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Serotonin receptor 2A gene moderates the effect of childhood maternal nurturance on adulthood social attachment

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The ability to form and maintain attachment relations with other people is crucial for mental health and well-being. The origins of attachment behaviors are often assumed to be in early experiences with other people, especially with primary caregivers. Preliminary evidence suggests that serotonergic system may be involved in attachment behaviors. We examined whether the T102C variant of the serotonin receptor 2A gene moderates the effect of childhood maternal nurturance on social attachment in adulthood. The participants were 1070 women and men from the Young Finns Study with 27-year follow-up and two measurement times for the outcomes ($n = 1836$ person observations). Mothers reported their relationship quality with their children (participants) in childhood or adolescence. Social attachment was assessed by participant's self-reports on two measures (reward dependence scale of the Temperament and Character Inventory and the Relationship Questionnaire). High childhood maternal nurturance predicted high reward dependence and low avoidant attachment in carriers of the T/T genotype but not in the T/C or C/C genotype groups, while low maternal nurturance was associated with low reward dependence and high avoidant attachment in T/T genotype carriers but not in C allele carriers. Our result suggests that T/T genotype carriers were more influenced by their childhood nurturing environment, than their C allele carrying counterparts, thus providing evidence for differential susceptibility to childhood nurturing environment associated with the *HTR2A* gene.

Keywords: Differential susceptibility, gene–environment interaction, genotype, *HTR2A*, maternal nurturance, serotonin, social attachment

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People form important attachment relations with significant others, including their parents, spouses, children and close friends. In psychological literature, the term attachment is often used narrowly to describe the relationship between parent and child, which may have long-term implications for other intimate relationships later in life (e.g. Collins & Feeney 2000; Feeney & Collins 2001). In behavioral biology, the broader term *social attachment* encompasses interpersonal attachment behaviors and emotions between various dyads besides parents and their offspring (e.g. Insel 1997; Insel & Young 2001). Social attachments are a central part of human life, and the ability to form and maintain such relations is crucial for mental health, as has been shown repeatedly (Baumeister & Leary 1995).

Attachment theory postulates that the development of childhood and adult attachment relations is affected by the quality of early relationships with primary caregivers (e.g. Bowlby 1988; Collins & Feeney 2000). The theory has received supporting evidence in many studies (e.g Dalton *et al*. 2006; Donnellan *et al*. 2005; Ruchkin *et al*. 1998; Schlette *et al*. 1998). However, not all studies have observed consistent associations between parental care and later attachment behaviors. In many studies, the effects have been small (Donnellan *et al*. 2005; Lopez *et al*. 2000) or completely absent (Difilippo & Overholser 2002; Lopez *et al*. 2000; Parker *et al*. 1992). While these inconsistencies may be related to the wide range of definitions and measures used to evaluate both parental care and social attachment, it is also possible that there is heterogeneity in how individuals respond to parental care. The influence of parenting may depend on child characteristics, such as genetic background (Belsky *et al*. 2007). This might help to explain the inconsistent results found in previous studies.

Genes underlying the functioning of the serotonergic system are likely to be associated with social attachment. Serotonin is an important neurotransmitter involved in emotion regulation, and it has also been linked with several social behaviors (Ebstein *et al*. 2010; Lesch 2007; Lucki 1998). Measures of social attachment, such as adult attachment style, have been previously associated with polymorphic variation in serotonergic genes, including the T102C polymorphism of serotonin receptor 2A (*HTR2A*) gene (Gillath *et al*. 2008) and the serotonin transporter gene (Caspers *et al*. 2009; Spangler *et al*. 2009).

The recent focus of behavior genetics has shifted from studying genetic main effects to exploring interaction effects between genes and environments (Belsky *et al*. 2007; Dempfle *et al*. 2008). It has been argued that genetic variation between individuals manifests itself particularly as individual

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differences in the sensitivity to environmental influences (Belsky & Pluess 2009; Keltikangas-Jarvinen & Salo 2009; Rutter *et al*. 2006; but see Risch *et al*. 2009; Uher & McGuffin 2008, 2010).

The differential susceptibility framework suggests that some individuals are more susceptible to negative and positive aspects of their environment and thereby show negative outcomes in unfavorable environments but beneficial effects in favorable circumstances (Belsky 1997; Belsky *et al*. 2007). This framework has proven to be a successful approach in studying child and adult development (Ellis *et al*. 2011), attachment (Bakermans-Kranenburg & van lJzendoorn 2007) and mental health (Jokela & Keltikangas-Järvinen, in press). In terms of differential susceptibility, the traditional view of genes as vulnerability factors may be extended to account for overall plasticity: genetic background may modify general susceptibility to environmental effects (Belsky *et al*. 2009).

In a recent series of studies, we have shown that the T102C polymorphism of *HTR2A* gene may moderate the influence of various environmental conditions on a range of psychological outcomes, such as depressive symptoms, temperament and hostility (Jokela *et al*. 2007a; Jokela *et al*. 2007b; Jokela *et al*. 2007c; Keltikangas-Jarvinen *et al*. 2008). These studies suggest that the T allele carriers of the T102C polymorphism are more sensitive to environmental conditions than their C allele-carrying counterparts. Furthermore, the T allele carriers seem to be more sensitive to both the positive and the negative aspects of the environment, implying that the T allele carriers may gain more from beneficial circumstances but fare worse in disadvantageous environments than C allele carriers, thus suggesting differential susceptibility. This polymorphism has also been related with adulthood attachment (Gillath *et al*. 2008), indicating that it may be involved in other important interpersonal outcomes besides symptoms of psychopathology.

In the present longitudinal study spanning over 27 years, we examined whether the T102C polymorphism of *HTR2A* gene moderates the association between childhood maternal nurturance and adult social attachment. Based on our previous findings, we hypothesized that T allele carriers of the T102C variant are more sensitive to the nurturing aspects of mother's behavior than the C allele carriers. We hypothesized the T allele carriers to express higher levels of social attachment in adulthood in response to high maternal nurturance in childhood and to express lower levels of social attachment in response to low maternal nurturance in childhood. We also examined whether this interaction effect was independent of the interaction effects reported previously in our studies of the *HTR2A* gene.

Materials and methods

Participants

The participants were 1070 women and men from the population-based Young Finns Study (Akerblom *et al*. 1991; Raitakari *et al*. 2008). The original sample consists of 3596 Finnish healthy children and adolescents derived from six birth cohorts, aged 3, 6, 9, 12, 15 and 18 years at baseline in 1980. To select a broadly representative sample in terms of sociodemographic background, Finland was divided into five areas according to locations of university cities with a medical school (Helsinki, Kuopio, Oulu, Tampere and Turku). In each area, urban and rural boys and girls were randomly selected on the basis of their unique personal social security number. The sample has been followed subsequently in seven follow-up phases in 1983, 1986, 1989, 1992, 1997, 2001 and 2007. A more detailed description of the cohort can be found in Akerblom *et al*. (1991) and Raitakari *et al*. (2008). The study was approved by local ethics committees, and all participants gave their written informed consent. The study procedure was in accordance with the Declaration of Helsinki. The present sample consisted of participants with genetic data, data on maternal nurturance in 1980 and 1983 and at least one measurement of the outcome variables that were assessed in 2001 and 2007 ($n =$ 1070 participants with a total of 1836 participant observations).

Measures

Social attachment was measured using two scales, the reward dependence temperament trait of the Temperament and Character Inventory (Cloninger 1987) and The Relationship Questionnaire (RQ) (Bartholomew & Horowich 1991), which the participants completed in two test settings 21 and 27 years after baseline, when the participants aged 24–39 and 30–45 years, respectively.

Reward dependence

People with high reward dependence are characterized as tender hearted, socially dependent, caring and affectionate (Cloninger *et al*. 1993). The scale consists of 24 items rated on a 5-point Likert scale ranging from totally disagree (1) to totally agree (5). The Cronbach's α reliabilities for the total scale was 0.80 (2001) and 0.82 (2007), and the correlations between the two measurements were $r = 0.75$.

Relationship Questionnaire

The RQ (Bartholomew & Horowitz 1991) is used to assess two essential dimensions of adult attachment styles, anxiety and avoidance, which reflect discomfort with closeness and anxiety about abandonment, respectively (Brennan *et al*. 1998). The RQ consists of four descriptive statements of four different attachment styles: secure, dismissing- avoidant, fearful and preoccupied. Participants rated how well each style described themselves on a 7-point Likert scale. These four styles represent four distinct attachment style categories that may be derived by combining the high and low ends of the two attachment dimensions anxiety and avoidance (Brennan *et al*. 1998). For example, a person categorized as secure may be described as having low avoidance and low anxiety, while a person categorized as dismissing is low in anxiety but high in avoidance. The two attachment dimensions, anxiety and avoidance, may be derived from the RQ scores (Brennan *et al*. 1998) as follows: anxiety = [(fearful + preoccupied) − (secure + dismissing-avoidant)] and avoidance = [(dismissing-avoidant + fearful) − (secure + preoccupied)]. The test–retest correlations with a 7-year interval were $r = 0.47$ ($P < 0.001$) for anxiety and $r = 0.54$ ($P < 0.001$) for avoidance. The validity of the RQ has been shown in young adults (Bartholomew & Horowitz 1991).

Maternal nurturance

Maternal nurturance was self-rated by the mothers of the particpants using a scale derived from the Operation Family Study (Makkonen *et al*. 1981) addressing the emotional significance of the child for the mother. The scale comprises four items ('My child is emotionally important to me'; 'I enjoy spending time with my child'; 'I am emotionally important to my child'; 'My child allows/enables me to fulfill myself'), which were rated on a 5-point scale ranging from totally disagree (1) to totally agree (5). The assessments were made at the baseline ($\alpha = 0.66$) and 3 years after the baseline ($\alpha = 0.78$). The Cronbach alphas calculated for each age group separately were 0.73 (year 1980)/0.75 (year 1983) at age 3, 0.71/0.78 at age 6, 0.71/0.81 at age 9, 0.67/0.81 at age 12, 0.71/0.75 at age 15, and 0.72/0.79 at age 18, indicating similar internal reliability at different ages. The correlation between the two measurements was $r = 0.37$ ($P < 0.001$) or $r = 0.52$ after correction for attenuation becuase of

measurement error. We used the mean of the two measurements as the maternal nurturance variable in the statistical analysis. The nurturance variable was negatively skewed and was corrected by a cubic root transformation. We then standardized the variable [mean = 0, standard deviation (SD) = 1] to facilitate the interpretation of the regression coefficients.

Covariates

As we have previously found an interaction effect between *HTR2A* and maternal nurturance on adulthood depressive symptoms (Jokela *et al*. 2007a), we used depressive symptoms as a covariate. We have also found an interaction effect between *HTR2A* and parental socioeconomic status (SES) on adulthood harm avoidance (Jokela *et al*. 2007c), so parental SES and harm avoidance were also controlled. This allowed us to assess whether the *HTR2A* had a moderating role independent of the associations we have reported in previous studies.

Depressive symptoms and harm avoidance were assessed concurrently with the main outcomes using a modified version of Beck's Depression Inventory (BDI) (Beck & Steer 1987; Jokela *et al*. 2007a). In the original version of the BDI, individuals are asked to choose one of the four alternative response statements, representing ascending levels of symptom severity, in each of the 21 items. In the modified version used here, the 21 items of the scale were the second mildest statements of the original BDI items (e.g. 'I often feel sad'). The participants were asked to rate each of the 21 statement items on a 5-point scale ranging from totally disagree (1) to totally agree (5). The second mildest statements of the original BDI items were selected for the modified scale because they were expected to most accurately measure individual differences in depressive symptoms in a normal population. The Cronbach α reliabilities for the scale were $\alpha > 0.90$ in both years studied. Harm avoidance was assessed with the Temperament and Character Inventory (Cloninger *et al*. 1993). The 35 items were rated on a 5-point Likert-type scale.

Parental SES was assessed at baseline using two indices: (1) the mother's and father's years of education and (2) the annual income of the household (measured on an 8-point scale). In the total sample, the correlation between the mother's and the father's years of education was $r = 0.66$, and the correlation between these two measures and household income was $r = 0.45$ and $r = 0.50$, respectively (all P values < 0.001). The SES indicator was constructed by first calculating the mean of the years of education of the mother and the father and then standardizing 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 SES (Jokela *et al*. 2007c).

Marital status and education level of the participants were added as sociodemographic covariates. Marital status was coded as a dichotomous variable (0 = not married/divorced/separated, 1 = married/cohabiting). Education was assessed on the basis of the highest achieved educational qualifications reported on a 7-point scale (1 = mandatory school, 7 = higher education).

HTR2A 102 T > C (Rs 6313) genotyping

Genomic DNA was extracted from peripheral blood leukocytes using QIAamp DNA Blood Minikit and automated biorobot M48 extraction (Qiagen Inc., Hilden, Germany). DNA samples were genotyped using the 5′ nuclease assay and fluorogenic TaqMan MGB probes (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, 6-carboxyfluorescein or 20-chloro-70-phenyl-l,4-dichloro- 6-carboxyfluorescein, were deduced from sequences deposited in the GenBank database and synthesized in conjugation with Applied Biosystems using the TaqMan Validated SNP Genotyping Assays (assay ID C_3042197_1). A polymerase chain 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 polymerase chain reaction amplification, 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. Random duplicates and known control samples were run in parallel with unknown DNA samples.

Statistical analysis

Given that each participant could contribute one or two measurements of the outcomes (in 2001 and 2007), we applied multilevel linear regression analysis in which the participant observations were nested within participants ($n = 1070$ participants and 1836 participant observations). The random-intercept multilevel regression modeling takes into account the nonindependence of the observations within participants and calculates standard errors of coefficients accordingly. *HTR2A* genotype was coded with two dummy variables with individuals carrying the T/T genotype being the reference group. To provide interpretable effect magnitudes and to make results comparable across scales, all regression coefficients were calculated for standardized scales of exposure and outcome variables (SD = 1).

Following Belsky *et al*. (2007), we tested whether our results indicated differential susceptibility in four steps. First, we tested the association between the susceptibility factor (*HTR2A*) and the outcome (social attachment), which should to be zero in the case of differential susceptibility. Second, we tested the independence of the susceptibility factor (*HTR2A*) and the predictor (maternal nurturance). Third, we examined the interaction effect. Fourth, we illustrated the interaction effect to assess whether our results reflected differential susceptibility. Given that we have observed other interaction effects with the *HTR2A* polymorphism, we did not test for the specificity of the interaction with other environmental measures (Belsky *et al*. 2007).

Results

Descriptive statistics for the analytic sample are shown in Table 1. The differences between the analytic sample and the main sample were small, the largest difference being observed for education (0.13 SD higher in the analytic sample) An attrition analysis of childhood characteristics indicated that older participants [odds ratio (OR) = 1.17, standard error (SE) = 0.04, $P < 0.001$] and women (OR = 2.33, SE = 0.62, $P = 0.001$) were more likely to be included in the analytic sample (i.e. they were more likely to participate in adult follow-ups), while maternal nurturance (OR = 1.09, SE = 0.14, $P = 0.52$) and parental SES (OR = 1.11, SE = 0.09, $P = 0.19$) did not predict this probability. The correlations between the study variables are reported in Table 2. *HTR2A* genotype frequencies, T/T (10%), T/C (45%), C/C (45%), did not deviate from Hardy–Weinberg equilibrium, $\chi^2(2) = 0.16$, $P = 0.92$. *HTR2A* was not associated with reward dependence or attachment behaviors (step 1, Table 3) or with maternal nurturance (step 2 Jokela *et al*. 2007a). Adjusted for sex, age and measurement time, high maternal nurturance was associated with high reward dependence ($\beta = 0.06$, SE = 0.03, $P = 0.02$) and avoidant attachment ($\beta = -0.07$, SE = 0.03, $P = 0.02$) but not with anxious attachment ($\beta = -0.04$, SE = 0.03, $P = 0.17$). In fully adjusted regression models, there was an interaction effect between *HTR2A* and nurturance when predicting reward dependence and avoidant attachment style (step3, Table 4), such that high maternal nurturance predicted these outcomes among carriers of the T/T genotype group ($\beta = 0.27$, SE = 0.08, $P = 0.001$ for reward dependence; $\beta = -0.32$, SE = 0.08, $P < 0.001$). Among the group of C allele carriers (T/C and

Table 1: Descriptive statistics for the analytic sample ($n = 1070$) and main sample ($n = 1593–3596$)

Variable	Analytic sample*	Main sample		Difference‡
	Mean (SD) or %	Mean (SD) or %	*n* (participants)†	Cohen's *d* or %
Sex (% women)	54.3	51.0	1593	3.3
Age at baseline	10.2 (4.9)	10.4 (5.0)	3596	−0.04
Age at final follow-up	37.2 (4.9)	37.5 (5.0)	2512	−0.06
Education	3.62 (1.89)	3.38 (1.87)	2606	0.13
Married or cohabiting (%)	83.7	81.0	2597	1.5
HTR2A genotype				
T/T (%)	10.4	9.8	156	0.8
T/C (%)	44.5	44.6	711	0.0
C/C (%)	45.1	45.6	726	−0.7
Maternal nurturance§	0.00 (0.98)	0.00 (1.00)	2736	0.00
Parental SES§	0.16 (1.61)	0.01 (1.67)	3424	0.09
Reward dependence	79.9 (10.2)	79.8 (10.7)	2508	0.01
Anxious attachment	9.53 (2.96)	9.65 (2.97)	2498	−0.04
Avoidant attachment	9.54 (3.55)	9.73 (3.70)	2498	−0.05
Depressive symptoms	42.2 (13.8)	43.4 (14.2)	2511	−0.09
Harm avoidance	89.7 (18.2)	91.3 (18.5)	2506	−0.09

*$N = 1070$ participants, 1836 participant observations.
†Number of participants varies depending on availability of data for the covariate.
‡Difference between analytic and main sample in SDs (Cohen's *d*) for continuous variables or in percentage points for categorical variables. Given that the analytic sample is nested with the main sample, no *P* values are calculated.
§Standardized variables.

Table 2: Correlations between study variables

	1	2	3	4	5	6	7	8	9	10	11
1. Male sex	—										
2. Age	0.02	—									
3. Education	**−0.06**	**−0.05**	—								
4. Married/cohabiting	−0.04	**0.19**	−0.04	—							
5. *HTR2A* (C alleles)	−0.02	−0.03	0.00	0.00	—						
6. Maternal nurturance	−0.04	**−0.10**	**0.07**	0.02	−0.01	—					
7. Parental SES	**0.05**	**−0.12**	**0.35**	**−0.07**	−0.01	0.04	—				
8. Depressive symptoms	**−0.13**	0.03	−0.03	**−0.06**	0.02	**−0.10**	**−0.07**	—			
9. Harm avoidance	**−0.20**	**0.05**	**−0.07**	−0.04	**0.06**	**−0.07**	**−0.12**	**0.59**	—		
10. Reward dependence	**−0.42**	−0.02	**0.09**	**0.09**	−0.04	**0.05**	0.04	−0.05	−0.04	—	
11. Avoidant attachment	0.13	0.03	**−0.07**	**−0.15**	**0.05**	**−0.07**	**−0.09**	**0.26**	**0.25**	**−0.49**	—
12. Anxious attachment	−0.03	0.00	**−0.12**	−0.01	**0.05**	−0.04	−0.11	**0.35**	**0.46**	**−0.06**	**0.21**

Statistically significant correlations ($P < 0.05$) are printed in bold font. $N = 1070$ participants, 1836 participant observations.

Table 3: Levels of reward dependence and attachment styles by serotonin receptor 2A (*HTR2A*) genotype groups

	T/T	T/C	C/C	*P*
Reward dependence	79.99 (0.84)	79.98 (0.40)	79.67 (0.40)	0.84
Anxious attachment	9.44 (0.25)	9.33 (0.12)	9.75 (0.12)	0.05
Avoidant attachment	9.06 (0.30)	9.49 (0.15)	9.72 (0.15)	0.11

Values are means (and SE). $N = 1070$ participants, 1836 participant observations from two measurement times.
P, *P* value for genotype group differences, adjusted for sex, age and assessment time.

C/C genotypes), maternal nurturance was not associated with reward dependence ($\beta = 0.04$, SE = 0.03, $P = 0.11$) or with avoidant attachment ($\beta = -0.04$, SE = 0.03, $P = 0.19$). Figure 1 illustrates these interaction effects, showing differential susceptibility (step 4).

Discussion

The purpose of this study was to examine whether the association between maternal nurturance in childhood and social attachment in adulthood is moderated by the T102C polymorphism of *HTR2A* gene. We found maternal nurturance experienced in childhood to be associated with adult social attachment, assessed with two different measures, in the

Table 4: Predicting reward dependence and attachment styles by *HTR2A* × maternal nurturance interaction

	Reward dependence	Anxious attachment	Avoidant attachment
Nurturance	0.23 (0.08)*	0.01 (0.08)	−0.26 (0.08)**
HTR2A			
T/T	(ref)	(ref)	(ref)
T/C	0.01 (0.09)	−0.10 (0.08)	0.09 (0.08)
C/C	−0.02 (0.09)	0.02 (0.08)	0.14 (0.08)
HTR2A × nurturance			
T/T	(ref)	(ref)	(ref)
T/C	−0.19 (0.09)***	−0.02 (0.08)	0.25 (0.09)*
C/C	−0.20 (0.09)***	0.01 (0.08)	0.26 (0.09)*

Values are standardized regression coefficients (and SEs) of multilevel linear regression analysis, adjusted for sex, age, assessment time, parental SES, adult depressive symptoms, harm avoidance, marital status and education. $N = 1070$ participants, 1836 participant observations from two measurement times.
*$P < 0.01$; **$P < 0.001$; ***$P < 0.05$.

expected way: high maternal nurturance predicted higher levels of reward dependence and lower levels of avoidant attachment. However, when stratified by genotype, these associations were observed only in T/T genotype carriers of the T102C polymorphism of *HTR2A* gene, while in C allele carriers the associations were not statistically significant. In other words, mother's nurturing behavior seemed to benefit mostly the T/T genotype carriers.

The present findings are in agreement with our previous studies of the differential susceptibility associated with the *HTR2A* gene, which have suggested that individuals carrying T alleles of the T102C polymorphism are most sensitive to both beneficial and adverse environmental influences than individuals carrying the C alleles (Jokela *et al*. 2007a; Jokela *et al*. 2007b; Jokela *et al*. 2007c; Keltikangas-Jarvinen *et al*. 2008; Keltikangas-Jarvinen *et al*. 2010). Here, the gene-dependent association was considerably stronger in homozygous T/T genotype carriers compared with others. Such an effect has been observed in some of our previous studies (Keltikangas-Jarvinen *et al*. 2008), while in others, the largest difference has been observed between homozygous and heterozygous T allele carriers compared with homozygous C/C genotype carriers (Jokela *et al*. 2007a; Jokela *et al*. 2007b; Jokela *et al*. 2007c). Crucially, the present interaction effect was independent of childhood parental SES and adult depressive symptoms and harm avoidance, which have previously been shown to be involved in the *HTR2A*–environment interactions.

The T allele of the T102C polymorphism of *HTR2A* gene has previously been associated with higher scores on avoidant attachment (Gillath *et al*. 2008). Our results show that the association of the *HTR2A* on social attachment may depend on early parenting experiences. Two other studies investigating the serotonin transporter gene showed that genetic variants in this gene may moderate the effect of maternal responsiveness on attachment disorganization (Spangler *et al*. 2009) and attachment insecurity (Barry *et al*. 2008) in infancy.

Reward dependence and avoidant attachment both capture similar aspects of interpersonal behavior, and they are strongly negatively correlated ($r = -0.49$). Individuals with high reward dependence have a strong desire to seek affectionate and close relationships with other people. Avoidant attachment, on the other hand, depicts the proximity-seeking aspect of adult attachment: closeness of contact, reliance on others and interpersonal orientation (Brennan *et al*. 1998). A person low in avoidance may be described as being comfortable with intimacy, seeking emotional closeness to others and expecting others to be available and supportive, while a person scoring high in avoidance avoids intimacy and close contact and is detached and cold.

In contrast to avoidant attachment, mother's nurturing behavior in childhood did not predict the child's later anxious attachment neither alone nor when the genetic information was taken into account. Anxiety represents a different aspect of adult social attachment compared with avoidant attachment. While attachment avoidance characterizes the interpersonal aspect of attachment, anxiety is more related to the internal or within-person aspects of attachment: sense

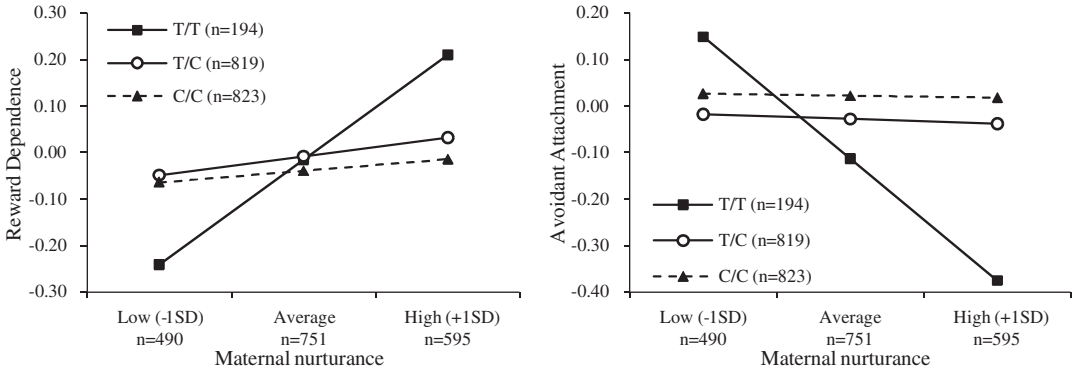

Figure 1: Predicted values of reward depednence and avoidant attachment by maternal nurturance and serotonin receptor 2A (*HTR2A*) genotype. See Table 4 for statistical details.

of self-worth, self-concept and anxiety experienced in close relationships (Brennan *et al*. 1998). In earlier retrospective and cross-sectional studies, adult attachment anxiety has been associated with low emotional warmth or responsiveness of parents (Cheng & Mallinckrodt 2009; Swanson & Mallinckrodt 2001), poor parental availability (Holman *et al*. 2009) and low levels of family's expressive atmosphere (Smith & Ng 2009). We suggest that the *HTR2A* moderated association between maternal nurturance and adult attachment may be more relevant to the interpersonal aspects of social attachment than to person's internal self-concepts.

Why are T/T genotype carriers more sensitive to their environmental conditions than C allele carriers? While the T102C variant does not alter the amino acid sequence of 5-HT2A receptors, it has been shown to influence gene expression and to affect the binding potential of serotonin 2A receptors (Khait *et al*. 2005; Polesskaya & Sokolov 2002; Turecki *et al*. 1999; but see Bray *et al*. 2004). The C allele has been associated with lower binding potential of the 5-HT2A receptors (Turecki *et al*. 1999). Hence, the mechanism might be related to the binding potential of serotonin 2A receptors. Studies of nonhuman primates have shown that early experiences and rearing conditions have different effects on later central serotonin functioning depending on the primate's genotype on a serotonergic gene (Bennett *et al*. 2002; Champoux *et al*. 2002). In a study using human subjects, the relation between serotonin transporter linked polymorphic region (*5HTTLPR*) and the participant's unresolved loss or trauma was dependent on the methylation density of 5HTT promoter region, suggesting that environmental experiences may have an epigenetic effect on later serotonergic functioning and that epigenetic marks (DNA methylation) may serve as the interface between environmental experiences and the developing infant (Van IJzendoorn *et al*. 2010).

Given that mothers and their children share common alleles with a 50% probability, the present results might also reflect a passive gene–environment correlation in which the parent and the child share common genes influencing both parental behaviors and child dispositions. An evocative gene–environment correlation, in which heritable characteristics elicit certain kinds of responses in the environment, would also be possible. For example, the *HTR2A* T102C variant has been associated with popularity in a novel social group in males (Burt 2008). However, the *HTR2A* genotype was not associated with maternal nurturance, suggesting that a gene–environment correlation was unlikely to explain the present results. In light of our previous studies (Jokela *et al*. 2007a; Jokela *et al*. 2007b; Jokela *et al*. 2007c) using various environmental measures that are unlikely to share common genetic background (maternal nurturance, SES and residential location), a gene–environment interpretation of the results seems most parsimonious.

The present study has several strengths. First, the study had a long, prospective follow-up time spanning from childhood to adulthood. Second, maternal nurturance was reported by mothers and adult attachment by the participants, so the results were not confounded by common informant bias. Third, the gene–environment interaction effect was observed with two different measures of social attachment, strengthening the reliability of the association. However, our study is limited by the fact that maternal nurturance and adult attachment were both assessed by questionnaires, which may yield only a limited measure of parental behavior and social attachment.

Together with earlier studies on gene–environment interactions and differential susceptibility (Belsky *et al*. 2007), our study further strengthens the hypothesis that the effect of environmental factors may be moderated by the person's genotype. Parental nurturing behavior has been considered a strong candidate in affecting child's social attachment (e.g. Bowlby 1988), although not all studies have provided supporting evidence for this relationship (Difilippo & Overholser 2002; Lopez *et al*. 2000; Parker *et al*. 1992). Studies of child temperament have shown how children with different temperaments are differentially susceptible to parenting and quality of child care (e.g. Pluess & Belsky 2009, 2010). The present results suggest that the inconsistent findings of some previous studies may, at least in part, be because of omitted data of genetic background that modify the influence of parent–child relationship on later behavior. It appears that some children benefit more than others from a warm and nurturing maternal behavior and also suffer more from the lack of it (Belsky *et al*. 2007). The nonsignificant effect of maternal nurturing behavior in individuals carrying the C allele of the *HTR2A* gene implies that some children may be at a risk of following unfavorable developmental pathways despite good and supportive parenting because of their genetic background.

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