Genes, Brain and Behavior
Official publication of the International Behavioural and Neural Genetics Society

Genes, Brain and Behavior (2011) **10:** 325–333 doi: 10.1111/j.1601-183X.2010.00671.x

Serotonin transporter allelic variation in mothers predicts maternal sensitivity, behavior and attitudes toward 6-month-old infants

V. Mileva-Seitz[†], J. Kennedy[‡,§], L. Atkinson[¶], M. Steiner[,††], R. Levitan[‡,§], S. G. Matthews[‡‡], M. J. Meaney[§§], M. B. Sokolowski[¶¶] and A. S. Fleming[*,***]**

[†]Institute of Medical Sciences, University of Toronto, Mississauga, Ontario, [‡]Center for Addiction and Mental Health, Toronto, Ontario, [§]Department of Psychiatry, University of Toronto, Mississauga, Ontario, [¶]Department of Psychology, Ryerson University, Toronto, Ontario, [**]Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, Ontario, [††]Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Ontario, [‡‡]Department of Physiology, University of Toronto, Mississauga, Ontario, [§§]Sackler Program for Epigenetics and Psychobiology at McGill University and Douglas Mental Health University Institute, Montréal, Québec, [¶¶]Department of Biology, University of Toronto, Mississauga, Ontario, and [***]Department of Psychology, University of Toronto, Mississauga, Ontario
**Corresponding author: Dr A. S. Fleming, Department of Psychology, South Building, Room 2037B, University of Toronto Mississauga, 3359 Mississauga Road North, Mississauga, Ontario L5L1C6, Canada. E-mail: alison.fleming@utoronto.ca*

Maternal behavior in the new mother is a multidimensional set of responses to infant cues that are influenced by the mother's early life experiences. In this study, we wanted to test if mothers' early life experiences and mothers' genotype have interactive effects on maternal behaviors and attitudes, something which has not been previously explored. In a sample of 204 mothers, we assessed maternal genotype at the serotonin transporter-linked polymorphic region (5-HTTLPR) and an adjacent upstream polymorphism (rs25531), together giving rise to three alleles: short (S), L_G and L_A. Controlling for maternal age and parity, we showed that this genotype can predict differences in maternal sensitivity at 6 months postpartum: mothers with an S (or the functionally similar L_G) allele were more sensitive than mothers who lacked the allele during a 30-min recorded mother–infant interaction (F (4, 140) = 3.43; P = 0.01). Furthermore, we found highly significant gene–environment interactions in association with maternal behavior, such that mothers with no S or L_G alleles *oriented away* more frequently from their babies if they also reported more negative early *care quality* (F (5, 138) = 3.28; P = 0.008). Finally, we found significant gene–environment associations with maternal attitudes; mothers with the S allele and with greater early care quality scored higher on ratings of their *perceived attachment* to their baby (F (5, 125) = 3.27; P = 0.008).

Keywords: Early experience, gene–environment interactions, maternal behavior, maternal sensitivity, serotonin transporter

Received 30 August 2010, revised 10 November 2010 and 3 December 2010, accepted for publication 15 December 2010

The quality of parental care children receive has clear consequences for their development (De Wolff & van IJzendoorn 1997; Rutter 1979; Sroufe 2005; Trickett and McBride-Chang 1995). In turn, maternal behaviors and attitudes vary within populations and are influenced by complex environmental and hereditary factors. On one hand, the quality of early life experiences predicts later maternal responsiveness (Gara *et al*. 1996; Newcomb & Locke 2001). On the other hand, twin studies suggest greater heritability for some dimensions of maternal behavior (Neiderhiser *et al*. 2004) and molecular studies suggest associations between genotype and maternal sensitivity, directly (Bakermans-Kranenburg and van IJzendoorn 2008) or in interaction with ongoing stressors (Van IJzendoorn *et al*. 2008). This study is the first to explore the interactive effects of mothers' genotype and early life experiences on the quality of later maternal behavior and attitudes.

We selected the serotonin transporter gene (*5-HTT*) as a candidate gene. *5-HTT* encodes for a presynaptic transmembrane protein involved in serotonin reuptake. This gene has been studied extensively in nonhuman primates and human populations and variants of the promoter-linked polymorphic region on this gene (known as 5-HTTLPR) have direct and interactive effects on many behaviors both in the young and in adults (Murphy *et al*. 2008). The 5-HTTLPR contains a 43 bp insertion/deletion in the promoter region of *5-HTT*, which in humans results in two functional alleles, long (L) and short (S). There is three times less *in vitro* basal transcription of 5-HTT mRNA found resulting from the S allele (Heils *et al*. 1996). In humans, the S allele has been linked with depression and other negative affective states in individuals with and without a history of early life adversity (Anguelova *et al*. 2003; Brown & Harris 2008; Caspi *et al*. 2003; Lee *et al*. 2005; Lesch *et al*. 1996; Osher *et al*. 2000; Thakur *et al*. 2009; Uher & McGuffin 2008; Risch *et al*. 2009). Furthermore, recent studies indicate that individuals who lack an S allele exhibit a potentially protective tendency to avoid

negative emotional stimuli and a concurrent bias for positive emotional stimuli not seen in S-carriers (Fox *et al*. 2009).

Conversely, S-carriers show greater amygdala activation in response to emotional stimuli and have greater difficulty disengaging from happy, fearful and sad facial expressions (Beevers *et al*. 2009; Hariri *et al*. 2002; Munafo *et al*. 2008). However, S allele carriers show improved performance on a variety of executive function tests compared with homozygous L individuals (Borg *et al*. 2009; Roiser *et al*. 2007; Strobel *et al*. 2007). Furthermore, the 5-HTTLPR genotype predicts differences in the activation of brain regions associated with imitation, social cognition and communication (Canli and Lesch, 2008); the S allele might be indicative of increased vigilance. In light of this evidence, we hypothesized that the S allele at 5-HTTLPR may have adaptive advantages in certain contexts, such as during mother–infant interactions.

In rhesus macaques, early life adversity in carriers of the S allele at the rhesus 5-HTTLPR homolog (rh5-HTTLPR) are associated with lower 5-HT metabolite levels than controls (Bennett *et al*. 2002). In turn, low 5-HT metabolite levels are predictive of maternal behavior quality in this species suggesting a gene–environment interaction on mothering (Cleveland *et al*. 2004). Moreover, S allele-carrying macaques also display increased social vigilance (Watson *et al*. 2009). Together, the human and macaque evidence suggests complex associations among genotype, early experiences, cognition and sociality. It is yet unknown if these associations relate to differences in human mothering.

We thus explored behaviors and attitudes in human mothers of 6-month-old infants. We hypothesized that mothers with one or two copies of the 5-HTTLPR S allele will exhibit differences in maternal behaviors from mothers lacking an S allele. We also hypothesized that these effects might be dependent on the mothers' early experience.

Methods

Participants

Subjects were part of the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) study, a longitudinal study following two cohorts of mothers and their infants. We examined the Hamilton, Ontario cohort for which 255 mothers originally enrolled. Relevant genotyping and experiential data were available for the 204 mothers included in this study. Fifty-one subjects were excluded for the following reasons: attrition between the recruitment visit and the 6-month postpartum follow-up ($n = 28$), premature delivery ($n = 18$), stillbirth or termination ($n = 3$) and involvement of the Children's Aid Society (CAS) ($n = 2$). Most subjects reported having a partner (94%). Ethnic descent of the sample was mostly Caucasian (90%), with 3% ($n = 6$) mixed ethnicity, 2% ($n = 4$) African, 1.5% Hispanic ($n = 3$) and 1% East Indian ($n = 2$); the rest were unknown or unspecified. This ethnic distribution is typical of the greater Hamilton region.

The subjects, aged 18–45 years, were recruited during the second trimester of pregnancy (weeks 12–24) from referrals to the St. Joseph's Health Center (SJHC) Women's Health Concerns Clinic and SJHC Ultrasound Department, Hamilton, Ontario, Canada.

Procedure

Subjects were approached during early pregnancy and asked to participate in a longitudinal study on maternal adversity, vulnerability and neurodevelopment. Written consent was obtained from each participant prior to recruitment. During 20 visits, beginning in the second trimester of pregnancy (weeks 12–24) and continuing until 72 months postpartum, the mothers and their children were assessed through questionnaires, diagnostic tools and behavioral tasks. Participants received $25 compensation after each visit.

Measures

Video-recorded mother–infant interaction

At 6 months postpartum, we recorded 30 min of non-feeding mother–infant interaction at the mothers' homes: 20 min of free interaction/play and 10 min during which mothers filled out a questionnaire in the presence of their infant. One hundred and fifty-eight of the 204 mothers agreed to be recorded. These mothers did not differ significantly from mothers who did not participate in the video recording on income, parity (whether the mother has had previous children), genotype frequency or depression. However, they were slightly better educated ($M = 4.94 \pm 2.28$ vs. $M = 3.83 \pm 2.44$ on a scale from 0 = not finished high-school to 10 = professional degree; $t(170) = -2.16$, $P = 0.03$) and older ($M = 31.6 \pm 4.75$ vs. $M = 28.7 \pm 5.53$ years of age; $t(201) = -2.13$, $P = 0.04$).

A single rater (V. R. M.-S.) coded the videos for *maternal sensitivity* using the Ainsworth maternal sensitivity scales (Ainsworth *et al*. 1978) ($n = 158$), which contain four subscales: cooperation, accessibility, acceptance and sensitivity. In comparison with an experienced rater, inter-rater reliability was high ($r = 0.83$ across all four subscales; $n = 17$). Intra-rater reliability was also high ($r = 0.93$ across all four subscales, $n = 10$). The primary rater was blinded at the time of rating to women's genotype and early experience status.

The first 20 min of the interaction were also coded by two raters using the Behavioral Evaluation Strategies and Taxonomies (BEST) coding system (Educational Consulting, Inc., Florida, USA) (Krpan *et al*. 2005). This analysis provides duration and frequency information for numerous maternal and infant behaviors. We focused on the frequency of maternal *orienting away from the infant*. This is a behavior characterized by the mother's gaze being directed at something other than the infant, including objects in the environment. Inter-rater reliability was high ($r = 0.80$, $n = 10$).

There was a negative correlation between maternal *sensitivity* and maternal *orienting away from the infant* frequency (Kendall's tau $= -0.13$, $P = 0.02$, $n = 169$) in both the present sample and in an independent sample of 88 mothers (Kendall's tau $= -0.22$, $P = 0.004$, $n = 88$, from the data set in Gonzalez *et al*. 2009).

Maternal attitudes

We assessed mothers' feelings and attitudes about a range of issues related to mothering and the infant through the *Childbearing Attitudes Questionnaire* (CAQ). From the CAQ, 18 factors were originally derived by factor analysis from two data sets (Fleming*et al*. 1988; Ruble *et al*. 1990). We used one of these factors, maternal 'perceived attachment' to the infant, a dimension calculated from scores on items including 'I would like to spend at least the first year with my baby', 'Often when I'm with other adults, all I can talk about is the baby' and 'I do not feel as close to my baby as I expected' (reverse scored). This measure has a Chronbach's alpha reliability of 0.67 (Fleming *et al*. 1988). The *perceived attachment* measure was not significantly correlated with either early experience measure in our sample.

Early experience

We used a modified version of the life history calendar (LHC; Caspi *et al*. 1996) to assess the number of experienced changes in primary caregiver during the subjects' first 18 years of life. We used the Childhood Trauma Questionnaire (CTQ; Bernstein *et al*. 2003), a retrospective self-report questionnaire, to assess five types of childhood trauma: physical, emotional and sexual abuse; emotional and physical neglect. Additionally, we used the Parental Bonding Instrument (PBI; Parker*et al*. 1979), a self-report, retrospective measure of quality of parenting experienced during the subjects' first 16 years of life. Although retrospective measures are open to criticism of biased recall, the PBI and CTQ have good

psychometric properties (Bernstein *et al*. 1994; Wilhelm *et al*. 2005). The LHC and CTQ were delivered at 12–24 weeks of pregnancy, whereas the PBI was delivered at 6 months postpartum. By using these three early experience questionnaires, we hoped to capture a greater spectrum of early experience and adversity, whereas the CTQ tends to assess more severe occurrences of trauma and neglect, the PBI and LHC assess more mild occurrences, including family transitions and parental bonding.

In order to constrain the multiple measures of experience from the three questionnaires (CTQ, PBI and LHC), we used principal component analysis (quartimax rotation) to derive two factors with eigenvalues >1, which appeared to reflect *care quality* and *care stability*, explaining 59% of the shared variance of the nine input variables (eigenvalues were 4.0 and 1.3, respectively). Early experience dimensions that loaded highly on *care quality* were the following: CTQ physical abuse, CTQ emotional abuse, CTQ physical neglect, CTQ emotional neglect, PBI maternal care and PBI maternal overprotection (intercorrelations between these six dimensions were significant and the absolute value Kendall's tau coefficients ranged between 0.25 and 0.56, $n = P < 0.01$ across all cases).

Dimensions with high loadings on *care stability* were LHC *number of primary caregiver shifts* experienced by mothers in the mothers' first 18 years of life and LHC *number of years of paternal presence in the home* (correlation between these two scales was highly significant; Kendall's tau $= -0.73$, $P < 0.001$). However, this method significantly reduced the sample size, because not all subjects successfully completed all three questionnaires. To compensate, we imputed values of the derived components with stochastic regression single imputation in SPSS, where the original nine CTQ, PBI and LHC variables were used as predictors and the *care quality* and *care stability* as the predicted variables.

Buccal cell swabs and genotyping

We collected subjects' DNA through buccal swabs. DNA extraction and genotyping for 5-HTTLPR were carried out at the Center for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada, according to previously published protocols (Praschak-Rieder *et al*. 2007).

Upstream of the 5-HTTLPR region, a single nucleotide polymorphism (A→G, rs25531) results in two functional variants of the L allele: L_A and L_G (Hu *et al*. 2006; Nakamura *et al*. 2000). The L_A/L_A genotype associates with higher mRNA expression *in vitro* (Hu *et al*. 2006) and greater binding potential in human putamen (Praschak-Rieder *et al*. 2007) and midbrain (Reimold *et al*. 2007) compared with genotypes containing one or two copies of L_G or S. On the basis of this literature, we used rs25531 in addition to the 5-HTTLPR polymorphism to maximize genotypic information for 5-HTT and assessed three alleles at 5-HTTLPR: S, L_A and L_G. We categorized mothers who carry an L_G allele with those who carry an S allele, given that L_A has been shown to be functionally different from both (Hu *et al*. 2006).

Analysis

We compared genotype groups for differences in age, combined family income at intake and the two derived components of early experience, *care quality* and *care stability* (see *Methods: Early experience*). Extreme outliers on these two dimensions were transformed by shifting the values to preserve rank but reduce spread.

We assessed the influence of 5-HTTLPR genotype and early experience on the outcome measures with linear regression in SPSS. For each outcome measure, we first entered maternal age and parity (known predictors of maternal behavior; Fleming*et al*. 2008; Krpan *et al*. 2005)), then the early care components (*care quality* and *care stability*, centered), then *genotype* and a multiplicative interaction term of genotype and the early care components. *Genotype* was dummy coded for the presence of the S allele: 1 = one or two copies of S or L_G and 0 = no copies of S or L_G.

For the attitudinal *perceived attachment* outcome, the distribution was severely skewed (skewness coefficient = −1.69 and skewness standard error = 0.19) and kurtotic (kurtosis coefficient = 3.53 and kurtosis standard error = 0.38). We corrected using an inverse transformation on the sample distribution, after reflecting all scores to preserve original directionality. Regression results and figures are based on the transformed distribution.

We performed the analyses on the entire sample (including all ethnic groups), as well as an on a restricted sample (Caucasian only). We used Fisher's *z*-test to compare the *r*-values for the regression models based on the Caucasian only and the full sample of subjects. For *sensitivity*, *orienting away* and *perceived attachment*, we obtained the following *z*-scores: 0.16, 0.05 and 0.00, which are below the critical value 1.96 for a two-tailed test, suggesting there is no difference between the outcomes of the two regression models. Here, we present the larger sample.

Results

Genotype frequencies in our cohort

Table 1 describes genotype frequencies and percentages in our cohort of 166 mothers. The frequency of mothers (25.9 %) with the L_AL_A genotype is consistent with the literature on other Caucasian populations (Hu *et al*. 2006).

Genotype does not predict differences in demographics or early experiences

Subjects did not differ in age, combined family income at intake into the study or early experience as a function of genotype (Table 2). The means in this analysis were compared using two-tailed tests, assuming equal variances, at a significance level, $\alpha = 0.05$; tests were adjusted for multiple comparisons using the Bonferroni correction.

Genotype predicts maternal behavior, but not maternal attitudes

We tested the association between maternal genotype and three dimensions of maternal responsiveness: *sensitivity, orienting away from the infant and perceived attachment to the infant*. We also tested whether the mother's early experiences moderated the effects of genotype on these maternal outcome variables, by including the two early experience dimensions, *care quality* and *care stability*, in our regression analyses. Table 2 shows significant differences in maternal *sensitivity* and *perceived attachment to the infant* by maternal genotype. These were explored in the regression analyses.

Preliminary analyses (not shown) indicated the *care stability* component of maternal early life experiences did not contribute significant variance to any of the three maternal outcome measures, alone or in interaction with genotype, so it was removed from later analyses. Therefore, we retained only the *care quality* early experience measure as a potential environmental moderator of genotypic effects. We used linear regression with IBM SPSS statistics 17.0 (IBM, Armonk,

Table 1: Triallelic 5HTTLPR polymorphism genotype frequencies

Genotype	L_AL_A	L_AL_G	L_GL_G	L_AS	L_GS	SS	Total
Frequency	43	18	1	67	6	31	166
Percentage	25.9	10.8	0.6	40.4	3.6	18.7	100

Table 2: Means (standard deviation) of demographic variables, predictor variables and outcome variables in mothers by 5HTTLPR and rs25531 genotype

	HTTLPR + rs25531 genotype	
	No S or L_G allele	One or two copies of S or L_G
Sample size, *n*	43	123
Age*	31.0 (5.4)	31.2 (4.8)
Parity† (%)	43.3	43.6
Income‡	13.9 (3.1) ($40–60 000)	13.6 (3.8) ($40–60 000)
Care quality§	−0.02 (1.0)	−0.01 (0.9)
Care stability§	0.22 (1.1)	−0.14 (1.0)
Maternal sensitivity¶	22.2 (6.3)	24.4 (5.1)‡‡
Orienting away from infant**	27.9 (18.2)	21.8 (11.4)‡‡
Maternal perceived attachment††	6.1 (0.7)	6.2 (0.6)

*Postpartum (6 months).
†Percentage of mothers with one or more previous children.
‡Combine family income reported during the prenatal visit, rated as a score of previous year's income, where 0 = no revenue, 3 = 'at least $10 000', 8 = 'at least $20 000', 12 = 'at least $40 000', 15 = 'between $60 000 and $80 000' and 17 = 'over $100 000'.
§Regression scores derived from principal component analysis on nine early experience dimensions (see *Methods: Early experience*), centered and with a range of 5.0 for care quality and 4.9 for care stability; lower values indicate more negative early experiences.
¶Total score on the Ainsworth maternal sensitivity scales (Ainsworth 1978) during a recorded 30-min mother–infant interaction at 6 months.
**The frequency of occurrences where mother orients away from the infant during a recorded 20-min mother–infant interaction at 6 months.
††Score on the *perceived attachment to the infant* dimension of the CAQ at 6 months postpartum.
‡‡Row means differed at $P < 0.05$, adjusted for multiple pair-wise comparisons within rows.

Table 3: Unstandardized regression beta coefficients (*t*-statistics in brackets) of linear regressions

	Sensitivity		Orienting away		Perceived attachment*	
Predictor	Step 1	Step 2	Step 1	Step 2	Step 1	Step 2
Maternal age	0.16 (1.72)	0.19 (2.03)*	−0.10 (−0.41)	−0.31 (−0.11)	−0.01 (−2.23)*	−0.01 (−2.37)*
Parity	−1.59 (−1.71)	−1.96 (−2.10)*	3.63 (1.56)	3.29 (1.44)	−0.32 (−1.04)	−0.21 (−0.70)
Care quality	–	−0.80 (−1.37)	–	1.76 (1.24)	–	0.05 (2.61)**
Genotype†	–	−2.15 (−2.10)*	–	6.23 (2.48)*	–	−0.04 (−1.28)
Genotype × Care quality	–	–	–	−7.93 (−2.79)**	–	−0.07 (−1.96)*
r^2 (adj)	0.02	0.06	0.00	0.07	0.04	0.08
F	2.58	3.43**	1.24	3.28**	3.58*	3.27**
df	(2, 142)	(4, 140)	(2, 141)	(5, 138)	(2, 128)	(5, 125)

Table coefficients were derived from conventional (forced entry) linear regression.
*Coefficients are based on analyses with the reflected inverse transformation of 'perceived attachment'.
†S or L_G allele vs. no S or L_G allele.
*$P \leq 0.05$; **$P \leq 0.01$.

NY, USA), inserting variables in the following order: Step 1, *maternal age*; *parity* (dummy coded as 0 = no previous children and 1 = one or more previous children); Step 2, *care quality, genotype and Care quality × Genotype*. In Step 2, *Care quality × Genotype* interaction terms were dropped if not significant. Table 3 shows the final regression models.

Controlling for the effects of maternal age, parity and early life experience, there was a significant effect of genotype on *maternal sensitivity*. Mothers with one or two copies of the S or L_G alleles were more sensitive in their interactions with their infants at 6 months. Furthermore, there were significant gene–environment interactions between genotype and *care quality* on both maternal behaviour (*frequency of orienting away from the infant*) and maternal attitudes (*perceived attachment*) (Fig. 1a). Mothers with an S or L_G allele less frequently oriented away from their infants and scored higher on *perceived attachment* to the infant as the reported *care quality* increased (Fig. 1b).

Discussion

We examined the influences of genotype and early life experience on the expression of individual differences in

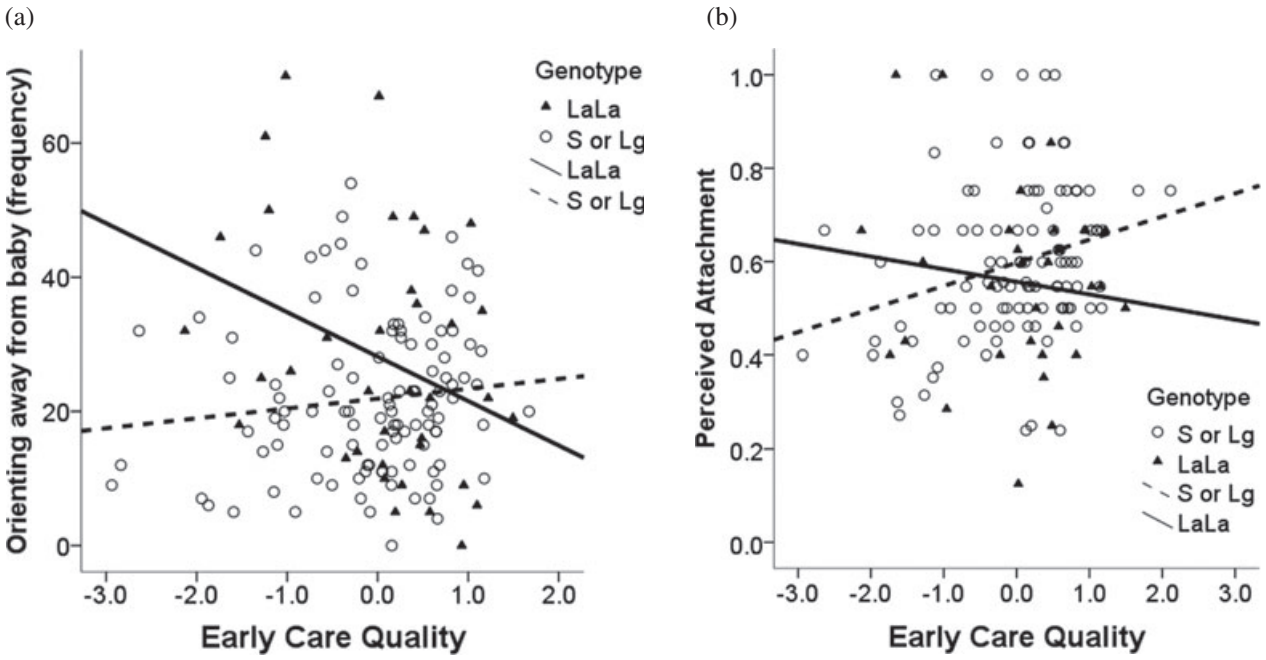

Figure 1: Relationship between *early care quality* (based on mothers' reports of their experiences in childhood assessed with CTQ, PBI and LHC and later reduced to regression scores along one dimension). (a) Frequency of maternal *orienting away from the infant* or (b) reported ratings of maternal *perceived attachment* to the infant. Cases are labeled by genotype.

three dimensions of maternal responsiveness: maternal sensitivity, maternal behaviour (*orienting away from the infant*) and maternal attitudes (*perceived attachment*). We assessed two polymorphic regions on the serotonin transporter gene, 5-HTT: the serotonin transporter-linked polymorphic region (5-HTTLPR) and an adjacent upstream polymorphism (rs25531), which together result in the S, L_G and L_A alleles. We found that mothers with an S or the functionally similar L_G allele were more sensitive than mothers lacking these alleles. We also found a highly significant gene–environment interaction effect on the other two mothering dimensions. With increasing *care quality*, mothers with an S (or L_G) allele tended to orient away from their babies less often and score higher on ratings of *perceived attachment*, whereas mothers lacking an S (or L_G) allele tend to exhibit increased frequency of *orienting away* and lower ratings on *perceived attachment* with increased early care quality.

Genotypes with one or two S alleles have been regarded as 'vulnerability' genotypes, because of increased susceptibility to mood disorders, particularly in conjunction with early stress. However, in the absence of early stress and perhaps even despite early stress, the S allele might in some contexts have adaptive advantages over the L allele. This fits well with the emerging theory that the S allele confers greater sensitivity to environmental signals (Taylor 2010), and that rather than a susceptibility allele, the S allele may be viewed as a plasticity allele (Belsky *et al*. 2009). Our results corroborate this view, as the S (or L_G)-carrying mothers in our sample were more sensitive to their infants, and with increasing early care quality, oriented away from their infants less frequently during interactions and scored higher on ratings of *perceived attachment* to their infants.

Orienting away from the baby is negatively correlated with sensitivity, both in our sample and in a previous sample (see *Methods*). This may be partially because of the relationship between orienting away from baby and maternal attention. For instance, studies in our laboratory have shown that orienting away from the infant during mother–infant interaction is negatively correlated with performance on attentional and cognitive tasks as assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Chico *et al*. in preparation). Mothers who better sustain attention to their infants might more frequently perceive and respond to infant cues. In this context, it has been shown that maternal attention is a necessary but insufficient condition for higher maternal sensitivity (Atkinson *et al*. 1995). More broadly, sensitivity involves openness to signals (Pederson *et al*. 1990). If mothers can more successfully perceive and respond to infants' cues, this might also increase mothers' feelings of competence and mothers' attitudes about parenting the infant. Although *perceived attachment* ratings increased with greater early care quality in our S or L_G mothers, there were no correlations between this attitudinal measure and *sensitivity* or *orienting away from the infant*. Therefore, this hypothesis warrants further investigation.

There is also a role of serotonin in attentional processes. For example, acute administration of the SSRI escitalopram results in decreased activation of the thalamus and frontal

areas of the brain during a sustained attention task (Wingen *et al*. 2008) and reductions in sustained attention (Drueke *et al*. 2009; Oranje *et al*. 2008). Although it is not clear whether such effects are related to 5-HTTLPR genotype, carriers of the S allele perform better on a number of cognitive and attentional tasks (Borg *et al*. 2009; Roiser *et al*. 2007; Strobel *et al*. 2007).

We have shown that maternal 5-HT transporter genotype can significantly predict differences in a wide range of mothering dimensions, from behavior (*oriented away*), through maternal sensitivity, to maternal attitudes (*perceived attachment*), and it is possible that these associations may be related to underlying neural and cognitive differences. There is an emerging evidence that the S allele predicts improved attentional processes (Roiser *et al*. 2007) and social cognition (Canli & Lesch 2007), both important components of mothering (Atkinson *et al*. 2009; Gonzalez *et al*. 2009; A. Gonzalez *et al*., under review; Donovan *et al*. 1997). The 5-HTTLPR genotype in humans is directly associated with differences in 5-HTT binding in the putamen (Praschak-Rieder *et al*. 2007) and in the midbrain (Reimold *et al*. 2007). In the midbrain, the ventral tegmental area (VTA) is the major site of dopaminergic projections of the mesocorticolimbic dopamine system, implicated in reward and motivation. The VTA is also crucial for the regulation of maternal behavior in rats (Numan 2007). Additionally, there appears to be direct serotonergic innervation of VTA dopaminergic neurons (Herve *et al*. 1987) and sustained 5-HT reuptake inhibition by application of SSRIs is associated with decreased dopaminergic signaling in the VTA (Dremencov *et al*. 2009). This is consistent with the theory that 5-HT inhibits dopaminergic neuron signaling (Guiard *et al*. 2008).

Using this evidence, it is possible to speculate that midbrain differences in 5-HTT function may be associated with differences in dopamine signaling downstream, differences which are known to affect maternal behavior. Furthermore, 5-HT reuptake inhibition with fluoxetine (Johns *et al*. 2005) has direct effects on maternal behavior in the rat, whereas serotonergic neurotoxin lesions in the median raphe, a major serotonin production site, impairs lactation and pup retrieval (Barofsky *et al*. 1983). In addition, 5-HTTLPR genotype may be important across a number of behavioral and cognitive functions, to the extent that it is associated with genotype-dependent serotonin function in relevant brain regions. In mice, mutations that disrupt 5-HTT function affect over 50 complex phenotypic traits, from biochemical to physiological anatomical to behavioral (Murphy & Lesch 2008; Murphy *et al*. 2008).

Although we found gene–environment interactions on maternal orienting away from the infant and maternal attitudes of attachment to the infant, the genotype effects on maternal sensitivity did not appear to be moderated by early environment. Although the S allele is commonly the focus in gene–environment interactions, the relationship among 5-HTTLPR genotype, early stress and later 5-HTT function and stress reactivity is not straightforward. Early stress in primates predicts increased adulthood 5-HTT expression across all *rh*5-HTTLPR genotypes (Kinnally *et al*. 2010), but it is the S-carrying individuals who exhibit heightened anxiety and stress responsivity (Barr *et al*. 2004). If, in humans, there is a higher theoretical maximum of 5-HTT expression for the L allele (Murphy *et al*. 2008), then it may be 'easier' for LL-carriers to attain that maximum with even lower levels of early stress. Hahn and Blakely (2007) suggest that as the L allele is more dynamically regulated (i.e. has a greater transcriptional activation), there might be situations in which the L allele would be associated with a 'disadvantageous sensitization to life stressors'. Therefore, for certain outcomes including our 'orienting away' maternal measure, it might be in the LL (or L_AL_A) mothers that we would expect to see the environmental moderation, especially given the non-severe nature of the early stress in our cohort of mothers.

One possible mechanism by which the environment could affect later mothering is through direct epigenetic effects on gene expression (Champagne *et al*., 2006; Roth, Lubin, Funk & Sweatt, 2009). Francis, Diorio, Liu & Meaney, (1999) found that in comparison to high-licking mother rats, mothers that lick their pups less have female offspring who as adults lick their offspring less. Moreover, in the medial preoptic area these female offspring show both reduced expression of the estrogen alpha receptor gene and higher DNA methylation of its promoter region (Champagne *et al*., 2006). A similar process may also affect the brain derived neurotrophic factor gene (Roth *et al*., 2009). Differential gene expression through methylation is one epigenetic mechanism by which the early environment could impact the long-term neural modulation of mothering behavior. Finally, as early adversity effects on methylation patterns in the brain of humans have also been reported (McGowan *et al*., 2009), it would also be interesting to know whether the GXE effects that we report in the present study in humans involve differential methylation patterns as a function of early 'adversity' in the different genotypes.

Bakermans-Kranenburg and van IJzendoorn (2008) report that independent of daily stress levels, S-carrying mothers are *less* maternally sensitive, which is opposite to this findings. However, methodological differences may account for this discrepancy. For example, in this study, we recorded interaction between mothers and their 6-month-old infants in their homes, whereas Bakermans-Kranenburg and van IJzendoorn (2008) recorded mothers and their 1–3-year-old children, interacting during problem-solving tasks in a laboratory setting. Maternal sensitivity can be plastic over time (Lohaus *et al*. 2004), particularly in mothers with depressive symptoms (Pauli-Pott 2008) which may relate to genetic factors. For example, sensitivity at 6 months postpartum might have genotypic associations that differ from those at 12 or 36 months postpartum. Additionally, home-observed mothers may be less stressed than laboratory-observed task-performing mothers and this may be true specifically for S allele-carrying mothers (Gotlib *et al*. 2008), for whom performance anxiety might result in lowered performance or lower maternal sensitivity. Additionally, there is an evidence of differences in mother–infant interaction in a laboratory vs. at home (Belsky 1980). To summarize, it is possible that S-carrying mothers are more sensitive than non-S-carrying mothers under conditions of low stress, but less sensitive under conditions of high stress. This hypothesis is consistent with arguments that genetic influences depend on

environmental conditions (Belsky *et al*. 2007). Nonetheless, the difference in findings serves as a caveat regarding the complexity of genetic influences and the need for further research in varied contexts.

One of the limitations to our study is the use of retrospective reports of early adversity. As with all retrospective measures, the early experience questionnaires in this study may be confounded with present stress or affect. However, both the PBI and CTQ have been shown to have good psychometric properties (Bernstein *et al*. 1994; Wilhelm *et al*. 2005) and have good predictive validity.

A possibility we did not explore here is that the g × e associations with mothering may be mediated by numerous other factors including maternal depression, reward-processing and attention. For instance, depression in mothers is related to decreased sensitivity (Milgrom *et al*. 2004; Murray *et al*. 1996). The S allele in combination with early adversity is associated with greater depression risk, but the mothers with one or two copies of this allele in our cohort had greater maternal sensitivity, which argues for a main effect of genotype regardless of early adversity. We are currently testing this hypothesis in greater depth in a manuscript (Mileva-Seitz *et al*. in preparation) on 'maternal genotype and maternal behavior: depression as a mediating factor'.

Overall, through our use of multidimensional measures of maternal behavior and attitudes, we have uncovered many gene or gene–environment interactions. Extensive phenotypic variation in association with polymorphisms in the serotonin transporter is found in mice mutant models (Murphy & Lesch 2008, Murphy *et al*., 2008) and a similar story is emerging in human association studies as well. We have presented evidence that human maternal phenotypes have complex associations with genotype and environment. These phenotypes, be they behavioral, physiological or attitudinal, are intricately related to underlying neural machinery, in ways not even remotely understood in humans. *5-HTT* is an important gene that likely acts within a large network of epistatic genes. Research into the *5-HTT* gene in animals and humans will provide insights into its role in mothering along with its described roles in psychiatric disorders.

References

Ainsworth, M.D.S., Blehar, M.C., Waters, E. & Wall, S. (1978) *Patterns of Attachment: A Psychological Study of the Strange Situation*. Lawrence Erlbaum, Hillsdale, NJ.

Anguelova, M., Benkelfat, C. & Turecki, G. (2003) A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. *Mol Psychiatry* **8**, 646–653.

Atkinson, L., Scott, B., Chrisholm, V.C., Blackwell, J., Dickens, S., Tam, F. & Godlberg, S. (1995) Cognitive coping, affective distress, and maternal sensitivity: mothers of children with Down syndrome. *Dev Psychol* **31**, 668–679.

Atkinson, L., Leung, E., Goldberg, S., Benoit, D., Poulton, L., Myhal, N., Blokland, K. & Kerr, S. (2009) Attachment and selective attention: disorganization and emotional Stroop reaction time. *Dev Psychopathol* **21**, 99–126.

Bakermans-Kranenburg, M.J. & van IJzendoorn, M.H. (2008) Oxytocin receptor (*OXTR*) and serotonin transporter (*5HTT*) genes associated with observed parenting. *Soc Cogn Affect Neurosci* **3**, 128–134.

Barofsky, A., Taylor, J., Tizabi, Y., Kumar, R. & Jones-Quartey, K. (1983) Specific neurotoxin lesions of median raphe serotonergic neurons disrupt maternal behavior in the lactating rat. *Endocrinology* **113**, 1884–1893.

Barr, C.S., Newman, T.K., Shannon, C., Parker, C., Dvoskin, R.L., Becker, M.L., Schwandt, M., Champoux, M., Lesch, K.P., Goldman, D., Suomi, S.J. & Higley, J.D. (2004) Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. *Biol Psychiatry* **55**, 733–738.

Beevers, C.G., Wells, T., Ellis, A.J. & McGeary, J.E. (2009) Association of the serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. *J Abnorm Psychol* **118**, 670–681.

Belsky, J. (1980) Mother-infant interaction at home and in the laboratory: a comparative study. *J Genet Psychol* **137**, 37–47.

Belsky, J., Bakermans-Kranenburg, M.J. & van IJzendoorn, M.H. (2007) For better *and* for worse: differential susceptibility to environmental influences. *Curr Dir Psychol Sci* **16**, 300–304.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B. & Williams, R. (2009) Vulnerability genes or plasticity genes? *Mol Psychiatry* **14**, 746–754.

Bennett, A.J., Lesch, K.P., Heils, A., Long, J.C., Lorenz, J.G., Shoaf, S.E., Champoux, M., Suomi, S.J., Linnoila, M.V. & Higley, J.D. (2002) Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatry* **7**, 118–122.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E. & Ruggiero, J. (1994) Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry* **151**, 1132–1136.

Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D. & Zule, W. (2003) Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abuse Negl* **27**, 169–190.

Borg, J., Henningsson, S., Saijo, T., Inoue, M., Bah, J., Westberg, L., Lundberg, J., Jovanovic, H., Andree, B., Nordstrom, A.-L., Halldin, C., Eriksson, E. & Farde, L. (2009) Serotonin transporter genotype is associated with cognitive performance but not regional 5-HT1A receptor binding in humans. *Int J Neuropsychopharmacol* **12**, 783–792.

Brown, G.W. & Harris, T.O. (2008) Depression and the serotonin transporter 5-HTTLPR polymorphism: a review and a hypothesis concerning gene-environment interaction. *J Affect Disord* **111**, 1–12.

Canli, T. & Lesch, K.-P. (2007) Long story short: the serotonin transporter in emotion regulation and social cognition. *Nat Neurosci* **10**, 1103–1109.

Caspi, A., Moffitt, T.E., Thornton, A., Freedman, D., Amell, J.W., Harrington, H., Smeijers, J. & Silva, P.A. (1996) The life history calendar: a research and clinical assessment method for collecting retrospective event-history data. *Int J Meth Psychiatr Res* **6**, 101–114.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A. & Poulton, R. (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**, 386–389.

Champagne, F.A., Weaver, I.C., Diorio, J., Dymov, S., Szyf, M. & Meaney, M.J. (2006) Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. *Endocrinology* **147**, 2909–2915.

Cleveland, A., Westergaard, G.C., Trenkle, M.K. & Higley, J.D. (2004) Physiological predictors of reproductive outcome and mother-infant behaviours in captive rhesus macaque females *(Macaca mullatta). Neuropsychopharmacology* **29**, 901–910.

De Wolff, M.S. & van IJzendoorn, M.H. (1997) Sensitivity and attachment: a meta-analysis on parental antecedents of infant attachment. *Child Dev* **68**, 571–591.

Donovan, W.L., Leavitt, L.A. & Walsh, R.O. (1997) Cognitive set and coping strategy affect mothers' sensitivity to infant cries: a signal detection approach. *Child Dev* **68**, 760–772.

Dremencov, E., el Mansari, M. & Blier, P. (2009) Effects of sustained serotonin reuptake inhibition on the firing of dopamine neurons in the rat ventral tegmental area. *J Psychiatr Neurosci* **34**, 223–229.

Drueke, B., Baetz, J., Moeller, O., Hiemke, C., Grunder, G. & Gauggel, S. (2009) Differential effects of escitalopram on attention: a placebo-controlled, double-blind cross-over study. *Psychopharmacology* **207**, 213–223.

Fleming, A.S., Ruble, D.N., Flett, G.L. & Shaul, D.L. (1988) Postpartum adjustment in first-time mothers: relations between mood, maternal attitudes, and mother-infant interactions. *Dev Psychol* **24**, 71–81.

Fleming, A.S., Gonzalez, A., Afonso, V. & Lovic, V. (2008) Plasticity in the maternal circuit: experience, dopamine, and mothering. In Bridges, R.S. (ed), *Neurobiology of the Parental Brain.* Academic Press, Burlington, MA, pp. 519–529.

Fox, E., Ridgewell, A. & Ashwin, C. (2009) Looking on the bright side: biased attention and the human serotonin transporter gene. *Proc Roy Soc B Biol Sci* **276**, 1747–1751.

Francis, D., Diorio, J., Liu, D. & Meaney, M.J. (1999) Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* **286**, 1155–1158.

Gara, M.A., Rosenberg, S. & Herzog, E.P. (1996) The abused child as parent. *Child Abuse Negl* **20**, 797–807.

Gonzalez, A., Atkinson, L. & Fleming, A.S. (2009) Attachment and comparative psychobiology of mothering. In de Haan, M. & Gunnar, M.R. (eds), *Handbook of Developmental Social Neuroscience.* The Guilford Press, New York, pp. 225–245.

Gotlib, I.H., Joormann, J., Minor, K.L. & Hallmayer, J. (2008) HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biol Psychiatry* **63**, 847–851.

Guiard, B.P., El Mansari, M., Merali, Z. & Blier, P. (2008) Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. *Int J Neuropsychopharmacol* **11**, 625–639.

Hahn, M.K. & Blakely, R.D. (2007) The functional impact of SLC6 transporter genetic variation. *Annu Rev Pharmacol Toxicol* **47**, 401–441.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M. & Weinberger, D.R. (2002) Serotonin transporter genetic variation and the response of the human amygdala. *Science* **297**, 400–403.

Heils, A., Teufel, A., Petri, S., Stober, G., Riederer, P., Bengel, D. & Lesch, K.P. (1996) Allelic variation of human serotonin transporter gene expression. *J Neurochem* **66**, 2621–2624.

Herve, D., Pickel, V.M., Joh, T.H. & Beaudet, A. (1987) Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. *Brain Res* **435**, 71–83.

Hu, X.-Z., Lipsky, R.H., Zhu, G., Akhtar, L.A., Taubman, J., Greenberg, B.D., Xu, K., Arnold, P.D., Richter, M.A., Kennedy, J.L., Murphy, D.L. & Goldman, D. (2006) Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet* **78**, 815–826.

Johns, J.M., Joyner, P.W., McMurray, M.S., Elliott, D.L., Hofler, V.E., Middleton, C.L., Knupp, K., Greenhill, K.W., Lomas, L.M. & Walker, C.H. (2005) The effects of dopaminergic/serotonergic reuptake inhibition on maternal behavior, maternal aggression, and oxytocin in the rat. *Pharmacol Biochem Behav* **81**, 769–785.

Kinnally, E.L., Tarara, E.R., Mason, W.A., Mendoza, S.P., Abel, K., Lyons, L.A. & Capitanio, J.P. (2010) Serotonin transporter expression is predicted by early life stress and is associated with disinhibited behavior in infant rhesus macaques. *Genes Brain Behav* **9**, 45–52.

Krpan, K.M., Coombs, R., Zinga, D., Steiner, M. & Fleming, A.S. (2005) Experiential and hormonal correlates of maternal behavior in teen and adult mothers. *Horm Behav* **41**, 112–122.

Lee, H.J., Lee, M.S., Kang, R.H., Kim, H., Kim, S.D., Kee, B.S., Kim, Y.H., Kim, Y.K., Kim, J.B., Yeon, B.K., Oh, K.S., Oh, B.H., Yoon, J.S., Lee, C., Jung, H.Y., Chee, I.S. & Paik, I.H. (2005) Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. *Depress Anxiety* **21**, 135–139.

Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H. & Murphy, D.L. (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **274**, 1527–1531.

Lohaus, A., Keller, H., Ball, J. Voelker, S. & Elben, C. (2004) Maternal sensitivity in interactions with three- and 12-month-old infants: stability, structural composition, and developmental consequences. *Infant Child Dev* **13**, 235–252.

McGowan, P.O., Sasaki, A., D'Alessio, A.C., Dymov, S., Labonte, B., Szyf, M., Turecki, G. & Meaney, M.J. (2009) Epigenetic regulation of hippocampal glucocorticoid receptor gene expression in human suicide victims. *Nat Neurosci* **12**, 342–348.

Milgrom, J., Westley, D.T. & Gemmill, A.W. (2004) The mediating role of maternal responsiveness in some longer term effects of postnatal depression on infant development. *Infant Behav Dev* **27**, 443–454.

Munafo, M.R., Brown, S.M. & Hariri, A.R. (2008) Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biol Psychiatry* **63**, 852–857.

Murphy, D.L. & Lesch, K.-P. (2008) Targetting the murine serotonin transporter: insights into human neurobiology. *Nat Rev Neurosci* **9**, 85–96.

Murphy, D.L., Fox, M.A., Timpano, K.R., Moya, P.R., Ren-Patterson, R., Andrews, A.M., Holmes, A., Lesch, K.-P. & Wendland, J.R. (2008) How the serotonin story is being rewritten by new gene-based discoveries principally related to SLC6A4, the serotonin transporter gene, which functions to influence all cellular serotonin systems. *Neuropharmacology* **55**, 932–960.

Murray, L., Fiori-Cowley, A. & Hooper, R. (1996) The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Dev* **67**, 2512–2526.

Nakamura, M., Ueno, S., Sano, A. & Tanabe, H. (2000) The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. *Mol Psychiatry* **5**, 32–38.

Neiderhiser, J.M., Reiss, D., Pedersen, N.L., Lichtenstein, P., Spotts, E.L., Hansson, K., Cederblad, M. & Elthammer, O. (2004) Genetic and environmental influences on mothering of adolescents: a comparison of two samples. *Dev Psychol* **40**, 335–351.

Newcomb, M.D. & Locke, T.F. (2001) Intergenerational cycle of maltreatment: a popular concept obscured by methodological limitations. *Child Abuse Negl* **25**, 1219–1240.

Numan, M. (2007) Motivational systems and the neural circuitry of maternal behavior in the rat. *Dev Psychobiol* **49**, 12–21.

Oranje, B., Jensen, K., Wienberg, M. & Glenthoj, B. (2008) Divergent effects of increased serotonergic activity on psychophysiological parameters of human attention. *Int J Neuropsychopharmacol* **11**, 453–463.

Osher, Y., Hamer, D. & Benjamin, J. (2000) Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israel sibling pairs. *Mol Psychiatry* **5**, 216–219.

Parker, G., Tupling, H. & Brown, L. (1979) A parental bonding instrument. *Br J Med Psychol* **52**, 1–10.

Pauli-Pott, U. (2008) Mothers with depressive symptoms: cross-situational consistency and temporal stability of their parenting behaviour. *Infant Behav Dev* **31**, 679–687.

Pederson, D.R., Moran, G., Sitko, C., Campbell, K. & Acton, H. (1990) Maternal sensitivity and the security of infant-mother attachment: a Q-sort study. *Child Dev* **61**, 1974–1983.

Praschak-Rieder, N., Kennedy, J., Wilson, A.A., Hussey, D., Boovariwala, A., Willeit, M., Ginovart, N., Tharmalingam, S., Masellis, M., Houle, S. & Meyer, J.H. (2007) Novel 5-HTTLPR allele associates with higher serotonin transporter binding in putamen: a [^{11}C] DASB positron emission tomography study. *Biol Psychiatry* **62**, 327–331.

Reimold, M., Smolka, M.N., Schumann, G., Zimmer, A., Wrase, J., Mann, K., Hu, X.-Z., Goldman, D., Reischl, G., Solbach, C., Machulla, H.-J., Bares, R. & Heinz, A. (2007) Midbrain serotonin transporter binding potential measured with [^{11}C]DASB is affected by serotonin transporter genotype. *J Neural Transm* **114**, 635–639.

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., Griem, A., Kovacs, M., Ott, J. & Merikangas, K.R. (2009) Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression, A meta-analysis. *JAMA* **301**, 2462–2471.

Roiser, M.U., Clark, L. & Sahakian, B.J. (2007) The effects of acute tryptophan depletion and serotonin transporter polymorphism on emotional processing in memory and attention. *Int J Neuropsychopharmacol* **10**, 449–461.

Roth, T.L., Lubin, F.D., Funk, A.J. & Sweatt, J.D. (2009) Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol Psychiatry* **65**, 760–769.

Ruble, D.D., Brooks-Gunn, J., Fleming, A.S., Fitzmaurice, G., Stangor, S. & Deutsch, F. (1990) Transition to motherhood and the self: measurement, stability, and change. *J Pers Soc Psychol* **58**, 450–463.

Rutter, M. (1979) Protective factors in children's responses to stress and disadvantage. In Kent, M.W. & Rolf, J.E. (eds), *Primary Prevention of Psychopathology: Vol. 3. Social Competence in Children*. University Press of New England, Hanover, NH, pp. 49–74.

Sroufe, L.A. (2005) Attachment and development: a prospective, longitudinal study from birth to adulthood. *Attach Hum Dev* **7**, 349–367.

Strobel, A., Dreisbach, G., Muller, J., Goschke, T., Brocke, B. & Lesch, K.P. (2007) Genetic variation of serotonin function and cognitive control. *J Cognitive Neurosci* **19**, 1923–1931.

Taylor, S. (2010) Mechanisms linking early life stress to adult health outcomes. *Proc Natl Acad Sci U S A* **107**, 8507–8512.

Thakur, G.A., Joober, R. & Brunet, A. (2009) Development and persistence of posttraumatic stress disorder and the 5-HTTLPR polymorphism. *J Trauma Stress* **22**, 240–243.

Trickett, P.K. & McBride-Chang, A. (1995) The developmental impact of different forms of child abuse and neglect. *Dev Rev* **15**, 311–337.

Uher, P. & McGuffin, P. (2008) The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Mol Psychiatry* **13**, 131–146.

Van IJzendoorn, M.H., Bakermans-Kranenburg, M.J. & Mesman, J. (2008) Dopamine system genes associated with parenting in the context of daily hassles. *Genes Brain Behav* **7**, 403–410.

Watson, K.K., Ghodasra, J.H. & Platt, M.L. (2009) Serotonin transporter genotype modulates social reward and punishment in rhesus macaques. *PLos One* **4**, e4156.

Wilhelm, K., Niven, H., Parker, G. & Hadzi-Pavlovic, D. (2005) The stability of the Parental Bonding Instrument over a 20-year period. *Psychol Med* **35**, 387–393.

Wingen, M., Kuypers, K.P.C., van de Ven, V., Formisano, E. & Ramaekers, J.G. (2008) Sustained attention and serotonin: a pharmaco-fMRI study. *Hum Psychopharmacol* **23**, 221–230.

Acknowledgments

This study was funded by a Canadian Institutes of Health Research (CIHR) trajectory grant for the MAVAN, principal investigators (PIs) M.M and S.M, by CIHR grants to A.S.F. and J.K. and by a Natural Sciences and Engineering Research Council Canada (NSERC) PhD scholarship to V.M-S. We would like to thank Amber Rieder and the team for their lead in the Hamilton project and to Maria Tampakeras and her team for assistance with genotyping.