The Neurogenetics of Nice: Receptor Genes for Oxytocin and Vasopressin Interact With Threat to Predict Prosocial Behavior

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The highly similar peptides oxytocin and vasopressin have emerged in the literature as promising candidates for the biological underpinnings of prosociality (for reviews, see Campbell, 2010; Ebstein et al., 2009). Research on oxytocin administration and on variation in the oxytocin receptor gene (OXTR) has suggested that oxytocin influences generosity in the context of economic games, as well as empathy, prosocial temperament (e.g., Bartz et al., 2010; Israel et al., 2008; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Mikolajczak et al., 2010; Tost et al., 2010), and interactions with close others (Bakermans-Kranenburg & van IJzendoorn, 2008; Ditzen et al., 2008; Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). Similarly, research on variation in the vasopressin 1a receptor gene (AVPR1a) has indicated that vasopressin influences generosity and endorsement of benevolent values in the context of economic games (Knafo et al., 2008), as well as pair bonding in men (Walum et al., 2008).

The same psychological mechanisms for the effects of oxytocin and vasopressin on prosociality and the scope of these hormones’ influence on prosocial behaviors outside the contexts of the laboratory and close relationships remain unknown. However, all prosocial acts require people to contend with concerns about potential exploitation or loss of resources (i.e., threats). If oxytocin and vasopressin moderate responses to such threats, they may influence a wide variety of prosocial behaviors, including those outside a laboratory context.

Oxytocin, Vasopressin, and Threat Moderation

Evidence suggests that oxytocin moderates responses to some threats (for a review, see Campbell, 2010). Oxytocin administration reduces amygdalar reactivity to negative stimuli (Kirsch et al., 2005; Petrovic, Kalisch, Singer, & Dolan, 2008), and amygdalar reactivity, in turn, mediates oxytocin’s effects on generosity in the context of an economic game (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008). The G/G genotype of the rs53576 single-nucleotide polymorphism (SNP) for OXTR also predicts lower cardiovascular reactivity to startle anticipation than do the A/A and A/G genotypes (Rodrigues, Saslow, Garcia, John, & Keltner, 2009).

Vasopressin also appears to moderate responses to certain threats. In nonhuman animals, vasopressin administration...
leads to increased behavioral displays of fear, but vasopressin deficiency is also associated with increased fear (see Jones & Gosling, 2008, for a review). In both humans and nonhuman animals, vasopressin administration increases not only physiological arousal (Ebstein et al., 2009; Shalev et al., 2011) but also approach-oriented emotions in response to potentially threatening faces (Thompson, George, Walton, Orr, & Benson, 2006). Notably, variation in the rs1 and rs3 AVPR1a polymorphisms moderates amygdala activity in response to emotional faces (Meyer-Lindenberg et al., 2008), as well as the startle response (Levin et al., 2009).

The Present Study: OXTR, AVPR1a, and Real-World Prosocial Behavior

Our goal in this study was to examine whether oxytocin and vasopressin interact with threat to predict prosocial behavior outside the contexts of the laboratory and close relationships. Examining individual differences in oxytocin and vasopressin function, as manifested by OXTR and AVPR1a variation, constituted an ideal way to do this. We examined three genetic variants previously shown to predict prosocial behavior: the G allele of the OXTR variant rs53576 (e.g., Bakermans-Kranenburg & van Ijzendoorn, 2008; Tost et al., 2010), which also predicts lower incidence of autism and social anxiety relative to the A allele (e.g., Wu et al., 2005), and the long forms of the AVPR1a variants rs1 and rs3 (Knafo et al., 2008).

We were interested in whether these genetic variants would predict two types of self-reported prosocial behaviors: engagement in volunteer work or charitable activities and commitment to civic duty. We also examined whether the polymorphisms interacted with perceived threats from the social world in predicting these prosocial behaviors. We investigated the following hypotheses:

1. First, the rs53576 G allele, relative to the A allele, should (a) predict greater levels of prosocial behavior (i.e., engagement in volunteer work or charitable activities and commitment to civic duty) and (b) should buffer the connection between perceived threat and prosocial behavior.

2. Second, long forms of the AVPR1a rs1 and rs3 microsatellites, relative to short forms, should predict greater levels of prosocial behavior.

Because of conflicting evidence about the effects of vasopressin on responses to threat, we did not make a prediction about the interactions of the AVPR1a rs1 and rs3 polymorphisms with threat, but we did explore these interactions.

Method

Participants and procedure

Data were collected via Internet-based surveys of a large, nationally representative U.S. sample (Silver et al., 2006) recruited by Knowledge Networks (http://www.knowledgenetworks.com). Knowledge Networks panel members are compensated with Internet access (if needed), points that can be used toward purchasing merchandise, and monetary rewards in return for completing certain surveys. Data used for this investigation were collected at several time points, described in the following paragraphs. Because genotype distributions differ across racial groups, our analyses focused on European Americans, who composed the largest racial group in the sample. For the present study, 518 European American participants (48.8% male, 51.2% female) were successfully genotyped for one or more polymorphisms of interest. Of these participants, 348 had participated in data collection at all time points and were included in our analyses.

Life-event surveys. All individuals in this study participated in a survey-based study on responses to life events (N = 2,792). Surveys were administered at six time points: November through December 2001; March through April 2002; September through November 2002; March through April 2003; September through October 2003; and September through November 2004.

DNA collection. At our request, in 2008, Knowledge Networks recontacted available participants from the life-events study (n = 1,296) and asked them to provide a saliva sample for DNA analysis. The majority of participants (54.9%; n = 711) agreed to do so; these participants received and returned Oragene (Ottawa, Ontario, Canada) saliva-collection kits (for more information, see http://www.dnagenotek.com) via mail. Kits were then sent to The Centre for Applied Genomics (Toronto, Ontario, Canada; http://www.tcag.ca) for genotyping.

Social and political survey. A subset of the original sample from the life-events study (n = 1,266) completed a Knowledge Networks–administered survey on social and political attitudes and involvement between April 2000 and March 2003. Most participants (74.8%) completed this survey after August 2002.

Measures

OXTR and AVPR1a polymorphisms. The OXTR variant of interest, rs53576, consists of a locus at which either the nucleobase adenine or the nucleobase guanine (abbreviated “A” and “G,” respectively) can occur. Because every person has one copy of each gene from each parent, there are three possible genotypes for this OXTR variant: A/A, A/G, or G/G. This variant was genotyped using TaqMan SNP-genotyping technology (Assays-by-Design Service; Applied Biosystems, Foster City, CA). Samples were analyzed using the ABI 7900HT Sequence Detection System (Applied Biosystems), and genotype calls were made using Sequence Detection System software Version 2.1 (Applied Biosystems). Table 1 shows the distribution of OXTR genotypes in the sample. Both AVPR1a variants of interest consist of genetic sequences that repeat a variable number of times. Polymerase-
chain-reaction genotyping was performed using fluoresceintly labeled primers on the genomic regions containing rs1 and rs3 (see Walum et al., 2008, for primer sequences), and fragment length was analyzed via capillary electrophoresis using the ABI 3730 DNA Analyzer (Applied Biosystems) and GenMapper software Version 3.5 (Applied Biosystems). For our analyses, we dichotomized fragment lengths at the median to obtain roughly equal numbers of alleles designated as “short” and “long” (as per Knafo et al., 2008). Because every person has one copy of each gene from each parent, there were three possible genotypes: short/short (s/s), short/long (s/l), and long/long (l/l; see Table 1 for the distribution of AVPR1a genotypes in the sample).

**Perceived threat.** Perceived threat was assessed at all waves of the life-events study with a reverse-coded, six-item version of Janoff-Bulman’s (1989) World Assumptions Scale. Items on the scale included “There is more good in the world than bad” and “Human nature is basically good”; participants responded to each item using a scale from 1, *strongly disagree*, to 5, *strongly agree*. Higher mean scores indicated greater disagreement that people and the world in general are good, and thus greater belief that the world is a malevolent and unsafe place (i.e., greater perceived threat). Because not all participants took part in each wave, we maximized the number of participants included in our analyses by computing each individual’s mean perceived-threat score across all waves for which he or she had data. These scores had high internal consistency both within waves ($\alpha_s = .83–.87$) and across waves ($\alpha = .81$).

**Civic duty.** Four items in the social and political survey assessed participants’ felt duty to make sacrifices on behalf of society: “It is a citizen’s duty to serve on a jury even if it interferes with his/her private life”; “It is a citizen’s duty to report a crime even if it might put him or her in some jeopardy”; “It is a citizen’s duty to pay taxes even if they seem unfair or too high”; and “It is a citizen’s duty to keep informed about politics even if it is time-consuming.” Participants responded to each item using a scale from 1, *strongly disagree*, to 5, *strongly agree*. The mean score for all items was used as an index of commitment to civic duty; this scale exhibited fair internal consistency ($\alpha = .61$).

**Charitable activities.** The social and political survey assessed whether participants had engaged in the following activities during the past 12 months: donating blood, giving money to or working for a charity, attending parent-teacher-association meetings, or attending community group meetings. The total number of activities a participant had engaged in was used as a measure of involvement in charitable activities.

### Results

#### Distribution of genes and descriptive statistics

Genotyping the OXTR SNP (rs53576) showed that the G allele was more common than the A allele (see Table 1). Genotyping the AVPR1a microsatellite repeats resulted in a range of fragment sizes (see Table 2) similar to those found in other recent studies (rs1: median = 310 repeats; rs3: median = 336 repeats; cf. Levin et al., 2009; Walum et al., 2008). Dichotomizing these ranges at the median resulted in the distributions of s/s, s/l, and l/l genotypes shown in Table 1. The rs1 and rs3 variants were in linkage disequilibrium. The OXTR rs53576, AVPR1a rs1, and AVPR1a rs3 polymorphisms were in Hardy-Weinberg equilibrium. Correlations among the key nongenetic variables were quite small, indicating that these variables all reflected distinct constructs (see Table 3).

#### Associations of OXTR and AVPR1a genes with threat and social behavior

We used one-way analyses of variance (ANOVAs) to test the associations among each polymorphism, perceived threat, and the two prosocial-behavior variables. Results indicated no significant main effects of OXTR or AVPR1a genotypes on either threat or social behavior.

The interactions of the OXTR and AVPR1a genotypes with perceived threat were tested using two multiple regressions, one predicting commitment to civic duty and one predicting involvement in charitable activities. Because the OXTR and AVPR1a genotypes were categorical, they were dummy-coded, with reference groups of G/G and l/l, respectively. Each model simultaneously tested all genotypes, perceived threat, and all Genotype × Threat interactions. For simplicity of presentation, we dropped nonsignificant variables (except those included in interaction terms) from the final models (see Tables 4 and 5).

The OXTR rs53576 SNP interacted with perceived threat to predict charitable activities (see Table 4). Using simple-slopes
Table 2. Distribution of Specific Vasopressin Receptor 1a (AVPR1a) Alleles in the Sample

<table>
<thead>
<tr>
<th>AVPR1a polymorphism and allele</th>
<th>Frequency (n)</th>
<th>Percentage of the sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1a rs1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>299</td>
<td>9</td>
<td>0.70</td>
</tr>
<tr>
<td>304</td>
<td>151</td>
<td>11.72</td>
</tr>
<tr>
<td>308</td>
<td>504</td>
<td>39.13</td>
</tr>
<tr>
<td>312</td>
<td>317</td>
<td>24.61</td>
</tr>
<tr>
<td>316</td>
<td>131</td>
<td>10.17</td>
</tr>
<tr>
<td>320</td>
<td>120</td>
<td>9.32</td>
</tr>
<tr>
<td>324</td>
<td>15</td>
<td>1.16</td>
</tr>
<tr>
<td>328</td>
<td>33</td>
<td>2.56</td>
</tr>
<tr>
<td>332</td>
<td>2</td>
<td>0.16</td>
</tr>
<tr>
<td>333</td>
<td>5</td>
<td>0.39</td>
</tr>
<tr>
<td>336</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>AVPR1a rs3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>319</td>
<td>13</td>
<td>1.03</td>
</tr>
<tr>
<td>323</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>325</td>
<td>4</td>
<td>0.32</td>
</tr>
<tr>
<td>327</td>
<td>7</td>
<td>0.55</td>
</tr>
<tr>
<td>328</td>
<td>2</td>
<td>0.16</td>
</tr>
<tr>
<td>330</td>
<td>80</td>
<td>6.32</td>
</tr>
<tr>
<td>332</td>
<td>104</td>
<td>8.21</td>
</tr>
<tr>
<td>334</td>
<td>311</td>
<td>24.57</td>
</tr>
<tr>
<td>336</td>
<td>274</td>
<td>21.64</td>
</tr>
<tr>
<td>338</td>
<td>134</td>
<td>10.58</td>
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<tr>
<td>340</td>
<td>155</td>
<td>12.24</td>
</tr>
<tr>
<td>342</td>
<td>44</td>
<td>3.48</td>
</tr>
<tr>
<td>344</td>
<td>18</td>
<td>1.42</td>
</tr>
<tr>
<td>346</td>
<td>68</td>
<td>5.37</td>
</tr>
<tr>
<td>348</td>
<td>32</td>
<td>2.53</td>
</tr>
<tr>
<td>351</td>
<td>16</td>
<td>1.26</td>
</tr>
<tr>
<td>352</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>353</td>
<td>2</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Note: The numbers assigned to the alleles indicate the number of repeats in the rs1 and rs3 fragments. Alleles are counted for each occurrence; because every individual has two alleles, there are twice as many alleles as participants.

Table 3. Descriptive Statistics and Correlations for the Key Nongenetic Study Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>M (SD)</th>
<th>Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Perceived threat (n = 518)</td>
<td>2.35 (0.54)</td>
<td></td>
</tr>
<tr>
<td>2. Commitment to civic duty (n = 307)</td>
<td>3.83 (0.57)</td>
<td>-0.26**</td>
</tr>
<tr>
<td>3. Charitable activities (n = 304)</td>
<td>1.55 (1.16)</td>
<td>-0.25**</td>
</tr>
</tbody>
</table>

Note: Scores on the measures of perceived threat and commitment to civic duty ranged from 1 to 5, with higher scores indicating greater perceived threat and greater commitment to civic duty, respectively. The number of charitable activities participants had engaged in ranged from 0 to 5. **p < .001.

Table 4. Results of the Regression Analysis Predicting Engagement in Charitable Activities (n = 264)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>b</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXTR rs53576 A/A genotype</td>
<td>-0.15 [-0.74, 0.44]</td>
<td>-0.03</td>
</tr>
<tr>
<td>OXTR rs53576 A/G genotype</td>
<td>-0.01 [-0.29, 0.28]</td>
<td>-0.00</td>
</tr>
<tr>
<td>Perceived threat</td>
<td>-0.15 [-0.53, 0.22]</td>
<td>-0.07</td>
</tr>
<tr>
<td>OXTR rs53576 A/A Genotype × Perceived Threat</td>
<td>-0.91 [-1.94, 0.11]</td>
<td>-0.11†</td>
</tr>
<tr>
<td>OXTR rs53576 A/G Genotype × Perceived Threat</td>
<td>-0.92 [-1.50, 0.34]</td>
<td>-0.24*</td>
</tr>
</tbody>
</table>

Note: Nonsignificant predictors were dropped from this model. All genotypes refer to the oxytocin receptor genotype (OXTR). The numbers in brackets are 95% confidence intervals. Perceived threat was centered for the purpose of calculating interactions. Adjusted $R^2 = .08$, $p < .001$. †p < .10. *p < .01.

analyses, we examined the main effect of perceived threat for each genotype by treating each genotype as the reference group (equal to 0) in its own regression; results showed that greater perceived threat predicted fewer charitable activities for A/A individuals ($β = -0.45, p = .03$) and A/G individuals ($β = -0.46, p < .001$), but not for G/G individuals ($p > .40$; see Fig. 1). In addition, the AVPR1a rs1 polymorphism interacted with perceived threat to predict commitment to civic duty (see Table 5). Specifically, greater perceived threat predicted lower commitment to civic duty for the s/l genotype ($β = -0.43, p < .001$) and marginally lower commitment to civic duty for the s/s genotype ($β = -0.16, p = .11$), which was substantially less common (found in 128 individuals) than the s/l genotype (found in 241 individuals). By contrast, perceived threat was unrelated to commitment to civic duty among individuals with the l/l genotype ($β = -0.00, p = .99$; see Fig. 2). The interaction between OXTR genotype and threat did not predict commitment to civic duty, and the interaction between AVPR1a genotype and threat did not predict engagement in charitable activities.

The AVPR1a rs3 polymorphism did not predict or interact with threat to predict either commitment to civic duty or engagement in charitable activities; this pattern of results held whether the genotype was long or short and whether the 334 base-pair allele examined in past research (e.g., Meyer-Lindenberg et al., 2008; Walum et al., 2008) was present or absent. Including age and gender as covariates in separate models did not substantively change the results. Moreover, there were no two- or three-way interactions of variables in the models that included age or gender.

Discussion

Our results suggest that oxytocin and vasopressin receptor genes predict prosocial behavior in theoretically meaningful ways. The hypothesized main effects of OXTR and AVPR1a genes on prosocial behavior were not present (see Tables 4 and 5), a result consistent with recent laboratory findings (Apicella...
et al., 2010); however, we observed significant interactions in the predicted direction. Specifically, OXTR and AVPR1a polymorphisms believed to enhance the function of oxytocin (e.g., Rodrigues et al., 2009) and vasopressin (e.g., Knafo et al., 2008) buffered the negative association between threat and prosocial behaviors.

### Threat moderation and prosocial behavior

Threat moderation may be a key component of prosocial behavior or altruism. Brown and Brown (2006) and Graziano and Habashi (2010) have argued that the caregiving behavioral system suppresses the avoidance response to potential costs of helping valued others. Our findings are consistent with the possibility that oxytocin and vasopressin are part of the biological underpinnings of this caregiving system. In fact, the lack of main effects of OXTR and AVPR1a variation on prosocial behavior may suggest that threat processing is the mechanism by which these genes affect prosocial behavior. It is even possible that the lack of observed effects for AVPR1a rs3—a departure from prior research—resulted from insufficient threat. Because we used a Web-based method of data collection, participants lacked a socially evaluative audience, the presence of which may enhance the effects of vasopressin (Shalev et al., 2011).

### Implications for social processes and well-being

It is widely accepted that having a strong social network and high-quality close relationships promotes physical and mental well-being (Uchino, 2009). Given the threat-reducing and prosociality-increasing effects of oxytocin, vasopressin, and their receptor genes, it is possible that some of the positive effects of relationships on health and well-being stem specifically from increased opportunities for prosocial behavior. Indeed, some research has indicated that behavior aimed at helping other people is a better predictor of health and well-being than are social engagement or received social support (for a review, see Brown & Brown, 2006).

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**Table 5.** Results of the Regression Analysis Predicting Commitment to Civic Duty (n = 283)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>b</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1a rs1 s/s genotype</td>
<td>−0.00 [−0.19, 0.19]</td>
<td>−0.00</td>
</tr>
<tr>
<td>AVPR1a rs1 s/l genotype</td>
<td>−0.02 [−0.18, 0.15]</td>
<td>−0.02</td>
</tr>
<tr>
<td>Perceived threat</td>
<td>0.00 [−0.28, 0.27]</td>
<td>0.00</td>
</tr>
<tr>
<td>AVPR1a rs1 s/s Genotype × Perceived Threat</td>
<td>−0.18 [−0.54, 0.17]</td>
<td>−0.09</td>
</tr>
<tr>
<td>AVPR1a rs1 s/l Genotype × Perceived Threat</td>
<td>−0.49 [−0.82, 0.15]</td>
<td>−0.29*</td>
</tr>
</tbody>
</table>

Note: Nonsignificant predictors were dropped from this model. All genotypes refer to the vasopressin receptor genotype (AVPR1a; s = short fragment length, l = long fragment length). The numbers in brackets are 95% confidence intervals. Perceived threat was centered for the purpose of calculating interactions. Adjusted $R^2 = .08$, $p < .001$. *$p < .01$.
Limitations and future directions

Limitations of this study suggest directions for further research. Although our data may provide evidence that oxytocin and vasopressin can reduce avoidance behavior, other interpretations are plausible. The observed Gene × Threat interactions could reflect epigenetic effects or other developmental effects if, for example, perceived threat results from adversity in early life. Experimental studies of threat and pro-social behavior could resolve this ambiguity.

The use of self-report assessments of prosocial behaviors, although common (cf. U.S. Bureau of Labor Statistics, 2010), leaves open the possibility that our results actually reflected social-desirability processes. Convergent evidence from both survey-based and laboratory methods is needed to strengthen the interpretation of these results. In addition, we studied a relatively small sample of self-reported European Americans, to reduce confounds caused by underlying population-structure differences (i.e., stratification). Future research should employ larger samples and use strategies such as family-based association tests to address concerns about stratification.

The importance of replicating these findings is highlighted by the fact that many Gene × Environment interactions are not subsequently replicated, which indicates that they were spurious when first identified (Duncan & Keller, 2011). In a recent study, we replicated the OXTR results reported here in a sample of college students (n = 117), using time spent helping friends, neighbors, or adult relatives as the outcome measure (for details about and results from the study, see the Supplemental Material available online). However, we did not have data for the same outcome measure for which we report AVPR1a findings in this article; therefore, pending exact replication, our findings with respect to vasopressin function are best characterized as preliminary.

In short, our findings suggest that oxytocin and vasopressin may moderate the relationship between perceived threat and real-world prosocial behavior. Future work is needed to replicate these findings and to clarify the psychological and biological mechanisms by which OXTR and AVPR1a polymorphisms may influence responses to threat. Convergent data from longitudinal surveys and laboratory research could shed new light on the role of these genes in social and individual well-being.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Supplemental Material

Additional supporting information may be found at http://psp.sagepub.com/content/by/supplemental-data

Notes

1. These surveys were originally conducted to assess responses to the September 11 attacks and included additional data not relevant to the present study.

2. Results were substantively unchanged when our analysis included only the wave with the most data (September through November 2002).

References


