

Psychother Psychosom 2018;87:58–61
DOI: 10.1159/000484143

Childhood Trauma and Functional Variants of 5-HTTLPR Are Independently Associated with Alexithymia in 5,283 Subjects from the General Population

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Existing evidence suggests that both genetic and environmental factors contribute to the development of alexithymia. However, the composition of environmental as well as genetic factors and their putative interaction are incompletely understood.

It has been proposed that childhood trauma represents a key factor in the development of alexithymia. For example, Bermond et al. [1] found increased measures of alexithymia in a sample of women with a history of severe childhood sexual abuse, while Zlotnick et al. [2] reported that childhood physical and emotional neglect rather than abuse were associated with alexithymia. Considerably, impaired emotion regulation of alexithymia arises in response to insufficient adaptive emotional learning and disturbed early attachment to primary caregivers. Other concepts propose that alexithymia serves as a defense mechanism in subjects with a history of childhood trauma [3]. In turn, deficits in emotion regulation and elevated physiological arousal may partly explain the increased risk for mental and physical disorders associated with alexithymia [4].

The serotonin reuptake receptor gene *SLC6A4* has gained attention as a potential candidate gene associated with alexithymia. The expression and, thereby, the function of *SLC6A4* is influenced by the so-called 5-HTTLPR polymorphisms located within the promoter region. It comprises a more efficient long allele (L-allele)

and a less efficient short allele (S-allele). The S-allele is associated with less re-uptake and higher serotonin concentrations in the synaptic cleft. More recently, the 5-HTTLPR haplotype has been extended by the single nucleotide polymorphism rs25531 (*SLC6A4*-1936 A > G), which is located within the long variant of 5-HTTLPR. This led to the concept of a triallelic 5-HTTLPR polymorphism with a high-expressing L_A-allele and low-expressing S- and L_G-alleles. Studies in the field of affective disorders found evidence for interactions between the 5-HTTLPR polymorphism and environmental factors (G × E effects) [5].

Using data from 5,283 subjects (general population), we sought to investigate direct and interactional effects of childhood trauma and the 5-HTTLPR (bi- and triallelic) polymorphism on alexithymia. We hypothesized that (i) childhood trauma and (ii) the low-expressing alleles (S, L_G) of the 5-HTTLPR polymorphism are independently associated with alexithymia. Additionally, we expected (iii) childhood trauma to interact with 5-HTTLPR such that alexithymia scores are higher in subjects with a history of childhood trauma when carrying the S- or L_G-allele.

Data from the “Study of Health in Pomerania (SHIP)” were used. A detailed description of the population and examinations can be found elsewhere [6]. The 2 subsamples SHIP-LEGEND (*N* = 2,400) and SHIP-TREND (*N* = 4,420) were used. A total of 1,537 subjects with missing data were excluded. The 2 samples were investigated jointly, forming the final analytic sample of 5,283 subjects (Table 1).

Alexithymia was measured using the German version of the 20-item Toronto Alexithymia Scale (TAS-20) [7]. The Childhood Trauma Questionnaire (CTQ) was used for self-report of childhood maltreatment [8]. Lifetime diagnosis of major depressive disorder was made according to the DSM-IV.

Based on previous reports on gene expression, we classified the genotypes of 5-HTTLPR into 3 functional “triallelic” genotypes: L_AL_A = LL; L_GL_A or S L_A = SL; L_GL_G or L_GS or SS = SS [9].

Linear regression analyses with 1,000 bootstrap replicates were applied to investigate the association between the genotypes of 5-HTTLPR and childhood trauma (CTQ score, abuse, neglect) with alexithymia scores. Direct effects and 2-way G × E interactions were performed based on a model which included both main effects as well as the product term between both variables. All analyses were adjusted for age, sex, cohort, and life-time diagnosis of depression (Table 2).

Statistical analyses were performed using STATA/MP software, version 13 (StataCorp LP, College Station, TX, USA). We used unstandardized beta coefficients referred to as “B”. A B coefficient of 2.759 means an increase in TAS total score of 2.759 when the predictor changes from 0 to 1.

Childhood trauma was a strong predictor of TAS-20 scores (*p* < 0.001; B = 0.212). Neglect (*p* < 0.001; B = 3.705) showed stronger effects on TAS-20 than abuse (*p* < 0.001; B = 2.759).

The L-allele of the biallelic 5-HTTLPR polymorphism was associated with reduced TAS-20 scores (*p* = 0.022; B = −0.591). Using

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Table 1. Sample characteristics and sample comparison for SHIP-LEGEND and SHIP-TREND^a

	SHIP-LEGEND (N = 2,048)	SHIP-TREND (N = 3,235)	p value
Age, years	55 ± 14	52 ± 15	<0.001
Sex			
Male	976 (48)	1,581 (49)	0.40
Female	1,072 (52)	1,654 (51)	
TAS-20	45.0 ± 9.6	41.5 ± 9.2	<0.001
DIF	12.7 ± 4.6	10.8 ± 4.0	<0.001
DDF	11.9 ± 3.4	10.5 ± 3.4	<0.001
EOT	20.5 ± 4.2	20.1 ± 4.4	0.003
MDD lifetime	338 (17)	585 (18)	0.14
5-HTTLPR (triallelic)			
SS	420 (21)	704 (22)	0.53
SL	1,038 (51)	1,602 (50)	
LL	590 (28)	929 (28)	
5-HTTLPR (biallelic)			
SS	299 (15)	502 (16)	0.67
SL	1,000 (49)	1,559 (48)	
LL	749 (36)	1,174 (36)	
CTQ	34.1 ± 9.9	33.3 ± 9.6	0.004
Neglect ^b	285 (14)	607 (19)	<0.001
Abuse ^b	185 (9)	240 (7)	0.033

Values are *n* (%) or mean ± SD, as appropriate. CTQ, Childhood Trauma Questionnaire; TAS-20, Toronto Alexithymia Scale-20; DIF, difficulties identifying feelings; DDF, difficulties describing feelings; EOT, externally oriented thinking; MDD lifetime, major depressive disorder – lifetime diagnosis. ^a Subsamples from the “Study of Health in Pomerania (SHIP).” ^b Dichotomized abuse/neglect variable based on the subdimensions of the CTQ (see Methods for details).

the triallelic 5-HTTLPR polymorphism revealed similar results ($p = 0.031$; $B = -0.593$), showing significant associations of the low-expressing alleles (S; L_G) with increased alexithymia. Results remained statistically significant when adjusting for multiple testing. Interaction terms of childhood abuse/neglect × 5-HTTLPR (bi- and triallelic) did not predict TAS-20 scores.

Our results showing strong associations of neglect and abuse and significant effects of the low-expressing alleles (S; L_G) of 5-HTTLPR with alexithymia confirmed our hypotheses (i) and (ii), while findings were in contrast to hypothesis (iii).

The finding that childhood abuse and neglect are strong predictors of alexithymia indicates that different etiological pathways may result in the development of alexithymia. Concepts that relate childhood neglect to alexithymia state that perceived lack of attention and insufficient exposure to adaptive emotional learning can lead to impaired emotion regulation of alexithymic subjects. Regarding associations between childhood abuse and alexithymia, it has been suggested that alexithymia serves as a defense mechanism against intolerable thoughts and feelings [3].

In contrast to previous studies on alexithymia, we found associations of the low-expressing alleles with increased alexithymia

scores. Still, in the majority of studies on mood and 5-HTTLPR, the S-allele was associated with negative affectivity [5]. Thinking of alexithymia as a personality trait associated with deficits in emotion processing and regulation, the findings of Pezawas et al. [10] may provide a susceptibility mechanism. The authors found carriers of the S-allele showing reduced gray-matter volumes in limbic regions including the anterior cingulate cortex and the amygdale, which are critical for the regulation of negative emotions. Moreover, results from functional neuroimaging analyses from the same study revealed an association of the S-allele with a relative decoupling of a feedback circuit involved in the extinction of negative affect. These results mesh well with our finding that variants of 5-HTTLPR were only associated with the affective factors of the TAS-20, i.e., DIF (difficulties identifying feelings) and DDF (difficulties describing feelings), which have been shown to be particularly relevant for impaired emotion regulation.

A common limitation to previous studies was that only the biallelic insertion polymorphism of 5-HTTLPR was analyzed. However, taking the triallelic polymorphism into account only slightly changed results, which further questions the relevance of the concept of a triallelic 5-HTTLPR variant.

Limitations include the exclusive use of self-rating instruments. Although well-established and widely used, it may be particularly challenging for alexithymic subjects to evaluate their psychological characteristics. Moreover, childhood trauma was assessed based on retrospective information. The ability to recall aspects of traumatic events during childhood may be reduced. Also, the stability of alexithymia in relation to time and psychological distress were called into question by different researchers. However, the majority of studies found evidence for a sufficient absolute and relative stability. In particular, highly alexithymic subjects have been linked with impaired memory performance for emotional stimuli, which may additionally influence their ability to accurately recall early emotional memories. Finally, we did not replicate our data with an independent sample.

In conclusion, our findings support the concept that both childhood neglect and abuse play a key role in the development of alexithymia. Significant effects of functional variants of 5-HTT suggest an involvement of the serotonin metabolism. As no interaction effects were found, our results suggest a coexistence of environmental as well as genetic factors, which may independently result in alexithymic personality traits.

Acknowledgments

This work was supported by the German Research Foundation (GR 1912/5-1), the Federal Ministry of Education and Research in Germany (01ZZ9603, 01ZZ0103, and 01ZZ0403), and the Ministry of Cultural Affairs and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. SHIP is part of the Community Medicine Research Net of the University of Greifswald, Germany. The funding sources had no influence on the collection, analysis, and interpretation of the data, or in the writing and submission of the article.

Disclosure Statement

J. Terock, S. Van der Auwera, A. Hannemann, D. Janowitz, and G. Homuth have no conflicts of interest to declare. H.J. Grabe has received funding from the German Research Foundation, the Ministry of Education and Research, and the DAMP Foundation. C.O. Schmidt has received funding from the German Research

Table 2. Direct effects and interaction effects of genetic variants and childhood abuse on the TAS-20 and its subscales, adjusted for sex, age, and life-time diagnosis of major depressive disorder

	TAS-20	DIF	DDF	EOT
<i>5-HTTLPR biallelic (reference group SS/SL carriers)</i>				
B	-0.591	-0.253	-0.227	-0.120
<i>p</i>	0.022	0.029	0.018	0.31
CI	-1.096, -0.085	-0.48, -0.026	-0.416, -0.039	-0.355, 0.114
<i>R</i> ²	0.1%	0.09%	0.11%	0.02%
<i>5-HTTLPR triallelic (reference groups SL_A; L_GL_G; L_GS; SS)</i>				
B	-0.593	-0.341	-0.218	-0.055
<i>p</i>	0.031	0.0061	0.034	0.67
CI	-1.13, -0.055	-0.584, -0.097	-0.418, -0.017	-0.315, 0.204
<i>R</i> ²	0.09%	0.14%	0.09%	0.0%
<i>CTQ total score</i>				
B	0.212	0.098	0.062	0.053
<i>p</i>	1.2E-39	8.8E-39	5.5E-29	2.5E-14
CI	0.181, 0.244	0.084, 0.113	0.051, 0.072	0.039, 0.067
<i>R</i> ²	4.71%	5.12%	2.91%	1.36%
<i>Childhood abuse</i>				
B	2.759	1.931	0.834	-0.027
<i>p</i>	6.6E-7	3.0E-13	1.7E-5	0.91
CI	1.676, 3.842	1.412, 2.45	0.454, 1.213	-0.496, 0.443
<i>R</i> ²	0.63%	1.57%	1.26%	0.01%
<i>Childhood neglect</i>				
B	3.705	1.557	1.023	1.132
<i>p</i>	3.5E-26	6.5E-21	6.5E-16	5.1E-13
CI	3.019, 4.391	1.232, 1.882	0.775, 1.271	0.825, 1.439
<i>R</i> ²	2.22%	1.99%	1.26%	0.97%
<i>CTQ^a × biallelic^b</i>				
B	0.029	0.015	0.007	0.007
<i>p</i>	0.34	0.27	0.51	0.63
CI	-0.031, 0.089	-0.012, 0.043	-0.014, 0.028	-0.022, 0.036
<i>R</i> ²	0.04%	0.05%	0.0%	0.02%
<i>Abuse^a × biallelic^b</i>				
B	1.366	0.955	0.190	0.282
<i>p</i>	0.21	0.068	0.62	0.57
CI	-0.766, 3.499	-0.069, 1.98	-0.567, 0.946	-0.69, 1.255
<i>R</i> ²	0.5%	1.1%	0.31%	0.03%
<i>Neglect^a × biallelic^b</i>				
B	-0.203	-0.178	-0.052	0.092
<i>p</i>	0.78	0.61	0.85	0.79
CI	-1.625, 1.219	-0.852, 0.497	-0.58, 0.476	-0.586, 0.769
<i>R</i> ²	0.88%	0.73%	0.55%	0.42%
<i>CTQ^a × triallelic^b</i>				
B	0.022	0.013	0.002	0.007
<i>p</i>	0.51	0.37	0.86	0.63
CI	-0.044, 0.088	-0.016, 0.042	-0.021, 0.025	-0.022, 0.036
<i>R</i> ²	0.02%	0.01%	0.0%	0.03%
<i>Abuse^a × triallelic^b</i>				
B	2.167	1.380	0.215	0.623
<i>p</i>	0.083	0.024	0.62	0.24
CI	-0.28, 4.614	0.185, 2.576	-0.641, 1.07	-0.419, 1.705
<i>R</i> ²	0.52%	1.15%	0.25%	0.02
<i>Neglect^a × triallelic^b</i>				
B	-0.638	-0.319	-0.262	0.016
<i>p</i>	0.40	0.37	0.35	0.96
CI	-2.137, 0.861	-1.022, 0.384	-0.809, 0.286	-0.669, 0.7
<i>R</i> ²	0.62%	0.6%	0.34%	0.3%

B, observed beta coefficient; CI, confidence interval; *p*, *p* value; *R*², increase in *R*² due to the predictor of interest; CTQ, Childhood Trauma Questionnaire; TAS-20, Toronto Alexithymia Scale; DIF, difficulties identifying feelings; DDF, difficulties describing feelings; EOT, externally oriented thinking. ^a CTQ/abuse/neglect interaction term. ^b Also adjusted for sex.

Foundation, the Ministry of Education and Research, EU funds (ESF/EFRE), and the TMF – Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V. H.J. Freyberger has received funding from the Stiftung Aufarbeitung, the Damp Foundation, and the German Research Foundation. H. Meyer zu Schwabedissen has received funding from the Swiss National Foundation and the German Research Foundation.

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