Variation in mothers' arginine vasopressin receptor 1a and dopamine receptor D4 predicts maternal sensitivity via social cognition

By: Esther M. Leerkes, J. Su, Susan D. Calkins, Vincent C. Henrich, and A. Smolen

This is the peer reviewed version of the following article:

Leerkes, E.M., *Su, J., Calkins, S.D., Henrich, V. & Smolen, A. (2017). Variation in mothers' arginine vasopressin receptor 1a and dopamine receptor D4 predicts maternal sensitivity via social cognition. *Genes, Brain & Behavior, 16,* 233-240.

which has been published in final form at https://doi.org/10.1111/gbb.12326. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Abstract:

We examined the extent to which the arginine vasopressin receptor 1a (*AVPR1a*) and dopamine receptor D4 (*DRD4*) were related to sensitive maternal behavior directly or indirectly via maternal social cognition. Participants were 207 (105 European-American and 102 African-American) mothers and their children (52% females). Sensitive maternal behavior was rated and aggregated across a series of tasks when infants were 6 months, 1 year and 2 years old. At 6 months, mothers were interviewed about their empathy, attributions about infant behavior and beliefs about crying to assess their parenting-related social cognition. Mothers with long alleles for *AVPR1a* and *DRD4* engaged in more mother-oriented social cognition (i.e. negative attributions and beliefs about their infants' crying, $\beta = 0.13$, $P < 0.05$ and $\beta = 0.16$, $P < 0.05$, respectively), which in turn predicted less sensitive maternal behavior ($\beta = -0.23$, $P < 0.01$). Both indirect effects were statistically significant independent of one another and covariates [95% confidence interval (CI): −0.22, −0.03 and $\beta = -0.03$ for *AVPR*; 95% CI: −0.20, −0.03 and $\beta = -0.04$ for *DRD4*]. There were no significant direct effects of *AVPR1a* or *DRD4* on maternal sensitivity ($\beta = 0.02$, $P = .73$ and $\beta = -0.10$, $P = .57$, respectively). The results did not vary for African-American and European-American mothers ($\Delta\chi^2 = 18.76$, $\Delta df = 16$, $P = 0.28$). Results support the view that one mechanism by which maternal genes are associated with parental behavior is via social cognition.

Keywords: Arginine vasopressin | AVPR1a | dopamine | DRD4 | infants | mothers | sensitivity | social cognition

Article:

In the last decade, interest in the genetic underpinnings of individual differences in parenting behavior has increased, largely influenced by compelling evidence that neurological and

hormonal factors are associated with parenting behavior among humans and other mammals (Barrett & Fleming 2011; Mileva-Seitz & Fleming 2011; Numan 2010). Although several studies have shown associations between specific genotypes and parenting outcomes, relatively few investigators have examined the role of dopamine receptor (DR) D4 (*DRD4*) and arginine vasopressin receptor 1a (*AVPR1a*) in relation to parenting (see Mileva-Seitz *et al.* 2016 for a review). Thus, additional examination of associations between these genes and parenting is warranted. Moreover, prior studies did not directly test the purported mechanism or endophenotypes, by which these genes are associated with sensitive maternal behavior. In this article, we directly test the possibility that these genes are related to maternal sensitivity via their association with maternal social cognition.

Maternal sensitivity and underlying skills

Sensitive mothers respond to their infants' signals promptly and consistently, and do so in a manner that is well matched to their infants' current state, developmental level and the context. According to Ainsworth, in order to respond sensitively a mother must be aware of her infants' signals and interpret them from her infants' point of view rather than distorting them based on her own mood, needs or desires (Ainsworth *et al.* 1978). Thus, maternal social cognitive skills should underlie sensitive maternal behavior. In our previous work, we have shown that mothers who engage in more infant-oriented social information processing, characterized by accurate identification of infant distress, appropriate attributions about the causes of crying, empathy for the infant and the endorsement of positive and infant-oriented beliefs about crying (i.e. crying communicates infant needs), were observed to be more sensitive (Leerkes *et al.* 2016). In contrast, mothers who engage in more mother-oriented social information processing, characterized by negative and non-emotional attributions about the causes of crying and negative, self-oriented beliefs about crying (e.g. crying should be minimized, responding to crying spoils infants), were observed to be less sensitive. Mothers' ability to engage in infant-oriented social cognition and related sensitive behavioral responses may be influenced by neural and hormonal processes which are tied to specific genotypes as elaborated below (Mileva-Seitz & Fleming 2011; Numan 2010).

The role of *AVPR1a*

The neuropeptide arginine vasopressin has been implicated as critically important in relation to social motivation and social cognition, pair bonding and parenting behavior among rodents and humans (Donaldson & Young 2008; Heinrichs *et al.* 2009). Thus, arginine vasopressin receptor genes are particularly relevant to our social information processing perspective on maternal sensitivity. In humans, allele variation in RS3, one of the three microsatellites in the promoter region of *AVPR1a*, has received particular attention. RS3 is a complex repeat located 3625 base pairs (bp) from the transcription start site. Sixteen alleles that vary in length have been identified, and carrying long alleles (i.e. 327 or 334 depending on genotyping method, or longer) has been associated with negative outcomes (Kim *et al.*2002). Specifically, carrying one or two copies of these long alleles has been linked with deficits in social cognition as indexed by autism (Kim *et al.* 2002), lower generosity (Avinun *et al.* 2011), lower empathy (Uzefovsky *et al.* 2015), greater amygdala arousal in response to emotion matching tasks, a correlate of social avoidance (Meyer-

Lindenberg *et al.* 2009) and relationship difficulties as evidenced by greater marital problems (Walum *et al.* 2008).

Of most relevance, two prior studies have shown associations between *AVPR1a* and maternal sensitivity. In one study, White mothers with two copies of the long allele were observed to be less sensitive interacting with their children (a toddler and older sibling were observed separately) than mothers with one or zero copies of the long allele (Bisceglia *et al.*2012). In another study, Israeli mothers who carried one or two copies of the 327/334 bp allele were observed to be less sensitive (i.e. engaged in less structuring and gentle guidance) during play episodes with their 3.5-year-old twins than mothers with no copies of the target allele (Avinun *et al.* 2012). Importantly, this difference held across both twins and while controlling for the children's *AVPR1a* genotype thus eliminating the possibility that observed differences are a function of evocative child effects. Thus, we predict that carriers of long *AVPR1a* alleles (327/334 bp or longer) will engage in more mother-oriented cry processing, less infant-oriented cry processing and behave less sensitively when interacting with their infants than non-carriers.

The role of *DRD4*

Numan (2010) proposed that dopamine activates a motivational system controlled by the nucleus accumbens that promotes appropriate responses to significant stimuli and is critically important to caregiving behavior. Consistent with this view, there is evidence that dopamine is released in the nucleus accumbens during maternal behavior and that injections of DR *agonists* in the nucleus accumbens activate maternal behavior, whereas injections of DR *antagonists* disrupt maternal responses in postpartum rats (Lonstein *et al.*2015; Numan 2010). In humans, *DRD4* is one of the several dopamine-related genes that has received a good deal of attention in relation to prosocial behavior. *DRD4* includes a 48-bp variable nucleotide repeat polymorphism in exon III of chromosome 11. Individuals may carry 2–11 repeat units, and individuals with one or two long alleles (7 repeats or more) show lower gene expression (Schoots & Van Tol 2003), which may in turn undermine social cognition and prosocial behavior. In fact, individuals who carry the long allele show lower altruism (Anacker *et al.* 2013) and theory of mind (Lackner *et al.* 2012) and higher psychopathy, which is characterized in part by limited empathy for others (Wu & Barnes 2013). However, in one study, carrying the long *DRD4* allele was unrelated to women's self-reported emotional empathy but was associated with their heightened cognitive empathy (Uzefovsky *et al.* 2014).

To our knowledge, three published studies have examined associations between *DRD4* and parenting and none have reported main effects of this genotype on parenting outcomes (Beach *et al.* 2012; Beaver *et al.* 2012; van IJzendoorn *et al.* 2008). However, moderating effects of *DRD4* on parenting were apparent in two of these studies. Specifically, in a sample of African-American parents of adolescents, parental negative mood was associated with more negative parent–child interaction only among parents with *DRD4* long alleles (Beach *et al.* 2012). In a sample of Dutch mothers of children aged 1–3 years, daily hassles were associated with lower maternal sensitivity only among mothers with *DRD4* long alleles coupled with another dopamine risk polymorphism (*COMTval158met*) (van IJzendoorn *et al.*2008). Thus, carriers of the long *DRD4* alleles appeared to be at elevated risk for compromised parenting under certain conditions. Given that parenting is a complex phenotype influenced by biological,

psychological and contextual factors, the absence of simple direct effects of single genes is not entirely surprising. On the basis of the prior literature, we predict that *DRD4* has indirect effects on maternal sensitivity via its associations with mothers' social cognition, but we test a direct pathway between *DRD4* and sensitivity as well.

Proposed pathways linking genes to sensitivity

In summary, we examine three pathways by which *AVPR1a* and *DRD4* may be linked with maternal sensitivity. The first is a direct pathway in which carrying the long allele for *AVPR1a*or *DRD4* will be associated with lower maternal sensitivity. Then, we consider indirect pathways in which carrying the long allele of *AVPR1a* or *DRD4* will be associated with (1) lower infant-oriented crying processing and/or (2) higher mother-oriented cry processing which in turn would predict lower maternal sensitivity. We control for race, adult attachment coherence and maternal education as prior research has shown that each is related to cry processing and/or maternal sensitivity in this and other samples (Leerkes *et al.* 2016). In addition, we control for infant's *DRD4* and *AVPR1a* genotypes to ensure observed associations are not a function of infant evocative effects. As a final step, we test race as a moderator of proposed pathways given half of our participants are African-American and half are European-American and differences in the frequency distribution of specific genotypes across groups can have implications for associations between genotypes and phenotypes (Haberstick *et al.* 2015).

Materials and methods

Participants

Participants in this study were 209 primiparous mothers (106 European-American and 103 African-American) and their children from the southeastern United States drawn from a larger sample of 259 mothers initially recruited during the prenatal period. Mothers in the analytic sample ranged in age from 18 to 44 years ($M = 25.5$) at recruitment. Twenty-three percent had a high school diploma or less, 31% had attended but not completed college and 46% had a 4-year college degree. The majority (59%) of mothers were married or living with their child's father, 23% were in a relationship but not living with their child's father and 16% were single. Annual family income ranged from less than $2000 to over $100 000 (median = $35 000). All participating infants were healthy; 52% were females. Initial participants who did not provide DNA (because of attrition and not refusal) were younger, less educated and rated somewhat less sensitive at 6 months than mothers who did provide DNA, but they did not differ on race, income, measures of cry processing, adult attachment or maternal sensitivity at 1 year.

Procedure

Expectant mothers were recruited at childbirth classes. Upon enrollment in the study, women provided written consent. Women completed the Adult Attachment Interview (AAI) prenatally in our laboratory. Mothers and infants visited our laboratory for a videotaped observation of mother–infant interaction when infants were about 6 months ($M = 6.39$ months), 1 year ($M = 13.90$ months) and 2 years old ($M = 27.32$ months). At each visit, mothers and infants engaged in a 7-min free play, followed by two to three tasks designed to elicit infant distress

(frustration and fear) further described in Appendix S1 (Supporting information). Immediately after the 6-month observation, mothers participated in an audiotaped video-recall interview in which they viewed the videotapes of each distress task and answered a series of questions to assess cry processing. Mothers' and infants' DNA were collected via saliva samples during the 2-year visit. Procedures were approved by the University of North Carolina at Greensboro's Institutional Review Board.

Measures

Covariates

At the prenatal visit, mothers completed the AAI (C. George, N. Kaplan & M. Main, unpublished manuscript), a semi-structured interview in which participants describe their early childhood relationships with their primary caregivers and the influences they perceive those experiences have had on them. The coherence of mind rating (1 = *not at all coherent* to 9 = *very coherent*), a summary measure of participants' ability to describe early attachment experiences and their influence on current functioning in an organized manner, was our criterion measure of adult attachment security (M. Main & R. Goldwyn, unpublished manuscript). Interrater reliability was significant (intraclass correlation = 0.75, $P < 0.001$) based on 50 double-coded transcripts. In addition, mothers self-reported their highest level of education and their race.

Cry processing

During the 6-month video-recall interview, mothers were asked to rate how strongly they felt 17 emotions (e.g. sad, concerned and sympathetic) during each interactive task on a 4-point scale (1 = *not at all*; 4 = *very strongly*). Then, mothers were asked to describe why they felt each emotion. Their reasons were coded as infant-oriented or mother-oriented (Dix *et al.*2004); kappa based on 40 double-coded transcripts was 0.94. *Empathy* was calculated by averaging mothers' intensity ratings for infant-oriented empathy, sympathy and sadness across the three tasks to yield a single score.

Second, mothers were asked to indicate how frequently infants were distressed during each interactive task on a 7-point scale from never to the whole time and to indicate all emotions the infant displayed during each task using a list of 20 emotion terms (e.g. happy, sad and angry). Mothers' responses were compared with ratings made by reliably trained infant affect coders. If an infant was distressed according to our raters, and the mother rated the infant as never distressed (under-rating) or failed to indicate the infant felt specific negative emotions such as sadness, fear and anger (under-identification), the number of seconds the infants was rated as distressed by us was recorded to reflect the egregiousness of her detection error. That is, not noting an infant was distressed if they cried for 30 seconds is a bigger error than not noting they only cried for 5 seconds. Mothers who did not make these errors were scored as 0. These scores were calculated for each caregiving task and then summed across tasks. The two types of detection errors correlated ($r_{206} = 0.20$, $P < 0.01$) and were averaged. This score was multiplied by −1 so high scores reflect more accurate *distress detection*.

Third, mothers rated the extent to which they agreed with 18 statements about why their infant behaved as he or she did during each task on a 4-point scale ranging from strongly disagree to strongly agree to assess their causal attributions. *Situational/emotional attributions* is the mean of four items (upset by the situation, no one was helping my baby, trying to show he/she needs help and had no way to feel better) averaged across the three tasks. *Emotion minimizing attributions* is the mean of five items (having a bad day, in a bad mood, tired, hungry and not feeling well) averaged across the three tasks. *Negative/internal attributions* is the mean of seven items (spoiled, difficult temperament, trying to make my life difficult, unreasonable, crying on purpose, selfish and just wanted attention) averaged across the three tasks.

Mothers completed the Infant Crying Questionnaire (Haltigan *et al.* 2012), a single time, to assess their beliefs about infant crying by rating the extent to which they believed 43 statements on a 5-point scale ranging from *never* (1) to *always* (5). *Infant-oriented cry beliefs* is the average of two subscales: *Attachment* (eight items; e.g. when my baby cries, I want to make my baby feel secure) and *Crying as Communication* (three items; e.g. when my baby cries, I think my baby is trying to communicate). *Mother-oriented cry beliefs* is the average of two subscales: *Minimization* (nine items; e.g. when my baby cries, I want my baby to stop because I can't get anything else done) and *Spoiling* (three items; e.g. how I respond when my baby cries could spoil my baby).

We created two manifest variables based on analyses presented in Leerkes *et al.* (2016) by standardizing and averaging the relevant scores. Infant-oriented cry processing is the average of empathy, distress detection, situational/emotional cry attributions and infant-oriented cry beliefs (Chronbach's $\alpha = 0.62$) and mother-oriented cry processing is the average of negative and minimizing cry attributions and mother-oriented cry beliefs (Chronbach's $\alpha = 0.61$).

Maternal sensitivity

Maternal sensitivity during each interactive task at each time-point was rated using Ainsworth's 9-point sensitivity scale from (1) highly insensitive to (9) highly sensitive (Ainsworth *et al.* 1978). At each time-point, 15–20% of videos were double-coded to assess interrater reliability via interclass correlation coefficients (ICCs). Mean ICC across all waves and tasks was 0.88. Maternal sensitivity correlated significantly across tasks and time (*r*ranged from 0.51 to 0.85, all $P < 0.001$). Thus, a single measure of maternal sensitivity was created by averaging maternal sensitivity across all tasks and time-points (Chronbach's $\alpha = 0.91$).

Genotyping

Mothers' DNA was obtained using Oragene kits (DNAgenotek, Ottawa, Ontario, Canada). Mothers deposited 2 ml of saliva into a vial (#OG-500), that when capped released a stabilizing lysis buffer. All saliva samples were sealed and given a bar-coded label before sending the tubes for DNA processing. Genotyping was conducted at the Institute for Behavioral Genetics at the University of Colorado under the supervision of A.S. The RS3 site in *AVPR1a* was genotyped using the method of Walum *et al.* (2008). The primer sequences were forward: 5′-6FAM′-CCT GTA GAG ATG TAA GTG CT-3′; and reverse: 5′-gtttcttTCTGGAAGAGACTTAGATGG-3′, which yielded polymerase chain reaction (PCR) products of 317–355 bp, amplicons that are 7 bp

larger than those given in Knafo *et al.*(2008). Our most frequent allele (332 bp) is equivalent to the most frequent (325 bp) allele reported by Knafo *et al.* (2008). For the primary analysis, alleles were grouped as 334 bp or longer (long) vs. 333 bp or shorter (short), and *AVPR1a* genotypes were classified into two groups according to the absence (coded as 0) or presence of the long allele (coded as 1).

The 48-bp variable number tandem repeat polymorphism in the third exon of the *DRD4*gene (van Tol *et al.* 1992) was genotyped following the approach of Anchordoquy *et al.*(2003). The primer sequences were forward: 5′-VIC-GCT CAT GCT GCT GCT CTA CTG GGC-3′; and reverse: 5′-CTG CGG GTC TGC GGT GGA GTC TGG-3′, which yielded PCR products from 279 (2R) to 663 (10R) bp. We followed previous strategies (Hutchison *et al.* 2002; Lerman *et al.* 1998) to classify DRD4 genotypes into two groups as presence (coded as 1) or absence of the long allele (i.e. seven repeats or longer) (coded as 0).

To address reliability, 10% of samples were randomly duplicated with 100% concordance. In addition, samples that did not amplify well (approximately 5%) were duplicated and resolved via consensus if needed. Among mothers in the analytic sample, DRD4 was successfully genotyped for 100% and AVPR1a for 99% (all but two). Among infants in the analytic sample, two provided insufficient DNA for any genotyping. Of the remaining 207 infants, DRD4 was successfully genotyped for all but one (99%) and AVPR1a for all but four (98%).

Analysis

Preliminary analyses were performed to examine the frequencies of *AVPR1a* and *DRD4*genotypes for mothers and infants. We conducted chi-square tests using spss version 23 to examine whether genotype frequencies varied across racial groups. We also conducted chi-square test to examine deviations from Hardy–Weinberg equilibrium (HWE). Descriptive statistics and correlations between study variables were also examined. Path analysis was conducted using Mplus version 7 (Muthén & Muthén 2012) to evaluate the pathways through which *AVPR1a* and *DRD4* affect maternal sensitivity. In the path model, *AVPR1a* and *DRD4*were specified as exogenous variables that predicted infant-oriented and mother-oriented cry processing and maternal sensitivity. Infant-oriented and mother-oriented cry processing were specified as predicting maternal sensitivity. Maternal education and coherence of mind were specified as exogenous control variables linked to maternal sensitivity. Race was specified as a covariate associated with infant-oriented and mother-oriented cry processing and maternal sensitivity to account for potential population stratification effects. Infants' *AVPR1a* and *DRD4* genotypes were also included as covariates associated with infant-oriented and mother-oriented cry processing and maternal sensitivity to take into account potential child effects because of evocative gene–environment correlation. Infants' genotypes were specified to be correlated with mothers' genotypes. Hypotheses related to indirect associations were evaluated using bias-corrected bootstrapped 95% confidence interval (CI) (MacKinnon *et al.* 2004). To examine the possible differences in path coefficients between European-American and African-American mothers, multigroup analysis was conducted by removing race from the path model and then comparing a model with all remaining paths constrained to equality with one that had all paths freely estimated across African-American and European-American women.

Table 1. Genotype frequencies and HWE tests

Genotypes	Mothers			Infants		
	Whole sample	European-American	African-American	Whole sample	European-American	African-American
AVPR1a						
L/L	76 (36.7%)	41 (39.0%)	35 (34.3%)	74 (36.5%)	39 (37.5%)	35 (35.4%)
L/S	100 (48.3%)	52 (49.5%)	48 (47.1%)	90 (44.3%)	48 (46.2%)	42 (42.4%)
S/S	31 (15.0%)	12 (11.4%)	19 (18.6%)	39 (19.2%)	17 (16.3%)	22 (22.2%)
DRD4						
L/L	10 (4.8%)	5 (4.7%)	5 (4.9%)	14 (6.8%)	8 (7.6%)	6 (5.9%)
L/S	72 (34.4%)	32 (30.2%)	40 (38.8%)	61 (29.6%)	27 (25.7%)	34 (33.7%)
S/S	127 (60.8%)	69 (65.1%)	58 (56.3%)	131 (63.6%)	70 (66.7%)	61 (60.4%)
HWE test						
AVPR1a	0.84	0.46	0.72	0.22	0.73	0.17
DRD4	0.96	0.61	0.56	0.07	0.09	0.75

$n = 207$ for mothers' *AVPR1a*, $n = 209$ for mothers *DRD4*, $n = 203$ for infants' *AVPR1a* and $n = 206$ for infants' *DRD4*. Genotype frequencies are provided by maternal race. *P*-values from HWE tests are presented.

Results

Preliminary analysis

Genotype frequencies for mothers and infants for the whole sample and by maternal racial groups are presented in Table 1. Chi-square tests indicated that genotype frequencies did not vary across racial groups for either *AVPR1a* ($\chi^2 = 2.17$, df = 2, $P = 0.34$ for mothers; $\chi^2 = 1.14$, df = 2, $P = 0.57$ for infants) or *DRD4* ($\chi^2 = 1.44$, df = 2, $P = 0.49$ for mothers; $\chi^2 = 1.63$, df = 2, $P = 0.44$ for infants). Genotype frequencies for both *AVPR1a* and *DRD4* were in HWE for the whole sample and for each racial group (*P* ranged from 0.07 to 0.96) for mothers and infants. Descriptive statistics and intercorrelations are presented in Table 2.

Table 2. Descriptive statistics and intercorrelations

	M or %	SD	1	2	3	4	5	6	7	8	9	10
1. Race (European-American)	51%	—	—									
2. Maternal education	3.94	1.78	0.37**	—								
3. Coherence of mind	5.39	1.43	0.30**	0.37**	—							
4. Infant AVPR1a risk allele	81%	—	0.08	−0.01	−0.02	—						
5. Infant DRD4 risk allele	36%	—	−0.07	0.02	−0.01	−0.03	—					
6. Mother AVPR1a risk allele	85%	—	0.10	−0.11	0.03	0.20**	−0.12	—				
7. Mother DRD4 risk allele	39%	—	−0.08	−0.12	−0.04	−0.10	0.40**	0.00	—			
8. IO cry processing 6M	0.00	0.64	0.13	0.16*	0.10	−0.00	−0.04	−0.09	−0.04	—		
9. MO cry processing 6M	0.00	0.73	−0.27**	−0.28**	−0.17*	0.11	0.03	0.14	0.16*	−0.10	—	
10. Maternal sensitivity 6M-2Y	5.58	1.35	0.53**	0.58**	0.38**	0.02	−0.14*	−0.02	−0.18*	0.26**	−0.42**	—

n ranges from 196 to 209.
IO, infant-oriented; M, months; MO, mother-oriented; Y, years.
* $P < 0.05$;
** $P < 0.01$.

Predicting maternal sensitivity

Statistically significant path coefficients are presented in Fig. 1; all path coefficients are reported in Figure S1 (supporting information). Consistent with preliminary analysis and prior research, higher coherence of mind and maternal education were associated with higher maternal sensitivity, ($B = 0.11$, SE = 0.05, $\beta = 0.13$, $P < 0.05$ and $B = 0.26$, SE = 0.04, $\beta = 0.37$, $P < 0.01$, respectively). Consistent with prediction, mothers' long allele of *AVPR1a* and *DRD4* were associated positively with mother-oriented cry processing ($B = 0.27$, SE = 0.14, $\beta = 0.13$, $P < 0.05$ and $B = 0.24$, SE = 0.11, $\beta = 0.16$, $P < 0.05$, respectively). That is, mothers who carried the long allele of *AVPR1a* and/or of *DRD4* were more likely to focus on their own needs and endorse negative cognitions about their infants during distressing tasks. In contrast, neither mother's *AVPR1a* nor *DRD4* genotype was associated with infant-oriented cry processing ($B = -0.19$, SE = 0.13, $\beta = -0.11$, $P = 0.13$ and $B = -0.02$, SE = 0.10, $\beta = -0.01$, $P = 0.87$, respectively). Consistent with the hypothesis, infant-oriented cry processing was associated with higher maternal sensitivity ($B = 0.26$, SE = 0.11, $\beta = 0.13$, $P < 0.05$), whereas mother-oriented cry processing was associated with lower maternal sensitivity ($B = -0.39$, SE = 0.10, $\beta = -0.23$, $P < 0.01$) above and beyond the effects of covariates. There were no direct effects of *AVPR1a* or *DRD4* on maternal sensitivity ($B = 0.07$, SE = 0.19, $\beta = 0.02$, $P = 0.73$ and $B = -0.08$, SE = 0.15, $\beta = -0.03$, $P = 0.57$, respectively). However, results indicated that the indirect effects of *AVPR1a* and *DRD4* on maternal sensitivity via mother-oriented cry processing were significant (95% CI: −0.22, −0.03, $B = -0.11$, SE = 0.06, $\beta = -0.03$ for *AVPR1a*; 95% CI: −0.20, −0.03, $B = -0.09$, SE = 0.05, $\beta = -0.04$ for *DRD4*). Thus, maternal *AVPR1a* and *DRD4* 'risk' genotypes were linked with mothers' heightened focus on their own needs, which in turn predicted lower sensitivity to infant distress. There were no statistically significant associations between infants' *AVPR1a* and *DRD4* genotypes and mothers' infant-oriented cry processing, mother-oriented cry processing and maternal sensitivity in the path model. Results of the multigroup analysis indicated that path coefficients did not differ significantly across racial groups ($\Delta\chi^2 = 18.76$, $\Delta df = 16$, $P = 0.28$).

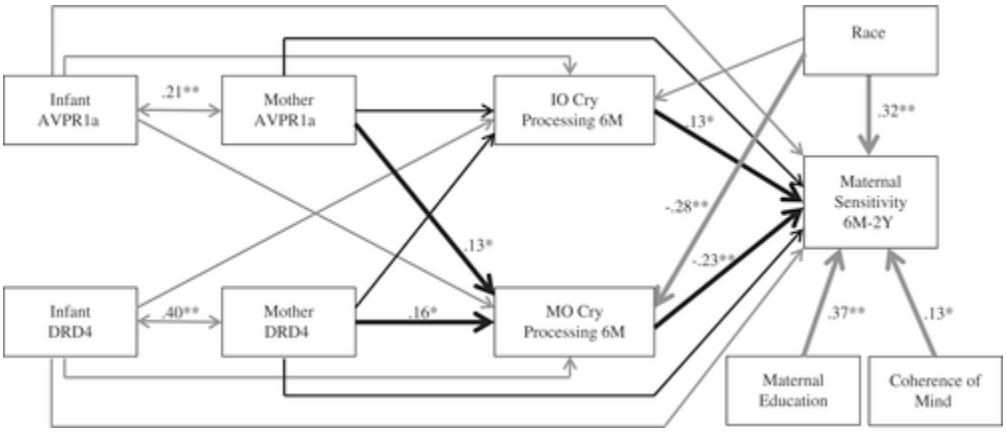

Figure 1. Effect of AVPR and DRD4 on maternal sensitivity via maternal cry processing while caregiving. Statistically significant standardized coefficients are presented. Race was coded (1, European-American; 0, African-American). The main paths for this study are in black and the paths for covariates are in gray. Statistically significant paths are given in bold arrows. *$P < 0.05$; **$P < 0.01$; $N = 209$. All coefficients are presented in Fig. S1. IO, infant-oriented; M, months; MO, mother-oriented; Y, years.

We examined statistical power by conducting *post hoc* Monte Carlo simulations in Mplus with the obtained model estimates used as population values and 10 000 replications. The power to detect direct and indirect effects of *DRD4* and *AVPR1a* on maternal social cognition and sensitivity was well below the threshold of 0.80 (all values ≤0.64).

Discussion

The goal of this article was to examine the extent to which *AVPR1a* and *DRD4* predicted maternal sensitivity directly and indirectly via mothers' social cognition. Consistent with prediction, the results showed that mothers who carried long alleles of *AVPR1a* or *DRD4* were more likely to engage in mother-oriented cry processing, characterized by negative beliefs and attributions about their infants' crying, which in turn predicted lower maternal sensitivity, and both indirect effects were significant independent of one another, infants' genotypes and important covariates. That mothers with long alleles of these two genes engaged in more negative social cognition about their infants is consistent with prior research linking these alleles with deficits in theory of mind (Lackner *et al.* 2012) and with negative personality traits (Wu & Barnes 2013). These two indirect pathways are consistent with the view that genes related to the vasopressin and dopamine systems, both part of the proposed maternal circuit (Numan 2010), are in fact related to mothers' social cognition. It appears that mothers with these two risk alleles have greater difficulty taking their infants' perspective and instead focus on their own needs in the moment undermining their ability to respond sensitively.

That neither *DRD4* nor *AVPR1a* were significantly associated with infant-oriented cry processing may be a function of the inclusion of mother's immediate emotional empathy which may be highly context specific, i.e. the extent to which a mother feels empathy may be more strongly driven by her infant's state in the moment than in her own genetically driven dispositions. In contrast, mothers' negative attributions and beliefs about crying may reflect a more stable tendency to minimize or downplay infant distress (Leerkes *et al.* 2016). The fact that women's *DRD4* and global emotional empathy were not significantly associated in a prior study (Uzefovsky *et al.* 2014) buttresses this argument.

The lack of direct effects of either gene on maternal sensitivity is not entirely surprising given the complexity of maternal sensitivity as a phenotype, and is consistent with prior research on *DRD4* and parenting in which main effects were not significant (Beach *et al.* 2012; Beaver *et al.* 2012; van IJzendoorn *et al.* 2008). However, the non-significant direct effect of *AVPR1a*on parenting is inconsistent with prior research (Avinun *et al.* 2012; Bisceglia *et al.* 2012). This difference is not attributable to our more conservative analytic approach which included multiple covariates given that inspection of the zero-order correlations indicates the association between *AVPR1a* and sensitivity was near zero prior to considering covariates. Discrepancies across studies could also result from differences in approaches to creating *AVPR1a* groups. But, *post hoc* analyses show that there are no differences in maternal sensitivity as a function of homozygozity vs. heterozygosity for the long allele (Bisceglia *et al.*2012) or when only the 334-bp alleles are considered risk rather than 334 bp and longer alleles (Avinun *et al.* 2012). Thus, this does not explain the either discrepancy suggesting additional research on the direct association between *AVPR1a* and maternal sensitivity is warranted.

Strengths of this research include the inclusion and simultaneous examination of two distinct genotypes related to different neural systems and our efforts to identify specific endophenotypes (two patterns of social cognition) that may explain associations between these genes and parenting behavior. To our knowledge, we are the first to present evidence that social cognition plays a role in linking specific genes to maternal behavior, although numerous others have proposed it would (Avinun *et al.* 2012; Barrett & Fleming 2011; van IJzendoorn *et al.* 2008). In addition, that we collapsed ratings of maternal sensitivity across time and tasks with varying demands likely yielded a highly reliable indicator of maternal sensitivity in contrast to relying on observations from a single time-point or task. Finally, we took a conservative analytic approach with multiple covariates. Controlling for maternal education and adult attachment coherence, both of which correlated highly with observed sensitivity, shows the robustness of the indirect effects of *AVPR1a* and *DRD4* over and above other predictors of sensitivity. Similarly, controlling for infants' genotypes eliminates the possibility that observed associations were a function of evocative gene–environment correlations.

Limitations of this research include the sample size. Although our sample is relatively large for developmental studies with extensive observational measures, it is quite small for molecular genetic research in which much larger sample sizes are desirable to detect small effects of specific genes on complex phenotypes such as maternal sensitivity. *Post hoc* power analyses show that we in fact had limited statistical power to identify genetic effects. In addition, although a diverse sample is often preferred for generalizability, in molecular genetic research, homogenous samples are preferred given concerns about potential confounding effects because of population stratification (Cardon & Palmer 2003). Thus, our sample is not ideal in this regard as it is composed of equal numbers of African-American and European-American mothers. But that genotype frequencies of *AVPR1a* and *DRD4* in our sample did not significantly differ across race, and that we included race as a covariate, reduce concern for population stratification in this study. However, our sample allowed us to formally test race as a moderator of genetic effects, and our multigroup analyses indicated the pathways did not vary across racial groups. Future work with non-Caucasian samples and with fathers in addition to mothers is needed. Such work should also consider gene–environment interaction (G × E) effects in which specific genes are examined as susceptibility factors that alter the links between mothers' childhood experiences, social cognition and maternal sensitivity, as there is more evidence for G × E effects than main effects of genes in relation to parenting outcomes (Mileva-Seitz *et al.* 2016). These efforts will require larger samples. Finally, the extent to which any gene is expressed is also dependent on epigenetics, which is determined in part by environmental experiences. Future work on the epigenetics of human parenting is still needed.

In conclusion, our results show that arginine vasopressin and dopamine-related ‘risk’ genes are related to mothers' compromised social cognition about their infants which in turn predicts less sensitive maternal behavior. These findings support the view that parenting is in part controlled by biological systems related to affect and cognition, and this is one way in which genes are linked with individual differences in maternal behavior.

Acknowledgments

This project was supported by the National Institutes of Health via R01HD058578 and R21HD073594. The contents of this article are the sole responsibility of the authors and do not necessarily reflect the views of the Eunice Kennedy Shriver National Institute for Child Health and Human Development. We are grateful to the participants for their time and Dr Regan Burney and project staff for their dedication. There are no conflicts of interest to report.

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