Correction

**PSYCHOLOGICAL AND COGNITIVE SCIENCES**

Correction for “Variation in the β-endorphin, oxytocin, and dopamine receptor genes is associated with different dimensions of human sociality,” by Eiluned Pearce, Rafael Wlodarski, Anna Machin, and Robin I. M. Dunbar, which appeared in issue 20, May 16, 2017, of Proc Natl Acad Sci USA (114:5300–5305; first published May 1, 2017; 10.1073/pnas.1700712114).

The authors wish to note, “We used the term ‘neuropeptide’ in referring to the set of diverse neurochemicals that we examined in this study, some of which are not peptides; dopamine and serotonin are neurotransmitters and should be listed as such, and testosterone should be listed as a steroid. Our usage arose from our primary focus on the neuropeptides endorphin and oxytocin. Notwithstanding the biochemical differences between these neurochemicals, we note that these terminological issues have no implications for the significance of the findings reported in this paper.”

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Variation in the β-endorphin, oxytocin, and dopamine receptor genes is associated with different dimensions of human sociality

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There is growing evidence that the number and quality of social relationships have substantial impacts on health, well-being, and longevity, and, at least in animals, on reproductive fitness. Although it is widely recognized that these outcomes are mediated by a number of neuropeptides, the roles they play remain debated. We suggest that an overemphasis on one neuropeptide (oxytocin), combined with a failure to distinguish between different social domains, has obscured the complexity involved. We use variation in 33 SNPs for the receptor genes for six well-known social neuropeptides in relation to three separate domains of sociality (social disposition, dyadic relationships, and social networks) to show that three neuropeptides (β-endorphin, oxytocin, and dopamine) play particularly important roles, with each being associated predominantly with a different social domain. However, endorphins and dopamine have a much wider compass than oxytocin (whose effects are confined to romantic/reproductive relationships and often do not survive control for other neuropeptides). In contrast, vasopressin, serotonin, and testosterone play only limited roles.

Significance

Social behavior in mammals is underpinned by a number of social neuropeptides. Most studies, however, focus on a single neuropeptide (often oxytocin), and invariably only in the context of reproductive relationships. Here, we examine the associations between the six main social neuropeptides (endorphins, oxytocin, vasopressin, dopamine, serotonin, and testosterone) and social indices in three separate social domains (disposition, dyadic/romantic relationships, and social network). We show that each neuropeptide is quite specific in its domain of influence, although endorphins and dopamine influence all three social domains. The results suggest that the social importance of endorphins may have been underestimated.


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OPRM1 variation explicitly related to fearful attachment styles (33). In addition, Gillath (34) found that, whereas variants of DRD2 are related to anxious attachment, HTR2A variation may be related to avoidant attachment.

Romantic relationship status, relationship quality, and sexual behaviors have been linked to OXTR variation in women and AVPR1a variation in men, although this sexual division is not always straightforward (12, 35–37). In addition, it has become

**Fig. 1.** Results for one representative SNP from each neuropeptide in each of the three domains of sociality (disposition, relationships, and wider network) for males (light shading) and females (dark shading). Significant gene effects on sociality are represented by plots with gray shaded plot areas and include the model parameter t value. *P < 0.05, **P < 0.01, ***P < 0.001.
clear that other neuropeptides also play a significant role in the formation and maintenance of sexual relationships. For instance, both the dopamine and opioid systems have been shown to interact to maintain monogamous pair bonds in prairie voles (15, 38). In humans, DRD2 and HTR2A variation has been linked to different “loving styles” (39) and DRD1 and DRD2 genotypes have been linked to age at first sexual intercourse (40), whereas HTRIA variation is associated with romantic relationship formation (41). In addition, OPRM1 and HTR2A have been associated with variation in mate-choice success differentially in the sexes in “speed-dating” situations (42). Furthermore, AR variation has been associated with relationship status and testosterone response in opposite-sex interactions (43, 44). Here, we examine variation in these genes in relation to both romantic relationship quality [Relationship Assessment Scale (RAS)] and sexual attitudes and behaviors [Sociosexual Orientation Inventory Revised (SOI-R)] more generally.

By comparison, with work on dyadic relationships, the role of neuropeptides in the wider social context beyond the dyad has been almost totally ignored. What little work has been done suggests that variation in OXTR can predict the size and diversity of social networks via its influence on social temperament (45), as well as being related to feelings of social connectedness (46) and “general sociality” (47). Other studies have, however, provided indirect evidence for a relationship between endorphins and social network size (48). Aside from these, little has been done to examine the influence of other neuropeptides on wider social network. The present study provides a significant attempt to evaluate the role these neuropeptides play at this larger social scale.

We genotyped 33 candidate SNPs from nine genes (SI Appendix, Table S1 and SI Materials and Methods) for 757 white British individuals (423 female) who did not report any previous psychological conditions for which they had received treatment. For analysis, we used PLINK, a software package for genetic analysis. PLINK allows us to test simultaneously for three alternative allelic conformations [additivity (add), dominance (domdev), and heterozygotic (geno_2df) effects]. We also checked for interactive effects with sex and age; whereas simple associations between sociality and sex or age are not themselves of direct interest in this study, we nonetheless report these results.

Results
There were significant associations (P < 0.05) between SNPs and all of the sociality measures across the three domains (SI Appendix, Table S2). Fig. 1 shows graphs for one representative SNP from each gene in each of the three domains of sociality, and Fig. 2 provides an overall summary of the significant results in the form of a heat map.

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Dyadic relationships</th>
<th>Wider network</th>
</tr>
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<tbody>
<tr>
<td>Testosterone</td>
<td>25.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>β-endorphin</td>
<td>30.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>12.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>4.0%</td>
<td>45.0%</td>
</tr>
<tr>
<td>Dopamine</td>
<td>12.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Serotonin</td>
<td>0.0%</td>
<td>0.0%</td>
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Fig. 2. Heat map showing percentage of SNPs for each neuropeptide that is significantly associated with behavioral indices of the three domains of sociality (disposition, relationships, and wider network). Number of SNPs in each case are as follows: testosterone, 1; endorphin, 5; vasopressin, 2; oxytocin, 10; dopamine, 4; and serotonin, 2. Number of scales are as follows: disposition, 4; relationship quality, 2; and network, 2.

Disposition. One OPRM1 SNP, rs3778151, showed a significant effect of genotype on anxious attachment (geno_2df, P = 0.025; Fig. 1), whereas another, rs648893, showed an interaction effect between the additive model and sex (add x sex, P = 0.049). One OXTR SNP (rs237897) also showed a significant positive effect on anxious attachment (geno_2df, P = 0.017). No SNPs showed significant associations with avoidant attachment. The AR SNP showed a significant negative additive effect on anxious attachment (add, P = 0.009, Fig. 1). Although the OPRM1 SNPs remained significantly associated with anxious attachment in models controlling for AR rs6152 or OXTR rs237897, neither the AR or OXTR SNPs were significantly associated with anxious attachment when controlling for the other SNP.

In terms of the empathy measures, OPRM1 rs3778151 was found to have a significant nonlinear relationship with Empathy Quotient (EQ) (domdev, P = 0.025), with the negative effect suggesting that the minor allele has lower EQ scores than expected from an additive model. In addition, the ANNK1 variant rs1800497 showed a significant effect on EQ (geno_2df, P = 0.46). OPRM1 rs3778151 also had a significant additive effect with sex on Reading the Mind in the Eyes Test (RMET) scores (add x sex, P < 0.001, as did AVP1ra1 rs11174811 (Fig. 1: add x sex, P = 0.021), whereas OXTR rs2228485 had a nonlinear effect on RMET (domdev, P = 0.049). The AVP1ra1 and OPRM1 SNPs remained significantly associated with RMET when controlling for OXTR rs2228485, but rs2268490 (Fig. 1), rs237887, and rs13316193 (Fig. 1) showed a significant partial relationship when AVP1ra1 was taken into account. AVP1ra1 remained significantly associated with RMET when OPRM1 rs1799971 was included in the model. However, OPRM1 rs3778151 SNP was not significantly linked to EQ once ANNK1 rs1800497 was included in the model, but the latter did not show a significant partial effect either.

Dyadic Relationships. Two OPRM1 SNPs showed significant effects on RAS scores of relationship quality (rs2075572: domdev x sex, P = 0.027; Rs648893: geno_2df, P = 0.036), as did two OXTR SNPS: rs2268490 (domdev, P = 0.032) and rs4686302 (geno_2df, P = 0.025), whereas a third OXTR SNP, rs2254298, showed a trend toward significance (geno_2df, P = 0.052). The OPRM1 SNPs remained significantly associated with RAS independently of the OXTR SNPs, but the opposite was not true.

Seven of the 10 OXTR SNPs were found to have significant associations with SOI-R scores: rs237887 (additive x sex, P = 0.014; Fig. 1), rs2268490 (geno_2df, P = 0.046), rs2254298 (geno_2df, P = 0.046), rs13316193 (geno_2df, P = 0.046), rs53576 (domdev, P = 0.035), rs237897 (domdev x sex, P = 0.034), and rs4686302 (add x sex, P = 0.047). DRD1 rs265981 was also found to interact with sex and be linked to SOI-R scores (domdev x sex, P = 0.039). OXTR rs237887, rs13316193, rs53576, rs237897, and rs4686302 remained significantly associated with SOI-R scores independently of the DRD1 SNP rs265981, and the latter remained significantly associated with SOI-R independently of the OXTR SNPs that were significantly linked to this measure.

Wider Network. In terms of personal network size, there were significant associations with OXTR rs237887 (geno_2df, P = 0.025), DRD2 SNP rs648893 (add x sex, P = 0.006), and the HTR1a SNP rs6295 (domdev x sex, P = 0.012, Fig. 1). Both DRD2 and HTR1a remained significantly associated with network size when models also controlled for OXTR variation, but OXTR SNPs did not show significant partial effects in these models.

For feelings of connection to their local community [measured using Aron’s Inclusion of Other in Self (IOS) scale] (49), significant associations were found for OPRM1 rs1799971 (domdev, P = 0.027), OXTR rs53576 (domdev, P = 0.025), and DRD2 rs1076560 (add x sex = 0.029, Fig. 1) and ANNK1 rs1800497 (downstream from DRD2; add x sex, P = 0.029). It should be noted that due to smaller numbers of minor allele homozygotes, the variance for this
group is greater than for carriers of the major allele for both rs1076560 (see Fig. 1) and rs1800497. Although OPRM1 rs1799971 did not remain significantly associated with IOS scores when controlling for the variance in OXTR and DRD2/ANKK1, both the OXTR and DRD2/ANKK1 SNPs remained significantly associated with IOS in models that controlled for rs1799971 or each other.

Overall Distribution. Running a large number of statistical tests risks inflating significance levels; however, we used an optimized permutation test that is generally considered to be conservative (SI Appendix). Moreover, less than 18% of possible relationships between genes and behaviors are in fact significant (many of which do not survive controlling for the influence of other neuropeptides).

Of greater interest, however, is whether the various neuropeptides are equally effective in all domains. To assess this question, we can treat the data in Fig. 2 as a straightforward contingency table, with a P value of 0.05 as a convenient criterion for inclusion. These data are not subject to multiple comparisons effects because the P value is simply a criterion for a binary partition of the dataset (SI Appendix). The distribution of significant effects shown in Fig. 2 is highly nonrandom ($\chi^2 = 51.7$, df = 10, $P < 0.0001$), with disproportionately higher frequencies than expected for endorphins, oxytocin, and dopamine. Partitioning $\chi^2$ for these three neuropeptides yields nonsignificant (i.e., random) distributions across the three social domains for endorphins ($\chi^2 = 4.7$, df = 2, $P = 0.097$) and dopamine ($\chi^2 = 0.7$, df = 2, $P = 0.716$), but a significantly nonrandom distribution for oxytocin ($\chi^2 = 7.5$, df = 2, $P = 0.023$). In sum, oxytocin is very specific in its functional domain (romantic relationships), whereas endorphins and dopamine both have broad spectrum effects.

Discussion

Hitherto, the majority of studies looking at genetic variation and sociality have focused on one neuropeptide (usually oxytocin), thereby ignoring confounds due to the potentially parallel roles of other neuropeptides. In addition, researchers have invariably focused on a narrow facet of sociality. As a result, it remains unclear whether particular neuropeptides have a general role in creating or sustaining social relationships or are more closely allied to specific domains of social engagement. By simultaneously comparing many of the candidate receptor genes previously independently linked to human social behavior, and in the context of three different social domains, this study provides a more nuanced picture.

Our results suggest that anxious, but not avoidant, attachment is associated with OPRM1, AR, and OXTR variation. Both measures of empathy were related to OPRM1 genotypes; there were significant associations with empathy (RMET) for three of five OPRM1 SNPs, one of which was also significantly associated with the EQ. However, only OPRM1 remained significant when controlling for other significant genes. Romantic relationship quality and sexual attitudes/behavior were significantly and strongly associated with variation in OXTR (70% of SNPs showing a significant effect on sexual orientation, SOI-R), as well as two OPRM1 SNPs and the DRD1 SNP. The OXTR SNPs rs2268490 and rs4686302 were linked to both RAS and SOI-R scores, and OXTR rs2254298 was significantly linked to SOI-R (and approached significance in relation to RAS, an index of relationship quality), though these relationships did not survive controlling for OPRM1. Vasopressin had a significant association only with RAS, confirming an earlier finding that it is predictive of high levels of promiscuity (39), but in a way suggestive of impulsivity or lack of inhibition rather than promiscuity per se (act first, and think about the consequences afterward). The two measures of engagement in a wider social network were related to variation in HTR1a (network size) and the dopamine genes DRD2 (network size: rs4648317; IOS: rs1076560) and ANKK1 (IOS), as well as one OPRM1 SNP (IOS) and two OXTR SNPs (one for IOS, one for social network size).

As has previously been found in both voles and humans, we found strong associations between oxytocin receptor variation and romantic relationships. Although a smaller number of OXTR SNPs were found to be linked to measures of wider social engagement (corroborating some previous findings) (50), it may be that this relationship is mediated through the partner’s network. An individual’s ability to empathize, and their typical way of relating in close relationships (their attachment style), is also likely to feed into their romantic relationships, and a small number of OXTR SNPs were found to be tied to attachment style in close friendships and measures of empathy in this study, echoing past work (30, 31). Whereas previous studies focused on empathy or attachment independently of other social domains, such that the unique effects of OXTR variation on different facets of sociability could not be assessed, the current study provides convincing evidence that the primary impact of OXTR variation in the human social sphere is specific to reproductive relationships (romantic/sexual and parent–child), as it is in voles and other small mammals. Note, however, that, despite its prominence in the literature, the significance of the role played by oxytocin often disappears when we control for endorphins, even in the context of romantic relationships, suggesting that endorphins may be more important than oxytocin even here. This finding may support the suggestion that the neurochemical mechanism underpinning long-term relationships is the endogenous opioid system rather than oxytocin (a neurochemical, which is incapable of maintaining a long-term impact on behavior and may exert most of its influence at the commencement of romantic relationships) (35, 51).

Dopamine receptor variants were most closely linked with social engagement beyond the dyad. Social network size was also the only index of sociability that showed a significant association with variation in serotonin receptor 1a. To our knowledge, dopamine function has never before been studied in relation to social interaction beyond the dyad, with past research showing links only to romantic relationships or parenting (13, 39, 40). By comparing different social domains, we provide the insight that variation in genes associated with dopamine receptor 2 may be predominantly linked to engagement in wider social groups. This relationship may reflect the fact that many of our behaviors involve activities (laughter, singing, dancing) (21, 22, 52) that are pleasurable. In contrast, variation in the DRD1 variant rs265981 was linked only to individual differences in socioeconomic orientation, and this relationship remained robust even when controlling for variance in OXTR. Whereas the second finding makes sense in terms of the well-known reward function of dopamine, the mechanism facilitating the first finding is not at all clear and begs investigation.

In contrast, OPRM1 variations were most strongly linked to individual differences in attachment style and the ability to identify emotional facial expressions (RMET), as well as a self-report measure of empathy (EQ). The density of μ-opioid receptors has previously been found to be related to attachment style, though mainly with the avoidance dimension (32). Importantly, OPRM1 variation was also associated with both dyadic relationship quality and community integration, which may reflect the way social dispositions affect these higher-level outcomes. Perhaps because of its role in the pain system, much previous work on β-endorphin has focused on “social pain” resulting from social rejection (53, 54). However, it is becoming increasingly clear that β-endorphin is also involved in the creation and maintenance of social relationships (19, 51), and this may be reflected in the finding that OPRM1 variation is linked to the extent to which individuals experience social rewards (31) rather than to pain per se. Recent PET work in humans has confirmed that the μ-opioid receptors are activated by touch by a
romantic partner (20), while, in synchronous group activities, endorphin release is thought to play a key part in bonding group members (21, 22). As with the effects of allostrogen in non-human primates (17, 18), it may be the reward effects of opiates that is important in this context or something to do with a sense of trust engendered by the opioid-induced feelings of relaxation and calmness in the presence of another individual. The finding that OPRM1 variation is most strongly linked to the ability to empathize hints at one mechanism by which β-endorphin creates social connections, namely through increasing the capacity to read others’ emotions and put oneself in their place. Variation in the ability to empathize likely impacts on romantic relationship quality as well, going some way to explaining our finding that OPRM1 variation was also associated with relationship quality (RAS) scores. Similarly, the fact that one of the OPRM1 SNPs and DRD2 variation correlates with degree of community integration may reflect known interactions between the dopamine and endorphin systems in both humans and rodents (40, 55, 56), whereby endorphin activation may itself trigger a dopamine response. It may be that variation in individuals’ capacities to empathize (linked with endorphin function) feeds into their dopamine-mediated ability to maintain support networks within their community.

In sum, three important conclusions emerge: (i) most neuropeptides are associated with one particular social domain, and (ii) only endorphin and dopamine are widely active across all three domains. These findings reinforce recent research suggesting the wide-ranging influence of both dopamine and endorphin in the formation of bonds within a range of social contexts. In part, this may reflect an interaction with oxytocin and testosterone and the close structural relationship between the oxytocin- and endorphin-producing neurons in the hypothalamus (19) and the limbic dopaminergic reward pathway (57).

Given the evidence that poor relationships and network disintegration lead to morbidity and mortality risks even greater than those of alcohol abuse, lack of exercise, and smoking (1), our findings have important practical implications. Whereas the deleterious effects of these other risk factors are well established in the public health literature, neurobiological underpinnings, and functional implications remain at best patchy at best. In addition, our results may have wider implications for understanding the evolution of sociality, in that it may be the reward effects of opiates that is important in this context or something to do with a sense of trust engendered by the opioid-induced feelings of relaxation and calmness in the presence of another individual. The finding that OPRM1 variation is most strongly linked to the ability to empathize hints at one mechanism by which β-endorphin creates social connections, namely through increasing the capacity to read others’ emotions and put oneself in their place.

Variation was also associated with SQRT ($\sqrt{P}$) for OPRM1, 3 SNPs for OXT (oxytocin), 3 SNPs for AVPR1A (vasopressin), 6 SNPs for OPRM1 (β-endorphins), 3 SNPs for DRD2, 3 for DRD2, 1 for ANKK1 (located downstream from DRD2) (dopamine), 1 SNP for HTR1A, 2 for HTR2A (serotonin), and 1 SNP for AR (testosterone).

Materials and Methods

For full details, see SI Appendix. For the data, see Dataset S1.

Participants. The final sample consisted of 757 individuals (423 female) aged 18–65 (mean 40.6) years who identified themselves as Caucasian, were physically healthy, did not use recreational drugs, were not on drug replacement therapy, or taking medication for a psychological condition. Ethics approval for the study was granted by the University of Oxford Central Ethics Committee (Ref: MS-IDREC-C2-2015-005). All participants provided written informed consent.

Questionnaires. Participants completed self-report questionnaires presented digitally on mobile devices. These included: the RMET, the EQ scale, and the Experiences of Close Relationships scale as indices of social disposition; the SOI-R and the RAS as indices of dyadic relationship quality; and the number of close friends and family index and the IOS scale as indices of wider network engagement. For details, see SI Appendix.

Genotyping. A single sample of saliva was taken from each participant using an OraGeneDNA collection kit (2 mL of saliva), which renders the samples acellular. The DNA was extracted using Kleargene technology. We genotyped 33 candidate SNPs from nine genes (SI Appendix, Table S1). These included 11 candidate SNPs for OXTR (oxytocin), 3 SNPs for AVPR1A (vasopressin), 6 SNPs for OPRM1 (β-endorphins), 3 SNPs for DRD2, 3 for DRD2, 1 for ANKK1 (located downstream from DRD2) (dopamine), 1 SNP for HTR1A, 2 for HTR2A (serotonin), and 1 SNP for AR (testosterone).

Analysis. Analysis was conducted using PLINK version 1.9 (SI Appendix shows further details). Participants with less than 90% coverage were removed (11 in total). All of the SNPs had at least 95% coverage. Only 4 of the SNPs differed significantly from Hardy–Weinberg equilibrium in the full sample (OXTR rs237897 $P = 0.048$, OXTR rs2228485 $P = 0.005$, DRD1 rs265981 $P = 0.007$, and OPRM1 rs648893 $P = 0.01$). Clustering according to linkage disequilibrium (LD) pruned 7 SNPs from the main sample and 2 were excluded due to very low minor allele frequencies, leaving 10 OXT SNPs, 2 AVPR1A SNPs, 5 OPRM1 SNPs, 1 AR SNP, 1 DRD1 SNP, 2 DRD2 SNPs, 1 ANKK1 SNP, and the HTR1A and HTR2A SNPs in the final analysis. We used an optimized permutation test to control for multiple testing. Genotypic models were applied to all of the diploid SNPs, including add, dom, and geno_Daf, as well as age, sex, and the sex * genotype interactions. To test the independence of associations between particular SNPs and specific social variables, we ran post hoc models that controlled for the effect of additional SNPs that also showed significant associations with the same social variable.

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