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Dopamine receptors D1 and D2 are related to observed maternal behavior

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The dopamine pathway and especially the dopamine receptors 1 and 2 (DRD1 and DRD2) are implicated in the regulation of mothering in rats. Evidence for this in humans is lacking. Here, we show that genetic variation in both DRD1 and DRD2 genes in a sample of 187 Caucasian mothers predicts variation in distinct maternal behaviors during a 30-min mother–infant interaction at 6 months postpartum. Two DRD1 single-nucleotide polymorphisms (SNPs rs265981 and rs686) significantly associated with maternal orienting away from the infant ($P = 0.002$ and $P = 0.003$, respectively), as did DRD1 haplotypes ($P = 0.03$). Two DRD2 SNPs (rs1799732 and rs6277) significantly associated with maternal infant-directed vocalizing ($P = 0.001$ and $P = 0.04$, respectively), as did DRD2 haplotypes ($P = 0.01$). We present evidence for heterosis in DRD1 where heterozygote mothers orient away from their infants significantly less than either homozygote group. Our findings provide important evidence that genetic variation in receptors critical for mothering in non-human species also affect human maternal behaviors. The findings also highlight the importance of exploring multiple dimensions of the complex human mothering phenotype.

Keywords: Dopamine, DRD1, DRD2, haplotypes, heterosis, maternal behavior, parental sensitivity, SNPs

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The dopamine (DA) system is among the most important biological regulators of mothering. In the rat brain, DA is released by midbrain neurons that project to the nucleus accumbens and prefrontal cortex, areas critical for motivation and attention. DA release into the accumbens occurs during maternal licking and grooming of pups (Afonso *et al*. 2009; Champagne *et al*. 2004; Hansen *et al*. 1993; Numan 2006, 2007) and variations in DA levels in the nucleus accumbens correlate closely with individual differences in licking and grooming (Champagne *et al*. 2004). Lesions of the nucleus accumbens or DA receptor antagonist infusion into this region disrupt maternal behavior in lactating rats (Numan *et al*. 2005; Parada *et al*. 2008). Overall, studies point to DRD1 and DRD2 as important for the manifestation of maternal memory and maternal behavior of rats. The genes coding for these receptors show widespread polymorphic variation with known associations to complex behavioral outcomes in humans (Hoenicka *et al*. 2007), making them excellent candidates for gene association studies.

Indirect evidence points to the possible involvement of the DA system in human mothering. In fMRI studies exposing mothers to infant stimuli, brain activity patterns coincide with regions of the mesocorticolimbic DA system, including the ventral striatum and the medial prefrontal cortex (Barrett & Fleming 2011). Furthermore, DA is involved in regulation of attentional, reward-processing and mood systems, which influence maternal responsiveness (Atkinson *et al*. 2009; Gonzalez *et al*. in press). Thus, mothers with better attention and working memory are more sensitive and prompt when responding to their infants (Atkinson *et al*. 1995; Gonzalez *et al*. in press). In addition, infant stimuli are salient and rewarding for new mothers, and become more so with time (Fleming *et al*. 1997a,b), implicating reward-processing as a facilitator of maternal attachment. Finally, depressed mothers are less interactive, less responsive and less vocal with their infants (Field *et al*. 2009; Tronick & Reck 2009). In non-maternal populations, variance in DA genes associates with individual differences in all three systems important to mothering: attention, reward-processing (Dreher *et al*. 2009) and mood (Guo & Tillman 2009; Lawford *et al*. 2006). Together, this evidence highlights a need

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to explore DA gene polymorphisms in relation to human mothering.

The possibility that genetic variation can contribute to individual differences in mothering has been largely ignored (Conger *et al*. 2009), although twin studies show differences in heritability of maternal behaviors (Kendler & Baker 2007) and gene association studies that examine mothering sometimes show significant effects (Bakermans-Kranenburg & van Ijzendoorn 2008; van Ijzendoorn *et al*. 2008; Lee *et al*. 2010; Mileva-Seitz *et al*. 2011; Mills-Koonce *et al*. 2007). Among the few studies addressing genetic associations with mothering, most rely on maternal sensitivity as the phenotypic outcome of interest. Maternal sensitivity is a global assessment of a mother's ability to promptly and adequately respond to infant cues, and it predicts child outcomes (De Wolff & van Ijzendoorn 1997; Isabella & Belsky 1991; Pederson *et al*. 1990). However, maternal sensitivity does not show the specific dimensions of maternal responsiveness that may be important to these outcomes. Here, we assessed two aspects of maternal responsiveness: (1) overall maternal sensitivity and (2) three classes of maternal behavior (maternal orienting away from the baby, infant-directed vocalizing, and general interactions including touching and toy playing with the baby). Two major outcomes of interest were the frequency of maternal 'orienting away from infant', which negatively correlates with maternal sensitivity (Mileva-Seitz *et al*. 2011), and duration of infant-directed vocalizing, which includes 'motherese', a widely used measure of maternal responsiveness (Fernald 1992).

In the present study, we explored associations between multiple single-nucleotide polymorphisms (SNPs) in the DRD1 and DRD2 genes and maternal responsiveness using the above-outlined measures of mothering.

Methods

Participants

Subjects were part of the Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) study. This is a longitudinal study following two cohorts of mothers and their infants with one in Montreal, QC, and the other in Hamilton, ON, Canada. At the time of these analyses, the data set from the Montreal cohort was incomplete, especially for measures that constituted the focus of the present study, the Behavioral Evaluation Strategies and Taxonomies (BEST) coding system (Educational Consulting, Inc., Hobe Sound, FL, USA) and sensitivity coding of mothering behavior (outlined below). Behavioral data were available for the Hamilton cohort, where subjects were recruited in their second trimester of pregnancy (weeks 12–24) from referrals to the St Joseph's Health Center (SJHC) Women's Health Concerns Clinic and SJHC Ultrasound Department, Hamilton, ON, Canada. Among the 255 mothers originally enrolled, 51 were excluded because of: attrition ($n = 28$), premature delivery ($n = 18$), stillbirth or termination ($n = 3$) or involvement of the Children's Aid Society ($n = 2$). Ethnic descent of the remaining Hamilton sample was mostly Caucasian (90%), with 3% mixed ethnicity, 2% African, 1.5% Hispanic and 1% East Indian; the remainder were unspecified. This ethnic distribution is typical of the greater Hamilton region. Allele frequency distributions can differ across ethnic groups (Kidd *et al*. 1998) and heterogeneous ancestry samples can reduce power (Tian *et al*. 2008). There is also evidence of an association between parenting and ethnicity (McLoyd & Smith 2002). Thus, we examined only the 187 Caucasian mothers in the Hamilton sample. Mean (±SD) maternal age was 31.2 (±4.9); mean maternal education was 4.81 (±2.3) on a scale of 0 through 10 where 0 represents 'not completed high school' and 10 represents 'post-graduate degree'. Most subjects reported having a partner (94%).

Procedure

Subjects signed written consent to participate in the MAVAN study. Ethics approval for this study was obtained from the ethics review boards at the University of Toronto and the St Joseph's Healthcare, Hamilton, ON. During 20 visits between the second trimester of pregnancy (weeks 12–24) and 72 months postpartum, mothers and their children were assessed through questionnaires, diagnostic tools and behavioral tasks. Participants received $25 compensation after each visit.

Measures

Video-recorded mother–infant interaction

We assessed maternal behavior and maternal sensitivity in a 30-min in-home video that recorded mother–infant interaction. The first 20 min were the *free-play* phase during which mothers were instructed to interact normally with their infants, but to refrain from nursing/feeding or diaper changing. The last 10 min were the *divided attention* phase (Pederson *et al*. 1990) during which time mothers completed self-report questionnaires in the presence of their infant. We gave mothers an opportunity to feed and change their babies prior to recording.

One hundred and fifty-eight of the 187 Caucasian-sample mothers agreed to be recorded. These mothers did not differ significantly from mothers who did not participate in the video recording with respect to having prior children or their prenatal household income. However, they were older ($M = 31.44 \pm 4.72$ vs. $M = 29.44 \pm 5.69$; $F(1, 184) = 3.84$, $P = 0.05$), and trended to be better educated ($M = 4.88 \pm 2.29$ vs. $M = 3.9 \pm 2.36$ on a scale from 0 = not finished high school to 10 = professional; $F(1, 156) = 3.21$, $P = 0.08$).

Maternal sensitivity. A single rater coded the full-length 30-min videos for *maternal sensitivity* using the Ainsworth Maternal Sensitivity Scales (Ainsworth *et al*. 1978) ($n = 158$), which contain four subscales: Co-operation, Accessibility, Acceptance and Sensitivity. Mothers received a rating (1–9) on each of these subscales, and they were then added to give a total score. Inter-rater reliability was high on these subscales ($r = 0.83$ across all four subscales; $n = 10$) in comparison with another experienced rater. Coding was performed blind to maternal genotype.

Maternal responsiveness during free-play. The first 20-min of the mother–infant interactions were coded by two raters using the BEST coding system (Krpan *et al*. 2005). This analysis generated duration and frequency data for multiple maternal behaviors by the use of a computer keyboard with keys indexed for each behavior. We limited the analyses to behaviors that were present in 15% or more of the mothers. Inter-rater reliability was high ($r = 0.80$, $n = 10$). We quantified the frequency and duration of the following eight maternal behaviors: orient-away from baby, show toy, kiss, vocalize to baby, poke, groom, stroke and play physically with a toy. From these, we used *orient-away from baby* (frequency) and *infant-directed vocalizing* (duration) as major outcomes. *Orienting away frequency* is the number of times a mother's gaze was not directed at the infant's head or body. This measure was positively skewed and was transformed with the natural log (Ln) transformation. *Infant-directed vocalizing* includes all infant-directed speech such as motherese, nonsense words and onomatopoeic sounds. All mothers vocalized in the span of 20 min. Finally, we quantified the frequencies of the rest of the above-outlined behaviors: show toy, kiss, poke, groom, stroke and play physically with a toy and these behaviors are collectively referred to as 'interaction frequency'.

Infant covariates. We quantified the durations of the following infant behaviors, derived with the BEST event-recorder system (see

above): *reaching toward mother*, *crying* and *smiling*. We added these three measures to obtain a combined *infant activity* duration, which we used as a covariate in regression analyses. All behavioral outcome variables were inspected for distributional properties and, where necessary, adjusted by transformation.

Buccal cell swabs and genotyping

We extracted DNA from buccal swabs. We chose DRD1 and DRD2 SNPs based on a combination of prior evidence of functional polymorphisms, positive associations with complex outcomes or successful haplotyping (Arinami *et al*. 1997; Batel *et al*. 2008; Chen *et al*. 2011; Comings *et al*. 1997; Del Zompo *et al*. 2007; Hirvonen *et al*. 2004; Misener *et al*. 2004; Noble 2003; Pohjalainen *et al*. 1998; Rodriguez-Jimenez *et al*. 2006; Xu *et al*. 2007).

The genotypes of the DRD1 and DRD2 polymorphisms were determined by the Taqman assay method using the ABI PRISM 7000 (Applied Biosystem, Foster City, CA, USA). The IDs for on-demand assays available from ABI were as follows: C___1011777_10 (DRD1 rs4532); C___1011775_20 (DRD1 rs265981); C__11157157_10 (DRD1 rs5326); C___3199294_20 (DRD1 rs265976); C__11339240_10 (DRD2 rs6277); C___7486676_10 (DRD2/ANKK1 rs1800497). Three of the SNPs required custom-made assays: DRD1 rs686 (3′-UTR), DRD2 rs1799978 and rs1799732. The SNPs have the following genomic context: rs4532, rs265981 and rs5326 are in the 5′ untranslated (UTR) region of the DRD1 gene; rs265976 and rs686 are in the 3′ UTR region of DRD1; rs1800497 is a missense mutation (Glu → Lys) on the ANKK1 gene ~10 kb downstream of DRD2, which associates with DRD2 receptor-binding levels in the brain (Pohjalainen *et al*. 1998); rs1799978 and rs1799732 are in the DRD2 promoter region, with association to differences in DRD2 expression for rs1799732 (Arinami *et al*. 1997); and rs6277 is a synonymous mutation (Pro → Pro) associated with differences in mRNA levels of DRD2 (Lawford *et al*. 2005).

Analysis

Genetic analysis

Hardy–Weinberg equilibrium (HWE) tests, linkage disequilibrium (LD) tests and haplotype analyses were performed with the 'haplo.stats' and 'genetics' packages in the open-source statistical framework R (http://cran.r-project.org). For HWE tests, we corrected *P*-value thresholds for multiple comparisons. haplo.stats (version 1.4.4) is designed for the analysis of indirectly measured haplotypes and uses a progressive insertion algorithm to calculate posterior probabilities of haplotypes. Haplotypes below a user-specified minimum frequency were grouped into a 'rare haplotype' group. haplo.design was used to model 'additive' or 'overdominance' haplotype effects. The function does this by first creating a design matrix for the possible haplotypes for each person, coded for the specified effect (where the presence of 0/1/2 copies of the haplotype is modeled as 0/1/2 for 'additive' and 0/1/0 for 'overdominance'), weighted by the posterior probability of those possible haplotypes per person and then collapsed back to a single row per person. Because of the complexity of LD patterning, we limited haplotype analyses to markers within the same gene (i.e. DRD1 gene haplotypes and DRD2 gene haplotypes). We set the threshold for common haplotypes at 5% for the regression analyses. Haplotypes were tested in the following sequence: first, we modeled haplotype heterosis using 'overdominance' effects, and then we modeled haplotype interactions using 'additive' effects. The 'additive' models have an intercept that includes only rare haplotypes or subjects who have *zero* copies of the major haplotypes in the model. The intercept can thus represent the mean effect for a reference group of very small sample size. For this reason, we grouped the least frequent of the major haplotypes with the intercept for the 'additive' analyses.

Multiple imputation

We imputed values for the behavioral outcomes because of missing scores (Little & Rubin 2002). Twenty-seven videos (14%) were missing for several reasons – mothers did not agree to videotaping because they felt that the taping was too invasive, time-consuming or, on occasion, taping was started but not completed during the session. Because the reasons for missing video are not systematically a result of any unmeasured variables, we can assume that they are missing at random for multiple imputation. Multiple imputation was performed over 10 iterations with the Hmisc package in R, using the areglmpute and fit.mult.impute functions. areglmpute uses predictive mean matching using the 'Bayesian approximate' method. The fit.mult.impute function fits the regression models over the 10 imputations and then computes imputation-adjusted variances and average beta coefficients. Predictor variables in the imputation model included all behavioral outcomes in this study, as well as maternal demographic and contextual variables, including maternal age, parity and prenatal income.

Validation of behavioral measures and covariates

There were some significant inter-correlations between outcomes, and between outcomes and potential covariates (Table 1). Frequency of *orienting away* was negatively correlated with both *infant-directed vocalizing* and *sensitivity* [Spearman rho (158) = −0.30, $P < 0.001$; and Spearman rho (158) = −0.19, $P = 0.02$, respectively], the latter correlation having been reported elsewhere (Mileva-Seitz *et al*. 2011). *Maternal education* was correlated with a number of the maternal outcomes (Table 1); as a result of its importance here and in the literature (Krpan *et al*. 2005), we retained this factor as a covariate in the analyses. We also included *infant activity during free-play* and *infant gender* as covariates in the models. Infant gender did not correlate with any mothering measures, but infant activity was significantly negatively correlated with maternal *orienting away* [Spearman rho (158) = −0.20, $P < 0.01$].

Results

Allele frequencies

Minor allele frequencies and genotype frequencies for all SNPs are shown in Table 2. SNPs within both DRD1 and DRD2 showed very high LD (Table 3). Additionally, rs1800497 (on the ANKK1 gene) was in high LD with SNPs in DRD2, which was consistent with its close location about 10 kb downstream of the DRD2 gene and previously documented LD with DRD2 (Kidd *et al*. 1998). There were three common haplotypes for both DRD1 (h1, h8 and h12) and DRD2 (h1, h2 and h3) (Table 4). Rare haplotypes accounted for 12% of the DRD1 and 13% of the DRD2 haplotypes (Table 4).

Single SNP associations

All markers were in HWE. We found a cluster of significant associations between DRD1 SNPs and maternal orienting away (Fig. 1a). Maternal *orienting away* differed significantly across genotype for both rs265981 and rs686 [Adj-R^2 = 0.07, likelihood ratio test $\chi^2(4, 163) = 15.49$, $P = 0.004$; and Adj-$R^2 = 0.06$, likelihood ratio test $\chi^2(4, 169) = 14.38$, $P = 0.006$, respectively]; these analyses included maternal age and infant activity as covariates. *Post hoc* comparisons with the Tukey's HSD test (using original non-imputed values) showed that the heterozygous group for both SNPs had significantly lower frequency of *orienting away* than either homozygote group (Fig. 1a). The data for another DRD1 SNP, rs4532, trended in the same direction [Adj-$R^2 = 0.02$, likelihood ratio test $\chi^2(3, 138) = 6.24$, $P = 0.10$].

There was an effect of DRD2 genotype on *infant-directed vocalizing* (Fig. 1b). rs1799732 genotype explained a

Table 1: Correlations between maternal responsiveness and maternal socioeconomic variables

	Orienting away	Infant-directed vocalizing	Interaction frequency	Ainsworth sensitivity
Orienting away	–			
Infant-directed vocalizing	−0.30***	–		
Interaction frequency	0.20*	0.10	–	
Ainsworth sensitivity	−0.19*	0.10	0.17*	–
Maternal age	0.04	−0.09	0.14	0.11
Education	0.05	−0.11	0.24**	0.16*
Income	−0.08	−0.04	0.16	0.13
Parity	0.15	0.00	−0.05	−0.12
Infant gender	−0.08	−0.02	0.06	−0.06
Infant activity during free-play	−0.20*	0.11	−0.10	−0.14

Values are Spearman's rho coefficients, two-tailed.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 2: Minor allele and genotype frequencies for DRD1 and DRD2 SNPs

		% Genotyped	Minor allele frequency	Genotype frequency		
DRD1	rs265981	90	G>A (0.36)	G/G (0.39)	G/A (0.50)	A/A (0.11)
	rs5326	90	G>A (0.16)	G/G (0.68)	G/A (0.32)	–
	rs4532	76	T>C (0.34)	T/T (0.46)	T/C (0.39)	C/C (0.15)
	rs686	93	A>G (0.37)	A/A (0.37)	A/G (0.51)	G/G (0.11)
	rs265976	95	G>T (0.21)	G/G (0.63)	G/T (0.33)	T/T (0.05)
DRD2	rs1799978	93	A>G (0.04)	A/A (0.92)	A/G (0.08)	–
	rs1799732	80	C>− (0.08)	C/C (0.85)	C/− (0.15)	−/− (<0.01)
	rs6277	97	C>T (0.49)	C/C (0.27)	C/T (0.49)	T/T (0.24)
ANKK1	rs1800497	82	G>A (0.20)	G/G (0.65)	G/A (0.29)	A/A (0.05)

Rs1799732 is an insertion/deletion polymorphism.

significant proportion of variance in maternal *infant-directed vocalizing* during free-play [Adj-$R^2 = 0.07$, likelihood ratio test $\chi^2(2, 145) = 12.81$, $P = 0.001$], even after covarying maternal age and infant activity [Adj-$R^2 = 0.05$, likelihood ratio test $\chi^2(3, 144) = 11.26$, $P = 0.01$]. rs6277 trended to explain a significant proportion of variance in *infant-directed vocalizing* in a model covarying maternal age and infant activity [Adj-$R^2 = 0.03$, likelihood ratio test $\chi^2(4, 175) = 9.12$, $P = 0.06$]. There were no significant associations with maternal sensitivity or other maternal behaviors.

Haplotype associations

Based on SNP analyses, we predicted a heterosis effect for DRD1 haplotypes on maternal *orienting away* frequency, such that having one copy vs. zero or two copies of a haplotype would be significantly predictive of *orienting away*.

DRD1 haplotype 12 ('overdominance' model) significantly predicted maternal *orienting away* [$\beta = -0.29$, $t(178) = -2.62$, $P = 0.01$] (Table 5), and the overall model including the other two haplotypes explained a significant proportion of variance in *orienting away* [Adj-$R^2 = 0.03$, likelihood ratio test $\chi^2(3, 178) = 8.67$, $P = 0.03$]. Maternal education was not a significant predictor and was dropped from the model. Covarying infant gender and infant activity during the mother–infant interaction period showed a persisting effect of haplotype 12 [$\beta = -0.29$, $t(175) = -2.39$, $P = 0.02$], an effect of infant activity [$\beta = -0.09$, $t(175) = -2.12$, $P = 0.03$] and a significant overall fit [Adj-$R^2 = 0.06$, likelihood ratio test $\chi^2(5, 175) = 15.36$, $P = 0.001$]. The additive analysis with haplotype 8 as part of the intercept term showed, as we had predicted, a significant interaction between haplotype 1 and haplotype 12 [$\beta = -0.34$, $t(178) = -2.33$, $P = 0.03$], and the overall fit approached significance [Adj-$R^2 = 0.02$, likelihood ratio test $\chi^2(3, 178) = 7.24$, $P = 0.11$]. Covarying infant gender and activity showed a trend of an interactive effect for haplotype 1 × haplotype 12 [$\beta = -0.28$, $t(175) = -1.94$, $P = 0.05$], a significant effect of infant activity [$\beta = -0.10$, $t(175) = -2.10$, $P = 0.04$] and a significant overall fit [Adj-$R^2 = 0.04$, likelihood ratio test $\chi^2(5, 175) = 3.31$, $P = 0.02$] (Table 5).

DRD2 haplotype 3 ('overdominance' model) significantly predicted *infant-directed vocalizing* [$\beta = 78.85$, $t(179) = 2.24$, $P = 0.02$] and together with the other haplotypes explained a significant proportion of variance in *infant-directed vocalizing* [Adj-$R^2 = 0.05$, likelihood ratio test $\chi^2(3, 179) = 9.01$, $P = 0.03$] (Table 6). When we covaried infant gender and activity during interaction, the effect of haplotype 3 remained significant [$\beta = 79.37$, $t(176) = 2.23$, $P = 0.03$], as did the overall fit [Adj-$R^2 = 0.04$, likelihood ratio test $\chi^2(5, 176) = 12.37$, $P = 0.03$]. No significant haplotype interactions were found with the 'additive' effects model (haplotype 3 grouped with the intercept, see *Methods*) (Table 6). Haplotypes were not related to other measures of maternal responsiveness.

Table 3: Pairwise linkage disequilibrium, D′, and correlation coefficients for nine DA SNPs across the MAVAN sample

		DRD1 rs5326	DRD1 rs4532	DRD1 rs686	DRD1 rs265976	DRD2 rs1799978	DRD2 rs1799732	DRD2 rs6277	ANKK1 rs1800497
DRD1 rs265981	D′	1.00	0.98	0.97	0.60	0.18	0.15	0.08	0.15
	Corr.	−0.33	0.94	0.96	−0.23	−0.03	0.06	−0.06	0.10
	$\chi 2$	34.63***	230.13***	301.73***	17.43***	0.24	0.93	1.27	2.75
DRD1 rs5326	D′		1.00	1.00	0.80	0.28	0.93	0.26	0.43
	Corr.		−0.31	−0.34	0.68	0.13	−0.12	0.12	−0.09
	$\chi 2$		26.75***	37.13***	150.83***	5.41**	4.10*	4.43*	2.59
DRD1 rs4532	D′			0.97	0.60	0.10	0.12	0.08	0.14
	Corr.			0.91	−0.22	−0.01	0.05	−0.06	0.10
	$\chi 2$			229.57***	13.91***	0.05	0.57	0.90	2.50
DRD1 rs686	D′				0.57	0.27	0.16	0.06	0.14
	Corr.				−0.23	−0.04	0.06	−0.05	0.09
	$\chi 2$				17.21***	0.59	1.08	0.78	2.37
DRD1 rs265976	D′					0.23	0.02	0.10	0.55
	Corr.					−0.02	0.01	0.05	−0.14
	$\chi 2$					0.19	0.06	1.03	5.88*
DRD2 rs1799978	D′						0.98	0.32	0.99
	Corr.						−0.06	−0.06	−0.10
	$\chi 2$						0.99	1.42	3.03
DRD2 rs1799732	D′							1.00	0.21
	Corr.							−0.29	−0.03
	$\chi 2$							24.90***	0.24
DRD2 rs6277	D′								0.61
	Corr.								−0.30
	$\chi 2$								26.74***

Table 4: Haplotype analysis for DRD1 and DRD2

	DRD1						DRD2			
Haplotype	rs265981	rs5326	rs4532	rs686	rs265976	Frequency	rs1799978	rs1799732	rs6277	Frequency
1	**G**	**G**	**T**	**A**	**G**	**0.415**	**A**	**C**	**C**	**0.403**
2	G	G	T	A	T	0.042	**A**	**C**	**T**	**0.474**
3	G	G	T	G	G	0.010	**A**	**–**	**C**	**0.082**
4	G	G	T	G	T	0.002	A	–	T	0.000
5	G	G	C	A	G	0.003	G	C	C	0.025
6	G	G	C	G	G	0.003	G	C	T	0.015
7	G	A	T	A	G	0.026	G	–	C	0.000
8	**G**	**A**	**T**	**A**	**T**	**0.136**	G	–	T	0.000
9	G	A	T	G	G	0.000				
10	A	G	T	G	G	0.000				
11	A	G	C	A	G	0.006				
12	**A**	**G**	**C**	**G**	**G**	**0.329**				
13	A	G	C	G	T	0.028				
14	A	A	C	G	G	0.000				
15	A	A	C	G	T	0.000				

Haplotypes in bold with frequencies significantly >5% were used in the analyses whereas the rest were grouped with the intercept term.

Discussion

Evidence from animal research shows that the DA receptors DRD1 and DRD2 contribute to the expression of maternal behavior and maternal memory, and this study is, to our knowledge, the first to show associations between genetic variation in DRD1 and variations in mothering in humans. We found an association between genetic variation in DRD1 and DRD2 and maternal *orienting away* and *infant-directed vocalizing*, respectively. Both of these behavioral outcomes were measures of maternal responsiveness during mother–infant interaction.

Pharmacological evidence shows that DRD1, compared with DRD2, has a preferential role in the visuospatial working memory of human females (Müller *et al*. 1998). Visuospatial skills have been correlated with executive functioning

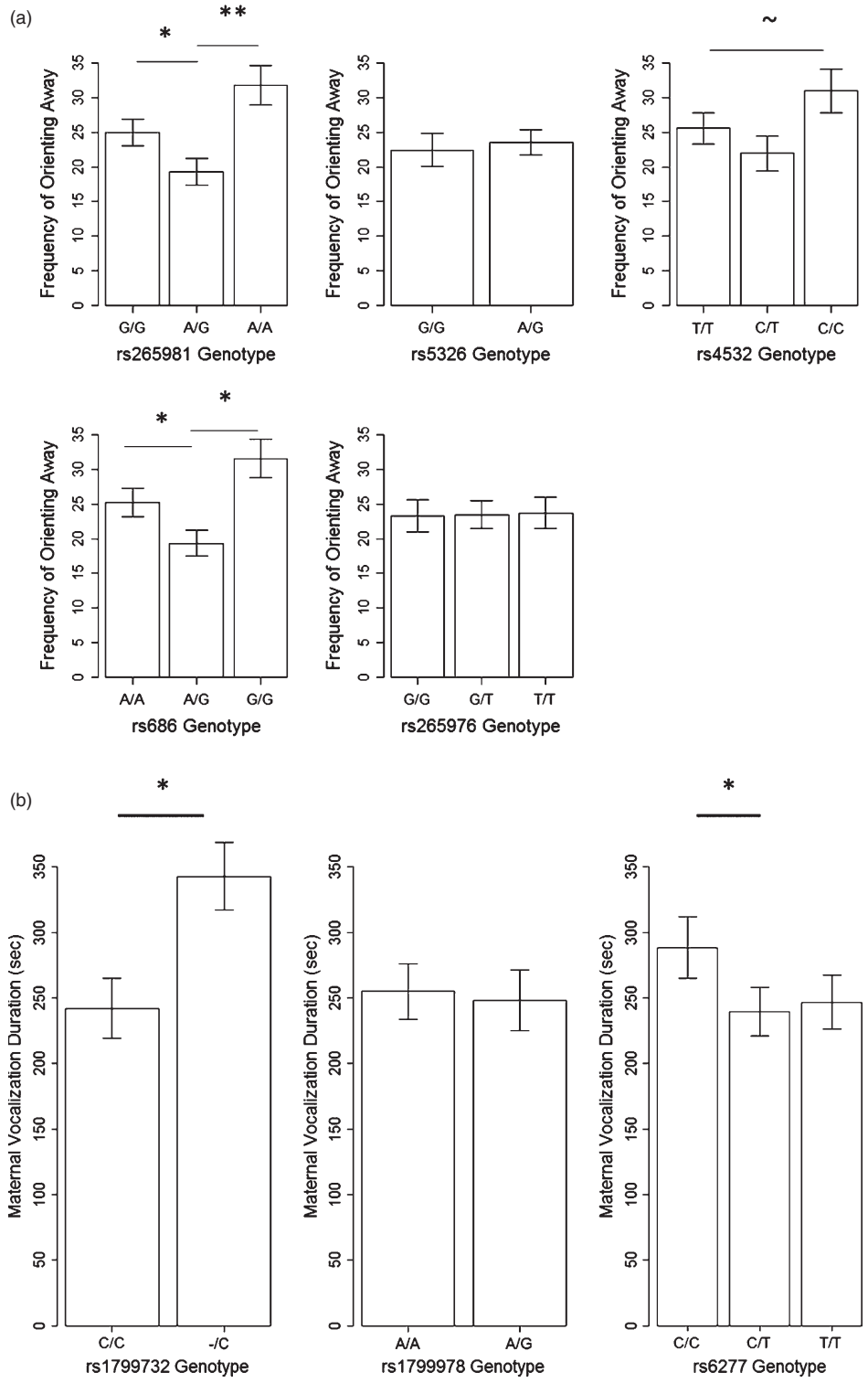

Figure 1: DA SNP associations with observed maternal behaviours. (a) DRD1 SNPs in association with maternal *orienting away*. ANOVAs with Tukey's *post hoc* tests showed the heterozygote group oriented away from the infant significantly less frequently compared with the other homozygous genotypes in rs265981 and rs686, and trended in the same direction for rs4532. (b) DRD2 SNPs in association with *infant-directed vocalizing* to the infant. $^{\dagger}P < 0.1$, $^{*}P < 0.05$, $^{**}P < 0.01$. Bars are means ± SEM.

Table 5: Unstandardized beta coefficients (*t*-statistic in brackets) for haplotype analyses with DRD1 and maternal orienting away, using overdominance and additive effect models

	DRD1 and maternal orienting away			
	Overdominance		Additive	
Intercept	3.01 (32.46)***	3.42 (17.27)***	2.92 (18.94)***	3.32 (13.63)***
h1	0.08 (0.74)	0.05 (0.44)	0.07 (0.70)	0.09 (0.82)
h8	0.10 (0.84)	0.14 (1.10)	–	–
h12	−0.29 (−2.62)**	−0.29 (−2.39)*	0.09 (0.65)	0.09 (0.65)
h1 × h12	–	–	−0.34 (−2.33)*	−0.28 (−1.94)†
Infant gender	–	−0.10 (−0.90)	–	−0.13 (−1.14)
Infant activity	–	−0.09 (−2.12)*	–	−0.10 (−2.10)*
R^2 (adj)	0.03	0.06	0.02	0.04
LR χ^2	8.67*	15.36**	7.24†	13.31*
df	(3, 178)	(5, 175)	(3, 178)	(5, 175)

For 'additive' models, the least frequent of the three major haplotypes for DRD1 (haplotype 8) was grouped with the intercept; likelihood ratio chi-square (LR χ^2) values are used to assess the overall fit; fit is significant for 'overdominance' models, indicating a significant effect of having just *one* copy of haplotype 12 in DRD1 on the frequency of orienting away; there is also a significant interaction between haplotype 1 and haplotype 12 ('additive' models), and the overall fit is significant when covarying infant behavior and gender.
†$P < 0.1$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 6: Unstandardized beta coefficients (*t*-statistic in brackets) for haplotype analyses with DRD2 and maternal infant-directed vocalizing, using overdominance and additive effect models

	DRD2 and infant-directed vocalizing			
	Overdominance		Additive	
Intercept	257.75 (15.71)***	203.06 (5.28)***	322.37 (6.97)***	267.21 (4.62)***
h1	−14.65 (−0.52)	−14.55 (−0.51)	−25.64 (−0.86)	−26.40 (−0.87)
h2	−9.11 (−0.32)	−11.69 (−0.41)	−34.32 (−1.24)	−34.23 (−1.22)
h3	78.85 (2.24)*	79.37 (2.23)*	–	–
h1 × h2	–	–	−28.71 (−1.22)	−31.16 (−1.32)
Baby gender	–	7.98 (0.37)	–	9.26 (0.42)
Baby activity	–	13.59 (1.55)	–	13.67 (1.56)
R^2 (adj)	0.03	0.04	0.03	0.02
LR χ^2	9.01*	12.37*	5.92	9.3†
df	(3, 179)	(5, 176)	(3, 179)	(5, 176)

For 'additive' models, the least frequent of the three major haplotypes for DRD2 (haplotype 3) was grouped with the intercept; likelihood ratio chi-square (LR χ^2) values are used to assess the overall fit; fit is significant for 'overdominance' models, indicating a significant effect of having just *one* copy of haplotype 3 in DRD3 on the duration of infant-directed vocalizing.
†$P < 0.1$; *$P < 0.05$; ***$P < 0.001$.

(Miyake *et al*. 2001). Moreover, DRD1-genotypic variation is related to brain metabolism (Potkin *et al*. 2003) and executive functioning (Floresco & Magyar 2006). Specifically, DRD1 action in the prefrontal cortex may modulate the balance between focus on current goals and competing, unrelated goals (Durstewitz & Seamans 2002). This supports previous evidence for a function of the DA system in distractibility (Braver *et al*. 1999). Together, this evidence of the executive function and working memory functions of DRD1 fits well with our current findings of an association between DRD1 and *orienting away*, which may be a measure of mothers' inattention (Mileva-Seitz *et al*. 2011). Maternal attention and working memory are important components of human maternal behavior (Deater-Deckard *et al*. 2010; Gonzalez *et al*. in press), further implicating the role of DA in mothering.

DRD1 and DRD2 receptors function together to regulate not only working memory but also behavioral flexibility (Floresco & Magyar 2006). In the current study, two of the DRD2 SNPs associated with *infant-directed vocalizing* during free-play with the infant: rs6277 and rs1799732. The former SNP is known to influence striatal DRD2 binding (Hirvonen *et al*. 2004) and predicts differences in working memory (Rodriguez-Jimenez *et al*. 2006; Xu *et al*. 2007) and reward-related impulsivity (White *et al*. 2009). The latter SNP is related to DRD2 expression (Arinami *et al*. 1997) and associates with substance dependence (Chen *et al*. 2011). Therefore, reward-related processes and, once again, working memory, both of which affect maternal behavior and potentially infant-directed vocalizations, are implicated in DRD2 genetic variation.

Interestingly, there was a significant negative correlation between *orienting away* and *infant-directed vocalizing*. Mothers who look away more frequently may have less opportunity, and perhaps less motivation, to engage with their infants vocally. Our findings of association between DRD1 and orienting away, and between DRD2 and infant-directed vocalization, provide support for the notion of dual regulation. Pharmacological evidence suggests that DRD1 and DRD2 have opposing functions in the striatum (an area important for maternal behavior regulation in rats) during a stop-signal reaction time task in rats (Eagle *et al*. 2011). In humans, this task is an index of inhibitory control and is closely related to attention and distractibility (Gambin & Swiecicka 2009). Relative changes in DRD1/DRD2 availability or binding may influence the balance between behavioral activation/inhibition (Eagle *et al*. 2011). Therefore, genetic variants that influence this DRD1/DRD2 balance may affect multiple behavioral activation/inhibition outcomes, including maternal outcomes.

We found a notable heterozygous effect for *orienting away* in three of the five DRD1 SNPs (rs686, rs265981 and rs4532) we examined and in the DRD1 haplotype analyses. For these three SNPs, the heterozygous group had *lower* levels of *orienting away*. In other words, mothers who were heterozygous at these SNPs tended to look away from their infants *less* often. Our haplotype analysis in DRD1 similarly showed that mothers carrying one copy of haplotype 1 and one copy of haplotype 12 had *lower* levels of *orienting away*. We argue that lower rates of orienting away are indicative of lesser maternal distractibility and greater maternal sustained attention on the infant, an argument strengthened by the negative correlation between orienting away and maternal sensitivity. A similar heterozygosity effect (or heterozygous advantage) is observed in a study of addictive behaviors where heterozygous individuals at the DRD1 rs4532 SNP score lower for addictive traits such as smoking and shopping than homozygotes (Comings *et al*. 1997). In the Comings *et al*. (1997) study, as well as in the present report, having two different alleles or haplotypes appears to confer a phenotypic advantage. This phenomenon is supported by the documented inverted-U model for optimal DRD1 activity levels in regulating prefrontal function and working memory, where too little or too much DA in the prefrontal cortex is less optimal (Seamans & Robbins 2010; Williams & Castner 2006). Moreover, inverted-U-shaped DA function may be important not only for cognitive function but also for maternal behaviors in rats (Numan *et al*. 2005).

We also investigated the Taq1 polymorphism of the ANKK1 gene because it associates with brain DRD2 receptor levels, glucose metabolism and cognitive functioning (Noble 2003; Pohjalainen *et al*. 1998), alcoholism (Smith *et al*. 2008), smoking (Styn *et al*. 2009) and altered striatal activation to food reward in obesity (Stice *et al*. 2008). Taq1 did not associate with any measure of maternal behavior, which is congruent with a prior study showing no effects on maternal sensitivity (Mills-Koonce *et al*. 2007).

Among the novel aspects of the present study was the use of haplotypes in relation to maternal behavior. Haplotype analyses in the DRD1 gene show associations with alcoholism (Batel *et al*. 2008), autism spectrum disorder (Hettinger *et al*. 2008) and attention-deficit/hyperactivity disorder (Misener *et al*. 2004). To our knowledge, the issue of haplotypic heterozygosity has not been addressed in these studies, and these haplotypes have never been examined as predictors of individual differences in maternal responsiveness. We believe that it is important to continue exploring haplotypes where possible, particularly when the functional roles of constituent SNPs are unknown. Haplotype analyses may have several advantages over single-SNP analyses, among which is the gain in statistical power (Akey *et al*. 2001; but see Clark 2004).

Another important consideration was the inclusion of 'child effects' in our models of parenting behavior. The human literature shows that child characteristics are important predictors of parental behavior (Lytton 1990). We included a measure of infant activity during free play (including infant reaching, smiling and crying) as well as infant gender. Although infant activity was negatively correlated to maternal orienting away, including this infant variable as a covariate in our models did not change the pattern of effects. Infant gender did not prove to be significantly correlated to any maternal outcome measure, or a significant covariate in the regression models. Thus, it appears that maternal genotype was more important than child characteristics in predicting maternal responsiveness. However, it is possible that other child effects (including temperament and personality) may have a greater role as influences on maternal behavior.

The significant associations we report here between DRD1/DRD2 and maternal behavior account for between 2% and 7% of the total variance in the outcomes. This, albeit small, proportion of explained variance is commonly found in studies of complex behavioral phenotypes in humans, where each variable is expected to contribute only a small part to explaining the overall individual variation in that trait. Furthermore, human studies in parenting that have reported R^2 values have a similar range of R^2 values to those found here (van Ijzendoorn *et al*. 2008; Mills-Koonce *et al*. 2007).

A limitation of the present study is its small sample size ($n = 187$) for a genetic study, particularly after exclusion of non-Caucasian mothers. However, this sample is comparable to other maternal samples with prominent time-intensive procedures such as recording and in-depth scoring of mother–infant interactions. Future genetic association studies should place primary importance on characterizing the complex maternal phenotype and should not rely exclusively on measuring maternal sensitivity. In the present study, DRD1 variation significantly associated with *orienting away*, but did not associate with maternal sensitivity. In our previous study, serotonin transporter gene variation alone predicted differences in sensitivity, and it interacted with early maternal experiences to predict differences in *orienting away* (Mileva-Seitz *et al*. 2011). These results suggest that specific behaviors (*orienting away*, *vocalizing*) are dissociable from global measures of maternal care (*sensitivity*) and should be treated as complimentary units of analysis in genetic studies. *Orienting away*, *infant-directed vocalizing* and *sensitivity* are likely separate but overlapping components of the complex maternal phenotype, akin to endophenotypes in psychiatric research. Support for this notion comes from child development research. Although

sensitivity is arguably the best known predictor of infant attachment and well-being, other behavioral dimensions, including maternal–infant synchrony and overall maternal stimulation, also influence infant outcomes (Belsky *et al*. 1984; Feldman *et al*. 2010; Isabella & Belsky 1991). A more phenotype-centered approach should also improve hypothesis generation and candidate gene selection.

Finally, we have a lot to learn about the potential moderating influences of mothers' early experiences, present stress and mood state on these gene–behavior relationships. We know, for instance, that maternal postpartum depression has numerous negative effects on maternal behavior (Beck 1995), and that early life experiences of abuse or neglect increase the risk of developing postpartum depression (Heim *et al*. 2004). Future examinations of the DA system of genes should take into account the influences of maternal mood and early life experiences. Future studies should also examine the involvement of other DA genes in mothering, including the DA receptor D4 (DRD4), a gene that appears important for attentional mechanisms and that may also confer 'differential susceptibility' to early life experiences (Belsky *et al*. 2009).

Taken together, these results provide an example of the power of translational research, where the initial impetus for the question is provided by an extensive animal literature that shows the importance of the DA system in the regulation of mothering. They extend these studies by showing a clear association between dopamine gene polymorphisms and human mothering, providing a rationale from the human research for subsequent studies on genetics of mothering in other animals – a topic that, to date, has received very little attention. Finally, we have shown the utility of assessing simultaneously multiple measures of mothering and multiple genes within a system, allowing us to discover both the gene–behavior associations and their dissociations. Working through the analysis of other genes within the dopamine pathway and the behavior of the mother in response to the developing offspring constitutes our next major challenge.

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