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The effect of 5-HTT gene promoter polymorphism on impulsivity depends on family relations in girls

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ABSTRACT

The short (S) allele of the 5-HTT gene promoter region polymorphism (5-HTTLPR), in combination with adverse environmental influence, leads to higher likelihood of depression. Impulsivity has been related to low serotonin turnover, poor regulation of affect, and problems in the family, including child maltreatment. The current study explored the effect of the 5-HTTLPR polymorphism in the serotonin transporter gene and adverse family environment on impulsivity in adolescents. Healthy adolescents participating in the Estonian Children Personality Behaviour and Health Study (n=483) filled the Adaptive and Maladaptive Impulsivity Scale (AMIS), Barratt Impulsiveness Scale (BIS-11), a scale measuring family relations, and were genotyped. While genotype alone was not associated with thoughtlessness, BIS-11 impulsiveness, fast decision-making or excitement seeking, 5-HTTLPR S allele carriers, however, had higher scores of disinhibition. In girls carrying the S allele, scores of thoughtlessness and disinhibition depended on family relations, being higher with less warmth in the family. Adverse family relations had no effect on impulsivity in girls with LL genotype. In boys, the effects of family relations on maladaptive impulsivity did not depend on genotype. However, the S allele and high maltreatment in the family both independently increased disinhibition and the BIS-11 score in boys. Family environment and the 5-HTTLPR genotype had no interactive effect on excitement seeking or fast decision-making. In summary, carrying the S allele may lead to high maladaptive impulsivity due to higher sensitivity to environmental adversity, which is more significantly expressed in girls.

1. Introduction

The 5-HT transporter gene (SLC6A4, *5-HTT*) has a polymorphism in the promoter region, which consists of a 20–23 base pair sequence that is repeated either 14 (short) or 16 (long) times. In functional studies of this variable locus, the SS and SL genotypes were functionally similar with regard to transcriptional activity, whereas the genotype homozygous for two long alleles (LL) displayed higher activity (Lesch et al., 1996; Lesch and Gutknecht, 2005). S allele carriers have lower neuronal density in brain regions regulating negative affect (Pezawas et al., 2005), and show higher amygdala reactivity to negative stimuli (Graff-Guerrero et al., 2005; Pezawas et al., 2005; Heinz et al., 2005). Clinical studies have demonstrated that carrying the S allele is associated with anxiety-related characteristics (Sen et al., 2004), depressive symptoms (Hoefgen et al., 2005) and other types of affective dysfunctions. In contrast, female subjects with obsessive–compulsive disorder have a higher frequency of LL genotype compared to controls (Baca-García et al., 2005).

Proneness for substance abuse and self-destructive behaviours have been demonstrated to be additional adverse outcomes of carrying S allele (Uher and McGuffin, 2008). Related findings include higher prevalence of the S allele in impulsive suicide attempters (Li and He, 2007) and in violent type 2 alcoholics (Hallikainen et al., 1999). Among individuals with antidepressant-induced mania, a state associated with impulsiveness, an overrepresentation of S allele carriers has been found (Masoliver et al., 2006). The studies on children have demonstrated an influence of S allele on aggressiveness (Haberstick et al., 2006) and higher novelty seeking and higher prevalence of smoking and illegal drug use in adolescents (Gerra et al., 2005a,b). Our own recent study demonstrated higher self-reported and performance impulsivity in adolescents carrying the S allele who also had low platelet MAO activity (Paaver et al., 2007).

The impact of 5-HTTLPR genotype on affect has been shown to depend on experience of environmental stressors. Depressive symptoms only appeared among those S allele carriers who suffered from stressful life events in the early age (Caspi et al., 2003), or had experienced a hostile family environment (Kaufman et al., 2006; Taylor et al., 2006). Subjects with the SS genotype and low perceived

Abbreviations: 5-HTTLPR, 5-HT transporter gene 20-23 base pair polymorphism; S allele, short allele; L allele, long allele; BIS-11, Barratt Impulsiveness Scale, 11th version.

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Table 1
The description and results of the factor analysis of the subscales of the Estonian Family Relationships Scale

Subscale	Number of items	Cronbach's α	Inter-item correlation	Factor loadings	Eigenvalue	Explained variance
Warmth						
Closeness	15	0.94	0.52	0.45–0.82	13.86	75%
Support	7	0.80	0.37	0.44–0.65	1.54	41%
Maltreatment						
Misprize	10	0.86	0.40	0.45–0.77	3.43	53%
Abuse	7	0.83	0.42	0.52–0.75	1.93	39%

parental care in childhood had much higher risk of becoming a cocaine user than subjects with other genotypes (Gerra et al., 2007). Furthermore, development of a less efficient serotonergic system was demonstrated in those 5-HTTLPR S allele carriers who had experienced adverse events during childhood (Lesch and Gutknecht, 2005) or who had been raised in families from low socio-economic background (Manuck et al., 2004). An analogous polymorphism is present in 5-HTT gene in monkeys, and a similar gene×environment interaction effect on the development of serotonergic system has been demonstrated in peer-reared rhesus macaques with the short rh5-HTTLPR allele, resulting in lower levels of cerebrospinal fluid levels of the serotonin metabolite 5-HIAA than in mother-reared monkeys (Bennett et al., 2002). An interactive effect of 5-HTTLPR and adverse rearing conditions on alcohol preference has been demonstrated in primates, but only in females (Barr et al., 2004b).

Olson et al. (1990) found in a longitudinal study that responsive, cognitively stimulating parent–toddler interactions in the 2nd year predicted later measures of cognitive non-impulsivity and ability to delay gratification. Straus and Mouradian (1998) found that corporal punishment was associated with impulsiveness in the child. Thus, development of impulsivity in 5-HTTLPR S allele carriers could be influenced by parenting styles.

The aim of the current study was to explore the effect of 5-HTTLPR and adverse family environment on different types of impulsivity in adolescents. It was hypothesized that the S allele induces higher impulsiveness in the presence of non-supportive family relations.

2. Methods

2.1. The sample

The sample was based on the younger cohort of the European Youth Heart Study (EYHS) conducted in Estonia in 1998/99, which was incorporated into the longitudinal Estonian Children Personality, Behaviour and Health Study (ECPBHS) (Harro et al., 2001). The present study was conducted during the follow-up in 2004 where we could recruit 83% (n=483) of the original sample, including 222 boys and 261 girls. Children and their parents gave their informed consent. Permission for the study was obtained from the Committee of Ethics of the University of Tartu, Estonia. The mean age of the subjects studied in 2004 was 15.3, SD=0.5.

2.2. Genotyping

The alleles at the 5-HTTLPR locus were amplified from genomic DNA using PCR as previously described (Paaver et al., 2007). The polymorphic region was amplified using the primers 5-HTTLPR-F: CAA CCT CCC AGC AAC TCC CTG TA, 5-HTTLPR-R: GAG GGA CTG AGC TGG ACA ACC AC, where the forward primer was fluorescently labeled with a 5′-FAM. Reagents and conditions for the PCR reaction were: 1×PCR buffer (Perkin Elmer, AmpliTaq Gold buffer II), 200 μM dNTP with 50% of dGTP replaced with 7-deaza-dGTP, 2 mM $MgCl_2$, 1 μM of each primer, 1 U Taq polymerase (Perkin Elmer, AmpliTaq Gold), and 20 ng genomic DNA, in a total reaction volume of 10 μL. The reaction started with 10 min at 95 °C, followed by 40 cycles with 30 s at 95 °C, 30 s at 59 °C, 30 s at 72 °C, and ended with 7 min at 72 °C. PCR products were then run on an ABI PRISM 3700 DNA analyzer (Applied Biosystems, USA), and scored using the software GeneMarker 1.5 (SoftGenetics, USA). All genotypes were manually checked on chromatograms to detect inconsistencies, and where needed, amplified and scored a second time. 5-HTTLPR genotype was assessed in 435 children and 191 (44%) of subjects were homozygous for L allele, 189 (43%) were heterozygous and 55 (13%) were homozygous for the S allele. Genotype frequencies were in Hardy–Weinberg equilibrium.

2.3. Psychological measures

Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) and Adaptive and Maladaptive Impulsivity Scale (AMIS) were used to measure different facets of impulsivity (fast decision-making, excitement seeking, disinhibition, thoughtlessness) as previously described (Eensoo, 2007; Paaver et al., 2006, 2007). Self-reported impulsiveness questionnaire AMIS was filled by 481 and BIS-11 by 429 children.

Relationships in the family were measured by a child-report scale (Tartu Family Relationships Scale). Forty nine items were included into the factor analysis. Principle component analysis was computed on a sample of 885 adolescents (43% boys and 57% girls). Their age range was from 14 to 21 years, mean age 16.14 years (SD=1.56 years). As a result, four subscales were extracted by factor analysis using the Cattell criterion (Cattell, 1966) and were named Closeness (15 items, e.g., "Our family is dedicated to each other", "The marriage of my parents is happy"), Support (7 items, e.g., "My family supports me", "Someone in the family helps (has helped) me to feel myself important and special"), Misprize (10 items, e.g., "I can make no decision on my own", "I am depreciated at home"), and (emotional and physical) Abuse (7 items, e.g., "Were you ever hit by someone in your family or have you experienced physical violence in your family?"). Items were presented in terms of 4 or 5-point Likert scale. More information about the subscales is presented in Table 1. Based on the similarity in results, in presented analyses the subscales of Closeness and Support were added together under a common name "Warmth in the family" and the subscales of Abuse and Misprize were added together under a common name "Maltreatment" in the presentation of data.

2.4. Statistical analyses

For detecting gene–environment interaction effects, subjects were divided into two groups according to the median score on family relations subscales. Pearson correlation analysis was used for detecting the interrelations between different psychological measures. The impulsivity

Table 2
Intercorrelations (Pearson r) between the measures of family relations and types of impulsivity

	(1)	(2)	(3)	(4)	(5)	(6)
Impulsivity measures						
Disinhibition (1)						
Thoughtlessness (2)	0.60***					
Excitement seeking (3)	0.24***	0.30***				
Fast decision-making (4)	0.12*	–	0.54***			
BIS-11 impulsiveness (5)	0.55***	0.60***	0.22***	–		
Family relations						
Warmth in the family (6)	−0.19***	−0.19***	–	0.10*	−0.30***	
Maltreatment in the family (7)	0.19***	0.19***	–	–	0.26***	−0.67***