Oxytocin receptor gene (*OXTR*) is related to psychological resources

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Psychological resources—optimism, mastery, and self-esteem—buffer the deleterious effects of stress and are predictors of neurophysiological and psychological health-related outcomes. These resources have been shown to be highly heritable, yet the genetic basis for this heritability remains unknown. Here, we report a link between the oxytocin receptor (*OXTR*) SNP rs53576 and psychological resources, such that carriers of the "A" allele have lower levels of optimism, mastery, and self-esteem, relative to G/G homozygotes. *OXTR* was also associated with depressive symptomatology. Mediation analysis indicates that the effects of *OXTR* on depressive symptoms may be largely mediated by the influence of *OXTR* on psychological resources.

Psychological resources refer to individual differences that are directly predictive of physical and psychological health (1–3). The most well-studied of these resources are optimism, mastery, and self-esteem (4–6). Optimism refers to the extent to which people hold favorable expectations about the future (4, 7); as a dispositional variable, it reflects positive expectations across a broad array of outcomes. Mastery involves the belief that one can determine one's own behavior, influence one's environment, and bring about desired outcomes; it also has a strong dispositional component (8). Self-esteem is a dispositional concept that refers to a person's overall evaluation of self-worth (9). Previous research has established that these three resources are closely interrelated (4, 6, 10) and, both independently and as a cluster, they are known to buffer the effects of stressful life events and experimentally manipulated stressors on physiological stress responses (for reviews, see refs. 2 and 5). Moreover, considerable research demonstrates that susceptibility to depression and other forms of psychological distress is lower among individuals high in optimism (4, 11, 12), mastery (13, 14), and self-esteem (15–17).

The model guiding the present research attributes the origins of psychological resources to developmental and genetic factors (2, 5). Aspects of the early environment that affect the development of these resources include family socioeconomic status (15, 18, 19), childhood adversities (20), and parental practices (18, 20). Psychological resources may continue to be influenced by life experiences in adolescence, young adulthood, and beyond (18), but less research is available on this question. Although we acknowledge the importance of these environmental factors in the developmental origins of psychological resources, the present research is primarily concerned with the second primary source: human genetics.

Twin studies have shown that a large proportion of the variance in psychological resources is heritable (21–25). The extant research suggests a narrow range for the heritability of optimism, with independent reports ranging from 20% (21) to 36% (24). Estimates for the heritability of self-esteem range more widely, from a low of 29% (23) to a high of 73% (22). Research on the behavioral genetics of mastery has not, to our knowledge, been conducted. Despite evidence for the heritability of psychological resources, the genetic bases of this heritability have yet to be elucidated.

The oxytocin system appears to play a role in socioemotional functioning and positive emotion (26–29). Located on chromosome 3p25.3, *OXTR* codes for the oxytocin receptor, the receptor by which the neurohormone oxytocin exerts a range of effects throughout the body and the brain (30; for review, see ref. 31). Several studies report associations of the SNP rs53576, located in intron 3 of *OXTR*, with stress-related and psychological traits, with the majority suggesting that carriers of the A allele (i.e., A/G and A/A genotypes) have an increased sensitivity to stress, reduced social skills, and more negative mental health outcomes relative to individuals with two copies of the G allele (32–38; but see ref. 39). For example, Lucht et al. (35) found that adult A/A homozygotes had lower self-reported positive affect and higher negative affect and loneliness. Another study found that G/G homozygotes outperformed carriers of the A allele of rs53576 on the ability to detect emotion from pictures of human faces showing only the eyes (37). Other research has found that among mothers of recently born infants, *OXTR* rs53576 A-allele carriers demonstrated lower maternal sensitivity relative to G-allele carriers (32). A subsequent study of reproductive-age women without children revealed greater heart-rate response to baby cries in GG women relative to A-allele carriers (36), which was interpreted as indicating greater sensitivity to the baby's needs and emotional state among GGs. Taken together, these findings suggest that *OXTR* rs53576 may play a role in human social behaviors and psychological resources (see also refs. 26–29).

Although these are intriguing and consistent findings, it is difficult to assess their meaning without a functional account of how variation at the rs53576 locus influences behavior via the circuits and networks of the brain. Although not complete, a picture has begun to emerge regarding the consequences of variation at this SNP for the structure and function of brain areas involved in a wide range of cognitive and social-cognitive processes. For example, Tost et al. (38) found that A-allele carriers had reduced volume of the hypothalamus and increased structural (correlated structure sizes) and functional (coactivation in response to faces picturing emotions) connectivity of the hypothalamus to both the amygdala and the dorsal anterior cingulate cortex (dACC). These brain regions have been tied previously to stress responses (10, 40, 41), which have also been associated with rs53576 (37) and vulnerability to social distress (dACC) (40–42). As such, these findings provide suggestive evidence for a biological stress-related phenotype associated with *OXTR* rs53576. The link between *OXTR* and the dACC is especially interesting in light of findings that self-esteem attenuates dACC activation in response to social rejection (42). The connection to the amygdala is consistent with previous research showing that intranasal administration of oxytocin modulates activation of the amygdala to emotional and neutral faces (42–46). Petrovic et al. (46) also found an effect of intranasal oxytocin on dACC activation. Thus, a growing literature supports a role for *OXTR* in the structure and function of the amygdala, hypothalamus, and

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dACC, structures of known relevance to psychological resources, and their influence on stress processes (10, 40–42).

On the basis of this literature, we hypothesized that variation in *OXTR* at rs53576 may be associated with psychological resources, such that self-esteem, optimism, and mastery would be higher among G/G homozygotes relative to carriers of the A allele. Additionally, because the A allele may confer risk for lower psychological resources, which are protective against stress and negative self-views, we predicted that *OXTR* A allele carriers would have higher levels of depressive symptomatology, which may potentially be mediated by (lack of) psychological resources.

Results

The distribution of genotypes for *OXTR* was 108 G/Gs (33.1%), 153 A/Gs (46.9%), and 65 A/As (19.9%). This distribution does not deviate from the Hardy-Weinberg equilibrium, $\chi^2(1) = 0.65$, $P = 0.419$.

To test the relation between *OXTR* and psychological resources and depressive symptomatology, we computed the scale means for the three resource measures and a sum-score for the depression measure (the Beck Depression Inventory-IA, BDI-IA) (47). In addition, we created factor scores for psychological resources and depressive symptomatology on the basis of an exploratory factor analysis (see *Methods*, *SI Text*, and Table S1 for more details). Descriptive statistics of the measures are presented in Table 1, along with the correlations between the different scales and factors.

Tests of the hypothesized association between *OXTR* and psychological resources are presented in Table 2. The results show that A-allele carriers (M = 3.53, SD = 0.85) were lower than G allele homozygotes (M = 3.74, SD = 0.79) in optimism [$t(324) = 2.17$, $P = 0.031$, $d = 0.26$, $R^2 = 0.016$], mastery [M = 3.06, SD = 0.47 vs. M = 3.17, SD = 0.44), $t(324) = 2.03$, $P = 0.043$, $d = 0.24$, $R^2 = 0.014$], and self-esteem [$M = 3.20$, SD = 0.54 vs. M = 3.38, SD = 0.46), $t(324) = 2.91$, $P = 0.004$, $d = 0.34$, $R^2 = 0.029$]. *OXTR* was also significantly related to the resources factor, such that A-allele carriers had lower levels of psychological resources relative to G-allele homozygotes: $t(324) = 3.07$, $P = 0.002$, $d = 0.36$, $R^2 = 0.032$. *OXTR* rs53576 appears to account for between 4.4% (0.016/0.360) and 8% (0.016/0.200) of the genetic variance in optimism. Likewise, *OXTR* may account for between 4% (0.029/0.730) and 10% (0.029/0.290) of the genetic variance in self-esteem. A-allele carriers also had significantly greater levels of depressive symptomatology for the measure of depression [for BDI-IA sum, $t(277.6) = 2.56$, $P = 0.011$, $d = 0.27$, $R^2 = 0.018$; for depressive symptomatology factor, $t(266.6) = 2.51$, $P = 0.013$, $d = 0.27$, $R^2 = 0.018$].Variances for the BDI-IA sum and factor score were significantly unequal between G/G homozygotes and A-allele carriers according to Levene's test for equality of variances. The *t*-statistics, *df*, and *P* values provided are corrected for this violation of the equality of variances assumption.

The allelic distribution differed between the Asian and non-Asian participants [$\chi^2(2) = 51.6$, $P < 0.0001$], with lower prevalence of G-allele homozygotes among Asians and conversely lower prevalence of A-allele homozygotes among non-Asians (Table S2). This difference is consistent with past reports in the literature (33, 34, 48). In addition, levels of psychological resources were lower and levels of depressive symptomatology were higher in the Asian participants (Table S3). The overall pattern of relations between *OXTR* genotypes and psychological resources, however, was the same for Asians and non-Asians (*SI Text* and Table S4). Additional analyses for ethnicity and analyses for sex appear in the *SI Text* and Table S5.

Mediation Analysis. The effect of *OXTR* on depressive symptomatology may be indirectly mediated by psychological resources, which are known to be protective against depression (4, 6, 11–17). We tested this possibility using mediation analysis (49). The hypothesized mediation model is presented in Fig. 1.

Simultaneous regression of the depressive symptomatology factor on *OXTR* and the psychological resources factor suggested that resources may fully mediate the effect of *OXTR* on distress. Specifically, the effect of *OXTR* on depressive symptomatology dropped from $\beta = 0.127$ ($P = 0.021$) without resources in the model to $\beta = 0.050$ ($P = 0.319$) with resources in the model, and the effect of resources on depressive symptomatology was highly significant, $\beta = -0.462$ ($P < 0.001$). The *OXTR* A allele carriers had lower levels of psychological resources, and the lower level of resources was in turn associated with higher levels of depression. These results are summarized in Fig. 1. The indirect effect of *OXTR* on distress as mediated by resources was significant (Sobel's $Z = 2.91$, $P = 0.004$). A model-based bootstrap (49) using 1,000 samples from the original data revealed a mean indirect effect of 0.0835 (SE = 0.0297), with a 95% confidence interval of 0.0295, 0.1442. Because the value 0 lies outside this interval, we can reject the null hypothesis of no indirect effect. As such, the findings are supportive of the hypothesis that *OXTR* affects depressive symptomatology by means of its influence on psychological resources.

An alternative model testing whether the relation of *OXTR* to psychological resources is mediated by depressive symptomatology suggested partial mediation, as the effect of the *OXTR* A allele on psychological resources remained significant ($\beta = -0.110$, $P = 0.026$; from $\beta = -0.168$, $P = 0.002$) when depressive symptomatology was added to the model, and yet the indirect effect remained significant (Sobel's $Z = 2.26$, $P = 0.024$). The *OXTR* A-allele carriers had higher levels of depressive symptomatology, which was in turn associated with lower levels of psychological resources. A model-based bootstrap using 1,000 samples from the original data revealed a mean indirect effect of −0.0610 (SE = 0.0244), with a 95% confidence interval of −0.0137, −0.1081. The fact that the value 0 lies outside this interval allows us to reject the null hypothesis of no indirect effect. Thus, al-

Table 1. Descriptive statistics for measures of psychological resources and depression

Scale	No. of Items	α	Range	Mean	SD	Correlations 1	2	3	4	5
Self-esteem	10	0.89	1.5–4.0	3.26	0.52	1.00				
Mastery	7	0.76	1.7–4.0	3.09	0.46	0.50	1.00			
Optimism	6	0.82	1.2–5.0	3.60	0.84	0.54	0.50	1.00		
BDI-IA, sum	20*	0.84	0.0–42.0	6.06	5.60	−0.54	−0.43	−0.47	1.00	
Psychological resources factor	21†	0.91	−3.3–1.9	0.00	1.00	0.90	0.73	0.80	−0.58	1.00
BDI-IA, factor	14‡	0.79	−1.0–6.6	0.00	1.00	−0.43	-0.39	−0.39	0.96	−0.47

*The BDI-IA contains 21 items; however, one item (suicidality) was dropped at the request of the Institutional Review Board.
†On the basis of the exploratory factor analysis (Table S1) (48), 21 items were used to compute the resources factor.
‡On the basis of the exploratory factor analysis (Table S1) (48), 14 items were used to compute the BDI-IA factor.

Table 2. Means for psychosocial resources by *OXTR* genotype

Scale	G/G (n = 108)	G/A/A/A (n = 218)	Significance
Self-esteem	3.38 (0.46)	3.20 (0.54)	P = 0.004
Mastery	3.17 (0.44)	3.06 (0.47)	P = 0.043
Optimism	3.74 (0.79)	3.53 (0.85)	P = 0.031
BDI-IA, sum*	5.05 (4.45)	6.56 (6.04)	P = 0.011
Psychological resources, factor score	0.238 (0.91)	−0.118 (1.02)	P = 0.002
BDI-IA, factor score*	−0.181 (0.83)	0.089 (1.07)	P = 0.013

Cell values indicate group means. SDs are in parentheses.
*For these variables, the equality of variances assumption was violated according to Levene's test. Corrected P values are provided.

though the indirect effect is smaller than in the previous analysis, there is evidence for partial mediation of the effect of *OXTR* on psychological resources by depressive symptomatology. However, because the direct effect of *OXTR* on resources is still significant when depressive symptomatology is in the model, the mediation is modest, whereas the results from the previous model suggest full mediation of the effect of *OXTR* on symptomatology via psychological resources.

Discussion

Psychological resources of optimism, mastery, and self-esteem have been found to be significant predictors of effective stress management, neurophysiological responses to stress, and physical and psychological health-related outcomes in previous research (2, 3, 5, 7). Researchers have long known that these psychological resources have genetic bases (21–25), but investigations have not previously identified which genes may be implicated. The present results suggest that *OXTR* is one gene that is linked to these resources. Carriers of the A allele of the *OXTR* SNP rs53576 were less optimistic, felt less personal mastery, and had lower levels of self-esteem. In addition, carriers of the A allele had higher levels of depressive symptomatology. Mediation analysis suggested that the effect of *OXTR* on depression may be mediated by psychological resources.

Previous research on *OXTR* and on the oxytocin system more generally has underscored connections between the oxytocin system and social affiliation and bonding (26–29), and links between oxytocin and positive emotional experiences have been explored primarily within a social context (cf. 26). To our knowledge, the present findings are unique in linking *OXTR* directly to individual psychological resources, suggesting an expanded role for the oxytocin system in the management of stress and distress that does not depend on social contact (see also refs. 33 and 37). Nonetheless, psychological resources are likely to facilitate social bonding, and this may be one route whereby the oxytocin system promotes social contact.

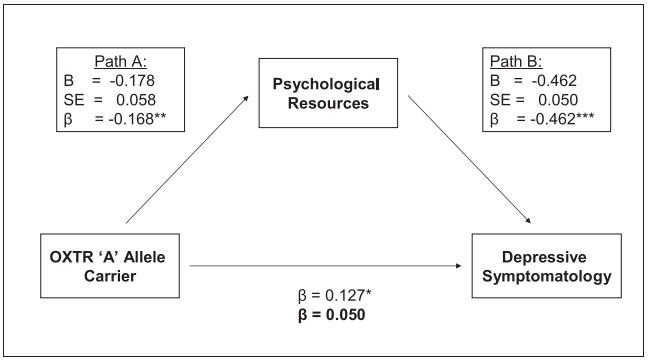

Fig. 1. Mediation model of *OXTR*, psychological resources and depression. For the path from *OXTR* to depressive symptomatology, the upper β-weight indicates the effect without resources in the model and the lower β-weight indicates the effect with resources in the model. *P < 0.05, **P < 0.01, ***P < 0.001.

The association of variation in intron 3 of the *OXTR* with psychological resources and depressive symptomatology is consistent with an emerging body of evidence associating variation in this region with similar psychological phenotypes (35, 50), psychological responses in experimental studies (33, 34, 37), and neural reactivity to emotional stimuli (38). Although the precise molecular mechanisms responsible for these associations are unclear, intron 3 is emerging as an important region in the regulation of *OXTR* expression. For example, variation in intron 3 has been associated with *OXTR* expression in both peripheral blood cells and the amygdala (51), a brain region exhibiting volumetric differences associated with *OXTR* intron 3 variation (52, 53). Further support for intron 3 being involved in the regulation of *OXTR* expression comes from epigenetic studies. Differential methylation of a CpG island within intron 3 is associated with relative levels of *OXTR* expression between peripheral blood cells and myometrial cells (54). Such effects may be relevant for *OXTR* expression in the brain, as Gregory et al. (55) found that methylation patterns within the *OXTR* were similar in peripheral blood cells and the temporal cortex. The methylation pattern within the *OXTR* promoter, but not intron 3, was associated with *OXTR* expression in this cortical area. The potential interacting influences of polymorphic variation and epigenetic modifications on *OXTR* expression will be an interesting area for future research.

The present study also highlights the need for additional research on the genetic bases of positive well-being and psychological flourishing. Ample evidence demonstrates the heritability of psychological resources and related constructs, yet few studies have explored the molecular genetic basis of this heritability. The results presented here represent a step toward understanding the genetics of positive well-being, but many unanswered questions remain. Consequently, this will likely be a source of productive research in the future.

Limitations to the present research should be noted. The cross-sectional design of the study precludes definitive conclusions regarding the causal relations among the *OXTR* polymorphism, psychological resources, and depression. In particular, the mediation analyses can only disconfirm hypothetical causal relations, not confirm their presence. Accordingly, one cannot completely reject the alternative model in which the effect of *OXTR* on psychological resources is mediated by depressive symptomatology. Nonetheless, only partial mediation was indicated, and some longitudinal research supports a causal relation between lower levels of psychological resources and subsequent increases in the incidence of depression (12, 16, 17).

In conclusion, scientists have long known that psychological resources protect against the psychological and physiological ravages of stress. Research has also made clear that there are genetic bases to these resources. The present study identifies

OXTR as one genetic contributor and also provides evidence that psychological resources may mediate the relation between *OXTR* and depressive symptomatology.

Methods

Sample. Participants were 344 students and employees of a large Western university recruited in two cohorts for participation in a study of stress and coping (further details on sample characteristics can be found in refs. 10 and 56 for cohorts 1 and 2, respectively). Data were collected between 2004 and 2007. The sample was genotyped for *OXTR* for the purpose of this study, and no previous publications have reported on this data. Participants were recruited via posted flyers advertising compensation of $125; the high level of compensation was because of participants completing several subsequent tasks that were not relevant to the present investigation. Recruitment and study procedures were approved by the University of California Los Angeles Institutional Review Board.

After excluding participants who were missing information for *OXTR* genotype ($n = 18$), the final sample consisted of 326 individuals. Ages for the final sample ranged from 18 to 36, with a mean of 21.3. There were 199 female participants (61.0%) and 127 male participants (39.0%). Of the participants, 117 (35.9% of the sample) were of Asian ancestry, 87 were Europeans or European-Americans (26.7%), 49 were Hispanic (15.0%), 9 were African-American (2.8%), 34 reported their ethnicity as "other" (10.4%) (usually Indian, Pakistani, or Middle Eastern ancestry), and 30 were "mixed" (9.2%).

Missing Data. To retain all successfully genotyped participants, missing responses to the psychological resources measures and the BDI-IA were imputed using the multiple imputation procedure, as implemented in AMELIA II (57). This procedure is preferred to more traditional approaches to imputation, such as mean replacement (cf. ref. 58). All statistics reported in the article and *SI Text* were computed using the imputed data.

Measures. Optimism was measured using the Life Orientation Test (LOT-R, 4), a six-item measure of dispositional optimism. Personal control was measured by the Pearlin Mastery scale, a seven-item measure of perceived control over one's circumstances and environment (8). Self-esteem was measured using the Rosenberg Self-Esteem Scale (9), a widely used 10-item measure of self-regard and perceived self-worth. Depressive symptomatology was measured with the BDI-IA (47), a 21-item inventory of depressive symptoms experienced in the past week. All of these measures are widely used and well-validated standardized instruments. Details regarding the internal reliabilities of the scales in the present sample are presented in Table 1, along with scale ranges, means, and SDs. Means were computed for the optimism, mastery and self-esteem scales, and the BDI-IA was summed to facilitate comparison with past studies using the BDI.

Factor Analysis and Factor Scores. Exploratory factor analysis was conducted on the items from the optimism, mastery, self-esteem, and BDI-IA questionnaires. Two factors were specified for extraction using principal axis factoring with direct oblimin rotation. This analysis yielded two factors corresponding to psychological resources and depressive symptomatology which were significantly negatively correlated ($r = -0.497$, $P < 0.001$) and combined to explain 28.6% of the variance in the 43 items.

Mediation Analysis. Sobel's Z was calculated using a Web-based interactive calculation tool available at http://quantpsy.org/sobel/sobel.htm. Unbiased estimates of the indirect effects and their 95% confidence intervals were obtained via bootstrap analysis using the SPSS macro provided by Preacher and Hayes (49).

Genotyping. In cohort 1, DNA was obtained using the Orasure oral specimen collection device (Orasure Technologies Inc.). Samples were immediately placed on ice in a cooler and transferred within the next few minutes to a freezer. The samples were stored at –20 °C for 12 to 18 mo before being extracted using the Puregene DNA purification kit (Gentra Systems, Inc.). All samples were whole-genome amplified using a GenomiPhi V2 DNA Amplification Kit (GE Healthcare) according to the manufacturer's instructions. For cohort 2, the DNA was collected from saliva with Oragene kits (DNA Genotek) and extracted according to the manufacturer's recommendations. The *OXTR* rs53576 SNP was identified using a 5′ nuclease assay to discriminate between the two alleles (Taqman SNP Genotyping Assay C_3290335_10; Applied Biosystems Inc.). Polymerase chain reactions were performed using 5-μL reaction volumes in 384-well plates with 5 ng of DNA. The standard protocol provided with the kit was followed. End point reads of fluorescence levels were obtained with an ABI 7900HT Sequence Detection System.

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