

ORIGINAL ARTICLE

Association of maternal dopamine transporter genotype with negative parenting: evidence for gene x environment interaction with child disruptive behavior

SS Lee¹, A Chronis-Tuscano², K Keenan³, WE Pelham⁴, J Loney⁵, CA Van Hulle⁶, EH Cook⁷ and BB Lahey^{3,6}

¹Department of Psychology, University of California at Los Angeles, Los Angeles, CA, USA; ²Department of Psychology, University of Maryland, College Park, MD, USA; ³Department of Psychiatry, University of Chicago, Chicago, IL, USA; ⁴Department of Psychology, State University of New York at Buffalo, Buffalo, NY, USA; ⁵Department of Pediatrics, University of Iowa, Iowa City, IA, USA; ⁶Department of Health Studies, University of Chicago, Chicago, IL, USA and ⁷Institute for Juvenile Research, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

Although maternal parenting is central to child development, little is known about the interplay between molecular genetic and environmental factors that influence parenting. We tested the association of the 40-bp variable number tandem repeat polymorphism of the dopamine transporter (*DAT1*; *SLC6A3*) gene with three dimensions of observed maternal parenting behavior (positive parenting, negative parenting and total maternal commands). A significant nonadditive association was found between maternal *DAT1* genotype and both negative parenting and total commands during a structured mother–child interaction task, even after controlling demographic factors, maternal psychopathology and disruptive child behavior during the task. Furthermore, the association between maternal *DAT1* genotype and negative parenting was significantly stronger among mothers whose children were highly disruptive during the mother–child interaction task, suggesting a gene–environment interaction.

Molecular Psychiatry (2010) 15, 548–558; doi:10.1038/mp.2008.102; published online 9 September 2008

Keywords: parenting; dopamine transporter gene; genetics; disruptive behavior; child effects

Introduction

Parenting style and practices are strongly correlated with important measures of child outcomes, including academic achievement, peer relationships and conduct problems.^{1–4} Although these correlations do not necessarily reflect the causal influence of parenting on children's development,⁵ interventions that reduce negative parenting and increase positive parenting are associated with reductions in child behavior problems,^{6,7} suggesting, but not confirming, a causal role of natural variations in parenting on child behavior and adjustment.

Because of the importance of parenting behavior for child development, it is essential to identify the variables that contribute to variations in parenting. One factor that strongly influences parenting is the child's behavior, a process referred to as 'child effects.'^{8–10} That is, not only do parents provide an important environment for their child, characteristics of the child also provide an important environment

for his/her parents. For example, mothers interact very differently with children who are compliant and obedient than with children who are defiant and disruptive.^{8,9} Variations in parenting behavior are also correlated with parental social support¹¹ and parental characteristics including negative affect,¹² personality traits such as neuroticism,¹³ and parental cognitive characteristics such as intelligence and attribution biases.^{14–16}

Parent-based designs, in which adult twins self-report on their parenting behavior with their own children, suggest that multiple dimensions of parenting behavior, including care and protectiveness¹⁷ and warmth and positivity¹⁸ are at least moderately heritable, although the one study that used observational measures of parenting found little genetic influence on negative parenting.¹⁹ Child-based designs, where adult twins report on the parenting received, also suggest genetic factors are involved in dimensions of parenting such as perceived support²⁰ and negativity.¹⁹ These heritability estimates could misrepresent the role of genetic factors in parenting and child development for at least two reasons, however. First, there is evidence that both passive and evocative gene–environment correlations (*rGE*) are involved in the association of parenting with child outcomes. That is, child genotype and parenting

Correspondence: Dr SS Lee, Department of Psychology, University of California, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA.

E-mail: stevelee@psych.ucla.edu

Received 30 July 2007; revised 25 July 2008; accepted 7 August 2008; published online 9 September 2008

environment may be correlated because parents both transmit genes to their offspring and provide parenting environments (passive rGE). Genetically influenced characteristics of children may also differentially evoke parenting behaviors (evocative rGE).²⁰ Passive and evocative rGE can distort heritability estimates from traditional twin studies, although the direction and magnitude of the effects are not always predictable.^{20–23} Second, gene–environment interactions ($G \times E$) may operate in the sense that parental genotype may be associated with parenting in different ways in different environments.

Only one study has found evidence of possible $G \times E$ involving parenting practices and the parent's genotype.²⁴ This study found a significant interaction between daily hassles in predicting sensitive parenting and a particular combination of alleles of two genes: the dopamine D4 receptor gene (*DRD4*) and the catechol-*O*-methyltransferase gene. The results of several additional studies were suggestive of $G \times E$ based on the child's genotype. Higher maternal sensitivity during infancy was associated with significantly fewer affective problems at age 3 years for children with the A_1+ allele of the dopamine receptor D2 (*DRD2*) gene, but not for children with the A_1- allele.²² Similarly, children with at least one copy of the 7-repeat allele of *DRD4* exhibited higher sensation seeking in the presence of low parenting quality, whereas there was no association between parenting and the offspring's sensation seeking in children without this allele.²⁵ Results were interpreted as being consistent with $G \times E$, although the authors acknowledged that the observed association may actually be genetic if parenting quality was genetically influenced. Furthermore, a recent study found that child *DRD4* genotype moderated the efficacy a randomized controlled trial to promote positive parenting, further suggesting interactive models for child genotype and parenting behavior.²⁶

In this study, we extend the existing literature by testing the association between maternal genotype and parenting behavior toward her young child using observational measures of parenting during a structured mother–child interaction task. We also test whether associations between maternal genotype and her parenting are moderated by two dimensions of child behavior (for example, parent and teacher ratings of attention-deficit/hyperactivity disorder (ADHD) symptoms during the past 12 months and disruptive behavior during the task). We genotyped the 40-bp variable number tandem repeat polymorphism located in the 3'-untranslated region in exon 15 of the dopamine transporter (*DAT1*; *SLC6A3*) gene. Genotypes at this locus consist almost entirely one or two copies of the 9-repeat or 10-repeat alleles, with 9/9, 9/10 or 10/10 genotypes being the most common. Each allele corresponds to the frequency of repeated DNA fragments of the 40-bp sequence.

Genetic variants that influence dopamine systems are good candidate polymorphisms for studies of maternal parenting behavior because dopamine plays

a key role in mood²⁷ and a wide range of affiliative behaviors, including maternal nurturing.^{28–30} Furthermore, dopamine is expressed in brain regions (for example, mesolimbic) that may be associated with individual differences in personality traits that may be related to parenting.³¹ In addition, dopaminergic neurons project from the ventral tegmental area and substantia nigra to regions such as the dorsal anterior cingulate that are implicated in executive functions such as response inhibition,^{32,33} which may be involved in well-modulated parenting. Studies of nonhuman animals also strongly support a role for dopamine in maternal behavior. Activation of the mesolimbic dopamine tract is necessary for maternal behavior in rats³⁴ and *DAT1* binding in the nucleus accumbens is correlated with maternal behavior in rats.³⁵ Furthermore, *DAT1* knockout mice show severely disrupted maternal behavior.³⁶

Materials and methods

Participants

Two cohorts of 3.8- to 7.0-year-old children, whose caregivers reported symptoms of ADHD, were recruited in consecutive years in Chicago and Pittsburgh. There was a total of 127 probands who met symptom criteria for ADHD (83% boys, mean age = 5.23, s.d. = 0.70, 65% Caucasian, 30% African American, 5.5% other). In addition, 126 matched control children who had never been referred for mental health problems and did not meet diagnostic criteria for ADHD were also recruited (81% boys, mean age = 5.17, s.d. = 0.77, 63.5% Caucasian, 31% African American, 5.5% other). A total of 259 parents gave written informed consent and all children gave oral assent. All procedures were approved by University of Chicago and University of Pittsburgh Institutional Review Boards.

Diagnostic assessments of the children

Trained interviewers administered the Diagnostic Interview Schedule for Children (DISC) to each child's biological mother to determine if the child met *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, Revised (DSM-III-R) diagnostic criteria for ADHD, oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorders, depression and dysthymia.³⁷ Additional questions from the DSM-IV Field Trials version of the DISC were asked to assess DSM-IV symptoms of disruptive behavior disorders (DBD) not in DSM-III-R.³⁸ In addition, teachers were sent the DSM-IV DBD Rating Scale by mail.³⁹ Following standard procedures, teachers indicated the presence of DSM-IV DBD symptoms with endorsements of behaviors at the level of 'pretty much' or 'very much,' whereas symptoms rated 'not at all' or 'just a little' were construed as absent. As in previous studies, DSM-IV symptoms of ADHD, ODD and CD were considered present if endorsed by either the parent or the teacher.⁴⁰

In a previous paper based on this sample,⁴¹ we reported a significant nonadditive association between the child's *DAT1* allele and combined parent and teacher reports of the child's symptoms of hyperactivity-impulsivity, but not inattention, ODD and CD, during seven annual assessments over 8 years. *Post hoc* comparisons of children with the three primary *DAT1* genotypes indicated that the 9/10 heterozygotes were consistently elevated on all four dimensions of ADHD and DBD relative to the homozygotes.

Assessment of maternal psychopathology

Mothers were interviewed about their current and lifetime history of psychopathology using the Structured Clinical Interview for DSM-III-R, Non-Patient edition.⁴² Mothers were asked about their DSM-III-R diagnostic symptoms of major depressive disorder and classified as meeting or not meeting criteria for the diagnosis. In addition, the mothers were asked about the number of DSM-III-R symptoms of CD that they exhibited before age 15, the number of DSM-III-R antisocial personality disorder symptoms that they exhibited since 15 years of age, and the number of their DSM-III-R ADHD symptoms.

Observational assessment of maternal parenting and child deviant behavior

Parenting behavior was assessed using observations of mothers and children during a structured laboratory protocol. Mother-child interactions were conducted in a standard room with a one-way mirror, chairs for the mother and child, magazines, toys and a TV monitor showing cartoons. For the first 10 min, the mother was directed to play freely with her child. Then, an interviewer entered the room and scattered clothes, papers and empty containers around the room. The interviewer handed the mother a list of instructions, an Etch-a-Sketch game, a cloth, worksheets, a magazine and a pencil. The interviewer quietly reviewed the instructions with the mother before leaving the room. These instructions asked the mother to instruct her child to complete the following tasks, which were designed to be moderately challenging, during the remaining 15 min: (1) return the toys to the shelf; (2) put the scattered clothes in a box; (3) place the scattered crumpled paper and empty containers in the waste basket; (4) sit at the table and count geometric shapes; (5) copy a set of geometric designs on paper; (6) dust the table with a cloth; (7) work cooperatively with the mother to draw a diagonal line on the Etch-a-Sketch and (8) choose one toy and play quietly whereas the mother reads a magazine and takes a 1 min telephone call from the interviewer.

Discrete mother and child behaviors were coded continuously from videotapes by coders who were blind to all information about the child. Each incident of the child's disruptive behavior (for example, non-compliance, disruptive/destructive behavior) and three mutually exclusive categories of parenting behavior

observed across the entire structured segment of the interaction were coded and summed into total scores: (1) negative parenting (for example, critical and negative statements and negative physical contact); (2) positive parenting (for example, praise, expressions of positive affect and positive physical contact) and (3) total number of maternal commands (for example, direct declarative commands, indirect suggestions and commands in the form of questions). These three categories of maternal parenting behavior have been found to discriminate children referred for behavior problems from matched healthy controls.^{43,44} Coders participated in 2 days of training until 80% agreement was achieved. Coders were supervised throughout the study with weekly telephone calls and monthly face-to-face meetings to resolve differences in rating difficult tapes, to avoid drift in coding and to maintain reliability. The primary coder scored all videotapes and the second coder scored a random 30% of the videotapes. Interrater reliability was excellent: Cohen's $\kappa=0.90$ for negative parenting, 0.95 for positive parenting, 0.95 for total commands and 0.92 for total child disruptive behavior.

Maternal genotypes

Saliva was collected in a later wave of this ongoing longitudinal study from 83% of the mothers and children. After one mother with a rare genotype (10/11) was excluded, a total of 207 maternal *DAT1* genotypes were available: 9/9 ($n=13$; 69% Caucasian, 15.3% African American, 15.3% other), 9/10 ($n=80$; 70.5% Caucasian, 26.9% African American, 2.6% other) and 10/10 ($n=114$; 62.2% Caucasian, 32.4% African American, 5.4% other). Allelic distributions were consistent with Hardy-Weinberg equilibrium ($\chi^2=0.04$, $P=0.98$) and were not significantly associated with race-ethnicity (European American vs non-European American: $\chi^2=1.37$, $P=0.24$; African Americans vs non-African Americans: $\chi^2=0.39$, $P=0.54$) or family income (linear: $\beta=-0.02$, $P=0.90$, nonadditive: $\beta=-0.003$, $P=0.97$).

Statistical analyses

The association between maternal *DAT1* and each observed parenting dimension was modeled using log-linear regression in SAS PROC GENMOD, specifying Poisson working distributions. Associations between the maternal *DAT1* 10-repeat allele and each of three dimensions of maternal parenting behavior (negative, positive and total commands) were tested separately. Both an additive term for *DAT1* (coded as -1, 0 and 1), which tested linear differences among mothers with 0, 1 or 2 copies of the 10-repeat *DAT1* allele, respectively, and a nonadditive (quadratic) term for *DAT1* (coded as -1, 2 and -1 for 0, 1 or 2 copies of the 10-repeat *DAT1* allele, respectively), which tested for any form of nonadditive genetic influence (that is, recessive, dominant or heterozygote disadvantage), were entered simultaneously.

Five classes of covariates selected on theoretical and empirical grounds were included in the analyses

of the association of maternal *DAT1* and her parenting behavior. First, because the sample consisted of a group of children with ADHD and demographically matched comparison children without ADHD, the number of child ADHD symptoms in the initial assessment was controlled. Second, given socioeconomic and racial-ethnic differences in parenting,^{45,46} total family income and the child's race-ethnicity were controlled. Third, age and sex of each child were entered as covariates because of reliable differences in parenting behavior associated with child age and sex.⁴⁷ Fourth, maternal psychopathology was controlled because *DAT1* variants have been associated with ADHD, oppositional behavior and conduct problems.^{41,48} Therefore, we controlled the mother's report of the number of her childhood ADHD symptoms, her number of childhood symptoms of CD, her current number of symptoms of antisocial personality disorder, and whether she met diagnostic criteria for major depression during the past 6 months. Without these controls, any association between maternal parenting and *DAT1* could reflect only the association of genes shared by the mother and child that are related to their correlated psychopathology. Fifth, because the parenting observed during the mother-child interaction could reflect the mother's responses to the child's disruptive behavior during the task (that is, child effects),^{8,10,44} we statistically controlled the child's disruptive behavior during the task.

Results

Association of maternal *DAT1* genotype and parenting
Negative parenting. The nonadditive term for maternal *DAT1* genotype was significant for the observed frequency of negative maternal parenting behaviors (additive term: $\beta = 0.22$, $P = 0.07$; nonadditive term: $\beta = 0.14$, $P < 0.005$). This indicates some form of nonadditive association between maternal *DAT1* and negative parenting, but it does not reveal the specific form of the association. Therefore, *post hoc* analyses were conducted to clarify the nonadditive association. Means for negative parenting for mothers with the three *DAT1* genotypes were: 9/10 heterozygotes ($M = 12.4$, $s.d. = 12.3$), 9/9 homozygotes ($M = 8.3$, $s.d. = 6.3$) and 10/10 homozygotes ($M = 10.5$, $s.d. = 7.7$). Two nonadditive models were compared using log-linear regression with the five sets of covariates described above. First, to test for a possible dominant effect of the 10-repeat allele (or recessive effect of the 9-repeat allele), mothers with at least one 10-repeat allele (9/10 and 10/10 genotypes combined) were compared to the 9/9 genotype mothers. Consistent with this model, mothers with the 9/9 genotype were observed to engage in significantly less negative parenting ($\beta = -0.52$, $P < 0.03$) and to issue fewer total commands ($\beta = -0.24$, $P < 0.04$) than mothers with at least one 10-repeat allele.

Second, the nonadditive 'heterozygote disadvantage' model was tested. Consistent with this model, heterozygous (9/10) mothers engaged in more negative parenting ($\beta = 0.25$, $P < 0.02$) than the two groups of homozygous mothers (9/9 and 10/10) combined. In addition, the 9/10 mothers engaged in less negative parenting behavior than the 9/9 genotype mothers ($\beta = -0.74$, $P < 0.01$) and less negative parenting than the 10/10 genotype mothers ($\beta = 0.21$, $P = 0.04$). Thus, the results of these *post hoc* comparisons were consistent with a dominant/recessive model for negative parenting, but more consistent with a heterozygote disadvantage model for negative parenting.

Total maternal commands. The nonadditive term for maternal *DAT1* genotype was significant for total maternal commands (additive term: $\beta = 0.11$, $P = 0.07$; nonadditive term: $\beta = 0.06$, $P < 0.02$). Means for total maternal commands were: 9/10 heterozygotes ($M = 75.1$, $s.d. = 35.1$), 9/9 homozygotes ($M = 62.3$, $s.d. = 29.3$) and 10/10 homozygotes ($M = 71.6$, $s.d. = 31.6$). The two nonadditive models were compared using log-linear regression with the five sets of covariates. Mothers with at least one 10-repeat allele (9/10 and 10/10 genotypes combined) were compared to the 9/9 genotype mothers. Consistent with a dominant/recessive model, mothers with the 9/9 genotype issued fewer total commands ($\beta = -0.24$, $P < 0.04$) than mothers with at least one 10-repeat allele. In contrast, mothers with the 9/10 *DAT1* genotype did not issue more total commands ($\beta = 0.08$, $P = 0.11$) than the two combined groups of homozygous mothers. Furthermore, although the 9/9 mothers issued fewer total commands ($\beta = -0.30$, $P < 0.05$) than the 9/10 genotype mothers, mothers with the 9/10 genotype did not issue more commands than mothers with the 10/10 genotype ($\beta = 0.06$, $P = 0.21$). Thus, the results of these *post hoc* analyses were consistent with a dominant/recessive model for total commands.

Positive parenting. Maternal *DAT1* genotype was not significantly associated with positive parenting behavior (additive term: $\beta = 0.05$, $P = 0.67$; nonadditive term: $\beta = 0.07$, $P = 0.17$).

Additional exploratory analyses were conducted to consider the possibility that the individual components of the positive parenting composite score might be associated with maternal *DAT1*. Using the same data analytic procedures and covariates, no significant associations between maternal *DAT1* and any individual component of the composite positive parenting dimension were detected, including positive physical maternal behaviors (additive term: $\beta = -0.05$, $P = 0.84$; nonadditive term: $\beta = -0.05$, $P = 0.69$), positive maternal affect (additive term: $\beta = 0.07$, $P = 0.68$; nonadditive term: $\beta = 0.09$, $P = 0.19$) and maternal praise of the child (additive term: $\beta = 0.08$, $P = 0.59$; nonadditive term: $\beta = 0.07$, $P = 0.23$).

Gene–environment correlation and interaction involving maternal *DAT1*

Because of the importance of child effects on maternal behavior,^{8–10} it is important to determine if child disruptive behavior was correlated with maternal parenting or moderated the association of maternal *DAT1* and her parenting behavior in this study. Separate tests were conducted for each measure of parenting to determine if the association between the mother's *DAT1* genotype and her parenting was moderated by two aspects of her child's behavior: (1) the total number of the child's DSM-IV ADHD symptoms reported by parents and teachers in the initial assessment and (2) the child's continuous level of disruptive behavior observed during the mother–child interaction task.

Because tests of $G \times E$ are ambiguous in the presence of rGE,⁴⁹ we first tested whether maternal *DAT1* genotype was correlated with the child's number of ADHD symptoms using log-linear regression, controlling the child's age, sex and race–ethnicity. The mean number of child ADHD symptoms in the three maternal genotype groups was: 9/9 ($M=12.2$, $s.d.=5.5$), 9/10 ($M=8.50$, $s.d.=7.0$) and 10/10 ($M=8.40$, $s.d.=6.8$). Maternal *DAT1* was not significantly related to the child's number of ADHD symptoms (additive term: $\beta=-0.18$, $P=0.08$; nonadditive term: $\beta=-0.05$, $P=0.26$), but there was a nonsignificant linear trend toward the children of mothers with fewer 10-repeat alleles exhibiting more ADHD symptoms. Thus, any significant interaction between maternal *DAT1* genotype and the child's number of ADHD symptoms should be interpreted cautiously.

We similarly tested for rGE between maternal *DAT1* genotype and the child's continuous level of disruptive and noncompliant behavior during the mother–child interaction task. The mean number of child disruptive behaviors was similar across the three maternal genotypes [9/9 ($M=14.9$, $s.d.=22.4$), 9/10 ($M=14.1$, $s.d.=18.4$) and 10/10 ($M=13.2$, $s.d.=16.3$)]. Maternal *DAT1* was not significantly related to the child's disruptive behavior (additive term: $\beta=-0.05$, $P=0.77$; nonadditive term: $\beta=-0.00$, $P=0.94$), indicating that the mother's *DAT1* genotype was not correlated with her exposure to her child's disruptive behavior during the mother–child interaction task. This means that the test of $G \times E$ (that is, moderation of the association between maternal *DAT1* and her negative parenting) was not substantially complicated by the presence of rGE between maternal genotype and the child's disruptive behavior during the task. In addition, we tested whether the child's *DAT1* genotype was associated with child disruptive behavior during the mother–child interaction task. No significant association was detected (additive term: $\beta=0.23$, $P=0.27$; nonadditive term: $\beta=0.09$, $P=0.28$), confirming that the mother's exposure to child disruptive behavior was not significantly correlated with the child's *DAT1* genotype. The results were essentially the same whether the child's ADHD

symptoms and demographic characteristics were controlled or not.

Tests of moderation by child ADHD. We tested the interaction between the child's number of DSM-IV ADHD symptoms reported by parents and teachers in the initial assessment and maternal *DAT1* to determine if the child's level of ADHD moderated the association between maternal *DAT1* and her parenting. Separate tests were conducted for each of the three categories of parenting behavior using the full set of covariates described above. None of the interactions was significant at the 0.05 level. The parameter estimates for interactions with the linear term for maternal *DAT1* for negative parenting, positive parenting and total maternal commands, were $\beta=-0.01$, $P=0.76$; $\beta=-0.02$, $P=0.57$ and $\beta=-0.00$, $P=0.52$; respectively. Similar patterns were observed based on the interaction with the quadratic term of the maternal genotype ($\beta=0.005$, $P=0.76$; $\beta=-0.01$, $P=0.16$ and $\beta=-0.003$, $P=0.55$; for negative parenting, positive parenting and total commands, respectively).

Tests of moderation by child disruptive behavior: negative parenting. We conducted similar separate tests for each dimension of parenting of the interaction between the continuous level of observed child disruptive behavior and maternal *DAT1*. Both the additive and nonadditive terms for *DAT1* were entered simultaneously in log-linear models with all five sets of covariates. For negative parenting, there was a significant interaction between the continuous level of child disruptive behavior and the nonadditive term for maternal *DAT1* and ($\beta=0.004$, $P<0.05$), but not the additive term for maternal *DAT1* ($\beta=0.01$, $P=0.16$). To provide an initial characterization of this interaction, we calculated the mean level of negative parenting for each maternal *DAT1* genotype above and below the sample median for child disruptive behavior during the mother–child interaction (median split). The cell sizes were as follows: 9/9 ($n=8$), 9/10 ($n=56$) and 10/10 ($n=58$); 9/9 ($n=5$), 9/10 ($n=44$) and 10/10 ($n=56$) for mothers with children above and below the sample median, respectively (see Figure 1).

The methods recommended by Aiken and West⁵⁰ also were used to probe the significant interaction between child disruptive behavior and the nonadditive term for maternal *DAT1* for negative parenting. Estimated regression lines for levels of negative parenting on the continuous level of child disruptive behavior in mothers with the three maternal *DAT1* genotypes are presented in Figure 2. At both the grand mean of child disruptive behavior and the grand mean -1 s.d., no significant mean differences in negative parenting were observed among the three genotype groups (Wald $\chi^2=5.44$, $d.f.=2$, $P=0.07$ and Wald $\chi^2=0.48$, $d.f.=2$, $P=0.79$, respectively). However, at the grand mean $+1$ s.d. for child disruptive behavior, significant mean differences in negative

parenting were detected among the three genotype groups (Wald $\chi^2=11.66$, d.f.=2, $P<0.01$). Because the distribution of child disruptive behavior was skewed, the interaction also was probed at the

grand mean + 2 s.d. Again, significant mean differences in negative parenting were detected among the three genotype groups (Wald $\chi^2=10.9$, d.f.=2, $P<0.01$).

Post hoc pairwise contrasts at the grand mean + 1 s.d. for child disruptive behavior revealed that both the 9/10 mothers (Wald $\chi^2=8.17$, d.f.=1, $P<0.01$) and the 10/10 mothers (Wald $\chi^2=4.04$, d.f.=1, $P<0.05$) used more negative parenting than 9/9 mothers. There was also a significant difference in negative parenting between the 9/10 and 10/10 mothers (Wald $\chi^2=5.56$, d.f.=1, $P<0.05$). At the grand mean + 2 s.d. for child disruptive behavior, the 9/10 mothers (Wald $\chi^2=7.54$, d.f.=1, $P<0.01$) and the 10/10 mothers (Wald $\chi^2=4.99$, d.f.=1, $P<0.05$) used more negative parenting than 9/9 mothers. In addition, the 9/10 mothers used more negative parenting than the 10/10 mothers (Wald $\chi^2=3.86$, d.f.=1, $P<0.05$).

Tests of moderation by child disruptive behavior: total maternal commands. For total maternal commands, there were nonsignificant trends toward moderation of the effect maternal *DAT1* genotype by the child's continuous level of observed disruptive behavior (additive term \times child disruptive behavior: $\beta=0.005$, $P=0.07$; nonadditive term \times child disruptive behavior: $\beta=0.002$, $P=0.07$). Because these nonsignificant trends for the interactions were in the same direction as for negative parenting, and because statistical power to detect interactions was modest in our sample, we conducted the same follow up analyses for total commands as we did for negative parenting in an exploratory spirit. We calculated the mean number of total commands issued by parents of each genotype with children above and below the sample median for child disruptive behavior (see

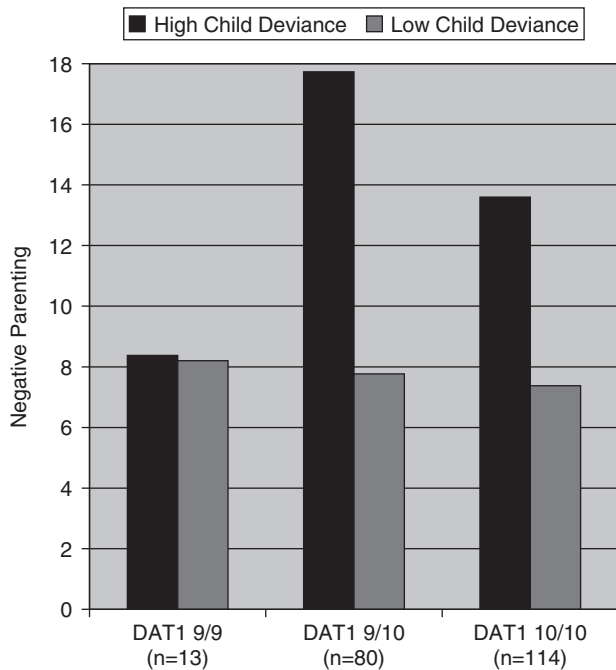


Figure 1 Maternal dopamine transporter (*DAT1*) genotype and the average number of observed negative maternal parenting behaviors as a function of her child's level of disruptive behavior during the mother-child interaction task. The significant nonadditive term for maternal *DAT1* and negative parenting suggests some form of nonadditive association, but the specific form of this nonadditive association was not determined.

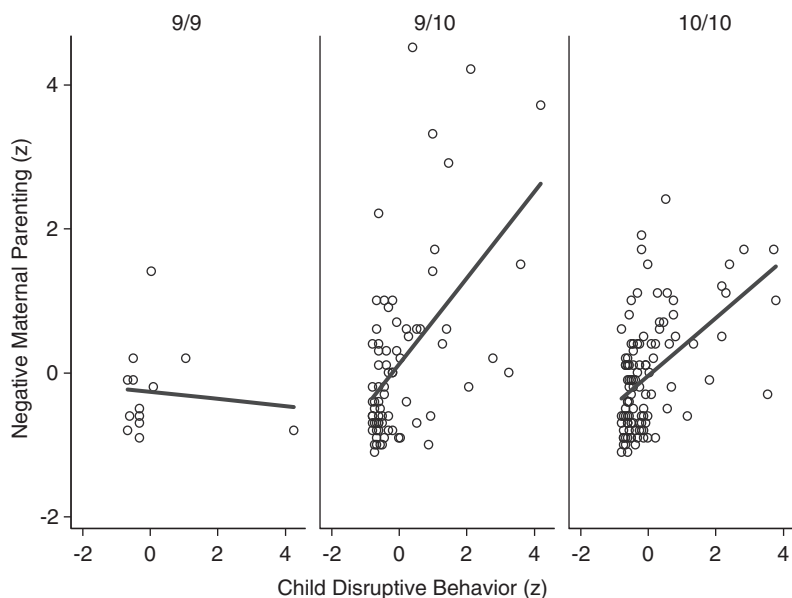


Figure 2 Regression lines for predicted levels of negative parenting (z score) for the interaction between maternal dopamine transporter (*DAT1*) genotype and the continuous level of child disruptive behavior (z score).

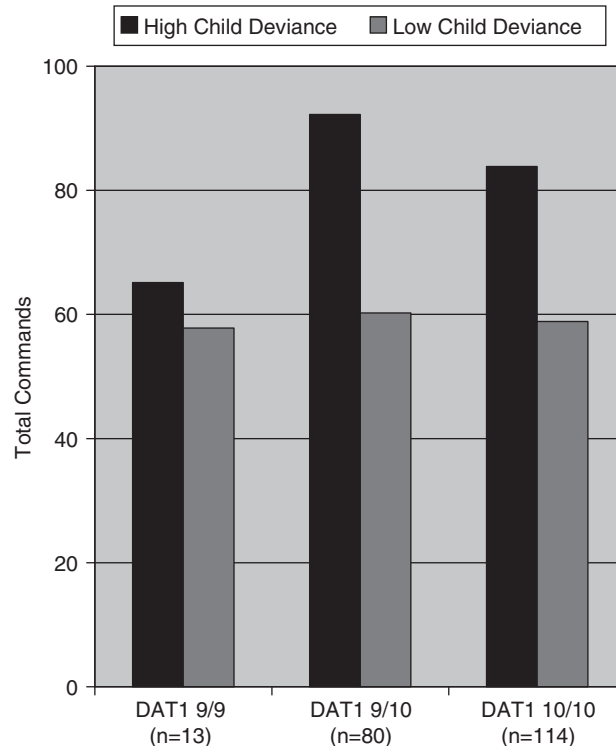


Figure 3 Maternal dopamine transporter (*DAT1*) genotype and the average number of observed maternal parenting commands during the mother–child interaction task. Parallel to the finding for negative parenting behavior, there was a nonadditive association of maternal *DAT1* and the number of parenting commands observed but no specific model of transmission was suggested.

Figure 3). We also probed the interactions using the Aiken and West⁵⁰ methods described above. Estimated regression lines for levels of total commands reflecting the borderline interaction between maternal *DAT1* genotype and the continuous level of child disruptive behavior are presented in Figure 4.

Parallel to the findings for negative parenting, no significant differences were found among the three maternal genotype groups at the grand mean and grand mean -1 s.d. of child disruptive behavior (Wald $\chi^2 = 3.60$, d.f. = 2, $P = 0.17$ and Wald $\chi^2 = 0.25$, d.f. = 2, $P = 0.88$, respectively). However, at the grand mean $+1$ s.d. and at the grand mean $+2$ s.d. for child disruptive behavior, significant mean differences in total commands were detected among the three genotypes (Wald $\chi^2 = 7.69$, d.f. = 2, $P < 0.05$ and Wald $\chi^2 = 7.63$, d.f. = 2, $P < 0.05$, respectively).

Post hoc pairwise comparisons revealed that at $+1$ s.d., the 9/10 and 10/10 genotype mothers each used more total commands than the 9/9 genotype mothers (Wald $\chi^2 = 8.12$, d.f. = 1, $P < 0.01$ and Wald $\chi^2 = 5.32$, d.f. = 1, $P < 0.05$, respectively), but there was not a significant difference between the 9/10 and 10/10 genotypes (Wald $\chi^2 = 1.39$, d.f. = 1, $P = 0.24$). At $+2$ s.d., there was an identical pattern whereby 9/10 and 10/10 genotype mothers used more total commands than 9/9 genotype mothers (Wald $\chi^2 = 7.60$, d.f. = 1, $P < 0.01$ and Wald $\chi^2 = 5.23$, d.f. = 1, $P < 0.05$,

respectively), but there was not a significant difference between the 9/10 and 10/10 genotypes (Wald $\chi^2 = 1.1$, d.f. = 1, $P = 0.30$).

Tests of moderation by child disruptive behavior: positive parenting. For positive maternal parenting, there were no significant interactions between maternal *DAT1* genotype and the child's continuous level of disruptive behavior (additive term \times child disruptive behavior: $\beta = 0.02$, $P = 0.89$; nonadditive term \times child disruptive behavior: $\beta = 0.09$, $P = 0.16$).

Discussion

The present findings suggest that a specific genetic polymorphism in women is associated with two specific dimensions of maternal parenting behavior. Maternal *DAT1* was significantly associated with the observed frequency of both negative parenting and total parenting commands during a structured mother–child interaction task with child and family demographic indices, maternal psychopathology, the child's ADHD symptoms, and disruptive behavior during the task controlled. We did not detect a significant association between maternal *DAT1* genotype and the mother's positive parenting, however. The present findings are consistent with earlier findings on the roles of the dopamine system, and the *DAT1* gene in particular, in maternal behavior in

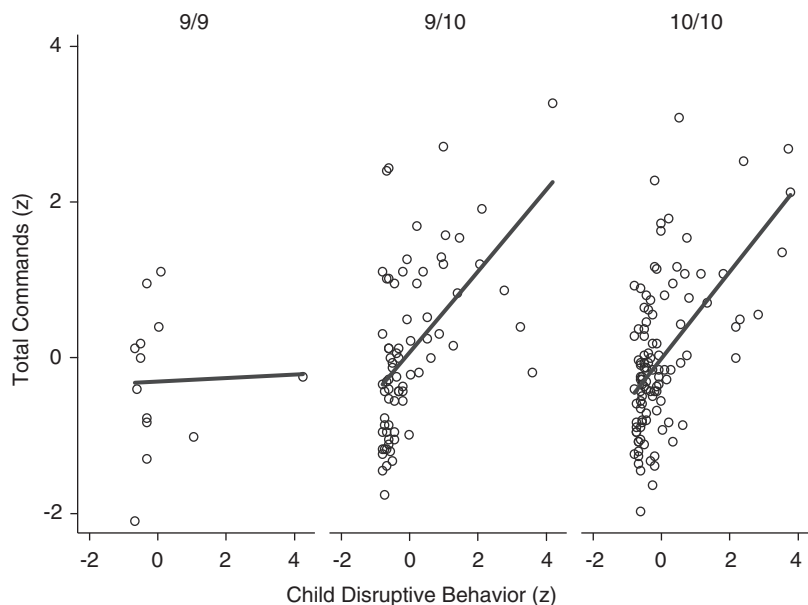


Figure 4 Regression lines for predicted levels of total commands (z score) for the interaction between maternal dopamine transporter (*DAT1*) genotype and the continuous level of child disruptive behavior (z score).

nonhuman animals, but this study provides the first evidence on the role of variations in *DAT1* in individual differences in observed maternal parenting behavior in humans.

This study also provides evidence of a $G \times E$ in which the level of disruptive behavior exhibited by the child during the mother–child interaction moderates the association between the maternal *DAT1* genotype and her negative parenting. Maternal *DAT1* genotype was significantly related to negative parenting among mothers of children who were highly disruptive and noncompliant during the mother–child interaction task, but not among mothers whose children were well behaved. There was a nonsignificant trend toward the same interaction for total maternal commands. Maternal *DAT1* genotype was not significantly correlated with the level of child disruptive behavior during the task, suggesting that the interaction between maternal genotype and child disruptive behavior was not an artifact of rGE.⁵¹

For both negative parenting and total maternal commands, the results suggested that a nonadditive model of transmission may be involved in their associations with maternal *DAT1*; however, the *post hoc* comparisons did not unambiguously indicate, which specific nonadditive model is involved. Mothers with the 9/10 genotype exhibited significantly more negative parenting than the combined group of 9/9 and 10/10 genotype mothers. This pattern of differences is consistent with a heterozygote disadvantage model, but a dominant/recessive model cannot be ruled out. The findings for total parental commands were consistent with both a heterozygote disadvantage model and a dominance model.

If future studies support a heterozygote disadvantage model for maternal *DAT1*, much would remain to be learned about this mechanism. It is possible that the two different alleles produce different gene products, but other explanations also are plausible. For example, what appears to be heterozygote disadvantage could actually reflect the influence of unmeasured genetic and/or environmental factors. For example, in the presence of one allele of another unmeasured polymorphism, mothers with one or more 9-repeat allele for *DAT1* might be at greatest risk for adverse parenting, but in the presence of another allele of the unmeasured polymorphism, mothers with one or more 10-repeat allele might be at highest risk. Depending on the frequency of the alleles of the unmeasured polymorphism, this could result in the 9/10 genotype being at highest risk when the unknown interacting locus is not considered. Similarly, apparent heterozygote disadvantage also could be result from the moderating influence of an unmeasured aspect of the environment.

Regardless of the nature of the association between maternal *DAT1* and parenting, it will be important to eventually understand the proximal mechanisms that mediate and/or moderate the association of the *DAT1* with parenting. Individual differences in personality traits, cognition and emotion regulation may represent pathways from genetic variation to differences in parenting behavior. For example, dopamine genes may be associated with personality traits such as novelty seeking,⁵² extraversion,⁵³ and harm avoidance⁵⁴ and epistatic effects between *DAT1* and brain-derived neurotrophic factor genes have been associated with neuroticism.⁵⁵ Considering the association of personality traits and parenting behavior⁵⁶

and the substantial heritability of personality dimensions,³¹ further exploration of personality traits as a mediator of genetic influences on parenting would be important to pursue further.

In addition to personality traits, emerging evidence from human and nonhuman neuroscience has supported the hypothesis that dopamine neurotransmission in regions that are associated with cognitive/affective processes be involved in individual differences in parenting. For example, the anterior cingulate cortex (ACC) is a dopamine-rich region of the brain that influences emotion regulation and simultaneously monitors competing behavioral responses in the presence of multiple task demands.⁵⁷ In particular, the caudal region of ACC has been associated with complex cognitive functions (for example, alerting, orienting and executive control) whereas rostral ACC has been implicated in affective processing and regulation.⁵⁸ In rats, dopamine (D1) receptors in ACC influence effort-based decision making and dopamine release into the forebrain is pivotal to the activation of voluntary maternal responses, including the decision to avoid or engage biologically relevant stimuli.^{34,59} Similarly, mesolimbic dopamine neurons in the ventral tegmental area and activation of reward circuitry through D1 dopamine receptors are strongly associated with maternal behavior in rats.⁶⁰ Moreover, the ACC may be vitally involved in the appraisal of initial conflict and coordination with other regions modulating cognitive control.⁶¹ Thus, because dopamine is centrally involved in cognitive and affective aspects of parenting and social behavior more generally, dopamine-related genetic variation may contribute to hypo or hyperactivation of neural regions underlying parenting behavior, particularly in the presence of complex cognitive and affective conditions.

Additional insight into dopaminergic influences on parenting, and the potential role of *DAT1*, might be found from studies utilizing dopamine agonists.⁶² For example, methylphenidate (MPH) blocks the *DAT1* and increases synaptic levels of dopamine. A number of studies have tested whether *DAT1* variants were related to the efficacy of MPH and associated side effects. The results varied considerably, but when the results are considered across studies, they suggest a nonadditive effect that is either consistent with a dominant effect of the 10-repeat allele^{63,64} or a heterozygote disadvantage effect in which children and adults with the 9/10 genotype experienced fewer side effects⁶⁵ and had a more favorable response to MPH.^{66,67} Finally, *DAT* knockdown mice respond to dopamine agonists differently than wild-type mice⁶⁸ in tasks sensitive to excitatory transmission in the corticostriatal pathway. In particular, *DAT1* genotypes may affect the limbic corticostriatal loop, which is strongly related to goal directed behavior and the appraisal of affective stimuli.⁶⁹ Future studies employing genetic dissection of parenting should be formulated within the context of cognitive and affective neuroscience to provide greater traction

on the mechanisms underlying complex social behavior.⁷⁰

Acknowledgments

This study was supported by National Institute of Mental Health Grant 2RO1 MH053554 to Benjamin B Lahey, T32 MH200065-01 to Elliot S Gershon and the Jean Young and Walden W Shaw Foundation to Edwin H Cook.

References

- 1 Maccoby EE, Martin JA. Socialization in the context of the family: parenting-child interaction. In: Mussen PH, Hetherington EM (eds). *Handbook of Child Psychology: Vol. 4. Socialization, Personality, and Social Development*. Wiley: New York, 1983, pp 1-101.
- 2 Baumrind D. Effective parenting during the early adolescent transition. In: Cowan P, Hetherington EM (eds). *Family Transitions: Advances in Family Research*. Erlbaum: Hillsdale, NJ, 1991, pp 111-164.
- 3 Campbell SB, Shaw DS, Gilliom M. Early externalizing behavior problems: toddlers and preschoolers at risk for later maladjustment. *Dev Psychopathol* 2000; **12**: 467-488.
- 4 Bates JE, Pettit GS, Dodge KA, Ridge B. Interaction of temperamental resistance to control and restrictive parenting in the development of externalizing behavior. *Dev Psychol* 1998; **34**: 982-995.
- 5 Harris JR. The outcome of parenting: what do we really know? *J Pers* 2000; **68**: 625-637.
- 6 Van Zeijl J, Mesman J, Van IJzendoorn MH, Bakermans-Kranenburg MJ, Juffer F, Stolk MN *et al*. Attachment-based intervention for enhancing sensitive discipline in mothers of 1- to 3-year-old children at risk for externalizing behavior problems: a randomized controlled trial. *J Consult Clin Psychol* 2006; **74**: 994-1005.
- 7 Webster-Stratton C, Reid MJ, Hammond M. Treating children with early-onset conduct problems: intervention outcomes for parent, child, and teacher training. *J Clin Child Adolesc Psychol* 2000; **33**: 105-124.
- 8 Bell RQ, Chapman M. Child effects in studies using experimental or brief longitudinal approaches to socialization. *Dev Psychol* 1986; **22**: 595-603.
- 9 Lytton H. Child and parent effects in boys' conduct disorder: a reinterpretation. *Dev Psychol* 1990; **26**: 683-697.
- 10 O'Connor TG, Deater-Deckard K, Fulker D, Rutter M, Plomin R. Genotype-environment correlations in late childhood and early adolescence: antisocial behavioral problems and coercive parenting. *Dev Psychol* 1998; **34**: 970-981.
- 11 Belsky J. The determinants of parenting: a process model. *Child Dev* 1984; **55**: 83-96.
- 12 Dix T, Gershoff ET, Meunier LN, Miller PC. The affective structure of supportive parenting: depressive symptoms, immediate emotion, and child-oriented motivation. *Dev Psychol* 2004; **40**: 1212-1227.
- 13 Clark LA, Kochanska G, Ready R. Mothers' personality and its interaction with child temperament as predictors of parenting behavior. *J Pers Soc Psychol* 2000; **79**: 274-285.
- 14 Snyder J, Cramer A, Afrank J, Patterson GR. The contributions of ineffective discipline and parental hostile attributions of child misbehavior to the development of conduct problems at home school. *Dev Psychol* 2005; **41**: 30-41.
- 15 Pinderhughes EE, Dodge KA, Bates JE, Pettit GS. Discipline response: influences of parents' socioeconomic status, ethnicity, beliefs about parenting, stress, and cognitive-emotional process. *J Fam Psychol* 2000; **14**: 380-400.
- 16 O'Callaghan MF, Borowski JG, Whitman TL, Maxwell SE, Keogh D. A model of adolescent parenting: the role of cognitive readiness to parent. *J Res Adolesc* 1999; **9**: 203-225.
- 17 Perusse D, Neale MC, Heath AC, Eaves LJ. Human parental behavior: evidence for genetic influence and potential

- implication for gene-culture transmission. *Behav Genet* 1994; **24**: 327–336.
- 18 Kendler KS. Parenting: a genetic–epidemiologic perspective. *Am J Psychiatry* 1996; **153**: 11–20.
- 19 Neiderhiser JM, Reiss D, Pedersen NL, Lichtenstein P, Spotts EL, Hansson K et al. Genetic and environmental influences on mothering of adolescents: a comparison of two samples. *Dev Psychol* 2004; **40**: 335–351.
- 20 Hur Y, Bouchard TJ. Genetic influences on perceptions of childhood family environment: a reared apart twin study. *Child Dev* 1995; **66**: 330–345.
- 21 Moffitt TE, Caspi A, Rutter M. Measured gene–environment interactions in psychopathology: concepts, research strategies, and implications for research, intervention, and public understanding of genetics. *Perspect Psychol Sci* 2006; **1**: 5–27.
- 22 Mills-Koonce WR, Propper CB, Gariepy J, Blair C, Garrett-Peters P, Cox MJ. Bidirectional genetic and environmental influences on mother and child behavior: the family system as the unit of analyses. *Dev Psychopathol* 2007; **19**: 1073–1087.
- 23 Plomin R, DeFries JC, Loehlin JC. Genotype–environment interaction and correlation in the analysis of human behavior. *Psychol Bull* 1977; **84**: 309–322.
- 24 van IJzendoorn MH, Bakermans-Kranenburg MJ, Mesman J. Dopamine system genes associated with parenting in the context of daily hassles. *Genes Brain Behav* 2008; **7**: 403–410.
- 25 Sheese BE, Voelker PM, Rothbart MK, Posner MI. Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Dev Psychopathol* 2007; **19**: 1039–1046.
- 26 Bakermans-Kranenburg MJ, Van IJzendoorn MH, Pijlman FT, Mesman J, Juffer F. Experimental evidence for differential susceptibility: dopamine D4 receptor polymorphism (*DRD4 VNTR*) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Dev Psychol* 2008; **44**: 293–300.
- 27 Ruhe HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatry* 2007; **12**: 331–359.
- 28 Depue RA, Collins PF. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behav Brain Sci* 1999; **22**: 491–569.
- 29 Depue RA, Morrone-Strupinsky JV. A neurobehavioral model of affiliative bonding: implications for conceptualizing a human trait of affiliation. *Behav Brain Sci* 2005; **28**: 313–395.
- 30 Young LJ, Lim MM, Gingrich B, Insel TR. Cellular mechanisms of social attachment. *Horm Behav* 2001; **40**: 133–138.
- 31 Congdon E, Canli T. The endophenotype of impulsivity: reaching consilience through behavioral, genetic, and neuroimaging approaches. *Behav Cogn Neurosci Rev* 2005; **4**: 262–281.
- 32 Arnsten AFT, Robbins TW. Neurochemical modulation of prefrontal cortical function in human and animals. In: Struss DT, Knight RT (eds). *Principles of Frontal Lobe Function*. Oxford University Press: New York, 2002, pp 51–84.
- 33 Williams SM, Goldman-Rakic P. Widespread origin of the primate mesofrontal dopamine system. *Cereb Cortex* 1998; **8**: 321–345.
- 34 Numan M. Motivational systems and the neural circuitry of maternal behavior in the rat. *Dev Psychobiol* 2007; **49**: 12–21.
- 35 Champagne FA, Chretien P, Stevenson CW, Zhang TY, Gratton A, Meaney MJ. Variations in nucleus accumbens dopamine associated with individual differences maternal behavior in the rat. *J Neurosci* 2004; **24**: 4113–4123.
- 36 Spieglewsky C, Roubert C, Hamon M, Nosten-Bertrand M, Betancur C, Giros B. Behavioural disturbances associated with hyperdopaminergia in dopamine-transporter knockout mice. *Behav Pharmacol* 2000; **11**: 279–290.
- 37 Shaffer D, Fisher P, Piacentini J, Schwab-Stone M, Wicks J. *Diagnostic Interview Schedule for Children*. Columbia University: New York, 1993.
- 38 Lahey BB, Pelham WE, Stein MA, Loney J, Trapani C, Nugent K et al. Validity of DSM-IV attention-deficit/hyperactivity disorder for younger children. *J Am Acad Child Adolesc Psychiatry* 1998; **37**: 695–702.
- 39 Pelham Jr WE, Gnagy EM, Greenslade KE, Milich R. Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. *J Am Acad Child Adolesc Psychiatry* 1992; **31**: 210–218.
- 40 Piacentini JC, Cohen P, Cohen J. Combining discrepant diagnostic information from multiple sources: are complex algorithms better than simple ones? *J Abnorm Child Psychol* 1992; **20**: 51–63.
- 41 Lee SS, Lahey BB, Waldman ID, Van Hulle CA, Rathouz P, Pelham WE et al. Association of dopamine transporter genotype with disruptive behavior disorders in an eight-year longitudinal study of children and adolescents. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144**: 310–317.
- 42 Spitzer RL, Williams JBW, Gibbon M. *User's Guide for the Structured Clinical Interview for DSM-III-R: SCID*. American Psychiatric Association: Washington, DC, 1990.
- 43 Robinson EA, Eyberg SM. The dyadic parent–child interaction coding system: standardization and validation. *J Consult Clin Psychol* 1981; **49**: 245–250.
- 44 Chronis AM, Lahey BB, Pelham WE, Williams SH, Baumann BL, Kipp H et al. Maternal depression and early positive parenting predict future conduct problems in young children with attention-deficit/hyperactivity disorder. *Dev Psychol* 2007; **43**: 70–82.
- 45 Lansford JE, Deater-Deckard K, Dodge KA, Bates JE, Pettit GS. Ethnic differences in the link between physical discipline and later adolescent externalizing behaviors. *J Child Psychol Psychiatry* 2004; **45**: 801–812.
- 46 Ispa JM, Fine MA, Halgunseth LC, Harper S, Robinson J, Boyce L et al. Maternal intrusiveness, maternal warmth, and mother–toddler relationship outcomes: variations across low-income ethnic and acculturation groups. *Child Dev* 2004; **75**: 1613–1631.
- 47 Keenan K, Shaw DS. Developmental and social influences on young girls' early problem behavior. *Psychol Bull* 1997; **121**: 95–113.
- 48 Young SE, Smolen A, Corley RP, Krauter KS, DeFries JC, Crowley TJ et al. Dopamine transporter polymorphism associated with externalizing behavior problems in children. *Am J Med Genet B Neuropsychiatr Genet* 2002; **114**: 144–149.
- 49 Eaves L, Silberg JL, Erkanli A. Resolving multiple epigenetic pathways to adolescent depression. *J Child Psychol Psychiatry* 2003; **44**: 1006–1014.
- 50 Aiken LS, West SG. *Multiple Regression: Testing and Interpreting Interactions*. Sage: New York, 1991.
- 51 Jaffee SR, Price TS. Gene–environment correlations: a review of the evidence and implications for prevention of mental illness. *Mol Psychiatry* 2007; **12**: 432–442.
- 52 Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D et al. Dopamine D4 receptor (*D4DR*) exon III polymorphism associated with the human personality trait of novelty seeking. *Nat Genet* 1996; **12**: 78–80.
- 53 Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. *Nat Genet* 1996; **12**: 81–84.
- 54 Serretti A, Mandelli L, Lorenzi C, Landoni S, Calati R, Insacco R et al. Temperament and character in mood disorders: influence of *DRD4*, *SERTPR*, *TPH*, and *MAO-A* polymorphisms. *Neuropsychopharmacology* 2006; **53**: 9–16.
- 55 Huunerkopf R, Strobel A, Gutknecht L, Brocke B, Lesch KP. Interaction between *BDNF Val66 Met* and dopamine transporter gene variation influences anxiety-related traits. *Neuropsychopharmacology* 2007; **32**: 2552–2560.
- 56 Belsky J, Jaffee SR. The multiple determinants of parenting. In: Cicchetti D, Cohen DJ (eds). *Developmental Psychopathology*, 2nd edn. Wiley: New York, 2006, pp 38–85.
- 57 Fan J, Hof PR, Guise KG, Fossella JA, Posner MI. The functional integration of the anterior cingulate cortex during conflict processing. *Cereb Cortex* 2008; **18**: 796–805.
- 58 Fossella J, Sommer T, Fan J, Wu Y, Swanson JM, Pfaff DW et al. Assessing the molecular genetics of attention networks. *BMC Neurosci* 2002; **3**: 14.
- 59 Schweimer J, Hauber W. Involvement of the rat anterior cingulate cortex in control of instrumental responses guided by reward expectancy. *Learn Mem* 2005; **119**: 1687–1692.
- 60 Brunton PJ, Russell JA. The expectant brain: adapting for motherhood. *Nat Rev Neurosci* 2008; **9**: 11–25.

- 61 Botvinick M, Braver T, Barch D, Carter C, Cohen J. Conflict monitoring and cognitive control. *Psychol Rev* 2001; **108**: 624–652.
- 62 Bellgrove MA, Hawi Z, Kirley A, Fitzgerald M, Gill M, Robertson IH. Association between dopamine transporter genotype (*DAT1*), left-sided inattention, and an enhanced response to methylphenidate in attention deficit hyperactivity disorder. *Neuropsychopharmacology* 2005; **30**: 2290–2297.
- 63 McGough JJ. Attention-deficit/hyperactivity disorder pharmacogenomics. *Bio Psychiatry* 2005; **57**: 1367–1373.
- 64 Stein MA, Waldman ID, Sarampote CS, Seymour KE, Robb AS, Conlon C *et al*. Dopamine transporter genotype and methylphenidate dose response in children with ADHD. *Neuropsychopharmacology* 2005; **30**: 1374–1382.
- 65 Gruber R, Joobar R, Grizenko N, Leventhal BL, Cook EH, Stein MA. Differential effects of dopamine transporter genotype on stimulant side effect factors in children with ADHD. *Manuscript Under Review* 2008 (unpublished manuscript).
- 66 Kooji JS, Boonstra AM, Vermeulen SH, Heister AG, Burger H, Buitelaar JK *et al*. Response to methylphenidate in adults with ADHD is associated with a polymorphism in *SLC6A3* (*DAT1*). *Am J Med Genet B Neuropsychiatr Genet* 2008; **147B**: 201–208.
- 67 Joobar R, Grizenko N, Sengupta S, Amor LB, Schmitz N, Schwarz G *et al*. Dopamine transporter 3'-UTR *VNTR* genotype and ADHD: a pharmacobehavioural genetic study with methylphenidate. *Am J Med Genet B Neuropsychiatr Genet* 2007; **32**: 1370–1376.
- 68 Wu N, Cepeda C, Zhuang X, Levine MS. Altered corticostriatal neurotransmission and modulation in dopamine transporter knock-down mice. *J Neurophysiol* 2007; **98**: 423–432.
- 69 Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: translation between preclinical and clinical studies. *Clin Psychol Rev* 2006; **26**: 379–395.
- 70 Caspi A, Moffitt TE. Gene–environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci* 2006; **7**: 583–590.