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The Serotonin Receptor 2A Gene Moderates the Influence of Parental Socioeconomic Status on Adulthood Harm Avoidance

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Abstract We examined whether the T102C polymorphism of the serotonin receptor 2A gene (HTR2A) moderated the influence of childhood or adolescence parental socioeconomic status (SES) on adulthood temperament trait harm avoidance (HA) in a population-based sample of 1246 healthy Finnish men and women, who were 24–39 years of age in the last follow-up phase. High parental SES predicted low adulthood HA. In addition, the C allele of the T102C polymorphism was associated with high HA in one of the two test settings, and with the mean of the two measurements. Most importantly, we found that the T102C polymorphism moderated the influence of parental SES, such that high parental SES predicted low adulthood HA in subjects with the T/T or T/C genotypes, while this was not true for those carrying the C/C genotype. The role of the T102C polymorphism was most pronounced among those with high parental SES. We conclude that the T102C polymorphism of the HTR2A gene may be involved in the development of temperament by moderating the influence of environmental conditions.

Keywords Temperament · Personality development · Gene-environment interaction · HTR2A · TCI · Childhood

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Introduction

In the biosocial model of personality proposed by Cloninger and colleagues (Cloninger et al. 1987, 1993), temperament refers to biases in automatic responses to emotional stimuli. This model distinguishes four temperament traits: novelty seeking, harm avoidance, reward dependence and persistence. The traits are postulated to have independent genetic and neurobiological bases and to modulate responses to reinforcement and different classes of emotional stimuli. Temperament is involved in a wide range of developmental processes such as socialization (Kochanska 1991), cognitive development (Raine et al. 2002) and physical health (Keltikangas-Järvinen et al. 1999). The most important outcome of temperament is adulthood personality (McCrae et al. 2000).

Temperament is of high relevance in the context of stress, since it may determine what individuals perceive as stressful and how they respond to stressful stimuli (Bolger and Schilling 1991). It may therefore play a role in individual stress vulnerability (Fanous et al. 2002).

Even though temperament has a genetic basis, appears early in life and is relatively stable over time (McCrae et al. 2000), its manifestation may depend on environmental factors (Fox et al. 2005). Parental socioeconomic status (SES) is one of the most extensively studied factors of children's developmental environment. Parental SES is a global construct reflecting the availability of social, financial and human capital for the child (Bradley and Corwyn 2002). The effects of parental SES are observed in almost every domain of development, including social, cognitive and somatic development (see Bradley and Corwyn 2002; Repetti et al. 2002). Concerning stress, parental SES has been associated with socio-emotional development and coping skills, so that children with high parental SES tend

to become more resilient to stress later in life than children with low parental SES (see Bradley and Corwyn 2002; Repetti et al. 2002).

Accumulating evidence from molecular genetic studies suggests that genes may moderate the influence of environmental factors on behavioral endpoints (Berman and Noble 1997; Ozkaragoz and Noble 2000; Caspi et al. 2003; Eley et al. 2004; Fox et al. 2005; Grabe et al. 2005). In the context of human behavior, the first molecular studies on gene-environment interactions were carried out by Noble and colleagues, who found the dopamine receptor gene DRD2 to moderate the impact of family stress on cognitive functioning (Berman and Noble 1997) and personality (Ozkaragoz and Noble 2000) in adolescent boys. The interaction between dopamine receptor gene DRD4 and hostile childhood environment has also been shown to result in high levels of novelty seeking (Keltikangas-Järvinen et al. 2004). Studies investigating the serotonergic system have shown that the serotonin transporter gene 5-HTTLPR polymorphism may moderate the impact of negative life events on depression (Caspi et al. 2003; Eley et al. 2004) and physical health (Grabe et al. 2005). In addition, Manuck et al. (2004) found the 5-HTTLPR to moderate the association between adulthood SES and serotonergic functioning.

The purpose of the present study was to examine whether allelic variation in the T102C polymorphism of the serotonin receptor 2A gene (HTR2A) moderates the association between parental SES in childhood and adolescence and temperamental harm avoidance (HA) in adulthood. According to Cloninger (Cloninger et al. 1987) HA refers to behavioral inhibition and reactivity to aversive stimuli, and individuals with high HA are characterized as inhibited, cautious and fearful. HA has been shown to be related to stress vulnerability (Puttonen et al. 2005), and high HA may increase the susceptibility to affective disorders, such as depression (Farmer et al. 2003). Cloninger (Cloninger et al. 1987) suggested that serotonin is the primary neurotransmitter underlying HA. This assumption has been supported by neuroendocrinological (Peirson et al. 1999, Hansenne and Ansseu 1999) and genetic (Munafò et al. 2005) evidence.

The HTR2A gene in particular may be considered as a candidate gene for HA, since the binding potential of the 5-HT_{2A} receptors has been associated with HA (van Heeringen et al. 2003) and related traits (Moresco et al. 2002). The T102C polymorphism of the HTR2A gene has been associated with the binding potential of the 5-HT_{2A} receptors (Turecki et al. 1999), and with 5-HT_{2A} receptor mRNA levels in postmortem brain (Polesskaya and Sokolov 2002). These findings suggest that there might be an association between the T102C polymorphism and HA. This suggestion has, however, not been supported by studies carried out this far (Kusumi et al. 2002; Schüssler et al. 2000). The functional significance of the T102C polymorphism has also been questioned by a study (Bray et al. 2004) that found no evidence of polymorphisms in the HTR2A gene affects mRNA levels in the adult brain. These conflicting findings emphasize the need for additional studies.

We hypothesized that the C allele of the T102C polymorphism and low parental SES in childhood and adolescence are associated with high adulthood HA, and that the association between parental SES and adulthood HA is moderated by the T102C polymorphism. In order to provide a more reliable assessment of temperament, temperament was measured in two test settings taken four years apart. The independent role of parental SES was evaluated by controlling for the subject's own adulthood SES.

Materials and methods

Subjects

The subjects were 1246 healthy men (n = 559) and women (n = 687) participating in the on-going population-based study of 'Cardiovascular Risk in Young Finns' (CRYF; Åkerblom et al. 1991). In this prospective epidemiological study, a randomly selected sample of 3596 Finnish healthy children and adolescents from six birth cohorts (aged 3, 6, 9, 12, 15 and 18 years at the baseline) has been followed since 1980, with a focus on the development of risk factors of coronary heart disease. In the present study, a subsample of 1593 participants was selected at random for genotyping and, depending on the availability of temperament assessments, 966–1246 subjects had complete data (see Tables 1 and 2). All the subjects gave their written informed consent and gave blood samples in accordance with the Helsinki Declaration.

Measures

Parental socioeconomic status was assessed at the baseline (referred to as Year 0, the subjects being 3–18 years of age). Following a method used by Pulkki et al. (2003) in an earlier CRYF study, SES was measured by two indices: (a) the mother's and father's years of education and (b) the annual income of the household (measured on an eight-point scale). In the CRYF sample the correlation between the mother's and the father's years of education was r = .66, and the correlation between these two measures and household income was r = .45 and r = .50, respectively (all P values < .001). The SES indicator was constructed by calculating first the mean of the years of education of the mother and the father and then standard-

Table 1 Descriptive statistics (n = 1246)

	n (%)	Mean (SD)
Gender		
Men	559 (45.9)	
Women	687 (55.1)	
HTR2A T102C genotype		
T/T	129 (10.4)	
T/C	548 (44.0)	
C/C	569 (45.6)	
Age at Year 0		10.9 (5.0)
Year 17 Harm avoidance		91.2 (18.0)
Year 21 Harm avoidance		90.0 (18.5)
Subject's education (years)		14.6 (3.0)
Mother's education (years)		10.0 (3.2)
Father's education (years)		9.7 (3.7)
Household income		4.8 (1.9)
SES indicator		0.0 (1.7)

Note: Household income was measured on a 8-point scale. SES indicator was created from standardized parental education and household income scores (see text)

Table 2 The number of subjects by gender and age at Year 21

Age	Gender		
	Women	Men	Total
24	90	91	181
27	137	72	209
30	107	97	204
33	122	85	207
36	118	116	234
39	113	98	211
Total	687	559	1246

izing the mean into a Z score. Twelve percent of the subjects were living in single-parent households, for whom parental education was determined by the years of education of the single parent. Next, the annual income of the household was standardized into a Z score, and then the Z scores of education and income were summed, resulting in an index of parental socioeconomic status.

In order to evaluate the stability of parental SES, it was also assessed in the first follow-up of the CRYF, three years after the baseline. The correlation between baseline and Year-3 parental SES was r = .94 (P < .001) in the total CRYF sample (n = 2174). Given the very high stability, statistical analyses were carried out with the baseline assessment only, for which we had complete data on all the participants.

Assessments of temperament were made 17 and 21 years after the baseline (Years 17 and 21, subjects being 20–35, and 24–39 years of age, respectively). Harm avoidance was measured with the Temperament and Character Inventory (TCI) developed by Cloninger et al. (1993). The HA scale consists of 35 items which were self-rated by the subjects on a five-point scale ranging from totally disagree (1) to totally agree (5). The Cronbach's alpha reliability was α = .92 for both Year-17 and Year-21 HA. The correlation between Year-17 and Year-21 HA was r = .78 (P < .001).

The subject's own adulthood socioeconomic status was measured by years of education of the subject. Data on the subject's adulthood income was not available.

HTR2A 102 T>C (34 S/S) genotyping

Genomic DNA was extracted from peripheral blood using a commercially available kit (Qiagen Inc., Hilden, Germany). DNA samples were genotyped by employing the 5' nuclease assay and fluorogenic TaqMan MGB probe (Livak 1999) using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA). The nucleotide sequences of primers and allele-specific probes, labeled with the reporter dyes FAM or VIC, were deduced from sequences deposited in the GenBank database and synthesized in conjugation with Applied Biosystems using the TaqMan® Validated SNP Genotyping Assay (SNP rs6313, assay ID: C-3042197-1). PCR reaction containing genomic DNA, 1 × Universal PCR Master Mix, 900 nM of each primer and 200 nM of each probe was performed in 96-well plates using the standard protocol in a total volume of 25 µl. After PCR amplification, the endpoint reading of the fluorescence signal generated from each probe was measured by the allelic discrimination analysis module, resulting in clear identification of three genotypes.

Statistical analysis

The main effects of the HTR2A gene were assessed with univariate analysis of covariance (controlling for age and gender) and the main effects of SES with linear regression analysis (controlling for age, gender and adulthood years of education). Multiple regression analysis was used to assess the association of the HTR2A gene (coded as a continuous variable representing the number of C-alleles: T/T = 0, T/C = 1, C/C = 2), parental SES and their interaction on harm avoidance, with gender, age and adulthood years of education as covariates. Three separate regression models were tested, with the dependent variables being (1) Year-17 HA, (2) Year-21 HA, and (3) the mean of those two measurements, which was calculated for subjects who had data on both assessment times.

Results

The descriptive statistics of the sample and study variables are shown in Tables 1 and 2.

Table 3 shows harm avoidance scores by genotype groups. There was a linear association between T102C polymorphism and Year-21 HA, such that the C/C genotype group had the highest and the T/T genotype group the lowest HA (P = .019, linear contrast P = .027). The other findings were in line with this. Even though there were no significant differences in Year-17 HA between genotype groups, the C/C genotype group tended to score slightly higher on HA than the others. The association between the T102C polymorphism and mean HA was significant (P = .038). This association was not linear (linear contrast P = .28) but the C/C genotype group had significantly higher mean HA than the others (P = .047; Table 3). The T102C was not associated with parental SES (P = .88) or with the subject's own education (P = .99), indicating that there was no gene-environment correlation between the T102C and indicators of socioeconomic status.

High parental SES predicted low adulthood HA (Year-17 HA: b = –.96, SE = .33, β = –.09, P = .004; Year-21 HA: b = –1.21, SE = .32, β = –.11, P < .001; Mean HA: b = –1.10, SE = .33, β = –.11, P < .001). The adulthood education level of the subject was also associated with lower Year-21 HA (b = –.51, SE = .17, β = –.08, P = .003) and Mean HA (b = –.43, SE = .18, β = –.08, P = .017), and there was a tendency in the same direction for Year-17 HA (b = –.29, SE = .18, β = –.05, P = .106). The correlation between parental SES and subject's adulthood education was r = .35 (P < .001). Controlling for subject's adulthood education did not alter the association between parental SES and HA (data not shown).

Next we examined whether the T102C polymorphism moderated the association between parental SES and adulthood HA. The interaction effect between the T102C polymorphism and parental SES on HA was statistically or marginally significant in each of the three models (Table 4), and showed that high SES predicted low HA in individuals carrying the T/T or T/C genotype (Year-17 HA: b = –1.36, SE = .50, β = –.12, P = .006; Year-21 HA: b = –1.52, SE = .46, β = –.14, P < .001; Mean HA: b = –1.40, SE = .49, β = –.14, P < .004), but not in those carrying the C/C genotype (Year-17 HA: b = –.44, SE = .51, β = –.04, P = .386; Year-21 HA: b = –.42, SE = .50, β = –.04, P = .403; Mean HA: b = –.39, SE = .52, β = –.04, P = .453).

The interaction effect between the T102C polymorphism and parental SES was further illustrated by categorizing the subjects according to level of childhood SES (low group = lowest 25%, high group = highest 25% of subjects), and examining the levels of HA as a function of the T102C within these two groups with analysis of covariance (Fig. 1). Among subjects with high parental SES, the level of HA was linearly dependent on the T102C

Table 3 Harm avoidance (Mean ± SD) by HTR2A T102C genotype groups

	T/T (n = 129)	T/C (n = 548)	C/C (n = 569)	ANOVA	η^2
Year-17 HA (n = 1107)	90.96 (18.11)	90.02 (18.54)	91.71 (17.82)	P = .405	–
Year-21 HA (n = 1246)	87.32 (18.90)	89.02 (18.29)	91.47 (18.42)	P = .019 [a]	.01
Mean HA (n = 966)	89.71 (17.14)	89.11 (17.24)	92.06 (16.70)	P = .038 [b]	.01

[a] Linear contrast P = .027;

[b] C/C > T/T & T/C P = .047

Table 4 Three separate linear regression models predicting Year-17, Year-21 and mean harm avoidance

Variable	Harm avoidance					
	Model 1: Year 17		Model 2: Year 21		Model 3: Mean	
	B (SE)	P	B (SE)	P	B (SE)	P
Gender	–5.31 (1.11)	0.000	–7.56 (1.05)	0.000	–5.54 (1.12)	0.000
Age	–0.01 (0.11)	0.897	0.04 (0.10)	0.677	0.07 (0.11)	0.549
Subject's education	–0.08 (0.20)	0.676	–0.34 (.018)	0.068	–0.28 (0.20)	0.165
HTR2A	0.75 (0.84)	0.375	2.15 (0.78)	0.006	1.73 (0.83)	0.036
Parental SES	–3.15 (1.22)	0.010	–3.32 (1.15)	0.004	–3.05 (1.20)	0.011
HTR2A × parental SES	0.94 (0.50)	0.058	0.99 (0.47)	0.035	0.90 (0.49)	0.065
Constant	99.18 (5.13)	0.000	101.58 (4.78)	0.000	98.09 (5.09)	0.000

Note: n(model 1) = 1107, n(model 2) = 1246, n(model 3) = 966

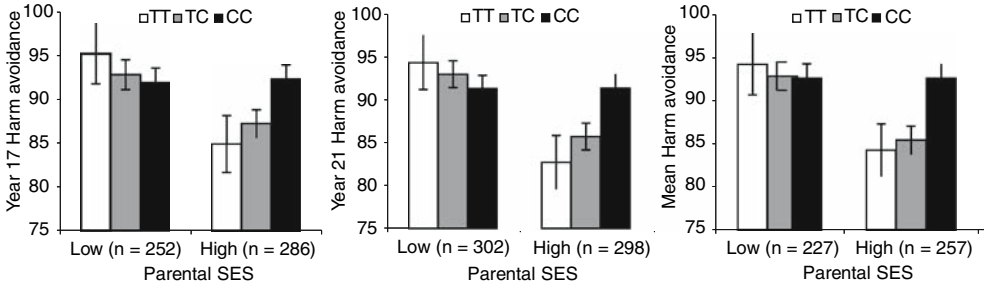

Fig. 1 Harm avoidance (Mean ± SE) by T102C genotype and childhood SES group

polymorphism, so that the number of C alleles was related to higher HA (Year-17 HA: $P = .029$, linear contrast $P = .044$, $\eta^2 = .03$; Year-21 HA: $P = .012$, linear contrast $P = .017$, $\eta^2 = .03$; Mean HA: $P = .003$, linear contrast $P = .017$, $\eta^2 = .05$). Among subjects with low SES there was some evidence for an association in the opposite direction (i.e. higher HA for T-allele carriers; Fig. 1) but this effect was not statistically significant (all P values $> .62$).

Discussion

The present findings suggest a role of parental socioeconomic status (SES), the T102C polymorphism of the serotonin receptor 2A gene (HTR2A), and their interaction in the development of harm avoidance (HA). First, we found that high parental SES in childhood and adolescence predicted low HA in adulthood independently of subjects' own adulthood educational level. Second, the C allele of the HTR2A T102C polymorphism was associated with high HA in one of the two test settings taken four years apart, and with the mean of those two measurements. The main finding was, however, an interaction between parental SES and T102C polymorphism, indicating that parental SES in childhood predicted HA in adulthood in the T/T or T/C genotype carriers, but not in carriers of the C/C genotype.

The main effect of the T102C polymorphism on HA was inconsistent (i.e., observed only in one of the two test settings), which has been the case across many molecular genetic studies examining only main effects (e.g., Munafò et al. 2005; see Ebstein 2006). In contrast, the T allele was consistently associated with low HA among those with high parental SES, while no statistically significant association was observed among those with low parental SES. The environmentally contingent association was more robust (i.e. observed in both of the two test settings) and greater in terms of magnitude than the main effect observed in the total sample (i.e. the T102C polymorphism accounted for 3–5% of the HA variance among individuals with high parental SES and only 1% in the total sample). This finding lends support for the argument that the association between a genotype and a phenotype of interest should become more robust when individuals are stratified by relevant environmental exposure (Ebstein 2006).

Harm Avoidance has been suggested to reflect individual differences in serotonergic functioning and reactivity to aversive stimuli (Cloninger et al. 1987), and high HA has been shown to correlate with high stress vulnerability. In a study by Puttonen et al. (2005) individuals with high HA showed a high level of emotional distress and high physiological reactivity in terms of autonomous nervous system activation during a task-induced stress.

Early life experiences have been shown to induce long-term alterations in serotonergic functioning which, in turn, may be associated with individual stress vulnerability (Sánchez et al. 2001) Rhesus macaques raised in adverse rearing conditions exhibit serotonergic dysfunctions and heightened behavioral and neuroendocrinological reactions to stress (Bennett et al. 2002; Barr et al. 2004). With specific regard to serotonin receptors, Pine et al. (1996) found that exposure to harsh parenting was inversely related to the density of 5-HT_{2A} platelet receptors in a sample of adolescent boys. Thus, our finding of an association between high parental SES and low adulthood HA is in line with studies demonstrating an association between early life experiences, serotonin functioning, and stress vulnerability. The influence of parental SES on adulthood HA in carriers of the T allele was relatively small, the standardized regression coefficient being approximately $\beta = -.14$.

Studies on rhesus macaques have shown that an adverse impact of early rearing conditions on serotonergic functioning and stress vulnerability may be moderated by the serotonin transporter polymorphism rh5-HTTLPR (Bennett et al. 2002; Barr et al. 2004), suggesting that some genotypes may be more susceptible to environmental influences than others. The present gene-environment interaction involving the T102C polymorphism of the HTR2A gene indicates that the development of temperament in the T-allele carriers is influenced by parental SES, while the C/C-genotype carriers may be insensitive to this aspect of the environment. This suggests that the C/C genotype might render the 5-HT_{2A} receptors, and thereby temperament

development, less susceptible to external influences. It would be of interest to examine this hypothesis in neurobiological studies measuring the function of 5-HT_{2A} receptors.

The C allele of the T102C polymorphism of the HTR2A gene has been associated with lower binding potential of the 5-HT_{2A} receptors (Turecki et al. 1999), and with lower 5-HT_{2A} receptor mRNA levels in postmortem brain (Polesskaya and Sokolov 2002), suggesting that the T102C polymorphism may have functional relevance, although this was not supported by a study by Bray et al. (2004). Furthermore, the T102C has been found to be in complete linkage disequilibrium with the –1438A/G polymorphism of the HTR2A gene (e.g., Bray et al. 2004, Spurlock et al. 1998). In a recent study, Myers et al. (2007) reported that variation in gene expression was associated with the –1438A/G polymorphism of the HTR2A, and that this association was further moderated by the –783A/G polymorphism. The interaction effect between the –1438A/G and –783A/G polymorphisms suggests that future behavior genetic studies of the HTR2A should consider the interactions between different polymorphisms of the HTR2A gene.

Children with high parental SES usually have better access to financial and social resources and are less likely to be exposed to stressful environmental influences than children with low parental SES (see Bradley and Corwyn 2002; Repetti et al. 2002). Here the association between the T allele of the T102C polymorphism and low HA was observed most clearly among individuals with high parental SES (see Fig. 1). We therefore suggest that a benevolent developmental environment may bring out the T102C allelic variance associated with HA. Conversely, the association between the T allele and low HA may be masked among individuals with low parental SES, where the environmental conditions necessary for this genetic association to manifest may not be available, and where all individuals tend to have high HA irrespective of their T102C genotype.

Findings of a single association study need to be interpreted with caution before they are replicated in other studies and samples. In another study with the same sample as here, we (Jokela et al. 2007) found that the T102C polymorphism moderated the association between exposure to maternal nurturance in childhood or adolescence and depressive symptoms in adulthood. High maternal nurturance predicted low depressive symptoms in individuals carrying the T/T or T/C genotype but not in those carrying the C/C genotype. In the CRYF sample the correlation between the maternal nurturance scale and parental socioeconomic status is nonsignificant (Year 0: r = -.03, P = .13) or low (Year 3: r = .09, P<.001; unpublished data), so our two studies provide evidence for the moderating role of the HTR2A gene with two largely independent measures of the environment. The correlation between HA and depressive symptoms is r = .45–.63 (P<.001; unpublished data, see Elovainio et al. 2004).

A recent meta-analysis (Abdolmaleky et al. 2004) concluded that there is an association between the C allele of the T102C polymorphism of the HTR2A gene and increased risk of schizophrenia. The T102C polymorphism has also been associated with suicidal behavior (Du et al. 2000) and depression, although inconsistently since different studies (Du et al. 2000; Eley et al. 2004) have associated both the T and the C alleles with increased risk of depression. Furthermore, the majority of studies of the T102C polymorphism have found no evidence for an association with depression at all (Anguelova et al. 2003). Our present finding may be relevant in the context of psychiatric disorders, since high HA is related to schizophrenia (Szöke et al. 2002) and depression (Farmer et al. 2003), among other outcomes. The association between the C allele and the development of psychiatric disorders found in previous studies might be due to limited responsivity of the C allele to the protective aspects of the environment. Moreover, the genetic risk may be highest among individuals with benevolent developmental environments, where the individual differences in T102C polymorphism of the HTR2A gene appear to be most pronouncedly expressed.

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