OR 4.1, 95%-confidence interval 1.5–10.9, $\chi^2 = 7.9$, (df), $P = 0.005$) and childhood environmental risk factors (OR 5.4, 95%-confidence interval 2.3–12.5, $\chi^2 = 15.3$, (df), $P = <0.0001$) independently increased the risk of ADHD in childhood. Further, an interaction of 5-HTTLPR and environmental risk factors in childhood was found (logistic regression, $\chi^2 = 4.1$, (df), $P = 0.04$). The final model correctly predicted 76.3% of the individuals with ADHD in childhood. Results remained stable but did not improve the model when diagnoses of antisocial personality disorder and substance use disorders were included into regression analysis in order to control for antisocial severity.

### Table 1

<table>
<thead>
<tr>
<th>Childhood ADHD</th>
<th>Age at assessment (Mean S.D.)</th>
<th>Persistent ADHD N (%)</th>
<th>Any personality disorder N (%)</th>
<th>Antisocial personality disorder N (%)</th>
<th>Substance use disorder N (%)</th>
<th>Child development environment index Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present (WURS-k ≥30) N=79</td>
<td>30.2 (9.9)</td>
<td>38 (48.1)</td>
<td>32 (40.5)</td>
<td>14 (17.7)</td>
<td>38 (48.1)</td>
<td>0.79 (0.65)</td>
</tr>
<tr>
<td>Not present (WURS-k &lt;30) N=105</td>
<td>37.0 (12.2)</td>
<td>0 (0.0)</td>
<td>32 (30.5)</td>
<td>16 (15.2)</td>
<td>43 (41.0)</td>
<td>0.37 (0.48)</td>
</tr>
</tbody>
</table>

$t$: t-statistic; $\chi^2$: $\chi^2$-statistic; $df$: degrees of freedom; S.D.: standard deviation, N: number of subjects, %: percentage.

* Data obtained from 174 subjects.

### Table 2

Influence of genotype and childhood adverse environment on childhood ADHD

<table>
<thead>
<tr>
<th>Risk factors**</th>
<th>WURS-k ≥30 versus WURS-k &lt;30*</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate (SE), Wald $\chi^2$, DF, $P$-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTTLPR: LL versus SS + SL</td>
<td>1.5 (0.5), $\chi^2 = 7.9$, (df), $P = 0.005$</td>
<td>4.1 (1.5–10.9)</td>
</tr>
<tr>
<td>Childhood adverse environment index</td>
<td>1.6 (0.4), $\chi^2 = 15.3$, (df), $P = &lt;0.0001$</td>
<td>5.4 (2.3–12.5)</td>
</tr>
<tr>
<td>5-HTTLPR by childhood adverse environment index</td>
<td>$-1.2$ (0.6), $\chi^2 = 4.1$, (1), $P = 0.044$</td>
<td>0.3 (0.01–0.97)</td>
</tr>
</tbody>
</table>

$df$: degrees of freedom; SE: standard error.

* Model with adjustment for age differences.
** Model $df=4$; Error $df=179$. 
The results of the model with 174 individuals were compared with results of three models with differentially implemented values for the missing CAEI data. Results of the four models were very similar (data not shown), with the 5-HTTLPR, the CAEI and an interaction of both risk factors influencing the rate of childhood ADHD independently in each model. In Table 2, results of the semi-conservative model setting the missing CAEI measures to 0.4 (median) are shown. Similar results were obtained for individuals with persistent ADHD. Again, the four models regarding the implementation of the CAEI showed comparable results (data not shown). In Table 3, results of the semi-conservative model setting the missing CAEI measures to 0.4 (median) are shown. The model correctly predicted persistent ADHD in 70.7%.

To further elucidate the interaction effect found in the logistic regression model, subjects with a history of childhood ADHD and subjects with persistent ADHD were compared regarding genotype and environmental risk factors (Table 4 and Fig. 1). Missing CAEI measures again were set to 0.4 (median). For the LL genotype, a high childhood adverse environment index did not increase the rate of childhood or persistent ADHD, whereas for the SS+SL genotypes, a strong effect of childhood adverse environment on the rate of ADHD was present. Regarding the 5-HTTLPR as risk factor, it can be seen from Table 4 that in individuals with low CAEI values, however, the LL genotype was associated with far higher rates of ADHD than the SL and SS genotypes.

### Table 3
Influence of genotype and childhood adverse environment on persistent ADHD

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Persistent ADHD *</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (SE),</td>
<td>(95% confidence interval)</td>
</tr>
<tr>
<td></td>
<td>Wald $\chi^2$, $df$, $P$-value</td>
<td></td>
</tr>
<tr>
<td>5-HTTLPR: LL versus SS+SL</td>
<td>1.2 (0.6), $\chi^2=4.0$, (1), $P=0.047$</td>
<td>3.2 (1.0–10.0)</td>
</tr>
<tr>
<td>Childhood adverse environment index</td>
<td>1.2 (0.4), $\chi^2=8.4$, (1), $P=0.004$</td>
<td>3.3 (1.5–7.8)</td>
</tr>
<tr>
<td>5-HTTLPR by childhood adverse environment index</td>
<td>$-1.6 (0.7)$, $\chi^2=5.0$, (1), $P=0.025$</td>
<td>0.2 (0.01–0.77)</td>
</tr>
</tbody>
</table>

* df: Degree of freedom; SE: standard error.

### Table 4
Childhood and persistent ADHD by genotype and childhood adverse environment index

<table>
<thead>
<tr>
<th></th>
<th>Low childhood environmental risk factors (index &lt;0.4)</th>
<th>High childhood environmental risk factors (index ≥0.4)</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of individuals with ADHD</td>
<td>Number of individuals with ADHD</td>
<td>$\chi^2$ ($df$)</td>
</tr>
<tr>
<td><strong>Childhood ADHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTTLPR: LL</td>
<td>13/29 (44.8)</td>
<td>19/32 (59.4)</td>
<td>$\chi^2=1.3$, (1)</td>
</tr>
<tr>
<td>5-HTTLPR: SL+SS</td>
<td>5/52 (9.6)</td>
<td>42/71 (59.2)</td>
<td>$\chi^2=31.2$, (1)</td>
</tr>
<tr>
<td><strong>Persistent ADHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HTTLPR: LL</td>
<td>5/29 (17.2)</td>
<td>8/32 (25.0)</td>
<td>$\chi^2=0.5$, (1)</td>
</tr>
<tr>
<td>5-HTTLPR: SL+SS</td>
<td>2/52 (3.9)</td>
<td>23/71 (32.4)</td>
<td>$\chi^2=15.1$, (1)</td>
</tr>
</tbody>
</table>

CAEI: Childhood adverse environment index.

### 4. Discussion

Despite strong evidence of the contribution of environmental risk factors in addition to genetic risk factors to the development of ADHD, to date there is a lack of systematic investigations concerning the evaluation of gene by environment interactions regarding ADHD etiology. In this study we (1) found evidence supporting prior findings of an association of the ADHD phenotype with the long allele of the 5-HTTLPR (Manor et al., 2001; Seeger et al., 2001; Kent et al., 2002; Retz et al., 2002; Zoroglu et al., 2002) and (2) demonstrated a significant impact of adverse childhood environment on childhood ADHD symptoms, which has been suggested in several previous studies (Biederman et al., 1995, 2002).
We further elicited an interaction between the 5-HTTLPR and adverse childhood environment. Analysis of this interaction showed that the rate of childhood ADHD in carriers of the LL-genotype was only slightly increased in high compared with low adverse childhood environment risk. With regard to carriers of the SS or SL genotype, a high childhood adverse environment index strongly increased the risk for ADHD in childhood compared to low environment risk. These results suggest that the 5-HTTLPR mediated risk for ADHD is moderated by environmental adversity and that the impact of the environment depends on an individual’s genetic background. The failure of some studies to replicate the association between ADHD and 5-HTTLPR (Kent et al., 2000; Johann et al., 2003; Langley et al., 2003) may be at least partially explained by differences in the environmental background and life experiences of the subjects under investigation.

Our finding is in agreement with experiments with 5-HTT knock-out mice, which exhibit an increased stress-responsive phenotype (Murphy et al., 2001). They also corroborate the findings of two longitudinal studies (Caspi et al., 2003; Wilhelm et al., 2006) that were able to demonstrate that the relation of stressful life events to affective disturbances is moderated by the 5-HTTLPR genotype with highest vulnerability in carriers of the SS-genotype. In our study, individuals with current affective disorder were excluded from the study, and only 2% of the assessed individuals had a history of affective disorders. Therefore, our findings are not related to depressive symptoms, but underscore the importance of gene–environment interaction with regard to the serotonin transporter gene for other psychiatric disorders. Interestingly, two recent studies (Eley et al., 2004; Sjöberg et al., 2006) found an interaction effect of the 5-HTTLPR and environmental effects with regard to depression in females only. In males, who were assessed in our study, the same genetic background and comparable environmental risk factors, therefore, might lead to differing psychopathology.

Interestingly, we did not find substantial differences concerning the role of genetic and environmental factors between subjects with lifetime ADHD and the subgroup of adults with persisting ADHD. This might suggest that serotonergic mechanisms and psychosocial adversity support the development of the ADHD phenotype, but they do not explain why ADHD core symptoms decline in some cases with age and in some others do not. Therefore, other genetic and environmental factors that might take effect at several stages of an individual’s development might be responsible for remission or persistence of ADHD with age.

In our study, male offenders were assessed. Since several lines of evidence suggest that disturbances in central serotonin function may play a role not only for ADHD but also antisocial and aggressive behavior (Lesch and Merschdorf, 2000; Retz et al., 2004), some caution should be used in generalizing the results to a non-forensic population. However, the genotype and allele frequencies found in this study correspond very well with those found in large population-based epidemiological studies (Lesch et al., 1996). Therefore, a study in a general male population might find similar results. Moreover, when we controlled statistical analysis for comorbid antisocial personality disorder, the regression model was stable, suggesting no relevant influence of this indicator for antisocial severity on the described associations.

A limitation of the study is the retrospective assessment of ADHD symptoms. Further, although each subject was interviewed carefully for psychosocial risk factors and history of ADHD by the use of standardized instruments, recall bias and invalid diagnoses due to missing information of parents or spouses cannot fully be excluded. It also should be noted that formal validation of the CAEI, which we used for assessment of childhood adversity, is still lacking. However, the criteria used in this instrument are well-documented risk factors for ADHD and also in validated rating scales (Rutter, 1999; Biederman et al., 2002). Moreover, the WURS-k is not specific for ADHD, but also comprises conduct problems, which do not correspond directly to the diagnostic criteria of ADHD. Therefore, our results might be due to the phenotype of ADHD plus conduct disorder, which is regarded as a subtype of hyperkinetic disorder according to ICD-10 (World Health Organization, 1992), rather than to pure ADHD. However, no differences in the rate of personality disorders between subjects with high and low WURS-k scores were found in our study. Similarly, Seeger et al. (2001), using a case-control study design, demonstrated a stronger association of the LL-genotype with hyperkinetic disorder (HD) without comorbid conduct disorder (CD) compared with HD with CD, indicating that this association truly refers to ADHD symptomatology.

Another limitation derives from difficulties regarding the separation of effects of genetic risk factors from environmental risk factors. We cannot exclude that environmental adversity also might be a result of an individual’s behavior. Insofar as behavior is genetically influenced, which is especially true for ADHD, genetic factors also affect the liability of an individual to experience negative reactions within his or her social environment (Rutter, 2005).
Accumulating evidence suggests that serotonergic neurotransmission underlies age-dependent changes (Zhou et al., 2000) and is influenced by environmental variables (Bennett et al., 2002; Manuck et al., 2004). Moreover, the 5-HTTLPR is involved in developmental and plastic processes within the serotonergic neurotransmitter system (Lesch and Gutknecht, 2005; Hariri et al., 2006) and also in other important neurodevelopmental disorders like autism (Conroy et al., 2004). In this study we made a first step toward the elaboration of gene by environment interactions in ADHD. Further investigations are required to elucidate the mechanisms of gene by environment interaction regarding serotonergic function and ADHD psychopathology. Much more research is needed regarding multiple gene by gene and gene by environment interactions in large populations, since multiple genes and environmental conditions – psychosocial and biological – contribute to the etiology of this complex disorder. Moreover, the pleiotropic effect of the 5-HTTLPR makes it necessary to assess this polymorphism for differential influence in males and females and in different psychiatric disorders or personality traits, which co-occur with ADHD.

In summary, our data suggest that environmental adversity and genetically determined variation of serotonin transporter function are associated with ADHD-related psychopathology and that there is a substantial gene by environment interaction concerning the development of this phenotype. However, because ADHD is a complex disorder, more work is needed to further elucidate such interactions.

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