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ORIGINAL PAPER

A gene–environment investigation on personality traits in two independent clinical sets of adult patients with personality disorder and attention deficit/hyperactive disorder

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Abstract While an interactive effect of genes with adverse life events is increasingly appreciated in current concepts of depression etiology, no data are presently available on interactions between genetic and environmental (G × E) factors with respect to personality and related disorders. The present study therefore aimed to detect main effects as well as interactions of serotonergic candidate genes (coding for the serotonin transporter, *5-HTT*; the serotonin autoreceptor, *HTR1A*; and the enzyme which synthesizes serotonin in the brain, *TPH2*) with the burden of life events (#LE) in two independent samples consisting of 183 patients suffering from personality disorders and 123 patients suffering from adult attention deficit/hyperactivity disorder (aADHD). Simple analyses ignoring possible G × E interactions revealed no evidence for associations of either #LE or of the considered polymorphisms in *5-HTT* and *TPH2*. Only the G allele of *HTR1A* rs6295 seemed to increase the risk of emotional-dramatic cluster B personality disorders ($p = 0.019$, in the personality disorder sample) and to decrease the risk of anxious-fearful cluster C personality disorders ($p = 0.016$, in the aADHD sample). We extended the initial simple model by taking a G × E interaction term into account, since this approach may better fit the data indicating that the effect of a gene is modified by stressful life events or, vice versa, that stressful life events only have an effect in the presence of a susceptibility genotype. By doing so, we observed nominal evidence for G × E effects as well as main effects of *5-HTT*-LPR and the *TPH2* SNP rs4570625 on the occurrence of personality disorders. Further replication studies, however, are necessary to validate the apparent complexity of G × E interactions in disorders of human personality.

Keywords ADHD · Personality disorder · Life events · G × E interactions · Serotonin

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Introduction

Twin and adoption studies suggest that 30–62% of the variance of anxiety and depression-related personality traits is due to inherited factors; furthermore, there is solid evidence that neuroticism is a risk factor for affective disorders and that personality disorders occur co-morbid to depression and anxiety [23]. In humans, non-human primates, and other mammals, preclinical and clinical studies have accumulated substantial evidence that serotonergic signaling is a major modulator of emotional behavior including fear and anxiety, and integrates complex brain functions such as cognition, sensory processing, and motor activity [28]. The diversity of these functions is due to the fact that serotonin (5-HT) orchestrates the activity and interaction of several other neurotransmitter systems. From the numerous genes encoding components of the serotonergic system, three are outstanding with respect to their

impact on human personality traits: the $5HT_{1A}$ receptor gene (*HTR1A*), the 5HT transporter (*5HTT*) and the enzyme which synthesizes serotonin in the central nervous system, tryptophan hydroxylase 2 (*TPH2*).

Evidence for a role of the 5-HT_{1A} receptor in the pathophysiology of anxiety and depression has come from several clinical studies as well as from animal models [7, 28]. The G(-1019) allele of the C(-1019)G *HTR1A* promoter polymorphism (rs6295) was reported to be associated with major depression, depression-related personality traits, and suicidal behavior in various samples [2, 13, 25]. In a study of Strobel et al. [36] carriers of the G allele showed significantly higher scores of neuroticism than individuals homozygous for the C variant. The effect was primarily due to associations with the neuroticism facets anxiety and depression. Carriers of the G allele also exhibited higher TPQ harm avoidance scores. Most noteworthy, this risk variant also led to decreased amygdala activation in a fMRI task assessing brain activation towards threatening stimuli further arguing for a role of this polymorphisms in the predisposition towards anxiety and related traits [14].

The tryptophan hydroxylase-2 gene (*TPH2*) has been linked to a spectrum of clinical populations characterized by emotional dysregulation including affective disorders. Significant associations of TPH2 single markers as well as haplotypes with emotional-dramatic cluster B and anxious-fearful cluster C personality disorders were demonstrated [18]. In both patient groups, an overrepresentation of the T allele of a polymorphism (G-703T, rs4570625) located in the upstream regulatory region of *TPH2* was observed which biases the responsiveness of the amygdale [3–5], a structure critically involved in the modulation of emotional behaviors. Furthermore, significant associations of *TPH2* variants with anxiety-related traits defined primarily by the TPQ harm avoidance were found in healthy individuals.

The low-activity variant of a serotonin (5-HT) transporter polymorphism (5-HTTLPR) is associated with the depression- and anxiety-related personality traits neuroticism or harm avoidance [27]. Meta-analytic findings confirm a modest association with affective disorders, suicidal behavior, and depression-related trait scores [29]. Individuals with one or two copies of the low-activity s allele of the 5-HTTLPR (l/s and s/s, respectively) exhibit greater neuronal activity of the amygdala in response to fearful stimuli when compared with individuals homozygous for the l allele, as assessed by BOLD functional magnetic resonance imaging (fMRI) [19].

In a seminal prospective-longitudinal study of a representative birth cohort, Caspi et al. demonstrated interactions of stressful experiences and genetic variation of the serotonin transporter (5-HTTLPR) on depressive symptoms, diagnosable depression, and suicidality. Individuals with one or two copies of the short (s) allele of the 5-HTTLPR exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long (l) allele. Furthermore, rates of major depression were found to be strongly influenced by the number of stressful life events in carriers of s alleles of the 5-HTTLPR, but not in those individuals with the l/l genotype [8]. Zalsman et al. [41] confirmed the finding by reporting that lower expressing transporter alleles, directly and by increasing the impact of stressful life events on severity, explain 31% of the variance in major depression severity. Gene–environmental interaction (G × E) between 5-HTTLPR and environmental adversity on the onset of depression in humans has been found in 15 independent studies [39]. However, negative findings have been reported in two large samples [11, 37].

We reasoned that genes encoding for important components of the serotonergic system might be implicated in G × E effects on personality and that these effects are apparent in clinical phenotypes. Personality disorders and adult attention deficit/hyperactivity disorders (aADHD) share many commonalities and formally spoken, aADHD even fulfills the diagnostic criteria of PD according to the DSM-IV criteria: experience and behavior that deviates markedly from the expectations of the individual's culture (criterion A); the enduring pattern is inflexible and pervasive across a broad range of personal and social situations (criterion B) and leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning (criterion C). The pattern is stable and of long duration and its onset can be traced back at least to adolescence or early adulthood (criterion D). Thus, it might be conceptualized that persistence of ADHD into adulthood might rather represent a narrow-defined form of personality disorder [20]. Both disorders feature a high degree of heritability: 0.60 for the emotional-dramatic cluster B consisting of antisocial, borderline, histrionic, and narcissistic personality disorders, 0.62 for the anxious-fearful cluster C personality disorders consisting of obsessive-compulsive, avoidant, and dependent personality disorders [38], and 0.76 for ADHD [15]. As the s allele of 5-HTTLPR, the T allele TPH2 SNP G-703T (rs4570625), and the G allele of HTR1A gene are all associated with negative emotionality, we hypothesized that these variants are associated with anxious-fearful cluster C personality disorders, as is an increased #LE and that this effect is increased by G × E.

Materials and methods

Participants and procedure

The sample of probands affected with aADHD consisted of 123 unrelated patients (58 females and 65 males; mean age

Table 1 Description of samples

	PD sample		aADHD sample		*p* value of comparison test
	N	%	*N*	%	
Total	183	100	123	100	
Males	71	38.8	65	52.8	
Females	112	61.2	58	47.2	0.019
Cluster A PD	28	15.3	14	13.2	0.73
Cluster B PD	138	75.4	74	69.8	0.335
Cluster C PD	72	39.3	51	48.1	0.175
	Mean	SD	Mean	SD	*p* value of comparison test
Age	37.15	13.0	35.11	9.6	0.270
Number of life events	10.99	8.2	9.19	5.6	0.107

35.11 ± 9.57 years) and the sample of probands affected with PD consisted of 183 unrelated patients (112 females and 71 males; mean age 37.15 ± 13.03 years). Both samples were recruited at the Department of Psychiatry, University of Würzburg. All subjects were of Caucasian origin. Table 1 contains descriptive statistics of the samples. A comparison of these characteristics revealed a nominally significant difference in the distribution of sex (38.80% male PD patients versus 52.85% male aADHD patients, $p = 0.019$), while the other variables did not differ significantly between the two samples.

All assessments were performed by an experienced psychiatrist (C.P.J.). Inclusion criterion of the aADHD sample was the diagnosis of attention deficit/hyperactivity disorders both in childhood and current according to the diagnostic criteria of DSM-IV. Inclusion criterion of the personality disorders sample was a diagnosis of a personality disorder according to the diagnostic criteria of DSM-IV. All participants were assessed with the structured clinical interview of DSM-IV personality disorders (SCID-II).

Personality dimensions were thereafter assessed by two different methods: the revised NEO personality inventory (NEO-PI-R) [10] and the tridimensional personality questionnaire (TPQ) [9]. TPQ and NEO-PI-R scores for each sample are given in Table 2 for those patients who do not suffer from combined cluster B/C PD. As expected [34], anxious-avoidant Cluster C personality disorders in both samples exhibited higher scores of anxiety- and depression-related personality traits (harm avoidance and neuroticism) than Cluster B personality disorders.

The evaluation for life events used the same items as the procedure performed by Caspi et al. [8]. Life events were retrospectively assessed with the aid of a life-history calendar, a highly reliable method for ascertaining life-event histories. Since the onset of personality traits occurs in late childhood or adolescence, and as stable, long duration of the symptoms in adulthood is required for establishment of a diagnosis of personality disorder (and even more so *adult* ADHD), we restricted the registration of stressful life events to the time period before the 21st birthday, i.e., up to the point of time when people had overcome puberty and reached stability in terms of personality traits.

The study was approved by the Ethics Committee of the University of Würzburg and written informed consent was obtained from all individuals after procedures and aims of the study had been fully explained.

Genotyping

Genomic DNA was extracted from EDTA blood following a routine method (Miller et al. 1988). Genotyping of candidate gene polymorphisms (*HTR1A* rs6295, *TPH2*

Table 2 Description of the samples with respect to personality dimensions (as evaluated by TPQ and NEO-PI-R)

	PD sample				aADHD sample			
	Cluster B only ($N = 106$)		Cluster C only ($N = 40$)		Cluster B only ($N = 33$)		Cluster C only ($N = 10$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
TPQ								
Novelty seeking	16.4	5.0	9.8	3.8	22.0	5.2	13.2	5.2
Harm avoidance	17.0	7.2	22.8	6.3	18.0	7.1	24.7	7.2
Reward dependence	18.9	4.0	18.5	4.2	18.3	4.7	18.4	4.2
NEO-PI R								
Neuroticism	98.9	25.6	112.7	24.9	117.7	23.3	122.3	32.5
Extraversion	109.4	21.1	80.4	19.7	115.5	23.3	84.8	20.8
Openness to experience	114.9	20.2	104.1	16.9	124.8	19.7	116.1	22.6
Agreeableness	116.8	14.4	124.6	17.3	111.3	14.7	124.9	18.0
Conscientiousness	113.4	19.8	119.1	17.2	92.2	17.4	102.9	15.5

Table 3 Sample sizes, genotype and minor allele frequencies (MAF) and *p* values of Hardy–Weinberg Equilibrium test (*p* HWE) for the investigated polymorphisms

Gene and marker	Sample	*N*	Genotype frequencies: *N* (%)						MAF (%)		*p* HWE
5HT1A	PD	183	GG	51 (27.9)	CG	86 (47.0)	CC	46 (25.1)	C	48.6	0.42
rs6295	aADHD	123		27 (27.6)		62 (50.4)		34 (22.0)		47.2	0.90
TPH2	PD	182	GG	104 (57.1)	GT	66 (36.3)	TT	12 (6.6)	T	24.7	0.73
rs4570625	aADHD	123		82 (66.7)		33 (26.8)		8 (6.5)		19.9	0.08
5-HTT/	PD	182	L/L	61 (33.5)	S/L	88 (48.4)	S/S	33 (18.1)	S	42.3	0.9
5-HTTLPR	aADHD	123		52 (42.3)		53 (43.2)		18 (14.6)		36.2	0.46

rs4570625, *5-HTT*-LPR) followed routine PCR protocols established in our laboratory as published earlier [18, 21, 33]. Table 3 contains information about genotype frequencies of the investigated genes in both samples. All genotype distributions were in Hardy–Weinberg equilibrium and did not differ between the samples (p values >0.07).

Statistical analysis

As a preliminary step, we compared descriptive characteristics of the two samples: sex, occurrence of cluster B and cluster C personality disorders as operationalized in DSM-IV (by Fisher's exact test) and age, number of life events (#LE) (by Mann–Whitney test, as implemented in SPSS 15). Chi-square tests were used to test whether the observed genotype distributions deviate from Hardy–Weinberg equilibrium. Genotype and allele frequencies between the two samples were compared using exact Cochran-Armitage test for trend and Fisher's exact test implemented in StatXact-6.

The analysis of genetic and environmental risk factors was performed in two stages: first, we investigated the main effects of each gene and of the environmental risk variable separately. Second, we explored possible gene–environment interactions. For the first stage, we preformed separate analyses for each genetic marker and the environmental variable (#LE) to assess an association with the dichotomous traits cluster B and cluster C personality disorder. For this, we used logistic regression models with one marker or #LE as predictor variable and one of the traits as response variable. We included sex and age as covariates in the regression models and assumed an allele-dose effect of the assumed risk alleles (i.e., three genotypes were considered). Analysis was performed using the R function glm().

At the second stage, we extended the simple main effects analysis models to investigate the joint effects of genetic and environmental variables. For each gene, we assessed whether a model with a genetic and an environmental main effect and a G × E interaction fits the data significantly better than the simple model. The improvement in model fit can be appraised by means of a likelihood ratio test (Chi^2 statistic with 2 degrees of freedom) for logistic regression analysis. Only those extended models which clearly provided an improvement in fitting the data were pursued further (LR-test nominal p value <0.05 in at least one sample). The respective main and interaction effects in these models are then evaluated. Additionally, in order to consider the simultaneous influence of all risk factors on cluster B and C, we included sex, age, all gene variants, life events as well as terms of gene–gene and gene–life event interactions into a comprehensive logistic regression model.

For the purpose of instructive graphical presentations only, the samples were grouped into high and low life stress groups (number of life events below or above the median); genotypes accordingly were grouped in presence or absence of the putative risk allele. Based on this, the frequencies of cluster B or C personality disorders in the resulting groups are presented.

All analyses were performed for both samples separately. We used a two-sided nominal significance level of 0.05. Note that the results of the present study are predominantly exploratory and not corrected for multiple testing.

Results

Number of life events in personality disorder and aADHD samples

First, we explored the psychometric characteristics of both samples. Figure 1 shows box plots of the distribution of number of life events stratified by age and sex groups among personality disorder and aADHD patients. A linear regression analysis of #LE including both sex and age as independent variables confirmed that the impact of age on #LE was positive in the personality disorder sample (regression coefficient $= 0.10$, SE $= 0.05$, $p = 0.032$) and negative in the aADHD sample (regression coefficient $= -0.13$,

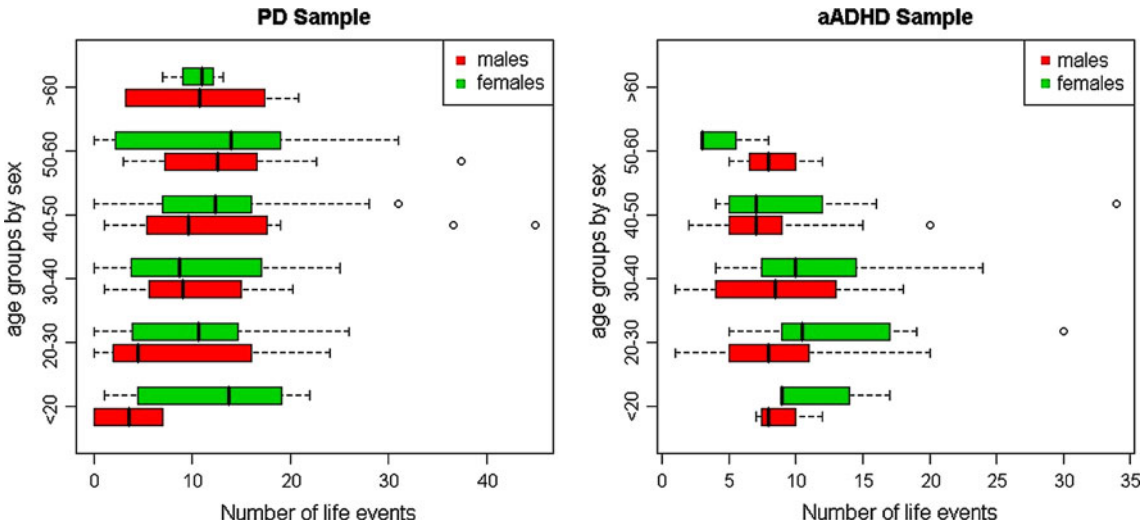

Fig. 1 Distribution of the number of life events by age and sex groups for PD and aADHD samples

SE = 0.05, $p = 0.014$). Furthermore, female aADHD patients seemed to have more #LE than male patients (mean difference = 2.72, SE = 0.98, $p = 0.006$).

The impact of risk genotypes and life events on cluster B and C personality disorders ignoring possible G × E interactions

In the first stage of analysis, we analyzed main effects of each gene and #LE on the different traits separately, ignoring possible G × E interactions, and adjusted for sex and age only. The rs6295 G allele of *HTR1A* significantly increased the risk of cluster B personality disorders in the personality disorder sample (OR 1.99, 95%CI 1.12–3.54, $p = 0.019$, Table 4) and decreased the risk of cluster C in the aADHD sample (OR 0.44, 95%CI 0.23–0.86, $p = 0.016$). In both cases, there is a small, non-significant trend in the same direction in the other sample (Table 4). The environmental variable #LE did not show an association with any of the investigated traits in the simple analysis.

The impact of the risk genotypes, #LE and their interactions on cluster B and C personality disorders

As a second step, we extended these simple models to investigate the joint effects of genetic markers and stressful life events (again adjusting for sex and age). These extended models may markedly better fit the data. Table 4 provides results of both the simple and extended analysis, in terms of odds ratios and confidence intervals for the gene and #LE main effects and their interaction. If the likelihood ratio test did not indicate an improved fit by an extended model ($p > 0.05$), results from the simple model are given, and if the LR-test indicates an improved fit ($p < 0.05$), results from the extended model are presented.

Effects of 5-HTTLPR on cluster B personality disorders in both samples

For the 5-HTTLPR polymorphism, we found a significantly better fit of such an extended model for cluster B personality disorders in both samples (LR-test $p = 0.046$ in personality disorder sample and $p = 0.03$ in aADHD sample). Both samples showed a significant interaction effect in the same direction (OR = 0.88, $p = 0.041$ in the personality disorder sample and OR = 0.79, $p = 0.036$ in the aADHD sample; Fig. 2). In both samples, as compared to carriers of the s allele, carriers of the l/l genotype are more likely to suffer from emotional-dramatic cluster B personality disorders if reporting an above average #LE in the childhood (∼85 vs. ∼70%). In contrast, l/l carriers reporting a below average #LE exhibited a similar risk in the personality disorder sample (∼79 vs. ∼77%) and even a strongly reduced risk for cluster B personality disorders in the aADHD sample (45 vs. 70%) as compared to carriers of the s allele. The 5-HTT-LPR polymorphism did not show an association with anxious-fearful cluster C personality disorders in either sample.

Effects of TPH2 rs4570625 in the personality disorder sample

For rs4570625 in the TPH2 gene, an extended gene–environment model for the occurrence of both cluster B and cluster C personality disorders in the personality disorder sample again yielded a significantly better fit (LR-test $p < 0.005$). For those with few life events, presence of the T

Table 4 Joint effects of genetic markers and stressful life events on cluster B and C personality disorders

Gene/marker	Traits	Effect type	PD sample					aADHD				
			LR-test[a]	OR	95%CI lower	95%CI upper	*p* value	LR-test[a]	OR	95%CI lower	95%CI upper	*p* value
5HT1A/	Cluster_B	Gene	0.730	1.99	1.12	3.54	**0.019**	0.202	1.53	0.79	2.97	0.212
rs6295	Cluster_C	Gene	0.170	0.92	0.57	1.48	0.740	0.618	0.45	0.23	0.86	**0.016**
5-HTT/5-HTTLPR	Cluster_B	Gene	**0.046**	1.44	0.63	3.28	0.385	**0.030**	6.10	1.56	23.85	**0.009**
		LE		1.10	0.97	1.24	0.147		1.21	0.98	1.49	0.072
		Gene × LE		0.88	0.77	0.99	**0.041**		0.79	0.64	0.98	**0.036**
	Cluster_C	Gene	0.104	0.99	0.61	1.62	0.970	0.300	1.75	0.92	3.35	0.090
TPH2/rs4570625	Cluster_B	Gene	**0.001**	3.53	1.13	11.05	**0.030**	0.480	0.63	0.29	1.38	0.250
		LE		1.07	0.99	1.15	0.078					
		Gene × LE		0.85	0.77	0.94	**0.001**					
	Cluster_C	Gene	**0.005**	0.37	0.14	0.97	**0.044**	0.670	1.08	0.52	2.23	0.840
		LE		1.00	0.95	1.05	0.948					
		Gene × LE		1.11	1.02	1.21	**0.012**					

[a] The reported results are either from the simple model, if *p* LR-test >0.05, or from the extended model, if *p* LR-test <0.05

Nominally significant effects are in bold

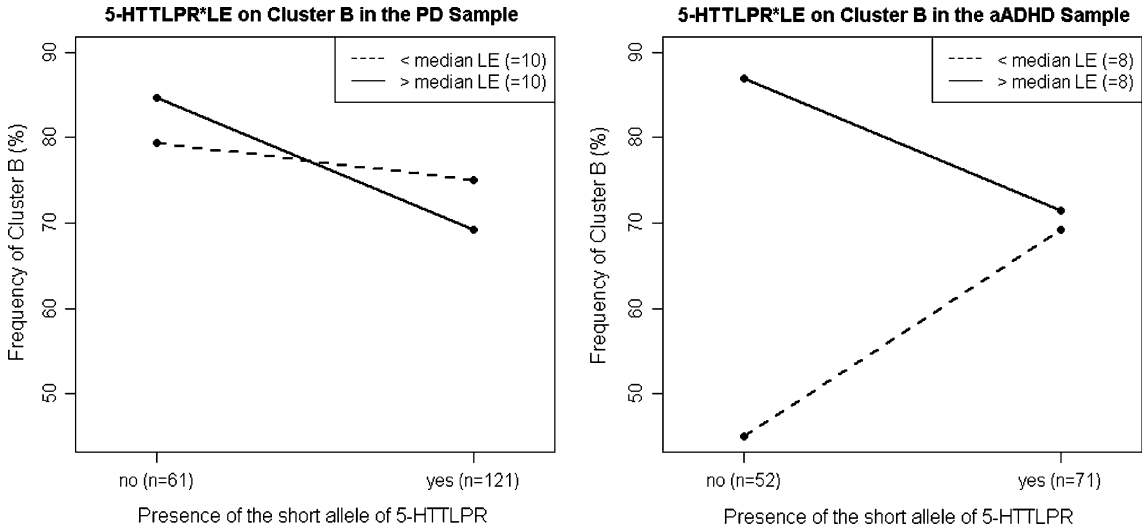

Fig. 2 Relative frequencies of Cluster B PD in the sample of PD and aADHD patients within the two life-event categories (*>median or <median number of life events*), depending on the presence of the s allele of 5-HTTLPR

allele slightly increased the risk for cluster B personality disorders, while it strongly decreased it in those with many life events (p interaction = 0.001, Fig. 3). An inverse relationship for anxious-fearful cluster C personality disorders was found: there was a significant genetic main effect (OR = 0.37, $p = 0.044$) and a significant interaction effect ($p = 0.012$) of *TPH2* rs4570625 on cluster C. In individuals without the T allele, the number of stressful life events did not seem to influence risk of cluster C personality disorders (~40% in both groups). Among carriers of the T allele, those with many stressful life events had a higher risk of cluster C personality disorders (~60%) as compared to those who experienced few such events (~25%).

Integrative model on gene–gene and gene–environment interactions

Finally, in a comprehensive model, we found no evidence for gene–gene interactions, while the effects of the individual genes and their interactions with life events were similar to those in the single-gene models. In such an extended model, inclusion of additional variables may reduce variance for the estimation of an environmental main effect even if no gene–environment interaction is apparent. Here, we found that stressful life events seemed to have a small positive independent effect on the development of cluster B in the aADHD sample (OR = 1.86,

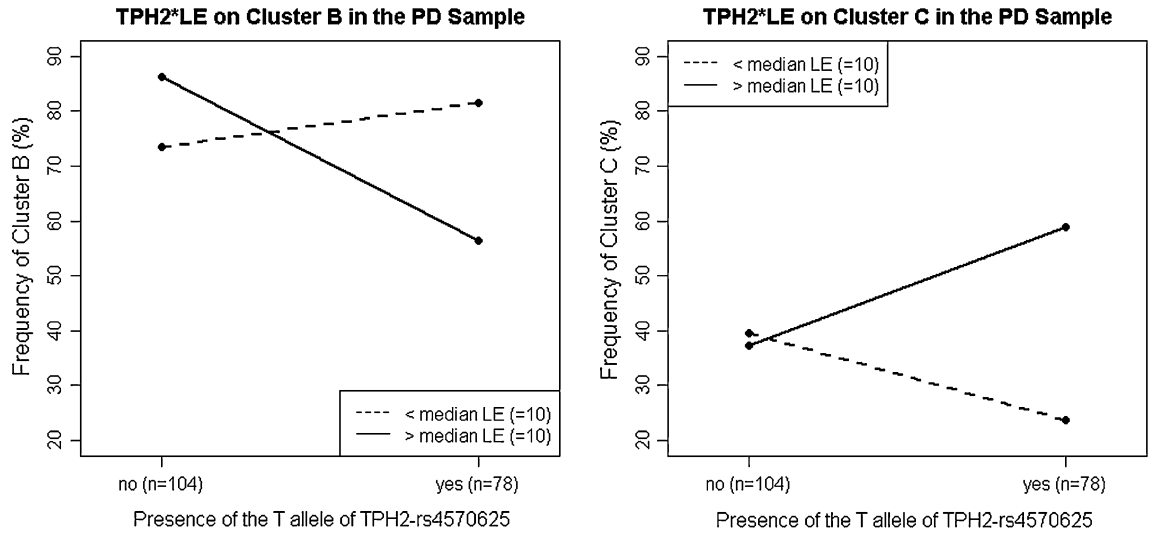

Fig. 3 Relative frequencies of cluster B and cluster C PD in the sample of PD patients within the two life-event categories (*>median or <median number of life events*), depending on the presence of the T allele of rs4570625 in TPH2)

95%CI 1.17–2.96, $p = 0.008$). Age had a slightly negative effect on cluster B in both samples (OR = 0.96 in personality disorders, $p = 0.008$ and OR = 0.94 in aADHD, $p = 0.03$), with older patients less likely to have cluster B personality disorders. Age had no effect on the risk of cluster C personality disorders. Sex also had no effect on the risk of cluster B and cluster C personality disorders in both samples.

Discussion

In the present study, we sought to explore the interaction between stressful life events and functional genetic variants in genes encoding key variants of the serotonergic system on personality traits. Taken together, our data supported an interaction of #LE and 5-HTT as well as TPH2 genotype on disorders related to personality, while we found a genetic main effect of the HTR1A G allele independent of LE. This allele significantly increased the risk of emotional-dramatic cluster B personality disorders in the personality disorder sample and decreased risk for cluster anxious-avoidant cluster C personality disorders in the aADHD sample. Previous studies demonstrated an association of HTR1A with major depression and anxiety/depression-related personality traits in various samples [2, 13, 25, 36] as reviewed by Le Francois et al. These studies are well in line with the notion that there is a continuum leading from anxiety depression-related personality traits to affective disorders and are underscored by recent data showing that the G allele leads to decreased amygdala activation towards threatening stimuli [14]. How our finding relates to this data, however, is more difficult to explain, as the G allele tended to increase cluster B, but to decrease the anxious-fearful cluster C personality disorders, an effect which was observable in both samples. However, it has to be stressed that hitherto no case–control association study on HTR1A with respect to categorical personality disorder has been published. Yet not only cluster C, but also cluster B personality disorders are characterized by increased levels in neuroticism; and furthermore, also cluster B personality disorders can be linked to the phenotypes associated with HTR1A (e.g., depression, suicidality, and panic disorders). Thus, it seems conceivable that the HTR1A risk allele operates on a clinical trajectory from increased neuroticism over cluster B personality disorders to various categorical axis-I disorders.

Not only for HTR1A, but also in general we mainly observed significant associations with respect to cluster B P personality disorders which most likely reflects the larger sample size and resulting power of this sub-sample, as 69% of all subjects studied suffered from cluster B personality disorders as opposed to 40% suffering from cluster C PD (Table 1). In cluster B PD, G × E interactions were evident for both TPH2 and 5HTT. Contrary to our initial hypothesis, the 5-HTTLPR polymorphism did not show an association with anxious-fearful cluster C personality disorders in either sample-neither as a genetic main effect nor as a G × E interaction. As outlined above, this could, however, also be due to the lack of statistical power of this sub-sample. To date, 17 studies have been published examining G × E with respect to 5-HTTLPR, producing conflicting findings yet converging to the notion that life stress interacts with 5HTT to produce psychopathology or distress [6, 39]. One of the reasons for all these conflicting findings may be the use of different characteristics of the study samples and different study designs such as

prospective cohort studies, cross-sectional surveys, combined cohort/case–control design, examination of individuals exposed to a major stressor and case-only design. In our sample the most meaningful result with respect to 5-HTTLPR was the finding that, in aADHD, carriers of the LL genotype had an increased risk to develop cluster B personality disorders when having encountered a high #LE.

For the promoter SNP rs4570625 in the TPH2 gene, we also found a significantly better fit of an extended gene–environment model for the occurrence of both cluster B and cluster C personality disorders in the personality disorder sample only. This polymorphism has hitherto been associated with panic disorder [24], ADHD [40], obsessive-compulsive disorder [30], anxiety-related traits [18, 32], and both cluster B and C personality disorder [18]. The polymorphism also affects cognitive control [1, 35] and amygdale reactivity [3]. No data on G × E, however, has been presented to date. In the presence of high life stress, risk allele (i.e., the T allele) carriers had less cluster B personality disorders in the personality disorder sample (which in turn means that they had more cluster C personality disorders, which, however, was not significant most likely due to the small sample size) while they had more cluster C personality disorders in the aADHD sample. Especially the latter finding fits well previous studies on the categorical association of the risk allele with cluster C personality disorders [18] and related conditions. It would be intriguing to see whether life stress also modulates these associations or not.

A drawback of our study is the retrospective assessment of life stress, which has to be considered when interpreting the results. The evaluation of life events was performed along the procedure used by Caspi et al. [8]. Life events to the time period before the 21st birthday were assessed, when people had overcome puberty and reached stability in terms of personality traits. It can reasonably be argued that younger subjects are able to better recall life events before the 21st birthday due to the shorter latency between event and recall. However, the positive impact of age on #LE we observed in our personality disorder study sample confutes this assumption. Another line of argumentation is that the recall of the actualities of critical life events is independent of time. From the present data it is impossible to resolve whether differences in reported #LE in the two samples, the different age groups and sexes are due to different recall or truly different experiences in youth; however, longitudinal studies are sparse and also retrospective studies are valuable given that the subjective level of live stress, which might well be the crucial variable, is assessed hereby.

Another disadvantage of the study is the number of patients, which might be too small to detect underlying genetic effects as the effect of a single allelic variation on personality traits is presumably small. Allelic variation in 5-HTT function was found to account for approximately 8% of inherited variance in anxiety- and depression-related personality traits in individuals as well as sibships [27]. Interestingly, two of the studies on 5HTT-LPR × E interactions in depression with very large samples were negative [17, 37] The sample size of some of the replication studies was too small to test the hypothesis [16, 26], since in general the sample sizes required for interaction studies are larger than those for genetic main effects [12]. This could either suggest publication bias with smaller negative studies remaining unpublished or could be explained by other systematic differences between negative and positive studies [39]. Anyhow, large-scale and preferentially longitudinal studies on G × E in personality disorders are clearly needed to uncover the apparently complex relationships between genetic risk, environmental variables, and their interplay to predispose the target range on the clinical continuum from non-average personality traits over personality disorder to axis-I disorder.

Summary

For two of three investigated polymorphisms, we found significantly better fit of the extended model, which incorporates genotypic as well as environmental data and their interactions. This fact indicates that the effects of *5-HTT* and *TPH2* variants on cluster B and C personality disorders may likely be modified by stressful life events. The results from the integrative model also support the presence of G × E interactions, and the main effect of stressful life events became only evident when susceptibility genotypes were taken into account.

Beside the above described methodological limitations, the necessity of research on personality traits has to be emphasized. According to a dimensional model of psychiatric disorders there is a continuum between personality traits, personality disorders, and axis I disorders. Especially, neuroticism and harm avoidance are viewed as a risk factor (or personality template) for mood and anxiety disorders. The research on gene effects and G × E interactions in personality traits may contribute to a better understanding of the etiology of personality disorders and axis I disorders [22, 31]. Further studies have to be performed to validate assessment methods of life events in personality traits and to untangle the apparent complexity of G × E interactions on human personality traits.

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References

1. Baehne CG, Ehlis AC, Plichta MM, Conzelmann A, Pauli P, Jacob C, Gutknecht L, Lesch KP, Fallgatter AJ (2008) Tph2 gene variants modulate response control processes in adult ADHD patients and healthy individuals. Mol Psychiatry. doi:10.1038/mp.2008.39. 22 Apr 2008 [Epub ahead of print]
2. Baune BT, Hohoff C, Roehrs T, Deckert J, Arolt V, Domschke K (2008) Serotonin receptor 1A-1019C/G variant: impact on antidepressant pharmacoresponse in melancholic depression? Neurosci Lett 436:111–115
3. Brown SM, Peet E, Manuck SB, Williamson DE, Dahl RE, Ferrell RE, Hariri AR (2005) A regulatory variant of the human tryptophan hydroxylase-2 gene biases amygdala reactivity. Mol Psychiatry 10:884–888 (see also p 805)
4. Canli T, Congdon E, Gutknecht L, Constable RT, Lesch KP (2005) Amygdala responsiveness is modulated by tryptophan hydroxylase-2 gene variation. J Neural Transm 112:1479–1485
5. Canli T, Congdon E, Todd Constable R, Lesch KP (2008) Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on neural correlates of affective processing. Biol Psychol 79:118–125
6. Canli T, Lesch KP (2007) Long story short: the serotonin transporter in emotion regulation and social cognition. Nat Neurosci 10:1103–1109
7. Carola V, Frazzetto G, Gross C (2006) Identifying interactions between genes and early environment in the mouse. Genes Brain Behav 5:189–199
8. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389
9. Cloninger CR, Przybeck TR, Svrakic DM (1991) The tridimensional personality questionnaire: U.S. normative data. Psychol Rep 69:1047–1057
10. Costa PT, McCrae RR (1998) Revised NEO personality inventory (NEO PI-R) and NEO five- factor inventory (NEO-FFI) professional manual. Psychological Assessment Resources, Odessa
11. Covault J, Tennen H, Armeli S, Conner TS, Herman AI, Cillessen AH, Kranzler HR (2007) Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. Biol Psychiatry 61:609–616
12. Dempfle A, Scherag A, Hein R, Beckmann L, Chang-Claude J, Schafer H (2008) Gene–environment interactions for complex traits: definitions, methodological requirements and challenges. Eur J Hum Genet 16:1164–1172
13. Domschke K, Braun M, Ohrmann P, Suslow T, Kugel H, Bauer J, Hohoff C, Kersting A, Engelien A, Arolt V, Heindel W, Deckert J (2006) Association of the functional -1019C/G 5-HT1A polymorphism with prefrontal cortex and amygdala activation measured with 3 T fMRI in panic disorder. Int J Neuropsychopharmacol 9:349–355
14. Fakra E, Hyde LW, Gorka A, Fisher PM, Munoz KE, Kimak M, Halder I, Ferrell RE, Manuck SB, Hariri AR (2009) Effects of HTR1A C(-1019)G on amygdala reactivity and trait anxiety. Arch Gen Psychiatry 66:33–40
15. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005) Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1313–1323
16. Gibb BE, McGeary JE, Beevers CG, Miller IW (2006) Serotonin transporter (5-HTTLPR) genotype, childhood abuse, and suicide attempts in adult psychiatric inpatients. Suicide Life Threat Behav 36:687–693
17. Gillespie NA, Whitfield JB, Williams B, Heath AC, Martin NG (2005) The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. Psychol Med 35:101–111
18. Gutknecht L, Jacob C, Strobel A, Kriegebaum C, Muller J, Zeng Y, Markert C, Escher A, Wendland J, Reif A, Mossner R, Gross C, Brocke B, Lesch KP (2007) Tryptophan hydroxylase-2 gene variation influences personality traits and disorders related to emotional dysregulation. Int J Neuropsychopharmacol 10:309–320
19. Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR (2002) Serotonin transporter genetic variation and the response of the human amygdala. Science 297:400–403
20. Jacob CP, Romanos J, Dempfle A, Heine M, Windemuth-Kieselbach C, Kruse A, Reif A, Walitza S, Romanos M, Strobel A, Brocke B, Schafer H, Schmidtke A, Boning J, Lesch KP (2007) Co-morbidity of adult attention-deficit/hyperactivity disorder with focus on personality traits and related disorders in a tertiary referral center. Eur Arch Psychiatry Clin Neurosci 257:309–317
21. Jacob CP, Strobel A, Hohenberger K, Ringel T, Gutknecht L, Reif A, Brocke B, Lesch KP (2004) Association between allelic variation of serotonin transporter function and neuroticism in anxious cluster C personality disorders. Am J Psychiatry 161:569–572
22. Jang KL, Livesley WJ (1999) Why do measures of normal and disordered personality correlate? A study of genetic comorbidity. J Personal Disord 13:10–17
23. Kendler KS, Gatz M, Gardner CO, Pedersen NL (2006) Personality and major depression: a Swedish longitudinal, population-based twin study. Arch Gen Psychiatry 63:1113–1120
24. Kim YK, Lee HJ, Yang JC, Hwang JA, Yoon HK (2009) A tryptophan hydroxylase 2 gene polymorphism is associated with panic disorder. Behav Genet 39:170–175
25. Koller G, Bondy B, Preuss UW, Zill P, Soyka M (2006) The C(-1019)G 5-HT1A promoter polymorphism and personality traits: no evidence for significant association in alcoholic patients. Behav Brain Funct 2:7
26. Lenze EJ, Munin MC, Ferrell RE, Pollock BG, Skidmore E, Lotrich F, Rogers JC, Quear T, Houck P, Reynolds CF 3rd (2005) Association of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) genotype with depression in elderly persons after hip fracture. Am J Geriatr Psychiatry 13:428–432
27. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274:1527–1531
28. Lesch KP, Zeng Y, Reif A, Gutknecht L (2003) Anxiety-related traits in mice with modified genes of the serotonergic pathway. Eur J Pharmacol 480:185–204
29. Levinson DF (2006) The genetics of depression: a review. Biol Psychiatry 60:84–92
30. Mossner R, Walitza S, Geller F, Scherag A, Gutknecht L, Jacob C, Bogusch L, Remschmidt H, Simons M, Herpertz-Dahlmann B, Fleischhaker C, Schulz E, Warnke A, Hinney A, Wewetzer C, Lesch KP (2006) Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in children and adolescents with obsessive-compulsive disorder. Int J Neuropsychopharmacol 9:437–442
31. Reif A, Lesch KP (2003) Toward a molecular architecture of personality. Behav Brain Res 139:1–20
32. Reuter M, Kuepper Y, Hennig J (2007) Association between a polymorphism in the promoter region of the TPH2 gene and the personality trait of harm avoidance. Int J Neuropsychopharmacol 10:401–404
33. Rothe C, Gutknecht L, Freitag C, Tauber R, Mossner R, Franke P, Fritze J, Wagner G, Peikert G, Wenda B, Sand P, Jacob C, Rietschel M, Nothen MM, Garritsen H, Fimmers R, Deckert J, Lesch KP (2004) Association of a functional 1019C>G 5-HT1A

receptor gene polymorphism with panic disorder with agoraphobia. Int J Neuropsychopharmacol 7:189–192
34. Saulsman LM, Page AC (2004) The five-factor model and personality disorder empirical literature: a meta-analytic review. Clin Psychol Rev 23:1055–1085
35. Strobel A, Dreisbach G, Muller J, Goschke T, Brocke B, Lesch KP (2007) Genetic variation of serotonin function and cognitive control. J Cogn Neurosci 19:1923–1931
36. Strobel A, Gutknecht L, Rothe C, Reif A, Mossner R, Zeng Y, Brocke B, Lesch KP (2003) Allelic variation in 5-HT1A receptor expression is associated with anxiety- and depression-related personality traits. J Neural Transm 110:1445–1453
37. Surtees PG, Wainwright NW, Willis-Owen SA, Luben R, Day NE, Flint J (2006) Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. Biol Psychiatry 59:224–229
38. Torgersen S, Lygren S, Oien PA, Skre I, Onstad S, Edvardsen J, Tambs K, Kringlen E (2000) A twin study of personality disorders. Compr Psychiatry 41:416–425
39. Uher R, McGuffin P (2008) The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. Mol Psychiatry 13:131–146
40. Walitza S, Renner TJ, Dempfle A, Konrad K, Wewetzer C, Halbach A, Herpertz-Dahlmann B, Remschmidt H, Smidt J, Linder M, Flierl L, Knolker U, Friedel S, Schafer H, Gross C, Hebebrand J, Warnke A, Lesch KP (2005) Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in attention-deficit/hyperactivity disorder. Mol Psychiatry 10:1126–1132
41. Zalsman G, Huang YY, Oquendo MA, Burke AK, Hu XZ, Brent DA, Ellis SP, Goldman D, Mann JJ (2006) Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. Am J Psychiatry 163:1588–1593