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Journal of Affective Disorders 112 (2009) 19–29

Journal of Affective Disorders

www.elsevier.com/locate/jad

Research report

Towards a genetically validated new affective temperament scale: A delineation of the temperament 'phenotype' of 5-HTTLPR using the TEMPS-A ☆

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Received 4 March 2008; received in revised form 19 March 2008; accepted 19 March 2008
Available online 1 May 2008

Abstract

Background: Although it has been described that affective temperaments are associated with the 5-HTTLPR, less attention was paid to the association between this polymorphism and subscales and items related to each affective temperament. The aim of our study was to investigate the association of affective temperament subscales and individual items with the s allele of the 5-HTTLPR.
Method: 138 psychiatrically healthy women completed the TEMPS-A questionnaire and were genotyped for 5-HTTLPR. Scores of subjects on the temperament scales, subscales and items in the three genotype and the two phenotype groups were compared using ANOVA. We selected items with significantly different mean scores between the three genotype groups and the two phenotype groups separately and performed item analysis.
Results: Subjects in the different 5-HTTLPR genotype and phenotype groups have significantly different score on scales measuring depressive, cyclothymic, irritable and anxious temperaments, and several subscales composing these temperamental scales. Subjects in the three genotype groups scored significantly different on 11 items, 8 of these remained in a derived genotype scale after item analysis. Subjects in the two phenotype groups had significantly different scores on 12 items, 9 of them were retained in a derived phenotype scale after item analysis.

☆ These studies were supported by the Sixth Framework Programme of the EU, LSHM-CT-2004-503474, the Ministry of Welfare Research Grant 460/2006, the Hungarian Research Fund Grants 022256/1997 and 032398/2000 and the PhD Fellowship Program of the Semmelweis University, Ministry of Culture and Education, Hungary.

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0165-0327/$ - see front matter
doi:10.1016/j.jad.2008.03.012

Limitations: Our sample was relatively small and included only women.
Conclusions: Our data provide support for the association of affective temperaments with the s allele. Although the cyclothymic temperament shows the strongest association, all temperaments within the depressive superfactor have a similar share in this association. The newly derived 5-HTTLPR Phenotype Scale shows strong association with 5-HTTLPR genotype and phenotype, therefore this scale should be further investigated in relation to psychiatric disorders, as well as psychological traits and temperaments.

Keywords: Depression; Affective temperaments; Polymorphism; 5-HTTLPR; Endophenotype

1. Introduction

Affective temperaments are by definition considered the subaffective, subclinical manifestations of affective disorders, and when present in a dominant form they indicate an increased risk towards the manifestation of major mood disorders (Akiskal, 1995, 1996; Akiskal and Akiskal, 1992). It has been found that dominant affective temperaments are significantly more frequent among affective disorder patients (Akiskal and Mallya, 1987; Brieger et al., 2003; Hantouche et al., 1998; Kesebir et al., 2005; Lotrich and Pollock, 2004). Recently there is increased attention towards the genetic background of psychiatric diseases and healthy psychological phenomena as well. The 5-HTTLPR functional polymorphism of the serotonin transporter gene has been described to be associated not only with affective disorders (Bellivier et al., 1998, 2002; Collier et al., 1996; Levinson, 2006), but also with subthreshold forms of depression (Gonda et al., 2005) and with affective temperaments within a healthy population (Gonda et al., 2006). According to our previous study, subjects carrying the s allele of the 5-HTTLPR score significantly higher on scales measuring those affective temperament which by definition carry a depressive component and are part of the depressive superfactor, that is, the depressive, cyclothymic, irritable and anxious temperaments (Gonda et al., 2006). While the factor structure of the questionnaire measuring affective temperaments (TEMPS-A) has been validated (Akiskal et al., 2005a,b; Rozsa et al., 2008), no research has so far been carried out on the association of the s allele and individual items related to affective temperaments. This analysis would give us a deeper insight to the relationship of the 5-HTTLPR and affective temperaments, both of which has been shown to play a role in the background of major and minor mood disorders (Gonda et al., 2005, 2006).

The aim of our present study was to investigate the association of the 5-HTTLPR s allele of the serotonin transporter gene with scales, subscales and individual items within the TEMPS-A questionnaire in a healthy population.

2. Methods

138 unrelated healthy Hungarian females of Caucasian origin participated in the study. Participants were aged between 18 and 64 years, the mean age of the participants was 32.20±1.02. All participants of the study were volunteers. Participants were recruited from the all levels of employees of the National Institute for Psychiatry and Neurology, Budapest, Hungary between 2003 and 2005. All participants were screened for neurological and psychiatric disorders using the MINI International Neuropsychiatric Interview and routine neurological testing, as well as a detailed questionnaire regarding current and past psychiatric and neurological disorders in case of participants and also in their families. Subjects with any neurological and current or lifetime DSM-IV Axis I psychiatric disorders were excluded. All study participants were female, because the frequency of dominant affective temperaments is different in males and females suggesting a possible gender difference in the background of affective temperaments. We included only women to ensure a homogenous sample. The study protocol was approved by the Scientific and Research Ethics Committee of the Scientific Health Council of Hungary in charge of genetic experimentation concerning human subjects. All subjects gave informed consent before participating in the study.

The participants completed the Hungarian standardised version of the TEMPS-A questionnaire (Rozsa et al., 2008). The questionnaire measures affective temperaments in five scales: depressive, cyclothymic, hyperthymic, irritable and anxious.

All participants were genotyped for 5-HTTLPR with PCR. PCR amplification of 5-HTTLPR was performed on genomic DNA extracted from buccal cells (Walsh et al., 1991), and 5-HTTLPR genotypes were identified as previously reported (Heils et al., 1996).

All statistical analyses were carried out using Statistica 7.0 for Windows. In all cases our subjects were divided into genotype groups (additive model; subjects with either of the 3 different genotypes: ss, sl, ll) and phenotype groups (dominant model; subjects

Table 1
Logistic regression: effect of TEMPS-A temperament scales on phenotype grouping (s allele-no s allele)

	df	Wald stat	*p*
Intercept	1	0.1706	0.6796
Depressive	1	0.7447	0.3882
Cyclothymic	1	1.2814	0.2576
Hyperthymic	1	0.6550	0.4183
Irritable	1	0.7304	0.3928
Anxious	1	0.1367	0.7116

carrying the s allele and subjects not carrying the s allele). We compared test scores in the sample according to both types of distribution of the subjects. To investigate the relationship between the five affective temperament scales and the presence of the s allele, we performed logistic regression. We used ANOVA to compare the scores of the genotype and phenotype groups on the TEMPS-A scales, subscales and individual items. 0.05 was accepted as level of significance. In case of the scale composed of the items with a significant difference, we performed item analysis and computed Cronbach alpha. Deviations from the Hardy–Weinberg equilibrium were calculated for our study sample.

3. Results

The frequency of the s allele in the population was 38.77% which parallels the results of earlier studies and is representative of the Caucasian population (Lesch et al., 1996). The frequency of sl, ll and ss genotypes were 50%, 36.23%, and 13.77%, respectively. The distribution of genotypes in our population followed the Hardy–Weinberg equilibrium ($\chi^2 = 0.38934$, $p = 0.8231$).

3.1. Association of the TEMPS-A scales with the 5-HTTLPR

We performed logistic regression to identify the association between the affective temperaments and presence of the s allele. In the logistic regression model the effect of none of the scales was significant (Table 1).

Table 3
Post hoc LSD tests for scales with significantly different scores in the three genotype groups (ss, sl and ll)

	sl vs ll *p*
Depressive	0.0132
Cyclothymic	0.0017
Hyperthymic	
Irritable	0.0103
Anxious	0.0190

In the next step we analysed our scales in a forward stepwise regression model. In this model, only cyclothymic temperament appeared to have a significant effect (Wald = 7.3705, $p = 0.0066$; Table 1).

In the next step we compared the scores of subjects in the different genotype and phenotype groups on the five TEMPS-A temperament scales. In accordance with our earlier results, there was a significant association between the 5-HTTLPR genotypes and those affective temperaments which carry a depressive component, i.e. depressive, cyclothymic, irritable and anxious (Table 2). There was no significant association in case of the hyperthymic temperament (Table 2) Mean score and SE of the temperament scales are shown in Table 2. In all cases, post hoc LSD tests indicated that the observed differences were significant between the sl and ll groups. Results of the post hoc LSD tests are shown in Table 3.

As for the comparison of the two phenotype groups, similarly there was a strong significant association for the depressive, cyclothymic, irritable and anxious temperaments, with no significant association in case of the hyperthymic temperament (Table 4).

3.2. Association of subscales composing the TEMPS-A scales with the 5-HTTLPR

There was a significant difference concerning the scores of the subscales composing the TEMPS-A scales according to genotype grouping. In case of the depressive temperament, there was a significant association in case of the Low self-esteem subscale. Within the cyclothymic

Table 2
Analysis of variance table for affective temperament scores associated with genotypes ss ($n = 19$), sl ($n = 69$) and ll ($n = 50$)

	Mean ± SE			SS effect	*df* effect	MS effect	SS error	*df* error	MS error	*F*	*p*
	ss $n = 19$	sl $n = 69$	ll $n = 50$								
Depressive	7.10±0.59	7.34±0.0.40	5,98±0,34	56.05	2	28.02	1162.42	135	8.61	3.25	0.0416
Cyclothymic	5.05±0.77	6.55±0.51	4,34±0,43	147.00	2	73.50	1871.24	135	13.86	5.30	0.0061
Hyperthymic	9.89±0.79	10.10±0.45	10,72±0,64	14.66	2	7.33	2174.16	135	16.10	0.46	0.6353
Irritable	3.58±0.60	4.87±0.45	3,30±0,38	77.95	2	38.97	1422.96	135	10.54	3.70	0.0273
Anxious	8.42±1.15	8.14±0.64	5,94±0,63	164.64	2	82.32	3378.00	135	25.02	3.29	0.0403

Table 4
Analysis of variance table for psychometric scores of subjects carrying the s allele ($n=88$) and subjects not carrying the s allele ($n=50$)

	Mean ± SE		SS effect	*df* effect	MS effect	SS error	*df* error	MS error	*F*	*P*
	Subjects carrying the s allele ($n=88$)	Subjects not carrying the s allele ($n=50$)								
Depressive	7.30±0.34	5.98±0.34	55.17	1	55.17	1163.30	136	8.55	6.45	0.0122
Cyclothymic	6.23±0.44	4.34±0.43	113.56	1	113.56	1904.68	136	14.00	8.11	0.0051
Hyperthymic	10.06±0.39	10.72±0.64	14.02	1	14.02	2174.80	136	15.99	0.88	0.3507
Irritable	4.59±0.38	3.30±0.38	53.13	1	53.13	1447.77	136	10.65	4.99	0.0271
Anxious	8.20±0.56	5.94±0.63	163.51	1	163.51	3379.14	136	24.85	6.58	0.0114

dimension, there was a significant association in case of the Variability, the Cyclicity, and the Intensity subscale. In case of the irritable dimension, there was a significant association for the Restlessness and the Aggression subscale. In case of the anxious temperament, there was a significant association for the Fear prone subscale (Table 5). There was no significant association with any of the hyperthymic subscales (Table 5). Post hoc tests indicated that the observed significant differences occurred between the ss and ll and sl and ll groups in

Table 5
Analysis of variance table and results of post hoc LSD tests for affective temperament subscale scores associated with genotypes ss ($n=19$), sl ($n=69$) and ll ($n=50$)

	SS effect	*df* effect	MS effect	SS error	*df* error	MS error	*F*	*p*	Mean±SE			Post hoc LSD *p*		
									ss	sl	ll	ll-sl	ll-ss	sl-ss
Depressive														
Introversion	1.02	2	0.51	123.80	135	0.92	0.56	0.5739	0.84±0.22	1.10±0.12	1.02±0.13			
Low self-esteem	**7.07**	**2**	**3.53**	**101.35**	**135**	**0.75**	**4.71**	**0.0106**	**1.00±0.23**	**1.13±0.11**	**0.64±0.10**	**0.0028**		
Pessimistic	2.53	2	1.26	75.88	135	0.56	2.25	0.1095	0.42±0.14	0.49±0.11	0.20±0.08			
Sensitivity	4.13	2	2.07	154.51	135	1.14	1.81	0.1683	1.42±0.23	1.54±0.14	1.16±0.13			
Altruism	0.90	2	0.45	44.21	135	0.33	1.37	0.2568	1.37±0.11	1.28±0.07	1.14±0.08			
Cyclothymic														
Variability	**15.19**	**2**	**7.60**	**333.80**	**135**	**2.47**	**3.07**	**0.0496**	**1.47±0.38**	**1.99±0.21**	**1.28±0.19**	**0.0170**		
Cyclicity	**11.10**	**2**	**5.55**	**224.81**	**135**	**1.67**	**3.33**	**0.0386**	**1.32±0.19**	**1.71±0.18**	**1.10±0.15**	**0.0120**		
Instability	3.37	2	1.69	90.87	135	0.67	2.51	0.0854	0.47±0.14	0.70±0.12	0.36±0.08			
Intensity	**8.16**	**2**	**4.08**	**169.06**	**135**	**1.25**	**3.26**	**0.0415**	1.63±0.26	1.93±0.14	1.40±0.15	0.0123		
Hyperthymic														
Fun loving	3.03	2	1.52	400.57	135	2.97	0.51	0.6010	3.58±0.25	3.52±0.16	3.84±0.32			
High self-esteem	5.65	2	2.82	320.50	135	2.37	1.19	0.3074	3.05±0.36	2.94±0.17	3.38±0.24			
Narcissistic	0.62	2	0.31	166.83	135	1.24	0.25	0.7779	1.42±0.27	1.62±0.13	1.60±0.15			
Risk taking	0.91	2	0.45	80.09	135	0.59	0.77	0.4673	0.95±0.19	1.07±0.10	0.90±0.10			
Sociable	0.04	2	0.02	78.28	135	0.58	0.04	0.9646	0.79±0.14	0.78±0.09	0.82±0.12			
Irritable														
Restlessness	**8.67**	**2**	**4.33**	**147.11**	**135**	**1.09**	**3.98**	**0.0210**	**1.21±0.29**	**1.06±0.14**	**0.58±0.11**	**0.0149**	**0.0266**	
Aggression	**6.23**	**2**	**3.11**	**136.35**	**135**	**1.01**	**3.08**	**0.0491**	**0.42±0.18**	**0.97±0.13**	**0.62±0.13**			**0.0165**
Critical of others	1.85	2	0.93	75.77	135	0.56	1.65	0.1957	0.47±0.16	0.83±0.10	0.76±0.10			
Dysphoric emotionally	0.21	2	0.11	30.69	135	0.23	0.47	0.6287	0.26±0.10	0.23±0.07	0.16±0.05			
Complaining	6.55	2	3.28	145.59	135	1.08	3.04	0.0512	0.63±0.17	1.10±0.14	0.68±0.13			
Anxious														
Worrying about kin	13.25	2	6.62	428.99	135	3.18	2.08	0.1284	1.63±0.42	1.81±0.22	1.14±0.24			
Inability to relax	3.17	2	1.58	175.22	135	1.30	1.22	0.2982	1.32±0.24	1.23±0.14	0.94±0.16			
Somatic anxiety	3.31	2	1.66	126.81	135	0.94	1.76	0.1752	1.11±0.20	1.22±0.12	0.88±0.14			
Fear prone	**24.81**	**2**	**12.40**	**343.08**	**135**	**2.54**	**4.88**	**0.0090**	**2.68±0.36**	**2.14±0.20**	**1.46±0.22**	**0.0222**	**0.0051**	
Autonomic anxiety	1.44	2	0.72	148.21	135	1.10	0.66	0.5201	1.00±0.25	1.23±0.12	1.04±0.15			

Subscales with $p<0.05$ are shown in bold letters.

Table 6
Analysis of variance table for psychometric scores of subjects carrying the s allele ($n=88$) and subjects not carrying the s allele ($n=50$)

	SS effect	*df* effect	MS effect	SS error	*df* error	MS error	*F*	*p*	Mean ± SE	
									Subjects carrying the s allele ($n=62$)	Subjects not carrying the s allele ($n=62$)
Depressive										
Introversion	0.02	1	0.02	124.80	136	0.92	0.02	0.8810	1.05±0.10	1.02±0.13
Low self-esteem	**6.81**	**1**	**6.81**	**101.60**	**136**	**0.75**	**9.12**	**0.0030**	**1.10±0.10**	**0.64±0.10**
Pessimistic	**2.45**	**1**	**2.45**	**75.95**	**136**	**0.56**	**4.39**	**0.0380**	**0.48±0.09**	**0.20±0.08**
Sensitivity	3.94	1	3.94	154.71	136	1.14	3.46	0.0650	1.51±0.12	1.16±0.13
Altruism	0.77	1	0.77	44.34	136	0.33	2.36	0.1265	1.30±0.06	1.14±0.08
Cyclothymic										
Variability	**11.29**	**1**	**11.29**	**337.71**	**136**	**2.48**	**4.55**	**0.0348**	**1.88±0.18**	**1.28±0.19**
Cyclicity	**8.79**	**1**	**8.79**	**227.13**	**136**	**1.67**	**5.26**	**0.0233**	**1.63±0.15**	**1.10±0.15**
Instability	**2.64**	**1**	**2.64**	**91.60**	**136**	**0.67**	**3.92**	**0.0498**	**0.65±0.10**	**0.36±0.08**
Intensity	**6.85**	**1**	**6.85**	**170.36**	**136**	**1.25**	**5.47**	**0.0208**	**1.86±0.12**	**1.40±0.15**
Hyperthymic										
Fun loving	2.98	1	2.98	400.62	136	2.95	1.01	0.3160	3.53±0.14	3.84±0.32
High self-esteem	5.47	1	5.47	320.68	136	2.36	2.32	0.1302	2.97±0.15	3.38±0.24
Narcissistic	0.01	1	0.01	167.44	136	1.23	0.01	0.9173	1.58±0.12	1.60±0.15
Risk taking	0.67	1	0.67	80.32	136	0.59	1.14	0.2871	1.05±0.09	0.90±0.10
Sociable	0.04	1	0.04	78.28	136	0.58	0.07	0.7897	0.78±0.08	0.82±0.12
Irritable										
Restlessness	**8.32**	**1**	**8.32**	**147.45**	**136**	**1.08**	**7.68**	**0.0064**	**1.09±0.12**	**0.58±0.11**
Aggression	1.72	1	1.72	140.86	136	1.04	1.66	0.1997	0.85±0.11	0.62±0.13
Critical of others	0.00	1	0.00	77.62	136	0.57	0.01	0.9405	0.75±0.08	0.76±0.10
Dysphoric emotionally	0.20	1	0.20	30.71	136	0.23	0.87	0.3517	0.24±0.06	0.16±0.05
Complaining	3.26	1	3.26	148.88	136	1.09	2.98	0.0864	1.00±0.12	0.68±0.13
Anxious										
Worrying about kin	**12.76**	**1**	**12.76**	**429.47**	**136**	**3.16**	**4.04**	**0.0464**	**1.77±0.19**	**1.14±0.24**
Inability to relax	3.06	1	3.06	175.32	136	1.29	2.38	0.1255	1.25±0.12	0.94±0.16
Somatic anxiety	3.13	1	3.13	127.00	136	0.93	3.35	0.0694	1.19±0.10	0.88±0.14
Fear prone	**20.48**	**1**	**20.48**	**347.41**	**136**	**2.55**	**8.02**	**0.0053**	**2.26±0.17**	**1.46±0.22**
Autonomic anxiety	0.64	1	0.64	149.01	136	1.10	0.59	0.4456	1.18±0.11	1.04±0.15

Subscales with $p<0.05$ are shown in bold letters.

Table 7
Items with significantly different scores in the three genotype groups (sl, ll and ss)

Item	Mean score			*F*	*p*	Post hoc LSD *p*		
	sl	ll	ss			sl-ll	ss-ll	sl-ss
17D—I would rather look for someone else than be the boss	0.59	0.36	0.58	3.5068	0.0328	0.0116		
23C—I get sudden shifts in mood and energy	0.43	0.26	0.16	3.6271	0.0292	0.0446		0.0229
29C—My mood often changes for no reason	0.35	0.14	0.11	4.7386	0.0103	0.0082	0.0263	
32C—I sometimes go to bed feeling great and wake up in the morning feeling life is not worth living	0.09	0.00	0.00	3.2143	0.0433	0.0216		
38C—The way I see things is sometimes vivid, but at other times lifeless	0.20	0.08	0.00	3.6970	0.0273	0.0480	0.0196	
39C—I am the kind of person who can be sad and happy at the same time	0.42	0.20	0.16	4.6406	0.0112	0.0094	0.0260	
64I—I am a grouchy (irritable) person	0.33	0.14	0.05	5.2531	0.0064	0.0115	0.0086	
73I—People tell me I blow up out of nowhere	0.33	0.16	0.11	3.5838	0.0304	0.0280	0.0381	
77I—I can get so furious I could hurt someone	0.33	0.16	0.05	4.6339	0.0113	0.0254		0.0097
98A—When someone is late coming home, I fear they have had an accident.	0.35	0.32	0.63	3.1676	0.0452		0.0171	0.0237
107A—I am an insecure person	0.49	0.28	0.58	3.8386	0.0239	0.0199		0.0242

Table 8
Items with significantly different scores in the two phenotype groups (subjects carrying and not carrying the s allele)

	Mean score		*F*	*p*
	Subjects carrying the s allele	Subjects not carrying the s allele		
4D I think things often turn out for the worst	0.1932	0.06000	4.6513	0.0328
7D I have always blamed myself for what others might consider no big deal.	0.4659	0.28000	4.6867	0.0321
17D I would rather work for someone else than be the boss.	0.5909	0.36000	7.0504	0.0089
24C My moods and energy are either high or low, rarely in between.	0.1364	0.02000	5.1760	0.0244
29C My mood often changes *for no reason*.	0.2954	0.14000	4.3056	0.0399
39C I am the kind of person who can be sad and happy at the same time.	0.3636	0.20000	4.0936	0.0450
42C I am the kind of person who falls in and out of love easily.	0.1932	0.06000	4.6513	0.0328
68I I often feel on edge.	0.3182	0.16000	4.2036	0.0423
69I I often feel wound up.	0.4546	0.26000	5.2203	0.0239
94A I often have an upset stomach.	0.3409	0.18000	4.1348	0.0440
100A I'm always thinking someone might break bad news to me about a family member.	0.1818	0.040000	5.8099	0.0173
107A I'm an insecure person.	0.5114	0.28000	7.2381	0.0080

case of all subscales except for the Aggression subscale, which is in line with the dominance of the s allele.

We also observed significant differences in temperamental subscale scores with respect to phenotype grouping. In case of the depressive temperament, there was a significant difference between the two phenotype groups on the Low self-esteem and Pessimistic subscales. In case of the cyclothymic temperament all four subscale dimensions showed a significant association: Variability, Cyclicity, Instability and Intensity. In case of the irritable temperament, there was a significant association with the Restlessness subscale. In case of the anxious temperament, there was a significant association for the Worrying about kin and Fear prone scales. There was again no association with any of the hyperthymic subscales (Table 6).

3.3. Association of individual items of the TEMPS-A with the 5-HTTLPR

In the next step, we selected the items with scores with a significant difference between the three genotype groups. Items, mean scores, *F* and *p* values and results of post hoc LSD test are shown in Table 7. We also selected items with significant difference for the two phenotype groups. Items, mean scores, *F* and *p* values are shown in Table 8. We performed item analyses on both of our new derived scales.

Table 9
Item analysis for the Genotype Derived Scale: items with significantly different scores in the 3 genotype groups (ss, sl and ll)

	All items with significantly ($p<0.05$) different scores in the three genotype groups (Original 5-HTTLPR Genotype Derived Scale) Standardized Cronbach alpha=0.6377					Items remaining after deleting items with item-total correlation less than 0.2 (5-HTTLPR Genotype Derived Scale) Standardized Cronbach alpha=0.6921				
	Mean if deleted	Variance if deleted	SD if deleted	Item-Total correlation	Alpha if deleted	Mean if deleted	Variance if deleted	SD if deleted	Item-Total correlation	Alpha if deleted
17D	2.5507	4.2474	2.0609	0.0313	0.6442					
23C	2.7246	3.4024	1.8446	0.5389	0.5192	1.5362	2.2342	1.4947	0.5999	0.5839
29C	2.8188	3.5686	1.8891	0.5034	0.5343	1.6304	2.3779	1.5420	0.5640	0.5994
32C	3.0145	4.2607	2.0641	0.3084	0.5914	1.8261	3.0277	1.7400	0.3276	0.6671
38C	2.9275	3.9078	1.9768	0.4060	0.5648	1.7391	2.7001	1.6432	0.4412	0.6375
39C	2.7536	4.1422	2.0352	0.1110	0.6221					
64I	2.8333	3.8635	1.9656	0.3195	0.5761	1.6449	2.6493	1.6277	0.3521	0.6541
73I	2.8188	3.8730	1.9680	0.3019	0.5796	1.6304	2.7112	1.6466	0.2909	0.6691
77I	2.8261	3.9263	1.9815	0.2735	0.5857	1.6377	2.7528	1.6592	0.2649	0.6750
98A	2.6812	4.0867	2.0216	0.1226	0.6218					
107A	2.6304	3.8127	1.9526	0.2611	0.5895	1.4420	2.6959	1.6419	0.2223	0.6935

Table 10
Item analysis: items with scores of significant difference in case of the two phenotype groups (standardized Cronbach alpha=0.661906)

	All items with significantly ($p<0.05$) different scores in the two phenotype groups (Original 5-HTTLPR Phenotype Derived Scale) Standardized Cronbach alpha=0.6619					Items remaining after deleting items with item-total correlation less than 0.2 (5-HTTLPR Phenotype Derived Scale) Standardized Cronbach alpha=0.6866				
	Mean if deleted	Variance if deleted	SD if deleted	Item-Total correlation	Alpha if deleted	Mean if deleted	Variance if deleted	SD if deleted	Item-Total correlation	Alpha if deleted
4D	3.1739	4.8683	2.2064	0.3967	0.6294	2.2174	3.4890	1.8679	0.4480	0.6524
7D	2.9203	4.4067	2.0992	0.4680	0.6090	1.9638	3.1219	1.7669	0.4858	0.6371
17D	2.8116	4.9645	2.2281	0.1769	0.6664					
24C	3.2246	5.1307	2.2651	0.2966	0.6452	2.2681	3.8484	1.9617	0.2341	0.6868
29C	3.0797	4.6821	2.1638	0.4033	0.6243	2.1232	3.4124	1.8473	0.3857	0.6608
39C	3.0145	5.2317	2.2873	0.0784	0.6805					
42C	3.1739	5.2596	2.2934	0.1393	0.6644					
68I	3.0580	4.8662	2.2059	0.2836	0.6447	2.1014	3.4970	1.8700	0.3119	0.6760
69I	2.9348	4.3508	2.0859	0.5033	0.6019	1.9783	3.0647	1.7506	0.5289	0.6265
94A	3.0362	4.7451	2.1783	0.3368	0.6354	2.0797	3.5661	1.8884	0.2547	0.6883
100A	3.1884	5.1674	2.2732	0.2140	0.6544	2.2319	3.7578	1.9385	0.2534	0.6843
107A	2.8913	4.6186	2.1491	0.3504	0.6327	1.9348	3.2784	1.8106	0.3790	0.6630

Table 11
Analysis of variance table for affective temperament scales and the derived scales associated with genotypes ss ($n=19$), sl ($n=69$) and ll ($n=50$)

	Mean±SE			SS effect	*df* effect	MS effect	SS error	*df* error	MS error	*F*	*p*	Post hoc LSD		
	ss $n=19$	ll $n=50$	sl $n=69$									sl-ll	ss-ll	ss-sl
Original Phenotype Derived Scale	3.58±0.56	2.04±0.23	4.17±0.29	133.51	2	66.75	640.47	135	4.74	14.07	0.000003	0.000001	0.0098	
Final Phenotype Derived Scale	2.68±0.48	1.42±0.21	2.96±0.26	70.73	2	35.36	509.16	135	3.77	9.38	0.000154	0.000038	0.0170	
Original Genotype Derived Scale	2.42±0.34	2.10±0.25	3.93±0.27	105.77	2	52.88	523.77	135	3.88	13.63	0.000004	0.000002		0.0037
Final Phenotype Derived Scale	0.47±0.19	0.94±0.17	2.07±0.22	57.84	2	28.92	314.20	135	2.33	12.43	0.000011	0.0001		0.0009

3.3.1. Item analysis

We considered items with significantly different scores in the three genotype groups as composing an Original 5-HTTLPR Genotype Derived Scale. We carried out item analysis to establish the internal consistency of this new scale. The Original 5-HTTLPR Genotype Derived Scale consisted of 11 items, standardized Cronbach alpha was 0.6377. In the next step we omitted items with item-total correlations less than 0.2 (items 17, 39 and 98). The resulting Final 5-HTTLPR Genotype Derived Scale composed of the remaining items consisted of 8 items, standardized Cronbach alpha was 0.6921 (Table 9).

We carried out items analysis also in case of the items with significantly different scores in the two phenotype

Table 12
Analysis of variance table for psychometric scores of subjects carrying the s allele ($n=88$) and subjects not carrying the s allele ($n=50$) on the derived scales

	Mean±SE		SS effect	*df* effect	MS effect	SS error	*df* error	MS error	*F*	*p*
	Subjects carrying the s allele $n=88$	Subjects not carrying the s allele $n=50$								
Original Phenotype Derived Scale	4.05±0.26	2.04±0.23	128.23	1	128.23	645.74	136	4.75	27.01	0.000001
Final Phenotype Derived Scale	2.90±0.23	1.42±0.21	69.62	1	69.62	510.26	136	3.75	18.56	0.000031
Original Genotype Derived Scale	3.60±0.23	2.10±0.25	71.96	1	71.96	557.58	136	4.10	17.55	0.00005
Final Genotype Derived Scale	1.73±0.19	0.94±0.17	19.76	1	19.76	352.28	136	2.59	7.63	0.0065

Table 13
The items composing the 5-HTTLPR Genotype Derived Scale

23C–I get sudden shifts in mood and energy
29C–My mood often changes for no reason
32C–I sometimes go to bed feeling great and wake up in the morning feeling life is not worth living
38C–The way I see things is sometimes vivid, but at other times lifeless
64I–I am a grouchy (irritable) person
73I–People tell me I blow up out of nowhere
77I–I can get so furious I could hurt someone
107A–I am an insecure person

groups. The Original 5-HTTLPR Phenotype Derived Scale consisted of 12 items. Standardized Cronbach alpha for the Original 5-HTTLPR Phenotype Derived Scale was 0.6619. After dropping items with item-total correlations less than 0.2 (items 17, 39 and 42), 9 items remained and composed the Final 5-HTTLPR Phenotype Derived Scale. Standardized Cronbach alpha for the Final 5-HTTLPR Phenotype Derived Scale was 0.6866 (Table 10).

3.4. Association of the scores of the derived scales with the 5-HTTLPR

We compared the scores of subjects in the three genotype groups (ss, sl and ll) in case of all four of the derived scales (Original 5-HTTLPR Genotype Derived Scale, 5-HTTLPR Genotype Derived Scale, Original 5-HTTLPR Phenotype Derived Scale, 5-HTTLPR Phenotype Derived Scale). Subjects in the three genotype groups had significantly different scores in all four derived scales (Table 11). Post hoc LSD test indicates that the significant difference occurred between sl and ll and also between ss and ll groups in case of the Phenotype Derived Scales, while there was a significant difference between sl and ll as well as ss and sl groups in case of the new Genotype Derived Scales (Table 11). Subjects in the two phenotype groups also had significantly different scores in all 4 derived scales (Table 12). The Final 5-HTTLPR Genotype and Phenotype Derived Scales are shown in Tables 13 and 14.

4. Discussion

With our present study we confirm and extend our previous results regarding the association of affective temperaments carrying more or less of a depressive component with the 5-HTTLPR polymorphism of the serotonin transporter gene (Gonda et al., 2006). We have found that depressive, cyclothymic, anxious and irritable temperaments, as well as several subscales related to them, are significantly related to both presence of the s allele and genotype grouping. No significant relationship between the 5-HTTLPR and hyperthymic temperament or any of its subscales was detected. In line with our previous results and our expectations, only cyclothymic temperament predicts significantly if a subject carries the s allele. Despite of this and that the strongest association for both phenotype and genotype grouping was found in case of the cyclothymic temperament, our results indicate that all affective temperaments within the depressive superfactor (depressive, cyclothymic, irritable and anxious temperaments) equally share the association with the 5-HTTLPR.

Our data in comparing the scores of three genotype groups on scales and subscales of the TEMPS-A instrument confirms the dominance of the s allele, since with the exception of the aggression subscale of the Irritable temperament, significant differences occurring between the three genotype groups were always between the ss and ll or sl and ll genotypes. So we proceed by analysing our results concerning the two phenotype groups.

It has been described that the s allele of the 5-HTTLPR is significantly associated with increased neuroticism and neuroticism-related scale scores (Hantouche et al., 1998; Katsuragi et al., 1999; Lesch et al., 1996; Mazzanti et al., 1998; Melke et al., 2001; Sen et al., 2004) and neuroticism-related psychiatric disorders (Bellivier et al., 1998, 2002; Bengel et al., 1999; Collier et al., 1996). Our group has also found evidence of the significant relationship between this allele and factors associated with neuroticism such as subthreshold depression (Gonda et al., 2005) and anxiety (Gonda et al., 2007) within a healthy population. Neuroticism is a complex phenomenon related to a tendency to experience negative emotional states encompassing such factors and characteristics as increased tendency towards depression and anxiety, increased emotional lability, increased tendency for somatization of psychological problems, tendency to experience guilt and hostility (Cartwright, 1974; Costa and McCrae, 2005; Eysenk,

Table 14
The items composing the 5-HTTLPR Phenotype Derived Scale

4D–I think things often turn out for the worst
7D–I have always blamed myself for what others might consider no big deal.
24C–My moods and energy are either high or low, rarely in between.
29C–My mood often changes for no reason.
68I–I often feel on edge.
69I–I often feel wound up.
94A–I often have an upset stomach.
100A–I'm always thinking someone might break bad news to me about a family member.
107A–I'm an insecure person.

1987; McCrae and Costa, 1996; Miller and Pilkonis, 2006). Increased affective lability and affective reactibility is conceived in affective temperaments as well. Affective temperaments also represent a continuum towards the manifestation of minor and major affective disorders (Akiskal, 1996). By definition, affective temperaments are subtle, subaffective manifestation of an increased tendency for affective disorder detectable in a healthy population, and in their dominant form they present a risk factor for the development of both unipolar and bipolar forms of affective disorder (Akiskal and Akiskal, 1992). Thus our results, besides further confirming the association of depressive affective temperaments with the 5-HTTLPR, also provide a bridge towards results concerning the significant association of this polymorphism with DSM-IV affective disorders, even on subaffective or temperamental level.

In our present study, however, we went further into investigating the relationship of the 5-HTTLPR polymorphism with affective temperaments and analysed this association in case of subscales composing each of the temperaments. We have found that all the subscales associated with the cyclothymic temperament were in a significant relationship with the presence of the s allele, again supporting that the cyclothymic temperament is the most strongly related to this polymorphism. In case of the other affective temperaments within the depressive superfactor, some but not all subscales showed a significant association, which is in line with the polygenic and multifactorial nature of the emergence and manifestation of affective temperaments, indicating a role for other genetic and environmental factors as well.

To have a deeper understanding of the nature of the association of the affective temperaments with the s allele, we investigated the association of each of the individual items with this polymorphism. We found that there were 12 items which significantly differentiated between subjects carrying and not carrying the s allele (Original 5-HTTLPR Phenotype derived scale). In case of all items, subjects carrying the s allele had a higher mean score meaning they were more likely to agree with the given item. After item analysis, 3 items were dropped (5-HTTLPR Phenotype derived scale). Our results indicate that both of these derived scales differentiate significantly between subjects carrying and not carrying the s allele and also that in case of these two derived scales the level of significance is much higher than in case of the original temperament scales. Both derived scales contain items from all four temperament scales composing the depressive superfactor, that is, the depressive, cyclothymic, irritable and anxious temperaments, indicating that despite of our previous results showing that the cyclothymic temperament is the one most strongly associated with the 5-HTTLPR, all of the above temperaments share this relationship. This indicates a general role of the 5-HTTPLPR in the development of subthreshold affective characteristics, rather then being associated with only one type of affective temperament. Also, what these four temperaments share in common is the depressive component, so it requires further investigation, whether it is only the depressive component incorporated in these temperaments that carries the association with the 5-HTTLPR. The fact that not the depressive, but the cyclothymic temperament shows the strongest association with the 5-HTTLPR, and also that all subscales of cyclothymic temperament are associated with presence of the s allele, argues against this.

Our results indicating that the 5-HTTLPR s allele is associated with cyclothymic, depressive, anxious and irritable temperaments and also with several types of anxiety and affective disorders suggests that presence of the 5-HTTLPR conveys a general vulnerability towards the manifestation of threshold and subthreshold anxiety and affective disturbances, which vulnerability is conceptualised in such trait and temperament concepts as neuroticism and affective temperaments. Keeping in mind the polygenic and multifactorial nature of both traits and temperaments on one hand, and psychiatric disorders on the other, we can expect that the exact type of symptomatology that will develop in the presence of the s allele depends on the effect of other genes, environmental factors, and the interactions between these.

The new 5-HTTLPR Phenotype Derived Scale we derived contains items related to pessimism (4), sensitivity (7), mood variability (24, 29), restlessness (68, 69), bodily reactions to anxiety (94), and fear proneness (100, 107). This in general composes a picture which is congruent with the description of people scoring high on the neuroticism scale. Taken together, although our results emphasize that 5-HTTLPR is most strongly related to the cyclothymic temperament, it seems that the presence of the s allele may lead to a general disposition towards the increased risk to manifest a more marked form of any one of affective temperaments composing the depressive superfactor, and differentiation within this factor, the relative prominence of the depressive temperaments will be a function of factors other than 5-HTTLPR genotype. Therefore it is an important development in the model of affective temperaments that it sensitively distinguishes within threshold and subthreshold neuroticism-related pathology. On the other hand, however, if personality components traditionally subsumed under the category

of neuroticism most strongly relate to the s allele of the serotonin transporter gene and so is cyclotyhmia (the core feature of bipolar mood disorder spectrum), then it may be worthy of consideration that neuroticism in its original sense should be modified from its traditional meaning to encompass the other extreme of mood lability, which seems to be an integral part of this concept, or a new "bipolarism" personality trait concept should be outlined and validated in terms of its association to personality components and the s allele.

Furthermore, our new derived scale may provide a behavioural endophenotype associated with the 5-HTTLPR genotype able to predict the presence of the s allele to a high degree. It warrants further investigation what role and what power our new derived scale has in differentiating between psychiatric patients with different affective symptomatology. The relationship of the new scale with subtypes of depression should be studied in further detail, as well as its differential association with suicidal behaviour in depression, since a significant association between the 5-HTTLPR s allele and suicide has been described (Li and He, 2007). Also, it has been described in several studies that 5-HTTLPR genotype is related to antidepressant drug response, with s allele carriers showing less favourable response to SSRIs (Lesch and Gutknecht, 2005; Murphy et al., 2004; Pollock et al., 2000; Serretti et al., 2007; Smeraldi et al., 1998; Zanardi et al., 2000). Our new scale showing a strong association with 5-HTTLPR genotype and the presence of the s allele therefore might have a role in predicting antidepressant response in patient groups. This association should also be investigated.

A limitation of our paper is that our sample included only women. However, the frequency of dominant forms of affective temperaments is different in males and females (Placidi et al., 1998; Rozsa et al., 2008), therefore we chose to include only women in order to obtain a homogenous sample. Further studies are needed to explore the relationship of TEMPS-A items with 5-HTTLPR genotype in males and to compare the results obtained with the two genders.

Role of the funding sources

Funding for this study was provided by the Sixth Framework Programme of the EU, LSHM-CT-2004-503474, the Ministry of Welfare Research Grant 460/2006, the Hungarian Research Fund Grants 022256/1997 and 032398/2000 and the PhD Fellowship Program of the Semmelweis University, Ministry of Culture and Education, Hungary.

The funding sources had no involvement in influencing the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

None of the authors have any conflicts of interests to declare.

Acknowledgements

These studies were supported by the Sixth Framework Programme of the EU, LSHM-CT-2004-503474, the Ministry of Welfare Research Grant 460/2006, the Hungarian Research Fund Grants 022256/1997 and 032398/2000 and the PhD Fellowship Program of the Semmelweis University, Ministry of Culture and Education, Hungary.

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