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ARTICLE

Oxytocin receptor genotype and low economic privilege reverses ventral striatum-social anxiety association

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ABSTRACT

Oxytocin receptor gene (*OXTR*) polymorphisms, lower ventral striatum (VS) response to social stimuli, and lower economic privilege have been independently associated with depression and anxiety. However, the interactions between these risk factors are unknown. One hundred and fifty-seven healthy adult participants genotyped for *OXTR* rs237915 completed a common emotion-matching task during functional magnetic resonance imaging. Past economic privilege and depression and anxiety symptoms were concurrently assessed through validated self-report measures. The data revealed an interaction between rs237915 genotype and economic privilege on the neural response to negative faces. C-carriers showed decreased VS activation and increased connectivity between the VS and ventromedial prefrontal cortex with *increased* economic privilege. TT homozygotes showed the reverse pattern. Low VS response to negative faces predicted increased social anxiety, but only for those with *either* lower economic privilege or the C allele. For those with *both*, low VS response was associated with paradoxically *lower* social anxiety. Findings suggest that economic privilege and *OXTR* rs237915 genotype may calibrate social motivational neural systems for better or worse. While lower VS response to negative faces may generally constitute a risk factor for social anxiety, lower response to social cues may be a benefit for those with dual risk.

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OXTR; rs237915; life history; economic privilege; ventral striatum; social salience; social anxiety

Introduction

Psychopathology is generally marked by disordered social functioning. Social demands are uniquely complex, requiring advanced abilities to recognize, manipulate and respond to socially relevant information. This includes the ability to construct representations between self and others and to use those representations to flexibly guide our own behavior. Disordered social information processing has been found in mood (Douglas & Porter, 2010) and anxiety (Clark & McManus, 2002) disorders. Accumulating data suggests that administering oxytocin promotes social behavior, such as eye gaze (Auyeung et al., 2015), emotion recognition (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), and decreases in social anxiety (Lim & Young, 2006). As such, intranasal oxytocin has been used as treatment for common psychopathology, but with mixed results (MacDonald & Feifel, 2013). Differential response to exogenous oxytocin may be moderated by individual differences in developmental experience and molecular background (Feng et al., 2015).

Administration studies often fail to account for variability in the endogenous oxytocinergic system, in particular that the effects of oxytocin are dependent on expression of its receptor, *OXTR* (Yoshida et al., 2009). Single nucleotide polymorphisms (SNPs) in *OXTR* have been associated with attachment (Strathearn, 2011), risk of mood disorders (Costa et al., 2009), as well as resilience in the face of adversity (Smearman et al., 2016), among others. These same SNPs have been associated with performance on social perception tasks such as face recognition (Skuse et al., 2014) and emotion perception (Lucht et al., 2013; Tost et al., 2010) that can be performed in a neuroimaging context. In turn, we can then assay the neural intermediaries between genetic risk and overt behaviors across the healthy to pathological spectrum (Loth, Carvalho, & Schumann, 2011).

Ventral striatum (VS) is rich in oxytocin receptors, and species-specific differences in social-affiliative behavior, including pair bonding and alloparenting, are related to the level of expression of this receptor (Ross et al., 2009). VS is thought to have generalized functions in the calculation of costs and value, but also plays a key role in responding to (Loth et al., 2014) and integrating (Báez-Mendoza & Schultz, 2013) social

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information. As part of the mesocortical limbic system, VS activation is blunted in anhedonia (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005) and social anxiety during social perceptual and reward tasks (Freitas-Ferrari et al., 2010). Even absent a disorder, blunted VS activation creates additional risk for depression for those who experienced early life stress (Hanson, Hariri, & Williamson, 2015) and in those with a family history of psychopathology (Luking, Pagliaccio, Luby, & Barch, 2016). Given this background, the VS is an obvious region of interest, but successful social information processing requires the coordinated efforts of many brain areas. A comprehensive examination therefore requires consideration of variability in whole brain response and how individual regions interact.

Early life stress interacts with both the oxytocinergic system and VS response to social information to influence individual differences in social behavior. Experiences of childhood maltreatment are associated with enhanced perception of angry faces(Shackman, Shackman, & Pollak, 2007), decreased oxytocin levels in cerebral spinal fluid (Heim et al., 2009), and decreased gray matter in cortico-striatal networks (Cavanagh et al., 2013). Childhood emotional neglect increases adolescent risk for depression, which may be partially mediated through VS response to reward (Hanson et al., 2015). Even in the absence of maltreatment, broad indicators of early life stress like lower economic privilege are associated with increased risk for psychopathology and altered social processing (Gonzalez, Beckes, Chango, Allen, & Coan, 2014). For example, lower neighborhood quality and lower subjective social status are associated with increased negative interpretations of ambiguous social situations (Chen & Paterson, 2006; Gonzalez et al., 2014), a bias found in mood and anxiety disorders. These indicators also moderate VS response to reward (Gonzalez, Allen, & Coan, 2016) and social stimuli (Ly, Haynes, Barter, Weinberger, & Zink, 2011).

Taken together, genetic variability in *OXTR*, neural variability in VS response, and differences in developmental economic privilege likely interact to influence mental health susceptibility. Recently, Loth and colleagues (Loth et al., 2014) identified that adolescent peer problems are independently associated with the interaction between *OXTR* SNP rs237915 and stressful life events, and the interaction between rs237915 and VS response to angry faces. There was also a main effect of genotype on the brain such that CC homozygotes showed attenuated VS activation. However, the study failed to find gene-environment interactions on VS activation or a gene-brain-environment interaction on the behavioral phenotype. Furthermore, despite including more well-researched *OXTR* SNPs in linkage disequilibrium (e.g., rs53576), Loth identified rs237915 as most related to neural variability within a social paradigm, suggesting that this SNP is a sensitive assay from which to probe gene by environment interactions on the brain. We sought to replicate and extend these findings using a confirmatory approach. Specifically, we examined the interaction between genotype, VS activation to negative faces, and economic privilege on mental health outcomes using validated clinical measures of anxiety and depression. We identified a gene-brain-environment interaction that supports a role for *OXTR* genotype, VS response to negative social stimuli, and economic privilege in conferring risk for common psychopathology. Furthermore, an interaction between *OXTR* genotype and economic privilege that influences VS connectivity emerged, suggesting that differences in network architecture may be influenced by this gene-environment interaction. These data highlight the necessity for considering both environmental influences and endophenotypes when exploring how behavioral phenotypes vary with genetic makeup.

Methods and materials

Participants

Participants were drawn from a larger epigenetics study (N = 212) consisting of self-reported Caucasian participants between the ages of 18 – 30. The sample was restricted to Caucasian participants to prevent population stratification. The study was approved by the University of Virginia's Internal Review Board for Health Sciences Research and all participant and data procedures were performed in accordance with guidelines and regulations. Participants were given thorough accessible written explanation of study procedures, and they signed informed consent forms in accordance with guidelines. Participants were then screened for MRI counter-indications such as possible pregnancy or ferromagnetic metals in their bodies. Only participants with genotype, fMRI, and Life History Questionnaire data where included in this analysis (N = 157, F = 75, Age = M: 21.3, sd = 2.59). After obtaining informed consent and completing a second screening for MRI counter-indications, participants completed MRI scanning, a blood draw, and questionnaire measures administered through Qualtrics.

Self-report measures

Life history questionnaire (LHQ)

We used an unnamed validated measure of relative socio-economic status as a measure of economic

privilege (Griskevicius, Tybur, Delton, & Robertson, 2011), which here we call the LHQ for ease of reference. The LHQ has been used as a proxy measure of the relative harshness and instability experienced in the developmental context to predict adult behavior (Griskevicius et al., 2013). It consists of six statements about past, present, and future estimations of economic privilege. Three questions ask about the past (e.g., "My family usually had money for things when I was growing up). Two questions ask about the present (e.g., "I don't worry too much about paying the bills") and one questions asks about future expectations (i.e., "I don't think I'll have to worry about money too much in the future"). Participants rated the extent to which they agreed with these statements on a 1 to 7 Likert scale (from 1 = Strongly disagree to 7 = Strongly agree). The creators of the measure reported a two-factor structure that separates items pertaining to past experiences of privilege versus current and future expectations (Griskevicius et al., 2011). Past subscores can range from 3 to 24, with higher scores indicating greater economic privilege during development (N = 155, Skew = -.84, Mean = 17.63, Median = 19, MAD = 2.97,). Given our interest in developmental context, we report results using the Past subscore, which we call economic privilege. Results using the omnibus score and the current status score are reported in the Supplementary Materials.

Social interaction anxiety scale (SIAS)

The SIAS (Brown, Turovsky, Heimberg, Juster, & Et Al, 1997) is composed of 20 statements about experiences of anxiety during social interactions (e.g., "I am tense mixing in a group"). Participants rate the degree to which statements could be applied to themselves on 4-point Likert scale (from 0 = Not at all true of me to 4 = Extremely true of me). Scores can range from 0 to 60 with higher scores indicating greater social anxiety. The SIAS is used as a screening measure for Social Phobia (fear to specific situations) and Social Anxiety Disorder (generalized fear of social situations) with cut off scores at 34 and 43 respectively. Twenty-seven participants were at or above the social phobia cut-off (N = 155, Skew = .97, Mean = 20.97, Median = 18, sd = 13.18). Scores on the SIAS are independent of trait anxiety.

State-trait anxiety inventory (STAI)

We used the Trait subscale of the STAI composed of 20 items indicative of general worry that is stable across situations (e.g., "I worry too much over something that really doesn't matter."). Participants rate how often events described in these statements happen to them on a 4-point Likert scale (1 = Almost never to 4 = Almost always). Scores range from 20 to 80 with greater scores being indicative of greater trait anxiety. Scores of below 50 suggest low anxiety while scores between 50 and 65 suggest moderate anxiety and scores above 65 suggest high levels of anxiety. Twenty-four participants were at or above the moderate level of anxiety (N = 129, Skew = .40, Mean = 39.91, Median = 39, sd = 10.16).

The center of epidemiological studies depression scale-revised (CESD-R)

The CESD-R (Eaton, Smith, Ybarra, Muntaner, & Tien, 2004) is a 20-item measure composed of affective and cognitive statements indicative of depression. Participants rate the number of days they have felt this way in the past week or so on a 0 to 4 Likert scale (0 = not at all or less than 1 day to 4 = Nearly every day for two weeks). However, for scoring purposes, the last two choices are given a score of 3 (4's are changed to 3's). Therefore, scores range from 0 to 60 with greater scores indicating greater depressive symptomology. Score of 16 and above indicates at least subthreshold depression. Thirty participants were at or above subthreshold depression (N = 129, Skew = 1.73, Mean = 11.30, Median = 8, sd = 10.46). This scale closely reflects the depression criteria from the DSM-IV.

OXTR rs237915 genotype

Blood collection and DNA extraction

Eight milliliters of blood were collected in mononuclear cell separation tubes (BD Vacutainer CPT with sodium citrate, BD Biosciences, Franklin Lanes, NJ) from each participant. Blood samples were immediately spun at 1800 RCF for 30 min to separate the mononuclear cell fraction per product protocol. The mononuclear cells were then lysed and DNA was extracted using the reagents supplied in the Gentra Puregene Blood Kit (Qiagen, Valencia, CA). DNA was stored at −20°C prior to further analysis.

Genotyping procedures

Ten nanograms of genomic DNA was used as a template for PCR using a Pyromark PCR kit (Qiagen, Valencia, CA) and 0.2 uM primers (5′-AAGGGAGGGTCAAAATCAGC-3′) and (5′-biotin-GGGGAGGTGATTTGGTTTTAG-3′). Samples were amplified on a C1000 Thermal Cycler (Biorad, Hercules, CA). This amplifies a region of the *OXTR* gene that contains rs237915. Successful PCR amplification of a single fragment that runs at 64 bp was confirmed using agarose gel electrophoresis for each sample.

Pyrosequencing was performed using primer (5′-GGGTCAAAATCAGCA-3′) on a Pyromark Q24 using PyroMark Gold Q24 Reagents (Qiagen, Valencia, CA) per the manufacturer's protocol. Genotype for *OXTR* SNP rs237915 breakdown was as follows: 4 CC homozygotes, 61 CT heterozygotes, and 91 TT homozygotes. Allele frequencies were consistent with those seen in the CEPH population (Data: C′ = .22, T′ = .78; CEPH: C′ = .33, T = .67) and the data are in Hardy-Weinberg equilibrium. CC and CT individuals were combined for analyses (C-carriers) versus TT homozygotes. Data from Loth and colleagues (Loth et al., 2014) indicate that the C allele, in particular, the CC genotype is most sensitive to interactions with the environment. Given the rarity of the CC genotype, we tested the hypothesis that the presence of the C allele increases risk for negative mental health outcomes and neural plasticity in response to adverse experiences. Therefore, we combined CC and CT individuals into a C-carrier group.

Fmri data acquisition and analyses

Participants completed a widely-used emotional face matching fMRI task (Hariri et al., 2002), and standard image acquisition and FSL preprocessing steps were followed Analyses were then conducted using FEAT (fMRI Expert Analysis Tool, version 6) from FSL. Participants used the left/right button box to match a target fearful or angry face from the NimStim (Tottenham et al., 2009) set of facial expressions displayed at the top of the screen with the same emotion portrayed in one of two faces shown at the bottom sides of the screen. Six blocks of this social perception task were interlaced with five blocks of an identical oval orientation matching task. A block is defined as 4 of the social or cognitive stimuli presented for 5s for a total of 20s per block.

Image acquisition

Participants were scanned using a Siemens 3 Tesla MAGNETOM Trio high-speed imaging device with a 12-channel head-coil, an integrated mirror, and head stabilizers. One hundred and seventy-six high-resolution structural T1-weighted magnetization-prepared rapid-acquisition gradient echo images were obtained before functional scans (1-mm slices, TR = 1900 ms, TE = 2.53ms, flip angle = 9°, FOV = 250mm; image matrix, 256 mm x 256 mm; slice thickness, 1 mm). We collected 130 functional T2-weighted Echo Planar images (EPI's) sensitive to BOLD contrast in volumes of twenty-eight 3.5-mm transversal slices coplanar to the anterior and posterior commisures covering the whole brain (1-mm slice gap, TR = 2000ms, TE = 40ms, flip angle = 90°, FOV = 192 mm, matrix = 64 x 64, voxel size = 3 x 3 × 3.5mm). Stimuli were presented with Psychophysics Toolbox in MATLAB and projected using an LCD AVOTEC projector on a screen behind the participant seen through the head-coil mirror.

Preprocessing

Imaging data were preprocessed and analyzed using FMRIB Software Library (FSL) software (Version 5.8; www.fmrib.ox.ac.uk/fsl). We assessed deviation using center of mass measures (BHX/XCEDE Tools, version 1.8.16, Bioinformatics Information Research Network) ensuring no greater than 3mm deviation on the *x, y*, and *z* dimensions. Motion was corrected using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), brain extraction performed using BET(Smith, 2002), spatial smoothing performed using a 5-mm full width at half-minimum Gaussian kernel, grand-mean intensity normalization by a single multiplicative factor, and high pass temporal filtering using a Gaussian weighted least-squares linear fitting with sigma equal to 50.0 s. Finally, functional imaging was registered to each individuals anatomical image and to the Montreal Neurological Institute (MNI) standard space, using FLIRT (Jenkinson et al., 2002).

Individual-level contrasts of faces > ovals were created and parameter estimates carried forward to group-level analyses using FSL's improved linear model with local autocorrection (Woolrich, Ripley, Brady, & Smith, 2001). Specifically, we modeled regressors for faces and ovals conditions by convolving the time course using a gamma hemodynamic response function (HRF), adding a temporal derivative, and applying temporal filtering.

Two sample co-variate analysis

We conduced a group-level, two-sample, co-variate interaction analyses using FSL's local analysis of mixed effects (FLAME) stage 1. This analysis tested the *a priori* hypothesis that SNP rs237915 genotype interacts with economic privilege to moderate task-specific activity in the bilateral VS. Using the same mask as Loth and colleagues (Loth et al., 2014), we defined the bilateral VS space based on a meta-analysis of reward processing (Liu, Hairston, Schrier, & Fan, 2011). To do so, mean faces > ovals activation and grand-mean centered LHQ scores were entered for C-carriers and TT homozygotes in the same generalized linear model while controlling for sex. We used a cluster-wise mixed effects strategy using estimated smoothness and Gaussian Field Theory to correct for multiple comparisons and to determine significant cluster size ($Z = 2.3$, $p = .05$).

We also conducted a second, exploratory whole-brain analysis with the same parameters.

Psychophysical interaction (PPI) analyses

To understand how SNP rs23915 genotype and economic privilege might be related to neural interactions involving the VS, we assessed task-based connectivity (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) between the whole brain and the VS mask used in the *a priori* analysis.

First level analyses where conducted using FEAT and FSL's improved linear model with local autocorrelation correction. For each participant, we created an HRF convolved task regressor by applying a double-gamma HRF to the regressor representing the faces > ovals contrast with a temporal derivative added and a temporal filtering applied. We then extracted the time course for the VS seed region. Finally, a PPI was generated through the interaction between the task regressor and the VS time series and added as the third regressor. To account for the shared variance between faces and oval conditions, we added the faces + oval contrast time course, which was also convoluted in the manner of the faces > ovals contrast, to the individual models. First level analyses generated task-dependent co-activity maps indicating individual level connectivity between VS and other brain regions. These activation maps were then entered into a higher-level group analysis carried out in the same manner as the whole-brain two sample covariate analyses described above. The model was corrected for multiple comparison using a more stringent cluster threshold of $Z = 2.57$, $p < .05$. This analysis strategy performed well in a recent meta-analysis (Eklund, Nichols, & Knutsson, 2016).

Gene-brain-environment effect on psychopathology analyses

Average level Z statistics were extracted from the *a priori* VS mask at the individual face > oval contrast for each participant. To assess the relationship among mental health symptoms, task-dependent VS activity, rs237915 genotype, and economic privilege, we completed three separate multiple regression analyses (one per questionnaire) using the general linear model. Each regression estimated independent and interaction effects of VS Z statistics, genotype, and economic privilege on one of the three mental health measures. All models were adjusted for sex. All statistics were completed in RStudio (V 0.99.03). Models were assessed for normality of residuals, linearity, heteroscedasticity, and influence (Cook's distance). All models met these assumptions and no outliers were found.

Significant interactions arising from the multiple regression models were then further probed for mediated and moderated moderation using the laavan (Rosseel, 2012) in RStudio (V 0.5) Structural Equation Modeling (SEM) package. Given that our hypotheses centered around the moderating effects of *OXTR* on the associations between economic privilege and VS activation and VS activation and social social anxiety, we used a moderated moderation model. We then calculated simple slopes using the method developed by Preacher and colleagues (Preacher, Curran, & Bauer, 2006) through their open-sourced online calculator (http://www.quantpsy.org/interact/mlr3.htm).

Test of moderated moderation

Significant interactions arising from the multiple regression models were then further probed for moderated moderation. Moderated moderation occurs when the relationship between x (VS Z statistics) and y (mental health measure) is dependent on the level of a moderator z (economic privilege) and the direction or magnitude is in part dependent on another moderator, w (Preacher et al., 2006) (rs237915 genotype). These relationships are expressed through the prediction equation:

$$\hat{y} = \hat{b}_0 + \hat{b}_1 x + \hat{b}_2 z + \hat{b}_3 w + \hat{b}_4 xz + \hat{b}_5 xw + \hat{b}_6 zw + \hat{b}_7 xzw$$

where $\hat{y}$ is the estimated mental health score as predicted by the model, $\hat{b}_0$ represents the model intercept, and $\hat{b}_1 - \hat{b}_7$ represent the sample estimates of the corresponding parameters and their interaction term. Moderated moderation was formally tested using path analysis and maximum likelihood estimation through laavan (Rosseel, 2012) in RStudio (V 0.5). Indicators were centered to control for multicollinearity. Two paths were entered into a multi group analysis with the first testing the linear association between mental health score, VS Z statistic, economic privilege and the product of the two independent variables (their interaction), and the second being a path testing the linear association between VS Z statistic and economic privilege. Genotype was added as the group variable. All continuous predictors were mean centered. Parameter estimates were bootstrapped and standardized to create a confidence interval and for reporting purposes.

Calculation of simple slopes

Following this, we further probed interaction effects through the simple slopes method developed by Preacher and colleagues (Preacher et al., 2006) through their open-sourced online calculator (http://www.

quantpsy.org/interact/mlr3.htm). The region of significance (the specific values of both moderators at which the relationship between mental health and VS become significant), simple intercept, and simple slope were calculated using one median absolute deviation (MAD) above and one MAD below the median of the life history measure. Deviation from the median was used for its relative robustness.

Results

Neural response to angry and fearful faces is dependent upon the interaction between OXTR genotype and economic privilege

The *a priori* region of interest analysis of bilateral VS indicated a significant interaction between rs237915 genotype and economic privilege. Specifically, VS response decreased for C-carriers as economic privilege increased while the inverse was true for TT homozygotes (Figure 1). Right VS peak activity (Z = 3.56) occurred at $x = 10$, $y = 6$, $z = -8$; $k = 229$. Left VS peak activity (Z = 3.51) occurred at $x = -16$, $y = 16$, $z = -10$; $k = 134$ (Table 1).

The exploratory whole brain analysis revealed five clusters that were significantly associated with the interaction between genotype and economic privilege. VS response decreased for C-carriers as economic privilege increased in multiple areas, whereas the opposite was true for TT homozygotes. The largest cluster encompassed mesolimbic areas with the peak voxel near left caudate ($x = -22$, $y = 26$, $z = -4$; $k = 1189$) and the center of gravity located in subcallosal cortex ($x = -0.14$, $y = 15.8$, $z = -5.22$). A second cluster was found in motor cortex areas with peak activation occurring in right supramarginal gyrus ($x = 28$, $y = -36$, $z = 42$; $k = 798$) with the center of gravity at precentral gyrus ($x = 31.7$, $y = -18.2$, $z = -46.1$; $k = 1144$). Two significant clusters were identified at right and left lateral occipital cortex extending to precuneus with peak coordinates at right lateral occipital cortex ($x = -14$, $y = -62$, $z = 56$, $k = 515$) and left supramarginal gyrus ($x = -20$, $y = -58$, $z = 64$, $k = 646$) respectively. Finally, a significant cluster was identified in left dorsal medial PFC (dmPFC) extending laterally with peak coordinates at left dmPFC ($x = -22$, $y = 34$, $z = 30$, $k = 604$).

Neural coupling with ventral striatum is dependent upon the interaction between OXTR genotype and economic privilege

Task-based connectivity analyses revealed genotype and economic privilege-dependent coupling between the VS seed region and regions of frontal and posterior cortex. Specifically, with increased economic privilege, C-carriers show decreased task-dependent connectivity between bilateral VS and a cluster in vmPFC (peak coordinates: $x = -6$, $y = 40$, $z = -22$; $k = 182$), and increased VS task-dependent connectivity in three unique clusters. These clusters were contained within

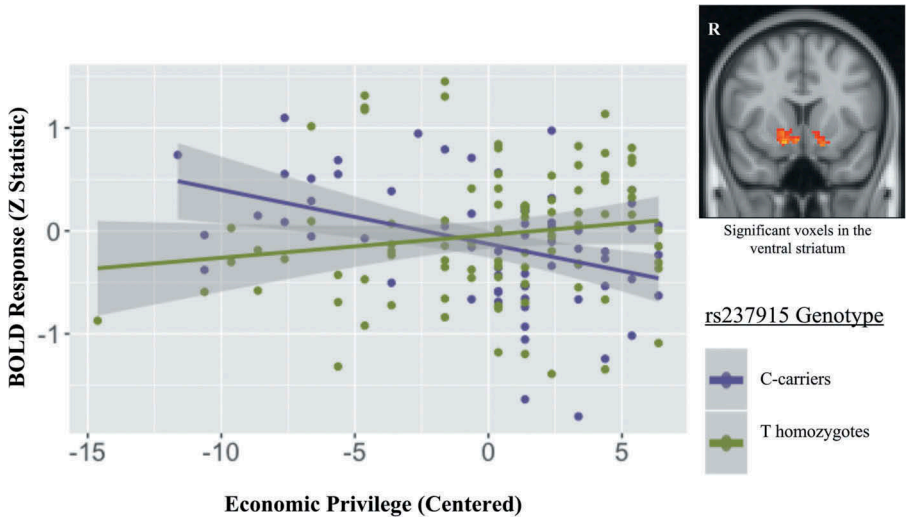

Figure 1. Ventral striatal response to angry and fearful faces is dependent upon the interaction between *OXTR* genotype and economic privilege. C-carriers (purple) show decreased VS BOLD response as a function of greater economic privilege while TT homozygotes (green) show the opposite. Mean Z statistics are plotted against economic privilege (mean centered raw Past Life History Questionnaire score; $n = 156$). Gray shading indicates 95% confidence interval around the line of best fit. Upper right: surviving clusters from ventral striatum region of interest in MNI standard space taken from Loth et al. peak coordinates surrounded by the 8mm sphere (Y = 12).

Table 1. Local maxima for C-carriers > TT homozygotes x Economic Privilege region of interest (ROI) and whole brain analyses using the Past LHQ score. ROI GRF-theory based thresholding corrected at p < .05. Whole-brain significant cluster threshold: Z = 2.3, p < .05.

				X	Y	Z
Anatomical region	*k*	P	Max Z	Local Maxima		
***A priori* ROI Analysis using economic privilege PAST scores**						
Right Ventral Striatum	229	0.00145	3.56	10	6	−8
Left Ventral Striatum	134	0.00805	3.51	16	16	−10
Exploratory whole brain analysis using economic privilege PAST scores						
Middle frontal gyrus	1189	2.92E-06	3.91	22	26	−4
Precentral gyrus	1144	4.47E-06	4.25	28	−36	42
Left Lateral Occipital Cortex	646	0.000891	4.09	20	−58	64
Left dmPFC	604	0.00147	3.98	22	34	30
Right Lateral Occipital cortex	515	0.00441	3.67	14	−62	56

left angular gyrus (peak coordinates: $x = -44$, $y = -44$, $z = 6$; $k = 687$), right lateral occipital cortex extending to the right occipital pole (peak coordinates: $x = 32$, $y = -88$, $z = 26$; $k = 247$), and right lateral occipital cortex extending to right angular gyrus (peak coordinates: $x = 34$, $y = -46$, $z = 30$; $k = 202$; Table 2, Figure 2).

Depressive symptoms and trait anxiety are associated with lower economic privilege

Higher depressive symptoms are associated with lower economic privilege

A multiple regression model predicting depressive symptoms (CESD-R) from VS activation, rs237915 genotype, and economic privilege was not significant (F (8,120) = 1.30, p = .25). However, we do find a significant negative relationship between economic privilege and depressive symptoms (t = −2.84, p < .01). No significant interaction effects with VS, genotype, or economic privilege emerged from this model.

Higher trait anxiety is associated with lower economic privilege

A multiple regression model predicting trait anxiety (STAI-Trait) from VS activation, rs237915 genotype, and economic privilege approached significance (F (8,120) = 1.29, p = .26). As above, we find a significant negative relationship between economic privilege and trait anxiety (t = −2.57, p = .01). No significant interaction effects with VS, genotype, or economic privilege emerged from this model.

Table 2. Local maxima for brain regions showing increased bilateral ventral striatum functional coupling for C-carriers by Economic Privilege.

Anatomical Region	*k*	Max Z	X	Y	Z
Left Angular Gyrus	212	4.11	−44	−56	32
Superior Parietal Lobule	134	3.88	−38	−50	54
Right Lateral Occipital Cortex	93	4.27	32	−88	26
Left Occipital Pole	72	4.05	−14	−98	20

Social anxiety is associated with the interaction between OXTR genotype, economic privilege and ventral striatal activation

A multiple regression model predicting social anxiety (SIAS) from VS activation, rs237915 genotype, and economic privilege was statistically significant (F (8:146) = 2.52, p = .01). We find a significant three-way interaction between VS activity, economic privilege, and genotype on social anxiety (t = −2.3, p < .01). To further probe this three-way interaction, we first tested for mediated moderation, or that the relationship between VS activation and social anxiety *can be explained by* the level of economic privilege, given rs237915 genotype. This test failed to show significance (B = .094, Z = .25, p = .80; CI 95%: -.64, .83).

We next tested for moderated moderation, or that the level of economic privilege *differentially influenced* the relationship between VS activation and social anxiety depending on *OXTR* genotype (Figure 3A). We find that TT homozygotes show a relationship between social anxiety and VS activation (B = -.24, Z = −2.50, p = .01) and an interaction (B = .28, Z = 2.64, p < .01) between economic privilege and VS activation on social anxiety. TT homozygotes with lower economic privilege (Figure 3B, solid green line) and low VS have greater anxiety, whereas TT homozygotes of high economic privilege (Figure 3B, dashed green line), show no relationship between VS activation and social anxiety. In contrast, C-carriers show a significant crossover interaction (B = -.36, Z = −3.10, p < .01) between economic privilege and VS activation (Figure 3A) such that those with lower economic privilege (Figure 3B, solid purple line) and high VS activation display greater social anxiety. However, C-carriers with high economic privilege (Figure 3B, dashed purple line) and high VS activation

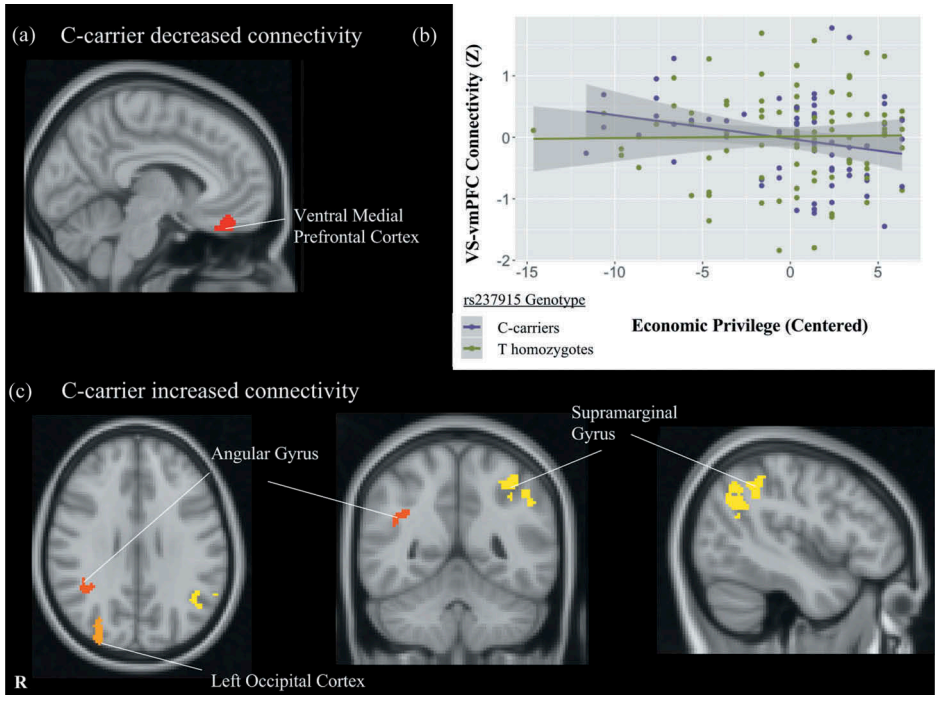

Figure 2. Ventral striatal connectivity in response to angry and fearful faces is dependent upon the interaction between *OXTR* genotype and economic privilege. With increased economic privilege, C-carriers exhibit decreased bilateral VS connectivity with vmPFC (A) and increased VS connectivity with right occipital pole, left lateral occipital cortex, angular gyrus and supramarginal gyrus (C). Inset: mean Z statistics for VS-vmPFC connectivity plotted against economic privilege. Significant cluster thresholding: $Z = 2.58$, $p < .05$. R = right (B).

display low social anxiety. The direction of these relationships was established by examining the simple slopes. The unstandardized simple slope for C-carriers was 4.49 ($t = 1.92$, $p = .06$) for those one median absolute deviation (MAD) above the median of the economic privilege measure and −6.45 ($t = -2.12$, $p = .04$) for those MAD below the median. In contrast, the unstandardized simple slope for TT homozygotes was 1.10 ($t = .45$, $p = .66$) for those one MAD above the median of the economic privilege measure and −5.02 ($t = -2.90$, $p < .01$) for those one MAD below the median.

Discussion

We find that increased VS activation to negative social stimuli largely acts as a protective factor against social anxiety. For those with a single risk factor, either genetic (C-carriers) or environmental (low economic privilege), failure to activate the VS was associated with a more socially anxious phenotype. This is in line with previous research showing that lower VS activation is a risk factor in mood and anxiety disorders, including social anxiety (Boehme et al., 2013; Freitas-Ferrari et al., 2010). Our results extend these findings, suggesting that genetic and environmental pathways interact to shape VS sensitivity to social stimuli.

A recent paper using an animal model identified a polymorphism in *OXTR* that was related to oxytocin receptor expression in the nucleus accumbens (King, Walum, Inoue, Eyrich, & Young, 2016). Furthermore, increased expression of the oxytocin receptor in the nucleus accumbens has been liked to resilience against early life experiences of social isolation in the same animal model (Barrett, Arambula, & Young, 2015). Though a similar relationship has not yet been identified in humans, perhaps rs237915 (or another SNP in linkage disequilibrium) may modulate oxytocin usage in the VS. Within this framework, rs237915 C-carriers' risk may be derived from a lower capacity to respond to oxytocin in the VS via reduced oxytocin receptor expression However, enriching experiences available in high economic privilege environments may help C-carriers mitigate risk either by epigenetically tuning *OXTR* expression (Puglia, Lillard, Morris, & Connelly, 2015) in the VS or via indirect action on other neurotransmitter systems, like dopamine (Baskerville & Douglas, 2010). In contrast, T homozygotes might benefit from increased oxytocin receptor expression in the VS and show resilience against early life adversity, with less benefit in this system from early life enrichment.

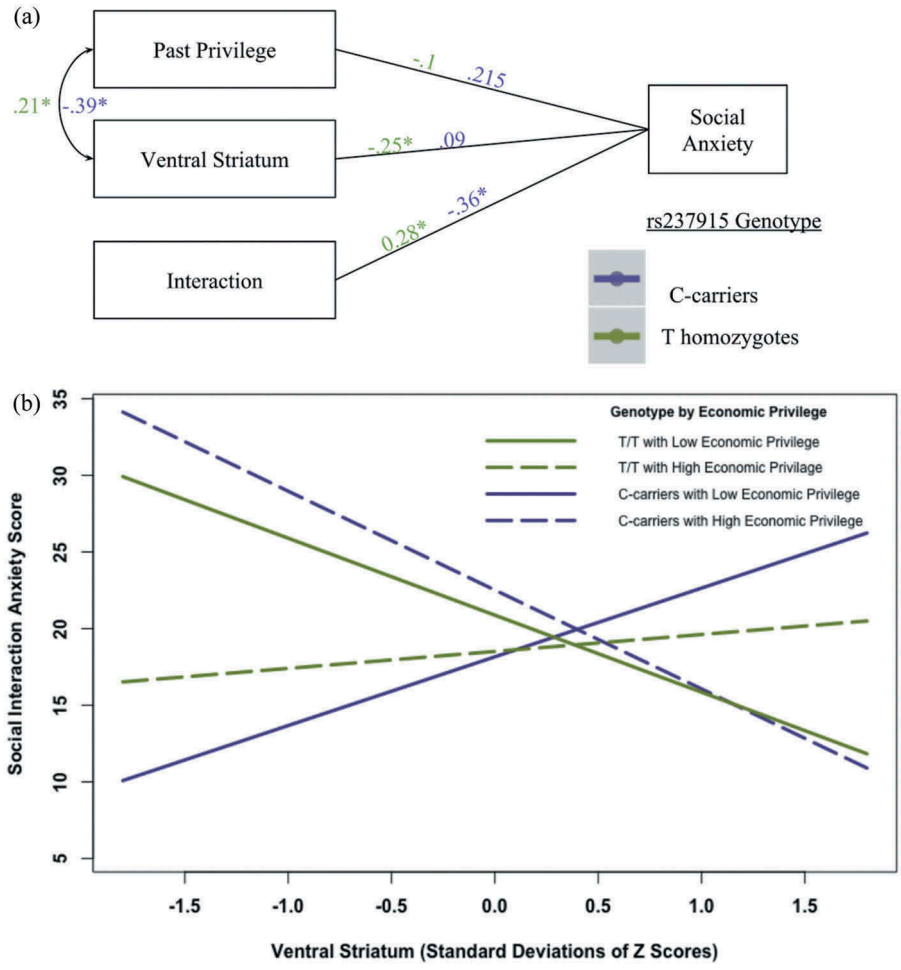

Figure 3. *OXTR* genotype, economic privilege and ventral striatal activation interact to influence social anxiety. A) Model showing how the relationship between predictors (and their interaction term) and social anxiety depends on rs237915 genotype. Unstandardized regression weights for TT homozygotes are in green while regression weights for C-carriers are in purple. B) Maximum likelihood ratio 3-way interaction among *OXTR* genotype, VS BOLD, and economic privilege on social interaction anxiety. Solid lines indicate one median absolute deviation (MAD) above the median of the economic privilege measure. Dashed lines indicate one MAD below the median of the economic privilege measure. Green lines indicate TT homozygotes and purple lines indicate C-carriers. Z statistics for the faces > ovals contrast is plotted at one standard deviation above and below the mean Z statistic for the entire sample.

Epidemiological research strongly supports that lower economic privilege itself is a risk factor for psychopathology. Our data follow this pattern, though only social anxiety was significantly associated with the interaction among *OXTR* genotype, VS response, and economic privilege. Examining this interaction in a larger sample might reveal that these risk factors impact additional mental health outcomes.

Paradoxically, for individuals with *both* genetic and environmental risk, *lower* VS activation was associated with *less* social anxiety. Analyses examining the connectivity between VS and vmPFC offer some clues as to other moderating neural structures involved in the processing of negative faces. In our exploratory analyses, C-carriers with low economic privilege generally showed higher mesolimbic activation, higher vmPFC activation, and also increased connectivity between VS and vmPFC. vmPFC is generally thought of as an evaluative area, involved in assessing risk, threat, and emotional valence (Roy, Shohamy, & Wager, 2012). While increased vmPFC activation has been related to down-regulating amygdala activation in response to threat (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015), its projections to VS also make it part of the reward and motivational salience network (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). Human and animal work indicate that vmPFC input is crucial in modulating reward-related VS activation (Ghazizadeh, Ambroggi, Odean, & Fields, 2012) and even density of the accumbens subsection of VS (Pujara, Philippi, Motzkin, Baskaya, & Koenigs, 2016). At the same time that this motivational salience system is sensitized in

low economic privilege for C-carriers, VS interactions with social cognitive areas, specifically angular gyrus and supramarginal gyrus (Bzdok et al., 2016), are decoupled. This encourages an emphasized motivational salience system and a de-emphasized social-cognitive evaluative system: a pattern that could leave one vulnerable to stress in response to even irrelevant social threat as in this paradigm. As such, lower VS sensitivity to social cues could be beneficial in reducing perceived threat (one aspect of social anxiety) in less privileged environments, though this may present a tradeoff for difficulties in other system functions. Targeted studies can be designed to test these models.

Whole-brain exploratory findings suggest that broader social cognitive and regulatory regions are also impacted by oxytocin genotype and experiences of economic privilege. Gene by environment interactions were found in angular gyrus and precuneus cortex. These areas are part of the Default Mode Network, associated with task negative activity, as well as with social cognitive processes such as social-understanding and self-referencing (Seghier, 2013; Utevsky, Smith, & Huettel, 2014). Importantly, these areas also show increased activation (Gentili et al., 2009) and altered resting-state connectivity (Zhu et al., 2017) in social anxiety disorders. Finally, occipital areas were also associated with this gene by environment interaction. Of note, previous research has found greater occipital activation in adults who had lower economic privilege in adolescence (Gonzalez et al., 2016). Emerging literature suggests that occipital activation may be related to salience and attentional deployment, especially in reward contexts (Padmala & Pessoa, 2011). Possibly, these system-wide differences indicate endophenotypic calibration based on gene by environment interactions which may reflect coping or disorder depending on context. Future research should investigate the meaning of these system-wide individual differences and how they relate to mental health phenotypes.

One possible application of the current findings is in the investigation of intranasal oxytocin therapeutic effects. Oxytocin treatments are inconsistent when applied to psychological disorders like social anxiety. Accounting for gene-environment interactions will likely improve our ability to predict which treatments work for whom (Bakermans-Kranenburg & Van Ijzedoorn, 2014). Furthermore, the addition of neuroimaging and in particular considering VS response and connectivity during social processing may better elucidate neural mechanisms underlying both pathology and treatment efficacy. The current study represents a stepping stone towards more integrated models of pathophysiology in social anxiety and perhaps other forms of psychopathology

Limitations to the current study include classifying both CC and CT genotypes as "C-carriers", potentially small cells sizes modeled in the simple slopes, and use of a retrospective measure. Future research should investigate these gene by environment relationships in a larger sample size or use a targeted sampling strategy where dosage of effects of both "risk" allele and economic privilege may be investigated. Future work should also test our model using a prospective longitudinal approach capturing multiple dimensions of privilege and broader assays of anxiety and depression phenotypes. *OXTR* rs237915 is largely understudied, individuals with lower economic privilege remain underrepresented in neuroimaging and genetic studies, and assays of context are underdeveloped, all of which obscure gene-environment interactions. These limitations are reflected in our own study which relied on self-reported data and a restrictive sample. In order to better understand the development of typical and pathological phenotypes, future work will need to consider these factors as well as epigenetic modifiers which are at the interface of gene-environment interactions.

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