

Variations in maternal 5-HTTLPR affect observed sensitive parenting

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Background: Little is known about the genetic determinants of sensitive parenting. Two earlier studies examined the effect of the serotonin transporter polymorphism (5-HTTLPR) on sensitive parenting, but reported opposite results. In a large cohort we further examined whether 5-HTTLPR is a predictor of observed maternal sensitivity and whether observed child social fearfulness moderates the effect of 5-HTTLPR on maternal sensitivity. **Methods:** The population-based cohort consisted of 767 mother–child dyads. Maternal sensitivity was repeatedly observed at the child's age of 14 months, 36 months and 48 months. Sensitivity was coded using the Ainsworth's rating scales for sensitivity and cooperation and the revised Erickson rating scales for Supportive presence and Intrusiveness. Child social fearfulness was observed using the Stranger Approach episode of the Laboratory Temperament Assessment Battery at 36 months. **Results:** Repeated measurement analyses showed a consistent main effect of maternal 5-HTTLPR on sensitivity; mothers carrying the *S*-allele were more sensitive toward their children ($p = .005$). This effect was not explained by the child's 5-HTTLPR genotype. We found no evidence that child social fearfulness moderated the effect of 5-HTTLPR on sensitivity. **Conclusions:** This study suggests that variations in maternal 5-HTTLPR genotype appear to be involved in the etiology of parenting behavior. The observed effects of this genetic variation are consistent with the notion that parenting may have a genetic component, but large studies are needed to find the specific small molecular effects. **Keywords:** 5-HTTLPR, serotonin transporter polymorphism, maternal sensitivity, parenting, social fearfulness.

Introduction

Sensitive parenting is predictive of children's attachment security (Bakermans-Kranenburg, Van IJzendoorn, & Juffer, 2003), social problem solving (Raikes & Thompson, 2008), executive functioning (Bernier, Carlson, & Whipple, 2010), and relationships with siblings and peers (McFarlane et al., 2010; Volling & Belsky, 1992).

Given the critical role of sensitive parenting in children's healthy development, a vast body of research has investigated the determinants of parenting. Belsky's (1984) widely cited process model of parenting distinguishes three main groups of determinants: parental characteristics, such as affective disorders and agreeableness (Bornstein, Hahn, & Haynes, 2011; Clark, Kochanska, & Ready, 2000), child characteristics such as negativity and difficult temperament (Mills-Koonce et al., 2007; Van den Boom, 1994; Vaughn, Bost, & Van IJzendoorn, 2008), and contextual sources of stress and support in which the parent–child relationship is embedded.

While substantial genetic influences may also be involved in parenting (Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000; Neiderhiser et al., 2004; Plomin, Reiss, Hetherington, & Howe, 1994), molecular genetic determinants have been studied to a far lesser extent (Swain, Lorberbaum, Kose, & Strathearn, 2007). In terms of Belsky's process model (1984), genetic factors may impact on parenting by their effects on parental and child characteristics.

In this study, we focus on the serotonin transporter polymorphism (5-HTTLPR), a polymorphic region in the promoter region of the serotonin transporter gene. In humans, 5-HTTLPR has two functional alleles, long (*L*) and short (*S*). The *S*-allele results in a decreased transcription of the serotonin transporter gene, and consequently in increased levels of serotonin in the synaptic cleft (Murphy & Lesch, 2008). Evidence shows that the *S*-allele is associated with higher levels of trait anxiety (Schinka, Busch, & Robichaux-Keene, 2004; Sen, Burmeister, & Ghosh, 2004), with selective attention to negative, threat-related stimuli (Pergamin-Hight, Bakermans-Kranenburg, Van IJzendoorn, & Bar-Haim, 2012), and with an increased risk of depressive disorders in the presence of environmental

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stress (Karg, Burmeister, Shedden, & Sen, 2011). Against this background, an association of the *S*-allele with less sensitive parenting may be hypothesized. However, the increased vulnerability of *S*-allele carriers for depressive symptomatology in the presence of stress also supports the increasing notion that the *S*-allele acts as a plasticity allele (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). That is, the *S*-allele confers vulnerability to psychopathology in stressful environments, but confers an advantage in low-risk environments (Belsky & Beaver, 2011). On the basis of the enhanced sensitivity to the social environment of *S*-allele carriers, we hypothesize that mothers carrying the *S*-allele may be more able of providing sensitive parenting. Furthermore, there is accumulating evidence showing that the *S*-allele is related to improved decision making and cognitive flexibility (Borg et al., 2009; Homberg & Lesch, 2011), and to social cognition (Canli & Lesch, 2007), which are fundamental components of parenting (Atkinson et al., 2009; Barrett & Fleming, 2011). This also provides initial support for the hypothesis that the *S*-allele may be positively associated with sensitive parenting. Because the *S*-allele was maintained throughout evolution in humans and rhesus macaques, it might be that positive effects of the allele offset negative ones (Homberg & Lesch, 2011).

Two previous studies focused on 5-HTTLPR and both found a direct effect of the polymorphism on observed sensitive parenting (Bakermans-Kranenburg & Van IJzendoorn, 2008; Mileva-Seitz et al., 2011). However, they reported opposite effects: In a sample of mothers with toddlers at high risk for behavioral problems, mothers carrying the *S*-allele had lower levels of sensitive parenting toward their toddlers (Bakermans-Kranenburg & Van IJzendoorn, 2008). In contrast, a general population-based study reported that mothers carrying the *S*-allele had higher levels of sensitive parenting (Mileva-Seitz et al., 2011). Moreover, Mileva-Seitz et al. (2011) found that mothers carrying the *S*-allele and reporting higher levels of early care quality, oriented away from the baby less frequently, which was positively associated with sensitivity.

In this study, we further examined the association between 5-HTTLPR and observed sensitive parenting. We used a four times larger sample than previous studies to increase the power to detect any effect of 5-HTTLPR. Precision of the findings was improved by assessing maternal sensitivity repeatedly at three different time points. We also assessed whether child social fearfulness moderated the effect of 5-HTTLPR on maternal sensitivity. It has been proposed that shy children are cognitively more challenged in new situations, eliciting maternal over involvement (Bates & Pettit, 2007). Also, previous research demonstrated that child characteristics such as shyness and approach withdrawal are associated with maternal intrusiveness and less warmth (Bates & Pettit,

2007; Brunk & Henggeler, 1984). Because social fear was previously associated with parenting, it is a good candidate factor (Moffitt, Caspi, & Rutter, 2005). In addition, we examined whether any associations between maternal 5-HTTLPR and sensitivity could be explained by the child's 5-HTTLPR genotype as maternal sensitivity includes reciprocal interactions between mother and child (Shin, Park, Ryu, & Seomun, 2008). Last, to test the specificity of any association between 5-HTTLPR and maternal sensitivity, we repeated all analyses with two other polymorphisms that have previously been examined in relation to sensitivity: the Val158Met polymorphism in the Catechol-O-Methyltransferase gene (COMT) and rs53576, a polymorphism in the oxytocin-receptor gene (OXTR).

Methods

Setting

The study was embedded within the Generation R Study, a population-based prospective cohort from fetal life onwards in Rotterdam, the Netherlands, which has been described in detail elsewhere (Jaddoe et al., 2010).

In a randomly assigned subgroup of Dutch pregnant women and their children, detailed assessments were conducted including observations of maternal sensitivity and child temperament. This subgroup is ethnically homogeneous to exclude confounding or effect modification by ethnicity. All children were born between February 2003 and August 2005 and form a prenatally enrolled birth-cohort. The study was conducted in accordance with the guideline proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam (numbers: prenatal, MEC 198.782/2001/31 and postnatal, MEC 217.595/2002/202). Written informed consent was obtained from all participants.

Study population

Mothers were considered eligible for this study if they had singleton pregnancies and gave full consent for postnatal follow-up ($n = 1079$). Of these, data on 5-HTTLPR genotype were available for $n = 919$ mothers. Within this group, information on observed maternal sensitivity was available for $n = 780$ (85%) mothers. A total of $n = 13$ mothers participated with two siblings. In these cases, data from one of the siblings were randomly excluded so that each mother was included with only one child. Thus, the cohort for analysis comprised $n = 767$ mothers. Of these mothers, the majority ($n = 584$, 76%) participated in 2 or 3 assessments of sensitivity.

To study the main effect, information on all 767 mother-child dyads were included in the analyses. As for the 5-HTTLPR \times child fearful temperament interaction effect, data on 604 mother-child dyads with assessments of child fearful temperament were available.

Nonresponse

Nonrespondents (i.e. mothers without any data on maternal sensitivity, $n = 139$) did not differ on the distributions of 5-HTTLPR genotypes, parity, or family stress compared to mothers included in the study. Nonrespondents were, however, less educated than mothers included (43.6% vs. 34.4%,

$\chi^2 = 4.22$, $p = .04$). The children of nonrespondents did not differ on social fearfulness compared to children of mothers included in the study.

Mothers included in the study (i.e. mothers participating in a subgroup of the Generation R Study) reported slightly less symptoms of psychopathology [0.36 (0.21) vs. 0.38 (0.24), $t = 2.41$, $p < .001$] and less family stress [1.18 (0.16) vs. 1.20 (0.17), $t = 3.68$, $p = .002$] compared to Dutch mothers participating in the total sample of the Generation R Study. Also, mothers included in the study were higher educated (65.5% vs. 56.3%, $\chi^2 = 21.9$, $p < .001$) than Dutch mothers participating in the total study group of Generation R.

5-HTTLPR genotyping

Maternal DNA was derived from blood samples at enrollment and child DNA was derived from cord blood samples at birth. The 43-base pair insertion/deletion in the promoter region of the 5-HTT gene was genotyped using Taqman allelic discrimination. Primer sequences were taken from Hu and colleagues (Hu et al., 2006). Reactions were performed in a 384-wells format in a total volume of 5 μ L containing 2 ng DNA, 120 nM FAM-probe, 80 nM VIC-probe, PCR primers (100 nM each), dimethyl sulfoxide (DMSO) (4% by volume), and 1 \times genotyping master mix (Applied Biosystems Inc., Brooklyn, NY). PCR cycling consisted of initial denaturation for 10 minutes at 95°C, and 40 cycles with denaturation of 15 seconds at 96°C and annealing and extension for 90 seconds at 62.5°C. Signals were read with the Taqman 7900HT (Applied Biosystems Inc.) and analyzed using the sequence detection system 2.3 software (Applied Biosystems Inc.). To evaluate genotyping accuracy of 5-HTTLPR, 225 random child samples were genotyped a second time. No discrepancies were found.

Maternal sensitivity

During the lab visit at the child's age of 14 months, maternal sensitivity was observed during 5 minutes free play ($SD = 2.0$). Maternal sensitivity was coded from DVD recordings with the Ainsworth's 9-point rating scales for sensitivity and cooperation (Ainsworth, Bell, & Stayton, 1974). The intraclass correlation (ICC) for intercoder agreement was .79 for sensitivity and .69 for cooperation ($n = 24$). Sensitivity and cooperation correlated strongly ($r = .84$). An overall 14-month sensitivity score was created by standardizing the two scores and computing the average.

During the lab visit at the child's age of 3 years and the home visit at age 4 years, maternal sensitivity was observed during two tasks that were too difficult for the child, considering his or her age: building a tower and etch-a-sketch. Mothers were instructed to help their child as usual. Maternal sensitivity was coded from DVD recordings with the revised Erickson 7-point rating scales for Supportive presence and Intrusiveness (Egeland, Erickson, Clemenhausen-Moon, Hiestler, & Korfmacher, 1990). An overall sensitivity score was created by reversing the Intrusiveness scale, standardizing the scores, and computing the average across both scales and both tasks. The two tasks were independently coded by 13 and 10 extensively trained coders, respectively. At 3 years, average ICC's for the subscales were .75 for the tower task ($n = 53$) and .79 for the etch-a-sketch task ($n = 55$). At 4 years, average ICC's for the subscales were .85 for the tower task ($n = 40$) and .79 for the etch-a-sketch task ($n = 40$).

Overall, coders were trained in approximately 7 sessions and regularly supervised during the coding process; interreliability between coders was not only assessed directly after the training, but also monitored during the coding process to avoid rater drift. Coders were unaware which of their DVDs would be assigned to a second coder.

Child social fearfulness

Child social fearfulness was measured using the Stranger Approach (SA) episode of the Laboratory Temperament Assessment Battery Preschool Version (Lab-TAB) during the lab visit at 3 years of age (Goldsmith, Reilly, Lemery, Longley, & Prescott, 1999). The Lab-TAB is a widely used, standardized instrument for observational assessment of early temperament. During the SA episode, the child has to deal with social fear when a novel, slightly threatening stranger approaches. The episode was modeled after real-life events: The child was left alone in a room. After 10 seconds, a stranger entered the room and asked the child standard questions in a neutral tone of voice.

Episodes were coded from DVD recordings according to the coding system described in the Lab-TAB manual. Coders were blind to all other measures. Each episode was divided into nine epochs. Eight parameters were scored in each epoch: Intensity of fear expressions, distress vocalizations, activity decrease, approach, avoidance, gaze aversion, verbal hesitancy, and nervous fidgeting. For each parameter, average scores were calculated by dividing the child's overall score for that parameter across the 9 epochs. The mean intercoder agreement ICC for these average scores was .84 ($n = 25$). An overall 'fearfulness' score was created by taking the mean of the standardized average scores of the different parameters. This fearfulness score ranged from 0 to 1 with higher scores indicating a more social fearfulness.

Other covariates

Maternal age, educational level, marital status, and parity were assessed using questionnaires at enrollment. Mothers were investigated what their highest completed level of education was. Educational level was dichotomized into 'lower education' (primary school, lower or intermediate vocational education) and 'higher education' (higher vocational education or university).

At 20 weeks of pregnancy, family stress was assessed by a subscale, General Functioning, of the Family Assessment Device (FAD), which is a validated self-report measure of health or psychopathology of the family (Byles, Byrne, Boyle, & Offord, 1988). The scores were square root transformed to approach a normal distribution. Maternal symptoms of psychopathology were assessed with the Brief Symptoms Inventory (BSI), a self-report instrument. The BSI is a short version of the Symptom Checklist 90 (SCL-90) (Derogatis, 1993). Good validity and reliability are reported (de Beurs, 2004, 2009). For this study, the overall summary score, the Global Severity Index score, was used. This score covers a broad range of symptoms of psychopathology: Next to depressive and anxious symptoms, symptoms of interpersonal sensitivity, and hostility are covered among other dimensions. The score was square root transformed to approach a normal distribution.

Amount of nonparental care was assessed using a questionnaire at the child's age of 1 year. Mothers were investigated for how many hours per week is your child been taken care of by (a) a babysitter, (b) an au-pair, (c) a host-parent, (d) neighbors or family members, (e) daycare, or (f) some-one else?'. The total hours of nonparental care per week was computed by summing the answers to the different items.

Statistical analyses

An additive model was used in the analyses with the 5-HTTLPR genotype, with $LL = 0$, $LS = 1$, and $SS = 2$. Using this model, an r -fold increased effect was assumed for LS , and a $2r$ -increased effect for SS . The genotypes were analyzed by the Armitage's test for trend (1 df). The 5-HTTLPR genotype was also analyzed by a general genetic model. Using this model, 5-HTTLPR was

analyzed per genotype using dummy coding with the *LL* genotype as the reference group (2 *df*).

Data were analyzed in three steps. We first assessed the main effect of maternal 5-HTTLPR on maternal sensitivity. To analyze the associations between the repeatedly measured sensitivity scores and 5-HTTLPR, we used unbalanced repeated-measurements regression analysis. These regression models enable studies of repeatedly measured outcomes taking into account the correlation between measurements, and allowing for incomplete outcome data (Twisk, 2003). The covariance parameters were estimated using Restricted Maximum Likelihood (REML). We used unstructured covariance structures.

We also tested whether 5-HTTLPR interacts with child age, that is whether the development of maternal sensitivity over time differs between mothers with different alleles of 5-HTTLPR. However, as this term was not significant ($p = .5$) it was not further included in the models.

To test whether any effect of 5-HTTLPR on maternal sensitivity was driven by a specific time point, we examined the per time-point associations between 5-HTTLPR and maternal sensitivity using multivariate linear regression analyses.

Second, we tested whether the interaction between child social fearfulness and maternal 5-HTTLPR predicted maternal sensitivity. To this end, the fearfulness score was standardized. Again, unbalanced repeated-measurement regression analysis was used to test the repeated associations and multivariate linear regression analyses were performed to examine the per time-point associations.

Third, because maternal and child genotype are highly correlated, we choose a two-step approach to examine the role of the child's genotype in the association between 5-HTTLPR and sensitivity: We first reran all analyses using only the child's 5-HTTLPR genotype. This enabled us to test whether any effect of maternal 5-HTTLPR on sensitivity could not be explained by an effect of the child's genotype. Second, we reran all analyses of the maternal 5-HTTLPR genotype, now additionally adjusted for the child's genotype if available ($n = 624$ out of $n = 767$). This allowed us to test whether the reported results for maternal 5-HTTLPR were independent of the child's genotype.

Bivariate correlations between the determinants, outcome, and possible confounding covariates were assessed using Pearson correlations for continuous variables and Spearman's rho for categorical variables (see Table S1). All analyses were additionally adjusted for the hypothesized covariates.

To exclude gene-environment correlations, we assessed whether maternal or child 5-HTTLPR was correlated with child social fearfulness.

To test the specificity of our findings for 5-HTTLPR, the analyses testing the main effect of 5-HTTLPR and the interaction effect with social fearfulness were repeated using COMT and OXTR.

To exclude possible false-positive findings due to population heterogeneity, analyses were reran in a sample of $n = 607$ mother-child dyads of which the children were of genetically Caucasian descent based on GWA data.

We used Multiple Imputation in SPSS 17 to impute the missing data on covariates (family stress 6.9%, educational level 0.8%, parity 0.1%, psychopathology symptoms 5.6%). All test statistics and regression coefficients were averaged over 5 imputed datasets. We used an alpha of .05 to indicate statistical significance. All repeated measurements analyses were carried out using the Statistical Analysis System version 9.2 (SAS, Institute Inc., Gary, NC), including the PROC MIXED procedure for unbalanced repeated measurements. All per time-point analyses and correlations were carried out using the Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Descriptive statistics of the mothers and children are presented in Table 1. Maternal and child 5-HTTLPR genotype distribution were both in Hardy-Weinberg equilibrium ($p = .6$ and $p = .6$, respectively). Correlations between predictor variables, maternal sensitivity, and covariates are presented in Table S1.

The repeated measurement analyses showed that, overall, with each additional *S*-allele of the mother, she was more sensitive toward her child [$B = 0.11$ (95% CI = 0.03, 0.18), $p = .005$] taking into account all covariates (see Table 2). Using a general genetic model, we found that mothers carrying the *SS* and *SL* genotypes were more sensitive toward their children than mothers with the *LL* genotype.

The results of the individual per time-point analyses are summarized in Table 2. Maternal 5-HTTLPR was associated with maternal sensitivity at 14 months and with maternal sensitivity at 4 years. These associations remained significant after adjusting for all covariates. Although 5-HTTLPR did not predict maternal sensitivity at 3 years, the association was in the same direction as the associations observed at 14 months and 4 years, and was not significantly different from those associations.

The repeated measurements analysis showed no evidence for an interaction between 5-HTTLPR and child temperament in predicting maternal sensitivity; $B = -0.08$ (95% CI = -0.17 , 0.01), $p = .08$ (see Table 3). Also, the per time-point analyses showed no evidence for a specific age-driven interaction effect between 5-HTTLPR and child temperament on sensitivity (see Table 3).

To test whether our results could not be explained by the child's 5-HTTLPR genotype, we first tested whether the child's genotype was associated with maternal sensitivity. Repeated measurements analyses showed that there was no main effect of the child's 5-HTTLPR on maternal sensitivity [$B = 0.05$ (95% CI = -0.03 , 0.13), $p = .2$], see Table S2. Next, we included both maternal and child's genotype as predictors of maternal sensitivity in the analyses. Results showed that maternal 5-HTTLPR genotype remained a significant predictor of sensitivity over and beyond the child's genotype: $B = 0.12$ (95% CI = 0.03, 0.21), $p = .01$. Also, we found no evidence for an interaction effect between the child's 5-HTTLPR and child fearfulness on maternal sensitivity. Furthermore, no evidence for an interaction effect between maternal and child's 5-HTTLPR was found (see Table S2).

To test the specificity of the findings for 5-HTTLPR, the analyses were repeated using COMT and OXTR. No main effects or interaction effects with social fear on maternal sensitivity were found (see Table S3).

We found no evidence of possible confounding by ethnicity: using a subsample ($n = 607$) of mother-child dyads of genetically Caucasian descent, effects of 5-HTTLPR on sensitivity remained essentially the same [$B = 0.13$ (95% CI = 0.04, 0.21), $p = .003$].

Discussion

This study investigated the effect of 5-HTTLPR on maternal sensitivity in a large population-based sample of mother–child dyads, using repeated measurements of sensitivity at different ages of the child. Mothers carrying *S*-alleles showed more sensitive behavior toward their children than mothers carrying *L*-alleles. No evidence for a moderating effect of child social fearfulness on the association between 5-HTTLPR and maternal sensitivity was found.

The findings of a direct effect of 5-HTTLPR on maternal sensitivity are consistent with the observations of Mileva-Seitz et al. (2011) who also found that the *S*-allele was associated with more sensitive parenting. The 5-HTTLPR polymorphism may exert its influence on parenting through its associations with maternal characteristics because the 5-HTTLPR polymorphism is associated with various aspects of cognitive functioning. Both rodent and human studies have suggested that *S*-allele carriers show improved cognitive functioning on a variety of tasks including cognitive flexibility, reversal learning, attention, and inhibition (Brigman et al., 2010; Homberg & Lesch, 2011; Jedema et al., 2010). Especially, cognitive flexibility and attention are important components of parenting behavior as sensitive parenting depends on the ability to accurately perceive children's signals and to respond to them in an adequate and prompt way (Ainsworth, Blehar, Waters, & Wall, 1978). For example, it has been shown that maternal attention deficit/hyperactivity disorder (ADHD) negatively impacts on maternal parenting practices (Chronis-Tuscano et al., 2008; Murray & Johnston, 2006). Also, poor working memory is predictive of observed reactive parenting (Deater-Deckard, Sewell, Petrill, & Thompson, 2010). Besides an effect on parenting via maternal characteristics, the 5-HTTLPR polymorphism may also exert a direct influence on parenting through underlying neural and hormonal influences. Both oxytocin and vasopressin appear to be of major importance for understanding differences in parenting behavior across species (Galbally, Lewis, Van IJzendoorn, & Permezel, 2011; Swain et al., 2007). The two hormones are secreted by the hypothalamic paraventricular nucleus (PVN) which is innervated by serotonergic fibers (Skuse & Gallagher, 2011). Furthermore, serotonin receptors are present in the PVN. Studies have indicated that through its receptors, serotonin influences the release of oxytocin and vasopressin (Jorgensen, Riis, Knigge, Kjaer, & Warberg, 2003). Therefore, through its associations with the oxytocin and vasopressin systems, 5-HTTLPR may influence maternal sensitive parenting.

Children inherit genes of the mother associated with sensitive parenting. These inherited genetic variants may evoke certain parenting behaviors (evocative rGE) (Rutter & Silberg, 2002). We showed that no effect of child genotype on sensitive parenting

Table 1 Sample descriptives ($n = 767$)

	Mean ^a (SD) ^a
Mothers	
5-HTTLPR (%)	
<i>LL</i> ($n = 257$)	33.5
<i>LS</i> ($n = 371$)	48.4
<i>SS</i> ($n = 139$)	18.1
Sensitivity at 14 months, mean (range) ^b	0.0 (−4.16, 2.58)
Sensitivity at 36 months, mean (range) ^c	0.0 (−2.75, 2.86)
Sensitivity at 48 months, mean (range) ^d	0.0 (−2.56, 2.42)
Psychopathology symptoms	0.36 (0.21)
Family stress	1.18 (0.16)
Educational level (% lower)	34.5
Parity (% nulli)	63.5
Age at intake	31.8 (3.74)
Nonparental care, hours per week	16.0 (9.93)
Children	
5-HTTLPR (%) ^e	
<i>LL</i> ($n = 205$)	26.7
<i>LS</i> ($n = 295$)	38.5
<i>SS</i> ($n = 124$)	16.2
Child's social fearfulness, mean (range) ^f	0.0 (−2.72, 3.67)
Child's gender (% boys)	50.1
Age at 14 month visit, months, median (95% range)	14.5 (13.4, 17.1)
Age at 3 years visit, months, median (95% range)	37.3 (35.5, 41.4)
Age at 4 years visit, months, median (95% range)	51.1 (49.8, 55.1)

^aUnless otherwise indicated.

^b $n = 537$.

^c $n = 574$.

^d $n = 524$.

^e $n = 624$.

^f $n = 604$.

was observed. Moreover, the effect of maternal 5-HTTLPR genotype on sensitivity was driven by the maternal genotype beyond the child's genotype, thereby confirming the independent effect of the maternal genotype on maternal sensitivity.

However, as parents and children share the same genes associated with both parenting behavior and child outcome (passive rGE), parenting behaviors may also be a marker for genetic heritage rather than a causal factor for child development. Therefore, passive gene-environment correlation needs to be carefully looked at in future studies assessing associations between parenting styles and child outcome.

Next to strengths, our study also has some limitations: Our results may be somewhat biased due to the overrepresentation of higher educated mothers. Second, the Generation R Focus Study is a relatively homogenous population-based cohort that mainly consists of low-risk families. While the homogeneity of the sample is advocated for validly testing genetic effects, results may be less generalizable to samples including high-risk families. Furthermore, we did not differentiate between *L* and *Lg* although *Lg* is

Table 2 Associations between 5-HTTLPR and maternal sensitivity

	Maternal sensitivity (per <i>SD</i>)			
	Unadjusted model		Adjusted model	
	B (95% CI)	<i>p</i>	B (95% CI)	<i>p</i>
Repeated measurements analyses				
5-HTTLPR	0.12 (0.04, 0.19)	.003	0.11 (0.03, 0.18)	.005
5-HTTLPR (general model)				
<i>LL</i>	0.00 (ref)	–	0.00 (ref)	–
<i>LS</i>	0.16 (0.04, 0.29)	.008	0.17 (0.06, 0.29)	.004
<i>SS</i>	0.21 (0.06, 0.37)	.007	0.19 (0.04, 0.35)	.01
Per time-point analyses				
Sensitivity at 14 months (<i>n</i> = 537)				
5-HTTLPR	0.13 (0.01, 0.25)	.04	0.12 (–0.00, 0.24)	.06
Sensitivity at 3 years (<i>n</i> = 574)				
5-HTTLPR	0.08 (–0.04, 0.19)	.2	0.07 (–0.05, 0.18)	.3
Sensitivity at 4 years (<i>n</i> = 524)				
5-HTTLPR	0.16 (0.04, 0.28)	.008	0.16 (0.04, 0.28)	.009

The adjusted model was adjusted for psychopathology symptoms, family stress, maternal educational level, parity, age at intake, amount of nonparental care, and child's gender. Unless otherwise specified, additive models were used.

Table 3 The moderating effects of social fearfulness on the association between 5-HTTLPR and maternal sensitivity

	Maternal sensitivity (per <i>SD</i>)			
	Unadjusted model		Adjusted model	
	B (95% CI)	<i>p</i>	B (95% CI)	<i>p</i>
Repeated measurements analyses				
Social fearfulness × 5-HTTLPR	–0.08 (–0.18, 0.02)	.1	–0.08 (–0.17, 0.01)	.08
Per time-point analyses				
Sensitivity at 36 months (<i>n</i> = 532)				
social fearfulness × 5-HTTLPR	–0.08 (–0.20, 0.04)	.2	–0.08 (–0.20, 0.03)	.2
Sensitivity at 48 months (<i>n</i> = 453)				
Social fearful × 5-HTTLPR	–0.07 (–0.19, 0.06)	.3	–0.08 (–0.20, 0.05)	.2

The adjusted model was adjusted for psychopathology symptoms, family stress, maternal educational level, parity, age at intake, amount of nonparental care, and child's gender. Furthermore, all models included the main effects of social fearfulness and 5-HTTLPR. Unless otherwise specified, additive models were used.

considered a low expressing genotypic variant of the 5-HTTLPR polymorphism (Hu et al., 2006). However, in Caucasian samples, the percentages of *Lg* have been found to be rather low (Zalsman et al., 2006).

Conclusion

In conclusion, we showed that the maternal 5-HTTLPR polymorphism most likely is associated with maternal sensitive parenting. This finding contributes to growing knowledge that parental behavior is a multifactorial concept. As noted by Swain et al. (2007), parenting can be viewed as an interaction among genes, past parenting, current experience, psychological state, neurobiological systems, and environmental constraints. Acknowledging and providing further insights into the multifactorial processes underlying parenting will provide a better understanding of parenting. In particular, investigation of possible mediators of the association between 5-HTTLPR and maternal sensitivity, such as cognitive flexibility and attention, may provide valuable insights into underlying biological pathways and provide further evidence for an association between

5-HTTLPR and parenting. Moreover, as for many complex traits, it remains challenging to find and recognize true genetic associations. Therefore, replication of the current association between 5-HTTLPR and sensitive parenting remains warranted.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Correlations among the variables.

Table S2 The role of maternal and child genotype.

Table S3 Associations between COMT, OXTR, and maternal sensitivity.

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Key points

- Little is known about the molecular genetic determinants of parenting behavior.
- Two earlier studies assessing the association between variations of the serotonin transporter polymorphism (5-HTTLPR) and maternal parenting reported opposite results.
- In this large, population-based cohort we further assessed whether variation in the maternal 5-HTTLPR genotype predicts maternal sensitivity.
- Maternal sensitivity was repeatedly observed, at three different ages of the child.
- Findings suggest that variation in maternal 5-HTTLPR genotype appears to be involved in the etiology of parenting behavior.

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